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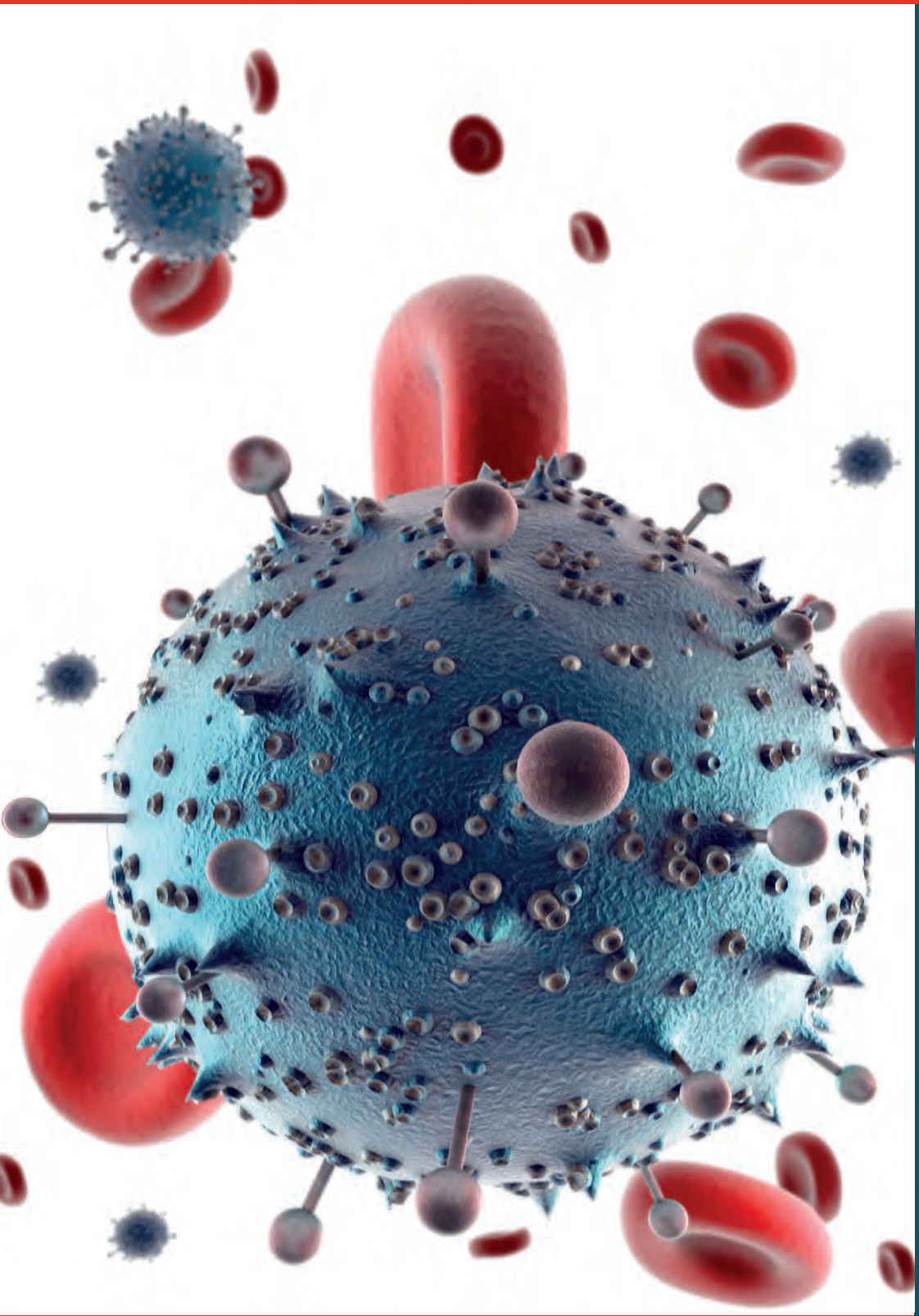

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Eftenem

efavirenz | emtricitabine | tenofovir

FIXED DOSE COMBINATION OF EFV/FTC/TDF

INDICATION[1]

For use alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults

Eftenem is a fixed-dose combination tablet containing 600 mg of EFV, 200 mg of FTC and 300 mg of TDF – ***the preferred agents for use in treatment-naïve HIV patients***[2,3,4]

...its all about trust

EFV = efavirenz; FTC = emtricitabine; HIV = human immunodeficiency virus; TDF = tenofovir disoproxil fumarate

REFERENCES: 1. EFTENEM package insert (13 August 2013). **2**. Killingley B, Pozniak A. The First Once-Daily Single-Tablet Regimen for the Treatment of HIV-Infected Patients. *Drugs of Today*. 2007;**43**(7):427-442. **3**. National Consolidated Guidelines for the Prevention of Mother-To-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults. National Department of Health, South Africa. April 2015. Available at: http://www.sahivsoc.org/upload/documents/ART%20Guidelines%2015052015.pdf. Accessed: 1 October 2015. **4**. Meintjes G, Black J, Conradie F, *et al*. Guideline: Adult antiretroviral therapy guidelines 2014 - Southern African HIV Clinicians Society. *S Afr J HIV Med*. 2014;**15**(4):121-143.

S4 **Eftenem**: Each film-coated tablet contains 600 mg efavirenz, 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate (tenofovir DF). Reg. No.: 47/20.2.8/0118. For full prescribing information refer to the package insert approved by the MCC. HCR: Specpharm (Pty) Ltd. Reg. No. 97/00203/07. Cnr 15th and Pharmaceutical Road, Halfway House, Midrand. PO Box 651, Halfway House, Midrand, 1685, Gauteng. Telephone: + 27 11 652 0400. **CERTIFICATION NUMBER:** EFTEN/22/28-09-2015.

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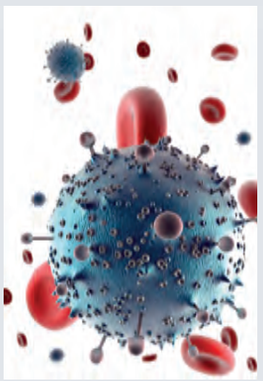

Virus cells in blood (photo: http://www.istockphoto.com/muzon).

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Care of HIV-exposed and HIV-infected neonates

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South Africa has implemented a successful prevention-of-mother-to-child-transmission (PMTCT) intervention programme. Important milestones achieved in 2012 include: (1) an estimated 83% of all pregnant women living with HIV in South Africa received antiretrovirals (ARVs) for PMTCT, (2) early vertical transmission of HIV in infants ≤ 2 months of age declined to 2.4% and (3) early infant HIV diagnosis coverage (i.e. coverage in infants < 2 months of age) reached 72.6%.[1,2]

Complete elimination of mother-to-child transmission (MTCT) will be hard to accomplish. However, further reduction in MTCT may be possible if newborns at high risk of acquiring HIV infection (high-risk infants) after intrapartum exposure are routinely identified and administered an intensified post-exposure prophylaxis (PEP) regimen comprising 2 or 3 ARVs.[3] The recently updated hospital-level Standard Treatment Guidelines and Essential Medicines List, and the 2014 National Consolidated HIV Guidelines, include risk stratification for newborns.[4,5] The latter document recommends one of several neonatal PEP regimens depending on the risk of MTCT: (1) for low-risk infants whose mothers were on lifelong antiretroviral therapy (ART) during pregnancy, daily nevirapine (NVP) for 6 weeks is recommended, (2) for high-risk infants because their mothers were on ART for < 4 weeks prior to delivery, or because their mothers were diagnosed with HIV infection within 72 h of delivery, or because their mothers tested HIV positive > 72 h post-delivery, daily NVP for 12 weeks is recommended if breastfed, (3) for infants of breastfeeding mothers with newly diagnosed HIV infection, dual NVP/zidovudine (AZT) prophylaxis is recommended with revision based on the infant's immediate HIV DNA polymerase chain reaction (PCR) result and (4) for high-risk infants born to mothers whose latest viral load results were > 1000 copies/mL, dual NVP/AZT prophylaxis is recommended.[5] These recommendations may be difficult for the average clinician to digest and remember. Consequently, the extent to which they are correctly administered in routine clinical practice requires evaluation. If implementation proves difficult, a simplified intervention for high-risk infants should be devised.

Identifying high-risk infants and initiating ART when needed is critical to reduce the associated HIV-related morbidity and mortality. A South African study that analysed post-neonatal deaths under 12 months of age identified a peak in mortality between 1 and 3 months owing to HIV infection.[6] Early survival was estimated in an analysis of pooled individual data from antiretroviral-naïve infants who had been enrolled in 12 sub-Saharan African studies. According to this analysis, net survival of perinatally infected infants declined from 99% at 28 days to 83% by 90 days of life, confirming that a significant mortality risk exists between 1 and 3 months of life.[7] The Children with HIV Early Antiretroviral Therapy (CHER) trial drew further attention to the vulnerability of HIV-infected infants, convincingly demonstrating that early ART significantly lowered the mortality and disease progression risks of HIV-infected infants. The CHER trial randomly assigned HIV-infected infants aged between 6 and 12 weeks with mild HIV disease (CD4 percentage ≥ 25% and CDC stage N or A disease) to receive ART either immediately (early ART cohort) or when the CD4% had declined to less than 20% (deferred ART cohort). The median age at which ART was initiated was 7.4 weeks in the early ART cohort, and 20 weeks in the deferred ART cohort.[8,9] Of 532 infants who were screened for eligibility for the CHER trial, 122 (22.9%) were excluded from the trial because they had a CD4 percentage < 25%, were symptomatic or had CDC stage C disease, implying that a sizeable proportion of young HIV-infected infants have advanced HIV disease.[8] A more recent analysis of 403 infants commenced on ART before the age of 12 weeks in public sector clinics in Cape Town and Soweto showed that, at ART initiation, 250 (62%) had advanced HIV disease.[10]

In June 2008, the World Health Organization (WHO) acknowledged the public health importance of the CHER trial's findings by recommending that, upon diagnosis, all HIV-infected infants (< 12 months of age) should commence ART as soon as possible, irrespective of their clinical stage or CD4 count.[11] South Africa was slow to embrace this recommendation; on 01 December 2009, 18 months after the WHO report, President Zuma announced in his World AIDS Day speech that the country would implement this intervention.[12]

Although the benefits of early treatment of HIV-infected infants are now well established, identifying these infants remains a challenge. South Africa's practice of routine HIV DNA PCR testing at 6 weeks of life for HIV-exposed infants fails to recognise HIV infection during the first 6 weeks of life, which may be too late to initiate ART at 7.4 weeks of age as per the CHER trial and has reduced sensitivity for detecting HIV infection in infants who receive a minimum of 6 weeks of ARVs for PMTCT.[3] Birth HIV DNA PCR testing of HIV-exposed neonates coupled with early ART initiation in HIV-infected neonates should be liberalised so as to reduce the observed increase in mortality between 1 and 3 months of age in untreated infants. In 2013, South Africa recommended birth HIV DNA PCR testing for HIV-exposed low birth weight infants, and the 2014 National Consolidated HIV Guidelines recently extended birth testing to 6 categories of newborns deemed to be at high risk of antenatal or intrapartum HIV infection.[4,5] It will be important to assess how well this recommendation is implemented, and whether it results in increased ART initiation during the neonatal period and reduced HIV-related infant morbidity and mortality.

Finally, recent studies suggesting additional benefits of early ART provide further motivation to identify and treat during the early neonatal period. When ART is initiated in infants less than 6 months of age, the period of viraemia is shortened and the size of the resting CD4+ T-cell latent HIV-1 reservoir is limited.[13] Continuous decay of this reservoir occurs, provided that virological control is sustained, suggesting that lifelong ART may not be necessary for all patients.[14] The clinical course experienced by the Mississippi baby suggested that ART initiation within 30 h of life may prolong the control of viral replication in the absence of ART.[15] However, this supposition was recently challenged by yet another case study. In that report, an HIV-infected neonate was initiated on ART within 30 min of birth, seroreverted and remained clinically well and virologically suppressed while on ART. At the age of 4 years, both HIV-1 RNA and DNA were undetectable. A few weeks later, ART was discontinued, on the assumption that functional cure had been achieved. However, evidence of viral rebound was detected within 7 days of ART discontinuation, raising concerns about the durability of virological control following early neonatal ART.[16]

The challenge for clinicians is the lack of pharmacokinetic and dosing information in neonates for some commonly used ARVs such as abacavir; safety concerns about lopinavir/ritonavir co-formulation in neonates < 14 days of age or infants less than a corrected gestational age of 42 weeks; and uncertainty about the optimal approach of transitioning a neonate from antiretroviral prophylaxis to ART.[17,18] Because of these limitations, a NVP-containing ART regimen should be administered during the neonatal period until it is safe to prescribe lopinavir/ritonavir co-formulation.[15,16,18]

South African clinicians are grappling with the prevention, diagnosis and management of HIV infection in neonates and a limited body of evidence to guide them. In February 2014, the Southern African HIV Clinicians Society convened a colloquium to review the state of knowledge regarding post-exposure prophylaxis for neonates who experienced high-risk HIV exposures during the intrapartum period, and HIV diagnosis and ART during the neonatal period. The meeting was attended by a group of South African paediatric HIV and AIDS experts (Appendix 1). Arising from this meeting are papers by Max Kroon, Gayle Sherman and James Nuttall addressing these very issues, published in this edition of the *Southern African Journal of HIV Medicine*. These papers provide comprehensive guidance for practising clinicians. The colloquium identified potential research questions, discussed in a separate paper by Mary-Ann Davies.

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Appendix 1

The following individuals, listed in alphabetical order, participated in the colloquium entitled 'Diagnosis and Treatment of HIV Infection in Neonates' which took place on 21 February 2014 and/or commented on the series of neonatal papers published in this edition of the *Southern African Journal of HIV Medicine*:

Theunis Avenant
Mo Archary
Ashraf Coovadia
Mark Cotton
Vivian Cox
Mary-Ann Davies
Nonhlanhla Dlamini
Nicolette du Plessis
Brian Eley
Lee Fairlee
Ute Feucht
Lisa Frigati
Ute Hallbauer
Sandy Holgate
Max Kroon
Louise Kuhn
Leon Levin
Aurelie Nelson
James Nuttall
Helena Rabie
Gary Reubenson
Gayle Sherman
Gillian Sorour
Karl Technau
Lloyd Tooke
Kerry Uebel

Evaluation of selected aspects of the Nutrition Therapeutic Programme offered to HIV-positive women of child-bearing age in Western Cape Province, South Africa

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Background: The Nutrition Therapeutic Programme (NTP) involves the provision of food supplements at primary health clinics (PHCs) to correct nutritional deficiencies in vulnerable groups. Although previous studies have identified problems with implementing the programme at PHCs, assessments of its efficiency have been scarce.

Objective: To evaluate implementation of the NTP at PHCs that provide antiretroviral therapy.

Methods: A cross-sectional, descriptive study was conducted at 17 PHCs located within 3 districts of Western Cape Province. Two target groups were chosen: 32 staff members working at the sites and 21 women of child-bearing age enrolled in the NTP. Questionnaires were used to obtain data.

Results: Only 2 women (10%) lived in food-secure households; the rest were either at risk of hunger (29%) or classified as hungry (61%). Most of the women knew they had to take the supplements to improve their nutritional status, but the majority only recalled receiving basic nutritional advice, and the information was mainly given verbally. Ten of the women had shared their supplements with others, mostly with their children. The study identified lack of clearly defined NTP responsibilities at the PHCs, causing confusion amongst the staff. Although many staff members expressed problems with the NTP, only 38% of them reported having routine evaluations regarding the programme.

Conclusion: Several aspects compromised the effectiveness of the NTP, including socio-economic factors leading to clients' non-compliance. The strategic organisation and implementation of the NTP varied between different PHCs offering antiretroviral therapy, and staff experienced difficulties with the logistics of the programme.

Introduction

In 1995, the South African government implemented the Integrated Nutrition Programme (INP) as a response to the poor nutritional status of the country's population. A targeted supplementary feeding programme termed the Nutrition Therapeutic Programme (NTP), as one component of the INP, involves the provision of food supplements at primary health clinics (PHCs) to correct nutritional deficiencies in vulnerable groups.[1] These groups include babies and children (0–18 years), pregnant and lactating women, and patients diagnosed with HIV/Tuberculosis (TB) and other chronic diseases (Table 1). Eligible adult patients are referred and admitted to the NTP based on the following criteria: body mass index (BMI) < 18.5 kg/m^2; unintentional weight loss > 10% over 6 months and unintentional weight loss > 5% in one month. After 6 months, patients are re-evaluated and, if they suit the exit criteria, they are taken off the programme.[2] However, studies have identified problems with implementing the NTP at PHCs, including insufficient financing, unclear responsibilities amongst staff, and knowledge gaps amongst the clients.[3,4,5]

South Africa is severely affected by HIV. Even though antiretroviral therapy (ART) coverage increases, the government still faces challenges in combating the spread of the disease. Good nutrition is crucial when infected with HIV, as both the disease itself and the treatment have metabolic consequences.[6,7] Also, a lowered BMI, which is associated with malnutrition, might increase mortality in HIV patients.[8]

TABLE 1: Current target groups, entry criteria and product options available for patients on the Nutrition Therapeutic Programme in Western Cape Province.

Target group	Entry criteria	Product
Birth < 6 months	Non-breastfed (medically/mentally unfit mother, mother on long-term medication/treatment contra-indicated for breast feeding or mother died)	Infant formula **ONLY** – whey dominant
6–12 months	Growth faltering or mid upper arm circumference (MUAC) = < 125 mm	Infant formula whey dominant **AND** maize-based infant cereal
1–13 years	Growth faltering or MUAC: • 1–5 years = < 135 mm • 6–9 years = < 155 mm • 10–14 years = < 185 mm	Maize-based instant porridge **AND** lactose-free energy drink **OR** maize-based Instant porridge **AND** lactose-free energy drink. Lactose-free energy drink **ONLY** Maize-based instant porridge **AND** RuTF
14–18 years	Growth faltering or MUAC (5–14 years)	Maize-based instant porridge **AND** lactose-free energy drink Maize-based instant porridge **AND** RuTF Lactose-free energy drink **ONLY**
Severe acute malnutrition (SAM) children: birth ≤ 5 years	On 'old' Road-to-Health chart: < 60% expected weight-for-age. On 'new' Road-to-Health booklet: -3SD for weight-for-age or weight-for-height MUAC (1–5 years)	**Infant: 0 – 12 months:** 0–6 months: infant formula **ONLY**: 6–12 months: infant formula **AND** rice/mealie-meal-based infant cereal **Children 1–5 years:** Maize-based instant porridge **AND** lactose-free supplementary drink
Pregnant women and lactating women (infant < 6 months)	Insufficient growth of fetus (symphysis-fundus graph) MUAC < 23 cm Lactating women with/without growth-faltering infant (< 6 months) and/or MUAC < 23 cm or BMI < 18.5	Lactose-free energy drink (with/without fibre) only **OR** maize-based instant porridge **AND** lactose-free energy drink Maize-based instant porridge **AND** RuTF
Lactating women (infant > 6 months)	Lactating women with/without growth-faltering infant (> 6 months) MUAC < 23cm or BMI < 18.5	**Mother:** Lactose-free energy drink only **OR** maize-based instant porridge **AND** lactose-free energy drink Maize-based instant porridge **AND** RuTF **Infant:** infant cereal
HIV and AIDS and TB and other chronic diseases	Birth – 60 months: Growth faltering or referred by dietician 5–18 years: growth faltering or referred by dietician > 18 years – BMI < 18.5 **OR** > 10% unintentional weight loss in 6 months **OR** > 5% unintentional weight loss in past month	**> 18 years:** Maize-based instant porridge **AND** lactose-free energy drink **OR** maize-based instant porridge **AND** RuTF drink Maize-based instant porridge **AND** RuTF drink Lactose-free energy drink only Maize-based instant porridge **AND** RuTF RuTF only

MUAC, mid upper arm circumference; BMI, body mass index; RuTF, ready-to-use therapeutic food.

The present study evaluated the NTP at PHCs offering ART, with particular focus on women, as this group had previously not been addressed.[3,4,5] As the NTP relies largely on compliance of the individuals receiving the supplements, it is important to understand how well the programme is implemented at clinic level and adhered to at household level, to ensure that the maximum number of patients reap the full NTP benefits. Therefore the main aim of the study was to establish the opinions, perceptions and current practices of HIV-positive female beneficiaries of the NTP. It was further necessary to investigate whether patients received adequate information and education regarding the NTP to utilise it effectively. Lastly, we also examined the opinions, perceptions and practices of staff members concerning the NTP and the resources at their disposal for effectively implementing and managing the programme.

Methods

A cross-sectional descriptive study was conducted in the City of Cape Town, Overberg and Cape Winelands districts from December 2009 to April 2010, and from March 2011 to February 2012. Ethical approval was obtained from the Health Research Ethics Committee at Stellenbosch University (ref no: N07/10/232), the Provincial Government of the Western Cape, the Municipality of the City of Cape Town, and the Norwegian Regional Committee for Medical and Health Research Ethics (ref. no. 2009/1364b).

Study sites and participants

Of the 52 registered PHCs that provide ART, 17 were randomly included. Twelve were within the City of Cape Town, and 5 in rural areas of the Cape Winelands and Overberg districts. Data obtained from urban and rural sites were pooled for analyses.

We targeted two groups: (1) various staff members (managers, nurses, dieticians) at the PHCs working with the NTP and (2) female clients (15–49 years old) enrolled in the NTP. Thirty-two staff members were included, with all PHCs represented. Clients were selected by convenience sampling as randomisation was not feasible. Clients eligible for inclusion were either approached on the day of a clinic visit, or identified by means of the NTP register. Twenty-one women were included from 10 of the sites, whilst no women were eligible at the remaining 7 sites.

Data collection methods

Questionnaires adapted from a previous study regarding the NTP conducted at PHCs were used.[4] The questionnaires for both clients and staff members were available in Afrikaans, English and isiXhosa. Clients' experience with and knowledge about the NTP were collected through an interviewer-administered questionnaire containing both option-based as well as open questions. A validated hunger questionnaire

was used as a proxy for food insecurity experienced in clients' households and was based on 8 questions addressing the availability of food and their ability to secure an adequate food intake.[9] Staff members were questioned about their training, knowledge, opinions, perceptions, practices and resources regarding the NTP, also through both open and option-based questions. In addition, sociodemographic data were obtained.

Results

Characteristics of the clients

The median age of the 21 clients included was 30 (range 16–46) years. Seventeen of them received ART, 5 had AIDS and 17 had TB.

Most of the women were unemployed (86%), and only 33% had grade 11–12 education or higher. Table 2 shows the income and money spent on food per household. Twelve (57%) of the women stated that they and/or their family received social grants, including child support (58%), old age pension (25%), disability grant (8%), or financial support from other family members (17%).

Food insecurity

Scores from the hunger questionnaire was used to identify household food insecurity. Thirteen out of the 21 women were classified within the *hungry* category. Four of these 13 women answered Yes to all 8 questions, indicating severe household food insecurity. Six women were *at risk of hunger*, and only 2 had scores that put them in the *food secure* category.

Clients' experiences of the Nutrition Therapeutic Programme

When clients were asked if they knew why they were receiving supplements, 19/21 (90%) answered Yes. Only 2 women said that they did not follow instructions given by staff members for use of the supplements.

Fourteen reported receiving nutritional advice before receiving supplements. Sixteen received verbal instructions on how to take the supplements and/or information as to why they had to take them. Only 4 had received any written information about the NTP and supplements, whilst 5 said that they had not received any information. Two women had experienced problems with the supplements owing to a lack of ingredients to mix them with. Regarding side-effects, 5 women reported nausea, but 3 of them specified that this occurred only when starting to use the supplements. None of the responders reported that they had ever sold their supplements, but 10 had shared the supplements with others, mainly their children.

TABLE 2: Income and food expenses per household.

Income and expenses	Rands†	Number of clients	
		n	%
Monthly income	Nothing	3	14
	1–500	6	28
	501–1000	3	14
	1001–3000	6	28
	3001–5000	2	10
	Do not know	1	5
Weekly food expenses	0–100	6	28
	101–200	7	33
	201–400	3	14
	> 400	2	10
	Do not know	3	14

†, 1 Rand ~ 0.09 US dollars ~ 0.07 Euro.

Staff members' characteristics

The positions of the 32 staff members (30 female and 2 male) were as follows: 8 facility managers, 10 professional nurses, 5 dieticians, 3 nursing staff, 2 medical doctors and 4 defined as *other* (2 health promoters, 1 nutrition adviser and 1 nutritionist). The median age of the staff members was 40 (range 26–56) years.

Knowledge, training and responsibilities of staff members regarding the Nutrition Therapeutic Programme

Twenty of the staff members had received training and/or education in implementing the NTP after their formal training, including oral lecture (65%), written material (45%) and practical demonstration (45%). Thirteen had received training once, whilst only 7 had regular training.

When asked what role staff had in the NTP, the categories most frequently answered were *Handing out supplements* (66%) and *Recording statistics* (66%), followed by *Storage* (44%) and *Ordering* (34%). Regarding storage, 71% of the staff with this responsibility had written guidelines on how to store the supplements, but 43% reported that their facility was inadequate because of space constraints. For handing out supplements, 90% with this responsibility had written instructions. All staff members indicated that they explained to clients the purpose of the supplements, but only 29% reported giving clients written information.

Staff found that clients receiving supplements were generally grateful. One of the stated reasons for poor compliance was clients failing to come back for follow-up appointments. Three staff members said this was because of ignorance; the rest thought that social factors (e.g. no funds for transport to the clinic, or important activities such as work) prohibited clients from attending scheduled appointments.

When asked to specify who were in charge of the different components of the NTP, staff members gave inconsistent answers (Table 3). There was a discrepancy between sites regarding which staff categories were assigned NTP responsibilities, but answers also differed between staff members working at the same site.

TABLE 3: Distribution of Nutrition Therapeutic Programme responsibilities amongst primary health clinics site staff categories.

Staff category	Ordering supplements	Storage of supplements	Deciding entry/ exit of NTP	Handing out supplements	Updating NTP register	Statistics and reporting
Facility manager	28	22	3	0	0	13
Professional nurse	25	34	50	47	47	50
Nursing staff	0	0	25	28	16	9
Pharmacist	6	19	0	6	0	0
Dietician	38	25	50	44	41	34
Others	16	22	22	25	13	6
Do not know	3	6	0	3	3	9

Note: Values refer to which staff categories the 32 staff members allotted the various responsibilities, and are expressed as percentages. For example, 28% of the 32 staff members answered that the facility manager was responsible for ordering the supplements. It was possible to allocate several staff categories for each area of responsibility.
NTP, Nutrition Therapeutic Programme.

Nineteen staff members stated that there was a lack of supplements within the last year. Reasons for this were mainly lack of stock in the clinic (32%) or lack of stock at the suppliers (63%). Five staff members said that the clinic's budget had been exceeded. Eight staff members said that they had tried to improve the nutrition budget with their superiors; 5 had succeeded. Twelve of the 32 staff members stated that their clinic had undergone evaluations of their NTP implementation routines. When asked to specify what problems they experienced with the NTP, 2 commented that a staff shortage was an issue, and said that staff had inadequate time to implement the programme properly. Five staff members said that inadequate clinic routines prohibited efficient utilisation of the NTP, and another 5 staff members attributed lack of success with the programme to clients' failing to come back for follow-up appointments.

Six of the 8 facility managers said that their staff had received training in implementing the NTP. Only 2 managers reported that the training took place regularly; this corresponded well with what staff members had responded about training. Seven facility managers had a separate budget for the NTP, and 2 stated that their budget was never adequate to cover expenses related to the NTP.

Discussion

Our results indicated that there were several aspects that potentially compromised the effectiveness of the NTP, including socio-economic factors leading to clients' non-compliance. The strategic organisation and implementation of the NTP varied between clinics, and staff experienced some difficulties with the programme logistics at PHCs.

Many of the women studied experienced food insecurity; this jeopardised their nutritional status and increased the need for supplementation, which could result in clients becoming dependent on supplements. In theory, these women should benefit from the supplements, but it was evident that many shared their supplements with others, indicating a shortfall in taking the advised dosage. This conclusion was further supported by findings from the hunger questionnaire that established that more patients reported reducing the size of their own meals rather than those of their children.

The long-term effectiveness of the programme depends largely on the ability of former clients to sustain nutritional status after they have been exited from the NTP. This is difficult for them as they have increased nutritional needs owing to HIV and AIDS and TB, and the task is made even more challenging when their socio-economic status is low. Malnutrition also hastens disease progression amongst such people and puts added pressure on healthcare services.

Educational levels affected the understanding and effective utilisation of supplementation amongst clients. Even though the women understood that they had to take the supplements to gain weight, more in-depth counselling, or use of illustrated instructions and/or written information in their own language, could have contributed to a better understanding of the programme and possibly promoted better adherence. Both the clients and staff experienced difficulties in implementing the programme. One of the main problems identified by staff members was poor compliance of the women in attending clinic. If client attendance reflects reality, it can be assumed that clients failing to attend follow-up appointments have increased the defaulter rate of the programme. It must be noted that client compliance was largely influenced by their socio-economic difficulties, which manifest as poor clinic attendance, despite the fact that most of the attending clients were perceived to be grateful for the supplements and support they received.

The lack of strategic organisation, and no clear responsibility distribution at clinic level, must be suspected of causing obstacles to efficiency and programme coverage. The scarcity of evaluation routines would indicate that any problems experienced with the programme would continue without being properly addressed; an example is the lack of supplements owing to poor ordering routines, which could easily be corrected.

Considering South Africa's burdens of malnutrition, the lack of food and nutrition security and the need for multisectoral interventions, the low health sector budgetary allocation by government to nutrition (less than 0.3% of the health budget) is a further problem. In current expenditure, most funds are spent on targeted supplementary feeding, including to HIV-infected individuals as a target group. Appropriate monitoring and evaluation of this programme is therefore of cardinal importance. There is a concern that the returns on nutrition expenditure are not as high as could be, owing to inappropriate interventions and poor implementation.[10]

The National Nutrition Directorate (NND) acknowledges the challenges that the programme faces, including: poor institutional co-ordination amongst various departments that are giving assistance to people facing food and nutritional insecurity; lack of proper mechanisms to facilitate referral of individuals across programmes; under-developed information management; different entry and exit criteria for nutritional support for people living with HIV and AIDS and TB; and little or no community involvement in nutrition support interventions for such people.[10] However, very little strategic guidance from the NND is provided to overcome these challenges.

Limitations

The main limitation of this study was the small number of eligible clients identified at the PHCs. The reason for the specific inclusion criteria was because these individuals form part of the vulnerable group in society of whom very little is known. Although most clinics had specific days on which the NTP supplements were handed out, and researchers made a concerted effort to remind them of their appointments, this did not ensure that clients would visit the clinic on those days. Despite the small number of participants, the data obtained were extensive. Through open questions, clients could freely express opinions and experiences, and thus provided us with a good understanding of whether they felt the programme worked optimally, both for staff members issuing supplements, and also for the clients receiving them. Notably, the study was performed in the Western Cape – one of the most affluent provinces in the country, and this fact might limit the generalisability of our findings.

Conclusion

Our results support the findings from previous studies that there are problems with the implementation of the NTP and that these problems are also evident at PHCs.[1,3,4] It is clear that the challenges experienced by staff members and clients are obstructing the effective implementation of the programme. It is therefore necessary to take note of the relevant challenges mentioned in this study and strive to solve the problems that, if left unattended, could ultimately result in clients not reaping the benefits of the programme, which in turn will lead to increased government expenditure and depletion of clinic funds in support of a programme that is ineffective, as patients are not reaching the goals set out in the programme. Therefore, to successfully implement nutrition interventions, sufficient capacity and resources, strategic management, evaluation routines and monitoring of results must be in place.[11,12,13] The findings from our study advocate for an increased effort in these matters when implementing the NTP at PHCs that provide ART in Western Cape Province and possibly also elsewhere in South Africa.

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Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

T.T.H. (Stellenbosch University), L.D. (Stellenbosch University), T.B. (Stellenbosch University), C.v.N. (Stellenbosch University) and L.T. (Stellenbosch University) collected and analysed the data. M.H. (Stellenbosch University), L.d.P. (Stellenbosch University) and P.O.I. (Stellenbosch University) designed the study and analysed the data. All authors co-wrote the article and accepted the final version and the decision to submit.

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Factors associated with retention in HIV care at Sediba Hope Medical Centre

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Background: Lost to follow-up (LTFU) is a major challenge that hinders the success of antiretroviral treatment (ART).

Objective: To identify factors conducted to a low LTFU rate.

Methods: We conducted a two-part descriptive and quantitative study. Part 1 comprised interviews with clinic staff to determine their perspectives on LTFU and to establish the clinic's follow-up procedures for patients on ART. Part 2 of the study was a retrospective review of clinic and patient records. LTFU patients were identified and those with contact details were contacted for telephonic interview to determine if they were still on ART and/or their reasons for becoming LTFU.

Results: A low LTFU rate (7.9%; *N* = 683) was identified. Work-related stress, and lack of transport and funds were reported reasons for LTFU. Monthly visits, non-adherent defaulters and LTFU patients were tracked by an electronic system (SOZO). Factors contributing to high rates of retention in care were: location of the clinic in the inner city, thus in close proximity to patients' homes or work; clinic operating on Saturdays, which was convenient for patients who could not attend during the week; an appointment/booking system that was in place and strictly adhered to; a reminder SMS being sent out the day before an appointment; individual counselling sessions at each visit and referrals where necessary; and a stable staff complement and support group at the clinic.

Conclusion: Achieving a low LTFU rate is possible by having a patient-centred approach and monitoring systems in place.

Introduction

Adhering to antiretroviral treatment (ART) is a lifelong commitment that requires patients to diligently adhere to daily medication dosing schedules and make regular clinic visits for care.[1] ART has improved the lives of many people living with the human immunodeficiency virus (HIV), but many challenges still exist before ART programmes might achieve total success in terms of patient outcomes.[1] Two of the major challenges and concerns for ART programmes are retention in care and patients who are lost to follow-up (LTFU).[1] Several studies have been conducted on these problems, investigating various ways to improve retention in HIV care and patient outcomes.[1,2,3,4]

'Lost to follow-up' refers to the disappearance of a patient from the programme, for no reported reason.[5] Definitions of when a patient is classified as LTFU vary widely across studies and countries.[6] In a pooled analysis of 111 facilities, a threshold of 180 days since the last clinic visit was recommended as a standard definition for LTFU.[7]

In sub-Saharan African countries, rates of LTFU vary extensively. According to a systematic review of patient retention following ART initiation, it was evident that 1 year after initiation approximately 25% of patients were no longer in care, with LTFU figures escalating to 40% after 2 years.[8] Lower LTFU figures (3.3%; *N* = 2548) were reported from a retrospective cross-sectional study of a community-based ART cohort in Cape Town, South Africa, which used a computerised tracking tool to manage patients in care.[9]

Sediba Hope Medical Centre (SHMC) is a nongovernmental organisation (NGO) clinic, situated in the city centre of Tshwane in South Africa. It caters for patients working and living in and around the city of Tshwane. The centre was previously known as Fountain of Hope (FOH), which was a Foundation for Professional Development (FPD) clinic funded by the President's Emergency Plan for AIDS Relief (PEPFAR) and the United States Agency for International Development (USAID). The clinic's budget allowance provided for a patient database of only 500 patients.

The main purpose of the FOH Clinic was to provide ART for HIV-positive patients living and working in the inner city. In 2011, FPD joined in a project with Participate Empower and Navigate (PEN), a non-profit, non-denominational, faith-based organisation, and subsequently the FOH Clinic became the SHMC. Since the name change, it has operated as an ARV site for the PEPFAR- and USAID-funded patients on ART and as a primary healthcare (PHC) private practice for patients using medical aid or paying privately. The move from the FOH Clinic to the SHMC had some implications for patients as they had to adapt to a new site, new processes, new staff and additional travelling distances for some patients. Patients living near the FOH Clinic had to walk an average of 1.4 km further to the SHMC, which represents approximately 17 minutes.

LTFU had not been evaluated at this site previously. In the present study, we aimed to quantify LTFU at the SHMC, investigate the factors that contributed to patients on ART becoming LTFU, and identify factors that could contribute to low LTFU rates and be implemented to improve retention in care.

Methods

Patient population and data collection

We conducted a two-part descriptive and quantitative study at SHMC between August and November 2013. The first part of the study included an individual interview based on a structured questionnaire with each of the nine staff members. We aimed to determine staff members' perspectives on the reasons for LTFU and to establish the procedures used at the clinic to monitor patients on ART and to identify and trace those who were LTFU.

The second part of the study was a retrospective review of clinic and patient records for the previous 4 years (2010–2013). The review included 'hard copy' patient files and an electronic patient management system, known as SOZO, which was developed by FPD in partnership with Infocare and John Snow International (JSI) in 2007. All patients on ART, who had become LTFU with no obvious reason for default, were identified. A patient record sheet was used to record LTFU patients' details from their files and the SOZO system. Patients identified as LTFU, with contact details in their records, were contacted telephonically for a structured telephonic interview to investigate reasons for LTFU.

Data analysis

Data were analysed with SPSS V21.0 statistical software. The percentage of LTFU patients was calculated with a 95% confidence interval. Patient demographics and clinical, treatment and social data were summarised descriptively. Associations between variables and differences in means were identified with Fisher's exact test and independent samples *t*-test as appropriate. Statistical significance was set at $p \leq 0.05$.

Ethical approval

Ethical clearance for the study was granted by the Medunsa Research Ethics Committee of the University of Limpopo. Permission to conduct the study at the SHMC was provided by FPD and the manager of SHMC. Written consent was obtained from staff members of SHMC and verbal consent from responding patients, prior to their participation in the interviews.

Results

SHMC is conveniently situated in the city centre; that is, close to home or work for most patients. The clinic operates on weekdays as well as Saturdays to accommodate patients who work or are unable to attend the clinic during the week. The previous FOH Clinic also hosted a support group with regular meetings every second Saturday, which were available to all patients from the time they started treatment.

Patient flow process and tracking of lost to follow-up patients

Interviews with staff members revealed that the clinic followed a structured patient flow process, according to which patients were seen by appointment only and according to bookings done on the SOZO system. According to the staff interviewed, patient waiting time was kept to a minimum,

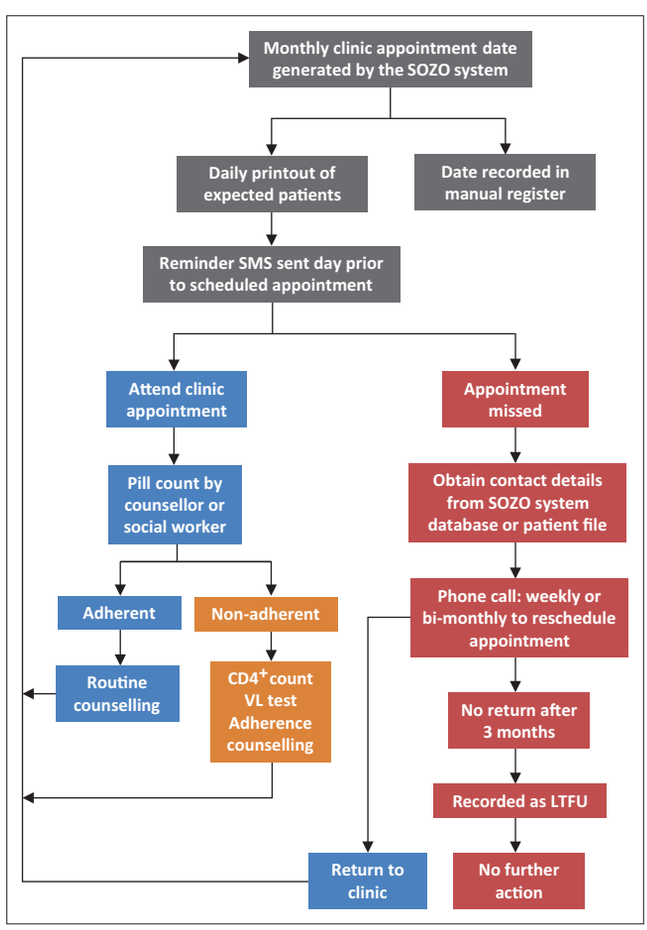


FIGURE 1: Flow process of monitoring and tracking patients on antiretroviral treatment at Sediba Hope Medical Centre.

as appointments were made according to a time schedule. The patient flow process and the tracking of LTFU patients at SHMC are illustrated in Figure 1.

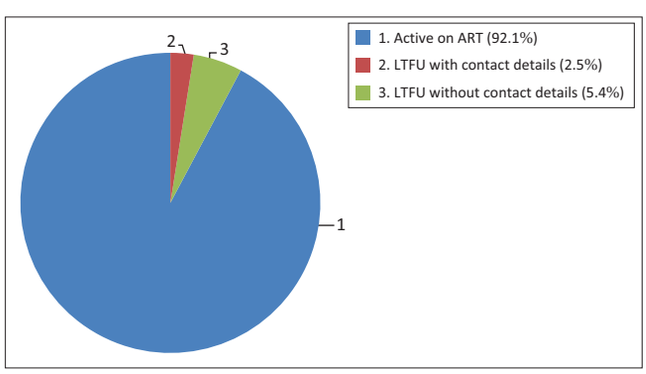
Patients at SHMC are sent a reminder short message service (SMS) the day prior to their scheduled appointment. A booking list is printed daily to track patients as they attend. The service received is personalised and, should patients not attend their appointment, follow-up phone calls are made.

When a patient on ART is identified as LTFU, the social worker phones the patient weekly or at least bi-monthly for a period of 3 months, in an attempt to reschedule an appointment and get the patient back into care. All phone numbers on patient records are contacted in an attempt to trace them. After 3 months of no success in tracing a patient, no further action is taken.

The staff complement at the previous FOH Clinic was stable for a period of 4 years and, consequently, patients interacted with the same healthcare worker at each visit. For this reason, patients felt comfortable and built good relationships with the staff.

Extent of lost to follow-up

Of the total number of 683 patient records reviewed, 54 (7.9%; 95% confidence interval [CI], 6.1%–10.2%) patients were identified as LTFU (Figure 2). Only 17 of the 54 patients had contact details in their records and were contacted for a telephonic interview. Sociodemographic characteristics of the 54 patients who were LTFU are summarised in Table 1.



N = 683.
LTFU, lost to follow-up; ART, antiretroviral treatment.

FIGURE 2: Overall proportion of patients lost to follow-up at Sediba Hope Medical Centre.

Disclosure of HIV status

According to the patient records, most patients (90.7%; *N* = 54) had disclosed their HIV status. Women preferred to disclose to a relative (82.1%; *n* = 28) rather than a partner (28.6%; *n* = 28) whilst men disclosed mainly to relatives (46.1%; *n* = 26) and their partners (42.3%; *n* = 26). Three male patients did not disclose their status to anybody.

Travelling distance to the clinic

Travelling distance to the clinic was known for 16 of the 17 LTFU patients who were contacted for an interview. Nine of them (56.3%) lived less than 1 km away from the clinic, and so required minimal travelling; 3 (18.8%) lived between 1 km and 5 km from the clinic; and 4 (25.0%) lived more than 10 km from the clinic.

Clinical profile of lost to follow-up patients: CD4⁺ cell count and viral load

Table 2 shows the gender distribution of LTFU patients, for whom CD4⁺ cell count test results were available within 6 months of their final clinic visit, prior to becoming LTFU.

The median CD4⁺ count for patients (*n* = 35) who had a test done within 6 months of their last clinic visit prior to

TABLE 1: Sociodemographic characteristics of lost to follow-up patients.

Sociodemographics	Characteristics	*n*	%
Gender	Male	26	48.1
	Female	28	51.9
Marital status	Single	28	51.9
	Married	21	38.9
	Widowed	1	1.9
	Divorced	1	1.9
Educational level	No education	2	7.1
	Primary education completed	1	3.6
	Secondary education not completed	9	32.1
	Secondary education completed	11	39.3
	Tertiary or vocational education	5	17.9
Employment status	Employed	23	42.6
	Self-employed	6	11.1
	Unemployed	20	37.0
	Student/scholar	2	3.7

N = 54.

TABLE 2: Distribution of patients according to CD4⁺ cell count results, based on testing done within 6 months of the patient's final clinic visit prior to becoming lost to follow-up.

CD4⁺ count (cells/µL)	Male†	%*	Female‡	%*	Total§	%
< 100	2	5.7	2	5.7	4	11.4
100–350	15	42.9	5	14.3	20	57.2
> 350	1	2.9	10	28.6	11	31.4
Range	11–1382		69–656		11–1382	
Median	255.0		431.0		289.0	
IQR	173.25–299.0		253.0–471.5		186–438	
Mean ± s.d.	287.8 ± 287.6		371.9 ± 167.0		328.6 ± 237.3	
Mean difference (95% CI)			84.1 (-247.1–78.9)**			

†, *n* = 18; ‡, *n* = 17; §, *N* = 35.
*, *p* = 0.001, Fisher's exact test; **, *p* = 0.302, independent samples *t*-test.

TABLE 3: Adherence patterns over the period of 3 months prior to becoming lost to follow-up.

Adherence level	Number (%) of patient visits							
	Third-last month†	%	Second-last month‡	%	Month prior to LTFU§	%	Total	%
Excellent adherence	10	23.9	4	9.1	2	4.3	16	12.0
Adherent	27	64.3	34	77.3	30	63.8	91	68.4
Non-adherent	5	11.9	6	13.6	15	31.9	26	19.6

N = 133; †, *n* = 42; ‡, *n* = 44; §, *n* = 47.

becoming LTFU was 289.0 cells/µL (interquartile range [IQR] 186–438), with a $CD4^+$ count below 350 cells/µL for the majority (68.6%) of them. Categorisation of $CD4^+$ count results available within 6 months of the final clinic visit prior to becoming LTFU showed a statistically significant association with gender (p = 0.001; Fisher's exact test). Being female was associated with the probability of a $CD4^+$ count > 350 cells/µL, and being male was associated with a probability of a lower $CD4^+$ count (100 cells/µL – 350 cells/µL) at the time of being LTFU.

A detectable viral load (VL) within 6 months of their final visit to the clinic was evident in 44.1% (n = 35) of patients, with more of the men (58.8%; n = 17) than the women (29.4%; n = 17) having a detectable VL. The association between gender and detectable VL was, however, not significant (p = 0.472; Fisher's exact test).

Antiretroviral treatment and adherence

At the time of their final visit, just more than half of LTFU patients (57.4%; n = 54) were on the current first-line regimen, comprising tenofovir (TDF), lamivudine (3TC) and efavirenz (EFV). Thirteen per cent of the LTFU patients were still on the previous Regimen 1A (stavudine [d4T], 3TC, EFV) and 11.1% on the previous Regimen 1B (d4T, 3TC, nevirapine [NVP]). Only 13% of LTFU patients were on the second-line regimen (TDF, 3TC or emtricitabine [FTC] and lopinavir/ritonavir [LPV/r]).

Adherence to ART at the SHMC was monitored at each visit by means of pill counts, conducted by the social worker or counsellor and recorded as descriptive notes in the patient files and on the SOZO system. Table 3 shows the adherence patterns for patient visits over the period of 3 months prior to becoming LTFU.

Reasons for lost to follow-up

Staff members' perceptions of the reasons for LTFU are summarised in Table 4.

Based on the contact details available in the files of patients identified as LTFU, only 17 patients could be contacted successfully for a telephonic interview. One patient was identified to have demised while on ART. Another patient had relocated to Europe, and it could not be determined whether he was still on ART or not.

Nine patients were confirmed to be still active on ART at other sites, of whom one patient was actually LTFU at SHMC before initiation on ART. This patient subsequently commenced ART at another site, as he moved from one city to another. Three patients indicated that they were using delivery services to obtain their ARVs. Explanations from the remaining five patients who continued treatment at a different ART facility were related to proximity and travelling time. Two of these patients reported that the alternative facility was closer to home, and three reported it as being closer to their workplace.

TABLE 4: Reported reasons for lost to follow-up, according to staff perceptions.

Reasons for lost to follow-up	Number
Work-related stress (e.g. cannot take leave to attend clinic)	7
Lack of transport	5
Only one month's supply of ART (opposed to 3 months' supply issued previously)	5
Strenuous/tedious to attend clinic every month	2
Stigma/shame	1
Foreigners going back home	1
Patients moving to other provinces	1
Domestic abuse	1

N = 9.
Some participants provided more than one reason.

Only six of the patients interviewed reported that they had discontinued ART altogether. All six patients provided transport costs as a reason for discontinuing treatment; 2 of these patients also mentioned the side-effects of ARVs, whilst one patient was using traditional or herbal medication instead of ARVs.

Discussion

The LTFU rate at the SHMC (7.9%; N = 683) was evidently much lower in comparison to most sub-Saharan countries.[1,9] This reasonably low LTFU rate could be attributed to various processes at the centre, one being the follow-up of patients from an early stage after a missed appointment at the clinic. A previous study confirmed that early active follow-up of patients can improve retention on treatment and programme outcomes.[9]

The use of an electronic patient management system (SOZO) facilitated patient follow-up and engagement, thus improving the efficiency of the system immensely. Appointments were booked electronically according to a time schedule which, according to the staff, minimised patient waiting time. A large ART programme in Malawi also considered time-specific appointments for each patient as an option to reduce waiting times.[2] In addition, the SOZO system identified patients due for appointment, and a reminder SMS was sent to them the day beforehand. Similarly, low LTFU rates (3.3%) were identified elsewhere in South Africa where a computerised pharmacy tracking system (iDART) was used to trace patients who failed to collect their medication.[9]

Most (90.7%) of the LTFU patients disclosed their HIV status, which was a positive finding and attributed to the fact that disclosure is encouraged during counselling. Disclosure of HIV status to one's spouse is known to be associated with good adherence.[10]

Women in our study had a higher $CD4^+$ count at the time of being LTFU. This could be expected as previous studies from sub-Saharan Africa have shown that women usually have a higher $CD4^+$ count at ART initiation and a better median $CD4^+$ count increase from baseline across all time periods after ART initiation, than men.[11]

It is evident that an elevated VL may be a factor to consider for LTFU, which is supported by the findings from other studies which demonstrated that unsuppressed viral loads at any time point in treatment are predictive of loss.[12]

Good adherence rates were supported by consistent pill counts and counselling sessions, which happened at each clinic visit. Having a stable staff complement at the clinic meant that patients saw the same counsellor or social worker at every visit, which facilitated good relationships between staff and patients. The staff perceived the regular support group meetings as a contributing factor to adherence. Support groups are known to encourage adherence and improve retention in care.[13]

From our findings, it was apparent that work-related stress, lack of transportation, and lack of funds for travel and food were reported as contributing factors to LTFU at SHMC. Travelling distance was the main reported reason why patients changed facilities and opted for a clinic closer to home or to work, or preferred the convenience of ART delivery services to their home or work. High transport costs and patients having to travel long distances to get to ARV clinics were identified as problems in a study conducted at Themba Lethu Clinic, Helen Joseph Hospital, in Johannesburg, South Africa.[3] Lack of transport and employment obstacles as reasons for LTFU are supported by a number of other studies conducted in South Africa and Mozambique.[3,14,15]

Lack of availability of contact details for all patients at SHMC made follow-up and tracing of LTFU patients difficult in our study. The majority of LTFU patients had incorrect information or no contact information at all. It is apparent that ART programmes should invest in obtaining accurate, complete and up-to-date contact details for patients to aid tracing. Availability of more updated contact information for all patients at SHMC may have resulted in an even lower number of LTFUs altogether.

Limitations

Our study was conducted at only one facility and the results can therefore not be generalised to other ART facilities in South Africa. Incomplete and incorrect patient records (manual and SOZO system) made it difficult to trace all LTFU patients and therefore negatively affected the number of LTFU patients interviewed. A limitation of the study itself was that the review did not include patients who remained in care. Consequently, comparisons between LTFU patients and those who remained in care were not possible. Furthermore, as a result of incomplete clinic records, information about the proportion of patients who did not become LTFU as a result of successful contact by social workers could not be determined.

Conclusion

From our study, it is evident that low LTFU rates and measures to prevent LTFU are possible. The flow through the clinic was efficient and patients in general were pleased with the services rendered at SHMC. Most patients had built good relationships with the staff, which made them feel comfortable and cared for. The complete functioning of SHMC took the form of a patient-centred approach and was much more than only having a computer system in place.

SHMC can be an example to similar ART sites with high LTFU rates. The SMS reminder service and tracking system may benefit other ART sites. Seeing patients on an appointment only basis proved to be beneficial. However, it might be difficult in facilities with larger numbers of patients.

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Competing interests

Two of the authors (N.R. and D.C.) are employees of the FPD, which provides facility-based technical assistance to SHMC, within its model for strengthening district health systems.

Authors' contributions

N.R. (Sefako Makgatho Health Sciences University) was a Master's student at the former University of Limpopo, Medunsa Campus, now Sefako Makgatho Health Sciences University. N.R. developed the methodology and collected the data. J.C.M. (Sefako Makgatho Health Sciences University) and D.C. (Foundation for Professional Development) supervised the Master's project. N.R. wrote the first draft of the manuscript. All authors discussed the results and implications and commented on the manuscript at all its stages.

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Outcomes from the implementation of a counselling model supporting rapid antiretroviral treatment initiation in a primary healthcare clinic in Khayelitsha, South Africa

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Background: Lengthy antiretroviral treatment (ART) preparation contributes to high losses to care between communicating ART eligibility and initiating ART. To address this shortfall, Médecins Sans Frontières implemented a revised approach to ART initiation counselling preparation (integrated for TB co-infected patients), shifting the emphasis from pre-initiation sessions to addressing common barriers to adherence and strengthening post-initiation support in a primary healthcare facility in Khayelitsha, South Africa.

Methods: An observational cohort study was conducted using routinely collected data for all ART-eligible patients attending their first counselling session between 23 July 2012 and 30 April 2013 to assess losses to care prior to and post ART initiation. Viral load completion and suppression rates of those retained on ART were also calculated.

Results: Overall, 449 patients enrolled in the study, of whom 3.6% did not return to the facility to initiate ART. Of those who were initiated, 96.7% were retained at their first ART refill visit and 85.9% were retained 6 months post ART initiation. Of those retained, 80.2% had a viral load taken within 6 months of initiating ART, with 95.4% achieving viral load suppression.

Conclusions: Adapting counselling to enable rapid ART initiation is feasible and has the potential to reduce losses to care prior to ART initiation without increasing short-term losses thereafter or compromising patient adherence.

Introduction

One-third of antiretroviral treatment (ART)-eligible patients are estimated to be lost to care between communicating ART eligibility and initiating ART[1] – the so-called 'third stage' of pre-ART care[2] – increasing the risk of morbidity and mortality.[3] Whilst patient education and adherence counselling are recommended to improve long-term adherence,[4,5] lengthy preparation processes before starting ART cause delays during this pre-ART stage, contributing to high losses to care.[6,7]

In practice, there are wide-ranging approaches to patient ART preparation within the South African public sector.[6] In 2012, the South African National Department of Health released a circular that recommended fast-tracking patients onto ART without unnecessary delay. It further recommended that patients with CD4 counts < 200 cells/mm^3 and pregnant women be started on the same day that ART eligibility is ascertained. Some facilities now provide minimal ART preparation owing to prioritising fast-tracking, whilst others continue to require prior attendance of 3 (and sometimes more when co-infected with TB) education and adherence counselling sessions.

Médecins Sans Frontières (MSF), along with its partners (see acknowledgements), developed a revised approach to ART initiation counselling which supports rapid initiation without failing to adequately prepare a patient for lifelong adherence to treatment, including those who are co-infected with TB or pregnant. The overall aim of the revised approach is to reduce the loss of patients prior to ART initiation without increasing losses post ART initiation or reducing adherence amongst such patients.

The aim of the present study is to describe the intervention and determine the retention outcomes during the third stage of pre-ART care and post ART initiation of patients who

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underwent this model of counselling. Secondary outcomes include viral load completion and suppression rates of those retained on ART.

Methods

Study design

This was an observational cohort study using routinely collected data.

Study setting

Khayelitsha is a peri-urban township on the outskirts of Cape Town, South Africa. It has a population of approximately 500 000 with high burdens of both HIV and TB. In 2011, the antenatal HIV prevalence was 34.3%[8] and the TB case notification rate at least 1500 per 100 000 population per year.[9]

The study site (Kuyasa Clinic) is a general primary healthcare facility run by the City of Cape Town's Health Department. HIV and TB related services include: HIV counselling and testing (HCT), pre-ART, ART initiation, ART management, ART adherence clubs[10] and both drug-susceptible and drug resistant TB services. According to 2013/2014 records, the clinic tests each month approximately 466 patients for HIV (2014), initiates approximately 50 patients on ART (2014), starts TB treatment for approximately 37 patients (2013) and had 2766 ART patients retained in care at the end of June 2014, with 772 (28%) receiving their treatment and care through ART adherence clubs.

Antiretroviral treatment management

In South Africa, ART eligibility is determined by World Health Organization clinical staging combined with CD4 cell count. Western Cape HIV clinical guidelines provided that, from August 2011, patients with WHO stage 4 disease or those with a CD4 count < 350 cells/mm^3 were eligible to start ART. Patients are due for their first and second viral loads at 4 and 12 months on ART respectively.

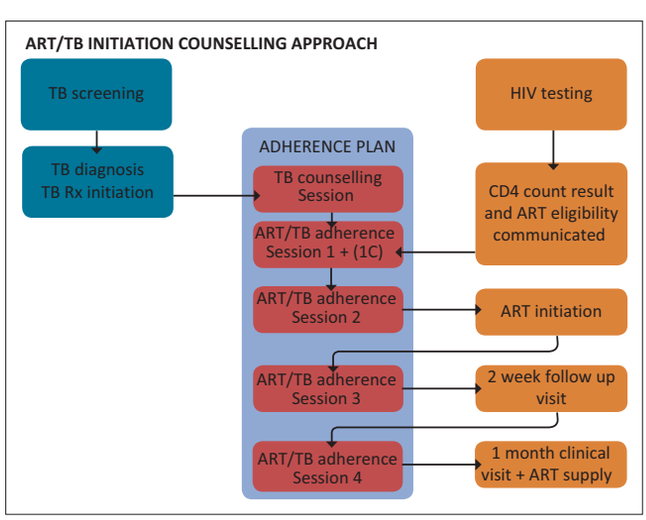
Antiretroviral treatment preparation education and counselling

Prior to July 2012, the ART initiation counselling model in place at Kuyasa Clinic consisted of three counselling sessions, scheduled at weekly intervals after communication of ART eligibility, followed by ART initiation. Co-infected TB/HIV patients were also required to undergo 3 TB counselling sessions, which at the time were not integrated within the ART preparation counselling process. Where a clinician indicated a need to rapidly initiate HIV or TB treatment for clinical reasons, counselling was condensed into fewer sessions. Counsellors were not trained on how to appropriately condense sessions – specifically on what information remained pertinent and necessary. Counselling was provided by lay counsellors, employed by a nongovernmental organization (NGO) funded by the Western Cape's Department of Health (WCDoH). The counsellors were trained by the WCDoH's AIDS Training, Information and Counselling Centre (ATICC) according to Egan's 'skilled helper' model of counselling.[11]

From July 2012, MSF supported the implementation of a revised ART initiation counselling model at Kuyasa Clinic. In summary, the lay counsellor provides a total of four counselling sessions: 1 session prior to ART initiation ('session 1') on the date when ART eligibility is communicated to the patient, 1 session on the day of ART initiation ('session 2'), and two sessions post ART initiation ('sessions 3 and 4') on subsequent clinic appointment/ART refill dates. Where the patient indicates at the end of session 1 that he/she is not ready to start, a further 'not ready to start' session is scheduled ('session 1C') that specifically aims to work through patient-identified barriers to initiating ART. Where it is appropriate for clinical reasons to initiate ART on the day that ART eligibility is assessed, it is possible to carry out the first two sessions on the same day. Where a patient is diagnosed with TB and HIV, one additional counselling session is added prior to session 1 to prepare the patient for starting and adhering to TB treatment. Each counselling session is designed to take 12 min – 18 min. Figure 1 outlines session timing. Where a patient is not able to return to the clinic 2 weeks after ART initiation, sessions 3 and 4 are combined and provided at the first ART refill date, which is 28 days after ART initiation.

The counselling approach is based on the Life Steps intervention to HIV medication adherence[12,13] in which cognitive behavioural, problem solving, and motivational interviewing techniques are used to enhance motivation and assist HIV-positive patients to develop better skills for adhering to HIV treatment. This model has shown favourable results in different settings.[14]

The Life Steps model was simplified and adapted to barriers and adherence planning requirements identified by MSF through its work with patients attending a second-line failure



ART, antiretroviral treatment.

FIGURE 1: Timing of counselling sessions.

clinic in Khayelitsha.[15,16] Patient education is limited to essential information to initiate ART and TB treatment, supported through the use of a visual aid and a take-home leaflet. The 14 most common barriers to start ART and adherence (Box 1) are addressed with all patients and are documented in each patient's adherence plan. The approach focuses on creating a patient-oriented motivation for commitment to lifelong treatment.

Session guides were developed, defining the content to address per session, and served as a working tool for both counsellor and counsellor supervisor. Both counsellors were trained, and fidelity to the intervention was assured through regular supervision by observation of sessions using a standardised observation checklist, and review of patients' adherence plans and counsellors' paper registers recording patients enrolled and counselling sessions provided. This supervision was performed by an NGO counsellor supervisor who covered a number of clinics and MSF staff.

For further details on the model, including session plans and tools, see ART/TB/PMTCT Initiation counselling model report and toolkit at http://bit.ly/197VDfb.

Study participants

From 23 July 2012 to 30 April 2013, all HIV-positive patients found to be eligible for ART initiation who attended session 1 were enrolled in the study.

Data collection and analysis

All data were collected (other than viral load results) at the end of January 2014, providing a minimum of 9 months of follow-up. Viral load data were collected on 30 September 2014. Variables collected included age, sex, CD4 count, TB at ART start, TB treatment start date, attendance of counselling sessions, ART initiation date, last visit date to the clinic for ART refill, reported transfers and deaths, and dates of first viral load and first viral load outcome.

Study outcomes were time taken and retention from session 1 to ART initiation, short-term retention on ART at 28 days (first ART refill) and 6 months (183 days) post ART initiation, viral load completion and suppression within 6 months of ART initiation, and viral load suppression at first viral load.

We defined retention at 1 month and 6 months as those patients whose last visit to the clinic or documented transfer date was more than 28 days and 6 months after the date of ART initiation. Viral load suppression was defined as < 400 copies/mL.

Descriptive analyses were done in STATA Version 13.[17]

BOX 1: Adherence steps addressed in antiretroviral treatment initiation counselling model.

14 adherence steps:	
Step 1:	Understanding HIV (and TB)
Step 2:	Identify support system
Step 3:	Planning future appointments
Step 4:	Readiness to start treatment
Step 5:	Creation of a medication schedule
Step 6:	Managing missed doses
Step 7:	Reminder strategies
Step 8:	Storing medication and extra doses
Step 9:	Dealing with side-effects
Step 10:	Planning trips
Step 11:	Dealing with substance use
Step 12:	Communication with treatment team
Step 13:	Learning from mistakes
Step 14:	Making goals: suppressed viral load (and TB continuation phase)

Ethics approval

Ethics approval was obtained from the University of Cape Town Human Research Ethics Committee. Permission to do the study was obtained from the City of Cape Town research committee.

Results

A total of 449 patients attended session 1 from 23 July 2012 to 30 April 2013, thereby enrolling in the study, of whom 300 (66.8%) were female and 137 (30.5%) of whom had TB at enrolment. Median age was 31 years (interquartile range [IQR] 26–37 years) and median CD4 count 242 cells/mm^3 (IQR 147 cells/mm^3 – 308 cells/mm^3) at enrolment. A further breakdown of age and CD4 count categories is set out in Table 1.

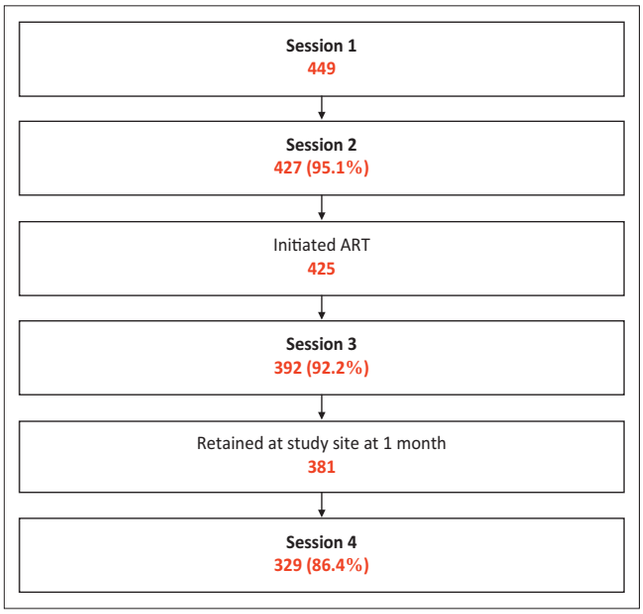
Figure 2 presents a summary of counselling session completion. Of those patients who enrolled in the study, 427 (95.1%) completed session 2, of whom two did not proceed to initiate ART. Session 3 was completed by 392 (92.2%) of those who completed session 2 and initiated ART and 329 (86.4%) of those patients who returned to the study site for their 28-day ART refill, completed session 4.

Figure 3 details retention in care from enrolment to 6 months post ART initiation. ART was initiated by 433 (96.4%)

TABLE 1: Demographic and clinical characteristics of patients included in study at enrolment.

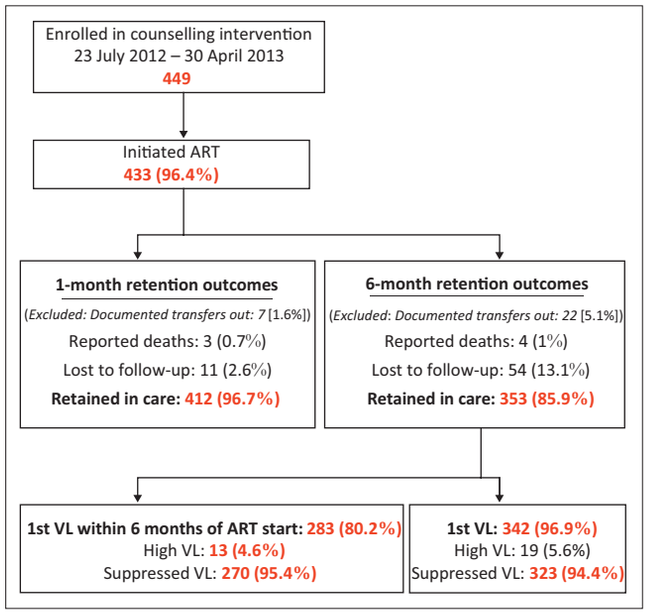
Characteristics	Number	%
Gender		
Male	149	33.2
Female	300	66.8
Age (in years)		
Median†	31	-
14–18	19	4.2
19–25	80	17.8
26–39	272	60.6
40–54	75	16.7
> 55	3	0.7
CD4 count‡ (cell/mm^3)		
Median§	242	-
≤ 50	33	7.4
51–200	131	29.6
201–350	224	50.6
351–500	36	8.1
> 500	19	4.3

N = 449.
†, IQR 26–37; ‡, missing three patients' CD4 counts; §, IQR 147–308.



ART, antiretroviral treatment.

FIGURE 2: Counselling session completion.



ART, antiretroviral treatment; VL, viral load.

FIGURE 3: Retention and viral load outcomes.

TABLE 2: Time from enrolment (session 1) to antiretroviral treatment start and first viral load.

Category	Subcategory	Number	Percentage
Enrolment (session 1) to antiretroviral treatment start†	Median (IQR)	5 days (IQR 2–14 days)	-
	Same day	49	11
	1–7 days	224	52
	8–14 days	55	13
	15–21 days	47	11
	22–28 days	16	4
	> 28 days	32	7
	Counselled after antiretroviral treatment start	5	1
	Restarted (treatment interrupters from other antiretroviral treatment sites)	5	1
Time from antiretroviral treatment start to first viral load‡	Median days (IQR)	134.5 (114–174)	-
	≤ 6 months	283	80.2
	6–9 months	33	9.3
	9–≤ 13 months	19	6.7
	> 13 months	7	2.0
	No viral load taken by 30 September 2014	11	3.1

†, *N* = 433; ‡, *N* = 353.

patients. Median time to the start of ART for all enrolled patients from session 1 was 5 days (IQR 2–14 days). Forty-nine (11%) patients started ART on the same day as session 1, indicating fast-tracking for clinical reasons including pregnancy, whilst 32 (7%) took more than 28 days to start (see further breakdown of time to ART start in Table 2 below). Patients with a concurrent TB diagnosis took a median of 18 days (IQR 14–29 days) from start of TB treatment to initiate ART. After excluding patients with documented transfers to other facilities, 412 (96.7%) and 353 (85.9%) patients were retained respective at 1 and 6 months post ART initiation.

The median time to first viral load was 4.4 months (134.5 days [IQR 114–174 days]). Of those patients retained at the study clinic, 283 (80.2%) had a viral load taken within 6 months of initiating ART, with 270 (95.4%) achieving viral load suppression. By 30 September 2014, 342 (96.9%) had their first viral load taken, with a 94.4% suppression rate. See Table 2 for a further breakdown of time to first viral load.

Discussion

By adapting ART initiation education and counselling to expedite the start of treatment, whilst addressing common barriers to patients' readiness to start ART, only 3.6% of patients were lost from care between their first counselling session and ART initiation. The proportion of patients initiating ART after being informed of their eligibility for treatment is substantially higher than estimates reported previously in South Africa and elsewhere in the region.[1,18] Our findings are comparable to the outcomes of a randomised controlled trial by Rosen et al. which reported pre-ART losses when rapid (2%) versus standard ART initiation (28%) took place.[19]

Reducing losses to care prior to ART initiation carries a potential risk of increased losses immediately after ART start, if patients are uncomfortable with starting quickly or are insufficiently prepared. Our study found limited losses

immediately after ART start, with 2.6% of those initiated not returning for their 1-month ART refill appointment. At 6 months after ART initiation, 85.9% of patients were retained, which is comparable to elsewhere in South Africa[20] and sub-Saharan Africa.[21,22] Whilst cohorts that started ART prior to 2008 in Khayelitsha were reported to have higher 6-month retention outcomes,[23] a recent study reporting on MSF cohorts has shown higher losses to care in more recently initiated cohorts, with the 2011 cohort retaining 85.5% (95% CI 84.5% – 86.4%) at this time point.[22] It is worth noting that it may not be appropriate to compare retention reported in older versus more recently initiated cohorts; this point is due to increasing unaccounted-for self-transfers hidden within the lost to follow-up (LTFU) outcome[24] and a bias towards better retention outcomes in older cohorts introduced by longer follow-up times, which allow transient treatment interrupters to return to care.[25]

It took less than a week for patients to initiate ART from starting ART preparation counselling. Whilst there is extensive evidence on the delay between ascertaining ART eligibility (date of CD4 count) and initiating ART, with a recent systematic review reporting a range of 22–108 days,[18] we could find no routine programme evidence specifically measuring the time from starting ART preparation counselling to ART initiation.

High rates of both viral load completion and suppression were achieved. These were higher than those previously reported for ART patients in Khayelitsha.[23] Focusing the ART initiation counselling sessions on making practical plans to overcome the most commonly experienced barriers to maintaining good treatment adherence, together with educating and motivating patients towards the goal of achieving an undetectable viral load, might have contributed to these high completion and suppression rates.

The use of motivational interviewing has been recommended to ensure behaviour change related to ART adherence[26] but, in resource-limited settings, major challenges exist to make lay counsellors proficient in using these more complex counselling techniques.[27,28] Whilst this model was based on principles of motivational interviewing, by engaging with all patients on planning around the same common barriers to adherence, the counselling model did not require lay counsellors to use more complex counselling techniques. Barriers to address with patients were predefined, and each adherence barrier was addressed in a standardised way by setting the goal, identifying the possible barriers to reaching that goal, and concluding on a plan per adherence barrier. Our experiences with the ART initiation counselling model suggest that this may provide a feasible approach to enhancing the counselling skills of lay counsellors, whilst taking their limitations into account. The present study is not comparable with a recently published study in South Africa that found no difference in patient adherence or virological suppression outcomes when assessing those who received only didactic education with those who received both didactic education and counselling utilising motivational interviewing skills.[29] Our study was carried out in an operational setting, provided a maximum of one session prior to the day of ART initiation, sessions were considerably shorter in length, and sessions were carried out by existing lay counsellors only, and not nursing staff.

Our results should be considered in the light of the following strengths and limitations: the principle strength of the study is demonstration of feasibility within an operational setting utilising existing lay counselling staff. There were a number of limitations, the first three relating to the study constraint of limited pre-ART routine data. Firstly, we were unable to provide a comparison group as a result of poor routine pre-ART data collection prior to implementation of the revised ART initiation counselling model, including attendance of ART counselling preparation sessions. Secondly, the date of baseline CD4 counts was not accurately captured, often reflected as the same date as ART initiation, limiting our capacity to calculate length of time from eligible CD4 count to ART start. Thirdly, whilst the intervention was designed for patients to attend session 1 immediately after being informed of their ART eligibility, we were unable to verify the date on which such communication took place. Further limitations should be noted: during the evaluation period described by the present study, the counselling model had not yet been specifically adapted for pregnant women initiated on ART. Whilst these women were enrolled in the study and accounted for some of the same-day ART initiations with high CD4 counts, we were unable to reliably identify those starting ART for PMTCT purposes. Their inclusion in the study cohort might have increased overall short-term losses to care as reported elsewhere.[30,31] Lastly, despite basic interventions to ensure fidelity, no specific data were collected to report on fidelity to the piloted model.

The present study highlights useful directions for future research. Most importantly, further evidence is required to determine the optimal ART initiation counselling model that can feasibly be implemented in settings with lay counsellors, who have no formal professional or paraprofessional degree in counselling and high numbers of ART patients. These models should ideally also evaluate pre- and post ART retention outcomes. To provide a better understanding of the counselling model, components such as timing, counselling provider, session length, content and measures to ensure fidelity to the intervention should always be described. In addition to counselling model research, more studies are required that report on the extent of delays and losses to care attributable to lengthy ART preparation processes prior to ART initiation. Lastly, whilst there is substantial evidence on optimal timing for starting ART after TB treatment initiation from a clinical perspective,[32,33] competing risk analysis would benefit from studies reporting on losses to care caused by delaying ART initiation for TB co-infected patients.

Conclusion

Adapting initiation education and counselling to enable the rapid start of ART, by addressing common barriers to

adherence and strengthening post-initiation support, is feasible. It has the potential to reduce losses to care prior to ART initiation without increasing short-term losses thereafter or compromising patient adherence. ART programmes should consider adjusting their ART initiation counselling to limit delays but ensure that fast-tracking does not result in patients receiving inadequate adherence support with possible negative long-term consequences.

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Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

L.W. (MSF) was involved in intervention design, paper conception, data acquisition, data analysis, interpretation and drafting the paper. H.D. (MSF, South African mission) was involved in intervention design, implementation and critical review of the paper. G.P. (MSF) did data acquisition and critical review of the paper. S.S. (MSF) and L.M. (MSF) were involved in intervention implementation and critical review of the paper. S.P. (City of Cape Town Health Department Khayelitsha) was involved in intervention design, implementation, and critical review of the paper. V.d.A. (City of Cape Town Health Department) undertook a critical review of the paper. S.B. (MSF) was involved in intervention design and critical review of the paper, and approved it for publication.

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Routine cranial computed tomography before lumbar puncture in HIV-positive adults presenting with seizures at Mitchells Plain Hospital, Cape Town

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Background: Current international guidelines recommend that a cranial computed tomography (CT) be performed on all HIV-positive patients presenting with new onset seizures, before a lumbar puncture (LP) is performed. In the South African setting, however, this delay could be life threatening. The present study sought to measure the number of cranial CTs that contraindicate an LP and to predict which clinical signs and symptoms are likely to pose an increased risk from LP.

Methods: The study was performed at a district level hospital in Western Cape Province. Data were collected retrospectively from October 2013 to October 2014. Associations between categorical variables were analysed using Pearson's chi-squared test. Generalised linear regression was used to estimate prevalence ratios.

Results: One hundred out of 132 patients were studied. Brain shift contraindicated an LP in 5% of patients. Patients with brain shift presented with decreased level of consciousness, focal signs, headache and neck stiffness. Twenty-five per cent of patients had a space-occupying lesion (SOL) (defined as a discrete lesion that has a measurable volume) or cerebral oedema. Multivariate analysis showed a CD4 count <50 (p = 0.033) to be a statistically significant predictor of patients with SOL and cerebral oedema. Univariate analysis showed focal signs (p = 0.0001), neck stiffness (p = 0.05), vomiting (p = 0.018) and a Glascow Coma Scale (GCS) < 15 (p = 0.002) to be predictors of SOL and cerebral oedema.

Conclusion: HIV-positive patients with seizures have a high prevalence of SOL and cerebral oedema but the majority of them are safe for LP. Doctors can use clinical parameters to determine which patients can undergo immediate LP.

Introduction

Background

New onset seizures in HIV-positive adults have been reported to have an incidence of around 6%.[1] Current guidelines, based on a number of international research articles,[2,3,4] recommend that cranial computed tomography (CT) be performed on all HIV-positive patients presenting with new onset seizures, before a lumbar puncture (LP) is performed. Cranial CT, in addition to being a diagnostic tool, is used to advise if an LP can be performed safely. The concern about performing an LP in this group is the risk of brain herniation secondary to raised intracranial pressure.

Raised intracranial pressure is defined, in the acute setting, as pressure within the cranial vault that exceeds 20 mmHg – 25 mmHg for more than 5 minutes (Roytowski).[5] Raised intracranial pressure *per se* has not been conclusively linked to the risk of brain herniation from LP.[3] LP is in fact used to treat symptoms of raised intracranial pressure, particularly in patients with a communicating hydrocephalus. Common examples of cases where LP is therapeutic are idiopathic intracranial hypertension and cryptococcal meningitis (CCM).

Brain shift, however, has been associated with an increased risk of brain herniation from LP, and can be measured by a CT scan. Cranial CT can demonstrate hemispherical shift and gross generalised brain swelling, both contraindications to LP.[6] Brain shift occurs when differences in pressure between brain compartments lead to areas of the brain being compressed against certain intracranial structures.[3] The brain can literally be pushed to the point where it can herniate through the foramen magnum; this can result in death from compression on the medulla oblongata in the brain stem, which controls cardiac and respiratory functions.[5] When performing an LP in patients with brain shift, downward pressure can increase and advance fatal brain herniation. Brain shift is usually caused by an expanding mass such as a space-occupying lesion (SOL), cerebral oedema or hydrocephalus.[5]

A prospective South African study performed at Chris Hani Baragwanath Hospital found that 53.3% of HIV-positive patients presenting with new-onset seizures had a SOL.[7] Many clinicians are of the opinion that a suspected SOL is an absolute contraindication to LP before CT Van Crevel et al.[3] have shown, however, that herniation from LP can only occur when a SOL is accompanied by brain shift. Brain shift usually declares itself by clinical symptoms such as a decreased level of consciousness, headache and vomiting, neck stiffness, focal neurology, bradycardia and apnoea.[3] The incidence of brain shift in an HIV-positive adult patient presenting with seizures is not known.

In developed countries, where CT scanners are readily available, it is feasible to scan all HIV-positive individuals presenting with seizures soon after presentation. In many South African hospitals, however, arranging a CT scan is time-consuming and is often not done after working hours. A working diagnosis and commencing treatment based on LP results can save time and lives whilst waiting for a cranial CT.

The purpose of the present study was to assess if current international guidelines that recommend a cranial CT before LP on all HIV-positive patients presenting with seizures, is applicable to the HIV-positive population of Western Cape Province, South Africa.

Methods

This was a cross-sectional, observational study conducted at Mitchells Plain Hospital (MPH) from October 2013 to October 2014. MPH is a large metro district hospital providing level one (district level) as well as some level two (general specialist) care to approximately 440 000 people from the areas of Mitchells Plain, Phillippi and Crossroads. The study population comprised HIV-positive patients with seizures, presenting for cranial CT. The CT request forms filed in the Radiology Department at MPH were used to identify patients to be included in the study. Initially, a broad manual search for any patient whose cranial CT was requested for seizures, was undertaken. The search was then streamlined to only include HIV-positive patients and seizures. Where there was doubt regarding HIV status, confirmation was sought via the National Health Laboratory Service (NHLS) database. Patients under the age of 18 and patients whose seizures were acutely trauma related, were excluded from the study.

Data were extracted onto a data collection sheet from patient folders, the NHLS database and the Radiology Department database where necessary. Patients' demographic details, CD4 count, risk factors for seizures, seizure history, seizure type, symptoms and signs of brain shift on presentation, CT information, LP findings (Figure 1), final diagnoses and prognoses were recorded. Criteria used for CT findings that would contraindicate an LP included any midline shift of the midline structures, effacement of any of the basal cisterns, and obliteration of the fourth ventricle. Diagnoses were the most likely diagnosis for the patient, recorded in the notes; this was not necessarily based on organism detection but also on doctors' clinical impressions.

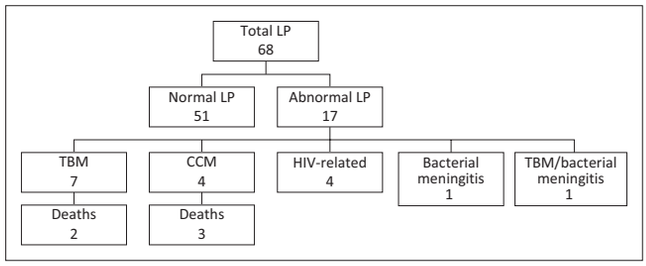


FIGURE 1: Lumbar puncture findings.

The data were then captured onto a Microsoft Excel spreadsheet and were analysed using STATA 13.0. Associations between categorical variables were analysed using Pearson's chi-squared test and prevalence ratios (PRs) with 95% confidence intervals (CIs). Variables that were considered as potential risk factors, such as age, gender, CD4, seizure history, type of fit and signs and symptoms of brain shift, were included in the model for 'generalised linear regression analysis' to estimate the PR. For all analyses, a p-value <0.05 and a 95% CI that did not span unity were considered the thresholds of statistical significance.

Ethical considerations

Ethical approval was obtained from the University of Cape Town research ethics committee, and the Western Cape Provincial Health Research Committee granted permission to conduct the study. Patients' identities were protected as their names were not recorded.

Results

A total of 132 CT request forms, for the period October 2013 – October 2014, identified suitable patients to be included in the study. This figure suggests a minimum of 11 cranial CTs performed monthly at MPH on HIV-positive patients presenting with seizures. The first 100 patients whose folders were accessed were studied.

Baseline characteristics of patients are presented in Table 1. Patients' ages ranged from 21–73 years, with the median age being 38. Twenty per cent (n = 20) of patients had advanced immunosuppression with a CD4 count <50. Patients who presented with seizures usually had some form of systemic illness such as TB or gastro-enteritis with renal impairment, which also placed them at risk for metabolic abnormalities, and hence seizures. New-onset, generalised seizures were most common. There were 42 patients who were asymptomatic at the time of presentation. Headache and a decreased level of consciousness were the most frequent clinical presentations. The presence or absence of papilloedema was recorded in 1 of the 100 folders. The assumption is that papilloedema was not checked for in the remaining 99 patients.

Brain shift was seen on CT scan in 5% of the patients. Details of these patients are given in Table 2. All of them had one or more signs and symptoms of raised intracranial pressure/brain shift on presentation. One patient with suspected meningitis had an LP before the cranial CT, which showed brain shift. No adverse effects were reported from the LP.

Results of cranial CTs are set out in Figure 2. More than half of the patients (n = 55) had an abnormal cranial CT.

TABLE 1: Baseline characteristics of patients.

Characteristics	*n* and years
Age	
Median	38 years
IQR	32–45 years
CD4 count	
<50	20
50–200	23
200–350	24
>350	32
Unknown	1
Risk factors for seizures	
Systemic illness	38
Alcohol/substance use	21
History of head injury	13
Abnormal chemistry	8
Seizure history	
New onset seizure	81
Known epileptic	19
Type of seizure	
Generalised	74
Focal	16
Undocumented	10
Clinical signs and symptoms suggestive of brain shift	
Headache	21
Vomiting	4
Visual disturbances	1
GCS < 15	38
Focal signs	11
Neck stiffness	10
Papilloedema	None documented

n, portion of total sample (N = 100).
IQR, interquartile range; GCS, Glascow Coma Scale.

Many of these abnormalities were old and untreatable. Patients with active SOLs, together with the patients with cerebral oedema (generalised and localised), were at risk of developing brain shift. This proportion comprised 25% of the study population. Calcified granulomata were categorised as inactive SOLs as they have no potential for growth and expansion. In our setting, a calcified granuloma is attributed to old TB, but there are a number of different causes. Nearly a quarter (n = 24) of patients had brain abnormalities that might have explained their seizures but were incurable, such as old infarcts, calcified granulomata and focal encephalomalacia.

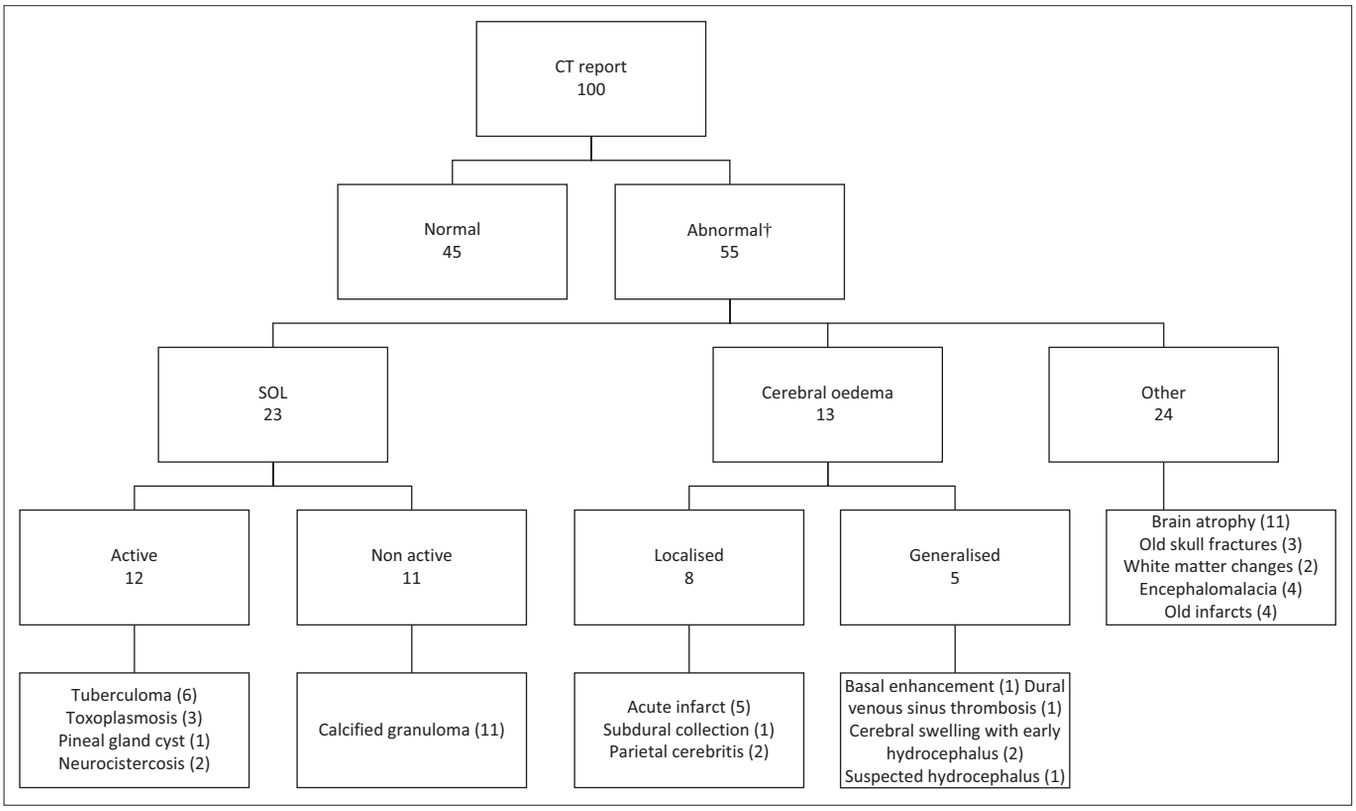
Generalised linear regression was used to predict patients with SOL/cerebral oedema (Table 3). Associations were initially found in the following categories: age, CD4 count, asymptomatic, focal signs, neck stiffness, vomiting and decreased level of consciousness. However, after multivariate analysis only, a CD4 count <50 was associated with an increased risk for SOL/cerebral oedema. All other variables such as age, gender, history of seizure, and type of seizure (whether localised or generalised) had no predictive value in at-risk patients. The group of patients with brain shift was too small to show any significant clinical predictors and they were therefore grouped together with patients with active SOLs and cerebral oedema.

LPs were performed on 68% (n = 68) of patients presenting with seizures. Despite international guidelines, 52% of these patients (n = 35) had an LP before cranial CT, with no adverse effects reported. A markedly abnormal cerebrospinal fluid (CSF) result was found in 24% of patients (n = 16) who underwent LP, of whom 75% (n = 12) were diagnosed with infective meningitis. Meningitis comprised more than half of the total study mortality (5 out of 9 deaths). Other causes of death were from renal failure (2 out of 9 deaths) and gastroenteritis (2 out of 9 deaths).

The proportion of patients who did not have a clear diagnosis on discharge comprised 23% (n = 23), 13 of whom had an LP and 10 of whom did not have an LP. Sixteen per

TABLE 2: Description of patients with brain shift.

Patient	CD4 count	Gender	Type of seizure	Symptoms	CT finding	LP done	Adverse effect from LP	Diagnosis	Prognosis
1	<50	Male	Generalised	Focal signs Impaired consciousness GCS 14	Active space-occupying lesion	No	Not applicable	Toxoplasmosis	Referred tertiary institution
2	50–200	Female	Focal	Focal signs Headache GCS 15	Active space-occupying lesion	No	Not applicable	Toxoplasmosis	Recovery and discharge
3	50–200	Female	Unrecorded	Impaired consciousness GCS 13	Generalised cerebral oedema	Yes, after second scan	No	Meningitis bacterial/TB	Recovery and discharge
4	200–350	Male	Generalised	Impaired consciousness Neck stiffness GCS not documented	Active space-occupying lesion	Yes, before scan	No	Tuberculoma/TB meningitis	Recovery and discharge
5	200–350	Female	Generalised	Impaired consciousness GCS 14	Localised cerebral oedema	No	Not applicable	Chronic haematoma/empyaema	Referred tertiary institution



SOL, space occupying lesion.

†, Patients might have had several pathologies.

FIGURE 2: Computed tomography scan findings.

TABLE 3: Univariate and multivariate analyses of potential predictors of patients with active space-occupying lesion and cerebral oedema.

Potential predictors for at-risk patients	Total number of patients	Percentage of patients with active SOL or cerebral oedema	Univariate			Multivariate		
			PR	95% CI	*p*-value	PR	95% CI	*p*-value
Age								
<40	58	32.8	2.3	1.0–5.2	0.0352	1.8	0.7–4.5	0.236
CD4								
> 350	32	3.1	1	-	-	1	-	-
200–350	24	25.0	2.3	1.4–3.8	0.0143	8.3	1.0–71.0	0.053
50–199	23	34.8	2.7	1.7–4.4	0.0017	7.5	0.9–62.0	0.063
<50	20	50.0	3.7	2.1–6.6	0.0001	10.1	1.2–85.4	0.033
Clinical presentation								
Asymptomatic	44	6.8	0.2	0.1–0.5	0.0002	0.3	0.1–1.3	0.118
Focal signs	11	72.7	3.8	2.2–6.7	0.0001	2.0	0.8–5.1	0.154
Neck stiffness	10	50.0	2.3	1.1–4.7	0.0543	1.0	0.4–2.8	0.995
Vomiting	4	75.0	3.3	1.7–6.4	0.0184	1.5	0.4–6.2	0.586
GCS < 15	38	42.1	2.9	1.4–5.9	0.0020	1.0	0.4–2.7	0.984

PR, prevalence ratio; CI, confidence interval; GCS, Glascow Coma Scale.

cent of patients had seizures attributed to the use of drugs or, alcohol, a previous head injury, a metabolic cause or a breakthrough seizure (in the known epileptic group).

Discussion

Uptodate,[8] the international evidence-based clinical decision support resource, has advised that patients with suspected meningitis be scanned first if they have any of the following: decreased level of consciousness, focal signs, papilloedema, preceding seizures and impaired cellular immunity. This recommendation was based on the study by Hasbun et al.[4] By strict international standards, all patients in the present study ought to have had a CT scan before LP. Our study sought to measure the risk of LP in patients with preceding seizures and impaired cellular immunity by measuring the number of CT scans that reported brain shift and hence contraindicated an LP. It is the first study to look at the prevalence of brain shift and patients at risk for brain shift (SOL/cerebral oedema) in this particular subset of patients. An attempt was also made to predict if clinical factors in this group could be used to decide which patients needed a preceding cranial CT.

Despite the expected increased prevalence of an active SOL (12%) and cerebral oedema (13%) in the population studied,

the actual number of patients who had a contraindication to LP on CT scan was small (5%). This finding prevented us from drawing any significant statistical conclusion from the descriptive results in Table 2. We were, however, able to show statistically significant associations, on univariate analysis, between clinical predictors and patients with an active SOL or cerebral oedema (Table 3). Active SOLs and cerebral oedema are disease processes that could lead to brain shift. It can therefore safely be assumed that patients with no clinical predictors of SOL and cerebral oedema will have a reduced probability of brain shift.

The present study confirmed recommendations that a decreased level of consciousness and focal signs are significant predictors of patients at risk for brain shift. It also found that vomiting and neck stiffness might also be positive predictors of SOL/cerebral oedema, in HIV-positive patients presenting with seizures. Of significance is the finding on multivariate analysis that a CD4 count <50 is associated with increased risk for SOL/cerebral oedema. A CD4 count <50 is a specific predictor and should be given more weight in clinical decision making. Two asymptomatic patients, with CD4 <50, underwent LP and subsequently had an active SOL on cranial CT. It must be stressed, however, that none of the asymptomatic patients was unsafe to LP.

Papilloedema has been described as a contraindication to LP. The patients in our study were almost entirely not examined for papilloedema; this may be owing to the fact that it is often difficult to perform ophthalmoscopy in a bright and busy emergency room, especially when doctors' experience with ophthalmology is limited. Papilloedema, however, is a late finding of raised intracranial pressure, and guidelines from Queens University recommend performing LP even when the optic discs cannot be visualised,[9] if there are no other contraindications to LP.

Extensive research was performed by the Swedish Infectious Disease Society regarding the comparative risk between immediate LP before CT and the risk of delayed LP (and inevitably delayed treatment) in adults with suspected acute bacterial meningitis. Hypothetical calculations of these risks, in different clinical settings with varying probabilities of cerebral mass lesions and acute bacterial meningitis (ABM), were presented. The authors worked on the premise that, although there is little evidence of an association between LP and brain herniation in acute bacterial meningitis, there is sufficient evidence of an association between LP and brain herniation in patients with cerebral mass lesions. The risk of brain herniation, associated with LP, in patients with cerebral mass lesions, however, is small and was assumed to be between 1% and 2%. It was concluded that where a patient had no clinical signs to indicate a SOL, an immediate LP will be advantageous; this would apply even where the probability of ABM is >0.5%. This research has led to the revised Swedish recommendation for early LP in 2009, which removed impaired immunity and new onset seizures as indications for a preceding cranial CT.[10]

An American study by O'Laughlin et al.[11] examined 1737 CT reports in various patients with both medical and trauma-related presentations, to assess the prevalence of CT scans that contraindicated LPs. It was found that 14.6% had ≥ 1 high-risk findings that would contraindicate LP, compared with our study where 5% of CT scans contraindicated LP. Their study also found no clinical correlation between clinical presentation and CT findings. It did, however, draw the conclusion that because brain herniation precipitates death, radiologists are becoming increasingly cautious when reporting on CT scans. This assumption is made because actual brain herniation from LP is very rare, whilst the number of CT reports that contraindicate an LP is relatively common. To support this statement, there have been reports from casualty staff at MPH of patients undergoing LP before CT which later reported that LP was contraindicated. These patients, as with the one reported in the present study, had no adverse event after the preceding LP.

Cranial CT provided a diagnosis for seizures in more than 50% of our patients and it should remain an important diagnostic tool in our population. What is questionable is the need to provide our patients with urgent cranial CTs to rule out brain shifts before performing an LP. There are substantial financial and clinical implications that arise from this recommendation. The Hasbun study[4] reported a 2-hour time delay to lumbar puncture and longer emergency department stays when patients underwent cranial CT before LP. In our setting, the time delays would be much longer, especially after hours when there is no CT service on site. The shortage of CT scanners and a lack of funding for staff has led to studies such as 'The Kimberly hospital rule for urgent CT of the brain in a resource limited environment'[12] and 'Appropriateness of computed tomography and magnetic resonance imaging scans in the Eden and Central Karoo districts of the Western Cape Province, South Africa'.[13] These studies, like ours, highlight the need to implement local, cost-effective CT guidelines.

Apart from the financial implications of arranging urgent CT scans, there is the clinical consideration. The highest number of deaths in our study was from CCM (3 out of 9 deaths), followed by tuberculous meningitis (TBM) (2 out of 9 deaths). The high case fatality rate in CCM, predicted by the WHO to be between 35% and 65% in sub-Saharan Africa prompted the recommendation that patients with a CD4 less than 100 have early screening for the disease.[14] LP and CSF analysis remain the key diagnostic test for CCM but, if LP needs to be delayed, an urgent serum cryptococcal latex antigen test (CLAT) must be performed on all patients suspected of CCM.[15] Patients with CCM often present with a severe headache and an isolated sixth nerve palsy. The *Southern African Journal of Infectious Diseases* (SAJEI) recommends that an LP be performed if meningitis is suspected despite the presence of isolated cranial nerve palsies.[6] Current guidelines recommend blood culture analysis and IV antibiotics in cases of suspected meningitis where LP is contraindicated. The administration of IV antibiotics is

intended to ensure that patients with bacterial meningitis are not deprived of emergency lifesaving treatment whilst waiting for lumbar puncture results. The prevalence of bacterial meningitis in our study was low in comparison with TBM and CCM. This is not unusual, as the causes of meningitis in a population with a high prevalence of TB and HIV, similar to our own, have already been described. The LP results of 4549 patients were studied between 2006 and 2008 at GF Jooste Hospital in the Western Cape and CCM followed by TBM were the most common causes of meningitis in this setting.[16] Delayed LP will delay treatment in such patients and worsen their outcome.

Limitations

The most significant limitation of the present study was the sampling strategy. Ideally, to measure the number of people who suffered immediate death after LP, it would have been necessary to identify all patients who had an LP. By identifying patients from their CT request forms, the study overlooked a possible group of patients who might have suffered immediate cerebral herniation post LP and never survived to have had a CT. Consultation with the Head of the Casualty Department, however, revealed that no patient, to his knowledge, suffered cerebral herniation from LP at MPH. Furthermore, at least 50% of our patients had an LP before CT and reported no complications.

The study design was adequate to report on the number of CT scans where LP was contraindicated. The small study sample and the small percentage of patients with brain shift prevented us from predicting any statistically relevant factors for brain shift. Enough information was available to describe these patients and it is not unreasonable to conclude that any decreased level in consciousness or focal signs, excluding isolated cranial nerve palsies, should contraindicate LP before CT in patients with HIV and seizures. Doctors working in hospitals with no CT scanners may benefit the remaining patients by performing LP before CT.

Another limitation is that our research conclusions are based on doctors' clinical impressions and not necessarily measurable information. Neck stiffness, for example, is a subjective clinical finding and should not be used in isolation to decide on management steps. Similarly, patient diagnoses were not based on hard facts, owing to the low detection of organisms on CSF microscopy and culture as well as the absence of histology on SOLs. In such cases, doctors used their clinical judgement as well as evidence of disease elsewhere to make a diagnosis and start treatment. CCM and toxoplasmosis were, however, definitive diagnoses, based on positive India ink staining or cryptococcal antigen testing and positive toxoplasmosis serology, respectively.

The present study was a retrospective folder review, with all CT scans reported by the same radiologist, and might have been more reliable if the scans had been seen by two radiologists, to reduce any interpretation bias.

Conclusion

HIV-positive patients with seizures have a high prevalence of SOLs and cerebral oedema but the majority of them are safe for LP. Indicators such as a decreased level of consciousness, focal signs, vomiting, neck stiffness and a CD4 count <50 should alert doctors to the possibility of at-risk patients. All the asymptomatic patients were safe for LP but should still have undergone non-urgent cranial CT owing to the limited occurrence of SOL and cerebral oedema in this group (6.8%). CCM accounted for the highest mortality, and doctors need to be more vigilant in performing serum cryptococcal latex antigen tests (serum CLATs) if LP is delayed. It is imperative that results of these tests be followed up promptly so that patients with CCM can be identified and treated early. There were no adverse events reported after any LPs performed on the patients in the present study.

Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

S.M. (University of Cape Town) contributed the bulk of the data collection, collation and interpretation; the literature review and the writing of the study. A.R. (Mitchells Plain Hospital) contributed to the interpretation of CT reports and general radiological concepts, provided the patients' CT request forms for source patient identification, and generally played a supportive and advisory role. E.d.V. (Mitchells Plain Hospital) was the official supervisor of the research, recommended the topic, assisted with the study methodology, checked data, assisted with statistical conclusions, and provided a mentor role throughout.

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A prospective study of demographic features and quality of life in HIV-positive women with cervical cancer treated at Tygerberg Hospital

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Background: Cervical cancer and human immunodeficiency virus (HIV) infection/acquired immune deficiency syndrome (AIDS) both have a high incidence in South Africa. Cervical cancer treatment of HIV-positive women poses challenges. Treatment-related changes in quality of life (QOL) of such women are important to future treatment protocols.

Aim: To examine demographic data of HIV-negative and HIV-positive women at diagnosis of cervical cancer and describe their changes in QOL as a result of treatment.

Methods and materials: All newly diagnosed patients with cervical cancer at Tygerberg Hospital were approached to participate in the study. The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) and the Cervix Cancer Module (QLQ-CX24) were used. General QOL was measured with the EORTC QLQ-C30 and cervical-specific QOL with the QLQ-CX24 questionnaire. The patients completed the questionnaire at diagnosis, on completion of treatment and at 3 months' follow-up.

Results: The study included a total of 221 women of whom 22% were HIV-positive; the latter were younger and of higher educational level than the rest. Mean monthly income and stage distribution was similar between the two groups. HIV-positive patients underwent radiation therapy more commonly than chemoradiation. HIV-positive women showed statistically significantly higher loss to follow-up during the study. HIV-positive women experienced no improvement in insomnia, appetite loss, nausea, vomiting, diarrhoea, social role or any of the sexual domains. In contrast, HIV-negative women experienced statistically significant improvement in all sexual domains other than sexual/vaginal functioning. The QOL improvement of HIV-negative women was statistically significantly greater than their HIV-positive counterparts in the majority of QOL domains. Global health improved in both groups, with HIV-negative women experiencing greater improvement. HIV-positive women experienced an initial decline of peripheral neuropathy (PN) symptoms post treatment with a return to pretreatment values at 3 months' follow-up. The change in PN was statistically significant between the HIV-negative and HIV-positive women.

Conclusion: Demographic differences exist between the HIV-negative and HIV-positive groups. The differential outcome in the QOL of HIV-positive and HIV-negative women treated for cervical cancer might be related to persistence of AIDS-related symptoms on completion of cervical cancer treatment.

Introduction

The quality of life (QOL) of human immunodeficiency virus (HIV)-positive women with cervical cancer is the result of both diseases and the impact of their respective treatments. Invasive cervical cancer is an acquired immune deficiency syndrome (AIDS)-defining condition (World Health Organization stage 4).[1] AIDS is endemic in sub-Saharan Africa. The South African population has a 12% – 18% incidence of HIV-positivity.[2] South Africa has a cervical cancer incidence rate of 26.8/100 000.[3] Most South African women present at an advanced stage of the disease. Cervical cancer and HIV infection are epidemiologically related owing to the sexual transmission of both conditions. Peripheral neuropathy (PN) in HIV-infected persons occurs in 50% – 60% of cases. At autopsy, PN can be shown in all HIV-positive persons despite their having no signs or symptoms during their lifetime. Antiretroviral medication (particularly didanosine, zalcitabine and stavudine) is directly neurotoxic and results in PN identical to AIDS-associated neuropathy. The disease and its treatment synergistically increase PN. Cisplatin is the drug of choice in chemoradiation (CR) treatment of cervical cancer. Cisplatin results, in a dose-dependent fashion, in sensory PN in the stocking-glove distribution.[4] Poor tolerance of chemotherapy for cervical

cancer by HIV-positive women results in substantially less completion of CR than their HIV-negative counterparts. The use of CR in advanced stage (III to IVA) cervical cancer in HIV-positive women has been questioned owing to the limited survival benefit.[5] A Cochrane review shows a statistically non-significant 3% benefit in 5-year survival of CR over radiation therapy (RT) in stage III to IVA.[6] Simonds et al.[5] suggest that the omission of chemotherapy in these HIV-positive women with cervical cancer would result in timely completion of the full dose of radiation therapy.

A limitation of the study by Simonds et al.[5] was the 15.4% (59 out of a cohort of 383) incidence of HIV-positive women.[5] Data on the impact of RT on QOL of HIV-positive women with cervical cancer are lacking. The aim of the present study was to examine demographic data for HIV-negative and HIV-positive women at diagnosis of cervical cancer and to describe QOL changes in these women after treatment for cervical cancer.

Methods and materials

Inclusion criteria

Patients referred to the Unit of Gynaecologic Oncology at Tygerberg Hospital who had newly diagnosed cervical cancer were approached to participate in the study. The unit is one of two tertiary referral units for public-sector patients in Western Cape Province. The province has a population of 5.8 million. Most (85%) of the population do not have private medical insurance and are dependent on public facilities provided by two tertiary hospitals (Tygerberg Hospital and Groote Schuur Hospital) for treatment of cervical cancer.[7] Patients were eligible for the study if they had histologically proven cervical cancer. Exclusion criteria included concurrent, or previous history of, cancers and medical disorders that might affect QOL, such as diabetes. Patients unable to provide informed consent owing to psychiatric disorders were excluded. Cervical cancer was staged according to international guidelines .[8] Clinical management included HIV testing and initiation of antiretroviral treatment. HIV-positive women did not receive chemotherapy if their CD4 count was < 200 cells/μL, or active tuberculosis was present.

Questionnaires

Patients completed the questionnaire in the language of their choice (isiXhosa, English or Afrikaans) after informed consent was obtained.[9] A research assistant helped illiterate patients. To exclude bias, the research assistant had no medical background and was not involved in clinical management of the patients. Questionnaires were completed prior to treatment, after initial treatment, and after a 3-month post-treatment period. The follow-up visits coincided with clinical follow-up of patients. Patients failing to attend visits were contacted telephonically where possible. Patient records were used to extract relevant clinical data. Ethical approval was obtained from the local committee (S12/06/174). Clinical management followed protocols as previously described.[5] The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (EORTC QLQ-C30) and the Cervix Cancer Module (QLQ-CX24) were both used. The EORTC QLQ-C30 consists of 30 items comprising 5 functional scales (physical, role, emotional, social and cognitive), 3 symptom scales (fatigue, nausea/vomiting and pain), an overall QOL scale, and 6 individual items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The EORTC QLQ-C30 was analysed according to the procedures recommended by the EORTC QOL Group. Higher scores on the QLQ-C30 functioning scales and the overall QOL scale indicate a better QOL. Higher scores on the symptom and individual item scales represent a decrease in QOL.[10] The EORTC QLQ-CX24 includes 3 multi-item scales (symptom experience, body image, and sexual functioning) and 5 single-item scales (lymphoedema, lower back pain, menopausal symptoms, tingling and numbness, and sexual enjoyment). Higher scores indicate a decrease in QOL except for items 49 and 54 (where higher scores indicate better QOL).[11] The questionnaires used were translated and validated for use in South Africa.[9]

Statistical analysis

Descriptive statistics were used to characterise the study sample in terms of the contextual factors of socio-demographic and medical variables. Data presented as medians were analysed using Kruskal–Wallis tests. Post hoc analyses were done with Fisher's least significant difference (LSD) test. Chi-square tests were used for categorical data. A p value < 0.05 was considered to be significant. Statistical analysis was performed with the use of STATISTICA version 12 software.

Results

Demographic characteristics

The study included a total of 221 women (Table 1). HIV-positivity of the study group was 22%. The mean age of the HIV-positive women was statistically significantly 7 years less than that of the HIV-negative women. Age had a normal distribution without any outliers. HIV-positive women had a higher educational grade. Racial distribution shows a statistically significant difference between black (40%), mixed race (12%) and white (0%) participants' HIV-positivity rates. Mean monthly income as well as the percentage of patients under the poverty line were not statistically significantly different between the HIV-positive and -negative groups. Single women had a statistically significantly higher rate of HIV-positivity than their married, widowed and divorced counterparts. The stage distribution of HIV-negative and HIV-positive cases was not statistically significantly different. HIV-positive patients underwent RT more commonly than CR.

Unemployed women had a statistically significantly higher HIV-positivity rate (26%) than the employed women (23%). The loss to follow-up of HIV-positive women v. HIV-negative women during the post-treatment (56% v. 34%) and 3-month

TABLE 1: Comparative demographic data of HIV-negative and HIV-positive women (poverty line as defined by the Western Cape Provincial Government).

Characteristics	HIV-negative *n* = 173	HIV-positive *n* = 48	*p* value
Age (years)	51.34	43.94	$p < 0.01$
Mean education level (grade)	7	8	$p < 0.05$
Race (%)	-	-	$p < 0.05$
Mixed race people	88	12	-
Black people	60	40	-
White people	100	0	-
Income (ZAR)	1450	1576	NS
Below poverty line of R3500 (%)	79	21	NS
Marital state (%)	-	-	$p < 0.05$
Single	68	32	-
Married	88	12	-
Widow	86	14	-
Divorced	94	6	-
Stage distribution	-	-	NS
Treatment (%)	-	-	$p < 0.05$
Radiotherapy	75	25	-
Chemoradiation therapy	88	12	-
Employment (%)	-	-	$p < 0.05$
Employed	77	23	-
Pensioner	93	7	-
Unemployed	74	26	-

Source: Western Cape Provincial Treasury. Regional development profile City of Cape Town. 2012 [cited 2014 Jul 23]. Available from: http://www.westerncape.gov.za/assets/departments/treasury/dc0_city_of_cape_town_sep-lg_profile_02_2013.pdf
NS, not significant.

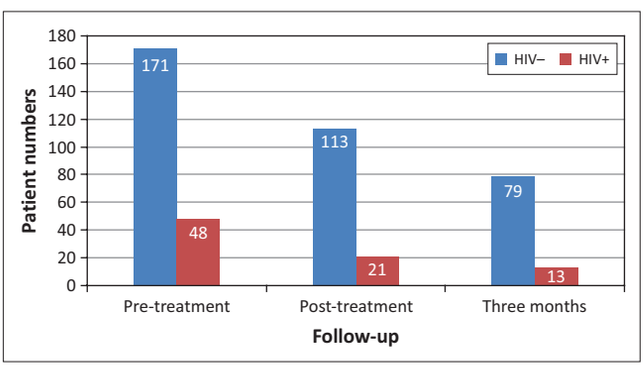

FIGURE 1: Follow-up of HIV-negative versus HIV-positive women over the study period.

(38% v. 30%) follow-up visits was statistically significantly higher for the HIV-positive women (Figure 1). Cause and confirmation of death could be accurately determined in 20 women in the total study population.

HIV status and change in quality of life over the study period

The domains of dyspnoea, financial difficulties, lymphoedema and menopausal symptoms remained unchanged during the study period. HIV-positive women experienced no improvement in insomnia, appetite loss, nausea and vomiting, diarrhoea, social role or any of the sexual domains over the study period. In contrast, HIV-negative women experienced statistically significant improvement in all sexual domains other than sexual/vaginal function. The improvement in QOL of HIV-negative women was statistically significantly more than their HIV-positive counterparts in all domains, with the exception of

TABLE 2: Change in quality of life during study period.

Quality of life domain	HIV- *n* = 173	HIV+ *n* = 48	HIV- versus HIV+
Physical function	$p < 0.01$†	$p < 0.05$†	$p < 0.05$
Role function	$p < 0.01$‡	$p < 0.01$‡	NS
Dyspnoea	NS	NS	NS
Pain	$p < 0.01$‡	$p < 0.01$‡	$p < 0.01$
Fatigue	$p < 0.01$‡	$p < 0.01$‡	$p < 0.01$
Insomnia	$p < 0.01$‡	NS	NS
Appetite loss	$p < 0.01$†	NS	$p < 0.01$
Nausea and vomiting	$p < 0.01$‡	NS	$p < 0.01$§
Constipation	$p < 0.01$†	$p < 0.05$†	NS
Diarrhoea	NS	NS	$p < 0.01$
Cognitive function	$p < 0.01$‡	$p < 0.05$‡	$p < 0.01$
Emotional role	$p < 0.01$‡	$p < 0.01$‡	$p < 0.05$
Social role	$p < 0.01$†	NS	$p < 0.05$
Financial difficulties	NS	NS	NS
Global health status	$p < 0.01$†	$p < 0.01$†	$p < 0.01$
Symptom experience	$p < 0.01$‡	$p < 0.05$‡	$p < 0.01$
Lymphoedema	NS	NS	NS
Peripheral neuropathy	NS	$p < 0.01$‡	$p < 0.01$
Menopausal symptoms	NS	NS	NS
Body image	$p < 0.01$†	$p < 0.01$†	$p < 0.05$
Sexual worry	$p < 0.01$‡	NS	NS
Sexual activity	$p < 0.01$†	NS	NS
Sexual/vaginal functioning	NS	NS	$p < 0.01$
Sexual enjoyment	$p < 0.05$†	NS	$p < 0.01$

NS, not significant.
†, Improved; ‡, decreased; §, HIV+ >HIV-.
All other *p* values in column HIV- >HIV+.

role function, insomnia, constipation, sexual worry and sexual activity (Table 2). Global health improved in both groups, with HIV-negative women experiencing a greater improvement. PN did not change in HIV-negative women but HIV-positive women experienced an initial decline in this symptom at post treatment with a return to pretreatment values at the 3-month follow-up visit. The change in PN was statistically significantly different between HIV-negative and HIV-positive women.

Discussion

The results of the study show significant demographic differences between HIV-positive and HIV-negative women with a diagnosis of cervical cancer. The former group is statistically younger, and has a higher educational level and higher unemployment rate than the latter. Black women have a statistically higher HIV-positivity rate than mixed race and white women. Single women had the highest HIV-positivity rate. Monthly income is similar in both groups. RT was more frequently used than CR in HIV-positive patients. The 22% HIV-positive rate in the current study is higher than previously reported rates. This change is the result of a general change in HIV-positive rates in the total population over time.[2] Black women had a higher HIV-positive rate than mixed race or white women. A previous study documented a higher incidence (30%) of positive syphilis serology amongst black women with cervical cancer than in their white and mixed race counterparts.[12] The younger age of HIV-positive cervical cancer patients confirms previous studies of HIV in cervical cancer cases. In previous studies, the difference in mean age between

HIV-negative and HIV-positive patients was reported as 10 years, whilst the current study shows a 7-year age difference.[5,13,14] The stage distribution in the current study was similar in HIV-negative and HIV-positive women. Despite the similar stage distribution, significantly more HIV-negative than HIV-positive women received CR. The selection by the presiding clinician of the inability of HIV-positive women to tolerate the chemotherapy because of low CD4 counts, gave rise to this difference.

The majority of QOL domains in HIV-negative women improved with treatment with prolonged effect up to 3 months' follow-up. Improvement of QOL domains in HIV-positive women was statistically less than in HIV-negative women. PN domain did not change in HIV-negative women. In HIV-positive women, initial improvement occurred in PN with relapse to pretreatment level at 3 months. Appetite loss in HIV-positive women initially improved after treatment and returned to pretreatment levels at 3 months' follow-up. HIV-negative women showed an improvement in appetite loss up to 3 months' follow-up. The QOL of HIV-negative women significantly improved in the majority of domains. HIV-positive women had fewer domains improved by treatment, and the magnitude of improvement was less than that amongst HIV-negative women. Temporary improvement of pain, fatigue and appetite loss after treatment in HIV-positive women reverted to pretreatment levels at 3 months' follow-up. Pain and fatigue are AIDS-related conditions that are prevalent in AIDS patients, despite adequate treatment. Depression is associated with these symptoms, and the difference in emotional functioning in the current study underlines the element of depression in the HIV-positive women.[15] The AIDS-related impact on QOL accounts for these relapses in QOL domains. Diarrhoea was significantly more in HIV-positive women than in HIV-negative women, and treatment did not change the incidence in either group. Diarrhoea is commonly associated with AIDS and can have numerous causes, both infectious and non-infectious, for example AIDS medication-related gastro-intestinal side-effects.[16] Constipation improved in both HIV-negative and HIV-positive women. Radiation is associated with increased stool frequency owing to radiation-induced mucosal rectal damage. PN paradoxically improved in both groups after treatment and reverted to pretreatment levels in HIV-positive women. Contrary to expected cisplatin-related toxicity, treatment did not result in an increase of PN. The dose of cisplatin, which did not reach the cumulative threshold dose > 250 mg – 350 mg/m^2, may explain the absence of PN. Cisplatin-associated PN may occur up to 8 months after exposure, and therefore longer follow-up may reveal PN.[17]

In the present study, higher rates of loss to follow-up occurred in HIV-positive women. A meta-analysis of sub-Saharan low- and middle-income countries' antiretroviral treatment programmes reports on causes of loss to follow-up. Self-transferring care to other facilities (18.6%), unreported death (38.8%) and stopping treatment were identified as the major reasons for loss to follow-up.[18] WHO AIDS stage 3 and 4 cases have a mortality rate of 72.12 per 100 person-years in the first 6 months after initiation of treatment. The mortality rate decreases to 7.9 per 100 person-years after 12 months.[19] The mortality rate is compounded by cervical cancer-related death. In a South African study, the mortality rate after treatment of stage III cervical cancer was the highest in the first 6 months after treatment.[12] In Kenya, a 41% loss to follow-up occurred in women receiving treatment for cervical cancer.[20] Tracking of women after missed appointments is not done routinely owing to resource constraints.[18] Verifying HIV-related deaths by checking death certificates is subject to 90% misclassification of HIV deaths in South Africa.[21]

Limitations of the present study include a short follow-up subsequent to completion of therapy. The short follow-up limits the conclusion to long-term effects of treatment. Prolonged follow-up may reveal an increased incidence of PN. The higher loss to follow-up rate of HIV-positive women during the study period precludes sub-analysis of smaller groups, for example treatment-related PN in those women undergoing CR.

In conclusion, the study documents the demographic difference in HIV-negative and HIV-positive women with cervical cancer with regard to a younger age in the latter group. The 5-year survival benefit of CR in comparison with RT in HIV-negative women with stage III to IVA is a statistically non-significant 3%.[6] The poor response of HIV-positive women to CR raises the question of whether CR is appropriate in these circumstances.[5] A significant difference exists in the short term in certain QOL domains of HIV-positive women with cervical cancer receiving RT or CR. In these circumstances, the different impact on long-term QOL of HIV-positive women with cervical cancer receiving RT or CR warrants further study.

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Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

G.d.T. (Stellenbosch University) was the project leader and designed the study, wrote the protocol, collected the data and wrote the paper. M.K. (Stellenbosch University) performed the statistical analysis and contributed to discussions. Both authors read and approved the manuscript.

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Impact of combination antiretroviral therapy initiation on adherence to antituberculosis treatment

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Background: Healthcare workers are often reluctant to start combination antiretroviral therapy (ART) in patients receiving tuberculosis (TB) treatment because of the fear of high pill burden, immune reconstitution inflammatory syndrome, and side-effects.

Object: To quantify changes in adherence to tuberculosis treatment following ART initiation.

Design: A prospective observational cohort study of ART-naïve individuals with baseline CD4 count between 50 cells/mm^3 and 350 cells/mm^3 at start of TB treatment at a primary care clinic in Johannesburg, South Africa. Adherence to TB treatment was measured by pill count, self-report, and electronic Medication Event Monitoring System (eMEMS) before and after initiation of ART.

Results: ART tended to negatively affect adherence to TB treatment, with an 8% – 10% decrease in the proportion of patients adherent according to pill count and an 18% – 22% decrease in the proportion of patients adherent according to eMEMS in the first month following ART initiation, independent of the cut-off used to define adherence (90%, 95% or 100%). Reasons for non-adherence were multifactorial, and employment was the only predictor for optimal adherence (adjusted odds ratio 4.11, 95% confidence interval 1.06–16.0).

Conclusion: Adherence support in the period immediately following ART initiation could optimise treatment outcomes for people living with TB and HIV.

Introduction

Adhering to a lengthy course of medication is difficult and poses a challenge to achieving health in people with chronic diseases. Poor adherence to treatment for infectious disease poses a risk to both the individual and community as it can lead to prolonged infectiousness, development of drug resistance, and poor treatment outcomes. Tuberculosis (TB) and the human immunodeficiency virus (HIV) present particular challenges as both are chronic diseases that mainly affect disadvantaged populations and involve complex treatment regimens with potentially severe side-effects.[1] Treatment adherence for TB and HIV is also affected by beliefs about the origins and transmission of TB and HIV, which can result in stigmatisation of those affected.[2]

The 2012 World Health Organization (WHO) and 2015 South African antiretroviral therapy (ART) guidelines recommend initiating ART in people with TB as soon as possible, within the first 2 weeks of initiating TB treatment for those with profound immunosuppression (CD4 counts < 50 cells/mm^3) and within the first 8 weeks of treatment in all TB patients.[3] Whilst initiating ART greatly improves the survival and quality of life of TB patients living with HIV,[4] it also poses challenges to patients and healthcare workers.[5] Early initiation of ART can result in clinical deterioration related to immune reconstitution inflammatory syndrome (IRIS), toxic effects of drugs, or drug interactions, and increased pill burden. The high pill burden of four anti-TB drugs, antiretroviral drugs, and antimicrobial prophylaxis (cotrimoxazole and fluconazole) against opportunistic infections, as well as possible drug interactions and toxic effects, may jeopardise the patient's adherence to treatment.[6] As a result, healthcare workers are often reluctant to start ART in patients receiving TB treatment. In 2012, only 57% of TB patients with HIV were started on ART,[7] and in the latter group, initiation of ART was often delayed.[8]

In the present study, we aimed to quantify changes in adherence to TB treatment associated with initiation of ART by prospectively measuring adherence to TB drugs immediately before and after initiation of ART.

Methods

Study setting and population

The study took place at Witkoppen Health and Welfare Centre, a primary care clinic in Johannesburg, South Africa. Adults (> 18 years old) diagnosed with pulmonary TB who were ART-naïve at the time of initiation of TB treatment and had a CD4 count between 50 cells/mm^3 and 350 cells/mm^3 were eligible for enrolment. Those with rifampicin-resistant TB (defined by Xpert MTB/RIF or culture-based drug susceptibility testing) were excluded as they are referred for care. Those with CD4 counts < 50 cells/mm^3 were excluded because ART should be initiated as an emergency, limiting the possibility of reliably establishing the level of adherence to TB treatment before ART initiation. Those with CD4 counts > 350 cells/mm^3 were excluded as these individuals were not eligible for ART, according to the 2010 South African Guidelines, which were current at the time of the study.

All care provision for TB and HIV, including the decision on timing of ART initiation, was performed by the routine clinic staff, without any input from study staff.

Study procedures

Eligible patients who signed informed consent completed a questionnaire collecting information on socio-demographic information, occurrence of side-effects, and adherence support. Medical files were reviewed to collect details of weight, height, results of TB diagnostics (Xpert MTB/RIF, smear microscopy and culture), TB treatment outcome, ART regimen and start date, and CD4 count and viral load (VL) at baseline and during the first 6–12 months of ART.

Ethical approval was obtained from the Institutional Review Board of the University of North Carolina (10–2317) and the University of the Witwatersrand's Human Research Ethics Committee (M10925).

Adherence measures

Participants were prospectively monitored for adherence, using pill count (primary measure of adherence), self-report, and an electronic Medication Event Monitoring System (eMEMS). Participants received their TB medication in a Securitainer fitted with an eMEMS lid (eMuM, GeoMed, Stellenbosch, South Africa). Participants were seen by study staff at each clinic visit; the number of visits varied and was determined by the routine clinic care provider. At each visit, the date of visit, number of pills distributed for TB treatment, and prescribed dosage were recorded. At each return visit, the number of pills remaining in the container was recorded, the eMEMS lid was connected to a computer to download data pertaining to when the Securitainer was opened, and the patient was asked, 'In the last week, have you missed any of your doses?' Participants with suboptimal adherence (according to self-report, pill count or eMEMS) were asked the reasons for non-adherence.

To reduce the effect of factors other than ART initiation on adherence to TB treatment, the primary outcome measure was adherence during the 28 days before and 28 days after ART initiation. The number of days included varied by participant because ART could be initiated sooner than 28 days after starting TB treatment, and the number of days between visits was not always exactly 28 days.

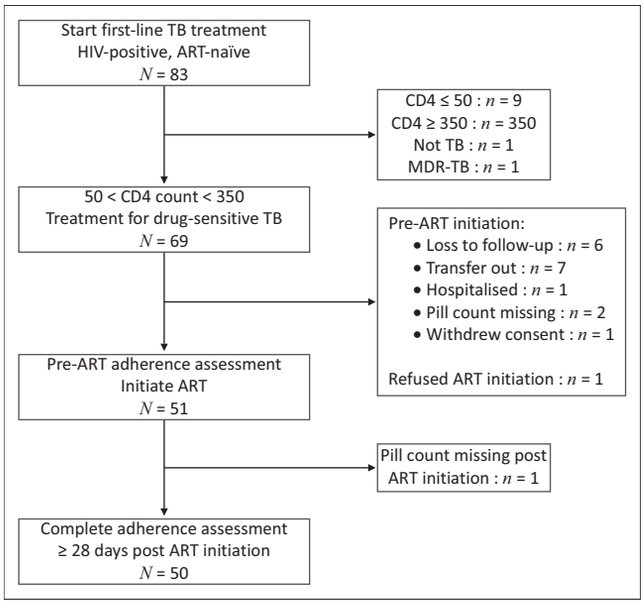
Pill count was used to calculate several adherence measures: percentage of the prescribed doses taken (100 × [number of pills dispensed minus the number of pills returned]/[number of days between clinic visits] × [daily dose]) and three binary indicators: whether adherence equalled 100%, ≥ 95% and ≥ 90%. eMEMS data were used to calculate additional measures of adherence: percentage of the prescribed doses taken (100 × number of days with bottle openings/number of days between clinic visits) and three binary indicators: whether adherence was 100%, ≥ 95% and ≥ 90%. The number of daily bottle openings were truncated to one to avoid overestimating adherence. Data from follow-up visit questionnaires were used to calculate the self-reported adherence (100 × [1 minus the number of missed doses]/number of days between clinic visits) and three binary indicators: whether adherence was 100%, ≥ 95% and ≥ 90%.

Statistical analysis

Participant characteristics are presented as absolute and relative frequencies for categorical variables and as medians and interquartile ranges (IQR) for continuous variables.

The effect of ART initiation on adherence to TB treatment was evaluated in two different ways. Firstly, the median change in percentage of prescribed doses of TB drugs taken before and after ART initiation was compared for each of the three continuous adherence measures (pill count, eMEMS and self-report) using the Wilcoxon matched-pair signed ranks test. Secondly, using the exact McNemar test for paired samples, the proportion of participants adherent to TB treatment before and after ART initiation was compared for all three binary adherence measures for each of the three methods (pill count, eMEMS and self-report).

To determine factors predictive of optimal adherence (100% adherence) in the first month after ART initiation, we first performed bivariate analysis to estimate crude odds ratios (OR) and 95% confidence intervals (CI). We subsequently ran a saturated logistic model containing all selected covariates to estimate adjusted ORs (aOR), and used stepwise backwards elimination to generate a final (reduced) predictive model. We conducted a sensitivity analysis to explore the effect of broadening the definition of optimal adherence to ≥ 95% and ≥ 90% adherence post ART. Crude ORs and aORs are presented with standard Wald 95% CI. All analyses were conducted using STATA 12.1 (Texas, USA).



TB, tuberculosis; ART, antiretroviral treatment.

FIGURE 1: Study flow chart.

Results

Study cohort characteristics

Between September 2011 and October 2012, 83 ART-naïve individuals initiating first-line drugs for pulmonary TB gave informed consent for study participation (Figure 1). Of these, 14 were excluded from the analysis for not meeting all inclusion criteria: CD4 count < 50 cells/mm^3 (n = 9), CD4 count > 350 cells/mm^3 (n = 3), erroneous TB diagnosis (n = 1), or MDR-TB diagnosis (n = 1). Prior to ART initiation, another 18 were excluded owing to loss to follow-up (n = 6), transfer to another facility (n = 7), hospitalisation (n = 1), refusal to start ART (n = 1), missing pill count (n = 2), and withdrawal of consent (n = 1). One additional participant was excluded because of missing pill count post ART initiation.

Among the 50 patients included in the analysis, median age was 32.5 years (IQR 30–38), 56% were female, 58% were unemployed, and almost half (48%) were not of South African nationality. The diagnosis of TB was bacteriologically confirmed in 80%. Median CD4 count was 124 (IQR 94–193). The median time to ART initiation was 27 days (IQR 13–48), and almost all (92%) participants initiated an ART regimen containing efavirenz, lamivudine and tenofovir. TB treatment outcome was successful in 82%. Only 56% of participants achieved viral load suppression, defined as a viral load < 400 copies/mL in the 6–12 months of ART (Table 1).

TABLE 1: Characteristics of 50 individuals included in the analysis of the impact of initiation of antiretroviral treatment on adherence to tuberculosis treatment.

Continuous variables	Group	Median *n*	IQR %
Gender	Male	22	44.0
	Female	28	56.0
Employed	Yes	21	42.0
	No	29	58.0
Nationality	South Africa	26	52.0
	Zimbabwe	21	42.0
	Mozambique	3	6.0
Education†	None	2	4.1
	Primary school	4	8.2
	Some secondary school	28	57.1
	Secondary school completed	15	30.6
TB diagnosis	Confirmed	40	80.0
	Clinical	10	20.0
ART regimen	EFV, 3TC, TDF	46	92.0
	EFV, 3TC, D4T	3	6.0
	EFV, 3TC, AZT	1	2.0
TB treatment outcome	Cure	9	18.0
	Treatment completed	32	64.0
	Treatment failed	0	0.0
	Died	1	2.0
	Lost to follow-up	5	10.0
	Not evaluated (transfer out)	3	6.0
ART outcome	Suppressed‡	28	56.0
	Failure to suppress‡	10	20.0
	Died	1	2.0
	Lost to follow-up	8	16.0
	Not evaluated (transfer out)	3	6.0
Age (years)		**32.5**	**30–38**
BMI at enrollment		**21.5**	**19–23**
CD4 count at enrollment (cells/mm^3)		**124**	**94–193**
Time from TB treatment to ART initiation (days)		**27**	**13–48**

BMI, body mass index; TB, tuberculosis; ART, antiretroviral treatment; IQR, interquartile ranges.
†, Education level missing for 1 participant; ‡, suppression is defined as viral load < 400 copies/mL within the first year of ART.

Adherence to TB treatment before and after antiretroviral therapy initiation

When measured by pill count or self-report, the median percentage of prescribed TB drug doses taken was 100% before and after ART initiation (Table 2). When measured by eMEMS, median percentage of prescribed TB drug doses taken was 93% before, and 82.5% (IQR 55–96) after, ART initiation. There was no change in the percentage of TB medication taken before and after ART initiation, with a median percentage change of 0 (IQR -4, +1) for pill count, 0 (IQR 0–0) for self-report, and minus 1.5 (IQR -25, +3) for eMEMS (all p values > 0.30).

When measured by pill count, the proportion of participants who were 100% adherent to TB treatment before and after ART initiation was 64% (41.7–70.3) versus 56.0% (50.2–77.8); increased to 68.0 (54.6–81.4) versus 78% (66.1–89.9) when adherence was defined as 95% of prescribed doses taken, and 78.0 (66.1–89.9) versus 88.0% (78.7–97.3) when adherence was defined as 90% of doses taken.

Self-reported adherence was high, with 100% of participants being adherent before and after ART initiation when adherence was defined as taking ≥ 90 or ≥ 95% of prescribed doses, and 96.0% (90.4–100) and 94.0% (87.2–100) being adherent before and after ART initiation, respectively, when adherence was defined as 100% of prescribes doses.

Owing to technical errors, power failures, equipment failures, and misunderstandings by pharmacists and patients, adherence data by eMEMS were only available

TABLE 2a: Adherence to tuberculosis treatment before and after initiation of antiretroviral treatment.

Adherence measure	% TB drugs prescribed taken before ART initiation†			% TB drugs prescribed taken after ART initiation‡			% change in TB drugs taken before and after ART initiation			
	N	Median	IQR	*N*	Median	IQR	*N*	Median	IQR	*p* value§
Pill count	50	100	96, 100	50	100	91, 100	50	0	-4, +1	0.55
Self-report	50	100	100, 100	50	100	100, 100	50	0	0, 0	0.64
Electronic MEMS	21	93	75, 100	20	82.5	55, 96	14	-1.5	-25, +3	0.31

MEMS, Medication Event Monitoring System; TB, tuberculosis; ART, antiretroviral treatment; IQR, interquartile ranges.
†, Period assessed is the period up to 28 days pre ART initiation; ‡, Period assessed is the 28-day period following ART initiation. If the first TB clinic visit occurred > 28 days following ART initiation, the entire time period between ART initiation and subsequent TB clinic visit was included; §, Comparison only possible between 14 patients who had MEMS data available both before and after ART initiation.

TABLE 2b: Hundred percent adherence to tuberculosis treatment before and after initiation of antiretroviral treatment.

Adherence measure	Proportion of patients with 100% adherence pre ART			Proportion of patients with 100% adherence post ART			Difference in proportion adherent post v. pre cART (%)	*p* value‡
	N	%	95% CI	*N*	%	95% CI		
Pill count	50	64.0	50.2–77.8	0.50	56.0	41.7–70.3	-8.0	0.50
Self-report	50	96.0	90.4–100	1.00	94.0	87.2–100	-2.0	1.00
Electronic MEMS	21	38.1	15.4–60.7	0.5†	10.0	0.4–24.4	-18.1	0.5†

MEMS, Medication Event Monitoring System; ART, antiretroviral treatment; CI, confidence intervals.
†, Wilcoxon matched-pair signed ranks test; ‡, Exact McNemar test for paired samples.

TABLE 2c: Ninety-five percent adherence to tuberculosis treatment before and after initiation of antiretroviral treatment.

Adherence measure	Proportion of patients with ≥ 95% adherence pre ART			Proportion of patients with ≥ 95% adherence post ART			Difference in proportion adherent post v. pre cART (%)	*p* value‡
	N	%	95% CI	*N*	%	95% CI		
Pill count	50	78.0	66.1–89.9	0.36	68.0	54.6–81.4	-10.0	0.36
Self-report	50	100	100–100	1.00	98	94.0–100	-2.0	1.00
Electronic MEMS	21	47.6	24.3–70.9	1.00†	30.0	8.0–52.0	-17.6	1.00†

MEMS, Medication Event Monitoring System; ART, antiretroviral treatment; CI, confidence intervals.
†, Wilcoxon matched-pair signed ranks test; ‡, Exact McNemar test for paired samples.

TABLE 2d: Ninety percent adherence to tuberculosis treatment before and after initiation of antiretroviral treatment.

Adherence measure	Proportion of patients with ≥ 90% adherence pre ART			Proportion of patients with ≥ 90% adherence post ART			Difference in proportion adherent post v. pre cART (%)	*p* value‡
	N	%	95% CI	*N*	%	95% CI		
Pill count	50	88.0	78.7–97.3	0.18	78.0	66.1–89.9	-10.0	0.18
Self-report	50	100	100–100	1.0	100	92.9–100	0	1.0
Electronic MEMS	21	61.9	39.3–84.6	0.63†	40.0	16.5–63.5	-21.9	0.63†

MEMS, Medication Event Monitoring System; ART, antiretroviral treatment; CI, confidence intervals.
†, Wilcoxon matched-pair signed ranks test; ‡, Exact McNemar test for paired samples.

for 21 participants pre ART, 20 participants post ART, and 14 both before and after ART initiation. The proportion of participants adherent to TB treatment after ART initiation was consistently lower than adherence before ART initiation: 10.0% (0.4–24.4) versus 38.1 (15.4–60.7); 30.0 (8.0–52.0) versus 47.6 (24.3–70.9) and 40.0 (16.5–63.5) versus 61.9 (39.3–84.6) when adherence was defined as 100%, 95% or 90% of prescribed doses taken, respectively.

Reasons for suboptimal adherence

Leaving house without tablets (n = 8) and running out of tablets between visits (n = 8) were the most frequently stated reasons for missing doses (n = 8), followed by forgetfulness (n = 3), dosing errors (n = 3), taking medication as prescribed whilst not using the eMEMS lid (n = 3), distractions (n = 2), medication side-effects (n = 2) and lack of transport money (n = 1).

Factors associated with optimal adherence to TB treatment after antiretroviral therapy initiation

Employment status was the only factor associated with optimal (100%) adherence following ART initiation. Compared with those not employed, participants who were employed had four times greater odds (aOR 4.11, 95% CI 1.06–16.0) of being fully adherent to TB treatment. Age and gender tended to be associated with optimal adherence, with a 13% (95% CI -1, +29%) increased odds for every year increase in age and men being less likely to optimally adhere to TB treatment (aOR 0.32, 95% CI 0.08–1.29), but these associations did not reach statistical significance. In sensitivity analyses, age and employment status were factors associated with 95% and 90% adherence, respectively (Table 3).

Discussion

In the present study of ART-naïve HIV-infected individuals receiving treatment for active TB, we observed a trend of decrease in adherence to TB treatment in the first month following ART initiation, with an 8% – 10% decrease in the proportion of patients adherent according to pill count and an 18% – 22% decrease in the proportion of patients adherent according to eMEMS, independent of the cut-off used to define adherence (90%, 95% or 100% of prescribed doses taken). The finding of reduced adherence soon after the introduction of ART is clinically relevant, as suboptimal adherence has been associated with poor treatment

TABLE 3: Factors associated with optimal adherence (100% of prescribed doses) following initiation of antiretroviral treatment in patients receiving treatment for active tuberculosis (pe 0.05; pr 0.15).

Factor	Characteristic	Crude OR (95% CI)	Adjusted OR full model (95% CI)	Adjusted OR final model (95% CI)
Age	Per year increase	1.12 (1.00–1.25)	1.11 (0.97–1.28)	1.13 (0.99–1.29)
Gender	Female	Referent	Referent	Referent
	Male	0.80 (0.26–2.45)	0.34 (0.60–1.95)	0.32 (0.08–1.29)
Nationality	South African	Referent	Referent	-
	Not South African	0.83 (0.27–2.55)	1.48 (0.30–7.14)	-
Education	Secondary school not complete	Referent	Referent	-
	Secondary school completed	0.36 (0.10–1.27)	0.37 (0.07–1.91)	-
Employment	Unemployed	Referent	Referent	Referent
	Employed	4.53 (1.30–15.77)	3.87 (0.80–18.8)	4.11 (1.06–16.0)
CD4 count	(per 100 cells/mm^3 decrease)	1.37 (0.61–3.00)	1.19 (0.43–3.30)	-
BMI	Per unit increase	0.98 (0.85–1.14)	1.01 (0.92–1.11)	-
Time between TB treatment and ART initiation	Per day increase	1.01 (0.98–1.02)	1.01 (0.98–1.04)	-
Adherence to TB treatment before ART initiation	< 100%	Referent	Referent	-
	100%	2.08 (0.64–6.73)	1.40 (0.28–6.87)	-
Family DOT post ART	No	Referent	Referent	-
	Yes	0.40 (0.12–1.25)	0.81 (0.16–4 .06)	-

BMI, body mass index; TB, tuberculosis; ART, antiretroviral treatment; DOT, directly observed treatment; OR, odds ratios; CI, confidence intervals.

outcomes and development of resistance, especially in the early phases of treatment when the bacillary load is highest. Whilst many have speculated that the increased pill count in patients with TB initiating ART could reduce adherence,[5,6,9] we could not compare our findings with others as we could not find published reports assessing this association.

Similar to findings of other studies,[2] reasons for non-adherence reported by patients were multifactorial and few independent predictors for optimal adherence could be identified. Except for employment, with those being employed having four times higher odds of remaining fully adherent when initiating ART, we could not identify patient factors associated with adherence.

In the present study, we used three different methods to measure adherence: self-report of missed doses, pill count, and eMEMS. We observed that adherence by self-report was always highest, pill count gave intermediate estimates, and eMEMS consistently resulted in the lowest estimates. Poor correlations between different adherence measures have been reported. For example, in a study of adherence to ART, Holzemer found that there was minimal correlation amongst adherence as measured by pharmacy refill, self-report, MEMS and pill count.[10] Overestimation of adherence by self-report is a consistent finding, probably related to social desirability or recall error.[11] eMEMS, on the other hand, can underestimate adherence when several doses of medications are removed from bottles at a single time, as was observed in the present and other studies.[12,13] Similar to what was observed in our cohort, self-reported rates of adherence are higher than the rates derived from electronic monitoring; however, the 40% – 50% difference between the two measures is greater than the 10% – 30% reported in other settings.[14,15] This result may be owing to limited validity of the eMEMS data, given the numerous challenges when implementing eMEMS into routine care in a resource-limited setting, including batteries of eMEMS caps running flat, power cuts during the transfer of eMEMS data to computer, errors made by pharmacists when filling the containers, and breakage of the container lids. In addition, some patients forgot or lost their Securitainer.

The present study has several limitations. Firstly, the small sample resulted in imprecise estimates and a lack of power to detect statistically significant differences, even when the differences observed were probably of clinical relevance. Secondly, the time between starting TB treatment and ART initiation in the study participants was short, (median of 27 days), and did not vary greatly between participants (IQR 13–48). As such, we could not assess the impact of timing of ART initiation on adherence. It is possible that delay of ART initiation until the end of the intensive phase, when patients feel better and side-effects of TB treatment have subsided, could lower the negative impact of ART initiation on adherence to TB treatment. This possibility would need to be weighed against the risk of poor treatment outcomes owing to the delay of ART initiation, and may therefore only be possible for patients with high CD4 counts at the time of TB diagnosis. Thirdly, we limited our assessment to the 28 days immediately before and after ART initiation to assess the impact of ART initiation on adherence to TB drugs. We could therefore not assess whether the observed changes in adherence were temporary or persisted throughout the TB treatment period. Finally, the clinic did not perform clinic-based directly observed treatment (DOT). Findings of the present study may therefore not be generalisable to settings where DOT is systematically implemented for all patients receiving TB treatment.

Conclusion

In the present small prospective cohort study, we observed a trend to decreased adherence to TB treatment following the initiation of ART. Our findings suggest that adherence

interventions in the period following ART initiation may be needed to optimise treatment outcomes for people living with TB and HIV.

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Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

M.K. (University of the Witwatersrand) collected the data and wrote the first draft. R.L.v.Z. (University of the Witwatersrand) was involved in project design, I.S. (Right to Care) made conceptual contributions, J.B. (Witkoppen Health and Welfare Centre) was involved in data collection, and A.v.R. (University of North Carolina) was involved in project design and statistical analysis. All authors reviewed the manuscript and gave scientific input.

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Visual loss in HIV-associated cryptococcal meningitis: A case series and review of the mechanisms involved

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Permanent visual loss is a devastating yet preventable complication of cryptococcal meningitis. Early and aggressive management of cerebrospinal fluid pressure in conjunction with antifungal therapy is required. Historically, the mechanisms of visual loss in cryptococcal meningitis have included optic neuritis and papilloedema. Hence, the basis of visual loss therapy has been steroid therapy and intracranial pressure lowering without clear guidelines. With the use of high-resolution magnetic resonance imaging of the optic nerve, an additional mechanism has emerged, namely an optic nerve sheath compartment syndrome (ONSCS) caused by severely elevated intracranial pressure and fungal loading in the peri-optic space. An improved understanding of these mechanisms and recognition of the important role played by raised intracranial pressure allows for more targeted treatment measures and better outcomes. In the present case series of 90 HIV co-infected patients with cryptococcal meningitis, we present the clinical and electrophysiological manifestations of Cryptococcus-induced visual loss and review the mechanisms involved.

Introduction

Meningitis owing to *Cryptococcus neoformans* remains a frequent human immunodeficiency virus (HIV)- associated opportunistic infection even in developing countries with effective antiretroviral therapy (ART) rollout programmes.[1] This is largely a result of failure of HIV testing by individuals with risky sexual behaviour, and late presentation for and poor compliance with ART. Therefore, it is not uncommon to still encounter severely immunocompromised patients presenting for the first time with opportunistic infections and CD4+ T-lymphocyte counts < 100 cells/μL. Headache, high fever, nuchal pain and stiffness, photophobia, confusion, nausea, vomiting and diplopia are the common presenting symptoms of cryptococcal meningitis (CM). Symptoms arise from raised intracranial pressure and meningeal inflammation, usually within 1–2 weeks of the onset of the illness. High cerebrospinal fluid (CSF) pressure, depressed level of consciousness and an acellular CSF are poor prognostic features. Effective antifungal therapy (amphotericin B, flucytosine and fluconazole) is not readily available in most developing countries.[2] Mortality remains high and contributes up to 20% of HIV-related deaths.[1] Complications in survivors are severe, with visual loss being the most disabling, yet are potentially preventable and reversible. Recognition of visual impairment in encephalopathic patients is difficult and therefore often neglected and underreported. In the following case series, we evaluated 90 patients with culture-confirmed CM. Their results and a discussion of the mechanisms implicated in Cryptococcus-induced visual loss are discussed. An illustrative case of the optic nerve sheath compartment syndrome (ONSCS) as a putative mechanism is also presented in the discussion.

Method

In a prospective study approved by the Greys Hospital and University of KwaZulu-Natal Ethics Committees, we consecutively recruited 90 patients with culture-confirmed CM between February 2008 and December 2011 (Table 1). Patients with reduced levels of consciousness were excluded (GCS < 14). All were HIV co-infected, provided informed consent, had full neuro-ophthalmological assessments and had magnetic resonance imaging (MRI) using standard imaging protocols. Patients were recruited within 4 weeks of the disease onset, during the induction and consolidation phases of CM treatment. Drug treatment and management of raised intracranial pressure were based on the 2007 South African HIV Clinician Society Guidelines.[3]

Eighty-six patients underwent electrophysiological testing that involved visual evoked potentials (VEP) and Humphreys visual fields (HVF). VEP involved testing of each optic nerve's functioning by requesting the patient to look at a screen one metre away that displayed an alternating full-field checkerboard pattern. The cortical responses thus obtained were detected by silver-surface electrodes placed over the occipital scalp. Averaging of the cortical responses provided a reliable and reproducible triphasic wave from which the P100 latency (the large

TABLE 1: Demographic data, cerebrospinal fluid pressure and CD4 count of 90 cryptococcal meningitis patients.

Patient characteristics	Patient data
Age in years: mean (range)	33.5 (18–51)
Male: *n* (%)	50 (55.6%)
CD4 count in cells/μL: mean (s.d.)	47 (10.1)
On ART: *n* (%)	22/90 (24.4%)
CSF pressure in cm CSF: mean (s.d.)	31.3 (13.5)

s.d., standard deviation; ART, antiretroviral therapy; CSF, cerebrospinal fluid.

positive wave that occurs at approximately 100 ms from the stimulus) and amplitude (the vertical height in μV between the largest positive P100 and negative N80 waves) were obtained in accordance with International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines.[4] HVF was performed using the SITA 30-2 standard protocol. Pattern deviation fields that fulfilled acceptable reliability indices were included for analysis. Flash VEP using LED goggles were used in patients who were delirious; however, HVF was not possible in such patients.

Statistics

Visual acuity, VEP latency and amplitude were dichotomised into abnormal and normal groups using standard normal references. One-sample *t* tests were used to compare mean latency and amplitude with laboratory references that have been previously described.[5] Tests for association between groups were analysed using a chi-square test or Fisher's exact test, as appropriate. Statistical analysis was done by STATA, version 12.

Results and discussion

Clinical findings

Visual loss occurred at any stage of the illness and occurred frequently before starting drug therapy. Subgroup analysis not reflected in Table 2 showed that the majority of cases occurred within 2–4 weeks of CM onset, regardless of drug therapy. Rex's landmark article in 1993 of Cryptococcus-induced visual loss suggested two main mechanisms: an early and sudden visual loss owing to optic neuritis, and a late and gradual visual loss owing to papilloedema. Such distinct mechanisms, however, do not exist in isolation and an explanation for visual loss where neither mechanism is in operation needs clarification.[6] Gradual, symmetrical and bilateral visual blurring associated with headache was the most common presentation in our series (Table 2). Sudden and catastrophic visual loss was rare, occurring in only one patient. Forty-six percent of patients had appreciable loss of vision (< 6/9 on Snellen) and profound visual loss of < 6/60 in 13%. Colour desaturation, pupillary reflex changes and pain on eye movement were relatively uncommon. Sixth nerve palsies owing to elevated intracranial pressure or meningitis occurred in 16% of patients. Bilateral and symmetrical cerebellar ataxia was common in this group and probably accounted for the impaired smooth pursuit and nystagmus – findings also commonly encountered in HIV-associated neurocognitive disorder.

TABLE 2: Neuro-ophthalmological manifestations of cryptococcal meningitis in 90 patients.

Examination parameter	Clinical findings	Proportion examined	
		Proportion	%
Best corrected visual acuity (Snellen)	< 6/9	41/90	46
	< 6/60	12/90	13
Mode of onset of visual loss	Bilateral/unilateral	34/41; 7/41	83; 17
	< 1 week	6/41	15
	> 1 week	35/41	85
	Sudden	1/41	2
	Pain on eye movement	1/41	2
	Colour desaturation	5/41	12
External ophthalmoplegia	Bilateral 6th nerve palsy	7/90	8
	Unilateral 6th nerve palsy	7/90	8
	Unilateral 3rd nerve palsy	1/90	1
Supranuclear eye movements	Impaired smooth pursuit	23/90	26
	Gaze-evoked nystagmus	20/90	22
	Convergence spasm	1/90	1
Swollen optic disc	Bilateral	26/90	29
	Unilateral	3/90	3
Pale optic disc	Bilateral and mild	2/90	2
Pupillary reflex	Reactive but sluggish	11/90	12
	No reaction	4/90	4
	RAPD	5/90	6

RAPD, relative afferent pupillary defect.

Electrophysiological findings

VEP testing and HVF defects were common in the series we reported, both in visually impaired and visually normal patients with CM (Table 3).[5] In the cross-section of 86/90 patients who underwent electrophysiological tests, VEP abnormalities were detected in visually impaired patients (68.9% of right eyes and 67.6% of left eyes), and in visually normal patients (56.5% of all eyes). In subgroup analysis, prolongation of the P100 latency was the predominant abnormality (42.3% of all eyes).[5] In the absence of demyelination, these findings were interpreted as resulting from conduction block caused by optic nerve compression. Optic nerve compression with secondary conduction block and optic nerve infiltration were both deemed likely from these findings. VEP amplitude changes suggesting axonal loss were less frequent (14.6%) in eyes tested. As shown in Table 3, HVF abnormalities were also very frequent in patients who could be tested (76.6% of right eyes and 71.1% of left eyes). The predominant field defects were peripheral constriction with large blind spots – field defects consistent with papilloedema-related optic nerve dysfunction (Figure 1).[5] Consequently, the interpretation of these findings was that the HVF defects supported raised intracranial pressure as an important cause of optic nerve dysfunction in Cryptococcus-induced visual loss.

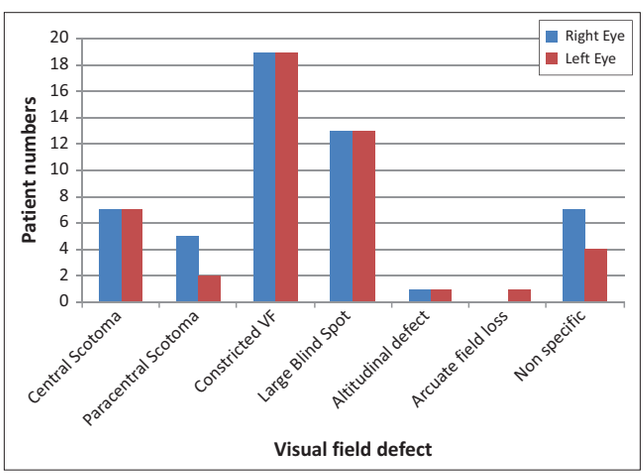
Mechanisms implicated

Rex's classification of visual loss was time based.[6] He suggested that early visual loss was a result of optic nerve infiltration/inflammation and occurred within 6 days of the onset of meningitic symptoms, whereas late visual loss occurred a few weeks into the infection and was the result of optic disc oedema from raised intracranial pressure

TABLE 3: Frequencies of abnormal visual acuity, visual evoked potentials and Humphreys visual fields in 86 patients tested.

Findings	Visual acuity: < 6/9		VEP				HVF			
			Right eye		Left eye		Right eye		Left eye	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Normal	46	53.5	23	31.1	24	32.4	11	23.4	13	28.9
Abnormal	40	46.5	51	68.9	50	67.6	36	76.6	32	71.1
Total	**86**	**100**	**74**	**100**	**74**	**100**	**47**	**100**	**45**	**100**

Source: Moodley A, Rae W, Bhigjee A, et al. Early clinical and subclinical visual evoked potential and Humphrey's visual field defects in cryptococcal meningitis. PloS One. 2012;7:e52895. PMID: 23285220, http://dx.doi.org/10.1371/journal.pone.0052895
VEP, visual evoked potential; HVF, Humphrey's visual fieldz



Source: Moodley A, Rae W, Bhigjee A, et al. Early clinical and subclinical visual evoked potential and Humphrey's visual field defects in cryptococcal meningitis. PloS One. 2012;7:e52895. PMID: 23285220, http://dx.doi.org/10.1371/journal.pone.0052895
VF, visual fields.

FIGURE 1: Frequencies of visual field defects.

(papilloedema). Remarkably, the rapid visual loss group in Rex's series had elevated CSF pressure (90%), thickened optic nerves on computed tomography (CT) scan (22%) and symmetrical visual loss (93%). The visual loss occurred before or soon after initiation of antifungal therapy and was severe and permanent. The slow visual loss group did not differ much, having elevated CSF pressure (83%), thickened optic nerves (22%) and symmetrical visual loss (93%). As to whether there was dilatation of the peri-optic CSF space or thickening of the optic nerve itself was not defined on CT scan for both groups in Rex's series. So, apart from the tempo of presentation, a clear distinction between these groups does seem artificial. We too have previously shown that raised intracranial pressure is common in CM-induced visual loss (69%), and that papilloedema was present in only 25%; but, in addition, we have shown that on MRI there is no difference between the optic nerve sheath diameter in patients with CM and that of a normal control group, regardless of CSF pressure.[7] None of the optic nerves demonstrated post-contrast enhancement either, reflecting a poor inflammatory response. Evidence for a third mechanism of optic nerve dysfunction was compelling.

Subsequent reports, as discussed below, have supported or refuted the findings of Rex with evidence for and against the optic neuritis and papilloedema models. However, his work certainly laid down the foundation for investigation into Cryptococcus-induced visual loss; and in fact much of our current understanding has resulted from his original observations.

Recovery of vision has always been documented as poor. Drug treatment alone is insufficient as demonstrated by Graybill et al. where steroids alone were ineffective but serial lumbar punctures and reduction of CSF pressure were more successful.[8] In Torres's meta-analysis of rapid and slow visual loss cases, the outcome was generally poor when only the underlying CM was treated and not the raised intracranial pressure.[9]

The papilloedema mechanism

Raised intracranial pressure in CM is well documented.[10,11] CSF outflow obstruction caused by plugging of the arachnoid granulations by the organism and/or polysaccharide capsule is postulated to result in the elevated intracranial pressure (Figure 2c).[10,12] Good support for obstruction at the arachnoid villi has come from Loyse et al. who demonstrated histopathologically that fungal loading (high fungal burden) occurs within the arachnoid villi and is positively correlated with elevated intracranial pressure.[12] Bicanic et al. have shown that higher fungal burden and higher cryptococcal antigen titres are associated with higher intracranial pressure and have therefore recommended early and aggressive fungicidal treatment with lowering of intracranial pressure by either serial lumbar punctures or lumbar drainage to lower morbidity and mortality in patients with CM.[13] In 1993, Garrity et al. performed optic nerve sheath fenestrations in two patients with visual loss and papilloedema.[14] Following the procedure, both patients had improved vision from lowering of intracranial pressure. Cryptococcal organisms were present in the dural sheaths of both patients. At autopsy of one of the patients, patency of the sheath fenestration was still present.

The evidence for visual loss resulting from raised intracranial pressure and papilloedema, and the benefit from CSF pressure lowering either by serial lumbar punctures,[8,10,15,16,17] acetazolamide,[17,18] lumbo-peritoneal (LP) shunt, lumbar drain,[18,19,20] ventriculo-peritoneal (VP) shunt[10,21] and optic nerve sheath fenestration[14,22] are well documented, but unfortunately mostly anecdotal. Comparative studies between surgical lowering of intracranial pressure and drug-only therapy to prevent or reverse visual loss in CM have not been done. Lowering of the raised intracranial pressure is shown to improve the overall prognosis of CM and therefore cannot be ethically withheld in a randomised controlled trial. Pharmaceutical approaches alone to control raised intracranial pressure in CM have not been shown to be effective. Surgically invasive methods to decrease intracranial pressure in CM also carry their own risks such as over drainage, shunt infection, distal catheter migration and need for shunt revision.[23] VP shunts are associated with lower risk of shunt obstruction and revision than LP shunts and are therefore recommended when serial lumbar punctures are ineffective or not an option.

CT and MRI scans show normal ventricular size in most cases of CM despite profoundly elevated CSF pressure. Presumably the equivalent pressures between the intraventricular fluid and the CSF surrounding the brain and the paucity of intraventricular fungal elements prevent ventricular dilatation, unlike tuberculous meningitis where hydrocephalus is often encountered from blockage at the Sylvian aqueduct or foramina of Lushka and Magendie.[10] Raised intracranial pressure and fungal loading are common and well described in CM patients, but inflammation is minimal if at all, regardless of HIV coinfection. The frequent finding of an acellular CSF in CM despite markedly elevated CSF pressure is a case in point. The significance of raised intracranial pressure cannot be underestimated in visual loss, and perhaps optic disc swelling and optic nerve infiltration/inflammation are secondary or co-occurrences. Reports of raised intracranial pressure-related visual loss are many in the literature, and the benefit of early lowering of intracranial pressure in reversing blindness in Cryptococcus-induced visual loss is well documented.[15,19,21,24]

The optic nerve infiltration/inflammation mechanism

Evidence for optic nerve infiltration by *C. neoformans* has come from case reports only. Lipson et al. first described two cases of AIDS-associated cryptococcal arachnoiditis resulting in bilateral visual loss secondary to an optic neuropathy (Figure 2b).[25] Ofner's claim of optic nerve infiltration in a patient with visual loss and elevated intracranial pressure was not robust.[26] Histology obtained from the optic nerve sheath showed fungal infiltration with inflammation, but optic nerve infiltration was only presumed. Histological evidence of cryptococcal infiltration of the intracanalicular segment of the optic nerve with associated necrosis was provided by Cohen et al. in 1993[27] and further supported by a histopathological case reported by Corti et al. in 2010.[28] Corti's case also showed a perineuritis, but in addition showed optic nerve infiltration by the fungus. By inference, Hoepelman[29] and Seaton[30] suggested that corticosteroids could only play a beneficial role in Cryptococcus-induced visual loss by reducing the optic nerve inflammation so induced by the organism. Further support for an optic neuritis model has come from De Schacht's report of a 26-year-old CM patient who developed an immune reconstitution illness with bilateral blindness after starting antiretroviral therapy.[31] Supposedly, the exaggerated optic nerve inflammation secondary to fungal infiltration caused the bilateral blindness. Unfortunately, such case reports in the literature are scanty and the evidence for optic nerve infiltration is mostly speculative.[32] In our cohort of patients, optic nerve infiltration was uncommon, as evidenced by the lack of nerve signal changes and enhancement on MRI, and the dissimilar magnetic resonance diffusion parameters to that of optic neuritis.[7] Optic nerve infiltration possibly results from direct cryptococcal invasion from the peri-optic CSF, or perhaps develops from retrograde extension of the meningo-encephalitis from the thalamus and other diencephalic structures that seem particularly susceptible to cryptococcal infiltration. The common finding of pseudocysts and dilated Virchow-Robin spaces in these regions supports this assertion.

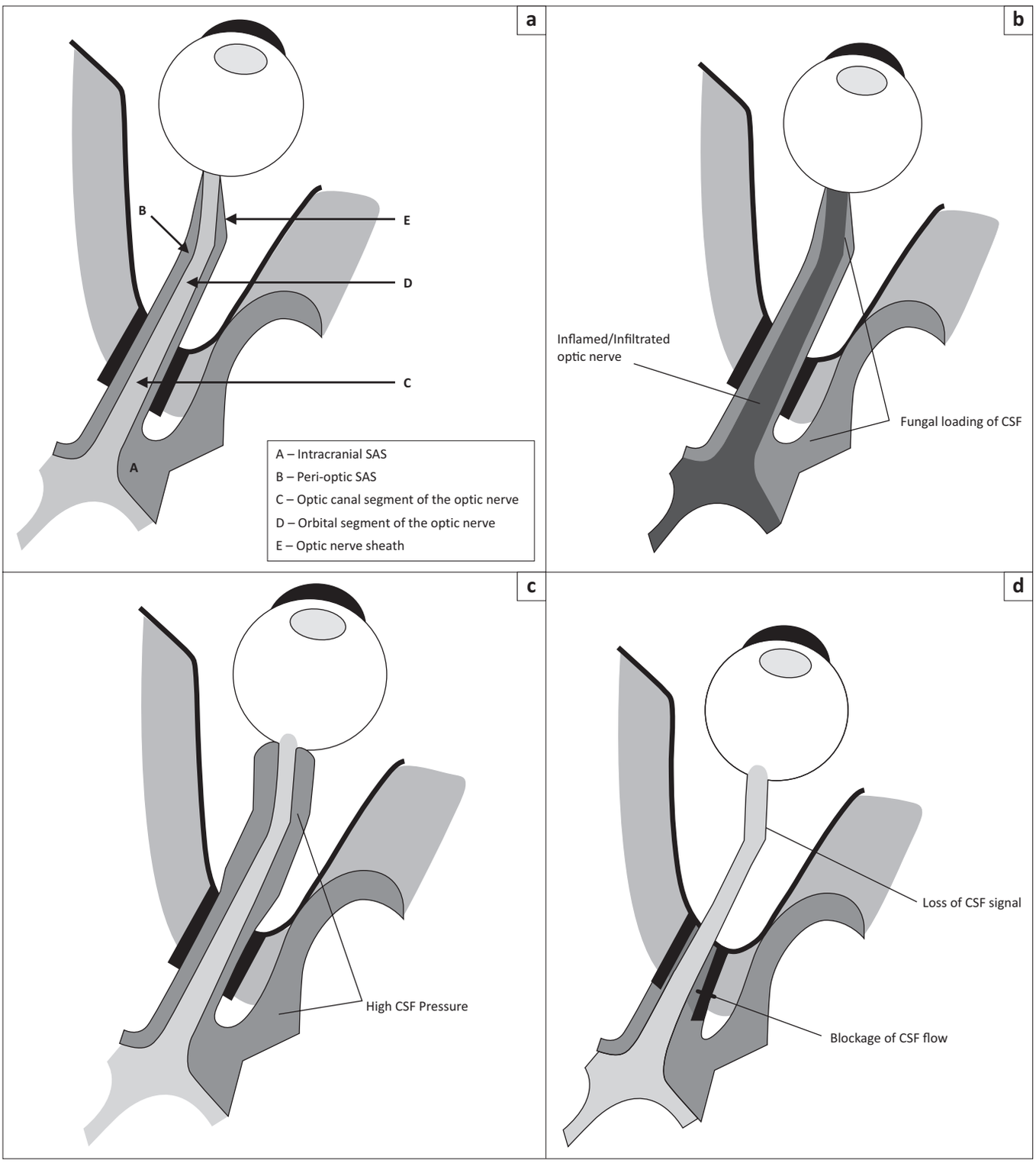
The optic nerve sheath compartment mechanism

We have reported a case that demonstrates the strong likelihood of ONSCS which we propose as a probable third mechanism of optic nerve dysfunction (Figure 2d). During elevated CSF pressure, there was loss of the peri-optic CSF signal on T2 MRI and return of the CSF signal following lowering of CSF pressure.[33] The stasis of contrast-filled CSF at the mid-orbital segment of the optic nerve sheath suggests complete plugging of the peri-optic space by cryptococcal fungal elements. We further postulate that a large pressure gradient resulted from blockage between the significantly elevated intracranial pressure within the intracranial subarachnoid space (SAS) and the pressure of the proximal peri-optic CSF space. An ONSCS thus followed, causing optic nerve compression, axoplasmic stasis and ischaemia. Optic nerve dysfunction ensued with visual blurring and visual loss.

A subsequent case of a 33-year-old HIV-infected patient with bilateral blindness from CM and elevated CSF pressure (> 50 cm CSF) also demonstrates this phenomenon. In addition to the blockage within the optic canals bilaterally, dilatation of the peri-optic CSF space ahead of the obstruction is visible on the left side (Figure 3). Notably, this case showed obstruction within the optic canal, unlike the previous case that showed mid-orbital obstruction. After lowering of the CSF pressure, there is return of the CSF to the orbital peri-optic space. We postulate that, following the blockage at the optic canal level, CSF from the orbital peri-optic space is drained by the peri-optic lymphatics and hence there is loss of the CSF signal on the T2 high-resolution scan. This is more plausible than loss of the CSF signal prior to CSF pressure lowering being the result of fungal loading alone, as the interval between the two scans was only 11 days and much too soon for all the fungal elements to clear from that space.

Cohen's histological description of intracanalicular necrosis of the optic nerve and obliteration of the intracanalicular peri-optic space by fungal loading provides the only credible histopathological evidence of a clear compartment syndrome in CM-induced visual loss.[27]

Killer et al. have shown by electron microscopy that the peri-optic SAS is not occupied by CSF alone but also by a network of trabeculae, septae and pillars comprising fibroblasts and blood vessels.[34] They provide histological evidence that the peri-optic SAS narrows in the mid-orbital segment where the delicate trabeculae change into broader septae and stout pillars that subdivide the SAS into compartments. The SAS within the intracanalicular segment is extremely narrow and consists of pillars and trabeculae only. Hence the potential sites of blockage to CSF flow are the mid-orbital and the intracanalicular segments of the peri-optic SAS.

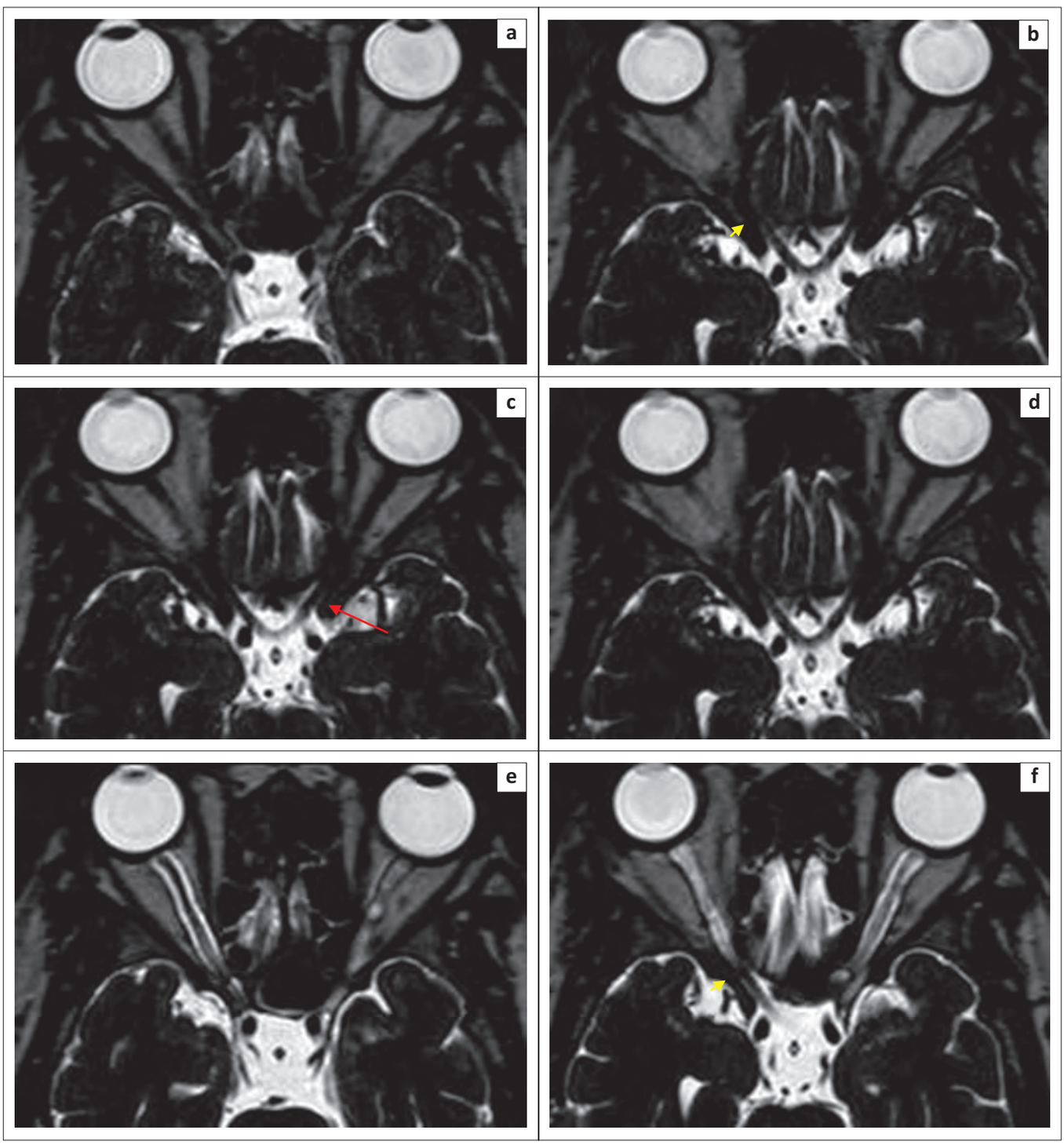


SAS, subarachnoid space; CSF, cerebrospinal fluid.

FIGURE 2: Proposed mechanisms involved in Cryptococcus-induced visual loss. (a) Normal, (b) inflammation/infiltration, (c) papilloedema and (d) compartment syndrome.

Killer et al. also suggest that the varying anatomy of these subarachnoid trabeculae, septae and pillars between the two optic nerves account for the asymmetrical papilloedema in idiopathic intracranial hypertension (IIH).[35] Asymmetrical pressure is transmitted to the laminar cribrosa of the two optic nerves. On the side with more trabeculae, septae and pillars, a lower pressure is transmitted to the optic nerve head and hence little or no papilloedema ensues. We have expanded on this theory in CM, where, in addition to raised intracranial pressure, there is loading of the peri-optic SAS with fungal elements (the organism and fragments of the polysaccharide capsule). CM is a pauci-inflammatory disorder, and hence fungal loading rather than inflammatory cell accumulation occurs. Fungal loading in the peri-optic CSF space has been shown by histology of the optic nerve sheath during optic nerve sheath fenestration.[22] Sequestration

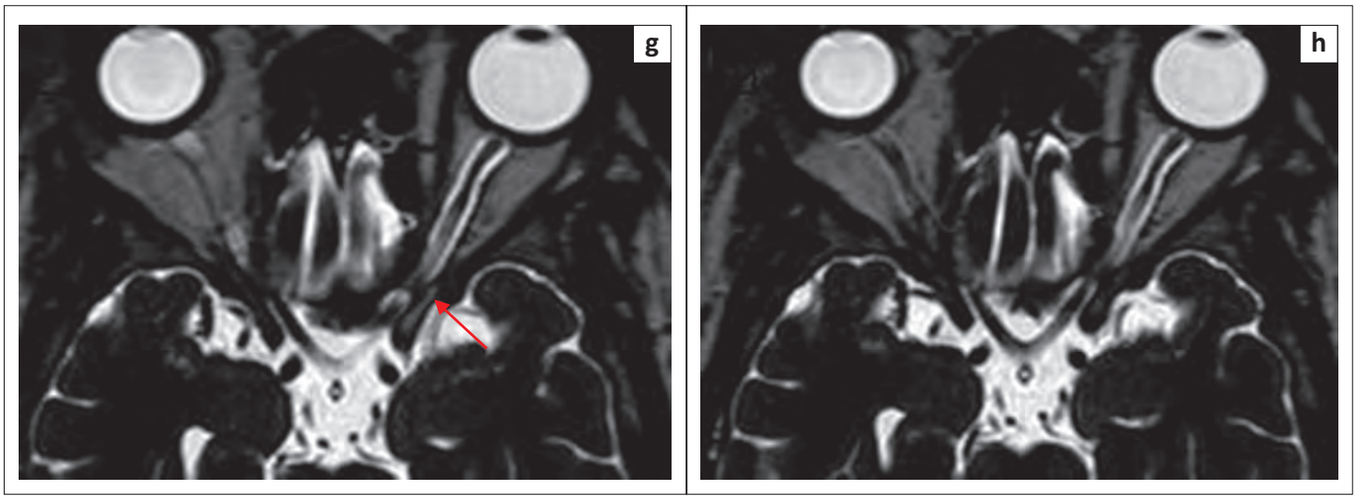
of CSF in the immediate retrobulbar space is not evident, and the contribution made by the fungal clumping needs exploration. We have not been able to demonstrate optic nerve sheath dilatation nor optic nerve thickening in the setting of CM with or without papilloedema and regardless of CSF pressure measured at the lumbar level.[7] It is conceivable that the retrobulbar segment of the nerve is subjected to toxic byproducts from the fungi, venous stasis, ischaemia from vascular compromise and axoplasmic stasis from mechanical compression. We propose therefore that these findings suggest axoplasmic stasis, mitochondrial dysfunction and ischaemia of the axons which develop from compression at the site of blockage. The end result is optic disc swelling that occurs in only 25% of CM patients, despite raised intracranial pressure occurring in 69% – 90% of CM patients. The blockage at the mid-orbital or intracanalicular segments from raised



Note: T2 high-resolution magnetic resonance imaging of the optic nerves in a patient with CM and bilateral blindness, showing return of the peri-optic CSF signal following CSF pressure lowering. The red arrows point to the site of blockage within the left optic canal, and yellow arrowheads point to blockage within the optic canal on the right. Re-dilatation of the peri-optic space beyond the obstruction following pressure lowering is seen on images e–h.

a–d, Day 1 CSF Pressure > 50 cm CSF; e–h, Day 11, Following 3 LPs, CSF Pressure = 28 cm CSF.

FIGURE 3: (a–h), Illustrative case of optic nerve sheath compartment syndrome.



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a–d, Day 1 CSF Pressure > 50 cm CSF; e–h, Day 11, Following 3 LPs, CSF Pressure = 28 cm CSF.

FIGURE 3 (Continues...): (a–h), Illustrative case of optic nerve sheath compartment syndrome.

pressure and fungal elements creates compartmentalisation between the peri-optic SAS and the intracranial SAS. We propose that the raised pressure and fungal loading cause apposition of the trabeculae, septae and pillars against each other, creating a block by a valve-like mechanism. When intracranial pressure is then lowered, reopening of the channels between the trabeculae and septae occurs, and re-establishment of CSF flow to the peri-optic space.

Furthermore, the lack of optic nerve sheath dilatation and optic nerve signal changes on MRI make papilloedema and optic nerve infiltration less likely to be the only pathogenic mechanisms in CM-induced visual loss. Magnetic resonance diffusion studies do not support optic neuritis as an early cause of visual loss in CM.[7] The co-occurrence of elevated CSF pressure, swollen optic disc and visual loss was in 15.4% of our cohort, visual loss and swollen discs in 17.3%, and visual loss and elevated pressure in 26.9%. Whilst visual loss was documented in 34.6% and elevated pressure was recorded in 69%, clearly disc swelling alone either from optic nerve infiltration or papilloedema was insufficient to account for all cases of visual loss. Elevated CSF pressure with an additional compromise of optic nerve function seems likely – not from axoplasma stasis at the lamina cribrosa but compression upstream. We postulate that this compression results from ONSCS. The steep pressure gradients at the optic canal or mid-orbital level and fungal elements trapped by subarachnoid trabeculae cause a functional block that reverses with pressure lowering. We prefer the term ONSCS to explain the above pathogenesis, which is in line with Killer's explanation of asymmetrical papilloedema in IIH,[35] but different to the optic nerve compartmentation he described in optic neuritis where CSF was trapped in the bulbar peri-optic space, causing disc swelling.[36] Our use of the term is also different from Orgul's description of optic nerve compartment syndrome.[37] Orgul uses the term to describe compartmentalisation in glaucoma where the slit-like pores in the lamina cribrosa cause venous congestion and constriction of the nerve fibre bundles.

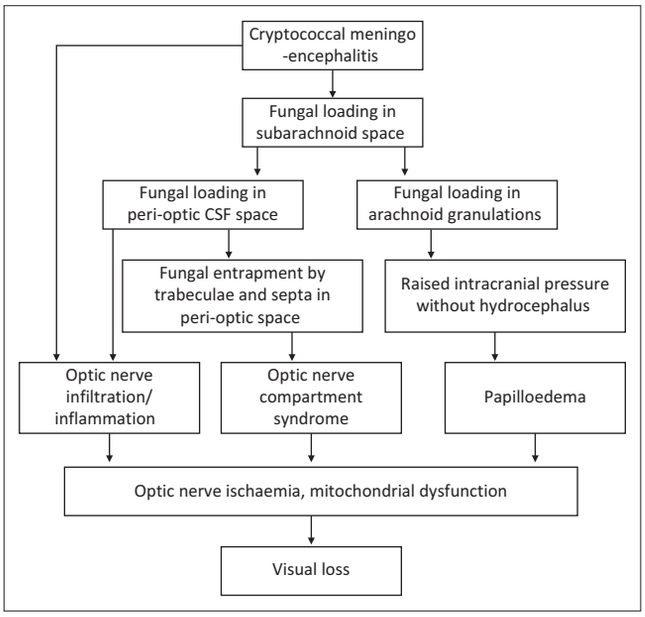
Management of visual loss

Early screening of vision in patients with CM is imperative. Screening should involve proper Snellen chart assessments with pinhole correction if required. Baseline documentation of visual acuity with weekly documentation during the first 4 weeks and bimonthly thereafter until the maintenance phase is complete is essential and should become standard practice. When there is doubt, VEP can be done to detect subtle and even preclinical optic nerve disease. HVF is useful and should be done at initiation of treatment and repeated 4 weeks later when cognition improves with treatment. Field defects are possible, even with intact visual acuity.

With raised intracranial pressure being the predominant mechanism by which visual loss occurs, it is prudent to address this complication in CM. Antifungal therapy alone is insufficient. Early and aggressive lowering of intracranial pressure not only improves the overall prognosis of CM but also definitely prevents, alleviates and reverses visual loss.[13] The benefit of intracranial pressure lowering is well documented by using serial lumbar punctures, lumbar drains, VP shunts and optic nerve sheath fenestration.[8,10,11,15,16,20,21,22] Reports of reversal of visual loss from CSF pressure lowering are encouraging. Medical management alone of raised intracranial pressure in lowering CSF pressure and thereby improving vision has been less satisfactory.[38] The latest recommendations by the Southern African HIV Clinicians Society (2013) are to remove 10 mL – 30 mL of CSF if opening pressure is > 25 cm CSF and daily LPs until symptoms of raised intracranial pressure settle.[39] Evidence for the benefit of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) to decrease optic nerve inflammation and thus improve vision has been anecdotal at best and is counter-intuitive, considering the pauci-inflammatory state of CM.[30]

Conclusion

The major limitations of our case series have been the lack of long-term follow-up and the exclusion of patients with



CSF, cerebrospinal fluid.

FIGURE 4: The pathogenesis of Cryptococcus-induced visual loss.

depressed levels of consciousness. However, we feel that the data from this cohort are compelling and certainly contribute to the improved understanding of Cryptococcus-induced visual loss. Visual loss in CM is common and varies from mild loss to no light perception. Bilateral involvement is usual and occurs at any time during the illness, regardless of drug therapy. Electrophysiology shows early and subclinical optic nerve dysfunction in CM. Three mechanisms seem to operate in the pathogenesis of CM-induced visual loss: (1) papilloedema, (2) optic nerve infiltration/inflammation and (3) ONSCS (Figures 2 and 4). Optic nerve infiltration/inflammation does occur but infrequently and is either a manifestation of the meningo-encephalitis that extends to the optic nerve by continuous spread from the diencephalon or a result of direct infiltration of fungi from the peri-optic CSF space. Raised intracranial pressure plays an important role in visual loss with or without papilloedema. When papilloedema and optic nerve infiltration are not demonstrable, raised intracranial pressure causes optic nerve dysfunction and visual loss, presumably by ONSCS. Fungal loading and obstruction of the peri-optic CSF space compartmentalising the intra-orbital peri-optic SAS from the intracranial SAS is probably the key mechanism but needs further investigation. Our understanding of Cryptococcus-induced visual loss has improved since Rex's initial contribution to the field. However, further studies are eagerly awaited – and preferably those that focus on CSF flow, the peri-optic and intracranial SAS compartments and the impact of pressure lowering measures on visual acuity.

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Competing interests

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Authors' contributions

A.M. (Greys Hospital) was responsible for drafting of the manuscript, project design, collection and analysis of data. W.R. (University of The Free State) made conceptual contributions and reviewed the manuscript. A.B. (University of KwaZulu-Natal) reviewed the manuscript.

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HIV counselling and testing in secondary schools: What students want

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Background: HIV counselling and testing (HCT) is an essential element in the response to the HIV epidemic. There are still major research gaps about the best ways to provide HCT, especially to the youth, and school-based HCT is a model that has been suggested. To make HCT youth friendly and to enhance access to the service, the particular needs of the youth need to be addressed.

Aim: To explore the expressed needs of students about school-based HCT service provision.

Method: The study was conducted in 6 secondary schools in Cape Town where a mobile HCT service is provided by a non-governmental organisation. In each school, two mixed-gender focus groups were held, one with grades 8 and 9 students and one with grades 10 and 11. A total of 91 students aged 13–21 were involved. The focus groups were conducted in the students' home language. All groups were audio-recorded, transcribed verbatim and translated into English.

Results: Content data analysis was done and the following themes emerged: (1) Where the students want HCT to be done, (2) How they want HCT to be done and (3) Who should do the counselling. Most students want HCT to be provided in schools *on condition* that their fears and expressed needs are taken into account. They raised concerns regarding privacy and confidentiality, and expressed the need to be given information regarding HCT before testing is done. They wanted staff providing the service to be experienced and trained to work with youth, and they wanted students who tested positive to be followed up and supported.

Conclusion: To increase youth utilisation of the HCT service, their expressed needs should be taken into account when developing a model for school-based HCT.

Introduction

HIV counselling and testing (HCT) has been advocated as a critical entry point for care and treatment services, including prevention and clinical management of HIV-related illnesses, and psychosocial support.[1,2,3,4,5] However, despite a national HCT campaign from 2010 to 2012 in South Africa, only 50.6% of youth aged 15–24 years reported testing, compared with 78.2% of adults aged 25–49 years.[6]

As part of the national HCT campaign, the South African Departments of Basic Education and Health announced that they intended to launch an HCT campaign specifically targeting secondary school students.[7] This announcement was met with widespread concern from child rights, human rights and AIDS organisations, who argued that the school setting was not conducive to providing HCT in a way that does not violate the rights of youth. Owing to these legal and ethical concerns, the Department of Basic Education put the campaign on hold until policies guiding HCT in schools could be developed.

Little research has been done on the school-based model of providing HCT, and it is not known if this model meets the needs of youth. School-based models have been described in Uganda, where the Kitovu Mission Hospital has provided a mobile HCT service in schools,[8] and the Tholulwazi Uzivikele HCT programme in Manguzi, South Africa, where HCT was offered in schools; drama used to raise awareness and encourage testing amongst the students.[9] However, these studies were descriptive and did not evaluate the acceptability or effectiveness of the programmes. The objective of the present study was to explore the expressed needs of secondary school students regarding HCT provision at schools, and to add the voice of youth to the discussion regarding school-based HCT.

Methodology

Setting

The study was done with a non-governmental organisation (NGO) in Cape Town, South Africa, which had been providing a school-based HCT service since 2005 (before the South African government announced the HCT campaign) in an attempt to make HCT more accessible to youth. The NGO provided mobile school-based HCT to schools that requested their service. With consent, students were tested class by class in the school hall (or similar space). They received individual pre- and post-test counselling and were tested by a nurse using a finger-prick rapid HIV test. Results were given 15 minutes after the test, and students who were found to be HIV-positive were referred to a health facility of their choice for further management. The team usually tested for a number of days at one school, depending on the size of the school and the demand for testing (personal communication with NGO project manager, 2010).

Sample

Six public secondary schools were purposively selected from a list of schools where the NGO provided the school-based HCT service. The six schools were selected so as to obtain the views of youth from diverse backgrounds in terms of their home language, ethnicity and school quintile.

One school was selected from quintiles 1–4 (schools A, B, C and D) and two schools from quintile 5 (schools E and F) because, even though they were in the same quintile, the socio-economic status and racial backgrounds of the students at the two quintile 5 schools were very different (Table 1). At the time of sampling, the NGO was not doing HCT at any quintile 1 secondary schools; however, one quintile 1 school was selected (school A), to gather the perspective of students who had not previously been exposed to HCT at school.

The Life Orientation ('the study of the self in relation to others and to society. It addresses skills, knowledge, and values about the self, the environment, responsible citizenship, a healthy and productive life, social engagement, recreation and physical activity, careers and career choices'[10]) teacher of each school was informed about the study purpose and asked to select students for two focus-group discussions (FGDs) at each school, one with grades 8 and 9 students and one with grades 10 and 11 students. The inclusion criteria were: students who were confident in groups; students who were able to express themselves well; and students who were not all leaders. The Life Orientation teacher was asked to select students from diverse population groups (where possible), and to ensure a similar number of male and female participants.

Data collection

In each of the six schools, two FGDs were conducted with students, with a total of 91 student participants (Table 2). All the groups were mixed-gender except for the grades 10 and 11 group at school D. None of the male students arrived for the FGD, even though they had signed consent to participate. Their reason for not attending was not established; the Life Orientation teacher felt that it was because the FGD was held after school hours.

Each FGD was conducted in the students' home language by a trained facilitator, who focused on the discussion process (guiding the discussion and encouraging equal participation by all students), and an assistant who took comprehensive notes and documented non-verbal communication. The

TABLE 1: Profile of selected schools.

School	Quintile†	HCT taken place at school	Home language	Racial groups‡
A	1	No	Xhosa	Black
B	2	Yes	Xhosa	Black
C	3	Yes	Xhosa	Black
D	4	Yes	English/Afrikaans	Mixed race
E	5	Yes	English	Black, mixed race
F	5	Yes	English	White, black, mixed race, Indian

HCT, HIV counselling and testing.
†, The South African Department of Education classifies schools according to relative poverty in five categories called quintiles. The quintile score is based on the national census data of the school catchment area and depends on income, unemployment rate and level of education. Schools from the poorest catchment areas are in quintile one, and from the least poor in quintile five.
‡, During the apartheid era, the South African government classified people into four major racial groups (black/African, mixed race, Indian/Asian and white/European). Post apartheid, many South Africans still identify themselves and others according to these groups.

TABLE 2: Sex and age of focus-group discussions participants.

School	Grades 8 and 9							Grades 10 and 11						
	Male		Female		Total	Age (years)		Male		Female		Total	Age (years)	
	n	%	*n*	%		Range	Mean	*n*	%	*n*	%		Range	Mean
A	2	29	5	71	7	14–16	15	4	44	5	56	9	16–19	17
B	3	29	4	71	7	14–16	15	4	50	4	50	8	16–20	18
C	4	44	5	56	9	13–16	15	3	50	3	50	6	17–21	18
D	7	70	3	30	10	14–15	14	0	0	5	100	5	17–18	17
E	3	33	5	63	8	13–15	14	1	17	5	83	6	15–17	16
F	4	50	4	50	8	13–15	14	4	50	4	50	8	16–17	16
Total	**23**	**47**	**26**	**53**	**49**	**13–16**	**14.5**	**16**	**38**	**26**	**62**	**42**	**15–21**	**17**

FGD, Focus-group discussion.

FGDs were held in one of the classrooms at the school involved. At the beginning of the FGD, a role-play was used to trigger the students' thinking. Students were divided into two teams and were asked to create a role-play which illustrated what they think happens when students go for school-based HCT. Once the teams had watched each other's role-play, the two teams came together for the FGD. A set of questions linked to the role-plays guided the discussion:

- What do you think will make students want to use this testing service?
- What do you think will make students *not* want to use this testing service?
- What would you like to experience when you go for HCT at school?
- Do you think the school is a good place to do HCT? Why do you say that?

Ethical clearance was obtained from the University of the Western Cape Senate Ethics Committee, and permission to conduct the study was given by the Western Cape Education Department as well as the schools' principals. Students ≥ 18 years old gave written informed consent to participate; those < 18 years gave assent, and written informed consent was obtained from their parents or guardians.

Data analysis strategy

Transcripts of the audio-recordings of the FGDs were loaded into Nvivo 8 and an inductive approach of content analysis was used to analyse the data. This involved close reading of the text, identifying segments related to the research question, coding these texts and assigning them to categories. A process of refining and revising the categories continued until three main themes emerged: (1) Where we (the students) want HCT to be done, (2) How we want HCT to be done and (3) Who should do the counselling (Table 3).

To improve the accuracy and validity of the coding and interpretation of the data, an independent researcher was asked to code the data, and member checks were done with the students who participated in the FGDs.

Results

The students' expressed needs were similar across schools, gender, age and grade, except where mentioned in the findings. There was also no difference between responses from the school where no HCT had ever taken place, and those schools where it had taken place. The responses from the all-female group were similar to the mixed-gender groups.

Theme 1: Where we want HIV counselling and testing to be done

When asked whether they thought their school was a good place to have testing done, most students stated that they would prefer to have HCT provided at their school during school hours. They explained that they would not find time after school to attend a clinic for testing. They also found it difficult to get to clinics because they were often located far from where they live:

> 'It is easy if it's done here at school, 'cause I would have never gone for testing if it wasn't.' (female student, age 14)

TABLE 3: Themes which emerged during data analysis.

Subcategory	Category	Theme
School accessible	At school	Where we want HCT to be done
School convenient		
Will not be seen by community members		
Will not be seen by other students	At clinic	
Service at clinic of better quality		
More private	At home	
Concern that others will assume HIV+	We do not want to be seen going for HCT	How we want HCT to be done
Concern that others will assume sexually active		
Do not want to be seen if upset by positive result	We want HCT to be done in a place that provides privacy	
Do not want others to hear result being given		
Need to know benefits of HCT	We want information about HCT before testing takes place	
Need to know procedure of HCT		
Do not want paper trail	We want confidentiality guaranteed	
Want counsellors to promise confidentiality		
Discomfort with being asked questions about sexual activity	We do not want to be asked too many questions	
Emotional support if positive	We want those who test positive to be supported	
Support with follow-up treatment		
Friendly service providers	We want service providers whom we can easily communicate with	Who should do the HCT
Non-judgemental service providers		
Patient service providers		
Experienced service providers	We want service providers who are competent to work with youth	
Specially trained service providers		
Service providers whom youth can relate to	We want service providers who are 'young'	
Service providers who can give advice and support		

HCT, HIV counselling and testing.

Students also would prefer testing at school rather than at a clinic, as they feared being seen at the clinic by community members who might tell their parents that they had gone for testing:

> '… [*T*]he other woman is going to say, "Oh no! Your child was at the clinic! What was she doing there? She was sitting on the other side for people who go to test."' (female student, age 17)

A few students felt that they would prefer being tested at a clinic. Reasons included not wanting to be seen by other students when going for testing; concerns about confidentiality at school; and perceiving the quality of service at the clinic as being better. One student felt that he would prefer being tested at home, as it was more private.

Theme 2: How we want HIV counselling and testing to be done

When stating that they would like to be tested at their school, students invariably added the proviso that it must be done 'in a right way'.

We do not want to be seen going for HIV counselling and testing

When describing what they meant by 'in a right way', students said that they did not want other students and teachers to know that they were going for HCT. They had huge concerns about what their peers and teachers would think of them if they were to be seen going for testing:

> 'Young people, they don't want this kinda thing [*going for HCT*] to be seen by others.' (female student, age 17)

> 'As a young person … something that is extremely important for us, is what people think about us.' (female student, age 16)

Reasons for concern about 'What people think' differed amongst the schools, which might have been linked to the students' racial groupings. Students from schools D (only mixed race students), E and F (students from various racial groups) were concerned that others would assume that they were sexually active if they went for testing. In contrast, students from schools A, B and C, where all the students were black, were concerned that, if they went for testing, others would assume that they were HIV-positive:

> '…[*b*]lack people … if you do go for a test, it's not because you want to know your status. It's because you are definitely [HIV] positive'. (female student, age 15)

A 15-year-old black male student at school A pointed out that male students do not want female students to see them go for testing, because it would be assumed that they were HIV-positive, and suggested that male students be tested on a separate day from female students:

> 'If you queuing there and you see a girl that you like … you are going to get shy if you are also there to test. You are going to think, "No, no."'

A 16-year-old black female student in the same FGD corroborated what he said:

> 'If maybe [*he*] goes in there to test, most girls are going to distance themselves from him, thinking that he is already positive … that is how most girls think.'

To avoid being seen, students suggested going for testing one at a time rather than class by class in the school hall (some suggested an appointment system).

We want HIV counselling and testing to be done in a place that provides privacy

The need for a space that provided visual and auditory privacy during the HCT process was consistently mentioned. Students specifically did not want to be tested in the school hall (the site where HCT took place at each of the schools). They explained that tents or cubicles were erected in the hall to try to provide visual and auditory privacy. However, they felt that the degree of privacy provided was not adequate, and preferred counselling in separate rooms:

> 'About the privacy, I do think they need a room, like different rooms for each counsellor … this cubicle thing is just too open. It's just too public … The whole grade [is] behind you, like a few meters behind you … and there you've just heard that you're positive, and the person [*is*] right behind you.' (male student, age 16)

After receiving their results, they had to face students waiting to be tested, and were afraid that they would not be able to hide the fact if they had just been told that they were HIV-positive:

> 'When I get told that I am positive, even if I keep quiet about it, I will have a facial expression that I make. If I am coming out, they are going to first look at me in the face, what facial expression I'm going to make, and then they know that if I am crying I am HIV-positive, and if I am smiling they know that I am not.' (female student, age 16)

Some students proposed that the counselling area should have a separate exit so that, after receiving their results, students did not have to face other students waiting in the queue.

We want information about HIV counselling and testing before testing takes place

Students attributed an 'it won't happen to me' attitude towards HIV as a reason for not testing. They believed that many students thought HIV and AIDS only affected older people, and thought it was necessary for students to be informed about the benefits, importance and procedure of HCT prior to testing taking place. Others felt that the fear of testing positive was a barrier to testing, and suggested that information be given about what to do if one should test HIV-positive, as they felt that this would reassure students and alleviate some of these fears.

We want confidentiality guaranteed

Students mentioned confidentiality as an important part of doing the testing 'in the right way'. They wanted staff to promise confidentiality up front, and preferred that only

counsellors (not nursing and administrative staff) knew the HIV results and that no 'paper trail' was kept of results.

We do not want to be asked 'too many questions'

In many of the FGDs, students said that they felt uncomfortable with being asked questions about sexual activity. They considered these questions to be 'private' and wanted their privacy respected:

> 'Sometimes they ask too much questions. Maybe they ask you now, "Are you sexually active?" Now you say, "Yes," then they ask you, "When last did you have sex?" You had sex yesterday last … you dunno how to tell her, because she's a big person [*an adult*] and you telling her now.' (female student, age 17)

We want those who test positive to be supported

Students felt it important that those who test positive be followed up and given support by the NGO. They wanted assistance with disclosing to family members, emotional support and encouragement with adherence if needing to take antiretrovirals:

> 'If they say you are positive … they should do check-ups to see … if you are coping.' (female student, age 17)

Theme 3: Who should do the counselling

We want to be counselled by staff whom we feel we can easily communicate with

Students said they wanted the counsellors to be people who are easy to talk to and who would make them feel comfortable. They felt it was essential that the counsellors were friendly, non-judgemental and treated youth with respect. They wanted the counsellors to be patient, and expressed the need to have enough time with the counsellor to have things explained properly, and to have the opportunity to ask questions.

We want to be counselled by staff who are competent to work with youth

It was important to students that the counsellor was experienced, behaved professionally and had received training to provide a youth-friendly health service (YFHS);

> 'The counsellor should be taught … about teenagers of today and how they function.' (female student, age 17)

We want HIV counselling and testing to be done by someone who is 'young'

Some students preferred the counsellor to be young (they defined 'young' as someone between the ages of 20 and 30). They felt that a younger counsellor would be easier to relate to, and would better understand them ('Older people don't know what we are going through.' [female student, age 17]). Some students preferred an older counsellor (they defined 'older' as someone in their 30s). Those who preferred an older counsellor felt that an older person would have more knowledge and experience, and therefore be better able to give advice. Students in one FGD favoured a counsellor under the age of 20 years, whereas other students in the same FGD specified that, though they preferred a younger counsellor, they did not want to be counselled by someone their own age, as they felt that their peers would only have as much knowledge as they did.

Discussion and implications

Findings suggest that most students (across socio-economic groups, racial groups, gender, age and grade) consider school-based HCT to be more accessible and convenient than a health facility-based HCT service, which is similar to the findings of Henry-Reid et al.,[11] who proposed that school-based HCT services are more accessible and acceptable to youth than other formal health settings; and Madiba and Mokgatle[12] who found that the acceptability of HCT at schools in Gauteng and North-West Provinces, South Africa, was high.

The students made it clear, however, that if HCT were to be offered at school, it has to be provided in a manner that takes into account their needs. They had very specific ideas about what they wanted and did not want. Most of their expressed needs were based on fear: fear of being seen going for testing, fear of testing positive, fear of their HIV-positive status being known and the stigma associated with it, fear of not being supported if they tested positive, and fear of being judged and not being understood. In fact, the few students who preferred testing at a health facility or at home favoured these settings owing to concerns regarding privacy and confidentiality at school.

Similar fears about being seen going for HCT have been expressed by African youth in other studies.[12,13,14,15] The need for auditory and visual privacy during counselling was also expressed by adolescents attending clinics that were part of a YFHS project in Zambia.[16] The guarantee of confidentiality was also mentioned as an important need by youth in studies done in other African countries investigating youth needs regarding YFHS.[16,17] The students' concerns about not receiving ongoing counselling for dealing with a positive diagnosis and to assist with access to treatment is echoed in the findings of MacPhail et al.[15] in their study with adolescents in two South African townships. Students' anxieties that they would be judged, disrespected and not understood by HCT service providers have also been described in previous studies.[15,17,18,19] Similarly, in a systematic review, healthcare providers' attitudes, communication skills and competency were cited by youth as indicators of youth-friendly health care.[20]

The expressed needs of students regarding school-based HCT, as described in the present study, coincide with some of the characteristics of a YFHS described by the World Health Organization (WHO)[21]; namely, that the service should have policies that guarantee privacy and confidentiality; that service providers are easy to relate to, non-judgemental, have good interpersonal and communication skills, and are competent to work with youth; and that testing facilities offer privacy. To be noted is the fact that students in the

present study did not mention youth involvement in service provision and assessment. Similarly, in the survey carried out by Erulkar et al.[18] amongst Kenyan and Zimbabwean youth, youth involvement was also not mentioned as a priority for providing a YFHS.

A number of limitations exist in the present study. All the groups, except one, were of mixed-gender, and all the facilitators were female, which might have affected responses by students. However, one group comprised only female students and their responses were similar to the responses in the mixed-gender groups. Also, all the schools were urban schools; therefore, findings might be different with students from rural schools. Because of these limitations and the fact that a purposeful sample was selected, data from the present study are not readily generalisable. However, care was taken to select schools and students that mirror the population groups in the area, and therefore the data allow valuable insights into the needs of students regarding school-based HCT.

One of the most important contributions that the present study could make is to afford youth a voice which has been lacking in discussions about the provision of HCT in schools. It should further contribute to the debate around the ethics and feasibility of providing HCT in South African schools, and can be used by governmental and NGO providers of HCT in schools to provide a youth-friendly service. Lastly, the present research adds to the limited existing body of literature regarding models of HCT provision to youth.

If HCT is to be provided in schools, service providers need to (1) address students' concerns regarding privacy and confidentiality, (2) provide information regarding HCT to students before HCT takes place, (3) ensure that staff are experienced and trained to work with youth and (4) that students who test positive are followed up and supported.

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Competing interests

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Authors' contributions

E.L. (Western Cape Department of Health) designed the study, conducted the focus-group discussions, interpreted the data and wrote the manuscript. P.S. (University of the Western Cape) and G.v.H. (Ghent University) supervised the development of the study, and helped in data interpretation and manuscript evaluation and editing.

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Attracting, equipping and retaining young medical doctors in HIV vaccine science in South Africa

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Background: HIV remains a significant health problem in South Africa (SA). The development of a preventive vaccine offers promise as a means of addressing the epidemic, yet development of the human resource capacity to facilitate such research in SA is not being sustained. The HIV Vaccine Trials Network (HVTN) has responded by establishing South African/HVTN AIDS Early Stage Investigator Programme (SHAPe), a programme to identify, train and retain clinician scientists in HIV vaccine research in SA.

Objectives: The present study sought to identify factors influencing the attraction and retention of South African medical doctors in HIV vaccine research; to understand the support needed to ensure their success; and to inform further development of clinician research programmes, including SHAPe.

Methods: Individual interviews and focus groups were held and audio-recorded with 18 senior and junior research investigators, and medical doctors not involved in research. Recordings were transcribed, and data were coded and analysed.

Results: Findings highlighted the need for: (1) medical training programmes to include a greater focus on fostering interest and developing research skills, (2) a more clearly defined career pathway for individuals interested in clinical research, (3) an increase in programmes that coordinate and fund research, training and mentorship opportunities and (4) access to academic resources such as courses and libraries. Unstable funding sources and inadequate local funding support were identified as barriers to promoting HIV research careers.

Conclusion: Expanding programmes that provide young investigators with funded research opportunities, mentoring, targeted training and professional development may help to build and sustain SA's next generation of HIV vaccine and prevention scientists.

Introduction

South Africa (SA) has one of the highest HIV prevalence rates globally.[1] Despite promising new developments in non-vaccine prevention modalities, a preventive vaccine against HIV offers the best hope to end the epidemic.[2]

Several large-scale HIV vaccine, and other prevention, trials will begin in SA in 2016.[3,4] These trials will utilise the strengths of South African investigative teams, requiring a wide breadth of research capacity. Whilst senior-level South African HIV vaccine researchers have developed enormous expertise, the number of junior clinician investigators entering the field has lagged. Since the early 1990s, SA has seen a decrease in the number of clinical researchers and an ageing of publishing scientists.[5,6] A concerted effort is required to increase the number of young medical doctors entering the HIV prevention and vaccine field to ensure the country's ongoing contribution to this critical effort.

In 2010, responding to the challenge, the HIV Vaccine Trials Network (HVTN), with support from the National Institute of Allergy and Infectious Diseases (NIAID) and the Fogarty International Center (FIC), established the South African/HVTN AIDS Early Stage Investigator Programme (SHAPe), a peer-reviewed medical doctors/PhD programme that recruits and supports young clinician investigators as they become independent investigators. Components of the programme, coordinated by the Desmond Tutu HIV Centre at the University of Cape Town, include 3-year salaried appointments at HVTN clinical trial sites; financial support for a mentored research project and research-related costs; targeted training and tuition for a concurrent PhD programme; travel to HVTN meetings and international HIV conferences; and facilitated integration into the HVTN scientific community via participation on scientific and governance committees.

To inform the SHAPe programme and future efforts, formative research was conducted to: (1) understand facilitators and barriers to attracting, equipping and retaining young South African

medical doctors in careers in HIV vaccine research, (2) develop recommendations to address identified challenges and (3) inform the design of clinician investigator development programmes, including SHAPe.

Methods

Sampling

During 2011, participants were recruited from clinical research sites and via referrals throughout SA. Target participants comprised a small group of specialised individuals and therefore purposive sampling with specific criteria was used. These groups were defined as: (1) senior investigators (SI) – those who led research teams and held the role of 'principal investigator' (PI) for at least 5 years, (2) junior investigators (JI) – those who had medical degrees and worked at clinical research sites for 10 years or less without assuming the role of PI and (3) young medical doctors (MD) – those who had received medical degrees no more than 12 years ago and expressed interest in research but had not pursued research careers.

Data collection

We used a qualitative approach and conducted semi-structured interviews and focus groups. K.B. underwent comprehensive training and utilised interview and focus group schedules to guide the sessions. Fifteen one-on-one, semi-structured, confidential telephone interviews were conducted, lasting approximately 1 hour and included five JIs, five SIs, and five MDs. Data collected during the interviews informed semi-structured questions used for three face-to-face focus groups, lasting approximately 1.5 hours and included four SIs, three JIs and four MDs in separate groups. All interviews and focus groups were conducted in English, recorded using a hand-held audio recorder, and transcribed in English. Demographics questionnaires were completed by those who participated in focus groups.

Data analysis

Three investigators independently coded five interview transcripts and then met as a team to review codes, resolve differences in coding by consensus, and create a codebook. The codebook was used to analyse subsequent interview and focus group transcripts, and generate new codes. Subsequent transcripts were assigned to three of the authors who independently cleaned and coded them using the codebook. The three investigators reconvened again to resolve differences in coding by consensus, analyse the transcripts, discuss patterns in the data and organise identifiable themes in ATLAS.ti.6.2.25 (GmbH Berlin). Data and investigator triangulation were utilised to enhance validity of the findings.[7]

Ethical considerations

All participants were over 18 years old and provided written informed consent. The study was approved by the University of Cape Town's Human Research Ethics Committee (IR File #128/2011) and the Fred Hutchison Cancer Research Center Institutional Review Board (IR File #7448).

Results

Participants (N = 18) were SIs (n = 5), JIs (n = 6), and MDs (n = 7). Sociodemographic characteristics of study participants are shown in Table 1.

The following themes were identified for each research objective and were endorsed by participants from all groups (JI, SI, MD) unless otherwise stated.

Attracting young doctors to research

Exposure to research early in medical training: Most participants believed there is little exposure to research in medical training and a majority of young doctors are not aware that research is a viable career option:

> '[*Clinical research*] is an unconsidered job because … it's not explored in medical school.' (MD)

Many participants indicated that even brief exposure to research (e.g. an investigator presenting their research to students and professors) can spark interest in a research career. There was wide agreement that incorporating research methodology courses and hands-on research with medical training early in the curriculum would help doctors to better understand research and fuel interest in this career option:

> '… integrate clinical researchers back into [*university*] departments. … people … could see … what fun research is and how research changes people's lives and become excited about doing this…' (SI)

Suggestions for supporting these activities included providing students with small mentored research projects, offering stipends to support projects, and combining a medical degree with a master's or PhD degree.

Several participants indicated that better integration of researchers into university academic departments would provide them with greater access to funding support,

TABLE 1: Sociodemographic characteristics of study participants.

Sociodemographic characteristics	*n*	%
Gender†		
Male	4	22
Female	14	78
Race or cultural group		
Black	6	33
Mixed race	1	5.5
Asian	2	11
White	3	17
African or Euro-African	5	28
Non-response	1	5.5
Employment category		
Medical doctor	7	39
Junior investigator	6	33
Senior investigator	5	28
Age, mean‡	42	8.52
SD	30–53	-
Total participants	**18**	**100**

†, N = 18; ‡, n = 17.

training and academic resources, whilst providing medical schools and other departments with faculty to teach research methodology, and opportunities for students to gain research experience:

> 'Clinical researchers are incredibly isolated in the university; even though they are driving the publications of the university and … the research agenda … [*they*] are isolated from [*their*] peers.' (SI)

Career development pathway: Most participants, particularly MDs, highlighted a lack of clarity around the career development pathway for clinical researchers as a deterrent to pursuing a career in this field:

> '… there isn't really a … [*formal*] progression… There's no hierarchy. Either, you're … the PI or you're not the PI …' (JI)

This is in contrast to the well-defined and regimented career pathway for clinical medicine:

> '[*In clinical medicine*]… determining your path is much more strict and clearly defined… [*clinical research*] has a lot of uncertainties…' (MD)

Comparable employment packages and job security: Nearly all participants agreed that, to attract and retain top research doctors, employment packages in clinical practice and research need to be comparable. Perceptions of researcher v. non-researcher salaries varied. To the best of our knowledge, there are no definitive data comparing salaries of medical doctors in clinical practice v. research. All SIs agreed that salaries have been historically lower for researchers, but recent efforts have been made to align salaries more closely; increasing awareness of this trend could help to attract doctors to research:

> '… making comparable salaries [*to doctors in clinical practice is*] important … We are really struggling to find doctors [*to bring*] into research…' (SI)

Increase awareness of the HIV prevention field: Many investigators reported that the subject of HIV prevention sparked their interest in research, citing the urgency and magnitude of the HIV epidemic and their desire and ability to make a difference in people's lives. Many participants suggested that increasing awareness amongst the medical community about developments in HIV prevention modalities, particularly vaccines, could stimulate interest in the field. Suggestions included presentations at medical conferences and in media frequented by clinicians:

> '… show [*doctors*] what the future holds for HIV/AIDS. To be able to see … the result, the impact in the community … it can be very satisfying for a career.' (JI)

Equipping and retaining doctors for careers in research

There was considerable overlap in themes identified as important for equipping and retaining doctors; therefore they are combined here.

Skill building, infrastructure and academic resources: To effectively equip JIs, SIs noted that they need specialised training. Most participants highlighted the importance of acquiring research knowledge and skills through academic courses in '… epidemiology, statistics, immunology… ethics … [*and*] research methods…' (SI). Some suggested courses in 'laboratory methods.' Most SIs recommended intensive training in '… manuscript and proposal writing …' and '[*giving*] presentations'. Participants also mentioned the importance of collecting data in the field and working in research units.

Nearly all participants agreed that, to train and retain new investigators, the investigators need access to academic resources such as journal subscriptions, educational opportunities, research symposia and networking to foster 'collaboration … [*with a*] wider scope of people …' (SI).

Mentorship: Structured mentoring was raised by most participants as a significant facilitator to equipping, retaining and supporting career progression for new investigators.

Nearly all participants proposed that fostering an environment with structure, clear objectives, dedicated time, and positive personal relationships is essential for a successful mentor-mentee experience:

> '[*we need a*] formal structure … the mentor and the mentee *[should*] draw up a contract that spells out … purpose… goals and targets … time frames … to guide this relationship.' (JI)

Despite the acknowledged importance of mentorship, most participants identified that lack of time hinders the mentoring process. All SIs emphasised that sufficient time for mentoring requires specific funding allocated for mentorship activities, but acknowledged the difficulty of earmarking research funding for mentorship.

Many investigators noted that they themselves had not been mentored and, as a result, some SIs conceded that they did not feel capacitated for this role. Several participants suggested the development of a mentorship training programme for all investigator levels to address this challenge:

> '… we need support. … mentors need coaching about how to be a good mentor because … [*we've*] never had one.' (SI)

Participants noted the importance of the JI and SI relationship in ensuring career progression and enhancing retention in the field. JIs mentioned the critical role that SIs play in providing linkage to resources, people and networks which can assist them in furthering their career. Most SIs and JIs recognised that if an SI was unwilling or unable to facilitate JI development and 'make space at the top', it could jeopardise career progression:

> '… if that chief person [*the SI*] … has no spirit of "Look, I'm on top, now I can pull you up to come join me." If that doesn't exist, it's a serious barrier.' (JI)

Adequate funding for research: All SIs and JIs expressed concerns about the inherently unstable nature of grant funding

and thought it deterred doctors from entering, progressing in, and retaining research careers because, in contrast, clinical practice salaries are thought to be 'guaranteed'. In addition, the limited availability of consistent and sustained government and university research funding in SA was a frequent theme:

> 'If you look at research, in general it's something that's run by donors, and if you go into that kind of career … you are not sure whether that job is secure…' (JI)

Because much research funding is sourced internationally and tends to be on a project or grant basis, the ability for long-term planning is affected. Financial concerns are perceived to hamper career progression, because the need to secure funding is constantly prioritised above the 'science':

> '… instead of spending my time thinking what's the next interesting research question, I'm thinking how the hell do I keep this funded? Sure, that dilutes efforts quite a lot.' (SI)

Some participants suggested seeking alternative funding sources, particularly from the South African government, to establish a more stable funding base to supplement grants:

> 'If the government is proactive in leading research … the private sector will also move in and pour in funds when they see there is commitment from the government.' (JI)

Clinician investigator development programmes

Most participants believed that it was critical for the clinical research field to create more clinical investigator development programmes that provide structured mentored research, training, and professional development opportunities:

> '[*Programmes like SHAPe offer*] something that is necessary. … people have to be given this opportunity, otherwise I don't see them paying their way through this kind of programme…' (JI)

Several participants emphasised that development programmes must provide the opportunity for young investigators to experience the full range of activities, and hone the practical skills needed to be a successful investigator:

> 'You're gonna need to give people the experience of doing all of it … if they're going to become the next generation PIs they do actually need to have that exposure and be able to do it.' (JI)

> '… things like regulatory [agency research review requirements], to understand how that process works … the practical experience of how to go about that.' (SI)

The South African/HVTN AIDS Early Stage Investigator Programme

Participants were asked to reflect on the design of the SHAPe programme and comment on the strengths and weaknesses of this model, and provide input on ways to improve the programme.

Most participants were enthusiastic about the SHAPe programme and agreed that it served an important role in providing an opportunity not previously available: to recruit and train young doctors in research. Participants identified SHAPe's strengths as providing a mentored research project and full-time salaries, incorporating a PhD degree programme, offering experience as a clinical trial doctor, and opportunities for travel to research meetings and conferences. Lack of awareness of the programme by the medical community was often identified as the most significant weakness:

> '… I'm actually thinking about [*applying to SHAPe*] … Nobody approached me before personally and said … this is what it entails … are you interested? Personal contact is the best [*way to recruit*].' (MD)

Participants suggested several ways to improve SHAPe. Most advocated greater involvement from SIs and JIs in publicising the programme and presenting research findings at medical schools and hospitals to increase interest in HIV vaccine research.

Most participants agreed that the best recruitment approach is multi-pronged and includes 'personal outreach', 'national publicity' and advertising through the 'provincial Departments of Health', 'newspapers', 'major medical journals' and 'medical association websites'. A few participants also advocated use of social media such as Facebook (SI), direct SMS (MD) and email (MD).

Some participants suggested expanding the programme to support independent research for mid-career HIV vaccine investigators. A few suggested increasing the number and location of sites where scholars can work.

Discussion

The present study identified factors influencing the attraction and retention of South African medical doctors into HIV prevention research; increasing the understanding of the resources and support needed to ensure their success; and eliciting suggestions to inform design of clinical research development programmes, such as SHAPe.

Of note is that findings were largely applicable to HIV prevention research generally and clinical research more broadly, increasing their value and impact in informing recommendations and future practice. Overwhelmingly, there was recognition from all groups that research was not adequately represented in the medical training curriculum and that this limited exposure discouraged interest in, understanding of, and entrance into this field. The overall shortage of doctors in primary healthcare is critical in SA[8,9,10] and requires urgent redress.[11] As a result, medical education has renewed its focus on primary healthcare.[12,13] Whilst necessary, this focus on primary healthcare has had a detrimental effect on the development of clinical research capacity and solid grounding in research skills[12]; and although medical schools

may include training on evidence-based medicine, it is not prioritised as a critical part of the curriculum.

Our study's findings highlight the need for a more clearly defined career pathway for MDs entering research, which includes research skill development, senior researcher mentorship, academic resource access, and networking opportunities. These findings mirror those of the Academy of Science of South Africa (ASSAF) report, which reviewed the overall state of clinical research in SA and indicated the inadequacies of these resources for clinical research.[12]

A major barrier to the attraction, retention and career progression of doctors in research is the perceived lack of secured and ongoing funding. With limited financial support from the South African government and academic institutions, the large amounts of money required to conduct HIV prevention trials are sourced outside SA. This project-based funding is competitive, subject to exchange rate fluctuations, and often short-term and unstable.

Based on these findings, several recommendations can be made.

Exposure to research:

- Enhance academic research modules, and develop more programmes where students at all levels can gain hands-on experience to spark interest in clinical research, including HIV vaccine research.
- Expand the number of programmes offering a combined MBBCh and PhD degree.
- Foster an awareness of research, particularly HIV prevention research and its impact, amongst both medical professionals and the broader community.

Training and mentorship:

- Develop coordinated training programmes for HIV clinical researchers at all levels, as well as a structured mentorship programme supporting researchers vertically and horizontally. Provide training on effective mentoring for JIs and SIs.
- Develop a more objective, standardised and clearly defined career development pathway for JIs with clear expectations, milestones and incentives (e.g. promotions, awards) and promote it widely.

Funding:

- Increase local/national funding (e.g. government, industry, corporate, donor).
- Address funding allocation to support projects, the researcher and designated time for mentorship activities.
- Ensure that salaries are comparable across research and clinical practice positions, and publicise this widely.

Clinical investigator development programmes:

- Expand programmes such as SHAPe that provide comprehensive support. Promote via personal outreach in medical schools, registrar programmes, hospitals and conferences. Advertise in journals, social media, medical bulletins, SMS and email from trusted sources.
- Create advancement opportunities for JIs. For example, create new PI roles at research sites, faculty positions and opportunities for independent research.
- Incorporate JI development programmes in networks, universities and other collaborative research environments to leverage research and academic infrastructures.

Study limitations

There are several limitations to the present study. The sample size was small, comprising 18 participants, most of whom took part in both one-on-one interviews and focus groups. Whilst this is considered an adequate sample size for qualitative research,[14] it possibly limits the generalisability of the present results. However, notably two of the three groups included in this study (SIs and JIs) are, by definition, small in size. HIV vaccine research is a specialised field and it is partly because of the small number of doctors entering this field that the present research was conducted. Consequently, particularly for SIs, our sample included a significant proportion of the total SI population involved in HIV vaccine research in SA.

In addition, given the small size of this research community in SA, it is possible that participants did not feel comfortable speaking freely and honestly, out of concern that they would be recognised, despite removal of identifiers. This risk might have been an issue particularly during focus groups, as many investigators are colleagues and collaborators. Nevertheless, all participants expressed an interest in and recognition of the importance of the topic, and were aware of the value of the research process, and it is hoped that this encouraged openness and honesty throughout.

Finally, factors identified by participants as significant in attracting, equipping and retaining doctors in HIV prevention science research were largely representative of their own needs rather than a broader impression of what might be required overall. Whilst inevitable, this may be viewed as a limitation.

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which may have inappropriately influenced them in writing this article.

Authors' contributions

D.F. (HIV Vaccine Trials Network) conceived the research study. D.F. and M.W. (Desmond Tutu Research Centre) were project leaders and led the qualitative study design, implementation, data analysis, interpretation and the writing of this article. D.F., M.W. and K.B. (Desmond Tutu Research Centre) coded transcripts. K.B. performed the interviews and led the focus groups, and assisted with data analysis and interpretation. L-G.B. (Desmond Tutu Research Centre) and J.K. (HIV Vaccine Trials Network) made conceptual contributions and provided edits to the manuscript. All authors contributed to the interpretation and writing of the article.

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HIV testing during the neonatal period

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Introduction

Testing for HIV in the neonatal period has been routinely recommended for all HIV-exposed infants in the developed world for over two decades. In 2015, birth testing for certain asymptomatic HIV-exposed infants was included in the South African National Consolidated Guidelines for the first time.[1] Questions remain concerning the optimal recommendations for and implementation of HIV testing in neonates to achieve improved outcomes for HIV-infected infants in South African and other low-resource settings.

Effect of evolving prevention of mother to child transmission interventions on 6-week HIV polymerase chain reaction diagnostic performance

The notion that a single HIV polymerase chain reaction (PCR) test performed at 6 weeks of age would detect virtually all *in utero* and intrapartum HIV-infected infants failed to recognise:

- the HIV-related mortality that occurs prior to testing at 6 weeks of age[2,3,4]
- the reduced sensitivity of HIV PCR tests as a consequence of the increase in the number and duration of drugs used for prevention of mother-to-child transmission of HIV (PMTCT) prophylaxis.

There is increasing evidence that both fixed dose combination (FDC) maternal PMTCT prophylaxis and daily dose nevirapine (NVP) infant prophylaxis (Option B or B+) contribute towards reduced detection of perinatal HIV infection at 6 weeks of age. The literature demonstrates that:

- a single perinatal dose of NVP reduced viral load to below the limit of detection in 38% and 17% of *in utero* infected infants at 5 days and 2 weeks of age respectively.[5,6] No HIV PCR sensitivity data for 6-week-old HIV-exposed infants, tested at discontinuation of 6 weeks of daily dose NVP, are available.
- the probability of a positive HIV PCR at age 6 weeks in perinatally HIV-infected infants is decreased with multi-drug maternal and/or infant PMTCT prophylaxis[7]
- in non-breastfed infants, HIV DNA and RNA PCR sensitivity at 1 month of age for perinatally infected infants was 89%[8]
- in formula-fed infants who received 6 weeks of postpartum zidovudine (AZT), with or without other antiretrovirals, 32% of intrapartum-infected infants tested HIV DNA PCR negative at 6 weeks of age but tested positive at 3 months of age[9]
- prophylaxis reduces HIV DNA concentrations at birth complicating early identification of infected infants for initiation of early treatment[10]
- there are case studies illustrating the challenges of 'false negative' and 'indeterminate' HIV PCR results in early infant diagnosis in the context of current PMTCT prophylaxis and calling for revised diagnostic guidelines.[11,12]

The 6-week test, conveniently scheduled at the same time as the 6-week expanded programme for immunisation (EPI) visit, is therefore too late and too early to detect all *in utero* and intrapartum HIV infections in the context of current PMTCT interventions. It is too late to diagnose infants who die prior to 6 weeks of age and to achieve early combination antiretroviral therapy (cART) initiation by 7.4 weeks of age as was done on the Children with HIV Early Antiretroviral Therapy (CHER) trial to reduce early morbidity and mortality.[13] It is too early to diagnose *in utero* and intrapartum infections suppressed by daily dose NVP and/or maternal prophylaxis via the placenta and/or breastmilk.

Diagnostic performance of HIV PCR at birth

The HIV PCR sensitivity at birth for detecting perinatal HIV infections (viz. *in utero* and intrapartum HIV infections) can never approach 100% because it detects *in utero* infection only

and cannot detect intrapartum infection, namely an infection transmitted at the time of labour and delivery and essentially in the window period at birth. Prior to the implementation of PMTCT and the use of standardised HIV assays, Dunn et al.'s meta-analysis demonstrated that 38% of all perinatal infections were detectable at birth.[14] With World Health Organization (WHO) Option A prophylaxis and a single dose of NVP at birth for infants, Lilian et al. demonstrated that 76% of all early HIV infections were detectable at birth.[15] This increase was attributed to more sensitive viral detection assays and a proportional increase in *in utero* to intrapartum infections as a result of PMTCT prophylaxis targeting intrapartum infections during late pregnancy and delivery. As the majority of women deliver in health facilities in South Africa, identifying all HIV-infected women at delivery coupled with birth HIV PCR testing would yield three-quarters of all perinatal HIV infections with close to 90% coverage.

With Option B or B+ including daily dose NVP for 6 weeks to the infant, the ratio of *in utero* to intrapartum infections detectable at birth and 6 weeks of age is not known but is likely to be similar to Option A.

When should birth and early neonatal HIV PCR be considered?

Because HIV testing of neonates is not performed unless a neonate is symptomatic, the HIV-related neonatal mortality rate in South Africa is unknown. In the presence of vertical transmission and without a birth diagnosis, it is neither possible to detect neonatal HIV infection nor to reduce HIV-related neonatal mortality by initiating antiretroviral therapy. Approximately 20% of infants known to be HIV-infected at birth in Johannesburg either died or were lost to follow-up by the time that 6-week HIV PCR testing was conducted.[4]

Modeling the ideal timing of HIV PCR tests in early infant diagnosis for South Africa,[16] considering birth, 6-, 10- and 14-week EPI visits, demonstrated that:

- when using 1 HIV PCR test, the same number of HIV-infected infants are identified when testing at birth or at 6 weeks of age
- when using 2 HIV PCR tests, the most HIV-infected infants can be identified by testing at birth and 10 weeks of age.

Additional evidence for the assumptions made in the model would assist in refining the optimal timing of HIV PCR tests.

The 2014 South African National Consolidated Guidelines recommend targeted birth testing, namely HIV PCR testing of only those HIV-exposed neonates identified as being at high risk of HIV transmission.[1] 'High risk' includes all premature (born before 37 weeks' gestational age), low birth weight (LBW < 2500 g) or symptomatic HIV-exposed neonates and those born to women who were unbooked or received a late diagnosis of HIV (e.g. at delivery) or received < 4 weeks of antiretroviral PMTCT prophylaxis or had viral loads > 1000 copies per millilitre or were co-infected with tuberculosis during pregnancy. The Western Cape PMTCT guidelines also recommend targeted birth testing that include additional and slightly modified high-risk factors.[17] These high-risk factors predict vertical transmission but not necessarily *in utero* transmission, and therefore the birth HIV PCR test may be negative.

Universal birth testing of all HIV-exposed infants may be simpler to implement than targeted birth testing. The cost of performing two early HIV PCR tests, to detect *in utero* and intrapartum infections, on every HIV-exposed infant can be offset by following 2010 WHO guidelines to use HIV rapid tests (HRT) from 9 months of age.[18] As the majority of HIV-exposed, uninfected infants demonstrate seroreversion by 9 months of age by testing HRT negative, only those with positive HRT would require HIV PCR tests.[19] This approach reduces the number of HIV PCR tests required for symptomatic infants or those requiring testing post-cessation of breastfeeding.

Optimal response to a birth or early neonatal HIV PCR result that is positive

To avoid morbidity and mortality, all positive HIV PCR results require urgent action to (1) confirm the HIV-infected status on a second blood sample and (2) initiate cART. Healthcare facilities require good communication with the laboratory to access positive results within 2–7 days and systems for patient follow-up to see all HIV PCR-positive patients as soon as possible. As neonates usually return to their primary healthcare clinic and not the maternity unit for follow-up after birth, ensuring that birth HIV PCR test results reach patients will be pivotal to successful implementation of birth testing. Point of care (POC) HIV diagnosis would facilitate same-day identification of HIV-infected neonates.

The results of the second, confirmatory viral detection assay should not delay cART initiation but should be obtained as early as possible because, once cART is initiated, it becomes progressively more difficult to detect HIV either by HIV PCR or viral load testing. The availability of two different POC assays for detection of HIV would facilitate same-day identification and confirmation of HIV infection in neonates.

Further testing if birth or early neonatal HIV PCR test result is negative

If the birth HIV PCR test is negative, an HIV PCR test at 10 weeks of age is recommended to detect as many cases of intrapartum infection as possible. If the HIV PCR test is repeated at 6 weeks of age, as per national guidelines,[1] fewer

cases of intrapartum infection may be identified owing to the viral load lowering effect of the daily dose NVP infant prophylaxis. The 2014 National Consolidated Guidelines cater for this in high-risk infants only by recommending a third HIV PCR at 16 weeks of age where prolonged infant prophylaxis (e.g. daily dose NVP for 12 weeks) has been used.[1] The probability that the sensitivity of diagnostic virological assays is affected by antiretroviral prophylaxis has prompted American guidelines to recommend an additional HIV PCR test be performed 2–4 weeks after combination antiretroviral infant prophylaxis has been discontinued if negative HIV PCR results were obtained during prophylaxis.[20] As for all HIV-exposed and uninfected infants, HIV PCR testing is recommended whenever clinical features suggestive of HIV infection are present and 6 weeks after cessation of breastfeeding (if < 18 months old). If, at 6 weeks after weaning, the child is ≥ 18 months old, a HRT or HIV enzyme-linked immunosorbent assay (ELISA) test should be performed instead of an HIV PCR test.

In an evolving PMTCT environment, ongoing monitoring is necessary to assess the impact of early diagnosis of HIV infection in neonates and to ensure that an evidence-based, effective diagnostic algorithm is deployed.

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HIV testing and antiretroviral therapy initiation at birth: Views from a primary care setting in Khayelitsha

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Background

Despite 95% coverage via the prevention-of-mother-to-child-transmission (PMTCT) programme, 14 000 children in South Africa became HIV-infected in 2012.[1] There are many reasons for this gap in PMTCT efforts. Late maternal diagnosis of HIV, late antenatal antiretroviral therapy (ART) initiation, seroconversion in pregnancy, and inadequate adherence to ART during gestation singly and collectively increase the risk of transmission. Early initiation of ART in the first few weeks of life significantly reduces the HIV-associated morbidity and mortality in HIV-infected infants, compared with deferred initiation[2,3] and may reduce the latent HIV-1 reservoir in children.[4] Furthermore, a recent South African study documents that 76% of babies who would have tested HIV positive via polymerase chain reaction (PCR) by 6 weeks could have been diagnosed at birth.[5] Therefore, the Western Cape Province (WCP) Department of Health adopted new guidelines[6] in June 2014 (and the South African Department of Health in December 2014[7]) to test 'high-risk' infants at birth. Infants testing PCR-positive are started on ART as soon as possible.

In March 2014, Médecins Sans Frontières, in collaboration with the University of Stellenbosch, started a pilot project in a community healthcare centre in Khayelitsha to establish the impact of very early infant diagnosis on ART initiation and to establish the feasibility of implementation in a primary care setting. To establish routine testing of high-risk HIV-exposed infants at the primary care level, the following steps were taken:

- training and mentorship of healthcare staff at the healthcare centre (midwives, nurses, doctors, counsellors) on the new guideline recommendations; the identification and management of high-risk infants; and the clinical management of ART initiation in a newborn
- routine counselling and consent from mothers for birth PCR testing
- initiation of nevirapine (NVP) and zidovudine (AZT) post-exposure prophylaxis on day one in high-risk infants
- PCR and confirmatory viral load testing via the routine courier system to the referring National Health Laboratory Service (NHLS) laboratory, with results available within 48 hours
- counselling all mothers regarding the PCR results at 48 hours of life, when the mother and infant return to the health centre for routine post natal care:
  - if the PCR result is negative, the mother is advised of the necessity to keep the infant in care for repeat HIV testing as per WCP guidelines as well as to continue post-exposure prophylaxis
  - if the infant is HIV positive, the nurse caring for the mother/infant pair provides standardised ART initiation counselling and ensures the infant is seen by a medical officer the same day
- initiation of ART on the same day as diagnosis for clinically well infants, according to interim infant ART treatment guidelines developed in consultation with infectious disease paediatricians, and referral to the district hospital for clinically unwell infants
- close follow-up of the infants on ART: weekly until 6 weeks of age and monthly until 2 years of age, including routine monitoring bloods and a repeat viral load at 4 months of age
- monitoring of further HIV test results in HIV-exposed infants testing negative at birth, to identify further HIV-positive infants and to assess the coverage of HIV testing per guidelines to 18 months of age.

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TABLE 1: Demographics and early outcomes of three HIV-positive infants diagnosed at birth in a primary care setting.

Demographics and outcomes	Case 1	Case 2	Case 3
Antenatal risk factors for transmission	Mother unbooked in labour (mother known ART treatment interrupter)	ART < 12 weeks in pregnancy (late booking at 25 weeks [HIV negative] and seroconverted at 32 weeks)	ART < 12 weeks in pregnancy (late booking at 31 weeks)
	-	-	Mother is a treatment interrupter
	-	-	Infant born prematurely at 36 weeks' gestation
Mother's results	Viral load (2 weeks after delivery): 484	Viral load (2 weeks after delivery): 302	Viral load not available
	CD4 162 on day of delivery	CD4 281 at 32 weeks	CD4 293 at booking at 31 weeks
Time from birth to ART initiation	16 days	2.5 days	2 days
WHO stage at initiation	Stage 2	Stage 1	Stage 1
Challenges at initiation	Fear of disclosure and stigma	Low socio-economic status	Low socio-economic status
	Distrust of healthcare system	Financially dependent on partner	No stable relationship
	Poor social support	-	-
	Low socio-economic status	-	-
	Financially dependent on partner	-	-
At ART initiation			
Viral load (copies/mL)	871 740	1015	Lower than detectable (LDL) (repeat at 10 days of life-on ART: 265)
CD4 cell count (percentage of total lymphocytes)	1731 (34%)	2082 (27%)	1364 (66%)
HIV drug resistance testing	No resistance	Amplification not possible owing to low viral load	Amplification not possible owing to low viral load
Feeding method	Formula feeding	Reverted to breast feeding when infant initiated ART	Reverted to breast feeding when infant initiated ART
First ART regimen	AZT/3TC/NVP	AZT/3TC/NVP	AZT/3TC/NVP
Second ART regimen: NVP replaced with LPV/r	3 weeks of age (gestational age unknown)	2 weeks of age (gestational age unknown)	6 weeks of age (42 weeks' gestational age)
Prophylactic medications	Co-trimoxazole (started at 4 weeks of age)	Co-trimoxazole (started at 4 weeks of age)	Co-trimoxazole (started at 4 weeks of age)
	Isoniazid (INH) for 6 months	-	-
Viral load (copies/mL) at 4 months†	1823	< 40 (month 3)	< 40
	-	AZT replaced by ABC	AZT replaced by ABC
Viral load (copies/mL) at 8 months	< 40	Not available yet	Not available yet
	AZT replaced by ABC	-	-
Mother VL 3–4 months after delivery	< 40	< 40	< 40
Adverse events	Hospitalised for bronchiolitis and to exclude TB (owing to presumed TB contact). Completed 6 months of INH.	Mild anaemia (Hb 10.4)	Hospitalised for initial high ALT at ART initiation (probably lab error). Repeat was normal.
Other challenges encountered	Transient migration to Eastern Cape over holiday period	Initial mix-up with ARV dosage despite extensive counselling	Mother claimed to be ART naïve at booking
	-	Transient migration to Eastern Cape over holiday period	-

†, Viral load recommended at 4 months after ART initiation as per Western Cape Government Department of Health prevention-of-mother-to-child-transmission clinical guidelines update.[6]
ART, antiretroviral therapy; NVP, nevirapine; AZT, zidovudine; INH, Isoniazid.

By the end of December 2014, we had identified 138 high-risk infants delivered at the primary healthcare centre and we tested 132 high-risk infants (95% of high-risk infants delivered at the centre had a birth PCR) of whom 3 had a positive HIV PCR. The 3 cases are summarised in Table 1 and the lessons learnt from them are described below.

Cases of positive HIV polymerase chain reaction: Lessons learnt

Case 1

Case 1 was complicated by a mother struggling with numerous psychosocial difficulties: low socioeconomic status, fear of stigmatisation and of disclosure to her partner/family, and deep mistrust of the healthcare system. Despite repeated attempts to contact her, she only returned to care when the infant was 9 days old after her perception of her baby being healthy changed after the infant developed conjunctivitis. This case was a good illustration of how barriers at the individual level (low socioeconomic background and psychological factors such as fear of disclosure and stigma) can prevent access to ART for the infant.[8] By addressing these barriers through individual counselling by healthcare providers and peer support from an organisation experienced in supporting HIV-positive mothers, the mother and infant returned to care and have remained in care to date (10 months later). They are both showing good adherence and viral suppression.

Case 2

Case 2 confirmed the higher risk of transmission with a presumed HIV incident infection in the mother, as reported in other studies such as that by Drake et al.[9] Good support and counselling allowed the mother to overcome her initial shock and to accept the need to initiate her infant on ART. She and her baby are suppressed and doing very well.

Case 3

Case 3 illustrates the importance of early booking as intrauterine HIV transmission to the infant could have been prevented if the mother had been diagnosed and started on ART earlier in the pregnancy. In this instance, too, extensive support and counselling assisted the mother in accepting the diagnosis and starting treatment for the infant. Both are now virologically suppressed.

So far, we have demonstrated that testing high-risk infants at birth is possible in a primary care setting, with 129 out of 130 mothers eager for their infants to be tested at birth (other high-risk infants were not tested for other reasons such as already being enrolled in another study, mother missed, etc.). Although concerns were expressed by healthcare providers and counsellors on the psychosocial readiness of the mothers to initiate ART, we found that it was possible and sustainable, with structured ART initiation counselling and adherence support. ART programmes aimed at the implementation of early infant diagnosis strategies should consider modification of the existing three pre-ART routine counselling sessions as essential, given the timing of ART initiation in newborns and the early challenges that both mother and infant are likely to experience in the first months on ART.

Prior to starting the pilot study, we had concerns about the timing of sample transport from the primary care setting to the central laboratory. In fact, the average turnaround time for PCR results has been 48 hours, allowing prompt initiation of babies on ART after birth. Programmatically, it may be more difficult in rural areas, where there may be a longer turnaround time to obtain results. Furthermore, in our pilot project, about 22% of women did not come back for the results of the baby's birth PCR. Using a point of care (POC) PCR machine at birth, with good sensitivity and specificity, could reduce the attrition of patients not returning for results and improve early management of HIV-exposed infants. More research is needed to look into which POC platform would be optimal and the feasibility of its use at a primary care level.

ART initiation in this pilot project was undertaken by a general medical officer in a primary care setting, with the telephonic support of infectious disease paediatricians. As described in an article by Nuttall[10] in the present issue of the *Southern African Journal of HIV Medicine*, initiating ART in a neonate is more intricate than for a 6-week-old infant in terms of available drugs, dosage and monitoring. An initial lack of confidence to initiate neonates on ART was observed during the mentorship of primary care medical officers, mostly related to lack of experience in calculating paediatric dosages and in blood draws in neonates. With the guidance of infectious disease paediatricians at our tertiary referral centre, we designed an interim guide on ART initiation at birth where we attempted to simplify blood tests for monitoring and the calculation of dosages. Modelled on existing ART drug dosing charts, the guide reduces the complexity of neonatal ART initiation and thus increases the confidence of clinicians managing well infants on ART at primary care level.

In addition to being well received by primary care doctors, mentorship on primary care ART initiation for stable infants was well received by the local district hospital, as it reduces the burden on their overstretched services. Furthermore, from the patient's point of view, previous studies show that accessing local clinics rather than distant referral hospitals leads to better retention in care,[8,11] which is what we experienced on the ground, with the above three patients' mothers being compliant with their appointments. The mother builds a trusting relationship with one or two health workers, which probably additionally promotes her retention in care. As we observed, assisting the very vulnerable mother-infant pair through the initial phase of ART may greatly assist long-term compliance with clinic visits.

The major difficulty encountered with ART initiation was for the mother to understand the dosage of syrups appropriately, particularly with the high number of changes in the first few months of treatment. This finding is corroborated by other MSF projects in which paediatric treatment failure has been linked directly to under-dosage by the caregiver (internal source). To overcome this difficulty, sufficient time must be spent counselling the mother on how to administer syrups; visual methods on how much of each syrup to give (using colour stickers and marked syringes) can be very helpful for mothers to understand the measurements. Assigning specific responsibility to the pharmacist, counsellor, nurse or doctor for this education on medication dosing is crucial for ART initiation in neonates to be rolled out effectively in a primary care setting.

Finally, whilst following up the birth PCR-negative babies, we observed that most women take their infants for a '6-weeks PCR' but very few of them actually come to clinics in the right time frame (6–8 weeks). Most of the '6-weeks PCR' tests are done at random times, showing that mothers return to clinics when it suits them, not when they are given a date. Further studies are needed to evaluate the impact of this observation as well as the reasons behind it, and how to adapt the existing system to the needs and demands of new mothers.

Conclusion

We started a pilot project in a primary care centre in Khayelitsha in March 2014 to establish the impact of very early infant diagnosis in reducing the age at ART initiation, and to investigate the feasibility of implementing both early diagnosis and early ART initiation in a primary care setting. So far, we have diagnosed 3 HIV-positive infants out of 129 high-risk HIV-exposed babies tested, and all 3 babies were initiated on ART from 2 days to 2.5 weeks after birth. They are currently doing well: all 3 infants are adherent to their medication and are virologically suppressed on ART. Overall, we have established the feasibility of testing newborns for HIV at birth and initiating ART in the first days

of life in a primary care setting with appropriate mentorship of healthcare providers and consistent adherence support for mothers. By promoting a decentralised model of early infant diagnosis at birth, programmes will ensure access to care for some of the most vulnerable patients with HIV infection.

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Authors' contributions

A.N. (Médecins Sans Frontières) contributed to the conception, design, data acquisition, interpretation, and co-drafting of the paper. J.M. (University of Stellenbosch) drafted the ethics protocol and contributed to the conception, intervention implementation and critical review of the paper. J.G. (Western Cape Department of Health) contributed to the critical review of the paper. L.F. (University of Stellenbosch) contributed to the intervention implementation and critical review of the paper. H.R. (University of Stellenbosch) contributed to the intervention implementation and critical review of the paper. G.v.C. (Médecins Sans Frontières) contributed to the conception and critical review of the paper. T.M. (Médecins Sans Frontières) contributed to the intervention implementation and critical review of the paper. N.J. (Médecins Sans Frontières) contributed to the intervention implementation and critical review of the paper. J.B. (Médecins Sans Frontières) contributed to the critical review of the paper. M.C. (University of Stellenbosch) contributed to the intervention implementation and critical review of the paper. V.C. (Médecins Sans Frontières) contributed to the conception, design and co-drafting of the paper and approved it for publication.

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Recognising and managing increased HIV transmission risk in newborns

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Prevention of mother-to-child transmission (PMTCT) programmes have improved maternal health outcomes and reduced the incidence of paediatric HIV, resulting in improved child health and survival. Nevertheless, high-risk vertical exposures remain common and are responsible for a high proportion of transmissions. In the absence of antiretrovirals (ARVs), an 8- to 12-hour labour has approximately the same 15% risk of transmission as 18 months of mixed feeding. The intensity of transmission risk is highest during labour and delivery; however, the brevity of this intra-partum period lends itself to post-exposure interventions to reduce such risk. There is good evidence that infant post-exposure prophylaxis (PEP) reduces intra-partum transmission even in the absence of maternal prophylaxis. Recent reports suggest that infant combination ARV prophylaxis (cARP) is more efficient at reducing intra-partum transmission than a single agent in situations of minimal pre-labour prophylaxis. Guidelines from the developed world have incorporated infant cARP for increased-risk scenarios. In contrast, recent guidelines for low-resource settings have rightfully focused on reducing postnatal transmission to preserve the benefits of breastfeeding, but have largely ignored the potential of augmented infant PEP for reducing intra-partum transmissions. Minimal pre-labour prophylaxis, poor adherence in the month prior to delivery, elevated maternal viral load at delivery, spontaneous preterm labour with prolonged rupture of membranes and chorioamnionitis are simple clinical criteria that identify increased intra-partum transmission risk. In these increased-risk scenarios, transmission frequency may be halved by combining nevirapine and zidovudine as a form of boosted infant PEP. This strategy may be important to reduce intra-partum transmissions when PMTCT is suboptimal.

Introduction

In South Africa, prevention of mother-to-child transmission (PMTCT) programmes have been very successful in reducing the vertical transmission of HIV, with resultant gains in maternal, infant and child health and survival.[1,2]

Complete elimination of mother-to-child transmission (MTCT) remains elusive, primarily because of incomplete programme uptake – owing to suboptimal patient care-seeking behaviour and inadequate health care access – but also because no current antiretroviral therapy (ART) regimen, even when started early in pregnancy, is 100% effective in preventing transmission. Maternal treatment failure resulting from inadequate adherence or drug resistance may also compromise PMTCT programme efficacy. In high-prevalence populations and serodiscordant partners, primary HIV infection in pregnancy (and breastfeeding), after initial negative HIV screening, may contribute disproportionately to transmission.[3] Delayed ART initiation and apparent incident infection may also be a consequence of false-negative initial testing, owing to procedural and quality issues with rapid antibody screening tests. Finally, resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) may compromise the efficacy of infant post-exposure nevirapine (NVP) 'mono-prophylaxis'.

Although further gains are possible by improving programme coverage and uptake (and this should be encouraged), high-risk vertical exposures at birth remain common and are responsible for a high proportion of transmissions. Recognition of increased-risk scenarios, enhanced labour management (including intra-partum antiretrovirals [ARVs] and caesarean section before labour), infant post-exposure combination ARV prophylaxis (cARP) and a more aggressive testing schedule may all reduce transmission risk and improve the linkage of HIV-infected infants to definitive management. Whilst it is also important for increased risk to be recognised and managed in pregnancy and labour, it is beyond the scope of this article to review obstetric management.

In the developing world, as capacity has grown, PMTCT programmes have evolved from simple, single-dose infant and maternal mono-prophylaxis, focused on intra-partum risk

through targeted maternal combination ART (cART), to the universal, lifelong 'treatment-as-prophylaxis' defined by the 2013 World Health Organization (WHO) guidelines. Each step in this evolution has resulted in progressive reductions in vertical transmission and improvements in maternal care. Infant prophylaxis has grown from post-exposure prophylaxis (PEP) for intra-partum risk to include post-partum peri-exposure prophylaxis (PEEP) intended to render breastfeeding safer. In the developing world, with the focus on reducing transmission during breastfeeding, little consideration has been given to quantification of the intra-partum risk or to boosting infant PEP for increased intra-partum risk scenarios.

In contrast, developed-world PMTCT guidelines routinely quantify intra-partum risk and recommend boosted infant PEP for increased-risk scenarios. In the event of no or minimal pre-labour prophylaxis, National Institutes of Health guidelines recommend the addition of 3 doses of infant NVP in the first week of life to the standard 6 weeks of infant zidovudine (AZT).[4] British HIV Association (BHIVA) guidelines recommend triple ARV prophylaxis for infants when the maternal viral load (VL) is > 50 copies/mL, and only recommend AZT mono-therapy if the maternal VL is fully suppressed from 36 weeks' gestation.[5] Both guidelines acknowledge a growing body of expert opinion that the benefits of infant post-exposure cARP exceed its risks when transmission risk is increased.

Ironically, pre-2010 South African guidelines provided for routine infant dual prophylaxis with single-dose NVP (sdNVP) and one week of AZT, and infants whose mothers had less than 4 weeks of pre-labour prophylaxis were assigned to sdNVP and 4 weeks of AZT.[6] This policy incorporated an element of risk recognition and response and was based on findings of the 'Thai long-short, short-long' and NVAZ studies.[7,8]

Quantifying risk

cART initiated early in pregnancy, with a resultant suppressed VL, and avoidance of breastfeeding virtually eliminate vertical transmission. However, even in the developed world, transmissions occur because of suboptimal antenatal care, failure of maternal and infant prophylaxis and primary HIV infection in pregnancy. These factors argue for an augmented approach to infant management in such increased-risk settings. Consequently, guidelines emanating from the developed world have incorporated elements of risk assessment and response.

In the absence of ARVs, HIV transmission rates are approximately 5% – 10% during pregnancy, 10% – 20% during the intra-partum period, and 10% – 20% during extended mixed breastfeeding.[9] Whilst transmission is minimal in early pregnancy, the frequency of infection increases significantly in the third trimester towards term, and peaks at 10% – 20% during the 8–12 hours of labour and delivery, making the latter the most intense risk period.[10] The intensity of risk is very low throughout breastfeeding, but the cumulative risk over time may be high. Factors strongly associated with increased transmission risk are: high maternal VL, low maternal CD4 count, the absence of maternal ART, and preterm labour with prolonged rupture of membranes.[11] Whilst the first three factors are associated with increased transmission in all risk periods, preterm labour, especially with prolonged rupture of membranes, appears only to increase intra-partum transmission risk.

The Women and Infant Transmission Study (WITS) found intra-partum transmission to be associated significantly with a lack of ART, an increased VL, a low CD4 percentage, young gestational age, low birth weight (LBW), prolonged rupture of membranes and hard drug use. Overall transmission, particularly the intra-partum proportion, has declined significantly over time, reflecting the success of peri-partum maternal interventions and infant PEP.[12] Consequently, the proportion of *in utero* transmissions is higher. In South Africa, the proportion owing to transmission during breastfeeding remains uncertain, as the uptake and duration of breastfeeding are unknown, and long-term follow-up to ascertain postnatal transmission rates has been difficult to achieve.

Intensity of risk varies during pregnancy and breastfeeding according to the timing of ART initiation, the duration of ART and the impact on VL by the time of delivery and breastfeeding. For example, a woman who is newly diagnosed immediately after delivery will be at high risk for transmission in the antenatal and intra-partum periods and will have some risk during early breastfeeding until maternal cART takes effect. In this scenario, infant ARV prophylaxis is critical for reducing transmission during labour and delivery, and exclusive breastfeeding, maternal cART and infant PEEP are vital for risk reduction in the first 3 months of breastfeeding. Heat-treatment of breast milk until an adequate duration of maternal cART or viral suppression has been achieved is an option to eliminate breastfeeding transmission risk entirely. This is especially important to preserve breastfeeding as an option for preterm/LBW infants who are more likely to experience serious adverse events in the first 6 months of life if replacement fed, even if not HIV exposed.[13]

In contrast, a woman who initiates ART from 34 weeks' gestation, has good adherence, is virally suppressed and delivers at 40 weeks' gestation will have some risk of transmission during pregnancy, but very little risk during labour and breastfeeding. Whilst a polymerase chain reaction (PCR) test at birth is indicated to detect pre-labour transmissions, infant cARP does not add much benefit and there is no real benefit in extending PEP beyond 6 weeks. It would be wrong to recommend replacement feeding in this case, unless the conditions for safe formula feeding were met.

It is difficult to incorporate this degree of risk assessment nuance into PMTCT programmes, and it may be better to

have a binary approach where any non-low-risk scenario, irrespective of risk period, attracts an enhanced response for intra-partum management, infant testing and cARP. The introduction of universal PCR testing at birth would simplify the issue and allow the focus to be solely on flagging increased intra-partum risk exposures for infant cARP. The definition of 'non-low risk' and extent of the response will need to be balanced against its cost and available resources. If this approach is adopted, then it is important to guard against the perception that all non-low-risk infants should avoid breastfeeding. Many infants in this category are at particularly high risk of formula-feeding-related morbidity and mortality; therefore, exclusive breastfeeding should be encouraged unless the criteria for safe replacement feeding are met.

The community living with HIV has had significant exposure to NNRTIs as part of first-line treatment and as single doses administered during labour. NNRTI resistance develops rapidly after limited exposure, requiring only a single base pair mutation, and vertical transmission of resistant virus has been described.[14,15] Primary and acquired resistance is not uncommon and, when NNRTI resistance is likely, it seems unwise to rely on NVP mono-therapy for infant PEP when intra-partum risk is increased, even if the mechanism of prophylaxis is different to that of treatment. In contrast, AZT resistance requires numerous mutations and takes longer to develop. Therefore, AZT is important to enhance infant PEP in order to reduce intra-partum transmission risk when maternal virus is likely to be NNRTI resistant.

NNRTI resistance is likely in women who are failing, or have failed, first-line ART, or are on second- or third-line regimens. In such circumstances, it seems logical, at least, to combine infant NVP with AZT if the maternal VL is not suppressed by delivery. The 2013 South African Paediatric Standard Treatment Guidelines recommend expert consultation if resistance is possible, but do not provide advice on reducing the peak risk during labour and delivery with boosted infant PEP.[16]

The following factors are likely to increase vertical transmission risk:

Maternal factors

- duration of maternal ART < 8 weeks (especially if no pre-labour ART)
- maternal VL > 1000 copies/mL close to term (not always available)
- maternal viral rebound (treatment interruption, poor adherence, true resistance)
- maternal co-morbidity (TB, opportunistic infections, chorioamnionitis)
- incident infection (initial HIV test negative, subsequently tests positive)
- likely NNRTI resistance (second-line ART, failing first-line ART; several sdNVP previously)
- adolescent pregnancy (recent/incident/vertically transmitted infection, more likely to have problems with follow-up)
- maternal substance abuse (alcohol or drugs).

Infant factors

- symptomatic (severe growth restriction, lymphadenopathy, hepatosplenomegaly, thrombocytopaenia, pancytopaenia, congenital cytomegalovirus, congenital syphilis, neonatal tuberculosis)
- preterm delivery (regardless of cause) and/or LBW infants (< 2500 g; < 37 weeks' gestation)
- abandoned infants (if Alere Determine or enzyme-linked immunosorbent assay [ELISA] positive).

PCR testing soon after birth will identify infants infected *in utero*, facilitate linkage to definitive care and, hopefully, reduce early mortality. Those not infected *in utero* will, in many instances, also have an increased intra-partum transmission risk and may benefit from enhanced infant PEP. In contrast to the peak risk intensity in labour and delivery, transmission risk intensity per breastfeeding session is extremely low but, owing to a relatively high cumulative risk over time, tends to be overstated. Therefore, the need for enhanced infant PEEP for breast milk exposure is less urgent than PEP for high-risk intra-partum exposure, and the cornerstone of risk reduction in this period remains the urgent optimisation of maternal cART. There is currently no evidence that infant cARP reduces breastfeeding transmission.

Post-exposure prophylaxis reduces transmission risk

ARV PEP, soon after HIV exposure in various settings, is well established as routine management to prevent transmission:

- In 1997 a case-control study reported that post-exposure AZT mono-prophylaxis reduces transmission in occupational exposures.[17] Since then, post-exposure cARP has become the standard of care for occupational exposures. Without prophylaxis, the risk of HIV infection from a penetrating injury with an HIV-contaminated needle is estimated at 0.3% compared with an estimated 15% vertical transmission risk in labour.
- Post-exposure cARP is established as the standard of care after sexual assault and after inadvertent exposure of an infant to another mother's HIV-infected breast milk.
- According to Wade et al. in 1998, when AZT was started before 48 hours of life for PMTCT, transmission was 9.3% (4.1% – 17.5%) and, when started on day 3 of life or later, it was 18.4%. Transmission was 26.6% (21.1% – 32.7%) in the absence of AZT.[18]
- A study of HIV-exposed, formula-fed infants whose mothers received no prophylaxis before delivery reported that infant sdNVP or 6 weeks of AZT were equally efficient at reducing vertical transmission. At 6 weeks, transmission was 5.3% with sdNVP and 6.4% with AZT – both considerably less than anticipated without prophylaxis.[19]

Infant prophylaxis probably contributes little to reducing transmission risk when maternal cART is started early and viral suppression is optimal by the last weeks of pregnancy. Extended or augmented infant PEP cannot compensate for suboptimal antenatal prophylaxis, and early maternal ART with VL suppression remains critical to prevent transmission at all times.

Ideally, patients with an increased risk of intra-partum transmission should be flagged for possible elective caesarean section to avoid intra-partum exposure. When maternal prophylaxis is suboptimal, the intra-partum risk peak is a critical opportunity for intervention and, importantly, its relative brevity makes it amenable to infant PEP. In non-breastfeeding settings, infant PEP targets intra-partum risk alone and is the key intervention for reducing intra-partum transmission when there has been no pre-delivery prophylaxis. In breastfeeding settings, infant cARP must include an ARV that reduces breast milk transmission risk (PEEP) as well. Infant AZT treatment has not been shown to be effective in this regard. PEP is usually only effective if initiated within 48–72 hours of delivery. Infant PEP is not effective in reducing *in utero* transmission, but should be commenced as soon as possible after birth to reduce intra-partum transmission.

In most situations, PEP duration is typically 4 weeks but, in the context of PMTCT, AZT for 6 weeks was established as standard by the PACTG 076 study.[20] In non-breastfeeding settings, there is no real evidence that AZT PEP for 6 weeks is superior to 4 weeks, and the shorter option may be associated with a lower incidence of anaemia and neutropaenia. Pundits for the longer course cite slow decay of transferred intracellular maternal virus as a reason for extending infant PEP.

Post-exposure combination antiretroviral therapy reduces transmission risk in increased-risk situations

Outside of PMTCT settings, exposures of considerably lower risk (occupational, sexual assault and inadvertent breastmilk exposures) routinely attract cARP. Whilst infant cARP for increased-risk MTCT scenarios is routine in the developed world, little consideration has been given to boosting infant PEP to prevent vertical transmission in the developing world.

If viral suppression by the onset of labour is suboptimal, the risk of intra-partum transmission is increased, and the relatively short duration of labour and delivery makes infant cARP an option for reducing transmissions.

Whilst data to support this approach are limited, there is some direct evidence that infant cARP is more effective than a single agent:

- In infants where maternal pre-labour ARVs were absent or minimal, the addition of 3 doses of infant NVP to the standard 6 weeks of AZT reduced intra-partum transmission from 4.8% (confidence interval [CI] = 3.2–7.1) to 2.2% (CI = 1.2–3.9; $p = 0.046$).[21]
- A study in Malawi by Taha et al. reported that the addition of 1 week of AZT to sdNVP reduced intra-partum transmission from 12.1% to 7.7% ($p = 0.03$).[22]

Post-exposure combination antiretroviral therapy options and recommendation for South Africa

There are two main potential benefits of cARP:

- reduced intra-partum transmission
- prophylaxis as very early treatment of HIV-infected infants while awaiting PCR results.

A potential disadvantage is consequent difficulty in confirming infection owing to the effect on VL, but this is already an issue with extended NVP mono-therapy in infants. A higher rate of anaemia owing to extended infant AZT argues for restricting the AZT component to 4 weeks.

Selection of appropriate ARVs for combination prophylaxis is problematic as there are limited pharmacokinetic, safety and efficacy data for the use of many agents in the neonatal period, and more so in combination and with preterm babies. Whilst the imperative of early treatment justifies the use of some of these agents in neonatal cART for newborns infected *in utero*, it is more difficult to justify their use as cARP in HIV-exposed neonates who, for the most part, remain uninfected.

The 2008 South African PMTCT programme recommended sdNVP and AZT extended to 1 or 4 weeks. Since 2010, extended infant daily NVP up to 12 months has been used as PEP and breastfeeding prophylaxis.

AZT, lamivudine (3TC) and NVP as infant prophylaxis are the most used and studied agents globally. There are good study data on the safety and efficacy of these agents as part of comprehensive PMTCT regimens.[23,24,25] BHIVA guidelines recommend these three drugs in combination for infant PEP when transmission risk is not minimal. If drug resistance is likely, consideration needs to be given to other agents not usually used for infant PEP, and then only under expert guidance and preferably with resistance genotyping.[26]

Lopinavir/ritonavir (LPV/r) has been associated with very significant toxicity and is not recommended for use before 42 weeks' corrected gestational age, limiting its usefulness as an option in cARP.[27] Where multidrug resistance is identified by maternal virus genotyping prior to delivery, serious consideration may need to be given to LPV/r use as infant cARP, but then only in a strictly controlled environment.

As extended infant NVP facilitates safer breastfeeding by HIV-infected infants, it makes sense to retain NVP as the

TABLE 1: Nevirapine doses for post-exposure prophylaxis in the first 6 weeks of life.

Birth weight	Age	Daily dosage	Daily volume
< 2.0 kg	Birth – 2 weeks	2 mg/kg	0.2 mL/kg
	2–6 weeks	4 mg/kg	0.4 mL/kg
2.0 kg – 2.5 kg	Birth – 6 weeks	10 mg	1 mL
> 2.5 kg	Birth – 6 weeks	15 mg	1.5 mL

Note: Nevirapine syrup (10 mg/mL).

TABLE 2: Zidovudine doses for post-exposure prophylaxis**.**

Birth weight/gestational age	Age	Dosage	Dose volume
< 2 kg and > 35 weeks	Birth – 4 weeks	4 mg/kg/dose 12-hourly	0.4 mL/kg/dose 12-hourly
> 2 kg and > 35 weeks	Birth – 4 weeks	12 mg 12-hourly	1.2 mL 12-hourly
If gestational age 30–35 weeks	Birth – 2 weeks	2 mg/kg/dose 12-hourly	0.2 mL/kg/dose 12-hourly
	2–4 weeks	3 mg/kg/dose 12-hourly	0.3 mL/kg/dose 12-hourly
If gestational age < 30 weeks	Birth – 4 weeks	2 mg/kg/dose 12-hourly	0.2 mL/kg/dose 12-hourly

Note: Zidovudine syrup (10 mg/mL).

core of infant prophylaxis and add 4 or 6 weeks of AZT and possibly 3TC. There is no evidence that extending AZT or 3TC beyond 6 weeks confers any further intra-partum transmission reduction, or that it affects breastfeeding risk. Both LPV/r and 3TC as single agents extended to 12 months of breastfeeding have recently been reported in the PROMISE PEP study to reduce HIV transmission during breastfeeding to very low levels.[28]

Currently, in South Africa, the two main options for cARP are for a two- (AZT, NVP) or three-drug (AZT, 3TC, NVP) approach. There is little evidence to support one over the other and, indeed, the three-drug approach in HPTN040 showed no clear benefit over the two-drug approach.

Dosage tables for NVP (Table 1) and AZT (Table 2) are given below. These tables are modified from the Western Cape 2014 PMTCT Guidelines, include doses for preterm infants, and differ slightly from doses provided in the current National Guidelines.

The recommended dosage for 3TC is 2 mg/kg for the first 4 weeks of life, irrespective of gestational age at birth.

Conclusion

The most intense period of risk for MTCT is during labour and delivery. This is accentuated by suboptimal maternal viral suppression and limited pre-labour cART duration.

An increased risk of intra-partum HIV infection can be reduced by boosted infant PEP. Newborns at increased risk can be identified by clinical and laboratory parameters at birth, be tested early, and receive post-exposure cARP if the birth PCR test is negative.

Risk of transmission during breastfeeding is low but, because of the cumulative risk over the whole breastfeeding period, tends to be overstated. Breastfeeding risk per month is very low with maternal cART and infant PEEP. In high-risk scenarios, maternal ART/adherence must be optimised urgently to reduce breastfeeding transmission risk and improve maternal health and survival. There are no data on the efficacy of cARP to prevent breastfeeding transmission of HIV in high-risk situations, and the potential toxicity of extended cARP means it cannot be recommended for this purpose.

PCR testing at birth is recommended for infants commencing cARP and when *in utero* transmission risk is high, to respectively exclude HIV infection and facilitate prompt linkage of infected infants to definitive treatment.

Appendix 1 contains commentary on the new South African *Consolidated guidelines for PMTCT and the management of HIV in children, adolescents and adults* that were released after the writing of this article.

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Competing interests

The author declares that he has no financial or personal relationships that may have inappropriately influenced him in writing this article.

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Appendix starts on the next page →

Appendix 1: Recognising and managing increased HIV transmission risk in newborns

In January 2015, the South African National Department of Health (NDoH) issued the new *Consolidated guidelines for PMTCT and the management of HIV in children, adolescents and adults*. This document includes risk criteria linked to more intensive testing and prophylaxis regimens.

Immediate PCR testing including birth testing is now recommended for many increased risk situations.

Infant post-exposure cARP with AZT and NVP for increased intra-partum risk is recommended for 6 weeks when the most recent maternal VLs are > 1000 copies/mL. If maternal ART duration is < 4 weeks or the diagnosis of maternal HIV is made during labour or after delivery, infant breastfeeding PEEP with NVP as a single agent is extended to 12 weeks.

Unfortunately, cARP is not recommended for the very situation where evidence for risk reduction is strongest: when there is no pre-labour ART and a current VL result is not available. Another important omission is the use of cARP for suspected maternal virus NNRTI resistance in instances where it does not make sense to rely solely on NVP for prevention.

Curiously, maternal seroconversion during breastfeeding does attract temporary cARP with AZT for 1 week and extended NVP, but this advice seems illogical and the evidence for benefit is lacking.

Unlike the 2013 WHO consolidated guidelines, the NDoH guidelines make no mention of ARV prophylaxis dosing for preterm and LBW infants. The NVP dosing schedule recommends 20 mg for all infants > 6 weeks old. Many preterm infants may weigh < 2 kg at 6 weeks, and the 20 mg dose may be too high. Moreover, the simplified AZT dosing schedule does not include recommendations for infants weighing < 2 kg.

Whilst the consolidated guidelines are a step in the right direction, they could be improved further, and clinicians should carefully consider whether patients with increased-risk intra-partum HIV exposure may benefit from enhanced prophylaxis. The adoption of universal birth PCR testing would simplify risk management and the selection of infants for cARP. Point-of-care nucleic acid testing in delivery facilities has great potential for routine maternal VL testing to determine intra-partum transmission risk and to facilitate universal birth PCR testing for HIV-exposed newborns.

Research gaps in neonatal HIV-related care

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The South African prevention of mother to child transmission programme has made excellent progress in reducing vertical HIV transmission, and paediatric antiretroviral therapy programmes have demonstrated good outcomes with increasing treatment initiation in younger children and infants. However, both in South Africa and across sub-Saharan African, lack of boosted peri-partum prophylaxis for high-risk vertical transmission, loss to follow-up, and failure to initiate HIV-infected infants on antiretroviral therapy (ART) before disease progression are key remaining gaps in neonatal HIV-related care. In this issue of the *Southern African Journal of HIV Medicine*, experts provide valuable recommendations for addressing these gaps. The present article highlights a number of areas where evidence is lacking to inform guidelines and programme development for optimal neonatal HIV-related care.

Research gaps in neonatal HIV-related care

The South African (SA) prevention of mother to child transmission (PMTCT) programme has made excellent progress in reducing vertical HIV transmission.[1,2] In addition,[1] paediatric antiretroviral therapy (ART) programmes have demonstrated good outcomes with increasing treatment initiation in younger children and infants, in response to South African and World Health Organization (WHO) guidelines expanding recommendations for immediate ART from infants to all children < 5 years old.[2,3,4,5,6,7,8,9,10] However, both in SA and across sub-Saharan African, lack of boosted peri-partum prophylaxis for high-risk vertical transmission, loss to follow-up (LTFU) for early infant diagnostic (EID) HIV-polymerase chain reaction (PCR) testing and receipt of results, and failure to initiate HIV-infected infants on ART before disease progression are key remaining gaps in neonatal HIV-related care.[11,12,13] The expert reviews on recognising and managing vertical transmission risk in the peri-partum period,[14] HIV diagnostic testing of newborns[15] and provision of neonatal ART[16] provide valuable recommendations for addressing these coverage gaps. They also highlight a number of areas where evidence is lacking to inform guidelines and programme development for optimal neonatal HIV-related care.

What is the best way to manage newborns at increased risk of intrapartum HIV transmission?

For many years, guidelines from developed countries[17,18,19] included identification of neonates at high risk of vertical transmission,[20,21] recommending multi-antiretroviral (multi-ARV) post-exposure prophylaxis (PEP) for these neonates. While two studies provide direct evidence that multi-ARV PEP is more effective than a single drug,[22,23] data are lacking on the best choice, number and duration of drugs.

Research is needed to inform guidelines that balance the prophylactic benefit of multi-ARV PEP with risks of toxicity and resistance that may increase with duration, as well as the programmatic challenges associated with effectively implementing more complex regimens for longer periods. Furthermore, longer-duration multi-ARV PEP may suppress HIV viral load,[23,24,25] making HIV diagnosis more challenging, with implications for EID algorithms. In wealthy countries with low maternal HIV prevalence, reduced sensitivity of HIV-PCR is of less concern as guidelines recommend EID testing at numerous time points in exposed infants. In contrast, in South Africa, routine testing in otherwise well infants will probably be restricted to two HIV-PCR tests per infant at most, hence the impact of reduced sensitivity of HIV-PCR testing is critical.

Research needs include determining the effectiveness of routine programmes in accurately identifying high-risk infants in need of multi-ARV PEP, as well as retention, adherence and transmission in routine care. For example, monitoring and evaluation of the implementation of the National and Western Cape provincial guidelines for multi-ARV PEP could provide valuable data to inform programme development.

What are the optimal algorithms for early infant diagnostic?

South African 2014 PMTCT guidelines provide for HIV-PCR testing at birth of HIV-exposed infants at high risk of vertical HIV transmission, including low-birthweight and premature infants as well as those born to mothers on ART for < 4 weeks or with HIV-RNA > 1000 copies/mL.[26] In addition, a WHO technical expert panel in 2013 reviewed the optimal timing of EID testing, and consideration was given to recommending either universal or risk-based birth testing.[27] Given the shift towards a greater proportion of in utero infections with improved coverage of more effective PMTCT regimens such as Option B/B+, and the proven efficacy of HIV-PCR at birth to identify 75% of infections detectable by 6 weeks of age, birth EID could be pivotal in mitigating against the high LTFU for EID testing and delays in starting infected infants on ART.[23,28] However, there are a number of questions regarding optimal EID guidelines.

What is the best time for a follow-up HIV-polymerase chain reaction test?

Birth testing necessitates a follow-up test, as 25% of early HIV infections are undetectable at birth.[23,28] Evidence is needed to inform the optimal timing of follow-up testing, which depends on test performance, morbidity and mortality without ART (and the effect of ART in reducing this), retention strategies and operational considerations of aligning follow-up with routine child health visits.[27,29] Whilst mathematical modelling suggests that, with two HIV-PCR tests per infant, the greatest number of infections can be identified at birth and 10 weeks of age, there is a need for more evidence to inform the model assumptions, such as the probable loss of HIV-PCR sensitivity owing to nevirapine PEP.[30] Of note, no studies to date have examined HIV-PCR test performance at birth and thereafter, now that triple ART is mandated for all women during pregnancy and breastfeeding together with extended infant NVP prophylaxis. These factors may all reduce test sensitivity at birth[31] and at 6 weeks of age.[25] For this reason, the 2014 South African PMTCT guidelines defer PCR testing to 16 weeks of age in infants who need 12 weeks of NVP PEP.[26] However, more data are needed on the duration and extent of reduced sensitivity post-PEP.[24] Delaying testing will improve sensitivity; however, attrition is likely to increase at longer post-partum durations.[32] The extent to which such attrition would be exacerbated by false reassurance of a negative result at birth is unknown.

In addition, the model assumes that ART very early in life is associated with improved survival. However, there are little data on the magnitude of the mortality benefit when ART is initiated very early, for example in the first days or weeks of life, especially in premature low-birthweight infants, compared with the benefit seen in the Children with HIV Early antiRetroviral (CHER) trial where the median age of ART initiation in the early group was 7.4 weeks.[33]

Is it efficient to test all infants routinely at birth, or should this be restricted to those at high risk of transmission?

Whilst the mathematical modelling study demonstrates a nearly 50% increase in the number of life years saved when adding a routine birth test to a single test at 10 weeks of age, more tests increase costs and reduce efficiency (measured in terms of new diagnoses per PCR) by approximately 35%.[30] The efficiency of restricting birth testing to those at high risk of transmission is unknown and may be programmatically more difficult to implement effectively. In particular, more data would be needed to identify easily implementable high-risk criteria that are predictive of a high likelihood of a positive birth test.

Although the specificity, and therefore positive predictive value (PPV) of currently used EID tests is very high, the proportion of false-positive tests increases with reduced transmission rates. Follow-up confirmatory testing with HIV-PCR or viral load may be difficult to interpret in infants on prophylactic therapy,[25] with careful counselling needed. Research is needed on how best to manage patients with false-positive or indeterminate test results, which may be resource-intensive and difficult outside specialist facilities.

How feasible is implementation of birth testing in routine care settings?

EID testing at 6 weeks and follow-up for results at the 10-week immunisation visit is currently performed at immunisation clinics. For a birth PCR, delivery facilities would be responsible for birth testing. The very high proportion of facility-based deliveries in SA favours birth testing, and routine postnatal follow-up within a few days of birth at many delivery facilities could facilitate receipt of results. However, the extent to which the additional workload can be absorbed by delivery facilities is unclear. This consideration is particularly important for high-burden facilities where women may be discharged within hours of delivery so that counselling and birth tests may need to be performed after hours or on weekends. There are encouraging early data from a pilot study comparing birth testing of high-risk infants in primary (Khayelitsha, Cape Town) and tertiary (Tygerberg Hospital, Cape Town) care delivery facilities, supporting the feasibility of implementing birth testing at primary care level.[34] There was no difference in median time-to-test results between the facilities despite no on-site laboratory at the primary care facility.[34] However, additional research staff supported the study and testing was limited to high-risk infants (about 25% of all exposed infants), therefore the results may not be generalisable to all infants in routine care settings.

Research is also needed on how best to counsel mothers of infants whose birth test is negative about the need to return for an additional test. Systems to ensure follow-up for a subsequent test require development. This approach may be challenging, especially in the absence of unique patient identifiers across the health service, as subsequent tests in infants born at a single delivery facility would probably occur in many different immunisation clinics.

How do we ensure that patients return for results and initiate antiretroviral therapy if indicated?

Irrespective of the timing of testing, there is a need to develop and evaluate systems for ensuring that positive infant results are received and ART is successfully initiated. Interestingly, in the modelling study, changing the timing of a second HIV-PCR test between 6 and 14 weeks of age had only a small effect on the proportion of perinatal infections diagnosed,[30] whereas the greatest reduction in missed diagnoses (11%) was seen if 100% of caregivers received test results, compared with the assumption of 66% based on previous studies.[35,36] Data from the Western Cape reassuringly suggest that the proportion of infected infants linked to HIV care has increased from 54% to 71% between 2005 and 2010.[37] It is likely that there have been further improvements, with rapid alerts of positive tests from laboratories to sub-district PMTCT co-ordinators and immunisation clinics, with follow-up tracing of infants. (Van Niekerk, personal comm.). In contrast, in rural KwaZulu-Natal in 2012, 45% of infants with positive HIV-PCR diagnoses never started ART and a number of challenges in tracing infected infants were identified, highlighting the need for better linkage systems in a range of settings.[38]

Point-of-care (POC) tests could maximise the proportion of infants receiving results, with a number of platforms currently under investigation.[29] A recent Mozambique study demonstrated 98.5% sensitivity and 99.9% specificity, comparing a POC nucleic acid test implemented in primary care clinics with laboratory tests.[39] Similar encouraging results were reported for a POC nucleic acid test in Cape Town, South Africa, with overall sensitivity of 97% and specificity of 100% for correctly identifying HIV-infected infants.[40] Sensitivity was slightly lower (93%) and the test error rate higher (10%) among 90 infants tested at < 7 days old.[40] Further studies of birth POC tests are ongoing. In addition, the throughput time for a single POC test may limit its use in busier facilities, especially if testing is done on all infants, and not only those at high risk.

Despite the research gaps and challenges described, implementation of routine birth testing in all infants with nearly 100% coverage could itself provide much-needed evidence of the real effectiveness of the PMTCT programme and monitor progress towards virtual elimination of vertical transmission of HIV. Mother to child transmission is probably currently under-estimated both by routine statistics and dedicated studies, as a high proportion of HIV-infected infants may be LTFU or deceased by 6 weeks of age.[2,28] Similarly, owing to current under-diagnosis of all neonatal infections, the true neonatal mortality in HIV-infected infants is unknown.[15]

What is the best management for HIV-infected neonates?

How soon after birth should antiretroviral therapy be started?

There is a spectrum of arguments favouring early infant ART ranging from the more conventional aims of reducing morbidity and mortality through effective therapy to the potential for modifying persistent HIV to facilitate later treatment-sparing or even eradication strategies.[41,42,43,44,45] Evidence for the traditional goal of reducing morbidity and mortality includes the high early mortality and rapid disease progression in HIV-infected infants,[46,47,48] the lack of prognostic markers for mortality in infants[49] and the substantial reductions in morbidity, mortality, neurodevelopmental delay and other HIV-related complications demonstrated in the CHER randomised controlled trial.[33,50,51] In addition, cohort studies report better growth, neurocognitive outcomes, immunological response and virological control in infants starting therapy at earlier ages than amongst older infants and children.[45,52,53,54,55,56,57,58,59]

Whilst early virological control in infancy is important for the conventional treatment goals of optimal long-term outcomes on ART, it may also moderate chronic HIV infection by reducing the latent HIV reservoir, paving the way for treatment-sparing strategies.[41,45,53,60] The case of the 'Mississippi child', who received triple therapy within hours of birth with early virological control and subsequent prolonged virological remission off ART,[61] has sparked interest in treatment-sparing or cure approaches. The final results of the CHER trial found that early therapy followed by interruption after either 40 or 96 weeks on ART had superior clinical and immunological outcomes and less overall time on ART than deferred continuous therapy.[44] However, it is not known whether longer duration or uninterrupted early therapy would have even better outcomes. In addition, detailed studies on the virological and immunological consequences of interruption, and predictors of the need to restart therapy in the interrupted groups, are still under way. Luzuriaga et al.[53] recently showed that early treatment at < 2.6 months of age with sustained virological control through to adolescence is associated with limited circulating pro-viral and replication competent virus with continuous decay of viral reservoirs, not seen in children starting ART at older ages. Nevertheless, whilst early virological control in infants may allow for later treatment interruptions or eradication strategies, it does not guarantee prolonged absence of viral rebound, which has occurred within days to weeks of stopping treatment.[62,63]

It is easy to merge the spectrum of arguments in favour of early infant ART into the general dictum 'the sooner, the better', especially with a shift towards birth EID testing. Indeed, the rapid disease progression and mortality in HIV-infected infants by 2–3 months of age and high mortality even in the early treatment arm of the CHER trial suggests that ART initiation before a median of 7.4 weeks of age should be beneficial.[33,46,64] However, we really do not know how soon is soon enough. There is no clear evidence on the optimal timing of ART between birth and 7.4 weeks for either reducing morbidity and mortality on ART, or later treatment-sparing approaches. Importantly, this evidence is also needed for pre-term and low-birthweight infants who comprise a substantial proportion of infants at risk of vertical transmission.[21,65,66] Of note, low-birthweight infants (< 2kg)

were excluded from the CHER study.[33] In addition, as studies demonstrating benefits of early infant ART to date have not distinguished between in utero and intrapartum infection, the optimal timing of ART initiation in these groups may differ.[47,67]

Which regimen should be used in the neonatal period?

The optimal timing of neonatal ART initiation must balance the benefits and risks of early therapy, and hence the lack of appropriate formulations or pharmacokinetic, dosing, safety and effectiveness data for drugs in neonates, especially premature neonates, as outlined in the companion article by Nuttall,[16] are research gaps. In particular, the use of a nevirapine-based regimen in neonates < 2 weeks of age is a concern with high prevalence of Non-nucleoside reverse-transcriptase inhibitors (NNRTI) resistance, even in the absence of reported PMTCT exposure.[68] Prevalence of resistance may be even higher than previously reported if more sensitive testing methods are used.[69] There is mixed evidence on the benefit of more aggressive regimens that hasten virological control, for example four-drug regimens.[54,70,71] Studies are warranted on the safety and effectiveness of different regimens, including triple-class four-drug regimens and integrase inhibitors. The role of these regimens may be particularly important if the goal of therapy is to allow for later treatment-sparing strategies.[41] In addition, as adult ART programmes mature, choice of regimen in infants born to mothers failing first-line ART is an emerging research need.

Evidence for which drugs to initiate should consider the likely characteristics and comorbidities in infants infected despite a comprehensive high-coverage PMTCT programme. In a case series of 20 infants initiating ART within the first 6 weeks of life at Rahima Moosa Mother and Child Hospital in Johannesburg, 70% had congenital infections and other illnesses requiring treatment.[72] Prematurity (70%), low birthweight (50%), and pre-treatment thrombocytopaenia (30%), anaemia (40%) and renal dysfunction (10%) were not uncommon.[72] Illnesses requiring treatment included congenital pneumonia, congenital syphilis, CMV and TB.[72] Similar results have been reported from a case series of infants diagnosed at birth at Mowbray Maternity Hospital, Cape Town.[73] Drug interactions may occur and drugs may require administration via nasogastric or orogastric tubes in sick pre-term infants, affecting dose delivery.[65]

Given the lack of data on many drugs in the neonatal period and probable comorbidities in infected infants, appropriate safety and dose monitoring requires determination. For example, published studies of treated premature neonates have closely monitored drug levels to determine dosing, and the extent to which this is required routinely is unclear.[65] Similarly, the optimal intensity of safety monitoring is unknown both for sick neonates in hospital as well as for those who are clinically well who could be treated in primary care settings.[74]

How do we initiate and retain children on antiretroviral therapy from the neonatal period onwards?

There are substantial challenges with initiating and retaining HIV-infected newborns on treatment. The mothers of HIV-infected infants will frequently have either never accessed PMTCT or been lost to care;[75,76,77] consequently, the likelihood of poor infant retention and adherence after ART initiation is high. Studies from both wealthy countries[78] and resource-limited settings[79] report substantial loss to follow-up and poor adherence on ART in infected infants, despite high coverage of an effective PMTCT programme. In a Johannesburg research cohort of 30 infants initiating ART at a median 16 weeks of age, < 50% were in care 68 weeks later, with four deaths.[79] The challenges that the caregivers of these infants may already face with accessing and remaining in care may be exacerbated by the tremendous stress experienced with EID.[80,81,82,83] Significant research gaps include understanding the tensions between maternal needs in the post-partum period, including the psychosocial readiness of the mother to initiate ART for her infant, and how neonatal ART services are delivered. Research is needed to investigate approaches to EID and neonatal ART initiation, such as the use of heath navigators, that best support engagement and long-term retention in care.

Future directions

As practice changes towards birth diagnosis and early infant ART, there is an opportunity to collect both programme-level and individual patient data to address some of the research questions related to early neonatal HIV care.[84] Just as studies of the first paediatric ART programmes in resource-limited settings were used to inform treatment guidelines and programme development,[85,86,87] careful collection and analysis of observational data from PMTCT, EID and neonatal ART programmes will provide valuable evidence to inform neonatal HIV care. Collaborative research across different sites and settings is needed owing to the small numbers of patients at individual sites and transfer of infants from PMTCT programmes to neonatal/paediatric and primary care ART programmes. Such observational research conducted within South Africa and in other resource-limited settings will be relevant both locally and globally.[84]

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Breastfeeding and the 2015 South African guidelines for prevention of mother-to-child transmission of HIV

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Breastfeeding, especially exclusive breastfeeding in the first months of life, is the cornerstone of good infant nutrition, health and survival. The various health benefits include the mother and also extend beyond infancy to protection against common noncommunicable diseases in adult life. These benefits take on even greater salience in low-resource settings.

Mother-to-child transmission (MTCT) of HIV through breastfeeding and the Centers for Disease Control's initial recommendation that HIV-infected women avoid breastfeeding their infants, threatened this key child health-promoting activity. Support for breastfeeding by HIV-infected women is steadily being reinstated, however. This change was prompted by numerous reports that formula feeding incurred significant harm[1] and was also facilitated by a 1999 report that showed significantly reduced postnatal HIV transmission if breastfeeding was exclusive.[2] Further impetus came from a demonstration that postnatal transmission is almost eliminated if maternal combination antiretroviral treatment (cART) or extended infant antiretroviral peri-exposure prophylaxis (PEEP) is provided during breastfeeding.[3] In 2012, even the British HIV Association (BHIVA) guidelines permitted breastfeeding under tightly controlled circumstances, if mothers insisted.

The 2010 South African Prevention of Mother-To-Child HIV Transmission (PMTCT) Guidelines incorporated this evidence and were broadly supportive of HIV-infected women breastfeeding their infants, but stopped short of adopting breastfeeding as the programme's default feeding choice. The Tshwane Declaration in August 2011 shifted South Africa squarely onto the breastfeeding restoration path. Besides promoting, protecting and supporting breastfeeding generally, the declaration specifically adopts breastfeeding as the default feeding method for HIV-exposed infants and promotes human milk banks to support breastfeeding and breast milk feeding. The Tshwane Declaration was followed by the promulgation of regulations (R991/2012) to enforce the international code on marketing of breast milk substitutes. Nevertheless, South Africa still lags behind many other African countries in the uptake and duration of breastfeeding and the duration of exclusive breastfeeding.[4]

New guidelines to improve PMTCT in South Africa have recently been released and recommend lifelong cART for all pregnant women and those who have delivered in the preceding 12 months, irrespective of disease and laboratory criteria.

Four important new dimensions provide greater attention to neonates, namely (1) birth polymerase chain reaction (PCR) testing of high-risk neonates, (2) extended infant antiretroviral (ARV) prophylaxis if early *breastfeeding risk is increased* owing to inadequate duration of maternal cART, (3) combination infant ARV prophylaxis (cARP) if *intrapartum transmission risk is increased* and (4) very early initiation of cART in infected neonates. In the present article, we discuss the implications of these new programme and policy developments for breastfeeding.

The first issue is the specific counselling needs of women whose infants are HIV-infected. The new birth PCR testing programmes will identify most HIV-infected infants much earlier than the old 6-weeks PCR testing programmes.[5] This approach provides a valuable opportunity for strengthening support for breastfeeding, which is essential to the survival and well-being of HIV-infected infants. HIV-infected infants should be breastfed for 2 years or more.

Secondly, by design, the new, targeted birth testing programmes will encompass a large proportion of preterm and low birthweight (LBW) neonates. Many challenges exist to maintain optimal breastfeeding and clinical care for this high-risk group, regardless of HIV exposure status. HIV clinicians will need to improve their skills and expertise in this area as caring for more of these vulnerable infants becomes their responsibility. In turn, neonatologists and paediatricians already caring for this clinical population will need to strengthen their skills and expertise in HIV-related interventions.

Thirdly, *risk estimation* linked to targeted testing or augmented infant prophylaxis will identify women with suboptimal cART, including those who have not yet accessed care, those who deliberately avoided care, those who are non-adherent, those who are failing cART, late starters, etc. Counselling around infant feeding for this group will need to balance HIV transmission risks against the adverse and potentially fatal outcomes associated with abstinence from breastfeeding, particularly in preterm and LBW infants.

HIV-infected neonates

Infant feeding counselling in PMTCT programmes has mostly ignored the scenario of known HIV-infected neonates. Typically, counselling has been directed at HIV-infected women with infants of unknown HIV status. Whilst antenatal counselling still has to keep this focus, postnatal counselling will now have the benefit of much earlier diagnosis of HIV infection than was previously possible. If a sample for a PCR test is collected at birth, the mother should be able to learn her infant's HIV status in a matter of days, depending on the turnaround time of the laboratory and the schedule of follow-up visits. This time could be reduced to a few hours if point-of-care (POC) tests are used routinely in the clinical setting. For an infant diagnosed as infected, earlier diagnosis offers a valuable opportunity for strengthening support for breastfeeding. Breastfeeding is crucial for the wellbeing of HIV-infected infants who are at exceedingly high risk of mortality.[6] Breastfeeding for two years or more can be unequivocally recommended and supported for the infected infant, as the risk of HIV transmission is no longer a consideration.

However, learning the infant's diagnosis is challenging for mothers. Many are distressed and experience feelings of guilt. They should be reassured that any 're-infection', should it even occur, will not accelerate disease progression in their infant and that the protective benefits of breastfeeding in an HIV-infected child far outweigh the minuscule possibility of harm.

Very early diagnosis also provides a window of opportunity to begin or restart breastfeeding for those who either decided to forgo all breastfeeding or who stopped before the infant's diagnosis. Healthcare workers and the community are often quite ignorant of the reversible nature of infant feeding decisions. An innovative programme in Soweto demonstrated that a modest relactation counselling program had reasonable success in achieving full lactation after infant HIV diagnosis, even in mothers who had abstained entirely from breastfeeding until infant diagnosis around 12 weeks of age.[7]

Preterm and low birthweight neonates

Preterm and LBW infants are generally at higher risk of perinatal HIV transmission than term, normal birthweight infants. They also may have biological reasons for increased susceptibility to enteral acquisition of HIV from breast milk. In addition, preterm birth before adequate passive transfer of maternal neutralising antibodies may cause reduced protection against postnatal HIV infection. This is why preterm birth and/or LBW is included as one of the criteria for targeted birth testing and, in the Western Cape, for cARP.

Few studies of extended infant prophylaxis include preterm infants, despite their higher risk of infection, and special dosage considerations are required in this group.[8] Nevertheless, combining infant PEEP with maternal cART is advisable in this group, as avoidance of breastmilk feeding increases morbidity and mortality significantly.

The immature, preterm gut is nowhere near as robust as the term gut with, initially, relative hypomotility, underdeveloped microvilli and brush border enzymes predisposing to malabsorption, stasis, bacterial overgrowth and inflammation, particularly if fed injudiciously. Very gentle graduated feeding with human milk reduces the risk of intestinal inflammation and necrotising enterocolitis (NEC). NEC is three times more common with formula milk than with donated human milk feeding.[9] Gut inflammation is likely to increase the number of CD4 cells and CCR5 receptor expression and increase vulnerability to HIV transmission. Additionally, HIV-exposed infants may be more at risk of developing NEC, worse grades of progressive NEC and mortality from NEC with worse outcomes after surgery.[10]

Consequently, whilst human milk feeding is critical to better outcomes in HIV-exposed preterm neonates, it may involve the risk of HIV transmission despite ARV prophylaxis. It may be advisable to complement infant PEEP and maternal cART to further reduce transmission risk. Consideration should be given to heat treatment of the infant's own mother's milk or feeding with human milk from an HIV-negative donor at least temporarily whilst feeds are being established and preterm gut matures in the first few weeks of life. Over-reliance on donated human milk should be discouraged, as this does not facilitate sustained breastfeeding after discharge whilst heat treatment of own mother's milk does.

Human milk banks have a critical role in supporting breastmilk feeding, and the South African Department of Health is currently developing regulations on milk banking. Some provinces and non-governmental organisation (NGOs) have already developed milk banks and milk bank networks.

One of the postulated mechanisms for the increased rate of transmission in mixed breastfeeding infants is that cow's milk protein or solid food causes low-grade gut inflammation, thus increasing susceptibility. This possibility may be especially true for the immature gut. Preservation of exclusive breastmilk feeding may be facilitated by the temporary use of donated human milk until lactation is fully

established or the next batch of own mother's milk is brought from home.

There are some data to suggest that heat treatment of expressed breast milk (EBM) at home may be implementable but this complicated approach requires a great deal of motivation from family and adequate support from the health service. The approach is worth considering in preterm neonates *in hospital* with additional risk factors such as mothers who fail therapy or who are drug resistant. The bulk of feeds would initially be by gastric tube, and this facilitates heat treatment of EBM. Cup feeding of heat-treated EBM may also be considered. It is probably safe to transition to suckling directly from the breast with extended infant ARP and maternal cART cover once the gut has matured and full enteral feeds are established and well tolerated. Minimally nutritive suckling may accelerate oro-motor maturation and should be encouraged.

Sustaining lactation in mothers of preterm infants can be challenging, particularly when faced with meagre lodging facilities, prolonged maternal-infant separation especially because of severe maternal illness, infrequent visiting owing to poverty or substance abuse, and inadequate support for sibling care especially in recently migrated impoverished families. In addition, postnatal depression and poor advice from healthcare workers may undermine sustained breastfeeding. Mothers should be informed that fortification of their milk to meet the increased nutrient demands of the preterm infant is preferable to special preterm formula. Whilst some infrastructure issues may be dealt with at a health systems level, commitment to the Mother and Baby Friendly Initiative (MBFI) principles, Kangaroo Infant Care and promotion of routine early and regular emptying of breasts by manual and mechanical expression are vital to support and sustain breastfeeding. Pharmacological interventions to optimise milk expression may also be helpful but, by and large, the most important component is parental education and 'buy-in' of the benefits of breastfeeding. An institutionalised belief that breastfeeding is a critical component of preterm care goes a long way to reverse the tendency to rely on formula milk as a short-term, quick-fix option.

This complex subset of preterm and LBW infants neonates poses many challenges for ensuring optimal and sustained breastfeeding and care whilst preventing HIV infection. HIV clinicians, neonatologists and paediatricians will have to rise to this challenge as these babies become the focus of intensified risk-based prophylaxis and, if infected, cART in the first weeks of life.

Some hospitals have sophisticated programmes to help support breastfeeding of preterm infants including kangaroo infant care, heat-treatment stations and active milk banks. Other hospitals, however, need to establish this capacity as soon as possible.

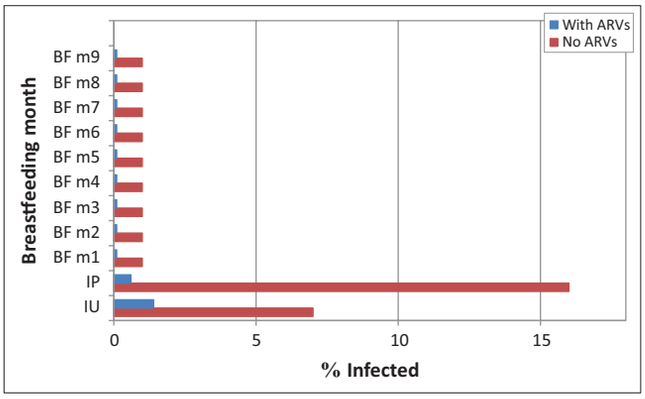
Neonates of mothers who are non-adherent or have drug-resistant virus

Infants whose mothers have had suboptimal ARV exposures will constitute the majority of high-risk infants identified for targeted testing or cARP. This group includes women who have only recently learned their HIV status; those who have deliberately absented themselves from programmes, are non-adherent or defaulters and those not yet able to access appropriate services. All of these characteristics point to challenging social circumstances. Ensuring that the mothers of these high-risk infants obtain HIV-related care and ARVs necessary for their own health is as important as ensuring the best available prophylaxis for their infants.

Given the probable social disadvantage of women who are partially adherent to cART, the new advice that women who are failing second- or third-line treatment should formula feed is, in most circumstances, ill-advised. There are no special reasons to avoid breastfeeding in this group. The same risk/benefit considerations for breastfeeding in all HIV-exposed infants apply to this subgroup, and many will have social circumstances that could amplify the adverse consequences of avoiding breastfeeding.

Invoking risk of transmission of drug-resistant virus through breastfeeding as the motivation for avoiding it is not logical. Concerns about transmission of drug resistance in this situation are overstated and confused. Almost all infants who fail PMTCT (i.e. become infected despite being exposed to ARVs) have virus resistance to a number of first-line ARVs.[11] The paediatric treatment guidelines already address this by recommending initiation with ritonavir-boosted lopinavir (LPV/r)-based cART for HIV-infected infants from 42 weeks' corrected gestational age and young children under 3 years of age. MTCT of resistance to LPV/r is exceedingly rare. We are aware of one report of transmitted LPV/r resistance to an infant via perinatal rather than postnatal transmission.[12] Trials using LPV/r for PMTCT have not observed frequent emergence of LPV/r resistance in either mothers or infants.[13] Even if it were to occur, the small risk of resistance applies only to the small population of infants who are infected. Avoiding breastfeeding for the benefit of a tiny minority places the majority of HIV-exposed uninfected infants at risk of poor health and development.

Fear of HIV transmission during breastfeeding looms large, and fear of transmission of drug-resistant HIV even larger. This fear seems to blind providers to the immediate risks of poor growth, pneumonia and diarrhoea, significantly more likely to be worse or fatal in the non-breastfed infant.[1] The risks of postnatal HIV transmission are almost 20 times less than during the pregnancy and delivery. ARVs given to the mother or to the infant reduce risks via all of these routes by a factor of more than 10 (Figure 1). In the event of suboptimal adherence to ARVs, the risk of HIV transmission



IU, intrauterine; IP, intrapartum; BF, breastfeeding; m, months; ARVs, antiretrovirals.

FIGURE 1: Risks of HIV transmission with (in red) and without (in purple) antiretroviral drugs occurring during the intrauterine, intrapartum and during months 1–9 via breastfeeding. The risks of transmission amongst mothers who are non-adherent, failing therapy or drug resistant are likely to lie between these two estimates.

does not exceed that observed in the absence of ARVs. Risks of transmission in this partially adherent group will be less than the risks when no ARVs are given.

The social circumstances and health service access issues associated with this subgroup tend to exacerbate the adverse effects of abstinence from breastfeeding. Formula feeding should only be considered in this group if all options of ensuring access to ARVs for mother and infant have been exhausted or there are absolutely no prospects of breastfeeding because serious maternal substance addiction will grossly interfere with it.

Conclusion

Risk recognition linked to improved testing and infant prophylaxis may further reduce transmission, diagnose infection earlier and improve linkage to definitive care and treatment. There is a danger that when transmission risk is increased, replacement feeding may be considered to prevent postnatal transmission despite breastfeeding being critical to infant health and survival. The few paediatric infections averted will be at the expense of harm to the majority who are HIV-exposed but uninfected.

Even with imperfect prophylaxis, less than 1% of infants become infected in each month of breastfeeding. Promoting replacement feeding denies breastfeeding benefits to the more than 99% of HIV-exposed infants who remain uninfected. Importantly, these benefits would also be denied to the high-risk infants infected during birth and only diagnosed at 6 weeks of age or older. Clinicians may struggle to keep this in mind when counselling the individual 'high-risk' patient on feeding choices, and should avoid inflating the real but tiny risk of transmission and understating the real harm from not breastfeeding.

At a public health level, occasional individual infections via breastfeeding are a small price to pay for a compelling benefit to the majority. The low frequency of transmission during breastfeeding, even when risk is increased, allows time to optimise maternal cART to reduce risk rather than promoting formula feeding.

A weak point in the old early infant diagnosis programme was a tendency towards early termination of breastfeeding around 10–12 weeks when receiving the negative result from the 6-weeks test. This pattern suggested a missed opportunity to support breastfeeding at this critical juncture. It is unclear whether counselling specifically encouraged women to stop breastfeeding or whether messaging around the need for retesting inadvertently failed to convey the importance of continued breastfeeding. Vigilance is needed when counselling mothers about the meaning of negative birth PCR tests to ensure that this counselling does not inadvertently discourage breastfeeding.

Breastfeeding and breastmilk feeding remain the best feeding method to optimise health outcomes in PMTCT, even when mothers are failing first- and second-line treatment. The counselling messages after birth testing must include clear support for breastfeeding if we are to leverage the full health benefits of very early HIV diagnostic testing and strengthened prophylaxis.

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Authors' contributions

The authors co-wrote the article.

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Reconciling the science and policy divide: The reality of scaling up antiretroviral therapy in South Africa

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With the world's largest national treatment programme and over 340 000 incident cases annually, the response to HIV in South Africa is hotly contested and there is sometimes a dissonance between activism, science and policy. Too often, policy, whilst well intentioned, is informed only by epidemiological data. The state of the healthcare system and sociocultural factors drive and shape the epidemic and its response. By analysis of the financial, infrastructural, human resources for health, and governance landscape in South Africa, we assess the feasibility and associated costs of implementing a universal test and treat programme. We situate a universal test and treat strategy within the governance, fiscal, human resources for health, and infrastructural landscape in South Africa. We argue that the response to the epidemic must be forward thinking, progressive and make the most of the benefits from treatment as prevention. However, the logistics of implementing a universal test and treat strategy mean that this option is problematic in the short term. We recommend a health systems strengthening HIV treatment and prevention approach that includes scaling up treatment (for treatment and prevention) along with a range of other prevention strategies.

Introduction

South Africa currently has the world's highest national incidence of HIV and AIDS, with 6.4 million people infected and over 340 000 incident cases annually.[1] The history of the epidemic and the political, economic and policy response has been well documented by academics.[2,3,4] In brief, the government refused from 1999 to 2004 to provide antiretroviral therapy via public facilities. The then Head of State, Thabo Mbeki, aided and abetted by Minister of Health Manto Tshabalala-Msimang, a few members of his cabinet and some of the provincial governments, questioned the causal link between the HI virus and AIDS, the effects of antiretroviral therapy (ART), and the motives of pharmaceutical companies.[5] Despite this opposition, drugs were made available by progressive provincial governments, health workers and activist organisations. Since those bleak days of AIDS denialism, and increasingly from 2005,[5] South Africa has expanded its HIV services and today has the world's largest ART programme, reaching about 2.1 million people.[1]

Like most countries in sub-Saharan Africa, South Africa tries to base its health policy on World Health Organization (WHO) recommendations. Their guidelines are based on the best available scientific evidence, but do not always speak to economic and social realities, especially regarding HIV and AIDS. The first WHO HIV treatment guidelines were released in 2002, and updated in 2006, 2010 and 2013. The latest WHO clinical recommendations promote treatment initiation for adults and adolescents > 10 years old whose CD4 count falls below 500 cells/mm^3 and immediate treatment for persons with active TB disease; hepatitis B virus (HBV) co-infection with severe chronic liver disease; pregnant and breastfeeding women with HIV; and those who are HIV-positive in a serodiscordant partnership.[6]

The South African National Department of Health adopted the 2010 recommendations to start adults on treatment at a CD4 cell count ≤ 350 cells/mm^3, and in 2015 partially adopted the new guidelines.[7] The only WHO recommendation not adopted in the new South African ART guidelines is the recommendation to initiate serodiscordant couples regardless of CD4 count; the discussion of whether or not to include this is ongoing. However, the government is hesitant to start all HIV-infected individuals on treatment irrespective of CD4 level.

Historically, WHO recommendations drive policy. In the light of the delayed and discrepant policy change in South Africa, it is worth examining the WHO recommendations and process with careful consideration of context. Whilst scientific evidence provides the foundation for the WHO's guidance on expanded treatment eligibility, scientific literature tends to be produced in a vacuum. Increasing the CD4 threshold has implications that reverberate across sectors: it affects budgets, infrastructure and human resources.

In the present article, we examine how policy has changed and existing constraints on the South African government. The policy debate has been articulated in the pages of this journal, but it is noteworthy that this is the only place where we have seen these arguments[7,8] as they are generally seen as politically incorrect and going against international norms.

We argue that policymakers must consider the possibility that a 'one-size-fits-all' approach to treatment may not be the most beneficial for patients' health and adherence to treatment, or the most cost-effective for the national budget.[7] Decisions to change the CD4 threshold in South Africa are not taken lightly, but we are not convinced that there has been sufficient consideration of the implications regarding capacity, adherence and the health of the population. We argue that the treatment agenda has been set outside the country and to unrealistic levels reflecting a dissonance between activism, science and policy.[9]

The success in translating evidence into practice depends on local context, resources, priorities and data. It is our view that the South African government's position is that it, reluctantly, has to change policy if not practice. This works for a relatively well-off country with a powerful political leadership, reasonable public health system, low (and falling) dependence on donors, and a reasonable public platform for debate. In many other settings, governments and ministries of health may be adversely affected by the decrees from Geneva or global capitals.

The present article identifies two major challenges faced in South Africa. First, modelling studies are being given too much emphasis and should not be used, in isolation, to dictate policy. Second, the issue of when to provide ART is being conflated with treatment-based prevention.

It is important, however, to understand the two pressures for treatment. First, it is seen by some as a 'right' that HIV-positive people should get the best available treatment, without considering the broader health context and the need to make choices. Second is the pressure of treatment as prevention. The seminal HPTN 052 study showed the effectiveness of ART in reducing HIV transmission in discordant heterosexual couples.[10] This study was a key driver for the WHO to revise its guidelines for ART initiation.[11] ART is recommended for HIV–positive, pregnant, breastfeeding women; all children under the age of five; people with TB or hepatitis B; and HIV–positive people with HIV-negative partners.[6]

For clarity, we include working definitions of Universal Access and Universal Test and Treat ART rollout strategies as well as treatment as prevention (TasP) (see panel). Papers[12,13,14,15] that model the cost-effectiveness of universal test and treat in South Africa, using various inputs and assumptions, yield different results. We include an overview of the findings and conclusions of these studies to show the different predicted outcomes and costs of universal test and treat.

Models are a mixed blessing – they can generate useful cost-effectiveness data if they are based on realistic assumptions and up to date biomedical data. However, achieving this often proves to be difficult, especially for long-term analyses, because even small inaccuracies or unforeseen costs may lead to very different results. Meyer-Rath and Over[15] warn about the shortcomings of ART scale-up models that do not account for the flexibility of costs over time. Their model showed that small-scale inefficiencies could lead to far higher costs in the long run.

Although prevention necessarily results from any treatment programme,[16] it is important when developing policy not to conflate TasP with universal test and treat. We critique universal test and treat in the context of governance, human resources for health, and infrastructural and fiscal constraints in South Africa. The response to the epidemic must be forward thinking, progressive and to make the most of the benefits from TasP. The logistics of implementing a universal test and treat strategy mean that this option is problematic in the short term. We recommend a health systems strengthening HIV treatment and prevention approach, which includes scaling up treatment (for treatment and prevention) along with a range of other prevention strategies.

Governance

South Africa's Constitution established three spheres of government–national, provincial, and local. Health policy is developed nationally and adapted to fit provincial needs. Healthcare funding, including that for HIV and AIDS, is allocated to provincial departments of health. This system has created and exacerbated health inequities between provinces. The political, socioeconomic and historical context in the nine provinces varies significantly, which affects service delivery (see Table 1).[17] We illustrate this point with data from the best and worst provinces: the well-resourced and well-governed Western Cape, and Limpopo which has a largely rural population, fewer human resources per capita and inefficient government.

The health profile in South Africa's nine provinces varies between these two extremes. HIV prevalence ranges from 4.75% in the Western Cape to 24.7% in KwaZulu-Natal – nearly double that in Limpopo. The number of annual new HIV infections varies by a factor of 30.[18] In this context, one-size-fits-all interventions cannot work; the gaps in health service facilities, especially staffing levels, are too great. A blanket universal test and treat strategy would be difficult to apply.

Human resources for health capacity

Human resources are a significant limitation on the ability to effectively deliver health and HIV services. Progress has been made; the number of public sector doctors increased from 7645 in 2003 to 13 614 in 2013, and the number of professional nurses registered with the South African Nursing Council from 96 715 to 129 015.[19] The number of

BOX 1: Definitions and models.

Definitions

Universal access: Treating 80% of HIV-infected individuals with CD4 count < 350 cells/μL, offering ART for discordant couples regardless of CD4 count[32]

Universal test and treat: Treating all HIV-infected individuals irrespective of CD4 count[13]

Treatment as prevention: HIV prevention methods that use ART in HIV-positive persons to decrease the chance of HIV transmission independent of CD4 count[11]

Models estimating the cost and cost-effectiveness of universal test and treat in South Africa

Granich R, Kahn JG, Bennett R, et al. Expanding ART for treatment and prevention of HIV in South Africa: Estimated cost and cost-effectiveness 2011–2050. PLoS ONE 2012; 7:e30216.

Findings:
- Model predicts universal access (at CD4 < 350 cells/μL) would reduce new HIV infections by an estimated 265 000 over 5 years and 1.4 million over 40 years.
- Universal access could reduce estimated deaths by 200 000 and save US$504 million over 5 years. Over 40 years, it could reduce deaths by 2.9 million, DALYs by 15.7 million, and costs by $3.9 billion.
- Achieving universal test and treat would result in a further decline of 3.3 million infections, 3.5 million deaths, 25.7 million DALYs, and would cost $10 million less over 40 years, compared with achieving universal access.
- Conclusion: A universal test and treat programme is an optimal implementation of TasP.

Wagner BG, Blower S. Universal access to HIV treatment versus universal 'test and treat': Transmission, drug resistance and treatment costs. PLoS ONE 2012;7:e41212.

Findings:
- Model finds that a universal test and treat strategy could eliminate HIV after 40 years and would cost $12 billion more than achieving universal access.
- Achieving universal access would prevent 4 million infections after 20 years and 11 million after 40 years.
- Conclusion: A universal access programme is a better implementation of TasP than universal test and treat.

Meyer-Rath G, Over M. HIV treatment as prevention: Modelling the cost of antiretroviral treatment—state of the art and future directions. PLoS Med. 2012;9: e1001247. http://dx.doi.org/10.1371/journal.pmed.1001247

Findings:
- Many existing models of TasP and ART scale-up do not use realistic assumptions about costs and cost structures, and therefore cannot accurately predict costs – especially in the long term.
- Conclusion: A universal test and treat programme in South Africa will cost 42% more than the cost predicted by the WHO model.

Bärnighausen T, Bloom DE, Humai S. Economics of antiretroviral treatment vs. circumcision for HIV prevention. PNAS. 2012;109:21271–21276.

Findings:
- Model finds universal access combined with high medical male circumcision coverage provides approximately the same HIV incidence reduction as universal test and treat, for $5 billion less over 2009 – 2020.
- Conclusion: Universal access and high MMC coverage is a better combination prevention strategy than universal test and treat, and better use of the benefits of TasP.

TABLE 1: Provincial inequality.

Indicator	Limpopo	Western Cape
Contribution to gross domestic product (2010)	7.2%	14.1%
Percentage of total population	10.4%	11.2%
Percentage of rural population	90%	10%
HIV prevalence (ages 15–49)	12.92%	4.75%
Number of people living with HIV	409 161	273 114
Number of private hospitals	8	34
Number of public hospitals	42	55
Number of public sector doctors per 100 000 population	20.7	34.8
Health professional vacancy rate	58.5%	29.0%

Data compiled from the public domain.

doctors and professional nurses per 100 000 people exceeds the WHO minimum.

The problem is the uneven distribution of human resources for health (HRH) across provinces; between urban and rural areas; and between the public and private sectors.[19] Only 12% of the country's doctors and 19% of its nurses work in rural facilities, serving 43.6% of the population.[20] These additional strains on an already overstretched health labour force compromise the ability of the health system to provide equal access and increased coverage of treatment and care for people with HIV.

Health facilities face other human resource problems. The real unit costs of labour have almost doubled over the last 15 years.[19] Put simply, this means that compensation has gone up more than productivity, hence more money has to be spent to achieve the same result. Attrition owing to AIDS and emigration has worsened the ratio of professional and enrolled nurses and doctors to population size in the public sector. There is an historical trend of a substantial proportion of doctors who qualified in South Africa emigrating to work abroad, and many leave the public sector to work in private practice.[20]

Responses include expanding and auditing the quality and relevance of training to meet the demand for health services, task shifting and developing strategies for ensuring an equitably distributed, long-term supply of HRH. Government's training targets may enable South Africa to reach universal ART, if the skewed distribution of HRH is addressed in conjunction with innovative, task shifting measures. Building human resource capacity to meet the needs of a universal test and treat programme will be a significant challenge in South Africa and will need to be an increasing priority as the treatment programme expands.

Infrastructural capacity

South Africa's healthcare infrastructure has improved since 1994, but regional and sectoral discrepancies persist (Table 1). Fifteen per cent of poor rural households live

more than one hour away from the closest clinic, and 20% live more than one hour away from the closest hospital.[21] The fragility of the health system was clearly illustrated in December 2012 when Médecins Sans Frontières had to step in to supply the Mthatha medical depot with ARVs for 50 000 HIV-infected patients. An estimated 5494 adults taking ARVs went at least one day without treatment owing to severe drug supply and delivery disruptions.[22,23] This service delivery crisis was a symptom of long-standing and systemic infrastructural, human resource capacity and financial mismanagement issues, which continue today.[24]

A universal test and treat programme would place strain on a fragile system, possibly particularly compromising rural healthcare where there may be fewer staff members, and also a dependence on urban-based supply chains. South Africa's public health infrastructure must be strengthened to support the demands of universal ART and the proposed National Health Insurance (NHI) plan.

Financial capacity

A good understanding of South Africa's healthcare spending shows additional constraints. Overall expenditure on public health grew from R16.4 billion in 2008/2009 to over R30 billion in 2013/2014.[25] A key component of the expanded health budget is the NHI plan, to be phased-in over 14 years. This plan aims to restructure and strengthen the public health system and improve quality of care. The NHI will require significant financial expenditure, imposing a further fiscal burden on taxpayers. NHI-related public spending increased from R119.3 million in 2008/2009 to R491.8 million in 2013/2014, and is expected to increase to R650.1 million by 2016/2017.[25]

This expense must be seen against a backdrop of rising HIV spending. Public spending on HIV and AIDS increased from R3.36 billion in 2008/2009 to R10.97 billion in 2013/2014.[25] Clinical care and treatment support from the President's Emergency Plan for AIDS Relief (PEPFAR), South Africa's largest bilateral donor, will come to an end in 2017, and the focus of this funding is already shifting from treatment to support and technical assistance. The government committed to increase its financing of the National Strategic Plan for HIV, STIs and TB (NSP) from R9.57 billion in 2012 (71% of NSP) to R15.2 billion in 2017 (88% of NSP).[26] Despite this outlay, the government is forecasting a widening funding gap; in 2013/2014 it was R2.67 billion. By 2015/2016 the projections are: resource needs of R29.86 billion, government funding of R19.8 billion, and development partners providing R5.02 billion – leaving a gap of over R5 billion.[27]

A universal test and treat strategy does not currently fit into South Africa's available financial resources and spending priorities. Although NHI expenditure will strengthen HIV services, it crowds out the feasibility of investment in a universal test and treat programme unless significant new money is allocated; this could come from re-allocation of national budgets but would require political will.

Treating the region?

There is evidence of an increasing burden on existing health resources because of 'medical tourists' in South Africa, especially from neighbouring countries. In 2012 there were 6 689 105 African or Middle Eastern visitors to South Africa, of whom 260 875 or 3.9% were defined as medical tourists. Not all are seeking public health; middle-class visitors may be coming for elective procedures or be covered by insurance; and some regional governments refer (and pay for) patients to attend specialised medical facilities and this is covered under the 1999 Southern African Development Community (SADC) Health Protocol.[28]

There is evidence to show that, as ART coverage improves across the border, so the number of people trying to access treatment in South Africa declines. In the case of Botswana, medical tourists grew from 40 000 to just over 50 000 between 2003 and 2008. Thereafter, the numbers fell to less than 20 000 in 2012. For Mozambique, the number of medical tourists grew rapidly from 8000 in 2003 to about 180 000 in 2010. With the expansion of ART coverage in Mozambique, the numbers fell and in 2012 were just less than 100 000.[28] The exception may be Zimbabweans who are primarily in South Africa for employment, and who are accessing ART. Of course, there is also evidence that South Africans are making it difficult for visitors to access treatment in the public sector, and the appalling April 2015 xenophobic attacks sent a message that foreigners are not welcome in the country for any reason. Nevertheless, providing ART to all makes public health sense.

The HIV endgame: An AIDS-free generation

Significant scientific advances coupled with political will have endowed the world with effective biomedical, behavioural and structural interventions. The conversation is shifting towards a foreseeable end to the epidemic. In the absence of a vaccine or cure, navigating the 'endgame' will be costly and ineffective if plans are designed without context and foresight.

The HIV epidemic in South Africa is driven by deeply entrenched social and structural factors including gender inequality, poverty and migration.[29,30] Even if the structural inadequacies of the healthcare system are addressed, a one-size-fits-all approach to HIV treatment and prevention will not work. The complexity of the epidemic necessitates a diverse range of interventions which are effective within the South African epidemiological and resource context.

Too often, health policy recommendations are prescribed with good intention but based primarily on modelled outcomes or international 'norms', with little attention paid to local context. Successful programmes that will make a real impact hinge on much more. Fiscal, infrastructural and human resources for health, political and sociocultural

factors drive and shape the epidemic and should inform its response.

Given these constraints, it is clear that a universal test and treat strategy, and a combination prevention and treatment approach that includes a strengthening of the health system, are mutually exclusive in the short term. A premature move to a one-size-fits-all policy will undermine the importance of other interventions that work. Rolling out a comprehensive treatment and prevention programme for HIV based on evidence for efficacy, cost-effectiveness and country-specific context must become a priority.

Strengthening the health system and increasing capacity for HIV treatment must remain high on the agenda, but a universal test and treat strategy cannot be pursued exclusively or to the detriment of other interventions that work, as we have shown elsewhere that there is the potential for a virtuous cycle to begin but it must be properly planned.[31]

In addition to medical interventions, there must be increased emphasis on gender relations and empowering women, especially young women. There needs to be social change, and it may be that requiring some form of payback for treatment – not financial but perhaps in terms of volunteerism – will contribute to this.

Conclusion

South Africa is achieving significant progress in the form of dramatically lower rates of mother-to-child-transmission, falling new infections in young adults, decreasing HIV-related mortality, and expanding ART coverage. We cannot risk derailing this momentum with premature policy decisions. Universal access should be the primary goal and, in this context, treatment will necessarily lead to prevention.

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Authors' contributions

A.W. (Balsillie School of International Affairs) developed an initial conceptual framework for this article. A.W. and J.C. (Harvard School of Public Health) and M.S. (University of KwaZulu-Natal) participated in conceptual development, literature search, writing and finalising of the article.

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Choice or no choice? The need for better branded public sector condoms in South Africa

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Condoms are one of the cornerstones to any response to the HIV epidemic. However, targeted marketing strategies that make condoms more attractive to people at high risk of infection are often overlooked. The South African National Department of Health has recently purchased more attractive condoms to distribute in higher-education settings free of charge, targeting at-risk youth including young women. The authors applaud this move but note the importance of expanding better branded condoms to young people elsewhere – for example, via youth clinics and in high schools. Exploratory, routine data from Médecins Sans Frontières in Khayelitsha are presented, showing the popularity of alternatives to the government's 'Choice' brand.

Introduction

Background

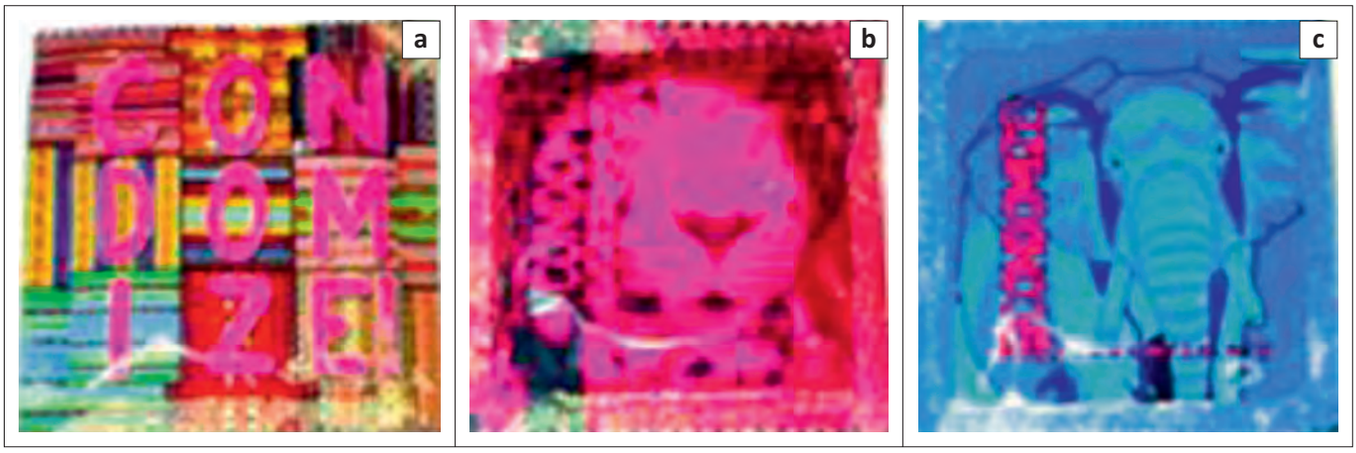
Condom distribution, promotion and social marketing represent a highly cost-effective HIV prevention strategy, given the low cost of condoms and their strong prevention efficacy. Self-reported condom usage is around 80% effective at preventing HIV for heterosexual couples, 70% effective for men who have sex with men (MSM), and much higher under laboratory conditions.[1] Condoms are advisable even for seroconcordant couples, to help prevent other sexually transmitted infections and unwanted pregnancy.[2] Lubricant is also advised for use with condoms. According to the World Health Organization, water-based lubricants are associated with either a decrease or no change in the rate of condom slippage or breakage. Female condoms are also considered safe.[3]

The latest Human Sciences Research Council behaviour survey,[4] however, found that self-reported condom use at time of last sex significantly declined in South Africa, from 45.1% (95% confidence interval [CI] 43.3–47.0) of adults in 2008, to 36.2% (95% CI 34.5–37.9) in 2012. This decline is in spite of increases in the total number of male condoms distributed by the public sector, over the same period, from 283 000 [5] to 501 000.[6] Female condoms still represent a small fraction of total condoms distributed.

Importantly, greater distribution of condoms does not ensure their increased and proper use, especially if divorced from a well-considered, segmented social marketing campaign. Such a campaign would ideally: (1) research the needs and preferences of high risk and general populations, (2) deliver heterogeneous products branded differently for different target groups and (3) provide public messaging promoting healthy behaviour appealing to the target audience.[7,8]

The South African government's free 'Choice' brand condoms, meanwhile, do not target any specific population or form part of any official marketing strategy. The main condom brands available at present are Choice (80% of the market) followed by Population Service International's subsidised 'Trust' and 'Lovers+'[9] brands.

Partly in response to such issues, Minister of Health Dr Motsoaledi announced in April 2014 that free, colourful and flavoured condoms would be provided in South African tertiary education institutions. The minister noted that this was to combat 'condom fatigue', referring to a lack of enthusiasm amongst young people for Choice.[10] Since this announcement, the National Department of Health awarded a tender for 50 million rebranded condoms for universities and further education and training colleges and has begun distributing them. However, by the age of 21, 50% of young people are not employed or enrolled in any form of education (20% at age 18) and thus do not benefit equally.[11] School age adolescents, particularly young women, are also vulnerable to HIV infection. A recent development is that the Department of Basic Education has drafted a policy to provide condoms in schools but faces backlash from school boards and religious groups who see this as encouraging sex,[12,13] rather than safe sex, despite a lack of evidence supporting this claim.[14]



Source: Authors' own photographs

FIGURE 1: Photo's of (a) Condomize regular, (b) flavoured and (c) extra-large.

The present editorial calls for the further expansion of attractively branded and marketed condoms via the public sector, especially to meet the needs of young, marginalised people, many of whom are not enrolled in tertiary education. Exploratory, routine data are presented from Médecins Sans Frontières (MSF) in Khayelitsha that adds weight to these arguments.

Condoms in Khayelitsha

Khayelitsha township has one of the most successful condom distribution programmes in the country, with approximately 1 million Choice condoms distributed per month by the Treatment Action Campaign to a population of 391 749.[15] With permission from the City of Cape Town, MSF conducted a trial on the popularity of alternatives to Choice in a youth clinic in Khayelitsha, using condoms donated by the organization 'Condomize'. Four condom types (Choice, Condomize regular with bright packaging, Condomize strawberry flavoured, and Condomize extra-large [Figure 1]) were placed in identical glass containers in the reception area of Site C Youth Clinic. Condom containers were refilled under the supervision of MSF's Patient Support team. Placing the condoms in the waiting area of the clinic allowed youth access with minimal interference from health workers. Clients could take as many or as few individually packed condoms as desired.

As shown in Figure 2, flavoured condoms proved the most popular, followed closely by extra-large condoms. Interestingly, even the regular condoms in bright packaging were far more popular than Choice, although their popularity seemed to decline slightly over time. Only 6% of condoms taken from the youth clinic were Choice condoms.

In discussions with youths about the new condoms at the clinic, the overall feeling was one of satisfaction. They preferred the colourful packaging, smell, fit and feel which some described as 'lighter'. Further remarks were 'Choice condoms are too thick and oily', 'we experienced pain due to the poor fit', and 'the old ones smelled awful and didn't fit well'. Some young women indicated that their boyfriends would sometimes buy condoms rather than use the freely available Choice condoms. This anecdotal evidence implies higher acceptability of alternative brands to Choice, at least in the short term.

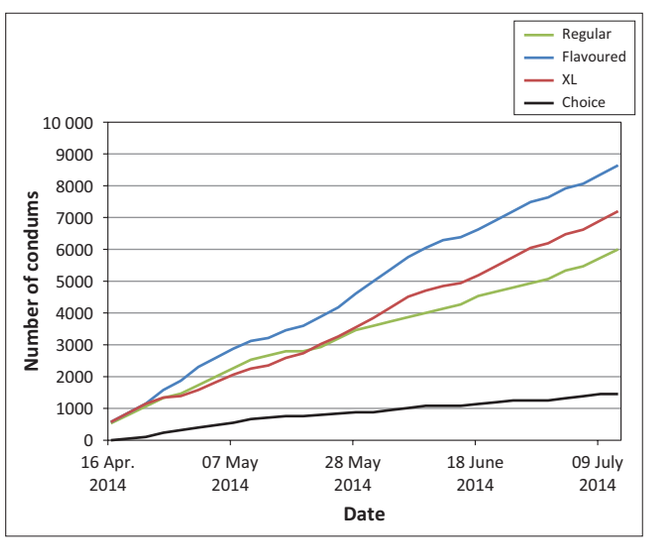


FIGURE 2: Cumulative total of condoms taken in Site C Youth Clinic: moving average.

Recommendations

Although the experience of Khayelitsha may not be generalisable to elsewhere in South Africa, changes to packaging and marketing of government condoms may nevertheless prove popular with South African youth. Repackaged, flavoured and extra-large condoms, in particular, appear to show some promise. The South African government should be praised for their introduction of such condoms to tertiary education institutions but must ensure wider distribution and reconsider their overall marketing strategy. MSF has seen high demand in its projects for alternative condoms, along with family planning, amongst school age adolescents. In terms of introducing condoms in schools and other outlets such as youth clinics, it is time to leave behind moralistic arguments about sex and focus

on addressing the public health crisis at hand. The costs of rebranding and marketing condoms should be weighed against the potential benefits of increased popularity and use.

In general, more research is needed to explore condom market dynamics in South Africa and elsewhere, including focusing on differences in design preference by gender, age and HIV risk. It is also important to identify whether alternative designs are preferred in the long term or whether there is a need for regular design changes to maintain novelty. Such research should inform a national condom marketing strategy that maximises the impact of free government condoms which might no longer capture the imagination of their intended users. Young people, but also sex workers, MSM and prisoners, may all require their own strategies, along with a new approach for the general population. Lubricant should also be considered for distribution along with condoms, especially for MSM, while there is also much scope for social marketing messages that promote correct and consistent condom use. It is unknown at present how many people who collect the various brands of condoms will actually use them. This point may be particularly important to consider in a setting where intimate partner violence and the inability of women to negotiate condom access are linked to HIV infection.[16]

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Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

J.A. (MSF) oversaw the project, analysed the data, and wrote most of the manuscript. R.H. (MSF) oversaw collection of routine data including patient feedback, and contributed significantly to the manuscript as well as project conception.

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Corrigendum: How ready are our health systems to implement prevention of mother to child transmission Option B+?

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The authors apologise for two oversights in Box 1: One was due to non-deletion of a bullet point; the other was an omission.

The June update of the new January 2015 South African (SA) PMTCT guideline states that infants should no longer be tested for HIV infection at 6 weeks.

Box 1 illustrates the PCR infant HIV testing time points. Six weeks testing has been removed from the revised Box (please see below).

Additionally, information about HIV infant test confirmation was omitted. This information has now been added as the last row in the revised Box (please see below). According to the new January 2015 SA PMTCT guideline a second infant HIV PCR test is used to confirm infant HIV infection following a first positive HIV PCR test. The new January 2015 SA PMTCT guideline no longer recommends infant viral load as a confirmatory test.

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Note: Doi of original article: http://dx.doi.org/10.4102/sajhivmed.v16i1.386

Please see below the revised Box.

BOX 1: Key changes between the 2013 and January 2015 South Africa prevention of mother to child transmission guidelines.

2013 South African PMTCT guideline	New January 2015 South African PMTCT guideline
No mention of HIV testing amongst children.	Children aged ≥ 12 years may self-consent to an HIV test if they are of sufficient maturity to understand the benefits, risk and social implications.
Re-testing of HIV-negative mothers or mothers of unknown HIV status: should be tested for HIV at 6 weeks, 3 months, 9 months and 1 year postpartum, particularly if they are breast feeding.	**Re-testing of HIV-negative mothers:** • 3-monthly through pregnancy • at labour/delivery • at 6-week infant immunisation visit (to identify newly exposed babies who need HIV testing) • 12-weekly throughout breastfeeding till 24 months if breastfeeding continued.
CD4 cell count ≤ 350 cells/μL used to guide eligibility for ART: amongst pregnant women without stage 3/4 disease or amongst non-pregnant HIV-positive patients with stage 3/4 disease. CD4 cell count used for monitoring of ART at 12 months post initiation.	**CD4 cell count not needed to determine ART eligibility amongst pregnant and lactating women:** Done for newly diagnosed patients at initiation to assess the need for: • ART prioritisation (CD4 < 200 cells/μL) • cotrimoxazole (CD4 < 200 cells/μL) • tests to diagnose Cryptococcus infection (CD4 < 100 cells/μL). (Amongst the non-pregnant HIV-positive population, the threshold CD4 cell count for ART has been increased to ≤ 500 cells μL.)
Initiate lifelong ART: • in all pregnant women with CD4 cell count ≤ 350 or stage 3/4 disease • all HIV-positive children < 5 years old – immediately for infants and within 2 weeks for children between 1 and 5 years • TB/HIV co-infected pregnant women. **Initiate 'feeding-dependent' ART** until 1 week after complete cessation of breastfeeding in women with CD4 > 350 without stage 3/4 disease.	**Initiate lifelong ART regardless of CD4 cell count for:** • HIV-positive pregnant, breastfeeding women, or women within 1 year post partum for life • HIV-positive women who attend for choice of termination of pregnancy (CTOP) (included in the 2015 PMTCT training package) • HIV-positive children < 5 years (discussed in more detail in the paediatric guidelines) • HIV/TB or HIV/hepatitis B co-infected women. **Duration of ART not dependent on feeding practice.**
Efavirenz (EFV) not used in first trimester of pregnancy amongst women on ART.	**Efavirenz (EFV)** used in first trimester of pregnancy amongst women on ART.
Viral load monitoring at first ANC if ART initiated before pregnancy and at 6 and 12 months post initiation.	**Viral load monitoring** at first ANC if ART initiated before pregnancy or within 3 months if ART initiated antenatally or during breastfeeding. Thereafter 6-monthly viral load monitoring.
Daily infant nevirapine for 6 weeks from as soon as possible post delivery.	As for 2013 plus **infant nevirapine could continue for 12 weeks if** maternal ART adherence has been suboptimal or maternal viral load > 1000 copies/μL or mother is newly diagnosed during breastfeeding. For newly diagnosed HIV-positive breastfeeding mothers, infant AZT and nevirapine should be initiated immediately. If infant PCR is negative, infant AZT can stop; but infant nevirapine should continue for 12 weeks. In HIV exposed infants < 18 months, infant nevirapine prophylaxis can be initiated if infant HIV rapid test result is not available or is positive, whilst awaiting infant's PCR result.
Infant PCR testing to be conducted at: • birth in symptomatic infants failing to thrive (includes low birth weight, haematological abnormality such as anaemia or thrombocytopaenia, congenital pneumonia, hepatosplenomegaly, extensive oral candidiasis, significant lymphadenopathy, any opportunistic infections) • 6 weeks in all HIV-exposed infants • 6 weeks post cessation of breastfeeding if aged < 18 months and rapid HIV test if aged ≥ 18 months • rapid HIV testing at 18 months. **Abandoned infants** should receive NVP < 72 hours post delivery and continued until HIV-exposure status has been determined. If the HIV rapid/ELISA test is positive, continue nevirapine until 6 weeks of age and do a PCR at 6 weeks. If the HIV rapid test result cannot be determined within 2 hours of encountering an abandoned baby, a stat dose of NVP is warranted.	**Infant PCR testing to be conducted at:** • birth, or as soon as possible after birth amongst all HIV exposed infants • 10 weeks in infants not testing HIV positive at birth • 16 weeks in infants receiving 12 weeks nevirapine • 6 weeks post cessation of breastfeeding if aged < 18 months and rapid HIV tests if aged ≥ 18 months • rapid HIV testing at 18 months for all HIV-exposed infants, for infants born to mothers of unknown HIV status, and for infants breastfed by a woman of unknown HIV status. For infants < 18 months, HIV rapid testing can be conducted to determine infant HIV-exposure. Abandoned infants – protocol as for 2013 guidelines.
Infant viral load: • used to confirm infant HIV infection following a first positive HIV PCR test	**Second infant HIV PCR test:** • used to confirm infant HIV infection following the first positive HIV PCR test, infant viral load not used.

How ready are our health systems to implement prevention of mother to child transmission Option B+?

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In January 2015, the South African National Department of Health released new consolidated guidelines for the prevention of mother to child transmission (PMTCT) of HIV, in line with the World Health Organization's (WHO) PMTCT Option B+. Implementing these guidelines should make it possible to eliminate mother to child transmission (MTCT) of HIV and improve long-term maternal and infant outcomes. The present article summarises the key recommendations of the 2015 guidelines and highlights current gaps that hinder optimal implementation; these include late antenatal booking (as a result of poor staff attitudes towards 'early bookers' and foreigners, unsuitable clinic hours, lack of transport to facilities, quota systems being applied to antenatal clients and clinic staff shortages); poor compliance with rapid HIV testing protocols; weak referral systems with inadequate follow-up; inadequate numbers of laboratory staff to handle HIV-related monitoring procedures and return of results to the correct facility; and inadequate supply chain management, leading to interrupted supplies of antiretroviral drugs. Additionally, recommendations are proposed on how to address these gaps. There is a need to evaluate the implementation of the 2015 guidelines and proactively communicate with ground-level implementers to identify operational bottlenecks, test solutions to these bottlenecks, and develop realistic implementation plans.

Introduction

Context and summary of 2015 prevention of mother to child transmission guidelines

South Africa has the highest HIV incidence rates globally, and is the largest provider of antiretroviral therapy in the world.[1,2] In January 2015, the South African National Department of Health (NDoH) released new national consolidated guidelines, including an approach akin to World Health Organization (WHO) Option B+ for the prevention of mother to child transmission (PMTCT) of HIV.[3] These guidelines harmonise triple antiretroviral treatment (ART) regimens for infants and young children, adolescents, pregnant and breastfeeding women, and adults to facilitate continuity of care. The guidelines stipulate lifelong ART for all pregnant and breastfeeding women and HIV-positive infants regardless of their CD4 cell count.[3] Box 1 summarises the main differences between the 2015[3] and 2013[4] PMTCT guidelines. Specific algorithms have been developed for women with comorbidities (e.g. active psychiatric illness, renal dysfunction and/or anaemia) and these remain unchanged compared with the 2013 South African guidelines.[3,4] The 2015 guidelines highlight the need to improve access to testing and treatment in general, to achieve the 90/90/90 target (90% coverage for HIV testing, 90% coverage for ART uptake amongst HIV-positive patients, and viral suppression of 90% of patients on ART) and to prioritise HIV prevention and treatment amongst adolescents.[3] Despite the complexity of the new policy, its 'treatment as prevention' approach amongst pregnant and breastfeeding women could move South Africa closer to achieving the fourth and fifth millennium development goals and the post-2015 sustainable development goals.

Health systems' readiness to implement the new guidelines

System gaps that may hinder successful implementation of the 2015 South African prevention of mother to child transmission guidelines

In our opinion, there are five main requirements for successful implementation of the 2015 PMTCT guidelines: (1) early presentation at the health facility to access care (i.e. early antenatal booking), (2) universal antenatal HIV testing based on high-quality standardised operating

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No mention of HIV testing amongst children.	Children aged ≥ 12 years may self-consent to an HIV test if they are of sufficient maturity to understand the benefits, risk and social implications.
Re-testing of HIV-negative mothers or mothers of unknown HIV status: should be tested for HIV at 6 weeks, 3 months, 9 months and 1 year postpartum, particularly if they are breast feeding.	**Re-testing of HIV-negative mothers:** • 3-monthly through pregnancy • at labour/delivery • at 6-week infant immunisation visit (to identify newly exposed babies who need HIV testing) • 12-weekly throughout breastfeeding till 24 months if breastfeeding continued.
CD4 cell count ≤ 350 cells/μL used to guide eligibility for ART amongst pregnant women without stage 3/4 disease or amongst non-pregnant HIV-positive patients with stage 3/4 disease. CD4 cell count used for monitoring of ART at 12 months post initiation.	**CD4 cell count not needed to determine ART eligibility amongst pregnant and lactating women:** Done for newly diagnosed patients at initiation to assess the need for: • ART prioritisation (CD4 < 200 cells/μL) • cotrimoxazole (CD4 < 200 cells/μL) • tests to diagnose Cryptococcus infection (CD4 < 100 cells/μL). (Amongst the non-pregnant HIV-positive population, the threshold CD4 cell count for ART has been increased to ≤ 500 cells μL.)
Initiate lifelong ART: • in all pregnant women with CD4 cell count ≤ 350 or stage 3/4 disease • all HIV-positive children < 5 years old – immediately for infants and within 2 weeks for children between 1 and 5 years • TB/HIV co-infected pregnant women. **Initiate 'feeding-dependent' ART** until 1 week after complete cessation of breastfeeding in women with CD4 > 350 without stage 3/4 disease.	**Initiate lifelong ART regardless of CD4 cell count for:** • HIV-positive pregnant, breastfeeding women, or women within 1 year post partum for life • HIV-positive women who attend for choice of termination of pregnancy (CTOP) (included in the 2015 PMTCT training package) • HIV-positive children < 5 years (discussed in more detail in the paediatric guidelines) • HIV/TB or HIV/hepatitis B co-infected women. **Duration of ART not dependent on feeding practice.**
Efavirenz (EFV) not used in first trimester of pregnancy amongst women on ART.	Efavirenz (EFV) used in first trimester of pregnancy amongst women on ART.
Viral load monitoring at first ANC if ART initiated before pregnancy and at 6 and 12 months post initiation.	**Viral load monitoring** at first ANC if ART initiated before pregnancy or within 3 months if ART initiated antenatally or during breastfeeding. Thereafter 6-monthly viral load monitoring.
Daily infant nevirapine for 6 weeks from as soon as possible post delivery.	As for 2013 plus **infant nevirapine could continue for 12 weeks if** maternal ART adherence has been suboptimal or maternal viral load > 1000 copies/mL or mother is newly diagnosed during breastfeeding. For newly diagnosed HIV-positive breastfeeding mothers, infant AZT and nevirapine should be initiated immediately. If infant PCR is negative, infant AZT can stop; but infant nevirapine should continue for 12 weeks. In HIV exposed infants < 18 months, infant nevirapine prophylaxis can be initiated if infant HIV rapid test result is not available or is positive, whilst awaiting infant's PCR result.
Infant PCR testing to be conducted at: • birth in symptomatic infants failing to thrive (includes low birth weight, haematological abnormality such as anaemia or thrombocytopaenia, congenital pneumonia, hepatosplenomegaly, extensive oral candidiasis, significant lymphadenopathy, any opportunistic infections) • 6 weeks in all HIV-exposed infants • 6 weeks post cessation of breastfeeding if aged < 18 months and rapid HIV test if aged ≥ 18 months • rapid HIV testing at 18 months. **Abandoned infants** should receive NVP < 72 hours post delivery and continued until HIV-exposure status has been determined. If the HIV rapid/ELISA test is positive, continue nevirapine until 6 weeks of age and do a PCR at 6 weeks. If the HIV rapid test result cannot be determined within 2 hours of encountering an abandoned baby, a stat dose of NVP is warranted.	**Infant PCR testing to be conducted at:** • birth, or as soon as possible after birth amongst all HIV exposed infants • 6 weeks in all HIV-exposed infants not testing positive at birth • 10 weeks in infants not testing HIV positive at birth • 16 weeks in infants receiving 12 weeks nevirapine • 6 weeks post cessation of breastfeeding if aged < 18 months and rapid HIV tests if aged ≥ 18 months • rapid HIV testing at 18 months for all HIV-exposed infants, for infants born to mothers of unknown HIV status, and for infants breastfed by a woman of unknown HIV status. For infants < 18 months, HIV rapid testing can be conducted to determine infant HIV-exposure. Abandoned infants – protocol as for 2013 guidelines.

Source: South African prevention of mother to child transmission Guidelines 2013 (South African antiretroviral treatment guidelines 2013. PMTCT guidelines: Revised March 2013 [cited 2015 Aug 27]. Available from http://www.sahivsoc.org/upload/documents/2013%20ART%20Guidelines-Short%20Combined%20FINAL%20draft%20guidelines%2014%20March%202013.pdf) and 2015 (South African National Department of Health. 2014 [cited 2015 Mar 02]. National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults. Available from http://www.sahivsoc.org/upload/documents/HIV%20guidelines%20_Jan%202015.pdf)
PMTCT, prevention of mother to child transmission; ART, antiretroviral treatment; ANC, antenatal care; PCR, polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

procedures, with repeat testing of HIV-negative women, (3) immediate referral into appropriate care and retention in care, (4) adequate coverage of appropriate laboratory systems and (5) uninterrupted drug supplies. These require appropriate actions within the health system and amongst sufficiently informed and empowered individual mother-infant pairs. Box 2 presents a summary of the main health system and community gaps in optimal implementation of the 2015 PMTCT guidelines; these are explained in more detail below.

Late antenatal booking

Since 2001, South Africa has improved access to antenatal care, HIV testing and ART provision for pregnant women. Currently, antenatal care uptake is over 95%; HIV testing is offered by over 95% of health facilities, and more than 87% of HIV-positive pregnant women receive some form of ART.[3,5] However, the District Health Information System shows that in 2011/2012 only 40.2% (range 33.6% in Eastern Cape to 56.2% in Western Cape) of pregnant women had their first antenatal booking visit before 20 weeks' gestation, highlighting the first key bottleneck to successful guideline implementation.[6] A study in North-West Province identified a variety of reasons for late booking, including late pregnancy disclosure amongst teenagers, fear of HIV testing, non-caring nurse attitudes, cultural beliefs that dissuade early revealing of pregnancy, lack of transport and unsuitable clinic opening hours.[6] These findings were corroborated by research in Johannesburg which showed that 54% of pregnant women sought antenatal care later than 5 months' gestation.[7] Solarin and Black found that almost half of new mothers interviewed reported that their first antenatal booking was not accepted by health facilities for various reasons including (1) they needed 'to make a booking appointment', (2) they did not have a South African identity document and (3) clinics had reached their quota for the day.[7] These obstacles delay first antenatal booking and thus HIV screening, ART initiation and detection of treatment failure amongst pregnant women on ART as recommended by the 2015 South African PMTCT guidelines.[3]

BOX 2: Summary of impediments to optimal prevention of mother to child transmission guideline implementation.

1. Late antenatal booking: • poor staff attitudes towards 'early bookers' and foreigners • unsuitable clinic hours • lack of transport to facilities • quota systems applied to antenatal clients • clinic staff shortages and insufficient capacity.
2. Poor quality HIV testing: • inadequate quality control • poor supervision • incomplete handling of discordant results • poor data quality/documentation.
3. Linkage and retention in care: • lack of service integration between (1) HIV-related care and routine maternal and child health services and (2) antenatal and postnatal services • poor information systems and documentation hinder tracking those lost to follow-up • weak referral systems.
4. Laboratory capacity: • insufficient staff training • limited staff capacity to handle increased demand as monitoring and numbers increase • challenges with quickly communicating positive infant PCR results (e.g. facility Internet access and working telephones).
5. Interrupted drug supplies: • inadequate supply chain management • corruption.
6. Community level: • late antenatal booking: > 50% book after 5 months' gestation • fear of HIV diagnosis • stigma associated with HIV infection and with teenage pregnancy • lack of demand for antiretroviral services owing to lack of awareness of benefits of treatment.

PCR, polymerase chain reaction.

Late HIV testing and poor quality HIV testing

There are grave concerns about quality control of HIV counselling and testing (HCT) at facilities, as shown by a study conducted in 455 sites (primary health care clinics, community healthcare centres and hospital gateway clinics) in Limpopo Province (Adrian Puren, personal communication, 11 March 2015). Poor quality control increases the risk of false-positive and -negative HIV results within the PMTCT programme. Concerns identified included inadequate training, frequent rotation of staff, lack of supervision and on-site quality control, incorrect storage of control samples, poor adherence to standard operating procedures (SOP) and improper stock control (Adrian Puren, personal communication, 11 March 2015). Anecdotal information gathered during healthcare provider (HCP) PMTCT guideline training found that HCPs are not waiting the required time before reading the HIV result, increasing the risk of false-negatives.

Late referral into care and poor retention in care

Appropriate, timely referrals and linkages to care are needed antenatally and post delivery to facilitate uptake of and retention in care. Over 90% of facilities assessed during a national South African Medical Research Council (SAMRC) review conducted in 2010 had a referral system for infant and adult ART clients.[5] Similarly, an Eastern Cape study found that 100% of facilities reported appropriate referral mechanisms for HIV-positive women.[8] However, in the MRC review, 38% of facilities did not make appointments for their patients at referral centres, and only 50% of clinics followed up whether clients engaged with care at the referral site.[5] From our research and clinical experience, postnatal loss to follow-up is particularly high in South Africa. Poor information systems and documentation contribute to difficulties with tracing such patients. In Malawi, loss to follow-up was five times higher for women who started ART during pregnancy and two times higher for women who started ART whilst breastfeeding than for women who started ART with WHO stage 3/4 disease or CD4 cell count ≤ 350 cells/μL.[9] These data highlight the risk of poor retention in care postnatally and emphasise the need for robust referral systems, integrated services and effective tracking mechanisms to retain, or re-engage, women in ART care post delivery.

Limited laboratory capacity

Laboratory capacity is needed for (1) viral load monitoring to identify poor adherence and treatment failure – a vitally important step in PMTCT programme success, (2) CD4 cell count to identify women who need cryptococcal antigen screening or cotrimoxazole prophylaxis, (3) routine antenatal bloods for ART toxicity monitoring and (4) repeated polymerase chain reaction (PCR) testing of HIV-exposed infants from birth (for symptomatic infants) to 18 months;[3] laboratory capacity is accordingly a critical component of the PMTCT programme, and is key to timely referral into appropriate care. Previous challenges to implementing laboratory-based HIV tests in South Africa included difficulties processing large numbers of HIV-related specimens, high staff turn-over, and insufficient training in PCR techniques and CD4 measurements.[10] Consequently, experienced staff carry the burden of training new staff[10] and processing high quantities of specimens.

Interrupted drug supplies

By mid-2014, an estimated 2.6 million people were on ART in South Africa.[3] This number will further increase following the 2015 guideline implementation, creating additional demand for ART stock. Sustaining such ART programme expansion will necessitate more efficient, effective supply chain management and increased human resources. Yet the healthcare system remains plagued by frequent HIV medicines stock-outs and clinic staff shortages. Inadequate supply chain management and 'corruption' contribute to avoidable stock-out-related treatment interruptions,[11] resulting in regimen modification at best or, at worst, drug discontinuation.[12] Considering the complexity of the new guidelines in part reflects South Africa's mature HIV epidemic, including increasing rates of highly experienced ART patients with treatment failure and drug resistance. The effects of recurrent stock-outs on adherence, viral loads and drug resistance should not be underestimated.

Recommendations

In light of the gaps identified above, we make several recommendations for optimal 2015 guideline implementation (Box 3).

BOX 3: Recommendations for optimal 2015 guideline implementation.

Within the health system:

1. Reduce the occurrence of late ANC booking:
- provide standardised training regarding benefits of early booking for all women, regardless of nationality
- provide adolescent-friendly sexual and reproductive health services
- review clinic opening times and conduct local situational assessments to match the demand and supply of services
- review clinic accessibility (physically and opening hours) and public transport routes
- provision of more or more frequent mobile facilities/services
- review use of quota systems in antenatal clinics.

2. Improve adherence to standard procedures for HIV testing:
- improve the competence and expertise of all levels of staff conducting HCT
- establish supervision and monitoring systems for rapid HIV testing quality assurance.

3. Strengthen linkages retention in care by establishing tracking systems:
- strengthen service integration
- establish patient tracking systems, utilising ward-based outreach teams, unique patient identifiers and/or e-systems such as MomConnect
- improve referral systems with pre-booking and feedback, using a unique identifier and engaging District Specialist Teams.

4. Increase laboratory capacity and reduce laboratory transport/feedback systems to reduce turnaround time:
- increase staffing levels and training
- improve communication (working telephones, computers, Internet access) to expedite results access.

5. Improve stock monitoring mechanisms and reduce drug stock-outs:
- ensure that all facilities are trained in stock management, re-ordering procedures and lag times to avoid ART stock-outs
- increase capacity at facility level to use DHIS data to identify gaps and address them through quality improvement processes
- facility managers and district coordinators to be held accountable where the PMTCT programme and maternal and child health outcomes are suboptimal.

Community level:
1. Improve awareness on importance of uptake of early antenatal care
2. Eliminate prejudice and discrimination by healthcare workers against people who test HIV-positive, and educate communities about the importance of knowing one's HIV status
3. Advocate at community levels to reduce fear and stigma around HIV and teenage/unwanted pregnancy and educate HIV-infected women regarding the treatment they should be able to access/demand
4. Increase awareness about PMTCT/antenatal and postnatal care at community level

ANC, antenatal care; HCT, HIV counselling and testing; ART, antiretroviral treatment; DHIS, District Health Information System; PMTCT, prevention of mother to child transmission.

Conclusion

The January 2015 PMTCT guideline recommendations are of a very high standard and based on the best intentions to improve the management of both HIV-positive and HIV-negative women. By implementing these guidelines, it should be possible to eliminate MTCT, improve maternal and infant outcomes, and ensure that women remain virologically suppressed and engaged in lifelong ART care. However, the implementation challenges might have been underestimated. Evaluation of the implementation process is needed to identify key bottlenecks and develop realistic implementation plans. A proactive process of communicating with ground-level implementers is needed to understand their challenges and to address these through well recognised, quality improvement processes.

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Competing interests

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Authors' contributions

P.N. (South African Medical Research Council) conceptualised and designed, drafted, wrote and finalised the article. N.D. (Wits Reproductive Health and HIV Institute) designed, contributed to and assisted with finalisation of the article. G.S. (National Institute for Communicable Diseases); S.B. (The United Nations Children's Fund) and V.R. (South African Medical Research Council), N.K.N. (South African Medical Research Council), T.R. (South African Medical Research Council), N.N. (South African Medical Research Council), V.M. (South African Medical Research Council), Y.S. (South African Medical Research Council) and D.N. (South African Medical Research Council) reviewed, commented on and approved the final version of the article. A.E.G. (South African Medical Research Council) conceptualised and designed, contributed to and assisted with finalisation of the article.

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Antiretroviral therapy during the neonatal period

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Rationale for initiating combination antiretroviral therapy during the neonatal period

Initiation of combination antiretroviral therapy (cART) at 6–9 weeks of age has been shown to reduce early infant mortality by 76% and HIV progression by 75% compared with cART deferred until clinical or CD4 criteria were met.[1] In the landmark Children with HIV Early Antiretroviral Therapy (CHER) trial, although the median age of starting cART in the early treatment arm was 7.4 weeks, one-third (10/30) of the overall mortality in the trial occurred in the early treatment arm.[1] In another study, 62% of 403 infants who initiated cART at median 8.4 weeks of age already had advanced HIV disease (CD4 < 25% or < 1500 cells/mm^3 or World Health Organization [WHO] Stage 3 or 4) at initiation.[2]

The above, with other findings describing the benefits of early cART, raise the question of whether even earlier cART initiation – immediately after birth or during the neonatal period – could further reduce morbidity and mortality rates, and confer greater benefits, particularly for infants who acquired HIV infection during the pregnancy and are consequently at highest risk of rapid disease progression.[3,4,5,6,7] The potential of early neonatal cART initiation in modifying the longer-term trajectory of HIV infection in an individual patient and need for lifelong cART is an area of intensive research.

The recent shift to targeted HIV polymerase chain reaction (PCR) testing at birth rather than only at 6 weeks of age allows for the earliest detection of neonates in whom intrauterine transmission of HIV infection has occurred and has opened the door to neonatal cART initiation. Availability of validated point-of-care HIV PCR testing will further increase the drive to initiate cART during the early neonatal period.

Safety and efficacy data on neonatal cART is currently very limited. There is even less experience with treating premature and low birth weight neonates with cART. Uncertainties relate to pharmacokinetics (PK), dosing, safety and choice of cART regimen. In addition, timing of the transition from prophylactic antiretroviral (ARV) regimens aimed at prevention of transmission to cART regimens aimed at long-term treatment requires further investigation.

Outline of pharmacokinetics, dosing and safety of antiretrovirals during the neonatal period

Nucleoside reverse transcriptase inhibitors

Abacavir

Despite the South African (SA) ARV treatment guidelines recommendation that Abacavir (ABC) should be used in all first-line cART regimens for children, there are insufficient safety data to recommend the use of ABC in infants < 3 months old.[8] There is also a lack of PK studies to guide dosing in this age group.[9]

Lamivudine

The SA ARV drug dosing chart (2013) recommends a Lamivudine (3TC) dose of 2 mL (20 mg) twice daily from 3 kg – 4.9 kg but advises expert consultation for neonates and infants weighing < 3 kg.[10] Although 3TC is not Food and Drug Administration (FDA) approved for use in infants < 3 months of age, it has been used and studied in neonates. The recommended dose for neonates (< 4 weeks of age) for either prevention of transmission or treatment is 2 mg/kg/dose twice daily. The recommended paediatric dose (age ≥ 4 weeks) is 4 mg/kg/dose twice daily to a maximum dose of 150 mg twice daily.[11] These recommendations are based on population PK analyses in infants < 6 weeks of age.[12,13] The higher WHO dosage recommendations (3 mL [30 mg] twice daily from 3 kg – 4.9 kg) result in increased plasma concentrations compared with the 2 mg/kg/dose recommendations and should be avoided in neonates.[14,15] There are no published data to guide dosing in premature neonates.

Lamivudine has generally been associated with minimal toxicity in older children and adults but studies suggest that haematological toxicity (anaemia, neutropaenia, thrombocytopaenia) increases when combined zidovudine (AZT)/3TC neonatal prophylaxis is used when compared with AZT alone, with increasing numbers of patients requiring treatment discontinuation or blood transfusions.[16] Lamivudine may be given without regard to food, and the oral solution may be stored at room temperature. Excretion is via the renal route, and dose adjustment is required in renal insufficiency.[11]

Stavudine

The recommended dose for neonates from birth to 13 days of age is 0.5 mg/kg/dose twice daily and, from 14 days onwards, 1 mg/kg/dose twice daily to a maximum of 30 mg twice daily.[11,17] Dose reduction is recommended if there is renal dysfunction. There are no published data to guide Stavudine (D4T) dosing in premature neonates.

The oral liquid formulation requires the addition of water to powder, has a concentration of 1 mg/mL, requires refrigeration and is stable for 30 days.[11] An alternative dosing method using opened capsules (available as 15 mg, 20 mg or 30 mg) with the contents dispersed in a small amount of water and the appropriate dose administered via oral syringe, has been investigated and plasma exposure shown to be equivalent to ingested whole capsules.[18] Stavudine is no longer included in SA treatment guidelines, and the oral liquid formulation is not readily available in the public sector.[8]

Although there is limited experience in the context of neonatal cART, D4T in older infants and children generally has minimal short-term toxicity and good efficacy.[11] It may therefore be a consideration for short-term use in neonatal cART when AZT is contraindicated or haematological toxicity has occurred. Alternative options for substitution of AZT are limited owing to lack of ABC safety and dosing information in infants < 3 months of age.

Zidovudine

There is considerable experience with the use of AZT in the neonatal period, although mostly for prevention of transmission. Although the landmark PACTG 076 study of prevention of mother-to-child transmission of HIV (PMTCT) used dosing of 2 mg/kg/dose 6 hourly, more recent data support twice-daily dosing.[19] Current USA guidelines recommend a dose of 4 mg/kg/dose twice daily for either prevention of transmission (4–6 weeks) or treatment (4 weeks) for neonates with gestational age ≥ 35 weeks.[11]

Western Cape (South Africa) PMTCT guidelines (2014) incorporate combination AZT/ Nevirapine (NVP) prophylaxis to prevent transmission in high-risk infants and recommend a standardised AZT dose according to birth weight (> 2 kg: 12 mg 12-hourly; < 2 kg: 4 mg/kg 12-hourly) or gestational age (< 35 weeks: 2 mg/kg 12-hourly) administered as post-exposure prophylaxis for 4 weeks.[20]

The SA ARV drug dosing chart (2013) and WHO weight band dosing (2010) recommend a dose of 6 mL (60 mg) twice daily from 3 kg – 5.9 kg which is equivalent to 10 mg – 20 mg/kg/dose or 172 mg – 300 mg/m^2/dose but advises expert consultation for neonates and infants weighing < 3 kg.[10,15]

It is recognised that the standard paediatric AZT dose (240 mg/m^2/dose twice daily) may lead to haematological toxicity (anaemia, neutropaenia, thrombocytopaenia), particularly in premature neonates with anaemia of prematurity and where other agents that may cause bone marrow suppression (e.g. ganciclovir, co-trimoxazole) are administered concurrently. Specific dosing based on PK studies in premature neonates is available and close monitoring of haematological parameters is recommended (at least every 2–4 weeks) during the neonatal and early infant period.[11,21] Switching from AZT to an alternative medication should be considered if signs of haematological or other toxicity are severe or persistent. Dosing adjustment is required in the setting of renal insufficiency or hepatic impairment.[11]

An intravenous (IV) AZT formulation is available. It is generally used in the setting of prevention of transmission when the neonate is unable to tolerate oral medication.[11] As no other IV ARV formulations are available, a fully IV treatment regimen is not feasible. Monotherapy with IV AZT as treatment in HIV-infected neonates is not recommended.

After 6 weeks of age, AZT dosing according to the SA ARV drug dosing chart (2013) is recommended.[10] Alternatively, body surface area-based dosing (240 mg/m^2/dose twice daily) may be used.[11]

Non-nucleoside reverse transcriptase inhibitors

Nevirapine

Although the use of NVP is well established for prevention of transmission, the optimal treatment dose for neonates < 14 days of age has not been established. The dose of oral suspension approved for treatment in neonates > 15 days of age and children is 200 mg/m^2/dose twice daily with a maximum dose of 200 mg (immediate-release formulation) twice daily.[11]

The standard practice of using a 14-day lead-in dose when initiating treatment with NVP in order to allow induction of cytochrome p450 metabolising enzymes and reduce occurrence of rash, can lead to subtherapeutic plasma NVP levels. This effect increases the risk of developing drug resistance and associated worse virological and clinical outcomes. Initiating cART with full-dose twice-daily NVP in black African children < 2 years of age without previous NVP exposure resulted in fewer subtherapeutic NVP levels than the 14-day dose escalation approach, and none of the children less than 2 years of age who received full-dose NVP developed rash.[22]

In HIV-infected neonates who are transitioning from once-daily NVP prophylaxis for prevention of transmission to cART containing NVP, it would seem appropriate to use full-dose

NVP with careful clinical and laboratory monitoring from the start of cART because some degree of induction of cytochrome p450 metabolising enzymes is likely to have already occurred. Further studies that include both neonates exposed to NVP prophylaxis for prevention of transmission and those without previous NVP exposure are required to validate the safety, efficacy and feasibility of full-dose NVP initiation. Based on PK modelling, the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1115 study will investigate a NVP treatment dose of 6 mg/kg/dose twice daily with full-dose initiation in full-term neonates < 48 hours of age.[23]

Nevirapine toxicities include rash, hypersensitivity reactions, and hepatotoxicity. Close monitoring for rash and liver function test abnormalities is required. NVP should not be administered to patients with moderate or severe hepatic impairment. In addition, drug-drug interactions are common and concomitant medications should be carefully reviewed prior to initiating NVP.[11]

Efavirenz, etravirine and rilpivirine are not approved for use in neonates and are not recommended.[11]

Protease inhibitors

Lopinavir/ritonavir

Lopinavir/ritonavir (LPV/r) co-formulated oral solution (Kaletra) was first approved by the USA's FDA in 2000 for the treatment of HIV-infected children ≥ 6 months old. In 2008, Kaletra oral solution was approved for use in children ≥ 14 days old.[24] The recommended dose of oral solution is 300 mg/m^2/dose twice daily.[11]

In January 2011, the FDA released a statement on Kaletra toxicity in neonates.[24] Post-marketing cases of toxicity were reported to the FDA's Adverse Event Reporting System (AERS) in September 2010 and were attributable to LPV and/or the inactive ingredients propylene glycol and ethanol. Kaletra oral solution contains 152.7 mg/mL of propylene glycol (15.3% w/v) and has a high ethanol content (356 mg/mL or 42.4% v/v).

A search of the AERS database revealed 10 reported cases with adverse events that might have been related to LPV, propylene glycol or ethanol. All 10 patients were neonates, and 8 of the 10 were premature neonates. Cardiac toxicity occurred in 7 of the patients and included bradycardia, sinoatrial block, complete atrioventricular block, congestive cardiomyopathy, cardiac failure and cardiogenic shock. An elevated lactate level was documented in 2 cases. Neuromuscular toxicity in 3 neonates included hypotonia, abnormal electroencephalogram (EEG), altered state of consciousness, somnolence and asthenia. Acute renal failure was seen in 5 neonates and an increased serum creatinine was documented in 1. Four neonates developed hyperkalaemia. Respiratory complications occurred in 3 neonates and included respiratory failure, pulmonary haemorrhage, respiratory arrest, dyspnoea and wheezing. Gastrointestinal events in 5 neonates included vomiting, failure to thrive, abdominal distension and ulcerative colitis. One of the 10 neonates died.[24,25]

Eight of the 10 neonates received their first dose of Kaletra within the first 2 days of life. The onset of toxicity occurred within 1–6 days in 8 of the neonates. A full-term infant showed the first signs of toxicity 20 days after birth. After Kaletra was discontinued, 6 neonates recovered within 5 days.[24,25] Transient asymptomatic elevation in 17-hydroxyprogesterone levels has been reported in term neonates treated at birth with LPV/r.[26]

As an appropriate dose in premature infants and neonates < 14 days of age is not known and the consequences of Kaletra toxicity in premature infants can be severe or possibly fatal, the FDA strongly recommends that Kaletra should be avoided in this age group:[11,24]

> If in the judgment of the health care professional, the benefit of using Kaletra oral solution in babies to treat HIV infection immediately after birth outweighs the potential risks, then the neonate should be monitored closely for increases in serum osmolality and serum creatinine and for toxicity related to Kaletra oral solution. These toxicities include hyperosmolality with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias, ECG changes and hemolysis.[24]

The IMPAACT P1030 study evaluated PK, safety and efficacy of LPV/r 300 mg/m^2/dose twice daily in combination with 2 nucleoside analogues in 10 HIV-infected infants with an age range of 3.6–5.9 weeks. Amongst 9 infants completing intensive PK evaluation on a median dose of 267 mg/m^2/dose (range 246–305) twice daily, the LPV area-under-the curve (AUC) was significantly lower than that in the 6-weeks to 6-months of age cohort. The LPV trough level (C_{min}) ranged from 0.99 µg/mL – 4.87 µg/mL which did not differ from the older children. A plasma LPV trough concentration of ≥ 1 µg/mL has been used as a correlate of efficacy in treatment-naïve adults. After 24 weeks' follow-up, adverse events were limited to transient neutropaenia in 3 infants, and only 2 of 10 infants met criteria for protocol-defined virological failure. Noting the low LPV exposure (AUC), the authors advised careful dose calculation and frequent dose adjustment for weight gain, and proposed studying a higher dose for very young infants.[27,28]

Taking into account the increasing usage of LPV/r administration to neonates at risk of perinatal or postnatal HIV transmission, Urien et al.[29] aimed to determine optimal dosing for LPV/r in the first weeks of life based on a population PK approach incorporating body weight, gestational age and postnatal age in 96 infants from France and the UK. Amongst the 96 neonates, 7 were on treatment for neonatal HIV infection. The median postnatal age was 2 weeks (range 1 day – 102 weeks), median gestational age was 38 weeks (range 27.3–41 weeks), median body weight was 3.3 kg (range 1.16 kg – 10.4 kg). A total of 163 LPV concentrations were available for analysis. The mean LPV dosage was 590 mg/m^2/day (range 106–1454) or 39 mg/kg/day (range 11–110) dosed between 1 and 3 times per day. A one-compartment model

described the data with body weight and age being the main influential covariates. The following dosage regimen was derived from the predicted LPV trough concentrations using a therapeutic range of 1 µg/mL – 8 µg/mL: 40 mg 12-hourly, 80 mg 12-hourly and 120 mg 12-hourly for 1 kg – 2 kg, 2 kg – 6 kg and 6 kg – 10 kg groups respectively.[29]

Holgate et al.[30] described the use of Kaletra-based cART in 8 HIV-infected premature neonates treated between 2006 and 2011 in Cape Town. The median gestational age at birth was 31 weeks (range 27–33), median age at initiation of LPV/r-based cART was 26.5 days (range 5–96), median corrected gestational age at cART initiation was 34.1 (range 31.6–44.7) and median dose of LPV/r at time of measuring LPV levels was 287 mg/m^2/dose or 23.1 mg/kg (range 235–325; 21.1–28.6, respectively). LPV trough levels were sampled a median 7 days after LPV/r initiation, 3 infants had subtherapeutic plasma levels (< 1 µg/mL), and in 1 infant the plasma level was above the recommended target range (> 4 µg/mL). The dose of LPV/r was adjusted in the 3 infants with low levels and a median dose of 533 mg/m^2 (range 400–540) resulted in plasma levels within the recommended therapeutic range. Overall, 5/8 infants required doses > 300 mg/m^2 to achieve plasma LPV trough levels within the recommended range. No adverse effects attributable to LPV/r solution were observed. The study highlighted the role of therapeutic drug monitoring in order to achieve target trough LPV levels. Although no toxicity was observed, the authors emphasised the need for extreme caution and careful monitoring of premature neonates treated with Kaletra.[30]

Although nelfinavir (NFV) has been used in ART regimens for prevention of transmission and treatment, it is not currently recommended for treatment in children < 2 years of age as there is significant inter-individual variation in plasma levels and insufficient PK data to support a standardised dosing regimen.[11]

Atazanavir, darunavir, fosamprenavir, indinavir, full-dose ritonavir (RTV), saquinavir and tipranavir are not approved for use in neonates and are not recommended.[11]

Integrase inhibitors

Raltegravir

There are currently no published data on safety and dosing of Raltegravir (RAL) in neonates. However, Phase 1 and 2 studies are underway. The IMPAACT P1097 study investigated washout PK in neonates born to HIV-infected mothers and showed that the neonatal half-life of RAL varied between 9 and 184 hours, most likely owing to reduced capacity for metabolism and elimination in newborns.[31] The Phase 1 IMPAACT P1110 trial is investigating the safety and PK of RAL suspension (granules for suspension) in HIV-exposed neonates at high risk of acquiring HIV infection. Different dosing strategies between birth and 6 weeks of age will be investigated with the option of continuing RAL beyond 6 weeks of age in infants found to be HIV-infected.[32]

The IMPAACT P1066 study investigated the use of RAL oral suspension in combination with an optimised background ARV regimen in 26 HIV-infected infants and young children aged 4 weeks to 2 years who had previously received ARV medication for prevention of perinatal transmission. Clinical outcomes were acceptable, there were no treatment discontinuations owing to adverse events, and PK parameters were similar to those achieved amongst cohorts of older children in the same study.[33] Raltegravir oral suspension is currently approved by the FDA for use in infants > 4 weeks of age and > 3 kg body weight.[11] In SA, RAL suspension is not currently registered by the Medicines Control Council. In the SA public sector, RAL has been restricted for use in third-line ART regimens.

Dolutegravir and elvitegravir are not approved for use in neonates and are not recommended.[11]

Choice of combination antiretroviral therapy regimen in neonates

Current SA HIV treatment guidelines recommend ABC+3TC+LPV/r as first-line cART for all HIV-infected children < 3 years of age; there are no separate recommendations for full-term or premature neonates.[8] There are currently no published clinical trial data comparing different cART regimens initiated during the neonatal period. Clinical trials in older infants and young children have informed treatment recommendations in these age groups and are important to consider in relation to cART initiation during the neonatal period.

The IMPAACT P1060 trial showed that LPV/r-based cART was virologically superior to NVP-based cART both in infants with previous exposure to NVP (6–36 months of age) and in infants without previous exposure to NVP (3–36 months of age).[34,35] One of the reasons proposed to explain the difference in virological efficacy between NVP and LPV/r is the dose escalation strategy used when initiating NVP, as this has been associated with subtherapeutic plasma NVP levels which could increase the risk of developing drug resistance and treatment failure.[22] Initiation of cART with full-dose NVP has been investigated and further studies are underway.[22,23]

An additional possible explanation for the difference in outcomes relates to the presence of drug resistance mutations prior to cART initiation. In settings of high nucleoside reverse transcriptase inhibitor (NRTI) exposure owing to the use of NVP for prevention of transmission and use of NRTI/ Non-nucleoside reverse transcriptase inhibitor (NNRTI) regimens during pregnancy, the presence of resistance mutations may compromise the efficacy of NVP-based regimens in the neonate. HIV drug resistance mutations in plasma virus were determined using population sequencing in 230 newly-diagnosed HIV-infected children < 2 years of age in Johannesburg in 2011. Two-thirds of the HIV-infected children had been exposed to maternal and/or infant PMTCT, 56.8% had NNRTI, 14.8% NRTI and 1.3% PI mutations. In children

with no reported PMTCT exposure, resistance to NNRTI was detected in 24%, to NRTI in 10.7% and to PI in 1.3%. In the children who were tested at ≤ 8 weeks of age, 85% had NNRTI drug resistant mutations present.[36]

The above data support the use of PI-based first-line cART in HIV-infected infants and young children regardless of PMTCT history. However, owing to potentially severe and life-threatening short-term toxicity concerns, Kaletra is currently not recommended in neonates < 14 days old and < 42 weeks corrected gestational age. Long-term toxicities of PIs, including effects on growth and lipid metabolism, have also been reported.[37,38]

Other studies have investigated whether 4 rather than 3 ARV drugs could improve outcomes based on the observation that young infants commonly have very high HIV viral loads and the hypothesis that increased regimen potency might achieve more rapid virological suppression, immunological recovery and better long-term treatment efficacy. However, the available studies are heterogeneous in nature and therefore difficult to compare directly, and 3 drug regimens have remained the standard-of-care in most guidelines.

The PACTG 356 study showed superior virological suppression rates of a 4-drug regimen comprising D4T/3TC/NVP/NFV compared with either AZT/3TC/ABC/NVP or AZT/3TC/NVP.[39] Prendergast et al.[40] showed that infants randomised to receive immediate or deferred (until CD4 count reached < 20%) 4-drug cART comprising AZT/3TC/NFV/NVP were able to achieve excellent adherence and virological suppression after one year by intention-to-treat analysis of 80%. The European Pregnancy and Pediatric HIV Cohort Collaboration (EPPICC) observational study of 437 infants initiating cART during the first year of life showed better virological and immunological responses among those starting 4-drug NNRTI-based regimens than 3-drug NNRTI-based and LPV/r-based regimens after median 5.9 years of follow-up.[41] The AntiRetroviral Research for Watoto (ARROW) trial conducted among 3-month – 17-year-old children in Uganda and Zimbabwe showed no long-term (72 weeks) immunological benefit to starting 4-drug cART (NNRTI +3 NRTIs) then simplifying to 3-drug cART (either NNRTI + 2 NRTIs, or 3 NRTIs) compared with starting 3-drug cART (NNRTI + 2 NRTIs), and there was increased toxicity with 4-drug cART.[42]

Further clinical trials comparing safety, tolerability and efficacy of different cART regimens, including consideration of 4-drug and triple class regimens, initiated during the neonatal period in high burden settings are warranted in order to better guide treatment recommendations.

Transition from antiretroviral prophylaxis to treatment

Neonatal ARV prophylaxis regimens vary between guidelines. In SA, prophylaxis regimens include NVP alone, AZT alone, NVP + AZT, and NVP + AZT + 3TC, and recommended duration ranges from 6 weeks to 3 months or more.[8,43] As a result, most neonates will be receiving ARV prophylaxis at the time that a positive birth HIV PCR test result is obtained.

Transition from neonatal ARV prophylaxis to neonatal cART requires adjustment to the number and choice of ARVs, dosage and dose frequency in most cases. Clinical assessment of the neonate, baseline investigations and careful counselling of the mother and family are pre-requisites to cART initiation. Although optimal strategies for transition from prophylaxis to cART have not been widely studied, it is recommended that a standardised approach applicable to the majority of HIV-infected neonates is adopted (Figure 1). Expert opinion and individualised guidance will still be required for certain categories of neonates; for example, low birth weight, premature or unwell neonates.

After obtaining a positive HIV PCR test result in a neonate, the following actions are required prior to consideration of cART initiation:

- A blood sample for confirmatory viral detection assay (second HIV DNA PCR test as per current National Department of Health [NDOH] SA guidelines or HIV RNA/viral load) must be submitted to the laboratory.[8,43] Initiation of cART should not be delayed on the basis that the result of the confirmatory PCR test has not yet been obtained. Rapid and systematic follow-up of birth HIV PCR tests that might have been submitted to the laboratory by the birthing facility or a referring clinic or hospital, and recall of HIV-positive neonates, is essential.
- The clinical condition of the neonate must be assessed. This includes determining the corrected gestational age (in weeks), postnatal age, birth weight and current weight, presence of any vital organ dysfunction including neonatal jaundice, hepatitis or renal dysfunction, and presence of other congenital or acquired infections including syphilis, tuberculosis (TB) and cytomegalovirus as indicated by the maternal history and clinical state of the neonate. Co-morbidities and their treatment may alter the timing of cART initiation and the treatment regimen required in the neonate. In neonates who are clinically unstable at the time that HIV infection is diagnosed, ARV prophylaxis should be discontinued and the neonate stabilised and treated as necessary prior to initiation of cART. In addition, neonates who are not fully established on enteral feeding are not eligible to initiate cART.
  - HIV-infected neonates who are also exposed to and/or infected with TB require evaluation as to the infectiousness and drug sensitivity profile of the contact, and assessment (clinical, radiological, bacteriological) of TB infection/disease followed by anti-TB chemoprophylaxis or treatment. HIV-infected neonates initiated on rifampicin and receiving LPV/r-based cART will require additional RTV (0.75 x LPV dose) to be added to the cART regimen although PK, safety and efficacy data for the super-boosting strategy in the neonatal age group is lacking. The PK,

TABLE 1: Antiretroviral drugs, formulations and dose recommendations for treatment of full-term neonates.

Inhibitor	ARV drug	Formulations	Dose	Comment
Nucleoside reverse transcriptase Inhibitors	Abacavir	20 mg/mL	Neonatal dose not known	Not FDA approved for infants < 3 months of age
	Lamivudine	10 mg/mL	Birth – 4 weeks of age: 2 mg/kg/dose twice daily ≥ 4 weeks of age: • If < 3 kg body weight: 4 mg/kg/dose twice daily • If ≥ 3 kg body weight: may be dosed according to SA ARV dosing chart	Not FDA approved for infants < 3 months of age but generally well tolerated. May contribute to haematological toxicity
	Stavudine	Oral suspension: powder for reconstitution with water 1 mg/mL; Capsules: 15 mg, 20 mg, 30 mg	Birth – 13 days of age: 0.5 mg/kg/dose twice daily ≥ 14 days of age: 1 mg/kg/dose twice daily	Consider use if AZT contraindicated or haematological toxicity Reconstituted oral suspension: requires refrigeration, stable for 30 days, no longer readily available Capsules may be opened, contents dispersed in water and appropriate dose administered
	Zidovudine	10 mg/mL	Birth – < 4 weeks of age (≥ 35 weeks gestational age): 4 mg/kg/dose twice daily ≥ 4 weeks of age: • If < 3 kg body weight: 12 mg/kg/dose twice daily or 240 mg/m²/dose twice daily • If ≥ 3 kg body weight: may be dosed according to SA ARV dosing chart	Monitor for haematological toxicity
Non-nucleoside reverse transcriptase inhibitor	Nevirapine	10 mg/mL	≤ 14 days of age: treatment dose is undetermined Investigational dose (IMPAACT P1115): 6 mg/kg/dose twice daily ≥ 15 days of age: • If < 3 kg body weight: 200 mg/m²/dose twice daily • If ≥ 3 kg body weight: may be dosed according to SA ARV dosing chart	Monitor for rash, hypersensitivity reactions, hepatotoxicity
Protease inhibitor	Lopinavir/ ritonavir (Kaletra)	80 mg/20 mg LPV/r per 1 mL	300 mg/m²/dose twice daily Doses may require adjustment based on therapeutic drug monitoring, if available	Contraindicated < 14 days of age and < 42 weeks corrected gestational age Refer to text for details on monitoring required

Source: Adapted from Ref. 11
Note: Body surface area (m^2) = (0.05 x weight [kg]) + 0.05.
ARV, antiretroviral; LPV/r, Lopinavir/ritonavir; SA ARV, South African antiretroviral; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trials; FDA, Food and Drug Administration; AZT, zidovudine.

safety and efficacy of rifampicin in combination with NVP-based cART in the neonatal age group is also not known. Expert advice should be obtained.

- Baseline blood investigations should be performed including full blood count and differential white cell count, urea and creatinine, and alanine aminotransferase (ALT).
- Careful and detailed counselling of the mother and if possible other family members who will be involved in the care of the neonate is required. The mother of the child might not have disclosed her own HIV status to other family members, and disclosure of the neonate's HIV status to the family should be discussed. In addition to providing support, counselling should include information about the HIV diagnosis in the neonate as well as details about cART. Information and guidance on infant feeding should be provided. Mothers who had chosen to breastfeed should be encouraged to continue breastfeeding whilst mothers who had chosen formula feeding should consider switching to breastfeeding if feasible.
- Ideally, a blood sample should be submitted for ARV drug resistance testing (genotyping) prior to initiation of cART in the neonate. This is particularly relevant when the neonate has been exposed to maternal cART or ARV prophylaxis prior to the diagnosis of HIV infection, and may assist in determining optimal ARV drug choices in future cART regimens for the child. Expert advice should be obtained to assist in the management of HIV-infected neonates born to mothers on 2nd- or 3rd-line cART regimens.

In neonates ≥ 15 days of age and ≥ 42 weeks corrected gestational age and with normal renal and hepatic function, an initial regimen of AZT+3TC+LPV/r is recommended. Refer to Table 1 and Figure 1 for guidance on dosing and monitoring.

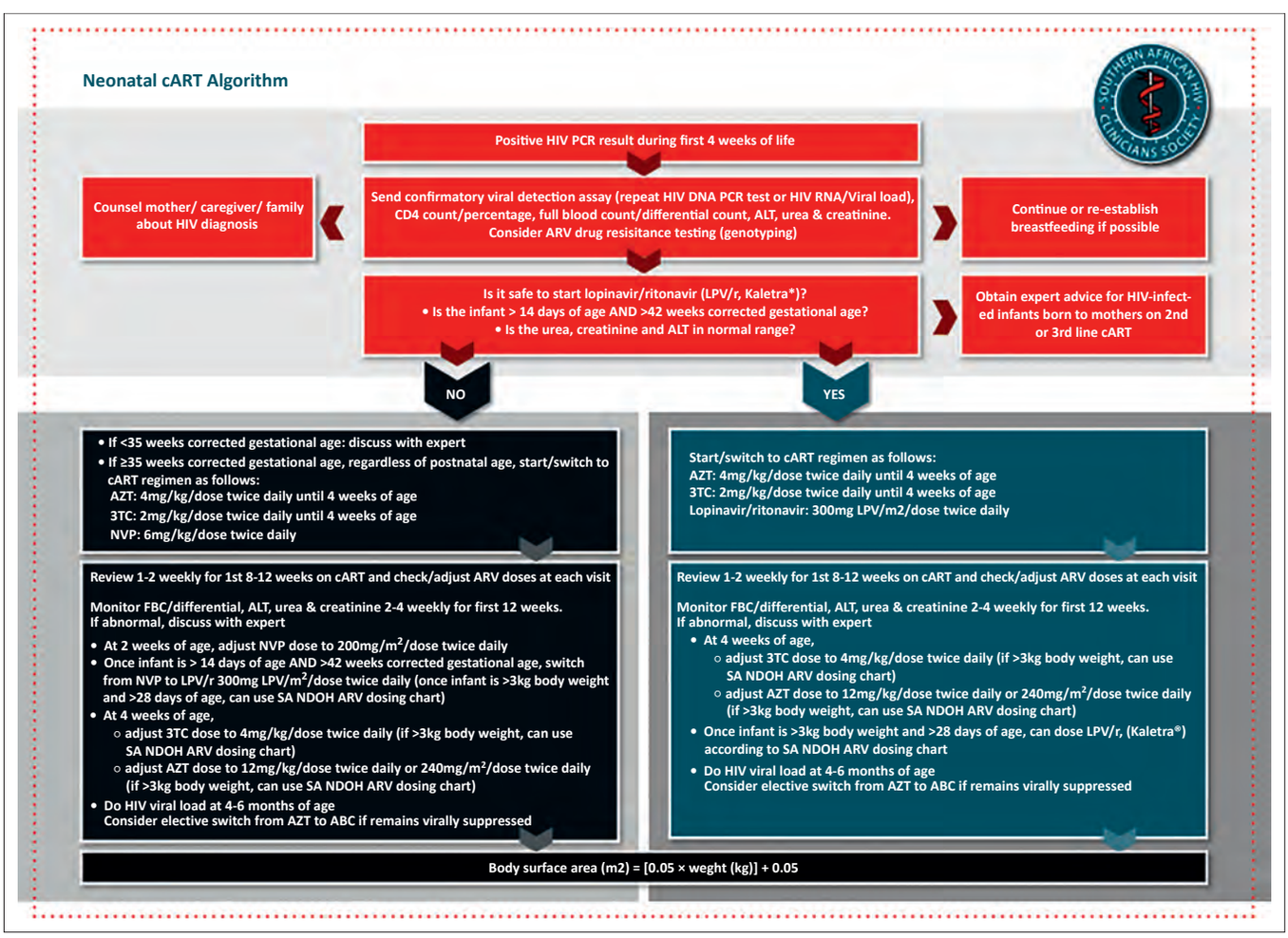
In full-term neonates ≤ 14 days of age, approved dosing recommendations are only available for AZT and 3TC. Treatment with only 2 drugs is not recommended. Based on a detailed review of available PK data, an NVP dose of 6 mg/kg/dose twice daily in full-term neonates initiating cART < 48 hours of age is under investigation in the IMPAACT P1115 study. Pending the results of this and other studies, a provisional recommendation to use an initial regimen of AZT+3TC+NVP dosed twice daily in neonates ≥ 35 weeks gestational age at birth, regardless of postnatal age, with normal hepatic function and appropriate monitoring for toxicity seems reasonable. Refer to Table 1 and Figure 1 for guidance on dosing and monitoring. As there are data for older infants and young children showing superior efficacy of LPV/r-based, compared with NNRTI-based, cART, these neonates should be considered for elective switch to AZT+3TC+LPV/r when they are ≥ 15 days of age and ≥ 42 weeks corrected gestational age.

The decision to initiate cART in premature neonates < 35 weeks gestational age involves assessing the relative risks and benefits of using unapproved dosing and the inherent concerns regarding drug toxicity. Dosing recommendations for premature neonates are currently only available for AZT. Treatment with AZT alone is not recommended and, based on currently available data, it is recommended that Kaletra should be avoided in this age group (refer to Table 2).

TABLE 2: Antiretroviral drugs, formulations and dose recommendations for treatment of premature neonates.

Inhibitor	ARV drug	Formulations	Dose	Comment
Nucleoside reverse transcriptase inhibitors	Abacavir	20 mg/mL	Appropriate dose for treatment of premature neonates is not known	Not FDA approved for infants < 3 months of age
	Lamivudine	10 mg/mL	Appropriate dose for treatment of premature neonates is not known	Not FDA approved for infants < 3 months of age but generally well tolerated. May contribute to haematological toxicity
	Stavudine	Oral suspension: powder for reconstitution with water 1 mg/mL; Capsules: 15 mg, 20 mg, 30 mg	Appropriate dose for treatment of premature neonates is not known	Reconstituted oral suspension: requires refrigeration, stable for 30 days, no longer readily available Capsules may be opened, contents dispersed in water and appropriate dose administered
	Zidovudine	10 mg/mL	• ≥ 35 weeks gestation: birth – < 4 weeks of age: 4 mg/kg/dose twice daily ≥ 4 weeks of age: If < 3 kg body weight: 12 mg/kg/dose twice daily or 240 mg/m2/dose twice daily If ≥ 3 kg body weight: may be dosed according to SA ARV dosing chart • ≥ 30 to < 35 weeks gestation: birth – < 2 weeks of age: 2 mg/kg/dose twice daily ≥ 2 weeks – < 8 weeks of age: 3 mg/kg/dose twice daily ≥ 8 weeks of age: 12 mg/kg/dose twice daily • < 30 weeks gestation: birth – < 4 weeks of age: 2 mg/kg/ dose twice daily ≥ 4 weeks – < 10 weeks: 3 mg/kg/dose twice daily ≥ 10 weeks of age: 12 mg/kg/dose twice daily	Monitor for haematological toxicity
Non-nucleoside reverse transcriptase inhibitor	Nevirapine	10 mg/mL	Appropriate dose for treatment of premature neonates is not known	Monitor for rash, hypersensitivity reactions, hepatotoxicity
Protease inhibitor	Lopinavir/ ritonavir (Kaletra)	80 mg/20 mg LPV/r per 1 mL	Appropriate dose for treatment of premature neonates is not known	Contraindicated < 14 days of age and < 42 weeks corrected gestational age. Refer to text for details on monitoring required

Source: Adapted from Ref. 11
Note: Zidovudine (AZT) is the only ARV drug for which dosing for treatment of premature neonates is approved. However, treatment with AZT monotherapy is not recommended. Body surface area (m^2) = (0.05 x weight [kg]) + 0.05.
ARV, antiretroviral; LPV/r, Lopinavir/ritonavir; FDA, Food and Drug Administration.



cART, combination antiretroviral therapy; AZT, zidovudine; 3TC, Lamivudine; NVP, Nevirapine; ARV, antiretroviral; ALT, alanine aminotransferase; LPV/r, Lopinavir/ritonavir; NDOH, National Department of Health; PCR, polymerase chain reaction.

FIGURE 1: Recommended process for initiation of combination antiretroviral therapy in neonates.

If cART is initiated in premature neonates, expert guidance on dosing and toxicity monitoring should be obtained.

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Corrigendum: Guideline on the management of occupational and non-occupational exposure to the human immunodeficiency virus and recommendations for post-exposure prophylaxis: 2015 Update

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The authors apologise for two oversights in Table 1: One was due to an incorrect recommendation; the other was an omission.

Table 1 states that, 'RAL is recommended as preferred third drug where available for HIV PEP in children. If RAL unavailable, then ATV/r is recommended.' This has been deleted and the correct recommendation made.

Please see below the revised Table 1.

Additionally, information about dosing was omitted. This information has now been added in Appendix 1 below.

TABLE 1: Summary of guidelines on post-exposure prophylaxis for HIV in adults, adolescents and children.

Guideline	Recommendation
Number of antiretroviral drugs	HIV PEP regimens should contain three drugs
Preferred PEP regimen for adults and adolescents	TDF + 3TC/FTC (preferably as fixed-dose combination) is recommended as preferred PEP backbone
	RAL is recommended as preferred third drug for PEP (except in pregnant women, where ATV/r is the recommended third drug)
	Alternative third drugs include ATV/r, LPV/r, DRV/r or EFV
Preferred PEP regimen for children ≤ 35 kg or unable to swallow tablets	AZT + 3TC is recommended as preferred backbone for HIV PEP in children ≤ 35 kg (substitute with d4T if AZT poorly tolerated)
	LPV/r is recommended as the third drug for HIV PEP in children. Where RAL is available, then it can be used in children over 2 years of age in preference to LPV/r due to better tolerability. In children over 6 years of age who can swallow tablets, ATV/r is another better tolerated alternative to LPV/r where available.†
Prescribing frequency	A full one-month course of antiretroviral drugs should be provided for HIV PEP at initial assessment
	Starter packs should not be used
Frequency of follow-up	Exposed individual should be seen at 2 weeks, 6 weeks and 3 months after exposure occurred
Adherence support	Enhanced adherence counselling is recommended for all individuals initiating PEP

PEP, post exposure prophylaxis; TDF, tenofovir; 3TC, lamivudine; FTC, emtricitabine; RAL, raltegravir; ATV/r, atazanavir/ritonavir; LPV/r, lopinavir/ritonavir; DRV/r, darunavir + ritonavir; EFV, efavirenz; AZT, zidovudine.
†, See dosing tables in Appendix 1 for dosages.

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Appendix 1
Dosing tables

FIGURE 1-A1: Stavudine (d4T); Lopinavir/Ritonavir (LPV/r); Zidovudine (AZT).[1]

Weight	Stavudine (d4T) Solution 1 mg/mL Caps 15 mg, 20 mg, 30 mg	Lopinavir/ Ritonavir (LPV/r) Solution 80/20/mL Adult tabs 200/50 mg† Paeds Tabs 100/25†	Zidovudine (AZT) Solution 10 mg/mL Capsules 100 mg Tablets 100 mg, 300 mg	Weight
3 kg – 4.9 kg	6 mL bd	1 mL bd	6 mL bd	3 kg – 4.9 kg
5 kg – 5.9 kg	**7.5 mg bd:** open 15 mg capsule into 5 mL water: give 2.5 mL	1.5 mL bd		5 kg – 5.9 kg
6 kg – 6.9 kg			9 mL bd	6 kg – 6.9 kg
7 kg – 9.9 kg	**10 mg bd:** open 20 mg capsule into 5 mL water: give 2.5 mL			7 kg – 7.9 kg
8 kg – 9.9 kg			100 mg bd (1 x 100 mg tab or cap) OR 12 mL bd	8 kg – 9.9 kg
10 kg – 13.9 kg	**15 mg bd:** open 15 mg capsule into 5 mL water	2 mL bd		10 kg – 13.9 kg
14 kg – 19.9 kg	**20 mg bd:** open 20 mg capsule into 5 mL water (If the child is unable to swallow a capsule)	Choose one option: -2.5 mL bd -100/25 mg **paeds tabs:** 2 bd -200/50 mg **adult tabs:** 1 bd	200 mg am and 100 mg pm OR 15 mL bd	14 kg – 19.9 kg
20 kg – 24.9 kg		Choose one option: -3 mL bd -100/25 mg **paeds tabs:** 2 bd -200/50 mg **adult tabs:** 1 bd	200 mg bd (2 x 100 mg cap or tab) OR 20 mL bd	20 kg – 24.9 kg
25 kg – 29.9 kg	**30 mg bd**	Choose one option: -3.5 mL bd -100/25 mg **paeds tabs:** 3 bd -200/50 mg **adult tabs:** 1 bd + 100/25 mg **paeds tabs:** 1 bd	1 x 300 mg tab bd	25 kg – 29.9 kg
30 kg – 34.9 kg		Choose one option: -4 mL bd -100/25 mg **paeds tabs:** 3 bd -200/50 mg **adult tabs:** 1 bd + 100/25 mg **paeds tabs:** 1 bd		30 kg – 34.9 kg
> 35kg		Choose one option: -5 mL bd -200/50 mg **adult tabs:** 2 bd		> 35kg

†, Do not crush or break lopinavir/ritonavir tablets.

Raltegravir[2]

- Chewable tablets and film-coated tablets are not equivalent.

Children aged 2 to < 12 years:

- < 25 kg: Chewable tablet twice daily (see dosing chart below)
- ≥ 25 kg and can swallow tablets: one 400 mg film-coated tablet twice a day
- ≥ 25 kg and can't swallow tablets: chewable tablets twice daily (see dosing chart below – maximum of 300 mg twice daily).

TABLE 1-A1: Raltegravir chewable tablets.

Weight (kg)	Number of chewable tablets (100 mg scored or 25 mg)
11 kg to < 14 kg	75 mg (3 x 25 mg) twice daily
14 kg to < 20 kg	1 x 100 mg twice daily
20 kg to < 28 kg	150 mg twice daily (1.5 x 100 mg)
28 kg to < 40 kg	200 mg (2 x 100 mg) twice daily
≥ 40 kg	300 mg (3 x 100 mg) twice daily

Atazanavir[2]

- Children ≥ 6 years and ≥ 15 kg.

TABLE 2-A1: Atazanavir capsules.

Weight (kg)	Once daily dose
< 15 kg	Capsules not recommended
15 kg to < 20 kg	Atazanavir 150 mg plus ritonavir† 100 mg, both once daily with food
20 kg to < 40 kg‡	Atazanavir 200 mg plus ritonavir† 100 mg both once daily with food
≥ 40 kg	Atazanavir 300 mg plus ritonavir 100 mg† both once daily with food

†, Either ritonavir capsules or ritonavir oral solution can be used
‡, Some experts would increase atazanavir to 300mg at ≥35kg especially when administered with tenofovir

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Guideline on the management of occupational and non-occupational exposure to the human immunodeficiency virus and recommendations for post-exposure prophylaxis: 2015 Update

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This guideline is an update of the post-exposure prophylaxis (PEP) guideline published by the Southern African HIV Clinicians Society in 2008. It updates the recommendations on the use of antiretroviral medications to prevent individuals who have been exposed to a potential HIV source, via either occupational or non-occupational exposure, from becoming infected with HIV. No distinction is made between occupational or non-occupational exposure, and the guideline promotes the provision of PEP with three antiretroviral drugs if the exposure confers a significant transmission risk. The present guideline aligns with the principles of the World Health Organization PEP guidelines (2014), promoting simplification and adherence support to individuals receiving PEP.

Key summary points

- Southern Africa differs from other regions, particularly in terms of very high HIV and hepatitis B virus (HBV) seroprevalence.
- Post-exposure prophylaxis (PEP) guidelines lack a substantive evidence base to guide advice. It is unlikely that this will change considerably, as randomised studies of different drug regimens for PEP are not feasible owing to the complexity of exposure, low event rate, and inability to ethically have a placebo group. Evolving basic science understanding, along with further studies on animals and prevention of mother-to-child transmission (PMTCT) findings, will continue to guide policy makers. In addition, data from pre-exposure prophylaxis (PrEP) studies will also provide valuable data relevant to PEP interventions.
- PEP guidelines prior to the Southern African HIV Clinicians Society's 2008 PEP guideline were not user friendly and rarely acknowledged the complex range of situations that occur with HIV.
- Selecting patients for appropriate PEP administration must be simplified. Algorithmic approaches for antiretroviral treatment (ART) regimens have simplified antiretroviral management at the treatment and management levels. The same approach is possible for PEP regimens in this region.
- The approach to occupational, sexual and other forms of HIV exposure (bites, assaults, trauma, injecting drug use, etc.) is similar.
- Cases of exposure are often not simple, do not lend themselves to simple categorisation, and require an individualised approach. However, concepts to guide the attending clinician are relatively simple and allow an effective intervention in most cases.

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Note: This guideline was compiled by the Southern African HIV Clinicians Society.

Disclaimer: Specific recommendations provided here are intended only as a guide to clinical management, based on expert consensus and best current evidence. Treatment decisions for patients should be made by their responsible clinicians, with due consideration for individual circumstances. The most current version of this document should always be consulted.

Update of: Bekker LG, Black V, Myer L, et al. Guideline on safer conception in fertile HIV-infected individuals and couples. S Afr J HIV Med. 2011;12(2), Art. #196, 14 pages. http://dx.doi.org/10.4102/sajhivmed.v12i2.196

Clinical approach

- Animal data, case control studies and PMTCT data suggest that PEP is highly effective if taken correctly for the full duration prescribed.
- Similarly, PrEP studies have indicated that, with high levels of adherence, PrEP is a highly effective intervention in the prevention of HIV transmission.
- The key outcome in HIV PEP is successful completion of one month of uninterrupted appropriate prophylaxis.
- Side-effect management is critical to completion, and is often under-managed. Zidovudine (AZT) and protease inhibitor (PI)-based regimens are associated with significant side-effects, and are therefore not preferred drugs in PEP regimens, except in special circumstances.
- The number of drugs used to treat PEP is often the focus of clinician attention. Whilst number of drugs and specific antiretroviral (ARV) prescribing are important, completing the full course, through active side-effect and anxiety management, remains the cornerstone of successful management.
- Side-effects owing to ART appear to be more common and severe in HIV-negative exposed people than in HIV-positive patients initiated on treatment, especially amongst healthcare workers (HCWs).
- There have been few documented failures of PEP. Many of these failures have been associated with poor adherence, suboptimal dosing or delayed ART.
- Anxiety management of the exposed individual must be actively addressed.

Drug selection

- Where ART is felt to be justified, a three-drug regimen should be used. However, this must never be at the expense of adherence. Single- or dual drug regimens are known to be effective and can be used as an alternative where necessary (e.g. to increase adherence when a three-drug regimen is not well tolerated).
- The preferred nucleoside reverse transcriptase inhibitor (NRTI) backbone for PEP is tenofovir (TDF) with lamivudine (3TC) or emtricitabine (FTC), preferably as a fixed-dose combination (FDC).
- The preferred third drug is raltegravir (RAL).
- Owing to a lack of safety data regarding the use of RAL in pregnancy, atazanavir/ritonavir (ATV/r) is the preferred third drug in pregnancy.
- AZT-containing PEP regimens are associated with significant side-effects, whereas stavudine (d4T) is well tolerated for short-term administration; in patients where TDF cannot be used, d4T should be given preferentially to AZT.
- Nevirapine (NVP) should never be used for PEP owing to its potentially severe side-effects.
- Boosted PIs should be used in cases where ARV resistance is suspected, with NRTI choices based on medication to which the patient has not been exposed. Expert guidance should be sought in these situations.
- Hepatitis B prophylaxis, often not considered after HIV exposure, must form part of any assessment.
- Follow-up must be actively pursued. Advice on further HIV and hepatitis testing; when it is safe to commence unprotected sex; and subsequent primary prevention, are critical. Post-exposure HIV status should be assessed through serial enzyme-linked immunosorbent assay (ELISA) testing at 6 weeks and 3 months after exposure occurred. Polymerase chain reaction (PCR) testing does not currently have a role in PEP assessment.

Public health issues

- Occupational exposure is usually avoidable. All cases should be investigated with a view to improving infection control.
- All health and allied institutions where exposure is an occupational risk should have clear, public and accessible PEP protocols.
- Hepatitis B vaccination programmes must be encouraged in all occupational health settings, as primary prophylaxis is very effective.

Introduction

In 2008, the Southern African HIV Clinicians Society published guidelines on PEP, which were bold, specifically with regard to three key recommendations: the removal of the distinction between occupational versus non-occupational exposure; the use of triple prophylaxis; and treatment for all exposures.[1] These points were in contrast to all other international guidelines at the time, and in fact it is only in the latest World Health Organization (WHO) PEP guideline that a similar approach to PEP has been promulgated.[2]

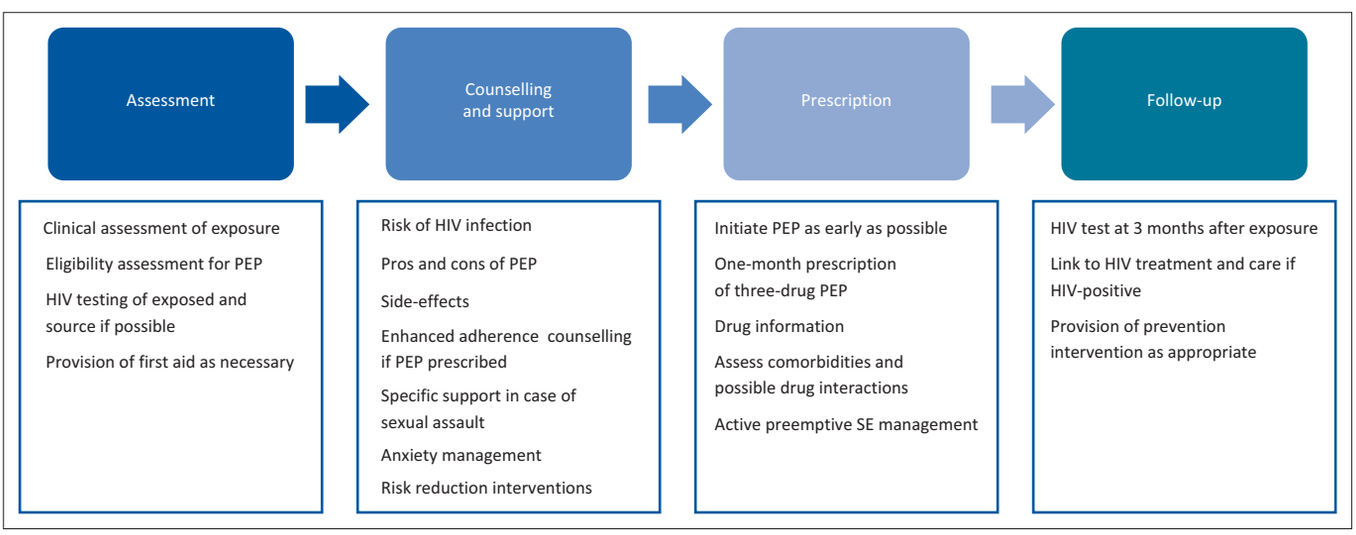
The present guideline updates the recommendations on the use of antiretroviral medications to prevent individuals who have been exposed to a potential HIV source, via either occupational or non-occupational exposure, from becoming infected with HIV. As in the 2008 guideline, no distinction is made between occupational or non-occupational exposure, and the guideline promotes the provision of PEP with three antiretroviral drugs if the exposure confers a significant transmission risk. There are strong recommendations with regard to the prevention of occupational exposure and the use of simplified approaches to PEP, with an emphasis on managing both the anxiety of the exposed individual, as well as a pro-active approach to side-effect management. See Table 1 for a summary of guideline recommendations.

Unfortunately, most of the data on which PEP guidelines are based are from different settings to the southern African region, and are largely derived from non-randomised control trial (RCT) data (except in the case of some of the PMTCT studies and more recently, the PrEP studies). Much of the data rely on retrospective register analysis, as well as extrapolation from animal data and individual clinical case studies. It is important to remember that these data from developed-

TABLE 1: Summary of guidelines on post-exposure prophylaxis for HIV in adults, adolescents and children.

Guideline	Recommendation
Number of antiretroviral drugs	HIV PEP regimens should contain three drugs
Preferred PEP regimen for adults and adolescents	TDF + 3TC/FTC (preferably as fixed-dose combination) is recommended as preferred PEP backbone
	RAL is recommended as preferred third drug for PEP (except in pregnant women, where ATV/r is the recommended third drug)
	Alternative third drugs include ATV/r, LPV/r, DRV/r or EFV
Preferred PEP regimen for children ≤ 35 kg or unable to swallow tablets	AZT + 3TC is recommended as preferred backbone for HIV PEP in children ≤ 35 kg (substitute with d4T if AZT poorly tolerated)
	RAL is recommended as preferred third drug where available for HIV PEP in children. If RAL unavailable, then ATV/r is recommended
Prescribing frequency	A full one-month course of antiretroviral drugs should be provided for HIV PEP at initial assessment
	Starter packs should not be used
Frequency of follow-up	Exposed individual should be seen at 2 weeks, 6 weeks and 3 months after exposure occurred
Adherence support	Enhanced adherence counselling is recommended for all individuals initiating PEP

PEP, post exposure prophylaxis; TDF, tenofovir; 3TC, lamivudine; FTC, emtricitabine; RAL, raltegravir; ATV/r, atazanavir/ritonavir; LPV/r, lopinavir/ritonavir; DRV/r, darunavir + ritonavir; EFV, efavirenz; AZT, zidovudine.



Source: Adapted from WHO PEP 2014 guideline (World Health Organization. Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: Recommendations for a public health approach: December 2014 supplement to the 2013 consolidated ARV guidelines. Geneva: World Health Organization; 2014)
PEP, post exposure prophylaxis; SE, side-effect.

FIGURE 1: Care pathway for individuals exposed to HIV.

world studies, where HIV epidemiology is significantly different and HIV prevalence considerably lower, may underestimate the risk of exposures in the southern African setting. However, due to ethical considerations and the numbers that would be needed to obtain RCT data, in the context of the relatively low rate of transmission associated with occupational exposure (if all parenteral exposures are considered together, the transmission risk is 0.3% per exposure),[3] we are unlikely to obtain much additional or quality 'pure PEP' data than what we currently have. In addition, PrEP studies consistently show that PrEP works when used properly, making it ethically questionable to conduct studies with PEP as a sole prevention intervention. In fact, there is a shift towards combination approaches to the prevention of HIV infection, of which PEP is only one component in a complex of prevention interventions.

Previous guidelines differentiated between occupational and non-occupational exposures. Given the very high background prevalence of HIV infection in the southern African region, HIV exposure risk outside the occupational setting is high, and the distinction between occupational and non-occupational exposure is less helpful for decision-makers. Further complicating the problem is the high rate of sexual assault in South Africa, and the large number of individuals with acute or primary HIV infection within the community. The generalised nature of the epidemic creates differences in risk group demographics that must be accommodated by local PEP guidelines. Finally, 'non-traditional' exposures, such as pre-mastication, tattoos, cuts from roadside barber's shears and other exposures listed below, often require clinician advice.

Whilst the actual management of exposure is the same whether the exposure was occupational or non-occupational, it is essential to document and manage occupational exposures appropriately, for possible subsequent compensation (including completion of the appropriate Compensation for *Occupational Injuries and Diseases Act* [COIDA] forms). This is also important in cases of sexual assault where legal and criminal proceedings may ensue.

The present update to the PEP guidelines seeks to harmonise with the WHO PEP guidelines (2014) by alignment with WHO principles, and promoting simplification and adherence support to individuals receiving PEP (see Figure 1).

The guidelines do not address PMTCT settings, PrEP or the comprehensive management of sexual assault. Local guidelines should be consulted as appropriate.

Scale of the problem

About 3 million percutaneous exposures to bloodborne viruses occur globally amongst HCWs annually. A survey of more than 2400 USA HCWs showed that more than half had experienced a percutaneous injury in their career, and almost a quarter in the last year.[4] A study in northern India demonstrated exceedingly high exposure rates, with 63% of participants reporting a percutaneous injury in the previous year, compared with the US data above.[5] Mucocutaneous and percutaneous exposures over the previous week in the Indian study were reported at 11% and 30% respectively. These figures are not uncommon in lower income countries, with 55% of HCWs in Uganda and 57% of injection providers in Mongolia experiencing a percutaneous exposure in the last year.[6,7]

Data from the southern African region are limited and poor. The largest study from three West African countries documented that 45% of HCWs had sustained at least one accidental blood exposure, over 60% of which went unreported.[8] In 2001, 69% of interns at Chris Hani Baragwanath Hospital in Gauteng, South Africa, had sustained at least one percutaneous injury, and 45% had sustained a mucocutaneous blood risk exposure.[9] Again in this cohort, over 60% of exposures were not officially reported. At Tygerberg Hospital, Cape Town, 91% of junior doctors reported needlestick exposures in the prior year, three-quarters of these 'after hours' or during calls.[10]

Despite regulatory frameworks being in place in some countries, management oversight regarding occupational accidental blood exposure is largely lacking in southern African institutions, especially as far as the handling of sharps disposal and training in safe exposure practices are concerned.

In terms of non-occupational exposure, HIV transmission data for rape (a common experience for women, children and not a few men) are poor. There are almost no data on other forms of exposure; however, the continued high incidence and prevalence of HIV in southern Africa amongst the general population suggests that exposure is ongoing and high risk. Advice is frequently sought from clinicians regarding PEP following assault, traffic accidents and other trauma-related events where blood exposure occurs.

Core principles of post-exposure prophylaxis

- Occupational exposure prevention requires strong management oversight in all settings.
- Non-occupational exposure requires an understanding of core transmission principles, combined with clinical common sense.
- In the southern African setting, all unknown source exposures should be assumed to be HIV-positive.
- Evidence regarding occupational and non-occupational risks of transmission for southern Africa is limited, and may underestimate transmission risk in our setting.
- Triple ARV regimens in treatment settings have been proven superior to mono or dual therapy regimens. However, in the setting of PMTCT and PrEP, mono and dual drug regimens have proven effective.
- It is recognised, however, that additional ARVs increase the potential side-effect and adherence burden. Risk of adverse effects and toxicities must be weighed against benefit in administering ARVs in the PEP setting. However, with increasingly well tolerated ARVs that are available, side-effects are becoming less of a problem. Nonetheless, side-effects must be treated rapidly, effectively and, where possible, avoided entirely. Ensure that the individual is aware of potential side-effects and has been advised how to deal with any that may arise. Patients should be advised that when in doubt they should rather see a healthcare provider as soon as possible and should only discontinue PEP under the guidance of a healthcare provider.
- PEP should be administered as soon as possible after exposure; efficacy after 72 hours is highly unlikely.
- To facilitate administering the first PEP dose as soon as possible after exposure, any ARV drug combination that is easily available can be used for the first dose, but the patient should not leave without a full month's supply (or prescription for a full month's supply) of the recommended regimen, namely TDF + FTC/3TC + RAL or TDF + FTC/3TC + ATV/r in pregnancy.
- Starter packs are not recommended owing to the high rate of default, as the exposed individual is often lost to care and does not return for the rest of the one-month supply.
- All PEP regimens must be administered for 28 days. Animal and case control studies suggest that administration for less than 2 weeks is associated with minimal efficacy; administration for more than 28 days confers no added benefit. Most ARVs are in packs of 30 tablets, and the full pack should be dispensed at the first visit.
- Regimens need to be selected using locally available ARVs.
- A comprehensive infrastructure of counselling and support for the exposed party is necessary to facilitate adherence to PEP regimens. Exposure is associated with substantial anxiety for most people; this must be dealt with actively. In many cases, anxiety is most significant for those who do not need PEP.
- Counselling must be available to deal with side-effects on an ongoing basis. AZT and PIs are commonly associated with side-effects.

Balancing risks and benefits in post-exposure prophylaxis

People with HIV infection have a near-normal lifespan provided that ART is not started too late, so the risks of PEP

need to be more carefully considered than in the past. On the other hand, newer antiretroviral drugs are considerably safer than most of the older agents. Most international guidelines on PEP, including those of the Southern African HIV Clinicians Society, recommend three antiretroviral drugs for both low- and high-risk exposures. There are no controlled data on the efficacy of any PEP regimen. There are also limited controlled data on the safety of ARVs in HIV-uninfected people, except for TDF + FTC from pre-exposure prophylaxis trials. It cannot be assumed that antiretroviral safety will be similar in HIV-infected and HIV-uninfected people, as illustrated by the severe toxicity of NVP when used in PEP. Therefore it is not possible to accurately determine risk-to-benefit ratios for PEP.

Life-threatening adverse drug reactions from currently recommended antiretroviral drugs are uncommon, probably occurring in about 1 in 1000 people, except for FTC and 3TC, which are considerably safer. People on the month-long course of PEP are at risk of life-threatening reactions, as many of them occur early (e.g. acute renal failure from TDF, severe hypersensitivity reactions). Therefore the number needed to harm (with life-threatening adverse drug reactions) may be similar to or lower than the number needed to treat to prevent one HIV infection when three-drug PEP is used following low-risk exposures.

In the absence of definitive data, clinical judgement needs to be exercised when balancing risks and benefits for PEP. It is reasonable to start three-drug PEP following an HIV exposure event. However, clinicians should have a low threshold to switch or stop offending antiretroviral drugs, should potentially severe adverse drug reactions occur. There may still be a place for two-drug PEP for very low-risk exposures.

Prevention of exposure

Awareness of the risks and activities related to transmission of HIV, as well as availability of PEP and support, is critical, especially in an occupational setting. HCWs in traditional exposure environments often receive training regarding this hazard. Other potential areas where PEP should be available include, but are not restricted to, home-based carers, day centres and crèches, schools and prisons, where PEP exposure and treatment training are often poorly available.

Exposure to HIV occurs in a variety of situations, which HCWs should be aware of (see Box 1).

Prevention of HIV exposure in the workplace

Prevention of exposure to HIV and other blood-borne viruses in the workplace is the responsibility of both employer and employee. It is a legal requirement in many southern African countries for employers to provide a safe working environment and to ensure that employees adhere to workplace guidelines for infection control. South Africa has an extensive legal framework and comprehensive codes and guidelines dealing with this issue. Employers have specific and numerous responsibilities with regard to workplace safety and staff support. The meticulous recording and reporting of incidents is critical; this responsibility usually rests with a medical practitioner.

BOX 1: Potential HIV exposure situations.

Exposure to HIV can occur in a vast variety of situations. Exposures where clinicians have requested advice regarding PEP, often where the source HIV and hepatitis status is unknown, include:

- Human bites or exposure to bloody phlegm during fights.
- Exposure at schools, including biting in crèche.
- Contact sports with blood exposure, such as rugby and boxing.
- Sharing needles during recreational drug use.
- Assaults with several people being stabbed with the same knife.
- Bullets travelling through one person and lodging in another.
- Animal attacks with repeated blood exposures on several people at once.
- Roadside and emergency services exposure – often not only by ambulance staff, but also police, bystanders who help.
- Exposure during home deliveries or during home-based care.
- Consensual sexual exposure, burst condoms, mucosal exposure during non-penetrative sex.
- Families, home-based carers.
- Catering, preparation and serving of food with blood contamination.
- Sitting on a needle in a movie theatre.
- 'Venoterrorism' – public attacks with needles.
- Unconscious drug user found in a room.

The following exposures do not require PEP:

- Exposed individual is already HIV-positive.
- Source is confirmed HIV-negative by laboratory ELISA test and the window period has been excluded.
- Exposure to bodily fluids that do not pose significant risk of HIV transmission: tears, non-bloodstained saliva, sweat and urine.

HIV, human immunodeficiency virus; PEP, post exposure prophylaxis; ELISA, enzyme-linked immunosorbent assay.

BOX 2: Who is at risk of occupational exposure to blood-borne viruses?

Healthcare workers

- Doctors
- Dentists
- Nurses
- Traditional healers
- Phlebotomists
- Laboratory workers
- Physiotherapists
- Occupational therapists
- Paramedics

Non-healthcare workers

- Firemen
- Commercial sex workers
- Teachers
- Prison warders
- Bar bouncers

A broad range of professionals practising within the healthcare service and outside the Department of Health is at occupational risk of blood-borne viral exposure (see Box 2).

Special situations: Healthcare situations

Occupational exposure involves potentially hazardous exposure to blood-borne viruses in the workplace:

- All occupational exposure should be regarded as preventable and hence deserving of investigation until proven otherwise.
- Standard precautions should be practiced in every setting where blood or infectious body fluid contact is possible. Gloves should be worn and, where appropriate, protective eyewear.

- Clean water or saline should be available to immediately irrigate any mucosal exposure or percutaneous injury. Use non-caustic soap. Only use water or saline if the exposure involves the eye.
- Needles should *not* be re-sheathed, and manipulation of the needle following withdrawal from the patient must be kept to the absolute minimum.
- Wherever possible, safety equipment for blood taking should be available, particularly in the hospital and clinic setting where the risk of exposure to HIV-infected blood is highest. It is imperative that the cost of cheaper equipment and disposal must be weighed against the potential increased risk of exposure that using such equipment entails.
- Needles and tools for any surgical practice, including traditional circumcision, should never be re-used without rigorous chemical disinfection/sterilisation according to national or local guidelines.
- All needles and sharp objects should be disposed of into a dedicated biohazard sharps bin. Syringes and other blunt instruments should *not* be disposed of in these bins, but rather in regulation biohazard bins for disposal of blunt biohazard objects.
- The number of sharps bins allocated to each workplace area will depend on the setting and the resources available. It is recommended that, in hospital settings, designated areas of high throughput of patients who require a large number of invasive procedures, such as intensive care and emergency departments, should have a ratio of sharps bins to beds of either 1:1 or 1:2. Isolation rooms should have their own sharps bins, as should any clinic area in which blood taking or invasive procedures are undertaken. The ratio of sharps bins to beds in open wards should ideally be 1:2, but at least one bin per bay.
- Once three-quarters full, the sharps bin should be sealed and disposed of to prevent obstruction of the opening; overfull bins are a risk factor for injury during subsequent sharps disposal (Figure 2). In resource-poor settings where sharps bins are unavailable, the safest and most practical method of sharps disposal should be practiced as per local or national guidelines.
- Within the hospital or clinic environment, it is the ultimate responsibility of that institution's infection control team to monitor and ensure that sharps bins are sealed when three-quarters full and disposed of correctly. However, on a day-to-day basis, this responsibility falls to the nursing sister in charge of the ward or clinic.
- Outside the healthcare setting, employers must take responsibility for such monitoring and enforce standard practice as laid out above.
- Best practice should be enforced with the aid of unions within the framework of occupational law to ensure that employers and employees create a safe working environment regarding prevention of blood-borne disease acquisition.

Source: Provided by the authors

FIGURE 2: Unsafe sharps bin.

Other situations

Post-sexual exposure prophylaxis is indicated for those who present within 72 hours of unprotected risky sexual activity including, but not limited to, penetrative intercourse and including, but not limited to, survivors of sexual assault. As a public health intervention, equal access to treatment of all sexual exposures, including rape, is essential to equality of prophylaxis and minimisation of HIV transmission:

- There is often considerable variation in clinical presentation of exposure situations, making it almost impossible to establish standard operating procedures for control of exposure, as may be possible in healthcare settings.
- The complications of criminal, civil and medico-legal elements, particularly in the case of criminally defined rape, are specialised elements of care that are beyond the scope of the present guideline. Applicable local guidelines should be consulted in such cases.
- PEP should be given as part of a package of care to women subjected to sexual assault, including support, emergency contraception and prophylaxis for additional sexually transmitted infections (STIs) in combination with psychological interventions (the details of this package of care are beyond the scope of this guideline – please consult applicable local guidelines).
- Other people who have been sexually assaulted need to have psychosocial issues addressed in combination with PEP as part of a package of care; this would include men, children and adolescents who have been sexually assaulted.
- Given the emotional and psychological trauma experienced by many of the patients who present after sexual assault, HIV-specific counselling may be appropriately delayed for 24–48 hours after onset of PEP regimens.
- It is recognised that the post-sexual assault situation has a high rate of therapy default, complicating all aspects of management.
- The choice of ARVs when several other agents are being utilised for pregnancy prophylaxis, STI syndromic

management, and various medications to treat side-effects of trauma, is complicated. Despite the strong empirical arguments for triple ARV prophylaxis in this setting, a default to dual therapy with minimal short-term side-effects may be considered in individuals where there are concerns regarding adherence, or where an integrase inhibitor is not available as a third drug, with full disclosure of the potential risk of this strategy to the patient. Alternatively, more ARVs with better tolerability profiles are available and consideration should be given to switching the offending agent to a different one. There is no real evidence that a third drug in PEP gives any additional protection. In addition, prophylactic management, such as anti-emetics and antidiarrhoeals, should be considered as upfront therapy, given the high rate of PEP defaulters.

Sexual exposure outside of a relationship, where disclosure concerning the exposure is not desired

This is a common and thorny problem faced by clinicians, with ethical and social implications. Marriage and long-term relationships are almost always assumed within our society to be monogamous, although 'straying' from the relationship is very common in all communities. Whilst a single episode of unsafe sex overall carries a low risk of HIV exposure, they may, should the exposed partner become positive, have a very high viral load during the seroconversion phase, and unprotected sex will carry a very high risk to the regular partner, whether PEP is given or not. We advise providing PEP for people who have had unprotected sex with a partner of known HIV-positive or unknown HIV status. Sudden cessation of regular sexual relationships or introduction of condoms can cause relationship disruption, and the exposed partner may be reluctant to do this. This situation raises issues concerning the duty of the HCW to disclose to the partner, and requires a very careful and individual approach. Any decision to disclose against the wishes of the exposed person to the partner must be carefully discussed with colleagues, representative organisations and medical defence organisations. Patients may require help with strategies around disclosure. Where the exposed individual is not putting their sexual partners at risk, for example by consistently using condoms, disclosure is not strictly necessary. Where the exposed individual is placing others at risk, the issue of disclosure or facilitated disclosure becomes relevant.

Children

Principles around exposure for children are biologically similar to those for adults. As in pregnancy, newer agents have often not been tested in children and dosages might not have been determined. Therefore, recommended medications and dosages may differ and it is important to check doses carefully. Psychological and legal consent issues may differ from adults, and clinicians should be guided by local legislation. Children often do not give accurate histories, and anxious parents, especially in the context of possible sexual assault, may require significant counselling and careful referral.

Pre-mastication of food is commonly practised in both developed and developing countries, and several cases of transmission from caregivers to children have been described in the USA. This practice should be actively discouraged.

Another source of potential infection, through breast milk, is using wet nurses, as well as milk kitchens (the practice of pooling breast milk, and then transferring to bottles in healthcare facilities).

Finally, children are exposed to other children's behaviours, which may theoretically have transmission risks, such as biting. Most cases of biting do not pose a risk of HIV transmission in children, but if there is blood in the mouth of the biting individual (e.g. bleeding gums owing to gingivitis), or if the skin of the bitten child is breached, there is a theoretical risk of transmission.

Principles of PEP in children are the same as in adults, although managing parent anxiety is often a huge challenge.

Selecting patients for antiretroviral interventions

Potentially infectious material

The following should be regarded as infectious material:

- blood (and *any* bloodstained fluid, tissue or material)
- sexual fluids
- vaginal secretions
- penile pre-ejaculate and semen
- tissue fluids
- any fluid drained from a body cavity, including ascites; cerebrospinal, amniotic, rectal, peritoneal, synovial, pleural or pericardial fluids; and wound secretions
- breast milk.

Parenteral or mucosal exposure requires antiretroviral PEP intervention, as described in the present guideline.

In the absence of super-contamination with the above fluids, the following may be considered non-infectious:

- sweat
- tears
- saliva and sputum
- urine
- stool.

Exposure to HIV occurs in a vast variety of situations, which healthcare professionals (HCP) should be aware of (see Box 2). Exposure to non-infectious material requires reassurance but no PEP. A special circumstance involves human bites and punching. Where a bite or a punch has resulted in opening of the skin, PEP should be advocated,

TABLE 2: Selecting patients for preferred for post-exposure interventions.

Type of exposure	Status of the source		
	HIV-positive	Unknown	HIV-negative
Percutaneous exposure to blood or potentially infectious fluids	Triple prophylaxis	Triple prophylaxis	No PEP
Mucous membrane exposure, including sexual exposure, mucocutaneous splash or open wound contact, with blood or potentially infectious fluids	Triple prophylaxis	Triple prophylaxis	No PEP
Mucous membrane exposure, including sexual exposure, mucocutaneous splash or open wound contact, with non-infectious fluids	No PEP	No PEP	No PEP

PEP, post exposure prophylaxis

bearing in mind that in the case of human bites, the possibility that both the person bitten and the person who inflicted the bite were exposed to blood-borne pathogens.

PEP should be offered and initiated as early as possible after exposure, ideally within 72 hours, to all individuals with exposure that poses a risk for HIV transmission, and should be continued for one month. In exceptional cases involving high-risk exposures, PEP may be considered up to 7 days after exposure. It is advisable to discuss such cases with an experienced HIV clinician.

Selecting antiretroviral regimens for post-exposure prophylaxis

Recommended post-exposure prophylaxis antiretroviral regimen

The choice of PEP combinations is based on available evidence in both prevention (including PrEP and PMTCT) and treatment settings; side-effect profiles; ease of use; local guidelines; and availability. In addition, the present PEP guidelines are aligned with the latest WHO PEP guidelines, released in December 2014, which now recommend three drugs as the preferred option for PEP, and no differentiation in regimen according to the type of exposure, namely occupational versus non-occupational. This approach is part of a move towards simplification of prescribing to improve availability of PEP and to reduce the time to PEP initiation. With the availability of less toxic and better tolerated drugs, providing a three-drug regimen supports simplified prescribing by removing the need to evaluate the risk of resistance, which was the basis upon which the decision to initiate two- versus three-drug PEP was previously made. While PEP completion rates are generally less than optimal, there is evidence that completion rates are similar when comparing two-drug to three-drug PEP (see Box 3).

BOX 3: Post-exposure prophylaxis recommendations.

In adults and adolescents ≥ 35 kg:

- The preferred backbone for PEP is TDF + FTC/3TC.†
- Raltegravir (RAL) is the preferred third drug (except in pregnant women, where ATV/r is the preferred third drug).
- Alternative third drugs include ATV/r, LPV/r, DRV/r or EFV.
- It is imperative that the first dose of PEP is administered as soon as possible after exposure; if the 3 recommended drugs are not immediately available, use whatever suitable ARV medication is available to start.
- All PEP regimens must be administered for one month.

PEP, post exposure prophylaxis; TDF, tenofovir; FTC/3TC, emtricitabine/lamivudine; RAL, raltegravir; ATV/r, atazanavir/ritonavir; LPV/r, lopinavir/ritonavir; DRV/r, darunavir/ritonavir; EFV, efavirenz; ARV, antiretroviral.
†, AZT is poorly tolerated in PEP settings, whilst TDF + FTC/3TC has a better safety profile, and is similar in cost to AZT + 3TC. TDF + FTC/3TC is also recommended for PrEP. Owing to poor tolerability of AZT in PEP, d4T is well tolerated in short-term use and should be used where TDF is contraindicated.

Justification for three versus two drugs and for choice of antiretrovirals preferred for post-exposure prophylaxis

As in the previous guideline, the present update recommends that, where PEP is to be provided, three drugs should be administered. The basis of this recommendation is manifold.

Current North American Centers for Disease Control and Prevention (CDC) and UK guidelines are based on risk assessments in low-prevalence settings, with presumed exclusive clade B data. In contrast, the southern African situation is one of extremely high HIV prevalence (clade C), high volumes of patients, and an attendant very high number of exposures. The individual and cumulative risk of HIV transmission in this setting has never been quantified. There are limited data suggesting that clade C is more infectious in the sexual exposure setting. We assume that this risk is significantly higher than in other settings, and the exposed individual should therefore be treated appropriately. For key populations, such as men who have sex with men (MSM), intravenous drug users, prison populations and others, the risk is even higher than penile-vaginal penetration, which adds further weight to this recommendation.

Whilst previous guidelines advocated two or three drugs based on clinician assessment of risk, the SA HIV Clinicians Society has recommended three drugs in all exposure situations since 2008. There is no evidence backing the use of two drugs over the single-agent AZT. We further note that the PMTCT trials suggest no added advantage of adding 3TC to AZT, a finding replicated in various cohort PMTCT studies. Several PrEP studies have shown TDF + FTC to be superior to TDF alone in preventing HIV infection occurring in study participants. In addition, the use of triple-therapy ART regimens has been shown to have significant benefit in comparison with dual therapy in treatment settings. Whilst no evidence exists to support the use of such combinations in humans in PEP scenarios, all current PEP guidelines advocate triple prophylaxis regimens in 'high-risk scenarios'. The argument is therefore not one of two or three drugs, but of what constitutes 'high-risk scenarios'. Southern Africa, with its high prevalence, large numbers of patients and high number of exposures, should be considered a high-risk scenario.

Of particular contention are mucous membrane exposures and oral sex scenarios, which are associated with lesser risk. The CDC guideline is based on a single known transmission out of almost 10 000 reported incidents. Again, no evidence of risk is available in our setting, but evidence of significantly higher exposures in comparison to the US setting (blood

spatters on eyeglasses, masks in low-, medium- and high-risk procedures) is available. Furthermore, blood risk exposures are chronically underreported, a factor that is likely to be particularly true of injuries that are deemed to carry a lesser risk, meaning the incidence may be greater than we think. For these reasons, coupled with the known high background HIV prevalence, we advocate three-drug PEP in these scenarios. However, the extremely low risk of transmission via these routes should be discussed with the exposed individual. On the other hand, the advocated PEP triple regimen is very well tolerated compared with previously used regimens, and the exposed individual may opt to take the PEP regimen despite the low risk of transmission via mucous membrane exposure.

Finally, the risk of side-effects increases when additional agents are added to PEP regimens. Three-drug regimens carry more risk of side-effects than two-drug regimens. With the availability of more tolerable drugs, potential side-effects are fewer, and can be anticipated and managed proactively, to ensure the full month of PEP is completed. Integrase inhibitors have minimal side-effects, and are a well tolerated third drug option.

Justification for choice of antiretrovirals preferred for preferred for post-exposure

AZT-containing regimens carry such a significant side-effect profile that this agent should be avoided, and with the reduction in cost of TDF combinations, the recommended NRTI backbone is now TDF with FTC/3TC, preferably in a FDC. There is no evidence that prevention of HIV transmission by AZT in the setting of PEP is effected by anything other than its inhibition of viral replication. This supports the use of TDF, whose potency of action is equivalent to AZT, yet which is far better tolerated over one month of therapy, as a recommended NRTI in PEP. Whilst the risk of adverse events is undeniably real, it must be balanced against the often unquantifiable but equally real risk of transmission associated with high HIV prevalence, high individual viral load levels, and high levels of exposures in occupational and non-occupational settings.

TDF is usually avoided in patients on ART with renal failure or eGFR < 50 mL/min. In the setting of PEP, the duration of TDF administration is short. Comparative data from three randomised trials for ART and PrEP and from observational studies with PEP support the use of TDF + FTC/3TC as the preferred backbone in PEP. Indirect comparisons between AZT + 3TC versus TDF + FTC/3TC across 15 studies demonstrate less PEP discontinuation due to adverse events in individuals receiving TDF + FTC/3TC than AZT + 3TC. However, where there are concerns regarding the use of TDF, d4T is very well tolerated when it is used for short periods and, given the poor tolerability of AZT in PEP regimens, would be the recommended NRTI to use in such cases.

There may be a risk of hepatic flares in individuals chronically infected with HBV who discontinue PEP containing TDF, 3TC or FTC, as has been seen in some patients on ART who switch away from these drugs. Such individuals should be monitored for hepatic flare if these drugs are not continued for HBV treatment. Where HBV testing is available, those with unknown HBV status should be tested for active HBV infection, to assess the need for ongoing HBV therapy.

In terms of third drug options, there are many agents which may be suitable for use in PEP but which may have limitations such as cost and availability in low- and middle-income countries, such as in the southern African region. There are studies that provide data on lopinavir + ritonavir (LPV/r), ATV/r, darunavir + ritonavir (DRV/r) and raltegravir (RAL) as part of triple-combination PEP, but offer little guidance on their efficacy.

The present guideline recommends using RAL as the third drug, with ATV/r, LPV/r, DRV/r or efavirenz (EFV) as alternatives where RAL is not available or cannot be used. RAL in combination with TDF + FTC/3TC (as an FDC) is the preferred PEP regimen on account of its tolerability, potency, convenience and minimal drug interactions. This regimen differs from WHO recommendations, which advocate the use of LPV/r or ATV/r as the third drug in PEP, as they are currently used in ART and are widely available in low- and middle-income countries, which is not always the case with RAL or DRV/r because of the higher cost of these agents.

If the three recommended drugs are not immediately available, this should not delay the initiation of PEP. It is imperative that PEP is started as soon as possible after exposure; in cases where the recommended 3 drugs are not immediately available, an alternative 3-drug combination can be given immediately. However, the patient must not leave without a full month's supply of the recommended 3 drugs.

There are other newer drugs that might be useful as part of a PEP regimen, but there are no data supporting their use in PEP specifically. The drugs include dolutegravir (high potency, tolerability and once-daily dosing); rilpivirine (high tolerability and low cost) and elvitegravir (tolerability and convenient coformulation). Once dolutegravir becomes available in South Africa, it is likely to replace RAL as the third drug of choice in PEP, with advantages being once-daily dosing (compared with RAL which is twice a day) and the possibility of dolutegravir-containing FDCs.

EFV is currently the preferred third drug in first-line ART, and is generally well tolerated in the long term; however, it is associated with early nervous system and psychiatric side-effects that limit its use in PEP. Owing to the possibility of high levels of anxiety in the exposed individual, EFV should only be used as the third drug where other drugs cannot be used.

Nevirapine (NVP) and abacavir (ABC) are not recommended for PEP, on account of their risk of serious side-effects.

Justification for duration preferred for post-exposure

A one-month prescription for ARVs should be provided for PEP. This is supported by animal study data that demonstrate that a full 28-day course is necessary to achieve maximum benefit from the intervention and prevent seroconversion.

Before the widespread availability of rapid HIV tests, starter packs of PEP were dispensed to ensure testing and counselling could be completed, accommodating the longer turnaround time of the available tests. However, it is now recommended that the full one-month course is dispensed to improve completion rates, which are lower amongst those exposed who received partial prescriptions than those receiving the full course at the initial visit.

Providing the full course removes the need for a 3-day follow-up visit, reducing the burden on facilities, as well as being more convenient for exposed individuals. However, they should be fully informed about the side-effects of the PEP regimen, and advised to return to the facility if they have any concerns, side-effects or adherence problems prior to their scheduled follow-up visit. A follow-up appointment for 2 weeks should be scheduled, and at this visit any side-effects should be proactively identified and managed, and appropriate counselling provided. The next appointment should be scheduled for 6 weeks post-exposure, where appropriate laboratory tests will be done (as per Table 4).

Routine baseline and follow-up investigations

Investigating the source individual

Where the source individual is known, every effort must be made to gain their voluntary, informed consent to have the necessary laboratory tests performed, in accordance with Health Professions Council of South Africa (HPCSA) guidelines and national policy regarding HIV testing. If the source individual is unknown, unavailable for testing, or refuses testing after appropriate counselling, the default position should be that the source is seropositive for HIV. If a source individual is unable to give consent because of an impaired level of consciousness, national guidelines allowing testing in such circumstances should be followed. Testing of the source should be undertaken as soon after the injury as possible. Testing of needles, sharps or other samples that have been implicated in the exposure is not recommended, even when the source is unknown or refuses testing. Such investigations are unreliable and pose a risk of further exposure to the HCWs undertaking the testing.

The tests that should be performed on blood from the source individual are shown in Table 4. If the source is found to be positive on any of the tests undertaken, they should receive post-test counselling and either be treated or referred to their local healthcare facility for further management.

TABLE 3: Doses of antiretrovirals for HIV preferred for post-exposure in adults and adolescents.

Generic name	Dose
Tenofovir (TDF)	300 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Emtricitabine (FTC)	200 mg once daily
Stavudine (d4T)	30 mg twice daily
Raltegravir (RAL)	400 mg twice daily
Atazanavir/ritonavir (ATV/r)	300/100 mg once daily
Lopinavir/ritonavir (LPV/r)	400/100 mg twice daily or 800/200 mg once daily†
Darunavir + ritonavir (DRV/r)	800/100 mg once daily or 600/100 mg twice daily
Efavirenz (EFV)	600 mg at night (400 mg if weight < 40 kg)

Source: Adapted from World Health Organization. Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: Recommendations for a public health approach: December 2014 supplement to the 2013 consolidated ARV guidelines. Geneva: World Health Organization; 2014
†, Once-daily dosing can be considered as an alternative for adults, but more data needed for children and adolescents.

HIV testing

A nationally approved HIV test should be performed by a HCW who is trained in this procedure, with pre- and post-counselling, and formally documented.

A positive rapid test should be confirmed, as per national guidelines, and the source patient managed as per guidelines. If the diagnosis of HIV is confirmed in the source patient, they must be linked with treatment and care services immediately.

For source patients on antiretrovirals, HIV RNA PCR should be performed where available. If the viral load is not fully suppressed, genotypic testing should be considered, although this is of uncertain value. This test should, however, not delay initiation of PEP. Detectable viral load results should be discussed with an expert. If viral load testing and/or genotyping are not available, and if resistance is suspected, a boosted PI should always be used as the third drug.

As the plasma viral load measures only the level of cell-free virus in peripheral blood and so an undetectable viral load does not exclude low-level viraemia, the possibility of transmission from a source patient with an undetectable viral

TABLE 4: Timing of bloods pre- and post-preferred for post-exposure.

Laboratory tests	Source: Baseline	Exposed			
		Baseline	2 weeks	6 weeks	3 months
HIV	Rapid test *plus* 4th-generation ELISA	Rapid test *plus* 4th-generation ELISA	-	4th-generation ELISA	4th-generation ELISA
HBV	HBsAg	HBsAb‡	-	-	HBsAg‡
HCV	HCV Ab†	HCV Ab§	-	HCV PCR§	-
Syphilis	RPR/TP Ab	RPR/TP Ab§	-	-	RPR/TP Ab§
Creatinine	-	If TDF part of PEP	If TDF part of PEP	-	-
FBC	-	If AZT part of PEP	If AZT part of PEP	-	-

HBV, hepatitis B virus; HCV, Hepatitis C virus; FBC, full blood count; ELISA, enzyme-linked immunosorbent assay; HBsAg, hepatitis B surface antigen; Ab, antibody; RPR, rapid plasma reagin; TP, *Treponema pallidum*; HBsAb, hepatitis B surface antibody; TDF, tenofovir; PEP, post exposure prophylaxis; AZT, zidovudine; PCR, polymerase chain reaction.
†, Only if high risk for HCV or source unknown; ‡, can be omitted if exposed individual known to be protected (natural immunity or vaccination); §, only if source patient was positive.

load is not eliminated. In such cases, the exposed individual should still be offered PEP and appropriate follow-up.

HIV and hepatitis B virus testing

Testing of the source for hepatitis B surface antigen (HBsAg) can be omitted when the exposed individual is known to be protected from hepatitis B acquisition by natural immunity or vaccination.

Hepatitis C virus testing

Hepatitis C virus (HCV) is rare in SA and we do *not* recommend testing unless the source individual is an intravenous drug user, MSM, haemophiliac or from a high HCV prevalence setting, or where the source is unknown. In such cases, the source should be tested for HCV Ab. If the source is HCV-negative, the exposed individual should be tested at baseline to assess their own HCV status, and no further HCV testing will be necessary in further follow-up. However, where the source is HCV-positive and the exposed individual is HCV-negative at baseline, HCV PCR testing should be done at 6 weeks.

Other blood-borne pathogens

Syphilis: routine testing of source should be performed. Malaria: malaria blood films should *not* be routinely sent from source patients, unless there is clinical suspicion that the source has malaria.

Investigating the exposed individual

It is strongly recommended that any investigation on the blood of an exposed person should be requested and taken by an independent third party. If infection is proven, baseline investigation for blood-borne viruses forms a vital part of any future compensation claim.

HIV testing

Pre- and post-test counselling should be offered to all exposed persons at all testing facilities. A baseline HIV rapid test, followed by 4th-generation ELISA as confirmation should be performed and the results carefully documented. As many cases have medico-legal or occupational claims implications, it is recommended that formal laboratory testing be done in all cases. Confirmatory testing of a positive result should be undertaken per standard guidelines.

Follow-up testing for HIV seroconversion should be undertaken at 6 weeks and 3 months post-exposure. We do not advocate routine testing of an exposed worker at 6 or 12 months, as current ELISA tests (4th generation) have reduced the window period considerably.

In exposed individuals, testing beyond 3 months is advised in the following settings:

- ongoing high-risk behaviour
- a specific exposure incident within the last few months can be identified
- HIV status at 3 months is indeterminate.

Viral load or p24 antigen testing is not recommended in the setting of PEP. Quantitative viral loads may yield false-positive results, and may cause substantial anxiety. Seroconversion on PEP is extremely rare; any exposed individual thought to be experiencing a seroconversion illness on PEP should be discussed with an HIV specialist physician for advice. If an exposed individual tests HIV-positive at any stage, they should be linked to treatment and care services as soon as possible.

Hepatitis B testing

The risk of transmitting the HBV is higher than that of HIV in most exposures, especially in the healthcare environment. If the exposed worker has had prior HBV infection or has been vaccinated and is a known responder, then no investigation or post-exposure therapeutic intervention for HBV is required.

If the source individual tests HBsAg-negative and the exposed individual is not vaccinated or does not know their vaccination/antibody status, they should be referred to a local facility for testing and vaccination. In the case of exposure to an HBsAg-positive source, the options for management of unvaccinated individuals or those whose status is unknown are as detailed in Table 5.

TABLE 5: Management of an individual exposed to an HBsAg-positive or unknown source.

Vaccinated status of exposed	HBV vaccine	HBIG (0.06 mL/kg)	HBsAb
Previous vaccination; known responder	None	None	Not done
Not vaccinated	1st dose stat and proceed to accelerated schedule (0, 1 and 6 months)	If HBsAb < 10 IU/mL, give stat HBIG and repeat at 1 month	If HBsAb > 10 IU/mL, no treatment
Incomplete vaccination or unsure	Complete depending on documentation, or restart 0, 1 and 6 months	Single dose stat	-
Vaccinated; unknown response	Single booster stat		
Non-responder to prior vaccination	1st dose stat and proceed to accelerated schedule 0, 1 and 6 months	1 dose stat, repeat after 1 month	HBsAb < 10 IU/mL
Previously vaccinated with four doses or two completed vaccine series; non-responder	Consider alternative vaccine	-	-

Comment: HBIG and HBV vaccine can be administered concomitantly at different sites.
HBV, hepatitis B virus; HIV, human immunodeficiency virus; HBIG, hepatitis B immunoglobulin; HBsAb, hepatitis B surface antibody.

Hepatitis C virus testing

- Only if the source individual is an intravenous drug user, MSM, haemophiliac or from a high HCV prevalence setting, or where the source is unknown.
- In such cases, the source should be tested for HCV Ab. If the source is HCV-negative, the exposed individual should be tested at baseline to assess their own HCV status, and no further HCV testing will be necessary in further follow-up.
- However, where the source is HCV-positive and the exposed individual is HCV-negative at baseline, HCV PCR testing should be performed at 6 weeks.

Other blood-borne pathogens

Malaria: routine testing of an individual who has been exposed to a source is *not* recommended unless the source is symptomatic.

Sexually transmitted infections

In cases of sexual exposure, exposure to other sexually transmitted infections might have occurred. If symptomatic, manage syndromically. Otherwise, appropriate prophylaxis should be provided to the exposed individual. However, these guidelines do *not* deal with the comprehensive management of sexual assault. Appropriate guidelines should be consulted for sexual assault cases.

Pregnancy

All exposed women should be screened for pregnancy at the time of the incident and subsequent follow-up. Emergency contraception should be offered to all women of childbearing age who present after accidental exposure or sexual assault, in line with relevant guidelines.

Tetanus

Individuals who have wounds such as abrasions, cuts or bites should be asked about their tetanus immunisation status, and be offered immunisation if appropriate.

Follow-up: Monitoring for adverse drug reactions

Side-effects

The present guideline's emphasis on appropriate choice of agents to minimise side-effects, on close management of the individual patient through the PEP process, and on the aggressive prophylactic and therapeutic management of side-effects, allows a great deal of amelioration of the side-effect risk. This approach then tips the risk/benefit balance back towards the use of the most virologically potent regimens available, namely three-drug regimens. Management guidelines to minimise exposure risk also form a large part of the present guideline, but once exposure has occurred, management of side-effects is almost always achievable, whilst the attendant risks are not. For common side-effects with the preferred and alternative PEP antiretroviral agents, see Table 6. Mainly shorter-term side-effects such as nausea, vomiting and headaches which are transient or can be managed have been included in the table. Longer-term toxicities that are unlikely to be seen with one-month PEP regimens are not included (e.g. lipoatrophy, hyperlactataemia, steatohepatitis).

Comorbidities

Patients with significant comorbidities should have regular monitoring of any relevant investigations during therapy. No additional investigations are warranted in otherwise healthy individuals.

Medical comorbidities and antiretroviral selection for preferred for post-exposure

Although many of the comorbid conditions listed in Table 7 do not preclude the use of certain ARVs, increased monitoring of the comorbid condition may be necessary during the one-month course of PEP. Moreover, whenever a safer regimen is available with equal efficacy, that regimen should be used in preference.

Drug safety in pregnancy

In pregnancy, the benefits of ARVs must be weighed against the risks of adverse events to the woman, foetus

TABLE 6: Common or severe adverse drug reactions of antiretrovirals that may be used for preferred for post-exposure.

Generic name	Drug class	Common or severe adverse drug reactions
Tenofovir (TDF)†	NtRTI†	Well tolerated. Nephrotoxicity: avoid in individuals with pre-existing renal disease†
Lamivudine (3TC)†	NRTI†	Well tolerated†
Emtricitabine (FTC)†	NRTI†	Well tolerated†
Raltegravir (RAL)†	InSTI†	Well tolerated. Occasional skin hypersensitivity, rhabdomyolysis (rare)†
Stavudine (d4T)	NRTI	Well tolerated
Zidovudine (AZT)	NRTI	Nausea, vomiting, headache, insomnia and fatigue common, anaemia, neutropenia
Efavirenz (EFV)	NNRTI	Central nervous system symptoms (vivid dreams, problems with concentration, dizziness, confusion, mood disturbance, psychosis, insomnia, somnolence), rash, hepatitis
Rilpivirine (RPV)	NNRTI	Well tolerated. Rash, hepatitis, central nervous system symptoms (all uncommon)‡
Atazanavir (ATV)	PI	Unconjugated hyperbilirubinaemia (visible jaundice in some patients), rash, hepatitis (uncommon)§
Lopinavir/ritonavir (LPV/r)	PI/r	Gastrointestinal intolerance, nausea, vomiting and diarrhoea are common§
Darunavir (DRV)	PI	Diarrhoea, nausea, headache. Rash (contains sulphonamide moiety: use with caution in patients with sulpha allergy)§

NtRTI, nucleotide reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; InSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PI/r, ritonavir-boosted protease inhibitor
†, Preferred antiretrovirals for post exposure prophylaxis; ‡, drug interactions need to be considered; §, must be boosted with ritonavir; drug interactions.

TABLE 7: Comorbidities affecting choice of antiretrovirals for preferred for post-exposure.

Comorbidity	Drug	Complication
Tuberculosis	LPV/r	Double the dose of LPV/r if patient is on rifampicin
Epilepsy	PIs	PIs increase the level of a number of commonly used anticonvulsants
	EFV	Increased risk of seizures
Psychosis	EFV	Increased risk of psychiatric symptoms
Insomnia	PIs	St John's Wort reduces all PI levels
Migraine	Migraine	All PIs increase risk of ergotism with ergotamine coadministration
Renal failure	NRTIs	Avoid TDF if creatinine clearance < 60 mL/min. Dose adjust AZT, d4T and 3TC
Hypertension	PIs	PIs increase levels of calcium channel blockers. RTV increases beta blocker levels
Asthma	PIs	PIs decrease theophylline levels
DVT/PE	PIs	Increase warfarin levels, leading to risk of bleeding

LPV/r, lopinavir/ritonavir; PI, protease inhibitor; EFV, efavirenz; NRTI, nucleoside reverse transcriptase inhibitor; TDF, tenofovir; AZT, zidovudine; d4T, stavudine; 3TC, lamivudine; RTV, ritonavir; DVT/PE, deep vein thrombosis/pulmonary embolus.

and newborn. Data regarding the use of most ARVs during pregnancy are limited, and usually not of high quality. Much of the information regarding the use of ARVs in pregnancy is from the Antiretroviral Pregnancy Registry that, by virtue of the voluntary nature of registration, introduces a selection bias.

As there is less information regarding the use of RAL in pregnancy than ATV/r, the present guideline recommends that ATV/r be the third drug of choice for PEP during pregnancy. Both ATV/r and RAL are Food and Drug Administration (FDA) pregnancy category C. Table 8 provides information on the use of the drugs recommended for PEP during pregnancy.

TABLE 8: Drug safety in pregnancy.

Drug	Comment
Tenofovir (TDF) Emtricitabine (FTC) Lamivudine (3TC)	High placental transfer. No evidence of human teratogenicity. All have anti-HBV activity, therefore risk of hepatitis flare if stopped.
Stavudine (d4T)	High placental transfer. No evidence of human teratogenicity.
	Do not use with ddI (risk of lactic acidosis) or AZT (both thymidine analogues).
Zidovudine (AZT)	High placental transfer. No evidence of human teratogenicity.
	Do not use with d4T (both thymidine analogues).
Raltegravir (RAL)	High placental transfer. Insufficient data to assess human teratogenicity.
	Case report of markedly elevated liver transaminases in late pregnancy.
Dolutegravir (DTG)	Unknown placental transfer. Insufficient data to assess human teratogenicity.
	No data on use in pregnancy.
Atazanavir (ATV)	Low placental transfer. No evidence of human teratogenicity.
	Increased dosing in T2/3?
	Non-pathologic neonatal hyperbilirubinaemia.
Lopinavir (LPV)	Low placental transfer. No evidence of human teratogenicity.
	Once daily dosing not advised during pregnancy.
	Avoid oral solution owing to alcohol and propylene glycol content.
Darunavir (DRV)	Low placental transfer. Insufficient data to assess human teratogenicity.
	Less experience in pregnancy than LPV/r and ATV/r.
Ritonavir (RTV)	Low placental transfer. No evidence of human teratogenicity.
	Not used for antiretroviral effect, but in lower doses as PI booster in combination with other PIs.
	Avoid oral solution owing to alcohol content.
Efavirenz (EFV)	Moderate placental transfer.
	Potential foetal safety concerns. No increase in overall birth defects with T1 exposure in humans.

HBV, hepatitis B virus; ddI, didanosine; T2/3, trimester 2/3; PI, protease inhibitor.

Key issues regarding counselling

Adherence

PEP studies report low completion rates, often less than 60% for all populations, but especially adolescents, and PEP following sexual assault. Adherence counselling has been shown to improve adherence in HIV-positive individuals starting ART. Three RCTs comparing standard care counselling to enhanced adherence packages in improving adherence to PEP were identified and reviewed. The enhanced package included individual baseline needs assessments, adherence counselling, and education sessions and telephone calls. The combined effect of the enhanced intervention improved adherence and completion rates compared with standard of care counselling. Based on this finding, it is likely that some of the methods used to improve ART adherence may well be effective in PEP, such as peer support, alarms, text messages and phone calls.

Anxiety management

Anxiety should not simply be dismissed as baseless with simple reassurance. HIV remains a 'dread disease', despite the success of ART, because it is sexually transmitted, still accounts for significant mortality and morbidity, and has extensive stigma associated with it.

Anxiety management must be part of the adherence or follow-up support, and may need several interventions. Simple telephonic contact and reassurance is almost always adequate.

The intervention must be individualised, but the following approaches should be integrated:

- Contextualise the risk: emphasise that acquisition of HIV is unusual through a single exposure, unless the injury is severe (sexual assault, blood transfusion of an infected unit, severe penetrating injury with infected tissue).
- Even in the case of severe exposure or injury, where PEP is used timeously and the course completed, the risk of transmission is extremely low.

Risk-taking interventions

Counselling should be non-judgemental, practical and solution-focussed. PEP is an ideal time to deal with risk-taking environments, whether unsafe sex (e.g. a one-night stand with unprotected sex), poor occupational health (e.g. overfull sharps bins) or other (e.g. injecting drug use). Addressing occupational risk must be practical (e.g. report overfull bins to infection control, do not tell an exhausted nurse to 'be more careful').

Secondary prevention to prevent harm to others (e.g. risk to a spouse after sex with a third party) must be addressed. Exposed individuals should be counselled on how to prevent transmission to others, until they undergo the three-month post-exposure test following PEP:

- use of condoms to protect sexual partners
- to prevent mother-to-child-transmission (MTCT), avoid pregnancy (provide emergency contraception if necessary) and avoid breastfeeding if possible (high risk of transmission via breast milk during the 3 months following seroconversion demonstrated in a study from Zimbabwe)
- safe injecting practices
- avoid blood and tissue donation.

Consider offering PrEP to exposed individuals where chronic exposure to HIV is unavoidable or likely to continue (e.g. sex workers). Current evidence indicates that PrEP is effective as part of combination prevention approaches, provided it is used correctly. For more information, consult the Southern African HIV Clinicians Society guidelines on the safe use of PrEP in MSM and the US Department of Health and Human Service DHHS clinical practice guideline.[11,12]

Acknowledgements

The previous iteration of the Southern African Clinicians Society PEP guidelines was convened by Dr Steve Andrews, and we acknowledge his contribution to HIV care and treatment in South Africa. The format of the previous guideline has been preserved, with additional information included, and the content updated in line with current evidence and recommendations.

Competing interests

All expert panel members have completed and submitted conflict of interest disclosure forms. Disclosure information represents the previous 3 years (updated 10 June 2014) and includes relationships with pharmaceutical companies and medical aids: L.G.B. has received honoraria from Merck (MSD) for participating in consultative meetings. V.B. has received research support from Standard Diagnostics and served as a consultant to Novartis. F.C. has received support from Abbvie, Aspen and Mylan to attend conferences; research support from Janssen; honoraria for speaking engagements from Abbvie, GlaxoSmithKline, Janssen and MSD; and acted as a consultant to Sanofi Aventis. M.M. has received honoraria for speaking engagements from Aspen and MSD. F.V. has received support to attend conferences from Adcock Ingram, MSD and Aspen; received honoraria for speaking engagements from MSD, Aspen, Abbott, Novogen, Adcock Ingram and GlaxoSmithKline; served on advisory boards for Johnson and Johnson, Mylan and Tibotec; and received drug donations for research projects from Gilead and Mylan. C.L.W. has received support from Roche Molecular to attend conferences; honoraria for speaking engagements from Abbvie, MSD and Janssen; and acted as a consultant to Celera. B.H., P.H., G.M., N.S.P., K.R. and G.S. report no conflicts of interest.

Authors' contributions

M.M. (Wits Reproductive Health & HIV Institute) is the first author, undertaking preparation of the first draft of the manuscript. The remaining authors were involved in the discussions that guided the development of the manuscript and also reviewed the first draft. All authors developed the recommendations.

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Southern African HIV Clinicians Society adult antiretroviral therapy guidelines: Update on when to initiate antiretroviral therapy

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The most recent version of the Southern African HIV Clinicians Society's adult antiretroviral therapy (ART) guidelines was published in December 2014. In the 27 August 2015 edition of the *New England Journal of Medicine*, two seminal randomised controlled trials that addressed the optimal timing of ART in HIV-infected patients with high CD4 counts were published: Strategic timing of antiretroviral therapy (START) and TEMPRANO ANRS 12136 (Early antiretroviral treatment and/or early isoniazid prophylaxis against tuberculosis in HIV-infected adults). The findings of these two trials were consistent: there was significant individual clinical benefit from starting ART immediately in patients with CD4 counts higher than 500 cells/μL rather than deferring until a certain lower CD4 threshold or clinical indication was met. The findings add to prior evidence showing that ART reduces the risk of onward HIV transmission. Therefore, early ART initiation has the public health benefits of potentially reducing both HIV incidence and morbidity. Given this new and important evidence, the Society took the decision to provide a specific update on the section of the adult ART guidelines relating to when ART should be initiated.

The 2014 guidelines

In the 2014 version of the Southern African HIV Clinicians Society's adult antiretroviral therapy guidelines, antiretroviral therapy (ART) was recommended for certain clinical indications (including WHO stage 3 and 4 disease, and other significant morbidities), for HIV-infected partners in serodiscordant relationships, and in all patients with a CD4 < 350 cells/μL. Further, these guidelines advised that if patients had two CD4 counts between 350 and 500 cells/μL, ART should be started if the patient was ready and motivated to start ART. However, in these guidelines it was advised that if a patient's CD4 count was > 500 cells/μL and the patient did not qualify on clinical grounds, then ART should be deferred. The rationale was that insufficient evidence existed to advise a 'test-and-treat' approach to HIV at that time, and it was stated that we awaited the results of the TEMPRANO and Strategic timing of antiretroviral therapy (START) trials.[1]

For patients diagnosed during acute HIV seroconversion, initiation of standard first-line ART was advised, provided that adherence requirements were met. For such patients, it was advised that ART should be continued for at least 3 years, but consideration should be given to continuing lifelong ART.

The strategic timing of antiretroviral therapy and TEMPRANO trials

Both the START and TEMPRANO trials enrolled patients with high CD4 counts (in START all participants had a study entry CD4 count > 500 cells/μL; in TEMPRANO, 41% had an entry CD4

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Note: This guideline was compiled by the Southern African HIV Clinicians Society.

Disclaimer: Specific recommendations provided here are intended only as a guide to clinical management, based on expert consensus and best current evidence. Treatment decisions for patients should be made by their responsible clinicians, with due consideration for individual circumstances. The most current version of this document should always be consulted.

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count > 500 cells/μL). A summary of the trials is presented in Table 1. Both trials involved randomisation to one of two strategies: immediate ART initiation, or to defer ART until the participant was eligible on the basis of CD4 count or clinical criteria. Patients were followed for about 3 years in each trial, and the primary endpoint was a composite endpoint that included AIDS events, serious non-AIDS events and death, with minor differences in specific aspects of the endpoint definition between the two trials.

Both trials demonstrated a statistically significant, approximate halving of events contributing to the primary endpoint when ART was started immediately. In TEMPRANO, this benefit was largely attributable to reductions in incident TB and invasive bacterial diseases (particularly pneumonia). In START, the benefit was related to a decrease in AIDS-related events (including TB) and serious non-AIDS events (including cancer). The relative reduction in the rate of primary endpoint events was greater in START (57% reduction compared with 44%). However, the absolute benefit of immediate ART was greater in the TEMPRANO trial (conducted in Cote d'Ivoire) than in the START trial (which was conducted in countries across the world), because the event rate in the control arms (mainly from TB and invasive bacterial infections) was higher in the TEMPRANO trial, reflecting the high co-infection risks that exist for individuals living with HIV infection in Africa, even with higher CD4 counts. No significant difference in mortality was observed between the study arms in either trial.[2,3]

There are two main concerns about ART initiation with CD4 counts > 500 cells/μL. Firstly, the risk of adverse events could outweigh clinical benefits. Secondly, adherence could be lower in asymptomatic patients. In both trials, immediate ART did not increase the risk of adverse events overall, nor did patients who started immediately have a higher risk of adherence problems, at least in the short term, as evidenced by the high proportion of patients achieving HIV viral suppression seen in the immediate arms in both trials (Table 1).

The HPTN052 trial[4] previously demonstrated that ART prevented onward transmission of HIV within serodiscordant couples, which suggested that ART at HIV diagnosis for all may be an important strategy to help prevent the growth of the HIV epidemic at a public health level. However, such an approach would be difficult to justify if there were no individual benefit and potential individual harm. What these two trials have demonstrated is that there is indeed individual clinical benefit with no signal of harm during ~3 years of follow-up, providing significant additional support for the 'test-and-treat' strategy.

TABLE 1: Summary of design, conduct and findings of the Strategic timing of antiretroviral therapy and TEMPRANO ANRS 12136 (Early antiretroviral treatment and/or early isoniazid prophylaxis against tuberculosis in HIV-infected adults) randomised controlled trials.

Trial	TEMPRANO	START
Countries	Cote d'Ivoire	35 countries (21% of participants enrolled in Africa)
Enrolment years	2008–2012	2009–2013
Number of participants	2056	4685
Inclusion criteria	≥ 18 years old	≥ 18 years old
	HIV-1 (or dual HIV-1 and 2)	ART naive
	CD4 < 800	No history of AIDS
	Not meeting WHO criteria for starting ART at the time (these criteria changed during the course of the trial)	General good health
	-	2 CD4 counts > 500
Comparison arms	*Immediate* ART	*Immediate* ART
	ART *deferred* until WHO criteria for starting ART met (these criteria changed over the course of the trial)	ART *deferred* until CD4 ≤ 350, AIDS diagnosis or other indication for ART (e.g. pregnancy)
Composite primary endpoint	AIDS, non-AIDS cancer, non-AIDS invasive bacterial disease or death	Serious AIDS-related event, serious non-AIDS-related event or death
Duration of follow-up	30 months for each participant	Mean 3.0 years (trial stopped early by DSMB)
Number of primary events	Immediate arm: 64	Immediate arm: 42
	Deferred arm: 111	Deferred arm: 96
Primary endpoint finding	44% reduction with immediate ART (aHR = 0.56, 95% CI = 0.41–0.76)	57% reduction with immediate ART (HR = 0.43, 95% CI = 0.30–0.62)
	Among patients with baseline CD4 ≥ 500, there was also a 44% in primary endpoint (aHR = 0.56, 95% CI = 0.33–0.94)	-
Main contributors to finding	Reduction in AIDS events (50%, mainly TB [50%]) and invasive bacterial disease (61%)	Reduction in AIDS events (72%, including TB [71%]), serious non-AIDS events (29%), cancers (64%) and bacterial infections (62%)
Deaths	Immediate arm: 21	Immediate arm: 12
	Deferred arm: 26	Deferred arm: 21
	Not significant: aHR = 0.60, 95% CI = 0.34–1.09	Not significant: $p = 0.13$
Viral load suppression	Viral load < 100 at 12 months on ART	Viral load < 200 at 12 months on ART
	Immediate arm: 84%	Immediate arm: 98%
	Deferred arm: 80%	Deferred arm: 97%
Adverse events	Overall, the 30-month probability of a Grade 3 or 4 AE did not differ between arms although it was 2.6 times higher in the immediate ART arm for the first 6 months	No difference between arms in terms of grade 4 events and hospitalisations for reasons other than AIDS

Note: In the TEMPRANO trial, there was a separate randomisation of participants to 6 months isoniazid preventive therapy (IPT) versus no IPT.
WHO, World Health Organization; DSMB, Data and Safety Monitoring Board; aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; AE, adverse event.

These were well-conducted randomised controlled trials with good participant retention and assured drug supply, and the vast majority of participants were on tenofovir/emtricitabine/efavirenz regimens in both trials. In less motivated patients, or in the context of inconsistent drug supply or different first-line ART regimens, these results should be treated with caution, as the modest benefits seen with early treatment may not be realised. In particular, if tenofovir (or abacavir) is unavailable and zidovudine or stavudine needs to be used in place, then the substantial side-effect profile of these drugs and effect on patients' quality of life may outweigh the benefit of early ART.

Isoniazid preventive therapy in patients on antiretroviral therapy

The TEMPRANO trial involved a separate randomisation of participants to 6 months of isoniazid preventive therapy (IPT) started one month after study entry, versus no IPT. The addition of IPT to ART provided added protection against active TB disease, even in these patients with relatively high CD4 counts. This finding was similar to those of a placebo-controlled trial conducted in Khayelitsha, South Africa, where 12 months of IPT prescribed to patients on ART reduced TB incidence by 37%.[5] Our December 2014 guidelines[1] recommended IPT for all patients on ART provided that there was no contra-indication to isoniazid, and active TB was not suspected based on symptom screen. Guidelines on duration of IPT based on tuberculin skin test results were provided. Given that southern Africa has the highest incidence rates of HIV-associated TB in the world, IPT as a TB-preventive strategy implemented within ART clinics should be prioritised.

Updated recommendations of SA HIV Clinicians Society regarding antiretroviral therapy initiation

Our updated recommendations are shown in Box 1. It is important to note that these are the guidelines of the SA HIV Clinicians Society, and clinicians working within national public sector ART programmes should continue to follow the guidelines that pertain to their programme. Whilst National Departments of Health are very likely to consider a change in ART initiation policy in the near future based on these study findings, such a change will need to factor the financial cost, adequate planning of drug supply and health service capacity. Sustaining funding for ART programmes in resource-limited countries is a huge challenge currently.[6]

Specific patient groups

For patients who are diagnosed with HIV during *acute seroconversion*, we continue to advise that those patients be counselled and initiated on ART. This should preferably be expedited ART initiation as there is evidence that this may limit the size of the HIV reservoir.[7] However, we no longer recommend that these patients should have ART interrupted after 3 years. Rather, once ART is started in this situation, this should be lifelong ART, and this should be discussed with the patient. Additional counselling once the patient is established on ART may be required for patients who start ART in this acute situation because there is limited time for extensive counselling pre-ART and there is often considerable psychological distress around this time.

Box 1: Indications for antiretroviral therapy in adults with HIV infection.

We recommend initiation of lifelong ART for all patients diagnosed with HIV infection. The CD4 count and clinical stage of the patient should no longer be a consideration in the decision to start ART.
For patients who are asymptomatic with CD4 > 350 cells/μL, additional time (weeks to a few months) can be spent counselling and preparing the patient for lifelong ART with good adherence before starting. In those with CD4 < 350 cells/μL (and especially < 200 cells/μL), or with clinical indication for starting, there should not be undue delay.
Within ART programmes, it is important to factor in that the absolute benefit of ART is much greater at lower CD4 counts (there is a mortality benefit at CD4 < 350 cells/μL.[10†] Therefore, planners and clinicians should prioritise and fast-track those with low CD4 counts (especially < 200 cells/μL); this is particularly relevant where there are ART shortages or anticipated stock-outs.

†, Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. N Engl J Med. 2010;363:257–265. PMID: 20647201, http://dx.doi.org/10.1056/NEJMoa0910370

A minority of patients (< 1%) have very effective immune control of HIV infection and are able to control HIV viraemia at undetectable levels in the absence of ART – termed '*elite controllers*'. An argument could be made that such individuals do not require ART if their CD4 count is > 500 cells/μL. The START and TEMPRANO trials did not specifically address the question of whether early ART was beneficial in such patients, and it is highly unlikely that any sufficiently powered randomised controlled trial could ever be conducted focused on these individuals. In the absence of such data, we rely on indirect evidence. Firstly, elite controllers still have evidence of chronic immune activation and inflammation that may drive non-infectious morbidities.[8] Secondly, elite controllers have been shown to have a higher rate of hospitalisation than patients who are virologically controlled by ART.[9] For these reasons, we do advise starting ART in elite controllers too, with the same caveats regarding the patient being prepared. One important consideration in such patients is that careful attention should be paid to confirming the diagnosis of HIV before starting ART. They are typically patients who have a positive HIV ELISA test, undetectable HIV viral load, CD4 count in the normal range and are clinically well. The possibility of a false positive HIV ELISA test should be excluded either by performing a qualitative HIV DNA PCR assay or a Western blot assay. If the patient at some point previously had a detectable HIV viral load, this would also serve as confirmation. Such patients should be discussed with a laboratory virologist to assist with confirmation of HIV infection status.

In patients with *active TB* or *opportunistic infections*, the 2014 guidelines included guidance as to when to initiate ART in relation to treatment of the TB or opportunistic infection. This guidance remains unchanged.

We recommend ART initiation without delay in all *HIV-infected women who are pregnant or breastfeeding*, irrespective

of CD4 cell count, to prevent mother-to-child transmission of HIV infection. We advise that such ART should be continued lifelong and not stopped after the pregnancy or weaning.

In *children and adolescents*, advice from the Society's Child and Adolescent Guidelines Committee is that the 'test-and-treat' approach is supported in principle for all ages. However, there is an absence of data for the 5–15-year-old age group. Adherence issues for adolescents in particular and the lack of a simplified first-line regimen make 'test-and-treat' for 5–15–year-olds complicated. Please refer to national Department of Health guidelines for further advice regarding children and adolescents.

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Authors' contributions

G.M. (University of Cape Town) is the first author, and undertook preparation of the first draft of the manuscript. The remaining authors were involved in the discussions that guided the development of the manuscript and also reviewed the first draft. All authors contributed to the review of the data informing the new recommendations, and to the development of the recommendations.

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A case of emmonsiosis in an HIV-infected child

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Opportunistic fungal infections can cause significant morbidity and mortality in immunocompromised patients. We describe a paediatric case of an unusual disseminated fungal infection. A three-year-old HIV-infected child with severe immunosuppression (CD4+ T-cell count 12 × 10^6/L) was admitted to hospital with pneumonia, gastroenteritis and herpes gingivostomatitis. Despite antibacterial and antiviral therapy, he experienced high fevers and developed an erythematous maculopapular rash and abdominal tenderness. The child's condition progressively worsened during the admission. A thermally dimorphic fungus was cultured from bone marrow and identified as an Emmonsia species on DNA sequencing. The patient made a good recovery on amphotericin B deoxycholate and antiretroviral therapy. Itraconazole was continued for a minimum of 12 months, allowing for immune reconstitution to occur. This case is the first documented description of disseminated disease caused by a novel Emmonsia species in an HIV-infected child in South Africa.

Introduction

Opportunistic fungal infections can cause significant morbidity and mortality in immunocompromised patients. The diagnosis and treatment of these infections may be challenging.[1,2] The manifestation of invasive fungal infection (IFI) is determined by numerous factors including the virulence of the fungal species, the adequacy of host immune responses, the size of the inoculum inhaled or disruption of mucosal barriers. Individuals at risk for IFIs include those who have received transplants, immunosuppressive therapy or chemotherapy for neoplastic diseases; HIV-infected patients; premature infants; and individuals with defects in neutrophil, monocyte, T-lymphocyte or B-lymphocyte function.[3] In the present report, we describe an unusual disseminated fungal infection caused by a novel Emmonsia species in an HIV-infected child.

Case report

A 3-year-old boy was admitted to Red Cross War Memorial Children's Hospital, Cape Town, South Africa, with acute gastroenteritis, pneumonia and herpes gingivostomatitis. Six months earlier, HIV infection was diagnosed at a primary health care clinic. Antiretroviral therapy (ART) was not initiated despite it being indicated for such patients by the South African ART guidelines. He was stunted (height 85 cm, height–age z-score – 3) but not wasted (weight 12.6 kg, weight-for-height z-score +1 [2006 WHO Child Growth Standards]). Blood results on admission showed a normocytic anaemia (haemoglobin 6.8 g/dL, reference range 10.7–13.1) and leucopaenia (white cell count [WCC] 2.71 × 10^9/L, reference range 6–18). The differential WCC showed that neutropaenia (1.22 × 10^9/L, reference range 2–5.5) and lymphopaenia (1.49 × 10^9/L, reference range 3.6–12) were present. A chest radiograph showed features of a bilateral pneumonia (Figure 1), for which he was commenced on ampicillin and gentamicin, and acyclovir, for the pneumonia and herpes gingivostomatitis, respectively. No supplemental oxygen therapy was required at admission and empiric treatment for *Pneumocystis jirovecii* pneumonia was not initiated. However, cotrimoxazole prophylaxis was commenced on admission.

He experienced high fevers, peaking at 40 °C. On day 6 of admission, he developed diffuse abdominal tenderness and a generalised erythematous maculopapular exanthem. Liver function tests (LFTs) showed normal total bilirubin (2 µmol/L, ref. range 0–21) and alkaline phosphatase (ALP 268 U/L, ref. range 104–345) concentrations, and elevated γ-glutamyl transferase (GGT 120 U/L, ref. range 3–22), alanine transaminase (ALT 223 U/L, ref. range 5–30) and aspartate transaminase (AST 1304 U/L, ref. range 0–56) concentrations. The C-reactive protein (CRP) was 58.2 mg/L (reference range 0.1–7.5). Owing to the persistent fever, antimicrobial therapy

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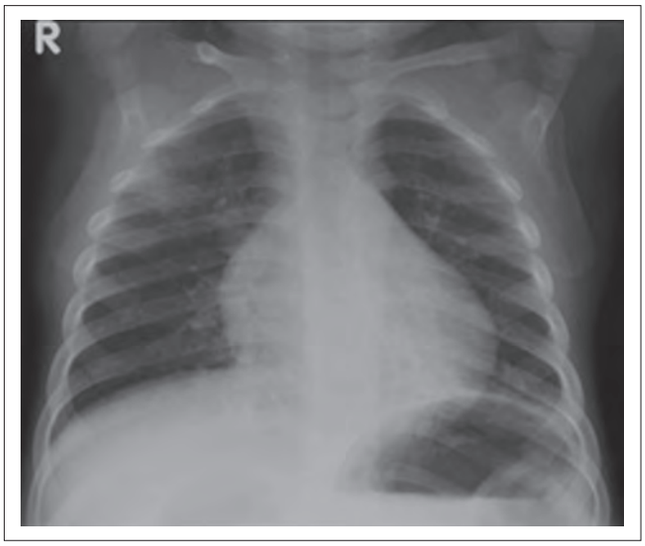


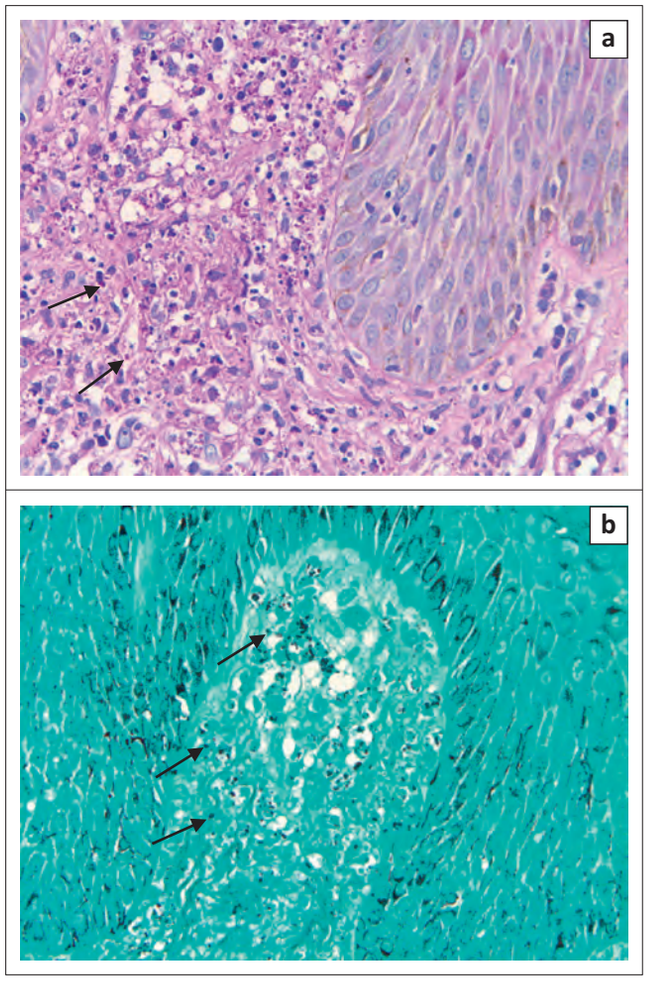
Source: Radiology Department, Red Cross War Memorial Children's Hospital

FIGURE 1: Chest radiograph on admission, with features of bilateral pneumonia.

was changed to ertapenem and fluconazole for presumed hospital-acquired infection. There was no growth on blood culture after 5 days of incubation, and a urine culture yielded mixed bacterial growth. Tuberculin skin testing (Mantoux method) and Xpert MTB/RIF (Cepheid, Inc., Sunnyvale, CA, USA) on induced sputum specimens were negative. Two days later, he had generalised tonic clonic seizures for which he received an intravenous loading dose of phenobarbitone. The antibiotic was empirically changed to meropenem for possible hospital-acquired meningitis. A cerebrospinal fluid specimen was bloodstained but there was no bacterial growth, and polymerase chain reaction (PCR) assays for entero- and herpesviruses were negative.

The fever and maculopapular rash persisted. Repeat CRP (88.4 mg/L), procalcitonin (5.3 µg/L, reference range 0.0–0.5), ferritin (91 705 µg/L, reference range 20–200) and triglyceride concentrations (4.7 mmol/L, reference range 0.3–1.1) were elevated. The differential diagnosis included haemophagocytic lymphohistiocytosis (HLH), disseminated tuberculosis and invasive fungal infection. The patient subsequently developed respiratory distress requiring supplemental nasal prong oxygen therapy. Repeat chest radiography was unchanged from admission with features not suggestive of tuberculosis or fungal infection. He was given packed red blood cell, platelet and cryoprecipitate transfusions for severe anaemia (Hb 5.6 g/dL), thrombocytopaenia (platelet count 52×10^9/L) and hypofibrinogenaemia (fibrinogen concentration 1.0 g/L, reference range 1.7 g/L – 4.0 g/L), respectively.

Skin and bone marrow biopsies were performed on day 10 in hospital. Skin histology showed extensive karyorrhexis and numerous dermal histiocytes containing cytoplasmic small fungal organisms. Grocott and Periodic acid–Schiff stains were positive and suggestive of dermal histoplasmosis (Figure 2). Skin culture did not grow fungi or mycobacteria. Bone marrow histology revealed histiocytosis and



Source: Dr Komala Pillay, Division of Anatomical Pathology, Red Cross War Memorial Children's Hospital

Note: The arrows identify the organism.

FIGURE 2: Skin histology biopsy demonstrating fungal elements measuring 1.5 µm × 2.5 µm using (a) Periodic acid-Schiff and (b) Grocott methenamine silver stains.

haemophagocytosis consistent with a diagnosis of HLH. Fungal stains showed scanty structures 1.5 µm × 2.5 µm in diameter and morphologically compatible with *Histoplasma capsulatum*. A diagnosis of disseminated fungal infection with secondary HLH was made and intravenous amphotericin B deoxycholate 1 mg/kg/day commenced 14 days later.

Culture of the bone marrow aspirate in a BACTEC MycoF/lytic bottle (Becton Dickinson, New Jersey) flagged positive after 17.6 days of incubation, and small yeasts were seen on Gram stain. The isolate was submitted to the National Institute for Communicable Diseases for further identification. The fungus was converted from the mycelial to yeast phase on brain heart infusion agar with 5% sheep blood (Diagnostic Media Products, Sandringham) at 35 °C and morphologically characterised based on DNA sequencing of the internal transcribed spacer region of the isolate's ribosomal gene. The isolate was identified as the thermally dimorphic fungus Emmonsia species. The DNA sequence was the same as those of previously described isolates of a novel Emmonsia species. An investigational urine Histoplasma antigen test (ImmunoMycologics, Norman, OK) was negative.

ART, comprising abacavir, lamivudine and efavirenz, was commenced 3 days before amphotericin B was started. The LFT concentrations had marginally improved at this stage with an ALT of 156 U/L, AST 560 U/L and GGT 102 U/L. The baseline CD4+ T-cell count (percentage) was 12 × 10^6/L (0.45%) and HIV-1 viral load 2 149 305 RNA copies/mL. After ART and amphotericin B were commenced, he made a remarkable recovery. Within 3 days, supplemental oxygen was discontinued and, after 5 days, the skin lesions and fever had resolved. The abdominal tenderness and abnormal LFTs resolved on day 11 and 12 of amphotericin B, respectively.

Daily amphotericin B was continued for 6 weeks via a central venous catheter. Adverse effects were minimised through pre-emptive hydration before amphotericin B infusions, close monitoring of renal function, potassium and magnesium concentrations and, where necessary, electrolyte replacement. Itraconazole 100 mg daily orally was commenced once amphotericin B had been discontinued. Because of its potential for reducing the bioavailability of itraconazole, efavirenz was replaced with a lopinavir/ritonavir co-formulation. Six months after commencing ART, the patient was well, virologically suppressed (HIV-1 viral load < 40 RNA copies/mL), had a CD4+ T-cell (percentage) of 884 × 10^6 cells/L (17.9%) and normal LFTs. At last evaluation, there was no clinical evidence of active fungal infection. The intention is to maintain him on itraconazole for a minimum of 12 months and until his CD4 count reaches 25%, before considering discontinuation of antifungal therapy.

Discussion

Emmonsia species, a group of dimorphic fungi, are found in soil, and some species can cause pulmonary infection in rodents.[4] The genus currently contains three species, namely *Emmonsia crescens*, *Emmonsia parva* and *Emmonsia pasteuriana.* Infection caused by Emmonsia species has been described in HIV-uninfected adults and one child. The infections were caused by *E. crescens* and *E. parva*, resulting in predominantly pulmonary adiaspiromycosis and occasional cutaneous manifestations.[4,5,6,7] More recently, invasive infection caused by a new species of Emmonsia closely related to *E. pasteuriana* was documented in 13 HIV-infected adults with advanced HIV disease in South Africa.[8] Our case is the first description of disseminated disease caused by this new Emmonsia species in an HIV-infected child.

All 13 adult patients presented with very low CD4+ T-cell counts, anaemia and widespread skin lesions. The skin manifestations ranged from erythematous papules to plaques and ulcers. Twelve had a documented fever and 8 of 9 who underwent LFTs had deranged liver enzymes, suggesting hepatic involvement. Our patient similarly developed severe immune suppression, anaemia, an erythematous papular eruption and deranged LFTs, and in addition had neutropaenia and lymphopaenia. In that series, the original histological diagnosis on skin biopsy samples morphologically resembled *H. capsulatum.* On gene sequencing, the fungus was identified as belonging to the genus Emmonsia.[8] Not all fungi require molecular diagnosis. However, Emmonsia species is difficult to diagnose by morphological appearance alone, necessitating molecular confirmation. The role of the Beta D Glucan assay in the diagnosis of emmonsiosis is currently not known. The assay is likely to be elevated but, as it detects most common fungi, is unlikely to be specific for Emmonsia species.

Our patient was empirically commenced on fluconazole during the course of his clinical deterioration. Fluconazole is less active than itraconazole against dimorphic fungi especially histoplasmosis, probably explaining the lack of clinical response until amphotericin B deoxycholate was commenced.[9,10] Currently there are no treatment guidelines for HIV-associated disseminated Emmonsia infection. Our regimen of amphotericin B deoxycholate followed by maintenance itraconazole therapy was extrapolated from treatment guidelines for other dimorphic fungal infections.[11] Duration of therapy depends on the extent of the disease. As our patient had disseminated fungal infection with severe immunosuppression, we elected to follow recommendations for treating disseminated histoplasmosis in HIV-infected patients. Lifelong antifungal prophylaxis may not be required in our patient because he has already had a good immunological response.[12]

Itraconazole is metabolised by the cytochrome P450 C3A4 enzyme. This pathway is also responsible for the metabolism of the non-nucleoside reverse transcriptase (NNRTI) class of antiretroviral drugs. Theoretically, levels of either the itraconazole or NNRTI could be affected. There is a paucity of literature describing the drug–drug interactions between itraconazole and the NNRTIs. A case report of an HIV-infected male patient with disseminated Histoplasma infection demonstrated reduced levels of itraconazole and an increase in the urine Histoplasma antigen level while he was receiving efavirenz. After switching to a protease inhibitor, the serum drug levels of itraconazole increased and the urine Histoplasma antigen levels declined.[13] Drug levels of itraconazole were not monitored in the case described because the test is not available in South Africa.

Conclusion

The recently published case series and the present case report confirm that emmonsiosis occurs among both HIV-infected adults and children in South Africa.[8] Prolonged incubation (up to 6 weeks) of the fungal culture may be necessary for the diagnosis. This infection should be considered in immunocompromised patients presenting with persistent fever and other clinical features suggestive of IFI.

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Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

H.L. (Red Cross War Memorial Children's Hospital), B.E. (Red Cross War Memorial Children's Hospital), N.P.G. (National Health Laboratory Service) and P.N. (Groote Schuur Hospital) reviewed, contributed to and approved the final submitted manuscript. K.P. (Red Cross War Memorial Children's Hospital) was involved in assessing the skin histology and preparation of the slides featured in the report. P.N. and A.R. (Groote Schuur Hospital) were responsible for the microbiological diagnosis. N.P.G. and T.M. (National Health Laboratory Service) carried out the molecular analysis for the final diagnosis.

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Neuroendocrine tumour in a patient with neurofibromatosis type 1 and HIV

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We report the case of an HIV-positive female patient with neurofibromatosis type 1 who was treated for recurrent peptic ulcer disease and later developed diabetes mellitus and chronic diarrhoea. A metastasising somatostatinoma was histologically proven and evidence of a concomitant gastrin-producing neuroendocrine tumour was found. Neuroendocrine tumours (NETs) are very rare neoplasms originating from a wide variety of endocrine and nervous system tissue with the ability to produce different hormones. A somatostatin- and gastrin-secreting NET in a patient with HIV has not been reported in the literature, to the best of our knowledge. We discuss oncogenic pathomechanisms related to the underlying conditions and propose stringent monitoring for tumours in HIV-positive patients with phakomatoses as well as initiation of antiretroviral therapy.

Introduction

Neuroendocrine tumours (NETs) are neoplasms originating from a wide variety of endocrine and nervous system tissues with the ability to produce different hormones. Pancreatic hormone-producing NETs are often associated with specific clinical manifestations, resulting from the excessive production and action of the respective hormone.

We report on a 30-year-old HIV-positive female patient with neurofibromatosis type 1 (NF1) who presented with Zollinger-Ellison syndrome and later developed diabetes mellitus and chronic diarrhoea. A somatostatinoma was proven histologically and we found laboratory evidence for the concomitant production of gastrin by the tumour. Somatostatinomas are very rare tumours, and a somatostatin- and gastrin-secreting NET in a patient with HIV has not been reported. We discuss oncogenic pathomechanisms related to the underlying conditions and propose stringent monitoring for tumours in HIV-positive patients with phakomatoses.

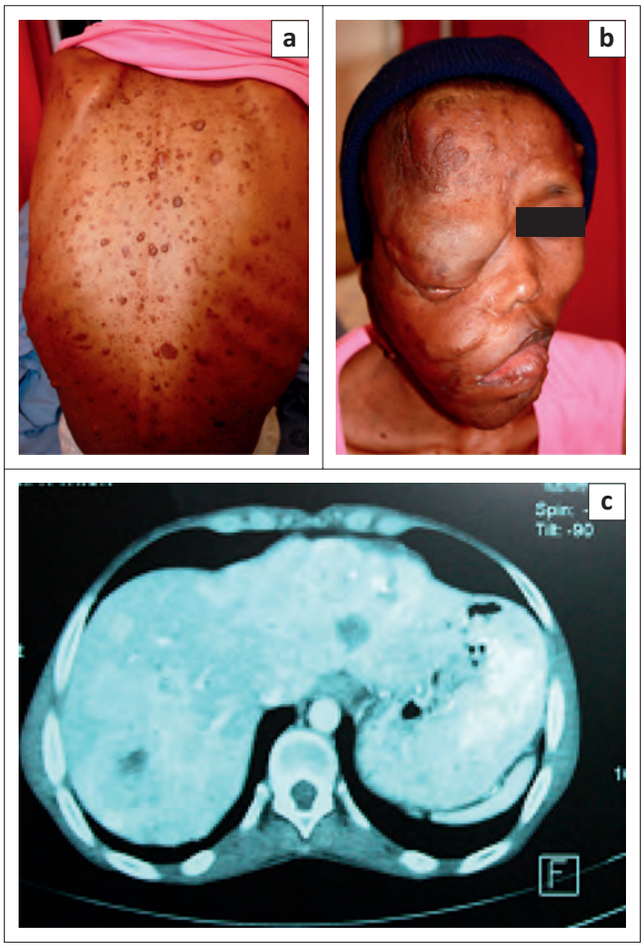
Case presentation

A 30-year-old woman had been seen at the Surgical Department over the past five years for recurrent upper gastro-intestinal bleeds. Peptic ulcer disease was proven gastroscopically on four occasions. She was repeatedly treated with proton-pump inhibitors and on one occasion received empiric triple therapy for *Helicobacter pylori* eradication. Her past medical history included visits to the Plastic Surgery Department for removal of a plexiform neurofibroma with enucleation of her right eye.

Clinically, with numerous neurofibromata, one big plexiform neurofibroma on the right side of her face, several café-au-lait spots and axillary freckling, she fulfilled the criteria for NF1.[1] She had tested HIV-positive a few months earlier, with a baseline CD4 count of 290 cells/µL. One week prior to admission, diabetes mellitus was diagnosed by the local primary healthcare clinic and she was started on metformin 850 mg bd. She then presented to the Medical Department with a four-day history of diarrhoea without melaena or epigastric pain.

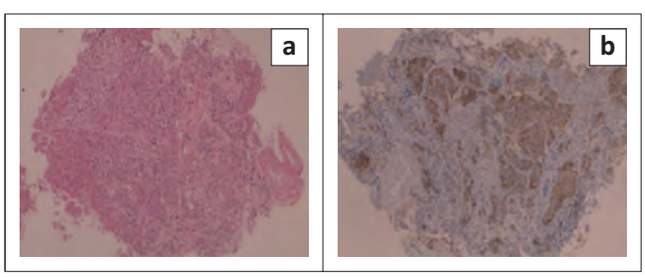
On admission, she was moderately dehydrated with features of NF1 (Figures 1a and 1b). The rest of the clinical examination was normal. A chest X-ray was unremarkable, and blood results were essentially normal except for a thrombocytosis of 614 x 10^9 cells/L. The patient received intravenous fluids and antibiotics. Insulin was commenced and antiretroviral therapy (ART) with TDF, 3TC and EFV was started.

Abdominal ultrasound demonstrated several solid, round lesions in the liver that were confirmed on computed tomography (Figure 1c). Liver biopsy showed polygonal tumour cells with granular eosinophilic cytoplasm and monomorphic nuclei, coarse dispersed chromatin and focal glandular formations. Synaptophysin and chromogranin stains were positive,



Source: Photographs of Patient and CT Abdomen taken by Juliane Hiesgen with the patient's consent

FIGURE 1: Clinical features of NF 1, with numerous neurofibromata (a), big plexiform neurofibroma over the right side of the face (b) and (c) CT image showing several hypodense lesions in the liver parenchyma, suggestive of metastases.



Source: Photographs of Histological Specimens by kind permission of Dr T. Omar

FIGURE 2: Histological slides from liver lesions: (a) HE staining showing polyglandular tumour cells with granular eosinophilic cytoplasm and glandular formation and (b) strongly positive immuno-histochemical synaptophysin stain (specific for neuroendocrine tumours).

compatible with a metastatic neuroendocrine carcinoma. Special somatostatin staining was positive, proving the somatostatinoma (Figure 2a and 2b). The excessively increased fasting gastrin level of 19 577 ng/L (13 ng/L – 115 ng/L) strongly suggested the additional hypersecretion of gastrin by the tumour.

A malignant, metastatic neuroendocrine tumour secreting somatostatin and gastrin was diagnosed. Unfortunately, the patient died soon after diagnosis.

Discussion

Somatostatinomas are extremely rare neuroendocrine tumours with an estimated annual incidence of 1 in 40 million per year, arising from the delta cells in the pancreas or, in about 40% of cases, from the duodenum.[2] Gender distribution is equal and mean age at presentation is between 51 and 53 years. Occasionally, additional hormones such as glucagon, calcitonin, insulin, gastrin or others are produced. Somatostatinomas often metastasise early and present late, resulting in a poorer prognosis.[2] Whilst non-metastatic somatostatinomas with full tumour resection can be cured, metastatic forms often have a fatal course as they are diagnosed late. Appropriate surgery combined with chemotherapy results in an average 5-year survival of about 59.9%.[2]

The association between NF1 and somatostatinomas is well documented. Fendrich et al. reported a case of NF1 and a duodenal somatostatinoma, and found 36 other cases in the literature until 2004, of which only 14 involved metastasis.[3] Somatostatinomas in NF1 occur with a higher frequency and are located more often in the duodenum than in patients without NF1, in whom pancreatic tumours dominate. NETs located in the duodenum tend to present less often with a somatostatinoma syndrome but rather with local or non-specific symptoms.[3]

Most somatostatinomas are symptomatic. The full clinical picture of the somatostatinoma syndrome, characterised as an inhibitory syndrome, was initially reported by Krejs et al. in 1979.[4] It comprises diabetes mellitus (suppression of insulin), steatorrhoea and cholelithiasis (inhibition of cholecystokinin and biliary motility). Additionally, patients often have general symptoms such as nausea and vomiting, abdominal pain and weight loss. Duodenal somatostatinomas might present with abdominal pain, duodenal obstruction, gastro-intestinal bleeding or jaundice, owing to local growth of the tumour.[2]

The differential diagnosis is wide, depending on the patient's presentation. It includes, amongst others, refractory diabetes mellitus and other endocrine conditions, carcinoids and gastro-intestinal malignancies, pancreatitis, inflammatory bowel disease, coeliac disease, irritable bowel syndrome or even depression.

NF1, originally described by Friedrich von Recklinghausen in 1882, is a fairly common hereditary disease that is autosomal-dominantly inherited and occurs in 1:3500 births. It forms part of the neuro-cutaneous syndromes or phakomatoses, a group of genetic conditions predominantly involving tissues of ectodermal origin, mainly the nervous system, skin and eye. NF1 is characterised by the slow evolution of tumour lesions in childhood and adolescence, as well as by a tendency to form hamartomas and a disposition to fatal malignant transformation. The mutated gene, encoding the protein neurofibromin (17q11.2), is a tumour-suppressor gene.

Involved mechanisms are rat sarcoma viral oncogene homologue (RAS)-mitogen activated protein kinase (MAPK),

mammalian target of rapamycin (mTOR) and P21 protein (Cdc42/Rac)-activated kinase (PAK1).[5] Patients with this disorder are predisposed to both benign and malignant tumours of neurogenic and non-neurogenic origin. NF1 reduces average life expectancy by 10–15 years, with malignant tumours being the most common cause of death.

In addition to NF1, our patient was HIV-positive with a low CD4 count. HIV infection is strongly associated with specific malignancies. Kaposi's sarcoma (KS), non-Hodgkin lymphomas (NHLs) and invasive cervical cancer are AIDS-defining illnesses.[6]

Several non-AIDS-defining malignancies appear more common amongst HIV-positive patients, and their incidence is increasing; these include invasive anal carcinoma, Hodgkin lymphomas, skin cancers, leukaemia, lung cancer, multiple myeloma, prostate cancer and others.[7,8,9,10,11]

Different pathomechanisms, direct and indirect, are involved in the oncogenesis in HIV. Opportunistic co-infections with oncogenic viruses can result in HIV-associated malignancies. Here the role of viral encoded micro-RNA is under investigation.[12] In particular, the associations of Kaposi's sarcoma and primary effusion NHL with human herpes virus type 8 (HHV 8), of primary CNS lymphoma and NHL with Epstein-Barr virus (EBV) and of invasive cervical cancer with human papillomavirus (HPV) are well documented.[13,14,15]

Immune deficiency itself seems to play a role in HIV malignancies.[16] Impaired T-cell surveillance in particular may lead to insufficient elimination of transformed cells, resulting in oncogenesis. Furthermore, the HIV TAT protein, a nonstructural protein secreted by infected cells and taken up by uninfected cells, seems to be involved in the pathomechanism of HIV-related malignancies. It has been found to deregulate cellular genes (as pRb2/p130) that work as onco-suppressor proteins.[17,18]

Recently, hyperactivation of mTOR has been found to play a role in different aspects of HIV pathology including HIV-associated nephropathy (HIVAN), HIV encephalopathy, and HIV-associated and non-HIV-associated malignancies.[19,20] As mentioned above, the mTOR pathway disinhibition is also one of the pathomechanisms involved in the oncogenesis in NF1. Additional mTOR activation in the setting of HIV infection as a compounding contributor may confer a 'second hit', leading to the question of the potential use of mTOR inhibitors in the treatment of these patients. This point also raises the interesting question of whether HIV patients with an increased risk for malignancies develop these at earlier ages and whether these tumours are more aggressive.

Conclusion

People living with HIV and/or AIDS have a significantly increased risk of developing malignancies, as have patients with neurofibromatosis (and other phakomatoses). Different mechanisms are involved in these two independent pro-oncogenic diseases, and there are no data on incidence or prevalence rates for patients affected by both conditions. We assume that these rates might be higher than for HIV or NF1 alone.

Therefore, in a setting of high HIV prevalence – such as South Africa – we suggest regular HIV testing in patients with NF1 and other phakomatoses. Frequent follow-up (e.g. 6-monthly) with close monitoring for malignancies and further diagnostic work-up, where a tumour is suspected, is encouraged. Because the risk resulting from the genetic condition is not modifiable, the aim can only be to reduce the tumour risk from HIV infection and immunosuppression. We therefore recommend starting ARVs irrespective of CD4 counts in such patients.

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Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

Both authors were the treating specialists of the patient. J.H. (University of Pretoria) collected the results and wrote the manuscript. E.V. (University of the Witwatersrand) edited the article and contributed, especially regarding the literature about oncogenesis in HIV.

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Gestational trophoblastic neoplasm and women living with HIV and/or AIDS

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The 2011 World Health Organization global report on HIV and/or AIDS estimated that sub-Saharan Africa comprised 67% of the global HIV burden, with a current estimate of 5.9 million cases in South Africa. Since the introduction of antiretroviral therapy, there has been an increase in the incidence of non-AIDS-defining cancers. Gestational trophoblastic neoplasm (GTN) is a rare pregnancy-related disorder with an incidence ranging from 0.12–0.7/1000 pregnancies in Western nations. The overall cure rate is about 90%. Response to treatment for GTN is generally favourable; but the sequelae of HIV and/or AIDS, the resultant low CD4 counts, comorbidities, poor performance status and the extent of metastatic disease in patients receiving chemotherapy, compromise the prognosis and survival.

Introduction

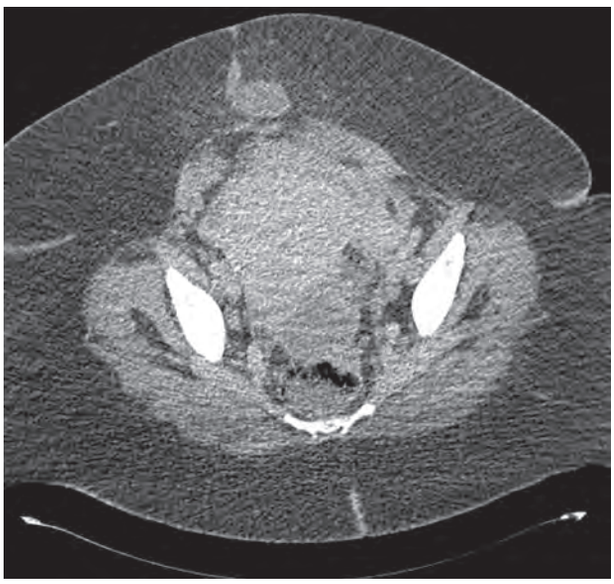
Infection with the human immune deficiency virus (HIV) in sub-Saharan Africa affected an estimated 22.5 million people, of whom 5.9 million were in South Africa, however, in the recent 2014 UNAIDS progress report, for the first time since 2009, a 17% decline was reported in the rate of newly diagnosed HIV cases for women of reproductive age, living in sub-Saharan Africa.[1] May et al. found that, between 1996 and 2008, the life expectancy of people receiving antiretroviral therapy (ART) had increased by an average of 15 years.[2] People with HIV infection live longer as a result of ART, and consequently are at risk of developing illnesses associated with ageing, chronic illnesses and malignancies.

Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL) and cervical cancer are the most observed AIDS-defining cancers. In the era of ART, a significant decrease in the incidence of AIDS-defining illnesses has been observed, whilst non-AIDS cancers (NADCs) are on the increase. An estimated 30% – 40% of HIV-infected patients are likely to develop a cancer during the duration of their disease.[3] An increased incidence was observed for anal, lung, certain head and neck cancers, and hepatocellular carcinoma, as well as Hodgkin's disease, whilst no increased risk was observed for breast, prostate and colorectal cancer in the HIV-positive cohort. No clearly established association between HIV and/or AIDS and gestational trophoblastic neoplasm (GTN) exists. Data from the Swiss HIV Cohort Study showed that 19% of all cohort deaths in the ART area were attributable to NADCs.[4]

GTN is a rare pregnancy-related disorder that derives from placental tissue and is clinically diagnosed if the B-HCG level fails to decrease or normalise in women when a normal pregnancy is excluded, and collectively includes: invasive mole, choriocarcinoma and placental site trophoblastic tumour (PSTT) that can lead to death if left untreated. Potential risk factors for the development of GTN include a history of a previous molar pregnancy, partial mole (0.5% risk) and a complete mole (15% risk), maternal age and a post-evacuation, persistent raised B-HCG level. Management includes careful dilatation and curettage (D&C), and the need for systemic treatment is guided by the International Federation of Gynecology and Obstetrics (FIGO)/WHO score that predicts if either single agent or combination chemotherapy is required. GTN is now one of the most curable solid tumours, with cure rates of more than 90% even in the presence of metastatic disease.[5,6] The occurrence of malignancy amongst people living with HIV and/or AIDS represents a management challenge. We present here two choriocarcinoma case studies of women with HIV and/or AIDS.

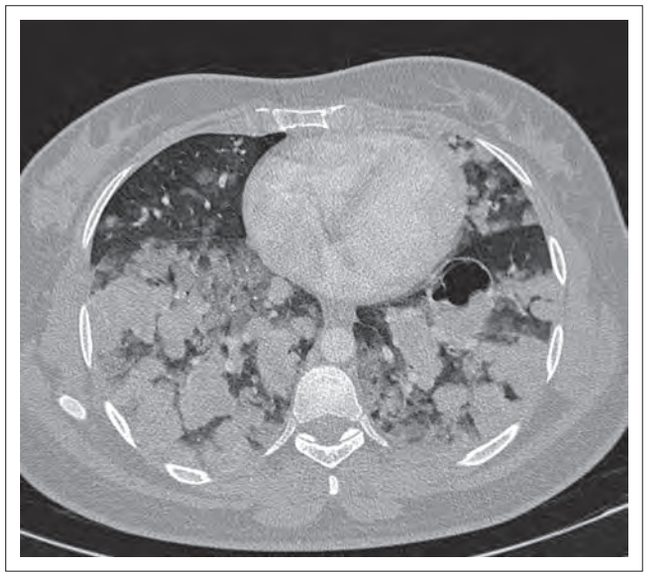
Ethics approval

The Human Research Ethics Committee (HREC) of Stellenbosch University approved the present report.



Source: Department of Clinical Oncology, Tygerberg Hospital

FIGURE 1: Computer tomographic scan of the abdomen demonstrating a grossly enlarged uterus and tumour mass extending through the anterior abdominal wall to the subcutaneous tissue.



Source: Department of Clinical Oncology, Tygerberg Hospital

FIGURE 2: Computer tomographic scan of the lung demonstrating bilateral diffuse soft-tissue nodules in keeping with metastatic disease. Note the large cavitating lesion in the left lower lobe, found in metastases from choriocarcinoma and resulting from tumour haemorrhage.

Case presentation

Case 1

A 33-year-old woman (gravida 5, para 2, miscarriage 3) presented post-evacuation for a miscarriage with persistent vaginal bleeding and a raised B-HCG value. She was living with HIV and/or AIDS and had been established on ART for one year. Clinical examination confirmed an abdominal uterine mass of 22 weeks' gestation with a foul-smelling vaginal discharge. Staging examinations included a computed tomography (CT) scan of the lungs, abdomen and pelvis and confirmed several bilateral lung metastases and an extensive tumour that involved the uterus and extended into the anterior abdominal wall (Figure 1). Abnormal laboratory studies revealed haemoglobin 4 g% (12.5 g% – 15 g%),a serum B-HCG level of 115 544 IU/L (<5 IU/L), and CD4 count of 290 cells/µL, (500 cells/µL – 2010 cells/µL). She was diagnosed as having a FIGO Stage III:12 high-risk choriocarcinoma.

Management included continuation with ART (tenofovir, efavirenz and lamivudine), intravenous antibiotics (piperacillin and amikacin), and low-dose chemotherapy with the alternating regime of methotrexate 50 mg alternative days (D1, 3, 5, 7) with leucovorin rescue. She completed one cycle without any adverse effects. However, a week post-chemotherapy she developed a neutropaenic fever. Abnormal laboratory studies then confirmed serum-creatinine 10.7 mmol/L (2.1 mmol/L – 7.1 mmol/L), urea 151 µmol/L (49 µmol/L – 90 µmol/L), and a pancytopaenia: white blood cells 0.13×10^9/L ($4.00–10.00 \times 10^9$/L), haemoglobin 6.6 g%, and platelets 15×10^9/L ($178–400 \times 10^9$/L). A follow-up CD4 count decreased to 29 cells/µL and the B-HCG value decreased to 50 296 IU/L. Supportive management included granulocyte-stimulating factor (G-CSF) and intravenous antibiotics according to the sensitivity of a positive blood culture (*Klebsiella pneumonia*). A vaginal pus swab cultured Candida species.

The outcome for the patient was unfortunate as she died owing to severe neutropaenic sepsis from a resistant Klebsiella and Candida sepsis that resulted in acute renal failure and severe immune suppression.

Case 2

A 20-year-old woman (gravida 2, para 0, miscarriage 1) presented with a history of haemoptysis, grade IV dyspnoea and a raised B-HCG level. She was known to have had a previous molar pregnancy, diagnosed three years previously. On clinical examination, symptoms and signs of thyrotoxicosis were present. Staging examinations included a lung CT that confirmed numerous bilateral, diffuse soft-tissue nodules throughout both lung fields in keeping with metastatic disease (Figure 2). Abnormal laboratory studies revealed a B-HCG value >898 400 IU/L (<5 IU/L), T4: 47 pmol/L (10.3 pmol/L – 21.9 pmol/L), and a CD4 count of 200 cells/µL (500 cells/µL – 2010 cells/µL); a HIV enzyme-linked immunosorbent assay (ELISA) test was positive. Direct microscopy for acid-fast bacilli was negative. She was diagnosed with a FIGO Stage III:15 high-risk choriocarcinoma in a newly diagnosed HIV-positive patient.

Management included commencement with ART (tenofovir, efavirenz and lamivudine) with the addition of trimetroprim-sulfamethoxazole for *Pneumocystis jiroveci* prophylaxis (PCP) as her CD4+ count was ≤200 cells/µL, intravenous antibiotic (clindamycin) and acute thyrotoxicosis therapy consisting of carbimazole and propranolol. Low-dose chemotherapy with methotrexate 50 mg alternated with leucovorin rescue on days 1, 3, 5 and 7 was initiated. However, she required admission into a high-care facility when spontaneous breathing became

problematic and a continuous positive airway pressure (CPAP) support system was needed. A standard blood culture confirmed Gram-positive cocci and a coagulase negative staphylococcal organism was isolated sensitive to vancomycin. A urine specimen cultured positive for *Candida albicans*.

When severe oxygen decompensation occurred, she was admitted to the ICU facility and intubation was necessitated. She died secondary to poor performance status, severe immune suppression, metastatic choriocarcinoma and a Staphylococcus and Candida sepsis when she developed acute respiratory distress syndrome (ARDS).

Discussion

Malignancy tends to occur at a younger age in people living with HIV and/or AIDS, and presents with atypical presentations, widespread metastatic disease, and aggressive tumour behaviour. In patients with immunodeficiency, physiological principles for the development of malignancy exist: (1) the lack of autoimmune surveillance, (2) an imbalance between cellular differentiation and proliferation and (3) a repeat antigenic stimulation by an oncogenic virus leads to the emergence and proliferation of abnormal cells. Amongst HIV-infected individuals, a 30% – 40% increase in the incidence of NADCs has been observed, and this contributes to morbidity and mortality in HIV-infected patients, now that survival is prolonged with the use of ART.[3,7]

Established chemotherapy regimens have resulted in a favourable response to GTN, and more than 90% of cases will be cured. Choriocarcinoma is generally associated with pregnancy but an estimated 25% occur after miscarriage, 25% after term pregnancy and the rest after a molar pregnancy. Choriocarcinoma is an aggressive form of GTN owing to its rapid growth and metastatic potential. In women, a high index of suspicion is needed to make a diagnosis based on an unexplained high B-HCG level in the presence of metastases in the lung, liver or brain. A high HCG level can also cause thyrotoxicosis. Delay in diagnosis with delay in starting chemotherapy treatment is a common cause of early death in patients with metastasis.[6]

Using the WHO/FIGO scoring system, patients are grouped into low- and high-risk categories. High-risk patients require combination chemotherapy as they are unlikely to be cured with a single agent. In high-risk patients, 50% of deaths occur within the first four weeks of initial treatment. Early deaths are attributed to respiratory compromise, haemorrhage secondary to a heavy tumour burden within the thorax, and rapid tumour destruction associated with full-dose chemotherapy treatment. Intubation in patients with very poor respiratory function should be avoided as far as possible as high ventilator pressures might trigger fatal intrapulmonary haemorrhage owing to friable tumour vasculature; and hence the introduction of low-dose therapy in the initial treatment of high-risk patients to gradually reduce tumour volume and significantly reduce the risk of haemorrhage to minimise the risk of early death.[8,9]

Because of extensive comorbidities, low-CD4 counts, poor performance status and the extent of metastatic disease, both our patients were offered initial low-dose chemotherapy to debulk tumour load. In the first case study, our patient developed post-chemotherapy neutropaenic sepsis. The outcome for her resulted in death secondary to a poor performance, severe immune suppression (CD4 count decrease from 290 cells/µL to 29 cells/µL), neutropaenic sepsis and extensive metastatic choriocarcinoma that resulted in acute renal failure. In the second case, the patient experienced severe oxygen desaturation owing to extensive lung metastases that necessitated intubation and ICU admission. The outcome for her was dismal as she died secondary to a poor performance status, severe immune suppression, sepsis and extensive metastatic choriocarcinoma when she developed ARDS.

Both our patients experienced severe immune suppression, had extensive metastatic disease and developed associated post-chemotherapy neutropaenia that increased their susceptibility to developing severe and fatal infections. Our cases also highlight previous findings of reported studies on GTN and HIV that confirm an associated poor outcome related to chemotherapy in women with HIV and/or AIDS if they present with low CD4 counts, have a poor performance status and an associated poor tolerance to chemotherapy treatment.[10,11]

Conclusion

Response to GTN is generally favourable with cure rates in excess of 90%. However, in patients with advanced immune suppression, medical management of non-AIDS-defining cancers can be compromised owing to their extent and aggressive tumour behaviour with associated treatment-related complications.

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Competing interests

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Authors' contributions

P.B. (Stellenbosch University) was responsible for the design, concept and preparation of the manuscript and was the project leader. M.R. (Stellenbosch University) also made conceptual contributions and was involved in preparation of the manuscript, and edited it.

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Reasons for failure of prevention of mother-to-child HIV transmission in a rural South African district hospital

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Further reduction of mother-to-child transmission (MTCT) of HIV requires improved understanding of the reasons for MTCT. We reviewed maternal and infant case notes for HIV-positive infants diagnosed by polymerase chain reaction at Bethesda Hospital. Nineteen cases were analysed. Median gestation at first antenatal consultation (ANC) was 22.5 (interquartile range [IQR] 19.25–24). Eleven (57.9%) mothers were HIV positive at first ANC, whilst eight tested negative and later positive (2 antepartum, 6 postpartum). Median maternal CD4 was 408 cells/μL (IQR 318–531). Six (31.6%) received no antenatal antiretroviral therapy (ART) because they were diagnosed as HIV positive postpartum; 9 (47.3%) received antenatal ART and 3 (15.8%) were never initiated on ART. At 6 weeks postpartum, 5 infants (26.3%) were not on prophylactic nevirapine (NVP) because their mothers had not yet been diagnosed. Maternal seroconversion in pregnancy and breastfeeding, and possibly false-negative HIV tests, were important reasons for prevention of mother-to-child transmission (PMTCT) failure.

Introduction

In 2010, the South African Department of Health (DoH) prevention of mother-to-child transmission (PMTCT) guidelines recommended World Health Organization Option A (prophylactic zidovudine [AZT] for women with a CD4+ count > 350 cells/μL and combination antiretroviral therapy [cART] for all pregnant women with CD4 < 350 cells/μL, with subsequent infant nevirapine [NVP] for a minimum of 6 weeks).[1] Option B (cART for all pregnant and breastfeeding women irrespective of CD4 count and postnatal infant NVP prophylaxis) was introduced in April 2013.[2] Using these guidelines, mother-to-child transmission (MTCT) in KwaZulu-Natal, South Africa, dropped from 20.8% at 6 weeks postpartum in 2005 to 2.1% in 2011,[3,4] with a national target of less than 2% by 2016.[5] Further reduction will require a better understanding of the reasons for PMTCT failure in local facilities. Seroconversion in pregnancy or breastfeeding, HIV diagnosis in pregnancy compared with diagnosis prior to conception, and health system-related factors have all been found to play a role in PMTCT failure.[6,7,8]

Bethesda is a rural district hospital serving approximately 115 000 people in Umkhanyakude District, KwaZulu-Natal Province, with an HIV prevalence of 41.1% amongst pregnant women in 2011.[9] HIV polymerase chain reaction (PCR) positivity at 6 weeks postpartum in 2013 was 2.3% for Bethesda Hospital (personal comm., Facility Information Officer, n.d.) and its eight peripheral primary healthcare clinics. Our aim was to identify reasons for these PMTCT failures.

Methods

We retrospectively reviewed maternal and infant case notes for HIV-positive infants identified by HIV PCR between February and September 2013 at Bethesda Hospital and its clinics.

Ethics approval

Ethics approval for the study was granted by the University of KwaZulu-Natal Biomedical Research Ethics Committee and the KwaZulu-Natal Health Research Committee.

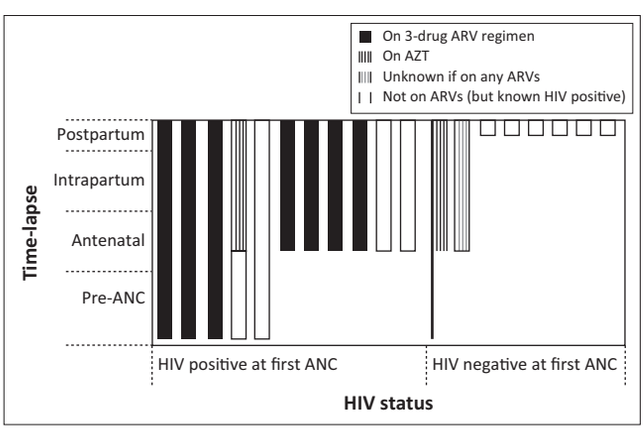
Results

A total of 25 cases of MTCT were identified in the study period. Data were available for analysis in 19 cases (Table 1). Notes were often incomplete, meaning data were not available for all 19 cases for some variables. Median maternal age was 22 years (interquartile range [IQR] 20.5–28). Median gestation at first antenatal consultation (ANC) was 22.5 weeks (IQR 19.25–24) and 9 (47.3%) women were known to have had their first ANC after 20 weeks' gestation. Five (26.3%) women were known to be HIV positive preconception. A further 6 (31.6%) tested HIV positive

TABLE 1: Maternal and infant characteristics.

Characteristics	Sub-characteristics	*n*	%	Median	IQR
Variable	Maternal age (years)	19	-	22	20.5–28
	Gestation at first ANC (weeks)	14 (5 unknown)	-	22.5	19.3–24
	Maternal CD4 (cells/μL)	14 (5 unknown)	-	408	318–531
	Weeks from infant diagnosis to ART initiation	13 (6 unknown)	-	5	3–11
Maternal HIV status at first ANC	Positive	11	57.9	-	-
	Negative	8	42.1	-	-
Period of maternal HIV diagnosis	Pre-conception	5	26.3	-	-
	Antenatal	8	42.1	-	-
	Postpartum	6	31.6	-	-
Antenatal ART regimen	None because diagnosed postnatally	6	31.6	-	-
	cART	7	36.8	-	-
	Prophylactic AZT	2	10.5	-	-
	No ART	3	15.8	-	-
	Unknown	1	5.3	-	-
Delivery	Normal vaginal delivery	12	63.2	-	-
	Caesarean section	5	26.3	-	-
	Unknown	2	10.5	-	-
	Gestation at delivery (weeks)	14 (5 unknown)	-	38	36–38
Infant NVP prophylaxis at 6 weeks postpartum?	Yes	8	42.1	-	-
	No†	6†	31.6	-	-
	Unknown	5	26.3	-	-
Infant feeding method at 6 weeks postpartum?	Exclusive breastfeeding	8	42.1	-	-
	Exclusive formula feeding	3	15.8	-	-
	Mixed feeding	2	10.5	-	-
	Unknown	6	31.6	-	-

N = 19.
n = number of cases per category; ANC, antenatal consultation; ART, antenatal antiretroviral therapy; cART, combination antiretroviral therapy; AZT, prophylactic zidovudine; NVP, nevirapine; IQR, interquartile range.
†, Five infants were not on NVP at their 6-week postnatal follow-up visit because their mothers had not yet tested HIV positive.



Note: The depth of the columns represents how early a maternity case was identified as HIV positive.

ANC, antenatal consultation; AZT, prophylactic zidovudine.

FIGURE 1: Period of maternal HIV diagnosis and initiation.

at first ANC. Eight (42.1%) tested HIV negative at first ANC, but two of these subsequently tested positive antenatally (1 and 3 weeks before delivery respectively). The remaining 6 (31.6%) women tested HIV positive postpartum. Median maternal CD4 at baseline was 408 cells/μL (IQR 318–531). Of the 13 who were known to be HIV positive before delivery, 1/13 (7.7%) had unknown antenatal antiretroviral therapy (ART) status, 3/13 (23.1%) were never initiated on ART before delivery, 3/13 (23.1%) were already on cART pre-conception, and 6/13 (46.2%) were initiated on ART antenatally (cART = 4, AZT monotherapy = 2) at a median of 28 weeks' gestation (IQR 26–30) and 0 days (IQR 0–16) after being diagnosed as requiring PMTCT. One of these patients had a documented history of poor adherence/defaulting. The six patients diagnosed postpartum did not have information on maternal ART initiation available. Of the three patients on cART pre-conception, 2 had viral loads taken antenatally and both were greater than 400 copies/mL. Five women had caesarean sections.

Regarding infants, 5 (26.3%) were not on NVP at their 6-week postnatal follow-up visit because their mothers had not yet tested HIV positive. Of the remaining 14 subjects, only 8/14 (57.1%) infants were documented to be on NVP prophylaxis, with 6/14 (42.9%) having no record of NVP administered. Two (10.5%) infants were documented as receiving mixed feeding at 6 weeks. One (5.3%) infant died before cART initiation, and 13 (68.4%) were known to have been initiated on cART at a median 5 (IQR 3–11) weeks after diagnosis.

Discussion

Maternal and infant ART have consistently been shown to be highly efficacious for PMTCT; consequently, omitting or delaying ART exposes infants to unnecessary HIV transmission risks.[10] In the present study, we repeat findings elsewhere[6,8] that initially testing HIV negative and subsequently positive in pregnancy or breastfeeding (leading to delays in ART initiation) is a major cause of PMTCT failure, occurring in 8 (42.1%) of the PMTCT failure cases in our study. We could not determine whether this was because of an initial false-negative test, or maternal seroconversion in the majority of cases. Current PMTCT guidelines advocate

a confirmatory second HIV rapid test if the initial test is positive. However, there is no confirmatory test if the first test is negative.[2] A study of 967 adults presenting for HIV testing in a clinic in Durban found that 2.1% of patients with a negative rapid HIV test had either acute HIV infection (which was missed by the rapid test because of falling within the 'window period') or chronic HIV infection (i.e. a false-negative rapid test).[11] In the context of further reducing MTCT to below 2%, potentially misdiagnosing 2% of mothers living with HIV is significant. Strategies to increase detection of all positive cases could include a second confirmatory rapid test as routine in all pregnant women (with an HIV ELISA confirmatory test for all discordant results). Furthermore, regular 3-monthly maternal HIV testing throughout the duration of pregnancy and breastfeeding, in accordance with DoH Guidelines,[2] or even reducing the repeat testing interval to 1- or 2–monthly, will be crucial to ensure that maternal seroconversion is detected as soon as possible.

Not documenting infant NVP prophylaxis when it is known to be indicated occurred in 6 (42.9%) cases in our study. However, this is probably higher than the true value as, from clinical experience, we note that infant NVP is often administered but poorly documented. Late booking after 20 weeks' gestation (also leading to late initiation of maternal ART) occurred in 9 (47%) of cases, although 75% of cases had booked before 24 weeks which should allow time for viral suppression by the time of delivery, assuming ART is initiated promptly.[10,12] Omitting maternal ART when it is known to be indicated occurred in 3 (15.8%) cases (we were unable to ascertain why), and virological failure despite maternal cART occurred in 2 (10.5%) cases. Both these cases had repeated viral loads > 400 copies/mL more than 1 month apart but were not switched to second-line cART. The third case had no viral load sampling during pregnancy.

Weaknesses of our study include lack of a control group, small sample size and incomplete or unavailable case notes. Data were too incomplete for analysis of several important variables (e.g. duration and means of rupture of membranes, elective versus emergency caesarean section, instrumental delivery, postpartum maternal ART adherence). Only descriptive analysis was possible and our results must be interpreted with caution.

Conclusion

PMTCT remains a focus programme in the South African healthcare sector. Better understanding of the reasons for MTCT can assist further reduction of MTCT rates to the target of less than 2%. Several causes for the failure of PMTCT in our sub-district have been identified. These correspond with reasons for MTCT from previous studies and available literature. Late first ANC, delayed or omission of maternal cART initiation, and poor management of women on cART contributed, amongst other factors, to our MTCT cases. Maternal seroconversion or an initial false-negative HIV test occurs frequently in PMTCT failures in our clinics, with subsequent late maternal ART initiation. This fact highlights the importance of preventing and promptly detecting maternal HIV infection in pregnancy and breastfeeding if MTCT is to be further reduced. Further research is needed to characterise the frequency of false-negative HIV testing in operational PMTCT programmes, and to identify cost-effective testing strategies to ensure early detection of acute maternal HIV infection in pregnancy and breastfeeding.

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Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

C.K. (Bethesda Hospital), L.C. (University of KwaZulu-Natal) and K.G. (Bethesda Hospital) designed the study. C.K., L.C., J.D. (Bethesda Hospital), G.M. (Bethesda Hospital) and K.G. collected data. C.K., L.C. and J.D. analysed the data. All authors were involved in drafting and critically reviewing the manuscript.

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New law on HIV testing in Botswana: The implications for healthcare professionals

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Background: Botswana is one of the countries with the highest HIV prevalence rates in the world. Innovative HIV testing strategies are required to ensure that those infected or at risk of infection become aware of their HIV status and are able to access treatment, care and support. Despite this public health imperative, HIV testing strategies in Botswana will in future be based around the principles in the new *Public Health Act* (2013). The present article describes the HIV testing norms in the Act, and sets out the strengths and weaknesses of this approach and its implications for healthcare professionals in Botswana.

Objectives: To compare international norms on HIV testing with the provisions governing such testing in the new Botswana *Public Health Act* and to assess the extent to which the new Act meets international human rights norms on HIV testing.

Method: A 'desktop' review of international human rights norms and those in the Botswana *Public Health Act*.

Conclusion: HIV testing norms in the new *Public Health Act* in Botswana violate individual rights and will place healthcare workers in a position where they will have to elect between acting lawfully or ethically. Law reform is required in order to ensure that HIV testing achieves the joint goals of public health and human rights.

Introduction

Botswana continues to have one of the highest HIV prevalence rates in the world.[1] Although the rate of new HIV infections has dropped, the prevalence rate remains high amongst certain populations, such as young persons with an estimated 23% of 15–49 year-olds being HIV infected.[1] In this context, increasing access to HIV testing as the gateway to HIV prevention and treatment is important, and international best practice requires innovative HIV testing strategies to reach those at risk.[2] It is against this background that the recently introduced *Public Health Act* (2013) which deals directly with HIV testing services in Botswana should be reviewed.[3] The present article maintains that the approach adopted by the *Public Health Act* does not follow a rights-based approach to accessing HIV testing as set out in international norms. The article describes some of the implications this approach has for healthcare workers (HCWs), and it concludes with recommendations for law reform.

HIV testing: The human rights framework

A rights-based approach has been defined as 'a conceptual framework for the process of protecting human rights, based on international human rights standards and operationally directed towards promoting and protecting human rights'.[4] This human rights approach is reflected in the well-established HIV testing norms at an international level. Although these standards have evolved over time, reflecting changing public health approaches, they have continued to be based on the fundamental human rights to exercise one's autonomy, to privacy and to access the highest attainable standard of healthcare.[5,6]

Early guidance was established in the HIV and Human Rights Guidelines, a set of international norms describing the way in which governments ought to respond to the epidemic.[7] Issued jointly by the United Nations Programme on HIV/AIDS (UNAIDS) and the United Nations Office of the High Commissioner for Human Rights in 1996, the guidelines provide that governments should review and reform their public health laws to ensure that they protect the right to consent, privacy and confidentiality during HIV testing.[7] In 2004, further guidance from UNAIDS and the World Health Organization (WHO) established the principle of a rights-based approach to HIV testing[3] by stating that the only form of acceptable mandatory screening is that done on donated blood.[8] It provided further that the '3 Cs' (consent, counselling and confidentiality) should form the bedrock of HIV testing services.[3] In this approach, the focus is on patients voluntarily electing to test for their HIV status.[8]

In 2007, there was a shift in the international guidance when UNAIDS and the WHO issued guidelines on Provider Initiated Counselling and Testing (PICT).[9] These proposed an approach in which HIV testing was to be recommended to all patients who present themselves at a healthcare facility with certain conditions.[9] If the offer of HIV testing was accepted, consent would be obtained for the test with the overriding principle being the best interests of the individual patient.[10] This approach requires the giving to individuals of sufficient information to make an informed and voluntary decision to be tested, maintaining patient confidentiality, performing post-test counselling and making referrals to appropriate services.[10] This shift was prompted by the new human rights goals of universal access to prevention, treatment, care and support services.[10]

The new legal framework regulating HIV testing in Botswana

The *Public Health Act* (No. 23 of 2013)[3] attempts to comprehensively address key public health concerns in Botswana by creating regulatory structures and setting normative standards on certain issues such as which diseases should be notifiable.[3] Part XII of the Act identifies HIV as a significant public health issue facing Botswana, and it sets a number of norms relating to HIV prevention and control.[3] These include seven norms for HIV testing, as follows.

Access to efficient HIV testing services

The *Public Health Act* provides that there is an obligation on the Minister of Health to ensure that confidential HIV testing facilities are available to all persons over the age of 16 (section 104).[3] Furthermore, the services ought to be efficient as every person has a right to receive their HIV test results as soon as they are approved (section 111).[3]

Consent must be provided for the testing

HIV testing may only be undertaken with the consent of the person or their parent (if they are under 16) (s 105) unless the test falls into one of the mandatory testing categories described below.[3]

Mandatory HIV testing

Nonconsensual testing may be done in six situations: (1) if a mentally disabled person is incapable of providing consent, they may be tested without consent (section 105[c]),[3] (2) if the HIV test is required under this or any other act, for example the compulsory HIV testing of any person convicted of rape or defilement under the Penal Code (section 108),[3] (3) if the person is unconscious and unable to give consent,[5] (4) where the medical practitioner believes that such a test is clinically necessary or desirable in the interests of that person (section 105[2]),[3] (5) all donated blood and tissue, (s 106–107) and (6) before any dental or surgical procedure (section 109). If a patient refuses to consent, the HCW may carry out the test without consent or refer the person to another HCW to do the procedure (section 109).[3]

A HCW who conducts an HIV test without consent is indemnified against any civil or criminal liability that may arise out of the nonconsensual HIV testing (section 105[3]).[3]

Pretest information

Pretest information should be provided to any person who is to undergo an HIV test (section 110).[3]

Confidentiality of HIV test results

Users of test services are entitled to confidentiality regarding both their test results and information on their sexual behaviour or the use of drugs.[3] Furthermore, the *Public Health Act* provides that all positive results must be confidentially recorded by HCWs in terms of the notifiable disease obligations (section 114).[3] Such information may only be disclosed with consent (section 115) or in terms of the circumstances described below.[3]

Nonconsensual disclosure of a person's HIV status

HCWs may disclose a person's HIV status without consent in three circumstances: (1) to a sexual contact or caregiver if after a reasonable period they have not made such a disclosure themselves (section 116[7]).[3] (2) after the death of the person (section 115) [3] and (3) where there may be disclosure to other HCWs directly involved in the care of the patient.[3]

HIV testing may only be undertaken at designated HIV testing centres

Section 119 provides that HIV testing may only be undertaken at a designated HIV testing centre.[3]

Review of the new legal framework for HIV testing in Botswana

The provisions in the new *Public Health Act* strengthen patient rights by providing, firstly, that there is a positive obligation on the state to provide confidential HIV testing facilities to all persons over the age of 16.[3] Given that HIV testing is the gateway to both HIV prevention and treatment, the Act makes access to these services a fundamental human right. If the State fails to make such services available, it could be held accountable for its inaction. Secondly, the testing services must be provided in a manner that respects rights, in that consent must be obtained from patients and their rights to privacy protected.[3] Furthermore, patients must be given information before the test and this promotes their rights to autonomy in the decision-making process. Thirdly, the service must also be efficiently provided as the test results should be made available to patients as soon as the result is obtained and approved, which promotes their right to the highest attainable standard of healthcare. Fourthly, in line with international norms, all donated blood and tissue must be tested for HIV. Fifthly, the Act lowers the age of consent to HIV testing to 16, so enabling young persons at risk of HIV infection to become aware of their HIV status independently.[5]

Previously this was not a legal right as the *Children's Act* is silent on the issue[11] but it was allowed in terms of the National Guidelines for HIV Testing and Counselling of 2009.[12]

Based on the above provisions, those in the new *Public Health Act* appear on the face of it to be in line with the '3Cs' as required in terms of international guidance issued by the WHO and UNAIDS. The Act also promotes a number of fundamental human rights as it protects the rights to autonomy and privacy. However, all of these rights are undermined by claw-back clauses in the Act. Firstly, the right to voluntarily consent to all forms of HIV testing is severely limited by the seven forms of mandatory or compulsory HIV testing that may take place in terms of the Act. As stated above, only one form of mandatory testing is allowed in terms of international HIV testing norms – the testing of donated blood. However, the drafters of the Act have created a further six circumstances in which testing may be undertaken without consent. It is particularly concerning that all persons undergoing surgical and dental procedures must be tested for HIV.[3] This means that all persons visiting healthcare services for routine dental check-ups or minor procedures such as the removal of an ingrown toenail will be subjected to mandatory HIV testing. The public health value of testing all persons before surgical or dental procedures is unclear, given the use of universal precautions. The personal benefit to the patient is also unclear as there is no direct obligation to provide post-test counselling or refer them for treatment. In addition to mandatory testing, the Act also allows HCWs to undertake HIV testing where they believe that the testing is clinically necessary or even simply 'desirable' in the interests of that person.[3] This creates a very low threshold at which HCW paternalism could override patient autonomy, which undermines the right to autonomy as it places the decision to test in the hands of the HCW. This opens the door to *inter alia* HIV testing practices being driven by, for example, stigmatising or discriminatory attitudes towards certain populations such as men who have sex with men, or sex workers.

Secondly, the right to privacy established in the Act is undermined by the sweeping powers of HCWs to disclose the HIV status of a patient to any sexual contact or caregiver of the patient if they become aware that the patient has not made such a disclosure themselves.[3] This power is out of step with international norms that would generally only require disclosure if the sexual partner or caregiver is at risk of HIV infection.[13] Mandatory disclosure not only violates the right to privacy, but it also places persons living with HIV at increased risk of stigma and discrimination. Furthermore, the Kenyan High Court recently found that the term 'sexual contact' in the Kenyan *HIV/AIDS Prevention and Control Act* (No. 14 of 2006) violated the principle of legality in that it was 'vague and overbroad and lacks certainty'.[14] The court was of the opinion that HCWs would not be able to comply with the provision as it was not clear who would be considered a sexual contact.

Thirdly, although the Act allows children of 16 and above to consent independently to HIV testing, this is an acontextual approach as there is nothing in the laws of Botswana which allow children of this age to independently consent to HIV treatment. This means that children will still require parental assistance, which may act as a barrier to some of them accessing antiretrovirals.

Fourthly, the approach taken in the Act to mandatory testing and disclosure places HCWs in an ethical dilemma. The Medical Council (Professional Conduct) (Amendment) Regulations provide that doctors have an ethical obligation to maintain confidentiality and may only violate this rule in limited circumstances, such as when ordered to do so by a court.[15] This means that doctors complying with the Act will be violating professional ethical obligations.

Finally, the narrow approach taken in the Act to limiting HIV testing services to designated facilities means that innovations such as home or self HIV testing cannot be rolled out in Botswana as they are expressly prohibited by law; this undermines the right to the highest attainable standard of healthcare.

Implications of the new HIV testing provisions for healthcare workers in Botswana

There are several implications of this new law for healthcare professionals working in Botswana, including that they:

- need to be aware that they may be asked to act unethically but legally in carrying out mandatory HIV testing, particularly before all surgical and dental procedures. In this regard, it is recommended that practitioners consult with their professional structures to obtain advice on what to do in such instances
- will be under a legal obligation to disclose the HIV status of, for example, pregnant HIV-positive women if they are not convinced that the patient has made the disclosure herself to her partner. This may place women at risk of domestic violence or other negative consequences[12]
- may lawfully disclose a patient's HIV status to other HCWs directly involved in the care of the patient
- will need to advise children over the age of 16 that, even if they consent on their own to an HIV test, they will need parental assistance to access HIV treatment
- will be unable to offer HIV testing to children under the age of 16 who do not have a parent or guardian to advise them as there is no provision in the Act for any alternative proxy consenter
- ought to provide pretest information but no legal obligation to provide post-test counselling
- cannot offer new innovations such as home HIV testing for these will be illegal as testing is limited to being done at authorised centres.

Conclusion

Sadly, the new 2013 *Public Health Act*[3] in Botswana goes against international best practices as laid out in instruments

such as the UNAIDS/WHO Policy Statement on HIV,[8] the HIV and Human Rights Guidelines,[7] and the PICT guidelines.[9] Although the Act provides a veneer of human rights, HIV testing will generally now be undertaken in a coercive manner, which undermines efforts to increase awareness of one's HIV status. The drafters of the Act have also misunderstood the shift in international norms as, although there is a focus on increasing access to HIV testing, it still requires such testing to be done in a way that is consistent with human rights norms. The Botswana legislature has elected to ignore this approach. It is unlikely that the current coercive approach to HIV testing as set out in the *Public Health Act* will result in greater individual awareness of HIV status, as most of the testing will be directed at HIV testing in the interests of the healthcare provider.

Recommendations

We submit that there is a need to reform the *Public Health Act* to ensure that HIV testing services are provided in a way that does not infringe people's rights. As a minimum, the power to test patients without their informed consent should be removed and the mandatory disclosure provisions limited to situations where a third party is at significant risk of HIV infection.

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Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

R.O.S. (University of KwaZulu-Natal) is the first author, undertaking the initial research and preparing a first draft of the manuscript. A.E.S. (University of KwaZulu-Natal) is second author; she reviewed the first draft and wrote the analysis of the *Public Health Act*. Both authors developed the conclusion and recommendations.

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Information for Authors and Readers

Focus and scope
The *Southern African Journal of HIV Medicine* is focused on HIV/AIDS treatment, prevention and related topics relevant to clinical and public health practice. The purpose of the journal is to disseminate original research results and to support high-level learning related to HIV Medicine. It publishes original research articles, editorials, case reports/case series, reviews of state-of-the-art clinical practice, and correspondence.

Peer review process
All manuscripts submitted to *Southern African Journal of HIV Medicine* will be reviewed by experts in the field and will undergo a double-blind review process.

Sponsors, endorsement and publication frequency
Southern African Journal of HIV Medicine publishes manuscripts on its website on a rolling basis throughout the year (i.e. as soon as they are ready for publication). In this way, *Southern African Journal of HIV Medicine* aims to speed up the process of manuscript publication, from submission to a manuscript's availability on the website.

Manuscript preparation and submission
All articles must be submitted online at http://www.sajhivmed.org.za.

Visit http://www.sajhivmed.org.za, click on 'Submit online'. If you are already registered, please proceed with the submission process by logging into the site. If not registered, please register with the website. Complete all the required fields and remember to tick the checkbox under 'Register as Author' at the bottom of the registration page. (You may also register here as a reviewer). Log in with your username and password and simply follow the easy five step process to upload your manuscript.

Abbreviation and referencing
The journal is officially referenced as *Southern African Journal of HIV Medicine.*

Distribution and Indexing
The journal is an online open access publication, available at http://www.sajhivmed.org.za to read. The hard copy is distributed to those individuals who order a copy from the publisher.

After publication in *Southern African Journal of HIV Medicine*, the complete text of each article is deposited immediately and permanently archived in major bibliographic databases:

- AOSIS Publishing Library
- Google Scholar
- Thomson Reuters Products
  - Science Citation Index
- GALE, CENGAGE Learning
- ProQuest
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Accreditation
The journal meets the criteria of the Department of Higher Education and Training (DoHET). It is therefore accredited and approved by the DoHET for its inclusion in the subsidy system for being a research publication for South Africa.

AOSIS
http://www.aosis.co.za

In an effort to facilitate the selection of appropriate peer reviewers for *Southern African Journal of HIV Medicine*, we ask that you take a moment to update your electronic portfolio on http://www.sajhivmed.org.za for our files, allowing us better access to your areas of interest and expertise, in order to match reviewers with submitted manuscripts.

If you would like to become a reviewer, please visit the journal website and register as a reviewer.

To access your details on the website, you will need to follow these steps:

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3. It is good practice as a reviewer to update your personal details regularly to ensure contact with you throughout your professional term as reviewer to the *Southern African Journal of HIV Medicine*.

Please do not hesitate to contact us if you require assistance in performing this task.

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Southern African Journal of HIV Medicine

The editorial team of *Southern African Journal of HIV Medicine* recognises the value and importance of the peer reviewer in the overall publication process – not only in shaping the individual manuscript, but also in shaping the credibility and reputation of our journal.

We are committed to the timely publication of all original, innovative contributions submitted for publication. As such, the identification and selection of reviewers who have expertise and interest in the topics appropriate to each manuscript are essential elements in ensuring a timely, productive peer review process.

We would like to take this opportunity to thank all reviewers who participated in shaping this volume of *Southern African Journal of HIV Medicine*.

We appreciate the time taken to perform your review successfully.

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