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Southern African Journal of HIV Medicine

- Gender inequality: Bad for men's health
- WHO guidelines should not change CD4 threshold for ART
- Transitioning behaviourally HIV-infected youths into adult care
- HIV and concurrency of sexual partnerships in SA language groups
- Overview of HIV-related lipodystrophy
- 2012 SA HIV Clinicians Society Conference (best abstracts)

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MESSAGE
From the Editor

HIV medicine is a rapidly evolving field, perhaps more so than many other areas of clinical practice. The optimal choice of medicines changes regularly, but more profound changes in strategies to manage (and prevent) HIV infection also emerge at frequent intervals. To keep pace with these changes, guidelines to support different aspects of HIV medicine are updated regularly, and indeed we are in the midsts of another season of international guideline revisions; most notably, at the World Health Organization (WHO).

Given the heavy burden of HIV in South Africa, and the major international contributions of South African research to the global evidence base, it is unsurprising that this edition of the Journal contains a number of pieces of commentary on key issues facing the WHO guidelines group. One of the key issues in adult HIV medicine is the 'best' CD4 threshold for ART initiation – recognising that the 'best' can be defined in terms of individual patient management, cost-effectiveness for public health services, and even in terms of impact on HIV prevention efforts. In his commentary, Geffen[1] touches on each of these concerns and arrives at a sensible position to maintain current CD4 starting points (i.e. with ART initiation below 350 cells/μl) until further evidence emerges. Meanwhile, the question of the most appropriate prevention of mother-to-child transmission (PMTCT) policy for South Africa was discussed in the previous issue[2] – focusing on the question of 'Option B+'. An editorial written in response by Coutsoudis and colleagues[3] is published here – and the question of whether South Africa should shift policy to universal initiation of lifelong ART for all HIV-infected women remains open. Finally, an issue that is not squarely in the sights of the WHO guidelines group – but perhaps should be – is the pervasive gender inequities in access to and outcomes of ART. As Cornell[4] notes in her commentary, this inequality favours female patients, in contrast to many of the commonly held assumptions about gender and HIV, raising concerns about men's health that many health services and policies are ill-equipped to address.

There are a number of other exciting contributions in these pages. Katusiime and colleagues[5] describe the evaluation of a novel Ugandan programme to transition HIV-infected adolescents to routine adult care services – one of the first of its kind in Africa. Given the growing number of adolescents in our care and treatment programmes, examples of South African services that meet this need are urgently required. Meanwhile, Kenyon[6] provides a creative analysis of HIV risk factors across language groups in South Africa, providing further indirect evidence for the role of sexual partner concurrency in the spread of the epidemic. Furthermore, Roussouw and colleagues[7] provide a useful overview of HIV-associated liopdystrophy. Finally, this issue of the Journal is the first since the very successful SA HIV Clinicians Society Conference, held in November 2012 in Cape Town. We have published several of the best abstracts[8] that were presented at the meeting, and look forward to seeing others published in *SAJHIVMED* soon.

Happy reading.

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MESSAGE
From the Executive

There is little doubt that 2012 ended on a high note. The inaugural conference of the Southern African HIV Clinicians Society was a resounding success; with over 950 attendees and excellent speakers (both local and international), I believe that we achieved our aim of 'Striving for Clinical Evidence.'

Even before the dust had settled on the conference, Dr Aaron Motsoaledi, South African Minister of Health Minister, announced two very important strides for our national antiretroviral therapy (ART) programme. Firstly, for the first time, fixed-dose combinations (FDCs) are going to be introduced. This means that most South Africans who are receiving first-line therapy will be taking one tablet a day. The price for the combination of tenofovir, emtricitabine and efavirenz is R89.37 – one of the lowest in the world. In the coming months, the Society will be training and educating healthcare workers and patients on when and how to change to FDCs. If that was not enough good news, at the same press conference Motsoaledi announced that all HIV-infected pregnant women will be given triple therapy – usually the single-dose FDC – irrespective of their CD4+ cell count.

The work is not over. Let's get these FDCs out there, enrol as many HIV-pregnant women on therapy as possible, and eradicate mother-to-child transmission of HIV.

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FORUM

World Health Organization guidelines should not change the CD4 count threshold for antiretroviral therapy initiation

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The World Health Organization (WHO) currently recommends that HIV-positive adults start antiretroviral therapy (ART) at CD4 counts <350 cells/µl. Several countries have changed their guidelines to recommend ART irrespective of CD4 count or at a threshold of 500 CD4 cells/µl. Consequently, WHO is currently revising its treatment guidelines and considering recommending ART initiation at CD4 counts <500 cells/µl. Such decisions are critically important, as WHO guidelines inform healthcare policies in developing countries and are used by activists in their advocacy work. Changing the CD4 initiation point from 350 to 500 cells/µl would, however, be premature and have profound cost implications on Global Fund, President's Emergency Plan for AIDS Relief (PEPFAR) and developing country health budgets. We should be willing to campaign for such a change in guidelines despite cost implications, *if* supported by evidence. However, the evidence remains outstanding.

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The World Health Organization (WHO) currently recommends that adults living with HIV start antiretroviral therapy (ART) when their CD4 counts fall below 350 cells/µl. Several countries have changed their ART guidelines to recommend treatment irrespective of CD4 count or at treatment thresholds of 500 CD4 cells/µl.[1] WHO is currently revising its treatment guidelines and considering recommending that treatment start at 500 cells/µl. The decisions taken by WHO on ART guidelines are extremely important, as these guide healthcare policies in developing countries and are used by activists in their advocacy work.

To understand the impact of the WHO guidelines, it is important to consider that there are more people living with HIV in Nigeria alone than in the whole of North America, Western Europe and Australia combined. Even a small country such as Zimbabwe has more HIV-positive people than in the whole of Western Europe.[2] Countries in sub-Saharan Africa, the Caribbean and Asia are strongly influenced by the WHO guidelines, much more so than by the Department of Health and Human Services (DHHS) guidelines published in the United States of America. This is especially the case for countries where treatment is primarily provided through funding from the Global Fund to Fight AIDS, TB and Malaria (GFATM) or the United States President's Emergency Plan For AIDS Relief (PEPFAR).

The evidence for changing CD4 initiation thresholds

When considering changing the CD4 threshold for ART initiation, or dispensing a threshold entirely, we need to consider the evidence to support such a change, for both an individual patient's health and for HIV prevention efforts at a population level.

Prevention

The HPTN 052 trial showed that ART greatly reduces the risk of an HIV-positive person transmitting HIV to his/her partner. This finding was consistent with compelling observational data.[3] There is also evidence from several places, including San Francisco, Vancouver and Taiwan, that reducing community viral load reduces HIV incidence.[4-6] There is also indication from mathematical models that ART may be reducing HIV incidence in South Africa.[7] WHO subsequently published guidelines regarding the role of ART in HIV prevention efforts.[8]

Nevertheless, in many settings it is not clear whether changing the CD4 initiation threshold to 500 CD4 cell/µl would have a significant effect on HIV incidence. In contrast to places in North America where reduction in community viral load has been shown to reduce incidence, the distribution of HIV in many sub-Saharan African cities is characterised largely by heterosexual epidemics of a much broader scale. It is likely that reducing viral load through widespread ART use will reduce incidence in sub-Saharan Africa, but this is not a given. Moreover, this approach has to be proven to policy makers, because there are enormous cost implications associated with this type of expanded treatment. Studies currently underway in African countries are looking at whether initiating treatment earlier does reduce community incidence.

Treatment

The benefit to the patient should be the salient consideration in the WHO treatment guidelines (as opposed to guidelines for sero-discordant couples, where preventing infection of the HIV-negative partner is the primary consideration). When empirical data on this question are appraised rigorously, as in the British HIV Association's guidelines, it emerges that the evidence for initiating treatment at a CD4 count >350 cells/µl is poor.[9]

One widely circulated myth that needs to be discredited is that the HPTN 052 trial showed a reduced disease progression when ART was initiated above 350 CD4 cells/µl: the initiation threshold was 250 CD4 cells/µl, and not 350 cells/µl. Data from clinical trials had previously shown that a treatment threshold of 250 cells/µl was inferior.[10,11] The question of whether a threshold of 350 CD4 cells/µl is optimal remains unanswered.

Guidelines in some wealthy countries have changed to-and-fro over the last decade and a half on the issue of when to initiate ART: from the 'hit hard, hit early' strategy promoted in the 1990s, to postponing ART initiation until lower CD4 thresholds more recently. This is precisely why the Strategic Timing of Anti Retroviral Therapy trial (START) (funded by the United States National Institute of Health) and the Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-positive Adults trial (TEMPRANO) (funded by the French National Agency for Research on AIDS and Viral Hepatitis) are being conducted: to answer once and for all when the best point is for patients to start ART.

There are three likely outcomes of the START and TEMPRANO studies: *(i)* that earlier treatment reduces disease progression; *(ii)* that there is no difference between the earlier v. later treatment arms; or *(iii)* that earlier treatment is harmful due to increased side-effects or reduced adherence. If the latter two outcomes emerge but WHO has already recommended earlier treatment, it will undermine the WHO treatment guidelines in general. At best, there would have been serious cost implications for developing country health budgets; and at worst patients might have been harmed. If WHO keeps its threshold recommendation unchanged and the first of the aforementioned outcomes is validated, then the organisation would have taken the correct action by having waited for the evidence.

Although clinicians and AIDS activists have different expectations of the trial results, these personal prejudices do not matter. The evidence is simply not yet available, and in this case, WHO needs to wait.

The issue of cost

Cost is profoundly important when considering public health interventions, and should always be a concern for activists. To ignore such implications is poor activism, not only because policy makers do not take activists who ignore cost seriously, but also because it is morally problematic. Public health policy involves making choices determined by cost. As ART becomes more nuanced, the relative cost per disability adjusted life-year (DALY) saved becomes higher and the arguments for using the money elsewhere become harder to refute. As an example of how cost has informed activism in a developing country, the Treatment Action Campaign (TAC) has been cognisant of cost in its campaigns, despite demanding that the South African (SA) government implements treatment and prevention programmes. In a court case that dealt with prevention of mother-to-child transmission of HIV in 2002, the TAC included an affidavit that showed that the intervention would be cost-saving.[12] The TAC later published research showing that ART would be affordable for the SA government. By considering cost, the TAC was able to make compelling arguments for the implementation of life-saving interventions.

The current WHO ART guidelines for adults and adolescents include two important changes, including provision (*i*) for ART to be initiated at 350 CD4 cells/µl; and (*ii*) for stavudine (d4T) to be replaced by tenofovir (TDF). Both of these changes have cost implications, but are supported by a very strong evidence base. Because the campaigns for these changes to be adopted by poor countries have been based on sound science, they have met some success. WHO guidelines should be seen as an achievable aspiration for poorer countries. Nevertheless, even today, several sub-Saharan countries initiate ART at 200 - 250 CD4 cells/µl with stavudine, largely due to resource limitations. This proves that cost is a critical factor – perhaps the most critical factor – in getting poorer countries to change their guidelines.

Conclusion

Changing the CD4 initiation point from 350 to 500 cells/µl in the new WHO guidelines would be premature. It would have profound cost implications on Global Fund, PEPFAR and developing country health budgets. We should be willing to campaign for such a change in guidelines despite cost implications *if* it was supported by evidence. But, the evidence is still outstanding. Expecting countries to move to a costly new CD4 threshold without sufficient evidence is a mistake.

Conflict of interest. The author serves on the Community Advisory Board of INSIGHT, the organisation that runs the START trial.

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FORUM
Is Option B+ the best choice?

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The success of prevention of mother-to-child transmission (PMTCT) programmes (Options A and B) in middle-income countries, together with clinical trial data on antiretroviral (ARV) treatment as prophylaxis, has emboldened UN agencies to aggressively promote lifelong ARVs for PMTCT (Option B+). Unsubstantiated claims submit that Option B+ is cost-effective at population-level, will protect HIV-negative male partners, improve maternal and infant health, and increase ARV coverage. We provide counterfactual arguments about the ethics, medical safety, programme feasibility and economic benefits of Option B+.

Option B+ offers no advantage to PMTCT and there are social hazards associated with privileging pregnant woman for treatment over men and non-pregnant women, especially with the absence of data to suggest that discordant relationships are more frequent among pregnant women or that they contribute disproportionately to the horizontal HIV transmission. The benefits and safety of long-term ARVs – including adherence and resistance – in mothers who do not need treatment for their own health, need to be considered, as well as, crucially, health service costs. The assumption that a decrease in efficiency caused by inappropriate targeting is compensated for by lower recruitment costs, is untested. Lives could be saved instead with appropriately targeted interventions. Countries should make individual decisions based on their HIV epidemiology, resources, priorities and local evidence.

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Advocacy of the extreme antiretroviral therapy (ART) Option B+ for pregnant women by some organisations and international agencies,[1,2] particularly at the AIDS 2012 conference in Washington DC, USA,[3] with little consultation, debate and discussion, is worrying.

Supporters of Option B+ argue that it is superior, owing to additional ART coverage (because CD4 cell count results are not needed), additional maternal health benefits, and protection of discordant male partners. However, these benefits have not been validated due to the fast pace and single-mindedness of advocacy. The business case,[2] which supports the use of Option B+ in resource-limited settings, does not fully address four critical considerations: ethics, medical safety and benefits, programme feasibility, and economic concerns (Table 1).

Options A, B and B+ have similar protective benefits with respect to the prevention of mother-to-child transmission (PMTCT) of HIV.[4,5] Data suggest that triple ART may provide maternal health benefits even up to CD4 cell counts of 600 cells/µl,[5,6] and that it reduces HIV transmission between discordant couples.[7]

However, these data alone do not justify favouring pregnant woman for treatment over men and non-pregnant women. If Option B+ is used because it may decrease mortality and disease progression in HIV-infected mothers with CD4 counts >350 cells/µl, then the justification should extend to the families, partners, friends and community of the pregnant women, and the whole HIV-infected population. The application of different treatment thresholds in sub-populations could create tensions

Table 1. Summary of PMTCT options and concerns with Option B+

PMTCT options	
Option A	

Mother	• CD4 count ≤350 cells/μl: triple ARVs starting as soon as diagnosed; continued for life
	• CD4 count >350 cells/μl:
	  • Antepartum: AZT from 14 weeks' gestation
	  • Intrapartum: single-dose (sd) NVP and AZT + 3TC
	  • Postpartum: AZT + 3TC for 7 days.

Infant	• Daily sd NVP for 6 weeks in non-BF infants or mother receiving ART or until 1 week after all BF has stopped.
Option B	
Mother	• All pregnant women will be started on triple ARVs regardless of CD4 cell count. • CD4 count ≤350 cells/μl: triple ARVs will be continued for life • CD4 count >350 cells/μl: triple ARVs will be started as early as 14 weeks' gestation, continued intrapartum and through childbirth and stopped if not breastfeeding or continued until 1 week after cessation of all breastfeeding.
Infant	• Daily NVP or AZT from birth to 4 - 6 weeks of age.
Option B+	
Mother	• All pregnant women will be started on triple ARVs regardless of CD4 cell count and this will be continued for life.
Infant	• Daily NVP or AZT from birth to 4 - 6 weeks of age.
Concerns with Option B+	
Ethical	• Should pregnant women be prioritised for treatment for reasons other than the immediacy of their medical condition? • Have the implications of introduction or exacerbation of intra-household and community tensions because of different treatment access been adequately considered? • Should selective test-and-treat interventions be considered ahead of achieving universal access for patients with CD4 counts <350 cells/μl? • Is it ethical to give women with high CD4 cell counts treatment for life without fully understanding the long-terms benefits and risks? • Will the rollout of ARVs for a selected group within the population compromise the provision of ARVs for other groups who need it for their own health in resource-limited settings or settings with drug-supply restrictions?
Medical	• Are there benefits for mother-to-child transmission and long-term infant HIV-free survival? • Are the benefits for maternal health worth the potential increase in drug resistance? • Will long-term exposure to ARVs in mothers reduce horizontal transmission and change the trajectory of the HIV epidemic? • Do we have enough evidence to suggest that pregnant women and new mothers are a risk group who have discordant relationships and contribute to the HIV epidemic?
Programmatic	• Can B+ be implemented in strained health systems without disruption of the introduction of treatment programmes? • Will the implementation of B+ need scarce resources such as personnel, laboratory support and drugs to be diverted from the drive towards universal access to HIV treatment or universal access to treatment for other non-HIV life-threatening conditions or infectious diseases? • Will the necessary levels of adherence be maintained?
Economic	• Is the assumption valid that economies of scope will favour this 3-in-1 intervention (i.e. PMTCT, treatment and treatment-as-prevention)? • If retention rates are not high, will the economic argument in favour of B+ be invalid?

between people with and those without access to treatment. If Option B+ is a phase-in of a universal test-and-treat goal, then this should be made explicit, and the ethics of early treatment initiation in the context of unmet need warrant discussion. Option B+ is being considered only in resource-limited settings with a high HIV burden, to target pregnant women for non-pregnancy-related interventions such as treatment-as-prevention and early treatment initiation. There are no data to suggest that pregnant women have above-average involvement in discordant relationships or that pregnant women contribute disproportionately to the horizontal transmission of HIV.

The medical benefits and safety of long-term antiretrovirals (ARVs) need to be considered, including adherence and resistance, in sub-populations of mothers and infants who do not need treatment for their own health. For example, increased exposure to ART, as will be experienced with Options B or B+, may increase adverse pregnancy outcomes such as pre-term delivery and low birth weight.[8] In resource-limited settings this may increase risk for infant death. Increased exposure to tenofovir may also increase potential for renal toxicity in mothers[9] and poor growth outcomes in infants.[10] Additionally, Option B+ is costly, owing to the need for additional drugs, laboratory tests, human resources

and other health-system expenditures. Furthermore, experience of Option B+ is restricted to Malawi and Rwanda; this is insufficient to measure universal feasibility. The success of Option B+ depends on the retention of women in treatment programmes, which increases pressure on already strained health systems.[11,12] Recent data show that adequate adherence drops from 75.7% (95% CI: 71.5 - 79.7%) during pregnancy to 53% (95% CI 32.8 - 72.7) postpartum among women who meet present ART criteria.[13] The public health implications (including resistance and potential for future treatment) of reduced adherence in Options B and especially B+ are unknown and likely to be concerning. Finally, although higher treatment thresholds may be necessary, particularly in regions with high fertility rates, it is unclear whether universal provision of ART for pregnant women only is appropriate.

The business case for Option B+ assumes that economies of scope are generated by implementation of the triple combination of PMTCT of HIV, treatment and treatment-as-prevention. If each intervention were to be introduced separately, except for PMTCT, then the targeting of pregnant women only would not be appropriate. The recommendation of Option B+ is based on the untested assumption that the decrease in efficiency caused by inappropriate targeting is compensated for by lower recruitment costs. Similar to the economic analysis of Test-and-Treat,[14] small changes to assumptions, particularly relating to retention, have large implications. Indeed, if the scope assumptions are incorrect, Option B+ will cost lives, which could have been saved with appropriately targeted treatment and treatment-as-prevention.

Advocacy is critical, and reliance only on what has been scientifically proven would result in slow progress. However, with so many unknowns, the strong push for countries to switch to Option B+ is premature. A switch now would be dangerous, ignoring severe ethical, safety, feasibility and economic concerns. Countries should make their own decisions based on their local situation, resources, priorities and evidence. International agencies should guide, but not pressure, ministries into making decisions, particularly where evidence is weak. A clear decision-making process is essential.

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FORUM
Gender inequality: Bad for men's health

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Men's increased risk of death in ART programmes in sub-Saharan Africa is widely reported but poorly understood. Some studies have attributed this risk to men's poorer health-seeking behaviour, which may prevent them from accessing ART, being adherent to treatment, or remaining in care. In a multicentre analysis of 46 201 adults starting ART in urban and rural settings in South Africa, these factors only partly explained men's increased mortality while receiving ART. Importantly, the gender difference in mortality among patients receiving ART (31% higher for men than women) was substantially smaller than that among HIV-negative South Africans, where men had twice the risk of death compared with women. Yet, this extreme gender inequality in mortality, both within and outside of ART programmes, has not given rise to widespread action. Here it is argued that, despite their dominance in society, men may be subject to a wide range of unfair discriminatory practices, which negatively affect their health outcomes. The health needs of men and boys require urgent attention.

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Sub-Saharan Africa is the centre of the HIV epidemic, with an estimated 68% of all people HIV-infected.[1] Over the past 10 years, largely through international aid programmes, there has been a dramatic increase in the number of HIV-infected individuals who have started antiretroviral therapy (ART) in the region. Despite early concerns that women may be disadvantaged in ART programmes, disproportionately more women than men have accessed ART in Southern Africa.[2] In South Africa, for example, 60% of eligible women were receiving ART by mid-2011 compared with 41% of eligible men.[3]

Men have a higher mortality than women when receiving ART.[4-8] Although the reasons for this are poorly understood, a number of possible explanations have been suggested; some implicitly blame men for their own poorer outcomes. For example, numerous studies have suggested that men's poorer 'health-seeking behaviour' may prevent them from accessing ART services, being adherent to treatment or remaining in care. But, is this based on evidence or is it an assumption that has gained currency through widespread usage?

To date, there has been no systematic attempt to understand the phenomenon of gender differences on ART. In the past year, we explored the issue in an analysis including 46 201 adults initiating ART in 8 large urban and rural South African cohorts between 2002 and 2009.[5] As 60% of our patients had civil identification (ID) numbers, it was possible to confirm their vital status through linkage to the National Population Register, estimated to capture over 90% of deaths nationally.[9] We were also able to track patients with IDs after they were lost to follow-up (LTF) and confirm whether they were alive or dead.

Men's increased mortality on ART unrelated to HIV/AIDS

At the start of treatment, on average men had lower CD4+ cell counts and more advanced HIV disease than women. After we adjusted for such gender differences at ART initiation, men still had a 31% higher risk of mortality than women over 36 months (adjusted hazard ratio (AHR) 1.31, 95% confidence interval (CI) 1.22 - 1.41). Men were more likely to be LTF than women (AHR 1.20, 95% CI 1.12 - 1.28), but not to die after being LTF (AHR 1.04, 95% CI 0.86 - 1.25). Virological responses to ART were similar between men and women and, even among virologically suppressed patients, men were still more likely to die. Women had slightly stronger immunological responses than men, but in analyses restricted to patients who had reached CD4+ cell counts ≥200 cells/μl, the gender difference in mortality persisted (AHR 1.37, 95% CI 1.03 - 1.83). Importantly, however, this difference was smaller than the gender difference in death rates (standardised by age) in a hypothetical cohort of HIV-negative South Africans, where men were *twice* as likely to die than women. It appears then that the observed differences in mortality while receiving ART may best be explained by background gender differences in mortality in the South African population that are unrelated to HIV/AIDS.

Some more equal than others?

The gender differences in mortality outside of ART programmes suggest a situation of extreme gender inequality. The World Health Organization (WHO) defines gender inequality as 'difference(s) between men and women which systematically

Table 1. Conceptualising discrimination as a determinant of population health

Aspects of discrimination	
Type	Defined in reference to constituent dominant and subordinate groups, and justifying ideology
Form	Legal or illegal; institutional, structural, interpersonal; direct or indirect; overt or covert
Agency	Perpetrated by state or by non-state actors (institutional or individuals)
Expression	From verbal to violent; mental, physical, or sexual
Domain	For example: at home; within family; at school; getting a job; at work; getting housing; getting credit or loans; getting medical care, purchasing other goods and services; by the media; from the police or in the courts; by other public agencies or social services; on the street or in a public setting
Level	Individual, institutional, residential neighbourhood, political jurisdiction, regional economy
Cumulative exposure to discrimination	
Timing	Conception; infancy; childhood; adolescence; adulthood
Intensity	
Frequency (acute, chronic)	
Duration	
Pathways of embodying discrimination (involving exposure, susceptibility and responses to)	
#1	Economic and social deprivation: at home, in the neighbourhood and other socio-economic regions
#2	Toxic substances and hazardous conditions (pertaining to physical, chemical, and biological agents): at home, at work, and in the neighbourhood
#3	Socially inflicted trauma (mental, physical or sexual, ranging from verbal to violent): at home, at work, in the neighbourhood, in society at large
#4	Targeted marketing of legal and illegal psycho-active/other substances (alcohol, smoking, other drugs, junk food)
#5	Inadequate healthcare, by healthcare facilities and by specific providers (including access to care, diagnosis, treatment)
Responses to discrimination (protective and harmful)	
Protective	Active resistance by individuals and communities (involving organising, lawsuits, social networks, social support) Creating safe spaces for self-affirmation (social, cultural, sexual)
Harmful	Internalised oppression and denial Use of psycho-active substances (legal and illegal)
Effects of discrimination on scientific knowledge	
Theoretical frameworks	
Specific hypotheses	
Data collection	
Data interpretation	

*From: Berkman LF. Social Epidemiology. London, UK: Oxford University Press, 2000:42; reproduced with permission from Oxford University Press.

empower one group to the detriment of the other' and which impact negatively on access to healthcare and health status.[10] Section 9 of the South African Bill of Rights states unequivocally that 'everyone is equal before the law'.[11] Equality includes protection against unfair discrimination (both direct and indirect) on the grounds of gender, and discrimination on any of the grounds mentioned is regarded as unfair unless proven to be fair. But, for many of us, discrimination seems a vague and unmeasurable concept. We have an intuitive sense of what it means, but how do we study it in order to address it? Krieger provides a useful framework to conceptualise how unfair discrimination affects population health (Table 1). On this basis it appears that, despite their dominance in society, men may be subject to a wide range of unfair discriminatory practices over their entire lives, through multiple pathways, with generally harmful responses.

There are few studies exploring the issue of discrimination towards men in health services. In contrast, there is a large body of literature

FORUM

HIV/AIDS and admission to intensive care units: A comparison of India, Brazil and South Africa

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In resource-constrained settings and in the context of HIV-infected patients requiring intensive care, value-laden decisions by critical care specialists are often made in the absence of explicit policies and guidelines. These are often based on individual practitioners' knowledge and experience, which may be subject to bias. We reviewed published information on legislation and practices related to intensive care unit (ICU) admission in India, Brazil and South Africa, to assess access to critical care services in the context of HIV. Each of these countries has legal instruments in place to provide their citizens with health services, but they differ in their provision of ICU care for HIV-infected persons. In Brazil, some ICUs have no admission criteria, and this decision vests solely on the 'availability, and the knowledge and the experience' of the most experienced ICU specialist at the institution. India has few regulatory mechanisms to ensure ICU care for critically ill patients including HIV-infected persons. SA has made concerted efforts towards non-discriminatory criteria for ICU admissions and, despite the shortage of ICU beds, HIV-infected patients have relatively greater access to this level of care than in other developing countries in Africa, such as Botswana. Policymakers and clinicians should devise explicit policy frameworks to govern ICU admissions in the context of HIV status.

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People living with HIV/AIDS (PLWHA) often become ill due to opportunistic infections such as *Pneumocystis jeroveci* pneumonia, necessitating hospitalisation and admission to intensive care units (ICUs). Resources allocated to specialised care in developing countries seldom match their demand, resulting in decisions having to be made about who benefits from treatment and who does not.[1] In resource-constrained countries, these value-laden decisions by critical care specialists are often made in the absence of explicit policies and guidelines, and are based on individual knowledge and experience, which may be subject to bias. In South Africa the general criteria for ICU admission in the public sector include whether the patient is 'too well or too ill', and whether there is a realistic prospect of 'reversibility of organ dysfunction'. This policy is equally applicable to PLWHA who require ICU admission.

We reviewed published information on legislation and practices related to ICU admission in India, Brazil and South Africa, to assess access to critical care services in the context of HIV status.

According to the 2012 UNAIDS Global Aids Report, the BRICS countries – Brazil, Russia, India, China and South Africa – increased domestic public spending on HIV by more than 120% between 2006 and 2011. These countries currently fund, on average, more than 75% of their domestic AIDS responses and have dealt with the HIV pandemic with varying levels of success.[2] The three countries reviewed face similar problems regarding resource constraints and the numbers of available ICU beds (Table 1). India is notable in that ICU care in the country is very limited, inaccessible and unaffordable to many citizens.[3]

The Constitutional right to intensive care for PLWHA

The Constitutions of Brazil, India and South Africa enshrine a patient's right to healthcare and their right not to be refused access to emergency treatment. Legal precedents to this effect exist in India and South Africa, where this Constitutional right has withstood legal review (Table 2). These case precedents apply equally to PLWHA and access to intensive care.

Table 1. Population to ICU bed ratio according to country

	Brazil	India	USA	South Africa
2012 population	199 million	1.2 billion	313 million	49 million
Number of ICU beds, *N*	25 367	70 000	94 000	5 500
Population : ICU bed ratio	~ 1:8 000	~ 1:14 000	~ 1:4 000	~ 1:10 000

Table 2. The right to healthcare and access to emergency care: Case precedents

Country	Case
India	P Rathnam v. Union of India 1994 (3); Supreme Court cases 394 - 430 Gian Kaur v. State of Punjab 1996 Supreme Court; 83: 12578 - 12564 Paschim Baga Khet Mansoor Samiti v. State of West Bengal; AIR 1996 SC 2426
South Africa	Government of the Republic of South Africa (RSA) and others v. Grootboom and others (judgment: 4 October 2000) Minister of Health and others v. Treatment Action Campaign (TAC) and others (judgment: 5 July 2002) Soobramoney v. Minister of Health (KwaZulu-Natal) 116 Case CCT 32/97 (judgement: 27 November 1997)

Professional ethical guidelines for ICU admission

The medical associations of India, Brazil and South Africa subscribe to the international guidelines of the World Medical Association's Declaration of Geneva, which provide a framework for the appropriate conduct of the medical profession globally.[4] Each country has a professional association that guides and regulates ethical conduct, particularly with regard to PLWHA. These guidelines protect PLWHA against stigmatisation and discrimination by health professionals, particularly with regard to access to healthcare, treatment and support programmes. Similarly, the Siracusa Principles[5] spell out five criteria concerning human rights and restrictions to public health based on resource limitations. The burden of proof still falls on those who want to restrict rights, and concrete scientific and public health evidence is needed, specifically with response to Siracusa Principle 5 which states that 'the restriction of the right of access to public health cannot be unreasonable or discriminatory in its application.'[5]

Lessons to be learnt from Brazil and India

The regulatory and ethical frameworks of Brazil and India provide a useful indication of the varied challenges faced by developing nations regarding PLWHA and their access to ICU care. An important contributor to the success of Brazil's response to the HIV/AIDS epidemic is its National Health Insurance Scheme, which has strengthened its public health system, including ICU bed availability. In Brazil, health services are provided by private-public partnerships, funded by the government and freely accessible to the patient, and extending to specialist and ICU care.[6] It is therefore evident that an HIV-infected patient in Brazil who requires admission to ICU would have easy access to such level of care. The Brazilian Society of Intensive Care[7] speaks of issues of informed consent, the need for comprehensive medical records, humanising the ICUs by improving communication with patients and their families, and establishing ICU admission and discharge criteria in keeping with the 'existing laws and institutional rules'. As such, failure to comply with the provisions under the resolution will be subject to 'civil liability, and administrative and criminal sanctions'.

There is no comprehensive legislation in India addressing HIV/AIDS and criteria for ICU admission. The number of ICU beds available is disproportionately low, in the private and public hospitals, and there is also considerable variation in the allocation and distribution of critical care services across the country, given that 70% of the country is rural.[3,8]

Notwithstanding explicit ICU admission policy at a macro level in South Africa, widespread anecdotal evidence seems to suggest that HIV status may be commonly used as an ICU exclusion criterion. This practice results in arbitrary decision-making and has no prognostic evidentiary basis, rendering such decision-making irrational. Furthermore, it is contrary to SA's legal and human rights policy frameworks.

Given the current state of affairs, policy-makers and clinicians in SA and further afield should devise explicit policy frameworks to govern ICU admissions in the context of HIV status.

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on discrimination and women's health,[12-21] possibly in response to the historic under-representation of women in research informing medical practice. In 1993 the United States National Institutes of Health (NIH) was mandated by law to ensure that 'women and minority groups' were included in clinical research.[22] While this was a welcome response to an important omission from international research agendas, is it possible that the pendulum has swung too far? It seems probable that we are unable to recognise gender inequality when it affects men.

The priorities and programmes of large funders appear to confirm the focus on women in HIV/AIDS programmes. For example, the Global Fund for HIV/AIDS, Tuberculosis and Malaria – the largest multilateral HIV/AIDS funding agency – states that equitable access to services is fundamental to its mission but does not include men's poorer access to ART as a key action area. The United States of America, the largest donor on HIV/AIDS, has provided funding for nearly 2.5 million people living with HIV through its President's Emergency Plan for AIDS Relief (PEPFAR) programme. Although disproportionately more women than men have accessed ART, PEPFAR does not prioritise increasing men's access to treatment.

In turn, funders' priorities may affect national ART programmes. In Zambia, 54% of those living with HIV, but 63% of adults starting ART, are women.[23] In South Africa, too, there is a gender gap: 55% of those living with HIV, but only an estimated 68% of those starting public sector ART, are women.[24] Yet, the national strategic plans for HIV/AIDS in both countries do not identify male access to ART as a priority, nor do they include action plans to address this gap urgently. The same is true for many other African countries.

This apparent lack of concern for men's needs extends beyond ART programmes to other arenas. Policy documents define gender as the 'socially constructed roles, behaviours, activities and attributes' considered appropriate for men and women in particular settings.[10] In practice, however, it seems that gender and women's issues are still regarded as interchangeable. For instance, South Africa has a ministry for women, children and people with disabilities, but nothing comparable for men. Similarly, the United Nations has an Inter-Agency Network on Women and Gender Equality and the third Millennium Development Goal for 2015 is to 'promote gender equality and empower women'. The UNAIDS's Operational Plan on gender addresses 'women, girls, gender equality and HIV', but none of the three action areas refers to the needs of men or boys. Clearly the initiatives listed above are vital, as are initiatives to address the health needs of men. In the words of WHO: 'no one should be sick or die because of gender inequality'.

One last point for readers to consider: Many international and national conferences, including the recent conference of the Southern African HIV Clinicians Society, include tracks on women's health, but not that of men. Is this because there are no HIV-related issues specific to men's health – or is it because the question was not asked?

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FORUM

Screening for HIV-associated neurocognitive disorders (HANDs) in South Africa: A caution against uncritical use of comparative data from other developing countries

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The prevalence of HIV-associated neurocognitive disorders necessitates community-based screening. In recent years, progress has been made in developing more localised comparative data for use in such screening on the African continent. These studies used measurements that are considered fair, easily accessible, and quick to administer. However, the variance in available international data limits their usefulness and poses a risk to the appropriate streaming of individuals. Here, examples are presented of variance in both cross-national and local demographic screening and neuropsychological test scores, with the aim of cautioning practitioners against undue reliance on general African data for classification of individuals. Recommendations are provided for the development of appropriate norms, specific to local communities.

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South Africa (SA) is home to the world's largest population of people living with HIV and AIDS (PLWHA), with an estimated HIV prevalence of 16.9% among SA adults (aged 15 - 49 years) in 2008.[1] Recent figures suggest that 17 - 25% of HIV patients in SA display cognitive impairment,[2,3] the diagnosis of which is largely dependent on the deviation of test scores from standardised norms. HIV-associated neurocognitive disorders (HANDs) are diagnosed using the Frascati model,[4] which requires neuropsychological scores to be compared with normative data using standard deviation (SD) as an indicator of impairment.

The classification of neurocognitive impairment requires clinical attention as it influences decisions on treatment initiation, the management of daily living, and so forth. Owing to the large number of people affected and the prevalence of impairment, large-scale screening is imperative and streams identified individuals towards further investigation. This process requires measurements that are fair, easily accessible and quick to administer. In this regard, the International HIV Dementia Scale (IHDS) and Grooved Pegboard (GP) are arguably the most widely used instruments for HAND screening in limited-resource communities,[5] and these have been shown to differentiate between the HIV statuses of asymptomatic patients in sub-Saharan Africa.[6,7]

The problem of variance

Data from the IHDS and GP tests, and from the rest of the World Health Organization (WHO) HIV battery, have been reported from various sites in sub-Saharan Africa. This is positive progress, as the developing world norms differ from those of industrialised countries,[8] and practitioners may need to use comparative data from Africa when no local data are available. However, despite these positive developments, the issue of data variability across countries has not been resolved.[9] An example of the range of scores for HIV-negative respondents on the IHDS and GP is provided in Table 1. Table 2 provides an example of the range of scores for HIV-negative respondents for some of the tests used across countries in Eastern and Southern Africa.

In terms of screening, there are some difficulties when comparing SA scores with other African data for local use. For example, the IHDS total score range equals an SD of ±1 across some countries (Table 1). Given that the recommended cut-off for streaming towards further investigation for possible neurocognitive impairment is ≤10,[7] this could have significant implications for individuals across different countries. Additionally, the range of the IHDS memory recall subtest differs noticeably between different demographic subgroups within one location.[12] The GP-non-dominant hand test (GP-NDH) also differs significantly across countries. This is an important HAND screening mechanism, and the variance in published data creates difficulties for interpretation and further streaming.

Similar problems are faced in terms of diagnosis. For example, the range of the Trail Making Test (TMT) scores differs by more than ±1 SD between different demographic subgroups within one location.[12] The Digit Symbol Modalities Test (DSMT) differs further by an SD of ±2 between countries.

Table 1. Scores for IHDS and GP-NDH tests conducted among HIV-negative respondents in East and Southern Africa

Country	Test	*N*	Mean	SD
Zambia[10]	IHDS total	57	10.10	
	IHDS memory recall	57	3.40	
	GP-NDH	57	97.50	
Uganda[11]	IHDS	25	11.10	±0.80
Uganda[7]	IHDS total	100	11.00	±1.00
	IHDS memory recall	100	3.60	±0.60
	GP-NDH	100	102.70	±25.20
South Africa[6]	GP-NDH	24	80.83	±9.20
South Africa[12]	IHDS memory recall (female; aged 18 - 29 years)		3.77	±0.47
	IHDS memory recall (male; aged 18 - 29 years)		3.39	±0.55
	IHDS memory recall (female; aged 30 - 50 years)		3.66	±0.48
	IHDS memory recall (male; aged 30 - 50 years)		3.19	±0.96

SD = standard deviation; IHDS = International HIV Dementia Scale; GP-NDH = Grooved Pegboard-non-dominant hand test.

Table 2. Scores for TGT, DSMT, TMT and DS conducted among HIV-negative respondents in East and Southern Africa

Country	Test	*N*	Mean	SD
Zambia[10]	TGT	57	12.3	
Uganda[7]	DSMT	100	31.10	±11.30
	TGT	100	6.95	±0.82
	DSF	100	5.30	±0.90
	DSB	100	3.50	±0.90
South Africa[6]	TMT-A	24	43.74	±12.40
	DSMT	24	50.54	±11.10
South Africa[12]	TMT-A (female; aged 18 - 29 years)		40.73	±17.40
	TMT-A (male; aged 18 - 29 years)		35.89	±8.94
All aged 18 - 29 years (*N*=68)	TMT-A (female; aged 30 - 50 years)		48.54	±18.70
All aged 30 - 50 years (*N*=42)	TMT-A (male; aged 30 - 50 years)		50.00	±13.60
	TMT-B (female; aged 18 - 29 years)		72.57	±26.00
	TMT-B (male; aged 18 - 29 years)		87.78	±26.50
	TMT-B (female; aged 30 - 50 years)		89.26	±28.40
	TMT-B (male; aged 30 - 50 years)		114.25	±43.10
	DSF (female; aged 18 - 29 years)		6.50	±1.38
	DSF (male; aged 18 - 29 years)		6.33	±1.12
	DSF (female; aged 30 - 50 years)		6.14	±1.40
	DSF (male; aged 30 - 50 years)		6.00	±1.07
	DSB (female; aged 18 - 29 years)		3.63	±0.97
	DSB (male; aged 18 - 29 years)		4.56	±0.73
	DSB (female; aged 30 - 50 years)		3.29	±0.83
	DSB (male; aged 30 - 50 years)		3.88	±0.99

TGT = Timed Gait Test; DSMT = Digit Symbol Modalities Test; TMT-A = Trail Making Test A; TMT-B = Trail Making Test B; DS = Digit Span; DSF = Digit Span Forward; DSB = Digit Span Backward.

Digit Span (DS) Forward and Backward scores also display ranges equalling an SD of ±1 between some countries (most notably Uganda and South Africa) and even within countries, based on demographics. The Timed Gait Test (TGT) score range equals an SD of ±6 between samples in Zambia and Uganda.[7,10] This is despite indications in the reported studies suggesting that the samples had broadly similar socio-economic and educational backgrounds.

While it is tempting to believe that the variance is simply due to inter-country differences, there may be a number of reasons why it may not reflect true cross-national or cross-cultural differences. Firstly, it is not always clear whether psychologists, primary healthcare nursing personnel or highly qualified researchers performed the assessments. Some tests (e.g. IHDS) were developed to be administered by primary healthcare workers, while others were (at least historically) firmly placed in the neuropsychological domain (e.g. GP, TMT). Secondly, there is a lack of demographic reporting. The effects of gender, age, education, and so forth, are well documented,[5,12] but not equally well-reported across studies, consequently limiting comparison. Thirdly, the samples are often small (N<50 in the case of the SA samples), which may not reflect the larger population.[13] Fourthly, viral subtypes may further limit comparison between HIV-1 clades.[8,14]

Using general scores from African samples may, therefore, not be appropriate when placing people in categories of impairment using SD from normative scores. The intention of this article is to caution researchers and practitioners against an over-reliance on cross-national 'African' data to create 'local' norms, which may result in inappropriate diagnostic classification.

Looking forward

Given the incidence of HANDs in SA, there is a critical requirement for valid norms to guide screening and eventual diagnosis. The problematic nature of comparing across national (and presumably cultural) borders emphasises the need for assessment that is fair to patients. This includes: firstly, the development of localised norms – in terms of specific communities – that, at the very least, are reported in terms of age, gender and education (socio-economic status, ethnicity and testing language may also be valuable); and secondly, the use of larger samples that have reasonable validity.[13] There are further concerns about the responsibility of test administration, in light of the possible effects of the tester on outcome variance.[15] Here, a balance must be struck between making assessment accessible to the community and maintaining the integrity of the neuropsychological nature of the tests. A tiered approach – i.e. screening with the IHDS by primary healthcare workers, referral to community-based psychologists for an expanded battery (e.g. WHO HIV battery), and further referral to specialist clinics for extended neuropsychological assessment – is recommended.

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ORIGINAL ARTICLE

Transitioning behaviourally infected HIV-positive young people into adult care: Experiences from the young person's point of view

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Background. There is limited literature on the transition of young people living with HIV/AIDS (YPLHIV) from adolescent/young adult HIV care to adult HIV care in sub-Saharan Africa.
Objective. We aimed to share the experiences of HIV-seropositive young adults transitioning into adult care, to inform best practice for such transitioning.
Methods. We conducted a retrospective evaluation of the transition of 30 young adults aged ≥25 years from our adolescent/young adult HIV clinic at the Infectious Diseases Institute, Makerere University, Kampala, Uganda, to adult HIV healthcare services between January 2010 and January 2012.
Results. Six major themes emerged from the evaluation: (*i*) adjustment to adult healthcare providers, (*ii*) the adult clinic logistics, (*iii*) positive attributes of the adult clinic, (*iv*) transfer to other health centres, (*v*) perceived sense of stigma, and (*vi*) patient-proposed recommendations. A model for transitioning YPLHIV to adult care was proposed.
Conclusion. There is a paucity of evidence to inform best practice for transitioning YPLHIV to adult care in resource-limited settings. Ensuring continuity in HIV care and treatment beyond young adult HIV programmes is essential, with provision of enhanced support beyond the transition clinic and youth-friendly approaches by adult-oriented care providers.

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There are a growing number of behaviourally HIV-infected young people who require HIV care and treatment in resource-limited settings. With improved coverage of HIV care, survival among vertically HIV-infected children is increasing. Consequently, an increase in the number of young people living with HIV/AIDS (YPLHIV) who are in need of HIV care and treatment services is inevitable.

YPLHIV, especially adolescents, are usually managed in adult HIV care programmes by providers who are not trained in the provision of adolescent services. This poses a major challenge as providers are often not fully aware of the most common, adolescent-specific challenges of antiretroviral therapy (ART) including adherence, drug-related toxicities (particularly lipodystrophy), HIV status disclosure, late presentation to care, and onset of sexual activity.[1]

Across Africa, there are few healthcare programmes tailored specifically for behaviourally HIV-infected young people; these YPLHIV are consequently under-served by the healthcare system.[2,3] Furthermore, with improved survival among YPLHIV, the need eventually arises to transition them into adult care services. Challenges in relation to such transition include the establishment of trusting relationships, which make paediatricians reluctant to transfer YPLHIV to physicians with adult-oriented healthcare models, and the difficulty most YPLHIV face in disclosing their HIV status to their families and caregivers.[2] Despite this, there is a scarcity of published information on the challenges faced and successes of transition clinics and models in sub-Saharan Africa.[3]

In Uganda, there are few adolescent healthcare services available outside of schools,[4,5] yet there is a national adolescent health policy in place.[6] Here, to begin to address this gap between policy and practice, we report on the experiences of YPLHIV who have been transited from our young adult HIV clinic into adult HIV care.

Methods

The Infectious Diseases Institute (IDI) at the College of Health Sciences, Makerere University, Kampala, Uganda, was

awarded a grant from the Civil Society Fund to provide specialised HIV/AIDS care to HIV-seropositive young adults. The weekly clinic, established and maintained since 2008, is run by a dedicated healthcare team comprised of doctors, nurses, counsellors and peer supporters specialising in adolescent/young adult HIV care. The main emphasis of the clinic is to bridge the gap between paediatric and adult HIV healthcare. This is achieved by offering HIV-seropositive young persons, aged 15 - 24 years, youth-friendly clinical services and psychosocial support.

Between January 2010 and January 2012, of 820 young persons enrolled in the young adult HIV clinic, 80 participants aged ≥25 years were transferred to adult healthcare services. Approximately 95% of the young adults acquired HIV through horizontal transmission. The remainder were likely to have been infected perinatally. In February 2012 we performed a retrospective evaluation of the transition of 30 of these young adults, aged 25 - 29 years, from our young adult HIV clinic to our adult HIV clinic.

The IDI young adult transition process

The IDI transition process for young adults from the young adult HIV clinic to full adult HIV healthcare is shown in Fig. 1. For participants, the transition commenced when the young adults reached 25 years of age; however, the timing of transfer was ultimately determined by patient readiness. The clinic counsellor conducted two exit-interview sessions with each young adult. The sessions, which lasted between 15 and 20 minutes on average, were conducted in the privacy of the counsellors' rooms. The first exit session was a one-on-one interaction to acquaint the young person with the subject of transitioning to the adult HIV clinic. During the second exit session, which was also a one-on-one session, an exit questionnaire was completed. The purpose of these sessions was to discuss the transition and to assess patient expectations and readiness (Appendix 1).

Data collection and analysis

One year after transition, a group evaluation was held to assess the participants' attitudes and perceptions of the transition process and to determine how they had adjusted to the adult HIV clinic. An evaluation during a peer-support meeting was selected as the best mode to conduct the research, because it closely resembled daily social interaction and was less intimidating than a one-on-one interview.

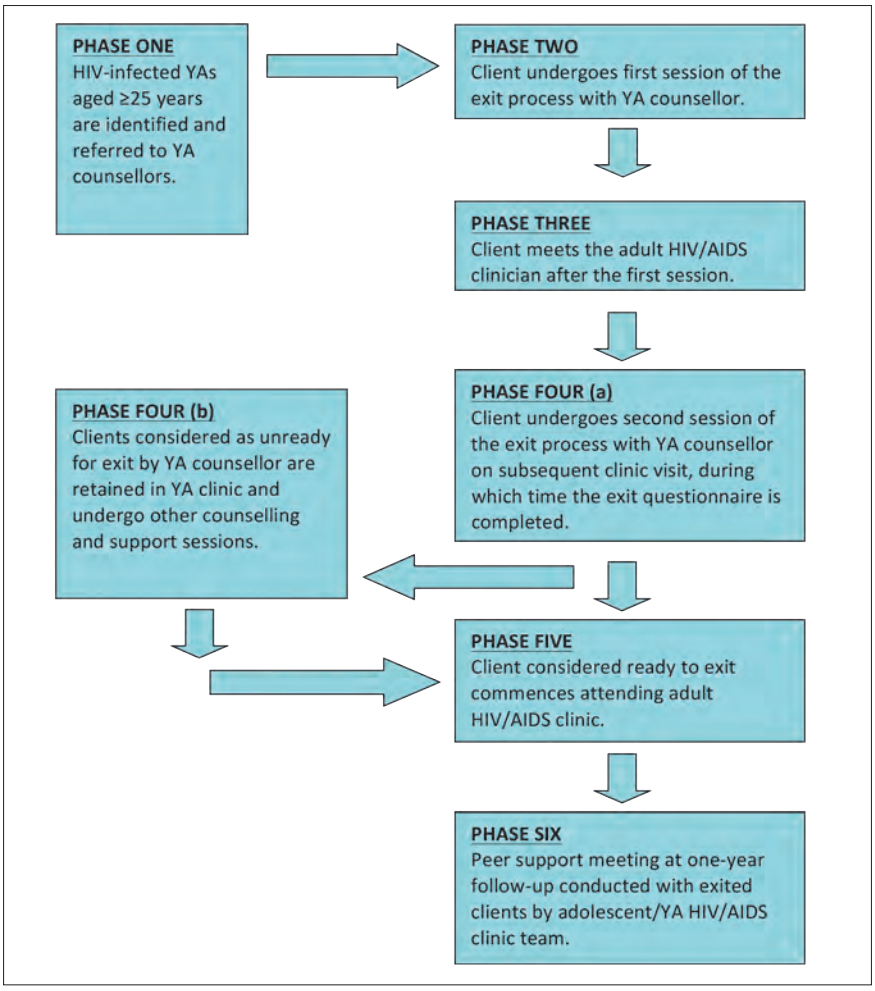

Fig. 1. The Infectious Diseases Institute (IDI) young adult HIV transition model. YA = young adult.

The participants were contacted telephonically prior to the event. The evaluation was conducted at the IDI premises and was facilitated by the co-ordinator and counsellors of the young adult HIV clinic. Participants were reimbursed approximately US$5 each for transportation costs.

The group evaluation lasted 4 hours and was audiotaped. Discussion was initiated by an open-ended question on the participants' experiences in the adult clinic. All participants provided written informed consent prior to the evaluation, and institutional ethical approval for the evaluation was obtained. Audiotapes were subsequently transcribed verbatim, and qualitative thematic content analysis was conducted by two independent coders: the investigator and a graduate public health student. Qualitative concepts were generated from the data from the evaluation. The two independent coders read the transcripts line-by-line and abstracted key ideas and themes.

Results

Of the 80 participants aged ≥25 years who were transited to adult HIV care between January 2010 and January 2012, 50 were unavailable for evaluation: 20 had provided incorrect telephone contact details and could not be reached; 15 had other obligations and could not attend the evaluation; 9 resided outside the Kampala district and were therefore unable to attend the evaluation; and 6 had been transferred to other partner clinics. All 30 participants who attended the evaluation had acquired HIV through sexual transmission. Nineteen (63%) of the 30 participants, aged 25 years, partook in the evaluation at approximately one year following the exit questionnaire interview. The remaining 11 (37%), aged 26 - 29 years, partook in the evaluation at 2, 3, 4 and 5 years, respectively, following the exit interview.

Six major themes emerged from the evaluation: (*i*) adjustment to adult healthcare providers, (*ii*) the adult clinic logistics, (*iii*) positive attributes of the adult clinic,

ORIGINAL ARTICLE

Overview of HIV-related lipodystrophy

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Lipodystrophy is a well-recognised adverse effect of HIV and antiretroviral therapy, with certain antiretrovirals, specifically thymidine analogues, implicated in the aetiology and pathogenesis. Lipodystrophy is often accompanied by metabolic complications, such as hyperlipidaemia and insulin resistance, which increase risk for cardiovascular disease. There are limited data on the effect of treatment modification, pharmacological interventions and surgical management on this condition.

Here we summarise the latest data on lipodystrophy, with the aim of facilitating informed decision-making in managing this condition. In light of the absence of cost-effective measures to treat lipoatrophy and lipohypertrophy, prevention remains the best option; we recommend targeted annual screening. Healthcare workers should be sensitised to early detection in patients on thymidine-based regimens, and affected patients should be switched to an appropriate regimen as soon as feasible. There is no evidence to support the use of new-generation ARVs, except in patients with significant hypercholesterolaemia, where atazanavir and raltegravir may present better options.

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The lipodystrophy syndrome is a well-recognised phenomenon in HIV-1-infected patients receiving antiretroviral therapy (ART). The syndrome is characterised by body habitus changes, most commonly a combination of lipoatrophy (LA) (loss of peripheral subcutaneous adipose tissue (SAT), usually in the face, limbs and buttocks) and lipohypertrophy (LH) (visceral adipose tissue (VAT) accumulation, gynaecomastia and, in some cases, lipomatosis, especially in the dorsocervical area, known as a 'buffalo hump').

Even though the aetiology remains unclear, the following factors have been implicated in the development of lipodystrophy: HIV itself, older age, female sex, genetic parameters and ART.[1] There seems to be consensus that peripheral LA and central LH have the same causes (HIV and ART), but are likely to be related to different fat depot physiologies.[2] It is speculated that LA is linked to severe mitochondrial dysfunction, oxidative stress and inflammation, while hypertrophy is related to mild mitochondrial dysfunction and cortisol activation, promoted by inflammation. Importantly, both LA in the lower part of the body and abdominal LH have been associated with metabolic changes akin to the metabolic syndrome, particularly dyslipidaemia and insulin resistance.[3]

Recent reports in the popular press have highlighted the psychological and social distress that patients experience as a result of lipodystrophy. Often, patients are left on offending regimens for too long, causing extreme and often irreversible body changes. It is imperative that healthcare workers familiarise themselves with this entity and understand the treatment options available to patients. Here we summarise the latest data on the topic, with the aim of facilitating informed decision-making in managing this condition.

Role of ART

Data on the effect of ART on lipodystrophy exist for the older nucleoside reverse transcriptase inhibitors (NRTIs) and unboosted protease inhibitors (PIs), but seem to be conflicting for the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and newer PIs, and are mostly unavailable for the new drug classes. Many studies have implicated stavudine (d4T) and zidovudine (AZT) in the development of lipodystrophy and this is generally uncontested. Abacavir (ABC) and tenofovir (TDF) have been shown to have minimal effect.[6] Initial studies did not reveal a role for efavirenz (EFV) in lipodystrophy, but the recent ACTG A5142 study[6] found that LA was indeed more relevant in EFV-treated patients when compared with boosted lopinavir (LPV/r)-treated patients. Another study, however, found only a minimal difference between EFV and another PI, atazanavir (ATV).[7] Taken together, these studies suggest that in terms of the development of LA, LPV may have a slight advantage over EFV when combined with TDF (up to 96 weeks) in treatment-naive patients. In terms of lipodystrophy, ATV may have a marginal advantage over EFV when combined with AZT (up to 48 weeks) in treatment-naive

patients. Importantly, ATV is known to have a better lipid profile than EFV and LPV/r and an argument could therefore be made for its preferential use in patients at high risk for cardiovascular disease.

The 2011 United States Department of Health and Human Services ART guidelines state that an increase in trunk fat has been observed with EFV-, PI-, and raltegravir (RAL)-containing regimens, but that a causal relationship has not been established.[4] There are very few data on the entry inhibitors and integrase inhibitors, although some early data indicate the possibility of an improved metabolic and lipid profile. There are currently no systematic reviews or meta-analyses comparing the effects of different antiretrovirals (ARVs) on lipodystrophy. The comparison of studies is complicated by different measurement standards for lipodystrophy, the use of different race and ethnic groups, and a general lack of control groups.

Table 1 summarises the current knowledge about the effect of different ARVs on lipodystrophy, lipids and glucose metabolism.

It is important to note that the number of patients changing ART regimens because of lipodystrophy appears to be decreasing over time. The Swiss HIV Cohort Study[5] followed 5 777 participants who started ART between 2000 and 2006, and compared rates of lipodystrophy between 2000 and 2002, and 2003 and 2006. The findings revealed that 4% of patients had changed ART regimens due to lipodystrophy during 2000 - 2002, whereas only 1% of patients changed during 2003 - 2006. This reduction was attributed to the decreased use of AZT (88% v. 64%) and d4T (4.2% v. 0.7%) and the increased use of TDF (0% v. 30%) over this time.[5]

The differential metabolic effects of the NNRTIs, NRTIs and PIs are depicted in Fig. 1. There is currently not enough long-term information on entry inhibitors and integrase inhibitors to allow for categorisation.

Metabolic consequences of lipodystrophy

Lipodystrophy is well known to cause significant psychological distress and has been identified as a risk factor for ART non-adherence.[9,10] There are, however, other consequences that may warrant treatment modification, especially metabolic complications. Fig. 2 shows that increased central fat and decreased limb fat are implicated in the development of metabolic complications. The basic pathology is postulated to be an increased release of cytokines and free fatty acids (FFAs) which, together with decreased adiponectin production by adipose tissue, lead to insulin resistance and triglyceride (TG) deposition in tissues such as the liver, skeletal muscle and heart. It seems that active lipolysis in SAT, combined with impaired fat storage capacity in the subcutaneous depot, drives the deposition of lipids in ectopic sites such as the viscera and other non-adipose sites. This leads to hepatic steatosis and increased lipid content in skeletal muscle, which contribute to systemic metabolic alterations, especially insulin resistance. The high levels of FFAs may also affect pancreatic function and thus contribute to impaired insulin release and a pre-diabetic state.

These metabolic changes ultimately result in impaired glucose tolerance and dyslipidaemia with decreased high-density lipoprotein cholesterol (HDL-C) and increased TGs. Metabolic complications are therefore responsible for increased cardiovascular and hepatic disease risks. These changes have also been linked to premature ageing. The hypothesis has been put forward that chronic HIV infection, combined with the use of some ARVs and lipodystrophy, may accelerate the normal ageing processes and lead to the early development of age-related co-morbidities.[2]

Table 1. The effects of different ARV drugs on fat and metabolism*

Drug	LA	LH	Dyslipidaemia	Insulin resistance
Stavudine (d4T)	+++	++	++	++
Zidovudine (AZT)	++	+	+	++
Didanosine (DDI)	+/-	+/-	+	+
Lamivudine (3TC)	0	0	+	0
Abacavir (ABC)	0	0	+	0
Tenofovir (TDF)	0	0	0	0
Emtricitabine (FTC)	0	0	0	0
Efavirenz (EFV)	+/-	+/-	++↑ HDL	+
Nevirapine (NVP)	0	0	+↑ HDL	0
Ritonavir (RTV)	+/-	+	+++	++
Indinavir (IDV)	+/-	+	+	+++
Lopinavir (LPV)	+/-	+	++	++
Saquinavir (SQV)	+/-	+	+/-	+/-
Atazanavir (ATV)	0	++	+/-	0
Darunavir (DRV)	0	+	+/-	+/-
Enfuvirtide (INN)	Insufficient data	Insufficient data	0	0
Maraviroc (MVC)	Insufficient data	Insufficient data	0	0
Raltegravir (RAL)	Insufficient data	Insufficient data	0	0

LA = lipoatrophy; LH = lipohypertrophy.

*Adapted from Caron-Debarle *et al.*[2]

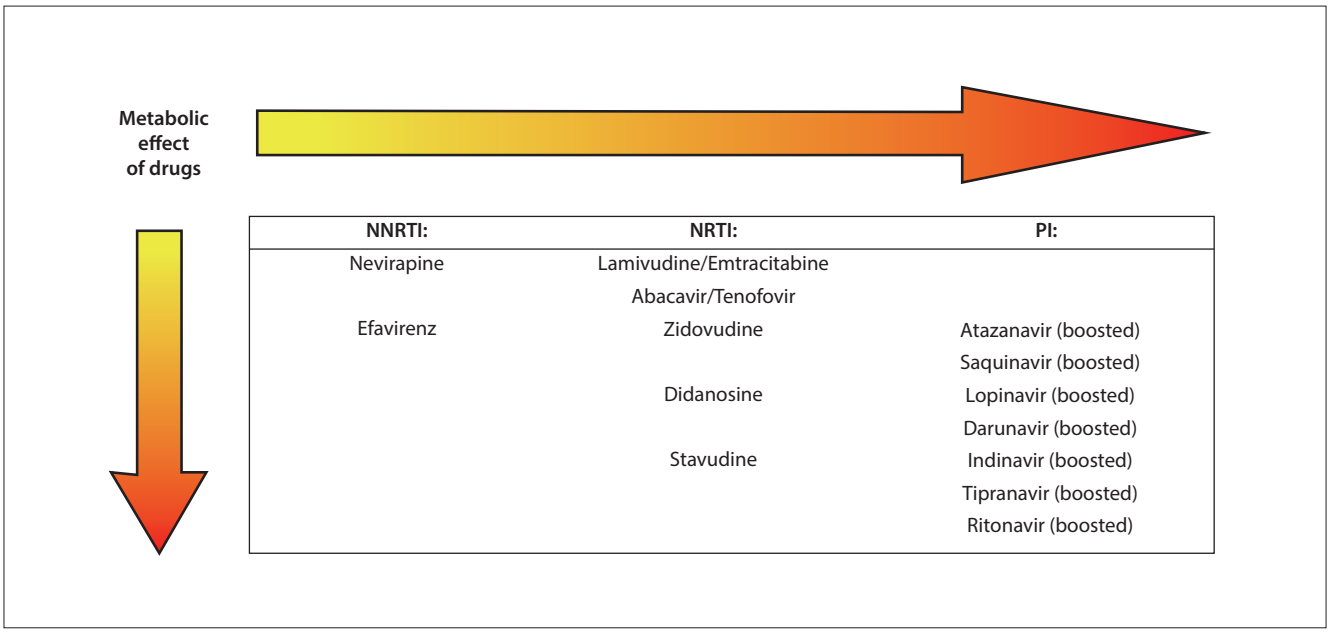

Fig. 1. Metabolic impact of ART classes and individual drugs.[8] *NNTRI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.*

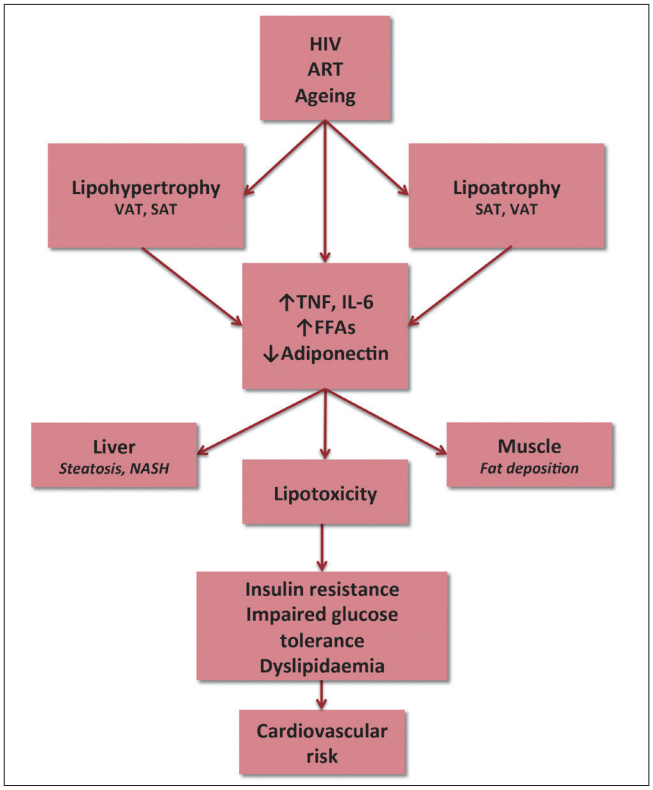

Fig. 2. Metabolic consequences of lipodystrophy. VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; TNF = tumour necrosis factor; IL-6 = interleukin-6; FFAs = free fatty acids; NASH = Non-alcoholic steatohepatitis.

Management of lipodystrophy

Changing ART

Lipoatrophy

The only ART modification that has been shown to partially reverse SAT loss is switching from d4T or AZT to ABC or TDF.[11,12] One small study comparing the effect of three ABC substitution approaches over 48 weeks showed that fat mass in the arms and legs improved significantly (41% and 52%, respectively) when d4T was replaced with ABC. There was, however, no improvement when treatment with a PI or NNRTI was stopped in favour of ABC.[13] On average, an estimated 400 - 500 g fat can be regained per year, but it is important to bear in mind that some patients may fail to demonstrate significant improvement due to possible exhaustion of the fat mesenchymal stem-cell pool. Furthermore, treatment modification may introduce risks associated with the new ART regimen, such as ABC hypersensitivity and TDF-associated nephrotoxicity; therefore, adequate monitoring should be in place. In light of the ongoing controversy regarding ABC and cardiovascular risk, ABC may best be avoided in patients with established cardiovascular disease (CVD). An alternative strategy is to switch to an NRTI-sparing regimen. This approach has also been shown to increase total limb fat by approximately 400 - 500 g per year, but has the disadvantage of possible increased dyslipidaemia (with all PIs except ATV). Furthermore, data on its long-term virological efficacy is limited.[8,14]

Lipohypertrophy

Weight gain is an expected consequence of successful ART. Weight reduction – or even better, avoidance of weight gain – through healthy diet and exercise may decrease VAT deposition and possibly improve insulin sensitivity and the lipid profile. There is, however, no information about the sufficient amount of diet and exercise needed to maintain this effect, and it may even aggravate LA. There are limited data on the effect of an ART regimen change on LH. In a trial of 201 HIV-infected patients with abdominal fat accumulation and viral suppression, a switch from a twice-daily ritonavir-boosted PI regimen to once-daily ritonavir-boosted ATV led to a non-significant difference in limb fat loss at 48 weeks.[15] Some anecdotal data do, however, hint that ATV may have some effect: a very small case series of three patients described regression of central fat accumulation after nelfinavir (NFV) was replaced with ATV.[16]

In a recent study by Lake *et al.*,[17] 39 virologically controlled women receiving TDF-FTC/ABC-3TC and either NNRTI- or PI-based ART, with LH, were randomised to immediate or delayed switch of the NNRTI or PI component to RAL. After 24 weeks, no statistically significant changes in VAT or SAT, anthropometrics, body mass index (BMI), glucose or C-reactive protein (CRP) were observed, but there were significant improvements in total and low-density lipoprotein (LDL) cholesterol (p=0.04).[17] There is therefore insufficient evidence to suggest that a change to the newer classes of drugs, such as integrase and entry inhibitors, may reverse LA or LH. The complexity of the data highlights the controversy of changing a treatment regimen for clinical and aesthetic reasons in the face of maximal virological suppression.

Novel treatment strategies

Lipoatrophy

Trials of the thiazolidinediones have shown that this drug class has very modest, if any, effect on lipoatrophic SAT. Although these drugs improve insulin sensitivity, they are known to induce harmful effects on blood lipids.[18] In a randomised controlled trial, pioglitazone was shown to increase the number and function of mitochondria and partially reverse peripheral fat loss in patients without thymidine NRTIs. This effect was, however, not noticeable to the patients.[19] Uridine, a pyrimidine nucleoside, has been postulated to protect fat cells from the adverse effects of thymidine analogues. After initial promising results, however, the drug failed to demonstrate improvement in limb fat in a subsequent multicentre clinical trial of 165 participants.[20] Pravastatin, a lipid-lowering 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitor that is thought to have anti-inflammatory properties, was shown to partially reverse lipodystrophy in 33 hypercholesterolaemic men.[21] However, it failed to show a beneficial effect in a randomised trial of men who had discontinued thymidine NRTIs.[22]

Lipohypertrophy

Growth hormone (GH) has been shown to decrease VAT, but it may worsen subcutaneous LA and insulin resistance.[8] Tesamorelin, a GH-releasing factor analogue, has been used to restore GH levels and has demonstrated a significant reduction in VAT hypertrophy. It has also been shown to improve the levels of TGs, HDL-C, adiponectin and insulin-like growth factor 1 (IGF-1), although a small but statistically significant worsening of glucose profiles was also evident. Based on these data, the US Food and Drug Administration (FDA) approved tesamorelin for the treatment of excess abdominal fat in HIV-infected patients in November 2010. The drug may only be used in patients without active malignancy and its widespread use is complicated by cost, the need for frequent monitoring of IGF-1 and glycosylated haemoglobin (HbA1c), and the lack of safety data beyond one year of use. Therapy should not be continued for longer than six months in the absence of a favourable treatment response, as assessed by a decrease in waist circumference.[23] Metformin is known to decrease VAT, especially in the presence of insulin resistance. It may, however, worsen subcutaneous LA and should not be used in patients with a low BMI. There are, however, not enough data to recommended its use in patients without diabetes mellitus (DM) at this stage. Anabolic steroids have not shown a beneficial response in the presence of normal blood testosterone levels and can also not be recommended at present.

Overall, in light of the high cost of these treatments, limited data showing minimal improvement, an absence of clear long-term benefits and the possibility of new complications of the therapy, none of these drugs can be recommended for the routine treatment of lipodystrophy at this stage.

Role of surgery

Lipoatrophy

Various surgical interventions have been proposed for the management of facial LA. There are, however, limited long-term data on the different approaches, and inadequate comparisons thereof. Polylactic acid (PLA) is a re-absorbable filler that is immunologically inert and causes only limited inflammation. Most patients report a good response after three to four injections. It is, however, prohibitively expensive. Hyaluronic acid and collagen produce equally favourable results, but the effects are less durable. Transplanting autologous harvested fat cells is becoming increasingly topical, but costs, the invasiveness of the technique and the requirement of general anaesthesia and hospitalisation limit its use.[24] Polyalkylamide (Bio-Alcamid) is a permanent filler and has been used with good effect, especially in cases of severe LA. Permanent fillers do not, however, have long-term safety data and have the disadvantage that, if LA progresses, then the edges of the filler may become visible. Conversely, if fat mass increases, the permanent filler may over-correct the original defect and hence become obvious and unsightly.[24]

Lipohypertrophy

Surgical interventions have been used for localised forms of LH, such as lipomas and buffalo humps. Options include standard surgical removal and liposuction. The duration of effect is, however, variable and up to half of the patients with dorsocervical disease experience a recurrence after 1 - 2 years. Surgery can also be considered when significant fat has accumulated around the breast tissue. Breast reduction surgery is invasive, requires anaesthesia and hospitilisation, and has a similar risk of fat return, especially if the patient cannot be established on a PI-sparing regimen. Surgery is not an option for patients with abdominal LH.

Screening for and managing metabolic complications

Suggested approach

Prevention of HIV-related lipodystrophy is the best strategy and all HIV-infected persons should be screened at regular intervals for a history of metabolic disease, dyslipidaemia, DM, hypertension and alteration of body composition (Table 2). Interventions to prevent CVD should vary in intensity according to a patient's absolute risk of ischaemic heart disease. A comprehensive, multi-disciplinary approach is preferred. This should start with lifestyle interventions – counselling to stop smoking, modified diet and regular exercise – and be followed with a change of ART if needed, and the use of lipid-lowering medication in high-risk patients. The prevention and management of type 2 DM and hypertension should be in accordance with guidelines used in the general population. When pharmacological interventions are considered, care should be taken to avoid detrimental pharmacokinetic interactions, such as between statins and PIs.[24]

Conclusion

Lipodystrophy remains a challenge in the long-term management of HIV-infected patients receiving ART, and should be regarded as part of a more pervasive pathology. We recommend approaching the condition with targeted annual screening. In light of the absence of

Table 2. Suggested annual screening for metabolic complications

History	• Family or personal history of CVD, DM or HT • Concomitant treatment for DM, HT or dyslipidaemia • Concomitant use of medication with risk for DM or dyslipidaemia • Lifestyle: smoking, alcohol, exercise, diet • Patient perception of change in body composition

Examination	• Body composition
	  • BMI
	  • Waist circumference
	  • Waist:hip ratio
	• Clinical signs of lipodystrophy
	• Blood pressure
	• Cardiovascular risk assessment

Bloods	• Lipids: fasting total cholesterol, TGs, LDL-C and HDL-C • Glucose (fasting) • Liver enzymes: ALT, AST, GGT, ALP • Renal function: eGFR
Special investigations	• ECG: men aged >40 years and women aged >50 years

CVD = cardiovascular disease; DM = diabetes mellitus; HT = hypertension; BMI = body mass index; TGs = triglycerides; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyl transpeptidase; ALP = alkaline phosphatase; eGFR = estimated glomerular filtration rate; ECG = electrocardiogram.

cost-effective measures to treat LA and LH, prevention remains the best option. Healthcare workers should be sensitised to the early detection of lipodystrophy in patients on thymidine-based ART regimens. Furthermore, affected patients should be switched to an appropriate regimen as soon as is feasible. There is currently no evidence to support the use of new-generation ARVs, except in patients with significant hypercholesterolaemia, where ATV and RAL may present better options.

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ORIGINAL ARTICLE

Association of HIV prevalence and concurrency of sexual partnerships in South Africa's language groups: An ecological analysis

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Background. There is considerable variation in HIV prevalence between different language groups in South Africa (SA). Sexual partner concurrency has been linked to the spread of HIV, but its effect on differential HIV transmission within SA's language groups has not been investigated quantitatively.
Objective. This ecological analysis was intended to explore the degree to which the variation in HIV prevalence according to language group can be explained by differential concurrency rates.
Method. Linear regression was used to assess the association between each language group's HIV prevalence and four risk factors: the prevalence of concurrency, multiple sexual partners in the preceding year, circumcision, and condom utilisation.
Results. In multivariate analysis, only the point prevalence of concurrency remained associated with HIV prevalence.
Conclusion. There is evidence of a high prevalence of point concurrency in sexual partnerships in SA's most HIV-affected language groups. Together with evidence that relatively small decreases in concurrency can lead to large declines in HIV incidence, this provides impetus for interventions to promote having only one sexual partner at a time.

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Although adult HIV incidence in South Africa (SA) has fallen somewhat, it remains alarmingly high – between 1% and 2%.[1] It is of great importance to ascertain what is driving this high incidence. One approach that has received little attention is to compare the potential risk factors for HIV in SA's various language groups. Since HIV prevalence varies widely among these groups, this offers an opportunity to determine which population-level factors co-vary most closely with this prevalence. The objective of this analysis was to determine the manner in which HIV prevalence varies according to SA's 11 major self-defined language groups, and to examine the ecological association of four risk factors (prevalence of concurrency, multiple partners in the preceding year, circumcision, and condom utilisation) with HIV prevalence in these groups.

Methods

Two nationally representative surveys were used for this study, namely the South African National HIV Prevalence, HIV Incidence, Behaviour and Communication Survey of 2008 (SABSSM III) and the National Communication Survey of 2009 (NCS 2009).[2,3] In both surveys, respondents were asked to verify which main language they spoke at home; responses were coded into 11 identical language options (Table 1). The HIV prevalence (dependent variable) and risk factors (independent variables: prevalence of concurrency, multiple sexual partners in the preceding year, circumcision, and condom utilisation) were calculated for each language group.

HIV prevalence

The HIV prevalence of each language group (among individuals aged 16 - 55 years) was obtained from the SABBSSM III survey.[2] This was the third and most recent of the SABSSM surveys, which are the only nationally representative HIV sero-surveys of South Africans of all ages. The survey used a multi-stage stratified sampling approach. When correctly weighted to account for the complex sampling design and HIV testing non-response, the sample was representative of the population in SA for the main reporting domains of sex, age, race and province.[2] Structured questionnaires were used to collect demographic, social and behavioural data. Dried blood-spot specimens were used for HIV testing using an algorithm that saw all samples initially being tested with an enzyme immuno-assay (Vironostika HIV Uni-Form II plus O, Biomerieux). Of 23 369 individuals, 20 826 (89.1%) completed the interviews and 15 031 (64.3%) agreed to provide blood for HIV testing. The mid-point of data collection was September 2008.

Risk factors

The four independent variables were derived from the NCS 2009[3] – a cross-sectional survey that utilised a multi-stage, stratified sampling approach (comprising three stages). Firstly,

Table 1. Prevalence of HIV[2] and various risk factors[3] per language group among South Africans aged 16 - 55 years

	SABSSM III[2]			NCS 2009[3]					
Language	*N*	Age median (IQR)	HIV prevalence % (95% CI)	*N*	Age median (IQR)	Concurrency % (95% CI)	Multiple partners per year % (95% CI)	Circumcision % (95% CI)	Condom utilisation % (95% CI)
IsiZulu	1 646	28 (21 - 40)	28.8 (24.3 - 31.8)	1 973	29 (23 - 38)	8.9 (7.3 - 10.9)	16.8 (14.4 - 19.7)	23.5 (20.0 - 27.3)	50.5 (46.2 - 54.7)
IsiZhosa	1 497	28 (20 - 40)	21.6 (17.6 - 24.6)	1 351	28 (22 - 39)	4.9 (3.5 - 6.9)	11.6 (9.4 - 14.2)	76.6 (72.3 - 80.4)	45.8 (42.1 - 54.7)
IsiNdebele	105	28 (21 - 41)	20.6 (9.4 - 38.5)	191	27 (22 - 36)	6.1 (3.0 - 12.0)	9.4 (5.0 - 17.0)	68.0 (52.9 - 80.1)	44.4 (33.7 - 55.5)
IsiSwati	251	28 (19 - 41)	23.9 (18.1 - 30.0)	365	25 (21 - 34)	5.3 (3.6 - 7.6)	7.7 (5.3 - 10.9)	32.9 (19.5 - 49.8)	51.7 (42.7 - 60.6)
English	1 847	32 (21 - 43)	1.5 (0.8 - 2.6)	370	36 (27 - 44)	1.4 (0.5 - 3.9)	3.1 (1.4 - 6.9)	31.9 (22.3 - 43.4)	22.8 (16.6 - 30.3)
Afrikaans	2 568	33 (21 - 44)	2.5 (1.8 - 3.3)	1 228	36 (26 - 44)	1.2 (0.6 - 2.4)	4.3 (2.8 - 6.6)	14.8 (10.3 - 21.0)	21.3 (17.0 - 26.3)
Sesotho	783	29 (21 - 40)	20 (16.6 - 22.9)	946	31 (23 - 40)	4.6 (3.0 - 7.0)	13.2 (9.9 - 17.5)	49.2 (42.5 - 56.1)	44.5 (39.6 - 49.5)
Sepedi	808	29 (20 - 42)	16.6 (11.4 - 21.6)	797	26 (21 - 35)	5.4 (5.0 - 7.5)	12.8 (9.1 - 17.8)	79.5 (72.5 - 85.0)	54.0 (44.9 - 62.9)
Setswana	852	29 (20 - 41)	18.4 (13.6 - 22.7)	699	31 (24 - 40)	4.6 (2.8 - 7.5)	11.0 (7.5 - 15.9)	31.6 (23.4 - 41.2)	49.2 (43.9 - 54.5)
Tshivenda	143	27 (20 - 41)	8.1 (3.2 - 17.8)	232	28 (22 - 36)	3.8 (1.5 - 9.5)	10.9 (6.5 - 17.5)	89.2 (77.4 - 95.2)	45.6 (38.1 - 53.2)
Xitsonga	331	28 (21 - 38)	17.6 (10.6 - 26.3)	374	27 (22 - 36)	5.4 (2.3 - 11.9)	11.8 (7.4 - 18.3)	70.1 (55.4 - 82.4)	39.5 (30.0 - 49.8)

SABSSM III = South African National HIV Prevalence, HIV Incidence, Behaviour and Communication Survey of 2008; NCS 2009 = National Communication Survey of 2009; IQR = interquartile range; CI = confidence interval.

400 primary sampling units (PSUs) were sampled using principles of probability proportional to size. PSUs comprised small areas from the 2001 National Census. The second and third stages, respectively, involved the selection of secondary sampling units or households, and the selection of one individual per household (aged 15 - 55 years) from eligible household members. The final sample comprised 9 728 individuals aged 16 - 55 years, who were representative of South Africans in this age band. The overall response rate was 58%. Data were collected between June and August 2009. See Johnson *et al.*[3] for further details of the methodology and possible bias introduced by differential non-response. The four independent variables were defined as follows:

- *Point concurrency:* The point prevalence of concurrency (i.e. having two or more overlapping sexual relationships) at the time of the survey was used as the indicator of concurrency, as this has been shown to best capture the effect thereof in increasing a sexual network's connectivity and, hence, HIV transmissibility.[4,5] For each language group, the point concurrency was determined by the percentage of persons who reported having two or more partners at the time of the survey. This variable was derived from the question: 'How many sexual partners do you currently have?'
- *Multiple partners per year:* defined as the proportion of respondents in each language group who reported having two or more sexual partners in the preceding 12 months.
- *Condom utilisation:* defined as the proportion of respondents in each language group who reported using a condom the last time they had sexual intercourse.
- *Circumcision:* defined as the proportion of male respondents who reported being circumcised (each male respondent was asked whether or not he was circumcised).

Statistical analyses

The HIV prevalence and independent variables were calculated for each self-defined language group using Stata version 12.0 (College Station, Texas, USA) and by applying the survey methodology to account for the multi-stage sampling strategies and varying non-response rates. Uni- and multivariate linear regression models were used to assess the association between the independent and dependent variables. All analyses were limited to sexually experienced individuals aged 16 - 55 years. The data were not age-standardised, as the differences in the age structure of each language group were relatively small (Table 1).

Results

Table 1 shows the variation in HIV prevalence between language groups, ranging from 1.5% (95% CI 0.8 - 2.6) to 28.8% (95% CI 24.3 - 31.8). These variations remained considerable upon analysis of the nine black language groups alone; ranging from 8.1% (95% CI 3.2 - 17.8) in Tshivenda speakers to 28.8% (95% CI 24.3 - 31.8) in isiZulu speakers.

Three risk factors were strongly associated with increased HIV prevalence per language group upon univariate analysis: multiple partners per year, point concurrency (Fig. 1) and lower condom utilisation rates (Table 2). Circumcision prevalence rates were not associated with HIV prevalence; however, this may have been driven by the effect of the English- and Afrikaans-speaking groups who had low rates of circumcision and HIV prevalence (Fig. 2). When the analysis was restricted to the nine black language groups, increasing circumcision rates were correlated with lower HIV prevalence rates (R^2=0.48; p=0.04).

Table 2. Univariate and multivariate linear regression analysis of the relationship between HIV prevalence per language group and risk factors[2,3]

	Univariate			Multivariate	
Risk factor	**β co-efficient**	**R^2**	***p*-value**	**β co-efficient**	***p*-value**
Concurrency	3.79	0.84	0.0001	3.50	0.046
Multiple partners/year	2.04	0.55	0.0061	-0.23	0.949
Circumcision	0.04	0.02	0.8132	-0.02	0.427
Condom utilisation	0.61	0.58	0.0165	0.24	0.267

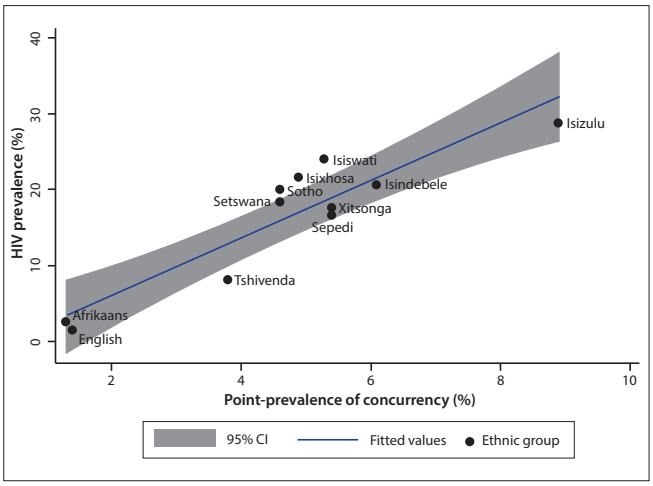

Fig. 1. Association between HIV prevalence (derived from SABSSM III) and the point prevalence of concurrency (derived from NCS 2009) for 11 language groups in South Africa (R^2=-0.84; p< 0.001).[2,3]

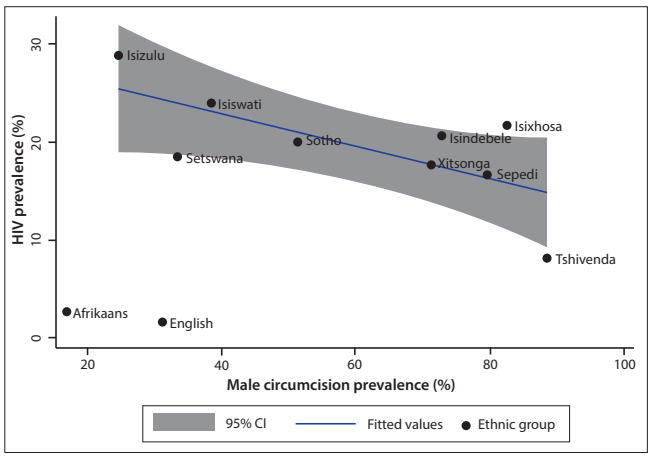

Fig. 2. Association between HIV prevalence (derived from SABSSM III) and the prevalence of male circumcision (derived from NCS 2009), for 11 language groups in South Africa (R^2=-0.02; p=0.70 for all 11 language groups and R^2=0.48; p=0.04 when analysis restricted to the nine black language groups).[2,3]

In multivariate analysis, only point concurrency remained associated with HIV prevalence (β co-efficient=3.5; *p*=0.03) (Table 2).

There was a high degree of overlap between language and self-reported ethnicity within the NCS 2009 sample. The proportion of coloureds, Indians and whites who spoke English or Afrikaans was 91.9%, 97.9% and 97.8%, respectively. The proportion of blacks who spoke English or Afrikaans as their home language was 1.6%. Omitting these individuals from the analyses made no difference to the results (data not shown). Moreover, it is possible that HIV prevalence may peak in different language groups at different times depending on the stage of the epidemic. To evaluate this, we repeated the analyses using the HIV prevalence rates from the 2002 and 2005 SABSSM surveys. The resultant difference to the results was negligible (data not shown).

Discussion

HIV prevalence is known to vary dramatically between South African language and racial groups.[2] This heterogeneity offers a useful opportunity to examine the reasons underpinning the country's generalised HIV epidemic. Great caution needs to exercised in the use of ethnic and racial categories in health research. This is especially the case in SA, where the uncritical use of racial categories in the apartheid era, combined with the concomitant lack of controlling for the effects of the widely divergent socio-economic conditions, served to exaggerate racial differentials in various health outcomes.[6-8] However, a wide range of evidence indicates that economic differences are not the predominant drivers of differential HIV spread according to racial group.[9] Furthermore, it is important to explain the considerable differences in HIV prevalence between language groups among black South Africans.

There is a high degree of homophilous partnering (like-with-like) among self-defined language groups in sub-Saharan Africa[10] and elsewhere.[11] Sexual networks would therefore be expected to cluster and segregate to a considerable degree along these lines, as has been demonstrated empirically.[10,11] These sexual networks may be, more or less, densely interconnected and these differences are believed by many,[4,12] but not all, epidemiologists[13] to be important in explaining differential HIV spread. Since network connectivity, as assessed by measures such as concurrency prevalence, is a network-level property, it is necessary and appropriate to investigate it at a network or ecological level.

A number of studies from SA, the USA and elsewhere have found that racial or ethnic variations in HIV prevalence are not explained by individual-level risk factors (e.g. multiple partners per year and lifetime number of sexual partners), but rather that network-level factors such as concurrency prevalence are important.[4,14,15] This is commensurate with global reviews of sexual behaviour which have shown that the average number of lifetime sexual partners is, if anything, lower in countries with generalised HIV epidemics than in countries with low HIV prevalence rates such as those in Western Europe.[16]

In the data described here, the relationship between circumcision and HIV prevalence is interesting, especially considering the significant association within the black language groups. Circumcision cannot, however, explain the low HIV prevalence rates in the English and Afrikaans groups, as they have the lowest circumcision rates. This is

mirrored globally. Eastern and Southern Africa have considerably higher circumcision rates than Latin America, and the non-Islamic countries in Asia and Europe, all of which have very low HIV prevalence rates.[17,18] Clearly, something else may be driving the higher HIV prevalence rates. The multivariate analyses presented here support findings from elsewhere which suggest that the degree of connectedness of the sexual network (here measured by point prevalence of concurrency) is playing a significant role in this regard.[4,14,15,19,20]

Study limitations

There are a number of weaknesses in this analysis, including the fact that the data for sexual behaviour and HIV prevalence were derived from different surveys. Both surveys were, however, conducted with nationally representative samples. The surveys were designed to provide representative data for the four racial groups in SA, but not for the eleven language groups. Ecological analyses, such as this one, assume a high degree of language group homophily as far as sexual partnering is concerned. This has been long been shown to be the case in the USA,[11] but only recently so in SA.[10] The data are derived from self-reported behaviour and circumcision statuses; however, these are prone to well-described biases.[11] In particular, self-described circumcision has been shown to over-estimate circumcision prevalence.[21] There is, however, no evidence to indicate that these biases vary between different language groups and, as such, they should not affect the validity of this study. Furthermore, ecological studies are susceptible to the ecological inference fallacy. This study, however, makes no inferences from the population to the individual level. Further work is necessary to evaluate whether partner concurrency is associated with an increased risk of HIV acquisition in prospective cohorts. Lastly, it is possible that the study's results may have been confounded by unmeasured variables.

Conclusion

In summary, evidence is presented here of a high prevalence of point concurrency in sexual partnerships in SA's most HIV-affected language groups. Other studies have found that these groups may be unaware of the dangers of concurrency.[22] These results combined with the evidence that relatively small decreases in concurrency can lead to large declines in HIV incidence provide further impetus for interventions to promote having only one partner at a time.[15,19,20]

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(*iv*) transfer to other health centres, (*v*) perceived sense of stigma, and (*vi*) patient-proposed recommendations.

Adjusting to adult healthcare providers

Most of the participants expressed a sense of difficulty with terminating their relationships with their young adult healthcare providers, because most of them had grown attached to them: 'The first time I came to IDI, I was placed in the young adult clinic and it had become my dad, my mum, my uncle, my auntie, my friend, my family and my life. I was at home in the young adult clinic. You cannot just take my family away from me.' (female, aged 25 years); 'I feel like I am being separated from my mother … I have been at home in the young adult clinic … The doctors in the adult clinic now view me like an old man.' (male, aged 26 years)

Some of the participants felt that they were not prepared appropriately for the changes in the adult clinic: 'They need to tell us that the doctors will not treat us like young people anymore. The doctors give us no special attention. If you are not sick, then you are not a problem. They will not even try to find out how your life is.' (female, aged 26 years)

Adult clinic logistics

The young adults described some logistical issues with the adult HIV clinic compared with the young adult HIV clinic. Specifically, they felt that the young adult clinic offered a less busy environment than the adult clinic: 'The waiting hours in the adult clinic are too long and yet in the young adult clinic waiting hours are much shorter.' (female, aged 27 years); 'Some of the health workers in the adult clinic are not youth-friendly and some bark at me. I am always worried about missing lunch.' (female, aged 25 years)

There were also logistical issues raised due to the large clinic size: 'At one of my clinic appointments, I was told that my file had gotten lost and was told to sit and wait. I sat at the waiting benches for almost the whole day and yet I had come at 8 a.m. in the morning and left at 3 p.m. in the afternoon. This had never happened to me in the young adult clinic.' (female, aged 28 years); 'Files begin to get lost when you are moved to the adult clinic and not when you are in the young adult clinic.' (male, aged 26 years)

Positive attributes of the adult clinic

Although most of the young adults acknowledged difficulties in coping with the transition, some appreciated the adult clinic services, the specialised healthcare and the tools that were used to decongest the adult clinic: 'Ever since I was transited into the adult clinic I have gotten special care ... maybe it is because at the time of transition, I was pregnant. I was given a special doctor to attend to my needs. My baby and I are healthy and well. I am happy with the services.' (female, aged 27 years); 'I have not faced any difficulties since I started attending the adult clinic. When I come to the clinic, I cancel all the day's programmes and devote the day to the clinic. I do not mind about the amount of time I spend at the clinic provided I have been seen by the doctor and gone home with my medications.' (female, aged 26 years); 'I have not had any problems in the adult clinic. As soon as I was transferred to the adult clinic, I was given a green card, which basically means that I see the health worker every 3 months. Every other month I get my drugs from a prescription window.' (male, aged 26 years)

Transfer to other health centres

Some of the young adults who had been transitioned from the young adult clinic expressed discontent when they had been transferred to other health centres: 'I was not happy when I was transitioned to the adult clinic. As soon as I was transitioned I was told that I had to be transferred to another health centre outside IDI. When I reported to that health centre, I was told that the centre only works on two days in a week and yet I have a job.' (female, aged 26 years)

Perceived sense of stigma

Some participants associated the adult clinic with stigma: 'I do not like the way the adult patients look at me in the adult clinic. They look at me in an accusing way … like I am someone who sleeps around.' (female, aged 26 years)

Some participants conveyed a fear that the adults may be a frightening group: 'It is very difficult for me to walk in the adult clinic … sit with adults and wait for my turn to see the doctor without being asked what I am doing in the clinic. I am a short, thin girl and usually get mistaken for being a teenager … when I sit in the adult clinic, I feel totally lost.' (female, aged 25 years)

Patient-proposed recommendations

Some participants felt that the adult HIV clinic healthcare providers needed to acquire skills specific to the treatment and management of YPLHIV: 'Some of the doctors in the adult clinic should work in the young adult clinic so that they can learn how to handle young people. Some of them treat us like adults and yet we are not … we need more time.' (female, aged 25 years)

One of the participants still felt the need for additional support extending beyond the adolescent and young adult HIV/AIDS care programme: 'I was among the first young adults to be exited from the young adult clinic. It would be good if you got us a special day – like Thursday or Friday – for the exited young adults, so that we can continue to meet others.' (female, aged 29 years)

Discussion

The transition process for YPLHIV to routine adult HIV care is a complex, clinical and psychosocial process that varies from patient to patient. Given the paucity of available data specific to this in resource-limited settings, we accordingly aimed to provide insight into and propose a model for such transitioning.

As much as transition into adult care is possible for YPLHIV, our evaluation showed that stigma still persists among these young people. The qualitative results of our study corresponded with similar findings by others when transitioning adolescents with other chronic diseases into adult healthcare in developed countries.[4-8] In our study, adjusting to the concept of adult care, an adult-oriented clinic environment and a perceived sense of stigma were some of the challenges faced by young people transitioning into the adult services. These findings were similar to those of others when transitioning adolescents with perinatally acquired HIV infection into adult care.[4-12] In contrast, a few participants acknowledged the benefits of the adult-oriented HIV clinic, reiterating that the process may vary for each patient.

Although the transition process itself did not involve caregivers, the importance of the social support system was emphasised during the exit process. The rationale for not involving caregivers in the transition process is to enhance patient autonomy. However, it is

possible that involvement of the caregivers would have provided more insight into some of the challenges faced by the young adults during and after transfer to adult care.

In the literature, there are a number of models that have been developed for transitioning adolescents and young adults with chronic health conditions into adult care. These models, however, have been developed in resource-rich, developed countries. The Maestro Project systems navigator model for diabetes mellitus and the Young Adults with Rheumatic Diseases (YARD) clinic transition model are two examples of disease-specific transition care programmes that were designed to provide support for youths with chronic diseases.[14] Other transition models that are not disease-specific were designed to link young adults with chronic conditions in general to adult care.[14,15] All of these models emphasise the importance of a social support system, including parents and families, in the transition care process. Each model also differs, as the principles that govern transition across these models differ. For example, the Maestro systems navigator model is governed by five principles: enhancement of patient autonomy, ensuring collaboration between healthcare providers, equipping with negotiation skills, providing community resources, and having a designated professional who takes responsibility for transition.[14] Other programmes emphasise the provision of developmentally appropriate care, shifting the responsibility to the adolescent, and the provision of a portable summary of the patient's healthcare needs and a clear transition plan in the patient's file.[14]

With regard to adolescent HIV care, the 'movin" out' model was developed by a special adolescent clinical team in the United States.[16] The model is essentially a transitioning protocol of 5 phases and is fluid, allowing a young person to revert to a prior phase or to become stagnant at a particular phase. The protocol necessitates that a multi-disciplinary transition team, comprising nurses, social workers, peer educators, psychologists and physicians, take charge of the process of transition.[16]

Against this backdrop, we formulated a transition model that would provide guidance for transitioning YPLHIV from young adult HIV programmes into adult HIV care in developing countries, on the basis of enhancing patient autonomy. Despite the limitations, the key findings of the evaluation were that moving to the adult clinic is difficult for YPLHIV. As an implication, there is the need for continual follow-up and for some of the adult care providers to be part of the adolescent/young adult team.

Study limitations

The study had several limitations. All 30 participants who partook in the evaluation had acquired HIV through sexual transmission. It is possible that there could have been major differences between sexually infected young people and perinatally infected young people. The results may, therefore, not be generalisable to vertically infected young people transitioning into adult HIV care. Secondly, there was a low response rate to participation in the evaluation (30/80; 38%); hence, the sample size was small. Adding to this, the study was based on a single-centre evaluation (one facility). As much as we sought to illuminate the area of transitioning young HIV-positive people into adult HIV care in the study, the data obtained in our evaluation may not be generalisable to other young adult HIV cohorts.

Conclusion

Ensuring that YPLHIV continue to access care beyond young adult HIV programmes is essential in assuring continuity in HIV care and treatment across Africa. The directions emerging from this study are clear: the provision of enhanced support beyond the transition clinic and youth-friendly approaches by adult-oriented care-providers to young people are both key to continuity of care.

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Author contributions. CK conceptualised the study, contributed to the data analyses, and prepared the manuscript. RPR helped with data analysis and manuscript preparation. AK managed the study and implemented the study protocol. All authors have read and approved the final manuscript for publication.

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SCIENTIFIC LETTER

Stavudine dosage reduction: Effect on symptomatic hyperlactataemia and lactic acidosis in patients at Dr George Mukhari Hospital, Pretoria

To the Editor: A range of studies have demonstrated that symptomatic hyperlactataemia and lactic acidosis are associated with antiretroviral combinations containing stavudine.[1,2] The HIV treatment programme in Khayelitsha, Cape Town, which began using stavudine as a first-line therapy in 2003, reported approximately 10% of patients switching from stavudine to the alternative drug after 12 months due to hyperlactataemia.[3] Following a meta-analysis showing that lower doses of stavudine are safer and as effective, the World Health Organization (WHO) issued a statement that only a low dose of stavudine (30 mg) should be used.[4]

This retrospective review included patients treated at the adult HIV clinic at Dr George Mukhari Hospital, Pretoria, South Africa. The study was approved by the Medunsa Research Ethics Committee (reference MP 156/2005). The records of 86 patients (aged 27 - 59 years) initiated on stavudine-containing antiretroviral therapy regimens between 2004 and 2006 were analysed: 66 females (29 received 40 mg stavudine; 37 received 30 mg stavudine) and 20 males (7 received 40 mg stavudine; 13 received 30 mg stavudine). Lactate levels were not routinely determined for all patients (only when a clinician suspected lactic acidosis or symptomatic hyperlactataemia on the basis of clinical symptoms). A serum lactate level >2.0 mmol/l was considered to be elevated. Lactic acidosis was defined by persistently increased blood lactate levels (>5 mmol/l) in association with acidosis (pH <7.35) and a bicarbonate level ≤ 20 mmol/l.[5]

Among female patients, elevated lactate levels developed in 18/29 (62%) treated with 40 mg stavudine, but only 13/37 (35%) treated with 30 mg of stavudine (range 2.3 - 9.8 mmol/l). Among male patients, elevated lactate levels developed in 2/14 (14%) treated with 30 mg stavudine and 2/7 (29%) treated with 40 mg stavudine.

Thirty-five patients (41%) had elevated lactate levels with signs or symptoms that obliged clinicians to cease treatment. The relative odds of developing elevated lactate levels when commencing treatment were 2.92 times higher in the group receiving 40 mg stavudine than in the group receiving 30 mg stavudine (95% confidence interval 1.10 - 2.51). The relative risk (RR) ratio was higher for female patients, with a greater risk for developing hyperlactataemia than males (RR 2.17 for 40 mg stavudine; RR 2.28 for 30 mg stavudine) (Table 1).

The onset of the first symptoms of elevated lactate levels occurred from 2 to 18 months following treatment initiation. Of the 35 patients with elevated lactate levels, 43% (n=15) were obese and 4 (11%) died due to complications of lactic acidosis.

This analysis demonstrated that stavudine dose reduction increased the odds of patients being more stable on treatment with fewer reported side-effects. Stavudine-containing regimens should be avoided in obese female patients. Low-dose stavudine (20 mg) may offer alternative solutions in poor or resource-limited settings, with a lower associated risk of toxicity and side-effects; however, virological non-inferiority to the first-line treatment option should be established.

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Table 1. Elevated lactate level in patients receiving 30 mg or 40 mg stavudine

	40 mg stavudine	30 mg stavudine	OR (95% CI)
Female, *n* (%)			3.02 (1.10 - 8.29)
Elevated lactate levels	18 (27)	13 (20)	
Normal lactate levels	11 (17)	24 (36)	
Total	29 (44)	37 (56)	
Male, *n* (%)			2.20 (0.24 - 20.00)
Elevated lactate levels	2 (10)	2 (10)	
Normal lactate levels	5 (25)	11 (55)	
Total	7 (35)	13 (65)	

OR = Odds ratio; CI = confidence interval.

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ABSTRACTS
'Striving for Clinical Excellence': Southern African HIV Clinicians Society Conference, Cape Town, 25 - 28 November 2012

A selection of the best abstracts from the first Southern African HIV Clinicians Society Conference, held in November 2012, is provided here. Presentations from the conference may be viewed online (http://www.sahivsoc2012.co.za).

First place

SALIVARY MUCIN MUC5B INHIBITS HIV-1 SUBTYPES A AND C IN AN *IN VITRO* PSEUDOVIRAL ASSAY

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Category: *Clinical laboratory science*

Background. Sub-Saharan Africa is the world's most HIV/AIDS-affected region. More interventions to manage this pandemic are urgently required. Transmission of the virus through saliva exchange is rarely known to occur. Using an *in vitro* pseudoviral assay, we sought to further describe findings that crude saliva and its purified mucins inhibit HIV-1. A robust assay is key to the identification of the mechanism involved in the inhibition of the virus by mucins. It could also help to identify a peptide sequence in mucins that could be used as a basis for the development of a microbicide.

Methods. Mucus was extracted in 4.0 M guanidinium hydrochloride and a cocktail of protease inhibitors (pH 6.5). Sepharose 4B gel filtration was used to separate MUC5B and MUC7 in saliva, and mucins were purified by density-gradient ultra-centrifugation in caesium chloride. Sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis and Western blotting were used to determine the size, purity and identity of the mucins. The inhibitory activity of crude saliva and purified MUC5B and MUC7, from HIV-negative (n=20) and HIV-positive (n=20) donors, was tested by their incubation with subtypes A and C HIV-1 pseudovirus and infection of susceptible epithelial tumour cells (genetically modified TZM-BL cells).

Results. Crude HIV-negative and HIV-positive saliva inhibited HIV-1 in an *in vitro* pseudoviral assay in a dose-response nature. Salivary MUC5B neutralised HIV-1 subtype C pseudoviruses CAP45 (KZN) and DU422 (Durban) and Q168a.2 (Kenya) of subtype A, when purified from HIV-negative and HIV-positive individuals. The neutralisation capability of MUC5B appeared greater than that of MUC7 for the HIV-negative group.

Conclusion. Crude saliva and its purified mucins from uninfected controls and HIV-positive individuals inhibited HIV-1 in an *in vitro* pseudoviral assay. The different inhibitory capabilities are postulated to be due to altered glycosylation of the mucins. Further work using liquid chromatography-mass spectrometry (LC-MS), to analyse glycosylation between mucin groups, is anticipated to reveal such differences.

Second Place

A RANDOMISED CONTROLLED TRIAL OF TWO SPUTUM SAMPLE ACQUISITION METHODS IN PERSONS WITH SMEAR-NEGATIVE OR SPUTUM-SCARCE TUBERCULOSIS IN PRIMARY CARE PRACTICE

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Category: *HIV complications*

Background. Sputum obtained either through dedicated healthcare-worker-provided instruction or sputum induction can improve tuberculosis (TB) case detection. However, the optimal initial sputum sampling strategy for adults with smear-negative or sputum-scarce TB in high-HIV-prevalent primary care practice is unknown.

Methods. Adults with suspected TB from 3 primary care facilities in Cape Town, South Africa, who were sputum-scarce or smear-negative, underwent open-labelled randomisation to receive induction (N=268; HIV-infected n=96) or healthcare-worker-provided instruction (N=213; HIV-infected n=75) to obtain sputum samples. An intention-to-treat analysis was undertaken and the primary outcome measure was time to treatment initiation. The study is registered with Clinicaltrials.gov (http://www.clinicaltrials.gov) (NCT01545661).

Results. Although a sputum sample >1 ml was acquired in a higher proportion of induced v. instructed participants (90% v. 76%; p<0.001) and culture-based TB case detection was higher in induced v. instructed participants (22% v. 14%; p=0.03), case detection was similar in both arms using either smear-microscopy or Xpert-MTB/RIF. However, given higher empirical treatment rates in instructed v. induced participants (62% v. 43%; p=0.04), a similar proportion in each group initiated TB treatment during the study (30% v. 29%), and at 10 days post-enrolment, a greater proportion of instructed v. induced participants had commenced treatment (75% v. 56%; p=0.03). Differences between groups were unchanged if the analysis was restricted to HIV-infected participants only, with the exception that culture-based case detection and empirical treatment rates were similar in instructed v. induced participants. The per-procedure sampling cost was lower for instructed than induced patients (US$2.14 v. US$7.88).

Conclusions. Healthcare-worker-provided instruction is the preferred initial sputum sampling strategy in primary care practice for adult participants with sputum-scarce or smear-negative TB, irrespective of HIV status.

Runners up

(alphabetical according to first author)

VIRAL RE-SUPPRESSION IN THE PRESENCE OF HIV-1 DRUG RESISTANCE MUTATIONS

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Category: *Antiretroviral therapy*

Background. HIV-1 drug resistance mutations present the most common reason for loss of antiviral activity and frequently herald a regimen change. However, small studies have demonstrated re-suppression without a switch in regimen, even in the presence of specific drug-resistance mutations. We aimed to identify the HIV genotypic background of patients who re-suppressed while remaining on the same regimen after initial failure.

Methods. Patients were enrolled in a prospective workplace HIV cohort (Aurum Cohort) with routine HIV RNA and CD4 monitoring. Suppression (HIV RNA <400 copies/µl), failure (viral load (VL) >1 000 copies/µl), and subsequent re-suppression were identified from serial HIV RNA values. First-line regimens were lamivudine (3TC) plus efavirenz (EFV)/nevirapine (NVP) with either stavudine (d4T) (75%) or zidovudine (AZT) (21%). Population-based sequencing was performed using plasma RNA and resistance mutations were identified with the Stanford HIV database.

Results. A total of 71 failing patients who re-suppressed on the same regimen were included. The average VL at failure was $\log_{10}$ 4.6 and the average time to re-suppression was 31.8 weeks. At failure, 31/71 (44%) patients had resistance-associated mutations, including M184V (58%), K103N (52%) and V106M (29%). Both the M184V and K103N mutations occurred in 9/31 (29%) of the re-suppressors. The prevalence of TAMs and other resistance mutations was <3%. The median VL at the time of genotyping was $\log_{10}$ 3.9 among those with resistance mutations and $\log_{10}$ 4.3 among those without mutations (p=0.02).

Conclusion. While the majority of patients who re-suppressed after virological failure were infected with wildtype virus, 44% had one or more drug-resistance mutations. Further work is needed to explore the long-term virological outcomes of patients who re-suppress despite resistance mutations.

HIGH RATE OF VIROLOGICAL RE-SUPPRESSION AMONG PATIENTS FAILING SECOND-LINE ART: A MODEL OF CARE TO ADDRESS ADHERENCE IN A RESOURCE-LIMITED SETTING IN KHAYELITSHA

K Conradie, G Patten, B Kerschberger, D Garone, G van Cutsem

Médecins Sans Frontières

Category: *Operational research*

Background. The rapid scale-up of antiretroviral therapy (ART) coverage in the last decade has improved access to treatment; however, it has coincided with an increasing number of patients failing treatment. In the public sector, patients failing their second-line regimens cannot access costly third-line drugs. Treatment failure may be due to poor adherence, rather than drug resistance. An intervention to improve adherence in patients failing second-line ART was introduced at a primary care clinic in Khayelitsha.

Methods. The intervention included counsellor-led support groups and adherence-focused clinical consultations. It aimed to identify and overcome practical and psycho-social barriers to adherence. Support groups allowed patients with similar difficulties to share experiences and solutions. The consultations were individual, addressing each patient's particular barriers. A descriptive analysis of patients' viral load history during July 2010 and December 2011 was undertaken using routinely collected data.

Results. A total of 69 patients were enrolled in the programme, 25 patients were excluded due to insufficient follow-up time. Four patients enrolled with known PI resistance and were switched to a third-line regimen. Of the remaining 40 patients: 27 (68%) went on to achieve virological suppression during 9 months of follow-up time and 5 patients left the programme (2 to death, 2 were lost to follow-up and 1 transferred). Seven patients (18%) continued to experience viraemia, either with known adherence problems or known to be treatment-sensitive following genotyping. One patient was resistant on genotype and switched to third-line treatment.

Conclusion. Poor adherence was the primary reason for virological failure among patients failing second-line ART. Identification of virological escape followed by simple, targeted adherence support can reduce treatment failure, improve treatment outcomes and decrease the need for costly and inaccessible third-line ART.

CHARACTERISTICS, SEXUAL BEHAVIOUR AND RISK FACTORS OF FEMALE, MALE AND TRANSGENDER SEX WORKERS IN SOUTH AFRICA

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Category: *Women's health*

Background. Information on the characteristics, sexual behaviour and health needs of sex workers in South Africa is limited. Current social, legal and institutional factors impede a safe working environment for sex workers and their clients.

Objectives. To describe the characteristics and sexual behaviour of female, male and transgender sex workers, and assess risk factors for unprotected penetrative sexual intercourse.

Methods. Repeat cross-sectional surveys among sex workers were conducted in Hillbrow, Sandton, Rustenburg and Cape Town. Sex workers were interviewed once and those reporting a re-interview were excluded from the analysis. Unprotected sex was defined as any unprotected penetrative vaginal and/or anal sexual intercourse with the last two clients.

Results. A total of 1 799 sex workers were interviewed between May 2010 and September 2010. Sex work was a full-time profession for most participants. Participants who reported daily or weekly binge-drinking

were 2.1-fold more likely to have unprotected sex than those who reported never binge drinking (adjusted odds ratio (AOR), 95% CI 1.2 - 3.7; p=0.011). Compared with females, male sex workers were 2.9-times more likely (AOR, 95% CI 1.6 - 5.3; p<0.001) and transgender people were 2.4-times more likely (AOR, 95% CI 1.1 - 4.9; p=0.021) to have unprotected sex. Sex workers in Hillbrow, where the only sex-work-specific clinic was operational, were less likely to have unprotected sex than those in other sites.

Conclusion. Tailored sex-work interventions should: explicitly include male and transgender sex workers and sex-work-specific clinics; focus on the risks of unprotected anal sex; and include interventions to reduce alcohol harms.

HIGH RATE OF ABACAVIR RESISTANCE IN CHILDREN LIMITS THE CHOICE OF NRTI USED IN SECOND-LINE ART

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Category: *Children and adolescents*

Background. Since 2010, initial antiretroviral therapy (ART) for HIV-infected children in South Africa has consisted of abacavir (ABC), lamivudine (3TC), and efavirenz (EFV), while second-line ART has comprised zidovudine (AZT), didanosie (ddI) and ritonavir-boosted lopinavir (LOP/r). We sought to determine the rate of virological failure (VF) and describe prevalent drug-resistance mutations among Clade C-infected children.

Methods. At the Sinikithemba Clinic at McCord Hospital in Durban, a retrospective chart review was performed to identify children who initiated ABC/3TC/EFV or were switched to this treatment without interruption between April 2010 and January 2012. Children receiving ABC/3TC/EFV for at least 24 months and with no prior history of VF (viral load >1 000 copies/µl following at least 6 months of ART) were included. Characteristics at ART initiation, virological outcomes and genotypic resistance patterns (using Trugene assay and the Stanford database) were recorded with a standardised instrument.

Results. A total of 221 children receiving ABC/3TC/EFV were identified; 154 (69.7%) were initiated on this treatment and 67 (30.3%) underwent an uninterrupted switch. Fourteen (6%) children experienced VF following a median treatment duration of 11 months (interquartile range (IQR) 8 - 13). Ten patients underwent genotyping: 4 (40%) had the K65R mutation, 4 (40%) had the L74V mutation and 1 (10%) had the L74I mutation. Nine (90%) patients had major non-nucleoside reverse transcriptase inhibitor (NNRTI)-resistance mutations.

Conclusion. Among children failing ABC/3TC/EFV treatment, a high level of resistance to ABC and NNRTIs was observed. Importantly, resistance mutations (L74V, K65R and L74I) are likely to reduce the activity of didanosine (ddI) in the second-line regimen. Based on these initial data, in the absence of resistance testing and following failure of ABC/3TC/EFV, we recommend that second-line ART comprises AZT/3TC/LPV/r in South Africa. The recycling of 3TC in the second-line regimen will help to minimise side-effects and preserve AZT hyper-susceptibility, and is likely to result in a reduction of viral fitness.

RETENTION IN CARE AMONG HIV-INFECTED PATIENTS WITH MENTAL ILLNESS IN JOHANNESBURG, SOUTH AFRICA

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Category: *Antiretroviral therapy*

Background. Retention in care is required for optimal clinical outcomes in patients with HIV infection. Reasons for loss to follow-up are not well understood, especially with regard to HIV-infected individuals with mental illness.

Methods. A retrospective analysis was conducted among adult patients with a history of mental illness at an urban HIV clinic in Johannesburg, South Africa, between July 2010 and September 2011. Patients discontinuing follow-up for at least 6 months were identified and traced through home visits to determine health status and reasons for discontinuing care.

Results. Of the 561 adult patients evaluated, 139 (24.8%) discontinued follow-up during the study period. Of those discontinuing follow-up, 48 were successfully traced by home visits. Among this group, 21 (43.8%) were not engaged in care, 12 (25%) had transferred care, 9 (18.8%) were deceased, 3 (6.2%) had relocated, and 3 (6.2%) were missing. Characteristics associated with death in those receiving ART were lower baseline CD4 cell counts (median 59 v. 133 cells/µl; p=0.036), lower most recent CD4 cell counts (median 147 v. 285 cells/µl; p=0.022), and higher most recent HIV RNA viral loads (median 151 828 v. 557; p=0.015). A significantly higher proportion of those who died had a history of tuberculosis compared with those who were living when traced (p=0.022). The most frequently cited reasons for discontinuing follow-up were: transportation costs and distances; conflicts with work or school schedules; and confusion regarding when to return for care.

Conclusion. Nearly 1/4 patients receiving care at Luthando Neuropsychiatric HIV Clinic over the 14-month review period had discontinued follow-up. However, one-quarter of the patients traced by home visits were engaged in care elsewhere, with the majority still receiving ART. Tracing patients through home visits proved to be an effective means by which to confirm the magnitude of patients lost to follow-up, ascertain their outcomes, and elucidate their reasons for discontinuing care.

PROFILE OF YOUNG CHILDREN DEVELOPING TUBERCULOSIS AFTER INITIATION OF ANTIRETROVIRAL THERAPY

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Category: *Children and adolescents*

Background. Young age and HIV co-infection interact to substantially increase the risk of developing tuberculosis (TB) among children from TB endemic settings. The effect of antiretroviral therapy (ART) on incidence and the clinical manifestations of TB in young children requires better description.

Methods. We retrospectively reviewed clinical and laboratory data of children aged <2 years who initiated ART at Tygerberg Children's Hospital Infectious Disease Clinic, Cape Town, South Africa, from January 2003 to June 2010. TB immune reconstitution (TB-IRIS) and incident TB were defined as TB treatment episodes within or following 3 months, respectively, of ART initiation. The observation period ended when children exited the hospital system for any reason. Time spent in trials of novel ART agents and prolonged isoniazid prevention therapy were reasons for exclusion from the observation period.

Results. ART was initiated in 531 children including 254 (48%) males. The median age was 7.9 months (interquartile range (IQR) 3.6 - 31.5) and median CD4 cell count (percentage) was 17.5% (IQR 11.5 - 26.2). The median follow-up time was 11.4 months (IQR 3.6 - 31.5). Fifty-one (9.6%) of the children died. ART was initiated during TB treatment in 125 (23%) children. Seventy-one new TB episodes (29 TB-IRIS) were recorded after ART initiation: 58 pulmonary, 5 miliary, 4 TB meningitis, 3 lymphadenitis, and 1 osteo-articular TB. Nine (13%) episodes were bacteriologically confirmed. The incident TB rate was 4.6 episodes/100 person years of follow-up. Among children who developed TB, the median age and CD4 percentage at ART initiation was 6.3 months (IQR 4.5 - 12.2) months and 18.0% (12.9 - 25.3), respectively. Baseline demographic and immunological characteristics were similar between children with TB-IRIS v. incident TB.

Conclusion. Young HIV-infected children remain at high risk of TB disease, including disseminated forms, despite a reduction in TB incidence with early ART initiation. Effective preventive strategies and improved diagnostic methods for TB in this vulnerable group could improve clinical outcomes.

SAFETY OF *SUTHERLANDIA FRUCTESCENS* IN HIV-SEROPOSITIVE SOUTH AFRICAN ADULTS: AN ADAPTIVE, DOUBLE-BLINDED, RANDOMISED, PLACEBO-CONTROLLED TRIAL

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Category: *HIV complications*

Background. *Sutherlandia fructescens* is widely used as a traditional medication by HIV-seropositive adults living in South Africa; however, the safety of the use of the plant has not been studied objectively. An adaptive 2-stage randomised double-blind placebo-controlled study was used to evaluate the use of *S. fructescens* in healthy HIV-seropositive adults with a CD4 T-lymphocyte count >350 cells/μl.

Methods. Fifty-six participants were randomised in stage 1 of the study to receive 400, 800 or 1 200 mg of *S. fructescens* twice daily or matching placebo for 24 weeks. No adverse events related to the consumption of *S. fructescens* were detected; subsequently an additional 77 participants were randomised to 1 200 mg *S. fructescens* or placebo. Data from stages 1 and 2 were combined so that a total of 106 participants were analysed with 53 in each arm, comparing 1 200 mg *S. fructescens* against placebo.

Results. *S. fructescens* was well tolerated; biochemical, haematological and electrocardiographic parameters remained within normal limits for the duration of the study. The changes in HIV viral load and CD4 T-lymphocyte count were similar in the two arms at 24 weeks ($p>0.3$). The questionnaire scores for physical vitality and energy were similar over the study period between the two arms ($p>0.1$). The burden of infection (BOI) (defined as the number of days of infection-related events experienced by each participant) was greater in the *S. fructescens* arm: mean 5.0 (5.5) v. 9.0 (12.7) days ($p=0.045$), and median 9.0 (12.7) v. 18.2 (25.4) days ($p=0.065$).

Conclusion. The implications of greater BOI observed in the *S. fructescens* arm need further evaluation. No other safety issues were identified in this cohort relating to the consumption of high-dose *S. fructescens.*

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CPD QUESTIONNAIRE

Vol. 14, No. 1

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True (A) or false (B):

Regarding HIV-related lipodystrophy:

1. The lipodystrophy syndrome is most commonly characterised by lipohypertrophy with lipomatosis.
2. In terms of the effect of antiretroviral therapy (ART) on lipodystrophy, an increase in trunk fat has been observed with efavirenz-, protease-inhibitor- and raltegravir-containing regimens, and a clear causal relationship has been established.
3. The metabolic complications of lipodystrophy are fully reversible through treatment modification.

Regarding partner concurrency and HIV:

4. It is widely accepted that partner concurrency (having more than one sexual partner in a given period of time) is a major determinant of the spread of HIV in South Africa.
5. Across South African language groups, multiple partners per year, point concurrency and lower condom utilisation rates are all associated with increased HIV prevalence by language group.
6. The spread of HIV is driven by the degree of connectedness of the sexual network.

Regarding stavudine dosing:

7. Obesity, female gender, age and duration of treatment are the risk factors increasing the possibility of severe hyperlactataemia and lactic acidosis when patients are on stavudine-containing ART regimens.
8. Following a meta-analysis showing that lower doses of stavudine were safer and just as effective, the World Health Organization (WHO) issued a statement that only a low dose of stavudine (30 mg) should be used.

Regarding screening for HIV-associated neurocognitive disorders (HANDs):

9. HANDs are commonly diagnosed by comparing neuro-psychological scores with normative data using standard deviation as an indicator of impairment.
10. Using general scores from African samples is appropriate when placing people in categories of impairment using standard deviation from normative scores.
11. Figures from South Africa suggest that up to 25% of HIV-positive individuals may display cognitive impairment.

Regarding adolescent HIV treatment services:

12. The transition for young people living with HIV from paediatric/adolescent HIV healthcare providers to adult HIV healthcare providers is a major challenge.
13. A large number of healthcare programmes are tailored specifically for behaviourally infected adolescents and young adults with HIV in sub-Saharan Africa. This group represents one of the few demographic groups adequately served by the various healthcare systems.
14. Adjusting to the concept of adult healthcare, adult-oriented clinic environments as well as a perceived sense of stigma are key challenges faced by young people transitioning into adult care services.

Regarding gender inequality in ART:

15. In African cohorts, women have higher mortality while receiving ART than men.
16. Disproportionately more women than men have accessed ART in South Africa – 60 % of eligible women were receiving ART by mid-2011 compared with 40% of eligible men.

Regarding the prevention of mother-to-child transmission (PMTCT) of HIV:

17. There is overwhelming global consensus that all HIV-positive pregnant women should be started immediately on lifelong ART regardless of CD4 cell count.
18. There is clear evidence that exposure to ART has no effect on pregnancy outcomes such as preterm delivery and low birth weight.

Regarding WHO guidelines for adult ART:

19. WHO currently recommends that adults living with HIV start ART when their CD4 counts fall below 500 CD4 cells/µl.
20. There are clear benefits to individual patient health associated with ART initiation above 350 cells/µl.

INSTRUCTIONS

1. Read the journal. All the answers will be found there.
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ADVICE DOCUMENT

Fixed-dose combination for adults accessing antiretroviral therapy

Southern African HIV Clinicians Society

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This document serves to guide clinicians and programme managers on how to switch from 3 separate antiretroviral (ARV) drugs to the new, single, fixed-dose combination (FDC) tablet containing tenofovir (TDF), emtricitabine (FTC) and efavirenz (EFV).

Summary

Transitioning from individual drugs to an FDC tablet needs to be managed carefully, particularly regarding stock management, ordering processes, supply-chain integrity and comprehensive patient counselling.

Priority groups

- Initially, FDC supply will be insufficient to provide for all FDC-suitable patients
- Therefore, the National Department of Health (NDoH) has recommended that the following patient groups be prioritised for FDC initiation/switch:
  - **Priority group 1**: All HIV-positive patients newly initiating ART – adults, adolescents and pregnant women (regardless of CD4 count (amendment to the guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) anticipated in April 2013) – and who do not have contra-indications to the FDC component drugs
  - **Priority group 2**: HIV-positive pregnant women **and** breastfeeding mothers currently stable on lamivudine (3TC), TDF and EFV
  - **Priority group 3**: Virologically suppressed patients on a stavudine (d4T)-based regimen and who have normal renal function
  - **Priority group 4:** Stable patients receiving individual TDF, 3TC and EFV and who have tuberculosis (TB) co-infection
  - **Priority group 5**: Stable patients receiving individual TDF, 3TC and EFV and who have other co-morbidites (e.g. hypertension, diabetes)
  - **Priority group 6**: Patients receiving individual TDF, 3TC and EFV and who request to switch to the FDC treatment
  - **Priority group 7:** Patients receiving individual TDF, 3TC and EFV and who, after counselling, agree to switch to the FDC treatment.

Important: Clinic staff must co-ordinate this process and only switch as many patients to the FDC tablet as stock allows. This should avoid patients being switched back and forth between FDC and individual drugs due to insufficient stock.

Note: The FDC tablet is not significantly larger than EFV or lopinavir/ritonavir (LOP/r) (Aluvia); therefore, swallowing should not be problematic.

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In 2012 Dr Aaron Motsoaledi, South Africa (SA)'s Minister of Health, announced the award of a new antiretroviral (ARV) tender – worth R5.9 billion – that, for the first time since the start of the ARV programme, includes a triple fixed-dose combination (FDC) tablet. The FDC tablet will contain 300 mg tenofovir (TDF), 200 mg emtricitabine (FTC) and 600 mg efavirenz (EFV). This is a significant step forward for SA's national ARV programme, as it enhances cost-effectiveness and simplifies the first-line regimen. It is anticipated that over 90% of new patients will be eligible to initiate this FDC treatment.

Advantages of FDCs

Regimen and stock management simplification

- ARV prescribing, dispensing and stock management is simplified because the first-line regimen is reduced from 3 separate drugs to 1 combined tablet.[1]
- From April 2013, all pregnant women, regardless of CD4 cell count, will be initiated on triple ARV therapy for the duration of pregnancy and breastfeeding, to enhance the prevention of mother-to-child transmission of HIV (PMTCT) programme. The FDC tablet will simplify the rollout of this change.

Adherence

- Reducing the pill burden of the first-line regimen to 1 pill once daily may, as reported in some studies,[2-4] improve adherence levels. However, the provision of intensive adherence counselling remains essential.

Efficacy

- The efficacy of TDF/FTC/EFV-based triple ARV therapy has been proven in randomised controlled trials.[5-7]

Guaranteed dosing and consistent dispensing

- There is a decreased risk of incorrect dosing due to patient misunderstanding and/or prescribing/dispensing errors.
- Patients are unable to default single drugs to avoid certain side-effects (e.g. some patients independently discontinue EFV because of dizziness or drowsiness).
- There is a reduced risk of patient exposure to dual therapy during single drug stock-outs.

Cost

The SA Government negotiated a cost of R89.37 per month for the FDC treatment.[8] This represents significant cost-saving compared with the old, single-drug tender.

Are 3TC and FTC interchangeable?

The majority of patients currently accessing ARVs are prescribed lamivudine (3TC). However, the FDC will contain **FTC**. FTC and 3TC are structurally very similar, FTC having just one additional fluorine molecule. In a recent technical update, the World Health Organization (WHO) concluded that 3TC and FTC are clinically and programmatically interchangeable.[9] Although few direct comparisons have been performed, 3TC and FTC appear to have comparable virological and clinical efficacy and safety. 3TC may rarely be associated with pure red-cell aplasia, which requires drug substitution, and FTC may occasionally cause palm discolouration, which is usually managed by reassuring patients. Both drugs are active against the hepatitis B virus. Therefore, WHO concludes that 'FTC is an acceptable alternative to 3TC' and that '3TC may substitute for FTC or *vice versa*'. Both 3TC and FTC are given as a single daily dose. Therefore, for those patients receiving stavudine (d4T), 3TC and EFV, switching to the FDC treatment can be considered as a single drug switch from d4T to TDF because 3TC and FTC are considered to be equivalent.

Supply chain management

It is imperative that all patients enrolled in the SA ARV programme are able to access a continuous supply of ARV treatment. Treatment interruptions, whether of single or multiple ARVs, are associated with poorer clinical outcomes, increased rates of virological failure and the emergence of drug-resistant HIV. Consequently, prescription of the FDC tablet will need to be managed carefully, particularly in terms of stock management, ordering processes and supply chain integrity. A gradual, phased approach to introducing the FDC treatment to new patients, pregnant patients and those receiving d4T should help to ensure a smooth transition.

District managers, facility managers, healthcare providers and pharmacy staff will need to work closely together to track how many patients are initiated on, or switched to, the FDC treatment, while also monitoring how many existing patients remain on various single drugs. Changes to monthly/quarterly orders must be kept in line with the needs of each facility's patient population. Facility staff will need support to manage the transition and to communicate effectively with the National Department of Health (NDoH) should shortages arise (preferably before complete stock-outs occur). As the proportion of patients on 'non-standard' regimens decreases, it will become increasingly important for facilities to manage their single drug stocks to avoid stock-outs which disadvantage patients who are not eligible for the FDC.

Switching patients to the FDC

SA's FDC producers will need time to maximise production. Considering that previous drug stock-outs arose when demand outstripped the manufacturers' capacity, it is imperative that FDC rollout is undertaken in a carefully controlled, phased approach. Under the January 2013 - December 2014 ARV tender, 30 million units of FDC will be produced for nationwide use. Due to the size of SA's ARV programme, this means that FDC provision will have to be limited to specific patient groups. Based on the existing tender, the NDoH has identified the following groups as eligible for FDC use. Currently, the Southern African HIV Clinicians Society recommends that clinicians adhere to these NDoH guidelines, to avoid FDC stock-outs occurring as a result of clinics over-extending beyond the anticipated maximum FDC availability during the current tender.

Priority patient groups (NDoH recommendations)

Priority group 1: All ARV-naive patients newly initiating ART

- All HIV-infected individuals identified as eligible for ART, including those with tuberculosis (TB) co-infection, should be initiated on the FDC treatment as long as there are no contra-indications to the component drugs (e.g. renal dysfunction precludes TDF use, and a recent psychotic episode precludes EFV use).
- This group includes new adults, adolescents and all HIV-positive pregnant women (to be initiated on triple therapy, as an FDC, regardless of CD4 count - as per the new PMTCT guidelines anticipated in April 2013)
- Women presenting in the first trimester who require urgent ART initiation for their own health should be managed according to NDoH guidelines. They may not be eligible for the FDC treatment.
- **Note:** Patients weighing <40 kg are unsuitable for the FDC treatment. These patients require **400 mg** EFV (unless concurrently receiving TB treatment). However, should they gain weight, they can switched to the FDC.

Priority group 2: All HIV-positive pregnant women

- HIV-positive pregnant women who are already stable on 3TC, EFV and TDF should be switched to the FDC treatment
- Breastfeeding women who are stable on individual TDF, 3TC and EFV should be changed to the FDC if they agree to do so.

Priority group 3: Established patients receiving d4T, 3TC and EFV

- All patients who are currently established on individual 3TC, d4T and EFV should be switched to the FDC treatment. Initially, while FDC stocks are built up, patients who display d4T toxicity (most commonly peripheral neuropathy or lipoatrophy) should be prioritised.
- The switch to the FDC treatment should be performed as per existing guidelines. Prior to the switch, clinicians must ensure that the patient has a recent (within 3 - 6 months) **undetectable viral load** and normal creatinine clearance.
- The clinician is effectively switching a single drug, d4T, to TDF; therefore, it is essential to ensure that the patient is virologically suppressed before switching.
- For patients with anaemia precluding AZT use, plus renal dysfunction precluding TDF use, special arrangements must be made to ensure access to d4T or abacavir (ABC).
- Patients should be counselled appropriately about the switch.

- Clinicians must remember to monitor creatinine clearance after 3 and 6 months, respectively, and annually thereafter.

Priority groups 4 and 5: Stable patients with TB co-infection and other co-morbidities

- There is concern that patients with co-morbidities (TB, hypertension or diabetes) may struggle with the combined pill burden.
- To lessen the potential for poor adherence, such patients should be offered the FDC treatment if they are already receiving TDF, 3TC and EFV.
- **Note: Multiple drug-resistant TB (MDR-TB**) patients are **excluded** as amino-glycosides and TDF have overlapping renal toxicity. Rather, these patients should be initiated on AZT or, if anaemic, d4T.
- **Important:** Clinic staff must carefully monitor FDC prescriptions and ensure that sufficient stock is available to secure a continuous FDC supply to all patients being initiated/switched. It is critical that patients do not find themselves being switched back and forth to individual drugs due to insufficient FDC stock.

What about other patient groups?

As SA's ARV programme continues to expand, clinics are experiencing burgeoning populations of stable patients who are clinically well and virologically suppressed. Long-term retention in care of this group is proving problematic and, increasingly, a shift to community-based, adherence club models is being advocated to streamline clinic services and improve patient retention. It is anticipated that successful implementation of such club models would be greatly facilitated by FDC availability, as this would simplify dispensing to club members. However, the NDoH has decided that clinically stable patients receiving TDF, 3TC and EFV are to be prioritised below other groups during the period of this current tender. After allocating FDC stocks to new patients, pregnant patients, d4T-receiving patients and those with co-morbidities, there may not be additional FDC available for stable patients falling into priority groups 6 and 7.

FDC side-effects

Patients taking the FTC/TDF/EFV FDC tablet are expected to experience the same side-effect profile as patients taking the 3 individual drugs. Patients should be counselled about potential side-effects as per usual. Anecdotally, upon switching from individual drugs to other FDCs, some patients report experiencing new or different side-effects. It is uncertain whether this may be associated with the binding components within the co-formulation or due to the psychological effect of changing medication. Most patients will settle with reassurance.

FDC-recipient patients who develop severe adverse events necessitating discontinuation of one agent (e.g. severe EFV-associated central nervous system (CNS) toxicity or TDF-induced renal dysfunction) should be managed as per patients taking individual drugs. Clinicians should adhere to existing guidelines when managing ARV-induced adverse events. If indicated, the FDC treatment should be discontinued to remove the offending agent. The FDC should be replaced with 3 individual drugs: the 2 tolerated drugs plus an alternative to replace the offending drug. The patient must be educated carefully about their new, more complex regimen, including matters such as dosing, expected side-effects and any additional monitoring required.

Note: For FDC-recipient patients who develop **MDR-TB,** clinicians should consider switching the TDF-containing FDC for the duration of aminoglycoside use. If the patient is retained on the FDC treatment, increased renal monitoring should be instituted during the MDR-TB treatment period.

Patient counselling

For patients, the switch from 3 tablets to 1 tablet may raise concerns about efficacy or quality. It is essential that healthcare workers educate patients about the FDC treatment.

Patient counselling messages

- The dosage is one pill once daily, not 3 pills once daily.
- Although the FDC is 'one pill once a day', it does contain 3 different ARV medications – it is easy to take, highly effective and in no way inferior to taking 3 individual drugs.
- Most patients initiating the FDC will not encounter problems, but if they experience any significant side-effects, they should consult their healthcare provider.
- Although the FDC is a large tablet, it is not significantly larger than EFV or LOP/r (Aluvia); therefore, swallowing should not create problems. There is no liquid FDC formulation currently on the market. **Crushing or dissolving the FDC**, which undermines bio-equivalence, **should be avoided**.[10]
- Patients (especially stable patients) who are not included in the priority groups for the FDC should be counselled so that they understand why they are not being switched to an easier option.

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