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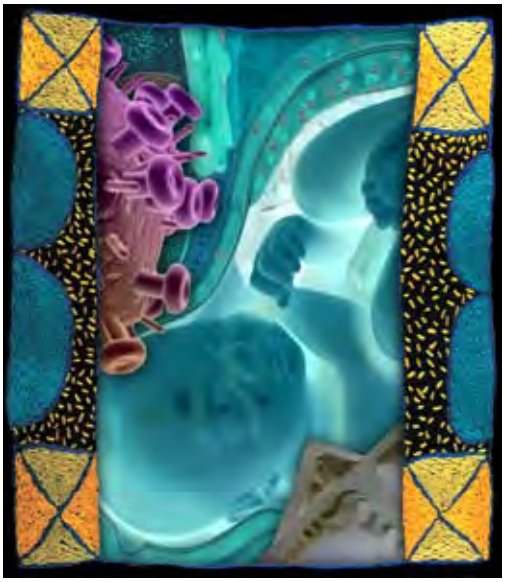

CONTENTS

Cover: *Across South and sub-Saharan Africa, the vast majority of HIV-positive individuals are adults of reproductive age. In the era of ART, HIV/AIDS has come to be viewed as a manageable chronic illness, and many HIV-infected women and men want to have children. The consensus guideline in this issue (p. 31) will help clinicians to identify patients' fertility desires and give safe and effective conception guidance.*

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FROM THE EDITOR

You may well be at the 5th South African AIDS conference in Durban as you read this! The conference promises to build on the resounding success of the previous four. In keeping with the mission of such conferences, the *Journal* continues to help you ensure not only fewer infections and longer lives but also better quality of life for your patients, both before and after commencement of antiretroviral therapy. This issue brings guidance on isoniazid prevention therapy in children and safer conception counselling and strategies for concordant and discordant couples. Guidance documents supported by the HIV Clinicians Society and published in this journal are the result of consensus among South African experts. Subjects are chosen that are considered areas of controversy or complexity or where clear evidence-based direction is lacking. Other topics covered include an overview of provider-initiated HIV testing and counselling. HIV testing has evolved since the onset of the era of successful treatment, and HIV testing is now less of a privacy issue and more of a health issue.

Nixon and colleagues remind us that rehabilitation and the rehabilitation sciences are important in HIV care. The co-epidemic of HPV in our population is resulting in a growing burden of cervical carcinoma in HIV-positive women, and Menon explores and discusses various cervical screening strategies in HIV-prevalent settings. Kirkcaldy and colleagues describe their original data from Mozambique on other sexually transmitted infections in HIV-infected women, and Abubakar and colleagues from Nigeria present a retrospective review of pericardial disease cases. Khan and colleagues remind us that TB can present in a range of tissues and organs in HIV, and describe a case of mammary TB. De Zoysa and colleagues from Sri Lanka present a patient with oesophageal carcinoma in whom oesophagectomy was performed.

This is the last issue of which I will be journal editor. I wish to thank all at HPMG for their extraordinary professionalism, the Clinicians Society staff, and Tammy, my PA who has held the fort through many a deadline.

I wish you all well as you continue to provide excellent HIV care, prevention, testing and management. May we in our lifetimes realise a southern African region in which not only AIDS but HIV is a receding threat.

LINDA-GAIL BEKKER
Editor

MESSAGE FROM THE EXECUTIVE

I hope you are reading this at the Durban AIDS Conference! The meeting is a major event on the conference circuit, and is jam-packed with exciting events, talks and seminars, as well as debates about everything from behaviour change to the responsibilities of donors. I'll be particularly interested in the sessions on the revamping of primary care in South Africa and on nurse-initiated ART (NiMART). We've made big gains in treatment, but we need to get more people into care and earlier, and for that to happen, we need all our primary care sites to be firing effectively.

For the unfortunates who can't be here, there's plenty more happening. The Annual Workshop in Advanced Clinical Care (AWAAC) will take place in Durban later this year (6 and 7 October 2011), co-ordinated by the Harvard academics, with local clinical experts Yunus Moosa and Henry Sunpath leading from the SA side. It's a hard-core conference for doctor and nurse clinicians, and the Society has managed to source some bursaries, so watch your e-mail and Transcripts for details.

FRANCOIS VENTER
President

OVERVIEW

PROVIDER-INITIATED COUNSELLING AND TESTING (PICT): AN OVERVIEW

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South Africa has the highest number of people living with HIV in the world. Despite this, many South Africans do not know their HIV status and uptake of voluntary counselling and testing (VCT) has been suboptimal. In clinical settings there are many missed opportunities for HIV diagnosis as most patients are not routinely offered HIV counselling and testing (HCT). Provider-initiated counselling and testing (PICT) has been introduced to ensure that HCT becomes the standard of care in all consultations with health providers. PICT promotes universal access to prevention, care and treatment services for all clients by increasing the utilisation and acceptance of HCT services.

This article outlines the rationale for PICT as well as providing an overview of the implementation protocol that will equip health care providers with the knowledge required to integrate HCT into routine medical care.

THE EPIDEMIOLOGY OF HIV

According to the World Health Organization (WHO), in 2007 more than 33 million people were living with HIV/AIDS with at least 2.7 million new infections being transmitted annually.[1] In a mid-term review of the National Strategic Plan 2007 - 2011, the Human Sciences Research Council reported that while the HIV epidemic in South Africa appears to have stabilised, a significant number of South Africans do not know their HIV status and testing is still primarily client initiated.[2] According to the South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2008, South Africa has an estimated national HIV prevalence of 10.6% (5.3 million people). Despite the availability of voluntary counselling and testing (VCT) services since 2000, many South Africans still do not know their HIV status. HIV-infected patients who consult their family practitioners are still being missed as opportunities to test are lost.

In 2007, the WHO made recommendations to introduce provider-initiated counselling and testing (PICT) in addition to client-initiated counselling and testing, also known as VCT, as an effective public health intervention to increase access to HIV counselling and testing (HCT) and reduce missed opportunities for testing.[3] With PICT the health care provider routinely offers and recommends an HIV test to all clients, irrespective of the medical diagnosis. The main objectives are to integrate HIV testing into routine medical care, thereby facilitating early diagnosis. By implementing PICT, family practitioners can not only learn the client's HIV status, allowing for appropriate clinical decisions to be made, but also enable all clients to know their status. Early diagnosis improves health outcomes of those who are HIV positive, while ensuring that they are provided with information to reduce transmission.

The recent HCT policy guidelines from the National Department of Health (NDoH)[4] emphasised the need to complement VCT through the implementation of PICT by all health care providers in both the public and private sectors. The overall goal of this strategy is to assist health care providers to expand access to HCT for their clients, thereby reducing the burden of disease in communities.

PICT AS A GATEWAY TO HIV PREVENTION, CARE, TREATMENT AND SUPPORT SERVICES

The availability of HIV rapid tests and same-day results has increased access to accurate, reliable and cost-effective diagnosis. HIV rapid tests allow medical practitioners to test their clients and provide results within a short space of time. The relationship between medical practitioners and their patients places them in an ideal situation to offer patient-centred care, allowing for better decisions to be made. For patients visiting medical practitioners, PICT is an important and effective model that forms part of the broader prevention strategy and acts as the gateway to accessing care, support and treatment services.

BEYOND VCT – DIFFERENCES BETWEEN PICT AND VCT

While there are many similarities between PICT and VCT, it is important for the medical practitioner to understand the differences between the two models (Table I).

SIMILARITIES BETWEEN PICT AND VCT

Both VCT and PICT are voluntary and require consent from the client. In both models testing is always performed in the client's best interests, in keeping with acceptable principles of medical ethics, and HIV results are always reported back to the client. In both models the client is supported to deal with the HIV test results. Counselling always precedes and follows testing.

BENEFITS OF PICT

Knowing the client's HIV status can have benefits for the individual concerned, the provider and the community. For HIV-negative people, knowing their status empowers them to protect themselves from becoming infected with HIV. It provides them with information on how to remain negative by assessing their own behaviour and providing solutions for behaviour change. For HIV-positive people, knowing their status ensures that they can be provided with the appropriate treatment, care and support services and assists them in living positively. Couples who know their HIV status are empowered to make safer choices with respect to sexual behaviour, e.g. condom use in discordant couples, implementation of positive living strategies, and accessing treatment for the prevention of mother-to-child transmission (PMTCT) of HIV.

PICT enables medical practitioners to treat their clients appropriately by identifying those who need treatment and/or wellness programmes early. This helps health care providers to improve the quality of medical care rendered to their clients and reduce morbidity and mortality.

PICT assists in reducing stigma in the community by making HIV testing the norm. It leads to the expansion of care and support services to deal with the demand for services.

PRINCIPLES OF PICT

PICT does not imply that people are coerced to test, nor does it constitute compulsory or mandatory testing. In implementing PICT medical practitioners should be guided by three principles, viz. consent, counselling and confidentiality, also known as the three Cs. Inappropriate use of PICT diminishes trust in health care providers and can lead to poor adherence to treatment and inadequate uptake of referrals.

INFORMED CONSENT

HIV testing by medical practitioners should only occur when the client or his or her legal surrogate, e.g. parent or guardian, has provided informed consent. The client must be provided with information that is understandable according to his or her language, disability and literacy. The client must also understand the nature of the test and its consequences and also understand the purpose of the exchange of information as being in the best interests of his or her own health, that of the partner, and in the case of a pregnant woman, the fetus or the infant being breastfed.

The PICT protocol

Implementing PICT in the medical practitioner's rooms has specific steps that need to be followed. The PICT protocol is set out in Fig. 1.

Health education

Education is aimed at providing basic information to clients on HIV and the PICT process. Education can be provided to an individual verbally and can be supported by other material, e.g. pamphlets and audiovisual tools. The client's right to refuse to be tested should be discussed. The content of health education should cover the following:

- the difference between HIV and AIDS
- how HIV is acquired and transmission
- HIV prevention measures and options for prevention, e.g. medical male circumcision, prevention with positives to prevent transmission to HIV negative partners, reduction in the number of concurrent sexual partners, correct regular condom use and PMTCT
- the advantages of testing and the importance of early diagnosis
- assurance that the process is confidential and of the right to privacy, and that only those directly involved in the person's care will be informed about their HIV status

TABLE I. DIFFERENCES BETWEEN PICT AND VCT

PICT	VCT
Individual is seeking medical care and HCT is recommended and performed by medical practitioner as part of the consultation	Individual chooses to seek HCT
Services provided are confidential and documented in medical record to ensure continuity of care	Anonymous or confidential services may be offered
Primary focus is on identifying HIV-infected people and linking them with prevention, care and treatment services	Primary focus is on preventing HIV acquisition through risk assessment, risk reduction and testing
Verbal consent is required and should be documented in the patient record	Written consent or thumb print for illiterate clients is required
First user of the test result is the health care worker to make a correct diagnosis and provide appropriate treatment	First user of the test result is the client, who uses the information to make personal life decisions

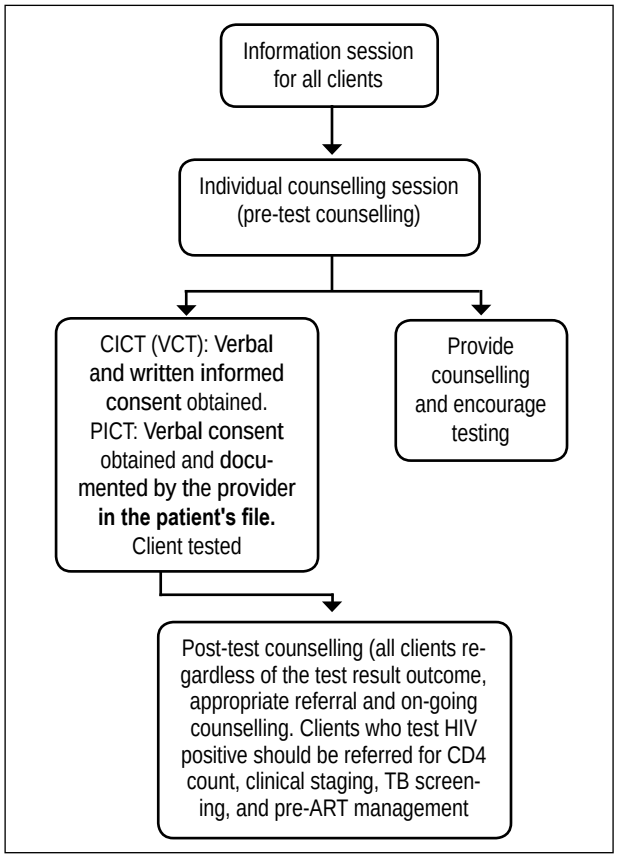

Fig. 1. The PICT protocol (source: HCT Policy Guidelines, 2010, NDoH[4]).

- the different types of rapid tests and the testing process
- understanding the results and that they are not an indication of the disease stage.

COUNSELLING

Pre-test counselling

Individual pre-test counselling must precede *all* HIV testing. For PICT a lengthy counselling session is *not* required, but the medical practitioner should be guided by the client's knowledge, needs or requests. Some of the key points in pretest counselling in adults are:

- assessing the client's understanding of information provided and reinforcing messages and concepts
- assisting the client to determine and assess their risk based on the information provided
- assessing the client's readiness for testing and possible results
- obtaining informed consent
- in the case of refusal, ascertaining reasons and responding to incorrect beliefs.

In addition to gauging whether the information that was given was understood, providers need to conduct a risk assessment with the client as part of the history taking. The aim is to assist the client to identify their own risk and the potential adverse events of their behaviour. A good risk assessment allows the family practitioner to

TABLE II. POST-TEST COUNSELLING

Positive	Negative

• Inform client of positive test result
• Explore client's understanding of results and their implications and supports client in adjusting to result, or refers client to on-site lay counsellor
• Inform client of need for HIV care, treatment, support and re-infection
• Advise client of need to get partner/s tested as partner/s may be negative
• Encourage disclosure to an at-risk third party; discuss to whom, when and how this will be done
• Offer tuberculosis questionnaire assessment and refers for investigation if necessary
• Perform WHO clinical staging
• Collect blood for CD4 count and make follow-up appointment for results
• Cervical screening (Pap smear) and pregnancy test for females
• Refer to appropriate support service as required
• Nutrition
• Psychosocial support
• For pregnant women, discuss:
  • plans for childbirth
  • the availability and use of antiretroviral drugs where indicated to prevent mother-to-child transmission
  • infant feeding options and support for the mother in implementing her infant feeding choice
  • HIV testing for the infant and the necessary follow-up
  • partner testing
• Record all information required in the client records
	• Inform the client of negative test result
	• Give client messages about prevention and how to remain negative, e.g. medical male circumcision, condom use, and reduction in the number of concurrent sexual partners
	• Guide client to develop a risk reduction and behaviour change plan
	• Advise client that partner needs to be tested
	• Offer tuberculosis questionnaire assessment and refer for investigation if necessary
	• Reinforce the need for annual testing
	• Make an appointment for retesting at 32 weeks for pregnant women
	• Refer client to nearby community-based resources for:
	  • partner testing
	  • window period retesting for people at risk of recent exposure
	  • additional prevention counselling

devise an individual risk reduction plan with the client. A risk assessment can be incorporated in the history taking and systemic enquiry about:[5]

- alcohol use
- drug use (especially intravenous drug use)
- domestic violence
- history of prison incarceration
- sexual history, including:
  - number of previous and current partners
  - history of unprotected high-risk sexual intercourse, anal and vaginal
  - rape or sexual assault
  - sexually transmitted infections.

Post-test counselling

All clients who have been tested should receive post-test counselling (Table II), irrespective of HIV results. The content of post-test counselling will be guided by the HIV test results.

Testing

HIV rapid tests are easy to perform with proper training. Results can be provided within 10 - 15 minutes during client consultation and are as reliable and accurate as enzyme immunoassays (EIA). All persons performing HIV rapid testing should follow a stipulated quality assurance programme to ensure accurate and reliable results. HIV testing should be conducted using the accepted national HIV testing algorithm using both a screening and a confirmatory test, as indicated in Fig. 2.

CONFIDENTIALITY AND DISCLOSURE

While HCT is a confidential process, clients should be encouraged to disclose their results to their sexual partners. The concept of shared confidentiality, i.e. that health care providers who contribute directly to the care of the person may have access to his or her results, should be discussed with the client. Medical practitioners may also offer to help clients to disclose to their partners. Medical practitioners should be cautioned against disclosing HIV results to third parties without either the client's written consent or a court order. Where any doubt exists about the appropriate course of action, medical practitioners should consult with senior colleagues for guidance.

Acknowledgements

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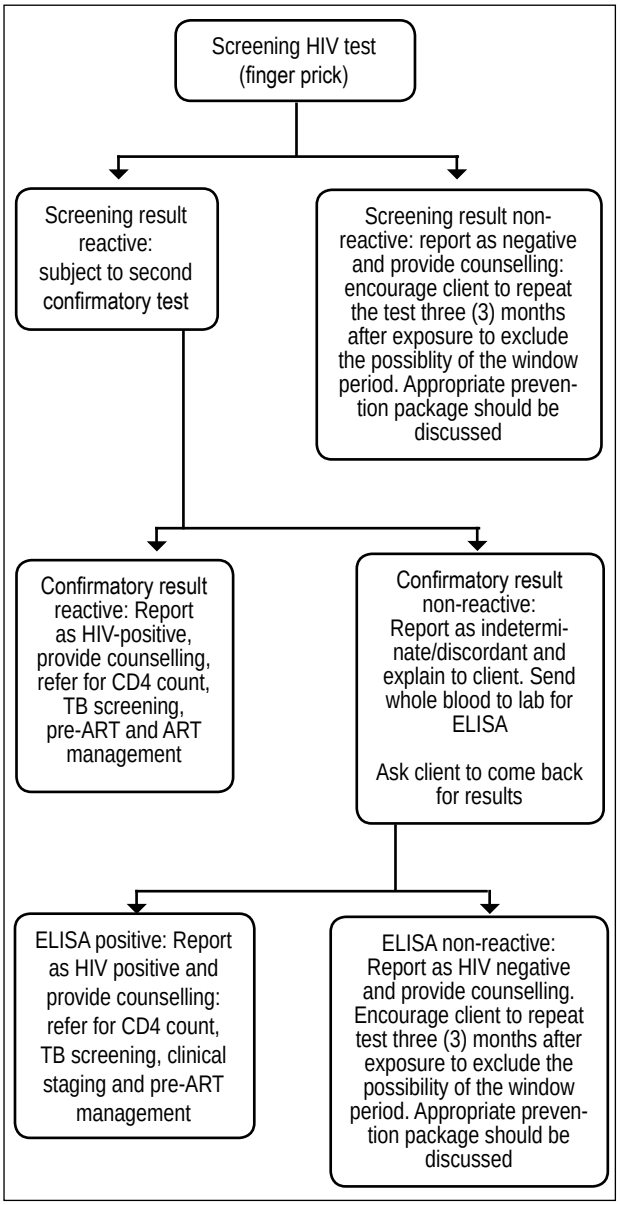

Fig. 2. National HIV testing algorithm (source: HCT Policy Guidelines, 2010, NDoH[4]).

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OPINION

REHABILITATION: A CRUCIAL COMPONENT IN THE FUTURE OF HIV CARE AND SUPPORT

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Provision of antiretroviral therapy (ART) is not an end in itself but a means to achieving improved wellness for people living with HIV. Rehabilitation, broadly defined, is another key contributor to wellness within this context. Understanding the potential for rehabilitation requires that one is able to consider HIV not only within a biomedical model that focuses on body systems, diagnoses and symptoms, but also within a rehabilitation framework that focuses on how these diagnoses and symptoms affect people's lives more broadly. Furthermore, rehabilitation is a human rights imperative, which deserves the energetic attention enjoyed by other aspects of HIV treatment and care. In particular, the United Nations Convention on the Rights of Persons with Disabilities (UNCRPD) is shining a long-overdue spotlight on the human rights imperatives associated with disability. For South Africa and other countries, proactively and meaningfully engaging rehabilitation in the HIV response will require major shifts on several fronts, including practice, education, policy and research. We argue that in settings where ART delivery is now widespread, HIV should be understood not only as a medical issue, but as a rehabilitation and disability concern. Whereas medicine adds years to life, it is rehabilitation that aims to add life to years.

THE LATE 1990s: THE BIRTH OF REHABILITATION IN THE CONTEXT OF HIV IN HIGH-INCOME COUNTRIES

Until 1995, an HIV diagnosis meant largely the same thing regardless of where one lived globally: people living with HIV typically experienced various HIV-related diseases that progressed steadily until death. In 1996, however, early forms of triple-combination antiretroviral therapy (ART) became available and life with HIV changed dramatically for people who could access and tolerate these medications – the vast majority of whom lived in high-income countries.

With the advent of ART, people with HIV began to live longer, which was a cause for great celebration.[1] However, the experience of living with HIV was not without continuing challenges. Along with their existing symptoms, many people living with HIV described an unexpected experience of disablement related to primary infection from HIV, HIV-related conditions, and side-effects of ART.[2,3] As their needs changed, so did the way that clinicians and advocates thought about HIV. In Canada, a key response came from the rehabilitation community.[4]

Rehabilitation as a field aims to help people address the life-related consequences of medical conditions. As such, an early response to the shift in experience brought about by the advent of ART was to reconceptualise HIV out of a biomedical model and into a rehabilitation framework.[5] In contrast to an exclusive biomedical focus on diagnoses, symptoms and medications, the World Health Organization's rehabilitation framework, the *International Classification of Disability, Functioning and Health* (ICF), served to refocus attention on the related 'impairments' (problems with body structure or function), 'activity limitations' (challenges at the level of the whole body) and 'participation restrictions' (challenges related to the person in her/his environment) associated with HIV.[6] Rehabilitation is broadly defined as any services, policies or other actions that respond to these challenges.

The reconceptualisation of HIV within a rehabilitation framework enabled people living with HIV and their advocates to articulate their experiences and needs differently.[7] This in turn encouraged health care providers to consider the rehabilitation care needs of their clients more comprehensively.[8] This reframing offered HIV researchers a strategy for measuring the prevalence of disability among people living with HIV, which was found to be strikingly high.[2,9] It also led researchers to explore novel dimensions of life with HIV in this new era, such as 'episodic disability'.[10-13] Finally, but not least, this re-orientation prompted policy-makers to meaningfully include rehabilitation and disability in their strategic responses to HIV.[14] Rehabilitation in the context of HIV is now well entrenched in the HIV response in Canada.[15]

THE LATE 2000s: THE REBIRTH OF REHABILITATION IN THE CONTEXT OF HIV IN LOW- AND MIDDLE-INCOME COUNTRIES

Since the mid-2000s, after years of dynamic activism to bridge profound inequities in treatment delivery, access to ART has at last begun to improve in many resource-poor countries with a high HIV prevalence.[16] ART is a crucially important advance in contributing to the health and well-being of people living with HIV. However, it has been hypothesised that the widespread scale-up of ART in sub-Saharan Africa will prompt experiences of disablement related to HIV, its secondary conditions and side-effects of medication, similar to those in Canada in the mid-1990s.[17,18] Indeed, the first studies exploring disablement among people living with HIV in southern Africa support this hypothesis: Myezwa, Van As and colleagues used the WHO-ICF framework to reveal a high level of disablement among 80 people living with HIV who were hospital inpatients,[19] as well as 45 clinic outpatients in South Africa.[20]

In addition to formal evidence, rehabilitation providers on the ground are witnessing the disabling effects of HIV and the medications used to treat it. For example, Handicap International, an international NGO that supports the development of rehabilitation services in 13 African countries, reports that their rehabilitation programmes in Kenya, Ethiopia and Mozambique are increasingly witnessing the arrival of people living with HIV seeking rehabilitation services. Similarly, the South African Disability Alliance in co-operation with the South African National AIDS Council identified that people living with HIV are at increased risk for developing disability.[21] Furthermore, a recent research meeting in KwaZulu-Natal identified the disabling effects of HIV as a priority.[22] We argue that this is the beginning of a trend that will see rehabilitation become a key component of HIV care. For South Africa and other countries, proactively engaging rehabilitation in the HIV response will require major shifts on several fronts.

ADVANCING OUR PRACTICE AND EDUCATION

Provision of ART is not an end in itself, but rather a means to achieve improved wellness for people living with HIV. Rehabilitation, broadly defined, is another key contributor to wellness within this context. Understanding and engaging rehabilitation requires that one is able to consider HIV not only within a biomedical model that focuses on body systems, diagnoses and symptoms, but also within a rehabilitation framework that refocuses on how physical and mental health diagnoses and symptoms affect people's lives. The World Health Organization's ICF contributed importantly to a paradigm shift in Canada. The ICF is also a leading rehabilitation framework in the global South that has much to offer HIV. Reconceptualising HIV through a rehabilitation lens highlights opportunities for enhanced HIV practice and education relevant for at least three broad populations.

First, people and organisations who provide HIV health services should come to understand the role of rehabilitation within the continuum of care. This is particularly true for HIV care providers who, as the point of contact with people living with HIV, are uniquely situated to provide referrals to rehabilitation services. HIV providers must be trained to understand the impairments, activity limitations and participation restrictions that can arise from HIV-related conditions, and the options available within the world of rehabilitation to address these concerns.

Second, we call on the rehabilitation and disability communities to recognise their role in responding to the needs of people living with HIV and their communities, including physiotherapists, occupational therapists, speech-language therapists, audiologists, prosthetics and orthotics specialists and the wide range of other rehabilitation providers for people living with HIV. However, education on the role of rehabilitation for people living with HIV also needs to reach community-based workers, health volunteers and community leaders, as these front-line workers are frequently the information links for people in need of rehabilitation. Shortages of all forms of health human resources demand a different approach to rehabilitation delivery to that in the North. However, existing models of community-based rehabilitation have been driving service delivery for decades and have a range of similarities with HIV home-based care. Overburdened health systems require that, like all aspects of the HIV response, we must seek synergies for providing rehabilitation within the broader health system, rather than implementing services within a purely vertical response.

Third, and arguably most importantly, is for people living with HIV and their advocacy partners to recognise the robust role that rehabilitation can play in the future of the HIV response and to include calls for action from stakeholders. Historically, it has been people living with HIV who were most effective at prompting change. Rehabilitation in the context of HIV needs to be recognised as a new target for advocacy and lobbying, which points to change at the policy level.

ADVANCING OUR POLICIES

Rehabilitation is a human rights imperative and therefore deserves the kind of energetic attention enjoyed by other aspects of HIV treatment and care. One major advantage for the rehabilitation response in this new era of ART scale-up is the recent passing of the United Nations

Convention on the Rights of Persons with Disabilities (UNCRPD), which is shining a long-overdue spotlight on issues of disability. The Convention requires states to recognise that where people living with HIV have impairments which, in interaction with the environment, result in stigma, discrimination or other barriers to their participation, they fall under the protection of the Convention.[23]

The South African government is an instructive example insofar as it is bound by the human rights imperative to rehabilitate under international and national law. South Africa has ratified the UNCRPD, which recognises people's right to habilitation and rehabilitation. This requires the state to take steps to allow people with disabilities to achieve maximum independence, full physical, mental, social and vocational ability, and full inclusion and participation in all aspects of life, including through comprehensive habilitation and rehabilitation services and programmes, particularly in the areas of health (article 26). This duty is reinforced in the prohibition of unfair discrimination on the grounds of disability in the South African Constitution (section 9.3), and within related protections contained in subsidiary legislation and policy, including the Social Assistance Act of 2004, the Employment Equity Act of 1998, and the Integrated National Disability Strategy of 1997.

As such, we need to ensure that recognition of rehabilitation and disability are reflected in national strategic plans for HIV and other health policy instruments.[24] Importantly, South Africa's 2007 - 2011 National Strategic Plan (NSP) introduced a disability sector plan in 2009.[25] Under the goal of mitigating the impact of HIV and AIDS, the NSP describes the need to improve treatment, care and support for people with disabilities. However, little guidance is given for addressing the disabling effects of HIV. Furthermore, roles for rehabilitation are not explicitly described, although dimensions of rehabilitation are considered, such as goal 6, which focuses on enabling people living with HIV to lead healthy and productive lives.[26,27]

Rehabilitation, therefore, is vital in terms of human rights, health outcomes and quality of life and needs to be integrated into HIV plans. Ushering in change will require 'double mainstreaming' insofar as national and provincial HIV offices will need to be aware of the rehabilitation needs of people living with HIV, and rehabilitation/disability-related authorities need to be made aware of their role in supporting people living with HIV.

ADVANCING OUR RESEARCH

Like all dimensions of the health response to HIV, evidence is required to inform effectiveness, efficiency and acceptability of potential interventions. The same is true of rehabilitation and its role as part of the HIV care continuum. This is an untapped research landscape; several examples can illustrate the potential within this field. First, good research drives not only practice but policy development and the wise distribution of scarce resources. We need to engage in research on the African continent that explores rehabilitative care as a cost-effective means of improving autonomy and quality of life for all people living with disability, including people living with HIV. Second, it is not known how the concept of episodic disability, which has been a cornerstone of the response in Canada, might play out in the context of hyper-epidemics in sub-Saharan Africa. Third, the ICF concept of participation squarely engages issues of stigma and discrimination, providing a bridge between rehabilitation researchers and those working in other anti-stigma paradigms. One final illustrative example involves forecasting models of human resource needs in rehabilitation based on increased access to ART, given the expected rise in demand.

CONCLUSION

Provision of treatment has necessarily been the central focus of HIV care in recent years. However, many countries including South Africa are now at the point of identifying and grappling with new questions related to HIV care, treatment and support in this new era of ART – a scenario that is reminiscent of the experience in Canada and other resource-rich countries in the late 1990s. While we must pay close attention to the differences between the two scenarios and the contexts in which they are based, we must also seek reciprocal lessons based on similarities. Importantly, we must understand HIV not only as a medical issue, but also as a rehabilitation and disability concern in settings where ART delivery is now widespread. Indeed, whereas medicine adds years to life, it is rehabilitation that aims to add life to years.

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OPINION

CERVICAL CANCER PREVENTION IN SETTINGS OF HIGH HIV PREVALENCE

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Despite being a preventable disease, cervical cancer is still the second most common cancer in women worldwide. HIV infection is associated with a higher incidence, more rapid progression, and increased recurrence rates of human papillomavirus (HPV)-associated cervical intra-epithelial neoplasia and invasive cancer. The disease burden in developing countries is the result of inadequate national health care infrastructures that cannot establish or sustain comprehensive screening programmes, together with a high prevalence of HIV infection, particularly in southern Africa. In this article, clinically relevant issues for primary prevention of cervical lesions by a quadrivalent HPV vaccine and the 'screen-and-treat' protocol in settings of high HIV prevalence will be explored.

HIV AND HPV CO-INFECTION

HIV is believed to increase the risk of HPV infection and cervical neoplasia, in part due to HIV-induced immunodeficiency and the resulting inability to control HPV infection.[1,2] HIV status, herpes zoster, oral candidiasis and tuberculosis have all been found to be associated with carcinogenic human papillomavirus (HPV), consistent with other studies that found HIV and HIV-associated immunosuppression to be independently associated with HPV positivity.[3]

Although it has been recognised that HIV plays a significant role in increasing the risk of persistent/latent HPV infection and/or rates of progression of precancerous lesions to high-grade cervical neoplasia and cancer, several key variables remain to be elucidated. These include a better understanding of the role of HPV viral load in the genesis of cervical neoplasia in HIV-infected women, and the relationship between early initiation of HAART and the possible inadvertent result of an increased risk of the acquisition of molecular changes characteristic of carcinoma *in situ*.

In contrast to a very small subset of the many immunocompetent women infected with oncogenic types of HPV who develop cervical cancer, women infected with HIV are thought to be 3 - 5 times more likely to develop cervical lesions that can become cancerous.[4] Both pre-invasive disease and invasive cervical cancer have been reported to have a much poorer outcome in HIV-infected women than in the general population.[5]

Similar to cervical disease progression, recurrent disease after treatment is correlated with low CD4 cell counts.[6] Although at least seven studies have examined the effects of highly active antiretroviral therapy (HAART) on the course of cervical lesions, it is still not clear whether HAART substantially affects the natural history of cervical squamous intra-epithelial lesions (SIL). The impact of HAART has led to some improved resolution of abnormal Pap smears, but has not made a significant impact on the risk of cervical cancer in HIV-infected women.[7] This may be because administration of HAART is most often offered to women with more advanced HIV disease status and higher HPV viral loads. HAART also prolongs survival in women with cervical pre-invasive lesions.[8]

In this article, it will be argued that while a 'one-visit-in-a-lifetime' strategy with immediate cryotherapy or the loop electrosurgical excision procedure (LEEP) as part of the minimum package for the high-risk age group of women between 35 and 50 years may have an impact in resource-poor settings, this protocol in areas of high HIV prevalence may not take into account the high rates of recurrence and cervical disease progression associated with low CD4 cell counts. Secondly, it will be explored how a HPV DNA-based screening programme in high HIV prevalence areas may result in overtreatment because of its low specificity. Finally, it will be argued why a vaccine-based cervical cancer prevention programme may not be sufficient to reduce cervical cancer in southern Africa.

DISCUSSION

SCREEN-AND-TREAT PROTOCOL IN SETTINGS WITH HIGH PREVALENCES OF HIV AND GENITAL ULCERATION

In developing countries, inadequate screening programmes have contributed to high incidences of cervical cancer. While in developed countries the introduction of large-scale cytological testing has resulted in a major decline in cervical cancer mortality, in low-resource settings the high specificity of cytological testing is offset by its lack of sensitivity for detection of precursors of invasive cervical cancer (ranging from 30% to 90%) and highly dependent on adequacy of sample collection, slide preparation and slide interpretation.

As part of an efficient cervical prevention programme, alternatives to cervical cytology have been sought but have not met a high level of specificity. Several recent

studies have demonstrated that direct visual inspection of the cervix with acetic acid (VIA) is a reasonably sensitive and a cost-effective alternative to cytological screening.[9] With a sensitivity of 76% in HIV-positive women, VIA is also a useful screening test for pre-invasive lesions of the cervix in low-resource settings.[10] However, the high prevalence of sexually transmitted infection (STI)-related genital ulcers in the African countries worst affected with HIV may lead to a relatively low specificity of VIA.[11]

HPV DNA testing has emerged as a convincing option for cervical cancer screening. A large study in India in 1999 on healthy women aged between 30 and 59 years found that a programme strategy based on a single round of HPV testing was associated with a 50% reduction in cervical cancer incidence and mortality, whereas strategies based on a single round of VIA or Pap screening had little, if any, effect on these outcomes.[12] It was recommended that since most HPV infections in young women regress rapidly without causing clinically significant disease, a single HPV testing round would be associated with a significant reduction in the numbers of advanced cervical cancers and death from cervical cancer if targeted at women aged over 30 years.[12]

A randomised controlled trial in South Africa in 2000 - 2002 led to recommendations that both VIA and HPV-based screening and immediate cryotherapy treatment were safe and decreased the prevalence of high-grade cervical cancer precursor lesions.[13] Several studies have been undertaken in low-resource settings to assess the optimal age group for cervical cancer screening to achieve the greatest public health impact. A cost-effectiveness modelling exercise comparing screening strategies in five developing countries predicted that for 35-year-old women screened only once in their lives, a 1 - 2-visit approach with the VIA method could reduce the lifetime risk of cervical cancer by 25%, and HPV DNA testing could reduce it by 36%.[14]

Although these recommendations may be effective in HIV-negative women, in whom there is the possibility of spontaneous regression of pre-invasive lesions because of their normally functioning immune systems, certain issues would need to be explored in resource-poor settings with a high prevalence of HIV.

HIV-positive women have high rates of SIL and concurrent HPV infections with a variety of genotypes in which the oncogenic risk is poorly documented. A high diversity of HPV genotypes was observed in HIV-infected women in Brazil. Many of these women infected with HPV were found to carry oncogenic genotypes, even when cytological evaluation showed normal results.[15]

Although HPV testing of cervical smears is more sensitive than cytological assessment, the specificity of HPV DNA testing may be unacceptably low in areas of high HIV prevalence. In one study, the specificity of HPV DNA testing for detection of high-grade squamous intra-epithelial lesions (HSIL) was 75% in HIV-seronegative women and 41% in HIV-seropositive women.[16]

In HIV-positive women, rapid progression of HPV may reduce the age at which women are 'at high risk'. In a study to determine the effect of the HIV epidemic on invasive cervical cancer in Kenya, HIV-positive women who presented with cervical cancer were found to be significantly younger than HIV-negative women.[17] These findings imply that screening of 35-year-old women only once in their lives may not reduce the lifetime risk of cervical cancer in a high HIV prevalence setting.

In Zambia, where the prevalence of HIV infection is one of the highest in the world and the incidence of cervical cancer the highest in sub-Saharan Africa,[18] it was found that in a resource-constrained environment it would be feasible to implement a system of referral of cryotherapy-ineligible patients for LEEP in a 'screen-and-treat' cervical cancer prevention programme targeting HIV-infected women.[19] A study conducted in Thailand between 2004 and 2008 demonstrated that HIV infection was not significantly associated with LEEP complications.[20]

PROPHYLAXIS-BASED SECONDARY CERVICAL CANCER PREVENTION PROGRAMME

Settings of high HIV prevalence such as Rakia, Uganda, where almost 50% of HIV-positive women are infected with strains of HPV that are associated with a risk of cervical cancer,[21] would stand to benefit most from a prophylaxis-based (vaccine) cervical cancer prevention programme aimed at HPV-naïve women.

A robust surveillance system capable of monitoring long-term safety, sustained immune responses, vaccine efficacy, and the epidemiological distribution of HPV oncogenic strains also encountered in HIV-positive women would be needed. Although the quadrivalent HPV vaccine against HPV 6, 11, 16 and 18 constitutes an important breakthrough in cervical cancer control in HIV-negative women in the developed world, the limited epidemiological data available suggest that a much wider variety of HPV types are involved in the pathogenesis of cervical neoplasia in developing countries.[22] Also, HIV-infected women in various geographical regions, such as Zambia, Brazil and Rochester, NY, appear to be infected with less prevalent types of HPV compared with the general population.[23]

Evidence suggests that different HPV types behave as independent infections, with no cross-reactive cell-mediated immunity that might potentially be able to keep the oncogenic non-vaccine types under control. In 2009 a double-blind randomised study in young women indicated that the immune response stimulated by HPV 16 and 18 may also confer individual cross-protection against genetically related HPV oncogenic types, such as HPV 31, 33 and 45.[24] Monitoring would be necessary to see whether individual cross-protection could extend some protection to HIV-infected women in sub-Saharan Africa, and whether the Af variants of HPV 16 and 18 common in women of African descent[25] impact on the effectiveness of the HPV 16 and 18 vaccine and on individual cross-protection.

CONCLUSION

This paper has explored issues regarding screening for cervical cancer in settings with a high prevalence of HIV and genital ulceration. While the new HPV test has proved to be a successful cancer screening tool in detecting 14 high-risk types of carcinogenic HPV with 90% accuracy when tested on a group of local women in Eastern China,[26] its effectiveness will also need to be assessed in a high HIV prevalence setting to ascertain its specificity and sensitivity in HIV-positive women.

Although in Zambia piggybacking on established HIV infrastructure has optimised resources and increased the efficiency of both HIV and cervical cancer programmes,[27] the once-in-a-lifetime screen-and-treat protocol focusing on women between 30 and 45 years of age recommended for sub-Saharan Africa may not adequately take into account what is already known about the epidemiology of HIV-HPV co-infection. Longer follow-up will be needed to assess the efficacy, cost-effectiveness and safety of VIA with same-visit treatment with LEEP in HIV-positive women.

It is important to keep in mind that the prophylaxis prevention programme would be implemented in a setting where malnutrition and decreased immunity due to HIV/AIDS result in far less spontaneous regression of cervical lesions than would be seen in industrialised countries. This fact underscores the need for prevailing strains to be fully characterised and linkage to be established between vaccination history, screening history and HPV exposure.

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ORIGINAL ARTICLE

BACTERIAL VAGINOSIS, ALTERATIONS IN VAGINAL FLORA AND HIV GENITAL SHEDDING AMONG HIV-1-INFECTED WOMEN IN MOZAMBIQUE

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Objectives. We investigated whether abnormal vaginal flora, including bacterial vaginosis (BV), are associated with detection of cervical HIV-1 RNA among HIV-infected women in Mozambique.

Methods. We obtained clinical data and vaginal specimens from HIV-infected women registering for their first visit at one of two HIV care clinics in Mozambique. We compared women with detectable cervical HIV viral load (≥40 copies/ml) with women with undetectable cervical HIV.

Results. We enrolled 106 women. Women with abnormal vaginal flora (intermediate Nugent scores, 4 - 6) were more likely to have detectable cervical HIV RNA than women with normal vaginal flora (adjusted odds ratio 7.2 (95% confidence interval 1.8 - 29.1), adjusted for CD4 count). Women with BV had a non-significantly higher likelihood of detectable cervical HIV than women with normal flora.

Conclusions. Abnormal vaginal flora were significantly associated with cervical HIV expression. Further research is needed to confirm this relationship.

HIV genital shedding enhances HIV transmission to sexual partners.[1] We investigated whether abnormal vaginal flora, including bacterial vaginosis (BV), are associated with cervical HIV-1 RNA expression among HIV-infected women in Mozambique.

METHODS

Women were enrolled from October 2007 to March 2008 as part of an evaluation of reproductive tract infections among HIV-infected individuals registering for a first visit at one of two HIV care clinics in Mozambique: Xai Xai Provincial Hospital and Mavalane General Hospital.[2] We collected demographic and clinical data, and plasma and vaginal specimens. Cervical lavage specimens were obtained by application of 10 ml of sterile saline to the cervix and collection from the posterior fornix after 3 minutes. Diagnosis of BV was based on Nugent's criteria. Diagnoses of *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Mycoplasma genitalium* were done by real-time multiplex polymerase chain reaction testing. HIV RNA levels were determined by nucleic acid sequence-based amplification assay, with a lower limit of detection of 40 copies/ml. Patients were treated according to the 2006 Mozambique Ministry of Health treatment guidelines and offered partner notification cards. The evaluation protocol, consent form and questionnaires were approved by Mozambique's National Health Bioethics Committee and the CDC Institutional Review Board.

Data were analysed using SAS version 9.2 (SAS Institute, Cary, NC). Nugent scores were categorised as normal (0 - 3), intermediate vaginal flora (4 - 6) and BV (7 - 10). Cervical HIV RNA was dichotomised as detectable (≥40 copies/ml) or undetectable. Women with detectable cervical HIV were compared with women without detectable cervical HIV by the chi-square or Fisher's exact test for categorical variables, and the

t-test for continuous variables. We used multivariable logistic regression models to test whether abnormal vaginal flora (intermediate vaginal flora or BV) were associated with detectable cervical HIV RNA. Plasma viral load, CD4 count, trichomoniasis and age were considered for inclusion; variables were excluded if they were not significant ($p \geq 0.05$) or disrupted the model's goodness of fit (e.g. CD4 count was included in the final model and plasma viral load was not). Missing data were excluded from the analyses.

RESULTS

Of 258 women enrolled in the larger study, 106 agreed to have cervical lavage specimens collected; there were no significant differences between women who agreed and did not agree to cervical lavage. The mean age of the 106 participating women was 33 years and most of them were from Xai Xai (Table I). None of the women was receiving antiretroviral therapy.

Lower CD4 counts ($p=0.01$) and abnormal vaginal flora ($p=0.04$) were associated with cervical HIV RNA detection (Table I). In multivariable logistic regression modelling, women with intermediate vaginal flora had higher odds of detectable cervical HIV RNA than women with normal vaginal flora (adjusted odds ratio (aOR) 7.2 (95% confidence interval (CI) 1.8 - 29.1), adjusted for CD4 count). Women with BV had non-significantly higher odds of detectable cervical HIV RNA compared with women with normal vaginal flora (aOR 2.7 (95% CI

TABLE I. CHARACTERISTICS OF ENROLLED WOMEN AND ASSOCIATION WITH DETECTION OF CERVICAL HIV RNA

		Detection of cervical HIV RNA		
	N	Yes (*N* (%))	No (*N* (%))	*p*
Total	106	75 (71)	31 (29)	--
Study site (*N*=106)				
Xai Xai	70	48 (69)	22 (31)	0.49
Maputo	36	27 (75)	9 (25)	
Education (*N*=84)				
No education	2	1 (50)	1 (50)	0.51
Primary	66	45 (68)	21 (32)	
Secondary or mid-level	16	10 (63)	6 (37)	
Marital status (*N*=81)				
Single	38	24 (63)	14 (37)	0.93
Unmarried, in relationship	32	22 (69)	10 (31)	
Married	2	1 (50)	1 (50)	
Widowed	9	6 (67)	3 (33)	
Prior antiretroviral therapy (*N*=84)				
Yes	1	0 (0)	1 (100)	0.15
No	83	56 (67)	27 (33)	
CD4 count (cells/µl) (*N*=106)				
<50	14	12 (86)	2 (14)	0.01
50 - 199	31	25 (81)	6 (19)	
200 - 349	26	21 (81)	5 (19)	
≥350	35	17 (49)	18 (51)	
HIV-1 plasma viral load (copies/ml) (*N*=76)				
<10 000	12	5 (42)	7 (58)	0.06
10 000 - 99 999	31	24 (77)	7 (23)	
≥100 000	33	24 (73)	9 (27)	
Abnormal vaginal flora categories* (*N*=106)				
Bacterial vaginosis	47	32 (68)	15 (32)	0.04
Intermediate vaginal flora	34	29 (85)	5 (15)	
Normal vaginal flora	25	14 (56)	11 (44)	
Mycoplasma genitalium† (*N*=103)				
Positive	14	9 (64)	5 (36)	0.62
Negative	89	63 (71)	26 (29)	
Trichomonas vaginalis† (*N*=103)				
Positive	54	41 (76)	13 (24)	0.16
Negative	49	31 (63)	18 (37)	
Chlamydia trachomatis† (*N*=103)				
Positive	1	1 (100)	0 (0)	0.51
Negative	102	71 (70)	31 (30)	
Neisseria gonorrhoeae† (*N*=103)				
Positive	1	1 (100)	0 (0)	0.51
Negative	102	71 (70)	31 (30)	

*Diagnosed by Nugent's criteria (normal 0 - 3, intermediate 4 - 6, bacterial vaginosis 7 - 10).

†Diagnosed by polymerase chain reaction of vaginal specimens.

0.8 - 8.7), adjusted for CD4 count). Mean Nugent scores of women with detectable cervical HIV were comparable to those of women without detectable cervical HIV (5.7 v. 5.3, *p*=0.64).

Compared with women with plasma viral loads of ≥100 000 copies/ml, women with plasma viral loads of <10 000 copies/ml more often had abnormal vaginal flora (58% v. 21%, *p*=0.049). On stratified analysis, there was a non-significant trend towards higher plasma viral load and cervical HIV RNA detection among women with normal Nugent's scores or BV, yet there was no association between plasma viral load and cervical HIV among women with intermediate vaginal flora.

CONCLUSIONS

We found positive associations between intermediate vaginal flora and BV and detection of cervical HIV RNA among HIV-infected women in Mozambique, suggesting that abnormal vaginal flora might enhance HIV genital viral shedding. Previously published work demonstrated associations between the presence of BV and detection of cervical HIV RNA,[3,4] possibly because of immune activation.[5] It was surprising that although intermediate vaginal flora were significantly associated with genital HIV expression, BV was not. It is possible that intermediate vaginal flora are more conducive to HIV viral shedding than BV, yet the explanatory mechanism is unclear. It is also possible that our study lacked adequate power to detect a significant association between BV and detectable cervical HIV due to a small sample size: this may be reflected in the wide confidence intervals. Limitations include that we did not control for menstrual cycle timing, contraceptive use, possible semen contamination of cervical specimens and herpes simplex viral infection, and cold-chain interruptions may have occurred. We did not find a clear overall association between plasma HIV viral load and cervical HIV expression, although the association may have been confounded by the presence of abnormal vaginal flora. Despite these limitations, these data suggest that abnormal vaginal flora might enhance HIV genital shedding and thus potentially enhance HIV transmission to sexual partners. Further research is needed to confirm this association.

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ORIGINAL ARTICLE

PATTERN OF PERICARDIAL DISEASES IN HIV-POSITIVE PATIENTS AT UNIVERSITY COLLEGE HOSPITAL, IBADAN, NIGERIA

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Rationale. Pericarditis has been reported as the most common cardiac complication of HIV disease, followed by pericardial effusion.

Methods. A retrospective review was conducted of all 68 patients treated for pericardial diseases between August 2003 and July 2008 at University College Hospital, Ibadan, Nigeria. HIV-positive patients (*N*=42) were compared with those who were HIV negative (*N*=26).

Results. More male than female patients presented with pericardial disease, and the HIV-positive patients were younger than those who were HIV negative. Pericardial effusion was the commonest mode of presentation, accounting for 20 HIV-positive patients (47.7%) and 13 HIV-negative patients (50%). Pericardiostomy was the commonest surgical intervention performed in HIV-positive patients (*N*=15), while the majority of HIV-negative patients had pericardiocentesis.

Conclusion. Pericardial effusion was the commonest cardiac presentation in HIV-positive patients in our setting. We recommend that patients with pericardial effusion be investigated for HIV infection.

Previous reports have described cardiac involvement in 28 - 73% of patients with HIV infection. This includes pericardial effusion, pulmonary hypertension and heart failure, infective endocarditis, tumours, myocarditis and left ventricular dysfunction.[1] The association between pericardial diseases and AIDS has been well documented.[2]

Of interest is the observation that the incidence of AIDS-related diseases found at autopsy studies is significantly higher than the incidence of abnormalities diagnosed clinically. It is therefore possible that many AIDS patients have cardiac abnormalities that are not recognised during the course of their illness.[3]

The number of HIV-positive patients with pericardial diseases has been reported to be increasing in Africa.[4] Pericarditis was reported to be the most common cardiac complication of HIV infection, followed by pericardial effusion.[5]

METHODS

We reviewed the records of all patients treated for pericardial diseases between August 2003 and July 2008 at University College Hospital, Ibadan, Nigeria. Data were obtained from medical, ward and theatre records. Demographic data, causes of pericardial diseases, treatment offered and outcome were recorded. Pericardial effusion was categorised into mild (<2 cm) and severe (>2 cm), based on echocardiographic evaluation of thickness. Comparisons were made between the HIV-positive and HIV-negative groups. The chi-square test was used to compare the two groups.

RESULTS

The total number of patients treated for pericardial diseases during the period under review was 68; 42 were HIV positive and 26 HIV negative. The mean age of the HIV-positive patients was 30 years and that of the HIV-negative patients 53 years (p=0.05). HIV-positive patients were three times more likely to be male and HIV-negative patients twice as likely. Diagnoses and the causations of pericardial disease in the two groups are set out in Tables I and II, respectively. Large effusions were seen in 80% of HIV-positive patients, but only 15% were categorised as large in the HIV-negative group (Table III). The treatment offered to the patients is shown in Table IV. Pericardiostomy was performed in 15 of the HIV-positive patients and 4 of the HIV-negative patients. Four of the HIV-positive patients and 1 HIV-negative patient died. Among the HIV-positive patients, 2 died after pericardiectomy, 1 following a complication of tube pericardiostomy, and 1 while being prepared for surgery because he was haemodynamically unstable.

TABLE I. DIAGNOSES IN 68 PATIENTS WITH PERICARDIAL DISEASE

Diagnosis	HIV positive	HIV negative
Pericardial effusion	20 (47.6%)	13 (50%)
Constrictive pericarditis	12 (28.6%)	7 (26.9%)
Effusive constrictive pericarditis	6 (14.3%)	2 (7.7%)
Pericarditis	4 (9.5%)	4 (15.4%)
Total	42	26

TABLE II. CAUSES OF PERICARDIAL DISEASE

Diagnosis	HIV positive	HIV negative
Tuberculosis	17 (40.5%)	10 (38.5%)
Malignant disease	7 (16.7%)	4 (15.4%)
Chronic inflammation	6 (14.3%)	10 (38.5%)
Unknown	12 (28.6%)	2 (7.7%)
Total	42	26

TABLE III. PERICARDIAL EFFUSION

	HIV positive	HIV negative
Large effusion*	16 (80%)	2 (15.4%)
Small effusion**	2 (10%)	8 (61.5%)
No report***	2 (10%)	3 (23.1%)
Total	20	13

Statistical significance was defined as $p<0.05$.
*$p<0.01$.
**$p<0.05$.
***$p<0.10$.

TABLE IV. TREATMENT OF PERICARDIAL DISEASE

Treatment	HIV positive	HIV negative
Pericardiostomy	15 (37.5%)	6 (23.1%)
Pericardiocentesis	6 (14.3%)	8 (30.8%)
Pericardiectomy	14 (33.4%)	8 (30.8%)
Nil	7 (16.7%)	4 (15.4%)
Total	42	26

DISCUSSION

The incidence of cardiac manifestations in the course of AIDS is increasing, although these manifestations are not often diagnosed clinically. Myocarditis and pericardial diseases have been reported to be the commonest HIV-related cardiac abnormalities.[6] The association of pericardial diseases and AIDS has been well documented.[1] Pericardial effusion was the commonest mode of presentation in our patients, which is in keeping with other studies.[7] Our study showed that HIV-positive patients were younger than HIV-negative patients. This has also been documented by Kwan *et al.*[8] The majority of our HIV-positive patients had large effusions, and pericardiostomy was therefore the commonest procedure performed in this group. Effusions in HIV-negative patients were small and were mainly drained by pericardiocentesis. This is in keeping with the findings of other studies.[9] Pleural effusion was associated with pericardial effusion, mainly in HIV-positive patients. This association has also been reported by Kaplan *et al.*,[10] and it may be related to the large size of the pericardial effusions. Other studies have reported pericarditis as the commonest pericardial condition.[11-14] Tuberculosis was the commonest cause of pericardial disease in our patients. The association of tuberculosis and HIV infection has been described,[9] although some reports suggest that tuberculosis is less common than opportunistic infections and neoplasms as a cause of pericardial disease.[5] Of the patients in our study, 7 had malignant pericardial disease (16.7% of HIV-positive patients). Most series have reported Kaposi's sarcoma to be the commonest malignancy in HIV patients, mainly as a result of the documented association between this malignancy and HIV infection.[15] Purulent pericarditis was noted in the majority of HIV-negative patients. This has previously been reported from our centre.[16]

Of the HIV-positive patients in our study, 4 (9.5%) died. Mayosi *et al.* reported a higher mortality rate (26%), and found mortality to be highest in those with clinical AIDS or who were haemodynamically unstable.[10]

CONCLUSION

Although not commonly looked for clinically, cardiac involvement in HIV-positive patients is a reality, with pericardial effusion being the commonest mode of presentation in our environment. We advocate that patients with pericardial effusion be investigated for HIV infection, and likewise that all HIV-infected individuals should undergo periodic cardiac evaluation, including echocardiography, in order to identify sub-clinical pericardial and cardiac diseases.

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GUIDELINE

INH PREVENTIVE THERAPY (IPT) IN HIV-INFECTED SOUTH AFRICAN CHILDREN

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HIV-infected children have a high risk of acquiring tuberculosis. The World Health Organization (WHO) has released isoniazid preventive therapy (IPT) recommendations for adults and children living with HIV, based on efficacy studies, mainly in adults. Data from children appear conflicting. IPT guidelines for children were developed in response to WHO guidelines at a local meeting, followed by discussions.

IPT should be given to all HIV-infected children after exposure to a source case if treatment for active disease is not required. For children whose mothers' HIV status was known antentally, when tuberculosis has been actively excluded in mothers and at infant follow-up, and when infants have commenced antiretroviral therapy in the first 3 months of life, IPT is not required. Otherwise, all infants and children should be given IPT for 6 months once active tuberculosis has been excluded.

HIV-infected children are at high risk of contracting tuberculosis (TB). An incidence of 24 cases per 100 HIV-infected children per year was documented in Cape Town during a period of limited access to antiretroviral therapy (ART).[1]

For HIV-infected adults, IPT is a cornerstone of TB management. IPT for HIV-infected adults refers to giving INH to those without active TB. IPT, together with intensified case finding and infection control, is collectively referred to as the '3 Is' strategy of the World Health Organization (WHO).[2] In a recent meta-analysis of 12 trials and 8 578 randomised HIV-infected subjects >13 years of age, TB preventive therapy (any anti-TB drug) versus placebo resulted in a lower incidence of active TB (relative risk (RR) 0.68, 95% confidence interval (CI) 0.54 - 0.85). This effect was more pronounced in individuals with a positive tuberculin skin test (TST) (RR 0.38, 95% CI 0.25 - 0.57). For adults with a negative TST, there was no statistically significant difference between treatment groups as the upper CI was >1 (RR 0.89, 95% CI 0.64 - 1.24). Compared with INH monotherapy, short-course multidrug regimens had more adverse effects. A reduction in mortality with INH monotherapy versus placebo was confined to those with a positive TST (RR 0.74, 95% CI 0.55 - 1.00).[3]

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The meta-analysis did not address the role of ART, which also reduces the risk of acquiring TB disease, as no randomised controlled trials have been reported in patients on ART. Lawn and colleagues have argued that ART and IPT have complementary roles, IPT being important in TST-positive individuals with higher CD4 counts and better immunity, and that ART (together with active case finding) is the most important component in immunosuppressed individuals.[4]

A meta-analysis from 2006 showed that IPT is not associated with production of INH resistance,[5] although resistance is a concern if patients have active disease before commencing IPT. It is also recognised that IPT is unlikely to prevent TB if a patient is infected with *Mycobacterium tuberculosis* resistant to INH.[6]

For children there are fewer data. The benefit of IPT after documented TB exposure or infection (TST positive) is undisputed, with the efficacy derived from studies in HIV-uninfected children.[7] Findings assessing the value of universal IPT before or in the absence of documented exposure to a source case (pre-exposure IPT) seem contradictory. Zar and colleagues showed benefit in a double-blind study comparing INH with placebo in children with limited access to ART in Cape Town.[1] Active TB was excluded at baseline and children already responding to TB treatment were randomised once TB treatment had been completed. Mortality was lower in the INH group (11 (8%) v. 21 (16%)) (hazard ratio (HR) 0.46, 95% CI 0.22 - 0.95, p=0.015). The incidence of TB was also lower in the INH group (5 cases, 3.8%) than in the placebo group (13 cases, 9.9%) (HR 0.28, 95% CI 0.10 - 0.78, p=0.005).[1]

A large multicentre trial set in Soweto, Cape Town and Durban enrolled infants between 3 and 4 months of age, after excluding all children with known TB contact.

It took place during expanding access to ART. There was no benefit from pre-exposure IPT compared with placebo, either in preventing TB or in reducing mortality in HIV-infected and HIV-exposed uninfected infants.[8,9] The apparent contradiction with the study by Zar *et al*.[1] could be explained by differences in the patient populations, excellent surveillance for TB exposure, and rapid institution of open-label INH for any documented exposure to a source case. The benefit of ART in reducing TB disease is well documented in children.[10,11]

New long-term data from Cape Town on children from the original IPT study recently reported additive benefit of ART and IPT over 5 years of follow-up. All children on placebo were switched to open-label INH and accessed ART through the public programme. INH reduced the risk of TB by 0.22 (95% CI 0.09 - 0.53) compared with placebo. ART alone reduced TB risk by 0.32 (95% CI 0.07 - 1.55). INH plus ART reduced the risk of TB by 0.11 (95% CI 0.04 - 0.32). Restricting the analysis to children receiving ART revealed a TB risk reduction of 0.23 (95% CI 0.05 - 1.00) when comparing INH with no INH.[12] This study suggests that IPT and ART have additive benefit in HIV-infected children.

1. WHO RECOMMENDATIONS

The WHO has recently published guidance on IPT for both children and adults, mainly based on adult data.[13] The recommendations for children are as follows:

1.1 Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB.
Strong recommendation, low quality of evidence

1.2 Children living with HIV and any one of the following symptoms – poor weight gain, fever, current cough or contact history with a TB case – may have TB and should be evaluated for TB and other conditions. Once TB is excluded, offer IPT regardless of age.
Strong recommendation, low quality of evidence
Comment: All suspected cases MUST be referred for exclusion of TB according to local guidelines. The timing of this screening is important to avoid excessive referrals. A review after 2 weeks may be useful before referral. In the complete absence of symptoms, no additional work-up is required.

1.3 Children living with HIV and >12 months of age and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case, should receive 6 months of IPT (10 mg/kg/d) as part of a comprehensive package of HIV prevention and care services.
Strong recommendation, moderate quality of evidence
Comment: The implication is that all HIV-infected children should receive IPT once active TB has been excluded, regardless of their underlying condition. This recommendation brings IPT guidelines for children in line with those for adults. However, in adults, while a duration of 6 months is regarded as the minimum period, there is support for 36 months or longer. In children, the duration was limited to 6 months, pending longer-term safety data. The risk for TB disease may not be at the time of giving IPT. Screening for TB must therefore take place at each clinic visit.

1.4 In children <12 months of age living with HIV, only those children in contact with a TB case and in whom active TB is excluded should receive 6 months of IPT.
Strong recommendation, low quality of evidence
Comment: The contradiction here is that children at greatest risk (HIV-infected infants) are not offered the same access to IPT as older children. HIV-infected infants have a 20 times higher incidence of TB than HIV-uninfected infants in a setting of expanding but inadequate early identification and access to ART.[14]

1.5 All children living with HIV who have successfully completed treatment for TB disease should receive INH for an additional 6 months.[15]
Conditional recommendation, low quality of evidence

2. THE IPT WORKING GROUP

The place of IPT for HIV-infected children in Southern Africa was debated at a small meeting held in Cape Town on 14 October 2010, sponsored by the HIV Clinicians Society of South Africa. Paediatricians from South Africa and Botswana and adult infectious diseases specialists with expertise in IPT attended. (During a review process, additional colleagues with expertise in childhood HIV and TB gave invaluable input.) The consensus was that IPT should be supported. There is a need to define the extent to which it should be included. There is a role for operational research on IPT. Integration of maternal and child health with TB and HIV programmes to accompany IPT (Infection control and Intensified case finding) is a key component for elimination of TB in children.
The following should be addressed:
2.1 Who takes responsibility for delivery of IPT?
2.2 How will it be monitored? Key indicators include:

- uptake
- adherence
- development of TB in children on or not on IPT.

3. RECOMMENDATIONS OF THE IPT WORKING GROUP

At each health care visit, every HIV-infected child must be reviewed for possible TB exposure and/or active disease and managed appropriately.
Always check the following:

- contact with a TB source case
- failure to thrive (monitor Road to Health Card (RTHC))
- present cough (non-remitting cough of ≥2 weeks' duration is suggestive of TB).

4. POST-EXPOSURE IPT

IPT should be provided after EACH documented TB exposure, unless the child is CURRENTLY receiving INH or TB treatment (Fig. 1).

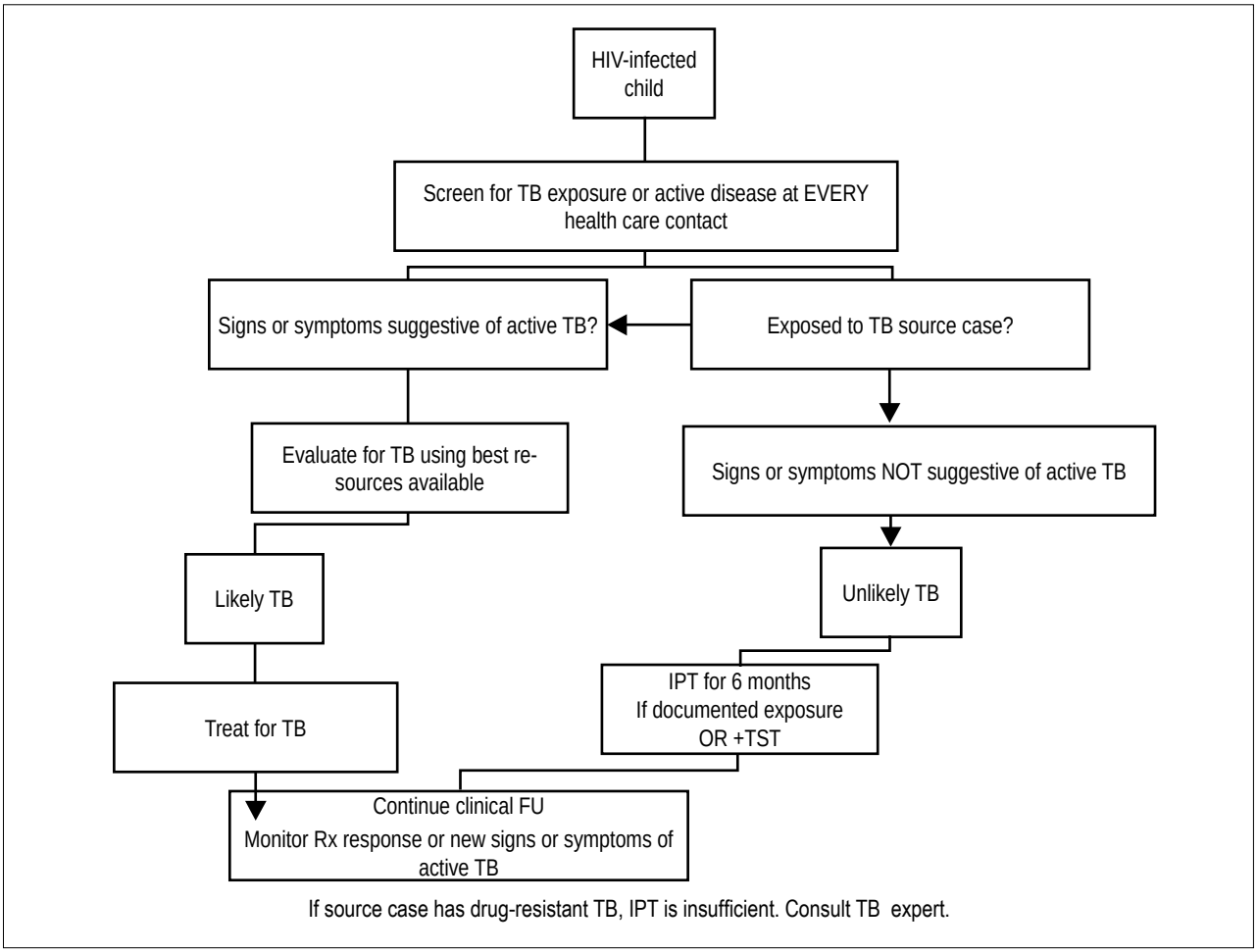

Fig. 1. Management of an HIV-infected child with documented TB exposure or suspected to have TB disease.

4.1 First exclude active TB (see below).
4.2 Give IPT to all HIV-infected children and all children less than 5 years of age, regardless of HIV status, after exposure to a source case of TB.
4.3 Give INH for 6 months (see dosing below).

Before giving post-exposure IPT, first make sure that the child does not have active TB.

- Completely asymptomatic children (no current cough, no failure to thrive, no signs of extrathoracic TB, active and playful) require no further investigation prior to IPT initiation. (All children receiving IPT and/or TB treatment should be followed up clinically while on therapy to evaluate for new symptoms or signs of disease.)
- Any symptomatic child should be carefully assessed (always plot weight and assess RTHC for failure to thrive). In the absence of a convincing clinical picture of TB or lethargy, and without easy access to chest radiography, first treat the most likely alternative diagnosis and re-assess the child after 2 weeks.
- Persistently symptomatic children must be assessed with at least a chest radiograph (antero-posterior or postero-anterior AND lateral). Respiratory specimens (gastric aspirates and/or induced sputa) for *M. tuberculosis* culture must be collected in all children with signs suggestive of TB on chest radiograph (prior to initiation of TB treatment).

NOTE: Evaluate for TB using the best resources available.

5. PRIMARY (PRE-EXPOSURE) IPT

Primary (pre-exposure) IPT should be given for 6 months (Fig. 2).

5.1 Give under the following circumstances:

- Active TB excluded (as for post-exposure IPT).
- Infant/child diagnosed with HIV or ART initiated after 3 months of age (or poor TB exposure screening expected).

5.2. Do NOT give if ALL of the following criteria are fulfilled:

- The mother is identified as HIV infected in antenatal clinic and screened for TB.
- No active TB is identified in close contact of the child such as member of the household/plot or a regular visitor.
- Infants are initiated on ART under both of the following circumstances:
  - ART initiated within the 1st 3 months of life when asymptomatic
  - active TB excluded.
- The infant is enrolled in the ART programme and seen at least every month for first 3 months and thereafter at least every 3 months (with screening for TB exposure or signs/symptoms of TB at each visit).

6. CATCH-UP PHASE FOR CHILDREN ALREADY ON ART FOR >6 MONTHS

At the time of implementation of the IPT guidelines (June 2011), there will be 50 000 children on ART. Data support

DOSAGE RECOMMENDATIONS FOR IPT (PRIMARY AND POST-EXPOSURE)		
Weight range (kg)	100 mg tablets per dose (total dose 10 mg/kg/d)	Dose given (mg)
<5	0.5	50
5.1 - 9.9	1	100
10 - 13.9	1.5	150
14 - 19.9	2	200
20 - 24.9	2.5	250
>25	3	300

Resources for drug-resistant TB: references 16 and 17.

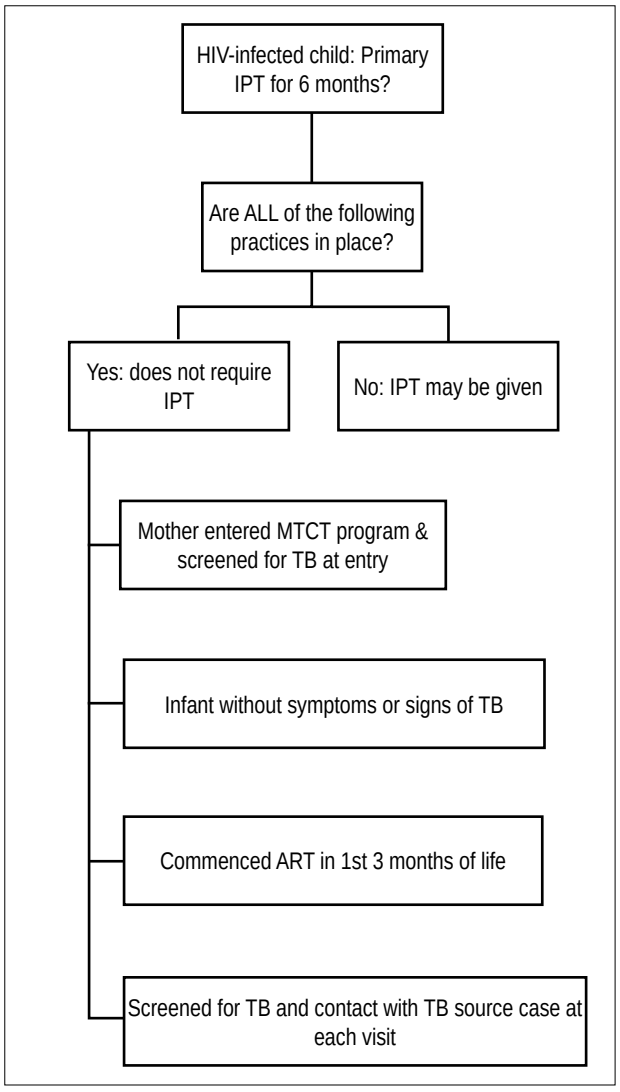

Fig. 2. Considerations for primary (pre-exposure) IPT.

IPT in children.[12] For children already well established on highly active antiretroviral therapy (HAART) (i.e. >3 months) and without active TB, there are two options:

6.1 IPT may be given for 6 months. (Apply guidelines for new contact with potential source case.) This is likely to be most beneficial for those who are TST positive (*note:* in the absence of ART, an induration ≥5 mm denotes a positive TST (Mantoux)).

6.2 Defer IPT and continue monitoring for new TB exposure and signs/symptoms of TB.

7. DOSAGE

7.1 INH 10 - 15 mg/kg/d.

7.2 Also give vitamin B_6 25 mg/d.

8. ADDITIONAL POINTS

8.1 In the absence of obvious TB disease, initiation of HAART takes precedence over IPT.

8.2 IPT must NOT complicate the HAART programme.

8.3 ANY child assessed for TB after contact with a TB source case must be screened for HIV.

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GUIDELINE

GUIDELINE ON SAFER CONCEPTION IN FERTILE HIV-INFECTED INDIVIDUALS AND COUPLES

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Ninety years ago the isolation of insulin transformed the lives of people with type 1 diabetes. Now, models based on empirical data estimate that a 25-year-old person with HIV, when appropriately treated with antiretroviral therapy, can expect to enjoy a median survival of 35 years, remarkably similar to that for someone of the same age with type 1 diabetes. It is high time we normalised the lives of people living positively with HIV. This includes the basic human right to conceive and raise children. HIV-positive individuals may be in serodiscordant relationships or in seroconcordant relationships. As health care providers, it is our responsibility to ensure we understand the opportunities and risks of natural conception in these scenarios, so that we can help our patients to make informed decisions about their own lives. Most of all, it is our duty to make family planning in the setting of positive prevention as safe as we can. This includes informed decisions on contraception, adoption, fostering, conception and prevention of mother-to-child transmission.

Some months ago a dedicated group of individuals, invited and sponsored by the Southern African HIV Clinicians Society, came together in Cape Town to devise guidance in this area, recognising that there are ideal strategies that may be outside the realm of the resource constraints of the public sector or health programmes in southern Africa. This guideline therefore attempts to provide a range of strategies for various resource settings. It is up to us, the providers, to familiarise ourselves with the merits/benefits and risks of each, and to then engage patients in meaningful discussions. All the above, however, is based on the premise and prerequisite that the subject of family planning is actively raised and frequently discussed in our patient encounters.

1. INTRODUCTION

Across South and sub-Saharan Africa, the vast majority of HIV-positive individuals are adults of reproductive age. Before universal access to effective antiretroviral therapy (ART), traditional medical wisdom generally discouraged childbearing because of the risk of HIV transmission (both to uninfected partners and from mother to child) and the reduced survival of infected parents and children. In the era of ART, HIV/AIDS has come to be viewed as a manageable chronic illness. In addition to leading to dramatic reductions in morbidity and mortality of HIV-infected parents, use of highly active antiretroviral therapy (HAART) in Europe and North America has driven the virtual elimination of paediatric HIV infection, and in southern Africa PMTCT programmes have greatly reduced paediatric infections.[1]

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We are indebted to Karin Richter and Polly Clayden for their insightful and helpful comments on this guidance document.

Although many patients feel uncomfortable discussing it with their health care providers, many HIV-infected adults are sexually active. In advanced HIV infection fertility is reduced, but the incidence of pregnancy increases with ART initiation,[2] through increased sexual activity and attitudinal changes in hopes and desires for the future. South Africa has an estimated 1 million births annually, and an estimated 29% of these occur in women living with HIV. Other southern African countries have similar antenatal HIV prevalence rates. A substantial proportion of these pregnancies are unplanned, despite effective contraception being a critical component of the prevention of mother-to-child transmission (PMTCT) of HIV/AIDS programme. However, many HIV-infected women and men want to have children, either immediately or at some time in the future. Reproduction is a basic human right,[3] and for many women having a child is part of their life plan. Indeed, in many parts of southern Africa being without a child attracts significant stigma.[4]

In this context, dealing with issues of fertility and childbearing should be seen as part of routine HIV care. Clinicians are responsible for identifying and supporting the fertility desires of their HIV-infected patients – both in the interests of 'normalising' the lives of people living with this chronic infection, and to help ensure that conception, pregnancy and delivery take place with the least possible risk to the mother, her partner, and the resulting child.

This consensus guideline for the Southern African HIV Clinicians Society has been formulated through a process of consultation with the South African health services in mind. It is designed to assist clinicians to identify patients' fertility desires, and to give safe and effective conception guidance to a presumed fertile couple where one or more partners are HIV infected. We have considered 'resource-intensive' clinical settings, such as the private sector, where technologically advanced assisted reproduction technologies may be available, as well as 'resource-limited' settings such as most public sector health facilities across the region. It is understood that these two levels are often not clearly demarcated, and it is recommended that providers should become familiar with which services documented here are available to patients in their setting. While we present the optimal management for safest conception, there is recognition that state-run and resource-limited clinical settings may not yet facilitate or fund these interventions. In these cases we have attempted to quantify the increased risk that not meeting these standards would incur for your patient. While specialist referral is not contraindicated for those couples in whom one or both partners are suspected of having compromised fertility, these advanced fertility interventions will not be covered in these guidelines.

The guideline is divided into three sections. The first section discusses how the clinician can raise the issue of childbearing and help identify the fertility desires of HIV-infected women and men, with a brief discussion on contraceptive strategies for women who do not wish to become pregnant. The second part focuses on the management of individuals and couples who do desire a pregnancy, with emphasis on the management of HIV disease and co-morbidities before attempting conception. This includes specific conception strategies for HIV-seroconcordant positive couples and serodiscordant couples. Finally, several key issues are discussed, and a series of illustrative scenarios have been appended to the guideline to assist with their understanding and implementation.

The guideline has been devised with an eye on international norms but also with a keen view to local resource issues. The change in the natural history of HIV infection and reduction in MTCT as a result of ART has led to a re-evaluation of the ethical and moral arguments previously used to deny assisted reproduction to HIV-infected patients. Increasingly, parenting is regarded as a realistic option for couples where one or both partners are infected, and the demand for reproductive management is rising. It is also imperative to provide some measure of protection to both the uninfected partner and the uninfected fetus. This guideline attempts to provide some pointers to how this can be done more safely in the southern African context.

2. DISCUSSING FERTILITY AND CHILDBEARING WITH HIV-INFECTED WOMEN AND MEN

The first step towards addressing the issues of fertility and childbearing is to regularly and repeatedly raise these with HIV-infected patients, to understand their desires and related health care needs (Fig. 1). Issues about fertility choices should be discussed with both

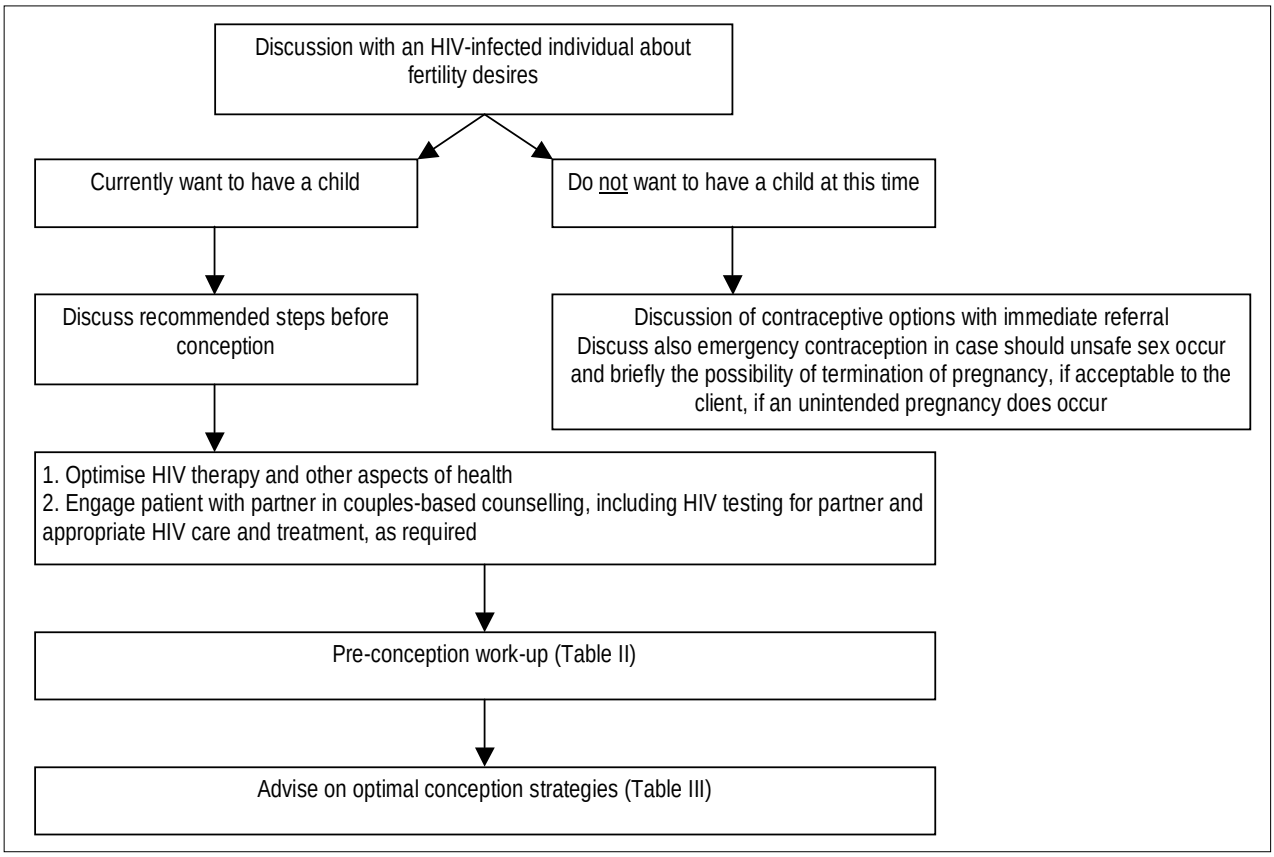


Fig. 1. Flow diagram to approach pregnancy-related issues in HIV-infected women and men.

men and women, and men should be encouraged to bring their partners in for further consultation should this be appropriate. Local research demonstrates that the majority of individuals attending HIV care and treatment services have never had an open discussion about fertility and childbearing with their health care providers.[5] When these discussions do take place, patients report that the tone is strongly judgemental – often discouraging individuals from childbearing regardless of their desires – with an exclusive focus on the need for contraception and condom use.[6]

Ensuring that patients have a basic understanding of HIV transmission and conception is fundamental to safer conception in HIV. Basic information for this can be obtained online in 'Pregnancy in our lives' at http//www.tac.org.za/community/files/file/TreatmentLit/2010/PregnancyInOurLivesEnglish2010.pdf

To introduce this topic, the health care provider may find the following discussion points useful and informative:

- the number of living children, the age of the patient's youngest child, and/or the number of other children the patient may help to care for, and how easy or difficult they find their child care responsibilities
- the health of their existing children, including whether any child is HIV infected
- the partnership status of the patient, the number of children the patient has with their current partner, and perceptions of a partner's desires.

Because of the stigma around sexual activity and pregnancy for HIV-infected individuals, raising issues of fertility and childbearing can be sensitive for many patients. In these discussions, the use of 'normalising' statements – for instance, pointing out that many other patients are grappling with these issues – may help patients to feel comfortable expressing their own thoughts and opinions.

Typically discussions will focus on female patients, but it is critical to note that male partners can have a strong influence on women's fertility-related desires and decisions. These issues are often highly relevant for male patients, and local studies have shown that HIV-infected men are at least as likely as women (often more so) to want another child.[7] Male or female patients may wish to return with their partners to discuss fertility and related issues with the health care provider, and we strongly recommend a couples-based approach to these issues (see below).

Throughout this discussion, the objective of the provider should be to assist patients in arriving at their own informed choice about their fertility desires. Key aspects of information that providers may share which can help the patient arrive at an informed decision include: the patient's current health status and their prognosis; their age; the possibility of HIV transmission if the partner is HIV negative; and the probabilities of having an HIV-negative child given appropriate interventions. Other topics the provider may raise with a patient include: current versus desired family size; partner, family and community influences on fertility desires; whether any existing children are HIV infected; and the current and future resources required in caring for a child. These discussions may include an evaluation of some of the alternatives to childbearing, including adoption (Box 1).

BOX 1. OTHER OPTIONS TO CONSIDER IN MAKING A DECISION AROUND FERTILITY AND CHILDBEARING

In discussing the desire to have a child with HIV-infected women and men, there are several potentially useful options that patients may not be aware of. These include:

- An HIV-infected male partner may consider HIV-negative sperm donations from an HPCSA-accredited facility in South Africa (appropriate accreditation bodies should be sought in other southern African countries), or in low-resource settings from an HIV-negative man.
- Adoption may be possible through an approved facility, or through a social worker. Note that chronic illnesses (including HIV) are not a contraindication, provided the illness is well controlled and the adopting parents are relatively healthy.
- Surrogacy may be an option (i.e. another woman carries the pregnancy for the couple), but this would only be acceptable if the male partner is HIV negative. Surrogacy is not widely practised in South Africa.
- Not to have or formally adopt a child, but to focus on becoming more involved in the care of children in the family or community.

Ultimately these discussions should help to identify the patient's current fertility intentions, which in turn indicate various possible health care interventions. Specifically, providers should encourage patients to decide between:

(a) wanting to become pregnant immediately (i.e. actively trying to conceive), versus
(b) not wanting a child now, but considering a possible pregnancy in the future, versus
(c) the desire to not become pregnant at all.

For patients who remain unsure of their choice, option (b) above (not wanting a child in the present, but reserving the possibility of a child in the future) may be a useful default position, as it holds options open and seeks to emphasise that individuals' fertility intentions may change over time. For example, an HIV-infected woman who does not want a child at present may decide to have a child in the future. Or, a couple who wants a child at present, and has one, may decide afterwards that they do not want more children. As a result, it is important to raise issues of fertility and childbearing at regular intervals during the course of chronic HIV care, even if these are brief discussions to confirm previous decisions. Briefly documenting the discussions between patient and provider can be useful as a reference for future consultations and as a cross-reference in a busy public sector clinic.

3. CONTRACEPTION FOR THE HIV-INFECTED INDIVIDUAL OR COUPLE WHO DOES NOT WANT A CHILD

While this guideline focuses on the needs of individuals and couples who wish to conceive, local research suggests that the majority of HIV-infected individuals are not actively trying to conceive and do not at present want a child.[5,6] HIV care and treatment services are ideally suited to address family planning needs.[8] A range of detailed resources are available on appropriate contraception among HIV-infected women and men (see references). However, a few key points emerge from the literature on this subject.

First, there are a number of effective contraception options that may be used safely by patients living with HIV.[9] Choices may be somewhat restricted in the public sector to barrier methods (such as male and female condoms), injectable progestins and combined oral contraceptive pills. Although availability in the public sector may be limited, intra-uterine contraceptive devices (both copper IUCDs and progesterone IUCDs) are very effective long-acting methods that can be used safely in HIV-infected women, and their use deserves further attention. Male or female sterilisation should be considered for individuals or couples who are certain that they do not wish to become pregnant in the future. In making recommendations about which method to recommend, the efficacy of the different methods should be considered. If a woman is unwell and a pregnancy could impact on her health, a highly effective method should be recommended. If she does not want to use these methods and an unplanned pregnancy would not be a problem, the condom should be considered.

Table I shows the relative effectiveness of the common contraceptive methods, the safety of using each method in HIV-infected women, and whether there is any increased risk of transmission to partners.

HIV-infected women will have the same general contraindications to use as the general population of women.[10]

For women who can negotiate condom use, we strongly recommend that all patients who require effective contraception be advised to practise dual method use – the concurrent use of a highly effective contraceptive method and a male or female condom. Because of the relatively high failure rates of condoms, this approach should be recommended even to women who report consistent condom use. Women who do not currently want a pregnancy but are reluctant to use contraception should be offered contraceptive counselling at every subsequent opportunity.[10,11]

4. THE HIV-INFECTED INDIVIDUAL OR COUPLE WHO WANTS A CHILD

A significant proportion of HIV-infected individuals will desire a child, and may be actively trying to conceive at the time of a clinical consultation. In consulting these individuals, there are several important considerations that the HIV clinician should keep in mind.

Natural conception – unprotected intercourse. The risks of HIV transmission depend on HIV plasma viral load, the presence of sexually transmitted infections, and the length and frequency of exposure.

TABLE I. EFFECTIVENESS OF THE COMMON CONTRACEPTIVE METHODS, AND THEIR SAFETY IN HIV INFECTION

Method	Failure rate/100 woman-years	Impact on disease progression	Increased HIV transmission to partner	Impact on HAART or tuberculosis treatment
Oral combined oral contraceptive	0.2 - 3	No conclusive evidence of harm: can use	No conclusive evidence of harm: can use	Drug interaction with some NNRTIs: do not use Drug interaction with rifampicin and related TB drugs: do not use
DMPA and NET-EN (injectable progestins)	0 - 2	No conclusive evidence of harm: can use	No conclusive evidence of harm: can use	HAART: can use, no need to increase dose or injection frequency TB drugs: can use, no need to increase dose or injection frequency
Male condom	Careful use: 0.4 - 8 Typical use: around 10	None: may prevent re-infection	Barrier method protects partner	N/A
Female condom	Careful use: 5 Typical use: 21	None: may prevent re-infection	Barrier method protects partner	N/A
Copper IUCD	0.1 - 0.3	Evidence on safety reassuring: can use	Limited evidence but reassuring: can use	No interactions
Levonorgestrel IUCD 20	0.1 - 0.3	Limited evidence of safety reassuring: can use	Little evidence but extrapolating from Cu IUCD can use	No interactions
Male and female sterilisation	Female 0 - 0.5 Male 0 - 0.2	No evidence but unlikely: can recommend	No evidence but unlikely: can recommend	N/A

NNRTI = non-nucleoside reverse transcriptase inhibitor.

The impact of HIV viral load. Plasma HIV-1 ribonucleic acid (RNA) levels can be correlated with the sexual transmission of HIV. Viral load is the single greatest risk factor for all transmission modes. ART reduces the plasma and genital HIV viral load in the infected individual to undetectable levels.[12] In a study of 415 HIV serodiscordant couples in Uganda, 21.7% of initially uninfected partners became infected over 30 months of follow-up, translating to a transmission rate of approximately 12 infections per 100 person-years.[13] No transmission events occurred in couples in which the infected partner had a plasma HIV-1 RNA level of less than 1 500 copies/ml, and the transmission risk increased as plasma HIV-1 RNA levels increased. For every 10-fold increase in viral load, there was a >2-fold risk of transmission. Plasma HIV-1 RNA levels generally correlate positively with the concentration of HIV in genital secretions, rectal mucosa and saliva, although inflammation can stimulate local replication.[14] Other studies have shown that transmission events may be observed at a very low plasma HIV-1 RNA level, suggesting that plasma HIV-1 RNA level is not the only determinant of transmission.[15,16] These data suggest that transmission probability drops markedly in people with naturally controlled viral loads or with ART controlled viral loads.[15,16]

Clinical research in discordant couples. Findings from a large multinational clinical study conducted by the HIV Prevention Trials Network (HPTN) recently showed that men and women infected with HIV reduced the risk of transmitting the virus to their sexual partners through initiation of oral ART. The study, known as HPTN 052, was designed to evaluate whether immediate versus delayed use of ART by HIV-infected individuals would reduce transmission of HIV to their HIV-uninfected partners and potentially benefit the HIV-infected individual as well. Findings from the study were reviewed by an independent Data and Safety Monitoring Board (DSMB). The DSMB concluded that initiation of ART by HIV-infected individuals substantially protected their HIV-uninfected sexual partners from acquiring HIV infection, with a 96% reduction in risk of HIV transmission.[17]

So what are the risks for natural conception and unprotected intercourse? One of the difficulties in counselling serodiscordant couples on natural conception methods involving unprotected intercourse is that the risk to the uninfected partner is difficult to quantify, but can certainly not be quoted as zero. Mathematical models cite a risk of 1 in 100 000 per act of intercourse. In practice, viral shedding in semen has been reported to occur even in men fully suppressed on ART.[18]

A recent retrospective study of 551 semen samples analysed in HIV-1-infected men undergoing sperm washing identified 15 cases of detectable HIV-1 in ejaculated semen in men with a long-term undetectable plasma viral load through use of ART, highlighting a need for caution when couples consider a natural conception approach.[19] In the case of serodiscordant couples where the woman is HIV-positive, the evidence is equally concerning: detectable HIV has been identified in follicular fluid and endometrial samples from a series of HIV-positive women undergoing *in vitro* fertilisation (IVF), even when plasma viral load was suppressed fully through the use of ART.[20]

Three studies have analysed infection risk in serodiscordant couples attempting to conceive naturally. The first was a prospective study conducted before the widespread use of ART and examining the risk of unprotected intercourse timed to the fertile window in 96 discordant couples where the male was infected. Four seroconversions were noted in the female partners, 2 during pregnancy and 2 post partum.[21] The seroconversions were identified in couples in whom condom use after conception and outside the fertile window was inconsistent. A more recent, retrospective study attempted to quantify the risks of unprotected intercourse in discordant couples where the man had an undetectable viral load through use of ART for at least 6 months. There were no seroconversions in 62 discordant couples who conceived.[22] Apart from the small sample size, the study is further weakened by the fact that seroconversions were not analysed in couples who failed to conceive, where the risk might be enhanced by repeated exposures. The only study to prospectively assess viral transmission risk in serodiscordant couples attempting to conceive naturally, where the man was fully suppressed on ART and additional pre-exposure prophylaxis (PrEP) was used in the female partner, involved only 22 couples.[23]

4.1 ENGAGING COUPLES

While we typically see patients in individual consultations, ideally HIV care and treatment services should discuss fertility and childbearing jointly with female and male partners. There are several distinct advantages to a couples-based approach. First, because partnerships have an important influence on fertility decisions, consulting with couples can be useful in helping individuals and their partners arrive at appropriate informed decisions about fertility. Second, the health of both partners is important towards safe conception and pregnancy, and delivering care to both partners may therefore be necessary. Third, if a couple is struggling to conceive, there are specific investigations and interventions for both women and men, and investigating and treating one partner only may lead to suboptimal outcomes. However, this entails disclosure of HIV status between partners, which can be a major challenge. At the minimum, the HIV status of both partners must be known and disclosed in order to manage this process safely and effectively

Despite the importance of a couples-based approach, there are circumstances where an individual desires a child but does not know the serostatus of their partner, or desires a child in the absence of a regular partner or a partner who is willing or able to attend the clinic. These situations present particular challenges (see 'Special issues', below).

WHAT SHOULD BE COVERED IN PRECONCEPTION COUNSELLING?

Preconception counselling should ensure an informed choice about reproductive options, including the inherent risks and costs of each treatment and the likely chances of success.

It must include:

- a summary of the available data on safety for each method together with advice on additional methods of reducing risk, such as limiting intercourse to the fertile window, or early initiation of ART
- regular screening for sexually transmitted infections
- the need to identify evidence of reduced fertility or sterility at an early stage in either or both partners
- the possible use of pre-exposure prophylaxis.

The discussion should balance the risk of natural conception with that of more established risk-reduction methods such as sperm washing or risk-free options such as donor insemination. Although timed unprotected intercourse may be the only option for discordant couples in resource-limited settings, this has risk.

Preconceptual counselling should also address:

- The possibility of treatment failure and how the couple would cope if they successfully had a child but the infected parent became more seriously ill or died.
- Those electing to have assisted conception with sperm washing have to understand that this is a risk-reduction method and not a risk-free method.
- When the female partner is HIV-positive they need to understand the risks of MTCT and the methods used.
- They should plan and agree to attend an antenatal clinic once pregnant to ensure that they receive the best possible advice to minimise MTCT risk.

4.2 OPTIMISING HIV THERAPY AND ADDRESSING OTHER HEALTH CONCERNS

As with any chronic condition, optimising the health status of an HIV-infected couple prior to conception is an important step both to facilitate conception and help ensure a safe pregnancy. In the case of HIV, this means:

4.2.1 Documenting the HIV status of both partners. The recommended strategies to conceive vary depending on the serostatus of both partners, with key differences in optimal strategies for HIV-seroconcordant positive couples, and for HIV-serodiscordant partners (where either the male or female partner is HIV infected). HIV counselling and testing is a prerequisite if the HIV status of both partners is not known.

4.2.2 Identifying and managing co-morbidities. This includes HIV-related co-morbidities, most notably opportunistic infections such as tuberculosis (TB), as well as other medical conditions that may influence the pregnancy, such as epilepsy or diabetes. For conditions with short-term management (e.g. TB or acute infections), we recommend delaying attempts at conception until treatment is completed. For chronic conditions that will require treatment throughout pregnancy, it is necessary to avoid potentially teratogenic medications and ensure optimal management before proceeding.

4.2.3 Determination of health status for HIV-infected partners. All HIV-infected patients should undergo thorough clinical assessment and have a CD4 count to determine eligibility for ART before conception. In settings where viral loads are available, these should be included as part of this work-up. However, it should be noted that an undetectable plasma viral load does not necessarily mean that there is an undetectable viral load in the genital tract.

4.2.4 ART initiation as appropriate. Given the benefits of ART in reducing viraemia and reducing the risk of HIV transmission (in addition to its benefits for adult health), ART initiation in eligible individuals and optimisation of appropriate therapy is necessary before proceeding. Ideally, given the data above, any HIV-infected patient wishing to conceive and therefore contemplating unprotected sex should have an undetectable viral load before doing so. This would imply ART for at least 3 - 4 months prior to sexual intercourse. World Health Organization (WHO) guidelines and a number of southern African countries have adopted short-course HAART for PMTCT regardless of CD4, stopping after delivery in women whose baseline count was >350 cells/μl and in whom formula feeding will be implemented, and after cessation of breastfeeding in those women who choose to do so. While current South African national guidelines call for ART initiation in pregnant women with CD4 cell counts <350 cells/μl, clinicians should consider the initiation of ART in a non-pregnant woman with a CD4 count of <350 (ideally this should be <550) cells/μl who is attempting to conceive. It is hoped South African PMTCT guidelines will adopt the strategy of HAART for all pregnant women, continuing HAART for maternal health in women with CD4 <350 cells/μl, and cessation of HAART after pregnancy or breastfeeding in women in whom CD4 counts are >350 cells/μl depending on the infant feeding method of choice. Care is needed in the selection of regimens preconception and in pregnancy, and the risks and advantages of using any antiretroviral with potential teratogenicity (such as efavirenz (EFV)) should be considered in the first trimester. In discordant couples where the man is infected, similar consideration should be given to initiating ART with CD4 counts of >350 (ideally 200 - 550) cells/μl if he and his negative partner are trying to conceive. It is hoped that with the HPTN 052 results[17] (HIV acquisition was reduced by 96% in discordant heterosexual couples where the HIV-infected partner commenced ART at CD4 levels between 350 and 550 cells/μl compared with those in whom it was commenced at 250 cells/μl or with onset of AIDS), the recommendations above can be modified to that described as 'ideal'.

For an ART-eligible HIV-infected woman who conceives while not on ART (and may be diagnosed in pregnancy), therapy should be initiated as soon as possible using pregnancy-friendly regimens (at least by the end of the first trimester), as the duration of ART received during gestation is an important determinant of MTCT risk.[24] For women who are not ART eligible (do not need ART for their own health), PMTCT interventions, focusing on short-course antiretroviral prophylaxis regimens according to national PMTCT guidelines, should be initiated when appropriate (see Box 2). Suggested pregnancy-friendly regimens would include a boosted protease inhibitor (PI) in the first trimester (if the CD4 count is >250 cells/μl) or an EFV-based regimen after the first trimester. A nevirapine-based regimen can be used throughout pregnancy if the starting CD4 count is <250 cells/μl.[25]

BOX 2. PRINCIPLES OF REDUCING MOTHER-TO-CHILD HIV TRANSMISSION

This is not intended to be a comprehensive guide to PMTCT. Please see the reference below for details.

- Ideally all HIV-infected women should already be on ART as part of preconception management; this should be continued throughout pregnancy and breastfeeding.
- If a woman is not on ART, initiate ART as soon as possible irrespective of CD4 cell count, using the appropriate antiretrovirals to avoid teratogenicity, and reduce side-effects and pill burden.
- Women with a baseline CD4 cell count ≤350 cells/μl should continue ART indefinitely for their own health.
- Women with a CD4 cell >350 cells/μl who elect to breastfeed should continue ART until the baby is weaned.
- Women with a baseline CD4 count >350 cells/μl may discontinue ART after delivery.
- In situations where the above cannot be applied, local PMTCT guidelines should be followed.

Additional reading

National Department of Health. The South African Antiretroviral Treatment Guidelines 2010 (2010). http://www.doh.gov.za/aids/index.html

4.2.5. Optimisation of ART. For male or female partners who are either initiating or already established on ART, evidence that therapy is optimised is required before attempting to conceive. This should include evidence of high levels of adherence and immune recovery, and preferably documented virological suppression for at least 4 - 6 months.

4.3 PRECONCEPTION WORK-UP

Table II shows recommended basic investigations that may be undertaken in primary care facilities in the preconception work-up of an HIV-infected couple who desires a child, with adaptations for resource-limited and resource-intensive settings. At a minimum, all women should receive HIV-related investigations as well as syphilis screening, haemoglobin measurement, and physical examination with visual inspection of the cervix for abnormalities and for signs of sexually transmitted infections. Consider a Papanicolau smear (Pap smear) in resource-intensive settings; this may be extended to include a full screen for TORCH infections (congenital infections: toxoplasmosis, rubella, CMV and herpes simplex and other congenital infections) and viral hepatitis, a Pap smear, and a full blood count.

In resource-intensive settings, patients who are struggling to conceive may be referred to specialist fertility services for further work-up, including assessment of luteinising hormone levels in women and sperm assessment in men. Couples found to be non-fertile may be candidates for assisted reproductive technologies.

4.4 SAFER CONCEPTION STRATEGIES

The tools at our disposal to make conception safer in seroconcordant and serodiscordant couples now include (some are proven, some experimental, and they are not listed in any particular order):

- HAART and viral load suppression in the positive partner(s)
- timed, limited, peri-ovulatory, unprotected sex
- intra-uterine insemination
- intravaginal insemination
- male circumcision
- sperm washing

TABLE II. PRECONCEPTION WORK-UP FOR HIV-INFECTED INDIVIDUALS DESIRING A CHILD IN RESOURCE-INTENSIVE AND RESOURCE-LIMITED SETTINGS

	Female partner	Male partner
Resource-intensive strategy	CD4, HIV viral load, hepatitis serology (A); investigations for syphilis, CMV, rubella, HSV, toxoplasmosis; full blood count; Pap smear If on HAART preconception, adaptation of regimen as needed; ensure undetectable HIV Viral load in blood *If difficulty conceiving:* lutenising hormone, referral for fertility assessment	CD4, HIV viral load, syphilis serology; laboratory investigations for other sexually transmitted infections If on HAART preconception, ensure undetectable HIV viral load in blood *If difficulty conceiving:* referral for sperm assessment; fertility assessment
Resource-limited strategy	CD4, syphilis serology, clinical assessment for other sexually transmitted infections; haemoglobin; visual inspection of the cervix ART and undetectable viral load also strongly advised	CD4, syphilis serology; clinical assessment for other sexually transmitted infections ART and undetectable viral load also strongly advised

CMV = cytomegalovirus; HSV = herpes simplex virus.

- surrogate sperm donation
- post-exposure prophylaxis (PEP) in the negative partner
- PrEP in the negative partner.

It is important to note that in deciding which strategies to use for safer conception while in an HIV-positive seroconcordant or discordant relationship, resources, risk and preference may play a role for both the patient and the provider.

Table III shows the recommended conception strategies for serodiscordant and HIV-infected seroconcordant couples, stratified for resource-intensive and resource-limited settings. In all cases where unprotected sex with a positive partner or vaginal insemination with potentially infected semen is considered, both partners should be counselled about the risk of transmission and measures such as ART or prophylaxis, male circumcision, sperm washing and donor insemination. Which of these options are utilised will be determined by available resources

TABLE III. OPTIMAL CONCEPTION SUPPORT STRATEGIES FOR RESOURCE-INTENSIVE AND RESOURCE-LIMITED SETTINGS, ACCORDING TO THE HIV STATUS OF THE COUPLE

	Seroconcordant (male and female HIV infected)	Serodiscordant (male HIV infected)	Serodiscordant (female HIV infected)
Resource-intensive strategy			
Female partner	If on HAART preconception, adaptation of regimen as needed; ensure undetectable HIV viral load in blood; no use of efavirenz in the first trimester among HIV-infected women trying to conceive Conception: consider sperm collection with intra-uterine insemination; self-insemination possible; peri-ovulatory unprotected sexual intercourse only in the face of demonstrated undetectable viral loads If not on HAART preconception, maternal HAART initiation as soon as possible with appropriate regimen	Repeated HIV PCR testing before pregnancy Conception: undectable viral load preferable; sperm washing and intra-uterine insemination Repeated HIV PCR during pregnancy with appropriate management if female partner becomes infected	If on HAART preconception, adaptation of regimen as needed; ensure undetectable HIV viral load in blood Conception: sperm collection with intra-uterine insemination If not on HAART preconception, maternal HAART initiation early in the second trimester
Male partner	Preconception HAART until un-detectable HIV viral load in blood and semen	Preconception HAART until undetectable HIV viral load in blood, semen Conception: sperm assessment; sperm washing with HIV PCR	Ongoing HIV testing; male medical circumcision where appropriate, especially if couple choose peri-ovulatory unprotected sexual intercourse for conception
Resource-limited strategy			
Female partner	If on HAART preconception, adaptation of regimen as needed; ensure high levels of adherence and CD4 monitoring; no use of efavirenz in women trying to conceive Conception: consider sperm collection with self-insemination; peri-ovulatory unprotected sex possible under safe conditions. This would include undetectable viral loads if possible, timed sexual intercourse and limited exposures (see text) If not on HAART prconception, maternal PMTCT initiation asap with appropriate antivirals	Repeated HIV antibody testing before pregnancy Conception: unprotected sex during the fertile period (preferably while on ART with viral load control) Repeated HIV antibody testing during pregnancy with appropriate management if female partner becomes infected Consider use of mono- or dual-therapy PrEP	If on HAART preconception, adaptation of regimen as needed; ensure high levels of adherence and CD4 monitoring; consider ART for conception and pregnancy regardless Conception: sperm collection with self-insemination at the time of ovulation (avoiding spermicide-containing condoms) If not on HAART preconception, maternal PMTCT initiation as soon as possible with appropriate regimen
Male partner	If required, preconception HAART for at least 6 months with intensive adherence support and CD4 monitoring and viral loads monitoring	If required, preconception HAART for at least 6 months with intensive adherence support and CD4 and viral load monitoring	Ongoing HIV testing; male medical circumcision where appropriate, especially if couple choose peri-ovulatory unprotected sexual intercourse for conception

PCR = polymerase chain reaction.

and will determine the level of risk of transmission. Where unprotected exposure is embarked upon this should be in the presence of reasonable expectations for fertility, e.g. no evidence of reduced ovarian reserve or tubal damage, and no more than 6 - 12 cycles of peri-ovulatory sex should be performed unsuccessfully without considering referral for infertility investigation.

4.4.1 Seroconcordant positive couples. In resource-limited settings, sperm conception with self-insemination may be considered. Limited peri-ovulatory unprotected sex is a feasible approach to insemination, although both partners must acknowledge the potential risks associated with superinfection, and have a good understanding of how to time intercourse to the peri-ovulatory window (see Box 3). Superinfection occurs when an already infected individual becomes 're-infected' with another strain of HIV that may or may not be drug sensitive. This is thought to be more common than first thought, although there are few case series. A study in Kenyan sex workers quantified the incidence at 4% per annum.[26] The implications may include increased viral load in someone not on therapy, or infection with a drug-resistant virus in someone who is. Ideally, even in resource-limited settings this risk can be further reduced in seroconcordant couples by ensuring viral load suppression during conception in both partners and self-vaginal inception. In resource-intensive settings, optimal conception may take place under the supervision of a specialist in reproductive medicine. In such contexts, sperm collection and intra-uterine insemination may be optimal. As discussed above, in all settings ART-eligible individuals should be stabilised on optimal therapy prior to conception.

BOX 3. HOW TO DETERMINE A WOMAN'S FERTILE PERIOD

When a couple is living with HIV and attempting conception, determining a woman's fertile period is necessary to time peri-ovulatory intercourse. There are various ways in which a woman's fertile period can be determined. The methods described here presume normal fertility and require minimal resources.

In situations where a woman's fertility may be impaired, more resource-intensive methods (such as day 21 progesterone measurements or serial ultrasound monitoring, with or without ovulation stimulation – clomiphene administration is usually performed in consultation with specialist services) may be used by a reproductive specialist. These more intensive methods may also be used in women living with HIV (who has presumed normal fertility) in order to increase her chance of fertility prediction.

Fertile dates

The average normal duration of a menstrual cycle is 28 days. The first day of a woman's menstrual period is considered to be day 1 of her menstrual cycle. Ovulation is assumed to occur half way through her cycle. Her fertile period would be from 5 days before predicted ovulation up until 1 - 2 days after ovulation. For example, in a woman whose cycle is 28 days long, this would mean that ovulation would be assumed on day 14. The woman's fertile period would therefore occur between days 9 and 16 of her menstrual cycle.

However, menstrual cycle length may differ considerably between women and may even differ from month to month for an individual woman. It is therefore essential that a woman keeps record of her menstrual cycle (typically taking into account the first day of her menstrual period) for at least 4 months in order to determine an average menstrual cycle length. It is important to explain to patients that regular menstrual cycles may not necessarily indicate that ovulation has occurred.

Ovulation prediction kits (for urine and saliva)

A number of over-the-counter products are available that enable ovulation prediction. These methods may utilise sampling and analysis of either urine or saliva, and detect the surge of luteinising hormone that occurs immediately before ovulation.

Basal body temperature (BBT) charting

A woman's body temperature increases by 0.25 - 0.5 ºC during ovulation. Charting a woman's BBT daily will therefore result in a pattern that may assist her in predicting ovulation. For this method of ovulation prediction to be accurate, it is essential that the woman plots her BBT at the same time every day (preferably between 6 and 8 a.m.), before getting out of bed or drinking or eating anything. Attempt conception after the first rise in BBT has been detected. The chances of conceiving after the 3rd day of raised BBT are greatly reduced.

Cervical mucus monitoring

In addition to BBT, a number of other physiological changes occur around the time of ovulation that may be used to help time intercourse. Cervical mucous changes are used most commonly. During non-fertile days, the cervical mucus is thick and acidic. In contrast, during fertile days, the mucus undergoes a change to become thin, profuse, transparent and 'stretchy' (*spinnbarkeit*). A woman's awareness of these changes in her cervical mucus may help her to predict her fertile period.

4.4.2 Serodiscordant couples where the male partner is infected. When the male partner is positive in a serodiscordant relationship he requires optimal medical therapy, including ART when indicated, to minimise the risk of transmission. In resource-limited settings, both partners should be counselled on the risks of transmission, and limited, timed, unprotected intercourse or sperm collection and self-vaginal insemination (Box 4) may be advised. In this scenario, the HIV-negative female partner requires regular HIV antibody testing throughout pregnancy to detect and manage possible seroconversion as soon as possible. In resource-intensive settings, a serodiscordant couple with a positive male partner is an indication for 'sperm washing' and intrauterine insemination, which affords the possibility of conception with minimal risk of male-to-female HIV

BOX 4. LOW-TECHNOLOGY SPERM COLLECTION AND SELF-INSEMINATION TECHNIQUES

Artificial insemination is the process whereby semen is introduced into the female reproductive tract other than by sexual intercourse. It may be intra-uterine or vaginal, the former being a specialist procedure. The latter is a low-risk procedure that can be carried out by a health care provider or by the patient herself.

It is advisable that vaginal insemination be attempted at the most fertile time in the menstrual cycle, which is approximately 2 weeks prior to menses. In a woman with a regular cycle this can be worked out per calendar, but other methodologies include using an ovulation predictor kit, which is commercially available and measures the LH surge. Other indicators include the quality of the cervical mucus and body temperature.

Semen needs to be provided in a clean receptacle, either by male ejaculation into a condom during intercourse or by male ejaculation into a clean specimen jar provided for the purpose. The semen (most men ejaculate 3 - 5 ml) should be inseminated as soon as possible.

Other equipment to carry out the vaginal insemination would include a 'turkey baster' (!), 5 ml plastic syringe or plastic discardable pipette. These items should be supplied to prospective female patients along with the instructions in the appendix.

transmission. PEP/PrEP may also be considered in this setting as protection for the HIV uninfected female partner although this is unproven (see later).

4.4.3 Serodiscordant couples where the female partner is infected. When the female partner is positive in a serodiscordant relationship, there are a wider range of options. It is beneficial for the uninfected male to have been circumcised. If he undergoes a male circumcision procedure, this should be at least 2 months before considering unprotected sex. With the woman's HIV management optimised (viral load undetectable on ART), couples in resource-limited settings may attempt timed peri-ovulatory unprotected sex with appropriate counselling on the risks of transmission. In this case, the male partner may benefit from PrEP or PEP and at the very least will require ongoing HIV testing to identify possible seroconversion. However, it is preferable and feasible to collect the semen of the uninfected male partner and perform vaginal self-insemination around the time of ovulation, thus avoiding the risk of female-to-male transmission. This procedure can easily be taught to the female partner and can be performed with ease in her own home. In addition, if a freshly collected seminal fluid specimen is brought to a clinic, vaginal insemination can easily be performed as a service. In resource-intensive settings, sperm collection and intra-uterine insemination in a female patient with undetectable viral load, would be a preferable option. See Appendix, 'Vaginal artificial self-insemination instructions'.

5. SPECIAL ISSUES

This guideline provides a general approach to safer conception and pregnancy in different situations involving HIV infection. However, there are several potentially common circumstances that are not directly addressed by the strategies described above.

5.1 IS IT EVER APPROPRIATE TO DISCOURAGE PREGNANCY IN AN HIV-INFECTED INDIVIDUAL OR COUPLE?

Ultimately the decision to have a child rests with the patient. However, there are several instances when a clinician may reasonably decide to discourage attempting to have a child. These may include:

- either of the couple has a viral load that cannot be suppressed
- non-disclosure of HIV status to a partner
- documented infertility in either partner
- conditions affecting fertility (although specialist fertility clinics may be able to intervene here)
- medical contraindications, such as active opportunistic/intercurrent infections.

5.2 WHAT IF AN HIV-INFECTED WOMAN DESIRES A CHILD, BUT DOES NOT HAVE A PARTNER?

This raises the question of insemination from alternative sperm sources such as sperm banks, surrogacy and adoption. Should this possibility arise, it is worth knowing what the resources in your area are, what the stipulated eligibilities are and what resources are required for these services. In addition, this situation might be addressed by a sperm donation from a friend, in which case the HIV status of that friend should first be established.

5.3 CAN WE USE PrEP AND/OR PEP TO FACILITATE CONCEPTION WITHOUT HIV TRANSMISSION IN SERODISCORDANT PARTNERS?

PEP for sexual assault survivors has been used for some time, and there is growing interest in PrEP to prevent transmission in serodiscordant partnerships. However, it is important to note that PrEP and/or PEP for discordant couples, initiated before or after sexual intercourse in situations where sperm washing/insemination is not available, have not been validated and could have significant implications for the health of the man, woman or a subsequent child.

While PEP efficacy has not yet been established in a randomised clinical trial, significant data have been collected from cohort studies that suggest that it is an effective intervention. PEP has been recommended for accidental exposure to HIV, either occupational or non-occupational, where the benefits of the medication clearly outweigh the risks. In the case of a serodiscordant couple wanting to conceive, the exposure would be planned. The use of PEP has been reported from a study in men who have sex with men (MSM) in Brazil, who were randomised to take PEP after a risky sexual exposure. The study, conducted by Schecter *et al.*,[27] demonstrated that people have difficulty recognising risk after the fact. This may be due to denial, substance abuse and other factors. Animal models have explored a number of different drug exposures both pre- and/or post-exposure.[28] Current PEP protocols generally state that antiretrovirals have to be given for 28 days after exposure. Some studies have

reported that side-effects related to PEP occur in as many as 77% of users. Currently, then, for every episode of unprotected intercourse, the HIV non-infected partner would take 28 days of antiretrovirals with possible ART-related side-effects.[29]

The evidence for PrEP is also still not well established. The most promising candidate drugs are tenofovir or emtricitabine/tenofovir disoproxil fumarate (FTC/TDF, Truvada). In November 2010, results from a phase III large-scale study, iPrEx, showed that PrEP provided an additional 44% protection from HIV acquisition in men exposed to HIV rectally.[30] The study enrolled 2 499 men and transgender women who have sex with men (who were all at high risk of HIV infection) from Peru, Ecuador, South Africa, Brazil, Thailand and the USA. Half the study subjects were given once-daily oral FTC/TDF and the other half was given a placebo. All subjects received monthly HIV testing and risk-reduction counselling. Among those taking FTC-TDF, 36 became infected with HIV during the trial, compared with 64 in the placebo group.

The FEM-PrEP clinical trial[31] – implemented by FHI in partnership with research centers in Africa – was designed to study whether HIV-negative women who are at higher risk of being exposed to HIV can safely use a daily dose of FTC/TDF to prevent infection. Following a scheduled interim review of the FEM-PrEP study data in March 2011, the Independent Data Monitoring Committee (IDMC) advised that the FEM-PrEP study would be highly unlikely to be able to demonstrate the effectiveness of FTC/TDF in preventing HIV infection in the study population, even if it continued to its originally planned conclusion. The FHI subsequently concurred and has therefore decided to initiate an orderly closure of the study over the next few months. There are a number of possible reasons for the study findings, including low adherence to the study regimen, a true lack of effect of the product among women (v. MSM), or other factors still to be determined.

There is more PrEP research being conducted (Table IV), with the studies on heterosexual transmission being undertaken in Africa in a variety of population groups. There is still much to be learned about effectiveness and real-life implementation, as well as cost-effectiveness.[32]

So what advice can be given to the serodiscordant couple with regard to PrEP? While the results among MSM are promising, and it is likely that PrEP may offer some protection (although whether this will be the case in heterosexual HIV transmission is unknown today), unprotected intercourse with an HIV infected person is never 'no-risk', even if PrEP is partially effective.

6. CASE STUDIES

Case study 1

LM is a 33-year-old woman initiated on EFV, stavudine and lamivudine in May 2005. She responded well to treatment and is currently receiving treatment and care at a down-referral primary health clinic. Her most recent viral load, May 2009, was lower than the detectable limit and her CD4 cell count in January 2010 was 797 cells/µl. She has two children, both over 12 years old, but has no children with her current partner of several years, to whom she has disclosed her status. He is HIV negative.

Initially the patient said that she had no desire to have more children. However, over time she indicated that she and her partner wanted to have a child together. Aside from her ART regimen, she was a good candidate for a safe conception. Upon indicating her intention to conceive, she was referred by study staff for a regimen change. She was told by clinic nurses that a referral was useless as she would need to be up-referred to her initiation site for a regimen change and that up-referrals for regimen changes were not being accepted for planned pregnancies; she should request a regimen change only *after* conceiving. At a subsequent visit on 3 June 2010, the patient had a positive pregnancy test and the same day was up-referred by the primary health centre to her ART initiation site for a regimen change. Upon presenting at the up-referral site with her referral letter, the clinic chose not to accept her back, saying that her current living address was outside their jurisdiction, and referred her elsewhere. The second clinic was willing to receive her, but would not change her regimen or provide an explanation for refusing a regimen change. After 10 weeks of going between clinics the patient was clearly distressed about potential harm that might have been caused to the baby by her current regimen, and after one more failed attempt to receive a regimen change she booked to terminate her planned pregnancy. She had a termination of pregnancy on 25 August, without seeking counselling and discussing her concerns with health care providers or study staff, who might have been able to assuage her fears about the EFV-related risks posed to the baby.

This situation would have been avoided if the patient had: (*i*) received a regimen change when she initially indicated that she was trying to conceive; or (*ii*) failing this, been received by the clinic she was referred to and given an immediate regimen change, as was the expected protocol. Furthermore, had any counselling been provided to her about the actual level of risk associated with EFV-based conceptions, the outcome would probably have been different.[25]

TABLE IV. PrEP RESEARCH IN PROGRESS [32]

Location	Population	Expected completion date
Thailand (CDC)	2 400 injecting drug users	2012
South Africa, Uganda, Zimbabwe (VOICE)	5 000 heterosexual women	2013
Kenya, Uganda (Partners for Prevention)	4 700 serodiscordant heterosexual couples	2013

It is important to note that EFV poses a risk to fetal neural tube development. Neural tube formation occurs at approximately 4 weeks' gestation. The practical point is that unless planned prior to conception, most women on EFV will present after this sensitive time period, making regimen changes both unnecessary and unhelpful. The alternative regimens may be more problematic, e.g. in the case of nevirapine in women with higher CD4 counts (>250 cells/µl), and much more difficult to adhere to in the case of lopinavir/ritonovir (Kaletra). A rule of thumb is not to change unless a pregnant woman on EFV presents at <12 weeks' gestation (first trimester), although one could argue that change is necessary in the case of presentation at >6 weeks.

Case study 2

A nulliparous, 33-year-old HIV-positive woman seeks counselling around safe conception. She had first tested positive for HIV 3 years previously and had been participating in wellness care as her CD4 cell count was still >200 cells/µl. Her partner is HIV positive and on ART. In 2009, the patient's CD4 count was 420 cells/µl. Her most recent CD4 count (June 2010) was 318 cells/µl; a viral load had not been done. The patient desperately wants to conceive, but is worried about MTCT as she is not on ART.

This woman's case is challenging, as she is not indicated to start ART under the national treatment guidelines until her CD4 count drops to 200 cells/µl. However, she is relatively healthy and it may be another year or more before she becomes eligible for ART. The patient understands that as her CD4 count decreases her viral load is rising, and she is worried about a large spike in her viral load around the time of pregnancy if she were to conceive now. On the other hand, if she *were* to conceive, under the new guidelines she would immediately be eligible to start ART as a pregnant woman, since her CD4 count is <350 cells/µl.

What is the best plan of action for this woman if she cannot get started on ART? She can wait for a year or so for her CD4 count to drop and her viral load to spike, start ART and then wait again for another 6 months to achieve virological suppression. At this point she will be 35 and potentially have lowered fertility due to the disease progression and increasing age. Alternatively, she can conceive before ART initiation, with a sub-optimal CD4 cell count and a rising viral load. In this situation she would hope to diagnose the pregnancy as soon as possible, and be initiated onto ART sooner rather than later. The second option allows her to maximise her fertility, particularly now while she is still relatively healthy, but may increase the risk of MTCT and infant mortality, the primary concerns for many HIV-positive women planning to conceive.[14,15] In a resource-intensive setting, the patient would be offered antiretrovirals immediately. There is a potential risk for hypersensitivity and/or hepatotoxicity with nevirapine at a CD4 count of 318 cells/µl. However, EFV is also contraindicated in the first trimester. In South Africa, it would be an option to commence treatment with a boosted PI such as lopinavir or atazanavir. It must be confirmed that both partners are virally suppressed before conception.

WHAT ART IS APPROPRIATE TO USE IN THIS SETTING?

Any woman with reproductive intent who has a CD4 count <250 cells/µl should commence with nevirapine and tenofovir plus lamivudine or FTC. If she is already pregnant and on EFV and presenting in the first trimester, consider changing EFV. If the CD4 count is <250, opt for nevirapine; if >250, opt for a PI, e.g. atazanavir or lopinavir. Note, however, the greater pill burden and possibly greater nausea and vomiting with the latter, especially in the first trimester. If necessary and for simplicity the PI can be changed to EFV in the second or third trimester.

Case study 3

A 24-year-old woman who had been on nevirapine, stavudine and lamivudine since January 2009 indicated that she did not currently want to have any more children. She had a CD4 count of 265 cells/µl and a history of irregular menstrual cycles since HIV diagnosis; she had not menstruated since giving birth 9 months previously. She had a positive pregnancy test during a routine clinic visit in November 2009. She was not prepared for another child and chose to terminate the pregnancy. During her subsequent visit she was encouraged to start family planning, as she indicated that she has difficulty negotiating condom use with her partner. In May 2010, she was diagnosed with a second pregnancy. At this point she went for a second termination of pregnancy in 6 months and was strongly counselled by medical staff to begin using family planning. At her next clinic visit she was still amenorrhoeic. She had a pregnancy test and was given the negative result to present to the clinic nurses in order to initiate an injectable method of family planning. However, she was refused family planning because she was not menstruating. She had a third pregnancy in September 2010.

Amenorrhoea is not uncommon in women, and prolonged amenorrhoea may be more prevalent among HIV-positive women, particularly those with lower CD4 cell counts.[16] Research also suggests that HIV-positive women may be more likely to be ovulating while amenorrhoeic than their HIV-negative counterparts.[17] Policies, whether formally written or just informally followed, to initiate family planning only on the first day of a woman's menstrual cycle are inconvenient for women and result in lower contraceptive uptake and increased rates of unplanned pregnancies. These policies also do not take into consideration HIV-related health concerns, such as an increased risk of amenorrhoea, specific to HIV-positive women. Clear guidelines must be in place to address fertility concerns related to family planning for HIV-positive women.

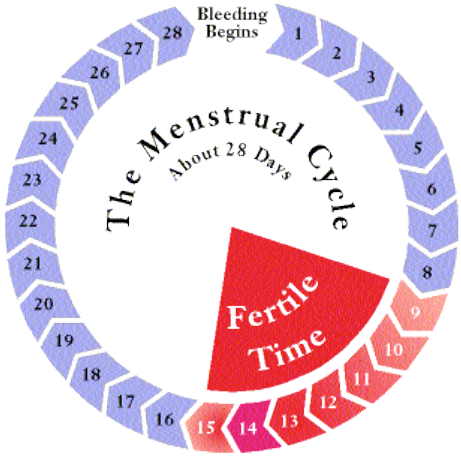
APPENDIX. VAGINAL ARTIFICIAL SELF-INSEMINATION INSTRUCTIONS

Vaginal artificial self-insemination is the process of placing sperm into your vagina without your partner's penis going inside you. This gives you the chance to get pregnant without the risk of passing HIV on to your partner.

Two important things will give you the best opportunity to get pregnant. Firstly, do the artificial insemination at the time of the month when you are the most fertile, and secondly do not wait too long to place his sperm inside you.

How do you know when it is your most fertile time?

The most fertile time in your menstruation cycle is 2 weeks before you get your period, or around day 14 of your cycle.



Other signs to look out for are an increase in your body temperature (if you have a thermometer) or changes in your vaginal discharge. The mucus will become more clear and sticky – you can pull it into strings if you rub it between your fingers.

What you need to do when the time is right.

The first thing to do is to get a sample of sperm from your partner. You can do this in two ways. You can have sex with a condom (don't use one with spermicide) and use the semen that is captured in the end of the condom. The other way is to get your partner to ejaculate into a clean container you can get from the clinic for this purpose. He can do this with your help or on his own.

Once you have the semen sample, don't wait too long. As soon as possible you need to draw the semen into a 5 millilitre (ml) clean plastic syringe without a needle or a bulb pipette (your local clinic can provide you with one). The next thing to do is to get yourself in the right position. Lie on your back with your knees bent. Place a cushion under your hips to get your back flat and your pelvis tipped up.

Make sure you have got all the extra air out of the pipette or syringe and place it into your vagina, a bit like you would a tampon. Don't push it up too far. (This should NOT be painful. If it is, stop what you are doing and report to your clinic.) Then slowly push the semen out of the syringe or pipette backwards into your vagina.

If possible try to stay in this position for an hour. The chance that you will get pregnant might be a bit better if you masturbate and bring yourself to orgasm while you are lying there, although this is not required if you are not used to it.

Lie on back with knees bent | Place a cushion under hips | Slowly push semen from syringe into vagina | Stay on your back for 1 hour

Realistically, the possibility that you will get pregnant is around 5 - 10%. You can try this technique 2 - 4 times during your fertile time. The more often you try, the greater your chance of success.

If you have any questions ask your counsellor or health care provider.

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CASE STUDY

UNUSUAL PRESENTATION OF EXTRAPULMONARY TUBERCULOSIS: A CASE REPORT ON MAMMARY TUBERCULOSIS

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This case study highlights an unusual manifestation of extrapulmonary tuberculosis (TB) in a person living with HIV, namely mammary TB. Clinicians practising in settings where HIV and TB are endemic need to be aware of the clinical presentation, diagnosis and management of mammary TB.

The incidence of extrapulmonary (EP) tuberculosis (TB) is increased in patients with advanced HIV infection.[1,2] Mammary TB is a rare manifestation of EPTB, and this report describes a case of TB mastitis and TB-associated immune reconstitution syndrome (IRIS) with advanced HIV infection.

CASE REPORT

A 34-year-old woman presented with a 2-month history of loss of weight, non-productive cough and painful swelling of the right breast. There was no past history of TB, and the patient did not know her HIV status. Clinical examination revealed a unilateral 10x8 cm mass in the upper outer quadrant of the breast, with no lymph node involvement. A fine-needle aspirate (FNA) was performed and the mass was then incised, drained and dressed. Acid-fast bacilli (AFB) were isolated from the FNA using an auramine stain, and the mycobacterial growth indicator tube culture was positive at 3 weeks. The *Mycobacterium tuberculosis* (MTB) strain isolated was sensitive to all anti-TB drugs. In addition, concurrent pulmonary tuberculosis (PTB) was diagnosed through a positive sputum AFB smear and compatible changes on the chest radiograph (CXR). The CXR also showed no communication between the lung and chest wall. The intensive phase (IP) of TB treatment, consisting of rifampicin, isoniazid, pyrazinamide and ethambutol, was commenced. An uneventful clinical course followed on TB treatment, and the breast mass resolved completely. The patient accepted counselling and testing for HIV on diagnosis of PTB and was found to be HIV infected.

Sputum smear reversion occurred 2 months after TB diagnosis. The patient was commenced on antiretroviral therapy (ART) after 3 months of TB treatment. A once-daily regimen of didanosine, efavirenz and lamivudine was chosen because of its substantial potency and tolerability with TB treatment. The patient presented 2 weeks after initiation of ART with a 4-day history of a painful sternal mass. Clinical findings included new-onset generalised lymphadenopathy, a 3 cm tender erythematous sternal mass with overlying desquamation, a 5 cm firm non-tender right breast mass recurring in the previous site, and two 10 cm soft, non-tender mobile masses, one over the left scapula and the other centrally over the spinal column. A full blood count demonstrated bicytopenia, neutropenia and normochromic anaemia with abnormally low folate levels. The patient's CD4 count was 163 cells/µl and her viral load 932 553 copies/ml (log 5.97).

Staphylococcus aureus was isolated from a pus swab of the sternal lesion and treated with a course of flucloxacillin. A Ziehl-Neelsen stain of an FNA of the breast mass isolated AFB but was culture negative. Cytology demonstrated thick inflammatory/necrotic debris with numerous epithelial granulomas, and no ductal cells.

The patient completed 7 months of TB treatment and uninterrupted ART. Eighteen months after ART initiation, her CD4 count was 480 cells/µl with an undetectable viral load. The sternal and breast masses had resolved completely. However, the patient refused excision biopsy for histologically confirmed lipomas on the posterior chest wall.

DISCUSSION

In the pre-AIDS era, incidence rates of TB mastitis were 0.1% and 3% of all breast lesions in developed and developing countries, respectively.[3] However, reports of TB of the breast are becoming more common with the advancing HIV epidemic, especially over the past decade (Table I).

In immunocompromised patients in particular, haematogenous spread of MTB from a primary focus can result in mammary TB. The primary site of TB in this report was the lung parenchyma. TB of the breast most commonly presents as a lump in the central or upper outer quadrant of the breast,[18] as in this case. Diagnosis is based on multiple factors including clinical history, examination, histological features, and in some cases response to empiric TB treatment. FNA of the breast lesion remains the single most important diagnostic method.[14] Histopathological examination reveals suppuration and

TABLE I. SUMMARY OF LITERATURE REVIEW OF TB MASTITIS CASES

Author, year	No. of cases	Isolation of MTB		
		Breast only	Co-morbid PTB	Pattern of drug-resistant TB, site
Kalaç *et al.*[4]	5	4	1	RI resistance, lung
Tewari and Shukla[5]	30	30	-	-
Khanna *et al.*[6]	52	52	-	-
Green and Ormerod[7]	10	5	5	IE resistance, breast
Morino *et al.*[8]	2	1	1	-
Sakr *et al.*[9]	10	10	-	-
Ahmed and Sultan[10]	10	2	8	-
Sriram *et al.*[11]*	1	1	-	-
Fadaei-Araghi *et al.*[12]	8	1	-	-
Kumar and Sharma[13]	1	1	-	RIS resistance, breast
Kakkar *et al.*[14]	164	164	-	-
O'Reilly *et al.*[15]	1	1	-	-
Al-Marri *et al.*[16]	13	13	-	-
Harris *et al.*[17]	38	33	5	-

*This was the only report that documented HIV status; the patient was HIV uninfected.
R = rifampicin; I = isoniazid; E = ethambutol; S = streptomycin.

a degree of necrotising inflammation that is uncommon in profoundly immunocompromised patients.[19]

The development of the breast mass after initiation of ART may be related to the unmasking of TB-associated IRIS. It is unusual for MTB-associated IRIS to present as a breast mass; commonly fever, lymphadenopathy or worsening pulmonary symptoms characterise MTB IRIS.

This case highlights the need for a high index of suspicion of EPTB presenting in unusual sites particularly against a background of high TB and HIV prevalence. It also demonstrates the clinical diagnostic and management dilemmas faced by clinicians in this setting.

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Conflict of interest: The authors declare that there are no conflicts of interest.

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CASE STUDY

TRANS-HIATAL OESOPHAGECTOMY IN AN AIDS PATIENT

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A 49-year-old man was diagnosed as HIV infected, with a CD4 count of 60 cells/µl. He was started on an antiretroviral treatment regimen comprising zidovudine, lamivudine and efavirenz. Following treatment, his CD4 count improved and the viral load was undetectable. He was subsequently found to have a moderately differentiated adenocarcinoma of the lower oesophagus.

CASE STUDY

A 49-year-old male security supervisor was admitted to hospital with recurrent chest infections. He was found to be HIV positive with a CD4 count of 60 cells/µl, and was started on an antiretroviral treatment regimen comprising zidovudine, lamivudine and efavirenz. Six months later the absolute CD4 count had increased to 249 cells/µl and the viral load was undetectable.

Nine months after initial HIV diagnosis the patient complained of progressive dysphagia for solids for 2 months and a weight loss of 5 kg during the same period. He denied loss of appetite, haematemesis or symptoms of gastro-oesophageal reflux disease. He weighed 76 kg with a body mass index of 25.9.

Clinical examination was unremarkable, with no evidence of an abdominal mass, hepatomegaly or left supraclavicular lymph nodes. Upper gastro-intestinal endoscopy showed a polypoidal growth of the abdominal oesophagus. There was no evidence of candidal oesophagitis. Histological examination revealed a moderately differentiated adenocarcinoma. A computed tomography (CT) scan showed a T2 tumour with no evidence of regional lymph node enlargement or hepatic metastases.

The patient underwent trans-hiatal oesophagectomy with a cervical oesophago-gastric anastomosis. A jejunostomy feeding tube was placed at the time of surgery in view of his dysphagia and poor oral intake. Three days after surgery, he developed a lower respiratory tract infection which was treated with intravenous co-amoxyclavulanic acid. He responded to treatment and was discharged on the 11th postoperative day. Histological examination showed a moderately differentiated adenocarcinoma with involvement of the para-oesophageal and left gastric lymph nodes. The feeding jejunostomy was removed.

The patient received an adjuvant regimen of two cycles of chemotherapy (5-fluorouracil 1 g/m^2 and cisplatin 100 mg/m^2) and concurrent local radiotherapy (45 Gy). Twelve weeks after the conclusion of his treatment course, a repeat CT scan of the chest and abdomen showed significant tumour regression and no evidence of metastatic disease. He was able to return to his occupation, and his quality of life was not affected.

At 2 months' follow-up the patient's absolute CD4 count had decreased to 117 cells/µl. At 6 months it had risen to 211/µl. He continued on antiretroviral therapy, but died of metastatic disease and opportunistic infections 16 months after surgery.

DISCUSSION

The commonest cause of dysphagia in patients with AIDS is candidal oesophagitis. Cytomegalovirus oesophagitis is less frequently seen.[1] Because oesophagitis is a common complaint in this group of patients, heightened awareness of the risk of malignancy and a low threshold for upper gastro-intestinal endoscopy are necessary to avoid a delay in diagnosis. Our patient was free of oesophagitis, and his symptoms were suggestive of mechanical oesophageal obstruction.

Oesophageal adenocarcinoma in HIV/AIDS has been reported, but very few of these patients have undergone a potentially curative resection.[2-4]

Demographic analysis of HIV/AIDS patients with oesophageal carcinoma is not possible owing to the paucity of reported cases. It is likely that improved survival in these patients has permitted the development of other disease processes. It is also possible that the immunosuppression associated with HIV/AIDS puts them at a higher risk of developing oesophageal cancer.

The impact of oesophageal cancer surgery, in terms of postoperative survival as well as quality of life, is still largely unknown. Clinical experience and the scarce existing literature both suggest that these patients find it difficult to return to their previous lifestyles and social activities, not just owing to the problems common to all malignant tumours but because of the specific dietary and digestive disturbances resulting from oesophageal cancer therapy.[5] Our patient was able to eat a normal diet and return to work and to his original lifestyle within 1 month after surgery.

The impact of oesophageal cancer and its treatment on survival in AIDS patients can only be ascertained with long-term follow-up. However, the recent improvement in life expectancy in AIDS patients means that oesophageal malignancies should be treated aggressively to ensure maximal survival in this challenging subgroup.

The treatment of HIV infection has undergone considerable change. When used as part of combination drug regimens, protease inhibitors and non-nucleoside reverse transcriptase inhibitors can profoundly suppress viral replication, with consequent repletion of CD4 cell counts.[6] Our patient responded well to antiretroviral therapy, both before diagnosis and after treatment of his oesophageal cancer.

Pre-operative status and co-morbidity are strong predictors of outcome. The prognosis for oesophageal carcinoma varies depending on the stage at presentation. A 2005 study showed 5-year survival rates of around 67% for resectable stage 0 - 1 oesophageal cancer, 33% for stage 2, and 8% for stage 3.[7]

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Concerning INH preventive therapy (IPT) in children:

1. True (A) or false (B):
   Tuberculosis (TB) must be excluded before commencing IPT in HIV-positive children.
2. True (A) or false (B):
   HIV-infected infants have a twofold greater incidence of TB than their HIV-uninfected counterparts.
3. True (A) or false (B):
   Failure to thrive is a strong consideration in deciding whether an infant is possibly infected with TB.
4. True (A) or false (B):
   Infant exposure to a TB case requires 3 months of IPT.
5. True (A) or false (B):
   IPT should only be given to children >5 years after a TB exposure.
6. True (A) or false (B):
   Children of mothers who did not receive screening for TB during antenatal care may require IPT.
7. True (A) or false (B):
   IPT may be given to children already on ART, especially if they are Mantoux positive and have no TB symptoms.
8. True (A) or false (B):
   In a child, a Mantoux induration of >2 mm is considered positive in the absence of ART.
9. True (A) or false (B):
   In the absence of TB disease, IPT must always be commenced before ART.

Concerning safer conception in HIV infected couples:

10. True (A) or false (B):
    Pre-exposure prophylaxis involves giving antiretroviral therapy to HIV-uninfected individuals to reduce the risk of HIV acquisition.
11. True (A) or false (B):
    HIV transmission is independent of HIV viral load in the blood.
12. True (A) or false (B):
    In discordant couples considering conception, it is important to know the HIV status of both individuals.
13. True (A) or false (B):
    In the case of an HIV-infected male partner, sperm can be washed to reduce the HIV viral load before insemination into a negative partner.
14. True (A) or false (B):
    In the case of a positive female partner, vaginal insemination can reduce the risk of HIV transmission to a negative male partner.
15. True (A) or false (B):
    Vaginal insemination is a technical procedure that requires a sterile environment and specialist input.
16. True (A) or false (B):
    In discordant couples, ensuring that the positive partner is well established on ART with an undetectable viral load is an effective way to reduce HIV transmission.
17. True (A) or false (B):
    ART is only safe in the third trimester of pregnancy.
18. True (A) or false (B):
    Efavirenz should be avoided throughout pregnancy.

Concerning human papillomavirus (HPV):

19. True (A) or false (B):
    Infection with HPV may result in cancerous transformation in the cervical mucosa.
20. True (A) or false (B):
    All strains of HPV are oncogenic.