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CONTENTS

FROM THE EDITOR

Sexual violence — the neglected epidemic

5

HORIZONS

Challenges ahead

7

CLINICAL

Immune restoration in the context of HAART

8

CONFERENCE COMMENTARY

What lessons have we learned? Proceedings of the 9th European AIDS Conference, Warsaw, 25 - 29 October 2003

15

Artworks in this edition come from the National Paper Prayers Campaign, initiated and co-ordinated by Artist Proof Studio. This is an initiative which gives South Africans a chance to respond positively and creatively to the AIDS epidemic. The idea of Paper Prayers comes from the Japanese custom of hanging up strips of paper as prayers for healing. Exhibitions have been held nationally and internationally and prayers are sold to raise funds for AIDS organisations. Workshops for health workers, teachers and people living with AIDS can be arranged by ringing Artist Proof Studio (011) 492 1278.

CONTENTS

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GUIDELINES

Medical management of a survivor of sexual assault/abuse

21

Updated guidelines for the use of rifamycins for the treatment of tuberculosis in HIV-infected patients taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors

28

ART IN RESOURCE-POOR SETTINGS

Provision of antiretroviral therapy in resource-limited settings — a review up to August 2003

34

MEDICO-LEGAL

An overview of some of the key legal developments in HIV/AIDS and the law — 2003

40

HIV/AIDS, law and ethics: A brief analysis of some pertinent issues

44

DRUG COSTS

Update on the pharmaceutical industry

46

CPD QUESTIONNAIRE

48



GlaxoSmithKline

Discovery Health



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FROM THE EDITOR



SEXUAL VIOLENCE — THE NEGLECTED EPIDEMIC

South Africa is thought to have one of the highest incidences of sexual assault in the world. About 50 000 rapes were reported in 2001 alone, although it is thought that this is just a small percentage of the total number. One of the main reasons that rape is so prevalent in South Africa is that the justice system is so ineffective in dealing with it. Most rapists walk free. Of 50 000 reported cases in 2001 only about 5 000 resulted in convictions. Similar statistics were reported by the South African police service in 2002, but a very worrying statistic is that more than 40% of survivors of sexual assault who reported their cases to the police between February 2002 and March 2003 were girls under 18, with 14% being 12 years or younger. This would mean that pre-teens and teenagers are at much higher risk of sexual assault than the population as a whole. In 2000 and 2001 the reported incidence of rape and attempted rape of children increased, even as the incidence among adults began to stabilise. Far too many girls have no safe haven from sexual violence, and many girls are coerced to have sex and subjected to sexual harassment by male relatives, boyfriends, schoolteachers and male classmates.¹

In 2002, a government study once again found that only 7.7% of reported rape cases resulted in convictions and that a large number of cases were still being withdrawn after having been registered, despite police instructions not to do so.

The causes put forward by sociologists in an attempt to explain the high incidence of sexual assault are many and varied. They include societal attitudes in a male-dominated

and patriarchal society, lack of empowerment of women, the culture of violence as a legacy of the apartheid years, and a number of 'rape myths', among the most hideous of which is that sex with a virgin is a cure for AIDS.

An important component of this neglected epidemic is sexual violence against both men and young boys. Between September 2000 and April 2003 a private hospital group that provides post-exposure prophylaxis (PEP) for survivors of sexual violence treated 67 male patients out of a total of 1 465 (4.5%).² Other private clinics have reported similar statistics. In the 2003 annual report by Judge Hannes Fagan (the inspecting judge of prisons) he said that South Africa has one of the highest proportions of prisoners for its population in the world, possibly the highest in Africa. Four out of every 1 000 South Africans are in jail and prisons hold 70% more people than they were designed to accommodate, which is known to contribute to the spread of HIV/AIDS. During the Jali Commission (investigating corruption in prisons) rape was said to be most prevalent among awaiting-trial prisoners because of overcrowding and the fact that there are no separate holding facilities for people who have been accused of different classifications of crime. Compounding these circumstances, most male prisoners do not report rape and awaiting-trial prisoners have no access to social workers or other professionals. During the commission interviews, police inspectors reported that they could not recall any prosecutions involving cases of sodomy in prison.

The HIV Clinicians Society has over the years been very concerned about this largely neglected field of patient management. The Society receives calls on a regular basis from members seeking guidance on how to deal with victims of sexual assault. We believe that to deal with the epidemic the justice system needs to be strengthened in order that more cases are brought to court and more rapists convicted of this heinous crime. We as doctors, however, have to play our part in providing the required evidence in a proper manner which will make the prosecutors' task so much easier. The other issue at stake is the provision of PEP for survivors of sexual assault. We believe that the article by Dr Adrienne Wulfsohn on p. 21 both addresses the issue of appropriate management of a case of sexual assault and also provides guidelines as to how forensic specimens should be obtained. This will empower doctors to deal more adequately with patients who have been sexually assaulted and play their part in combating this neglected epidemic.

DES MARTIN

*Editor, Southern African Journal of HIV Medicine
President, Southern African HIV Clinicians Society*

1. See, e.g. Human Rights Watch, *Scared at School: Violence Against Girls in South African Schools* (New York: Human Rights Watch, 2001).
2. Human Rights Watch interview with Mandé Toubkin, Johannesburg, 19 May 2003: Mandé Toubkin, 'Rape: A Social Responsibility Project. Can It Be Managed in The Private Health Care Environment?', Power Point presentation, 2003.

CHALLENGES AHEAD

'Lack of access to antiretroviral therapy is a global health emergency. To deliver antiretroviral treatment to the millions who need it, we must change the way we think and change the way we act.' Wise words spoken by Lee Jong-wook, Director General of the World Health Organisation. The 3 by 5 initiative was created by WHO because the six million people currently infected with HIV in the developing world need access to antiretroviral therapy to survive. Only 400 000 people worldwide have this access. So WHO has set the targets at 3 million on treatment by 2005, and time is marching on. WHO has developed a strategic framework for this based on five pillars:

- Global leadership, strong partnership and advocacy
- Urgent sustained country support
- Simple standardised tools for delivery
- Effective reliable supply of medicines and diagnostics
- Rapidly identifying and reapplying new knowledge and successes.

We have just returned from an antiretroviral meeting in Dakar, Senegal, a vibrant interesting city where there is clear evidence of political leadership and support in the area of HIV. Health care professionals from West and Central Africa were keen to share experiences and discuss standardised strategies, and hungry for new knowledge and lessons learned. Very exciting developments are taking place in so many countries. Even in a country as battered as Zimbabwe we were told of a number of projects already enabling people to receive ART, and plans are in place for expansion.

Indeed, as we look back at more than a year of the Usapho Lwethu project in Gugulethu, Cape Town, I am so excited. It can be done – we *can* deliver treatment, people *will* take drugs faithfully, lives *can* be turned around and the progression of this horrible disease halted. The challenge for us all now is how to do this on a much greater scale. We need 53 sites in South Africa to be up and running in the next 6 months and 1.4 million HIV-infected people to be on treatment by 2007 to meet government targets.

There seems to be a hive of activity, but things will never move quickly enough, to which anyone who is HIV-infected and facing AIDS will bear testimony. There remains concern whether roll-out is happening at the same rate in all provinces – it is well known that some provinces have more to do than others, but there is no doubt that overall there is a huge amount of work to be done.

Pillar five is interesting and poses some challenges, since the field of HIV medicine is an incredibly fast moving one. No sooner

is a paper or concept published than it is out of date. One needs to be on the conference circuit continuously to keep one step ahead of the most recent data.

Some interesting nevirapine data have recently come to light. A study published in the *Journal of the Acquired Immune Deficiency Syndrome* describes a higher rate of severe hepatotoxicity in non-HIV-infected than in HIV-infected individuals, and the rate in the latter group was higher with higher CD4 counts. The study therefore recommended that the use of post-exposure regimens containing nevirapine should be discouraged.¹

Montaner and colleagues² have published findings that the risk of serious hepatotoxicity may be increased in individuals co-infected with hepatitis B and C, abnormal liver enzymes at baseline or higher CD4 counts (> 350/ μ l).² A worrying paper from the Paris meeting by Lyons *et al.*³ entitled 'Nevirapine tolerability in HIV-infected women in pregnancy – a word of caution' indicates that there is a significant risk of nevirapine-associated hepatotoxicity in pregnant women, especially those with high CD4 cell counts, and that the progression to severe hepatotoxicity may be explosive and not predicted by the patient's enzyme level at baseline. The risk of nevirapine-related hepatotoxicity and rash, which seems to be caused by an acute and idiosyncratic hypersensitivity reaction, increased with increasing CD4 cell counts. Hence women with CD4 counts > 250 and men with CD4 counts > 400 or persons with recent exposure to HIV and therefore relatively normal immune responses are at particular risk.³

For these reasons, the Centers for Disease Control recommends against the use of nevirapine as post-exposure prophylaxis.⁴ While the 'once dosing' regimen used in South Africa for PMTCT is unlikely to cause hepatotoxicity, the data also suggest that the use of nevirapine in patients and pregnant women with high CD4 counts may be problematic and it may be necessary to measure CD4 counts before commencing a long-term nevirapine-containing regimen.

LINDA-GAIL BEKKER

Managing Editor

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IMMUNE RESTORATION IN THE CONTEXT OF HAART

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The advent of highly active antiretroviral combination therapy (HAART) has resulted in significantly improved survival of patients and a reduction in the progression of human immunodeficiency virus (HIV) infection.¹

At the root of these clinical benefits is a dramatic reduction in HIV viral load. HAART induces a sustained effective suppression of HIV replication in most patients and leads to a preservation or restoration of immune function.

The restoration of an impaired immune system is assessed by clinical parameters, immunological changes which can be measured in the laboratory and a marked reduction in the morbidity and mortality of patients. To understand the features of immune restoration it is necessary to review the immunopathogenesis of HIV infection and highlight areas where improvement of function occurs with HAART.

THE IMMUNOPATHOGENESIS OF HIV INFECTION

It is important to remember that the destruction of the immune system is related to the kinetics of viral replication. In most cases increased viral replication is associated with a more rapid destruction of the immune system and a more rapid progression of HIV disease.

The hallmark of HIV infection is a loss of CD4+ lymphocytes. The loss of lymphocytes occurs for a variety of reasons, among them direct destruction of CD4+ cells, immunologically mediated CD4+ loss and apoptosis (programmed cell death), which is related to the intense and ongoing immune activation invariably present throughout the course of HIV disease. In early disease the loss of CD4+ cells is compensated for by an increased output and the CD4+ lymphocyte homeostasis is largely maintained. This situation continues for the first few years, but progressive events occur in lymphoid tissue which compromise the output of CD4+ lymphocytes.

MECHANISM OF CD4+ CELL LOSS

- Direct cytotoxic effect of viral replication
- Immunologically mediated destruction
- Apoptosis mediated by immune activation
- Bone marrow stem cell failure
- Thymic failure of CD4+ cell programming

IMMUNE RESPONSES TO HIV INFECTION

Cytotoxic T cells (CTLs)

Studies in persons with chronic HIV-infection have detected both cellular and humoral immune responses to HIV.² As in other chronic viral infections cytotoxic T lymphocytes are generated in response to infections that inhibit virus replication by at least two mechanisms. In the first instance direct killing of cells infected with HIV occurs. Small peptide fragments form complexes with class 1 HLA molecules and these are presented on the cell surface to trafficking CTLs. The presence of a viral peptide (usually 9 - 10 amino acids in length) within the peptide-binding cleft of a class 1 molecule is a signal to the immune system that a foreign pathogen is present within that cell. This then triggers the CTL to kill the infected cell through a direct recognition mediated by the T-cell receptor (TCR) on the CTL. The killing of the cell results from a production of perforins and granzymes secreted by the CTL.

The second mechanism exerted by the CTL is the release of soluble antiviral factors via the activated CTL. These include the beta-chemokines (RANTES, MIP-1alpha and MIP-1beta). There is also a further soluble factor, which is in the process of being defined. This factor, termed the CD8+ antiviral factor (CAF), is thought to suppress viral replication at the transcriptional level. This occurs in a non-major histocompatibility complex (MHC) manner.³

Each HLA class 1 allele is slightly different and therefore there is variation in the viral peptides that are able to bind

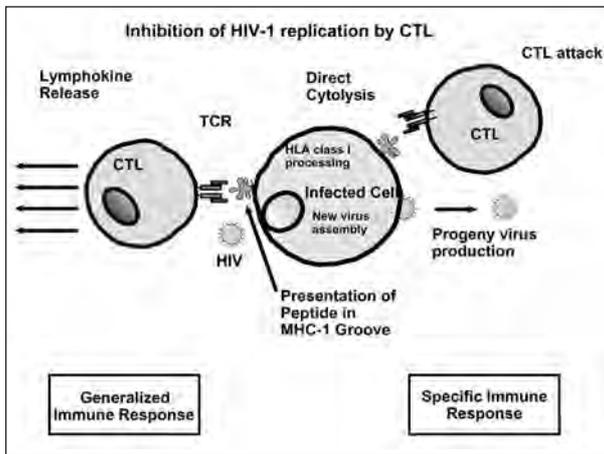


Fig. 1. Inhibition of HIV-1 replication.

to a specific allele. As over 50 class 1 alleles have now been defined it can be seen that many different viral peptides can be bound and presented, and consequently there is a considerable variation between individuals with regard to their immune response. The importance of CD8+ CTLs is seen throughout the course of HIV disease. It is an important mechanism to curtail HIV replication at primary infection, and high levels of CD8+ cells are especially seen in persons who are slow progressors (so called long-term non-progressors).

Virus-specific T-helper cells

In addition to CTLs the cellular immune response is also associated with the generation of virus-specific T-helper cells. These cells are required for the maintenance of CTL function. CD4+ T-helper cells recognise viral proteins that have been taken up in lysosomes of antigen-presenting cells (APCs). There they are processed to smaller peptides and then presented at the cell surface within the peptide-binding groove of class 2 HLA molecules. The presence of

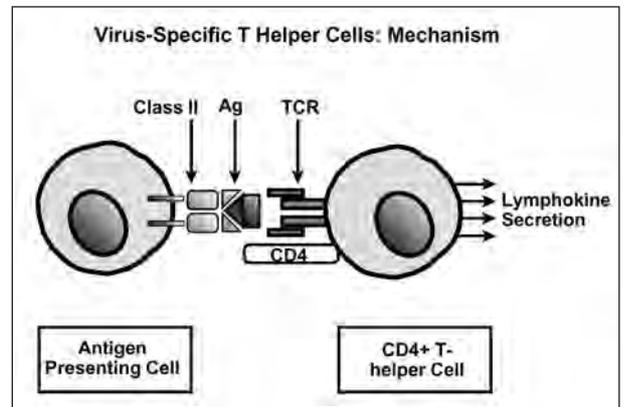


Fig. 2. Virus-specific T-helper cells mechanism.

a viral peptide in the class 2 binding group elicits a CD4+ helper response, which in turn orchestrates an overall immune response. The CD4+ helper effect is mediated by direct cell-to-cell interactions and the release of a number of cytokines. The viral peptides that service targets for the T-helper response tend to be larger than those involved in CTL recognition (12 - 15 amino acids in length).

Antibodies

Neutralising antibodies are detected in HIV infection and are targeted against a number of different epitopes. These include antibodies directed against portions of the envelope protein that are involved in virus entry to the cell (V3 loop antibodies) and in CD4+ binding (CD4+ binding site antibodies).⁴ One of the limitations of neutralising antibody responses is that they are typically type-specific. This means that antibodies generated against one particular virus may not cross-react with others. This has implications for immune control since viruses continue to mutate within the infected host and are constantly escaping immune detection.

IMMUNE ACTIVATION		
<p>Positive consequences</p> <ul style="list-style-type: none"> ■ Expression of activation antigens – HLA-DR, CD38 ■ Activation of monocytes ■ Lymph node hyperplasia ■ Increased cytokine expression ■ Antiviral effects ■ Removal of infected cells normal vigorous immune response 	<p>Negative consequences</p> <ul style="list-style-type: none"> ■ Promotes reverse transcription ■ Viral integration ■ Upregulates viral replication ■ Induces expression in latently infected cells ■ Spread to activated cells ■ Anergy of immune cells ■ Perturbation of T-cell repertoire chronic immune activation 	<p>Immunodeficiency</p> <ul style="list-style-type: none"> ■ Chronic immune system dysfunction ■ Reduction of function of macrophages, neutrophils, dendritic cells and NK cells leading to decrease in chemotaxis, microbial killing, altered cytokine expression and antigen presenting function ■ Decreased CD4+ responses to recall antigens, allo-antigens and mitogens ■ Decreased cytokine production especially IL-2 ■ Decreased CD8 responses and CTL functions immune exhaustion

IMMUNE ACTIVATION

One of the hallmarks of HIV infection is a chronic immune activation, which persists for years. Immune activation is a necessary component in any immune response to infecting pathogens, but after the acute event the immune activation usually subsides. In HIV disease the persistent generation of both humoral and cellular escape mutants means that in effect the immune system is constantly facing a new pathogen, and this leads to a persistent state of immune activation. The negative consequences of immune activation are induction of activation of cells, which in turn leads to productive infection of latently infected cells and also makes uninfected cells more susceptible to infection. Immune activation also promotes apoptosis of uninfected CD4+ lymphocytes and thus contributes to the overall CD4+ cell loss.

Both CD4+ and CD8+ cells all have surface expression of molecules such as CD38 and HLA-DR that are associated with immune activation. Recent studies⁵ have shown that high-level expression of CD38 on CD8+ cells is a powerful predictor of HIV disease progression. CD38 expression also correlates with lymphocyte susceptibility to programmed cell death.

IMMUNE PHENOTYPIC CHANGES

The CD4+ lymphocyte compartments consist of two functional subsets separated on the basis of expression of certain cell surface markers. Naïve cells express CD45RA and CD62L whereas memory cells express CD45RO. In principle, naïve cells are newly generated through a selection process in the thymus. Naïve cells have the potential to generate immune responses to newly encountered antigens but are not particularly capable of cytokine expression or of effector cell activity. After exposure to antigenic peptides expressed on cell surface class 1 MHC molecules (CD8+ cells) or those on cell surface class 2 MHC molecules (CD4+ cells), naïve cells evolve into effector cells and will eventually express the memory phenotype. These cells are capable of an array of cytokine expression and also possess effector cytolytic activity. After antigenic exposure the majority of effector cells die by apoptosis and a minority revert to the memory state. These cells are capable of rapid responses to previously encountered antigens providing the classic secondary or anamnestic response to previously encountered antigens. In healthy adults approximately 50% of circulating cells are of the naïve phenotype and 50% of memory cells.

CYTOKINES-TH1/TH2 AXIS

T-helper lymphocytes consist of two distinct subsets designated TH1 and TH2. The differentiation into the subsets is based on the cytokine profiles elaborated by the

individual subsets. Cytokines are soluble factors produced by immune cells that subserve immunological functions. The TH1-subset is associated with the production of interleukin-2 (IL-2) and gamma interferon (IFN- γ). The TH1-response promotes cell-mediated immunity and enhances CD8+ lymphocyte function. This is seen in early disease and is also part of immune restoration after HAART is initiated. The TH2-response is associated with the production of IL4, IL5, IL6 and IL10. The TH2-response is linked to an enhanced humoral activity with activation of B cells. There is a cross-regulation between the two functional subsets (Fig. 3). During progression of HIV infection there is a switch from a TH1 to a TH2 cytokine profile, which is often reversed following the increase in CD4+ cell numbers and function with HAART.

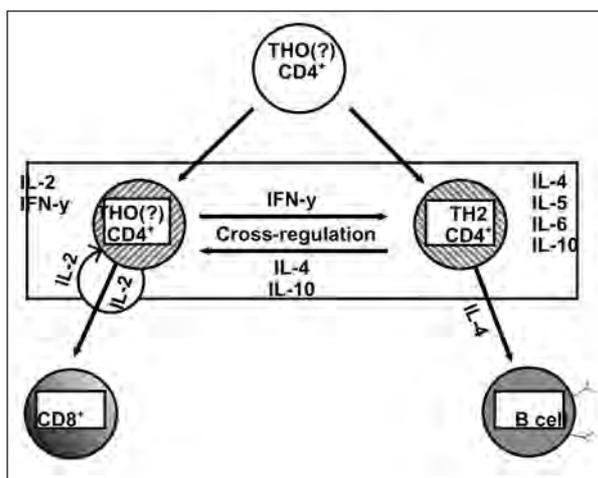


Fig. 3. TH1 and TH2 model.

THE T-CELL REPERTOIRE

An enormous diversity of foreign antigens, approximately 10^{13} to 10^{15} , are recognised by T cells through the T-cell receptor to antigen (TCR). This comes about following intrathymic maturation by the diversity of recombination in the gene fragments that encode the TCR, with each TCR providing the specificity for a given antigen. The overall diversity of the T-cell repertoire decreases with age and also following chronic exposure to antigens. This process is accelerated throughout the course of HIV infection because of the state of immune activation and also because thymic output decreases once the thymus gland itself becomes infected. The introduction of HAART improves the diversity of the TCR repertoire via both a thymic regeneration of naïve cells and a decrease in immune activation, which is associated with consumption of T-cells.

THYMIC FUNCTION

It is a long-held view that thymic function decreases with age and is not present at all in adults. This view has been challenged in recent times.⁶ It has been observed in HIV-infected persons that thymic responses occur as measured

by increase in thymic size in patients on treatment and also by an increased thymic output of naïve cells.

IMMUNOLOGICAL CHANGES WITH DISEASE PROGRESSION

- Decreased CD4+ lymphocyte count
- Increased CD8+ lymphocyte count (from sero-conversion to late-stage disease)
- Decreased naïve CD4+ lymphocytes (CD45RA)
- Decreased memory CD4+ lymphocytes (CD45RO)
- Increased activation markers
 - Increased HLA-DR on CD8+ lymphocytes
 - Increased CD38+ on CD8+ lymphocytes
- Decreased HIV-specific CD4+ lymphocytes
- Decreased TCR repertoire diversity
- Switch from TH1 to TH2 cytokine profile

IMMUNE RESTORATION FOLLOWING HAART

The benefits of HAART can be shown not only in the clinical context but also by following certain laboratory parameters that relate to immune function. The introduction of HAART has led to a marked decrease in the incidence of opportunistic infections and it has also been shown that certain categories of opportunistic disease may disappear without specific therapies. Complete or partial resolution has been reported in the following conditions:

- progressive multifocal encephalopathy
- Kaposi's sarcoma
- oral hairy leukoplakia
- oral/oesophageal candidiasis
- cryptosporidiosis/microsporidiosis.

ENHANCED IMMUNE FUNCTION

After commencement of HAART there are at least two phases of changing numbers of circulating lymphoid cells. The first-phase increase in the CD4+ cells is composed of memory cells that lack markers of cell proliferation, suggesting that these cells have been redistributed from other lymphoid sites into the general circulation. This comes about as a result of suppression of viral replication in lymphoid tissue and CD4+ lymphocytes are thus 'freed' from being sequestered in these sites. The early (often impressive) CD4+ lymphocyte increases are therefore mainly composed of memory cells. This is supported by measuring the expression of the KI67 antigen, which is selectively expressed in proliferating cells. This nuclear antigen was only found to be present after 2 - 3 months on HAART, suggesting that new lymphocyte proliferation begins at this time.⁷

The rapid initial increase of peripheral blood CD4+ lymphocytes is of the order of 1 to 5 cells/ μ l/day. Since the

peripheral blood lymphocytes represent only 2% of the total lymphocyte compartment a minimal virus reduction in lymph tissue following HAART mobilises enough CD4+ cells to substantially increase the peripheral numbers. This phenomenon is more noticeable when treatment is commenced during late-stage disease.

The second-phase increase in T-cells is a much slower process and involves an increase in naïve cells, which require programming in the thymus gland and also possibly in some, as yet undefined, extra-thymic sites. These cells therefore represent a true and meaningful restoration of the immune system. Direct evidence for a thymic participation is the T-cell regenerative process provided by the detection in CD45RA+ T cells of DNA circles produced by TCR rearrangements during thymic maturation. These T-cell receptor excision circles (TRECs) can be quantified by polymerase chain reacton (PCR) and are a good measure of thymic output of naïve cells. Another measure of active thymus involvement involves a measure of thymic size by imaging, utilising a CT scan.

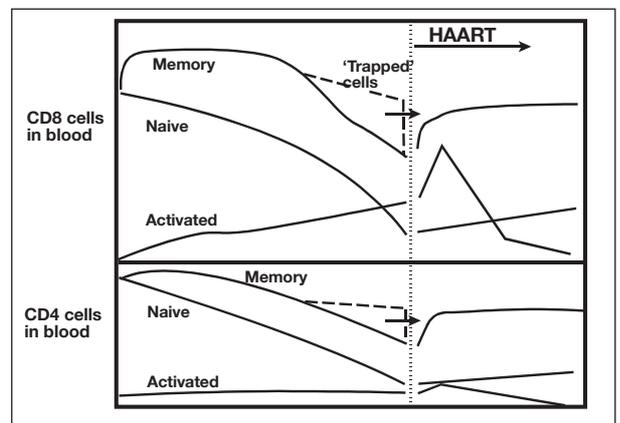


Fig. 4. HIV immune reconstitution.

Another consequence of the introduction of HAART is a decrease in the high level of immune activation. This can be demonstrated by a reduction and expression of the memory HLA-DR and CD38 activation markers on both CD4+ and CD8+ T cells. A reduction in the expression of Fas was also observed.⁸ Fas is an expression marker of cells undergoing apoptosis. There is also a return of markers indicating immune competence and function of T-helper cells such as CD28 and CD7. The return of memory CD4+ cell reactivities against pathogens such as CMV and *Mycobacterium tuberculosis* can lead to an immune reconstitution inflammatory syndrome.

Ultimately the reconstitution of the immune response can lead to the discontinuation of primary or secondary chemoprophylaxis for opportunistic pathogens. One of the disappointing features of immune restoration is the lack of increase of CD4+ helper cells specific for HIV. In a few patients treatment initiated at the time of primary

infection can preserve this important cell group. These cells, it is to be emphasised, are the key to a co-ordinated immune response and their loss leads to significant immune dysregulation.

MARKERS OF IMMUNE RECONSTITUTION AFTER HAART

- Increase in CD4+ memory cells (CD45RO)
- Increase in naïve CD4+ cells (CD45RA62L+)
- Increase in CD8+ naïve cells (CD45RO)
- Decrease in activation markers (CD38 and HLA-DR)
- Increase in TCR repertoire
- Increase in T-cell receptor excision circles (TRECs)
- Cytokine profile – TH1-response restored.
- Improved lymph node architecture
- Renewed responses to antigens

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

Within the first few weeks of commencing ART, the immune system begins to recover and may respond to certain infections that have been present in tissues in a dormant form. With the recovery of the immune system the antigens become recognised and an acute inflammatory response ensues.

This situation is seen when patients begin treatment when their CD4 counts are very low, usually < 50 cells/ μ l. For patients with tuberculosis, the syndrome is characterised

by fevers, lymphadenopathy, worsening pulmonary lesions and expanding CNS lesions. These reactions are commonest in the intensive phase of treatment and are typically self-limiting.

IRIS has been described in the following situations:

- cytomegalovirus (CMV) retinitis
- mycobacterial disease
- hepatitis B or C
- cryptococcal meningitis.

It has been noted in the clinical situation that 15 - 20% of new AIDS diagnoses occur in the first few months after commencement of HAART in patients whose CD4 counts are < 50/ μ l. It is important that HAART should not be discontinued just because the patient develops an immune reconstitution syndrome, and steroids may be useful to suppress the acute inflammatory response.

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WHAT LESSONS HAVE WE LEARNED?

Proceedings of the 9th European AIDS Conference, Warsaw,
25 - 29 October 2003

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These days there seems to be a plethora of meetings devoted to HIV and antiretroviral (ARV) therapies. Many of us suffer from 'conference fatigue'; however, each meeting seems to make progress in understanding the various facets relating to these complicated therapies. Old items such as when to initiate therapy continue to appear on the agenda, and conferences seem to have their own unique 'hot topics'. This conference offered an impressive variety of interesting and important presentations.

APPROACHES TO THE INITIATION OF ANTIRETROVIRAL THERAPY

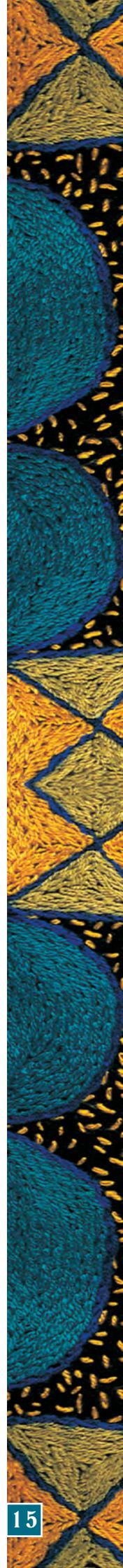
Currently most international guidelines reflect an approach to deferment of ARV therapies. On the one hand we have the World Health Organisation (WHO) guidelines for ARVs in resource-poor settings, and on the other we have guidelines that reflect practice in the industrialised world. Clearly these guidelines, at both extremes, reflect a delicate balance between the availability of drugs, drug toxicities and operational programmatic issues. The very fact that we are constantly revising and changing our guidelines reflects the experiences that are gained in various settings. For some time to come we are likely to have different guidelines for different economic settings. Dr Andrew Phillips of the Royal Free and University College Medical School in London delivered a plenary lecture on when to start therapy. Most guidelines suggest that anti-HIV treatment should be initiated when a patient's CD4+ cell count is between 200 and 350 cells/ μ l. Data from observational studies conducted by Professor Phillips and colleagues¹ at the Royal Free Hospital have shown that for a patient with a CD4+ cell count of 350 cells/ μ l and a plasma viral load of 20 000 copies/ml, it will take a mean of 6 years to observe a decline in CD4+ cell count to 200 cells/ μ l; this period is shortened to 18 months or less when the plasma viral load is 300 000 copies/ml. In the short term, in a 45-year-old patient with these parameters, the risk of progressing to full-blown AIDS is 3% over 6 months. This supports the statement

that treatment decisions should be individualised, and not blindly linked to a single CD4+ cell count parameter applied to all patients. This is important information as guidelines are really to guide decisions and not cast in stone, and therefore should be individualised to the particular situation. Rigid application of guidelines can be to the detriment of an individual patient.

PROTEASE INHIBITORS AS FIRST LINE?

Daniel Podzamczar of the Hospital Princesps d'Espanya in Barcelona, Spain, discussed the various therapeutic options that are available to patients once a decision is made to initiate treatment. It has been common practice to use non-nucleoside reverse transcriptase inhibitors (NNRTIs) as a component of first-line regimens together with dual nucleoside reverse transcriptase inhibitors (NRTIs) as the backbone, and the most frequently recommended NNRTIs have been efavirenz and nevirapine. Dr Podzamczar stated there may be a role for protease inhibitor (PI)-based combinations (especially those including lopinavir/ritonavir) in patients with more advanced immune deficiency, where some experts feel the response to NNRTI-based therapies may not be as robust. There has been a general view that among the NRTIs most combinations are equivalent, except for those known to be antagonistic (d4T/AZT), or when toxicities are cumulative (d4T/ddI) or in which the efficacy is sub-optimal (tenofovir/abacavir). It is also emerging that stavudine (d4T) may no longer be a preferred choice owing to its long-term toxicity. This is sobering because d4T is a frequent component of first-line regimens currently in use in South Africa including the national roll-out programme.

To address this issue, important data were presented on the combination of efavirenz, lamivudine and the new extended-release (XR) formulation of stavudine as a novel once-daily combination (DART-11 study).² Stavudine-XR produces pharmacokinetics with a peak concentration



that is 50% lower and a trough concentration that is 2- to 3-fold higher than with immediate-release (IR) stavudine. A number of studies have shown it to be better tolerated (50% reduction in peripheral neuropathy) and just as effective. In 64 patients in the DART-11 study, 78.1% (intention-to-treat) had a plasma viral load < 50 copies/ml at 24 weeks, with only 3 discontinuations due to adverse events. This is very promising. Further, in a randomised study ($N = 20/\text{group}$) of patients on a stavudine-IR-containing regimen and with good levels of virological suppression,³ a switch from stavudine-IR to stavudine-XR was not associated with virological breakthrough (v. staying on stavudine-IR).

ONCE-DAILY REGIMENS

This strategy is particularly attractive, which is likely to improve adherence, and more importantly, lends itself to directly observed therapy (DOT). A number of studies targeted at certain patient groups in which adherence has always been problematic, such as intravenous drug users (IVDUs), were presented. In one study of 70 patients who received this regimen⁴ virological failure occurred in only 15% of patients in total and in only 4% of those who started therapy with CD4+ cell counts > 100/ μl .³ Of note, there was only 1 case of grade 3 hepatotoxicity associated with nevirapine. These results are in keeping with those of another study of nevirapine-based therapy in a group of drug-naïve patients, 49% of who were IVDUs.⁵ At 24 weeks, 44 of 53 patients (83%) receiving nevirapine plus 2 NRTIs had a plasma viral load < 50 copies/ml. In another study, efavirenz was used, in combination with didanosine and lamivudine, in potentially non-adherent patients.⁶ Of 39 patients (21 of whom were ARV-naïve), 56% maintained virological suppression at 12 months. A further small study of 14 patients suggests that the combination of lamivudine, abacavir and efavirenz might also be effective in an IVDU population: 8 patients had sustained virological suppression over 48 weeks.⁷

FUTURE OF TRIPLE-NUCLEOSIDE THERAPY

Triple-nucleoside therapy seems to be an attractive option for simplification of treatment regimens in that one pill twice a day was all the dosing that was required. Previous studies had suggested that its efficacy is reduced if the plasma viral load was > 100 000 copies/ml, thus restricting the indications for use. Astriti and colleagues⁸ of Pitie Salpetriere Hospital, Paris, France, conducted a retrospective analysis of 120 drug-naïve patients who received Trizivir. The study authors reported that at week 48, 85% of those still on treatment (76 subjects) had maximal virological suppression. However, this figure was reduced to 75% in those beginning with a plasma viral

load > 100 000 copies/ml, and to only 59% by intention-to-treat analysis. In a separate study of IVDUs receiving Trizivir as a 'simple' initial regimen, only 20 of 52 (38%) subjects ever achieved plasma viral loads < 50 copies/ml.⁹ Although it can be argued that virological failures in these cases were not associated with the emergence of resistance mutations that would greatly limit second-line therapeutic options, the low success rates reported here do not justify the consideration of Trizivir as an equipotent option for initial HAART.

UPDATE ON LOPINAVIR/RITONAVIR

The use of lopinavir/ritonavir in drug-naïve patients has been a long-term success story. Sixty-eight patients who were enrolled in the original phase 3 study (M97-720) have now been on lopinavir/ritonavir-based regimens for 5 years, with 64 (94%) of these patients continuing to have plasma viral load measures < 50 copies/ml.¹⁰ With this type of success in mind, investigators have explored a number of innovative approaches to the use of this drug. A study of 190 drug-naïve individuals has now been completed in which lopinavir/ritonavir was given once daily ($N = 115$) or twice daily ($N = 75$) in combination with emtricitabine and tenofovir.¹¹ After 24 weeks, intention-to-treat analysis demonstrated maximal virological suppression in 57% of participants in both groups. However, 11% of patients in the once-daily arm had to discontinue therapy due to gastrointestinal toxicity (v. 3% in the twice-daily arm). This may represent a significant problem. There is a need to confirm the safety and efficacy of once-daily lopinavir/ritonavir in a larger trial.

Studies have started to emerge with the use of lopinavir/ritonavir monotherapy as first-line therapy in treatment-naïve subjects. In a study conducted at a single urban clinic in the USA, 30 patients with fairly advanced HIV infection began LPV/RTV therapy.¹² The mean CD4+ count was 170 cells/ μl (range 7 - 425 cells/ μl) and the mean viral load 262 000 copies/ml (range 4 161 - > 750 000 copies/ml). Twenty-one patients (70%) began therapy with a CD4+ count < 200 cells/ μl . The dosage varied according to body weight, with patients < 70 kg receiving 400/100 mg twice daily and those > 70 kg receiving 533/133 mg twice daily. At 24 weeks of follow-up only 1 patient failed to reach a viral load < 400 copies/ml. However, 8 other patients dropped out of the study or had to add another drug (intention-to-treat virological success rate of 70% with a viral load of < 400 copies/ml at 24 weeks). A further study in 32 patients¹³ shows that 6 patients had to discontinue therapy owing to adverse events but of the remainder, 25 of 26 patients maintained virological suppression during long-term follow-up, extending from 57 to 122 weeks on the

monotherapy at least in 12 patients enrolled in the initial study group. Further Federal Drug Administration (FDA)-approved studies are planned for the near future.

THERAPEUTIC SIMPLIFICATION (INDUCTION-MAINTENANCE THERAPY)

Therapeutic simplification is receiving increasing attention because of the long-term problems related to adherence and toxicities. With this strategy patients are given four drugs to achieve virological control and then treatment is simplified and an assessment of virological control, over time, is carried out. In one small study of patients who achieved maximal virological suppression on an initial regimen of Trizivir plus nelfinavir, nelfinavir was discontinued at week 48 or later.¹⁴ At last follow-up (after 48 weeks on Trizivir alone), 11 of 14 patients on therapy had maintained virological suppression 96 weeks after their regimen was simplified to Trizivir alone.¹⁵ Perhaps there is a role for Trizivir in this setting, following up on the data of Martinez and colleagues,¹⁶ which showed that a change from a PI-based regimen to a regimen that included 2 NRTIs plus abacavir was safe and effective, as long as the patient had not experienced a previous virological breakthrough while receiving NRTIs.

Although it has not been studied in the context of induction/maintenance therapy, atazanavir has the potential to play a role in treatment simplification. According to the results of one study, atazanavir is most effective in patients with prior drug resistance if combined with low-dose ritonavir.¹⁷ In another small study, good success rates were observed for unboosted atazanavir, in combination with other agents, in patients who did not carry isolates with PI resistance mutations.¹⁸ It would be interesting to see studies of atazanavir/ritonavir simplification therapy, as this regimen could be given once daily, would in all likelihood have a lower pill count than lopinavir/ritonavir, and would probably not have any metabolic toxicity, based on the results of clinical trials presented to date.

TREATMENT MODIFICATION

Treatment modification involves substitution of one drug for another in the face of toxicities despite good virological suppression or for simplification of a regimen to optimise adherence. In a study of 31 patients, one group demonstrated that it is safe and effective to substitute efavirenz for a PI in a patient who is responding to a PI-based regimen, despite the fact that the patient had experienced virological failure on a previous PI-containing regimen.¹⁹ In another study, 127 patients with sustained virological suppression were switched to the

combination of didanosine, tenofovir, and efavirenz to allow for once-daily therapy.²⁰ Distressingly, only 68% remained suppressed on this regimen at 6 months. This was largely due to side-effects. In these latter patients, nevirapine could prove to be a good alternative. In a separate study, 37 patients with long-term virological suppression and CNS side-effects on efavirenz-based therapy had nevirapine substituted for efavirenz.²¹ To ensure that therapeutic drug levels were maintained during the entire period of observation, nevirapine was started at 200 mg/day for 2 weeks while efavirenz was continued. After 2 weeks, nevirapine was increased to 400 mg/day, and efavirenz was discontinued. In 24 patients, CNS toxicity subsided; virological suppression was successfully maintained in all cases.

THE CURRENT APPROACHES TO SECOND-LINE AND SALVAGE THERAPY

For patients who have not received lopinavir/ritonavir as part of their initial HAART regimen, lopinavir/ritonavir is a favoured agent for later stages of therapy. In the MaxCmin2 study,²² it was compared with saquinavir/ritonavir in a total of 335 treatment-experienced patients (48% of whom had previously received a PI) and proved to be superior. In an intention-to-treat analysis, 65% of patients in the lopinavir/ritonavir arm achieved plasma viral load measures < 50 copies/ml at 48 weeks compared with 57% in the saquinavir/ritonavir group.

Concerns have been expressed regarding the long-term toxicity of tenofovir. In a careful review of almost 700 patients who received tenofovir in phase 2/3 trials, the incidence of discontinuation due to adverse events was 13%, a relatively low number for 2/3 trials.²³ With respect to nephrotoxicity, only a single case of Fanconi syndrome was observed. At any one time, 49 patients presented with elevated creatinine levels (always within 0.5 - 2.0 mg/dl of baseline values), although this effect only persisted in 6 (0.9%) of all patients included in the analysis, and creatinine levels never rose more than 2.0 mg/dl higher than baseline measures. This should allay our fears regarding the danger of renal impairment on tenofovir. This was confirmed by the results of Gilead Science's 903 Study (presented by Joel Gallant²⁴ of Johns Hopkins University at the recent ICAAC meeting), which demonstrated similar renal safety for tenofovir and stavudine (each in combination with lamivudine and efavirenz) among patients who received either drug for 96 weeks.

Tipranavir is the first of the PIs developed for use against viral isolates that have become resistant to other PIs. In a phase 2, open-label, randomised trial, a group of 41

NNRTI-naïve patients with at least 2 occurrences of therapeutic failure while on a PI were given tipranavir (boosted with ritonavir) along with efavirenz and a new NRTI.²⁵ Patients were followed up for 80 weeks, at which time 25 patients remained on therapy, with 16 (64%) having plasma viral load measures < 50 copies/ml. The relatively high drop-out rate in this study may be attributable to the fact that the tipranavir doses used were too high and thus too toxic. In this light, a double-blind dose-optimisation study²⁶ was conducted in triple-class-experienced patients who received optimised background therapy plus 1 of 3 tipranavir/ritonavir combinations administered twice daily: 500 mg/100 mg (*N* = 73); 550 mg/200 mg (*N* = 72); 750 mg/200 mg (*N* = 71). Over 24 weeks, there was a 40% to 45% response rate (defined as a decrease in plasma viral load >1.0 log₁₀ copies/ml) in the 500/200 mg and 750/200 mg groups; there were nearly twice as many treatment discontinuations (15.5% v. 9.7%) in the patients on the higher tipranavir dose. Based on these results, the dose of 500 mg/200 mg was carried forward into pivotal phase 3 trials, the results of which should be presented in 2005.

STATUS OF STRUCTURED TREATMENT INTERRUPTIONS (STIs)

As more data become available there is increasing evidence that there is no benefit for the use of STIs in chronic established HIV infection. Of importance were the data derived from the CPCRA 064 study²⁷ that showed an alarming frequency of clinical events among patients who interrupted treatment.

Conversely, the GIGHAART study (ANRS 097) demonstrated a benefit of treatment interruption in patients with advanced immune deficiency and few remaining therapeutic options.²⁸ The REVERSE study, of 23 patients, was conducted in an attempt to replicate these findings.²⁹ Outcomes were largely unsuccessful, thought to be a result of greater frequency of reversion of HIV to wild-type associated with precipitous decreases in CD4+ cell counts. The investigators suggested that a shorter period of treatment interruption (less than 24 weeks) should have been used. These results are discouraging, as they further narrow the scope of application of treatment interruption as a therapeutic option.

It would appear that the best indication for treatment interruptions would be in patients who start HAART at CD4+ cell levels above those recommended by present guidelines. Christina Mussini³⁰ of the University of Modena, Modena, Italy, presented the results of an observational study of 140 individuals with nadir and

current CD4+ cell counts of > 250 and > 500 µl, respectively, 60% of whom had undetectable plasma viral loads at entry. These individuals discontinued HAART and remained under close observation. Over a median period of 104 weeks, half resumed therapy, equally divided between those who chose to do so and those whose CD4+ cell counts had declined to < 350 µl. Of note, the majority of patients who had a nadir CD4+ cell count < 350 µl and who had virological suppression for < 12 months had to resume therapy. These findings appear to be consistent with those of a recently published study by Van Sighem and colleagues³¹ which showed that high (> 90%) 5-year survival probabilities could be maintained in the context of delayed or interrupted antiretroviral therapy only in patients with high CD4+ cell counts (> = 450 µl). It would be interesting to perform a clinical trial involving patients who initiated HAART with CD4+ cell counts > 350 µl and discontinued it after their plasma viral loads had been undetectable for 1 year or longer, in order to test whether such individuals would be able to stay off therapy indefinitely.

HAART IN AFRICA

It was heartening to note the contribution from Africa, from the rural Maun region, offering HAART to adults with full-blown AIDS and/or a CD4+ cell count < 200/µl. Almost 600 patients have been enrolled and data are available for 156 of these.³² The most common regimen is zidovudine/lamivudine plus either efavirenz or nevirapine. Of 101 patients available for follow-up at 9 - 12 months, a staggering 88% have plasma viral load measures < 400 copies/ml and a mean CD4+ cell count increase to 256 - 276/µl (from 98 and 141/µl in drug-naïve and previously treated patients, respectively). This is strong evidence of a hopeful future for HIV-infected persons living in Africa, even in the hardest-hit countries (e.g. Botswana) and hardest-to-reach communities like the Okavango Delta.

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MEDICAL MANAGEMENT OF A SURVIVOR OF SEXUAL ASSAULT/ABUSE

Including Post-Exposure Prophylaxis and the Forensic Kit

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I. MEDICAL MANAGEMENT

1. INTRODUCTION

(a) It is important to remember that survivors of sexual assault are patients like any other patients but with special needs. The basics of good clinical medicine should therefore apply including good history taking, clinical examination, special investigations and appropriate management.

(b) Every patient should be seen and managed in a comfortable and compassionate environment.

(c) The appropriate Crime Kits for the medico-legal examination should be available in hospitals and doctors' rooms, as South African Police Service (SAPS) personnel do not always have easy, quick access to the kits. This is one of the many reasons why a positive and co-operative working relationship with the relevant local SAPS is vital.

(d) All health care staff should undergo basic training in counselling and should have been trained in general medico-legal procedures regarding rape/sexual assault.

2. PROCEDURES

(a) If the patient is a priority 1 (immediate life-threatening injury = code red) or priority 2 (limb/potential life-threatening injury = code yellow) they should be managed in the resuscitation room according to Advanced Trauma Life Support protocols.

(b) If the patient is a priority 3 (non-limb or life-threatening injury = code green) they should be treated in a dedicated, private room.

(c) A registered nurse and a medical doctor should commence by taking the medical history *and* details of the actual sexual assault.

(d) Once the history has been taken, the medical procedures that will be necessary should be explained to the patient in detail.

(e) If the patient decides to lay a charge, the appropriate medico-legal examination should be explained in detail.

(f) If the patient is treated in a hospital, all injuries should be attended to, and patient transferral should be kept to a minimum.

(g) However, referrals may be necessary in certain circumstances, e.g. a child with vaginal tears requiring suturing under general anesthesia by a specialist surgeon.

(h) If the patient requires special investigations, e.g. x-rays, or requires admission for specialised medical treatment, this should be carried out.

(i) Where appropriate antibiotic prophylaxis should be commenced, as soon as possible.

(j) If possible, a facility should be made available where the patient can shower/bath and change their clothing on completion of the full medico-legal examination.

(k) Follow-up examinations should take place at 6 weeks, 3 months and 6 months after the assault. The choice of whether to attend for regular annual follow-up visits should be left to the patient.

3. COUNSELLING

(a) A trained counsellor should be called in for every case of sexual assault. He or she would be in a position to assist the family, friends, spouse and victim throughout the entire procedure and then provide follow-up counselling on a regular basis, according to the patient's needs.

(b) The patient has a right to lay a charge against the perpetrator(s). This should be facilitated with the relevant SAPS. Statistics from one large Johannesburg Hospital Trauma Unit show that less than 48% of patients are accompanied to casualty by a member of the SAPS. It may therefore be necessary to call in a SAPS officer for unaccompanied patients wishing to lay a charge. Data indicate that over 70% of sexual assault patients lay

charges against the perpetrator(s), with appropriate treatment and explanations.

(c) Experience has shown that patients who see a counsellor at the initial event have improved follow-up rates for themselves and their families.

II. POST-EXPOSURE PROPHYLAXIS (PEP)

(a) A component of the initial history taking should include pre-test counselling for an HIV test.

(b) Consent for the management and procedures to be undertaken should be obtained.

(c) Informed consent for the baseline HIV enzyme-linked immunosorbent assay (ELISA) should be obtained. If the patient is under age the appropriate parent/guardian should be approached. If they are unavailable the attending SAPS officer will assist. If reliable rapid tests are available these may be used.

(d) The HIV ELISA results should be available within 3 hours.

(e) In circumstances where the results of conventional HIV ELISA tests may be delayed the use of rapid antibody tests is endorsed. A positive rapid test result would need to be confirmed by the use of a conventional ELISA test.

(f) Every patient should be told about PEP.

(g) If the ELISA test is negative, patients seen within 72 hours of the sexual assault should be offered antiretroviral (ARV) PEP. This should consist of a 28-day course of AZT and 3TC (Combivir), one tablet twice daily. Children and the elderly, who may find capsules difficult to swallow or require a lower dosage than provided by Combivir, can be given AZT/zidovudine (Retrovir) and 3TC/lamivudine syrup.

(h) Patients presenting more than 72 hours after the sexual assault should be counselled and offered routine blood testing, counselling and follow-up for HIV/AIDS and the rape incident.

(i) If the patient's HIV ELISA is positive, he or she should be counselled and referred to relevant centres for HIV-AIDS treatment.

(j) A pregnancy test should be done if necessary.

(k) Adherence to PEP does not appear to be problematical among survivors of sexual assault.

(l) The follow-up rate is excellent within the first 3 months and may only decline thereafter.

(m) The unit should provide patient follow-up for other medical problems, as well as counselling.

OTHER CONCOMITANTLY PRESCRIBED MEDICATION

Prophylactic antibiotics. In addition to the ARVs the patients should be given prophylactic antibiotics for other sexually transmitted infections:

■ Penicillin 2 million units intramuscularly (IM)
OR

Ciprobay 2 g stat.

■ Flagyl 2 g p.o. stat
OR

Flagyl 500 mg intravenously (IV) should the patient be vomiting or nauseous.

■ Zithromax 1 g p.o. stat
OR

Tetracyclines 500 mg q.i.d. for 10 days.

Patients who are allergic to penicillin should be given erythromycin.

Other medication to consider:

■ The 'morning after' pill should be given if appropriate and necessary. This should be given at least 1 hour before giving the antibiotic prophylaxis.

■ A vaginal douche should be provided to take home.

■ Anti-emetics should be prescribed if necessary.

■ Analgesia/anti-inflammatory medication should be prescribed if necessary.

III. THE FORENSIC KIT – DIRECTIONS FOR USE

The following steps should help you to understand the kit and make it easier to work with.

GENERAL

(a) It is imperative that from the commencement to the completion of the medical examination, a correct chain of events (evidence) is adhered to.

(b) It is therefore desirable that a second health care professional is present during the course of the forensic examination.

THE CRIME KIT

The new Crime Kit consists of:

1. The Evidence Collection Form and

2. The Crime Kit itself, which contains 7 sections. (Not all 7 sections will necessarily be used in all rape cases.)

1. The Evidence Collection Form

(a) The form (1 page) needs to be completed in triplicate.

(b) The first section of the document requests all of the particulars of the examining doctor.

(c) The second section asks the patient when he/she last had consensual intercourse. It is vital that this question be asked, although it may prove difficult, because if consensual intercourse has taken place within 5 - 7 days before the assault semen from the consenting partner may still be present. This can make the forensic examination difficult to interpret.

(d) Should consensual intercourse have taken place within 5 - 7 days before the assault the justice system may request a blood sample, for DNA testing of the initial consenting partner, prior to going to court

(e) The third section requests all of the patient's details.

This is a vital part of the form that must be completed, as it is the only piece of documentation showing the patient's name and details, since these cannot be reflected on the outside of the forensic collection box.

(f) The fourth section requests the doctor or examiner to list the specimens that have been taken.

(g) The doctor and patient both need to sign the form.

(h) The first copy of the form should be placed in the Crime Kit box.

(i) The doctor retains the second copy in the patient's file for medico-legal purposes should the case go to court.

(j) The third copy, together with the forensic evidence bag, is handed to the member of the Family Crime and Sexual Violence Unit (FCS) unit or SAPS unit who collects the kit.

2. THE CRIME KIT

A. Section 1. The oral swab

This is used to detect any seminal fluid present in the buccal cavity if the patient has been forced to perform oral sex .

The kit contains the following:

- A swab box
- A swab
- An evidence seal.

NB: the swab must not be moistened.

Procedure:

Swab the following areas with the same swab:

- Under the tongue
- Along the inner, outer, upper and lower gum line
- The cheek
- The palate.

There are extra swabs if necessary. Then:

- Place the swab in the box
- Fold as instructed
- Seal with an evidence seal.

B. Section 2. Collection of underwear

The kit contains the following:

A brown paper bag for the panties (or panties and/or pad) worn during or immediately after the assault. *NB: sanitary pads attached to panties should be left attached.*

Procedure:

The instructions request:

- Collection of the patient's panties and/or sanitary pad that she may have been wearing during or immediately after the assault.
- If the pad is separate from the panties, cover the adhesive (outside) side of the pad with the wax strip provided.
- If the victim is a man or boy, the underpants must be collected.
- Place all items in the bag.
- Seal the bag by removing the self-adhesive backing from the bag.
- Place the evidence sticker where the lip and the body of the bag meet.
- If the patient was wearing a tampon, see Section 7 (Tampon collection).

C. Section 3. Collection of other evidence from the patient's body

This section provides for the correct removal of evidence from the patient's body.

There are two steps (C.1 and C.2) to this part of the kit.

C.1. Collection of evidence from the patient's body, e.g. foreign debris and/or dried secretions

The kit contains the following:

- Sterile swabs
- Sharp-pointed sterile swabs (2)
- Sterile water
- Ruler
- Box for swabs
- A catch paper for reference samples.

Procedure:

- Look for any areas on the body on which there may be dried secretions, and also ask the patient if they feel any area(s) of dried and/or caked secretions on their body.
- To identify secretions, ask the patient if she/he knows where they might be. Ask the patient if the perpetrator kissed, licked or bit her/him anywhere. Those areas should be swabbed.
- To prevent destroying any evidence, one evidence source should be swabbed at a single time.

- This means one 'stain' per swab. *This is to prevent mixing evidence if there was more than one attacker.*
- The swab should be moistened with the sterile water provided before swabbing the body area.
- If the patient reports having scratched the perpetrator, fingernail scrapings must be taken. Before swabbing under the fingernail(s) loosen the debris with a sterile blade (2 swabs with sharp points are provided in the kit) which can be used to swab under the nail(s). The swab must be moistened with the sterile water provided.
- Any bruise(s)/bite mark(s) should be measured with the ruler provided.
- Pack the swabs in the box provided.
- Break off the ends and close with an evidence seal.

C.2. Collection of evidence from the patient's hair

The kit contains the following:

- A comb
- A catch paper for the head combings
- A catch paper for reference samples.

Hair combing procedure:

- Place the catch paper under the patient's head.
- Comb the hair so that any loose hair or debris fall onto the catch paper marked '**head hair combing**'. Ensure that there are sufficient samples.
- Comb hair in a downward direction to ensure that any foreign debris falls onto the catchment paper.
- You may use your fingers to ruffle the hair to loosen any debris that may be stuck in the hair.
- Fold the paper with the comb inside it .
- Place in pack.
- Seal the pack with an evidence sticker.

Reference head hair:

- Pull at least 5 hairs from the top, back, front, left and right side of the head.
- Place the hair on the catch paper marked pulled '**reference head hair**'.
- Fold the paper and seal with an evidence seal.

D. Section 4. Collection of debris that will link the patient to the location of the assault

The kit contains the following:

- Catch paper marked '**debris A**' for matted hair from the head or body which might indicate blood/semen
- Catch paper marked '**debris B**' for debris taken from the body.

Procedure for collecting samples:

Debris A:

- Look for matted hair on the head and/or body that may indicate blood/semen.
- Cut the hair over the catch paper marked '**debris A**'.

- Fold the paper and seal with the evidence seal.

Debris B:

- Collect any debris such as soil, leaves, grass and hair that may be present during the examination.
- Use a spatula and remove the debris from the patient's body.
- Place it on the catch paper marked '**debris B**'.
- Fold the paper.
- Seal with the evidence seal.

E. Section 5. Collection of pubic hair and reference hair

This is done to attempt to identify the perpetrator.

This section contains two sub-sections: E1 for samples of pubic hair and E2 for reference hair.

The kit contains the following:

- A comb
- Catch paper marked '**pubic hair combing**'
- Catch paper marked '**reference pubic hair**'.

E.1. Pubic hair combing

Procedure for collecting pubic hair combings:

- Place the catch paper marked '**pubic hair combing**' under the patient's buttocks.
- Comb the hair in a downward direction over the catch paper.
- Comb with your fingers to assist in loosening debris.
- If matted hair is noted, cut it off over the catch paper.
- Fold the paper.
- Seal with evidence seal.

E.2. Reference hair

Procedure for collecting reference pubic hair combings:

- This is needed for microscopic screening
- With the patient's consent, pull out about 10 pubic hairs.
- Place the hair into the catch paper marked '**reference pubic hair**'.
- Fold.
- Seal with the evidence seal.

F. Section 6. Collection of anal samples (used in anal rape)

NB. The ano-rectal examination should be carried out before the vaginal examination to prevent cross-contamination of evidence.

The kit contains the following:

- Two swabs
- An amp of sterile water
- Racks marked '**A**' and '**B**'.

Procedure for collecting samples from the external anal area and the rectum:

External anal area:

- Put the patient into a comfortable position, e.g. left lateral position.
- Moisten the swab with the sterile water provided.
- Swab the external anal area, extending slightly into the anal canal.
- Place the swab in the rack marked 'A'.

Rectum:

- Apply gentle lateral tension to the peri-anal area for about 3 minutes to dilate the anal sphincter.
- After dilatation has taken place, use one swab to swab the rectal canal.
- Place the swab in the rack marked 'B'.
- Fold pack.
- Close with evidence seal.

G. Section 7. Collection of vaginal swabs (used in vaginal rape)

The kit contains the following:

- Three swabs
- An amp of sterile water
- Racks marked 'A', 'B' and 'C'
- Box marked 'Tampon'.

Procedure for collecting vaginal biological material for DNA testing that may identify the perpetrator: (NB: Swabs are taken of three areas: external genital area, vagina and cervix).

External genital area swab:

- Moisten the swab with the sterile water provided.
- Swab the external and internal surface of the labia majora and minora including the clitoris, peri-urethral area and fosse navicularis.
- Place the swab in the rack marked 'A'.

Vaginal swab:

- *This must be done before the internal clinical examination.*
- Insert an unlubricated speculum
- Swab the anterior and posterior vaginal fornices
- Place the swab in the rack marked 'B'.

Cervical swab:

- Swab the inside of the cervical os.
- Collect as much of the mucous plug as possible.
- Place the swab in the rack marked 'C'.
- Fold.
- Seal the box with the evidence seal.
- Place sellotape around the box.

Tampon collection:

If a tampon was present during the rape or inserted after the rape, it should be retained for evidence. The procedure for collection is:

- Remove the tampon
- Place in the box marked 'Tampon'
- Seal the box with the evidence seal.

Additional items

Collection of reference DNA specimen – which need *not* be included in the kit.

- This provides the forensic laboratory with a sample of the patient's blood.
- Once the blood has been taken and put in the purple-capped tube, insert the cannula provided.
- Press the cannula onto the cassette. Only one drop of blood is needed.
- Place the cassette in the bag provided.
- Seal with an evidence seal.

Box closure

- Once all the specimens have been taken, place them in the box.
- Leave the unused packs in the box.
- The front page of the evidence collection form is placed on top of the specimens.
- On the outside of the box is a space to write the police station and case number.
- There are three stickers with numbers on, on the upper left corner of the box.
- One sticker goes onto the J88 form.
- The second sticker goes onto the retained copy of the form which is stapled onto the inside cover of the patient file.
- The third sticker stays on the box.
- The box is then sealed with the evidence sticker provided.
- Place sellotape around the box to keep it closed.



UPDATED GUIDELINES FOR THE USE OF RIFAMYCINS FOR THE TREATMENT OF TUBERCULOSIS IN HIV-INFECTED PATIENTS TAKING PROTEASE INHIBITORS OR NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Centers for Disease Control and Prevention
National Center for HIV, STD and TB Prevention
Division of Tuberculosis Elimination

Two previously published reports provided guidelines for managing the pharmacological interactions that can result when patients are treated with protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) for human immunodeficiency virus (HIV) infection together with rifamycins for tuberculosis (TB).^{1,2} This article presents current data pertaining to interactions between these agents, with recommendations for their use from a group of Centers for Disease Control (CDC) scientists and outside expert consultants; these include initial recommendations for the PIs lopinavir/ritonavir, atazanavir, and fosamprenavir (a phosphate ester prodrug of amprenavir).

MECHANISMS OF RIFAMYCINS-ANTIRETROVIRAL DRUG INTERACTIONS

The principal locus of these drug-drug interactions is the cytochrome P450 (CYP) system in the intestinal wall and liver, specifically the iso-enzyme CYP3A4.³ Rifamycins are antituberculosis agents that induce the activity of CYP3A4 and may thereby substantially decrease serum concentrations of PIs and NNRTIs. The available rifamycins differ in potency as CYP3A4 inducers, with rifampin (rifampicin) being the most potent, rifapentine being intermediate, and rifabutin being the least potent inducer.⁴ As such, rifabutin can be safely used with most PIs and NNRTIs, except saquinavir and delavirdine (see Table II). Unlike rifampin (rifampicin) and rifapentine, however, rifabutin is also a substrate for CYP3A4; its serum concentration is therefore affected by the degree to which CYP3A4 is inhibited or induced by PIs and NNRTIs. Rifapentine, a long-acting rifamycin, is not recommended for the treatment of TB in HIV-infected persons because of its association with acquired rifamycin resistance in such patients.⁵



Among the available antiretroviral (ARV) agents, ritonavir has the highest potency in inhibiting CYP3A4, a quality that increases the serum concentrations of other co-administered PIs,⁶ although it can also increase concentrations of rifabutin and a rifabutin metabolite to toxic levels.⁷

RIFAMPIN (RIFAMPICIN) AND ANTIRETROVIRAL THERAPY (TABLE I)

Initial guidance from the CDC stated that use of rifampin (rifampicin) was contraindicated for persons taking NNRTIs and PIs.¹ Subsequent data, however, have supported the use of rifampin (rifampicin) with certain combinations of ARV agents. These include:

- ritonavir with nucleoside/tide reverse transcriptase inhibitors (NRTIs)⁸
- efavirenz with NRTIs.⁹⁻¹¹

Alternative, less supported, ARV combinations for use with rifampin (rifampicin) include:

- ritonavir (400 mg twice daily) and saquinavir (400 mg twice daily) with NRTIs¹²
- ritonavir (400 mg twice daily) and lopinavir (400 mg twice daily) with NRTIs (when the current co-

formulated lopinavir/ritonavir combination is supplemented with additional ritonavir, see Table I)¹³

- nevirapine with NRTIs¹⁴⁻¹⁷ (and Boehringer Ingelheim, Viramune Product information, 2002)
- triple NRTIs.¹²

It is noteworthy that the ritonavir dose typically used for pharmaco-enhancement of co-administered PIs (i.e. 100 mg or 200 mg twice daily),¹⁹ though less likely to produce adverse events than higher doses, still results in net CYP3A4 induction when used with rifampin (rifampicin)¹³ (and BMS Virology, Reyataz package insert, 2003). Data are lacking for other PIs co-administered with rifampin (rifampicin) and ritonavir 400 mg twice daily. The use of nevirapine and NRTIs with rifampin (rifampicin) is of particular importance in countries with limited resources where rifabutin may not be available, and for pregnant patients, in whom efavirenz cannot be used. Despite pharmacokinetic data showing a significant reduction in nevirapine concentrations when co-administered with rifampin (rifampicin),¹⁴⁻¹⁷ two small studies demonstrated a favourable clinical and virological response.^{16,18} Nonetheless, until additional data are available, rifampin (rifampicin)- and nevirapine-containing ARV regimens

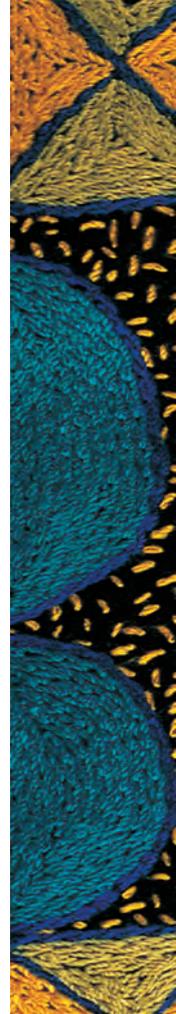


TABLE I. RECOMMENDATIONS FOR CO-ADMINISTERING PROTEASE INHIBITORS AND NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS WITH RIFAMPIN (RIFAMPICIN) – UNITED STATES, 2004*

Single PIs	Antiretroviral dose change	Rifampin (rifampicin) dose change*	Comments
Ritonavir	None	None (600 mg/d)	Ritonavir AUC ↓ by 35%; no change in rifampin (rifampicin) concentration
Amprenavir	Rifampin (rifampicin) and amprenavir should not be used together		Amprenavir AUC ↓ by 82%, Cmin ↓ by 92%
fos-amprenavir	Rifampin (rifampicin) and fos-amprenavir should not be used together		See amprenavir
Atazanavir	Rifampin (rifampicin) and atazanavir should not be used together		Interaction studies not performed, but marked decrease in atazanavir concentrations predicted
Indinavir	Rifampin (rifampicin) and indinavir should not be used together		Indinavir AUC ↓ 89%
Nelfinavir	Rifampin (rifampicin) and nelfinavir should not be used together		Nelfinavir AUC ↓ 82%
Saquinavir	Rifampin (rifampicin) and saquinavir should not be used together		Saquinavir AUC ↓ 84%
Dual PI combinations	Recommended change in dose of antiretroviral drug	Recommended change in dose of rifampin (rifampicin)	Comments
Saquinavir / ritonavir	Saquinavir 400 mg + ritonavir 400 mg twice/day	None (600 mg/day)	Limited clinical experience ¹²
Pharmaco-augmented lopinavir/ritonavir (Kaletra®) Note: Additional ritonavir required	Lopinavir/ritonavir (Kaletra®) – 3 capsules + 300 mg ritonavir twice/day	None (600 mg/day)	Limited clinical experience. Increased hepatotoxicity from ritonavir is likely ¹³
Lopinavir/ritonavir (Kaletra®)	Rifampin (rifampicin) and lopinavir/ritonavir (Kaletra®) should not be used together. If Kaletra® is used with rifampin (rifampicin), additional ritonavir is required (see above)		Lopinavir AUC ↓ by 75 % & Cmin ↓ by 99%
Non-nucleoside reverse transcriptase inhibitors	Recommended change in dose of antiretroviral drug	Recommended change in dose of rifampin (rifampicin)	Comments
Efavirenz	↑ to 800 mg/day [†]	None (600 mg/day)	Efavirenz AUC ↓ by 22%; no change in rifampin (rifampicin) concentration
Nevirapine	200 mg twice daily	None (600 mg/day)	Nevirapine AUC ↓ 37% - 58% and Cmin ↓ 68% with 200 mg 2x/day dose ¹⁴⁻¹⁶ (and Boehringer Ingelheim Viramune product information). Limited, though favorable data for efficacy of 200 mg BID dose, although should only be used if no other options exist and clinical and virological monitoring possible. ^{16,17} May consider 300 mg BID only if close biochemical monitoring feasible; however, no clinical, pharmacokinetic, or safety data available for 300 mg BID dose
Delavirdine	Rifampin (rifampicin) and delavirdine should not be used together		Delavirdine AUC ↓ by 95%

*References proved for combinations with either inconclusive or limited data.
[†]May ↓ to 600 mg/day if 800 mg dose not easily tolerated.

should only be used when no other options are available and close clinical and virological monitoring can be performed.

RIFABUTIN AND ANTIRETROVIRAL THERAPY (TABLE II)

Rifabutin can be used with most PIs, including atazanavir and fos-amprenavir, provided the dose of rifabutin is reduced (Abbott Laboratories, Kaletra package insert, 2003

revised). Use of rifabutin with saquinavir alone is not advised given the significant decrease in saquinavir concentration; however, rifabutin may be used with saquinavir if co-administered with ritonavir. Other PI/ritonavir combinations, including lopinavir/ritonavir, can be safely co-administered with rifabutin as long as the dose of rifabutin is decreased.²⁰ Conversely, as a CYP3A4 inducer efavirenz can reduce concentrations of rifabutin, necessitating an increase in the dose of rifabutin.²¹

TABLE II. RECOMMENDATIONS FOR CO-ADMINISTERING PROTEASE INHIBITORS AND NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS WITH RIFABUTIN – UNITED STATES, 2004

Single protease inhibitors	Antiretroviral dose change	Rifabutin dose change*	Comments
Amprenavir	None	↓ to 150 mg/day or 300 mg 3x/week	Rifabutin AUC ↑ by 193%; no change in amprenavir concentration.
fos-amprenavir	None	↓ to 150 mg/day or 300 mg 3x/week	Comparable to amprenavir.
Atazanavir	None	↓ to 150 mg every other day or 150 mg 3x/week†	Rifabutin AUC ↑ by 250%
Indinavir	↑ to 1 000 mg q 8 h	↓ to 150 mg/day or 300 mg 3x/week	Rifabutin AUC ↑ by 204%; indinavir AUC ↓ by 32%.
Nelfinavir	↑ to 1 000 mg q 8 h	↓ to 150 mg/day or 300 mg 3x/week	Rifabutin AUC ↑ by 207%; nelfinavir AUC ↓ by 32%
Ritonavir	None	↓ to 150 mg every other day or 150 mg 3x/week	Rifabutin AUC ↑ by 430%; no change in ritonavir concentration
Saquinavir	Rifabutin and saquinavir should not be used together		Saquinavir AUC ↓ by 43%
Dual protease inhibitor combinations	Antiretroviral dose change	Rifabutin dose change*	Comments
Lopinavir / ritonavir (Kaletra™)	None	↓ to 150 mg every other day or 150 mg 3x/week	Rifabutin AUC ↑ by 303%; 25-O-des-acetyl rifabutin AUC ↑ by 47.5-fold
Ritonavir (any dose) with saquinavir, indinavir, amprenavir, fos-amprenavir, or atazanavir	None	↓ to 150 mg every other day or 150 mg 3x/week	
Non-nucleoside reverse transcriptase inhibitors	Antiretroviral dose change	Rifabutin dose change†	Comments
Efavirenz	None	↑ to 450 mg/day or 600 mg 3x/week	Rifabutin AUC ↓ by 38% Effect of efavirenz + protease inhibitor (s) on rifabutin concentration has not been studied
Nevirapine	None	300 mg/day or 300 mg 3x/week	Rifabutin and nevirapine AUC not significantly changed
Delavirdine	Rifabutin and delavirdine should not be used together		Delavirdine AUC ↓ by 80%; rifabutin AUC ↑ by 100%

*If CD4 count is greater than 100 cells/ul, may consider twice weekly administration of rifabutin with amprenavir, fos-amprenavir, indinavir, nelfinavir, efavirenz, and nevirapine.
†Recommendation as per package insert.

OTHER DRUG INTERACTION ISSUES

Further study is needed regarding the co-administration of other complex ARV combinations (e.g. the concurrent use of CYP3A4 inducer and inhibitor, such as efavirenz and a PI) with rifabutin and rifampin (rifampicin). One observational study found that the use of rifabutin with such complex ARV regimens was associated with low serum concentrations of rifabutin, particularly when the rifabutin dose was reduced to 150 mg twice weekly for use with ritonavir-containing regimens.²¹

The NRTIs, which include zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir and emtricitabine, are not metabolised by CYP3A4, so NRTIs and rifampicins may be co-administered without dose adjustments. However, ARV therapy consisting exclusively of NRTIs appears to have reduced potency compared with

regimens that contain either a PI or an NNRTI, and current guidelines recommend NRTI-based regimens only if PI-based or NNRTI-based regimens cannot be used.²² As with NRTIs, *in vitro* and pharmacokinetic data suggest that CYP3A4 is not involved in the metabolism of either the NRTI tenofovir or the fusion inhibitor enfuvirtide, and each is therefore considered safe to use with any of the rifamycins²³ (and Gilead Sciences Inc., Viread package insert, 2002).

ACQUIRED RIFAMYCIN RESISTANCE

Rifamycin resistance has developed during the treatment of TB in HIV-infected persons, and has been associated with all rifamycins, particularly with highly intermittent administration (once or twice weekly). Rifapentine, which can be administered once a week, is not recommended for HIV-infected patients because of their risk of developing

rifamycin resistance.⁵ In addition, rifamycin resistance has developed in patients who have advanced HIV disease (i.e. CD4 count < 100 cells/μl) and are receiving rifampin (rifampicin) or rifabutin twice weekly.²⁴⁻²⁶ To prevent acquired rifamycin resistance in persons with advanced HIV infection and TB, more frequent therapy (thrice weekly or daily) with either rifampin (rifampicin)- or rifabutin-based TB regimens is recommended.

As new ARV agents and additional pharmacokinetic data become available, recommendations for the use of these agents during the treatment of TB are likely to be revised and updated. More general information on ARV drug interactions can be obtained at <http://www.aidsinfo.nih.gov/guidelines> and <http://www.hiv-druginteractions.org>.

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This document (updated 20 January 2004) is on the CDC Division of Tuberculosis Elimination website at www.cdc.gov/nchstp/tb/TB_HIV_Drugs/TOC.htm

PROVISION OF ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS – A REVIEW UP TO AUGUST 2003

World Health Organisation (WHO) and Department for International Development, UK

Improved prospects for expanded access to antiretroviral therapy (ART) in resource-poor settings are the result of reduced costs of antiretroviral drugs (ARVs), increased availability of cheaper generics and access to funds such as the Global Fund to Fight Acquired Immunodeficiency Syndrome (AIDS), Tuberculosis and Malaria (GFATM), private foundations, non-government organisations (NGOs), corporate initiatives, government budgets and other multilateral and bilateral donors, with the prospect of additional funding from the United States Millennium Challenge Account.

Increased affordability together with the political will has seen a rapid increase in the number of countries introducing or scaling up ART programmes.

The paper aims to elucidate the requirements for ART programmes in resource-poor settings by using existing pilot experience and lessons learnt with particular regard to:

- The feasibility of ART in resource-poor settings.
- The different approaches being taken to delivery of ART.
- The issues to be considered in scaling up ART provision.

FEASIBILITY AND IMPACT OF ART IN RESOURCE-POOR SETTINGS

Pilot studies conducted in South Africa, Uganda, Cameroon, Cote d'Ivoire, Kenya, Malawi, Senegal and India demonstrate the feasibility and effectiveness of highly active antiretroviral therapy (HAART) in a range of resource-poor settings with limited evidence of resistance. There is little evidence outside of these small studies.

Positive outcomes (good adherence, decreased viral load, increased CD4+ count, decreased opportunistic infections and side-effects) from the pilot studies compare favourably with rich countries. Patient commitment has been shown to be strengthened by careful counselling of both patients and families before commencement of therapy, ongoing support; local government and community support,

Précis by Penny Penhall.



and recovery from AIDS illnesses.

Patients on HAART do better than those who because of cost considerations are given dual nucleoside therapy. Dual therapy has limited durability and may promote more rapid emergence of drug resistance.

Effects of HAART on mortality differ. In Brazil, where there is universal access, there has been a 50% decrease in HIV-related deaths since 1996 and a median survival increase from 18 to 58 months. Improvements have been recorded at sites in most countries with the exception of the Médecins Sans Frontières (MSF) Homa Bay site in Kenya, where late presentation played a major role.

ART has decreased the risk of tuberculosis (TB) by as much as 80% in Brazil and South Africa.

In Brazil, the positive impact of HAART includes a decrease in health

service expenditure, where an estimated 358 000 hospital admissions were avoided between 1996 and 2002, saving US\$2.2 billion. Two years after introducing a comprehensive HIV/AIDS programme with ART, a Cote d'Ivoire private sector company noted a fivefold increase in company-based voluntary counselling and testing (VCT), a 94% decrease in absenteeism, an 81% decrease in HIV-related hospitalisation, a 78% decrease in new AIDS cases, and a 58% decrease in HIV-related mortality. The company saved approximately US\$750 000 in health care, funeral costs and absenteeism.

Debate on the impact of HAART on risk behaviour and implications for the spread of disease continues, but in Brazil no increase in unsafe behaviour has been reported. In Cote d'Ivoire it was found that unprotected sex was associated with *not* being on ART treatment. South Africa's Khayelitsha project confirmed this finding, with increased condom use in those on treatment.

APPROACHES TO DELIVERY OF ART

NATIONAL PLANS AND STRATEGIES

Brazil, Thailand and Botswana have national ART programmes, and Mozambique, Malawi and Kenya have developed strategic plans for scaling up (as has South Africa). Focus has differed from country to country; some have concentrated on service delivery and access to ART rather than on strategic planning, and others are reviewing their legal and policy framework.

Experience in African countries indicates that clear goal setting and integrating ART programmes into national HIV/AIDS strategic plans, with multisectoral national review, helps to define priorities for scale-up.

A review of national HIV strategic plans in five sub-Saharan countries identified a number of weaknesses in national plans and priority setting processes:

- Unrealistic resource allocation – designed for resource mobilisation.
- Priority setting by donors instead of by considerations of cost-effectiveness.
- The balance between prevention and care being determined arbitrarily.

The key issue being, *not* whether to include ART or not, but the balance between prevention and care and different care interventions.

Many large organisations suggest that HIV/AIDS programmes be included or considered in poverty reduction strategies, as they believe that addressing the epidemic is central to poverty reduction. This is not always easy in practice as organisations are not always aligned,

poverty reduction programmes do not always identify HIV/AIDS strategies, and there is concern that combining projects may distort planning and budgeting processes.

MODELS OF DELIVERY

Many countries have a wide variety of ARV providers and programmes within one country, which operate in different settings, and have different financing, logistical and clinical structures. This makes it difficult for policy makers to evaluate coverage, quality of services and equity impact.

Experience indicates that scaling up is best achieved through co-ordination and collaboration with the existing operational mix of providers, e.g. private sector (private health care facilities, private physicians, company schemes) combined with NGOs, and local and international organisations including mission hospitals, religious networks and community organisations. Systems need to be appropriate to the national context and the health system.

A literature review indicates that in most countries the public sector uses one or a combination of three models, i.e.

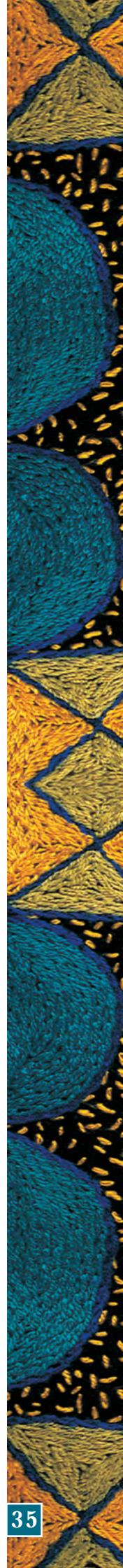
- provincial and regional hospital delivery
- district level delivery
- community clinic or community-based delivery.

PUBLIC HEALTH SECTOR

Most countries in sub-Saharan Africa are using public sector hospitals in a phased, scale-up approach beginning with selected regional or provincial hospitals, e.g. Ghana began with 2 hospitals, Botswana with 4 sites and Nigeria with 25. A number of countries use district facilities for counselling, testing, treatment of opportunistic diseases, prevention of mother-to-child-transmission (PMTCT) and monitoring and as referral points, and major public hospitals (often teaching hospitals) as the entry point for ARV treatment, e.g. Ghana, Senegal, Botswana and Nigeria. A second phase, comprising inclusion of all regional hospitals, is then undertaken. Mozambique is to make ARV available through multi-purpose Integrated Health Networks (IHNs).

NON-GOVERNMENT AND COMMUNITY ORGANISATIONS

In some countries NGOs are at the forefront of the provision of ARV treatment through pilot schemes and community programmes. A number of NGOs, e.g. MSF and AIDS Healthcare Foundation, run such pilot programmes in a number of African countries including South Africa. Faith-based networks also play a role. The number of patients treated varies from as few as 50 - 60 through to 300 or more.



Community-based organisations (CBOs) are being considered in some countries e.g. Uganda (through TASO and CDC) as a result of the successful, perhaps best-known, Haiti CBO, documented by Farmer in 2002, which provides HAART through directly observed therapy (DOT) to approximately 60 patients.

The importance of good information and adequate ART training has been shown to be essential for NGOs and CBOs.

PRIVATE SECTOR

Even in very poor countries ART has been available through the private health care sector for some time at a range of (mostly) high prices. High prices are not a guarantee of quality, as doctors sometimes prescribe according to patient affordability and local availability of ARVs. Some studies have shown that prescribing is consistent with international standards and others that drug regimens and frequency of monitoring are sub-standard. Concerns include monotherapy, resistance development, poor adherence, and unreliable drug supply leading to intermittent treatment and regimen switching.

Multinationals providing ARVs to their staff include soft-drinks manufacturers (Coca-Cola), breweries (Heineken), car manufacturers (Daimler Chrysler, Ford) and mining companies in Botswana and South Africa (e.g. Anglo American). Electricity companies in South Africa (Eskom) and Cote d'Ivoire also provide ART.

Some evidence from Africa suggests a cost saving for companies providing ARV, although studies suggest that affordability is more important than cost saving in influencing the initiation of the provision of ART.

A trend towards shifting the burden to households and to government through cost-sharing models including pre-employment screening and restructuring of employee benefits, has been identified.

ISSUES IN SCALING UP ART PROVISION

SELECTION OF BENEFICIARIES

Coverage

In December 2002, the World Health Organisation (WHO) estimated that < 1 in 18 people in middle- and low-income countries, thought to be in need of ART, were on treatment. Nearly two-thirds of these were in Latin America and the Caribbean. In sub-Saharan Africa, only 50 000 of 4.1 million needing ART were on treatment.

Eligibility criteria

WHO guidelines for resource-poor settings recommend

treatment for the following categories of HIV-positive people:

- diagnosed with AIDS
- with a CD4+ count of < 200/ μ l, or fulfilling the guidelines based on clinical diagnosis where CD4+ testing is not available. In countries with inadequate resources to treat all people requiring ART, additional criteria are required in the decision-making process.

Clearly defined economic, social and biomedical criteria are required to determine eligibility for free treatment to ensure equitable access. Communities need to be made aware of these criteria. MSF in South Africa has established clear criteria which include living in the geographical catchment area, number of dependants, health status, income, disclosure and activism.

Equity and priority target groups

Scale-up programmes should be informed by equity issues and consideration given to the poor, different geographical regions, rural v. urban populations, specific population groups, gender and children. Socio-economic determinants for free and subsidised ARVs need to be carefully defined to ensure equitable access. Experience has shown that many of the poor may not be able to afford ART even if it is heavily subsidised as the lowest cost of triple therapy can be as much as twice the average monthly formal sector wage, e.g. in Mozambique. In cost sharing systems, levels of charging, means testing and waiver systems need to be addressed.

Countries' objectives differ. Some aim to achieve the widest possible geographical coverage while others target key groups which vary by country, e.g. HIV-positive people with serious immune system damage, continued treatment of HIV-positive mothers identified in PMTCT strategies and their male partners, post-exposure prophylaxis (PEP) for health care workers, patients with TB, and victims of sexual assault.

Inclusion and free access criteria need to be flexible and evolve in accordance with changes in drug prices, availability and financial resources.

HEALTH SYSTEMS

Systems strengthening

There is limited information on the impact of HIV/AIDS on already constrained health systems of developing countries. Scaling up has the potential to strengthen systems and improve outcomes for non-HIV-related conditions if investment is used to address infrastructure, human resources and logistical weaknesses, e.g. in Thailand. Improving clinical services can boost staff morale, e.g. in Haiti. Conversely ART programmes could

weaken poor health systems without appropriate investment in systems strengthening. Situational assessments of regional and district facilities to identify needs and gaps and system strengthening requirements have been undertaken by certain countries, e.g. Kenya.

Integration of services

It is generally accepted that ART needs to be delivered as part of a comprehensive approach to prevention, care and support services including voluntary counselling and testing (VCT), PMTCT, diagnosis and treatment of opportunistic infections (OIs) and other HIV-related illnesses. Integration and co-ordination of services is advised by WHO as opposed to setting up new parallel structures. Lower levels of the system can act as entry points to regional treatment centres offering ART, or VCT and TB programmes can act as entry points.

Infrastructure

Limited infrastructure is a major constraint to scaling up of ART. There is a lack of clarity regarding the minimum infrastructure requirement, its costs and efficiencies of scale. Laboratory, pharmacy and clinical facilities are required for successful ART delivery.

Kenya is one of the few countries to have conducted a comprehensive situational assessment of public health facilities.

Human resources

Staff shortages are a major constraint to scaling up and in many of the worst-affected countries the health sector is facing a crisis in skilled human resources due to migration to the private sector and other countries and exacerbated by HIV/AIDS-related attrition.

Innovative ways to address lack of human capacity include lay counsellors, reduced frequency of visits for stable and adherent patients, prescribing of ARVs by district hospitals but collection of drugs and monitoring at satellite health centres using simplified clinical review guidelines and simple but effective record keeping and drug monitoring systems.

Training for clusters of doctors, nurses and other health care workers is critical, as is a common approach and message. Training strategies and methods need rethinking in order to incorporate responsive continued education given the rapidly evolving nature of ART.

Improved staff management (capacity to co-ordinate, supervise and monitor the scaling up process at all levels) would substantially increase staff productivity within the broader contexts of decentralisation and health sector reform.

Drugs and supplies

Effective ART programmes require regular and timely supplies of competitively priced quality drugs, laboratory reagents and related supplies, and drugs for OIs. This requires buffering against uncertainties in funding to minimise risks of interrupted supplies and prevent resistance.

Countries planning a scale-up need clear drug procurement, storage and distribution policies to prevent misuse. Secure supply chains and storage systems need strict monitoring to prevent leakage from public programmes.

Some drug registration processes may be slow and complex and procurement hampered by lack of drug information and corruption. Import taxes and duties add to the cost of ARVs and reagents, so local production (as in Brazil, India, Thailand, China) and the use of generics (Kenya, Mozambique, South Africa, Ethiopia and Ghana) are preferred options.

Assessment of challenges

Recent research has identified the following challenges in countries wishing to scale up ART: weak public sector management of essential drugs, poor storage facilities, weak transportation systems, problematic customs processes, diversion of products, inadequate training, lack of information systems, inaccurate quantification and forecasting (often based on consumption rather than morbidity data). The trend towards decentralisation requires support for district level planning and informed decision-making and drug budgeting.

Key logistics management issues

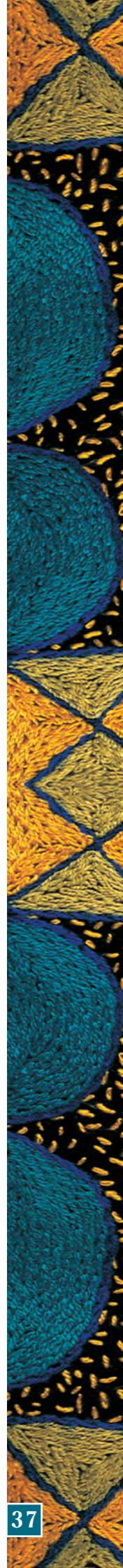
Key management issues listed by WHO/UNAIDS include the role of public v. private sector, supportive policies and legal environment, harmonised or standardised procurement, quality assurance and control, criteria for quantification and forecasting, standard treatment guidelines and inclusion in essential drug lists (EDLs), inventory control systems, secure transportation and storage, monitoring of prescribing patterns, dispensing patterns and stock levels.

Logistics management information systems need to be user-friendly and a minimal burden to health workers, to provide timely data, and to respond flexibly to consumption and regimen changes and drug substitution.

CLINICAL MANAGEMENT

Standard guidelines

Guidelines reduce treatment complexity and the cost of treatment and monitoring, and increase access to ART,



especially in resource-poor countries. In addition, local guidelines simplify eligibility criteria for initiating therapy and standardise first- and second-line therapy.

Some research in Zambia and Mexico indicates that lack of enforcement of guidelines, cost of triple therapy, and poor training of prescribers can lead to poor prescribing habits.

Alternative treatment regimens

Despite price decreases, HAART remains expensive relative to many other treatment modalities and remains complex in spite of the introduction of treatment regimens.

Simpler and more affordable regimens are being sought and studied, including structured treatment interruption, which appears the most promising option at present.

Clinical and laboratory monitoring

Laboratory monitoring is essential for the accurate assessment of the outcomes of ART and requires adequate facilities and well-trained staff to conduct accurate CD4+, viral load, and basic safety tests for side-effects. In most resource-poor countries laboratory services require strengthening.

While the price of ART has decreased, the price of tests has not (though in South Africa there have been reductions). Reduced prices for tests and reagents need to be negotiated, cheaper generic alternatives sourced, and new technologies and assays developed. Simplified and less frequent monitoring methods (e.g. one CD4+ every 6 months) and the use of low-cost alternatives to CD4+ tests are being studied. These require more reliance on clinical markers such as weight and early detection of any deterioration in health, e.g. OIs. It has been suggested that viral load testing be confined to monitoring of resistance at national referral centres.

Alternatives to the present CD4+ testing methods include dynabeads and cytospheres (counts measured by flow cytometry and non-flow cytometry), but their disadvantages include being labour intensive and requiring trained technicians, limiting the number that can be processed per day. The WHO recommends further studies before any recommendations are made for developing countries. Alternatives to polymerase chain reaction (PCR)-based and bDNA-based viral load assays are also being evaluated.

Drug resistance

The development of drug resistance is a commonly cited concern regarding rapid scale-up programmes in resource-poor settings, although a World Bank meeting in June 2003 concluded that there was no empirical evidence that it is more problematic in developing countries than developed

countries. They concluded that concerns should not delay programmes but recommended the promotion of rational drug use and good patient adherence.

Most developing countries cannot afford resistance testing for individual patients and most laboratories are not equipped to perform resistance tests. The WHO and various partners are working towards a global HIV drug resistance surveillance programme to record prevalence, identify contributory factors and strategise to minimise and limit the spread of resistant organisms.

DEMAND AND ADHERENCE

Uptake of ART

Availability and lowered cost of ART does not guarantee access, as uptake is influenced by financial, organisational, physical and social factors.

As many people are unaware of their HIV status, providing and improving access to VCT is an initial and vital step in increasing uptake. A study conducted in Kampala, Uganda, found that despite decreased ARV prices, uptake did not increase because of the limited knowledge and negative attitudes to ARVs of health care workers and patients. Subsequent training of health care workers and the use of people taking ARVs to educate others increased the number of patients. ARV availability and usage in PMTCT programmes has increased uptake of VCT in certain settings such as South Africa and Haiti.

The provision of free-of-charge diagnosis, drugs and monitoring improves uptake, although payment for OIs may remain an obstacle. Where patient co-payments are required, assessments on willingness to pay, ability to pay and impact of payments on households should be undertaken. In households in which more than one person is infected, cost is even more problematical.

People with private health insurance may not wish to claim for reimbursement due to fear of disclosure and discrimination.

Barriers to access include lack of transport, fear of disclosure, stigma and discrimination. There is however evidence that ART availability increases uptake of services, changes community perceptions of AIDS and reduces discrimination.

Community education is essential in improving uptake and successful implementation of programmes.

Adherence

Concerns regarding patient adherence to ART in resource-poor settings have been proved unfounded, programmes such as the MSF pilot programme in Khayelitsha, South

Africa, having demonstrated adherence of > 95% after 3 months of treatment. The programme combines patient-centred education with individual, peer and practical support.

Brazil attributes high rates of adherence to affordability, fixed-dose combinations, community participation, involvement of civil society organisations and adherence-support groups and support houses.

Other factors promoting adherence include affordability, disclosure of status to partners and family and regimens with limited numbers of pills. Poor clinical management and side-effects can adversely affect adherence.

More research is required and a study to identify the main determinants of adherence, barriers to adherence and the identification of effective interventions, is being undertaken in Mombasa, Kenya.

Community involvement

Experience indicates that uptake and adherence are improved in communities that have been adequately prepared for scaling-up programmes (highlighted at a WHO/UNAIDS meeting recently). Planning and budgeting for health care provider training and capacity building in communities is critical to the success and sustainability of expanded ART programmes.

In Brazil and South Africa civil society organisations have played a key role in advocacy and community mobilisation, e.g. the Treatment Action Campaign. In countries in which ART is not universally available, community involvement is becoming increasingly important in ensuring that decisions are made in a transparent and equitable manner.

AFFORDABILITY AND FINANCING

ARV prices

Increased competition and generics have substantially decreased ARV prices, enabling more governments to provide ART through the public sector. In May 2003 the least expensive *brand name* combination recommended by the WHO for low-income countries cost approximately US\$675 per person per year and the least expensive *generic* combination just under US\$300 per person per year.

In resource-poor countries, local manufacture and imported generics from Brazil, India and Thailand have made significant contributions to increased affordability.

Costing and sustainability

Developing countries with a high HIV incidence face or anticipate considerable difficulties regarding cost of public

programmes. Most governments will continue to require external aid to provide free or highly subsidised ART for some time to come. Only 7 of 19 Accelerating Access Initiative (AAI) countries have been able to fully subsidise ARV therapy.

Geffen *et al.* recently reported that a fully comprehensive HIV/AIDS response was feasible in South Africa, including ARV drugs, training and improvement in infrastructure (subsequently the price of ARVs has decreased and locally produced generics are soon to be made available). There is significant potential for ARV costs to be offset by reductions in hospitalisation and treatment of OIs (US\$400 million in 2001 – National Treasury of the Republic of SA, 2001).

Financing mechanisms

Long-term funding of programmes through the public sector is unrealistic in most resource-poor countries and multi-funding approaches are needed. A range of such strategies include drug and laboratory cost reduction, graduated cost sharing with the assistance of NGOs and private sector enterprises (based on ability to pay), national government exchequer funds, employer treatment schemes, health insurance scheme coverage of ART, social insurance funds, and donor support.

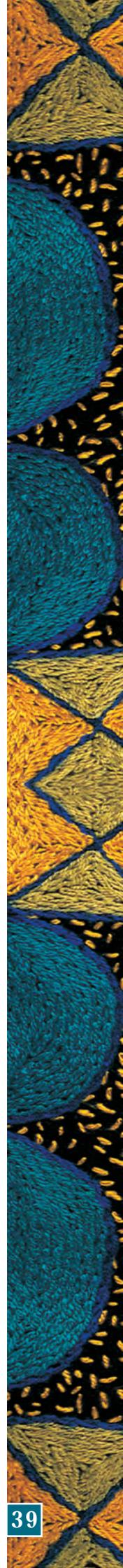
MONITORING AND EVALUATION

ART programme monitoring and evaluation (M&E)

M&E will assist in the identification of challenges and speed up the application of lessons learned. They need to identify inefficiencies, obstacles and adverse effects and address feasibility and cost issues and consider ART within the context of comprehensive care. In addition to clinical outcomes M&E will need to include equity, quality of care, and impact on risk behaviour issues.

Methods of patient and drug monitoring differ by country but include paper-based identity or photo cards, health facility registers, smart cards, finger-print readers, bar-coded drug packaging and electronic databases and sophisticated computer technology and fixed and mobile telephone-based links to central monitoring points.

Journal 15 will contain a précis of the 'Review of Experience' section of the original report prepared by the Health Systems Resource Centre for the UK Department for International Development in collaboration with the World Health Organisation.



AN OVERVIEW OF SOME OF THE KEY LEGAL DEVELOPMENTS IN HIV/AIDS AND THE LAW — 2003

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South Africa has a strong legal framework that offers a high level of protection to people living with HIV/AIDS. Although the Constitution does not explicitly refer to HIV/AIDS, it does prohibit unfair discrimination on the grounds of disability. International jurisprudence has developed a broad definition of 'disability', which goes beyond so-called functional disability and has successfully accommodated HIV-related discrimination cases in Australia, Canada and the USA. It is likely that South African courts will ultimately do the same.

Employment legislation does refer specifically to HIV-related discrimination and prohibits unfair discrimination on the grounds of HIV status in the workplace. Pre-employment and employment HIV testing is prohibited, unless the permission of the Labour Court is obtained before to testing takes place. There are other laws, dealing with the provision of medical aid services, access to education and health care, that also prevent HIV-related discrimination.

Despite this, however, people with HIV/AIDS continue to suffer high levels of discrimination and prejudice. The disclosure of HIV status remains a fearful experience for many South Africans and may well be accompanied by violence and economic and social deprivation.

This article examines some of the most important cases that have come before the courts and other tribunals in 2003 and have sought to establish the rights of people with HIV/AIDS to live lives of dignity without fear.

CHILDREN

As the epidemic has developed, issues relating to children and the impact of HIV have begun to gain prominence. The two cases described below illustrate some of the complexities involved in children's rights and HIV/AIDS.

THE RIGHT TO EQUALITY IN ACCESS TO EDUCATION

The Buccleuch Montessori Nursery School case garnered much publicity when it was argued in September 2002. The case concerned the right of Tholakele Nkosi, then 3 years old, to attend the private nursery school. The applicant in the case, Karen Perreira, Tholakele's foster mother, had elected to disclose Tholakele's HIV status to the school, believing that it was in the child's best interest for the school to be aware of her medical condition.

The response of the school was extraordinary in the context of a severe AIDS epidemic well into its second decade — fears were expressed about the risks of transmission as a result of biting, scratching insect bites and sharing sweets. The school also indicated that it did not consider itself

equipped to admit a child with HIV as none of its teachers had received any training in this regard.

In order to counter these allegations, expert affidavits dealing with the risks of HIV transmission in the school setting, evidence regarding the non-discrimination policy of the Department of Education and international case law were put before the court.

A dispute existed between the parties as to whether Tholakele's application for admission was actually rejected. According to the school's own version, however, it conceded that a recommendation had been made to defer the application until such time as the school considered itself ready to admit children with HIV and until Tholakele was 'past the biting stage'. It was argued that this conduct, on its own, constituted unfair discrimination against Tholakele.

Judgment was handed down more than a year later, in September 2003. Disappointingly, Judge Lucy Mailula found that since the school had not made a final decision

to exclude Tholakele, its conduct did not amount to unfair discrimination. The judge did not deal with the implications of the recommendation to defer Tholakele's admission and the discrimination inherent in such conduct and dismissed the application with costs.

In my view, the judgment is a dangerous one as it allows a school to effectively exclude a child with HIV as long it 'defers' the application, rather than rejects it outright. The judgment provides no guidance as to the basis on which such a deferral may take place, how long the application may be deferred and what steps a school should take to accommodate children with HIV. The judgment may also serve as a precedent for other settings where service providers wish to exclude people with HIV.

The judgment is currently being appealed.

CHILDREN AND CONSENT TO HIV TESTING AND TREATMENT

South African law requires that parental consent be obtained before any medical treatment can be given to a child below the age of 14 years. The Child Care Act 74 of 1983 permits the Minister of Social Development to consent to the treatment in the absence of consent from a parent or legal guardian, and a medical superintendent may consent in urgent cases. The High Court, as the upper guardian of all children, may also be approached to provide consent.

The Wits Paediatric HIV Working Group (WPHWG) provides treatment and care to children in the public sector and to children and infants in children's homes. Increasing numbers of children with HIV who require treatment and care are presenting at hospitals without parents or legal guardians. For these children, there is no person who is legally capable of providing consent to treatment and HIV testing. A similar situation has arisen in children's homes, where there are significant numbers of children, particularly newborn babies, who have not been lawfully placed in the custody of the homes.

The WPHWG wished to provide a high level of treatment and care to these vulnerable children and was extremely concerned about how the requirement of consent could be dealt with. It was the view of the WPHWG that consent plays a crucial role in empowering patients and their caregivers to participate in decisions about their health and also protects the health worker.

Three cases were brought in 2003, dealing with consent. The first two merely sought permission from the court for five orphans without legal guardians to commence anti-retroviral treatment. Although both applications were

successful, it was clear that it would be difficult, time-consuming and expensive to approach the High Court for each child in respect of whom consent could not be obtained. Attempts were then made to use the mechanism created by the Child Care Act that allowed for ministerial consent to be obtained where parental consent could not. The Minister of Social Development responded promptly to the first request and gave his permission for the children named in the letter to receive treatment. However, he failed to respond to any further requests and a third court application was then brought.

The third application attempted to create a mechanism that would facilitate the care of these children, without eroding the need to obtain consent, and was much broader in scope than the first applications. The order granted by the court permits the doctors associated with the WPHWG to obtain consent from the person who has daily care of the child, once they have certified that the test or treatment is in the best interests of the child. This approach is in line with the current proposals in the Children's Bill (a draft act that has not yet been enacted), which gives limited legal recognition to caregivers and allows them to consent to medical treatment.

Although the case represents an important victory for children, its application is limited to the WPHWG and it will not assist other doctors. It is unlikely that the Children's Bill will become law in the near future and it is therefore extremely important that the issue of consent be dealt with in the interim period. If it is not, doctors who treat children with HIV will be forced to either exclude children without legal guardians, or to act without consent. Neither situation is desirable.

HEALTH CARE

VRM V. THE HPCSA

A key case dealing with the role of the Health Professions Council of South Africa (HPCSA) in regulating the medical profession was finalised in 2003. The case concerned a pregnant woman with HIV who was tested during her pregnancy without her consent. The doctor who performed the test did not disclose the results of the test to his patient and failed to advise her of the steps she could take to reduce the risk of perinatal HIV transmission. The patient subsequently delivered a stillborn baby and was advised that she had HIV shortly after the birth.

A complaint was referred to the HPCSA, and although the doctor conceded that he had tested the patient without her informed consent and had not disclosed her test result, the HPCSA declined to convene a disciplinary hearing. Its

Committee of Preliminary Enquiry accepted the version of the doctor, that he had acted 'out of compassion', and declined to take the matter any further.

The judgment on appeal criticised the failure of the HPCSA adequately to consider the facts of the case and indicated that the procedures of the Committee of Preliminary Enquiry were flawed. The judgment examined the role of this committee and indicated that it did not have the power to merely accept the version of the doctor over that of the patient, which it routinely does, unless the evidence provided by the doctor is corroborated. The matter has been referred back to the HPCSA for proper consideration.

Several other complaints, which the HPCSA had also failed to deal with properly, will also be reconsidered in light of the judgment.

A civil claim for damages against the doctor is pending.

ACCESS TO AFFORDABLE ANTIRETROVIRAL MEDICINES

In September 2002, a complaint was lodged with the Competition Commission against two major pharmaceutical companies, GlaxoSmithKline and Boehringer Ingelheim, on behalf of various applicants, including four people living with HIV, the Treatment Action Campaign, COSATU and the AIDS Consortium.

The complaint alleged that the two companies were acting unlawfully by charging excessive prices for certain antiretroviral drugs. The complaint stated that the prices charged were directly responsible for the 'premature, predictable and avoidable deaths of women, men and children living with HIV/AIDS'.

In October 2003, the Commission announced that it had decided to refer the complaint to the Competition Tribunal for adjudication.

On 9 December 2003, a landmark agreement was reached between the two companies and the activists. The terms of these agreements will open the market to generic competition. The companies have agreed to license four additional companies to manufacture or import generic AZT and lamivudine products, with three companies being licensed to manufacture and/or import generic nevirapine products.

The agreements will have the effect of allowing government to procure antiretroviral drugs from a range of generic manufacturers without having to issue compulsory licences or negotiate voluntary licences first and will have a significant impact on prices.

OUTSTANDING CASES

GAZI V. THE MINISTER OF PUBLIC SERVICE

Dr Gazi, a medical practitioner in the Eastern Cape and the then spokesperson for health for the Pan African Congress (PAC), was found guilty of misconduct after he made various negative comments regarding the failure of the first Minister of Health to put an PMTCT programme in place. Dr Gazi appealed against the finding as well as the sentence, which amounted to a reprimand. The case has important implications for the rights of doctors who work in the public sector to speak out in the public interest and in the interests of their patients.

The case was argued in 2003 and a judgment is expected in 2004.

A PREVIEW OF 2004

A number of important cases will be heard in 2004. These cases will, it is hoped, continue to develop the law relating to HIV/AIDS and also empower people with HIV/AIDS to use the law to redress unfair discrimination.

NEGLIGENCE

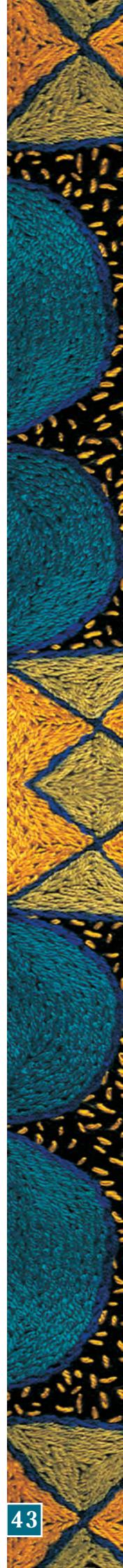
Three important cases dealing with medical negligence in the context of HIV are likely to be finalised in 2004. One case deals with the transplantation of a kidney from an infected person to a recipient without HIV. Despite requesting that HIV testing be conducted on both parties, medical practitioners performed the transplant without confirming the HIV status of the donor. A claim for damages is pending against the hospital.

A second case concerns a newborn baby who was infected in hospital. A claim for damages, including access to anti-retroviral therapy, is currently underway.

The third case concerns the failure of medical practitioners to ensure that HIV test results were communicated to a couple who were attempting to conceive a child. One partner was positive and subsequently inadvertently infected his partner, who was negative at the time of the test.

SOUTH AFRICAN NATIONAL DEFENCE FORCE

The SANDF continues to conduct pre-employment HIV testing and to exclude job applicants with HIV. The SANDF is excluded from the Employment Equity Act, which prohibits HIV testing in the workplace. It is our view that such testing is unlawful and unconstitutional, and a case challenging the requirement that new recruits are HIV negative will be argued in 2004.



HIV/AIDS, LAW AND ETHICS: A BRIEF ANALYSIS OF SOME PERTINENT ISSUES

Elsabé Klinck

Director: Research, Compliance and Counselling, Foundation for Professional Development

LAW AND ETHICS

In no other field is the role of law and ethics as crucial as in the field of HIV/AIDS. Health care professionals are in a unique situation, as both legal and ethical rules apply to a single HIV-related situation faced by them. Legal and ethical rules sometimes overlap, but sometimes differ. The South African Constitution and its Bill of Rights complicates matters further in that it is the highest law, and even ethical rules and rulings may be challenged as being justifiable limitations to human rights principles.

Perhaps the most well-known rule of medical ethics is 'do no harm'. In South Africa the Health Professions Council has issued a variety of ethical rules and its professional boards have made various rulings further concretising the application of these ethical rules. This body of rules and rulings is supplemented by policy statements, such as the Guidelines for the Management of Patients with HIV Infection or AIDS and the Policy Document on Undesirable Business Practices, which also contains various provisions on managed care.

HUMAN RIGHTS AND RESPONSIBILITIES

The following human rights play an important role for people living with HIV:

- The right to (substantive) equality and non-discrimination
- The right to privacy (confidentiality)
- The right to human dignity
- The right to security of the person (to make informed decision about one's body)
- The rights of access to health care and access to social security (welfare and insurance)
- The right of access to information.

These rights do, however, also entail responsibilities. The right of access to health care implies the responsibility to take care of one's own health and to follow the instructions of one's practitioner; the right of access to social security in the form of health care funding implies the duty not to abuse benefits awarded by schemes.

COUNSELLING AND INFORMED CONSENT

Pre- and post-test counselling form an integral part of the process of obtaining informed consent from a patient. Not only does it show respect for the physical integrity and human dignity of the patient, it prepares the patient for the potential outcome of a test and issues that may arise from such an outcome.

A typical pre-test counselling session could include:

- What the test is
- How it is done
- All advantages and disadvantages of undertaking a test and knowing the results
- What a positive result means
- What a negative result means
- The chances and implications of an incorrect result
- Appropriate support structures available, etc.

Concerns on funding of further health care may also be high on a patient's list of questions and should be addressed. Some of the issues raised during such sessions may indeed necessitate legal support. Practitioners may find it useful to have a list of support organisations and telephone numbers available for patients.

Post-test counselling should revisit the above points, and, in general, serve to facilitate patients' decision-making on future health care. The health care options and effects of each need to be discussed, as well as the ongoing and longer-term health care planning of the patient.

The National Health Act of 2003, which is not yet in force, sets the following prerequisites for informed consent:

- The range of diagnostic procedures and treatment options available to the patient
- The benefits, risks, costs and consequences generally associated with each option
- The right to refuse services, but also the implications, risks and obligations accompanying such refusal.

It also sets a whole new requirement in that where health services have been provided without consent, the provincial head of a health department must be informed of such fact within 47 hours.

The requirement to obtain a patient's informed consent may be disposed of where a law so authorises or a court so orders. The National Health Act of 2003 also authorises treatment without consent where failure to treat the patient will result in a serious risk to public health. This clause may, albeit unjustifiably, be used in the HIV setting. Another contentious section involves circumstances in which it would be justifiable for a professional not to discuss a patient's health status with him or her, i.e. if there is substantial evidence that the disclosure would be contrary to the best interests of the user. As these sections may indeed limit the rights of patients, both should be narrowly construed and applied.

Although not mandatory, it is advisable to obtain written consent. A typical consent form should include that the patient received the required information (listed in the document) and has understood such information, and that the patient provides his or her informed consent for the test and/or to be informed of the results thereof and/or treatment. If the form refers to treatment, the patient has to declare that s/he understands the requirements set in terms of compliance and the effects of the failure to comply. Patients may also be requested to agree to the anonymous use of their data for purposes of practice profiling, epidemiological data or files-based research projects.

CONTENTIOUS ISSUES

Needle-stick injuries remain a bone of contention. However, in the absence of legislation authorising testing without consent, it is submitted that the patient's consent

should be obtained, failing which post-exposure prophylaxis (PEP) should be commenced.

Testing in the pre-operative setting should serve to protect the health care, and especially the postoperative health care decisions, of the patient. Testing solely to 'protect other health care workers' may result in a false sense of security and a violation of ethics (acting in the best interest of the patient) and human rights (obtaining informed consent).

A third contentious area is where patients have been tested accidentally. It is advisable to discuss the circumstances with the patient and explain the importance of knowing one's HIV status.

Patients who are unwilling to undergo testing also present a particular difficulty to practitioners, especially where a practitioner strongly suspects that the patient is HIV-positive. The clinical signs of HIV may be explained to the patient, but it may be advisable to get to the root of this unwillingness, if necessary by means of counselling.

Other unresolved areas include disclosing HIV status for a known sex partner, accessing medical scheme benefits and insurance products, and access to health care in the public sector.

The well-known nevirapine case provides us with a good guideline on the issue of access to treatment in that the Constitutional Court ruled that if a medical practitioner is of the opinion that nevirapine is clinically indicated, it should be provided to the patient. Patients living with HIV and whose rights are in jeopardy may be greatly assisted if practitioners fight to retain their clinical independence.



UPDATE ON THE PHARMACEUTICAL INDUSTRY

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The *Sunday Times Business Times* published a supplement on the pharmaceutical industry on 30 November 2003. This has been an extremely dynamic environment and one that will be affected by impending legislative change. The objective of the survey was to provide some insight into the current status of the industry – special attention was paid to costs of medication, generic medication and antiretroviral therapy. This article aims to provide a summary of the publication and provide background information where necessary.

GENERIC MEDICINES

Generic medicines are copies of branded (original) medicines that are produced and sold at lower costs once the originator's patent protection period has lapsed. Multinational companies invest significantly on the research and development of new medicines. It is quoted that, of a batch of 10 000 molecules investigated, only one will make it to market, with a research and development cost of hundreds of millions of dollars. In order to allow the originating multinational pharmaceutical company to recoup research and development costs, a 20-year patent protection period is allowed. This period is often significantly reduced as extensive safety testing needs to take place before marketing of the new medication.

Once the patent has lapsed, producers of generic drugs are able to manufacture generic copies of the medication. These are invariably sold for a much lower price, bringing about a saving for the consumer.

While much is said about the spiralling costs of medicines, there has been a reduction in the prices of many medicines. This has been brought about largely by the emergence of generics and its effect on costing models. It is acknowledged, however, that multinationals need to be afforded some protection, as they play a major role in the development of innovative new medications.

It is widely accepted that generic medications have a role to play in providing high-quality, affordable health care. Uptake of generic medication in South Africa still lags behind that of other developed markets.

Country	Generic medication as a % of market
South Africa	19%
UK	70%
USA	75%
Germany	74%

The comparatively low use of generic medicines in South Africa has been attributed to mistrust on the part of doctors and patients, who have historically held the view that these medications are inferior because they are cheaper. The generic market is growing rapidly in South Africa, however, and it is anticipated that impending legislation will expedite this process.

MEDICATION PRICING LEGISLATION

Amendments to the Medicines and Related Substances Control Amendments Act (Act 90), intended for implementation in May 2004, have been made to provide a transparent costing model for medication, with the objective of reducing medication costs.

The new legislation will set a single factory exit price for each medication – this price list will be in the public domain. Medicine dispensers (doctors and pharmacists) will not be able to add a mark-up, but will instead charge a regulated professional fee for their service. In this way the consumer knows how much is being paid for the medicine and what is being paid for the dispensing and distribution.

Currently dispensers of medicine receive a percentage mark-up on medications – this clearly provides an incentive to use more expensive medicines in order to maximise profit margins. The price list, as well as the professional fees, will be determined by a pricing committee appointed by the Minister of Health.

There has been mixed reaction to the impending legislation, with some applauding the initiative as a bold step by the Government, while others criticise the practicality of the legislation.

Supporters believe that the legislation will provide a transparent pricing system that will not tolerate perverse incentives, back-handers and excessive profit margins. Detractors feel that implementation is likely to encounter a few practical difficulties and ignores the high likelihood of cost shifting. If an individual/pharmacy is currently earning a specific quantum of revenue, and this is cut, it is not impossible that profits will be recouped by increasing costs in non-regulated areas. In this case, the consumer pays the same (or more) and does not necessarily receive that appropriate care. If this has an adverse effect on the health of the patient, total health care expenditure increases.

It appears that there is still a lack of clarity about final implementation details, and the industry will need to wait for further information and assess the situation at the time of implementation.

ANTIRETROVIRAL THERAPY

The issue of the provision of affordable antiretroviral therapy (ART) received special focus in the survey, with an emphasis on generic medications in South Africa.

There has been good news on the issue of generic antiretroviral medication, with widespread availability of these drugs being predicted in the near future. This has been brought about through agreements between multinational pharmaceutical companies and generic medication manufacturers. On the one hand the need for affordable ART is too great to apply the patent protection period of 20 years, and on the other, the multinationals need to reap some benefit in order to fund further research and development.

A rational solution to this problem has been arrived at through the granting of voluntary licensing agreements by multinationals to generic manufacturers whereby the generic manufacturer is able to utilise the applicable intellectual property for a small royalty fee, or by limitation of the licence to a stipulated geographical region.

Additional good news reported on was the announcement by the Clinton Presidential Foundation of an initiative aimed at reducing the cost of antiretroviral drugs in developing countries. The initiative involves a venture with two Indian pharmaceutical companies and a South African

generic medicine manufacturer (Aspen Pharmacare). These companies will be manufacturing generic antiretroviral medication – funding from the Foundation will allow a further reduction in price. A target annual cost quoted is US\$140 for HAART.

MANAGING HIV/AIDS IN THE WORKPLACE

BMW South Africa have had considerable success with their workplace-based HIV/AIDS programme. An article on this outlined the comprehensive approach that this organisation has taken, including prevention, voluntary counselling and testing (VCT) and treatment of HIV- infected employees.

Ian Robertson, Managing Director of BMW SA, emphasised the need to see AIDS as a business issue that needs to be addressed with the same vitality as would be the case with other risks facing the business. It is clearly this attitude which has contributed to the success that has been achieved in the programme.

A notable success has been the uptake rate in the company's VCT initiative, with 87% of staff having participated over a period of 20 months. VCT is a crucial element of a comprehensive programme, providing the link between prevention and treatment. Once an individual is aware of his/her HIV status he/she is empowered to act

appropriately – if HIV-negative, to take action to remain negative, and if positive, to access management of the condition.

The point is well made in the article that implementation of an effective HIV/AIDS programme in the workplace is not necessarily a costly initiative. Much can be done to manage the epidemic at fairly low cost. In order to assist companies in this endeavour, the South African Business Coalition of HIV/AIDS (SABCOHA) will be launching an HIV/AIDS Workplace Programme toolkit in the first quarter of 2004.

CONCLUSION

The *Sunday Times Business Times* survey of the pharmaceutical industry gave valuable insights into a small but important range of issues affecting the health care industry.



CPD QUESTIONS

Journal 14

Two CPD points are awarded for the correct completion and submission of the questions below.

Please complete and post to: Southern African HIV Clinicians Society, Suite 233, PostNet Killarney, Private Bag X2600, Houghton, Johannesburg, 2041, or fax to (011) 453-5059

NAME	QUALIFICATION
ADDRESS	
.....	
.....	POSTAL CODE
HPCSA NO	
TELEPHONE	FAX
CELL NO	E-MAIL

PLEASE INDICATE WHICH OF THE FOLLOWING STATEMENTS ARE TRUE:

- It has been common practice to use non-nucleoside reverse transcriptase inhibitors (NNRTIs) as a component of first-line regimens together with dual nucleoside reverse transcriptase inhibitors (NRTIs) as the backbone. The most frequently recommended NNRTIs have been efavirenz and nevirapine.
 - It has been uncommon practice to use non-nucleoside reverse transcriptase inhibitors (NNRTIs) as a component of first-line regimens together with dual nucleoside reverse transcriptase inhibitors (NRTIs) as the backbone. The most frequently recommended NNRTIs have been efavirenz and nevirapine.
 - It has been common practice to use non-nucleoside reverse transcriptase inhibitors (NNRTIs) as a component of first-line regimens together with protease inhibitors.
- There has been a general view that among the NRTIs most combinations are equivalent, except for those known to be symbiotic (d4T/AZT) or when toxicities are cumulative (d4T/ddI) or in which the efficacy is optimal (tenofovir/abacavir).
 - There has been a general view that among the NRTIs most combinations are equivalent, with no exceptions.
 - There has been a general view that among the NRTIs most combinations are equivalent, except for those known to be antagonistic (d4T/AZT) or when toxicities are cumulative (d4T/ddI) or in which the efficacy is sub-optimal (tenofovir/abacavir).
- In rape/sexual assault, in addition to antiretrovirals, appropriate cases should be given the following prophylactic antibiotics:
 - Penicillin 2 million units intramuscularly (IM) OR Ciprofloxacin 1 g stat
 - Flagyl 4 g p.o. stat OR Flagyl 500 mg intravenously (IV) should the patient be vomiting or nauseous
 - Zithromax 2 g p.o. stat OR Tetracyclines 500 mg q.i.d. for 10 daysPatients allergic to penicillin should be given erythromycin.
 - In rape/sexual assault, in addition to antiretrovirals, appropriate cases should be given the following prophylactic antibiotics:
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 - Flagyl 1 g p.o. stat OR Flagyl 1 000 mg IV should the patient be vomiting or nauseous
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 - Zithromax 1 g p.o. stat OR Tetracyclines 500 mg q.i.d. for 10 daysPatients allergic to penicillin should be given erythromycin.
- Adherence with prophylactic antiretrovirals is a serious problem in post-exposure prophylaxis (PEP) following rape/sexual assault. The follow-up rate declines dramatically at 3 months, with a further steep decline after 6-month follow-up.
 - Adherence with prophylactic antiretrovirals does not appear to be problematical in PEP following rape/sexual assault. The follow-up rate only declines after 3 months, with a further decline after 6-month follow-up and testing.
 - Adherence with prophylactic antiretrovirals is of concern in PEP following rape/sexual assault. The follow-up rate declines at 3 months, and few patients attend the 6-month follow-up visit.
- It is unnecessary for all private and public hospitals, casualty units, trauma units, doctors' rooms and clinics to have Crime Kits in stock as South African Police Service personnel have quick access to kits in order to provide them, on request, in all rape emergency cases.
 - It is necessary for all private and public hospitals, casualty units, trauma units, doctors' rooms and clinics to have Crime Kits available at night as South African Police Service personnel only have quick access to kits during office hours, for rape emergency cases.
 - It is necessary for all private and public hospitals, casualty units, trauma units, doctors' rooms and clinics to have Crime Kits in stock as often South African Police Service personnel have no quick access to kits in order to provide them, on request, in all rape emergency cases.
- There are 4 sections in a rape Crime Kit in addition to the vital Evidence Collection Form.
 - There are 6 sections in a rape Crime Kit in addition to the vital Evidence Collection Form.
 - There are 7 sections in a rape Crime Kit in addition to the vital Evidence Collection Form.