SOUTHERN AFRICAN
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ISSUE TWELVE

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*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.*



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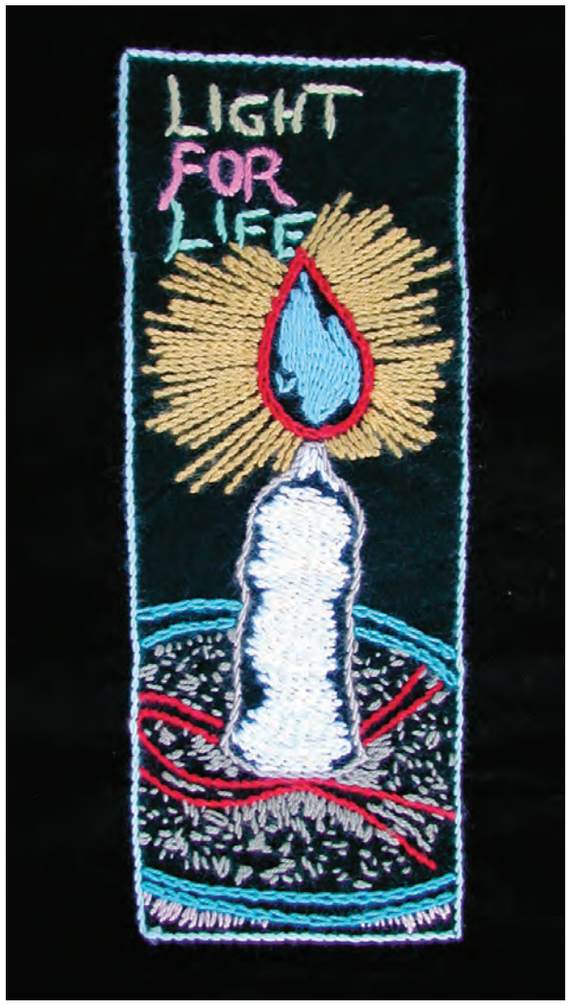
# FROM THE EDITOR

This month has seen an important event taking place in Durban, namely the first South African AIDS Conference. Prior to the conference many medical personnel were complaining of conference overload and groaning 'Not another AIDS conference!' This sentiment extended into the community of sponsors, whose budgets, already severely curtailed by declining profit margins in South Africa, have been overloaded by requests to support HIV meetings. The question may then be asked whether we needed a conference, or more pointedly, what was the likely impact of such a conference. It is quite clear that this conference was a resounding success, for the following reasons.

In the first instance, it carried forward the flame from Durban 2000 and focused the energies spawned by that conference into creative research work relevant to the local situation. It was the largest national medical meeting to have taken place in South Africa, its entire focus was on South African issues, and the majority of presentations were given by South African researchers. A word of congratulation needs to go to Dr Gustaaf Wolfaardt, Chief Executive Officer of the Foundation for Professional Development, and his organising committee, for the excellent programme. There was no dilution of the conference by global issues, problems of the north, and topics irrelevant to our local situation. The high quality of the presentations given by our young researchers was noteworthy. I have no doubt that the 180° turnaround of our government regarding provision of antiretroviral therapy (ART) in the public sector was a direct result of the focus brought about by the 3 000 delegates at this conference. Government intransigence with regard to the question of ART was evident even in the Minister of Health's opening address at the conference, and this was in complete contradistinction to the cabinet announcement which followed a few days after the conference ended. I believe the critical mass of medical and activist opinion came to a point during those momentous few days. It is therefore clear that the impact of this conference was to open the door for standard of HIV care for our people.

The willingness of the Southern African HIV Clinicians Society to lend assistance to the task team is on record and has recently been communicated both to the Minister of Health and to the cabinet National Task Team. The Society is willing to provide whatever assistance the National Task Team requires in its very important task in overseeing the roll-out of ART in South Africa. Dr Anthony Mbewu, the chairperson of the government National Task Team, has warmly welcomed these sentiments and has stressed the need to call upon the expertise of the Society in the near future.

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



## 'NO PLACE FOR NO TREATMENT' — A NEW ERA DAWNS

Well, just in case we thought it was all an impossible dream — a task team from the Department of Health has actually been travelling around the country, asking about capacity, sites, capability and protocols. It looks as if antiretrovirals really are on the agenda and the DOH is doing everything possible to make the deadline for a working national ARV plan in a month. I have picked up so many mixed feelings, with some people wondering what the catch is, some excited that it all seems to have come right at last, some suddenly getting cold feet — maybe it isn't such a great idea, and some seizing the opportunity to use the momentum to get more done in the war against HIV.

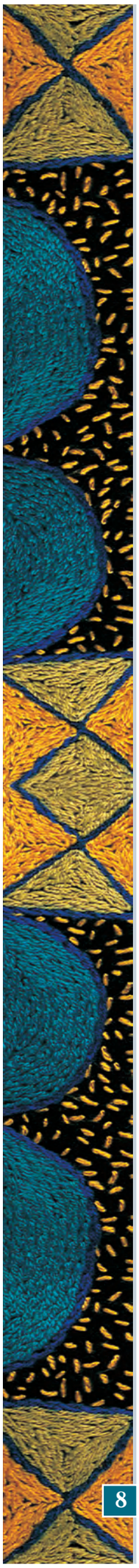
What an interesting experience it was to be at the first South African Conference in Durban last month. I guess it also reflected the very interesting times we live in at present — with the nevirapine deregistration issue hot on the front burners, the conference became the place for public debate, with opinions from civil society, the medical research community, the Medicines Control Council and international funders all being voiced in the same session. Even then it was hard to know what the real truth was, and one wonders how the average lay person in South Africa must be feeling about the vast spectrum of 'truths' that seem to abound about HIV-related issues. By the last session of the conference there seemed to be a real sense that the call to action was not one to fight each other but rather to join forces and find solutions and ways forward together. Indeed, Kgosi Letlape's call to our president to lead us in the fight is echoed in many hearts, and we hope he is truly in the lead in this new initiative to find ways to provide antiretrovirals to all South Africans in need of therapy as soon as possible. The fear is that if whole-hearted support is not felt from the very top, all efforts may be doomed to failure. We wish Tony Mbewu and his appointed task team wisdom and strength in the very important task of formulating a national ART roll-out plan.

Another important event over this period was the Treatment Action Campaign AGM. At this meeting a unanimous decision was taken to encourage and support the TAC leader, Zackie Achmat, to end his ART fast. Zackie had undertaken not to take ART for his own infection until ART was provided for the public sector. As it happened the AGM occurred just days before the announcement that the South African cabinet had approved antiretroviral roll-out and tasked the DOH to come up with a plan. We have all grown to love and respect Zackie — he has become an icon both in our nation and around the world, and we salute his courage and selflessness and wish him a trouble-free, event-free antiretroviral experience.

Some of you may have read a book published by Oxford University Press in 2000 called *AIDS Doctors — Voices from the Epidemic* by Gerald Oppenheimer and Ronald Beyer. It recounts the story of more than 50 doctors and their experiences around the HIV epidemic in the USA, especially early on when the epidemic was just unfolding. It makes interesting reading. Well, Gerry and Ron have been collecting South African voices at the conference and other places and may have more than 80 when they are done. They plan to roll this together into a South African story, and with our chequered AIDS history it should be just as fascinating.

So, as we stand, we hope at the dawn of a new era, I am again overawed at the enormous challenge before us. Dr Fareed Abdullah from the Western Cape AIDS Directorate will be remembered for his quote at the HIV conference: 'There are only two possibilities for South Africa — treatment success or treatment failure — there is no place for no treatment.' The implementation of antiretroviral treatment must happen, but it must happen without distraction from the programmes that provide condoms, STD treatment, safe sex education, life skills programmes for children and prevention of mother-to-child transmission. A programme of this scale and complexity requires a nationwide concerted and enthusiastic effort. We have the resources and the expertise — we now need one common goal, and that is treatment success!

**LINDA-GAIL BEKKER**
*Managing Editor*



IMMUNOLOGY

# HAART-MEDIATED IMMUNE RECONSTITUTION — IS IT A REALISTIC GOAL?

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HIV infection leads to a severe decrease of CD4+ T lymphocytes and generalised immune activation with subsequent development of opportunistic infections and malignancies. Administration of highly active antiretroviral therapy (HAART) has been successful in reducing HIV plasma viraemia to extremely low levels. This leads to an improvement of immune function and to a dramatic reduction in the incidence of both opportunistic infections and HIV-related mortality. However, the ability of HAART to restore immunocompetence appears incomplete, especially in patients with chronic and advanced disease; also, its extended use is not without drawbacks, including reduced adherence, toxic effects and viral resistance. Development of any complementary approaches, particularly those able to compensate for the limitations of HAART, would be of interest. Additional therapeutic strategies with cytokines, immunomodulators or therapeutic immunisations are currently being investigated and their benefit in HIV patients receiving HAART is under evaluation.

Host defence against pathogenic microbes requires various responses, depending on the character of the pathogen and on the tissue under attack. The host has evolved both innate and adaptive immune mechanisms to respond to and eliminate pathogenic micro-organisms. The fully integrated immune response draws elements from many effector systems to tailor a response to the specific invading pathogen: dendritic cells are essential to initiate the response by presenting foreign antigens to T cells; CD4+ T cells play a central role in orchestrating the immune response and are instrumental in eliminating intracellular pathogens (viruses, some bacteria) through the generation of cytotoxic CD8+ T cells and stimulation of natural killer (NK) cells; furthermore, B cells defend against extracellular pathogens by producing antibodies. The interaction among T cells, B cells, dendritic cells, and natural killer cells constitutes the fundamental defence network of the host. The failure of any of these components severely breaks the integrity of the immune system and its ability to mount the most appropriate immune response.

Infection by the HIV is characterised by a progressive loss of CD4+ T cells associated with dysregulation of immune function. The immunopathogenesis of HIV infection involves multiple interactions between the virus and the host's immune response to HIV.[1]

## IMMUNOLOGICAL ABNORMALITIES IN HIV INFECTION

Immunological abnormalities observed in HIV-infected patients are characterised by broad alterations in the adaptive and innate immune responses (Table I), including decrease in the number of circulating naïve and memory CD4+ T cells, alterations in CD4+ and CD8+ T-cell repertoires, decrease in lymphocyte proliferative responses (LPA), diminished delayed-type hypersensitivity (DTH) responses to antigens, B-cell dysfunction with decreased antibody responses after immunisation, dysregulation of the cytokine network and functional impairment of dendritic, NK and natural killer T cells (NKT cells). However, the decline in the number of and alterations in the function of CD4+ T lymphocytes is the hallmark of HIV infection.[1]

The dysregulation of the immune response appears early during HIV infection when individuals gradually lose their T-lymphocyte-proliferative responses to recall antigens, alloantigens and mitogens, before the reduction in CD4+ T-cell count. In addition to CD4 T-cell depletion, HIV replication might impair immune function directly through the immunosuppressive effect of viral proteins or indirectly through heightened immune activation.[2]

Chronic HIV infection is characterised by a state of uncontrolled immune activation that leads to

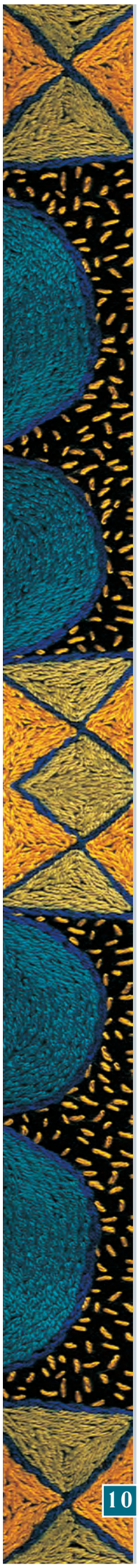


**TABLE I. IMMUNOLOGICAL ALTERATIONS OBSERVED DURING HIV INFECTION**

**Adaptive immune response**

- Decreased number and function of CD4+ T cells
- Dysfunctional cytotoxic CD8+ T cells
- Chronic activation of CD4+ and CD8+ T cells
- Decreased proliferative response to antigens, alloantigens and mitogens
- Abnormal expression of surface molecules: CD28, CD25
- Dysregulation in cytokine network:
  Enhanced proinflammatory cytokines
  Decreased Th1 response: IL-2, IFN-γ
  Increased Th2 response
- Abnormal production of antibodies:
  Hypergammaglobulinaemia
  Elevated serum IgE
  Low specific-antibody responses

**Innate immune response**

- Reduced number of pDC and low production of IFN-α
- Reduction in number of NKT cells
- Abnormal activity of NK cells
- Low expression of perforin in cytotoxic cell granules from lymphoid tissues
- Defects in antigen presentation by mDC and macrophages
- Decreased expression of costimulatory molecules: CD80, CD86
- Functional alterations in neutrophils: low chemotactic response, abnormal respiratory burst

pDC = plasmacytoid dendritic cells; mDC = myeloid dendritic cells; NK = natural killer cells; NKT = natural killer T cells.

immunosuppression and accelerated CD4+ T-cell death, resulting in severe immunodeficiency. In this phase of infection, the lack of HIV-specific responses is one of the most important defects of the immune system, especially reduced activity of HIV-1 specific CD8+ effector cells.[1,3] Perforin and granzyme A constitute major effector molecules within cytotoxic granules that induce apoptosis and lysis of virally infected cells. In HIV-infected individuals, perforin expression is impaired at local sites of HIV replication within lymphoid tissue, which may limit the ability of cytotoxic lymphocytes to eliminate HIV-infected cells in lymphoid tissues.[4]

## IMMUNE RECONSTITUTION WITH HAART

The current drug treatment for HIV infection is highly active antiretroviral therapy (HAART), which produces dramatic decreases in plasma HIV RNA levels and increases in CD4+ T-lymphocyte count leading to marked decreases in the incidence of opportunistic infections and in mortality.[5] However, after HAART is discontinued there is a rebound in viral load and a decrease in CD4+ counts to similar levels as before HAART administration. Also, potent antiretroviral therapy administered for several months is unable to eliminate HIV tissue reservoirs effectively.[6]

Besides the virological effects, HAART has improved immunological function in advanced, moderate and early HIV disease, as demonstrated by improved *in vitro* responses to recall antigens and polyclonal mitogenic stimuli.[7-10] Despite these beneficial effects of HAART, discordant results have been reported with regard to improvement of immunological functions in HIV-infected individuals receiving this regimen.[10,11] HAART has still not normalised all immune system parameters, such as CD4 and CD8 T-cell activation status. It is controversial whether HAART leads to recovery of the CD4+ and CD8+ T-cell repertoire, and it is likely that this is a delayed and incomplete process.[12,13]

With the aim of determining the level of immune reconstitution with HAART, one recent study evaluated whether immunisation results in the restoration of responses to recall antigen, or the development of responses to neoantigens. Most patients with moderately advanced HIV infection treated with HAART developed antibody, DTH and LPA responses following immunisation to both recall and neoantigens; however, LPA response to tetanus toxoid tended to increase only modestly and transiently. Response was related to the number of naïve and memory CD4+ T-cells and to the expression of the costimulatory molecule CD28 on CD4+ cells. Response was inversely related to the degree of immune activation and to plasma HIV-1 RNA levels.[14]

### WINDOW OF OPPORTUNITY: IMMUNE RESTORATION IN EARLY DISEASE

It is predicted that HIV-infected individuals early in the course of the disease are the most likely group to achieve immune reconstitution following HAART. Results from a recent investigation showed that in these patients there was a significant increase in total, naïve and memory CD4+ T cells, and reduction of total and activated CD8+ T cells and activated CD4+ T cells. The proliferative response to anti-CD3/CD28, antigenic and allogeneic stimulation was restored; also, the HIV-specific Th1 response was preserved.[9] Unfortunately, this strategy lessens the intensity of the HIV-specific CD8+ cytotoxic T-cell response. These findings suggest that early intervention with potent HAART may reverse most of the immune defects induced by HIV infection, and delay in HAART initiation can result in sustained functional immune impairment, even in persons with optimal CD4+ T-cell increases and sustained viral suppression. The issue currently under evaluation is that of lifelong therapy with HAART and the resulting problem with drug toxicity and development of resistance.

## IMMUNE RECOVERY IN ADVANCED DISEASE

HIV-infected individuals with advanced disease respond both virologically and immunologically to therapy with a potent antiretroviral regimen, as has been established by an increase in total, naïve and memory CD4+ T lymphocytes and a decrease in the proportion of activated CD8+ DR+ CD38+ T cells. However, individuals older than 40 years of age demonstrated less immunological recovery.[15]

Little recovery of HIV-1-specific CD4 responses is found in patients with moderate or advanced disease, in contrast to patients with early disease, who showed an improved response to specific HIV proteins such as p24 after the administration of HAART.[9,16,17] Also, CD8+ cytotoxic T lymphocytes specific for HIV were shown to decline after chronic suppression of viral antigens by HAART.[8,18] Therefore, immune-based therapy strategies may be the best option in conjunction with HAART-mediated potent HIV suppression to restore immunity in advanced HIV disease, but the question remains whether sufficient immune reserve is available.

## ROLE OF THE THYMUS IN IMMUNE RECOVERY

The mechanisms leading to incomplete T-cell regeneration in HIV-infected individuals are still a matter of debate. HIV-infected older subjects, who have an age-related decrease in thymic function, demonstrate reduced naïve T-cell restoration with HAART, despite similar virological responses to those in young individuals. It is likely that impaired thymic function contributes to the failure to completely restore T cells; thymus size, as measured by CT scans, is significantly associated with the number of naïve CD4 cells in HIV-infected adults.[19-21]

Frequency of T-cell receptor excision circles (TRECs, a marker of thymic function) in CD4 T cells from untreated HIV-infected subjects is often lower than levels found in age-matched healthy controls.[22,23] The decrease is probably due to two major factors: HIV-induced inhibition of thymic production of naïve T cells, or increased immune activation and increased cell turnover leading to dilution of TRECs. To enhance thymic output with hormones or cytokines might be important in HIV-infected patients receiving HAART. Currently, there is evidence for the role of IL-7 in thymic rebound in adult HIV-infected patients.[24]

## IS THERE A NEED FOR IMMUNE-BASED THERAPY?

In conclusion, despite the fact that HIV RNA levels in patients treated with HAART can be suppressed to < 50 copies/ml, eradication has not been achieved. Furthermore, HAART alone does not lead to full recovery of the immune system, and the goals of immune reconstitution should not be only to increase CD4 numbers and reduce T-cell activation but also lead to production of functional T cells. In addition, the cost and complexity of HAART regimens, the growing list of long-term side-effects, and the eventual development of resistance have underscored the immediate need for additional therapeutic approaches. Considerable efforts are under way to complement HAART with therapies that improve the immune system function and overall clinical outcome.

## IMMUNE-BASED THERAPIES IN HAART-TREATED PATIENTS

New approaches for managing HIV infection are focusing on cell-mediated immune responses, including the potential for improved immunological control over HIV replication. The complexity of HIV immunopathogenesis has prompted multiple strategic approaches to re-establish normal cellular immune responses (Table II), including the blockage of immune activation, the enhancement of T-cell production and function, and the induction of specific anti-HIV immunity. Here, we review the key facts of the

**TABLE II. IMMUNE-BASED THERAPY FOR HIV-INFECTED PATIENTS IN TREATMENT WITH HAART**

**Strategies of immunotherapy**

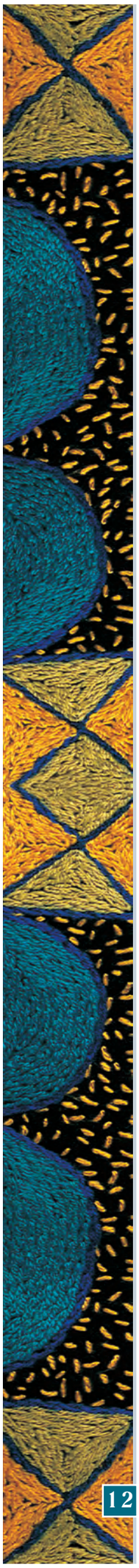
**1. Blocking immune activation and apoptosis**
- Cyclosporin A
- Corticosteroids: Prednisone
- IL-10
- TNF inhibitors: mAbs, thalidomide
- Mycophenolate
- Hydroxyurea
- Fas/Fas ligand inhibition

**2. Enhance T-cell production, expansion or functional activity**
- IL-2
- IL-7
- IL-12
- IL-15
- IL-16
- GM-CSF
- Growth hormone
- Adoptive immunotherapy

**3. Induction of specific anti-HIV immunity**
- Therapeutic vaccines
- Structured therapeutic interruptions
- Adoptive immunotherapy

**4. Other immunomodulators**
- CpG ODNs
- IFN-$\alpha$

mAbs = monoclonal antibodies.



most important immunotherapeutic strategies currently evaluated to complement the benefits obtained with HAART in HIV-infected patients.

## INTERLEUKIN 2

HIV infection significantly impairs interleukin 2 (IL-2) production, and it was thought that the exogenous administration of IL-2 could help to restore immune function in HIV-infected individuals. IL-2 is synthesised by activated CD4+ T cells and has several immunomodulatory effects, including the differentiation and proliferation of CD4+ and CD8+ T lymphocytes.

Several studies have demonstrated that administration of IL-2 to HIV-infected patients induces a significant expansion of CD4+ T lymphocytes with increase of both naïve and memory cells, enhances the expression of CD28 and helps to restore the *in vivo* proliferative response to mitogens and recall antigens.[25-28] A major concern with the use of IL-2 was the risk that this cytokine could stimulate HIV replication. However, randomised studies in patients receiving HAART showed no significant increases in HIV RNA plasma levels in subjects who received IL-2.

The effects of IL-2 therapy in combination with HAART in asymptomatic HIV-infected patients were reported recently.[29] Compared with patients receiving HAART alone, those who received IL-2 combined with HAART had a greater increase in CD4+ T cells and a similar control in HIV replication and viral load. IL-2 induced a greater increase of naïve and memory CD4+ T lymphocytes and enhanced the expression of CD28 and CD25. Patients treated with IL-2 combined with HAART experienced greater restoration and/or a preservation of functional immunity towards memory antigens and a higher *in vivo* antibody response to tetanus vaccination.[29] Clinical end-point trials are currently underway to evaluate the role of IL-2 in early (SILCAAT) and advanced (ESPRIT) HIV disease.

## INTERLEUKIN 7

There are several pathways for T-cell reconstitution in HIV-infected patients, including stimulating thymic differentiation, extrathymic differentiation and peripheral expansion. IL-7 appears to be a cytokine that can accomplish two of these tasks: enhance new T-cell synthesis by acting directly on the source of new T cells (the thymus) and expand the pre-existing pool of T cells.[30]

IL-7 is a key cytokine, along with IL-15, in the maintenance of memory CD8+ T cells. It can also lead to expansion of naïve T cells without altering their naïve phenotypic integrity.[31,32] IL-7 also exerts an antiapoptotic effect via increased expression of bcl-2, which contributes to the positive effects of IL-7 on naïve T-cell expansion prior to T-cell-receptor rearrangement.

In HIV-infected children and adults it was found that a strong inverse correlation exists between serum IL-7 levels and CD4 counts,[33] which indicates that IL-7 may be important in T-cell expansion *in vivo*. On the other hand IL-7 may have negative effects by enhancing infection of naïve T cells; this effect has been seen *in vitro* and needs to be confirmed *in vivo*.[31]

## INTERLEUKIN 15

IL-15, a cytokine that shares some activities with IL-2, is produced by activated monocytes and macrophages and supports the proliferation of activated T and B lymphocytes and the cytotoxic function of CD8+ T cells and NK cells. IL-15 can also enhance *in vitro* production of IFN-γ and IL-12 during an immune response.

IL-15 was found to enhance the *in vitro* proliferative capacity of peripheral mononuclear cells and purified CD4+ T cells from HIV-infected patients, on stimulation with mitogens, recall antigens, and HIV-specific antigens.[34] It was also reported that IL-15 enhances the cytotoxicity of CD8+ T lymphocytes and NK cells from HIV-infected patients.[35,36] It is not clear how viral load may be affected during *in vivo* administration of IL-15.[37]

## THERAPEUTIC VACCINES

In most subjects with chronic HIV infection treated with HAART, HIV-specific immune responses are not restored. An approach to stimulate HIV-specific immune responses is therapeutic vaccination in the setting of continued HAART therapy. The aim is to restore stronger and durable T-helper activity and higher and broader cytotoxic responses, and to achieve a state where patients can interrupt therapy and control viral replication.[38]

The encouraging results obtained in patients with primary HIV infection support the rationale for combining interrupted drug therapy with immunological interventions such as immunisations.[39,40] Boosting immunity to HIV with vaccines before interrupting HAART may allow the virus to be maintained in a low steady state both in primary and chronic HIV infection. The idea is to restore strong and diverse Th1 and cytotoxic T-cell responses against HIV before, and not after, the virus rebounds.[41]

Because exposure to HIV antigens may be necessary to maintain HIV-specific immunity, therapeutic vaccination may prime the naïve T lymphocytes as well as stimulate a response in the memory T cells. The current strategies include HIV genes expressed by viral vectors, subunit vaccines (attenuated HIV, viral peptides) and naked DNA vaccine.

## CPG ODNS

Unmethylated CpG motifs are prevalent in bacterial but not in vertebrate genomic DNAs; they are recognised by the Toll-like receptor 9 (TLR9) and can activate host defence mechanisms leading to innate and acquired immune responses. Oligodeoxyribonucleotides containing CpG motifs (CpG ODNs) are synthetic molecules of unmethylated DNA that mimic bacterial DNA and are also recognised by TLR9.[42]

Cells that express TLR-9, which include plasmacytoid dendritic cells (pDCs) and B cells, produce Th1-like proinflammatory cytokines, interferons and chemokines in response to stimulation with bacterial DNA and CpG ODNs. Certain CpG motifs (CpG class A) are especially potent at activating NK cells and inducing interferon alpha (IFN-α) production by pDCs, while other motifs (CpG classs B) are especially potent B cell activators.[43]

CpG ODNs administration has been shown to enhance immune effector responses through stimulation of pDCs and production of cytokines as IFN-α, IL-12, IL-15 and IL-18.[44-46] It is well known that CpG ODNs are potent activators of different innate cells such as dendritic cells, monocytes, macrophages, and NK and NKT cells. A potential role of NKT cells in the regulation of immunity has been hypothesised because of their capacity to rapidly release large amounts of IFN-γ and IL-4 upon activation. Indeed, NKT cells have been shown to play crucial roles in various types of immune responses, including antitumour, autoimmune and antimicrobial.[47-49] NKT cells bridge innate and adaptive immune responses and have been reported to exert antiviral effects via IFNs, which are also capable of inhibiting HIV replication. It has been suggested that the activation of NKT cells by CpG ODNs may play a role in the regulation of immune response of HIV-infected patients (Fig. 1).

The effect of synthetic immunostimulatory CpG ODNs as an adjuvant for an HIV-1 immunogen was evaluated recently.[50-53] In one study, the addition of CpG ODNs to HIV-1 antigens in incomplete Freund's adjuvant was the optimal combination for the production of HIV-1-specific immune responses, as measured by IFN-γ, RANTES and IgG antibody production.[50] These results suggest that the addition of CpG ODNs immunostimulatory sequences to HIV antigens may optimise HIV-1-specific immune responses.

## CONCLUSION

Infection with HIV leads to a complex and severe alteration of both the adaptive and innate immune responses. The restoration of host immunity may be an important factor in controlling HIV infection and slowing or preventing disease progression. HAART can partially, but not completely, achieve this goal. However, HAART in combination with

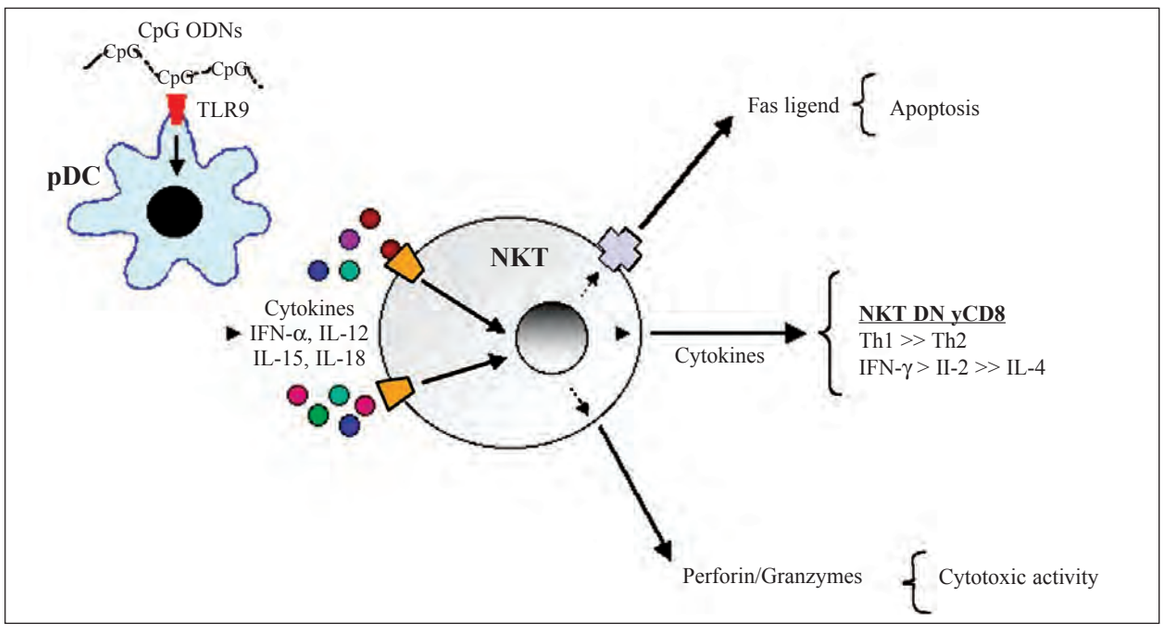



*Fig. 1. Modulation of innate immune response in HIV-infected patients: role of synthetic oligodeoxynucleotides with CpG motifs. CpG ODNs have been shown to enhance innate immune responses through the stimulation of pDCs, which induces the production of cytokines as IFN-α and IL-12. These cytokines, in turn, activate NKT cells inducing the secretion of cytokines that modulate the adaptive immune response and the production of cytotoxic and proapoptotic molecules; these functional responses of NKT cells may have direct anti-HIV effect and help to develop Th1-specific anti-HIV immune response. The improvement of immune function with CpG ODNs may be predictive of immune restoration and may be a goal for immunotherapy to enhance viral control. CpG ODN = oligodeoxynucleotides with CpG motifs; TLR9 = Toll-like receptor 9; pDC = plasmacytoid dendritic cells; NKT = natural killer T cells; DN = double negative cells (CD4-/CD8-).*

immune-based therapies has demonstrated the ability to increase the number and improve the function of CD4 lymphocytes in both early and advanced HIV disease. Also, the restoration of the innate immune function with CpG ODNs may be a goal for immunotherapy and ultimate viral control.

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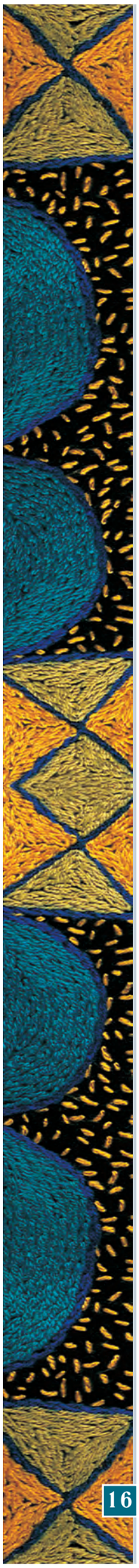

CLINICAL REVIEW

# *MYOBACTERIUM AVIUM* COMPLEX (MAC) INFECTION IN HIV DISEASE

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Disseminated infection with organisms of the *Mycobacterium avium-intracellulare* complex (MAC) was rare before the advent of acquired immunodeficiency syndrome (AIDS). In the early years of AIDS, the strong association between impaired cellular immunity and infections with organisms viewed as intracellular pathogens was recognised. Mycobacteria quickly emerged as part of the end-stage complications of HIV disease.[1] MAC plays the predominant role in the group of non-tuberculous mycobacteria (NTM) that cause disease in advanced AIDS.

MAC disease significantly decreases life expectancy.[2] MAC may eventually infect most if not all HIV-positive patients who do not die from other HIV-related events. Treatment can reduce or suppress bacteraemia and alleviate the symptoms of the disease.[3]

## INCIDENCE

The incidence of MAC disease in HIV ranges from 12% to 24% in the absence of prophylaxis and potent antiretroviral therapy.[4,5]

It appears that the incidence of disseminated MAC infection in AIDS patients is proportionate to the duration and severity of immunosuppression caused by the underlying HIV disease.[6] The incidence of *M. avium* bacteraemia increases exponentially as the CD4+ cell count approaches zero cells/µl. HIV-infected patients with CD4+ cell counts below 50 cells/µl have a 45% chance of developing MAC bacteraemia in the following year. The risk of bacteraemia is up to 60% greater in a year if the organism is isolated from the respiratory or gastrointestinal tract.

Systemic disease therefore becomes inevitable if the patient lives long enough. MAC disease develops in virtually no patients with CD4+ cell counts above 100 cells/µl,[4,5] but usually develops when the CD4+ cell count decreases to below 50 cells/µl. In one study the median CD4+ cell count was 13 cells/µl.[4]

Other risk factors identified are prior opportunistic infections, high plasma HIV-1 RNA levels, anaemia, time since onset of AIDS-defining condition and interruption of antiretroviral treatment.

There are no data available on the incidence of *M. avium* infection in the southern African HIV-positive population, since physicians often do not actively investigate for *M. avium* disease and postmortems are rarely performed.

## EPIDEMIOLOGY

Whereas pulmonary or disseminated tuberculosis originates from an initial primary focus, the NTM appear to originate from the environment.[7,8] With tuberculosis, humans are the reservoir and tuberculosis spread is from person to person. NTM are ubiquitous and can be isolated from soil, dust, plants and water. *M. avium*, as implied by the name, can be isolated from birds, but may also be found in pigs and cattle and is, indeed, an important disease in poultry and swine. The organisms are excreted in the faeces of infected animals and persist in soil for long periods of time.[9]

*M. avium* enters the human host through the gastrointestinal tract, and this is the most common route of infection in the human host. The organism may also enter via the respiratory tract and isolation of the organism in respiratory secretions is a predictor of the development of systemic disease.[10] MAC is transmissible, but the occurrence of disease is so thoroughly determined by host factors that an infection is not generally regarded as contagious.[11] It is, therefore, not necessary to isolate the patient or to investigate the family for possible MAC infection.

## PATHOGENESIS AND PATHOLOGY

The pathogenesis of disseminated MAC in AIDS is not clearly and fully understood.[12] Patients with advanced AIDS acquire new infections rather than reactivation of previous infections.

On histology of the gastrointestinal submucosa, numerous bacilli-filled macrophages or foam cells are seen.[13] The disease then spreads from the gut to the local lymph nodes with involvement of Peyer's patches and the mesenteric lymph nodes.

Colonisation of the stool can be shown to correlate with disseminated disease. It has been postulated that an initial bacteraemia from infection in the gut leads to diffuse infection of the reticuloendothelial system and eventual high-level bacteraemia spilling over from tissue infection. Intermittent bacteraemia has been demonstrated in early infection and persistent or high-level bacteraemia appears to be unusual in the absence of tissue infection.[12]

The organs most often affected are the liver, spleen and reticuloendothelial system. The histological picture of intracellular organism in the macrophages and the histocytes extends to these organs.

In an HIV-negative person, host immune mechanisms are responsible for preventing MAC from disseminating. Patients with advanced AIDS, owing to the deficiency of their immune mechanisms, fail to contain *M. avium* successfully. The macrophage-induced cytokine secretion, activation of CD4 lymphocytes, secretion of interferon-gamma (IFN-γ) and intracellular killing of *M. avium* by macrophages are impaired.[12]

## CLINICAL PICTURE

The presentation of MAC disease in patients with AIDS differs from that of non-HIV-positive patients. Most non-HIV-positive patients are elderly and have underlying obstructive airways disease. The symptoms are more limited to the respiratory tract and include cough and haemoptysis. Fever is an uncommon clinical sign.

In the context of HIV, MAC rarely causes pulmonary disease *per se*. In early disease the chest X-ray may show fleeting lung infiltrates. *M. avium* can be cultured from the sputum, but it must be remembered that *M. avium* can also colonise the airways without causing pulmonary disease. Should the smear be positive for acid-fast bacilli, it is usually *M. tuberculosis*.

*M. avium* lymphadenitis has been described in patients after initiation of highly active antiretroviral therapy (HAART). It is probably due to immune reconstitution in patients who had subclinical MAC infection before initiation of treatment.[14] The acid-fast bacilli on the biopsy of the lymph gland may be mistaken for *M. tuberculosis*, which more commonly affects lymph glands.

Disseminated *M. avium* disease is usually a late opportunistic infection. Some of the symptoms are quite non-specific. The patients might have severe fatigue and chronic malaise. Weight loss with a clinical picture of wasting is also common. Fever might be of low grade initially, but goes up to above 39°C and can be accompanied by rigors. The patient can experience drenching sweats, even if the fever is controlled by antipyretics.

Diffuse nonspecific abdominal pain is also a feature. If present, diarrhoea, which ranges from mild to severe, is watery and contains no white blood cells. Clinical examination of the abdomen may reveal organomegaly.

Routine laboratory tests may assist the clinician in suspecting *M. avium* disease. Unfortunately all of the abnormalities can also fit in with *M. tuberculosis*, although tuberculosis is often an earlier feature of HIV infection. Although patients with advanced disease are anaemic, even without an opportunistic infection being present, anaemia is more prominent with the presence of mycobacterial disease and a precipitous decline in the haemoglobin concentration should alert the clinician. Neutropenia and indeed pancytopenia can also occur. Measurement of the erythrocyte sedimentation rate may not contribute much.

Abnormalities in liver function test results include a decline in albumin, as well as raised alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT). Although the transaminases may be disturbed, the picture is not that of hepatitis.

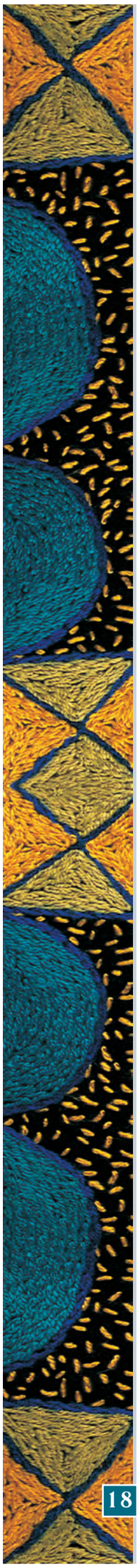
## DIAGNOSIS

The treating physician must have a high index of suspicion. If the patient is willing to accept the diagnosis and able to afford treatment, further laboratory investigations must be performed and a diagnosis actively pursued. A distinction must be made between colonisation and infection.

Radiometric or non-radiometric mycobacterial blood culture bottles are used to diagnose disseminated *M. avium* disease. Cultures may take from 1 to 3 (or even 4) weeks to yield positive results. Positive blood cultures contain from 10 to 500 colony-forming units/ml and the concentration rises in the absence of treatment. The higher the concentration of *M. avium* in blood, the higher the load in tissue, and this correlates with treatment difficulties.[12]

An earlier diagnosis may be possible by performing polymerase chain reaction (PCR) on tissue biopsies of liver, bone marrow, lymph nodes, duodenum and rectum, which should also be cultured.

On culturing the acid-fast mycobacteria, one needs to differentiate between *M. tuberculosis* complex, *M. avium* and other NTM species. Modern molecular techniques, such as PCR with genus-specific amplification of mycobacterial genes followed by species-specific differentiation, can be done in the laboratory.[15]



Respiratory tract specimen and stool cultures cannot be used as screening tests for disseminated infection, because of their low sensitivities.[16] Recovery of *M. avium* from sputum or bronchial washing, duodenal aspirates, biopsy or stool has to be interpreted against the patient's clinical picture as well as the CD4+ cell count. It may reflect either colonisation or infection. Culture of *M. avium* from these sites in a patient with symptoms and signs fitting in with infection would not be interpreted the same as in an asymptomatic patient with a CD4+ cell count of below 50 cells/µl.[10,16,17]

## SUSCEPTIBILITY TESTING

*In vitro* susceptibility testing of MAC is of limited value because of the poor correlation with clinical outcome.[18] Exceptions are the macrolides and azolides, because these drugs have proven clinical and microbiological efficacy in prophylaxis and treatment. Macrolide resistance develops rapidly on monotherapy. A positive clinical and microbiological response is obtained when the minimum inhibitory concentration (MIC) for clarithromycin and azithromycin is no more than 4 and 32 µg/ml respectively.[18]

It is unnecessary to perform macrolide/azolide susceptibility testing on initial MAC isolates, but if the patient relapses, susceptibility testing on either clarithromycin or azithromycin may assist in deciding whether to add other drugs. For drugs other than these two (which are cross-resistant), susceptibility testing has not proved to be a useful clinical or therapeutic tool.[9]

## TREATMENT

Several factors have to be weighed in the decision to treat or not to treat. The patient's wishes and attitude towards the disease should be considered. The toxicity of the individual agents and possible side-effects have to be taken into account. Unfortunately the multiple drug regimen is expensive and often unaffordable for patients. Improving the immune system by controlling the viral load through antiretrovirals is essential for control of *M. avium* disease.

As with *M. tuberculosis* treatment, combination therapy is used. Table I summarises the drugs available.

The backbone of any regimen should be a macrolide/azolide, either clarithromycin or azithromycin. The preferred first drug is clarithromycin. As monotherapy both will reduce bacteraemia and thus symptoms, but resistance may emerge.

The macrolide/azolide should be combined with a second agent. The choice is usually ethambutol, because it is cheap and easy to administer.

Critically ill patients may benefit from a third agent.

**TABLE I. TREATMENT REGIMENS FOR *M. AVIUM* DISEASE**

**Preferred regimen**
Clarithromycin 500 mg b.d.
+
Ethambutol 15 mg/kg/d

**Alternative regimen**
Azithromycin 600 mg/d
+
Ethambutol 15 mg/kg/d
±
Rifabutin 300 mg/d

**Alternative regimen**
Combination treatment with two backbone drugs
Amikacin 10 - 15 mg/kg/day IV
or
Ciprofloxacin 500 - 700 mg b.d.

b.d. = twice a day; IV = intravenously.

Rifabutin can be considered in combination with azithromycin, but not with clarithromycin, owing to drug interaction leading to a higher incidence of uveitis.[19] The dosage of rifabutin needs to be adjusted when used in a patient on a protease inhibitor-containing regimen.

If oral absorption of drugs is a problem, or hepatitis develops, intravenous amikacin can be used. Ciprofloxacin is another drug to be considered as part of an alternative regimen.

Duration of treatment is indefinite in the absence of HAART and immune reconstitution. However, in patients on HAART, studies suggest that MAC treatment may be discontinued after 1 year if the patient is asymptomatic, the CD4+ cell count is above 100 cells/µl for more than 3 - 6 months, and bone marrow and blood cultures are negative.[20]

Gastrointestinal intolerance is the most frequently reported side-effect, and may include vomiting, diarrhoea and hepatitis. Neutropenia is the most common adverse haematological side-effect.

## PROPHYLAXIS

No specific interventions to reduce environmental exposure to MAC have been established. The principal approaches for prevention therefore focus on chemotherapeutic prophylaxis and control of HIV-1 viral replication.

Primary prophylaxis for opportunistic infections, including *M. avium* disease, is instituted on the basis of CD4+ cell count thresholds for increased risk of the specific infections. Prophylaxis for *M. avium* disease is recommended when the CD4+ cell count declines to below 50 cells/µl, the threshold for increased risk of *M. avium* infection.[21]

Macrolides/azolides can be used as primary prophylaxis.[19,22,23] Azithromycin is preferred because its pharmacokinetics allows for convenient weekly dosing, thus improving patient compliance. The dosages would be as follows:

- azithromycin 1 200 mg/week
- clarithromycin 500 mg twice a day.

Active mycobacterial disease should be ruled out before initiation of prophylaxis.

It is standard therapy to use co-trimoxazole or alternatively dapsone for the prophylaxis of *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP) infection. There are additional benefits when azithromycin is used for *M. avium* disease prophylaxis in combination with either of the standard regimens for PCP prophylaxis: there is a further decrease in the risk of primary PCP infection as well as of bacterial infections.[23,24]

Despite the clear benefits of primary prophylaxis of *M. avium* disease, we are still faced with the limits that financial resources place on our abilities to treat patients, resulting in most not receiving prophylaxis. Furthermore, it is an unfortunate reality that many of our patients cannot afford treatment for the disease once they acquire it.

Improved immune function dramatically decreases the rates of *M. avium* disease. Primary prophylaxis can safely be discontinued in patients taking HAART when the CD4+ cell count increases to above 100 cells/µl for more than 3 months.[25,26] Secondary prophylaxis (where a patient was previously treated for *M. avium* disease) may be discontinued when the CD4+ cell count is above 100 cells/µl and the patient is on HAART for 6 - 12 months or more.

## PROGNOSIS

Median survival is 4 - 5 months after the first positive blood culture in untreated patients.[2,4,5] The outcome is much poorer in patients with pre-existing underlying opportunistic infections such as PCP or *Toxoplasma gondii* infection.

In the pre-HAART era median survival was less than 1 year, even with optimal antimycobacterial treatment.[20] Nowadays life expectancy can exceed 1 - 2 years with early diagnosis and aggressive treatment. That of course depends on whether or not the patient develops another opportunistic infection or cancer. Data indicate that disseminated MAC infection can be cured by prolonged antimycobacterial therapy in some patients who experience sustained CD4+ cell count increases while receiving HAART.[20]

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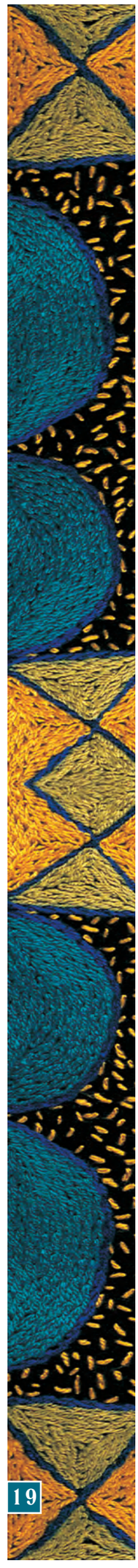

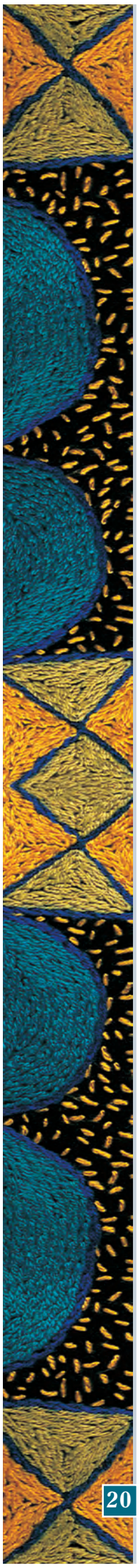

CLINICAL REVIEW

# ADHERENCE OUTCOMES IN RESOURCE-POOR SETTINGS

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Adherence is the term used to describe how well patients take their treatment. In the case of antiretroviral (ARV) therapy adherence is the key to maintaining suppression of the virus.[1-6] Viral benefit can be achieved with adherence of better than 80%, but to sustain long-term virological and clinical benefit with little development of viral resistance, adherence of 95% or more may be required.[4] In practical terms this means missing no more than 3 doses a month, which is less than 1 a week. Achieving and maintaining such high levels of adherence requires effort on the part of both the prescriber and the patient.

A number of people have expressed doubt as to whether people living with HIV in Africa will be able to sustain the high levels of adherence necessary for longstanding treatment benefit.[7,8] Can people adhere amidst poverty? Until now there have been few ARV adherence data from hospitals in Africa and none from clinics providing primary health care.[9]

This paper will describe adherence levels achieved in three public sector health care settings where ARVs are provided in Cape Town – one secondary level hospital and two primary health care facilities. The processes in place to support the patients in taking ARV tablets at each site will be detailed and recent results outlined.

## METHODS

The three sites to be described include:

1. Cape Town AIDS Cohort (CTAC), Somerset Hospital, Cape Town

2. Médecins Sans Frontièrs (MSF) ARV therapy programme, Khayelitsha, Cape Town

3. Hannan Crusaid Treatment Centre, Guguletu, Cape Town

Each site used different methods to collect adherence data. The CTAC data, collected at the HIV Research Unit, Somerset Hospital, between 1996 and 2001, were based on the counting of tablet returns. All patients at this site were participating in phase III multi-centre ARV trials, with strict medication control. All tablets dispensed were recorded and patients were asked to bring all medicines back at every visit. Tablet returns were carefully counted. Adherence was calculated by comparing the tablets actually taken with the number that should have been taken between the dates of each visit. Details of this study are published elsewhere.[10]

For this cohort adherence input was limited to pre-trial education with reinforcement by nursing and medical staff at routine visits to the unit. There were no dedicated adherence staff and no off-site or home visits. Although the data collection took place over 48 weeks, adherence at 12 weeks is described here as well in order to aid comparison with the other sites.

At the MSF sites in Khayelitsha, where ARV therapy has been offered in a primary care setting since April 2001, adherence data were collected at 1, 3 and 12 months into therapy using an adapted version of the AIDS clinical trial group (ACTG) self-reported 4-day recall questionnaire, detailing doses missed in the last 4 days. These questionnaires are a well-used tool for subjective adherence assessment.[11,12] MSF have had the questionnaire translated into Xhosa and piloted locally. The data were collected by Xhosa-speaking interviewers who were fully trained to administer the questionnaire and who were not involved in the routine health care of the patients on ARVs.

Dedicated lay counsellors, who are Xhosa-speaking, give adherence support in the clinic setting. In addition, each patient has a friend or family member trained by the

**TABLE I. COMPARISON OF THE DATA FOR THE THREE COHORTS**

| | *N* | Time on treatment (mo.) | > 95% adherence (%) | Virological suppression (%) |
|---|---|---|---|---|
| CTAC cohort | 270 | 3 | 63 | 73 (< 400 copies/ml) |
| MSF cohort | 177 | 3 | 89 | 91 (< 50 copies/ml) |
| Hannan Crusaid cohort | 43 | 4 | 95 | 93 (< 400 copies/ml) |

counselling staff as a treatment assistant for continued off-site adherence support. Three-month data will be presented here.

The Hannan Crusaid Treatment Centre has been providing ARVs from a local primary care clinic to patients in the Nyanga district of Cape Town since September 2002. Every 4 months patients had their adherence monitored by the same 4-day recall questionnaire as used by MSF as well as by tablet counts. Tablet counts of returned medications were completed at clinic visits, as with the CTAC cohort, but in addition, a surprise home tablet count was taken every 4 months.

Therapeutic counsellors, themselves HIV-positive and living in the local community, provide both on-site and off-site education in the home language of the patients and are responsible for adherence support. They collected the surprise tablet count information and completed the adherence questionnaires at the routine clinic visits. Four-month data are presented here.

## OUTCOME

The CTAC cohort included 289 people, 80% of whom did not speak English as a first language; 42% of the cohort lived in poor socioeconomic circumstances (total household income < R15 000 per annum).[13] The mean CD4 count at baseline was 268 cells/µl.

At 12 weeks (*N* = 270) the mean adherence was 94.1% with 63% of the cohort taking more than 95% of their medication. Seventy-three per cent of the cohort was virologically suppressed (< 400 copies/ml) on triple therapy at this time, with a mean 2.53 log drop in viral load.

At 48 weeks (*N* = 244) the mean adherence was 87.2%, with 56.1% maintaining the ideal adherence of more than 95%. Seventy per cent had a viral load of < 400 copies/ml.[10] Multivariate logistic regression analysis revealed decreased dosing frequency (twice compared with 3 times daily), older age, and speaking English as factors protective of adherence. Socioeconomic status had no impact on adherence.

The MSF cohort of 177 people had a low baseline mean CD4 count of 48 cells/µl. At 3 months 89% of the population reported ideal adherence (> 95%); only 4% reported adherence below 80%. Virological suppression (< 50 copies/ml) was achieved in 91% of the cohort, with a mean CD4 increase of 115 cells/ml.[14]

At the Hannan Crusaid Treatment Centre, the first 43 people on triple therapy had a mean CD4 count of 88 cells/µl at baseline. At 4 months the mean adherence of the group was 98.2% by tablet return, 98.4% by questionnaire and 90.3% by surprise tablet count. Ninety-five per cent of the cohort achieved ideal adherence, and 93% had virological suppression to < 50 copies/ml. The mean CD4 cell increase was 137 cells/µl and the mean drop in viral load was 3.13 logs.

## DISCUSSION

All three of these public sector cohorts show excellent adherence and virological outcomes. Objective outcomes for similar cohorts in the developed world show mean adherence ranging from 53% to 93% and mean virological suppression ranging from 35% to 78%.[1-5,11,15] Although the data collected from these three cohorts were not designed to be directly comparable, each set of results stands alone in showing the excellent adherence achieved by the patients and health care staff involved. While data collection times vary, and endpoints such as virological suppression differ slightly, the methods used to collect adherence data, i.e. tablet counts and 4-day recall questionnaires, are valid methods of assessing adherence.[2,3,16]

The data from the two primary care cohorts, MSF and Hannan Crusaid, were collected early on in the programmes. It might be expected that these results would taper off as duration of therapy increases. There was a slight decrease from 12 to 48 weeks in both mean adherence and percentage with virological suppression in the CTAC cohort, but the variation seen was relatively slight (< 10%). A similar 10% reduction in adherence for the other two cohorts would still leave them with results comparable worldwide.

The remarkable adherence to therapy in the two community cohorts may well reflect the value of both dedicated adherence input and education in a language used by the patient population. The CTAC cohort was supported by staff who largely spoke English. Xhosa-speaking counsellors supported both the community cohorts.

The benefit of pretreatment education should not be underestimated. Spending time explaining the HIV disease process and the do's and dont's of therapy is crucial. Whoever provides this information needs to be familiar with the medication, but does *not* necessarily need to be a doctor or nurse. Peer counsellors may in fact be more appropriate people to provide this education, many speaking from their own experience, with the advantage of belonging to the same community and speaking the same language as the patient.

A recent article reviewing HIV disease management in the South African private sector showed a mean drop in viral load of just 1.2 - 1.7 logs at 3 - 6 months into therapy.[17] This should be compared with the 3.13 log drop in the Hannan Crusaid group and the 2.53 log drop in the CTAC cohort, both at 4 months. Structured public sector programmes are showing better virological outcomes than private sector programmes. Private sector programmes offer less in the way of non-prescription qualitative support and could improve virological and clinical benefit by dedicating more health care worker time to pretreatment education and on-treatment adherence issues.

There are multiple obstacles to achieving successful ARV therapy, including the cost of the medication, the lack of health care expertise and infrastructure and the lack of political will. The data from the three different cohorts presented here show that, within structured ARV programmes, concerns about poor adherence to therapy are unfounded. Poor adherence can no longer be considered a barrier to successful ARV therapy in this country and must not be used as grounds to withhold life-saving treatment from the South African public sector population.

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# MEMBERSHIP

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Do you practice in Southern Africa? ❑ YES ❑ NO ❑ OTHER .....RURAL/CITY

Place of practice? .....

For how many years have you been treating HIV patients? .....

Is your area of HIV practice in: ❑ PRIVATE SECTOR ❑ PUBLIC SECTOR

Do you have any formal training in HIV Medicine? ❑ YES ❑ NO If 'Yes' please specify, .....

.....

Approximately how many of your patients are currently receiving antiretroviral therapy? .....

Would you like to become a member of the HIV Clinicians Provider Network? ❑ YES ❑ NO

## MEMBERSHIP BENEFITS

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- Discounted attendance at sponsored conferences
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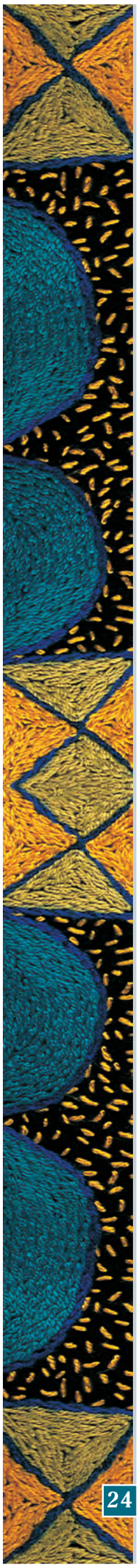

CLINICAL REVIEW

# EXPOSURE TO HIV AND OTHER BLOODBORNE PATHOGENS — GENERAL SAFETY MEASURES

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These guidelines will offer both individuals and institutions the necessary safety measures and universal precautions to follow in the event of an exposure to blood and body fluids. The contents of the first-aid box will be discussed and highlighted. Contact on the sports field will also be addressed, as will injuries caused by fights and accidents that may occur at various institutions.

South Africa currently has the highest number of individuals infected with the human immunodeficiency virus (HIV) globally, estimated at about 4.5 million.[1] Although risk groups that will be more susceptible to infection have been identified, the sheer volume and extent of this epidemic mean that it will affect everyone in South Africa.[2] In the early years of the South African HIV epidemic health care professionals were the group most concerned about the risks of potential transmission of blood-borne pathogens in the workplace setting. Today the fear of acquiring HIV from other forms of contact and exposure is a reality for all South Africans and needs to be addressed in their day-to-day activities. This article will discuss the risks of transmission of HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV) and recommend general precautionary measures that can be applied universally. These general guidelines could be applied at institutions, schools, boarding houses, university residences, community social services, sports clubs and other related areas.

## VIROLOGY OF HIV, HBV AND HCV

Of these three blood-borne viruses, HBV is the most infectious and the most hardy. However, there is a safe and effective preventive vaccine available and susceptible individuals should be vaccinated. This recommendation also applies to sexual partners or family contacts of individuals who are carriers of hepatitis B.

The actual infectivity of HCV is unknown and can only be estimated at this stage. However, care must be taken not to acquire infection with this virus, as the vast majority of individuals who become infected will remain carriers. In addition, there is currently no effective preventive vaccine and protecting the individual with immunoglobulins after exposure has been proven to be unsuccessful.

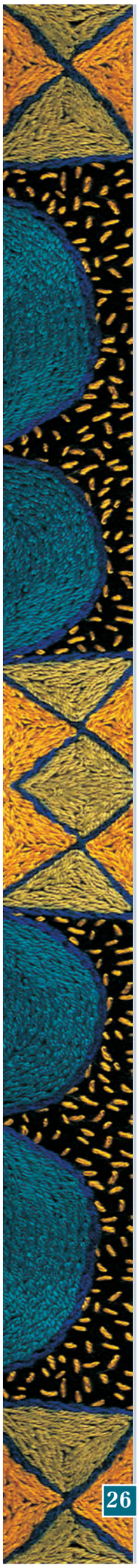
HIV, in comparison, is a fragile virus that dries out quickly and is extremely sensitive to disinfectants and alcohol, so its survival outside the body is short-lived and fluids and blood that have dried are not infectious. However, a great deal of anxiety and concern surrounds HIV. In view of the fact that HIV is spread primarily by sexual intercourse and contact with blood, persons are not at risk of being infected in the course of normal institutional and educational activity. HIV cannot be spread by sharing accommodation, swimming pools, toilets, bedding, furniture, transport, telephones, eating utensils, towels or clothes with an individual who is HIV-infected. Casual contact such as hugging and kissing on the lips will also not spread the infection. The infection is not spread by mosquitoes, bed bugs, ticks or fleas.

## RISK OF TRANSMISSION OF HIV, HBV AND HCV (Table I)

### HIV

In comparative terms HIV is not a highly infectious virus, yet it can be transmitted under the following circumstances:

- Via the sexual route (by anal, vaginal and oral intercourse). Oral sex is not considered a safe sex practice and the potential still exists for transmission.
- From mother to child, *in utero,* during delivery, or by breast-feeding.
- From contact with blood products. Such contact would include blood transfusion, penetration exposures from blood-contaminated instruments or blood splashes.



Although blood is the most common body fluid for HIV, HBV and HCV transmission, other body fluids can also transmit these three viruses. The occupational risk of acquiring HIV infection is low and is given statistically as 0.3% (confidence interval (CI) 0.005 - 0.9%).[3] This figure was derived from a retrospective multinational surveillance study on the risks of acquiring HIV among health care workers who reported occupational exposure events. The same figure of 0.3% risk has also been used to determine the risk of sexual transmission after vaginal sexual intercourse when both sexual partners do not have any other underlying sexually transmitted disease.[4] However, the type of exposure is important; for example, with sexual assault the risk may be as high as 15%.[4]

**TABLE I. RISK OF TRANSMISSION FOLLOWING PERCUTANEOUS EXPOSURE**

| | |
|---|---|
| HIV | 0.3% |
| HBV sAg+ eAg– | 3% |
| HBV sAg+ eAg+ | 30% |
| HCV | 2 - 10% |

It is important to note that HIV CANNOT penetrate through intact skin, so blood splashes onto intact skin of the hands are not deemed to be infectious.[3]

As there is currently no preventive vaccine for HIV, any exposure event must immediately be reported and managed. The exposed individual must immediately be referred to a medical practitioner for post-exposure prophylaxis in the form of antiretroviral drugs. Testing the source individual, if possible, can only be done after counselling and obtaining written informed consent to draw their blood. If the source is unknown, the matter must be referred to a medical practitioner or relevant authority for professional advice and further management.

### HBV

Although an effective preventive vaccine is available, this virus is important as currently South Africa still has at least 2.5 million carriers who are potentially infectious.[5] HBV is transmitted in the same way as HIV, namely via the sexual route or contact with blood. However, HBV is much more infectious than HIV. The average risk on exposure to an individual expressing the hepatitis B surface antigen (HbsAg) is about 3%, but the average risk when an individual is highly infectious and also expressing the nuclear antigen (HbeAg) is at least 30%.[3]

It is therefore clear that every South African should be vaccinated.

### HCV

The virus is predominantly transmitted via the blood, but sexual transmission can occur. However, there are still some uncertainties – all the modes of transmission of HCV are not known and the risk of transmission reported in various studies varies from 2% to 10%.[3] To make matters worse, there is currently no effective preventive vaccine available and response to treatment is variable.

## TYPES OF EXPOSURE EVENTS IN SOUTH AFRICA

There are currently three types of exposure occurring in South Africa. A few years ago health care professionals and workers were deemed to be at greatest risk and needle-stick injuries were the most common mode of exposure. Nowadays more and more people are encountering exposure and presenting for management. The following three categories have been identified:

- Exposure events and injuries within the occupational setting.
- Sexual assault and rape.
- Community-derived exposure is becoming more common through a wide range of circumstances.

## UNIVERSAL PRECAUTIONARY MEASURES

Although HIV prevention is classically associated with use of condoms, behavioural changes, prevention of mother-to-child transmission and post-exposure prophylaxis in the setting of occupational exposure and sexual assault, this article will address the issues of general preventive measures necessary in the community setting. These measures can be applied in a wide range of circumstances, namely within the household, at school or nursery school premises, in the workplace or in the general community setting:

- Guidelines on how to prevent and manage such exposure events should be clearly displayed and readily accessible, and the appropriate individuals must be informed about them.
- Designated staff members, employers or identified individuals must be available to assist with exposure events. The identification of a dedicated individual is a useful strategy as it ensures uniformity of management.
- Any exposure to blood or body fluids must be managed immediately. This often entails wound management and cleaning spillages or droplets of blood or body fluids. To achieve this, first-aid boxes must be correctly stocked and maintained and be readily visible and easily accessible. It has been suggested by some that individuals, including schoolchildren, carry with them a small yet effective wound aid kit containing basic items.
- Each individual or child should be aware of their HBV serostatus and whether they have been vaccinated or not. A proper vaccination schedule should be available to all.

- Education on the risks of blood exposures should be carried out and a culture of good hygiene practices must be cultivated. This is particularly important within the food and catering environment.
- Work and other area restrictions should be maintained.
- Promotion of good health care is an essential component of daily activities.

## EQUIPMENT FOR FIRST AID (Table II)

Every institution should have readily accessible first-aid kits. The following items should also be readily accessible:

- A bottle of household bleach. This simple disinfectant inactivates most micro-organisms.[6]
- Intact plastic bags. In resource-constrained areas these bags are very useful to protect the hands.

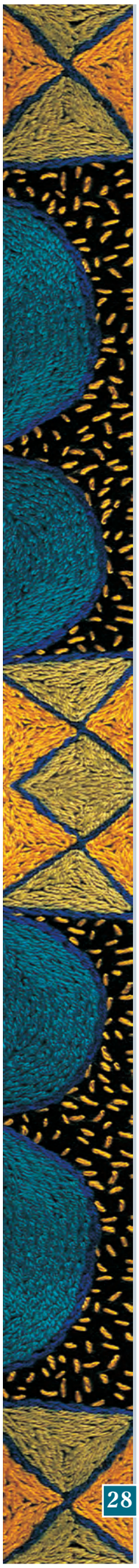
**TABLE II. CONTENTS OF FIRST-AID KIT**

- Four pairs of latex gloves (two medium, two large)
- Four pairs of rubber household gloves (two medium, two large)
- Materials to cover wounds, lacerations or abrasions (for example lint or gauze and waterproof plasters)
- Disinfectant, such as household bleach
- Scissors
- Cotton wool, tape for securing dressings and tissue paper
- A mouthpiece for mouth-to-mouth resuscitation
- Plastic eye goggles

- A container for water. Resource-constrained areas may not have access to running water, and a 25-litre drum of clean water should be kept for emergency use.

## MANAGEMENT OF ACCIDENTS AND INJURIES IN THE INSTITUTIONAL SETTING

- Avoid direct contact with blood and body fluids.
- Use latex gloves when attending to individuals bleeding from an injury or nose bleed.
- Gloves should be worn when blood is being cleaned from a floor, surfaces or clothes. The same precautions should be applied to other body fluids or excreta. If gloves are not available, intact plastic bags can provide protection.
- Pupils should be taught to avoid contact with blood and wounds and ask for help from a member of staff if there is an injury or a nosebleed.
- If a person is bleeding, the first action must be to try to stop the bleeding by applying pressure directly over the area with nearest available cloth or towel. Unless the person is unconscious or very severely injured, they should be encouraged to do this themselves.
- Grazes and wounds should be washed with clean water and antiseptic. If no antiseptic is available, household bleach (one part bleach, nine parts water) may be used.



- Wounds should be covered with a waterproof dressing or plaster. People should be encouraged to keep all wounds, abrasions or lesions (where the skin is broken) covered at all times.
- Any skin exposed to blood must be cleaned promptly with running water. If there is no running water, clean water from a container should be poured over the area. The area should be cleaned with antiseptic or household bleach diluted in water.
- If blood is splashed on the face, particularly the conjunctiva of the eyes or the mucous membranes of the nose and mouth, these should be flushed with running water for 3 minutes.
- Contaminated surfaces or floors must be cleaned with bleach and water (one part bleach, nine parts water).
- Bandages and cloths that become blood-soiled should be sealed in a plastic bag and incinerated or sent to an appropriate biohazard material disposal firm.
- Any contaminated instruments or equipment should be washed, soaked in bleach for an hour and dried.
- Ensure that bathrooms and toilets are clean, hygienic and free from blood spills.
- Every institution or school should ensure that there are arrangements for the disposal of sanitary towels and tampons. All female staff and pupils should know of these arrangements so that no other person comes into contact with these items.
- In severe injuries such as a stabbing or exposure of broken skin to HIV-infected blood, give first aid immediately and refer to an appropriate medical facility for expert assessment.

## FIGHTS, ACCIDENTS AND INJURIES IN THE INSTITUTIONAL SETTING

There is a possible risk of HIV, HBV and HCV transmission through contact with infected blood. However, the risk is negligible if good basic first aid is applied. Universal precautions should be the basic principle of management.

## THE SPORTS ARENA

- Risk of transmission is very low if the steps outlined for injuries are followed.
- First-aid kits containing rubber gloves should be available during every sports session or match.
- No one should play sport with uncovered wounds or flesh injuries.
- If an abrasion or injury occurs during play, the injured person should be called off the field of play and given first aid and only allowed to return when the injury has been treated and covered.
- Bloodstained clothes should be changed.

## COMMONLY ENCOUNTERED PROBLEMS

**Unknown source material, device or individual.** An expert professional should be identified and their contact details should be clearly displayed or readily accessible for consultation in these circumstances. Alternatively a 'hotline' source can be identified.

**Blood or fluid splashes onto the hands when there are nail-bed fissures**. Although viruses cannot penetrate through intact skin, when fluids run over the fingers and minor tears are noted the question whether a risk exposure has occurred arises. The risk is obviously very low, and a professional person should examine the extent of the actual tears.

**Human bites.** A human bite remains a serious injury, as the human mouth carries many dangerous bacteria and even fungi. The actual risk for transmission of blood-borne viruses is low, and the extent of the bite wound or contact must be assessed by an experienced individual.

**Needles left lying around.** Inadvertent injuries can be caused by unsheathed needles, for example when needles are left lying around after a medical procedure or fall into the bedclothes. There have been reports of malicious injuries. Referral to a professional person must take place. However, on a reassuring note, the needle contents have probably dried out and the contents are probably no longer infectious. The risk for transmission would then be negligible.

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# NEUROCOGNITIVE PROBLEMS IN HIV-INFECTED CHILDREN

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Central nervous system involvement contributes significantly to the morbidity and mortality of paediatric HIV infection. The spectrum of CNS morbidity varies from minor developmental disabilities to severe, progressive encephalopathy. Antiretroviral therapy may arrest or even reverse neurocognitive and motor deficits associated with HIV infection. Regular developmental evaluation should therefore be regarded as an essential component of the overall care of HIV-infected children. Although repeat neuropsychological testing is the most reliable measure of developmental delay, limited screening using a checklist may help identify those children in need of more comprehensive evaluation and intervention. Studies are needed to establish the extent and spectrum of developmental disabilities in HIV-infected children in sub-Saharan Africa.

Children whose developmental progress and performance fall outside the normal range should be targeted for specialised evaluation and intervention. The earlier developmental disabilities are recognised, whether they are due to physical, developmental or psychological causes, the better the outlook for the child, provided that correct management and appropriate placement are implemented.

## DEVELOPMENTAL ASSESSMENT

The purpose of a developmental assessment is to provide appropriate treatment, not to predict future intelligence. The assessment includes establishing the preceding pattern and rate of development, observing the child's present performance and completing a detailed physical examination. In evaluating a young child many factors may influence performance and must be taken into consideration (Table I). A developmental evaluation determines how a child behaved on a particular day. Ideally repeat observations are needed for accurate assessment, particularly when circumstances were not optimal. Serial evaluations should be done, as observations over a short period of time merely indicate the child's developmental achievements but do not determine the rate at which development is proceeding. Numerous tables have been published indicating what milestones normal children should achieve in the areas of gross motor, fine motor, speech, hearing, and personal/social development. Although these charts are reasonable guidelines, the development of normal children may vary (Table II). When a premature infant is assessed, the corrected gestational age should be used to determine developmental achievements. Development is a series of sequential events

**TABLE I. FACTORS THAT MAY INFLUENCE NEUROCOGNITIVE PERFORMANCE**

- Test environment
  - Noise level or other distractions
  - Extended hospitalisation
  - Previous painful experiences in hospital
  - Current hospitalisation
  - Non-child-friendly
- Child's physical well-being
  - Fluctuating health
  - Intercurrent infection
  - Hunger
- Unco-operative during evaluation
  - Child's emotional state
  - Overprotective or anxious parents
  - Ailing parents or caregiver
- Other
  - Child with attention/behavioural limitations
  - Examiner phobia

**TABLE II. AREAS OF DEVELOPMENT**

- Gross motor
  - Sitting
  - Ambulation: crawling, walking, running
  - Ball: kicking, throwing, catching
- Fine motor
  - Manipulation of objects (blocks, etc.)
  - Visual motor co-ordination
  - Drawing
  - Puzzles
- Speech/hearing
  - Expressive: use of words
  - Receptive: comprehension of spoken language
- Personal/social
  - Feeding
  - Dressing
  - Toilet training
  - Play and independence

that lead from one milestone to the next, so a new milestone or ability cannot be acquired unless the previous one has been mastered.

Although serial neuropsychological tests evaluating cognition and behaviour are considered the most reliable measures of developmental delay, the diagnosis may be established by completing a neurological and developmental assessment, taking into consideration parental observations and using standardised developmental screening checklists, which assess both motor and language skills.[1] Tests that are used for developmental screening (Table III) have been standardised for a particular community or setting. It is therefore important that the tests selected are appropriate for local settings, especially when using language-based tests. Test results may be influenced by previous experience or exposure to the test material, the socioeconomic environment from which the child originates, prior education, emotional state and cultural background. Attempts have been made to devise 'culture-free' tests, but there is no agreement among experts that such tests are truly neutral.

A comprehensive testing battery that is quick to administer is the ideal. The examiner should not only be skilled in administering these tests, but should also be able to use age-appropriate tests if indicated and should reschedule appointments if the situation is not optimal. Assessment instruments should cover all the areas of potential problems. Language and cultural barriers are common problems encountered in sub-Saharan Africa and this should be taken into consideration when choosing a battery of tests.

## CNS MANIFESTATIONS

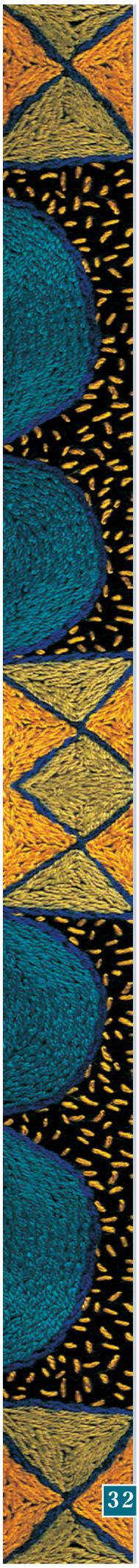
Central nervous system (CNS) involvement contributes substantially to the morbidity and mortality of paediatric HIV infection. The spectrum of CNS morbidity varies from minor developmental disabilities to severe, progressive encephalopathy (Table IV).[2-4] A significant proportion of infants with HIV infection show early and marked cognitive and motor delays or declines, that may predict rapid disease progression.[5] These abnormalities are associated with HIV infection and are not attributable to other risk factors for developmental delay, i.e. biological or environmental risk factors.[6] Central nervous system damage is caused by direct and indirect mechanisms associated with HIV infection. Indirect mechanisms, particularly neuronal attrition secondary to apoptosis, are believed to be the predominant mechanism of neuronal damage.[7]

**TABLE IV. CNS INVOLVEMENT IN PAEDIATRIC HIV INFECTION[3,4]**

- Normal neurological findings
- HIV-related CNS compromise – overall cognitive functioning within normal range with impairments in selective neurodevelopmental functions
- HIV-related encephalopathy
  - Static encephalopathy
  - Progressive encephalopathy
    - Subacute progressive course – rapid regression
    - Plateau course – less severe, no regression and no gain

**TABLE III. NEUROCOGNITIVE ASSESSMENT TOOLS – SUMMARY OF A FEW TESTS**

| Area assessed | Test | Age range | Advantages | Limitations |
|---|---|---|---|---|
| Cognitive | Bayley Scales of Infant Development, Mental & Motor | 20 - 30 months | ■ Standard scores<br>■ Developmental ages<br>■ Motor subset | ■ Hard to score<br>■ Not normed for handicapped children |
| | Griffiths Scales | 0 - 6 years | ■ Validated for language and culture<br>■ DQ and subquotients | ■ Unreliable under 1 year<br>■ Time-consuming to administer |
| | Ravens | 3.5 -11 years | ■ Easy and rapid administration<br>■ Non-verbal intelligence | ■ Prior exposure to picture/book material<br>■ Psychologist only |
| | DAP (Draw-a-Person) | 3 -15 years | ■ Easy administration<br>■ Developmental age | ■ May be affected by prior limited exposure to picture/ book material |
| Motor | Beery VMI/VP/MC | Ages 4 and up | ■ Brief administration<br>■ Easy to score | ■ Only tests fine motor skills |
| Communication | TROG (Test of Receptive Grammar) | 4 - 12 years | ■ Receptive language test | ■ Not expressive or articulation testing<br>■ Not validated for African languages |
| Adaptive behaviour | Vineland Scales<br>ABC (Aberrant Behaviour Checklist – community) | Birth - 19 years<br>School-age child | ■ Easy administration<br>■ Checklist for: irritability, lethargy, stereotypy, hyperactivity and inappropriate speech | ■ Hard to score<br>■ Not formal psychological testing |



Developmental delay may be the initial CNS manifestation of paediatric HIV infection. However, the presentation may be extremely variable. HIV encephalopathy is the most severe CNS presentation, which results in a wide range of developmental abnormalities including cognitive, motor, linguistic, psychosocial, sensory and perceptual deficiencies. Children with HIV infection may present with developmental delays at birth or remain relatively asymptomatic for several months or years before presenting with developmental compromise. A large proportion of HIV-infected children will ultimately acquire some form of CNS abnormality during the course of their lifetime.[2] Most HIV-infected children with developmental disabilities experience an intermediate pattern of plateaus and deteriorations with an overall declining course.[8]

HIV encephalopathy may be static or progressive. Children with static encephalopathy continue to gain new skills and abilities, but their scores on standardised tests are usually below normal and remain stable over time. Children with progressive encephalopathy usually have global developmental impairment. The subacute, progressive form is frequently encountered during infancy and early childhood. These children tend to regress, i.e. they lose previously acquired skills. Children who experience a plateau course fail to acquire new skills, but do not lose previously acquired milestones (Table IV).[3,4]

The manifestations of progressive encephalopathy include:

- Impaired brain growth or acquired microcephaly determined by serial head circumference measurements or brain atrophy confirmed by computed tomography (CT) or magnetic resonance imaging (MRI).
- Decline or regression in cognitive and neurobehavioural performance, verified by test scales.
- Progressive motor dysfunction or acquired symmetrical motor deficit manifested by two or more of the following: paresis, pathological reflexes, ataxia or gait disturbances.[9]

Before CNS manifestations are ascribed to HIV infection, other causes of neurological dysfunction should be considered, including the effects of maternal substance abuse, congenital CNS infection such as cytomegalovirus (CMV) and toxoplasmosis, and other causes of early static encephalopathy such as prematurity, birth trauma or genetic mechanisms.[3,7] Additional factors that may affect development adversely in HIV-infected children include low birth weight, poor antenatal care, malnutrition, limited environmental stimulation, prolonged hospitalisation, social isolation and limited parental education. Families who can afford to buy toys and household utensils to stimulate the child may facilitate the development of manipulative and spatial-perceptual skills.[3,10]

Both the age at which HIV infection is diagnosed and the severity of symptomatic infection are important prognostic determinants. The more advanced the disease, the higher the risk of developing encephalopathy. Between 70% and 80% of children with Centers for Disease Control (CDC) category B or C disease will develop encephalopathy. The risk is greater for those children diagnosed with HIV infection within the first 48 hours of life.[11] CNS disease progression is associated with significant immune suppression, rapidly declining CD4 count, high viral load, basal ganglia calcification, early age of HIV diagnosis and shortened survival. Advanced CNS involvement signals extremely poor outcome.[6,7,12,13] Early and persistent delay in motor development or regression in late infancy distinguishes many HIV-infected children from those who are HIV-exposed but uninfected.[14]

## ASSESSING HIV-INFECTED CHILDREN

A thorough neurological examination is the most sensitive method of detecting neurological impairment in HIV infection.[15] Impaired brain growth or microcephaly may be identified by serial head circumference measurements.[9] Although repeat neuropsychological testing is the most reliable measure of developmental delay, neurological and developmental observations, parental report and standardised developmental screening checklists are collectively very accurate.[8]

Neuroimaging remains an important aspect of the evaluation.[7] Radiological features, including cerebral atrophy, basal ganglia calcification, calcified microangiopathy and white matter changes, may be identified with CT or MRI scans.[3,8,15] CT scan abnormalities are particularly associated with gross motor delays and cognitive changes are especially pronounced in children with progressive brain atrophy.[16]

Nonspecific abnormalities are found on electro-encephalography (EEG) and cerebrospinal fluid (CSF) analysis in children with developmental delay. CSF analysis is important to exclude non-HIV causes of CNS involvement. Interestingly, the CSF HIV RNA concentration (or viral load) correlates with progressive neurological disease in HIV-infected children.[17] Neurological complications secondary to vascular events, neoplasms or opportunistic infections are less common in HIV-infected children than in infected adults.[3,4,18]

## ANTIRETROVIRAL THERAPY AND DEVELOPMENT

Highly active antiretroviral therapy (HAART) may arrest or even reverse neurocognitive and motor deficits associated with HIV infection.[7] Early use of antiretroviral therapy may be beneficial and a decision to start HAART may well be

influenced by the presence of subtle neurological abnormalities, as these may indicate a poorer prognosis and hence a need for therapy.[19] HAART may not necessarily reverse all the CNS manifestations. Once a child has HIV encephalopathy, the response to HAART is variable. However, some children do improve significantly.[20] Choice of HAART regimen may also affect the response to treatment. Triple therapy frequently includes a protease inhibitor (PI). There are limited data on the effectiveness of PIs in children with HIV encephalopathy.[12] Furthermore, some antiretrovirals may not inhibit viral replication adequately in CNS tissue because of limited CSF/CNS penetration. Large dosages may be required to achieve adequate CNS concentrations, but are impractical because of the increased risk of toxicity.[21]

For many children, HAART has transformed HIV infection from a terminal illness to a chronic disease. Despite the fact that the introduction of HAART has resulted in a decline in the prevalence of HIV encephalopathy, prolonged survival may well mean an increased prevalence of other neurological complications, such as seizures, CNS lymphoma, and cerebrovascular accidents.[3,22] The long-term neurological consequences of HAART are still largely unknown. The CNS may in fact be relatively vulnerable to neurological deterioration if antiretrovirals with limited cerebral penetration are administered. Furthermore, neuropathological improvement may be transient and revert if antiretroviral resistance develops.[20]

## DEVELOPMENTAL ASSESSMENT IN AFRICA

Studies have not adequately addressed the developmental disabilities of HIV-infected children living in sub-Saharan Africa, or indeed in South Africa. Anecdotal evidence suggests that these children may be at a greater risk for developmental problems than HIV-infected children living in rich countries, mainly because of unfavourable socioeconomic circumstances. Regular assessment (3 - 12-monthly, depending on the age of the child) is recommended using an adequate screening checklist and neurological examination. Primary health care workers should be trained to do the initial screening as part of routine clinical practice. Once a problem is detected the child can be referred for a formal appraisal and appropriate intervention. Furthermore, children with severe developmental disabilities may benefit from child dependency grants. The World Health Organisation recently published its recommendations for treating HIV-infected individuals in resource-limited settings with antiretroviral therapy. This document emphasises the importance of clinical monitoring, including regular developmental assessment of children on antiretroviral therapy. Therefore, regular developmental evaluation should be regarded at an essential component of the overall care of all HIV-infected children.[23]

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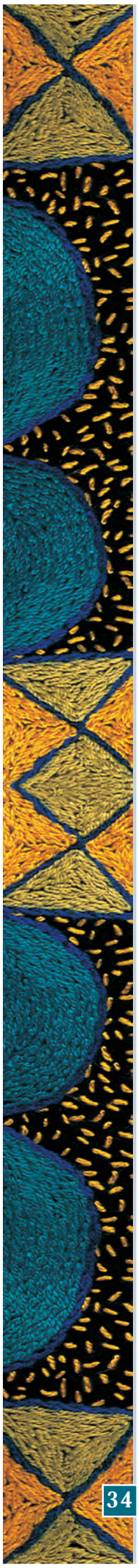



# APPROPRIATE SCIENTIFIC CRITERIA FOR EVALUATION OF HIV-1 VACCINE CANDIDATES

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As discussed in previous editions of this journal, South Africa is to embark on a process of testing HIV-1 vaccines. The primary objective of the first phase of trials is to test the safety of the candidate vaccine, which is of paramount importance. Many of the vaccine candidates in the pipeline for approval are 'prototype vaccines' in that they may contain single HIV-1-derived genes in novel vectors. Consequently, the first string of trials will also be 'proof-of-concept', where the goal would be to develop candidates containing multiple genes. For example, the first HIV-1 vaccine candidate to be approved by the Medicines Control Council (MCC) is AVX101, a Venezuelan equine encephalitis (VEE) virus attenuated and containing only one HIV-1 gene, subtype C *gag*. Such a candidate has been untested in human volunteers and the first phase of this vaccine is now taking place in the USA. Once the initial low dose of this vaccine has been shown to be safe in the US, approval to commence in South Africa will be given, making this the first vaccine trial to occur in parallel, using the same product, on two different continents.

Apart from safety, we also require information regarding immunogenicity: does the vaccine elicit an immune response in the volunteer that would mark the vaccine candidate as immunogenic? Although the first phase of a vaccine trial is not statistically powered to measure immunogenicity, this aspect of the vaccine is considered as a secondary endpoint measurement in phase I and then a primary endpoint in phase II clinical trials. The effectiveness of the vaccine will ultimately be tested in large phase III clinical trials. The scientific criteria used to decide whether a vaccine candidate should proceed beyond a phase II clinical trial are based on immunogenicity data.

## WHAT IS IMMUNOGENICITY?

The immunogenic nature of a candidate HIV-1 vaccine is how well it can cause the vaccine recipient immune system to produce anti-HIV gene antibody responses (humoral immunity) and/or anti-HIV gene T-cell responses (cellular immunity). This means that an immunogenic vaccine will induce immune responses specifically directed at the proteins, or antigens, expressed by the genes in the vaccine. It is hoped that these responses will provide primed immunity that will cross-react with the live pathogen in the event that the vaccine recipient ever becomes exposed to or infected with HIV-1. In phase I and II clinical trials, we wish to measure safety and the degree of immune priming. The purpose of this article is to demystify some of the terminology used to describe these immune responses and to describe them in the context of vaccine trials. By way of example, the AVX101 VEE vaccine candidate is used to highlight the types of immune responses expected and how we measure them in the laboratory.

The VEE vaccine contains a self-amplifying RNA, or replicon, in which the HIV *gag* gene replaces the structural protein genes of VEE. The replicon RNA is packaged into vaccine replicon particles (VRP) and after they enter cells the HIV-1 *gag* gene is abundantly transcribed leading to high-level expression of Gag proteins.[1] VEE replication is limited to a single cycle within the infected target cell resulting in viral antigens being expressed endogenously though the major histocompatibility complex (MHC) class I pathway.[2] These events result in Gag being presented to the immune on the surface of VEE-infected cells. Endogenous antigen processing is required to elicit a CD8+ T-cell response in the vaccine recipient, and it is known that these cells provide protective immune responses to viral infections.[3] We therefore anticipate that volunteers receiving this vaccine will mount CD8+ T-cell responses directed at subtype C Gag proteins. CD8+ T-cells are very important cells and are the smaller sub-population of T cells in the peripheral blood, with CD4+ T cells making the larger subset of cells in healthy vaccine recipients. While CD4+ T cells are central to the normal functioning of the immune system, by releasing cytokines and facilitating antibody production, it is the CD8+ T cells that have evolved to combat viral infections.[4] They function by recognising short linear fragments of viral proteins, termed epitopes, on the surface of other T cells or antigen presenting cells, and once recognised these target cells are killed and eliminated from the blood and lymphatic circulation. What we wish to observe with the VEE vaccine

candidate is whether CD8+ T cells are mobilised recognising subtype C Gag epitopes. It is anticipated that these cells would serve as long-lived memory T cells and provide us with a marker that the immune system of the vaccine recipient has been primed.[5] If such a scenario were to be observed, the VEE vaccine would be considered immunogenic.

## HOW DO WE MEASURE CD8+ T-CELL IMMUNOGENICITY?

Three different methodologies will be used to measure CD8+ T-cell responses in vaccine recipients. The first method will be the interferon-γ IFN-γ) ELISPOT assay,[6,7] an endpoint measurement now used for virtually all vaccine candidates designed to elicit T-cell immune responses. The ELISPOT assay is highly sensitive and quick to perform and measures T-cell cytokine secretion in response to the vaccine candidate. The assay is based on the same principle as the enzyme-linked immunosorbent assay (ELISA), although the ELISPOT measures the number of cytokine-secreting cells, rather than the concentration of the cytokine produced. The quantity of cytokine-secreting cells is measured by counting the imprint of cells after short-term stimulation with peptides matching proteins expressed by the vaccine. The imprint remaining is counted as a spot on the membrane of the ELISA plate and using a specialised digital counting system, we can quantify the IFN-γ spots. This will provide an *ex vivo* frequency of T cells elicited in response to the vaccine candidate and is now used as the primary end-point assay for HIV-1 vaccine trials. One important feature of this assay is that it can be subjected to quality control and assurance and allows different laboratories to be validated with each other as well as specifically for each vaccine trial.

The second method will measure the functional killing capacity of CD8+ T cells, also known as cytotoxic T lymphocytes (CTLs), using radioactive $^{51}$Cr release.[8] This assay is based on culturing peripheral blood cells with vaccine-matched proteins so that any priming of CTL by the vaccine can be detected after expanding these cells *in vitro*. These CTL assays are used to measure the frequency of vaccine-specific T-cell populations using $^{51}$Cr-labelled vaccine recipient immortalised B-cell lines as surrogate target cells. The basis for this assay is a 9 - 14-day *in vitro* stimulation using vaccinia-infected peripheral blood cells and interleukin 2 and 7.

The third method will use flow cytometry and intracellular cytokine staining.[9] Similar to the ELISPOT assay, peripheral blood is stimulated for a short time with vaccine-matched peptides and T-cell subsets expressing cytokines (IFN-γ, for example) are identified using fluorochrome-conjugated monoclonal antibodies to CD4 or CD8 cells. This method has been used successfully to identify the magnitude and breadth of antigen-specific CD4+ and CD8+ T cells in HIV-1 infected individuals. The major disadvantage of this method is that the lowest threshold of the flow cytometry-based assay is approximately 0.05% (or 1/2 000 CD8+ T cells), whereas it is possible to detect 1/50 000 cells using the ELISPOT assay. This may be a very important limitation of the method if the vaccine elicits low frequency of responses.

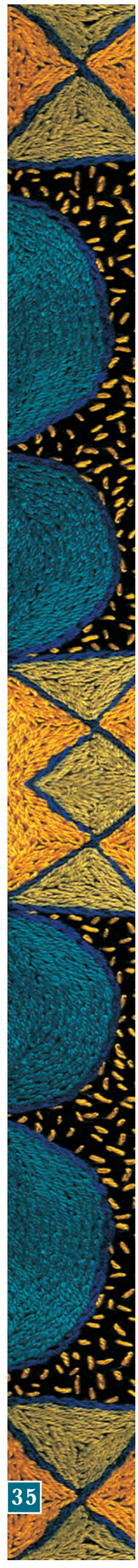
## WHAT ABOUT CD4+ T-CELL RESPONSES AND ANTIBODIES?

CD4+ T-cell responses are measured by testing the ability of cells to proliferate to vaccine-matched antigens *in vitro*. The ability of CD4+ T cells to divide in response to specific antigen is a measure of vaccine-specific CD4 responses and provides important information on how well the vaccine primes cellular immunity. The contribution of CD4+ T-cell responses to the ELISPOT, CTLs and intracellular cytokine assays can also be determined.

The first batch of prototype vaccines to undergo trials in South Africa are CTL-based. However, it is important to measure the levels of anti-Gag IgG binding antibodies in response to each immunisation. If no cellular responses can be detected, the levels of binding antibodies to the vaccine may become an important marker of a vaccine response. As the vaccine pipeline widens to include candidates containing *env* genes, it would then be expected that neutralising antibody responses might be elicited. Antibodies that interfere with the ability of gp41 to bind to the surface of CD4- and co-receptor-bearing cells will neutralise viral entry into cells and halt viral infection.[10] These responses are therefore highly desirable, and for a vaccine to offer sterilising immunity, the *env* gene needs to be included. An ideal HIV vaccine should therefore prime both humoral and cellular immunity.

## WHAT IMMUNOGENICITY RESPONSES ARE CONSIDERED POSITIVE?

There are two interrelated levels of defining positive immunogenicity responses. The first is at the assay level and the second is at the clinical trial level. One of the central issues of all the described methods for measuring immunogenicity is how to define cut-offs in the assay.[11] A cut-off is a threshold value in each of the three assays that defines what is to be considered a positive immune response. If this level is falsely high or low, it may lead to erroneous conclusions about the immunogenic nature of the vaccine. In a phase II trial, this would be extremely important as immunogenicity (a primary end-point) would determine whether the vaccine candidate enters phase III trials. All three assay cut-offs have been defined in the




context of assessing positive responses in HIV-1-infected individuals and, with the exception of the CTL assay, is undefined in the context of vaccine trials. This lack of clarity is probably related to poor immunogenic vaccine candidates that have previously been in clinical trials. The expectation is that the new vaccine candidates, including AVX101, will elicit strong responses that will allow positivity in each of the assays to be more clearly defined.

## CONCLUSIONS

Performing clinical vaccine trials is a complex process and measuring immune responses to vaccine candidates and defining immunogenicity adds to this complexity. Decisions as to whether vaccine candidates will move through to phase III trials in the future will be based on laboratory measurements of primed immunity – both humoral and cellular. How well immune responses are elicited will be partially based on the design of the vaccine construct. Laboratory capacity in South Africa for assessing immune responses has been built up through the HIV Vaccine Trials Network (HVTN) and the South African AIDS Vaccine Initiative. The immunology laboratories at the National Institute for Communicable Diseases is one of four Central Immunology Laboratories of the HVTN, working closely with the Fred Hutchinson Cancer Research Center, Seattle, Duke University, North Carolina, and the Department of Health Sciences in Richmond, California. This network of laboratories are working through a process of proficiency testing and protocol-specific validation to adequately define cut-offs in all the assays used that would allow correct decisions to be made regarding the immunogenicity of vaccine candidates and whether they should proceed further to phase III trials.

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# MEDICINES CONTROL COUNCIL APPROVES FIRST HIV VACCINE TRIAL IN SOUTH AFRICA

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The South African Medicines Control Council (MCC) has approved the first human clinical trial for an HIV vaccine in South Africa. This is a phase I human clinical trial of the AlphaVax replicon Vector (ArV) clade C candidate HIV-1 vaccine to assess the safety and immune system responses induced by this new vaccine technology. The trial will involve a small number of volunteers in the USA and South Africa.

ArV is cutting-edge vaccine technology that was awarded the World Technology Forum Award for biotechnology in 2001. It utilises virus-like particles, containing parts of an attenuated strain of Venezuelan equine encephalitis (VEE) virus and a gene from a South African strain of HIV, to deliver the vaccine to the immune system. This is the first trial of the ArV technology in humans.

The HIV Vaccine Trials Network (HVTN) is conducting the trial, which will take place at two clinical trial sites in South Africa – the Perinatal HIV Research Unit at the Chris Hani Baragwanath Hospital in Soweto and the SAAVI Vaccine Research Unit at the Medical Research Council in Durban. The US trial sites are Johns Hopkins University, Columbia University, the University of Rochester and Vanderbilt University.

As the vaccine contains only a copy of a small section of genetic material from HIV, and does not include the genetic elements needed to reconstitute live HIV, there is no possibility of the vaccine itself causing HIV infection. The vaccine material is also designed in such a way that its VEE components cannot generate VEE virus or cause VEE infection.

This ArV vaccine technology was originally developed by researchers at the University of North Carolina (UNC) and the US Army Medical Research Institute of Infectious Diseases, and has been applied to HIV by an international collaboration of researchers from UNC, the University of Cape Town, the Medical Research Council in South Africa, and AlphaVax, a North Carolina biotechnology company. The International AIDS Vaccine Initiative (IAVI) was also a key supporter of the programme earlier in the collaboration. The organisations involved in conducting and funding the trial in the USA and SA include the US National Institutes of Health (NIH), the HVTN and the SAAVI consortium partners in South Africa. The National Institute of Allergy and Infectious Diseases (NIAID)-funded HVTN is conducting the trial. AlphaVax developed the vaccine, produced the vaccine material, and submitted the regulatory applications in both countries.

A total of 96 participants will be involved in the trial – 48 in the US and 48 in South Africa. Twenty-four volunteers are required at each South African site and recruitment activities are continuing in preparation for the first vaccinations. Volunteers will be healthy, HIV-negative adults who are willing and able to give informed consent. Intensive pre-recruitment educational and community awareness activities have been conducted at both sites in South Africa. The study that has been approved will begin by enrolling 12 volunteers in the US, and additional volunteers will be enrolled in the US and SA once initial safety data from these 12 volunteers have been reviewed.

Potential volunteers will be supplied with detailed information about the candidate vaccine. Volunteers will undergo intensive risk-reduction counselling and clinical monitoring on an ongoing basis throughout the trial to ensure their safety and that they do not expose themselves to unnecessary risk.

SAAVI SOUTH AFRICAN AIDS VACCINE INITIATIVE

AlphaVax™

HIV VACCINE TRIALS NETWORK

## About the VEE candidate vaccine

The vaccine is based on alphavirus replicon vector technology. A vaccine vector is a biological delivery system for a vaccine. This is a *replicon vaccine*, which uses parts of the Venezuelan equine encephalitis (VEE) virus. In replicons, the genes for the VEE viral structural proteins are removed and replaced with a gene or genes cloned from the HI virus. Instead of producing its own structural proteins, the VEE replicon RNA is used like a machine to produce large amounts of HIV protein in the person vaccinated. It is hoped that the HIV protein will induce immune responses protective against HIV infection.

To deliver the replicon RNA into the body, it is packaged into an artificial virus-like particle, a VEE vaccine replicon particle (VRP). The VRP is used as a vector for the HIV gene. In making this vaccine, the genetic material of the VEE virus is weakened and restructured. Important parts are removed to make a vaccine particle that can express the proteins from the inserted HIV gene but cannot make more VEE virus, and therefore cannot cause VEE infection. Multiple, layered safety features are designed into the system and rigorous safety testing of each vaccine batch ensures that VRP preparations are safe. This has been confirmed in various laboratory and animal studies.

The vaccine does not contain killed or weakened HIV. It contains only a copy of a small section of genetic material from HIV, known as the *gag* gene derived from the clade C virus circulating in South Africa. It does not include the genetic elements needed to reconstitute live HIV. Therefore there is no possibility of the vaccine causing HIV infection.

This gene is a promising target for the cellular immune responses thought to be a prerequisite for a successful HIV vaccine. The *gag* gene selected conforms closely to the South African consensus sequence for this gene, and is therefore characteristic of the circulating clade C virus. A single gene was selected for the lead project to simplify the development and expedite initiation of clinical trials. Work on a multi-gene product is also proceeding with the hope of entering clinical trials by late 2004.

The same technology is also being studied in other disease models – including herpes and certain cancers.

A phase I trial is a safety trial, which aims to confirm that the test vaccine does not produce significant side-effects in human volunteers. Volunteers in this study will be closely monitored over a 12-month period. This test vaccine has already been extensively tested in laboratory and animal studies. The phase I clinical trial protocol has also been reviewed and approved by the US Food and Drug Administration (FDA) as well as by multiple ethics committees in South Africa and the USA.

Volunteers will be involved in the trial for about a year and it is anticipated that with data analysis the trial will last approximately 2 years.

This is the first HIV vaccine trial to be approved in South Africa and the first in the world to test a subtype C vaccine.

LEGAL UPDATE

# ONCOLOGY BENEFITS AND HIV — A BRIEF LEGAL AND ETHICAL ANALYIS

**Elsabé Klinck**

*Director: Research, Compliance and Consulting, Foundation for Professional Development, South African Medical Association*

It has been reported that authorisation for oncology treatment has been made made dependent on the patient's HIV-negative status. In order to solve this issue in terms of the law, it is necessary to start with the general principles applicable to medical treatment.

Informed consent from the patient is required for any medical treatment, investigation or consultation. Informed consent has been entrenched in South African law as a legal principle for over a century, and will soon be detailed in the National Health Bill of 2003. The requirement for consent can only be disposed of where, for example, a law or court order authorises this. In general, the Medical Schemes Act and regulations do not interfere with this principle. Even where schemes suspect certain conditions in certain patients, no patient can be forced to submit to any test, treatment or investigation without giving informed consent.

The second important principle is that of confidentiality. This means that after an investigation the results may not be made known to any third party unless the patient has consented to such a disclosure. In terms of the Medical Schemes Act and regulations, a scheme is only entitled to all the medical records of a patient in terms of a managed care agreement between the specific medical practitioner or practitioner's group and the medical scheme, as provided for in Regulation 15J(2)(c).

The Medical Schemes Act, however, also provides that all schemes have to fund the treatment of the so-called 'Prescribed Minimum Benefits'. Most oncology treatments form part of this list of conditions, attached to the Regulations as 'Annexure A', to which a list of 'Explanatory notes and definitions' is attached. The first important note refers to the fact that treatment of the prescribed minimum benefit conditions should be provided for in terms of 'predominant public hospital practice, as outlined in ... clinical protocols, where these exist'. Where they do not exist, consultation should take place with authorities on what predominant practice is.

In cases where more than one condition is present, Note 6 states that 'certain ... specified categories shall take precedence over others'. HIV is one such category. In very simple terms, this means that a medical scheme could decline to pay for a prescribed minimum condition if the patient is HIV-positive. However, this provision does not authorise testing or disclosure without informed consent. In practice, this means that a patient who is HIV-positive and who has consented to that fact being made known to the medical scheme, is *only* entitled to treatment of opportunistic infections as prescribed in Annexure A.

In constitutional and human rights terms, this provision of the Act and its application is open to legal challenge. The reason why a person would not be able to access treatment would relate solely to his or her HIV status. The basis for such a challenge can be found in either the equality or the access to health care clauses in the South African Constitution or the provisions of the Promotion of Equality and Prevention of Unfair Discrimination Act and its Schedule of Illustrative Unfair Practices.

# PALLIATIVE CARE — A CLINICAL APPROACH FOR ADULTS WITH HIV/AIDS

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The purpose of this article is to:

- define palliative care and understand its place in the management of HIV infection
- briefly review palliative care clinical guidelines for important HIV-related conditions
- identify some clinical challenges in the provision of palliative care and areas for research and open a debate on these issues.

## WHAT IS PALLIATIVE CARE?

Palliative care is an approach that improves the quality of life of patients and their families who are facing the problems associated with life-threatening illness. It does this through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychological and spiritual.[1]

The aim of palliative care is to heal when we cannot cure, and to achieve the highest possible quality of life for patients and their families.

## THE IMPORTANCE OF PALLIATIVE CARE IN AIDS

Pain in AIDS is likely to be under-diagnosed or under-treated. Pain in individuals with HIV is highly prevalent (62 - 87%) and varied in syndromal presentation. It is associated with significant psychological and functional morbidity, so negatively impacting on the patient's quality of life.[2,3] One study noted that, disturbingly, the more severe the pain, the more often doctors underestimate it.[2]

A local study found that people with AIDS have on average three pains at any particular point in time, as well as multiple symptoms.[4]

*'You matter because you are you, you matter to the last moment of your life, and we will do all we can not only to help you die peacefully but to live until you die.'*

*Cicely Saunders, founder of modern hospice*

## LACK OF RESEARCH AND DEVELOPMENT

In the pre-highly active antiretroviral therapy (HAART) era there was research into and interest in developing programmes for the palliation of AIDS. The introduction of HAART saw the closure of most of the AIDS hospices in the developed world, and palliative care virtually dropped from the AIDS research agenda. Because of exponentially increasing numbers of people dying with AIDS in South Africa, currently 600 per day,[5] this country should have a high level of activity in this area.

However, there seems to be little recognition of this need, either internationally or locally, when we examine current research being done in this field. For example, at the XIVth International AIDS Conference in Barcelona in 2002, of the 8 719 abstracts accepted only 53 were about palliative care or home-based care, 5 from Africa and none from South Africa.

## WHEN TO USE PALLIATIVE AND WHEN TO USE CURATIVE TREATMENT FOR AIDS-RELATED ILLNESSES

The WHO framework of integrating curative and palliative care helps us to implement appropriate care (Fig. 1).[6] Care can be directed towards curative treatment of opportunistic infections, palliative management of symptoms, or both at any time. For example, the management (palliation) of nausea and vomiting from side-effects of antiretrovirals (ARVs) may be a key aspect of promoting good adherence to ARV therapy.

Conversely, treating cytomegalovirus (CMV) retinitis in a dying patient with intraocular or intravenous ganciclovir to preserve sight may be an important quality of life issue for that person.[7]

However, in real life decisions such as whether or not to aggressively diagnose and treat opportunistic infections with antibiotics, to perform surgery, or to offer radiotherapy can be extremely difficult.

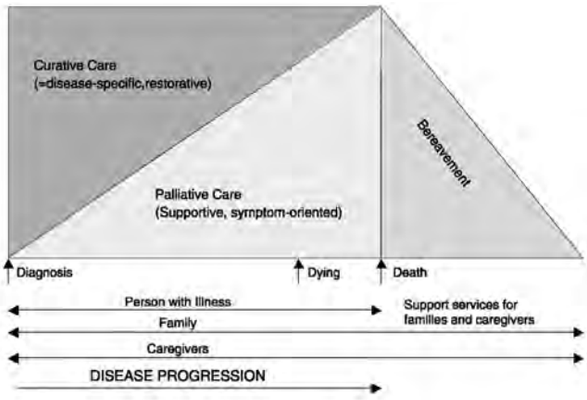



*Fig. 1. Integrated model including both curative and palliative care for chronic progressive illness. (Source: World Health Organisation.* Cancer Pain Relief and Palliative Care, Report of a WHO Expert Committee *(Publication #1100804). Geneva: World Health Organisation, 1990.)*

Asking the question 'Will this make a difference to the quality of this person's life?' can help guide us on when to use diagnosis-treatment algorithms, and when to make decisions based on goals of care.

This definition assumes a palliative component to care from the time of diagnosis, and not only when the patient is terminally ill, thus providing comprehensive care of the patient. Realistic goals of care will also be set if pain and symptoms are addressed from diagnosis. Patients and their families will understand that the doctor cannot perform miracles, and will often just ask that they are not abandoned in their time of greatest need.

### NEED FOR A MULTIDISCIPLINARY APPROACH

The palliative approach recognises the concept of total pain. This means that as well as relief of physical pain and symptoms, attention should be paid to the alleviation of psychosocial and spiritual problems. This necessitates the involvement of other disciplines and recognises the role of both patient and family in the healing process.

**Causes of pains in AIDS**

- Effect of specific opportunistic infections
- Effects of the HIV itself
- Effects of medication
- Nonspecific effects of chronic debilitating illness

### PREVALENCE OF AIDS SYMPTOMS (Table I)

Note that the prevalence of symptoms may not necessarily correspond to the degree of debility that is caused by a symptom.

**TABLE I. PREVALENCE OF SYMPTOMS IN AIDS**

| Symptom | Fantoni *et al.*[7] (Italy) *N* = 1128 rank (%) | Norval[4] (Soweto) *N* = 103 rank (%) |
|---|---|---|
| Fatigue | 1 (55%) | 10 (43%) |
| Weakness | | 5 (66%) |
| Anorexia | 2 (34%) | 3 (71%) |
| Loss of weight | | 2 (81%) |
| Cough | 3 (32%) | 9 (45%) |
| Pain | 4 (29%) | 1 (98%) |
| Nausea and vomiting | 5 (22%) | 8 (45%) |
| Respiratory symptoms | | 6 (19%) |
| Pruritus or dry skin | 7 (17%) | 6 (56%) |
| Diarrhoea | 8 (11%) | 7 (53%) |
| Visual loss | 9 (12%) | |
| Low mood | | 4 (70%) |

**Five most prevalent pains in patients with advanced AIDS in Soweto[4]**

Lower limb pain
Mouth pain
Headache
Throat pain
Chest pain

## A CLINICAL APPROACH TO PALLIATIVE CARE IN AIDS

Often palliation for people with AIDS is best achieved by treating the agent causing opportunistic infections. The most appropriate management is not always available to patients, however, and symptomatic options may be the only ones available.

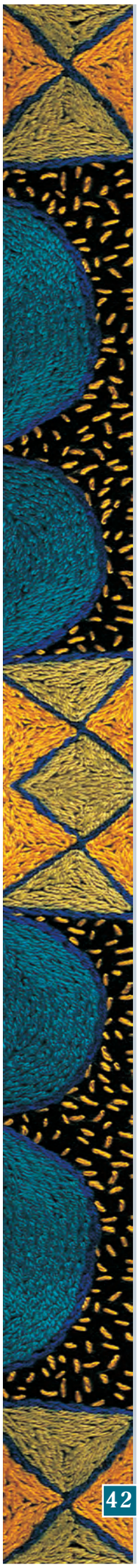
We review symptom management using a syndromic approach, and will indicate when treatment of the causative agent may be most appropriate. Texts on treatment of opportunistic infections and the use of ARV therapy are available so this topic will not be addressed here in detail.

### PAIN

Pain and other symptoms are by definition subjective, and should always be measured in this way, i.e. pain and symptoms are *always* what the patient says they are.

When diagnosing and reviewing pain:

- Remember non-AIDS-related causes of pain.
- Look for emotional and psychosocial causes of pain.
- Explain the cause and implications to the patient.
- Pain should be given a score, and pain relief reviewed against that score.
- New pains should be sought at each review.



### Principles of pain relief

*'By the mouth, by the clock and by the ladder, for the individual and attention to detail.'*

- Analgesics should be given regularly.
- Analgesics used must be appropriate for the severity of pain.
- If pain does not respond to a weak opioid, a strong one must be used.
- Except in the presence of chronic diarrhoea, all patients taking opioids must be prescribed a laxative.
- Additional methods of pain control must be considered in all patients, since pain may be caused by factors such as fear, constipation or infection.
- Review and reassess regularly.

### WHO ladder for management of pain

- **Step 1 for mild pain**

Acetominophen 1 g 4 - 6-hourly, max. 4 g in 24 h p.o.
Ibuprofen 200 - 600 mg 4 - 6-hourly, max. 2 400 mg daily p.o.
+/- adjuvants

- **Step 2 for moderate pain**

Tramadol 50 - 100 mg 6-hourly p.o.
Codeine phosphate 30 - 60 mg 4-hourly p.o. PLUS step 1
+/- adjuvants

- **Step 3 for severe pain**

Start morphine sulphate solution 5 - 10 mg p.o. 4-hourly* (administer at 06h00, 10h00, 14h00 and 18h00, and give a double dose at 22h00) PLUS step 1
+/- adjuvants

Constipation when taking morphine is inevitable, so start morphine together with liquid paraffin 5 - 20 ml daily. One may add senna 15 - 30 mg once daily.

### Prescribing morphine for chronic pain

Morphine is the strong opioid of choice, and will be the only strong opioid considered here, although in the case of morphine intolerance an alternative can be used.

The aim is to have the patient pain-free and mentally alert. When used in an appropriate dose for pain, morphine does not have a sedating effect.

There are no contraindications, if titrated carefully against the patient's pain.[8]

- Dose varies between individuals. Reduce the dose if drowsiness persists after 2 days.
- Titrate upwards until pain is relieved, by increasing the dose by 50% every 2 - 3 days if pain is not relieved or if more than 2 breakthrough doses are required in 24 hours.
- The titration can be increased gradually until the pain has been lessened or there are unpleasant side-effects. There is no maximum dose. In rare cases patients have required more than 1 000 mg in 24 hours.
- After 2 - 3 days add the total dosage required in 24 hours and divide by 2. Then switch to morphine MST (sustained release morphine). The MST should not be crushed or broken. If the patient remains drowsy, reduce the dosage.
- **Breakthrough pain.** The importance of receiving a dose for breakthrough pain cannot be over-emphasised. Administer an extra dose equal to the 4-hourly dose.

Warn patients of possible side-effects:

- Nausea – usually temporary. Give haloperidol 1.5 - 3 mg *nocte*.
- Sedation – usually wears off. Ensure adequate hydration if patient is drowsy. Often patients who have been exhausted by severe pain will have a long sleep once pain is relieved.

**Stopping morphine.** If the cause of the pain is addressed adequately, the morphine can be withdrawn. If it has been given for more than 5 days, reduce the dose by 25% each day.

Morphine is also effective for suppression of cough, and for chronic diarrhoea.

Concerns about respiratory depression have sometimes limited the use of opioids in the past. Current evidence indicates that as long as opioids are carefully titrated against symptoms for real pain or dyspnoea, respiratory depression does not present a serious danger.

Morphine does not lead to addiction when used for palliative care.

### Adjuvant drugs

Adjuvant drugs are used to enhance pain relief and to treat the adverse effects of analgesics. They include corticosteroids, antidepressants, antiepileptics, *N*-methyl-D-aspartate (NMDA)-receptor channel blockers, antispasmodics, muscle relaxants and bisphosponates.

Pain-relieving modalities also include radiotherapy, orthopaedic surgery, spinal opioids, nerve blocks, physiotherapy, transcutaneous electrical nerve stimulation and psychotherapy.

## TREATMENT OF PAIN IN AIDS

Treatment options for pain and symptom relief in AIDS are outlined in Tables II and III. Currently there are few evidence-based guidelines available for effective

*In our busy hospital setting we have found better pain control is achieved if morphine is prescribed and given 6-hourly, simply because staff implications of administering the 4-hourly doses meant that more doses were skipped than if the drug was prescribed 6-hourly.

**TABLE II. TREATMENT OF PAIN IN AIDS**

| Pain | Comments | Management |
|---|---|---|
| Peripheral neuropathy | This is a neuropathic pain caused by damage to the nerves. It is described as burning in the hands or feet, but may also be stabbing or shooting in nature, worse at night | Opioids are not very effective for this pain.<br>*Drug approach:*<br>1. Amitriptyline. Start with 10 - 25 mg *nocte*; titrate upwards every 2 - 3 days to maximum 75 mg *nocte*. Pain relief can be biphasic relieved within hours to days, then again after a month or two<br>2. According to response add or substitute carbamazepine 100 mg b.d. Can increase every second week to max. 400 mg b.d. NB: drug interactions and side-effects, and it is difficult to titrate<br>3. Dexamethasone 8 mg daily; if no improvement stop after 5 days<br>4. NSAIDs. Use with care, can cause serious GIT events (may use misoprostol), affect platelet function, and impair renal function. Note that GIT irritation is increased with concomitant use of corticosteroids<br>*Non-drug interventions* include giving the patient socks to wear |
| Post-herpetic neuralgia | | Use carbamazepine or amitriptyline.<br>Studies have shown opiates to be effective,[9] consider nerve blocks or EMLA cream or topical lignocaine |
| Generalised body pains | Include muscle pain often associated with bed-ridden state | Start WHO ladder. If pain is not controlled, morphine should be started. Consider diazepam 2.5 - 5 mg t.d.s. |
| Mouth pain | Treat cause as far as possible; this is often *Candida*. Fungizone lozenges – dissolve 1/4 on tongue 2-hourly | For the *prevention* of acute necrotising gingivitis, advise regular rinsing with chlorohexidine mouthwash for 1 minute twice daily as well as regular brushing using a soft toothbrush. Note that prolonged use of chlorhexidine can cause altered taste, discoloured tongue. May also rinse with copious amounts of salt water |
| Apthous ulcers | | Predisolone 5 mg, place tablet on ulcer and dissolve, chlorohexidine mouthwash t.d.s. |
| Acute necrotising gingivitis | Occurs early in AIDS, very painful, prevents eating, severe halitosis | Metronizadole 200 mg t.d.s. x 5 d, amoxicillin 250 mg t.d.s. x 5 d and rinsing with chlorohexidine. Andolex mouthwashes are also thought to provide an analgesic effect |
| Mucositis, glossitis, perleche | | Vitamin B co. 2 tabs b.d. OR pyridoxine 25 mg, plus thiamine 100 mg and folate 5 mg/d supplements can help the sore mouth. Vitamin C 500 mg, warm salt water |
| Dysphagia and odynophagia | Should be treated aggressively; almost all oesophageal infections are treatable | |
| Biliary tract or pancreatic pain | Often severe | WHO ladder – often requires step 3 |
| Abdominal pain | Consider constipation | For colic give hyoscine butylbromide 20 - 40 mg 6-hrly |
| Headaches | Exclude meninigitis as cause for headache | Use WHO ladder |
| Bone pain | If sudden in onset and severe consider possible fracture and refer | NSAID at maximum dose plus opioid. It is best to use a NSAID which has no effect on platelet function and low gastrotoxicity, e.g. ibuprofen. Consider dexamethasone, bisphosponates if tumour metastases present |
| Proctitis | | Anal sepsis: Savlon sitz baths, proctitis secondary to chronic diarrhoea: predsol enema b.d. 3 days, zinc oxide paste to skin.<br>Use WHO ladder |

NSAIDs = non-steroidal anti-inflammatory drugs; GIT = gastrointestinal.

treatments. Anecdotal evidence suggests that pain in AIDS patients often responds to lower doses than required in other patients. If patients are on ARV therapy, drug interactions should be considered.

## MEDICAL CARE IN ADVANCED AIDS

Consider referral to hospice care for home visits, respite or placement. Hospital admission for some conditions may be appropriate if they add to quality of life and if resources are available.

## PREPARING FOR DEATH AND THE LAST 48 HOURS

Facilitate these conversations for a 'peaceful death':

'Thank you'

'Forgive me'

'I forgive you'

'I love you'

'Goodbye'.

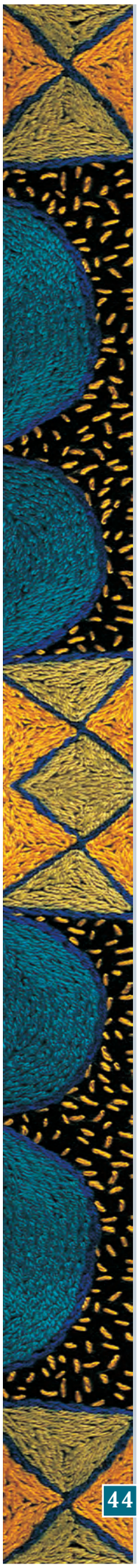


**TABLE III. TREATMENT OF SYMPTOMS OTHER THAN PAIN IN AIDS**

| Symptom | Comment | Management |
|---|---|---|
| **Constitutional** | | |
| Wasting | Mechanisms include diminished intake, excessive nutrient loss, metabolic dyregulation. Intake can be improved if mouth pain and oesophageal pains are addressed | e-pap (a nutritional supplement)<br>Appetite stimulants can be offered, but not on a long-term basis. For example dexamethasone 4 - 16 mg p.o. once daily, megestrol acetate, testosterone are under investigation. Both have significant side-effects |
| Fatigue | Common | Methylphenidate 2.5 - 5 mg in the morning and at noon, good for depression as well, avoid in anxiety and agitation.<br>Facilitate the patient's re-evaluation of goals and expectations.<br>Dexamethasone 4 - 16 mg p.o. once daily has been shown to be effective in patients with progressively disseminated MAC. Exclude depression: treat depression with fluoxetine. Paroxetine has been shown to be a highly effective analgesic for the treatment of diabetic neuropathy |
| Fevers and sweats | Exclude sudden withdrawal of opioids<br>If possible and appropriate, treat the underlying causes | Acetaminophen 650 - 1 000 mg p.o. 6-hourly.<br>NSAIDs: note potential side-effects.<br>Cimetidine 400 - 800 mg p.o. b.d. for sweats |
| **GIT** | | |
| Anorexia | | Soluble vitamins particularly B and C group.<br>High calorie intake, fluids.<br>Magnesium/calcium/selenium/potassium supplements.<br>Corticosteroids, e-pap |
| Nausea and vomiting | | Haloperidol 1.5 - 3 mg *nocte*<br>Metoclopramide 10 mg p.o. 8-hourly |
| Chronic diarrhoea | Refer if diarrhoea bloody and patient pyrexial | Oral rehydration 300 mg 2-hourly (1 litre water/8 tsp sugar/1 tsp salt).<br>Loperamide 2 mg after each loose bowel movement, not to exceed 16 mg in 24 h.<br>Morphine or codeine phosphate. Care of perineum: use zinc and castor oil ointment as a barrier cream |
| Cachexia, anorexia and dyseugia (food tastes bad) | | Artificial feeding in AIDS has not been shown to increase survival, can promote suffering; can distract families from issues of emotional support |
| **Respiratory** | | |
| Cough | Treat cause | PCP prevention with co-trimoxazole.<br>Use morphine |
| Dyspnoea | Titrate carefully against the patient's perception of dyspnoea, not against an increased respiratory rate or effort | Use morphine.<br>If dyspnoea is felt to reflect a component of anxiety, fear or stress, give diazepam or lorazepam |
| Haemoptysis | | Morphine.<br>Dark-coloured towels may lessen anxiety of patient and carers |
| Pulmonary secretions | | Hyoscine butylbromide 20 mg s.c. *stat* |
| **Skin** | | |
| Prurigo, dermatoses | Avoid prolonged, frequent hot baths | Antihistamine — chlorphenamine 25 mg t.d.s.,<br>UEA — betamethasone 4:1 to affected areas daily |
| Dry skin | | UEA and aqueous cream as soap |
| Kaposi's sarcoma | | Treatment of malodorous wounds: use crushed metronidazole (amount 10 - 20) tablets depending on odour, not size of wound, together with Intrasite gel and Flamazine, apply daily. Give adequate analgesia |
| Fungal and other infections | Treat aetiologically where possible | |
| **Genitourinary** | | |
| Incontinence | Can be distressing to patient. Exclude or treat treatable causes. Prevent skin breakdown. Can iron plastic bags together with a cool iron for mattress protection. Do not place patient on the plastic | Nappies, wash and dab dry do not rub, use barrier creams, zinc and castor oil ointment |
| **Psychiatric** | | |
| Delirium | | Haloperidol 0.5 - 5 mg *nocte* |
| Depression | Feelings of intense sadness, withdrawal anger, anxiety, early morning waking | Fluoxetine 20 mg *nocte* |

MAC = *Mycobacterium* avium complex; PCP = *Pneumocystis carinii* pneumonia; UEA = ungeuntum aqueous.

- Legal and financial issues should have been addressed while the patient was well.
- Memory boxes can help the bereavement process, especially when children are bereaved of their parents.
- Spiritual care may become extremely important.
- Physical presence of the carer at the bedside can reduce fear and loneliness.
- The death rattle may be distressing to carers and can be reduced (see Table III, pulmonary secretions).
- Bereavement can be normal, pathological or prolonged. Bereavement counselling may be indicated, especially in families with multiple deaths, orphans and AIDS-associated stigma.
- Care of the carer is recommended as a routine activity.

## CHALLENGES IN THE PROVISION OF PALLIATIVE CARE FOR PEOPLE WITH AIDS

The challenges are many and mostly pertain to the lack of clear policy guidelines, funding allocations, health systems and training, and access to required medication. Contributing factors include the sheer scale of the epidemic, lack of linkages and referral criteria between primary health care services, non-health sector organisations providing home and hospice care, and welfare and other support organisations.

The clinical challenges include:

- The lack of access to ARV therapy.
- Deciding whether to treat aetiologically at all, or when to stop aetiological treatment, for example in cryptococcal meningitis. Often this decision is influenced by non-clinical considerations, such as cost of care.
- Many cancers cause a fairly straightforward and progressive decline in health and functionality. AIDS, however, runs an erratic course, and even when the patient seems extremely ill, even terminal, with good care they may recover enough even to return to work. Prognoses are therefore often unpredictable. Data are scarce, but the rates of change of serial viral load, CD4 count and serum albumin have been used as laboratory prognostic indicators, and severe neurological defects and weight loss of over 20% as clinical indicators of a poor prognosis. In a small study the Karnofsky performance scale was shown to be a reliable prognostic indicator.
- The range of symptoms and multiplicity of pains require a good knowledge base of pharmacology and potential drug interactions between ARVs, other AIDS-related medications and palliative medicine.
- Working effectively in a multidisciplinary team that includes non-health professionals and even the patient and his or her family is something that the current health systems are not structured to accommodate. Acquiring up-to-date knowledge of local agencies to refer to can be time-consuming.

The stigma associated with AIDS means that many people are reluctant to be seen accepting hospice- or home-based care services, and will refuse care. Stigma also means that it is difficult to address denial, and patients and their families tend to insist that recovery is possible and seek aggressive therapies.

Lastly, the psychological impact of multiple deaths in a community and the prolonged period of debilitation exhausts resources. The physical and emotional burden on carers is enormous.

## CONCLUSION

Although some complicated syndromes in pain and symptom management would benefit from the input of a palliative care specialist, in most cases primary care providers and physicians can diagnose and treat a wide range of AIDS-related symptoms using standard palliative medicine strategies. Most of these pains and symptoms can be alleviated using a combination of drugs (all available on the South African EDP), as well as non-drug interventions.

Thank you to Terri Cohen, Regional Public Health Advisor, Johannesburg Oral Health Services, Gauteng Department of Health.

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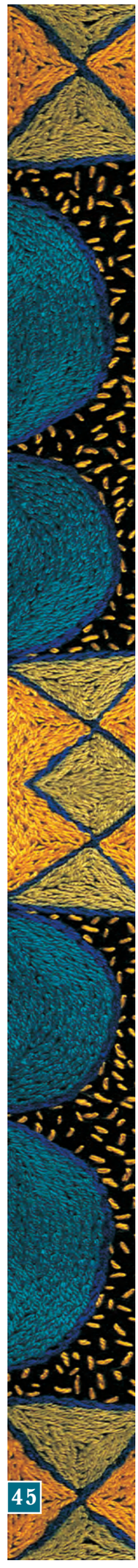

# HIV INFECTION IN INDIA — FOLLOWING IN THE FOOTPRINTS OF SOUTH AFRICA?

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*'from the moment she is born, an Indian female is seen as a liability rather than as an asset' (Becktell, 1994)*

## BACKGROUND

Since the first human immunodeficiency virus (HIV)-infected patient was diagnosed in 1986 in Chennai, in the south of India, the Indian subcontinent has witnessed an explosive increase in the number of HIV-infected individuals. Figures released in 2001 from the World Health Organisation and UNAIDS estimate that approximately 3.97 million people are currently HIV-infected, making India the second highest country globally in terms of sheer numbers of cases.[1] The top position goes to South Africa, where it is estimated that there are about 4.5 million HIV-infected individuals.[1] However, experts believe that the official figures quoted for India represent only about 50% of the actual number. Under-reporting, cultural taboos and scarcity of HIV testing sites cast doubt on the credibility of the official figures.[1] Although the prevalence rate of 0.7% may appear trivial, India has a population of more than a billion people,[1] so a miniscule increase of 0.1% means that 500 000 more people are infected. According to the 2001 annual national survey South Africa appears to have an HIV prevalence rate of approximately 24%, but only 8 years ago recorded a rate of less than 10%.[2] The latest South African survey (December 2002) has revealed an increase in prevalence to more than 30% among pregnant women in the age category 25 - 29 years.[3] However, there is evidence that in Ethiopia and South Africa the prevalence rate among younger teenage girls has dropped.[3] In India and South Africa diverse societal patterns and marked distinctions between rural and urban areas mean that there is an awful similarity between these two countries. India has just started to see the beginnings of the HIV epidemic, but they have a powerful role model in South Africa, and urgent measures must be instigated to prevent the Indian subcontinent from achieving the same infection prevalence rate.

## DISCRIMINATION, STIGMATISATION AND DENIAL

In India, as elsewhere, HIV infection is considered a disease of 'others', with the inevitable outcome of the 'discrimination, stigmatisation and denial' (DSD) syndrome, which affects life in families, communities, the workplace and health care settings. People in marginalised groups — female sex workers, *hijras* (castrated males dressing as

females and providing forms of entertainment) and homosexual men – are often stigmatised in India for also being members of socially excluded groups. In addition, the mainstream women's movement in India has not embraced the rights of women in prostitution as a high priority. A wide range of human rights abuses associated with HIV/AIDS has been reported in India.[4] Such abuses include discrimination against HIV-positive individuals in employment and in access to health care, education, housing and legal services; violation of confidentiality of HIV testing; and disinheritance, abandonment and physical and verbal abuse of wives and widows of men with HIV/AIDS.[4]

## IS DISASTER INEVITABLE?

Ten years ago, South Africa and Thailand had exactly the same HIV prevalence rates. Today, Thailand has a overall rate of 2.5% while South Africa's stands at 25%.[3] HIV infection is not only about CD4 counts, viral loads and vaccines. It is about moral decay, the physical and sexual abuse of women, and the rape of the young and vulnerable, including children and babies.

In both South Africa and India there is still a window of opportunity to turn the HIV epidemic around by responding effectively and timeously to infection trends. Socioeconomic status, traditional social ills, cultural myths regarding sex and sexuality and a large population of marginalised people have made both South Africa and India extremely vulnerable to this epidemic. Every avenue should be explored and every effort made at every level to combat the spread of HIV.

## FACTORS THAT MAKE A PERSON VULNERABLE TO HIV INFECTION

### FEMALE SEX WORKERS

There is a widespread belief in India that prostitutes are primarily responsible for the origin and spread of HIV infection. This reflects a lack of knowledge. There is a very low level of condom use among female prostitutes in India, and sex without a condom commands a higher fee. The main problem lies in the persisting unwillingness of the clients to use a condom, and the prostitute's powerlessness to insist on its use or to reject the client.[4]

### POVERTY

One of India's most striking characteristics is its material poverty, with an estimated 40% of the population living in poverty[4] – in other words, 400 million people do not have necessities for basic survival such as food, clothing and shelter. This desperate poverty has the following consequences:

- Women turn to prostitution in order to obtain material possessions they could not otherwise afford.
- Malnutrition has a disruptive and destructive effect on the immune response.
- Treatment of sexually transmitted disease (STD) is beyond the reach of the poor.
- Resources are often not available for condoms and other forms of protection.
- Illiteracy is widespread, as girls are often deprived of education because they are seen as a liability to the family. Raising a girl in India is regarded as 'watering the neighbour's garden'.[4]

### MIGRATION

Owing to limited employment opportunities, population migration has become a key factor in the spread of HIV infection in India. Migrant labourers are said to comprise 30 - 40% of the population of large cities, and their wives commonly become innocent victims of HIV infection.[4] More than 95% of Indian housewives are in monogamous relationships. The wife cannot under any circumstances demand the use of a condom by her spouse, as this would imply accusing him of infidelity, with dire consequences of physical and verbal abuse.[4]

### URBANISATION

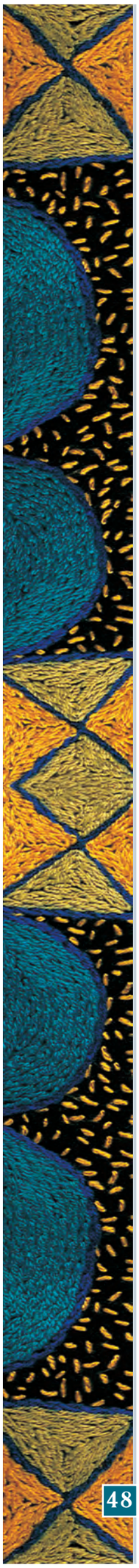
One of the disadvantages of the tremendous economic growth India is currently enjoying is rapid urbanisation, resulting in large slum populations inhabited by construction workers, casual landless labourers and child workers. In 1996 it was estimated that there were 100 million people living in slum areas, a figure expected to increase to 110 million by 2001.[1] Poverty, ignorance and violation of human rights in these slums create fertile ground for the spread of HIV infection.

### INJECTED DRUG USE

Certain states in India, such as Manipur, are experiencing a huge crisis in respect of the increased illicit use of injected drugs. This is compounded by lax Indian regulations which mean that drugs and non-sterile syringes and needles are obtainable from the unlicensed drug stores present on almost every corner. Government's reluctance to recognise this mode of transmission of HIV infection has aggravated the spread of the virus from the addicts to their sexual partners and spouses.

### MEN WHO SLEEP WITH MEN

Very little is known about the practice of homosexuality in India. A survey done in 1993 by Row-Kavi, activist and self-proclaimed homosexual, showed that more than 50 million men in India may be exclusively or predominantly homosexual.[4]



*Hijras.* These castrated males are becoming increasingly engaged in male prostitution and play a definite role in the spread of HIV infection in India. The total population of *hijras* in India is unknown; in censuses many are registered as females. Almost nothing is known about the sexual techniques *hijras* practise or are asked to practise when they perform the role of prostitute. It is very likely that they are often passive partners in unprotected anal intercourse. This makes them very vulnerable to HIV and other STDs.

**Male prostitutes.** In addition to the *hijra* community, many full-time and part-time male prostitutes offer services in metropolitan cities. Furthermore, thousands of homeless poor boys and young men employed in various establishments are compelled to provide sexual services to their male bosses in return for job security. Young men who work as helpers to truck drivers on their long trips also provide them with sexual favours.

### HOUSEWIVES

Important factors increasing transmission of HIV in India have previously been identified as migrant workers, long-distance truck drivers, commercial sex workers, blood donors and intravenous drug users.[1] The new victim of HIV transmission is the ordinary Indian wife and mother. HIV infection is spreading among young, monogamous, married women who are infected by their husbands.[5] A research study revealed that 13.6% of 391 ordinary Indian women attending STD clinics, who were not sex workers, were infected with HIV with their only significant risk factor being sexual contact with their partner.[5] Sociocultural reasons for the vulnerability of Indian women have their roots in historical traditions and culture. Benign neglect of female children, the fragility of the dowry status within the Indian family, inadequate access to appropriate health services, minimal access to educational resources and poverty are some of the manifestations of women's disadvantaged social and economic status.

## BOLD STEPS ARE STILL REQUIRED

Although the Indian Government has responded immediately and efficiently through its National AIDS Control Organisation and Programmes, efforts should be made at every level. The following recommendations have been suggested as a practical approach to try to slow down this epidemic:

- HIV research should be a universal priority. Africa and Asia must be ready to challenge the future spread of the virus. New conceptual frameworks and integration of research surveillance and management are urgently required.
- Empowerment of women. As the use of condoms is non-negotiable in many societies, women require greater independence to determine their other options, such as virucidals.
- Access to HIV testing. In some areas this may require promotion of rapid HIV tests and counselling.
- Street committee. Youth and street committees could play a valuable role in promoting awareness among their 'peers'.
- Sex education at schools. This area of education requires urgent attention. It must be started early and reinforced throughout the school career.
- Alcohol and substance abuse. It goes without saying that these areas must be tackled as aggressively as the sex education component.
- STD treatment. Decreasing the prevalence of STDs decreases transmission of HIV infection, and both female and male sex workers must receive attention.
- Government level. Smallpox was successfully eradicated mainly because of a powerful global commitment. Although HIV is a very different virus, prevention principles still remain sound and must be cultivated.
- Destigmatisation. South Africa and India both enjoy their national sports. Key figures can contribute to awareness with inspirational and educational messages.

## CONCLUSION

The world is now entering its third decade of the HIV/AIDS epidemic, the impact of which is far-reaching and profound and for many communities now part of the expected way of life.[6] Determining the prevalence rate in the adult population, the means most commonly used to measure the scale of the epidemic, does not give a clear indication of its recent trends.[6] South Africa and India could at this stage have different prevalence rates but still be experiencing the same epidemic. It has recently been stressed that the window of opportunity for bringing the epidemic under control is closing rapidly in the Asian regions.[6] Although global commitment is obviously required, efforts at every level of society are mandatory.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# CPD QUESTIONS

## Journal 12

**PLEASE COMPLETE AND RETURN TO:**

Southern African HIV Clinicians Society, Suite 233, PostNet Killarney, Private Bag X2600, Houghton, Johannesburg, 2041

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## PLEASE INDICATE WHICH OF THE FOLLOWING STATEMENTS ARE TRUE:

1. (a) Viral benefit can be achieved with adherence of better than 80%, but to sustain long-term virological and clinical benefit with little development of viral resistance, adherence of 95% or more may be required. In practical terms this means missing no more than 3 doses per month, which is less than 1 per week.
   (b) Viral benefit can be achieved with adherence of better than 90%, but to sustain long-term virological and clinical benefit with little development of viral resistance, adherence of 98% or more may be required. In practical terms this means missing no more than 2 doses per month, which is less than 1 per week.
   (c Viral benefit can be achieved with adherence of better than 75%, but to sustain long-term virological and clinical benefit with little development of viral resistance, adherence of 90% or more may be required. In practical terms this means missing no more than 3 doses per month, which is less than 1 per week.
2. (a) *Mycobacterium avium* complex (MAC) disease develops almost exclusively in patients with CD4+ cell counts of 100 - 200 cells/µl.
   (b) MAC disease develops almost exclusively in patients with CD4+ cell counts of < 100 cells/µl.
   (c) MAC disease may develop in patients with CD4+ cell counts as high as 300 cells/µl.
3. (a) Palliative management of mild pain in HIV may consist of acetominophen 1 g 4 - 6-hourly (maximum 4 g/24 h p.o.) and ibuprofen 200 - 600 mg 4 - 6-hourly (maximum 2 400 mg/d p.o.).
   (b) Palliative management of mild pain in HIV may consist of tramadol 50 - 100 mg 6-hourly (maximum 4 g/24 h p.o.) and ibuprofen 200 - 600 mg 4 - 6 hourly (maximum 2 400 mg/d p.o.).
   (c) Palliative management of mild pain in HIV may consist of codeine phosphate 30 - 60 mg 4-hourly (maximum 4 g/24 h p.o.) and ibuprofen 200 - 600 mg 4 - 6-hourly (maximum 2 400 mg daily p.o.).
4. (a) The occupational risk for HIV infection is low and is given statistically as 0.3% (confidence interval (CI) 0.005% to 0.9%); the same risk has been determined for vaginal sexual transmission, whereas the risk after sexual assault may be as high as 11%.
   (b) The occupational risk for HIV infection is low and is given statistically as 0.3% (CI 0.005% to 0.9%); the same risk has been determined for vaginal sexual transmission, whereas the risk after sexual assault may be as high as 15%.
   (c) The occupational risk for HIV infection is low and is given statistically as 0.3% (CI of 0.005% to 0.9%); the same risk has been determined for vaginal sexual transmission, whereas the risk after sexual assault may be as high as 20%.
5. (a) The Medicines Control Council has approved the first local human phase I HIV vaccine clinical trial using the AlphaVax replicon Vector (ArV) clade C candidate HIV-1 vaccine. Its safety and immune system responses will be tested in a small number of volunteers from the USA and South Africa.
   ArV utilises virus-like particles, containing parts of an attenuated strain of Venezuelan equine encephalitis (VEE) virus and a gene from a South African strain of the HI virus, to deliver the vaccine to the immune system.
   As the vaccine contains only a copy of a small section of genetic material from HIV, there is only a slight possibility of the vaccine itself causing HIV infection.
   (b) The Medicines Control Council has approved the first local human phase I HIV vaccine clinical trial using the AlphaVax replicon Vector (ArV) clade C candidate HIV-1 vaccine. Its safety and immune system responses will be tested in a small number of volunteers from the USA and South Africa.
   ArV utilises virus-like particles, containing parts of an attenuated strain of Venezuelan equine encephalitis (VEE) virus and a gene from a South African strain of the HI virus, to deliver the vaccine to the immune system.
   As the vaccine contains a small section of genetic material from HIV, and does not include all of the genetic elements needed to reconstitute HIV, there is only a slight possibility of the vaccine itself causing HIV infection.
   (c) The Medicines Control Council has approved the first local human phase I HIV vaccine clinical trial using the AlphaVax replicon Vector (ArV) clade C candidate HIV-1 vaccine. Its safety and immune system responses will be tested in a small number of volunteers from the USA and South Africa.
   ArV utilises virus-like particles, containing parts of an attenuated strain of Venezuelan equine encephalitis (VEE) virus and a gene from a South African strain of the HI virus, to deliver the vaccine to the immune system.
   As the vaccine contains only a copy of a small section of genetic material from HIV, and does not include the genetic elements needed to reconstitute live HIV, there is no possibility of the vaccine itself causing HIV infection.
6. (a) Although an effective preventive hepatitis B vaccine is available, this virus is important as currently South Africa has at least 2.5 million carriers. HBV is transmitted in the same fashion as HIV, namely via the sexual route or contact with blood. However, HBV is much more infectious than HIV. The average risk of exposure in an individual expressing the hepatitis B surface antigen (HbsAg) is about 3%, but the average risk of an individual who is highly infectious and also expressing the nuclear antigen (HbeAg) is at least 30%. It is therefore clear that every South African should be vaccinated.
   (b) Although an effective preventive hepatitis B vaccine is available, this virus is important as currently South Africa has approximately 1.5 million carriers. HBV is transmitted in the same fashion as HIV, namely via the sexual route or contact with blood. However, HBV is almost as infectious as HIV. The average risk of exposure in an individual expressing the hepatitis B surface antigen (HbsAg) is about 0.27%, but the average risk of an individual who is highly infectious and also expressing the nuclear antigen (HbeAg) is at least 0.3%. It is therefore clear that every South African should be vaccinated.
   (c) Although an effective preventive hepatitis B vaccine is available, this virus is important as currently South Africa has at least 4 million carriers. HBV is transmitted in the same fashion as HIV, namely via the sexual route or contact with blood. However, HBV is much more infectious than HIV. The average risk of exposure in an individual expressing the hepatitis B surface antigen (HbsAg) is about 2%, but the average risk of an individual who is highly infectious and also expressing the nuclear antigen (HbeAg) is at least 25%. It is therefore clear that every South African should be vaccinated.