

Topics in HIV Medicine™

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Perspectives

Viral Binding and Fusion—The Next Targets in Antiretroviral Therapy 4

Eric Hunter, PhD

Characteristics of HIV Binding and Fusion • Inhibition of CD4 Binding • Inhibition of Coreceptor Binding • Inhibition of Conformational Changes in Membrane Fusion

Where Do Strategic Treatment Interruptions Fit in the Management of HIV Infection? 9

W. Keith Henry, MD

Terminology • Immunologic Focus • Virologic Focus • Focus on Reducing Drug Exposure in Chronic Infection

Special Contributions

Current Strategies for Antiretroviral Therapy: Panel Discussion of Clinical Cases 14

Michael S. Saag, MD, and Jeffrey L. Lennox, MD

HIV in India 19

Suniti Solomon, MD, and Aylur Kailasam Ganesh, ACA

Tracking the Spread of HIV Infection • Government Responses • Social Precursors of HIV Infection • Issues in HIV Testing and Diagnosis • Issues in HIV Treatment and Care

About This Issue

This issue includes 2 *Perspectives* articles based on the International AIDS Society–USA continuing medical education courses held in New York and Chicago in March and April 2002. Eric Hunter, PhD, discussed steps in HIV binding and entry to host cells that present targets for antiretroviral drug development. W. Keith Henry, MD, reviewed recent findings in studies of strategic treatment interruptions in acute HIV infection, chronic infection, and the management of virologic failure, with a discussion of the implications of these findings for clinical practice.

At the Atlanta course, Michael S. Saag, MD, and Jeffrey L. Lennox, MD, presented case studies and moderated an interactive panel discussion by course faculty and audience members. The strategies for managing antiretroviral therapy are summarized in this *Special Contribution* article.

Finally, Suniti Solomon, MD, and Aylur Kailasam Ganesh, ACA, look at the work of the government-sponsored National AIDS Control Organization, and offer a commentary on the current status of the HIV epidemic in India, focusing on epidemiology, the government response, and diagnosis and treatment.

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HIV in India 19

Suniti Solomon, MD, and Aylur Kailasam Ganesh, ACA

Guidelines for Authors and Contributors 25

Subscription Request 26

Educational Programs of the IAS–USA 27

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Perspective

Viral Binding and Fusion—The Next Targets in Antiretroviral Therapy

At the International AIDS Society–USA course in New York in March 2002, Eric Hunter, PhD, discussed steps in HIV binding and entry to host cells that present targets for drug development.

Currently available antiretroviral agents exert their anti-HIV effects at 2 post-entry stages of viral replication. The nucleoside and nonnucleoside reverse transcriptase inhibitors act to block viral DNA synthesis, whereas the protease inhibitors inhibit a late step in the process of viral budding from the host cell. Viral binding and fusion to the host cell is a multistep process that offers a number of potential targets for intervention. Agents that target viral entry to the host cell might complement the effects of those inhibiting post-entry events.

Characteristics of HIV Binding and Fusion

It has long been recognized that HIV entry into susceptible cells involves the interaction of CD4 molecules on the host cell surface with the HIV envelope glycoproteins gp120 and gp41. More recently, it was found that interaction of the virus with coreceptors on the cell surface is crucial to entry, with the predominant coreceptors being the chemokine receptors CCR5 and CXCR4. In general, viral tropism is determined by which receptors are used by a virus, how well the receptor is used and with what affinity, and the degree of tissue expression of receptors. Late in HIV disease, a shift in viral tropism from the CCR5 to the CXCR4 coreceptor is often observed, probably in association with relatively greater availability of target cells expressing this coreceptor.

Molecular studies have greatly facili-

tated the understanding of the process of HIV entry into host cells. Nonspecific attachment of the virus to the target cell (eg, through interaction of gp120 carbohydrates with cell receptors) permits specific binding of the viral envelope with the CD4 molecule. The binding of CD4 induces a conformational change in both gp120 and gp41, so that the CD4-modified gp120 can bind chemokine coreceptors with a 100- to 1000-fold greater affinity. Coreceptor binding is

Viral binding and fusion to the host cell is a multistep process that offers a number of potential targets for intervention

necessary for the completion of conformational changes in the viral glycoproteins (Env) that are initiated by CD4. New antigenic epitopes in gp120 and gp41 are exposed after CD4 binding, consistent with the proteins having undergone an alteration in conformation.

These changes in the viral envelope proteins recapitulate those induced in the influenza virus hemagglutinin (HA) during low pH activation in the endosome. The similarities suggest that the mechanism by which viral-cell membrane fusion occurs is similar for the 2 viruses. In the case of the trimeric influenza virus HA, the HA2 domain, corresponding to the HIV gp41, undergoes a structural rearrangement in the acid pH of the endosome that results in

the formation of a trimeric coiled-coil structure. The formation of this structure enables the fusion peptide to be extended approximately 100 angstroms from its original position and allows its interaction with the target cell membrane. It is believed that a similar process is triggered by CD4 and coreceptor binding in HIV fusion. The extracellular domain of the gp41 contains a fusion peptide region and 2 potentially helical regions, the N-terminal heptad region (HR1) and the C-terminal heptad region (HR2). The HR1 regions of the Env trimer appear to form a trimeric coiled-coil structure similar to that of HA following interaction of the glycoprotein with cell receptors, forcing the fusion peptides into the target cell membrane (Figure 1). The second heptad-repeat regions then bind to the outside of the HR1 coiled-coil structure to form a 6-helix bundle, or hairpin, that mechanically brings the viral and target cell membranes together.

Rational drug discovery is based on an understanding at the molecular level of the process to be inhibited. Since the induction of membrane fusion by HIV is a complex process, there are discrete steps at which interference with the process can be attempted. Since there are several possible targets, there is also potential for the development of drugs with synergistic effects in inhibiting viral entry. The precedence for developing compounds that block viral entry is provided by the observation that naturally occurring neutralizing antibodies can be very effective in inhibiting this process. Three major steps in viral entry have been targeted for drug development: inhibition of CD4 binding, inhibition of coreceptor binding, and blocking of the gp41 conformational changes that permit viral fusion.

Inhibition of CD4 Binding

The binding of HIV to CD4 is an attractive drug target, both because the CD4

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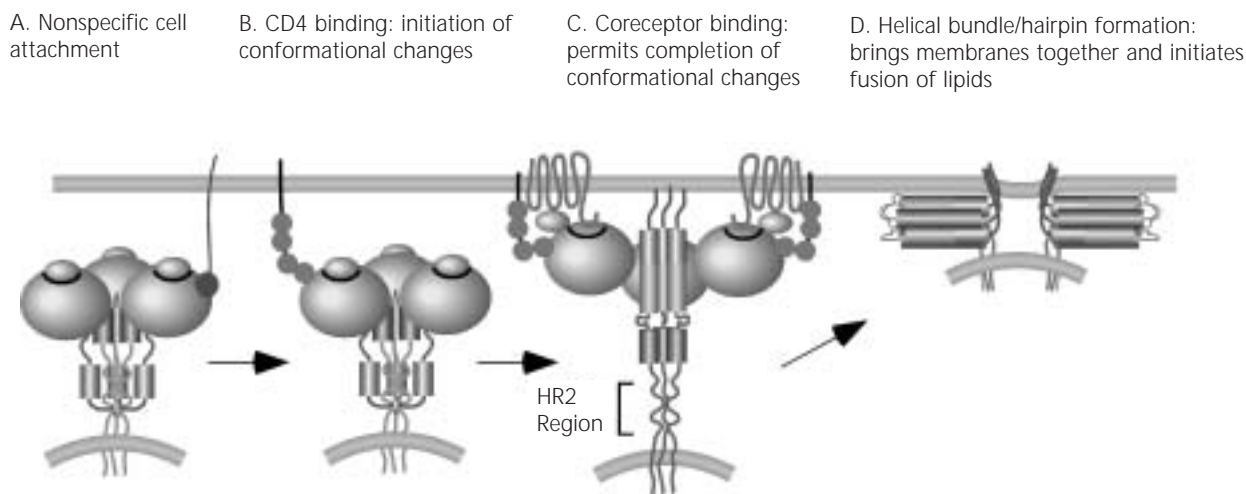


Figure 1. General schema of HIV binding and fusion with target cell. HR2 indicates C-terminal heptad region.

binding site is highly conserved and because it is known that neutralizing antibodies can effectively block this step. The first attempts to block CD4 binding in the clinical setting involved the use of soluble CD4. From 1988 to 1990, several investigators showed that soluble CD4 could block entry of laboratory-adapted strains of HIV into target cells and prevent Env-mediated syncytium formation in vitro. Initial clinical investigations indicated that soluble CD4 was associated with minimal toxicity and dose-dependent reductions in viral load, but only at very high doses (5-10 mg/kg) and in patients in which virus was susceptible to soluble CD4 neutralization (Schacker et al, *J Acquir Immune Defic Syndr Hum Retrovirol*, 1995). This apparent contradiction between laboratory and clinical results was in part explained when it was shown that CD4 binding triggered the very conformational changes in the HIV envelope glycoproteins that induce fusion, and that soluble CD4 could potentiate infection by some primary HIV isolates (Sullivan et al, *J Virol*, 1998).

Ongoing study of this approach has resulted in the development of a novel chimeric molecule consisting of domains of CD4 critical to gp120 binding combined with an immunoglobulin molecule. This tetravalent CD4-IgG, Pro 542, binds to gp120 with nanomolar affinity and neutralizes primary HIV isolates. Pro 542 has been shown to reduce

viral infectivity by 90% in vitro at a concentration of 20 µg/mL and to protect against HIV infection in the hu-PBL-SCID mouse model (Franti et al, 9th CROI, 2002). Initial clinical investigations in HIV-infected adults and children indicate that it is well tolerated and produces modest reductions in plasma HIV-1 RNA levels of approximately 0.5 to 0.7 log₁₀ copies/mL (Jacobson et al, *J Infect Dis*, 2000; Shearer et al, *J Infect Dis*, 2000). There is hope that this agent may prove useful in combination antiretroviral therapy.

Attempts have been ongoing to develop inhibitors of the CD4 binding pocket that do not induce the same conformational changes in the HIV envelope glycoproteins induced by CD4. Small-molecule inhibitors have recently been described that bind to gp120 and competitively inhibit CD4 binding; these formulations are orally available and appear to be safe in the animal studies conducted thus far (Lin et al, Abstracts 9 and 10, 9th CROI, 2002).

Inhibition of Coreceptor Binding

Approaches to inhibiting viral entry by interfering with viral binding to the CCR5 and CXCR4 coreceptors include the development of inhibitors that bind the coreceptor and block binding to gp120 through steric or allosteric hindrance or by inducing receptor down-

regulation, and also the development of inhibitors to block the coreceptor binding site on gp120.

Points in favor of the approach of inhibiting the coreceptor (Table 1) include: first, proof of concept, since chemokines and chemokine derivatives that use the CCR5 receptor can effectively block HIV infection via this receptor; second, the considerable experience with receptors of this type (7-transmembrane receptors) in pharmaceutical development; third, the potential to inhibit the receptors without triggering functional activity; and fourth, the fact that individuals homozygous for deletions in the gene for CCR5 ($\Delta 32$) are highly resistant to HIV infection and exhibit no adverse consequences of this deletion, which suggests that inhibition of CCR5 might not be associated with adverse effects on normal cellular function. On the other hand, potential disadvantages (Table 1) include the possibility that coreceptor inhibition will drive the virus to use alternative coreceptors, and the fact that the consequences of blocking chemokine pathways remain unknown (notwithstanding the absence of adverse effects in individuals with CCR5 deletions). With regard to the latter issue, it is known, for example, that CXCR4 is important in vascularization and organogenesis, and it is unclear what effects in this regard might be produced by inhibition of the receptor.

A number of CXCR4 antagonists have

Table 1. Selected Pros and Cons of Inhibition of CCR5 and CXCR4 Coreceptor Binding

Pro	Con
<ul style="list-style-type: none"> • Proof of concept • Considerable experience with 7-transmembrane receptors in pharmaceutical development • Potential to inhibit receptors without triggering functional activity • Inhibition of CCR5 may not be associated with adverse effects on cellular function 	<ul style="list-style-type: none"> • Coreceptor inhibition may cause virus to use alternative coreceptors • Consequences of blocking chemokine pathways are not known

been developed (ALX40-4C, AMD-3100, T22), but none is currently being pursued in the clinical setting. Although one of these compounds, AMD-3100, proved to be a potent inhibitor of CXCR4-using HIV in vitro, an unpublished phase 1a/2b trial of the agent was discontinued as a result of observation of abnormal cardiac activity in 2 patients at higher doses and absence of significant anti-HIV activity at lower doses (Hendrix et al, 9th CROI, 2002). CCR5 inhibitors that have been developed include TAK-779 and the SCH-C and SCH-D compounds; the former is not orally bioavailable and is not being pursued in the clinical setting. The SCH-C compound has shown potent inhibition of CCR5-using virus in vitro and is orally available (Strizki et al, *Proc Natl Acad Sci USA*, 2001). In early-phase clinical testing, some cardiac abnormalities involving prolongation of the QTc interval have been noted at higher doses of 400 to 600 mg per day; a 0.7- \log_{10} reduction in viral load was observed at lower doses of 50 mg per day (Reynes et al, 9th CROI, 2002), and phase 2 trials are proceeding. A second generation of this type of molecule, SCH-D, has already entered clinical evaluation (Chen et al, 9th CROI, 2002).

The approach of targeting the coreceptor binding site on viral gp120 is attractive, since it would involve targeting of a viral component rather than a cellular molecule. However, the coreceptor binding site on gp120 is a broad area consisting of a bridging sheet between 2 gp120 domains, and it is unclear how efficiently this region can be targeted for inhibitor development.

Inhibition of Conformational Changes in Membrane Fusion

Initial studies on the potential for blocking conformational changes that mediate HIV fusion with susceptible cells showed that mutations in the HR1 region of gp41 resulted in loss of viral fusion and that peptides corresponding to the HR1 and HR2 regions of gp41 (T-21 and enfuvirtide [T-20], respectively) inhibited fusion and infectivity of both cell culture-adapted and primary HIV isolates in vitro. Enfuvirtide was shown to have very low viral inhibitory concentrations in vitro and has undergone extensive clinical investigation. It is

believed that enfuvirtide exerts its effect by competitively inhibiting the HR2 binding site on the gp41 trimeric coiled-coil structure, thereby preventing the folding of the molecule that brings the viral and cell membranes together.

In a phase 1/2 trial, intravenous enfuvirtide produced a 1.5- \log_{10} decrease in plasma HIV-1 RNA level at the highest dose examined (100 mg twice daily) after 15 days of treatment in patients who had undergone a drug washout period (Kilby et al, *Nat Med*, 1998). Subsequent phase 2 studies have included a chronic administration safety study and assessment of an improved formulation that allows twice-daily subcutaneous administration. Pivotal phase 3 studies were initiated in July 2001 and are fully enrolled.

T-1249 represents the second generation of peptide inhibitors; this agent is a synthetic compound utilizing non-native sequences corresponding to the HR2 region. T-1249 has a longer plasma half-life than enfuvirtide and has been shown to inhibit enfuvirtide-resistant virus. The effects of this agent given subcutaneously have been assessed in a 14-day, dose-escalation study in 63 patients with a mean plasma HIV-1 RNA level of 5.3 \log_{10} copies/mL and mean CD4+ cell count of 121/ μ L. As shown in Figure 2 (Eron et al, 8th CROI, 2001), a dose of 25 mg twice daily produced a mean reduc-

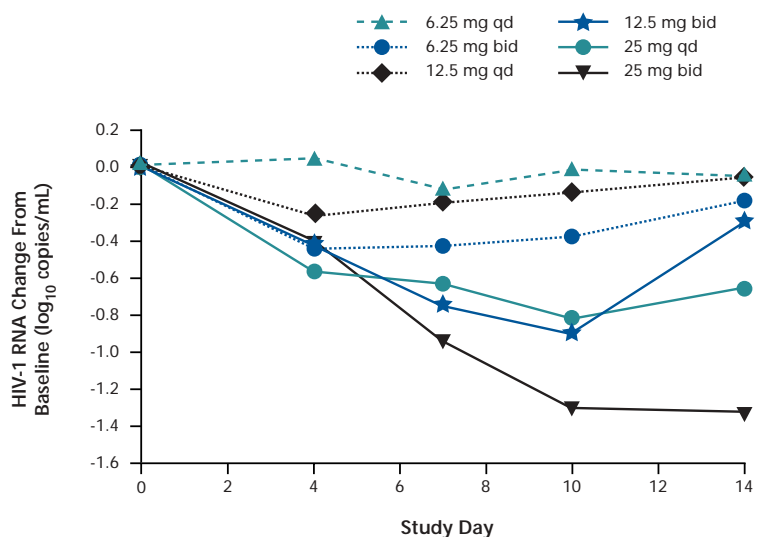


Figure 2. Mean changes in plasma HIV-1 RNA level according to dosage of subcutaneously administered T-1249. Adapted with permission from Eron et al, 8th CROI, 2001.

tion in plasma HIV-1 RNA level of 1.3 log₁₀ copies/mL.

Influence of Coreceptor Binding on Sensitivity to Peptide Inhibitors

Anecdotal observations from the initial clinical studies of enfuvirtide suggested that a majority of HIV that utilized the CXCR4 coreceptor (X4 viruses) were more susceptible to this agent than HIV that utilized CCR5 (R5 viruses). Testing of a panel of R5, X4/R5, and X4 viruses showed that the enfuvirtide 50% inhibitory concentration for the X4 viruses was 67 ng/mL, compared with 400 ng/mL for R5 viruses. Testing of chimeric viruses (produced by substitutions in the V3 loop of gp120 that switched binding tropism from CXCR4 to CCR5) also showed coreceptor modulation of enfuvirtide sensitivity, with susceptibility being reduced by 4- to 6-fold (Derdeyn, *J Virol*, 2000; Derdeyn, *J Virol*, 2001).

In addition to what they indicate about possible effects on enfuvirtide susceptibility, these findings also suggest differences in the fusion process based on HIV coreceptor affinity. It is known that HIV binds to CXCR4 with lower affinity than to CCR5. It can be hypothesized that HIV with low coreceptor affinity binds to CD4 normally, with the pre-hairpin structure of gp41 (the enfuvirtide target) being triggered normally. However, because gp120 would take longer to engage the coreceptors, formation of the hairpin structure would be delayed, with fusion occurring more slowly; since the enfuvirtide target is longer-lived in this case, the virus would be predicted to be more sensitive to enfuvirtide. In contrast, HIV strains with high coreceptor affinity would quickly engage coreceptors, with fusion occurring more rapidly; in this case, the enfuvirtide target is shorter-lived, and the virus would be less sensitive to enfuvirtide. Preliminary evidence supports this hypothesis (Reeves et al, 9th CROI, 2002).

However, it should be noted that other investigators have not found differences in sensitivity between X4 and R5 viruses, and the clinical significance of such differences is not clear.

Conclusions

HIV entry to susceptible cells is a multi-step process offering many opportunities for therapeutic intervention. The effects of first- and second-generation peptide inhibitors in blocking conformational changes necessary for viral fusion provide proof of principle that the entry process is a viable target for therapeutic intervention. Inhibitors of CD4 and coreceptor interactions with gp120 have been identified that exhibit potent effects in vitro and are strong candidates for continued clinical development. It is of considerable interest that studies in vitro suggest the potential for synergistic interactions between drugs targeting different steps in viral entry. For example, synergistic effects have been reported for coreceptor inhibitors and enfuvirtide (Tremblay et al, *J Acquir Immune Defic Syndr*, 2000) and for enfuvirtide and Pro 542 (Nagashima et al, *J Infect Dis*, 2001). It is therefore hoped that combination therapies targeting viral entry steps can be developed to maximize viral suppression at this stage of viral replication. Finally, it is likely that continued study of agents designed to inhibit viral entry will provide new insights into the mechanisms of the fusion process itself.

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Suggested Reading

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Updated Recommendations for Antiretroviral Therapy

Updated recommendations for antiretroviral therapy in adult HIV-1 infection, written by an International AIDS Society–USA panel of experts, appear in the July 10, 2002 issue of the *Journal of the American Medical Association*.

To access the recommendations online, please visit:

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Perspective

Where Do Strategic Treatment Interruptions Fit in the Management of HIV Infection?

At the International AIDS Society–USA course in Chicago in April 2002, W. Keith Henry, MD, reviewed recent findings in studies of strategic treatment interruptions in the settings of acute HIV infection, chronic infection, and the management of virologic failure. He discussed the implications of these findings for clinical practice and the need for further research in this area.

From the beginning of the AIDS epidemic until 1996, the major focus of HIV clinical research was the development of effective antiretroviral therapy. The introduction of potent antiretroviral therapy regimens and the availability of quantitative plasma HIV-1 RNA measurements revolutionized the treatment of HIV infection in resource-rich countries (Palella et al, *N Engl J Med*, 1998; Mellors et al, *Ann Intern Med*, 1997). Until that time, the concept of stopping effective therapy understandably received little attention.

Studies of the immunology of HIV infection led to new understanding about the typical consequences of the use of potent antiretroviral therapy in the setting of established HIV infection. In most instances, potent antiretroviral therapy results in reconstitution of much of the immune system except for HIV-specific immunity (Pitcher et al, *Nat Med*, 1999). Additional research revealed that a reservoir of HIV persists in patients treated with potent antiretroviral therapy, and projections for the time needed before a theoretical cure could be achieved ranged from 10 years to infinity (Finzi et al, *Science*, 1997). Coupled with new concerns about the long-term toxicity of antiretroviral therapy (Carr et al, *Lancet*, 2000), these

insights provided incentive to explore alternatives to the use of early, continuous potent antiretroviral therapy for the long-term management of HIV infection.

The description of the “Berlin patient” (Liszewicz et al, *N Engl J Med*, 1999), in whom interruption of antiretroviral therapy was followed by spontaneous control of HIV infection, introduced the concept of treatment interruption following use of potent antiretroviral therapy soon after HIV infection. Since then, there have been several other reports involving discontinuation of potent therapy either in the setting of chronic HIV infection (Ortiz et al, *J Clin Invest*, 1999) or with a focus on immunologic factors associated with control of HIV viremia (Papasavvas et al, *J Infect Dis*, 2000). The concept of strategic treatment interruptions (STIs) as a strategy to be studied prospectively was introduced in the clinical setting of acute human HIV infection (Rosenberg et al, *Nature*, 2000) and in the laboratory setting of acute simian immunodeficiency virus infection (Lori et al, *Science*, 2000). Soon thereafter, STIs were studied in patients receiving successful treatment for chronic HIV infection (Dybul et al, *Proc Natl Acad Sci USA*, 2001; Hirschel et al, 9th CROI, 2002, Abstract 528-M) and in patients with highly resistant HIV in whom potent therapy was failing (Miller et al, *AIDS*, 2000; Deeks et al, *N Engl J Med*, 2001). Finally, the use of intermittent therapy was proposed as a way to reduce drug exposure, thus possibly reducing toxicity and costs, but without the intention of stimulating enhanced anti-HIV immunity.

Terminology

An increasing number of terms are being used to refer to different aspects of stopping and starting potent antiretroviral therapy. There is no consensus as to precise definitions to describe different scenarios. “Strategic treatment interrup-

tion” is often used as an all-encompassing term to describe situations in which potent antiretroviral therapy is stopped in a planned manner for a specific purpose. Some have proposed that “STI” be used only in situations in which the objective of the treatment interruption is to boost anti-HIV immunity. The terms “intermittent therapy” and “pulse therapy” have been used to refer to treatment interruption with the aim of decreasing drug exposure to minimize cost and toxicity. Use of treatment interruption in the management of virologic failure, also termed “salvage therapy,” has a more virologic or clinical focus; the goal in this setting is to induce reversion of the principal HIV quasi species to the drug-sensitive wild-type, thus increasing the chances for successful viral suppression with the use of recycled drugs. For the purposes of this discussion, the topic of treatment interruptions is organized according to immunologic focus (boosting HIV-specific immunity), virologic focus (managing treatment failure), and the focus of decreasing drug exposure to reduce cost and toxicity.

Immunologic Focus

Acute Infection

A number of small studies of treatment interruption in patients with acute HIV infection have been reported. Walker and colleagues, for example, found that plasma viremia rebounds tended to become smaller with successive interruptions, with 5 of 8 patients initially studied maintaining a plasma HIV-1 RNA level of less than 5000 copies/mL after 5 to 9 months off therapy (Rosenberg et al, *Nature*, 2000). Patients showed evidence of stimulation of HIV-specific CD4+ helper T cell and CD8+ cytotoxic T lymphocyte (CTL) response. Similar findings have been reported elsewhere (Yu et al, 9th CROI, 2002; Hoen et al, 9th CROI, 2002).

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Chronic Infection

The relative success observed with STIs in acute HIV infection led to interest in applying a similar strategy to patients with chronic HIV infection with long-term, high-level viral suppression on potent antiretroviral therapy. The Swiss-Spanish Intermittent Therapy Trial (Hirschel et al, 9th CROI, 2002, Abstract 528-M; Hirschel, 9th CROI, 2002, Abstract S18) may be the best study of treatment interruption in chronic infection to date. This study examined the effect of 4 off/on cycles (2 weeks off then 8 weeks back on potent antiretroviral therapy) in 133 patients with initial plasma HIV-1 RNA levels below 50 copies/mL and CD4+ counts above 300 cells/ μ L. At the end of the 4 cycles (40 weeks), treatment was stopped until viral rebound occurred (>5000 copies/mL). A primary study measure was the proportion of patients maintaining plasma HIV-1 RNA levels of less than 5000 copies/mL at week 52.

Patients had received no antiretroviral treatment before initiating potent therapy, and in order to prevent the promotion of high-level resistance with treatment interruption, they did not receive nonnucleoside reverse transcriptase inhibitors (NNRTIs). Prior to beginning potent antiretroviral therapy, patients had a median CD4+ cell count of 398/ μ L and a median plasma HIV-1 RNA level of 4.5 \log_{10} copies/mL. They had been receiving therapy for a median of 26 months and had maintained plasma HIV-1 RNA levels below 50 copies/mL for a median of 21.5 months. At the start of the study, median CD4+ cell count was 740/ μ L.

Of the 133 patients, 43 dropped out of the study during the initial 40-week period of STIs and another 23 withdrew during the 12-week period after stopping therapy. Of the 67 remaining patients, 23 were considered responders for maintaining plasma HIV-1 RNA levels of less than 5000 copies/mL at week 52. Responders had a significantly lower median plasma HIV-1 RNA level prior to treatment than did nonresponders (4.09 \log_{10} vs 4.57 \log_{10} , $P=.002$), as well as a nonsignificantly greater median CD4+ count (441 vs 392 cells/ μ L). Absence of viral rebound during the first 2-week treatment interruption significantly pre-

dicted response at week 52 (odds ratio, 5; $P<.001$). At week 2, 15 (65%) of 23 responders had no viral rebound, compared with 30 (27%) of 110 nonresponders.

Among 61 patients with week-52 data, there was a significant increase in levels of HIV-specific CTLs from the start of the study, suggesting induction of HIV-specific immune response. However, responders had significantly lower HIV-specific CTL levels than did nonresponders. This finding indicates that increased CTL response is associated

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with exposure to the HIV antigen during viremia, but is not predictive of low viremia after treatment interruption.

The overall conclusion of the Swiss-Spanish Intermittent Therapy Trial was that use of STIs to stimulate HIV immunity (ie, "autovaccination") in the setting of chronic HIV infection cannot be recommended. Other small trials have also found little evidence of virologic or immunologic benefit with STIs in chronic infection (Carcelain et al, *J Virol*, 2001; Ruiz et al, *AIDS*, 2001). However, reports of the concept's demise might be premature. It could be that the criterion of plasma HIV-1 RNA level less than 5000 copies/mL was too stringent a standard for response and that longer follow-up would have revealed reductions in plasma HIV-1 RNA level in additional patients over time. It would also have been of interest to investigate the effects of interruptions on CD4+ cell

counts over time in these patients to determine whether there were potential immunologic benefits to the approach.

Virologic Focus

A substantial number of patients experience failure of successive antiretroviral regimens. For many of these patients, resistance studies indicate that their predominant HIV strain is resistant to most or all of the available drugs and their treatment options are very limited. The concept of interrupting antiretroviral therapy in the setting of persistent or increasing viremia as a means to reestablish a dominant population of drug-sensitive virus is attributed to Miller and colleagues (*AIDS*, 2000). They reported data from a cohort of 48 patients with treatment failure and multidrug-resistant virus who underwent a treatment interruption of at least 2 months. During the treatment interruption, plasma HIV-1 RNA level increased by a mean of 0.7 \log_{10} and CD4+ count decreased by a mean of 89 cells/ μ L. A complete shift to wild-type virus was observed in 28 of the 45 subjects with phenotypic data at baseline and follow-up and was associated with a higher baseline CD4+ count (mean of 192 vs 59 cells/ μ L, $P=.007$). Better response to reinitiation of therapy was related to lower baseline plasma HIV-1 RNA levels prior to treatment interruption, number of active drugs used, and shift to wild-type virus.

In a subsequent study, Miller and colleagues (Sabin et al, 8th CROI, 2001) assessed the effect of treatment interruption and reinitiation of therapy in 252 patients in whom prior treatment had failed. At baseline, prior to the treatment interruption, patients had a median CD4+ cell count of 207/ μ L and a median plasma HIV-1 RNA level of 4.84 \log_{10} copies/mL. The pretreatment nadir CD4+ cell count was 70/ μ L with a median peak plasma HIV-1 RNA level of 5.9 \log_{10} . The median length of the treatment interruption was 4.3 months. A median of 3 drugs were restarted. The median CD4+ cell count at the end of the treatment interruption was 93/ μ L with a median increase in plasma HIV-1 RNA level of 0.45 \log_{10} . Multivariate analysis of the data from 182 subjects reinitiating treatment identified CD4+ count and plasma

HIV-1 RNA level at the start of the treatment interruption and the number of drugs started as independent predictors of treatment response.

Observations from the original cohort indicate, however, that there is significant risk associated with treatment interruption. While virus is recovering drug susceptibility, plasma HIV-1 RNA levels increase and CD4+ cell counts fall, with the decrease in the original cohort being from 155/ μ L to 49/ μ L over 12 weeks. Such decreases pose considerable risk for opportunistic disease.

Deeks and colleagues reported on the use of STI in the setting of chronic failure of a protease inhibitor-based regimen (*N Engl J Med*, 2001). For 22 subjects studied, the baseline median CD4+

Use of treatment interruptions in failing therapy to induce a shift in predominant HIV species from drug-resistant to drug-susceptible has some merit but considerable clinical risk

cell count was 217/ μ L and plasma HIV-1 RNA level was 4.6 log₁₀ copies/mL (minimum of 2500 copies/mL). The patients had been on protease inhibitor-based therapy for 36 months and virologic failure had been present for 31 months. During STI of a median duration of 20 weeks, there was a median increase in plasma HIV-1 RNA level of 0.74 log₁₀ copies/mL and a median decrease in CD4+ cell count of 88/ μ L. A complete shift to drug-sensitive virus at around week 6 to week 8 was seen for protease inhibitors in 18 subjects and nucleoside reverse transcriptase inhibitors in 16

subjects. However, resistant virus was still detectable in the circulating lymphocytes of most patients. Forty-eight weeks of salvage therapy in 23 patients resulted in a 2.9-log₁₀ median decrease in plasma HIV-1 RNA level and a median increase in CD4+ cell count of 121/ μ L. The overall change in plasma HIV-1 RNA level from baseline (before STI) was a 2.1-log₁₀ decrease. However, the increase in CD4+ cell count during salvage therapy produced no net change in count from the pre-STI baseline. Clinical events did occur during the CD4+ cell nadir period of the STI, including *Pneumocystis carinii* pneumonia, non-Hodgkin's lymphoma, progressive Kaposi's sarcoma and death, and advanced AIDS and death.

The conclusions of the study by Deeks and colleagues were that antiretroviral treatment produces immunologic and virologic benefit despite persistent viremia and reduced drug susceptibility of virus during chronic antiretroviral failure. The benefit reflects continued antiretroviral activity and the maintenance under antiretroviral pressure of resistant strains. These resistant strains have reduced replicative capacity compared with the drug-susceptible strains that are present before therapy and that reemerge upon treatment interruption. Durable resuppression was achieved if the new regimen after STI contained at least 1 drug active against pre-STI isolates.

Experience with "drug holiday" treatment interruptions comes from the EuroSIDA study population (Lundgren et al, 9th CROI, 2002). Among 3610 patients starting potent antiretroviral therapy, 565 (10%) stopped therapy, with 49% restarting treatment. After adjustment for demographic variables, the relative risk for an AIDS-defining event or death was 6 for 3 months off treatment. After adjustment for the most recent CD4+ cell count and plasma HIV-1 RNA level, the relative risk was 2.4 for 6 months off treatment. Overall, risk was closely linked to CD4+ cell count, and was highest for CD4+ cell count less than 200/ μ L.

These studies suggest that the use of treatment interruptions in the setting of failing antiretroviral therapy as a strategy to induce a shift in predominant HIV species from drug-resistant to drug-sus-

ceptible has some merit but considerable clinical risk. More studies are needed to further evaluate which patient populations might benefit from such a strategy and to determine the long-term risks and benefits.

Focus on Reducing Drug Exposure in Chronic Infection

For the large number of patients with chronic HIV infection who are doing well on antiretroviral therapy, there is interest in developing strategies to decrease drug costs and toxicities by decreasing the time on treatment. One such approach was used in a pilot study of 10 subjects utilizing short on-and-off cycles of therapy (1 week on and 1 week off) (Dybul et al, *Proc Natl Acad Sci USA*, 2001). That approach was selected based on observations from other STI studies indicating that the time to detectable viremia when fully suppressive therapy was stopped usually exceeded 1 week. The results of that study demonstrated the feasibility of reducing the amount of antiretroviral therapy by 50% over a 1-year period while maintaining suppression of HIV, preserving CD4+ cell counts, and reducing markers of toxicity. Four subjects in that study utilized an NNRTI-based regimen and 6 subjects used a protease inhibitor-based regimen. No resistance was observed, although there is concern about using NNRTI-based regimens in situations in which longer on-and-off cycles are employed. Some benefit in terms of reduction in metabolic toxicity was also observed in the form of significant reductions in serum triglyceride and low-density lipoprotein cholesterol levels.

Another approach to decreasing drug exposure is to focus on the CD4+ cell count as the key marker for starting and stopping therapy. In order to consider such an approach, data are needed regarding the effect on CD4+ cell counts of stopping suppressive therapy. One study (Tebas et al, 1st IAS Conf, 2001) examined CD4+ cell count changes in 72 patients who interrupted suppressive therapy. These patients had a median baseline plasma HIV-1 RNA level of 108,146 copies/mL and maintained levels below the limit of assay detection for 36 weeks. The median CD4+ cell count at the time of stopping therapy was 571/ μ L.

and the prior nadir count was 272/ μL .

During a mean follow-up of 45 weeks after stopping therapy, the average drop in CD4+ count was 16 cells/ μL per month (interquartile range, -6 to -34 cells/ μL per month). The CD4+ cell decay was more rapid during the first several months off therapy, as was observed in the Swiss-Spanish Intermittent Therapy Trial. The plasma HIV-1 RNA level almost always rebounded to the pretreatment level. On multivariate analysis, only the CD4+ cell count gain on therapy significantly predicted the rate of decay—that is, the patients who gained more cells on therapy lost more cells after stopping therapy. Eleven patients restarted therapy and viral suppression was initially achieved in each, although viral rebound subsequently occurred in two. Four patients whose CD4+ cell counts dropped below 200/ μL while off therapy developed an AIDS-defining event or serious infection (sepsis in one, wasting in one, and *Pneumocystis carinii* pneumonia in two). None of the patients developed acute retroviral syndrome.

A recent observational study examined outcomes when treatment was discontinued in patients with marginal indications for starting treatment (Parish et al, 41st ICAAC, 2001). All patients had CD4+ cell counts that never fell below 200/ μL and no history of AIDS-defining events, and all had the intention to resume therapy based on plasma HIV-1 RNA or CD4+ cell count criteria or clinical criteria. Among the 62 patients studied, the major reasons for stopping therapy were lack of indication for treatment (44%), nonadherence (18%), and toxicity (18%). After stopping therapy, plasma HIV-1 RNA level returned to pretreatment levels.

Sixteen (26%) of the patients resumed therapy after a mean of 36 weeks, and 46 patients (74%) were still off therapy after a mean of 64 weeks. The major reasons for resuming therapy were increased plasma HIV-1 RNA level alone (37%) and increased plasma HIV-1 RNA level with decreased CD4+ cell count (31%). The pretreatment CD4+ cell count nadir for the patients resuming therapy was 389/ μL versus 442/ μL for the patients not resuming therapy. The estimated time to CD4+ cell count of less than 200/ μL after stopping therapy,

based on the observed rate of decay, was a median of 0.8 years in those resuming treatment and a median of 2.7 years in those not resuming treatment. With multivariate analysis, pretreatment plasma HIV-1 RNA levels were associated with resumption of therapy and pretreatment CD4+ cell count nadir was associated with the rate of CD4+ decline during treatment interruption. Viral suppression to pre-interruption levels occurred in most of the patients resuming treatment, although not all patients had sufficient follow-up to determine whether maximal reductions had occurred. Among patients in whom plasma HIV-1 RNA level was reduced to less than 50 copies/mL, reduction to this level occurred at an average of 20.1 weeks after resuming treatment. Among patients with suppression to 50 to 400 copies/mL, reduction to this level occurred at an average of 12.3 weeks.

Findings in these studies suggest that the best candidate patients for pulse therapy or treatment interruption are those with lower plasma HIV-1 RNA levels and higher CD4+ cell counts at baseline prior to starting therapy. However, these approaches require examination in randomized controlled trials.

Conclusions

Large randomized trials are needed to further evaluate the potential roles of STI. A number of studies are already in progress. The Strategies for Management of Antiretroviral Therapy (SMART) Study is a randomized trial examining long-term (7- to 9-year) clinical outcomes in 6000 patients assigned to a viral-suppression arm or a drug-conservation arm. The viral-suppression strategy is continuous use of potent antiretroviral therapy to achieve the lowest plasma HIV-1 RNA levels possible. The drug-conservation strategy consists of using potent antiretroviral therapy when the CD4+ count falls to less than 250 cells/ μL and stopping therapy when the CD4+ count is greater than 350 cells/ μL .

In the STACCATO trial, 600 patients with viral suppression on antiretroviral therapy are being randomized to 1 of 3 treatment arms: continuous therapy; 1 week on therapy, 1 week off therapy; and pulse therapy based on CD4+ cell counts (treatment only if CD4+ cell

count is $<350/\mu\text{L}$). All patients will receive potent antiretroviral therapy from month 24 to month 27. The primary study outcome measures are the proportion of subjects with plasma HIV-1 RNA level below 400 copies/mL and the proportion of subjects with CD4+ counts above 350 cells/ μL at month 27. In addition, the AIDS Clinical Trials Group Study A5102 is examining whether increases in CD4+ cell count induced by interleukin-2 can prolong treatment pauses. The purpose of this study is to assess the rate of CD4+ cell count decline after stopping treatment in 80 patients receiving 24 weeks of potent antiretroviral therapy with or without 3

The best candidate patients for “pulse therapy” may be those with lower HIV RNA levels and higher CD4+ counts at baseline prior to starting therapy

1-week cycles of moderate-dose interleukin-2. Treatment is to be resumed when CD4+ cell counts fall to below 350/ μL .

The relative dearth of controlled study data on STIs makes it difficult to answer the question of whether treatment interruption has a role in current clinical management. STI can be used in the setting of primary HIV infection, but use in a research setting is recommended until any utility of the approach is proved. The strategy should not be used in the setting of chronic infection as a way of stimulating HIV-specific immunity. It may be used to minimize drug exposure in the setting of chronic infection in patients with high nadir pretreatment CD4+ cell counts (eg, $>350/\mu\text{L}$) and lower pretreatment HIV-1 RNA levels (eg, $<100,000$ copies/mL); however, it is prudent to use the approach only in the research setting since its long-term

safety is unproven. Recent data (Douek et al, *Nature*, 2002) has demonstrated that HIV-specific CD4+ T cells are preferentially infected by HIV in vivo, suggesting that viremia during treatment interruptions results in further impairment of HIV-specific immunity. Use of this approach only in the research setting is especially recommended for patients with lower pretreatment CD4+ cell counts and higher plasma HIV-1 RNA levels. Extreme caution is warranted in the use of STI in treatment-experienced patients, particularly in patients with low CD4+ cell counts. In this setting, the virologic benefit achieved may come at a high immunologic and clinical cost. If use of the strategy in this setting is contemplated, enrollment in a research study would be the best option.

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Special Contribution**Current Strategies for Antiretroviral Therapy:
Panel Discussion of Clinical Cases**

As part of an International AIDS Society–USA course in Atlanta in March 2002, course faculty participated in an interactive panel discussion addressing strategies for managing antiretroviral therapy. Michael S. Saag, MD, and Jeffrey L. Lennox, MD, presented cases and moderated discussion of clinical questions by an 8-member panel (see list of panel members below), as well as comments from the audience. The following article summarizes selected comments drawn from the discussion of clinical cases.

Case 1

A 44-year-old man is found to be HIV-seropositive during a routine insurance exam. He has a history of hypertension, which has been controlled with diet. He understands the benefits and complications of antiretroviral therapy and is ready to start therapy at your recommendation. His plasma HIV-1 RNA level is 30,000 copies/mL and his CD4+ cell count is 350/μL. Do you recommend starting therapy?

Dr Thompson: We have struggled for years with the question of when to start therapy and there still is no certain answer. It is clear that therapy should be initiated once the CD4+ cell count drops below 200/μL. Current guidelines state that in patients with plasma HIV-1 RNA levels as low as 30,000 copies/mL and CD4+ counts above 350 cells/μL, it may be reasonable to defer therapy and monitor. The CD4+ count range between 200 and 350 cells/μL is a gray area.

Dr del Rio: If this patient had said that he is undecided about antiretroviral therapy or that he is not ready to start, I would explain that we could wait, monitor his laboratory results, and plan to initiate therapy before the CD4+ cell count reaches 200/μL. However, since he stated that he is ready to start therapy, I would be comfortable recommending antiretroviral therapy at a CD4+ count of 350 cells/μL.

Dr Lennox: At 30,000 copies/mL, this patient's viral load is in the intermediate range and does not indicate initiation of therapy. We are still learning which drugs are associated with long-

term metabolic complications, one of the main adverse effects of antiretroviral therapy. In the next few years we may know more about the causes of these complications and how to prevent them, and some of the newer agents becoming available may be less likely to be associated with known adverse effects. In this case, it might be reasonable to wait to initiate antiretroviral therapy and monitor the CD4+ cell count and viral load.

Dr Saag: Current treatment guidelines recommend less emphasis on viral load and much more emphasis on the CD4+ cell count for monitoring disease progression. Earlier data and guidelines supported an emphasis on the use of viral loads, but those data were from untreated patients and reflect the natural history of HIV disease before therapy. In the era of highly active antiretroviral therapy (HAART), the CD4+ cell count appears to be the more important of the 2 laboratory tools.

In their cohort study, Montaner and colleagues demonstrated that among patients starting their first HAART regimen, 91% of those with baseline plasma HIV-1 RNA levels above 200,000 copies/mL survived at 2 years. In comparison, among patients with baseline CD4+ counts below 50 cells/μL, 78% were alive at 2 years. Data from the Multicenter AIDS Cohort Study (MACS) suggest that the viral load serves as an indicator of how rapidly the CD4+ cell count will fall per year. In general, patients with higher viral loads will experience a more rapid decline in CD4+ cell counts than those with lower viral loads.

Dr Gulick: Many people have referred to these cohort data as evidence that we could delay starting antiretroviral therapy in all patients until the CD4+ cell count is below 200/μL. I think that this is a misinterpretation of these data because the end point in this analysis was the proportion of patients surviving. In fact, I do not think that these data support deferral of therapy until the CD4+ cell count is 200/μL because of the increased risk of death, particularly in those with plasma HIV-1 RNA levels greater than 100,000 copies/mL.

Dr Saag: Chen and colleagues conducted a similar study at the University of Alabama at Birmingham, but had 4 years of patient follow-up. At 2 years, 78% of patients with an initial CD4+ count

Panel Participants and Participant Affiliations: Michael S. Saag, MD (Co-Moderator), The University of Alabama at Birmingham School of Medicine; Jeffrey L. Lennox, MD (Co-Moderator), Emory University, Atlanta, Ga; Carlos del Rio, MD, Emory University, Atlanta, Ga; Roy M. Gulick, MD, MPH, Weill Medical College of Cornell University, New York, NY; Colleen M. Hadigan, MD, MPH, Harvard Medical School, Boston, Mass; Victoria A. Johnson, MD, The University of Alabama at Birmingham School of Medicine; H. Clifford Lane, MD, National Institute of Allergy and Infectious Diseases, Bethesda, Md; Mark S. Sulkowski, MD, The Johns Hopkins University School of Medicine, Baltimore, Md; Melanie A. Thompson, MD, AIDS Research Consortium of Atlanta, Atlanta, Ga; Glenn J. Treisman, MD, PhD, The Johns Hopkins University School of Medicine, Baltimore, Md.

below 50 cells/ μ L were alive. For patients with 200 to 350 CD4+ cells/ μ L, survival at 2 years was approximately 97%. At 4 years, the survival rate was 65% among patients starting HAART with a CD4+ count below 200 cells/ μ L. These data also suggest that waiting for a CD4+ cell count of 200/ μ L is too late.

Dr Thompson: Monitoring the CD4+ cell percent value is also important. All of our data tend to focus on absolute CD4+ cell counts. We see patients with *Pneumocystis carinii* pneumonia (PCP) who have CD4+ cell counts of 300 to 350/ μ L and CD4+ cell percent values of 12% to 14%, as was shown in the original data on PCP prophylaxis. It is important to take into account that patients with a CD4+ cell count of 300/ μ L might have a percent of 12, which is essentially equivalent to a lower CD4+ cell count.

Dr Lennox: In some places, the question of starting antiretroviral therapy at 350 CD4+ cells/ μ L or waiting until 200 CD4+ cells/ μ L is moot. In Atlanta, by the time most patients are diagnosed as HIV-seropositive, they already have clinically defined AIDS or advanced disease. This tendency for late presentation raises an important challenge: how do we encourage people to be tested earlier? We frequently see patients who are ultimately diagnosed with HIV-related PCP but who had presented to the emergency department, walk-in clinic, or some other medical clinic within the past year or two and had not been tested for HIV.

Dr Saag: I would add that if the decision is to initiate therapy, it is important to take adherence issues into account immediately, at the time of initiation of the first antiretroviral therapy regimen. We will not know in advance if a patient will tolerate one particular drug or another, but it is important to try to tailor the regimen based on potency and likely tolerability. Some considerations include history of neuropathy, gastrointestinal intolerance, and diarrhea. In our experience, stopping the first regimen because of virologic failure is uncommon; more typically, patients stop because of toxicity or tolerability issues. Chen and colleagues showed that among people on their first HAART regimen, only 66% are still on that first regimen after 1 year, and only 33% are still on the regimen after 3 years; at the end of the second year of HAART, 14% to 15% of patients are on their fourth regimen.

Case 2

A 26-year-old man presents with PCP and is diagnosed with HIV infection. His CD4+ cell count is 33/ μ L and his plasma HIV-1 RNA level is greater than 750,000 copies/mL. He does not have any other medical or mental health problems. Would you start antiretroviral therapy? With how many drugs? Which ones?

Dr del Rio: This is a fairly typical case of the presentation of advanced HIV disease. There are some data suggesting that an initial 4-drug regimen may be better than a 3-drug regimen in patients presenting with advanced HIV disease. Analysis from

AIDS Clinical Trials Group Study 388 by Fischl and colleagues shows that among patients taking 2 nucleoside reverse transcriptase inhibitors (nRTIs) and indinavir, 2 nRTIs and nelfinavir plus indinavir, or 2 nRTIs and efavirenz plus indinavir, the group that took the latter regimen had a better virologic response than the other groups. These findings suggest that this patient should perhaps start with 4 drugs, including a protease inhibitor and an nRTI, but we do not have a lot of clinical trial data on this issue.

Dr Saag: The data on using 2 drugs plus lopinavir/ritonavir are promising, and this regimen seems to work in patients with higher viral loads. There also are data on 2 drugs plus efavirenz suggesting that this regimen is effective in patients with higher viral loads. I think that current data suggest that a regimen of 3 nRTIs is not as effective in patients with plasma HIV-1 RNA levels above 100,000 copies/mL.

Dr Gulick: We do not have enough information on this issue. There are some initial data from 2 studies that evaluated a triple nRTI regimen and a regimen of 2 nRTIs and indinavir. There are practitioners in New York who will swear by a combination of fixed-dose lamivudine/zidovudine/abacavir and tenofovir or fixed-dose lamivudine/zidovudine/abacavir and efavirenz, but we do not have the clinical trial data to support this. There are numerous studies showing that 3 drugs are more effective than 2 drugs, but in studies of 4 drugs versus 3, it is not clear which option is better. In one study, Eron and colleagues showed that 3 drugs actually were better than 4 because most of the people taking 4 drugs simply could not tolerate them as well.

Dr Lennox: We may never know if 4 drugs are better than 3 in advanced-stage disease because there are always new regimens emerging, so the comparison regimens become obsolete.

Dr Thompson: There are some small studies evaluating fixed-dose lamivudine/zidovudine/abacavir and a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor (NNRTI) as an initial therapy in patients with higher viral loads. Once the patient's viral load is suppressed for approximately 6 months, he or she continues on fixed-dose lamivudine/zidovudine/abacavir without the protease inhibitor or the NNRTI. These studies are not well-controlled, but it is a strategy that people are using. The advantage may have to do with adherence to the regimens over time.

Dr Saag: The bottom line is that the potency of the first regimen is crucial. We must choose regimens that are likely to reduce the plasma HIV-1 RNA to less than 50 copies/mL. At the same time, drugs have no potency if they are not taken, so adherence is an equally important factor in choosing the first regimen.

Case 3

A 73-year-old HIV-seropositive woman has been taking stavudine/lamivudine/efavirenz for approximately 2 years. Her plasma

HIV-1 RNA level, which was consistently less than 50 copies/mL, has increased to approximately 6500 copies/mL. A genotype shows the M184V mutation but virus is otherwise wild-type. Would you add or replace an nRTI, add a protease inhibitor, add a new nRTI and a protease inhibitor, or recommend something else?

Dr Saag: A couple of years ago, we would have said “stay the course,” but there are now compelling data that show that when the M184V mutation is the first nRTI mutation to emerge, subsequent mutations will follow. Whether to change or add drugs depends on how this patient is tolerating the regimen and how adherent she is. Typically, you might not discontinue lamivudine, but assuming her adherence is good, you might intensify the regimen by adding tenofovir. That would involve just 1 extra pill per day and would not add any significant risk for new resistance mutations, especially if her plasma HIV-1 RNA level returns to less than 50 copies/mL.

Dr Gulick: We could also argue to change 2 drugs in this patient’s regimen. By adding 1 drug to the regimen in someone with a plasma HIV-1 RNA level of 6500 copies/mL, there is a risk of creating a sequential monotherapy-like approach. I think the best chance for resuppressing the virus to less than 50 copies/mL is to replace 2 drugs.

Dr Lane: We do not know the CD4+ cell count for this patient. Given her age, if she has a relatively high CD4+ cell count, you could make the case for waiting and watching. Even though it may be difficult to resuppress the viral load, protease inhibitors are still an option.

Case 4

A 22-year-old woman has been on antiretroviral therapy for approximately 5 years. Her current CD4+ count is 290 cells/μL and her plasma HIV-1 RNA level is 54,000 copies/mL. She has taken every antiretroviral drug available, and has been on and off therapy at various times. Her current regimen is didanosine/zidovudine/efavirenz. Genotypic testing shows major reverse transcriptase mutations at positions 41, 215, and 103 and protease inhibitor mutations at 46, 90, and 84. Would you order phenotypic testing, use lamivudine in the next regimen since there was no M184V mutation, or use tenofovir in the next regimen?

Dr del Rio: This is a complex genotype that is hard to interpret. A phenotype may help, but even if the M184V mutation is not present in a patient who is not currently taking lamivudine, the mutation may surface when he or she starts lamivudine again.

Dr Lennox: Findings from a recent study by Parkin and colleagues showed that for some drugs there is a sizable discordance between phenotype and genotype. This was observed in the laboratory, and the clinical utility of these findings is not clear. In this patient, it may be useful to order phenotypic testing to determine if there are drugs that by genotype appear to be ineffective, but by phenotype may be useful.

Audience Comment: The issue of ordering a phenotype for this patient is the same as that of ordering a genotype: the patient currently is not taking all of the drugs to which her virus has been previously exposed. Can you really obtain useful information from a drug resistance assay if she is currently taking only didanosine, zidovudine, and efavirenz?

Dr Lennox: The utility and reliability of phenotypic or genotypic testing results are not clear in this setting.

Dr Johnson: Ideally, resistance test results would reflect the archival history of drug exposure, not just the current exposure. It is difficult to sort out discordance between genotype and phenotype by drug because patients may have numerous mutations; we do not fully understand the net clinical effect of a given set of resistance mutations. In the “old days,” virus with lamivudine resistance mutations could become resensitized to zidovudine. Now, for example, if 3 or more nRTI-associated mutations and the M184V mutation are present in virus, there may be dual resistance.

Audience Comment: The issue with this case may not be a biochemical one. When you see drug failure like this, your first, second, third, and fourth thoughts should be about adherence. Only after exploring potential adherence problems should you discuss a new regimen.

Case 5

A 31-year-old man with HIV infection is seropositive for hepatitis C virus (HCV) infection. His CD4+ count is 118 cells/μL and his plasma HIV-1 RNA level is 76,000 copies/mL. He is taking trimethoprim-sulfamethoxazole for PCP prophylaxis. After 10 weeks of zidovudine/lamivudine/abacavir, his aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels have increased from 65 and 80 U/L to 185 and 250 U/L, respectively. The total bilirubin and albumin levels are normal. He reports no use of alcohol, dietary supplements, or any other medications that may be increasing his AST and ALT levels. Would you recommend stopping antiretroviral therapy, or continuing antiretroviral therapy and adding interferon alfa and ribavirin?

Dr Sulkowski: When a patient develops hepatitis, defined as an increase in liver enzymes suggesting increased hepatocellular necrosis, the first step is to generate differential diagnoses. Hepatitis A virus and hepatitis B virus are also very common. If these tests are negative, then you should suspect the antiretroviral therapy as the cause of the hepatitis.

Data from the Swiss Cohort Study show that approximately 60% of patients who developed a grade 3 or 4 toxicity and continued to take the same regimen did not experience an adverse outcome. This finding has been supported by results of other cohort studies; many patients have favorable outcomes with observation only. One argument in favor of continuing the regimen would be that the zidovudine/lamivudine/abacavir regimen has been associated with a relatively low rate of hepatotoxicity of any combination antiretroviral therapy regimen.

Dr Gulick: What about the immune reconstitution syndrome with concomitant HCV infection?

Dr Sulkowski: Immune reconstitution syndrome refers to the observation that after starting antiretroviral therapy, there may be a specific anti-HCV immune reaction leading to increased hepatocellular cytolysis. There are no data firmly supporting this effect. Some data indicate that the HCV viral load increases after initiation of HAART, suggesting that liver cells are being destroyed. However, there are no studies that show specific cytotoxic T-cell immunity to HCV in the liver, so the immune reconstitution syndrome in HCV infection remains an unproven hypothesis.

Dr Gulick: How would you otherwise account for the increase in HCV levels in the blood?

Dr Sulkowski: The reason for increased levels of HCV is not clear. In the case of cytomegalovirus (CMV), for example, the CMV viral load decreases with initiation of antiretroviral therapy. Research shows that an HIV-seropositive patient population has a higher HCV viral load than an HIV-seronegative population, so you would expect that if you added HAART and improved immune system function, the HCV viral load would decrease. We do not yet understand the effect, in part because studies that incorporate liver biopsies before and after the initiation of antiretroviral therapy have not been conducted. There is some evidence to suggest that immune cells in the liver may be different than those found in the peripheral blood.

Dr Lennox: There is controversy over whether measuring levels of HCV RNA predicts tissue damage in the liver.

Dr Sulkowski: Indeed, there are no studies that show that HCV viral load in the blood correlates with hepatic inflammatory activity, ALT levels, or fibrosis. In HIV disease, HCV viral load is not a good marker of disease progression. Liver biopsy may be helpful, but often we do not have biopsy results in this kind of clinical scenario.

Case 6

A 32-year-old woman was diagnosed with HIV infection in 1995. At that time, her CD4+ count was 520 cells/ μ L and her plasma HIV-1 RNA level was approximately 11,000 copies/mL. She began taking stavudine/lamivudine/indinavir and has had 1 episode of nephrolithiasis (successfully treated). For the last 4 years, her plasma HIV-1 RNA level has been less than 50 copies/mL. Her current CD4+ count is 840 cells/ μ L. She has heard about the long-term complications of HAART and is concerned. Do you maintain the current regimen, substitute a drug for indinavir, substitute zidovudine for stavudine, replace both indinavir and stavudine, or stop her current therapy and observe?

Dr Thompson: This patient began therapy in 1995 with a CD4+ cell count and plasma HIV-1 RNA level that would have indicat-

ed deferral of therapy under current treatment guidelines. I might consider stopping therapy because I am concerned about the long-term adverse effects of antiretroviral therapy in such patients. If we stop therapy, we may be able to spare this patient several years of therapy, but we would have to monitor the CD4+ cell count very, very closely. Her CD4+ cell count is 840/ μ L now, but it could decline rapidly if she stops therapy. It would be ideal to enroll this patient in a clinical trial.

Dr Hadigan: The first thing that I would recommend is checking her cholesterol, lipid, glucose, and insulin levels, as well as her body shape and appearance. It is also important to ask if she has noticed physical changes or has specific concerns. There are some data that suggest that if a patient has been on this regimen for this length of time and has not developed any problems, it is unlikely that he or she will do so in the future. If she has tolerated this combination for several years and has a fasting cholesterol level less than 200 mg/dL, a low-density lipoprotein cholesterol level of less than 160 mg/dL, a reasonable triglyceride level (<300 mg/dL), and has not experienced any significant changes in body fat distribution, I would recommend that she stay on this regimen. Some patients tolerate regimens very well for periods of 5 or more years.

Case 7

A 20-year-old woman was found to be HIV-seropositive during a prenatal work-up. Her CD4+ count was 540 cells/ μ L and her plasma HIV-1 RNA level was 12,000 copies/mL. She started zidovudine, lamivudine, and nevirapine and had a genotype indicating wild-type virus. Her plasma HIV-1 RNA level was less than 50 copies/mL at delivery, and she gave birth to a healthy, HIV-seronegative baby. She presents 2 months later and does not have a strong opinion about continuing antiretroviral therapy or not. She is not breastfeeding. Would you recommend continuing or stopping therapy?

Dr Treisman: I would suggest stopping therapy. It is important to explore other issues that for individual patients may have a more profound impact on treatment decisions than CD4+ cell counts or viral load. For example, this woman does not have a strong opinion about antiretroviral therapy. Does she have a long-term partner? Does having an undetectable viral load mitigate her concerns about transmission? Does she have concerns about the drugs that are coloring her opinion?

Dr del Rio: Data have shown that pregnant women adhere to antiretroviral therapy regimens very successfully during pregnancy, but that severe adherence problems begin after delivery. Two of the drugs this woman is taking are lamivudine and nevirapine, to which she could develop resistance very rapidly. If the recommendation is to continue therapy, it is essential to work on adherence.

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Special Contribution

HIV in India

Suniti Solomon, MD, and Aylur Kailasam Ganesh, ACA

Although it is estimated that there are fewer than 4 million cases of HIV infection in India, the general consensus is that there are growing localized epidemics. The challenge to the country's infrastructure to respond to this epidemic and the issues of stigma and discrimination faced by HIV-infected persons appear daunting. After initial denial, the government set up the National AIDS Control Organization, which initiated a large-scale surveillance program for prevalence of HIV infection throughout all the states of India. The National AIDS Control Organization also brought significant improvements to blood supply safety in the country. The nongovernmental sector is active in prevention and care; people living with HIV are beginning to organize themselves for advocacy and activism; epidemiologic, interventional, and clinical research have moved forward; yet more could be done. Diagnosis of HIV infection remains a challenge. There are unresolved ethical, technical, and programmatic issues around voluntary counseling and testing. Availability of highly active antiretroviral therapy is not an issue since antiretroviral drugs are manufactured in the country and exported elsewhere, but their affordability and the feasibility of monitoring patients taking the drugs are in question. Almost none of those living with HIV infection receive these medications from the government, except when nevirapine is provided to prevent mother-to-child transmission, or from the nearly nonexistent health insurance sector.

This commentary offers a perspective on the current status of the HIV epidemic in India, focusing on epidemiology, the government response, and diagnosis and treatment.

Introduction

We often hear 2 different descriptions of the HIV epidemic in India. The official version is that the total number of HIV infections in the country is still fewer than 4 million¹ and that the efforts by the government and other public agencies to prevent a rapid escalation of HIV infection are effective. However, a second version asserts that the official account does not present the true picture of the magnitude of the epidemic and the efforts to address it.

No matter which school of thought one believes, those who know India as a country that is populous, large, culturally complex, and economically diverse will agree that HIV adds to its woes. In 1978, India joined other nations in signing the World Health Organization's Alma Alta Declaration, which set the goal of "Health for All by the Year 2000."² Although India has not real-

ized this goal, the failure leaves valuable lessons for the health sector to learn about HIV infection.

HIV has yet to cause dramatic, visible turns in the Indian economy or the health sector. Such good fortune may not continue. The first documented HIV infection was among sex workers in Chennai, Tamil Nadu, in 1986,³ and the 15-odd years since this initial report may have been the best opportunity for response. This first case report and subsequent reports, including those from northeastern India describing HIV infection among injection drug users (IDUs), were received with skepticism and denial by academicians, politicians, and sociologists, thus diluting the promise for an effective response. Some speculate that India is now on the verge of a catastrophe.

Tracking the Spread of HIV Infection: The HIV Sentinel Surveillance System

The National AIDS Control Organization (NACO) is a government institution that was established in 1992 for planning and implementing HIV prevention, control, and management. A NACO brochure titled *India Responds to AIDS* states, "AIDS presents the most serious public health problem in India today."⁴ Reports from NACO's sentinel surveillance system present a grim picture. The sentinel surveillance system uses anonymous unlinked sample screening for HIV antibodies to estimate prevalence of HIV in various states and population groups. Surveys are conducted annually, and survey sites include sexually transmitted disease (STD) clinics, antenatal clinics, sites that target IDUs, and those that target men who have sex with men.¹ Table 1 provides surveillance data from 1995 to 1999; in the samples screened, which comprised both individuals at low and high risk for HIV infection, approximately 25.84 per 1000 were infected with HIV as of 1999. A large majority of these infections were attributed to heterosexual transmission, although bisexual and homosexual transmissions were likely underestimated. Possible sources of infection for AIDS cases reported from 1986 to 2001 are listed in Figure 1.

HIV testing is offered by government institutions and by private hospital-based or independent clinical laboratories. There is no national information grid that collects HIV testing information from clinical laboratories in the private sector, so prevalence estimates are based solely on the sentinel surveillance mechanism. Further, all over the country, individuals dying from opportunistic infections associated with HIV are not being test-

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Table 1. Surveillance for HIV Infection in India

For Period Ending	2/1995	3/1995	3/1996	9/1996	3/1997	9/1997	12/1999
No. Persons Screened	1,273,829	2,679,033	2,798,521	2,787,136	2,941,825	3,170,084	3,572,144
No. Persons HIV-seropositive	6683	19,754	22,389	46,503	52,802	67,067	92,312
Seropositive Persons Per 1000	5.25	7.37	8.00	16.10	17.80	21.15	25.84

Adapted from National AIDS Control Organization, 2000-2001.

ed for HIV infection. Families of those who die from known HIV infection often request that the cause of death be attributed to a cause other than HIV, and physicians oblige. The suboptimal HIV reporting system may thus preclude planners from shaping effective responses.⁵

Based on sentinel surveillance data, HIV prevalence in the adult population can be broadly classified into the 3 following groups of states and union territories in the country (Figure 2). States and union territories not listed below include those for which data are insufficient to estimate prevalence of HIV infection in antenatal women.

- High HIV Prevalence States: Includes Maharashtra, Tamil Nadu, Karnataka, Andhra Pradesh, Manipur, and Nagaland, where prevalence of HIV infection is 1% or higher in antenatal women.
- Moderate HIV Prevalence States: Includes Gujarat, Goa, and Pondicherry, where prevalence of HIV infection is 5% or higher among high-risk groups, but lower than 1% in antenatal women.
- Low HIV Prevalence States: Includes remaining states, where prevalence of HIV infection is lower than 5% in any of the high-risk groups and lower than 1% among antenatal women.

The virus is spreading rapidly along India's coasts and inward to all parts of the country, both rural and urban.⁶ The epidemic varies widely among regions, a reflection of the country's great diversity. A survey of randomly selected households in Tamil Nadu found that 2.1% of the adult population living in the countryside had HIV infection compared with 0.7% of the urban population.⁷ In the northeastern state of Manipur, HIV has already reached epidemic proportions among IDUs.⁸

Early descriptions of HIV epidemiology created a general perception that HIV infection was largely restricted to sex workers, truckers, and IDUs.⁶ The rest of the population was, and in many cases, still is, in denial; meanwhile, the infection has spread further into the general population. For example, HIV infection rates are reported to be increasing among monogamous women, through unprotected sex with infected spouses.^{9,10}

Poverty creates conditions ripe for HIV transmission. Economic growth has caused rapid urbanization in India, with large urban slum populations composed of migrants, manual laborers, and child laborers.¹¹ Currently, 260 million persons in India (26% of the population) live below the poverty line.¹² Those

with low incomes cannot afford to buy condoms or treatment for STDs. Poor families send their young women into prostitution to make ends meet. Too illiterate to understand prevention messages and with little access to information, the poor succumb to STDs. Untreated STDs increase the risk of HIV transmission, as these infections cause mucosal ulceration with an easy entry for HIV. India has a very high rate of STDs; the current estimates are about 6% to 9% of the population, with more than 40 million new infections per year.^{6,13}

Government Responses

The National AIDS Committee, which supervises the work of NACO, was set up under the Union Ministry of Health and Family Welfare in 1986. The committee's objective: ". . . to lead and catalyze an expanded response to the HIV/AIDS epidemic in order to contain the spread of the infection, reduce people's vulnerability to HIV, promote community- and family-based care to people with HIV/AIDS within an enabling environment without any stigmatization and discrimination, and alleviate the epidemic's devastating social and economic impact." NACO is headed by a project director and consists of an additional technical project director, subject specialists, and other technical and administrative staff.

Each state now has a State AIDS Control Society (a body with programmatic and financial autonomy), with a program

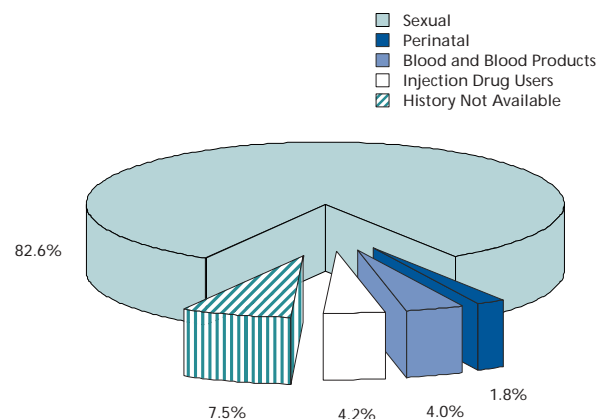


Figure 1. Probable sources of infection for AIDS cases reported in India from 1986 to 2001. Adapted from National AIDS Control Organization, "Combating HIV/AIDS in India 2000-2001."

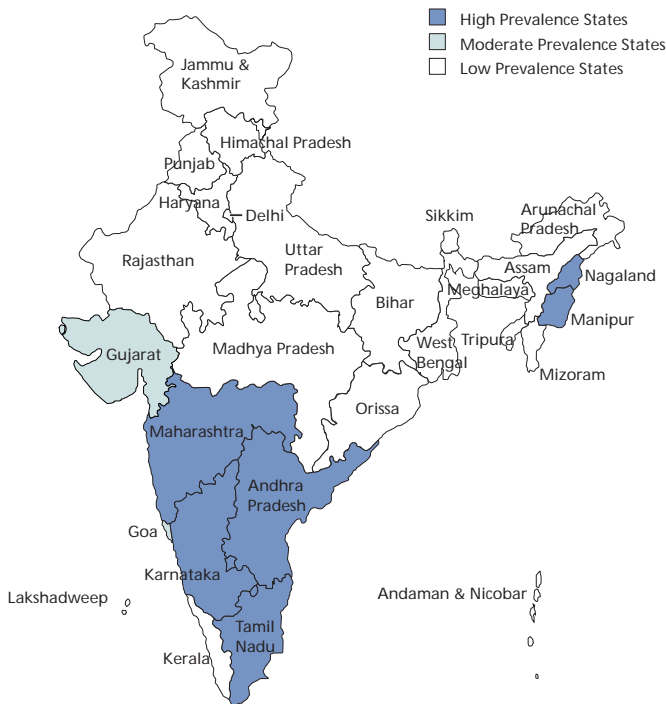


Figure 2. HIV prevalence in adults in India, 2000. Adapted from National AIDS Control Organization, "Combating HIV/AIDS in India 2000-2001."

officer supported by technical staff. Tamil Nadu was the first state to set up such a cell, the Tamil Nadu State AIDS Control Society (TNSACS), followed by Pondicherry. Their successes led the government of India to ask the other states and union territories to adopt this model.

The strengths of the TNSACS model are program management with flexibility and autonomy; participation of nongovernmental organizations (NGOs) and people living with HIV in the decision-making process; a strategic information, education, and communication campaign; a transparent process of funding NGOs; and the provision of funds for patient-care activities and support groups such as the Indian Network of People Living with HIV (INP Plus).

The efforts of NACO, augmented by the state AIDS societies, include surveillance, information, education, and communication campaigns for HIV prevention, safe blood supply, strengthening STD treatment services, expanding availability of condoms, preventing mother-to-child transmission of HIV, and providing community-based care for those living with HIV. NACO promotes its objectives by working with representatives of people living with HIV and bringing together government, NGOs, and private institutions to tackle HIV infection at various levels.

Of note, in 1989 the government of India declared a ban on the acceptance of blood from professional blood donors—individuals who accept a monetary compensation in return for donating blood. However, this ordinance has not been entirely effective. Although blood banks refuse to transact commercially with these donors, the friends and relatives of those who require blood transfusions regularly bring these donors to blood banks,

declaring them voluntary donors or close relatives, and complete the payment to donors elsewhere.

Social Precursors of HIV Infection

In ancient times, Indian culture offered the world the renowned treatise on sexuality *The Kamasutra*. Sexual imagery found a pride of place in temple sculptures. Elaborate rituals covered marriage, nuptial nights, pregnancy, and childbirth, recognizing sex and reproduction as part of the social processes that surrounded them. Such openness about sex and sexuality is now near absent. Talking about sex is taboo, and efforts by policy makers to introduce sex education in schools are half-hearted.¹⁴

There are many social precursors for the rapid spread of HIV in the country, including inability to talk openly and learn about sex and sexuality, pressures from family to give birth to an heir and an implicit threat to the marriage when a woman is unable to become a mother, the high prevalence and acceptability of domestic violence against women, the moral double standard imposed on men and women, and the lower status of women in general. The pressure to be a mother is so intense that when a woman has to choose between being HIV-seronegative but without children and possible conception with possible HIV infection, she often chooses the latter.¹⁵⁻¹⁷

Issues in HIV Testing and Diagnosis

Attitudinal Issues

It is important for every nation to have effective, voluntary counseling and testing services for HIV infection. Benefits include early management of HIV infection and thus improvement in quality of life, and the primary and secondary prevention of HIV infection. Only a fraction of persons living with HIV are aware of their infection, and those who do receive clinical testing are usually not provided with counseling.

Health counseling is a new concept in India. Patients here are much less proactive in seeking health care than in developed countries. In the context of HIV-test counseling, the process of building a risk inventory involves discussing the sexual lifestyle of the client. This falls into the realm of taboo. Worse, high-risk behavior is viewed as morally wrong; hence, few visit the voluntary counseling and testing (VCT) centers.

At the other end of the spectrum are health care facilities that test without consent. HIV testing is performed either as part of a differential diagnosis or, in the case of surgical candidates, to provide reassurance for surgeons. Hospitals are widely known to refuse to perform any invasive procedures on persons with HIV infection. Anecdotal evidence indicates that hospital staff commonly tell HIV-seropositive patients, "You have a problem in your blood. Come back once it is treated."

Hence the majority of HIV testing in India is not accompanied by pretest or posttest counseling.¹⁸ Individuals who receive an HIV-seropositive result are handed a virtual death sentence when they are told, "You have AIDS."

Another issue for any person undergoing an HIV test is realizing that his or her test is neither anonymous nor confidential.

With scant regard for the privacy that such clients are entitled to, laboratories readily provide test results over the telephone or share them with families and workplace supervisors.

The story of Mr V, who worked for a very large government-run company, is heartrending. Following frequent illness and a prolonged hospital admission, an HIV test performed on him without his consent was seropositive. The test result was shared with the company physician, who was excited by his “first” HIV case. Sadly, when Mr V returned to his workplace, he came to know of his HIV serostatus from a doorman who refused entry to him. Mr V attempted suicide but did not succeed.

By yielding a seropositive result or just by its very use, an HIV test can be stigmatizing. Appropriate skills and attitudes could reduce this stigma. At the Y R Gaitonde Centre for AIDS Research and Education (YRG CARE), an AIDS service organization in Chennai City, several thousand people have received HIV counseling and testing, and follow-up services if seropositive. The organization preserves its clients' anonymity by assigning each client a unique serial number on entry. The steady increase in the numbers of persons who have sought counseling and testing over the years reflects the positive reception of this program in the community.

Cost Issues

When laboratory resources are limited, consideration should be given to using total lymphocyte count (TLC) levels in lieu of CD4+ levels, at least for decisions on treatment initiation. In a study at YRG CARE, researchers found a high degree of correlation between 650 paired CD4+ and TLC counts ($r=0.744$).¹⁹ The cost of a single CD4 test is US \$30 versus US \$0.80 for a single TLC count, which translates into a substantial annual cost saving.

Many clinicians use plasma HIV RNA testing to monitor HIV infection; however, inexpensive assays with faster turnaround time are needed in resource-limited settings. The p24 antigen level is of potential, but has not been validated as a prognostic tool.^{20–24}

Quality Issues

The majority of the laboratories in India do not take part in quality-assurance and quality-control exercises for HIV testing, and poor techniques are commonplace.¹⁸ HIV test results are often inaccurate for several reasons: test kits are used after the expiration dates; kits are not stored at the correct temperature; electricity is shut down at night; air-conditioning for the testing equipment is erratic; poor-quality water is used; and tubes, tips, and other equipment are often recycled. With makeshift laboratories that have scant respect for quality control or assurance, patients cannot necessarily be sure of their test results, especially when these laboratories do not provide patients with an opportunity to discuss their lifestyles and risk histories with a counselor who could then help them place the result within that context.¹⁸

In a 2001 survey (unpublished and under further compilation) in Chennai City, conducted in association with the Brown-Tufts Fogarty Program, 972 laboratories were studied, of which 64% (n=619) offered HIV testing. More than 50% (n=510) offered

HIV test results on the basis of a single rapid test. A fourth (n=249) performed the enzyme-linked immunosorbent assay (ELISA), a tenth (n=24) of which offered, on request, confirmation by Western blot. There was a small percentage of laboratories (n=15) that either performed HIV RNA polymerase chain reaction assays or branched DNA assays, or acted as collection centers for others that did these tests. About 1% of the laboratories offered p24 antigen tests.

In a previous study that described the first 5 years of YRG CARE,¹⁸ 9% of clients (n=156) accessed services for reconfirming a prior HIV-seropositive test result. Of this group, only 78% (n=122) tested seropositive under the clinic's conditions for quality assurance and quality control.

Issues in HIV Treatment and Care

A wide spectrum of opportunistic infections has been documented in those living with HIV in India (Figure 3). Emerging opportunistic infections include *Pneumocystis carinii* pneumonia, toxoplasmosis, and cryptococcal meningitis. HIV infection has made tuberculosis, syphilis, and herpes more aggressive.

The standard of care that NACO supports is limited to the provision of drugs for treatment of opportunistic infections.¹ Resource constraints limit the distribution of drugs to those institutions that qualify through a NACO state-level selection process. Unfortunately, since there are additional people living with HIV who only have access to the centers not selected to receive drugs, the provision of drugs for opportunistic infections is limited.

A spate of antiretroviral drugs, evolving incrementally but rapidly and being approved at a brisk pace, has changed the treatment horizon. However, these drugs were not within reach of even middle-class Indians until recently, and they are still inaccessible to most. For example, only about 15% of YRG CARE's patients can afford antiretrovirals. Although antiretrovirals do not offer a definitive cure, the appropriate use of these

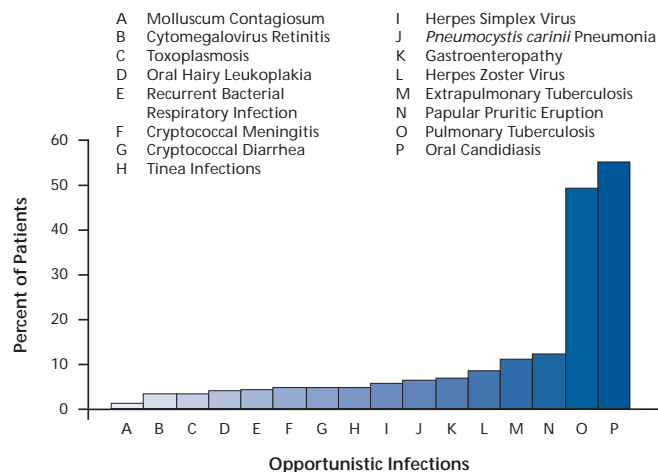


Figure 3. Spectrum of opportunistic infections at Y R Gaitonde Centre for AIDS Research and Education, Chennai, Tamil Nadu, India. Adapted with permission from: Kumarasamy N. *Studies on Human Immunodeficiency Virus Disease Progression in South India* (PhD thesis). Chennai, India: University of Madras; 2001.

drugs in combination has demonstrated a significant decrease in mortality and substantial clinical improvements and has helped individuals lead healthier, longer lives and enjoy a better quality of life.

These new drugs can also prevent mother-to-child transmission of HIV infection and prevent development of the infection in health care workers following occupational exposures to the virus or in cases of other exposures such as rape. To this extent, these drugs are definitely recommended. With regard to use of antiretroviral drugs in the setting of occupational exposure, NACO recently ordered hospitals to stock postexposure prophylaxis kits. Detailed guidelines on postexposure prophylaxis have been distributed to all the hospitals.¹ With regard to prevention of mother-to-child transmission, there are 27 million pregnancies a year in India and an overall estimated 0.3% prevalence rate of HIV infection among pregnant women; it is estimated that about 100,000 HIV-infected women deliver each year. In January 2000, a pilot study was initiated in 11 antenatal clinics to assess the feasibility of administering zidovudine for the prevention of mother-to-child transmission; a subsequent study of nevirapine was initiated in October 2001 in the same 11 clinics. The option of breast feeding was left to the mothers.²⁵

The major Indian pharmaceutical companies have changed the landscape of drug availability and affordability by taking advantage of Indian laws that protect process patents but not product patents. In a rare show of boldness and business wisdom, drugs that cost no less than \$8000 to \$12,000 a year in the United States are now being offered in the Indian and international markets for only a few hundred dollars a year. Whether the recent dramatic reductions in the pricing of AIDS drugs will make a difference to the very few who already know their HIV serostatus, and whether they foretell a standard of care in India on par with that in the developed world, remain contentious issues.

Treatment with antiretroviral therapy of 1 or perhaps more than 1 person in a family presupposes large savings, disposable incomes, or a benevolent government. Contrast these assumptions with the real current situation: a US \$400 per capita income and a government program allocating \$0.06 per capita per year on HIV/AIDS until 2004.¹

In a country where only a small portion of physicians have willingly learned about HIV infection and its management, finding a competent opinion on HIV treatment options may not be easy. Further, in India, where prescription drugs are available over the counter, some wonder how much longer it will be before HIV treatments are available for self-medication.

The viability of implementing wide-scale antiretroviral therapy in the country cannot be generalized. Although in urban centers there is remarkable excitement over the new combination antiretroviral therapies, this should not obscure the other elements of quality medical care for patients infected with HIV for whom antiretroviral therapy is out of reach. Affordability of antiretroviral drugs aside, logistical and financial challenges hinder access to CD4+ cell count and HIV RNA measurements. Drug supply logistics are convoluted; for example, only a small percentage of Indian households own or have access to refrigerators to store those drugs that require refrigeration. Drugs tend to be available only in urban centers, as those centers have more purchasing power than rural towns, where the demand for

the drugs is lower and the cost of stocking them, which may involve use of refrigerators, is high.

Low levels of literacy require additional effort from an overburdened, and more importantly, reluctant medical system to make the complex drug regimens more easily understood. In the absence of quality adherence counseling, both the rich and the poor are not adherent. When HIV-infected patients attain a good quality of life, usually after about 6 months of initiating therapy, the rich take a break and the poor run out of money.

We have important lessons to learn from the indiscriminate use of antibiotics, which has led to many a microbe winning the war. The global concern that suboptimal use of antiretroviral drugs may result in resistant strains of the virus is valid; however, there are as yet no facilities in India that perform resistance-testing assays.

The viability of implementing wide-scale antiretroviral therapy is not determined solely by the cost of the medications. It is affected by the public health infrastructure, site-specific natural history, costs of monitoring, and adherence levels. Data on these cofactors are incomplete and merit independent studies.

Pervasive Magic Cures

Although India predominantly follows the medical system practiced in the West, there are many conditions, such as viral hepatitis, that are treated with Indian traditional medicine.²⁶⁻²⁸ Although the Western medical system is often relied upon, if the condition does not respond to treatment, faith in that system becomes fatigued. Families turn to traditional systems as the last hope, and this moment has been seized by a number of self-proclaimed "experts" offering magic cures for HIV. India is in the grip of such a mania. These drugs often masquerade as natural and herbal, though anecdotal reports suggest that they contain steroid-like additives as well as minute quantities of heavy metals. After an initial sense of well-being, the health of persons who take such drugs deteriorates and they end up with life-threatening conditions. While the government is battling vagrant "healers" through legislation, demand from the general public fuels their greed. This is an ongoing and contentious issue, as drugs that are based on traditional systems do not have an approval process and often have never been investigated, even when compelling evidence of harm is presented.

What Is Relevant?

Pilot study data suggest that when antiretroviral therapy becomes universally available in India, there will be less morbidity and mortality from opportunistic infections.²⁹ However, even in the absence of antiretroviral therapy, opportunistic infections could be managed and prevented through improved health-seeking behaviors as well as shifts in the attitudes of medical establishments, in terms of friendliness to clients and adherence education. Simple chemoprophylaxis protocols effectively prevent the occurrence of opportunistic infections.³⁰

HIV Presents a New Opportunity

The time has come for India to change the way it treats its sick. Perhaps HIV will be able to jolt the health system awake and

pave the way to holistic treatment. Experiences from around the world clearly show that patients and their families require extensive education on nutrition, stress reduction, and exercise, as well as counseling and emotional support, to improve their quality of life.

India should begin to invest in promoting good practices in HIV/AIDS VCT, use of related drugs, routine clinical approaches, and relevant treatment guidelines. India also should promote a change in attitudes toward HIV/AIDS. It is a shame that HIV-infected persons continue to live in a secret world, hoping to shield themselves from the stigma, scorn, and discrimination of the members of their community by not talking about their infection. To them, even government support of antiretroviral drugs would be of little relevance.

Conclusion

The exploding epidemic in India calls for radical and courageous steps, and a departure from previous public health planning. We need to remind ourselves of the enormous task at hand: the establishment of quality-assured HIV testing centers, expansion of clinical facilities that provide HIV care, increased access to drugs with attendant laboratory facilities, and enhanced psychosocial support for those living with or affected by HIV. Additional resources are urgently required to tackle the raging twin epidemics of HIV and tuberculosis.

Investment in areas of research such as in the prevention of mother-to-child transmission of HIV infection and primary prevention of HIV transmission among women, perhaps using women-friendly and women-controlled methods (such as the female condoms or microbicides), and development of low-cost alternatives to laboratory markers such as the CD4+ cell count^{31,32} and plasma HIV-1 RNA level must be encouraged and accelerated.

The HIV situation in India may not have been alarming at first glance; however, a small percentage-point rise in HIV incidence must be viewed in absolute numbers as a multiple of a billion inhabitants.

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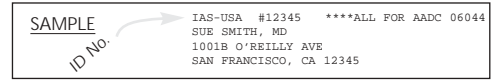


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