IN THIS ISSUE

Immune Reconstitution Strategies
Opportunistic Infections in the Era of Potent Antiretroviral Therapy
Metabolic Complications of Antiretroviral Therapy
HIV in Africa
ABOUT THIS ISSUE...

The articles in Issue 5 of Improving the Management of HIV Disease summarize presentations given at the Los Angeles, San Francisco, and Cleveland courses of the International AIDS Society–USA winter/spring CME program, HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management.

In Los Angeles, Dr Ronald T. Mitsuyasu reviewed current knowledge of the immunology of HIV infection and potent antiretroviral therapy and discussed the prospects for immune reconstitution using strategies based on this knowledge. In San Francisco and Cleveland, Dr Judith A. Aberg and Dr Steven K. Grinspoon discussed old and new complications of HIV disease and antiretroviral therapy; Dr Aberg examined the status of opportunistic infections and new data and guidelines on their treatment, and Dr Grinspoon discussed the emerging spectrum of metabolic complications of antiretroviral therapy.

The fourth article is the second in a 2-part series on the status of HIV in Africa. Following Dr Susan A. Allen’s article in the September issue on the prospects for effective antiretroviral therapy in Africa, this article summarizes a presentation in San Francisco by Dr David A. Katzenstein on the epidemiology of HIV-1 in Africa and the divergence of viral subtypes.

Articles in upcoming issues of IMHD will review new data on neurologic manifestations of HIV infection and will highlight several presentations given this October and November at the International AIDS Society–USA’s fifth annual fall course series, Current Challenges in HIV Disease: A Case-Based, Advanced Course in Clinical HIV Management.

For information on the International AIDS Society–USA fall and winter/spring CME course series, as well as other upcoming activities, please see pages 25 to 27.

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Unrestricted educational grants supported this issue of Improving the Management of HIV Disease and the 1999 HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management program.

We gratefully acknowledge:

Major, continuing grant support since 1992 from
Bristol-Myers Squibb Company
Glaxo Wellcome Inc.
Roche Laboratories

Substantial grant support from
Abbott Laboratories
DuPont Pharmaceuticals Company
Merck US Human Health

Generous grant support from
Agouron Pharmaceuticals, Inc.
Gilead Sciences
Pharmacia & Upjohn Company
Roxane Laboratories/Boehringer Ingelheim Inc.
Contents

Presentation Summaries

Immune Reconstitution Strategies in HIV Infection ........................... 4
Ronald T. Mitsuyasu, MD

Immune Defects in HIV Infection...Immune Changes with Potent Antiretroviral Therapy...CD4+ Cell Function...Strategies for Enhancing HIV-Specific Immunity

Opportunistic Infections in the Era of Potent Antiretroviral Therapy .................. 9
Judith A. Aberg, MD

Paradoxical Worsening of OIs Under Antiretroviral Therapy...
Dynamics of Cellular Restoration after Antiretroviral Therapy...
Prophylaxis/Maintenance Therapy after Initiation of Antiretroviral Therapy...Recommendations on Discontinuing Prophylaxis/Maintenance Therapy

Metabolic Complications of Antiretroviral Therapy .......................... 14
Steven K. Grinspoon, MD

Potential Pathophysiologic Mechanisms...Insulin Resistance and Hyperglycemia...Triglyceride and Lipid Abnormalities...
Clinical Management

HIV in Africa:
Epicenter of the Global Pandemic .................................. 20
David A. Katzenstein, MD

Announcements

Cases on the Web:
An Online CME Activity ..................................... 25

The Science and Treatment of HIV:
An Advanced CME Course for Clinicians .................. 26

Activities of the International AIDS Society–USA .................. 27
IMMUNE RECONSTITUTION STRATEGIES IN HIV INFECTION

The immunopathogenic mechanisms of HIV-1 infection involve multiple complex interactions of the virus with the host's immune response to infection. Delineation of some of these mechanisms has led to development of immunologic strategies to better control HIV infection and to augment immune reconstitution observed with potent antiretroviral therapy. Strategies for improving or hastening immune reconstitution in the setting of potent antiretroviral therapy were discussed at the Los Angeles course by Ronald T. Mitsuyasu, MD.

IMMUNE DEFECTS IN HIV INFECTION

The primary immunologic defect in HIV-1 infection is the decline in CD4+ cell number and function, with decreased CD4+ cell function indicated by decreased delayed-type hypersensitivity reaction to recall antigens, decreased lymphoproliferative (LPA) responses to antigens, and decreased production of Th1 cytokines, including interleukin-2, interleukin-12, and interferon gamma. Other defects include chronic immune activation resulting from ongoing viral replication, as evidenced by increased numbers of CD38+ and HLA-DR+ CD4+ T cells and CD8+ T cells, and increased production of proinflammatory cytokines (eg, interleukin-1, interleukin-6, and tumor necrosis factor). Perturbations of CD4+ and CD8+ T-cell repertoires may reflect clonal deletion or clonal exhaustion with ongoing HIV infection. The CD4+ cell repertoire abnormalities are relatively limited during early infection and worsen over time. The CD8+ cell repertoire appears to expand during early infection, possibly as a result of differentiation in response to HIV antigens, but subsequently exhibits a dramatic reduction. The decline in CD4+ cell count consists of declines in both memory (CD45RO+) and naive (CD45RA+, CD62L+) phenotypes. An increase in CD8+ cells during early infection, which is likely attributable to an increase in activated cells, includes an increase in memory cells and is followed by declines in overall cell number and both memory and naive phenotypes.

IMMUNE CHANGES WITH POTENT ANTIRETROVIRAL THERAPY

Potent antiretroviral therapy is associated with significant increases in CD4+ cell count. Ongoing investigation into immune reconstitution in this setting is examining the degree of immune reconstitution with continued viral suppression, specific quantitative and qualitative immune changes during therapy, the degree to which improved host immunity might play a role in regulating HIV replication and spread, and whether host immunity to HIV and other pathogens can be enhanced by specific immune interventions.

Compelling clinical evidence of functional improvement in host immunity is provided by data showing significant decreases in the incidence of opportunistic infections and mortality with the use of protease inhibitor-containing combination regimens (Figure 1). The significant increase in CD4+ cell count with potent antiretroviral therapy has now been shown by many investigators to be biphasic, consisting of an initial rapid increase (4 to 12 weeks after initiation of treatment) followed by a more gradual increase (Figure 2). It appears that the first phase increase is attributable to redistribution of cells from lymphoid tissue and to decreased activation-induced apoptosis; this initial increase is due largely to increased numbers of

![Figure 1. Impact on mortality of the use of protease inhibitor-containing potent antiretroviral regimens among HIV-infected patients with CD4+ cell counts of less than 100/μL. Adapted from Faella F Jr et al. N Engl J Med. 1998;338:853–860. Copyright 1998 Massachusetts Medical Society. All rights reserved.](image-url)
memory cells. The second phase increase appears to be due to increased proliferation of cells, characterized by a gradual and persistent increase in naive cells. The CD8+ cell population also exhibits a rapid early increase of both memory and naive cells, followed by a decline in total and memory CD8+ cell number but a persistent increase in naive CD8+ cells.

A number of findings now indicate that the increase in CD4+ cell number following the initial rapid rise reflects true expansion. Along with the increase in number of cells of naive phenotype, an increase in the number of cells positive for Ki67 (a marker of rapid cell proliferation) and an expansion of CD4+ T-cell repertoire have been demonstrated. Increases in newly-produced T cells after initiation of potent antiretroviral therapy have also been demonstrated using assays to measure incorporation of deuterated glucose into DNA of newly-produced cells.

Other recent studies have shown that there is a T-cell progenitor defect in HIV infection with an increase in thymic-derived cells after initiation of antiretroviral therapy, suggesting that effective treatment may be associated with improved thymic function. These studies use T-cell receptor rearrangement excision circles (TREC), produced during processing of T cells in the thymus, as a marker of thymic output. They have shown that (1) although thymic function declines with age, there is substantial output into late adulthood; (2) HIV infection is associated with decreased TREC levels in peripheral blood and lymphoid tissue; and (3) potent antiretroviral therapy results in a rapid and sustained increase in thymic output in the majority of patients. Other studies have shown that increases in thymic mass detected by computed tomography are associated with increases in naive CD4+ T cells in patients receiving potent antiretroviral therapy. The latter findings suggest both the potential contribution of the thymus to overall immune reconstitution and the potential for reconstitution of elements of the T-cell repertoire that may be lost through HIV infection. Available evidence indeed suggests that CD4+ T-cell repertoire normalizes to some degree during follow-up of patients receiving potent antiretroviral therapy; as noted, it has been observed that an initial expansion of the T-cell repertoire in CD8+ T cells is followed by a reduction in repertoire that does not improve during months of subsequent follow-up.

**CD4+ CELL FUNCTION**

Functional improvement of CD4+ T-helper cells with potent antiretroviral therapy has been demonstrated in a number of studies. Research has shown improved delayed-type hypersensitivity responses and increased proliferative responses to some recall antigens, including cytomegalovirus (CMV), *Candida*, and tuberculin antigens. However, functional reconstitution in patients with chronic HIV infection is incomplete with regard to LPA response to HIV antigens. For example, in a study of 39 patients taking potent antiretroviral therapy for 3 years with plasma HIV RNA maintained below 10,000 copies/mL, improved recall response to CMV, tuberculin, and *Candida* antigens but not to tetanus or HIV antigens was observed. Another study in patients with prior CMV retinitis and CD4+ cell counts below 100/μL has shown after 5 to 6 months of potent antiretroviral therapy improved LPA responses for CMV and *Candida* (in 70% of patients), *Mycobacterium avium* complex (in 50% of patients), and *Toxoplasma* and herpes simplex virus (in 20% of patients). One group of investigators has proposed that improved LPA response to mitogens and recall antigens may be due to a transient (in interleukin-2 production seen with the rapid decrease in viral replication upon initiation of potent antiretroviral therapy. They proposed that initiation of antiretroviral therapy may produce a switch in

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Figure 3. Strategies for enhancing HIV-specific immunity.

HIV suppression with potent antiretroviral therapy with subsequent increase in viremia may result in increased HIV-specific CD4+ T-helper cell and CTL responses in some patients, suggesting that the capacity for heightened HIV-specific immune responses may be stimulated with reexposure to viral antigens in vivo.

STRATEGIES FOR ENHANCING HIV-SPECIFIC IMMUNITY

It is possible that maintained effective antiretroviral therapy might ultimately allow reconstitution of HIV-specific immune responses; however, based on available data in patients followed for relatively long periods, this prospect seems unlikely in patients with chronic HIV infection. Two additional strategies for enhancing or hastening reconstitution of such responses are (1) immunizing with HIV-specific immunogen(s) and (2) using Th1 cytokines to improve cell-mediated immunity (Figure 3). Improved control of viral replication over the long term may also permit better overall immune restoration.

Early investigation of therapeutic vaccination in combination with dual nucleoside reverse transcriptase inhibitor (nRTI) treatment yielded disappointing results regarding augmentation of immune response. However, a recent study of an HIV-specific, gp120-depleted, whole virus inactivated vaccine (Remune), in conjunction with potent antiretroviral therapy, has suggested the potential for significant immunologic improvements. The vaccine is an inactivated (heat- and chemical-treated and irradiated), whole virus immunogen derived from the HZ321 HIV strain (clade A Env and clade G Gag). The vaccine exhibits broad immune cross-reactivity with several viral subtypes, including clades A, B, and E. In a study reported by Valentine and colleagues, 43 patients with CD4+ cell counts above 350/μL were randomized to receive vaccine that contains incomplete Freund’s adjuvant or adjuvant alone at weeks 4, 16, and 28 after initiation of potent antiretroviral therapy. At week 32, patients in the vaccine group exhibited significantly greater LPA responses to gp120-depleted HZ321 (P=0.005), native p24 antigen (P=0.0002), and clade B whole virus (P=0.007), as well as an increase in levels of the beta chemokine, MIP-1β, and a significant increase in delayed-type hypersensitivity skin test responses to p24 antigens compared with controls. The increase in MIP-1β may further decrease HIV spread in these vaccine-stimulated patients. Responses to HIV antigens were at least equal to those observed in long-term nonprogressors. Further, although the study was not designed to show differences in effect on viral load, a significantly greater proportion of vaccine recipients exhibited reduction of plasma HIV RNA (to below 40 copies/mL (94% vs. 75%, P=0.0007). This
study has provided one of the first demonstrations of the ability to improve HIV-specific immune response through immune intervention in the presence of effective viral suppression. Additional study of this approach is needed to determine durability of response, effect on HIV-specific CTLs, and potential long-term virologic and clinical effects. Additional trials with this vaccine and several others are planned.

Other recent studies have assessed the effects of administering interleukin-2 with potent antiretroviral therapy. Early studies of interleukin-2 treatment indicated significant increases in CD4+ cell count but no additional effect on plasma viral load compared with antiretroviral therapy alone. In a recent study reported by Davey and colleagues, 78 patients with CD4+ cell counts of 200 to 500/µL were randomized to potent antiretroviral therapy with or without interleukin-2 at a dose of 7.5 MU twice a day for 5 days every 8 weeks for 6 cycles. At the end of treatment, mean CD4+ cell count had increased by 112% (from 355 to 739/µL) in interleukin-2 recipients compared with 18% (from 341 to 405/µL) in control patients, with similar magnitudes of increase being observed at all strata of baseline CD4+ cell count. Further, there was a trend toward reduction of viral load below the limits of assay detection in a greater proportion of interleukin-2 recipients. The proportion of patients with plasma HIV RNA levels below 50 copies/mL increased from 39% before treatment to 65% after treatment in the interleukin-2 group and from 31% to 36% in the control group. Other recently reported studies of interleukin-2 dose and schedule in this setting have also indicated sizable increases in CD4+ cell count compared with antiretroviral therapy alone, with some studies also suggesting improved virologic response.

A report from the National Institutes of Health indicates that prolonged interleukin-2 treatment may result in an inability to recover viral DNA from pooled peripheral cells in some patients. The long-term durability of this effect will need to be addressed. Substudies of the fully accrued ACTG 328, a randomized controlled trial of interleukin-2 in patients on potent antiretroviral therapy with CD4+ cell counts of 50 to 350/µL, will evaluate the long-term benefit of interleukin-2 on CD4+ cell quantitative and functional recovery, effects on latently-infected cells, durability of viral suppression, frequency and rapidity of development of antiretroviral drug resistance, and expansion of naive CD4+ cells and TREC-positive cells. Other trials of interleukin-2 in combination with potent antiretroviral therapy have been initiated to evaluate whether improvements in quantitative or functional immune response translate into prolonged virologic effect and clinical benefit.

CONCLUSIONS

Preserving and restoring host immunity is important to regulating HIV expression and preventing opportunistic infections in HIV-infected individuals. Antiretroviral therapy increases CD4+ T-cell populations and reduces chronic activation of T cells, but does not appear to fully reconstitute normal T-cell function in patients treated during chronic infection. Studies with therapeutic immunization in the setting of potent antiretroviral therapy suggest that HIV-specific immune response may be improved with immune-based interventions. Studies combining interleukin-2 treatment with antiretroviral therapy also suggest that HIV-specific immunity may be enhanced through exogenous Th1 cytokine treatment. Ongoing investigation will provide additional information on the characteristics of these responses, and future studies are likely to combine these approaches in an attempt to achieve more effective immune restoration and better control of HIV.

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**Suggested Reading**


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(continued)
SUGGESTED READING (continued)


OPPORTUNISTIC INFECTIONS IN THE ERA OF POTENT ANTIRETROVIRAL THERAPY

Issues regarding the incidence and presentation of opportunistic infections (OIs) in patients taking potent antiretroviral regimens and the prospects for discontinuing OI prophylaxis or maintenance treatment after CD4+ cell count increases under such therapy were discussed by Judith A. Aberg, MD, at the San Francisco course.

The incidence of opportunistic infections (OIs) has decreased dramatically since the introduction of potent antiretroviral therapy. Decreases in incidence, however, were observed prior to the use of these potent regimens, likely in association with earlier intervention with OI prophylaxis and use of dual nucleoside reverse transcriptase inhibitor (nRTI) treatment. Recently, a modest increase in incidence of several OIs has occurred at San Francisco General Hospital. Although some of these incidences reflect infections in previously untreated patients, others are associated with virologic failure of treatment or consist of unusual manifestations of infections following initiation of potent antiretroviral therapy. These unusual manifestations have been observed by other investigators as well.

PARADOXICAL WORSENING OF OIS UNDER ANTIRETROVIRAL THERAPY

In a report by Narita and colleagues, paradoxical worsening of tuberculosis was observed in 12 of 33 HIV-1-infected patients treated simultaneously with an antituberculosis regimen and antiretroviral therapy, characterized by increased lymphadenopathy, fevers, and pleural effusion. By comparison, paradoxical worsening was observed in only 1 of 55 HIV-seronegative patients and in 2 of 28 HIV-infected patients receiving antituberculosis treatment but not antiretroviral therapy. The paradoxical responses were observed sooner in patients receiving simultaneous treatment (15 days) than in those who did not (109 days). Among the patients receiving simultaneous treatment, no differences in CD4+ cell count were observed between those who exhibited paradoxical worsening and those who did not. Tuberculin antigen testing in 8 of the patients receiving simultaneous treatment showed a positive test in 1 patient prior to initiation of treatment and the development of a positive response in 6 of the remaining 7 patients during follow-up, suggesting that some immune reconstitution had occurred during antiretroviral therapy.

Phillips and colleagues reported 9 cases of Mycobacterium avium complex (MAC) lymphadenitis in patients within 12 weeks of beginning potent antiretroviral therapy. These patients had a mean nadir CD4+ cell count of 37/µL and a mean count at presentation of 150/µL. Only 1 patient developed mycobacteremia. It is probable that these cases reflect the consequence of a restored pathogen-specific immune response to subclinical localized infection at the time of initiation of antiretroviral therapy. In other cases reported by Woods and colleagues, subclinical cryptococcal infection has appeared to rapidly present as meningitis soon after initiation of antiretroviral therapy. In 1 patient, meningitis occurred after 4 days of triple therapy and an increase in CD4+ cell count from 5 to 70/µL. In another, meningitis occurred 15 days after the addition of saquinavir and stavudine to existing lamivudine treatment and an increase in CD4+ cell count from 30 to 110/µL. In a third patient with a history of cryptococcal meningitis who had received acute treatment and was receiving itraconazole, culture-negative meningitis occurred 10 days after initiation of triple antiretroviral therapy and an increase in CD4+ cell count from 40 to 240/µL.

DYNAMICS OF CELLULAR RESTORATION AFTER ANTIRETROVIRAL THERAPY

A number of studies have reported that the initial rise in CD4+ cell count is comprised primarily of memory CD4+ T cells, with a more gradual rise in naive CD4+ T cells occurring after 12 to 24 weeks and continuing for years. A study and colleagues observed reduction in CD8+ activation indicated by eventual decline in memory CD8+ T cells, as well as an increased lymphoproliferative response to CMV and tuberculin recall antigens. In ACTG 315 similar dynamics were observed. Treatment with ritonavir followed at day 10 by zidovudine/lamivudine in patients with CD4+ cell counts of 100 to 300/µL resulted in an initial increase in all lymphocytes except natural killer cells, followed by a gradual increase in naive CD4+ and CD8+ T cells. Levels of memory CD8+ T cells declined after an initial
**TABLE 1. SELECTED CLINICAL TRIALS EVALUATING THE DISCONTINUATION OF PROPHYLAXIS OR MAINTENANCE THERAPY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target Accrual (No. Patients)</th>
<th>Schema</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG 360*</td>
<td>300</td>
<td>Prospective observational study of development of CMV in patients who have had CD4+ &lt;500/µL within past 24 months and no history of active CMV disease</td>
</tr>
<tr>
<td>ACTG 362*</td>
<td>636</td>
<td>MAC prophylaxis study: azithromycin versus placebo in patients whose CD4+ counts were once &lt;500/µL and are now &gt;100/µL on potent antiretroviral therapy</td>
</tr>
<tr>
<td>CPCRA 048</td>
<td>850</td>
<td>Similar to ACTG 362, but also evaluating risk of bacterial pneumonia</td>
</tr>
<tr>
<td>ACTG 379</td>
<td>125</td>
<td>Discontinuation of CMV maintenance therapy</td>
</tr>
<tr>
<td>ACTG 393</td>
<td>50</td>
<td>Discontinuation of MAC maintenance therapy</td>
</tr>
<tr>
<td>ACTG 888*</td>
<td>250</td>
<td>Discontinuation of primary and secondary prophylaxis</td>
</tr>
<tr>
<td>ACTG 5038*</td>
<td>50</td>
<td>Discontinuation of histoplasmosis therapy</td>
</tr>
<tr>
<td>CFAR</td>
<td>10</td>
<td>Discontinuation of cryptococcal maintenance therapy</td>
</tr>
</tbody>
</table>

ACTG indicates AIDS Clinical Trials Group. CPCRA indicates Community Programs for Clinical Research of AIDS. CFAR indicates Center for AIDS Research Pilot Study.

*ACTG 360 and 362 and ACTG 888 primary prophylaxis arm have been fully accrued and are closed to enrollment. ACTG 5038 opened in April 1999.

Adapted from Aberg JA. Formulary. 1999;34:418–434.

Increase, likely reflecting decreased activation in the context of reduced viral antigen.

Return of cell-mediated immune response has been observed by several investigators. Komanduri and colleagues compared CMV antigen-specific CD4+ T-cell responses measured by flow cytometry in 4 groups: HIV-infected patients with active CMV retinitis, those with quiescent CMV retinitis in whom increased CD4+ cell counts had permitted withdrawal of maintenance therapy, those who were CMV antibody-positive without disease, and subjects who were HIV-seronegative and CMV-seropositive. Patients with quiescent CMV disease had responses similar in magnitude to HIV-infected patients who were CMV-seropositive only and to HIV-seronegative/CMV-seropositive subjects. Patients with active CMV disease had reduced responses. Torriani and colleagues also found increased CMV-specific CD4+ cell proliferative response on lymphoproliferative assays in 8 of the 11 patients in whom CMV maintenance therapy was withdrawn after increases in CD4+ cell count. Of the 3 patients without an initially observed response, 1 developed retinitis, 1 developed a CMV-specific CD4+ cell response 6 months later, and 1 has exhibited neither response nor relapse of CMV disease. In the additional relapses in this group, the decline in CD4+ cell count to below 500/µL was associated with loss of the CMV-specific CD4+ cell response. In addition to indicating that the CD4+ cell count increase under potent antiretroviral therapy is associated with restoration of antigen-specific responsiveness, these studies suggest that use of assays to determine when such a response is present may provide a means of determining when prophylaxis or maintenance therapy for OIs can safely be withdrawn. However, other studies using such assays to determine in vitro antigen-specific responses have yielded disparate results, indicating absence of clear correlation of assay findings with clinical status. Thus, until immunocassays are standardized and validated, it remains unclear if they can be used to predict which patients might be at risk of disease development or recurrence.

Despite evidence that CD4+ cell count increases are protective and associated with reconstitution of antigen-specific responses, basic questions remain about the nature of immune reconstitution associated with potent antiretroviral therapy, including the degree to which naive cell increases may contribute to restoration of “lost” immune response; whether immunization can be active in restoration of lost response; the degree to which immune restoration continues with continued suppression of viral load; and the immunologic consequences of viral rebound during antiretroviral therapy.

**PROPHYLAXIS/MAINTENANCE THERAPY AFTER INITIATION OF ANTIRETROVIRAL THERAPY**

The observation of immune reconstitution following initiation of potent antiretroviral treatment for some OIs can be safely withdrawn with sustained increases in CD4+ cell count.

Data indicate that prophylaxis or maintenance treatment for some OIs can be safely withdrawn with sustained increases in CD4+ cell count.
1999 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus

In 1995, the USPHS and the IDSA developed guidelines for preventing OIs in persons infected with HIV. These guidelines, written for health care providers and patients, were revised in 1997. Because important new data concerning the prevention of opportunistic diseases have emerged since 1997, the USPHS and the IDSA reconvened the Prevention of Opportunistic Infections Working Group on March 4 and 5, 1999, to determine which recommendations warranted revision. Much attention was focused on recent data related to the advisability of discontinuing OI prophylaxis (primary prophylaxis and prophylaxis against recurrence) among persons whose CD4+ cell counts have increased to above prophylaxis thresholds because of potent antiretroviral therapy. The OI Working Group also addressed 2 pathogens not previously considered—human herpesvirus type 8 and hepatitis C virus. In addition, working group members reviewed data concerning the prevention of all common HIV-associated OIs.

Primary Changes in Recommendations

Primary changes in the disease-specific recommendations include:
- The addition of statements concerning discontinuation of prophylaxis against specific OIs when the CD4+ cell count increases in response to potent antiretroviral therapy
- New recommendations regarding human herpesvirus type 8 and hepatitis C virus.
- New recommendations concerning injection drug users.
- New recommendations about short-course chemoprophylaxis against tuberculosis in HIV-infected persons with positive tuberculin skin tests.
- Changes in secondary prophylaxis (chronic maintenance therapy) recommended to prevent the recurrence of Mycobacterium avium complex and cytomegalovirus disease.
- Caution against using fluconazole during pregnancy.
- Statements concerning the use of varicella and rotavirus vaccines among HIV-infected infants.

These guidelines were made available for public comment through announcements in the Federal Register and the MMWR. The final document is endorsed by the USPHS and IDSA as well as by the Infectious Diseases Society of Obstetrics and Gynecology and the National Foundation for Infectious Diseases.

A complete copy of the new recommendations can be found on the CDC Web page at http://www.cdc.gov/mmwr/mmwr_rr.html.


For disseminated MAC disease after initiation of antiretroviral therapy resulted in increases in CD4+ cell counts to above 100/μL. Sterile bone aspirate and peripheral blood cultures for MAC were obtained prior to discontinuation of antiretroviral therapy. CD4+ cell counts were 4 to 5/μL at the time of diagnosis of disseminated MAC disease in these patients and 137 to 301/μL at the time of discontinuation of MAC therapy; plasma HIV RNA levels were below 500 copies/mL in 3 patients and 1250 copies/mL in 1 patient when MAC therapy was discontinued. No relapses have been observed in these patients during 17 to 22 months of follow-up. Dr Aberg and colleagues are participating in the ongoing ACTG 393 study of withdrawing MAC therapy; in early follow-up, no relapses have been observed in the first 16 patients enrolled.

In a report by Tural and colleagues, 7 patients who discontinued maintenance therapy for cytomegalovirus (CMV) retinitis after 3 months of potent antiretroviral therapy had increased CD4+ cell counts to greater than 150/μL and maintained plasma HIV RNA levels at less than 200 copies/mL. No relapses were observed in these patients during 9 to 12 months of follow-up; subsequently, 1 patient has relapsed in association with a decrease in CD4+ cell count to below 50/μL. Investigators at the University of California San Diego reported that 11 patients who discontinued CMV maintenance therapy after antiretroviral therapy had increased CD4+ cell counts from a median of 42/μL to a median of 183/μL; only 3 of the 11 patients had plasma HIV RNA levels below the limit of assay detection. No relapses were observed in these patients over a period of 6 to 18 months of follow-up, despite absence of maximal suppression of viral load. Subsequently, relapse has occurred in 3 patients in association with CD4+ cell count declines to below 50/μL.

A number of reports indicate the absence of occurrence of Pneumocystis carinii pneumonia (PCP) following withdrawal of primary or secondary prophylaxis in patients with CD4+ cell count increases above 200/μL on potent antiretroviral therapy. For example, investigators from the Netherlands reported no occurrences of PCP over 7 to 14 months following withdrawal of primary prophylaxis in 62 patients and secondary prophylaxis in 16 patients with CD4+ cell count increases above 200/μL; at the time of discontinuation, the mean CD4+ cell count was 346/μL and plasma viral load was below assay detection limit in 61 patients. Two patients reinitiated prophylaxis when their CD4+ cell count dropped below 200/μL.
RECOMMENDATIONS ON DISCONTINUING PROPHYLAXIS/MAINTENANCE THERAPY

Updated guidelines on discontinuing OI prophylaxis or maintenance therapy were recently developed by the USPHS/IDSA (see sidebar, page 11). The guidelines suggest that primary prophylaxis for PCP and MAC disease and chronic suppressive therapy for CMV disease can be withdrawn in the context of CD4+ cell count increases to more than 200 cells/µL for PCP and more than 100 cells/µL for MAC and CMV. There are insufficient data to support recommendations regarding withdrawal of secondary prophylaxis for PCP, MAC disease, and systemic fungal disease. A number of clinical trials are evaluating discontinuation of prophylaxis or maintenance therapy (Table 1, page 10). These trials may provide more definitive data on risk associated with treatment withdrawal. Patients currently having primary prophylaxis or maintenance therapy withdrawn should be closely monitored. Patients discontinuing MAC maintenance therapy should be followed for symptoms and probably do not need to be routinely followed with blood cultures in the absence of symptoms. Patients having primary PCP prophylaxis withdrawn should also be followed for signs and symptoms, as should patients discontinuing maintenance therapy for cryptococcosis. Frequent ophthalmologic exams should be performed in those discontinuing maintenance therapy for CMV retinitis. Some practitioners are using CMV polymerase chain reaction to detect development of CMV viremia. Since Histoplasma antigen testing results correlate well with risk of recurrence, patients discontinuing histoplasmosis maintenance therapy should be followed by periodic testing.

Dr Aberg is Assistant Professor of Medicine at the University of California San Francisco and Co-Principal Investigator at the AIDS Clinical Trials Unit at San Francisco General Hospital.

SUGGESTED READING


(Continued)
SUGGESTED READING (CONTINUED)


METABOLIC COMPLICATIONS OF ANTIRETROVIRAL THERAPY

Characteristics of metabolic complications observed in patients receiving potent antiretroviral therapy were discussed at the Cleveland course by Steven K. Grinspoon, MD.

The body fat abnormalities and metabolic derangements that constitute the so-called "HIV lipodystrophy syndrome" were initially reported in patients receiving protease inhibitor-containing antiretroviral regimens. However, the metabolic abnormalities associated with HIV-1 disease have also been reported in protease inhibitor-naive patients, suggesting a complex pathophysiologic mechanism related only in part to protease inhibitor therapy. The syndrome is characterized by (1) changes in body composition ("fat redistribution"), including dorsocervical fat deposits (buffalo hump) and truncal obesity, facial and peripheral fat atrophy, and breast enlargement in women; (2) insulin resistance and hyperglycemia; and (3) lipid abnormalities ("dyslipidemia") including hypertriglyceridemia and reduced high-density lipoprotein (HDL) levels. However, there is significant heterogeneity in the presentation of HIV lipodystrophy syndrome, with variable prevalence estimates depending on the definition of the syndrome. One group has reported a prevalence of 83% among patients receiving protease inhibitors based on self-reporting and clinical examination, whereas others have reported prevalence rates of 12% based on dual-energy x-ray absorptiometry (DEXA) scans. A prevalence rate of 16% was shown in women based on self-assessment in a preliminary study. At the current time, no consensus exists for the most appropriate terminology to describe and define the metabolic changes and body fat abnormalities that have been observed.

Figure 1. Insulin sensitivity among HIV-seronegative controls (n=180) and patients with HIV infection receiving antiretroviral regimens containing a protease inhibitor (+PI; n=13) or not containing a protease inhibitor (-PI; n=61). Adapted from Walli R, et al. AIDS. 1998.

POTENTIAL PATHOPHYSIOLOGIC MECHANISMS

A number of mechanisms have been proposed to account for HIV lipodystrophy syndrome. Carr and Cooper have posited that abnormalities in fat redistribution result from protease inhibitor suppression of chylomicron and triglyceride uptake by the endothelial lipoprotein-related peptide (LRP)-lipoprotein lipase complex and inhibition of CRABP-1 (cis-retinoic acid binding protein-1)-mediated adipocyte differentiation and apoptosis, resulting in increased peripheral fat deposition and redistribution. However, a number of other groups have observed the syndrome in protease inhibitor-naive patients. It has thus been suggested that pathophysiologic mechanisms may include interaction of underlying metabolic abnormalities due to HIV disease itself and weight gain resulting from potent antiretroviral therapy. For example, hypertriglyceridemia has long been associated with HIV disease, and may worsen in association with weight gain and use of potent therapy.

Other potential mechanisms contributing to the observed metabolic abnormalities in HIV lipodystrophy syndrome include the effects of cytokines and/or hormonal factors. The buffalo hump and centripetal fat deposition observed in the syndrome are similar to the clinical picture of Cushing's syndrome, which is associated with hypercortisolism. The association of the syndrome with elevated cortisol levels, however, remains unclear, with some studies indicating elevated serum and urine cortisol levels and other studies indicating primarily normal levels and appropriate...
suppression testing in patients with borderline elevated cortisol levels. It is currently unknown whether, in the absence of systemic cortisol elevations, there are abnormalities in regional cortisol metabolism in affected patients.

INSULIN RESISTANCE AND HYPERGLYCEMIA

Hyperglycemia was previously observed in patients with HIV disease primarily in association with pentamidine or megestrol acetate use. The recent increase in prevalence of hyperglycemia is associated with use of potent antiretroviral therapy, with one study documenting fasting blood glucose levels above 120 mg/dL in 14% of patients receiving protease inhibitor-containing regimens. Further, impaired glucose tolerance was detected by oral glucose tolerance testing in 41% of patients on protease inhibitor-containing regimens. Insulin sensitivity in those taking protease inhibitor-containing regimens was significantly lower than in patients not receiving protease inhibitors or in HIV-seronegative controls (Figure 1).

Increased truncal fat may account for the insulin resistance observed in HIV-infected patients on potent antiretroviral therapy. In a recent study by Hadigan and colleagues of 75 HIV-infected women, fasting morning insulin levels were significantly higher in the HIV-infected patients compared with body mass index (BMI)-matched noninfected controls. No difference in insulin levels was observed between patients who had received a protease inhibitor and those who had not, or between patients who were less than 90% or more than 90% of ideal body weight, both of whom exhibited elevated insulin levels compared with controls. However, insulin levels were most significantly elevated in those patients with truncal adiposity (>2 standard deviations from controls in the relative ratio of trunk fat to extremity fat) (Figure 2). These findings suggest (1) the presence of underlying metabolic abnormalities in HIV-infected patients, and (2) that the degree of truncal obesity may be a primary determinant of fasting hyperinsulinemia in HIV-infected women. The available data thus indicate that relative truncal adiposity occurs even in patients not receiving protease inhibitors and may make patients prone to the metabolic effects of these drugs.

TRIGLYCERIDE AND LIPID ABNORMALITIES

Prior to the era of potent antiretroviral therapy, hypertriglyceridemia was commonly observed among HIV-infected patients and was shown to result from increased production of very low density lipoprotein and decreased triglyceride clearance. Correlation of hypertriglyceridemia and interferon levels suggest a potential cytokine-mediated mechanism for hypertriglyceridemia in HIV disease. In the setting of potent antiretroviral therapy, however, the frequency of lipid abnormalities has greatly increased. Hypertriglyceridemia is more common than hypercholesterolemia in this setting and is often associated with decreased HDL levels, with data indicating a sequential increase in triglyceride levels over 12 months of protease inhibitor-containing treatment. Other data indicate that of the currently available protease inhibitors, ritonavir is associated with greater severity of hypertriglyceridemia, with decreasing comparative effects observed for ritonavir/saquinavir, nelfinavir, indinavir, and

![Figure 2. Fasting morning insulin levels in HIV-seronegative controls (C; n=20) and HIV-infected patients (HIV; n=70) and according to whether HIV-infected patients had <90% (n=21) or >90% (n=49) ideal body weight, had truncal obesity (+TR; n=13) or not (-TR; n=57), and were receiving (+PI; n=16) or not receiving (-PI; n=54) a protease inhibitor. Adapted from Hadigan C, et al. Fasting hyperinsulinemia and changes in regional body composition in human immunodeficiency virus-infected women. J Clin Endocrinol Metab. 1999;84:1932-1937. Copyright The Endocrine Society.]

NS indicates not significant.
** P<0.01; *** P<0.001, patients versus controls; +++P<0.001, patients with versus patients without truncal adiposity.
saquinavir, in that order (Figure 3). One study has documented changes in lipid levels within 3 months of initiating protease inhibitor treatment, with less severe changes in patients receiving non-protease inhibitor-based regimens. It has also been shown that lipid abnormalities in patients receiving potent antiretroviral regimens correlate with central adiposity. Taken together, these data suggest exacerbation of hypertriglyceridemia due to protease inhibitor therapy in HIV-infected patients, which may result from increased truncal adiposity or direct effects of protease inhibitor therapy on lipid metabolism.

CLINICAL MANAGEMENT

Hyperglycemia/Insulin Resistance

Management of the metabolic abnormalities must be individualized for each patient and consideration must be made of the virologic as well as immunologic status of the patient. An option in the case of hyperglycemia is switching antiretroviral drugs. Preliminary data indicate that nelﬁnavir is less frequently associated with hyperglycemia than other protease inhibitors. However, the glycemic effects of protease inhibitor therapies may relate to their relative antiretroviral potencies. At the current time, insufficient data are available to recommend switching antiretroviral therapy based on metabolic abnormalities. Dietary measures such as restriction of total calorie and carbohydrate intake may also be effective. For patients with severe hyperglycemia, use of oral antidiabetic drugs or insulin may be necessary. Preliminary data indicate the potential utility of insulin-sensitizing drugs to reduce insulin levels and truncal fat in HIV lipodystrophy syndrome. The efficacy of insulin-sensitizing drugs in the syndrome is now being assessed in clinical trials.

Lipid Abnormalities

In the case of lipid abnormalities, discontinuation or switching of protease inhibitors is a potential management option, although the time course to return to normal lipid levels has not been well de-

fixed. In addition, determination of whether treatment for lipid abnormalities is warranted should take into account the fact that long-term complications of hyperlipidemia in HIV-infected patients remains undefined. Excessively high triglyceride levels are associated with risk of pancreatitis. It may thus be prudent to initiate treatment with lipid-lowering drugs if triglyceride levels are above 750 mg/dL. Gemfibrozil was shown to produce moderate decreases in cholesterol (104 mg/dL) and triglycerides (635 mg/dL) in 15 patients with initial cholesterol levels of nearly 400 mg/dL and initial triglyceride levels of greater than 1800 mg/dL (Figure 4); newer ﬁbric acid derivatives may also prove effective in this regard. Niacin may be effective in lowering triglyceride levels but may increase glucose levels and is associated with flushing and liver abnormalities. HMG-CoA reductase inhibitors have a greater effect on cholesterol than on triglycerides, and may be useful in patients with elevated levels of both; these drugs may also exhibit potent effects when used in combination with gemﬁbrozil. In a recent study, the combination of gemﬁbrozil 600 mg twice a day and atorvastatin 10 mg daily resulted in a 30% decrease in cholesterol level and 60% decrease in triglyceride level after 6 months in patients with baseline cholesterol and triglyceride levels of 314 mg/dL and 1359 mg/dL, respectively. In the same study, patients with less severe hypercholesterolemia (mean, 245 mg/dL) and hypertriglyceridemia (mean, 269 mg/dL) exhibited reductions of 11% in cholesterol level and 21% in triglyceride level with a 6-month diet and exercise program. Monitoring of muscle enzymes is recommended with combination HMG-CoA and ﬁbric acid therapy. Few data on the effects of dietary measures alone are available.

Body Composition

As with other aspects, the decision regarding treatment of body composition changes must be made with consideration of the potential advantages and disadvantages of changing antiretroviral treatments. Observation may be appropriate if there is no signiﬁcant morbidity associated with the body composition changes. In this regard, long-term data are not yet available on the consequences of fat redistribution in HIV lipodystrophy syndrome. Liposuction has been used to remove fat from dorsocervical fat deposits; fat supplementation has also

Figure 3. Changes in cholesterol and triglyceride levels in 232 patients receiving ritonavir (RTV), ritonavir/saquinavir (RTV/SQV), neﬁnavir (NFV), indinavir (IDV), or saquinavir (SQV). Courtesy of F Chang, Los Angeles, CA.
Metabolic Complications

occasionally been used in patients with facial wasting, but results have tended to be poor, with the reemergence of fat atrophy. Use of anabolic steroids to reduce fat is currently being investigated. Testosterone reduces fat and builds muscle mass in hypogonadal HIV-infected men. However, the safety and effectiveness of testosterone treatment in eugonadal patients, who would likely constitute the majority of men with the syndrome, have not been established; the effects of testosterone treatment in this setting currently are being investigated in clinical trials. The oral anabolic steroid oxandrolone was associated with significant hepatotoxicity at doses greater than 20 mg/d in one study, and thus far no clinical trial data on its efficacy in reducing fat are available; testosterone and other anabolic steroids may also lower HDL levels. Growth hormone has also been used to reduce overall fat mass in a small number of

![Graph showing changes in cholesterol and triglyceride levels](image)

Figure 4. Changes in cholesterol and triglyceride levels in 15 patients receiving gemfibrozil. Courtesy of K Henry, MD, St. Paul, Minnesota.

The safety and effectiveness of testosterone treatment of body composition changes in eugonadal patients have not been established and are currently being investigated

months, high doses of recombinant human growth hormone (4 to 6 mg) resulted in a 25% to 75% reduction in buffalo hump and abdominal girth with no change in total body fat; no effects on peripheral lipodystrophy or lipid levels were observed, and no data on effect on glucose levels were reported. Use of such high doses of growth hormone may have been motivated by findings of growth hormone resistance in patients with HIV-associated wasting; however, growth hormone resistance has not been shown in patients with HIV lipodystrophy. Study of lower growth hormone doses that may reduce fat without adversely affecting insulin resistance is necessary.

Changing Antiretroviral Regimens

A number of small preliminary studies have assessed the effects of changing the antiretroviral regimen in patients with the syndrome. In one study, discontinuation of protease inhibitors in 20 patients, 16 of whom substituted the NNRTI nevirapine, was associated with improvements in triglyceride and cholesterol levels and insulin resistance (but not HDL levels) after 3 months. Plasma viral load remained below the limits of detection in 11 of 15 patients for whom measurements were available. In an additional 12 patients switching to nelfinavir from indinavir or ritonavir/saquinavir, no improvement in these measures was observed. In another study, 23 patients with CD4+ cell counts less than 200/µL receiving 2 nRTIs plus a protease inhibitor replaced the latter with nevirapine. After 7 months, cholesterol level had decreased by 21%, triglyceride level by 56%, glucose level by 16%, and insulin level by 46%, and suppression of viral load was maintained during nevirapine therapy. However, only minor changes in fat distribution were observed. In a study in 13 indinavir-treated patients with plasma HIV RNA levels below 500 copies/mL, substitution of efavirenz for a protease inhibitor resulted in increased weight, decreased abdominal girth, and decreased glucose levels, but increased triglyceride and cholesterol levels, with continued suppression of viral load. Although available data thus suggest that there may be some benefit in switching from protease inhibitor-containing regimens, determination of the virologic consequences and effects on metabolic and body composition abnormalities of switching antiretroviral therapy requires longer-term study in additional trials.
CONCLUSIONS

The metabolic abnormalities being observed are related in part to the effects of protease inhibitors, and also to metabolic derangements from HIV disease itself. In addition to the distress caused by body composition changes and other short-term morbidity, there is concern that many of the abnormalities may be associated with long-term morbidity. Studies of the long-term consequences of HIV lipodystrophy syndrome have not yet been performed. However, in non HIV-infected populations, hyperlipidemia, truncal obesity, and insulin resistance are known to be associated with increased cardiovascular morbidity and mortality. Early cardiovascular morbidity has been reported anecdotally among patients with HIV disease. There is thus an important need for continued research on the syndrome to clarify the pathophysiologic mechanisms involved and to develop effective therapeutic strategies.

Dr Grinspoon is Assistant Professor of Medicine at Harvard Medical School and Assistant Program Director, General Clinical Research Center, MIT.

SUGGESTED READING


SUGGESTED READING (CONTINUED)


HIV IN AFRICA: EPICENTER OF THE GLOBAL PANDEMIC

The epidemiology of HIV-1 infection and the divergence of viral subtypes occurring in sub-Saharan Africa were discussed at the San Francisco course by David A. Katzenstein, MD.

There is persuasive evidence that HIV originated in primates in central Africa. Researchers have isolated viruses similar to HIV-1 from chimpanzees and to HIV-2 from sooty mangabees. Available serologic evidence indicates that HIV-1 was present in humans in central Africa in the 1960s; numerous hypotheses regarding the migration and global spread of virus thereafter have been put forward, including the role of international travel in the spread of the HIV-1 B subtype that predominates in the United States and Europe and among infected homosexual men and intravenous drug users. Figure 1 shows the estimated numbers of adults and children living with HIV-1 infection as of the end of 1998; sub-Saharan Africa accounts for nearly two-thirds of these cases and more than 5 million new infections are projected to occur this year. Figure 2 shows the proportional increase in global HIV prevalence rates between 1994 and 1997. Figure 3 shows the spread of HIV infection and increase in prevalence rates between 1982 and 1997 in sub-Saharan Africa, with cases clustering around Lake Victoria initially and spreading outward thereafter.

The impact of HIV infection in sub-Saharan Africa has been catastrophic, with more than 10 million deaths from HIV disease. Life expectancy has undergone a sharp reduction in many countries as a result of mortality from HIV in both children and adults, returning to levels present before the institution of immunization and other public health programs. Figure 4 (see page 22) shows the estimated impact of HIV-1 disease on mortality in children less than 5 years old in selected countries.

In many countries, obstetric and prenatal clinic programs have provided a great deal of epidemiologic data on HIV, which indicate that the epidemic is not increasing at equivalent rates in all countries. Seroprevalence rates among pregnant women in areas in East Africa and West Africa appear to increase more gradually than rates in the southern cone of the continent. In some of these areas, seroprevalence exceeds 30% in prenatal clinic populations. A recent finding indicating that pregnancy rates in Uganda are lower among HIV-1-infected women (14.2%) than among uninfected women (21.4%) suggests that estimates of seroprevalence in women of childbearing age may be underestimated by prenatal clinic
**Behavioral Factors Associated with Rapid Heterosexual Spread of HIV in Africa**

**Transport and Work Patterns**

Drivers often purchase sex along overland truck routes through East Africa. Large numbers of men, separated from their families and working in mines and factories, may be housed adjacent to their work place in “single men’s hotels” encouraging concomitant (sexual) partnerships with a small group of commercial sex workers.

**Migration**

Movement from rural to urban areas because of employment opportunities or agricultural disaster has led to loss of traditional structures of monogamy and polygamy and enforcement of sexual taboos. Incursions of armies and guerrillas and mass migration of civilian populations in civil war contribute to a breakdown in traditional sexual relationships.

**Demographics**

The majority of the population in Africa is under the age of 15. Large numbers of women entering adolescence may seek (or be sought by) older male sexual partners (who have a high prevalence of HIV infection). The average age of first pregnancy in most African countries is 17 to 18, suggesting many young women are sexually active.

**Sexually Transmitted Diseases**

Acquisition of gonorrhea, syphilis, chancroid, and herpesvirus are associated with risk for HIV infection.

**Sexual Networks**

Sexual networks map the numbers of concomitant or serial sexual relationships within a community or group. The example of the small number of commercial sex workers who supply sexual services to a large community of men working in mines and factories has been examined as a model that may lead to high prevalence of HIV among sex workers and their male partners.

Other data indicate that more than 25% of men and women in their 20s are infected in Zimbabwe, Malawi, Rwanda, Burundi, parts of South Africa, Zambia, and Botswana. Among sexually transmitted disease patients, commercial sex workers, the military, and the police, infection rates of greater than 50% are common.

It remains unclear to what degree the rapid spread of the epidemic in Africa is associated with ecologic factors—the environmental and behavioral dynamics in societies—and with biologic factors—the pathogenetic and genetic factors in both host and virus. Ecologic factors include transport routes, migration, changes in demographics, and influence of sexually transmitted diseases and sexual networks (see sidebar). Biologic factors include human and viral genetic variation and diversity of immune response. However, it is known that a large diversity of viral subtypes has emerged, and it is becoming increasingly clear that such factors as cellular tropism, viral regulatory genes, and the contribution of other infections to viral shedding and susceptibility to infection may play a role in the dynamics of HIV infection in Africa.

Currently, there are 10 known subtypes of HIV-1, designated as A through J, in the major (M) group. These subtypes differ from each other by more than 10% in nucleoside sequences for the viral envelope, the key region for cellular receptor binding. They are more closely related to each other, however, than they are to the outlier subtypes O and N of HIV-1 and the more distantly related HIV-2. Many of these major subtypes are present in Africa. Whereas most infected homosexual men in North and South America, Europe, and Australia are infected with the subtype B virus, this subtype is relatively infrequent in Africa. Heterosexual transmission of infection has been predominantly associated with subtypes A, C, D, and E. Most of the isolates from infected individuals in Uganda, Kenya, and equatorial West Africa are subtypes A or D, with subtype C consti-

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**Figure 3.** Spread of HIV infection and increase in prevalence rates between 1982 and 1997 in sub-Saharan Africa. Courtesy of UNAIDS, http://www.unaids.org.

... tuting a minority. Subtype C, however, is the predominant viral subtype throughout southern Africa (Figures 5 and 6), where infection rates are increasing most rapidly, and in Ethiopia. This subtype has also recently entered India and China, where it can be expected to be the dominant virus in the coming years. Research by Van Harmelen and colleagues in South Africa has shown that the infecting virus in the white homosexual community is predominantly subtype B, whereas subtype C predominates among black and colored men and women with heterosexual risks. This phenomenon, suggesting separate epidemics for different viral subtypes, has also been observed in Thailand, with separate epidemics of B and E subtypes in separate groups. HIV-2 appears to have remained relatively confined to parts of West Africa and Portuguese-speaking African nations.

Zimbabwe has the second-highest prevalence of HIV-1 infection in the world, after Botswana, both involving infection with subtype C virus. In Zimbabwe, among a population of 10 to 12 million, seroprevalence studies indicate infection rates of 1.0% and 0.3% in 17- to 20-year-old female and male blood donors, 18% to more than 30% in prenatal women, 15% to 30% in factory workers, 90% in commercial sex workers, 60% to 75% in sexually transmitted disease patients in city clinics, and 66% to 80% in tuberculosis inpatients.

Differences in HIV prevalence within Africa may be explained by behavioral or biological factors. A recent study by Kanki and colleagues provides evidence that subtype C virus infection may lead to more rapid disease progression compared with other viral subtypes. The study found that in Senegal, where subtype C virus is still a minority subtype, women infected with subtype C virus exhibited a more rapid progression to AIDS compared with women who acquired infection with other subtypes (Figure 7). It should be noted, however, that cross-sectional studies comparing prevalent infection with subtypes A, B, C, and D among Swedes and Africans in Sweden did not find a difference in disease severity. A study of the shedding of HIV in semen, conducted by Cohen and colleagues in Malawi, provides another example of a possible difference between subtype C and other subtypes. It showed that the presence of gonococcal urethritis in males is associated with higher seminal HIV virus load, with a significant decrease in viral shedding being observed after antibiotic treatment. Comparing the levels of viral RNA detected in semen in

Figure 5. Distributions of subtypes by region in serologic studies. Adapted from Janssens W, et al. The puzzle of HIV-1 subtypes in Africa. AIDS. 1997; 11:705–712.
men in Malawi before and after treatment, it was further observed that seminal viral load in those with subtype C virus is strikingly higher than that observed in subtype B infection, although these comparisons are made across studies in Africa and Europe.

A distinct feature of subtype C viruses has been identified in the structure of the regulatory region of the long-terminal repeat, which may explain the increased levels of genital virus in association with sexually transmitted disease in subtype C infection. Studies of subtype C isolates from Ethiopia, Zimbabwe, and Botswana demonstrate repeated NF-κ binding sites in a pattern that is distinct from other subtypes. Subtype C virus have 3 or sometimes 4 κ-B binding sites in the long-terminal repeats. In vitro, these result in increased transcription in response to cellular activation by tumor necrosis factor-α and other inflammatory cytokines that increase cellular NF-κ-B activity.

Subtype C isolates are also different in their nearly exclusive use of CCR5 as a coreceptor as the predominant second receptor with CD4 for viral entry. In several studies of subtype C, including patients with advanced HIV disease, nearly all subtype C isolates were CCR5-tropic (X5 viruses), while in advanced disease it is common in subtypes A, B, and D infection to find a phenotypic switch to CXC4 (X4) tropism.

In addition to potential viral factors underlying the establishment of subtype C infection in a population of more than 100 million people south of the equator, there are a number of other factors that may explain the rapid spread of HIV-1 infection. These include frequency of multiple sexual partners; attitudes, practices, and beliefs regarding condom use; and the role of patriarchy and disempowerment of women. In addition, spousal separation may be involved; men move away from their families to work for heavy industries and mining operations in urban areas, and the concentration of men living apart from their families encourages casual sexual partnerships and commercial sex provided by a relatively small number of women. Additional biologic risk factors include the prevalence and incidence of sexually transmitted diseases and genital ulcers; circumcision practices; prevalence of bacterial vaginosis; and the use of intravaginal agents and practice of “dry” vaginal intercourse.

Effective prevention of HIV-1 infection in Africa depends on education, counseling, testing, provision of condoms, and the treatment of other sexually transmitted diseases. The institution of programs for prevention depends largely on local initiatives and conditions. In some countries, programs targeting sex workers or other segments of the population have resulted in demonstrable benefits in reducing transmission rates. However, the only real hope for widespread prevention in the foreseeable future is the development of an effective vaccine; this endeavor is itself fraught with formidable obstacles, including the genetic variability of HIV-1. Overall, there are enormous challenges inherent to providing prevention and treatment services in countries that are among the poorest in the world. The HIV pandemic is likely to prove the severest test of global cohesion and cooperation across economic and social divides in the coming century.

Dr Katzenstein is Associate Professor of Medicine at Stanford University.
Suggested Reading


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IDSA INTERACTIVE SESSION

International AIDS Society–USA Interactive Session at the IDSA 37th Annual Meeting: Antiretroviral Therapy Decision Making in the Combination Therapy Era

Philadelphia, Pennsylvania, Saturday, November 20, 1999
5:15 PM to 7:15 PM

Chairs: Constance A. Benson, MD, and Paul A. Volberding, MD

Faculty: Judith A. Aberg, MD, Scott M. Hammer, MD, Victoria A. Johnson, MD, Michael S. Saag, MD, and Robert T. Schooley, MD

The session is co-sponsored by the IAS–USA and the IDSA. Topics will include initial therapy, opportunistic infection prophylaxis, current complications of HIV, strategies for antiretroviral failure, and resistance testing. Expert faculty will use clinical decision points as a springboard for discussion of new data. Open to all participants of the IDSA meeting.

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