

A publication of the
International AIDS Society-USA

IMPROVING THE MANAGEMENT OF HIV DISEASE

IN THIS ISSUE—

Recent Advances In...

- **Prevention and Treatment of Perinatal HIV Infection**
- **Kaposi's Sarcoma-associated Herpesvirus**
- **Complementary Therapies for HIV Disease**

Plus...

- **A State-of-the-Art Review of HIV Resistance to Antiretroviral Drugs**
- **Clinical Guidelines for Antiretroviral Therapy for HIV Infection: Special Insert**

VOLUME 4 ISSUE 3

SEPTEMBER 1996

International AIDS Society-USA

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In This Issue

This issue of *Improving the Management of HIV Disease* highlights selected presentations from the International AIDS Society-USA advanced courses in Atlanta, San Francisco, and Chicago. Dr Yvonne J. Bryson presents an update on maternal-fetal transmission of HIV infection, with an emphasis on prevention with zidovudine for HIV-infected mothers during pregnancy and delivery and for the newborn, and on early intervention with potent combination therapy for HIV-infected infants. In her update, Dr Bryson also highlights advances made in identifying the risk factors associated with vertical transmission and with disease progression in HIV-infected infants. Dr Donald E. Ganem summarizes recent findings on the etiology and pathogenesis of Kaposi's sarcoma (KS), highlighting the association of the herpesvirus with KS. And Dr Donald I. Abrams and Dr Charles Steinberg discuss complementary approaches currently in use and under investigation for HIV disease, as well as the controversies regarding their use.

As a supplement to the summaries from the IAS-USA courses, this issue includes a state-of-the-art review article by Drs Stefano Vella and Marco Floridia on HIV resistance to antiretroviral drugs, in which they discuss the general mechanisms of and the latest findings on viral resistance to nucleoside and nonnucleoside reverse transcriptase inhibitors, protease inhibitors, as well as resistance in combination therapy. Drs Vella and Floridia highlight our current understanding of and the progress made in delaying, suppressing, and reversing viral resistance, and the implications of complex viral resistance patterns for the care of patients with HIV/AIDS—all of which appear to underscore the importance of initiating treatment early in the course of infection when the virus is most homogeneous to induce and maintain maximal viral suppression and to help prevent the emergence of resistant viral strains.

Finally, this issue includes a reprint of the clinical recommendations for use of currently (mid 1996) available antiretroviral drugs in HIV-infected persons. When to start therapy, what to start with, when to change therapy, and what to change to are addressed. A 13-member panel representing international expertise in antiretroviral research and HIV patient care was convened by the International AIDS Society-USA, and the recommendations of the panel were published in the July 10, 1996, issue of *The Journal of the American Medical Association*.

A Special Welcome...

The International AIDS Society-USA is pleased to announce the appointments of Constance A. Benson, MD, and Peter C. Cassat, JD, to its Board of Directors. Renowned for her research in infectious diseases, especially in the pathogenesis, prevention, and treatment of opportunistic infections in HIV-infected persons, Dr Benson, Associate Professor of Medicine at Rush Medical College in Chicago, has made significant contributions to the field of HIV disease. Dr Benson has been involved in the educational efforts of IAS-USA since the formation of the organization, and her contributions have helped to further the mission of the IAS-USA. Mr Cassat, Associate General Counsel with *U.S. News & World Report* in Washington, DC, generously donated his time and efforts to help the IAS-USA receive its 501(c)(3) not-for-profit status during the initial formation of the organization, and he has continued to provide guidance on corporation and legal issues.

Dr Benson and Mr Cassat, welcome to the IAS-USA Board of Directors!

About The International AIDS Society-USA

The International AIDS Society-USA (IAS-USA) is a 501(c)(3) not-for-profit organization committed to improving the treatment, care, and quality of life of persons with HIV disease by providing balanced and relevant information to physicians. The IAS-USA programs are particularly intended to bridge clinical research and patient care. This publication is part of the ongoing efforts by the International AIDS Society-USA to provide information for physicians involved in HIV/AIDS care.

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Reprint of Carpenter CCJ et al for the International AIDS Society-USA. JAMA. 1996;276:146-154.

ADVANCES IN THE PREVENTION AND TREATMENT OF PERINATAL HIV INFECTION

Recent information on the prevention and treatment of perinatal HIV infection was discussed at the Chicago conference by Yvonne J. Bryson, MD, from the University of California, Los Angeles School of Medicine. In her presentation, Dr Bryson highlighted advances in our knowledge of the risk factors associated with vertical transmission and with disease progression in HIV-infected infants.

In the US and around the world, the majority of pediatric HIV infection occurs by maternal-fetal transmission, with transmission rates varying by population and geographic area. In the US and Europe, the transmission rates in women not treated with antiretroviral therapy are estimated at 25% to 30%, and at 13%, respectively. In Africa, HIV transmission rates were estimated at 40% by epidemiological studies earlier in the epidemic; however, more recent studies using better methods for early diagnosis of HIV in infants have reported transmission rates of approximately 25%. Heterosexual transmission of HIV is the most common route of transmission to women worldwide, and at present intravenous drug use is the most common risk factor among HIV-infected pregnant women in the United States. The number of women with HIV disease continues to rise, and as it does, the incidence of perinatal HIV infection is expected to increase if no intervention is employed.

As demonstrated in the AIDS Clinical Trials Group (ACTG) protocol 076, zidovudine given to HIV-infected pregnant women during gestation and at delivery who were previously untreated with antiretroviral drugs and to the infant during the first six weeks of life reduced perinatal transmission by approximately 70%. In this study, the transmission rate was 25.5% in the placebo group and 8.3% in the zidovudine-treated group. The reduction in transmission is most likely achieved by either or both of the following mechanisms: reduction of maternal viral load and prophylaxis of the fetus and infant.

The results of ACTG 076 provided proof of concept that vertical transmission can be significantly reduced with the use of antiretroviral therapy. Zidovudine has become the current antiretroviral drug of choice in the US for pregnant women with HIV to prevent perinatal transmission. Based on this concept, with the recent availability of new and more potent antiretroviral drugs, investigators expect to be able to reduce perinatal transmission even further, with a goal of less than 2% transmission. However, a number of key questions remain: Which specific aspects, if any, of this multifactorial process can be used to help predict those women who are at highest risk for transmitting the virus? Why do more than 70% of infants born to untreated HIV-infected women avoid infection themselves? At what point during gestation and delivery and by what means is transmission most likely to occur? Is there an increased risk associated with early breast-feeding? Ongoing international studies have been designed to address the relative importance of prenatal, intrapartum, and postpartum drug administration and other practical and cost-effective prevention strategies in reducing vertical transmission and the results will help to identify optimal approaches for its prevention.

Risk Factors Associated with Vertical Transmission of HIV

Risk factors and the timing of HIV infection. Viral, immunologic, and clinical factors in both the mother and the infant all play a role in the multifactorial process of vertical transmission of HIV disease. These factors, and, therefore, the efficacy of different interventions vary according to the timing of transmission. There is evidence supporting transmission before birth (in utero), during labor and delivery (intrapartum), and after birth (postpartum: breast-feeding). (See Table 1.) In non-breast-fed infants, the working definition of transmission in utero is based on a positive culture and/or polymerase chain re-

action (PCR) assay in infants within 48 hours of life. Intrapartum transmission is defined by a negative culture and DNA-PCR assay in infants within 48 hours of life and by a positive culture and DNA-PCR assay after 48 hours of life and up to 90 days after birth (see Suggested Reading: Bryson et al. *N Engl J Med.* 1992). An HIV-1 DNA-PCR assay was used to assess the relative contribution of intrauterine and intrapartum transmission of HIV in 271 HIV-infected infants. In this study, 38% had a positive DNA-PCR within 48 hours of birth, which is consistent with infection in utero. Within 28 days after birth, 96% of all of the infected infants had a positive DNA-PCR.

Intrauterine HIV transmission. Although the exact timing of in utero infection is unknown, most evidence points to transmission in late gestation in the majority of live-born infants. However, transmission has been documented in the first trimester based on finding HIV in aborted fetuses. A recent study suggested that there may be a higher frequency of HIV infection in spontaneous fetal loss. Risk factors that have been potentially associated with perinatal transmission during gestation include high maternal viral load (see below), decreased CD4+ cell counts, and stage of disease (primary infection and advanced maternal clinical HIV disease). Several small studies have shown that a lack of autologous neutralizing antibody in the mother is associated with a higher risk of perinatal HIV transmission, and that many women who transmit do not have neutralizing antibody to the infant's virus. It is also possible that HIV-infected mothers who do not transmit the virus to their infants may have a broader neutralizing antibody. In a study by Bryson and colleagues, both the presence and titer of autologous neutralizing antibody were decreased in women who transmitted in utero.

Intrapartum HIV transmission. Factors associated with intrapartum transmis-

Table 1. Potential Risk Factors Associated with Perinatal Transmission According to the Timing of Infection.

"In utero" transmission

- Increased maternal viral load (cell-free, cell-associated)
- Advanced maternal clinical disease
- Primary infection during pregnancy
- Lack of neutralizing antibody
- Decreased maternal CD4+ cell count
- Cell-mediated immunity (CTL, CD8+ cell suppression)
- Syncytium-inducing viral phenotype/tropism
- Placental breaks
- Maternal-fetal transfusion
- HIV or other infection of the placenta
- Spontaneous fetal loss

"Intrapartum" transmission

- High maternal viral load
 - In blood (cell-free, cell-associated)
 - In cervicovaginal secretions
- Prolonged ruptured membranes (>4 h)
- Infant exposure to blood/secretions
 - Swallowing
 - Mucous membranes
 - Maternal-fetal transfusion
- Delivery mode (vaginal vs cesarean section)
- Trauma
- Placental factors
 - Abruptio
 - Chorioamnionitis
 - Co-infections
- Infant prematurity
- First-born twin

"Postpartum" transmission

- Breast-feeding
- High risk during primary maternal infection

sion of HIV may also include maternal viral load in both plasma and in cervicovaginal secretions. It is estimated that 30% of HIV-positive women may have virus in cervicovaginal secretions detectable by PCR and/or culture and that these findings may not necessarily correlate with levels of maternal plasma HIV RNA (see Suggested Reading: Nielsen et al. *J Infect Dis.* 1995). HIV has recently been detected in the gastric aspirates of HIV-infected newborns, which may also be a risk factor for infection.

Intrapartum HIV transmission may occur despite the presence of maternal autologous neutralizing antibody. In the study mentioned above, Bryson and colleagues found no significant difference in the mean autologous neutralizing antibody titer in those women transmitting the virus intrapartum compared with that in women who did not receive zidovudine and did not transmit the virus. This suggests that the protective effects of antibody may be overcome and that virus may be transmitted cell to cell or by the oral route. The question of whether the passive transfer of neutralizing antibody can modify viremia and HIV disease course in infants infected intrapartum requires further investigation.

Other factors associated with intrapartum HIV transmission include the mode of delivery, trauma (particularly for premature infants), the duration of ruptured membranes, and placental factors, such as abruptio or coinfections. In the European Collaborative Study, the vertical transmission rate was reduced from 17% (127/727) in vaginal deliveries to 12% (21/172) in elective cesarean sections and to 10% (7/67) in emergency cesarean sections. These findings represent an approximately 50% reduction in vertical transmission of HIV for women undergoing a cesarean section ($P = .005$). This study, however, was not randomized, and other studies have not shown the same results. A recently published study by Landesman and colleagues for the Women and Infants Transmission Study (WITS) group showed that in the absence of antiretroviral treatment there was a significantly increased risk of transmission in women who had ruptured membranes for more than 4 hours regardless of the mode of delivery. There is no current rec-

ommendation for cesarean section for the prevention of perinatal transmission.

Maternal viral load and risk of perinatal transmission. A number of studies have demonstrated that high levels of HIV in pregnant women as measured by several different assays including ICD p24 antigen, HIV-limiting dilution co-culture, DNA-PCR, and plasma HIV RNA have been associated with an increased risk of vertical HIV transmission. Most recently, plasma HIV RNA assays have been shown to be the most sensitive. Plasma HIV RNA levels greater than or equal to 50,000 copies/mL were associated with a more than 50% risk of vertical HIV transmission in one study and were most highly associated with transmission in utero. In a study by Weiser and colleagues, all women (8/8) transmitting HIV had plasma HIV RNA levels at or above 100,000 copies/mL compared with only 2 of 22 women who did not transmit the virus ($P = .001$).

Dickover and coworkers showed that 75% (15/20) of pregnant women transmitting HIV had plasma HIV RNA levels greater than 50,000 copies/mL compared with 5.3% (4/75) of HIV-infected pregnant women who did not transmit the virus ($P < .0001$). The risk of transmission increased with higher plasma HIV RNA levels (Figure 1). The median plasma HIV RNA level at delivery was 94,054 copies/mL for women who transmitted HIV and 4596 copies/mL for those who did not ($P < .0001$).

The maternal use of zidovudine in this cohort significantly reduced maternal plasma HIV RNA levels in the drug-naïve women who did not transmit the virus, with a median six- to eightfold reduction from initiation of therapy to the time of delivery. Several patterns of viral load were observed in this cohort. Women who did not receive zidovudine and did not transmit HIV had stable and consistently low plasma HIV RNA levels. Approximately 50% of the untreated transmitters had unexplained increases in plasma HIV RNA prior to delivery, which points out that a low level of plasma HIV RNA early in pregnancy cannot be used to predict a low risk of vertical transmission. This study also revealed that 4 of 22 HIV-infected women given zidovudine did transmit the virus despite treatment,

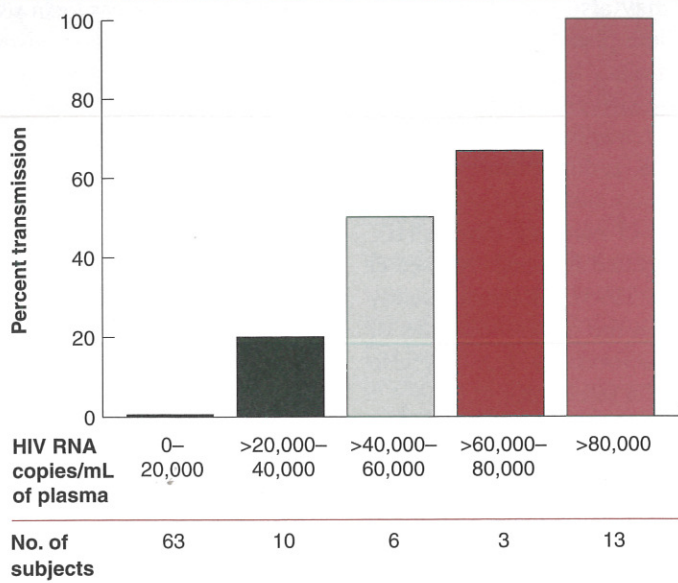


Figure 1. Risk of vertical HIV transmission by maternal plasma HIV RNA level at delivery in a cohort of 95 HIV-infected pregnant women. Adapted with permission from Dickover RE et al. JAMA. 1996; 275: 599-605. Copyright 1996, American Medical Association.

and this finding was associated with high plasma HIV RNA levels at delivery without evidence of zidovudine-resistant virus in maternal or infant samples. According to Dr Bryson, plasma HIV RNA levels in this subgroup were very high and the modest reductions achieved with zidovudine use may not have been enough to significantly reduce maternal viral load or to protect the infant. Since the majority of infants in this study as well as in a recent larger study of more than 180 women did not receive zidovudine after birth, maternal treatment prior to delivery may be most critical.

It is of interest that all of the women with lower plasma HIV RNA levels (less than 50,000 copies/mL) at delivery transmitted intrapartum. Preliminary analysis of plasma HIV RNA levels in women enrolled in the ACTG 076 study revealed that risk of transmission increased with increasing plasma HIV RNA levels; however, transmission occurred in some women with lower plasma HIV RNA levels. At present it is unknown if transmission at lower levels occurred intrapartum and/or resulted from cervicovaginal viral shedding or from other factors related to delivery. The ACTG 076 study also demonstrated that use of zidovudine was associated with reduced vertical HIV transmission in women with all levels of

plasma HIV RNA, underscoring the ability of the drug to protect the fetus and infant from infection by a mechanism other than reduction of maternal plasma HIV RNA levels.

Questions remain about the relationship of plasma HIV RNA levels to vertical transmission. Several recent studies have shown that transmission can occur at lower plasma HIV RNA levels. The question is why and if this transmission may be associated with events at the time of delivery or with other viral factors. It is also premature at this time to identify any specific HIV RNA copy number with risk of transmission since plasma HIV RNA measurements vary. The proper collection and processing of blood prior to assay is also important to avoid loss of HIV RNA. Both the choice of anticoagulant and rapid separation of plasma within 4 to 6 hours will help to ensure accurate results. Collection in heparin will result in a 38% decrease in HIV RNA levels compared with baseline levels in EDTA if processed immediately and a greater than 70% decrease in levels will occur if processing is delayed up to 24 hours. Clearly, a high maternal plasma HIV RNA level is an important risk factor, but it is not the only risk factor. According to Dr Bryson, current data support the use of antiretroviral therapy in pregnant HIV-

positive women at any level of plasma HIV RNA.

Approaches to Preventing Vertical HIV Transmission

At present, antiretroviral therapy is recommended for pregnant HIV-infected women during gestation and delivery, and for infants postpartum. While most research has been conducted with zidovudine monotherapy, proposed trials include studies of a combination of zidovudine/nevirapine during labor and delivery. Phase I trials with a variety of combined antiretroviral drugs are under way, including zidovudine and lamivudine, alone and combined with several of the protease inhibitors, as well as other investigational nucleosides. An efficacy study is planned for early 1997, based on results of these phase I studies. Drug combinations that prove to be safe, well-tolerated, cross the placenta, and maximally reduce maternal viral load will be chosen for this study. Phase I studies of nevirapine have been completed. Owing to its long half-life, a single dose of nevirapine given during labor results in significant drug levels in the infant for 3 days and may help prevent intrapartum transmission. This approach may be very attractive as a practical and cost-effective strategy to reduce intrapartum transmission in developing countries. Outside of the US, various regimens of reduced courses of zidovudine are being evaluated in mother/infant pairs, and in the mother or the infant alone. Studies of zidovudine/lamivudine in combination are also under way in Africa.

Immune-based therapies are also being investigated for use in pregnant HIV-infected women and in infants born to HIV-infected mothers. In the ACTG 185 protocol, pregnant HIV-infected women have been randomized to receive zidovudine and HIV intravenous gamma immunoglobulin (HIVIG) or intravenous gamma immunoglobulin (IVIG). To date, more than 250 women and infants have been enrolled in this efficacy trial. Phase I studies are under way in infants born to HIV-infected women to evaluate broadly-neutralizing monoclonal antibodies, and to evaluate tolerance to and immunogenicity of new vaccines. Studies evaluating a combination of vaccine and antibody therapy are planned.

Local approaches, such as vaginal washing, are also in use outside of the US. A large study in Africa evaluated the effectiveness of vaginal washing at delivery with chlorhexidine in more than 3000 deliveries and found no effect in terms of perinatal transmission. Topical and/or oral treatment of the infant may be other options.

Disease Progression in HIV-infected Infants

Although the majority of perinatally-infected children survive less than eight years, there are long-term pediatric survivors, and significant variation in disease progression and in life span in this population. A number of factors are assumed to effect disease progression, including the timing of perinatal infection, the viral load, the infant's immune response, and the virulence of the virus itself.

In a prospective cohort of 34 HIV-infected infants followed from birth, Dr Bryson and colleagues have conducted ongoing analyses on the risk factors for clinical progression. Rapid progression was defined as the onset of symptoms with disease progression within 6 months, an AIDS diagnosis within 2 years, and a significant and sustained fall in CD4+ cell counts. Slow progression was defined as no symptoms for at least 6 months, stable CD4+ cell counts, and no disease progression for at least 2 years. A third category, intermediate progressors, had early onset of symptoms, a transient fall in

CD4+ cell counts, and no disease progression for 2 or more years. Most infants in this latter category received early antiretroviral therapy. Of the 34 infants followed, 18 were infected in utero (PCR- and culture-positive at birth), 13 intrapartum (PCR- and culture-negative at birth), and 3 had no birth samples available.

Early onset of symptoms and rapid progression was associated with high levels of plasma HIV RNA at birth and during the first 6 months of life, rapid and sustained loss of CD4+ cells, and in utero HIV infection. A peak plasma HIV RNA level greater than 10^6 copies/mL was associated with an onset of symptoms within 6 months ($P = .002$); a persistent level of plasma HIV RNA greater than 10^6 copies/mL was associated with early onset of symptoms ($P = .0002$), a diagnosis of AIDS within 2 years ($P = .003$), and a survival time of less than 2 years ($P < .02$). Those infants with CD4+ cell counts less than $1000/\mu\text{L}$ and those with an age-adjusted CD4+ cell count less than 50% of the normal median were also significantly more likely to experience the onset of symptoms within the first 6 months ($P = .005$).

Early, aggressive antiretroviral therapy in perinatally-infected infants may alter the rate of disease progression, and, subsequently, the long-term prognosis, by reducing viral load and preserving the immune system during this primary infant

infection. Studies using the combination of zidovudine/nevirapine, or the triple combination of zidovudine/didanosine/nevirapine, have produced promising early results, including the ability to reduce the viral load below detectable levels for up to 9 months in some infants. Studies of protease inhibitors in children with HIV are currently under way. Studies of treatment of infants upon diagnosis of HIV with potent combinations of antiretroviral drugs including protease inhibitors to maximally reduce viral load during primary infection are planned.

Summary

There is cause for optimism in the prevention of perinatal HIV infection. Effective antiretroviral therapy can significantly reduce the risk of vertical transmission and clinical trials currently under way will help to identify optimal drugs, doses, and timing. In addition, early intervention in neonatal primary infection may potentially alter disease outcome for those infants who are infected with HIV. Raising awareness, providing education, translating scientific advances into clinical practice, and making effective interventions accessible worldwide remain the greatest challenges.

Yvonne J. Bryson is Professor of Pediatrics at the University of California, Los Angeles School of Medicine.

Suggested Readings

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KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS

Recent findings on the etiology and pathogenesis of Kaposi's sarcoma (KS) and on the association of a novel herpesvirus with KS were discussed at the San Francisco conference by Donald E. Ganem, MD, from the University of California San Francisco.

Characteristics of Kaposi's Sarcoma

Kaposi's sarcoma (KS) is an atypical tumor; indeed, KS should probably not be thought of in the same way as most cancers. Whereas most tumors derive from the clonal outgrowth of a single malignant cell, KS tumors do not appear to evolve in this manner. The exact events involved in their formation remain unclear. In advanced lesions, the predominant cell is the spindle cell. It is now generally believed that spindle cells are of endothelial origin, although precisely where in the endothelial cell lineage these cells originate remains the subject of investigation and debate. Spindle cells lack many of the markers of mature endothelial cells, with a very small percentage (2% to 5%) having the canonical factor VIII marker. Other evidence suggests that spindle cells are heterogeneous: 80% to 85% of these cells are positive for the endothelial cell marker CD34 and a similar proportion is positive for the CD36 marker. However, 5% of spindle cells are positive for smooth muscle actin. Thus it has been proposed that spindle cells may be derived from primitive, bipotential mesenchymal cells that can become either vascular smooth-muscle cells or vascular endothelial cells.

The complexity of KS lesions is underscored by the fact that they contain many infiltrating plasma cells, lymphocytes, and other inflammatory cells, as well as spindle cells. In addition, KS lesions are characterized by a profusion of aberrant slit-like neovascular spaces with extravasated red blood cells. Furthermore, KS often presents in multicentric fashion, with lesions appearing simultaneously at different sites. Kaposi's sar-

coma is also characterized by an unusual propensity for regression or exacerbation, which is again atypical of most cancers. Lesions have been found to regress with reduced immunosuppression in posttransplantation patients and in patients treated with protease inhibitors for HIV disease. Tumors in KS have been reported to progress very rapidly following severe episodes of sepsis or *Pneumocystis carinii* pneumonia (PCP) in patients with HIV disease.

Early studies of the pathogenesis of KS showed that cultured spindle cells require growth factors for their proliferation and that they produce a host of

It has been proposed that spindle cells may be derived from primitive, bipotential mesenchymal cells that can become either vascular smooth-muscle cells or vascular endothelial cells.

growth factors and factors with some angiogenic potential. Interestingly, cultured human spindle cells are nontumorigenic in nude mice: complete involution of these cells occurs within 1 to 2 weeks. However, prior to their involution, these cells lead to the development of lesions consisting of aberrant blood vessels and infiltrating inflammatory cells of murine origin. These neoangiogenic, KS-like lesions resolve following the involution of the human spindle cells. These findings led to the currently favored model of histogenesis in which the proliferation of spindle cells is accompanied by the pro-

duction of growth and angiogenic factors, which in turn, results in the formation of new blood vessels and the presence of plasma cells and lymphocytes.

Role of HIV in KS Pathogenesis

What triggers spindle cell proliferation? Early attention regarding this issue focused on the role of HIV. HIV infection is associated with a 20,000-fold increased risk for KS, and models proposed to explain the role of HIV in KS have greatly influenced studies of KS pathogenesis. In one proposed model, HIV-infected cells produce cytokines and other growth factors (eg, basic fibroblast growth factor and oncostatin M) that trigger the proliferation of spindle cells. The researchers who formulated this model showed that HIV-infected cells also release small quantities of Tat protein, which can bind to cell-surface receptors of the integrin family and stimulate spindle-cell proliferation.

One problem with a model that requires only the effects of HIV infection to induce KS is that KS tracks poorly with HIV infection within the cohort of patients with AIDS. A number of investigations have shown that the prevalence of KS varies in patients with AIDS: 15% to 35% in male homosexuals, 1% to 3% in transfusion recipients and in persons with hemophilia, and less than 1% in children with vertically transmitted HIV disease. This variability in the prevalence of KS suggests the presence of an etiologic cofactor other than HIV, as does the fact that KS occurs in HIV-negative populations, including elderly Mediterranean men, residents of certain areas in Africa, and transplant recipients. The pattern of KS cases in AIDS is most consistent with the cofactor being sexually transmissible.

Association of Human Herpesvirus 8 with KS

Given the epidemiology of KS, a number of research groups began to search for a viral etiologic agent in KS.

The approach that succeeded was to identify viral DNA in KS tissue that was not present in non-KS tissue. Two small exogenous DNA fragments—300 kilobases (kb) and 600 kb in length, respectively—were found to track closely with KS. In one series, these viral markers were found in more than 95% of AIDS patients with KS, in 10% of lymph node samples from AIDS patients without KS, and in no tissue samples from subjects without HIV infection. The DNA sequencing revealed that these DNAs derive from a novel herpesvirus, termed KS-associated herpesvirus (KSHV) or human herpesvirus 8 (HHV8). These DNA sequencing studies have shown that HHV8 is related to the gamma herpesviruses, or lymphotropic herpesviruses, of which the Epstein-Barr virus (EBV) is the best-known agent in humans. However, HHV8 is much more closely related to the simian virus *Herpesvirus saimiri* than to EBV. (The typical host of *H saimiri* is the squirrel monkey in which it causes asymptomatic infec-

Findings indicate that HHV8 infection precedes the clinical onset of KS, suggesting that HHV8 infection is not a superinfection of the KS lesion.

tion. In the related owl monkey, however, this virus causes an aggressive T-cell lymphoma.) It has subsequently been shown that the HHV8 DNA sequences originally found in AIDS-KS tissues are also present in KS tissues from patients without HIV infection.

The association of HHV8 with KS was further supported by findings in a study that used a polymerase chain reaction (PCR) assay for viral DNA in peripheral blood mononuclear cells (PBMCs). This assay is positive for HHV8 in approximately half of patients with KS. Whitby and colleagues tested stored samples of PBMCs from HIV-positive pa-

tients who did not have clinical KS at the time of sampling to examine the relationship between the presence of viral DNA and subsequent development of KS. In a cohort of 143 AIDS patients without KS, 11 subjects had PBMC samples that were positive for HHV8. Of these 11, 55% subsequently developed KS. Of the 132 AIDS patients whose PBMC samples were negative for HHV8, 9% subsequently developed KS. These findings indicate that HHV8 infection precedes the clinical onset of KS, suggesting that HHV8 infection is not a superinfection of the KS lesion.

Subsequent cloning of the HHV8 genome has shown that it is 160 kb in length. Dr Ganem and colleagues are currently attempting to identify the genes produced in the KS tumor as a means of better understanding the pathogenesis of KS lesions. Previous studies of cultured spindle-cell lines indicated that the viral genome was not present in spindle cells, and some investigators speculated that the lymphoid cells in KS were the likely target of HHV8 infection. However, Dr Ganem and colleagues as well as other researchers have found that spindle cells are in fact the *in vivo* target of HHV8 infection. Probes were developed by identifying and cloning the most abundant viral messenger RNA (mRNA) fragments in KS and using them in *in situ* hybridization studies. These investigations showed that there are at least two different transcriptional programs occurring in KS. Most spindle cells (80% to 90%) are latently infected. A minority of these cells (1% to 3%) seem to be lytically infected by HHV8, and, therefore, are likely to be producing virus. The latently infected cells are only expressing a small subset of viral genes, and studies are ongoing to identify all of these genes. The role of the lytically infected subset of cells is at present unclear.

Initial Seroprevalence Findings

Dr Ganem and colleagues have recently developed a system for viral growth in cell culture that will allow a better understanding of HHV8 replication and should facilitate studies of the pathogenesis and epidemiology of KS. Human herpesvirus 8 has been found in AIDS patients with rare B-cell lymphomas (ie,

body-cavity based lymphomas). These lymphomas do not involve bulky lymphadenopathy; instead they are characterized by malignant effusion usually of the pleural space or peritoneum consisting of a monoclonal population of malignant B-cells. It was initially believed that HHV8 was always present with EBV in these

HHV8 infection is not ubiquitous in the general population as are many other herpesviruses, and there is a strong association between markers of sexual activity and acquiring HHV8 infection.

lymphomas; however, recent investigations have shown that HHV8 can be present without EBV in such tumors. A cell line for HHV8 culture has been developed from one of these cases of lymphoma in which EBV was not present. The cells, which replicate *in vivo* as an ascites tumor, grow readily in culture medium.

Using this cell line, Dr Ganem and colleagues have developed an immunofluorescence test for HHV8 antibodies that is not complicated by the presence of EBV antibodies, which are nearly ubiquitous in the population. This assay, which in its current form has been found to detect HHV8 antibody in approximately 85% of AIDS patients with KS, has been used in initial seroprevalence studies. In a cohort of 150 blood donors who were negative for HIV and for hepatitis B and C viruses, Dr Ganem and colleagues found that the prevalence of HHV8 antibody was approximately 1% to 2%. In a group of 120 HIV-negative men with positive Venereal Disease Research Laboratories (VDRL) test results who presented to a sexually trans-

mitted disease (STD) clinic, 8% were found to be positive for HHV8 antibody. In still another cohort of 125 HIV-seropositive men, most of whom were gay, Dr Ganem and colleagues found that 31% were positive for HHV8 antibody. In contrast, only 2% to 3% of 300 HIV-positive persons with hemophilia were found to be HHV8 seropositive. These findings suggest that HHV8 infection is not ubiquitous in the general population (as are many other herpesviruses) and that there is a strong association between markers of sexual activity and acquiring HHV8 infection. In addition, they show a striking link between HHV8 infection and risk of KS. Taken together, the evidence strongly suggests that HHV8 is the sexually transmitted cofactor predicted by the epidemiology of KS.

Implications for Prevention and Treatment of KS

What are the implications of this research for the prevention and treatment of

KS? Clearly, if further evidence confirms that HHV8 infection predisposes a patient to the development of KS, strategies aimed at preventing this infection will assume a high priority. Investigators need to determine which specific practices confer the greatest risk of transmission. With such detailed information not yet available, it seems prudent to add HHV8 to the list of reasons for adhering to current safer-sex guidelines. Development of a vaccine for HHV8 infection will also need to be initiated in parallel. A successful vaccine has been developed for at least one herpesvirus infection (for the varicella-zoster herpesvirus, which causes chickenpox and shingles); thus, success is possible in principle. In practice, however, there are many potential obstacles and development of a vaccine for HHV8 infection is not likely within the next ten years.

An important question concerns the role of antiviral drugs. Since most KS spindle cells are latently infected, it is not likely that conventional antiviral therapy

will have a dramatic effect on established KS tumors, even though available anti-herpesvirus drugs target lytic viral growth. However, it is possible that such therapy could have an impact on the natural history of HHV8 infection in asymptomatic HHV8-seropositive patients. For example, reducing the number of infectious virions may reduce viral spread to susceptible spindle-cell targets. Over time, sustained therapy may reduce the risk of subsequent development of KS. However, it is to be emphasized that at present there is no solid evidence for such a scenario. Moreover, such a regimen would require an orally-active drug with an exceptionally favorable side effect profile, since therapy would presumably have to be protracted. None of the currently available drugs that are active against HHV8 meet this standard.

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Suggested Readings

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**Antiretroviral Therapy for
HIV Infection in 1996
Recommendations of an International Panel**

International AIDS Society - USA

Consensus Statement

Antiretroviral Therapy for HIV Infection in 1996

Recommendations of an International Panel

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Objective.—To provide clinical recommendations for antiretroviral therapy for human immunodeficiency virus (HIV) disease with currently (mid 1996) available drugs. When to start therapy, what to start with, when to change, and what to change to were addressed.

Participants.—A 13-member panel representing international expertise in antiretroviral research and HIV patient care was selected by the International AIDS Society—USA.

Evidence.—Available clinical and basic science data, including phase 3 controlled trials, clinical endpoint data, virologic and immunologic endpoint data, interim analyses, studies of HIV pathophysiology, and expert opinions of panel members were considered. Recommendations were limited to drugs available in mid 1996.

Process.—For each question posed, 1 or more member(s) reviewed and presented available data. Recommendations were determined by group consensus (January 1996); revisions as warranted by new data were incorporated by group consensus (February–May 1996).

Conclusions.—Recent data on HIV pathogenesis, methods to determine plasma HIV RNA, clinical trial data, and availability of new drugs point to the need for new approaches to treatment. Therapy is recommended based on CD4⁺ cell count, plasma HIV RNA level, or clinical status. Preferred initial drug regimens include nucleoside combinations; at present protease inhibitors are probably best reserved for patients at higher progression risk. For treatment failure or drug intolerance, subsequent regimen considerations include reasons for changing therapy, available drug options, disease stage, underlying conditions, and concomitant medication(s). Therapy for primary (acute) infection, high-risk exposures to HIV, and maternal-to-fetal transmission are also addressed. Therapeutic approaches need to be updated as new data continue to emerge.

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IMPORTANT ADVANCES in understanding the biology and treatment of human immunodeficiency virus (HIV) infection have occurred during the past 18 months. As a result, new scientifically sound approaches to therapy have been developed that offer new options for persons with HIV infection. The relevant recent advances fall into 4 major categories: (1) a better understanding of the replication kinetics of HIV throughout all stages of disease; (2) the development of assays to determine the viral load in individual patients; (3) the availability of several new effective drugs; and (4) the demonstration that

combination therapy is more effective than zidovudine monotherapy.

In light of these advances, the recommendations of earlier state-of-the-art guidelines^{1,2} are no longer applicable to clinical decision making in 1996. Therefore, an international panel of clinical investigators experienced in HIV patient care was selected and convened by the International AIDS Society—USA to develop current recommendations for the clinical management of HIV-infected individuals.

The panel addressed 4 central questions about antiretroviral therapy: when to initiate therapy, which types of drugs to use, when to change therapy, and which types of drugs to use when a change in therapy is indicated. In addition, the treatment of primary HIV infection, prevention of vertical transmission, and postexposure prophylaxis were addressed. The recommendations are not solely based on the results of controlled clinical trials with well-defined clinical endpoints. Developing clinical guidelines in the HIV field at this time requires an approach firmly anchored in data from controlled, double-blind clinical trials when available, but must also include information from trials in progress and available virologic and immunologic endpoint data, as well as extrapolations from studies of the pathophysiology of HIV infection. Clinical decisions must be made for best use of up to 8 available antiretroviral drugs, at a time when long-term studies with clinical endpoints have been completed for only a few possible combinations.

The recommendations herein reflect the panel's agreement on the importance of plasma HIV RNA measurements for predicting risk of clinical progression as well as of the recent demonstration from clinical trials of combination therapies that reductions in plasma HIV RNA

levels are associated with increased survival and decreased progression to AIDS. The recommendations do not provide precise algorithms for treatment of specific clinical situations, because available data do not define a single first-line regimen for any given indication. Acknowledging the paucity of clinical trial experience with some drug combinations and with all of the newly available protease inhibitors, the goal of the recommendations is to provide enough information to permit rational decisions for regimens and strategies in mid 1996.

INITIATING ANTIRETROVIRAL THERAPY

Background

Recent data have shed important light on the virologic and immunologic dynamics of HIV infection (reviewed in reference 3). Early infection of lymphoid tissue,^{4,5} with continuous high-level viral replication throughout the course of the disease, is well documented.⁶⁻⁸ Half of the virus population in plasma is turned over within hours, which translates to billions of virions produced and destroyed daily.^{7,9} Several billion CD4⁺ cells are likewise produced and destroyed each day.

The rate of virus replication stabilizes after primary infection at a particular level or "set point" in each individual. This level appears to be between 10² and 10⁶ HIV RNA copies/mL of plasma and remains relatively stable in asymptomatic patients over months and possibly years.¹⁰ Although it is convenient to measure viral RNA in plasma, it should be emphasized that these RNA levels are an indirect reflection of the number of productively infected cells in the body as a whole, and that most viral replication occurs in extravascular fixed lymphoid tissues. It is this viral replication in lymphoid tissues rather than circulating virus per se that is mechanistically linked to the progressive immunologic depletion that characterizes the illness. Although there appears to be a proportionality between plasma viral RNA and the amount of virus in fixed lymphoid tissues, the total amount of virus in the body cannot be directly calculated from the plasma viral RNA level. The set point is strongly associated with rate of disease progression and time to death, with a continuum of increased risk with increased plasma HIV RNA level. At one extreme of this continuum, a small proportion of subjects with very long-standing HIV infection have low HIV RNA levels and near-normal CD4⁺ cell counts and appear to have a particularly prolonged course. At the other extreme, those with

high levels of plasma viremia (>50 000-100 000 HIV RNA copies/mL) are at a greatly increased risk of clinical progression.

Several observational studies and treatment trials have confirmed this gradient of risk according to baseline plasma HIV RNA level.¹¹⁻¹⁴ With remarkable agreement between 2 recent studies, subjects in the lowest quartile (the 25% of subjects with the lowest viral load; <5000 HIV RNA copies/mL of plasma) had the lowest risk of progression to clinical acquired immunodeficiency syndrome (AIDS) and death. Subjects with a plasma virus level of more than about 30 000 to 50 000 HIV RNA copies/mL (the highest quartile) were at the greatest risk of progression.^{11,12}

HIV RNA levels appear to be more predictive of progression than CD4⁺ counts, particularly in asymptomatic patients with cell counts higher than 0.350 × 10⁹/L (350/μL).^{11,15} The CD4⁺ cell numbers may be difficult to interpret because the number at any point in time is only a partial indicator of the risk of AIDS.¹⁶ The onset of HIV-related symptoms is a strong predictor of further progression to serious opportunistic diseases.

Until recently, entry criteria for most clinical trials of antiretroviral drugs have centered on pretreatment symptom status, prior treatment history, and entry CD4⁺ cell count. Overall, zidovudine monotherapy was shown to be effective in advanced symptomatic disease, in mildly symptomatic disease, and in asymptomatic patients with CD4⁺ cell counts less than 0.500 × 10⁹/L.¹⁷⁻²⁰ In patients with CD4⁺ cell counts higher than 0.500 × 10⁹/L, zidovudine monotherapy reduced CD4⁺ cell loss but had no significant effect on clinical progression to AIDS or on survival compared with initiation of the drug at CD4⁺ cell count at or below 0.500 × 10⁹/L.²¹

More recently, plasma HIV RNA assays have permitted smaller and more efficient trial designs using viral load measurements in addition to or instead of clinical and CD4⁺ cell endpoints. Because of the important new insights gained from the use of these assays, strategies for earlier treatment with more potent combination antiretroviral regimens in asymptomatic disease are being considered.^{11,12,22-28}

In addition to the usefulness in assessing prognosis and guiding the initiation of therapy, HIV RNA levels are of potential value in assessing response to therapy (see next section). Reductions of HIV RNA titer generally occur within 4 weeks of starting or changing treatment. Several of the more potent combinations of antiretroviral drugs are

capable of inducing such profound reductions in viral replication that virus is no longer detectable in plasma with currently available techniques. Although studies of the relationship between changes in viral RNA in plasma and changes in the levels of virus in fixed lymphoid tissues are fragmentary, those that have been completed suggest that changes in the plasma compartment are an indirect reflection of events in fixed lymphoid tissues.^{29,30} A reduction in plasma viral RNA to levels that are below those detectable by current techniques does not necessarily reflect complete suppression of viral replication. As an estimated 10⁹ to 10¹⁰ virions are produced daily, it is highly likely that HIV-1 replication continues in lymphoid tissues following a reduction in plasma viral RNA by 2 to 4 log₁₀, albeit at a significantly lower rate.⁹ Even at these lower replication rates it would be expected that viral variants with reduced susceptibility to antiretroviral drugs will evolve over time. In that viral variation begins with the first cycles of replication during primary infection, as HIV-1 infection proceeds a subpopulation of viral variants that is resistant to antiretroviral drugs evolves, even in the absence of selective pressure. The prevalence of such mutants in the population of virus prior to the initiation of antiretroviral therapy is a function of the number of prior rounds of viral replication, the mutation rate, and the selective advantage (fitness) possessed by wild-type virus over variants that have incorporated mutations conferring drug resistance.^{31,32} Such considerations add further support to the concept that earlier initiation of therapy would be expected to result in a more durable response than would be expected in later stages of illness when a broader array of drug-resistant mutants would be expected to be present. Reductions in plasma viremia correlate with increased CD4⁺ cell numbers and AIDS-free survival.^{12,15} Treatments that achieve a greater and more durable suppression of HIV replication are assumed to be of greater clinical benefit. However, the magnitude and durability of the clinical benefits associated with plasma viral RNA suppression to undetectable levels have not been established.

Antiretroviral-Naive Patients.—Several trials have shown improvement based on laboratory indices or clinical benefits of combinations of 2 nucleoside analogues for initial therapy in HIV infection (Table 1). Three trials compared combination therapy with zidovudine and didanosine or zidovudine and zalcitabine with monotherapy regimens. In the US AIDS Clinical Trials Group

Table 1.—Results of Selected Recent Controlled Clinical Trials of Nucleoside Analogues: Studies With 250 Patients or More Observed for 48 Weeks or More

Regimen*	No. of Studies (References)	Approximate No. of Patients	Maximum CD4 ⁺ Cell Count Increase, $\times 10^9/L$ †	Maximum HIV RNA Reduction, \log_{10} Copies/mL‡
Trials in antiretroviral-naïve subjects				
Zidovudine/didanosine	3 (12, 27, 33-35)	1000	0.085	1.4
Zidovudine/zalcitabine	3 (12, 27, 33-35)	1000	0.085	1.1
Didanosine	1 (12, 33)	250	0.040	0.8
Zidovudine/lamivudine	2 (24, 36, 107)	300	0.085	1.7
Trials in antiretroviral-experienced patients†				
Zidovudine/didanosine	3 (12, 33-35, 108)	1000	0.040	1.1
Zidovudine/zalcitabine	3 (12, 22, 33-35)	800	0.020	0.9
Didanosine	1 (12, 33)	350	0.035	0.7
Zidovudine/lamivudine	2 (41, 56, 109)	275	0.032	1.5

*Each of these regimens except zidovudine/lamivudine has been shown to be superior to zidovudine monotherapy in delaying disease progression or death. Comparable data on the effect of zidovudine/lamivudine on clinical outcome are pending, but not yet available.

†For regimens evaluated in more than 1 trial, the maximum value is the highest mean peak value reported. HIV indicates human immunodeficiency virus.

‡The populations in the studies of antiretroviral-experienced patients vary considerably in terms of stage of disease and extent of pretreatment at entry.

(ACTG) 175 study, previously untreated patients with CD4⁺ cell counts of 0.200 to $0.500 \times 10^9/L$ at entry randomized to combination therapy had sustained clinical benefits and plasma HIV RNA and CD4⁺ count improvements^{12,33}; very similar results were obtained in the European-Australian trial, Delta 1, in patients with CD4⁺ cell counts of less than $0.350 \times 10^9/L$ at entry.^{34,35} In ACTG 175, didanosine monotherapy was as effective as the combinations and was superior to zidovudine monotherapy; didanosine alone was not evaluated in the Delta 1 study. In other studies, initial combination treatment with zidovudine and lamivudine reduced plasma HIV RNA levels and raised CD4⁺ cell counts more than either drug alone^{24,36} for longer than 76 weeks in some patients. These trials were not powered to detect differences in rates of clinical endpoints.

There are limited data on other initial nucleoside analogue-containing regimens that do not include zidovudine. In a small study of asymptomatic patients with CD4⁺ cell counts of less than $0.500 \times 10^9/L$, the combination of stavudine and didanosine had laboratory effects comparable to any of the other 2-drug combinations studied to date and modest toxic effects.³⁷ The combination of stavudine and lamivudine may have similar antiretroviral potency and tolerability, but no data are currently available on the combination. Stavudine monotherapy is also being investigated for initial therapy, and preliminary data indicate antiretroviral activity comparable to zidovudine.³⁸

Antiretroviral-Experienced Patients.—Results of some clinical trials in antiretroviral-experienced populations are considered because they provide insight into potential regimens for initial treatment. The US Community Programs for Clinical Research on AIDS (CPCRA) 007 trial compared combination therapy (zidovudine/didanosine or

zidovudine/zalcitabine) with zidovudine monotherapy in patients with CD4⁺ cell counts less than $0.200 \times 10^9/L$ or with AIDS at entry.³⁹ Overall, there were CD4⁺ cell count increases but no clinical benefit with combination therapies. However, most patients had prior zidovudine therapy (median, 12 months) and the risk of disease progression or death increased proportionally to the duration of prior zidovudine therapy for both combinations. In the subset of antiretroviral-naïve patients or those with less than 12 months of prior therapy, clinical progression or death was reduced in the zidovudine/didanosine group.

Combinations of nucleoside analogues with or without protease inhibitors appear to have more potent antiretroviral activity than monotherapy and may also delay or prevent the emergence of drug resistance. Several recent trials of protease inhibitor-containing combinations have been reported. In patients with moderately advanced disease, there were more substantial effects on laboratory markers with the combination of zidovudine, zalcitabine, and saquinavir than with the combination of zidovudine and saquinavir or the combination of zidovudine and zalcitabine.²² In 1 large phase 3 study, patients with CD4⁺ cell counts of 0.050 to $0.300 \times 10^9/L$ and at least 16 weeks of prior zidovudine therapy, the combination of saquinavir and zalcitabine was associated with significantly better clinical ($P=.002$) and survival ($P=.002$) outcomes than either saquinavir or zalcitabine alone.⁴⁰ These effects were, however, less striking than those seen subsequently with better absorbed protease inhibitors. In a small study, the combination of zidovudine, lamivudine, and indinavir resulted in a greater than 2.5 \log_{10} HIV RNA reduction at 16 weeks; more than 90% of those patients had reductions to fewer than 500 HIV RNA copies/mL at 6 months.⁴¹ The triple-drug combination was as well

tolerated as indinavir alone or zidovudine/lamivudine. The combination of zidovudine, zalcitabine, and ritonavir exhibited antiretroviral activity comparable to zidovudine, lamivudine, and indinavir.⁴² In a large trial in patients with very advanced HIV disease (median CD4⁺ cell count of $0.018 \times 10^9/L$), the addition of ritonavir to an existing regimen (including no current therapy) reduced progression to AIDS and mortality by approximately 50%.^{43,44} As yet, however, there are very few data from long-term (≥ 52 weeks), large (≥ 250 patients) controlled clinical trials of any protease inhibitors.

Lead compounds in the nonnucleoside reverse transcriptase inhibitor (NNRTI) class, nevirapine, delavirdine, and loviride, are extremely potent in vitro, but are associated with rapid development of viral resistance. Efforts are continuing to reduce the clinical impact of viral resistance by using higher drug doses and combination therapy with nucleoside analogues and protease inhibitors and evaluating these drug combinations for initial therapy.

When to Initiate Therapy

Ideally, therapy of HIV infection should be initiated before irreversible immunologic damage has occurred. The decision of when to initiate therapy should be based on the assessment of disease progression risk. Natural history studies and treatment trials demonstrate a continuum of increased risk with higher viral load and lower CD4⁺ cell count. As such, the experts differ somewhat with regard to the precise trigger point for recommending therapy (Table 2).

Clinical trial data support the initiation of therapy in patients with CD4⁺ cell counts below $0.500 \times 10^9/L$ (or a CD4⁺ percentage of <25). Some experts would defer therapy in a subset of patients with stable CD4⁺ cell counts between

Table 2.—Recommendations for When to Initiate Treatment

Status	Recommendation
Symptomatic HIV disease*	Therapy recommended for all patients
Asymptomatic, CD4 ⁺ cell count <0.500×10 ⁹ /L	Therapy recommended†
Asymptomatic, CD4 ⁺ cell count >0.500×10 ⁹ /L	Therapy recommended for patients with >30 000-50 000 HIV RNA copies/mL or rapidly declining CD4 ⁺ cell counts Therapy should be considered for patients with >5000-10 000 HIV RNA copies/mL

*Symptomatic human immunodeficiency virus (HIV) disease includes symptoms such as recurrent mucosal candidiasis, oral hairy leukoplakia, and chronic and unexplained fever, night sweats, and weight loss.

†Some would defer therapy in a subset of patients with stable CD4⁺ cell counts between 0.350 and 0.500 × 10⁹/L and plasma HIV RNA levels consistently below 5000-10 000 copies/mL.

0.350 and 0.500×10⁹/L (eg, counts that remain at the same level for 18 to 36 months) in whom plasma HIV RNA levels are consistently less than 5000 to 10 000 HIV RNA copies/mL.

Available clinical trial results do not define the optimal treatment strategy for asymptomatic patients with CD4⁺ cell counts above 0.500×10⁹/L. In such patients, treatment is recommended for those with more than 30 000 to 50 000 HIV RNA copies/mL or with rapidly declining CD4⁺ cell counts (ie, a greater than 0.300×10⁹/L loss over 12 to 18 months), based on the very high progression risk. Treatment should be considered for patients with HIV RNA levels higher than 5000 to 10 000 copies/mL based on the high progression risk. However, any decision to initiate therapy at CD4⁺ cell counts above 0.500×10⁹/L must be tempered by the fact that there are no available clinical data to support treatment at this stage of HIV disease, and that such earlier therapy carries with it potential problems related to long-term toxicity, tolerance, acceptance, expense, and the possible induction of drug-resistant virus.

Antiretroviral therapy should be initiated in all patients with symptomatic HIV disease (eg, recurrent mucosal candidiasis; oral hairy leukoplakia; chronic or otherwise unexplained fever, night sweats, or weight loss).

Initial Antiretroviral Regimens

A central question in the choice of an initial antiretroviral regimen is whether to use the most potent antiretroviral therapy available first in all patients or to reserve such therapy for patients with a higher pretreatment progression risk or for those progressing after initial therapy has been instituted. At this time, both approaches are defensible. Based

on current virologic and immunologic data, the most potent treatment regimen at this time would probably include 2 nucleoside analogues and a potent protease inhibitor; however, experience with protease inhibitors as initial therapy and in early HIV disease is still limited. Until longer-term clinical trial data from initial regimens with protease inhibitors are available, most patients in whom therapy is indicated should probably begin with 1 of the nucleoside analogue-containing regimens described below (Table 3).

The nucleoside analogue combinations with the most demonstrated clinical benefits are zidovudine/didanosine and zidovudine/zalcitabine (Table 1). Zidovudine/lamivudine may be better tolerated and appears to have comparable antiretroviral potency, but supporting clinical endpoint data are not now available. Also, there is some concern that initial lamivudine therapy with resulting resistance mutations at reverse transcriptase codon 184 may impair later response to didanosine or zalcitabine, should they be required.

Although emerging data support combination therapy, didanosine monotherapy is also a reasonable option,^{12,33} particularly for patients who cannot tolerate or who refuse zidovudine. This approach may allow the possibility of adding zidovudine at a later time or switching to zidovudine/zalcitabine or zidovudine/lamivudine, although there are no published data regarding the efficacy of these regimens in patients previously treated with didanosine monotherapy.

Initial therapy with other non-zidovudine-containing combinations are less well supported by clinical trial data. Stavudine/didanosine has antiretroviral potency that appears comparable to other 2-drug combinations³⁷; careful monitoring is clearly indicated for neurotoxicity, especially in more advanced disease. Stavudine/lamivudine is well tolerated, particularly for patients with limited bone marrow reserve who are poor candidates for zidovudine-containing regimens. However, no formal evaluation of the pharmacokinetics, safety, or activity of the combination has been completed. Stavudine monotherapy is also well tolerated, but available information does not permit adequate comparisons with other initial monotherapies (zidovudine or didanosine). Zalcitabine and lamivudine are not satisfactory single-drug therapies.

As noted, it may be reasonable to include a protease inhibitor in the initial regimen for any patient in whom therapy is indicated, particularly for patients at higher risk for progression. In this strategy, a protease inhibitor could be added

for symptomatic patients, patients with lower or rapidly falling CD4⁺ cell counts, and those with high plasma HIV RNA levels. The choice of a protease inhibitor should be made on the basis of efficacy and potency, safety and tolerability, durability of antiviral effects, drug resistance patterns, the potential for limiting future treatment options, and cost. Saquinavir, the first approved protease inhibitor, is well tolerated but has limited bioavailability and thus potency in its currently available formulation. A new formulation with improved bioavailability is under study. Indinavir is very potent and well tolerated. Toxic effects include benign hyperbilirubinemia and a 3% to 4% rate of nephrolithiasis (stones are primarily composed of precipitated indinavir). Ritonavir is comparable in potency to indinavir; it has more frequent adverse effects including gastrointestinal disturbance (20% to 25% of patients), hepatotoxicity, headache, and transient circumoral paresthesia. Ritonavir is a particularly efficient inhibitor of the hepatic enzyme cytochrome P450, which complicates its use with other drugs metabolized by this pathway. This may be particularly difficult in patients with advanced HIV disease in whom 1 or more of these drugs are commonly required.

The choice of initial therapy, including use of nucleosides and protease inhibitors, may be guided by emerging data on cross-resistance between drugs.⁴⁵ In the case of nucleosides, cross-resistance among lamivudine, didanosine, and zalcitabine based on codon 184 mutations provides an example of these concerns. The frequency of selection for viruses that are cross-resistant in vitro to some protease inhibitors suggest that an initial drug may limit future options for additional or alternative protease inhibitors.⁴⁶ Limited data from in vitro and sequential treatment studies support the hypothesis that ritonavir and indinavir select multiple mutations that often confer cross-resistance between these drugs. The mutations most commonly selected by saquinavir therapy in vivo are different and less numerous and may not confer cross-resistance in vitro.⁴⁶ However, some of the saquinavir-selected mutations have also been seen in subjects receiving indinavir and ritonavir, and the clinical consequences of initiating one protease inhibitor with respect to possible future benefits of another have not yet been fully defined. The clinical correlates of protease inhibitor resistance and cross-resistance will only be defined by careful analysis of current and future studies. It is important to maintain continuous drug administration at the optimal dosage level with all protease inhibitors, as dose re-

Table 3.—Recommendations for Initial Therapy Regimens

Zidovudine/didanosine, or zidovudine/zalcitabine, or zidovudine/lamivudine, or didanosine monotherapy*	If a protease inhibitor is added to a nucleoside analogue-containing regimen, the choice of protease inhibitor should be based primarily on antiretroviral potency and secondarily on other considerations as described in the text†
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*Didanosine monotherapy may be less effective as initial therapy in patients with more advanced human immunodeficiency virus (HIV) disease. Other possible non-zidovudine-containing regimens include didanosine/stavudine, stavudine/lamivudine, and stavudine monotherapy, although these regimens are less well studied.

†Antiretroviral potency refers to plasma HIV RNA and CD4⁺ cell count responses associated with these drugs at approved doses and with currently available formulations.

duction will contribute to the development of resistance to these drugs. When drug toxicity develops it is generally better to stop the protease inhibitor drug than to reduce its dose.

CHANGING ANTIRETROVIRAL THERAPY

Reasons for Changing Therapy

The initial antiretroviral regimen is of critical importance; however, few patients will remain on that treatment for prolonged periods of time. In general, there are 3 primary reasons for considering a change in antiretroviral therapy:

1. Treatment failure. Increased viral replication, due at least in part to the emergence of drug-resistant viral variants, is directly linked to immunologic and clinical progression. Treatment failure is indicated by increases in viral load (eg, a return toward or within 0.3 to 0.5 log₁₀ of pretreatment plasma HIV RNA levels), decreases in CD4⁺ cell count or percentage, or clinical progression. Ideally the patient should be monitored frequently enough that the decision to change the regimen can be made before symptomatic disease progression occurs.

Plasma HIV RNA assays have provided precise and compelling data on the relative magnitude and durability of effects of antiretroviral regimens. These data underscore the potential of plasma viral load levels, in conjunction with CD4⁺ cell counts, for guiding treatment decisions. Preliminary guidelines are available for using plasma HIV RNA levels in individual patient management.⁴⁷ If used, plasma HIV RNA level should be measured 3 to 4 weeks after initiating or changing therapy, and then periodically on the same schedule as CD4⁺ cell counts (eg, every 3 to 6 months). The minimum reduction in HIV RNA titer indicative of antiretroviral activity is 0.5 log₁₀ or more (about 3-fold) from pretreatment value (based on intra-assay variability of about 0.2 log₁₀ and biologic variation of about 0.3 log₁₀). The HIV RNA levels measured within about 1 month after immunizations or active intercurrent illnesses may show substantial but transient elevations associated with these events, which will resolve without alteration in therapy.⁴⁸⁻⁵⁰

CD4⁺ cell enumeration has been ex-

tensively used to guide treatment decisions. As with plasma HIV RNA measurements, it is not possible to strictly define CD4⁺ cell changes that definitely indicate that a change in therapy should be made. Most experts would view a return of CD4⁺ cell counts to pretreatment values as evidence of a loss of drug effect. Other factors, such as rate of decline of CD4⁺ cell count and extent to which additional treatment regimens are available, should also be considered.

The occurrence of HIV-associated clinical complications is considered evidence of treatment failure. The goal of using virologic and immunologic parameters to guide therapy is to prevent clinical disease progression, as clinical indicators of progression are, at best, insensitive and late indicators of treatment failure. Decisions to change treatment are often made relatively late, perhaps in part because of limited options and access to drugs, the general conservatism of many physicians, and the implication that altering therapy acknowledges disease progression. However, accumulating evidence suggests that earlier decisions to change therapy are more likely to have a significant impact on disease progression.^{34,35,39,51-54}

2. Toxicity, intolerance, or nonadherence. Each of the available antiretroviral treatments is associated with dose-limiting toxic effects. In general, they occur more frequently in individuals with advanced disease; in addition, overlapping toxicities with other drugs are more likely to encroach on therapeutic options in patient populations with more advanced disease. Physicians and patients must maintain an open dialogue about toxic effects and adherence to drug regimens.

3. Current use of a suboptimal treatment regimen. Zidovudine monotherapy is a suboptimal regimen and treatment should be reevaluated in any patient who is receiving it.

What to Change to

Several factors must be considered in determining which drugs should be added or substituted when a decision is made to change therapy, including the primary reason for changing, prior treatment history, currently available options, stage of disease, underlying conditions

(eg, neuropathy), concomitant medications, and cost and reimbursement issues associated with the regimens. An essential consideration relates to why a change in therapy is being made. For toxicity or intolerance, finding a regimen that a patient will tolerate and be willing to take on an ongoing basis is crucial. For treatment failure, drugs with greater potency, with different mechanism(s) of action, and those without cross-resistance should be sought.

With an expanding number of available antiretroviral drugs, opportunities will arise for continuing modification of the antiretroviral regimen, and the decision to use a particularly potent therapy early in treatment should be weighed against the type of regimen that can be employed at later stages of HIV disease. As with the recommendations for initial treatment, the most appropriate regimen cannot be defined specifically for each clinical scenario. In general, a change to the most potent regimen available is recommended, based on the virologic, immunologic, and clinical characteristics of the individual patient. Table 4 provides some representative options for subsequent regimens.

Patients currently on zidovudine monotherapy should be reevaluated as to whether a more potent antiretroviral regimen (eg, adding didanosine, zalcitabine, or lamivudine to the zidovudine regimen, or switching to didanosine monotherapy) should be recommended.^{12,34,35,51,53-55} In patients with advanced disease and those with extensive zidovudine experience, adding lamivudine to zidovudine or switching to another type of nucleoside analogue combination with or without a protease inhibitor may be beneficial. In patients with advanced disease, switching to zalcitabine or adding zalcitabine provides no additional benefit over zidovudine monotherapy.^{39,52,56} The benefits of adding didanosine are more modest than those observed with the initial use of this combination and are less demonstrable or absent in patients with extensive zidovudine experience or advanced disease.^{12,34,35,39,51,53} In such patients, new combinations of nucleoside analogues plus a protease inhibitor are appropriate.

In patients who have received a combination of 2 nucleoside analogues, such as zidovudine/didanosine, zidovudine/zalcitabine, or zidovudine/lamivudine, a change to combination therapy with at least 2 new drugs, such as 1 or 2 nucleoside analogues and a protease inhibitor (indinavir, ritonavir, saquinavir) may be appropriate. For patients for whom initial regimens included a protease inhibitor, subsequent regimens should include at least 2 new drugs; there are currently insufficient data on viral resistance pat-

Table 4.—Some Selected Options for Changing Therapy Owing to Treatment Failure or Drug Intolerance*

Initial Regimen	Subsequent Regimen Options
Treatment Failure	
Zidovudine†	Zidovudine/didanosine ± protease inhibitor Zidovudine/lamivudine ± protease inhibitor Didanosine ± protease inhibitor Didanosine/stavudine ± protease inhibitor
Didanosine	Zidovudine/lamivudine ± protease inhibitor Zidovudine/didanosine/ protease inhibitor Stavudine/protease inhibitor
Zidovudine/didanosine	Zidovudine/lamivudine ± protease inhibitor Stavudine/protease inhibitor
Zidovudine/zalcitabine	Zidovudine/lamivudine ± protease inhibitor Stavudine/protease inhibitor Didanosine/protease inhibitor
Zidovudine/lamivudine	Didanosine/protease inhibitor Stavudine/protease inhibitor Didanosine/stavudine Lamivudine/stavudine
Drug Intolerance‡	
Zidovudine†	Didanosine Didanosine/stavudine Lamivudine/stavudine Stavudine
Didanosine	Zidovudine/lamivudine Lamivudine/stavudine Stavudine/protease inhibitor
Zidovudine/zalcitabine Intolerance to zidovudine	Didanosine Didanosine/protease inhibitor Didanosine/stavudine Stavudine/protease inhibitor
Intolerance to zalcitabine	Zidovudine/lamivudine ± protease inhibitor
Zidovudine/lamivudine	Didanosine/protease inhibitor Stavudine/protease inhibitor Didanosine/stavudine

*For patients whose initial regimen includes a protease inhibitor, subsequent regimens should include at least 2 new drugs chosen from among nucleoside analogues, nonnucleoside reverse transcriptase inhibitors (if available), and protease inhibitors (one should be selected for which there is likely to be little or no cross-resistance to the initial protease inhibitor).

†Considered a suboptimal regimen; all patients on zidovudine monotherapy should be reevaluated.

‡A protease inhibitor could be added to the nucleoside analogue regimens listed.

terms to be able to provide specific recommendations for additional or alternative protease inhibitors in this setting.

Considerations for Stopping Antiretroviral Therapy

Stopping antiretroviral therapy may be appropriate in patients with very advanced disease for whom there are significant toxicity and quality-of-life issues associated with continued antiretroviral therapy. Data on viral dynamics⁷⁻⁹ support the need for continuous therapy with continued monitoring and reevaluation of

the antiretroviral regimen. The consequences of drug withdrawal are immediately evident (within days) in terms of increases in plasma HIV RNA levels.^{6,57} In light of this, efforts should be made to manage drug-related toxicity before all therapy is abandoned.

SPECIAL CONSIDERATIONS

Treatment of primary (acute) HIV infection, prophylaxis for the prevention of HIV transmission by accidental exposures, and the prevention of maternal-fetal transfer are discussed below. The latter 2 settings have been covered in detail by others.⁵⁸⁻⁶⁰ The recommendations herein address these 3 areas with regard to recent insights into HIV pathogenesis and clinical trials of newer and more potent antiretroviral treatments.

Primary Infection

Background.—Primary HIV infection refers to the 4- to 7-week period of rapid viral replication immediately following exposure. The number of virions produced during primary infection is similar to that produced during several subsequent years of established, asymptomatic infection.⁶¹ Roughly 30% to 60% of individuals with primary infection develop an acute syndrome characterized by fever, malaise, lymphadenopathy, pharyngitis, headache, myalgia, and sometimes rash.^{62,63} Following primary infection, seroconversion and a broad HIV-1 specific immune response occur, usually within 30 to 50 days.⁶

Primary HIV infection is characterized by high plasma HIV RNA levels (10^6 to 10^8 copies/mL). Each individual seems to establish a plasma HIV RNA set point that is highly predictive of subsequent progression risk.^{10,61,65} Theoretical reasons to treat during primary infection include the opportunity to intervene before the infection is fully established with the possibility of lowering the viral set point and the opportunity to intervene when the genetic diversity of HIV in each individual is more restricted.

Little information is available to guide treatment in primary HIV infection. Patients with primary infection and very recent seroconverters treated with zidovudine monotherapy (250 mg twice a day) for 6 months had slower progression to minor clinical endpoints and better CD4⁺ cell counts than did patients without antiretroviral treatment.⁶⁶ Reductions in plasma HIV RNA levels were more pronounced in the treated group.

Recommendations for Primary Infection.—To increase antiretroviral treatment effect and minimize or delay emergence of drug resistance (also, primary infection may have been with a

drug-resistant virus), treatment of primary infection with the most potent combination therapy available seems warranted. If enrollment in a clinical trial is not possible, a combination of at least 2 nucleoside analogues is recommended (eg, zidovudine plus didanosine, zalcitabine, or lamivudine). The addition of a protease inhibitor or an NNRTI, if available, should also be considered. Preliminary investigations of 2- and 3-drug combinations are under way.

At this time, the appropriate duration of antiretroviral therapy for primary infection has not been determined. It is recommended that treatment continue for at least 6 months, the duration of the only published study.⁶⁶ Until more data are available, further treatment should be guided by clinical judgment, weighing factors including plasma HIV RNA levels and CD4⁺ cell counts, as well as patient acceptance, long-term drug toxicity, and cost.

Postexposure Prophylaxis

Background.—Risk of HIV transmission through occupational exposure in health care workers is approximately 0.3% from a percutaneous injury from a needle or other device.^{67,68} Variables apparently related to risk of HIV transmission include volume of blood involved in the exposure (for example, 90% of transfusion recipients receiving HIV antibody-positive blood seroconvert); stage of disease and plasma HIV RNA level in the source patient; and site and mechanism of exposure.^{68,69,71} The risk of transmission in other types of accidental exposure, ie, that among HIV laboratory workers, between sexual partners of infected individuals, and from human bites, is less well characterized.⁷²⁻⁷⁴

Zidovudine has been the predominant drug evaluated for postexposure prophylaxis. Animal data on its protective effect have been inconclusive.⁷⁵⁻⁷⁸ There is limited experience with zidovudine prophylaxis in humans.⁷⁹⁻⁸³

In a recently reported case-control study from public health authorities in France, Great Britain, and the United States, experience with zidovudine prophylaxis was reported for 31 cases of seroconversion and for 679 controls with no seroconversion.⁷¹ Risk factors associated with seroconversion were deep injury; visible blood on needle or device involved; procedures involving a needle placed directly into a vein or artery; and terminal illness in the source patient. Prophylaxis with zidovudine (1000 mg/d for 3 to 4 weeks) was shown to reduce risk of transmission by nearly 80%. Caution should be used in interpreting these results, however, as data were collected retrospectively; the study used case con-

trols rather than placebo controls; cases and controls were identified from different sources; and reporting or ascertainment bias is possible.

Recommendations for Post-exposure Prophylaxis.—Despite limited data, post-exposure prophylaxis is recommended in occupational and accidental situations in which there is a definite high risk for transmission.⁷¹ Clinicians may be faced with decisions regarding prophylaxis in less well-studied exposures, such as transplantation of an HIV-positive donor organ, rape, or accidents in HIV laboratories. A level of risk per episode at least analogous to that of percutaneous needle-stick injury can be assumed to exist in these settings, and a similar consideration of prophylaxis may be appropriate. Previously published guidelines on post-exposure prophylaxis recommend zidovudine, 200 mg every 4 hours for 3 days, then 100 to 200 mg every 4 hours for the next 25 days.⁵⁸ Current guidelines have been proposed by the Centers for Disease Control and Prevention Task Force.⁸⁴

Maximal benefit of prophylaxis can be expected if therapy is begun as soon as possible after exposure (ie, within hours). It is strongly recommended that each institution develop a specific regimen and have available standard prophylaxis kits for use in occupational and nosocomial exposures. In view of the greater efficacy of combination therapy in patients with established infection and the increasing incidence of zidovudine resistance in source patients,⁸⁵⁻⁸⁷ potent combination therapy may confer more protection than monotherapy. If possible, at least 2 drugs that have not been used in the source patient should be considered. Alternatives to zidovudine monotherapy include therapy with at least 2 nucleoside analogues (Table 3). Three or more drug regimens that include a potent protease inhibitor or an NNRTI, if available, may also be considered. Newer treatments may soon provide more choices.^{23,25,26,88-92}

The specific time courses (ie, 4 to 6 weeks) for prophylaxis that have been evaluated are largely based on outmoded concepts of viral pathogenesis.^{59,71} Based on the current understanding of viral replication, it may be that shorter, more intensive courses of therapy (eg, 2 weeks of triple-combination therapy) are more appropriate, but this needs further evaluation before it can be recommended.

Vertical Transmission Prophylaxis

Background.—Without antiretroviral intervention, 15% to 35% of infants born to HIV-infected mothers will acquire HIV infection.⁹³⁻⁹⁶ Factors associated with increased risk of vertical transmission in-

clude the rupture of membranes for more than 4 hours and events that expose the infant to maternal blood.^{60,94,97} There appears to be no threshold for maternal plasma HIV RNA levels above which transmission always occurs or below which it does not occur.⁹⁸⁻¹⁰¹

The effectiveness of antiretroviral therapy in preventing maternal-to-fetal transmission has been demonstrated in women with CD4⁺ cell counts above 0.200×10⁹/L and little or no prior zidovudine experience.^{95,99} Zidovudine therapy for the mother during the antepartum and intrapartum period and for the newborn for 6 weeks after birth reduced transmission by approximately two thirds, from 24.9% to 7.8%. Recent observational studies have also shown reduced transmission associated with zidovudine therapy.¹⁰²⁻¹⁰⁴

Recommendations for Vertical Transmission Prophylaxis.—Counseling and HIV testing should be offered to all pregnant women.⁶⁰ Perinatal prophylaxis is recommended for all HIV-infected women, as is treatment for the newborn regardless of whether the mother is treated. All women currently receiving antiretroviral therapy should continue to receive therapy during pregnancy. Following the guidelines of the AAP,¹⁰⁵ HIV-infected women, if local conditions permit, should be encouraged to bottle-feed their newborns as HIV can be transmitted in breast milk.¹⁰⁶

There are insufficient data on efficacy, safety, or possible teratogenicity to permit recommendations of any regimen other than zidovudine for preventing vertical transmission at this time.¹⁰²

CONCLUSIONS

More effective treatment of HIV disease is now possible, and treatment decisions have become more complex, requiring an understanding of viral pathogenesis, antiretroviral resistance patterns, and use of laboratory markers of HIV disease progression and antiretroviral efficacy. These recommendations are designed to assist clinicians in making informed decisions regarding the treatment of HIV disease and will necessarily change as new data are generated. The panel intends to update the recommendations as warranted.

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COMPLEMENTARY THERAPIES IN HIV DISEASE

Overviews of alternative or complementary therapies were presented at the San Francisco conference by Donald I. Abrams, MD, from the University of California San Francisco, and at the Atlanta conference by Charles Steinberg, MD, of the Beacon Clinic in Boulder. The following summary highlights some of the complementary approaches currently in use and under investigation for HIV disease.

Many approaches outside of mainstream western medicine, including traditional Chinese herbs and acupuncture, foreign pharmaceuticals, vitamin supplements, massage, and spiritual healing, have been explored for the treatment of HIV disease and its associated symptoms. Although little data from formal controlled clinical trials exist, complementary or alternative therapies are widely used by persons with HIV and other diseases or conditions. In a report published by Eisenberg and colleagues in 1993, a survey of 1539 adults in the US revealed that 34% used at least one unconventional treatment in the past year; one third of the 34% made an average of 19 visits to providers of unconventional therapy during the preceding year. In this study, those reporting use of complementary therapies were more likely to be non-African-Americans, 25 to 49 years of age, and to have higher levels of income and education, indicating that they had the access and resources necessary to explore unconventional strategies. It is important to note that 72% of those who reported using complementary therapies had not discussed their use with their primary care physicians.

Studies from around the world on the use of complementary or alternative therapies in persons with HIV disease have revealed an even higher prevalence: 40% to 70% are seeking unconventional treatments in addition to (ie, complementary), or in place of (ie, alternative), conventional treatment. There have been distinct fluctuations in the search for and use of unconventional therapies for HIV disease,

which, according to Dr Abrams, reflect the availability of effective conventional drugs. Through the 1980s, limited options and disappointing data from trials of traditional drugs fueled an upward trend in the use of complementary therapies. With an expanded indication for zidovudine and the availability of didanosine and zalcitabine, interest in alternative compounds leveled off until discouraging results from the Concorde study spurred renewed interest. Now, with the availability of stavudine, lamivudine, and the potent protease inhibitors, the focus in the complementary/alternative therapy movement may be shifting toward investigating therapies for HIV-related symptoms or conditions for which few effective prescription drugs are available.

In addition to introducing a wide variety of nonconventional treatments, the complementary/alternative therapy movement in HIV disease has exerted influence in the political and regulatory arenas. Bans on importing drugs for personal use have been lifted in certain circumstances and buyers' clubs have been established. Widespread use of complementary therapies has also contributed to the modification of trial protocols to in-

clude patients with prior alternative-drug experience, the development of expanded access/parallel track programs for investigational drugs, and the accelerated drug approval policy.

Given the widespread use of complementary therapies and the strength of the complementary/alternative therapy movement in HIV disease, it is important that physicians and other healthcare providers working in mainstream western medicine be aware of these treatments, the risks and benefits associated with their use (see Table 1), and the role they may play in a comprehensive, holistic approach to managing HIV disease.

Selected Complementary Therapies

Vitamins and supplements. At present, there are no formal data from prospective, placebo-controlled, clinical trials evaluating the use of vitamins and supplements in persons with HIV disease.

Antioxidants, including vitamins A, C, E, beta-carotene, zinc, selenium, glutathione, and coenzyme Q-10, may reduce the level of free radicals in the body. A dose-ranging trial of vitamin C (ascorbate) is under consideration at the National Institutes of Health (NIH) to evalu-

Table 1. The Potential Risks and Benefits of Complementary Therapies for HIV Disease.

Potential risks	Potential benefits
<ul style="list-style-type: none">• Immune stimulation or suppression• Interaction with prescribed medication• Exclusion from orthodox clinical trials• Invalidation of clinical trial data• Strain on physician-patient relationship• Financial hardship• Potential for quackery or fraud	<ul style="list-style-type: none">• Evaluation of more potential treatments• Community education on scientific methods and clinical trials• Increased sense of patient hope and empowerment

ate its effect on plasma HIV RNA levels. A pilot study of beta-carotene has shown possibly suggestive short-term but not statistically significant improvement in CD4+ cell counts. In a number of recent trials in older non-HIV-infected adults, the use of beta-carotene supplements appeared to be associated with a higher death rate.

Dinitrochlorobenzene. Dinitrochlorobenzene (DNCB), a chemical used in color photography, was one of the first unconventional therapies used in HIV disease. A topical sensitizer for anergy testing and the treatment of warts and alopecia areata, DNCB was used at underground clinics in the early 1980s as a topical therapy for Kaposi's sarcoma (KS) lesions. Recently, there has been renewed interest in DNCB, based on anecdotal reports of the ability of the compound to enhance cutaneous—and subsequently—systemic, cellular immune response to HIV. Treatment involves painting a 2- to 4-inch patch of DNCB on the skin; the solution is diluted as sensitivity increases. Severe skin irritations have been observed, and findings from an observational cohort study have proven inconclusive.

Tumor necrosis factor (TNF) inhibitors. Another group of drugs widely available through underground treatment networks are those believed to inhibit TNF, including N-acetylcysteine (NAC), procysteine, pentoxifylline, peptide-T, and thalidomide. High concentrations of TNF in some in vitro systems activate HIV, inducing viral replication and increased destruction of the immune system. In addition, TNF-inhibitors may be useful in treating other cytokine-mediated symptoms of HIV disease, such as fever and wasting. N-acetylcysteine, a cysteine precursor available as a mucolytic agent in Europe, was evaluated by the National Institute of Allergy and Infectious Diseases (NIAID) and was found to have no effect on plasma cysteine levels, CD4+ cell counts, or viral load. Despite disappointing trial results and poor oral bioavailability, NAC remains popular at buyers' clubs. Pentoxifylline was evaluated in an AIDS Clinical Trials Group (ACTG) protocol and was found not to have any beneficial clinical effects.

Thalidomide inhibits TNF by interfering with messenger RNA (mRNA) production; it is being evaluated for the treatment of wasting and aphthous ulcers. Studies in the US and Thailand in persons with HIV and tuberculosis (TB) demonstrated that the addition of thalidomide to anti-TB medications increased weight gain. In an ACTG placebo-controlled study that evaluated thalidomide for the treatment of oral and esophageal ulcers, 95% of patients with oral ulcers had either complete or partial resolution compared with 10% of patients given placebo. The oral-ulcer component of the study was terminated; evaluation of thalidomide for the treatment of esophageal ulcers is ongoing. The primary side effect associated with thalidomide is sedation. The well-documented teratogenic side effects require that women of child-bearing age who are given thalidomide use strict methods of birth control. Based on early promising reports, thalidomide was being widely distributed through the underground buyers' club networks until prohibited by the Food and Drug Administration (FDA). Because of the controversies in the past regarding its use in pregnant women, emotional reactions to the use of thalidomide, particularly in HIV-infected women and minorities, have hampered its evaluation in larger clinical trials.

Complementary Therapies for Wasting

The lack of available effective interventions for HIV-associated wasting has spurred an increased use of complementary therapies in this area. In addition to thalidomide, testosterone, given by injection or patch, testosterone-like agents, and anabolic steroids are also being widely used for their potential to increase lean muscle mass. Efforts are under way to conduct clinical trials on nandrolone and decadurabolin through the ACTG; a study that would compare IM nandrolone with oral oxandrolone has been proposed by the Community Programs for Clinical Research on AIDS (CPCRA). Trials on these and other steroids are needed to examine their potential as immunosuppressants. There have been anecdotal reports from the alternative underground of more rapid HIV disease progression in persons using injected anabolic steroids; specifi-

cally, there is an increasing number of reports of cytomegalovirus (CMV) disease developing in patients with CD4+ cell counts higher than would normally be expected.

Dehydro-3-epiandrosterone (DHEA), an adrenal steroid present in decreased amounts in persons with HIV, has been reported to have antiretroviral and immunomodulatory effects in vitro. In a phase I dose-escalation study, 31 subjects were given the drug in doses ranging from 250 to 750 mg tid for 16 weeks. No changes were observed in CD4+ cell counts, β_2 -microglobulin levels, or p24 antigen levels. A transient decrease in serum neopterin levels was noted. There were no consistent side effects; rare instances of insomnia, fatigue, and nasal congestion were observed. At present, DHEA is the largest selling agent in the San Francisco Buyers' Club, and is used by persons with HIV for wasting and by HIV-negative consumers because of its reputation as a "smart drug," with alleged anti-aging, anti-obesity, and anti-cancer properties.

Ketotifen, an antihistamine widely used in Europe, is a best-selling item in the New York buyers' clubs as another potential treatment for wasting. Interest in ketotifen was sparked by a small German study suggesting decreased levels of TNF- α and a six-pound weight gain in HIV-infected patients with wasting during the 12-week treatment period. In addition to lowering TNF- α levels and stimulating the appetite, ketotifen may also have anti-inflammatory properties. Associated side effects include temporary drowsiness and dry mouth.

Marijuana, either inhaled or ingested in the form of dronabinol capsules, has also been widely used as an appetite stimulant by persons with HIV disease. As of July, the Cannabis Buyers' Club in San Francisco (shut down in August) made this drug available to approximately 8000 people with HIV disease and other life-threatening medical conditions. Based on reports of patients' preferences for inhaled marijuana because of the ability to titrate onset of appetite and duration effect, researchers at the University of California San Francisco designed a clinical trial to compare three strains of inhaled marijuana with dronabinol. Although the

study protocol was approved by the FDA and the institutional review board, questions regarding the source of the marijuana to be used have caused significant delays. An intensive inpatient evaluation of 15 adults using inhaled marijuana has been designed and submitted to the NIAID. Outcome measures will include food intake and impact on the lungs, the immune system, and viral load.

Chinese Medicine

Chinese medicine is used by more than 20% of the world's population. Focusing on the whole person rather than specific pathogens, these ancient methods of healing combine acupuncture and herbal treatment to realign the balance of energy in the body. Although a number of treatments have been evaluated for use in patients with HIV disease, primarily for their effect on constitutional symptoms, formal clinical trials remain a challenge, largely owing to the individualized nature of these approaches.

In studies involving persons with HIV, the use of acupuncture and herbs has been reported anecdotally to yield improvements in symptoms such as fever, night sweats, fatigue, and weight loss. No consistent beneficial effects on laboratory parameters such as CD4+ cell count and viral load have been observed. In a recent study, investigators at San Francisco General Hospital collaborated with practitioners of traditional Chinese medicine at the Quan Yin (a traditional Chinese medicine clinic) to conduct a 12-week randomized, double-blind, placebo-controlled trial using a combination of ENHANCE™ and CLEAR HEAT™. The combination comprised 31 herbal ingredients in a 650-mg tablet. Thirty HIV-positive patients with CD4+ cell counts of 200 to 500/μL and HIV-related symptoms but with no diagnosis of AIDS were given 28 herbal or placebo tablets daily. The results from 29 patients are presented in Table 2. Adherence was high, with patients in both groups taking an average of 26 pills daily. One patient discontinued treatment after two weeks due to diarrhea, one patient had a transient increase in hepatic transaminase levels, and one patient refused to return for follow-up; all three of these patients were in the placebo group.

Table 2. Results from a Placebo-controlled Trial of ENHANCE™ and CLEAR HEAT™.

Outcome measure	Herbal group (n = 15)	Placebo group (n = 14)	P-value
Mean life satisfaction score	0.86	0.20	<.05
Mean change in number of symptoms	-2.2	+0.3	<.05
Mean change in CD4+ count (cells/μL)	-30	-11	NS
Mean increase in weight (lb)	0.04	0.31	NS

NS, not significant.

Data from Burack JH et al. *JAIDS*. 1996.

The results of this collaborative trial proved inconclusive, and the methodology used was criticized by practitioners of both western medicine and traditional Chinese medicine. Western concerns included the small sample size, the short duration of the study, and the subjective outcome measures. The practitioners of traditional Chinese medicine also expressed concern about the trial's short duration, as well as the lack of a Chinese diagnosis and of complementary acupuncture, and the use of herbal extracts rather than the herbs themselves. Clinical trials are also under way for Source Qi, an herbal preparation for the treatment of patients with chronic *Cryptosporidium*-negative diarrhea, and for Marrow Plus, an herbal combination treatment for patients with mild-to-moderate anemia. In addition, the CPCRA is conducting a randomized, placebo-controlled study of acupuncture and amitriptyline for the treatment of peripheral neuropathy.

Complementary Therapies with Reported Antiretroviral Activity

An extract of the Boxwood evergreen with purported antiretroviral effects, SPV-30 has recently received much positive publicity. A placebo-controlled study at the Pasteur Institute in Paris demonstrated a modest increase in CD4+ counts in a cohort of about 30 patients with 250 to 500 cells/μL and no previous antiretroviral therapy. In patients given SPV-30, mean CD4+ counts increased by 94 cells/μL compared with a decrease of 43 cells/μL in patients given placebo. No toxicities were reported, and patients

given SPV-30 reported a decrease in fatigue. To date, more than 150 subjects have been enrolled in a larger follow-up phase II/III study in France; results were reported at the International Conference in Vancouver. The group that received a low dose of SPV-30 had fewer therapeutic failures (defined as progression to ARC or AIDS, or a CD4+ cell decline) than the placebo or high-dose SPV-30 groups. The authors concluded that "this trial shows that [SPV-30] slows down progression of disease." However, these results have been considered inconclusive, at best. In the US, an informal, community-based study of SPV-30 enrolled 400 HIV-infected persons with CD4+ cell counts of 0 to 700/μL and plasma HIV RNA levels of 0 to 10⁶ copies/mL. Participants added SPV-30 to their existing antiretroviral therapy, completed questionnaires, and supplied samples for laboratory testing every two months. Preliminary analysis of the study was presented in Vancouver. There was no CD4+ count benefit and only mild plasma HIV RNA activity; hence, these results are similarly considered inconclusive.

Cytolin, a mouse monoclonal antibody directed against the LFA-1 adhesion molecule of CD8+ cells, has been investigated for its ability to down-regulate cytotoxic CD8+ cells. HIV-induced cytotoxic CD8+ cells mediate the destruction of the immune system by killing CD4+ expressing cells. The cytotoxic CD8+ cells are covered with adhesion molecules, which are the primary immunologic lesions. Cytolin, targeted at the LFA-1 adhesion molecule of CD8+

cells, is postulated to block the killing of CD4+ cells. A pilot study conducted by the Search Alliance, a community-based trial group in Los Angeles, demonstrated decreased plasma HIV RNA levels, remission of early disease symptoms, and resolution of refractory molluscum. Additional data are currently being collected. Of concern is the potential for anaphylaxis and for the development of human anti-mouse antibodies (HAMAs) from using a foreign-protein product. In addition, some investigators question the use of LFA-1 as a target molecule. Critical for the attachment of CD8+ cells to virus-infected and cancer cells, blocking expression may promote the development of cancers and the spread of opportunistic viral infections in patients with HIV. Animals injected with anti-LFA-1 have shown markedly decreased cellular immune response.

Sho-Saiko-To (SSKT), a traditional Japanese medicine, is a precise mixture of 7 herbs and has been reported to have in vitro anti-HIV activity via reverse transcriptase inhibition. A trial of this drug conducted at Columbia University using lymphocyte cultures found that the degree of anti-HIV activity correlated with disease stage.

Summary

Given the widespread use of complementary or alternative therapies, it is important that physicians and other health care providers maintain open communication with their patients on issues relating to these unconventional therapies. Awareness of the drugs and compounds being used, the rationales for their use, and their potential toxicities, allows physicians to monitor treatment effects, prevent potential drug interactions, ward off fraud, and educate patients on treat-

ment issues. Such unconventional therapies should be subjected to the same rigorous, systematic assessment of risks and benefits as are the more conventional interventions. Complementary or alternative therapy may be one part of an integrated and individualized treatment program. For the person with HIV disease, seeking information on all available options and making informed treatment decisions are important components of keeping hope alive.

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HIV RESISTANCE TO ANTIRETROVIRAL DRUGS

STEFANO VELLA, MD, AND MARCO FLORIDIA, MD

New insights into HIV pathogenesis, the development of quantitative plasma HIV RNA testing, and the increased availability of antiretroviral drugs have significantly changed our approach to treating HIV infection over the last year or two. Moreover, recent results of two large controlled trials (the European-Australian DELTA trial and the US AIDS Clinical Trials Group [ACTG] 175 study)—although different in design, pretreatment characteristics of the patients, and primary endpoints—provided the long-awaited proof of concept that a significant and sustained reduction of viral replication is associated with improved clinical outcome.

The emergence of HIV resistance has been described for all classes of antiretroviral drugs used in monotherapy or in dual combination regimens and has continued to be considered an inevitable factor that ultimately determines the loss of efficacy of antiretroviral treatment, even though treatment failure is complicated by the concomitant interaction of virologic factors other than resistance. In this article, the general mechanisms of the development of resistance to antiretroviral drugs are reviewed together with recent findings in the field, and the latest advancements that have been made toward overcoming resistance.

Virology of Drug Resistance

The high rate of viral replication found throughout the course of HIV infection and the high frequency of virus mutations occurring during each replication cycle (a phenomenon common to all single-stranded RNA viruses) due to the lack of proofreading mechanisms, are the basis for the emergence of drug-resistant variants under the selective pressure of antiretroviral drugs. In fact, a "Darwinian" model can be applied to HIV dynamics, with the continuous production of variants and the continuous selection of the "fittest" virus.

Unfortunately, with daily production of perhaps 10^8 to 10^{10} virions and a mutation rate of 3×10^{-5} nucleotides per replication cycle, it is likely that any single mutation already exists before any drug is introduced. The relative level of viral mutants at a given point in time is probably determined by the forward mutation frequency (the amount of copying errors at a particular codon) and the cost of the mutation to the replicative capability of the virus.

Drug resistance, which in reality, can be better described as altered drug susceptibility, is clearly a relative characteristic, and is defined as the alteration of the drug concentration needed to inhibit *in vitro* growth of the virus. Virus susceptibility is usually quantified in terms of the concentration of a drug that is needed to inhibit 50% or 90% of viral growth, which defines the IC_{50} or IC_{90} , respectively. If the IC_{50} (or IC_{90}) value that is characteristic of the so-called wild-type virus is known, the IC_{50} (or IC_{90}) value for a resistant virus will be X-fold greater. The increase in the IC_{50} value needed to define a virus as resistant to a particular drug is often empirically established. For example, a virus highly-resistant to zidovudine is assumed to have an IC_{50} value at least greater than 1.00 μM , while wild-virus generally have an IC_{50} value of about 0.01 μM to 0.05 μM .

Drug susceptibility of the virus harbored by an HIV-infected individual can be assessed by isolating the virus, preferably from plasma (which will better represent the actively growing virus population), in the presence of various concentrations of the drug under study (phenotypic analysis of resistance). However, because phenotypic resistance is the consequence of specific mutations in the genes for the target enzymes (ie, reverse transcriptase [RT] or protease), polymerase chain reaction (PCR) assays

and gene sequencing methods have been developed to detect these mutations directly (genotypic analysis of resistance). The relationship between phenotypic and genotypic analyses of resistance is often direct, but can be altered in some cases by the fact that the emergence of resistance is a dynamic process, and multiple strains of virus with various susceptibilities frequently coexist in the patient.

Because resistant variants may exist before treatment is initiated and may evolve under selective pressure, therapy can address viral resistance in three ways: (a) maximizing the suppression of viral replication; (b) using drugs when multiple mutations are required for resistance; and (c) forcing the emergence of variants with attenuated replication or decreased virulence.

Resistance to RT Inhibitors

Resistance to nucleoside analogues. HIV variants with decreased susceptibility to zidovudine were first reported in 1989. Viral variants with different levels of drug resistance to other nucleoside analogues subsequently have been described (see Table 1).

In general, advanced disease-stage, baseline low CD4+ cell counts, and high plasma HIV RNA levels predict the development of resistance to zidovudine, and this is likely to be true for all other antiretroviral drugs.

TABLE 1. SOME GENOTYPIC CHANGES ASSOCIATED WITH THE *IN VIVO* USE OF ANTIRETROVIRAL DRUGS.

Reverse transcriptase inhibitor	Codon mutations in the reverse transcriptase gene	Protease inhibitor	Codon mutations in the protease gene
Nucleoside			
Zidovudine (ZDV)	41, 67, 70, 215, 219	Saquinavir	10, 48, 63, 71, 90
Didanosine (ddI)	65, 74, 184	Ritonavir	20, 33, 36, 46, 54, 71, 82, 84, 90
Zalcitabine (ddC)	65, 69, 184	Indinavir	10, 20, 24, 46, 54, 63, 64, 82, 84, 90
Lamivudine (3TC)	184		
Stavudine (d4T)	75 (rare)		
Nonnucleoside			
Nevirapine	103, 106, 108, 181, 188, 190		
Loviride	103, 181		
Delavirdine	181, 236		

Although resistance to zidovudine appeared to be related to the ordered emergence of viral variants with mutations at RT codons 70, 215, 41, 67, and 219, high-level resistance to didanosine has not been reported to date; also, diminished susceptibility to zalcitabine and stavudine *in vivo* has not been well documented. There is not a clear explanation for these findings, although it has been hypothesized that it may be related to the greater similarity of these compounds to the natural substrate. The pattern of viral mutations associated with didanosine has been further investigated by several groups, and their results substantially confirm that susceptibility is reduced when strains with one or more of the L74V, K65R, and M184V mutations emerge. One exception to the above statements are the recently described isolates that are highly cross-resistant to zidovudine, didanosine, zalcitabine, and stavudine on the basis of a distinctive set of mutations in the RT, the most important being at codon 151. This multiple resistance associated with unique genetic patterns has also been observed in HIV strains isolated from patients given combination therapy with nucleoside analogues, especially zidovudine and didanosine.

Cross-resistance has been reported between zidovudine and other 3'-azido-nucleosides. Reduced susceptibility has been described among zalcitabine, didanosine, and lamivudine (involving the K65R, V75T, and M184V mutations) and between didanosine and zalcitabine (L74V). Although zidovudine resistance was shown to predict more rapid progression of HIV disease, the clinical significance of resistance to the dideoxynucleosides and the clinical correlates of *in vitro* cross-resistance within this class are still not completely defined.

Resistance to lamivudine occurs rapidly *in vivo*, and is associated with substitution at codon 184. This mutation leads to high-level resistance to lamivudine, as well as to some cross-resistance to didanosine and zalcitabine. This mutation antagonizes zidovudine resistance mediated through the 215 (and 41) mutations, restoring phenotypic sensitivity to zidovudine.

The genetic profile of resistance to the new carbocyclic nucleoside 1592U89 has also been investigated in patients in early clinical trials. Some mutations common to other nucleosides have been observed (M184V, K65R, L74V), but their role has not yet been fully established.

Resistance to NNRTIs. The rapid development of reduced susceptibility to nonnucleoside reverse transcriptase inhibitors (NNRTIs) when used in monotherapy or in dual combination regimens initially suggested a limited use for these drugs in clinical practice. However, very interesting results were obtained using one drug

in this class, nevirapine, as part of triple combination regimens in antiretroviral-naïve patients. Effects on CD4⁺ cell counts and plasma HIV RNA levels were sustained for at least one year in many of the patients. Interim results of the Boehringer Ingelheim 1046 trial in antiretroviral-naïve patients given either zidovudine/didanosine, zidovudine/nevirapine, or zidovudine/didanosine/nevirapine demonstrated that in the triple combination arm the majority of isolates obtained from patients who were compliant with all three of the medications remained sensitive to nevirapine. Patients who were poorly compliant with the medications had detectable nevirapine-resistant isolates. These findings again prove the concept that resistance occurs as a direct consequence of viral replication. When the regimens used do not completely suppress HIV, resistance emerges in the presence of plasma levels of the drug.

Treatment with another NNRTI, delavirdine, has induced the emergence of variant strains with K103N and Y181C mutations and occasionally with the P236L mutation. The pattern of resistance may vary according to the extent of the genetic pressure of the drug, with some mutations being preferentially selected by more gradual increases in drug concentrations (V106I, G190T) and others being selected by greater increases in drug concentrations with every subsequent passage (G190E).

Cross-resistance is a common phenomenon with NNRTIs. *In vitro* studies have revealed several mutations common to different compounds: A98G (pyridinones); L100I (TIBOs, pyridinones, BHAPs); K103N (TIBOs, pyridinones, nevirapine, BHAPs); V106A (TIBOs, BHAPs, HEPTs, nevirapine); V108I (nevirapine, pyridinones); Y181C (nevirapine, TIBOs, pyridinones, BHAPs); Y188H (nevirapine, TIBOs, BHAPs); and Y188C (nevirapine, HEPTs). Most of these mutations also have been observed *in vivo* following treatment with these drugs as monotherapy.

Resistance to Protease Inhibitors

Resistance or reduced susceptibility has been reported with all available protease inhibitors, and appears to be associated with a loss of therapeutic effect. Results clearly indicate the frequent selection of strains exhibiting cross-resistance to different protease inhibitors following *in vitro* or *in vivo* drug exposure. The patterns of mutations for protease inhibitors, however, appear to be more complex than for RT inhibitors, with a greater number of sites involved, and greater variability in the temporal patterns and in the combinations of mutations leading to phenotypic resistance. This finding suggests that the protease gene may be able to adapt more easily than the RT gene under the

genetic pressure induced by drugs. Although about 20 codons have been identified as sites of mutation, some changes appear to be more frequent and can therefore help to define subgroups of protease inhibitors according to different genetic profiles.

A phenomenon that has been frequently observed with protease inhibitors is that viruses selecting for a compromising mutation may survive under the pressure of protease inhibitors by selecting compensatory mutations that restore original levels of viral replication. In other words, two kinds of mutations are often seen during protease inhibitor therapy. The first type of mutations are active-site and non-active-site mutations that reduce inhibitor binding. The second type are nonspecific mutations that can restore impaired enzymatic activity.

The issue of resistance to protease inhibitors is also complicated by the fact that the protease enzyme cleaves itself out of the wider *gag-pol* precursor and that the replicative disadvantage conferred by specific mutations may be complemented by adaptive mutations in the *gag* gene whose sequence is recognized by the protease enzyme. This has been shown for the V82F/I84V mutations, whose significant negative impact on replication is apparently reversed by the presence of some mutations in the p17 *gag* region, such as E52Q and Q63E. Interestingly, these mutations do not necessarily involve known protease cleavage sites.

The V82T mutation has been confirmed as a leading viral mutant in reducing binding of the HIV protease to indinavir, although it seems that resistance to indinavir develops as a consequence of multiple changes in the protease gene (eg, V82A,F, or T, plus M46I,L) and the number of subsequent mutations correlates with the degree of resistance. Viral isolates from patients given indinavir showed a very high occurrence of cross-resistance to other protease inhibitors. Cross-resistance was invariably present between indinavir and ritonavir. A 60% to 80% rate of cross-resistance was observed between indinavir and saquinavir or VX478/141W94.

Resistance to ritonavir also occurs as a consequence of the stepwise accumulation of different mutations in the protease gene. Mutations in codon 82 appear to be the critical initial mutations, but additional changes in the protease gene are necessary for high-level resistance to develop. These mutants, including M46I and I84V, are also common to indinavir. The V82T mutation has been found to determine a reduction in replicative efficacy; however, this observation needs confirmation. Cross-resistance to indinavir and to a more limited extent to

saquinavir has been reported in samples from patients given long-term ritonavir.

With respect to saquinavir, the association of G48V and L90M has been confirmed as a double mutation with significant impact on the drug's activity—an impact that is greater than that of the two mutations alone. In patients given saquinavir, mutations at residues 10, 54, 63, and 71 may also contribute to resistance. The low incidence of resistance mutations in patients treated with saquinavir (approximately 50% at one year) may be an inherent attribute of the drug; however, it may also be the result of the low selective pressure exerted on the virus by saquinavir in its present formulation.

During *in vitro* selection with VX478/141W94, the I50V mutant is associated with an eightyfold reduction in affinity to VX478/141W94, but with only a minor reduction in affinity to saquinavir and indinavir.

Nelfinavir is another protease inhibitor that seems to be characterized by some distinct genetic pattern of mutations; the D30N mutation is associated with a sevenfold reduction in sensitivity *in vitro* (after 22 passages at increasing drug concentrations). The same mutation has also been observed in samples from patients given nelfinavir in clinical trials. Other less common mutations include M36I, L63P, V77I, and N88D. The L90M mutation has rarely been observed with nelfinavir, and other mutations, such as G48V, V82A,F,T, and I84V, common to other protease inhibitors have not been detected. However, only results from preliminary studies are available.

Resistance in Antiretroviral-naïve Patients

Pretreatment genotypic resistance in antiretroviral-naïve patients in the DELTA1 and ACTG 175 trials suggests a low incidence of preexisting resistant virus (10 of 173 [6%] patients in the DELTA1 study had mutations in codons 70 or 215; 13% of patients in the ACTG 175 study had mutations in codon 215). These results, which need to be confirmed by sequencing, may indicate an unreported previous use of zidovudine; however, they are consistent with data from seroconverters (a mutation in codon 215 was found in about 10% of patients who seroconverted), which indicates transmission of zidovudine-resistant strains.

Multidrug Resistance

The patterns of mutations observed during combination therapy may be substantially different from those observed using the same drugs as monotherapy. Assessment of the genotype of HIV strains from patients given different antiretrovirals has also shown that although still rare, multidrug resistance can occur. The ge-

netic basis of this phenomenon is currently being investigated. Some sets of mutations responsible for multiple high-level resistance to dideoxynucleosides—particularly to zidovudine, didanosine, zalcitabine, and stavudine—have been described, including V751, F77L, F116Y, A62V, and Q151M. The Q151M mutation, which appears to be the critical first mutation in this set, is somewhat uncommon in untreated patients, and seems to arise via a two-step process—through a Q-L change that precedes the L-M change. The prevalence of this mutation appears to be about 5% in patients treated with combinations of zidovudine and didanosine.

Reversal, Delay, and Suppression of Drug Resistance

As a general rule, drugs that rapidly induce high-level resistance have been expected to have limited clinical use. However, at least two issues have recently modified this view: (a) the theoretical possibility that higher drug dosages can partially overcome resistance (provided that the drug has a very high therapeutic index); and (b) the possibility that the selection of resistance mutations can become a positive tool, if the resistance pattern of one drug can restore or increase the sensitivity to another drug.

Several *in vitro* experiments have shown that depending on the combinations of mutations, both multiple resistance and restored sensitivity are possible. Most of these studies have been conducted in zidovudine-resistant virus (specifically, with the T215Y mutation alone or in association with the M41L mutation). Interestingly, in these studies, the effect of a second drug-induced mutation was potentially different, according to the genetic pattern of zidovudine resistance. The L74V mutation, associated with didanosine exposure, has been shown to restore zidovudine sensitivity in the presence of the T215Y mutation alone; resistance to both zidovudine and didanosine was induced when both the T215Y and the M41L mutations were present. The addition of the V106A mutation to this set (V106A being associated with exposure to nevirapine and other NNRTIs) conferred added resistance to nevirapine. In contrast, the Y181C mutation confers added resistance to nevirapine, but restores zidovudine sensitivity in the presence of the T215Y mutation.

Zidovudine/lamivudine has become an attractive combination, based on the observed suppression of zidovudine resistance in lamivudine-resistant strains with the M184V mutations. In the antiretroviral-naïve population of the NUCB3001 trial, the combination of zidovudine/lamivudine induced significant CD4+ increases and viral load reductions, with both responses being greater in magnitude than

would be expected with this nucleoside combination. The rapid emergence of variant strains with the M184V mutation was observed in almost all patients, indicating rapid selection of lamivudine-resistant strains. At week 24, the proportion of patients who maintained wild-type strains with respect to zidovudine-associated mutations was significantly greater in the zidovudine/lamivudine arm than in the monotherapy arm (75% vs 31%, respectively). This finding suggests that a delay in zidovudine resistance may contribute to the sustained antiretroviral effects of this combination. In this trial, the possibility of reversing zidovudine resistance by adding lamivudine could not be evaluated, because the study population was zidovudine-naïve. This important issue has been investigated in other trials of zidovudine-pretreated individuals. Preliminary results, although confirming that resensitization to zidovudine also can occur *in vivo*, have shown that resistance to both zidovudine and lamivudine can occur with the loss of activity of the combination.

Mutually counteracting mutations have been detected also among NNRTIs. The P236L mutation, associated with the BHAP compounds delavirdine and atevirdine, apparently reverses resistance to nevirapine, TIBOs, and L697,661 conferred by the Y181C mutation. Unfortunately, the Y181C mutation confers resistance to delavirdine and atevirdine as well, so the combined use of NNRTIs selects for virus with mutations conferring resistance to all of the components of the combination.

As discussed above, there was enough evidence only a few months ago to assume that resistance would occur with any effective antiretroviral drug, even when given in combination regimens. However, results, although anecdotal, emerged from the recently reported preliminary analyses of trials of zidovudine/lamivudine/indinavir and zidovudine/didanosine/nevirapine to suggest that a sustained high-level suppression of viral load can significantly delay or even prevent the emergence of resistance.

As a consequence of these experiments, it has been hypothesized that after some years of theoretical “zero viral replication,” HIV infection may even “burnout” as chronically infected cells die off (described as viral eradication). However, reducing viral load to below the level of detection of the assays does not necessarily mean that HIV is absent from the body. Although it is generally accepted that an undetectable viral load level is the optimal target, this target cannot be achieved in all patients, even with highly effective regimens. Also, resistance can occur theoretically even at plasma HIV RNA levels below the current limits of detection, if some level of

replication occurs in "reservoir" tissues. Further studies are clearly needed to investigate these issues.

Clinical Implications

The increased number of available anti-HIV compounds is opening new perspectives and new questions for the design of therapeutic strategies. With about 15 drugs now in clinical practice or in clinical trials, the potential number of combinations is remarkable, and rational criteria must be adopted to select the combinations with the greatest likelihood of efficacy.

The level and durability of antiretroviral activity (ie, viral load and CD4+ cell count changes) is undoubtedly a good criterion for selection of regimens, but other factors, including the resistance characteristics of the drugs, are also important considerations. Although further studies are necessary to assess the complex implications of the resistance patterns for the care of patients with HIV/AIDS, some of the information already available can be used in clinical practice. As a general rule, combinations of drugs that share clear cross-resistance properties should be avoided. Switching between such drugs should also be performed with caution, considering the possibility of a reduced efficacy with the new regimen.

Ideally, therapy with regimens able to induce and maintain maximal viral suppression must be started early to prevent the emergence of resistant strains. Because even complete inhibition of viral replication may not prevent the selection of resistant mutants in the long term if

they exist at a sufficiently high frequency prior to therapy, there is a compelling rationale for treating the patient very early in the course of infection, when the virus is most homogeneous. There is current interest in whether determination of resistance patterns in patients' isolates would be useful in clinical practice. Such information might theoretically be useful for planning treatment on the basis of pretreatment susceptibility or of cross-resistance profiles.

However, a number of issues limit the use of resistance information as a longitudinal marker in clinical management, including: differences among the labor-intensive and time-consuming techniques used; difficulties in quantifying the drug-resistant virus by PCR assays; and the uncertain clinical meaning of drug resistance for many of the currently used anti-HIV drugs. It is also not known to what extent cross-resistance in vitro precludes sequential use of drugs characterized by common mutation profiles. Further clarification of these issues, together with the development of simpler tests that could be used in clinical practice, would be required before drug sensitivity information would have a role in planning and managing antiretroviral therapy for individual patients.

Summary

The possibility of preventing or counteracting the emergence of drug-resistant strains still represents a major issue in antiretroviral therapy. The mechanisms and patterns of resistance development in combination therapy appear to

be more complex than those in monotherapy, and their clinical implications remain only partially known. Although dual combination treatment does not seem to avoid the emergence of resistance, at least in some cases it has been shown to limit or to delay it, or to lead to the selection of less pathogenic quasiespecies, all of which may yield a positive impact on the progression of HIV disease. An issue currently being evaluated in clinical trials is the efficacy of combination regimens based on mutually counteracting, drug-induced mutations, which may convert the unavoidable selection of mutant viruses into an at least partially favorable phenomenon.

Finally, there is hope that the prevention of the emergence of resistance may be achieved by using combinations of drugs that completely inhibit viral replication. This strategy has been shown to be effective in vitro. Data emerging from triple combination regimens with enhanced antiretroviral potency suggest that the emergence of resistance is reduced when viral replication is effectively suppressed, with the subsequent hope of prolonging the antiretroviral effects of future therapeutic strategies.

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AUDIOTAPES OF IAS-USA PRESENTATIONS: Improving the Management of HIV Disease

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