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OPTIMIZING CARE FOR AFRICAN-AMERICAN AND LATINO HIV PATIENTS



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EXECUTIVE SUMMARY

This supplement to the *Journal of the National Medical Association* highlights a number of issues of importance to African-American and Latino healthcare providers. First, and foremost, is the impact of HIV/AIDS in communities of color. In the United States, approximately 1 million persons are living with HIV. Unfortunately, African Americans and Latinos are disproportionately affected. From 1985 to 2002, the proportion of reported AIDS cases among African Americans increased from 25% to 50% compared with a decrease from 60% to 28.3% for whites.¹ These trends are particularly disturbing considering that African Americans comprise only 12.3% of the U.S. population, compared with 75.1% for whites.² Similarly, Latinos represent approximately 13% of the U.S. population but accounted for 20% (8,220 of 41,211) of AIDS cases reported in 2001.¹ While the situation is also dire in the Caribbean and South America, it is even more so in Africa. Worldwide, approximately 77% of AIDS deaths and 68% of new infections are in sub-Saharan Africa.³ Further, the region is home to more than 90% of children infected with HIV.³

Thus, even providers who do not care for HIV patients need to be aware of the significant potential for HIV to be in our communities—not only among African Americans and U.S.-born Hispanics but among immigrants as well. At a minimum, these providers should be able to recognize the manifestations of HIV, know how to screen for it, and know where to refer HIV-infected patients for state-of-the-art care from culturally sensitive providers experienced in treating HIV infection. Clinicians who care for HIV/AIDS patients must stay abreast of the ever-changing treatment guidelines and realize that much of the data used to formulate these recommendations comes from studies involving few minority patients.⁴ To that end, the goal of each article in this supplement is to provide information, where available, that is relevant to our community. Supplements such as this are only the first step, however. Locally, we must attack the HIV/AIDS epidemic on several fronts:

Improve access to and quality of care

We must encourage HIV prevention efforts, including the use of rapid testing, and we must offer care in the communities where it is needed. In addition, that care must be provided by people who are knowledgeable about and sensitive to the populations that we are treating. To ensure that their patients are receiving appropriate care, clinicians should seek consultations when appropriate from physicians in other specialties that have experience with HIV/AIDS, including cardiology, endocrinology, and obstetrics/gynecology.

Encourage the design of relevant clinical trials

Traditionally, clinical trials have been designed to take place in a university or hospital setting. Often, however, data produced by such trials may be only marginally relevant to the needs of African-American and Latino patients. Further, even when minorities are referred to clinical trial sites, they are often not enrolled.⁴ To obtain relevant information, studies must be designed in a way that allows them to be performed in the practices where this population exists.

Address the alarming rate of HIV in U.S. prisons

Although not specifically addressed in this supplement, the prevalence rates for HIV and hepatitis C are high among African-American prison inmates.⁵ As many incarcerated people with HIV will eventually return to the community and are at risk for spreading the virus, we must call for greater use of prevention interventions, such as clean needles, condoms, and drug detoxification in American prisons.

Influence policy-making decisions

Locally and nationally, we must become more active and make our voices heard at the policy-making level. For example, throughout the country, states have reduced funding to HIV care due to budget constraints, a situation that, again, disproportionately affects African Americans and Latinos. International groups, such as those financed by the Global Fund—an important source of funding for programs attempting to combat HIV/AIDS in many developing countries—can be negatively impacted by political efforts at the national level. Greater input and lobbying efforts from healthcare providers of color can help ensure that policy and funding decisions are made fairly and equitably.

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DISPARITIES AND GAPS IN HIV RESEARCH AND CARE

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Key words: racial disparity ♦ clinical trials ♦
HIV/AIDS ♦ epidemiology ♦ antiretroviral
therapy

The HIV/AIDS epidemic has impacted people of African descent worldwide. Of the estimated 40 million (range 34–46 million) adults and children currently living with HIV/AIDS,¹ more than half (25.0–28.2 million) live in sub-Saharan Africa. Further, approximately 1.3–1.9 million reside in Latin America, 350,000–590,000 live in the Caribbean, and 790,000–1.2 million reside in North America. It is well documented that African Americans are significantly over-represented among individuals with HIV/AIDS in the United States.² What is less well known, however, is that African Americans are dramatically under-represented in HIV/AIDS research studies. A recent Medline search revealed that of more than 48,000 articles published on HIV/AIDS between January 1996 and January 2003, only 1.4% of articles refer to African Americans and/or blacks (K.Y.S., unpublished data, 2003). This under-representation is striking considering that African Americans accounted for 38.4% of the 816,149 cases of AIDS reported to the Centers for Disease Control and Prevention from 1985 through 2001 and for 50.2% of the 35,575 newly diagnosed cases of HIV reported in 2001 alone (Figure 1).²

Given the impact of HIV/AIDS in our com-

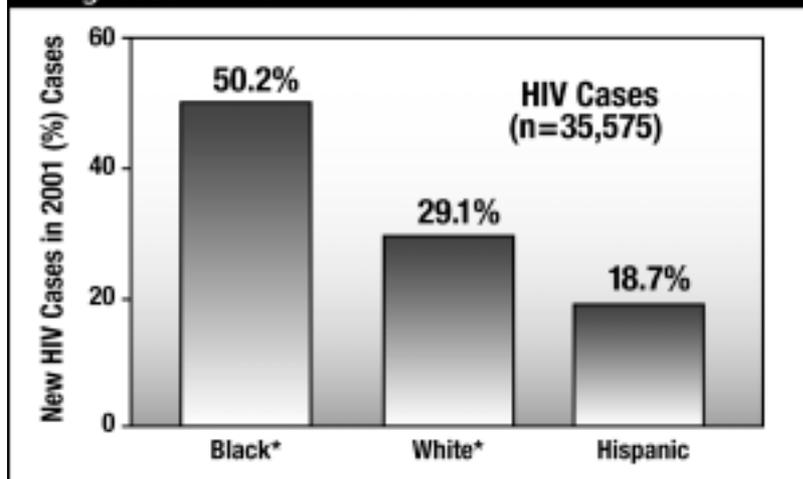
munities, it is critical that efforts to find a cure and optimize treatment strategies focus on these populations. Historically, however, African Americans have been less likely to participate in clinical trials than whites. One recent study revealed that 14% of adults receiving HIV care participated in clinical trials, and 24% received experimental medications.³ However, African Americans were 50% less likely than whites to be clinical trial participants or to receive experimental medications. Among those who sought experimental medications, whites received them more often than African Americans—77% and 69%, respectively ($P=0.03$).

As a result, African Americans have less access to investigational state-of-the-art drugs and treatment strategies than whites, a situation that appears to be leading to higher rates of viral transmission and, ultimately, to the ever-increasing incidence of HIV infection in our communities. Further, this lack of participation in clinical trials denies African-American and Latino patients the benefits of treatment—including lower rates of morbidity and mortality—that are derived by patients receiving state-of-the-art care. Several studies have shown that African-American and Latino patients infected with HIV receive suboptimal care compared with whites.^{4,5} Increasing the numbers of patients who participate in clinical trials can help overcome this disparity.

A separate but equally disturbing issue is that studies in which African Americans are not adequately represented may have limited clinical relevance because of the under-recognized differences between African Americans and other groups and because of the issues that disproportionately impact people of color. For example, the HIV Outpatient Study (HOPS) reported that whites were significantly more likely to develop lipatrophy than nonwhites, and blacks were sig-

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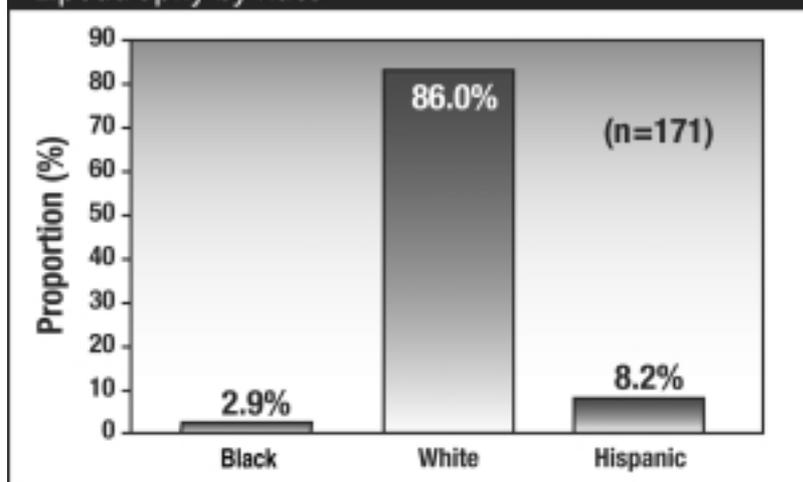
Figure 1. Demographics of New HIV Cases Diagnosed in 2001



*Not Hispanic.

Adapted from CDC: Surveillance Report, 2002.²

Figure 2. Proportion of Moderate to Severe Lipoatrophy by Race



Adapted from Lichtenstein KA, et al. *AIDS*. 2001;15:1389-1396.⁶

nificantly less likely to do so than nonblacks, even after adjusting for age, HIV disease status, duration of antiretroviral therapy, and use of particular antiretroviral agents.⁶ Of the 1,077 subjects in this study, 72% were white, 9% were black, and 13% were Hispanic. Moderate or severe lipoatrophy was reported in 171 patients of whom 5% were black and 18.9% were white. The proportion is

densely populated by these groups and when a safe and secure clinical trials environment is provided for patients to participate in clinical research.

A dearth of African-American and Latino physicians is another important factor contributing to inadequate representation. While 12.3% of the U.S. population is black, only 2.5% of

shown in Figure 2. This finding differs from the anecdotal experiences of clinicians who treat large numbers of black patients with HIV, which suggest that lipoatrophy is a common problem. Are blacks truly less likely to experience lipoatrophy than whites as the HOPS findings suggest, or are the results due to under-representation of blacks in the trial? Accurate answers will only come when African Americans are adequately represented in these studies.

One group addressing this concern is the Women's Interagency HIV Study (WIHS) Collaborative, which has enrolled 2,628 adult women (2,059 HIV-seropositive, 569 HIV-seronegative).⁷ Of the women enrolled, 57% were African American, 22% were Hispanic/Latina, and 18% were white—proportions that more closely mirror the current demographic profile of women infected with HIV. The efforts of the WIHS investigators clearly demonstrate that it is possible to recruit sufficient numbers of African Americans and Hispanics/Latinos to obtain information relevant to these populations. Recruitment of persons of color is improved when clinical trial centers are located in cities

physicians are black and an even smaller number of that group is involved in treating patients with HIV/AIDS.^{8,9} The situation is only slightly better for Hispanics, who comprise 12.5% of the U.S. population but only 3.4% of physicians. One encouraging note is that the percentage of blacks and Hispanics graduating from medical school is increasing. In 2001–2002, 7.2% of graduates were black and 6.1% were Hispanic compared with 5.3% and 5.5%, respectively, in 1992.^{8,9} Enrollment in medical school has increased for both groups as well during the same period. Nevertheless, greater efforts must be made to both increase the number of African-American and Latino physicians and, in particular, to increase the number involved in HIV/AIDS clinical research and care. Greater diversity among investigators could shift the focus of HIV/AIDS research toward the populations who have been disproportionately affected by the current epidemic and substantially improve the quantity, quality, and variety of studies involving these patients. A larger pool of clinicians of color could also help mitigate lingering issues of mistrust of the medical community among African Americans. One recent study in the *Archives of Internal Medicine* found that 727 of 909 (80%) blacks surveyed nationally feared they would be used as guinea pigs for medical research.¹⁰ In addition, clinicians of other cultures who treat blacks and Latinos must learn to deliver culturally competent care in an environment that is safe and comfortable.

Last, but not least, greater efforts must be devoted to providing education on prevention methods that have been shown to reduce transmission among other high-risk populations, such as gay white men and commercial sex workers, including regular use of condoms and repeated HIV testing.

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HIV/AIDS PREVENTION IN LATINO AND AFRICAN-AMERICAN COMMUNITIES

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Key words: HIV testing ♦ prevention ♦ antiretroviral therapy ♦ racial barriers

Recent recommendations from the Centers for Disease Control and Prevention advise all healthcare providers to make HIV testing a part of routine medical care and to work with infected patients to modify their behavior.¹ The goals of this approach are to prevent the spread of disease to noninfected individuals and to reduce the risk of reinfection and resistance among HIV-positive patients. In African-American and Latino communities, HIV prevention discussions must be culturally sensitive. This means physicians should provide facts in neutral ways that do not challenge the values and beliefs of any group or individual. Using this type of nonjudgmental approach helps patients hear and understand lifesaving information more easily and allows them to decide how to apply the information to their own lives within the context of their own values, attitudes, and beliefs. Table 1 lists additional elements of an effective HIV-prevention program targeted toward minority populations.

Discuss Strategies to Reduce Risk

At a minimum, physicians should appraise each patient's risk of contracting or spreading HIV and, for those who are at risk, discuss strategies to reduce that risk. One method is to suggest interventions that promote and reinforce safe behavior. For example, condom use should

be discussed with all patients at risk for HIV infection. Prospective studies have demonstrated that latex condoms, used consistently and correctly during sexual intercourse, can reduce a person's risk of acquiring or transmitting HIV infection by 70% to 100%.²⁻⁴

For patients already on antiretroviral therapy, encourage adherence. Evidence shows that HIV concentration in semen decreased in patients on antiretroviral therapy, thereby reducing the risk of transmission.^{5,6} One study from the Italian Study Group on HIV Heterosexual Transmission⁵ demonstrated a 50% reduction in the risk of HIV transmission. Mother-to-fetus transmission of the virus is also significantly reduced in HIV-infected women on zidovudine therapy. The Pediatric AIDS Clinical Trial Group Study 076 demonstrated a reduction from 22.6% to 7.6% when zidovudine (ZDV) was administered to HIV-infected pregnant women late in the third trimester of pregnancy, and when one dose of ZDV was given to the newborn.⁷ Between 1994 and 1999, there was a 75% decrease in perinatal transmission of HIV (Figure 1).⁸ More recently, fewer than 100 infants in the United States were born HIV-positive.⁹

Patients who participate in behaviors that put them at increased risk for HIV infection or reinfection—such as injection drug use—may benefit from harm reduction counseling. Such measures are aimed at reducing the harm associated with drug use, without necessarily requiring a reduction in consumption. Key concepts of this strategy are: 1) The user's decision to continue injection drug use is accepted as fact but does not imply approval. 2) The user is treated with dignity and respect. 3) The attitude toward the long-term goals of intervention is neutral, although the eventual goal might include abstinence. Any

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Table 1. Critical Elements of Culturally Sensitive HIV Prevention Programs

- Show respect for the community
- Hire culturally appropriate workers who speak the language of the target population
- Provide services in a culturally appropriate, nonjudgmental atmosphere
- Develop community peer education training programs and hire participants as peer educators
- Address clients' survival needs and work on building trust
- Promote confidentiality and anonymity
- Include lesbian, gay, bisexual, and transgender communities
- Do not permit staff to make assumptions based on appearances
- Post hours of operation and accept walk-in appointments

change that reduces harm is viewed as a step in the right direction. For these patients, improvement in quality of life and well-being are the criteria for measuring success.

For some patients, a dual approach to risk reduction may be useful. This strategy gives the patient the option of choosing between abstinence (the first choice of risk reduction) and—if this is not accepted—safer sex behavior, which is the second choice.

Offer Testing

While knowledge of serostatus is an important factor in preventing HIV transmission, many people fail to return for their results from traditional enzyme immunoassays (EIA).¹ Use of a rapid test that provides same-day results can substantially increase the number of persons who receive their test results, improving the delivery of counseling and treatment services and reducing the risk of further disease transmission.¹ A study conducted at Cook County (IL) Hospital demonstrated that use of a rapid test in conjunction with pre- and post-test counseling nearly doubled the number of people who received their results.¹⁰ Of 299 patients tested, 296 (99%) received their results and post-test counseling on the same day. Of that group, 85.7% went to a clinic appointment within an average of 10 days after learning their results. By comparison, only 50% of those

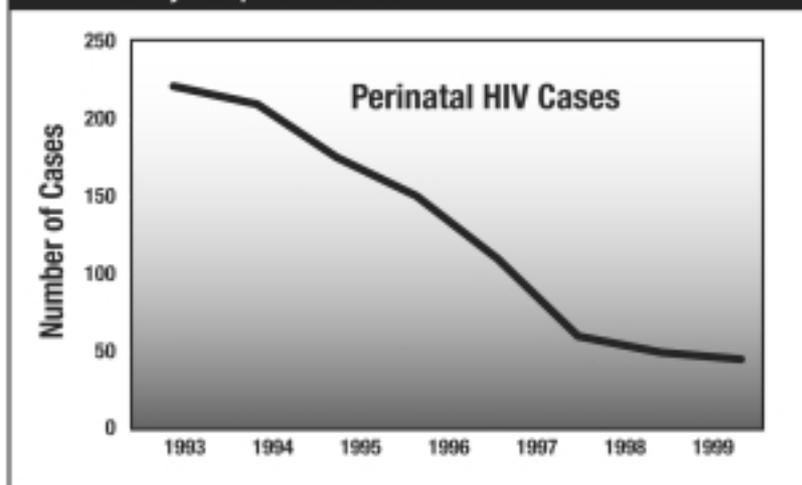
tested by EIA prior to this study received post-test counseling.

Currently, the only FDA-approved rapid point-of-care test, OraQuick[®], can detect antibodies to HIV-1 in fingerstick whole-blood specimens and provides results in approximately 20 minutes.¹ According to data submitted to the FDA by the manufacturer, the sensitivity of OraQuick was 99.6% (95% confidence interval [CI]=98.5%–99.9%) and the specificity was 100% (95% CI=99.7%–100%), which is comparable to FDA-approved EIAs in widespread use.¹¹ While the rapid test is highly accurate, every person with a positive rapid test result should be counseled about their true likelihood of being infected with HIV and about precautions to prevent transmission of the virus. In addition, all results should be confirmed by Western blot testing or EIA.¹

Potential Barriers to Testing and Counseling

It is not uncommon to encounter resistance to HIV counseling and testing from some patients. For some African Americans, reluctance may be due to significant mistrust of the medical community, engendered by the infamous Tuskegee syphilis study. The stigma of AIDS as well as homophobia and denial can also be powerful barriers to testing for African Americans. While language is the most obvious barrier for some

Figure 1. Success of Vigilant Testing and Treatment: Perinatally Acquired AIDS



Adapted from CDC. Surveillance Report. 2002.⁸

Latinos, other culturally significant barriers must also be considered. For example, attempts to educate some Latino men regarding the risk factors for HIV may be affected by an attitude of machismo, which encourages males in the society to have an active sexual life and to seek the services of prostitutes.¹² Because this is viewed as normal behavior, Latino men may not see themselves as at risk for transmission. It may be difficult to reach some Latino women—particularly recent immigrants—with a prevention message, as much of their day-to-day activities are focused in and around the home. Another consideration is that, historically, Latinos have not practiced the concept of preventive care, including getting regular Pap smears, mammograms, and HIV tests.¹³ Providing services in a culturally sensitive context can help overcome these barriers. The use of culturally sensitive multimedia measures to convey the importance of recognizing high-risk behavior may make a significant impact in reducing or eradicating HIV transmission in communities of color.

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INITIATING ANTIRETROVIRAL THERAPY IN ASYMPTOMATIC HIV PATIENTS

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Key words: antiretroviral therapy ♦ HIV/AIDS
♦ CD+4 cell counts

Questions regarding initiation of antiretroviral therapy have yet to be resolved, and researchers continue to seek ways to maximize the benefits of therapy while minimizing the risk of disease progression, drug toxicity, and drug resistance. A growing body of evidence suggests that delayed initiation of therapy is associated with increased risk; and newer drug regimens with improved tolerability and less complexity may make earlier initiation of therapy more appealing.

When to Start Therapy

Guidelines from the U.S. Department of Health and Human Services recommend that treatment be offered to asymptomatic patients with CD4+ cell counts <350 cells/mm³ or plasma HIV-1 RNA level $>55,000$ copies/mL by reverse transcriptase polymerase chain reaction [RT-PCR] or $>30,000$ copies/mL by branched-chain DNA.¹ The International AIDS Society (IAS) 2002 recommendations for antiretroviral therapy suggest a more conservative approach of delaying therapy until CD4 cell counts approach 200 cells/mm³ in asymptomatic individuals.² In making the updated recommendation, the IAS panel cited several cohort studies, including one from Johns Hopkins HIV clinic that demonstrat-

ed an increased risk of mortality when antiretroviral therapy (ART) is initiated in subjects with CD4 cell counts <200 . These studies were unable to demonstrate a clear benefit from initiating ART at higher CD4 cell counts.^{3,4} In addition, the panel relied heavily on an evaluation of the risk of disease progression within three years based on CD4+ cell count and plasma viral load in patients enrolled in the Multicenter AIDS Cohort Study (MACS).⁵ In this study, the risk of progression to AIDS within three years was $<16\%$ for individuals with CD4+ cell counts between 350 and 500 cells/mm³ and plasma HIV-1 RNA $<55,000$ copies/mL (by RT-PCR). However, a dramatic increase in risk (up to 40%) was seen in individuals with CD4+ cell counts between 201- and 350 cells/mm³ or a viral load $>55,000$ copies/mL.

Recent data raise new questions regarding the risks associated with delaying therapy. An updated analysis of the Johns Hopkins HIV Clinic cohort, which had previously found no benefit to initiating therapy at CD4 cell counts >350 , reveals that longer follow-up led to different results.⁶ Among all persons initiating highly active antiretroviral therapy (HAART), persons with CD4 cell counts <200 were significantly more likely to experience an AIDS-defining event or death than those whose CD4 cell counts ranged from 201 to 350 and >350 . An AIDS-free survival advantage was also seen for subjects who initiated therapy at CD4 cell counts >350 , compared with those with CD4 counts of 201 to 350. Confirmation of these findings comes from Ferrer and colleagues.⁷ They conducted a prospective observational cohort study of 573 patients and found that individuals who started therapy with CD4 cell counts >350 cells/mm³ had an extremely low risk (approximately 2%) of disease pro-

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gression after five years, compared with patients who started with counts between 201- and 349 cells/mm³ (approximately 11%). This study examined multiple potential prognostic factors, including baseline CD4 cell count, viral load, type of HAART, etc.; and, in a multivariate analysis, found that only a baseline CD4 <350 was independently associated with AIDS/death (RR 14.7, 95% CI 3.5–60.5, $P < 0.001$).⁷

Importantly, the Hopkins' cohort is quite representative of the group of patients currently being diagnosed with HIV. Of the 1,130 patients studied, 70% were male, 75% were black, 44% were injection-drug users, and 31% were men who have sex with men (MSM).⁶ In contrast, the MACS cohort is 100% male and approximately 80% caucasian.⁵ Clearly, this group is not representative of most individuals diagnosed with HIV today—who are more likely to be black, Hispanic, and/or female—and it is uncertain whether the findings can be generalized to these patients. In fact, recent data suggest that women may have a greater risk of disease progression than men at similar HIV-1 RNA levels.⁸ The DHHS guidelines, which emphasize that the optimal time to initiate antiretroviral therapy remains unknown, suggest that clinicians may wish to consider using a lower threshold for starting treatment in women with CD4+ cell counts >350.¹ It is clear that the optimal time to initiate HAART will vary depending on many individual characteristics of each patient. These recent studies demonstrate a clinical benefit from early therapy.

Immune Reconstitution

Clinical data demonstrating the benefit of early therapy are not surprising, in light of the findings of numerous studies examining immune reconstitution in HIV disease following HAART. One such study is ACTG 315/375, which demonstrated that after the first three years of treatment of individuals with moderate immune compromise (defined as CD4+ cell counts between 100- and 300 cells/mm³), CD4+ lymphocytes of both memory and naïve phenotype increased significantly.⁵ However, most of the increase in CD4+ lymphocytes occurred dur-

ing the first year of treatment. After more than three years of treatment, absolute CD4+ cell counts remained below normal levels.⁹

Other studies of immunologic recovery in individuals with wider ranges of CD4+ cell count at baseline have found that after two years of therapy, CD4+ cell counts remain lower in subjects who started treatment at lower CD4+ cell count levels than in those who started at higher CD4+ cell counts.^{10,11} Among individuals in the DuPont 006 study who started therapy with CD4+ cell counts <200 cells/mm³, 30% still had counts below this level after two years of treatment.¹⁰ Of note, however, is the finding that individuals who initiated treatment when their CD4+ cell count was between 200- and 350 cells/mm³ were at low risk of experiencing a decline in CD4+ cell count to <200 cells/mm³.

Importantly, a recent study examining immunologic and virologic responses to a HAART regimen consisting of lopinavir/ritonavir, stavudine, and lamivudine revealed that subjects with low CD4 cell counts (<50 and <200) could attain good immune recovery that was similar to that seen in subjects with higher baseline CD4 cell counts (>200) after four years of suppressive therapy.¹² These data are encouraging, particularly since many patients present with late-stage disease; thus, the decision regarding early versus late treatment has already been made. In situations where we have the option of early treatment, however, a significant immunologic benefit may be gained from early treatment.

Role of the Thymus

It is well established that the thymus in healthy adults is essentially nonfunctional due to age-related involution. In patients with HIV, viral destruction further contributes to this state. While limited thymus function is of little consequence in healthy adults, in patients with HIV, diminished thymus function may limit the regeneration of T cells. This has been clearly demonstrated in patients undergoing ablative chemotherapy, where younger individuals recover T cells more quickly and completely than older individuals.

Similar results have been seen in HIV disease. A recent study by Viard and colleagues

examined immunologic responses to HAART in individuals of different ages.¹¹ After controlling for other variables, the investigators found that increasing age at the start of therapy was associated with a decreased likelihood of achieving at least a 200-cell increase in CD4+ cell count. Individuals who were older than 37.2 years when they began treatment were 30% less likely to achieve such a CD4+ cell count increase than individuals younger than 37.2 years. Thus, substantial delays in initiating treatment could mean that some individuals will have poorer immune restoration due to their advancing age.

Durable Viral Suppression

Evidence from Sterling and colleagues' observational analysis of the Johns Hopkins HIV Clinic cohort suggests that durable viral suppression is also associated with higher CD4+ cell counts.¹³ In this group, 597 patients (53%) had durable virologic suppression (defined as having more undetectable [<400 copies/mL] than detectable viral loads after the start of therapy), and 533 (47%) did not; the median duration of durable suppression was 19 months. While the individuals who achieved durable viral suppression were significantly more likely to be male and MSM, those who did not were more likely to be female, black, and have a history of using injection drugs. In subjects who achieved durable viral suppression, the median baseline CD4+ cell count was significantly higher than in those who did not—189 and 131 cells/mm³, respectively ($P<0.001$); and the baseline viral load was significantly lower—46,000 and 65,000, respectively ($P<0.001$).

Notably, in subjects who initiated HAART with a CD4+ cell count <350 cells/mm³, the likelihood of disease progression was associated with durable viral suppression: 75% with durable viral suppression did not experience an adverse event (a new opportunistic infection or death), compared with only 35% of those without durable viral suppression. By comparison, among individuals with baseline CD4+ cell counts >350 cells/mm³, the proportion who remained event-free was approximately 85% among those with or without durable viral suppression.

This analysis also found that in patients with baseline CD4+ cell counts <350 cells/mm³ and durable suppression, disease progression did not differ significantly among those with initial CD4+ cell counts <50 , 51–200 ($P=0.83$), or 201–350 cells/mm³ ($P=0.32$). However, longer follow-up suggested that even among those with durable suppression of HIV RNA, starting therapy when the CD4 cell count was >200 cells/mm³ was associated with longer survival than starting treatment after the CD4 count was <200 cells/mm³.

Improved Adherence

An important argument for proponents of delaying therapy has been that poor adherence to complicated suppressive regimens leads to the development of drug resistance over time due to suboptimal suppression of viral replication. Newer regimens with improved potency, tolerability and low complexity, and pill burden are being designed to address this issue, and two important studies reported recently demonstrate that patients taking these regimens achieve undetectable HIV RNA levels.^{12,14}

The four-year follow-up of the Abbott 720 study demonstrated the durability of viral load suppression to <50 copies/mL in 72 treatment-naïve patients.¹² Patients in this study received stavudine + lamivudine combination plus one of three doses of lopinavir/ritonavir (coformulated) for an initial 24 weeks; all patients were later crossed over to open-label treatment with lopinavir/ritonavir 400/100 mg twice daily. At 204 weeks, 99% and 97% of patients (on-treatment analysis) had viral loads <400 and <50 copies/mL, respectively. Intent-to-treat analysis (ITT; missing values=treatment failure) found that 71% and 70% of patients had a viral load <400 and <50 copies/mL, respectively. In addition, there was a mean CD4 cell count increase of 440 cells/mm³ from baseline by week 204.

The Gilead 903 study demonstrated the efficacy of a novel low pill burden (three tablets once per day) regimen incorporating the recently approved nucleotide RT inhibitor, tenofovir DF.⁹ This randomized, double-blind, placebo-controlled study compared a regimen of tenofovir DF + lamivudine + efavirenz with that of stavudine + lamivudine +

efavirenz in 600 previously treatment-naïve HIV-positive patients. At 96 weeks, ITT analysis (missing values=treatment failures) found that between 74% and 78% of patients in both arms achieved suppression to <50 copies/mL.¹⁴

These and other studies that demonstrate the success of low complexity, low pill burden, and high tolerability regimens will improve our ability to offer patients the benefit of HAART with minimal negative impact on their quality of life. Currently, the preferred regimens for treatment-naïve patients recommended by the U.S. Department of Health and Human Services are lopinavir/ritonavir + lamivudine + (zidovudine or stavudine) or efavirenz + lamivudine + (zidovudine or tenofovir DF or stavudine). However, the safety of efavirenz in pregnant women has not been established, and regimens containing this agent are not recommended for women who are pregnant or who have pregnancy potential.¹

CONCLUSION

Taken together, these data emphasize the advantages of treating HIV disease well before advanced immunodeficiency. With the availability of newer, effective low-pill burden regimens, poor adherence and the development of resistance may, in the future, no longer be considered risks of early therapy.

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MANAGING THE METABOLIC AND MORPHOLOGIC COMPLICATIONS OF HIV

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Key words: hyperlipidemia ♦ metabolic complications ♦ morphologic complications ♦ highly active antiretroviral therapy

Clinicians have long been aware of metabolic and morphologic derangements associated with HIV and are becoming increasingly knowledgeable about abnormalities putatively associated with highly active antiretroviral therapy (HAART). While much remains to be learned about the etiologies of these complications, effective interventions are available. This article reviews current guidelines for monitoring and recommendations for treatment. It is important to note that these recommendations are based on findings from studies and experiences involving relatively few minority patients. Future studies with more diversified study populations are needed to provide more definitive guidance.

LIPID METABOLISM

Studies performed in the pre-HAART era showed multiple abnormalities in lipid metabolism among people infected with HIV. These abnormalities included decreased plasma concentrations of high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), as well as increased plasma levels of very-low-density lipoprotein cholesterol (VLDL-C).¹⁻⁴ Since the initiation of HAART, elevations in triglyceride and LDL-C levels have been report-

ed.⁵ The association between lipids and specific HIV treatment regimens and their long-term effect on cardiovascular health is unclear; however, the benefits of HIV therapy clearly outweigh the risks.⁶

Assessment and Treatment

Few studies have been completed regarding how to best monitor HIV-infected patients with or at risk for lipid abnormalities. An International AIDS Society-USA consensus panel recommends that physicians perform a fasting lipid panel (triglyceride, total cholesterol, HDL-C, and LDL-C levels) prior to initiating or switching HAART and to repeat it periodically (three to six months).⁵ There are growing data to suggest that the lipid abnormalities associated with HIV infection and treatment carry the same risk for cardiovascular disease as those in seronegative individuals.⁷ Even less is known about the implications for HIV-infected patients with pre-existing hyperlipidemia.

There are some data to suggest that certain antiretroviral drugs are associated with adverse cardiovascular events, although there are no studies to show head-to-head comparisons of specific regimens.⁸ Until further studies provide such information, physicians should assess cardiovascular risk in HIV patients with lipid profile alterations in light of other risk factors, such as smoking status, presence of diabetes, hypertension, family history, and menopausal status. Most experts advise following the National Cholesterol Education Program (NCEP) III guidelines to determine when to recommend lifestyle changes and/or initiate medical therapy for hyperlipidemia.⁹

In patients with pre-existing risk factors for cardiovascular disease, hyperlipidemia, or a fam-

© 2004. From the Integrated Minority AIDS Network, Inc. (IMANI), Dallas, TX (Rawlings); Boriken Health Center, East Harlem, NY (Santos). Send correspondence and reprint requests for *J Natl Med Assoc. February Supplement 2004*; 96:17S-20S to: M. Keith Rawlings, MD, Integrated Minority AIDS Network, Inc. (IMANI), 400 S. Zang Blvd., Suite 1220, Dallas, TX 75208; phone: (214) 942-5400; fax: (214) 942-7230; e-mail: mkrawlings@imanihiv.org

ily history of cardiovascular disease, consider initiating or switching to a regimen with no associated lipid problems. Keep in mind, however, that switching nucleoside therapy when lipoatrophy has developed on an nucleoside reverse transcriptase inhibitor (NRTI)-based regimen has not been shown to make a significant improvement in lipoatrophy.¹⁰⁻¹² When options are limited, antiretroviral therapy agents that can lead to lipid elevations should not be withheld.¹³

As no specific dietary interventions have been evaluated for reducing the cardiovascular risk of antiretroviral-induced hyperlipidemia, most experts recommend following NCEP dietary guidelines to lower cholesterol in adults.⁹ Recommendations include weight loss, exercise, reduction in alcohol intake, and smoking cessation. Lipid-lowering agents are appropriate for patients whose triglyceride levels are 500 mg/dL or higher to reduce the risk of pancreatitis.⁵ Fibrin acid analogues (gemfibrozil and fenofibrate) are effective in reducing triglycerides in patients on HAART. HMG-CoA reductase inhibitors (statins) effectively reduce total cholesterol and LDL-C levels.¹⁴ Based on the risk of potential interactions, pravastatin and atorvastatin are preferred.¹⁴ Omega-3 fatty acid supplements have shown a modest triglyceride lowering effect.¹⁵ While niacin is also hypolipidemic, it has been associated with adverse effects (cutaneous rash, insulin resistance) in patients on protease inhibitor (PI)-containing regimens.¹⁶

GLUCOSE ABNORMALITIES

On average, African Americans are twice as likely and Hispanics are 1.9 times as likely to develop diabetes mellitus as whites, regardless of HIV status. In addition, up to 40% of patients on certain PI-containing regimens have had glucose intolerance due to insulin resistance.^{13,17} Individuals with traditional risk factors for type-2 diabetes mellitus who take some PIs may be at particularly high risk for fasting hyperglycemia and diabetes.¹⁸

Assessment and Treatment

There are limited data on optimal HIV-1 management in patients with fasting hyper-

glycemia. Initiating therapy with some PIs may induce or exacerbate pre-existing problems with glucose tolerance. Therefore, fasting glucose levels should be determined prior to initiating PI-containing HAART and every three to six months during treatment. Consider avoiding PI-based regimens as initial therapy or substituting alternatives, when possible, in patients with pre-existing abnormalities of glucose metabolism or in patients with first-degree relatives with diabetes mellitus.⁵ Treatment of hyperglycemia should follow American Diabetic Association guidelines for HIV-negative patients, including eating a healthy diet, getting regular exercise, losing weight, and smoking cessation.¹⁹ Medical therapy should focus on insulin-sensitizing agents (metformin or a thiazolidinedione). However, physicians should monitor for hepatic dysfunction in patients on thiazolidinediones and for lactic acidosis in those taking metformin.⁵ Use of NRTIs—particularly d4T—has been associated with an increased risk of hyperlactatemia and lactic acidosis—a potentially life-threatening complication.^{20,21} Therefore, concomitant use of these agents and metformin should be avoided. Physicians should also be aware that several of the complications of diabetes—such as neuropathy, retinopathy, and renal disease—overlap those of HIV disease or its treatment. Therefore, it is important to rule out diabetes as a cause of these problems.

MORPHOLOGIC COMPLICATIONS

Weight loss and wasting remain common complications associated with HAART regimens. Both complications occur in patients who have been treated with HAART, who have failed HAART, and who are HAART naïve.⁵ While wasting is commonly thought of as a progressive decrease in body weight of more than 10% from baseline, some patients may gain fat while losing muscle mass, causing their weight to remain steady.

A variety of fat redistribution abnormalities have also been reported, and prevalence estimates vary. Dorsocervical fat deposit, commonly known as buffalo hump, has been reported in 0.4%–5.0%, increased breast size in 1.0%–

37.0%, and increased abdominal girth in 1.0%–56.0% of patients on HAART regimens.²² Together, these three abnormalities are referred to as fat accumulation syndrome. In the lipoatrophy syndrome, facial lipoatrophy is seen in 1.0% to 24.0% of patients, while peripheral atrophy has been reported in 6.0% to 11.0% of patients. Combined syndromes have been reported in 1.8% to 83.0% of patients.²² Physicians should keep in mind that a number of factors, including age, baseline BMI, duration of HIV-1 infection, baseline degree of immunodeficiency and subsequent immune restoration, have been associated with fat distribution abnormalities.⁵

Regardless of the cause, the psychosocial and clinical effects of these changes are profound. Initially, patients report poor self-esteem and feel stigmatized—emotions that, in some patients, lead to depression. Adherence may also become an issue if patients stop taking their medication to avoid these side effects. Clinically, patients with buffalo hump may report neck pain. Those with increased abdominal girth may report respiratory difficulty, umbilical hernia, or gastroesophageal reflux disease. Patients with increased breast size may report pain associated with the enlargement.

Assessment and Treatment

Wasting is an independent predictor of death. Consequently, it is very important to regularly check weight and to obtain chest, bicep, waist, hip, thigh, and calf measurements. Anthropometric measurements, which can be performed easily and inexpensively, should be performed quarterly. Regular measurements can also help identify and document lipodystrophic changes. If wasting or weight loss is noted, conduct a dietary assessment. Asking basic questions, such as “Are you eating?” or “Do you have food?” can identify patients whose weight loss is due to limited access to food. Inadequate calorie intake may also be due to anorexia, anxiety, depression, malabsorption, gastrointestinal dysfunction, diarrhea, or altered metabolism (growth hormone resistance or deficiency, opportunistic infections, malignancies, and cytokine dysregulation). These conditions must be ruled out or treated, if present.

Although few controlled trials have been reported, clinicians are currently assessing a number of therapies for these wasting and fat abnormalities. In addition to dietary modification and exercise, potential interventions include growth hormone, testosterone replacement, oxandrolone, appetite stimulants, and modification of HIV therapy. Of these, growth hormone treatment seems most promising, having demonstrated significant and prolonged increases in weight and lean body mass and reductions in wasting-associated mortality.²³ Side effects may limit its use, however.⁵ Studies using objective measurements have failed to demonstrate consistent reversal of central fat accumulation abnormalities when PI therapy was switched or discontinued.⁵ Consequently, for patients with isolated fat accumulation, this approach is not recommended. For patients whose primary complaint is lipoatrophy, withdrawal of stavudine and substitution of abacavir or AZT is associated with statistically significant improvement, but clinically no changes could be appreciated.

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THE IMPACT OF SUBSTANCE ABUSE ON THE CARE OF AFRICAN AMERICANS AND LATINOS WITH HIV/AIDS

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Key words: substance abuse ♦ injection drug use ♦ HIV/AIDS ♦ hepatitis C ♦ antiretroviral therapy

Approximately one-third of all AIDS cases in the United States are among active or former injection drug users (IDUs).¹ Among African-American men and women, injection drug use is the second leading cause of HIV infection (after heterosexual contact); 30% of all new AIDS cases among African-American men and women in 2001 were the result of HIV transmission from injection drug use.² HIV transmission related to substance abuse is also a significant problem among Hispanics, particularly among those of Puerto Rican origin. Among Hispanics born in Puerto Rico, 43% of AIDS cases reported in 2001 were the result of HIV transmission from injection drug use.² By comparison, 6% of cases reported among Hispanics born in Mexico and 17% of cases reported among Hispanics born in the United States were the result of injection drug use.

While needle-sharing is the primary behavior associated with HIV virus transmission, substance abusers* are also more likely to engage in high-risk practices, such as having unprotected intercourse, multiple sex partners, or exchanging sex for drugs. Individuals who abuse alcohol and noninjection drugs are also likely to participate in these types of risky behaviors. For substance-abusing HIV patients, treatment of the substance abuse is a critical component of care,

as it can help reduce the likelihood that patients will engage in these practices.³ Treating these patients is particularly challenging given the number of pharmacologic agents needed to address multiple concomitant problems. This article reviews important prescribing issues that must be taken into consideration when treating this population.

ADHERENCE

Resistant viral variants emerge under antiretroviral drug selective pressure, especially with incomplete suppression by some antiretroviral regimens, resulting in a diminished magnitude and duration of response to antiretroviral therapy. However, resistance is less likely to develop when patients adhere to their prescribed regimen. Unfortunately, both active drug and alcohol use have been associated with lower rates of adherence.⁴ Further, the high prevalence of psychiatric, cognitive, and social problems in these patients increases the risk of noncompliance. There are, however, a number of strategies that can be employed to improve adherence.

Directly observed therapy (DOT) has been shown to improve adherence and may be an option for patients who are actively engaging in illicit substance abuse.⁵ For patients who take methadone, DOT can be administered through the methadone program, enabling both regimens to be taken in the same place under supervision. Alternatively, twice-daily regimens can be administered in the morning and evening in the physician's office. For patients who self-administer, it is helpful to have the first set of medications mailed to the physician's office. This enables the healthcare provider to review instructions and helps ensure that the patient understands them. Other helpful strategies

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include written or pictorial instructions; use of a timing device, such as a beeper, to help ensure that medications are taken on schedule; and reinforcement with a support network, such as the pharmacist, nurse, support groups, case manager, and family members. With this type of reinforcement, some patients have sustained virologic control for more than five years (unpublished data, A.V.). Others have also reported sustained virologic control with DOT. Fischl and colleagues demonstrated that at 48 weeks, 100% of HIV-infected inmates (n=50) on DOT had HIV RNA levels below 400 copies/mL compared with 81% of HIV-infected patients (n=50) in an outpatient research program who self-administered therapy.⁶

Most experts agree that any HIV-infected patient with a detectable viral load who is ready to begin treatment should do so at once.³ However, some HIV patients who are actively abusing drugs may need to delay starting highly active antiretroviral therapy (HAART) until they can get treatment for their substance-abuse problem. The rationale is that patients who are constantly worried about procuring drugs will not comply with treatment. If the patient is not ready to commit to the regimen (thereby increasing the risk of nonadherence and the development of resistance) and has a high CD4 count, HAART can be withheld for several months.

Each patient must be evaluated individually, however. Some patients who use drugs daily can be very adherent. Anecdotal experience has shown that when survival needs (such as food, shelter, and safety) are addressed, substance abusers can be as adherent as nonusers. Stressing the benefits of HAART and the risks of non-compliance can help patients understand the importance of adherence.

PRESCRIBING CONSIDERATIONS

With the need for so many medications in this population, the potential for drug interactions is high. The following section reviews a few of the issues of concern to providers caring for HIV-infected substance abusers.

Two commonly used non-nucleoside reverse transcriptase inhibitors (NNRTIs)—efavirenz and

nevirapine—induce the hepatic cytochrome P450 metabolism of methadone.^{7,8} This leads to lower blood levels of methadone, which, in turn, can induce symptoms of opiate withdrawal. Increasing the daily dose of methadone by 10 mg every one to two days beginning on the day NNRTI treatment is initiated can prevent this problem. The protease inhibitor (PI) nelfinavir may produce a similar reaction, but studies have produced conflicting results.⁸ The combination of saquinavir plus ritonavir and the coformulated lopinavir/ritonavir can be used without routine dose adjustments.⁹

Nevirapine and efavirenz are associated with an increased risk of hepatitis, necessitating more aggressive patient follow up.^{3,10} The central nervous system side effects associated with efavirenz can mimic symptoms associated with drug use.³ In some instances, these feelings may trigger patients to begin using drugs again or to stop using efavirenz because they fear it may trigger use. In addition, some patients abuse efavirenz to boost their high.

Rifampin, given for the treatment of tuberculosis, may decrease the effectiveness of methadone by potentially inducing the rapid onset of classic opioid withdrawal symptom when these agents are coadministered.³ Gradually increasing the daily dose of methadone when rifampin treatment is initiated can prevent this problem. Rifabutin, phenytoin, and phenobarbital have similar effects on plasma methadone levels.³ In addition, rifampin may increase the risk of liver toxicity and should be avoided in patients taking PIs.³

Many substance-abusing HIV patients are coinfecting with hepatitis C. Some medications used to treat HIV may elevate liver enzymes, thereby worsening underlying chronic hepatitis C and B.¹¹ Nucleoside reverse transcriptase inhibitors have been associated with mitochondrial toxicity, while NNRTIs and PIs have been associated with an increased risk of hepatitis.¹¹

Less is known about interactions with alternative therapies. However, St. John's wort, which is used to treat depression, was shown to decrease the effectiveness of PIs and to decrease methadone blood levels.^{12,13} Until more is known about these alternative therapies, it may be advisable to tell patients to discontinue their use of alter-

native medicines when they begin HIV therapy. In addition, therapeutic drug monitoring may be appropriate when initiating antiretroviral therapy with coadministration of other hepatic-metabolized medications in this patient population to ensure therapeutic drug levels.

Patients with HIV who abuse alcohol—particularly those who are coinfecting with hepatitis C virus (HCV)—present a special challenge. Coinfection has been associated with more rapid progression to fibrosis and cirrhosis and to an increased risk of hepatocellular carcinoma (See *HIV/HCV Coinfection: Management Update*, page 25S). Thus, a reduction in alcohol use is crucial, and abstinence is recommended during antiretroviral therapy for HCV. Referral to substance abuse counselors is essential in addressing the complex problems these patients face.

Despite all of the challenges discussed above, it can be extremely rewarding for physicians and other healthcare providers to work with highly motivated former and active substance abusers who are HIV positive. These patients educate themselves about their medical condition, successfully complete substance abuse treatment, adhere to their healthcare regimen, and strive to help others to prevent HIV infection. Often, such patients become part of the treatment team, serving as peer advocates who help others who are reluctant to obtain HIV counseling and testing, supporting their entry into medical and substance abuse treatment, and providing continued support throughout the course of therapy.

** For the purposes of this article, substance abuse is defined as excessive use of addictive or abused substances and includes both substance abuse and substance dependence as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV).*

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HIV/HCV COINFECTION: MANAGEMENT UPDATE

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Key words: hepatitis C ♦ HIV/AIDS ♦
coinfection ♦ antiretroviral therapy ♦
pegylated interferon.

Of the estimated four million persons in the U.S. infected with hepatitis C virus (HCV), approximately one million are coinfecting with HIV.¹ Among injection drug users, between 50% and 90% are coinfecting.² HCV infection is substantially more prevalent among African Americans than among other racial groups.³ Based on these reports, all HIV-infected people should be screened for hepatitis C (as well as hepatitis B) during the routine physical examination. Vaccination is recommended for patients with chronic liver disease with negative antibodies against hepatitis A and/or B.

Screening for HCV can be performed by multi-antigen antibody testing using the enzyme immunoassay (EIA-2 or EIA-3) method. In high-risk populations, a positive test should be considered diagnostic, even without an abnormal alanine aminotransferase (ALT) level. However, all patients who test positive for HCV should have a test to detect HCV RNA in order to confirm the chronicity of the infection. Spontaneous RNA clearance of HCV occurs in around 15%–20% of infected subjects; these rates are lower in African Americans compared with Caucasians.⁴ False-negative results may occur in the early stages of acute hepatitis C infection (window period) and in HIV-infected patients with low CD4 counts who have lost detectable antibody due to severe immunosuppression. Anti-HCV antibodies can

re-emerge in the setting of highly active antiretroviral therapy (HAART)-induced immune reconstitution.^{5,6} When EIA results are negative but coinfection is highly suspected (for example, a history of drug abuse, transfusion, hepatitis C-infected partner), a test for hepatitis C virus RNA should be performed. While a liver biopsy is not absolutely required before initiating treatment,⁷ in this population, biopsy results provide a more accurate assessment of disease severity than hepatitis C virus PCR levels, ALT, or clinical staging.⁸ Currently, liver biopsy should be offered to most patients in order to make decisions about starting HCV therapy.

In hepatitis C-infected patients who do not have HIV, criteria for treatment include persistently elevated liver enzymes, detectable hepatitis C virus RNA, and portal or bridging fibrosis and at least moderate inflammation and necrosis on biopsy.⁷ Whether to treat patients at lower risk for cirrhosis is unclear. However, aggressive treatment of hepatitis C is recommended for HIV patients due to more rapid progression to fibrosis and cirrhosis and to the increased risk of hepatocellular carcinoma in this population. A National Institutes of Health consensus panel recommends that hepatitis C therapy be considered for coinfecting patients with good functional status, a stable antiretroviral regimen, and a sustained HIV virologic response.⁷ Treatment of patients with clinically compensated cirrhosis is controversial due to an increased risk of side effects and decreased efficacy of the current regimens in this group. Patients with decompensated liver disease should not be treated, however.

Most African Americans with hepatitis C infection are infected with the genotype-1 subtype.⁹ Unfortunately, this is the least responsive genotype to therapy. African Americans might

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also be less responsive to HCV treatment due to the higher iron load in this racial group.¹⁰ Ideally, therapy should be initiated: 1) before significant HIV-induced CD4 cell loss occurs, as lower CD4 counts diminish the likelihood of successful response to hepatitis C treatment, or 2) after immune restoration is achieved by successful HAART. Patients with genotype 1 should be treated for at least 48 weeks with high doses of ribavirin (1,200 mg/d).¹¹ A shorter duration of treatment or a lower dose of ribavirin decreases the likelihood of achieving a sustained virologic response. It is likely that coinfecting patients with genotype 2-3 should also be treated for at least 48 weeks.¹²

Treatment of HIV is also important. Tedaldi and colleagues demonstrated that HAART use among coinfecting HIV/HCV patients is a strong predictor of survival.¹³ This finding suggests that treatment of HIV is more important to survival than HCV coinfection status.

Even though the short-term hepatotoxicity of HAART is increased in subjects with HCV, the long-term consequences of this treatment in the progression of liver disease are more controversial. Small retrospective studies associate HAART with improved, worsening, or no effect on liver damage. The effect of HCV on the efficacy of HAART has also been studied. Several studies suggest that virologic response to HAART is unaffected by HCV status.¹⁴ Other cohort studies had shown worse response to HAART in subjects with HCV, although these findings were sometimes attributed to lower rates of adherence and more psychosocial issues in this population. However, immunologic response to HIV therapy may not be as good in coinfecting patients.

Providers treating HIV/hepatitis C coinfecting patients need to be aware of the potential for drug interactions and drug toxicity. For example, when ribavirin is combined with HIV regimens incorporating didanosine, patients are at increased risk for pancreatitis, symptomatic hyperlactatemia/lactic acidosis, and peripheral neuropathy. Zidovudine should be used with caution because it could potentiate the risk of anemia induced by ribavirin. Because of the complex nature of hepatitis C infection in patients with HIV, clinicians should develop collaborative

relationships with appropriate specialists for providing care for coinfecting patients.

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IMPROVING ADHERENCE TO HAART

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Key words: adherence ♦ HIV/AIDS ♦ highly active antiretroviral therapy

Following the introduction of highly active antiretroviral therapy (HAART) for HIV/AIDS in 1996, HIV-related morbidity and mortality in the United States dramatically declined. Although maximum and durable suppression of HIV plasma virus load is required to maintain the long-term effectiveness of HAART, in clinical practice, 50%–60% of patients fail to achieve this goal.^{1,2} Suboptimal adherence (i.e., taking medications <95% of the time)—particularly among patients receiving initial regimens—is the primary reason for failure.

While several studies have shown that race, gender, disease stage, and history of substance abuse are not predictive of adherence,^{3–5} a number of potentially modifiable characteristics have been found to be predictors. Knowledge of these characteristics can help clinicians develop a comprehensive strategy to enhance adherence.

Although demographic characteristics remain inconclusively linked to adherence to HAART, several other patient factors have been consistently linked to poorer adherence. Both heavy alcohol use and active injection drug use consistently predict nonadherence to HAART.⁵ In contrast to active injection drug users, however, former substance abusers appear to have rates of adherence to HAART that are similar to individ-

uals with no history of substance abuse. Depression also consistently predicts nonadherence to HAART.⁵ It should be noted that depression has been found to be among the strongest correlates of poor adherence to treatment for other medical illnesses as well.⁶ Because of the impact of untreated depression on adherence, all patients with HIV should be screened for depression prior to initiating therapy.

Belief in the effectiveness of HAART has been shown to be an important predictor of adherence.^{5,7} Recent results from a qualitative study of 44 persons with AIDS (28 men, 16 women), including 17 persons of color, demonstrated that most patients who were excellent adherers (i.e., took their medication consistently 90%–100% of the time) believed that this high level of adherence was necessary to benefit from the medication.⁷ Further, excellent adherers were more likely than nonadherers to have nondetectable viral loads; 73% of patients with excellent adherence had nondetectable viral loads compared with only 35% of those with suboptimal adherence. These findings underscore the importance of providing patients with information about the consequences of failing to maintain high levels of adherence.

The physician–patient relationship also appears to have a significant impact on adherence, with a better relationship associated with better adherence.^{7,8} For example, in a recent study, Malcolm and associates found that excellent adherers reported having a great degree of respect for their primary care providers.⁷ In addition, they were comfortable sharing personal information and trusted their providers' clinical recommendations. By comparison, suboptimal adherers were less likely to trust their providers and were more likely to be suspicious of their providers'

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intentions. These findings suggest that in clinical practice, providing care in warm and supportive settings in which patients feel comfortable and are cared for by knowledgeable, culturally competent providers may help improve adherence among African-American and Latino patients. In addition, asking patients about their attitudes toward HAART may help uncover any misperceptions or negative perceptions about treatment. Use of a support group, peer educator, or treatment buddy can be helpful yet non-threatening ways to clarify any misunderstandings the patient may have.

Characteristics associated with the medication regimen have also been shown to affect adherence. These, too, have the potential to be modified to improve adherence. A meta-analysis of HAART regimens by Bartlett and colleagues found that pill burden was the most significant negative predictor of viral suppression.⁹ Superior virologic response was associated with regimens involving the least number of pills ($P=0.0085$). In the Perspectives on Adherence and Simplicity for HIV+ Patients on Antiretroviral Therapy (PASPORT) survey,¹⁰ investigators found that of 10 characteristics evaluated by patients with HIV for their anticipated impact on adherence (total pills per day, dosing frequency, side effects, dietary restrictions, pill size, number of refills, number of insurance copayments, number of prescriptions, number of medication bottles, and bedtime dosing), total pills per day—with a mean attribute importance score of 14%—was the most important.

Dosing frequency also appears to be an important obstacle to adherence. Regimens requiring three-times daily or more dosing have been associated with lower adherence than twice-daily regimens.^{11,12} In the PASPORT survey, participants evaluated seven frequently prescribed triple-drug combination regimens, including three regimens comprising agents that could be administered on a once-daily basis.¹⁰ While once-daily dosing was viewed as the most desirable dosing schedule, unless such a regimen could be taken at one time as one combined product with no more than two pills and no

dietary restrictions, it was no more likely to improve adherence than existing twice-daily regimens consisting of one pill per dose.

Earlier studies have also reported that dietary restrictions may negatively impact adherence. Stone and colleagues demonstrated that the need to take one or more medications on an empty stomach was associated with an increased risk of skipping doses (OR=1.5; 95% CI, 0.9–2.6).¹² A number of investigators have reported finding an association between the occurrence of side effects during treatment with HAART and decreased adherence.^{13–15}

Physicians with experience treating HIV/AIDS patients report incorporating at least one activity to enhance adherence into their practices.¹⁶ Regimen-related strategies used by these experts include:

- Simplifying the regimen to the degree possible while incorporating the necessary potency.
- Informing patients, in advance, what side effects may be experienced and how to manage them.
- Avoiding medications that cause very unpleasant side effects, when possible.
- Providing written information to help ensure that patients understand how to take their medication. A dosing schedule with photographs can be very helpful.
- Recommending counseling by a nurse, pharmacist, or peer counselor.
- Dispensing devices, such as a pill box, beeper, or medication diary.

As discussed above, a number of factors influence a patient's ability to adhere to the prescribed treatment plan. By communicating openly and effectively with patients, physicians can help improve patient satisfaction, which, in turn, should help improve adherence and, ultimately, outcome.

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COMBATING ANTIRETROVIRAL RESISTANCE

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Key words: resistance ♦ HIV/AIDS ♦ highly active antiretroviral therapy ♦ potency ♦ durability ♦ boosted protease inhibitors

The disparity in HIV-associated morbidity and mortality among African Americans and Latinos is well known. However, clinicians on the frontlines of care can help reduce the risk of treatment failure by considering the impact of pharmacokinetic factors, in addition to factors, such as regimen complexity and side effects and their impact on adherence, when selecting an initial highly active antiretroviral therapy (HAART) regimen.

Two strategies that have been used to aid therapeutic decision making in this regard are the “sequence” model and the “probabilistic” model. In the sequence model, which should be considered only when selecting treatment for relatively healthy patients (high CD4 count, low viral load) who will be on long-term therapy, the physician selects an initial regimen not on the basis of potency, but on the ability to provide salvage therapy in the event of treatment failure. In other words, initial agents are chosen on the basis of their salvageability (i.e., mutations are unlikely to confer cross-resistance). In this case, antiretroviral therapy is chosen to maximize future options and takes into account which regimens would later be used in the event that virologic failure occurs.

The development of resistance remains an important issue for patients on HAART. Two studies provide examples of resistance at time of

first HAART failure in treatment-naïve patients. Havlir and colleagues¹ showed lamivudine resistance was present at the time of a first viral rebound in virus from 82.3% (14/17) of patients receiving triple-combination therapy with zidovudine + lamivudine + indinavir. The M184V mutation was present in virus from all 14 patients; protease inhibitor (PI)-resistant virus was recovered from only 1 of 26 patients receiving either triple-combination therapy or indinavir monotherapy. Similarly, Rusconi and colleagues² showed lamivudine resistance was found in virus from 87.5% of patients who experienced a first viral rebound while receiving zidovudine + lamivudine + amprenavir.

Thus, an important caveat to choosing an agent on the basis of having a salvageable resistance profile is that as soon as treatment failure becomes apparent, it is essential to change to a salvage regimen to prevent the emergence of drug-resistant HIV strains, which could possibly render other drugs less effective over the long-term.

An alternative approach for choosing an initial antiretroviral regimen is demonstrated using a probabilistic model. With this approach, the prescriber assumes that some drugs are more likely to produce resistance than others. Using this rationale, the prescriber selects agents that are more likely to be highly potent and to achieve durable viral suppression for the initial regimen.

Such drugs have a lower potential for failure and provide minimal opportunity for the development of possible mutations. Thus, regimen choices are made on the basis of the probability of avoiding resistance for the long-term.

Because most PIs are rapidly metabolized, trough levels of drug can fall below the concen-

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tration necessary to inhibit viral growth at the end of the dosing interval. Repeated or prolonged exposure to subtherapeutic concentrations of PIs may allow eventual emergence of resistance. One way to increase the trough levels of PIs is by co-administration of a second PI (or a coformulated agent), which inhibits the metabolism and hence increases plasma concentration of the first agent. Such a strategy avoids the subtherapeutic concentration of an unboosted PI and delays or entirely prevents the emergence of PI resistance. For example, Bernstein and colleagues³ showed that in patients experiencing first viral rebound while on stavudine +lamivudine +lopinavir/ritonavir therapy, none had protease resistance but 37.2% had resistance to lamivudine. Kempf and colleagues evaluated patients receiving either nelfinavir or lopinavir/ritonavir in combination with stavudine and lamivudine.⁴ They found that at 108 weeks, despite the use of identical NRTIs, there were significantly more patients in the nelfinavir arm with resistance to lamivudine and PIs and thymidine-associated mutations (TAMs) than in the lopinavir/ritonavir arm. However, neither TAMs nor PI resistance developed in the lopinavir/ritonavir arm.

In conclusion, antiretroviral resistance is responsible for a large portion of treatment failures. Among other factors, clinicians must also consider the long-term risks associated with subtherapeutic drug levels when choosing a treatment regimen.

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