Volume **11** Issue **2** March/April **2003**

Topics in HIV Medicine®

A publication of the International AIDS Society–USA

Perspectives

Review

Special Contribution

The International AIDS Society–USA

Educational grants supported this issue of *Topics in HIV Medicine* and the 2003 *HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management* program. Additional support was received for the November 2002 course in San Diego, *Current Challenges in HIV Disease: A Case-Based, Advanced Course in Clinical HIV Management*. We gratefully acknowledge:

Major Grant Support

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Additional Support
(for the San Diego course in November 2002 and this issue)

HIV/AIDS Bureau of the Health Resources and Services Administration, US Department of Health and Human Services (subcontract to grant #6 H4A HA 00058) as a subcontract with Pacific AIDS Education and Training Center

About This Issue

This issue features 3 *Perspectives* articles based on presentations given at the International AIDS Society–USA continuing medical education course held in San Diego in November 2002. Charles W. Flexner, MD, reviewed advances in HIV pharmacology; Wm. Christopher Mathews, MD, MSPH, discussed criteria for routine screening for human papillomavirus-associated anal dysplasia; and Kathleen A. Clanon, MD, outlined management strategies for HIV and hepatitis C virus coinfection. In a review article, Ighovwerha Ofotokun, MD, and Claire Pomeroy, MD, discuss differences between men and women in adverse reactions to antiretroviral drugs. Also included is an International AIDS Society–USA special contribution outlining the work of 8 US and international organizations that provide HIV care in developing countries. This information, collected through an International AIDS Society–USA survey, is intended to help address the growing number of questions asked at our continuing medical education courses about efforts to address the global HIV epidemic.

The upcoming May/June issue will feature summaries of new research presented at the 10th Conference on Retroviruses and Opportunistic Infections, which was held February 10 to 14 in Boston, Mass. As in previous years, these articles will highlight topics such as HIV pathogenesis and vaccine development, new insights in basic science, and management of antiretroviral therapy. To make this year's summaries available to readers as soon as possible, the articles will also be posted online at www.iasusa.org prior to print publication.

Topics in HIV Medicine®

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Current and previous issues of *Topics in HIV Medicine* are available online at www. iasusa.org.

ISSN 1542-8826
Printed in USA • March 2003

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Advances in HIV Pharmacology: Protein Binding, Pharmacogenomics, and Therapeutic Drug Monitoring

Developing better antiretroviral drugs, individualizing therapy through patient genetic profiling, and maintaining effective drug concentrations with therapeutic drug monitoring (TDM) represent 3 current areas of interest in the field of HIV pharmacology. This article first examines antiretroviral drug binding to plasma proteins, a factor that affects the amount of free drug available to enter cells. Protein binding influences drug development, raising questions about whether the drug levels required for appropriate therapeutic effect can be achieved at tolerable doses. Second, individualized antiretroviral therapy has generated considerable interest, but much work remains in the area of pharmacogenomics before this strategy finds a place in clinical practice. Finally, studies are mixed on the benefits of TDM; although such monitoring may be appropriate in some settings, such as pregnancy and pediatrics, data are currently lacking to support its routine use in HIV care. Although data on these pharmacologic strategies do not currently support their widespread clinical application, ongoing research of such strategies offers hope for future improvement of the efficacy of antiretroviral therapy. This article summarizes a presentation given by Charles W. Flexner, MD, at the November 2002 International AIDS Society–USA course in San Diego.

Developing antiretroviral therapy that is more potent, safer, and better tolerated by patients requires consideration of several factors, including drug binding to plasma proteins, which affects the amount of free drug available in the body. Individualizing drug therapy through patient genetic profiling and therapeutic drug monitoring (TDM) are also areas of interest in HIV pharmacology. Each of these topics is discussed below.

Plasma Protein Binding

Antiretroviral drugs differ in the degree to which they are bound to plasma proteins. Plasma protein binding is a concern in drug development because, in general, only free drug can penetrate cells or tissues and exert its therapeutic effect. In the case of antiretroviral drugs, any factor that reduces free-drug concentrations could in theory reduce drug activity and thus promote HIV resistance.

For the most part, studies of plasma protein binding assess binding to alpha$_1$-acid glycoprotein (AAG) or albumin. AAG, which accounts for only about 1% to 3% of plasma proteins, binds drug molecules with low capacity but high affinity, with the latter characteristic making dissociation of the drug molecule from AAG more difficult than from albumin. Although albumin is a major protein component of plasma, it is a high-capacity but low-affinity binder. Studies of protease inhibitors (PIs) that test how much the inherent fluorescence of AAG is quenched by binding to drug molecules have shown a wide range of drug binding affinities for AAG (Bakker et al, 12th World AIDS Conf, 1998). Of PIs tested in these studies, indinavir had the lowest affinity for AAG, with an equilibrium association constant of less than 1×10^{1} M^{-1}, followed by ritonavir at 1×10^{4} M^{-1}, nelfinavir at 2×10^{5} M^{-1}, saquinavir at 8×10^{5} M^{-1}, and the investigational drug SC-52151 at 2×10^{6} M^{-1}. SC-52151 thus had a binding affinity approximately 2 million times greater than indinavir and approximately 200 times greater than ritonavir. The potential effect of greater binding affinity on activity against HIV is indicated by studies showing that the 50% inhibitory concentrations (IC_{50}) of PIs in the presence of AAG in vitro were correlated with reported binding affinities: those drugs with higher AAG binding affinity showed less potent inhibition in the presence of that protein (Lazdins et al, *J Infect Dis,* 1997; Zhang et al, *J Infect Dis,* 1999). Albumin also was found to increase PI IC_{90} values, but to a lesser degree than AAG (Molla, *Virology,* 1998).

Given the inverse correlation between binding affinity and drug activity in vitro, the question is whether protein binding affects in vivo performance of highly protein-bound drugs. There are some direct consequences of protein binding in terms of clinical use. For example, cerebrospinal fluid concentrations of many highly protein-bound drugs, including highly bound PIs, correlate better with plasma concentrations of free drug than with total drug plasma concentrations. For a few highly protein-bound drugs, such as phenytoin, procainamide, and lidocaine, free drug concentration correlates better with activity than does total plasma concentration. However, for a number of reasons, plasma protein binding does not generally need to be compensated for in clinical use. These reasons include the fact that many drugs can be dosed high enough to achieve therapeutic levels of free drug even if they are highly protein-bound, and that drug concentrations are significantly affected by other aspects of drug pharmacokinetics.

Protein Binding In Vivo

Drugs that bind to plasma proteins bind to and dissociate from those proteins at particular rates, termed association and dissociation rates. At equilibrium, as much drug is associating with protein as is dissociating at any given time, and there is a constant concentration of free drug. However, protein binding is not the sole determinant of the amount of free drug that is available for therapeu-

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tic activity. For example, a highly protein-bound drug may be as potent in vivo as a drug that is less protein-bound, since greater amounts of the latter may be available for elimination or for entering therapeutically irrelevant sites (eg, molecules, cells, or organs other than the target sites).

With regard to the impact of metabolism and elimination on therapeutic activity as it relates to protein binding, the average time to circulate plasma through the liver of an adult is 9 seconds. In an average individual, every molecule of a drug, even drugs that are highly protein-bound, is estimated to be free in the liver every few minutes, providing ample opportunity to clear free drug for those agents that are metabolized. In short, determining clinical potency of a drug is much more complicated than would be represented by consideration of protein binding alone.

Modulating Protein Binding

Some drugs are known to affect AAG levels (eg, phenobarbital increases AAG levels in cats), and it is possible that antiretroviral protein binding could be modulated through use of drugs that upregulate or downregulate AAG. Studies to determine whether PIs that are cytochrome P450 (CYP 450) inducers affect AAG levels found that, after 5 weeks of treatment (during which steady state was achieved in all patients), neither nelfinavir nor ritonavir altered AAG levels in HIV-infected patients (Flexner et al, 12th World AIDS Conf, 1998). There was some variability in AAG response among patients, with levels increasing in some and decreasing in others; however, no supraphysiologic AAG levels that might have substantially reduced free drug were observed in any patients. Other studies of the effects of drugs or HIV disease on AAG levels similarly suggest that in most cases the impact is not sufficient to substantially alter free drug concentrations long term.

For the most part, the problem of protein binding is solved during clinical drug development, by ascertaining whether therapeutically meaningful drug levels and good therapeutic effect are achieved at tolerable doses. Development of the investigational PI SC-52151, for example, was stopped not because of the drug's high degree of protein binding but because the drug could not be dosed to achieve an adequate anti-HIV effect in vivo. This was largely due to the drug's poor water solubility, which required SC-52151 to be administered in an elixir that contained large amounts of ethanol and thus limited dose (Fischl et al, *J Acquir Immune Defic Syndr Hum Retrovirol,* 1997).

Individualizing Treatment: Pharmacogenomics

There is considerable enthusiasm about the prospect of individualizing antiretroviral therapy based on genetic profiling of patients. However, much research remains to be done before this prospect becomes reality. In a recent study performed by Mallal and colleagues (*Lancet,* 2002) in a relatively homogeneous population of individuals of mostly English or Irish descent in Western Australia, 14 (78%) of 18 HIV-infected patients with hypersensitivity to abacavir had HLA type HLA-B5701, compared with only 4 (2.4%) of 167 patients with abacavir tolerance, yielding an odds ratio for sensitivity among the former of 117. The combination of the 3 genetic markers HLA-B5701, HLA-DR7, and HLA-DQ3 was present in 13 (72%) of the abacavir-sensitive patients and in none of the abacavir-tolerant patients, yielding an odds ratio for the former group of 822. This association is similar in strength to the link between the HLA-B27 marker and ankylosing spondylitis, which is one of the strongest recognized genetic associations for a common disease. However, another study that was performed in a larger and more heterogeneous population, reported at about the same time, found that only about 45% of patients with abacavir sensitivity had the HLA-B5701 marker (Hetherington et al, *Lancet,* 2002).

> A problem in translating genetic findings into clinical practice is that many associations do not pinpoint a single gene responsible for a biologic effect

Other studies of genetic markers have indicated weaker associations and yielded findings that are more difficult to interpret than those in the Mallal study, which may prove to be more typical of data emerging in this field. One study examined the association of mutations in the gene encoding the P-glycoprotein drug transporter (the gene associated with multidrug resistance in cancer chemotherapy) with outcomes of antiretroviral treatment in HIV-infected patients (Fellay et al, *Lancet,* 2002). The investigators found that having the thymidine-thymidine (TT) genotype at position 3453 of the gene, rather than cytidine-thymidine or cytidine-cytidine (CC), was associated with lower trough concentrations of nelfinavir and efavirenz but higher CD4+ cell counts after 6 months of treatment. The TT genotype is found in 25% of white patients and in 13% of African-American patients, and a smaller study (Wegner et al, 9th CROI, 2002) suggested that efavirenz, one of the drugs affected by the TT genotype, may be less effective in African-American patients than in white patients. African-American patients receiving efavirenz had a significantly less durable plasma HIV-1 RNA response and a 2- to 3-fold higher risk of relapse than did white patients, with the time to treatment failure being approximately 400 days versus 1400 days. The study concluded that these disparities were probably not associated with differences in drug concentrations or adherence, and no comparable racial differences were observed with nelfinavir or indinavir.

Several factors may make it difficult to assess the effect of the TT genotype on antiretroviral treatment. This genotype is associated with lower efavirenz concentrations but better CD4+ cell count responses. It is linked with lower concentrations of some drugs (eg, fex-

ofenadine, as well as efavirenz) but higher concentrations of others (eg, digoxin). Further, the TT/CC polymorphism is "silent" in that it does not affect the sequence or structure of the protein produced. Finally, the odds ratio for the impact of the TT mutation on the anti-HIV effect of efavirenz is weak, suggesting a weak association; indeed, a number of studies that have yet to be published have not found an association between this genotype and antiretroviral drug concentrations.

A major problem in translation of genetic findings into clinical practice is that many associations do not pinpoint a single gene that is responsible for a biologic effect. Rather, they represent an association between a previously identified marker and a biologic effect; it often remains to be determined whether the marker is linked to another locus that is actually responsible for the biologic effect. Figure 1 shows a comparison of all marker variants in the abacavir-sensitive and abacavir-tolerant patients studied by Mallal and colleagues. The study found a fair amount of overlap and lack of specificity between these 2 patient groups in the HLA-B5701 locus. However, in another part of this immune response region of the chromosome, encoding genes for heat shock proteins, there was no overlap, suggesting that the gene responsible for abacavir hypersensitivity actually resides in this region. Thus, HLA-B5701 is tightly linked to the trait for abacavir hypersensitivity but is not the gene responsible for this biologic effect. The specific causative gene remains to be identified.

Guaranteeing Success: TDM

There is considerable interest in monitoring antiretroviral drug levels in HIV-infected patients to maintain concentrations that provide maximal therapeutic effect with the least possible toxicity. Particularly with regard to PIs, trough serum concentrations are often predictive of virologic outcome. There is a clear rationale for TDM for PIs, since they are highly metabolized by the CYP 450 system, particularly CYP 3A4, with some PIs being CYP 450 inducers, some inhibitors, and some both. Levels of PIs can be affected by the many other drugs metabolized via the 3A4 enzyme system and by the inherent variability of metabolism via this route.

A number of studies have evaluated use of TDM in patients receiving PI-based antiretroviral therapy. In the PharmAdapt study, 256 treatment-experienced patients were randomized in unblinded fashion to HIV genotyping or genotyping plus pharmacokinetic analysis (Clevenbergh et al, 8th CROI, 2001; Clevenbergh et al, 41st ICAAC, 2001). Genotyping and pharmacokinetic analysis were performed at week 4, with treatment modified on the basis of this information at week 8. Overall, there was no difference between the 2 groups with regard to virologic response at 12 weeks, with plasma HIV-1 RNA levels below assay detection limits in 43% of patients in the genotyping/TDM arm and in 50% of patients in the genotyp-

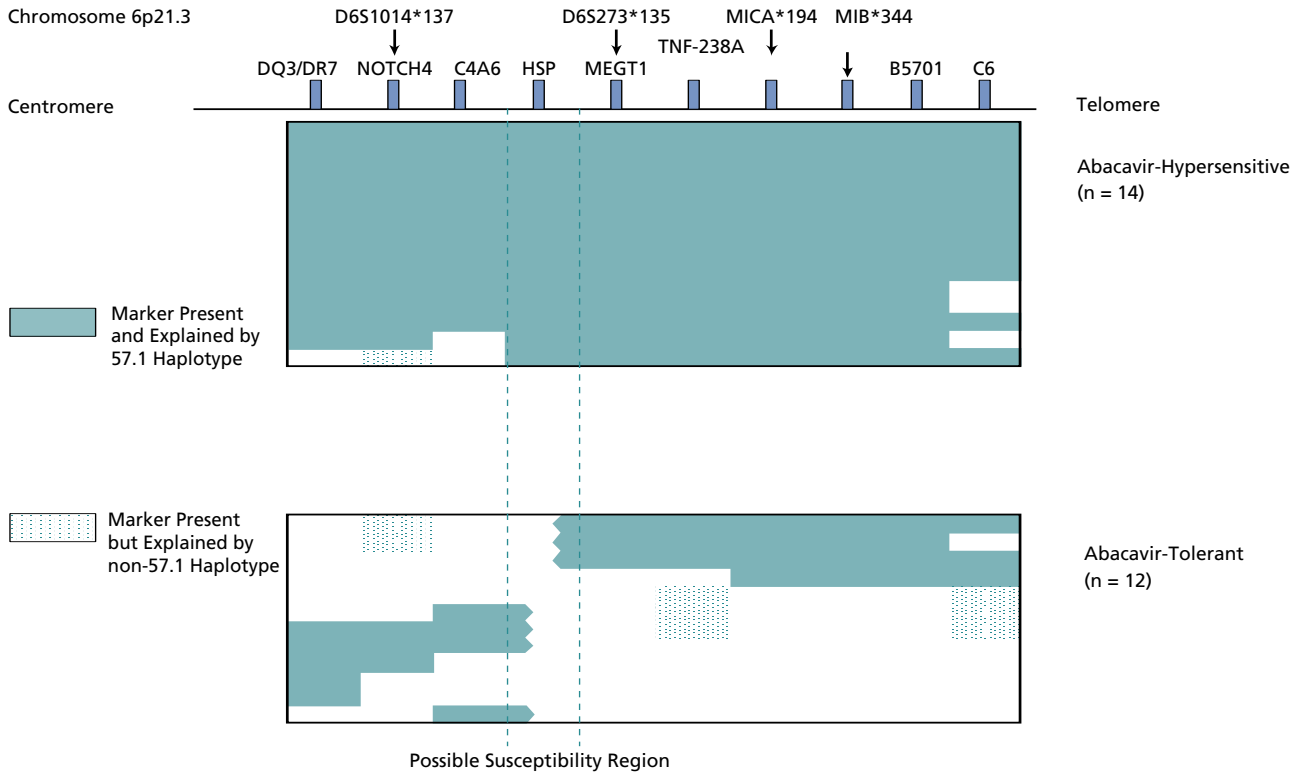

Figure **1.** Genetic mapping of the abacavir hypersensitivity region in abacavir-treated patients with polymorphisms as indicated. Adapted with permission from Mallal et al, *Lancet,* 2002.

ing-only arm. However, a number of factors make these findings difficult to interpret. First, the target drug concentrations were relatively low, equivalent to the protein-adjusted IC_{50}. In addition, about 60% of patients in both arms were receiving ritonavir, which acts pharmacokinetically to boost levels of other PIs. Finally, since 8 weeks of treatment elapsed prior to changes based on the pharmacokinetic analysis, modifications based on this information may have been made too late to prevent development of viral resistance. It should also be noted that there was intrasubject variability with regard to drug levels, with some patients moving from "suboptimal" to "optimal" concentrations between week 4 and week 8 with no change in drug dose.

The GENOPHAR study had a design similar to PharmAdapt (eg, genotyping and pharmacokinetic analysis of treatment-experienced patients at week 4 and change in regimen at week 8), although it was conducted in blinded fashion (Bossi et al, 9th CROI, 2002). This study also showed no difference in virologic outcome between genotyping/TDM and genotyping alone; as with the PharmAdapt study, however, target drug levels may have been too low and changes at week 8 based on pharmacokinetic analysis may have been made too late. A third study performed in treatment-experienced patients, the GART study, also showed no benefit of treatment based on optimal PI levels. (Baxter et al, *AIDS*, 2000)

The ATHENA study has provided some evidence of benefit of TDM in treatment-naive patients. In this "blinded" study, all patients underwent TDM, with their physicians given either dosing advice based on monitoring or no advice (Burger et al, 1st IAS Conf, 2001). Advice resulted in significant decreases in discontinuation rates at 1 year among patients receiving nelfinavir (2.4% vs 17.6% with no advice) or indinavir (9.5% vs 40.0%). However, results of this study are also difficult to interpret, since many practitioners who received advice based on TDM did not institute it. Further, while virologic response improved among patients receiving nelfinavir, no virologic benefit of TDM was observed among patients receiving indinavir, and no benefits of TDM at all were observed in patients receiving indinavir/ritonavir.

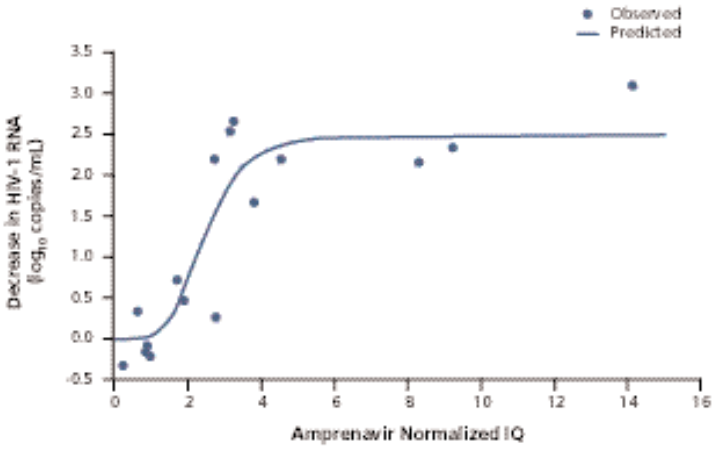

Figure **2.** Association of decrease in plasma HIV-1 RNA levels with amprenavir normalized inhibitory quotient (IQ) in patients receiving amprenavir. Adapted with permission from Piscitelli, ECCATH, 2001.

On balance, the available data suggest that a somewhat different approach to TDM is needed in treatment-experienced patients. Three recent studies reported a better correlation between drug concentrations and treatment outcome in treatment-experienced patients if correction was made for the level of drug resistance in the patient's viral population. Methods by which this correction can be achieved include measurement of the inhibitory quotient (IQ), which is the trough concentration divided by the IC_{50} for the drug; the virtual IQ, which is the trough concentration divided by the virtual IC_{50} derived from a virtual phenotype database; and the normalized IQ, which is the patient's virtual IQ divided by a population mean virtual IQ for a patient with drug-sensitive virus. Figure 2 shows the correlation between amprenavir normalized IQ and decrease in plasma HIV-1 RNA level found by Piscitelli and colleagues (ECCATH, 2001) indicating greater decreases in viral load with higher IQ values.

Much work remains to be done before clinical guidelines for TDM can be developed. Until then, such monitoring may be of benefit in some clinical situations. These include the settings of pregnancy and pediatrics, in which drug concentrations can change rapidly and are difficult to predict; use with phenotyping to determine optimal drug concentrations in salvage treatment, as noted above; in patients with renal or hepatic dysfunction; and in documentation of adequate drug levels in the presence of other drugs known to induce or inhibit the CYP 450 system.

Presented by Dr Flexner in November 2002. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Flexner in February 2003.

Financial Disclosure: Dr Flexner has received grants and research support from Abbott, Agouron, and Merck.

Suggested Reading

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Perspective

Screening for Anal Dysplasia Associated with Human Papillomavirus

Anal dysplasia associated with human papillomavirus (HPV) infection occurs in substantial proportions of HIV-infected men and women and poses risk for anal carcinoma. Whether to routinely screen for HPV-associated anal dysplasia in this population, however, remains a debated question. Anal dysplasia is detectable by Pap screening and colposcopic biopsy; as Pap testing results have relatively low reproducibility, 2 baseline tests may be prudent. Screening should also ascertain risk factors for dysplasia, including HIV infection, degree of immunosuppression, and history of prior anal disease. Although treatment options for anal dysplasia are limited by morbidity and high recurrence rates, early detection may permit better tolerance of therapy, and current estimates indicate that routine screening for the condition would be cost-effective. In addition, emerging immunologic therapies offer hope of more effective future treatment. This article summarizes a presentation given by Wm. Christopher Mathews, MD, MSPH, at the November 2002 International AIDS Society–USA course in San Diego.

Evidence-based public health decisions regarding whether screening programs for a particular health condition should be recommended are influenced by a number of factors:

1. How important is the health condition to be sought in terms of frequency, morbidity, and mortality?

2. How good is the screening test in terms of accuracy, safety, simplicity, acceptability to patients and health care practitioners, labeling effects (ie, social and psychologic effects on the patient from positive test results), and cost?

3. How strong is the evidence that outcome of the condition is improved if treatment is given after screening versus at the time the patient presents with symptoms?

Human papillomavirus (HPV)-associated anal dysplasia is a common condition in HIV-infected patients and is associated with increased risk for anal carcinoma. Whether to routinely screen for HPV-associated anal dysplasia remains a debated issue.

Dr Mathews is Professor of Clinical Medicine at the University of California San Diego Medical Center and Director of the UCSD Owen Clinic and of the UCSD AIDS Education and Training Center.

What Is the Incidence, Morbidity, and Mortality of HPV-Associated Anal Dysplasia?

Cervical cancer serves as a biologic and an epidemiologic model for anal carcinoma and its precursors. The current incidence of cervical cancer in the United States is approximately 8 cases per 100,000 people. The incidence of anal cancer in men who had sex with men (MSM) prior to the HIV epidemic was 35 per 100,000—an incidence rate similar to that of cervical cancer before routine Pap testing was implemented for the latter (Daling et al, *N Engl J Med*, 1987). The rate of anal cancer in HIV-infected MSM is approximately twice that in HIV-seronegative MSM (Goedert et al, *Lancet*, 1998).

Cervical and anal cancers have similar histologies, with both frequently arising in the squamocolumnar junction (transformation zone) and both being strongly associated with oncogenic strains of HPV. High-grade squamous intraepithelial lesions (HSIL) are a proven precursor to cervical cancer and are strongly suspected to be a precursor to anal cancer. HPV types include low-risk types (6 and 11) associated with low-grade squamous intraepithelial lesions (LSIL) and condyloma, intermediate-risk types (31, 33, 35, 45, 51, 52, and 56), and the high-risk types (16 and 18) that are found in approximately two-thirds of cases of invasive cervical cancer.

The newly revised Bethesda System of cervical cytologic classification (Solomon et al, *JAMA*, 2002) also applies to anal intraepithelial neoplasia. In this system, atypical squamous cells (ASC) are classified as "of undetermined significance" (ASCUS) or as "cannot exclude HSIL" (ASC-H). Squamous intraepithelial lesions are graded as LSIL, HSIL, or squamous cell carcinoma. LSIL indicates mild dysplasia (HPV cellular changes) and is equivalent to the cervical intraepithelial neoplasia (CIN) 1 category in the World Health Organization (WHO) histopathologic classification system. HSIL is categorized as either moderate dysplasia, equivalent to CIN 2 in the WHO system, or severe dysplasia, equivalent to CIN 3. The distinction between severe dysplasia and carcinoma in situ, also CIN 3, is very narrow, and the same lesion might be judged as severe dysplasia by one pathologist and carcinoma in situ by another. Cytologically, ASCUS is characterized by features of both LSIL and HSIL with the features being diagnostic of neither. LSIL is characterized by relatively little basal cell proliferation and atypia; the effects of HPV are observed as "koilocytes," featuring an irregular enlarged nucleus with a clear halo. Most LSILs spontaneously regress. HSIL is characterized by increasingly severe atypia, abnormal mitotic activity in the superficial layers, and immature basaloid cells.

Under the Bethesda System, it is recommended that patients with ASCUS findings on Pap testing undergo HPV testing. HPV-positive patients should undergo colposcopy or repeat Pap testing at 6 and 12 months, and HPV-negative patients should have

repeat Pap testing at 12 months. Patients with ASC-H should be immediately referred to colposcopy without HPV testing.

Data on the natural history of CIN, derived from 64 studies involving 15,473 CIN cases and 274 carcinoma cases followed for less than 1 year to 12 years, are shown in Table 1 (Östör, *Int J Gynecol Pathol,* 1993). Progression to carcinoma in situ or invasive disease is more frequent in the CIN 2 and CIN 3 categories. Comparable progression rates for anal intraepithelial neoplasia are unknown but likely to be similar.

HPV and Anal Dysplasia in HIV-Infected Patients

The cell-mediated immune response to HPV modulates the development of squamous intraepithelial lesions. A study in women with cervical HPV-16 showed that those with HPV-specific immune response were less likely to develop squamous intraepithelial lesions. HIV-induced expression of cytokines (eg, interleukin-6) may modulate HPV gene expression, and the HIV Tat protein may potentiate expression of HPV E6 and E7 gene products that are considered to be crucial in inducing chromosomal instability.

In a study reported in 1994 (Williams et al, *Obstet Gynecol*), 77% of 54 HIV-infected women had HPV infection detected by polymerase chain reaction (PCR) test. Of those with both cervical and anal HPV, the same HPV types were found in only 50%. In another study reported in 1996 (Melbye et al, *Int J Cancer*), 12.1% of 124 women had abnormal anal cytology. Risk factors for anal intraepithelial neoplasia were HIV seropositivity, low CD4+ cell count, and HPV positivity by PCR. Data on HPV infection in MSM in the pre-potent antiretroviral therapy era indicate that 93% of HIV-infected men and 61% of HIV-seronegative men had anal HPV detected by PCR, with HPV-16 being the most common type. Infection with multiple HPV types was found in 73% of HIV-infected men, with the frequency increasing with lower CD4+ cell counts, and in 23% of HIV-seronegative men (Palefsky et al, *J Infect Dis,* 1998). Palefsky and colleagues (*J Acquir Immune Defic Syndr Hum Retroviral,* 1998) found that LSIL or HSIL was present in 124 of 346 (36%) HIV-infected MSM compared with 19 of 262 (7%) HIV-seronegative MSM. Compared with HIV-seronegative patients (relative risk 1.0), relative risk for LSIL or HSIL increased with decreasing CD4+ cell count in HIV-infected patients, to 3.9 at cell counts greater than 500/µL, 5.6 at 200 to 500/µL, and 7.3 at less than 200/µL.

Figure 1 shows the prevalence of LSIL or HSIL in approximately 650 HIV-infected patients screened at the University of California San Diego Owen Clinic according to sex, MSM status, and CD4+ cell count. These data show a high frequency of LSIL or HSIL among male patients not reporting sex with men as a risk factor, suggesting that screening of only MSM would result in missing anal dysplasia in a significant proportion of patients. The relationship between LSIL or HSIL and CD4+ cell count is consistent with other studies. In 49 biopsies performed at the Owen Clinic, carcinoma in situ was found in 0 of 2 patients with normal Pap findings, 0 of 2 with ASCUS, 4 of 20 (20%) with LSIL, and 4 of 25 (16%) with HSIL (16% overall; Mathews et al, 9th CROI, 2002). The Owen Clinic's screening policy now is to refer any patient with ASCUS, LSIL, or HSIL for colposcopy.

Table **1.** Natural History of Cervical Intraepithelial Neoplasia (CIN), by World Health Organization Histopathologic Classification

Classification	Regression	Persistence	Progression to Carcinoma in Situ	Progression to Invasive Disease
CIN 1	57%	32%	11%	1%
CIN 2	43%	35%	22%	5%
CIN 3	32%	<56%	–	>12%

Adapted from Östör, *Int J Gynecol Pathol,* 1993.

Impact of Potent Antiretroviral Therapy on Anal Squamous Intraepithelial Lesions

Potent antiretroviral therapy leading to immune reconstitution including HPV-specific response might induce regression of anal squamous intraepithelial lesions and thus reduce rates of progression to anal cancer. On the other hand, if treatment-related immune reconstitution does not affect pathogenesis of HPV-associated dysplasia, prolonged survival in HIV-infected patients is likely to be accompanied by increased frequency of anal cancer. Anecdotal observations currently suggest that the frequency of invasive anal cancer has increased with greater patient longevity. One study reported by Palefsky and colleagues (*Semin Oncol,* 2000), however, indicates some potential for disease regression. Evaluation at 6 months after the start of potent antiretroviral therapy in 28 men with HSIL at the start of treatment showed no change in 57%, LSIL in 21%, ASCUS in 18%, and normal findings in 4%. Patients who showed regression had higher CD4+ cell counts at baseline than those who did not show regression.

Although these are the only available data on the effects of potent therapy in patients with anal squamous intraepithelial lesions, Minkoff and colleagues (*AIDS,* 2001) have reported findings on cervical squamous intraepithelial lesions in the Women's Interagency HIV Study of 741 HIV-infected women with at least 1 oncogenic HPV strain. These women were followed with biannual Pap smears, and findings in consecutive pairs of tests were analyzed according to potent therapy status. Patients were defined as "off therapy" if they were not receiving therapy or were seen prior to therapy and as "on therapy" during any visit after start of therapy. This study found that women with persistent HPV were more likely to have lesion progression. After adjustment for CD4+ cell count and Pap status, patients on potent therapy were 40% more likely to have lesion regression and had an odds ratio of 0.68 for lesion progression compared with those off therapy.

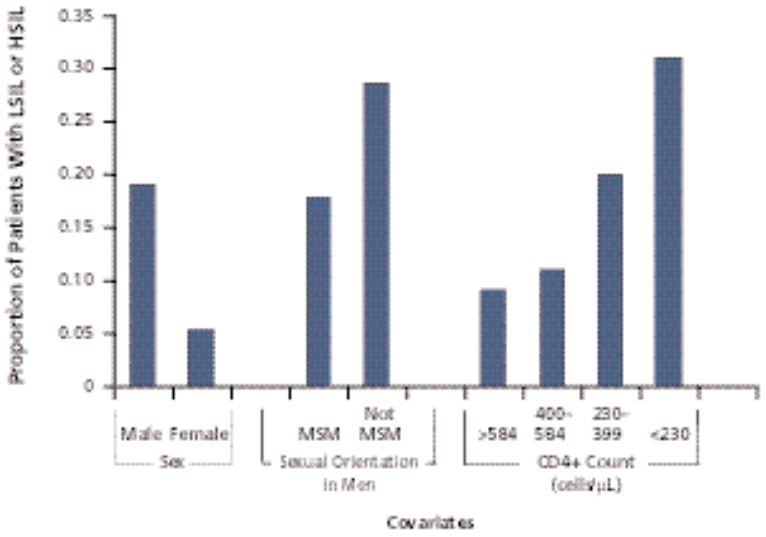

Figure **1.** Prevalence of low-grade squamous intraepithelial lesions (LSIL) or high-grade squamous intraepithelial lesions (HSIL) among approximately 650 HIV-infected patients by sex, classification as men who have sex with men (MSM) versus not MSM for men only, and CD4+ cell count. *P*=.036 for sex; *P*=.088 for MSM; *P*<.0001 for CD4+ cell count. Adapted with permission from Mathews et al, 9th CROI, 2002.

What Are the Efficacy and Effects of Anal Dysplasia Screening Tests?

The decision regarding who to screen for anal dysplasia depends on the probability of finding the disease in particular populations. There is a clear rationale for screening both HIV-infected and HIV-seronegative MSM. There is also a clear rationale for screening HIV-infected women with a history of anal receptive intercourse, anogenital warts or HPV infection, or cervical dysplasia. However, a case can also be made for screening all HIV-infected men and women, particularly given the unreliable nature of histories of sexual behavior. (Chin-Hong and Palefsky, *Clin Infect Dis*, 2002).

Components of screening evaluations include Pap tests (performed via conventional methods or using the liquid medium technique), digital rectal examinations, and high-resolution anoscopy. HPV testing has an uncertain role in screening. With regard to reproducibility of Pap testing, the sensitivity of cervical cytology to detect CIN 2 or 3 is estimated at a reliability coefficient of 0.67 to 0.76. Dr Mathews and colleagues have found that the reproducibility of anal Pap testing is lower, with a kappa statistic agreement of 0.30 between single repeat tests for HSIL/LSIL versus ASCUS/normal cytology found in testing of 42 patients (9th CROI, 2002). The Owen Clinic has thus instituted a practice of obtaining 2 baseline anal Pap tests in all patients screened.

Screening for anal squamous intraepithelial lesions begins with ascertaining risk factors, including HIV status and degree of immune suppression; history of anogenital warts, anal receptive intercourse, and prior cervical or anal squamous intraepithelial lesions; symptoms such as discharge, pain, or bleeding; and history of tobacco use. Risk factors for other anal sexually transmitted diseases should also be ascertained. Dysplasia screening presents an opportunity to screen for other anal sexually transmitted diseases, and Dr Mathews and colleagues are currently studying the diagnostic yield and cost-effectiveness of such joint screening. Use of the liquid medium technique for Pap testing allows use of the same sample for PCR testing for gonorrhea and chlamydia infections. Since dysplasia is not confined to the anal canal, physical evaluation should include examination of the perianal area, perineum, and genitalia, including the inguinal nodes. The Pap smear should not be taken after douching, enema, or anal intercourse, since any of these might remove the superficial abnormal cells being sought. The sample should be taken using a Dacron, rather than cotton, swab moistened with ordinary tap water. The swab should be inserted at least 1.5 to 2 inches into the anal canal (best results might be achieved by insertion to the posterior wall of the rectum) and withdrawn slowly while rotated in a spiral fashion. The swab should be rolled quickly across a slide, which should then be dipped in fixative.

High-resolution anoscopy should be performed after digital rectal examination using a lidocaine and water-based lubricant mixture. After insertion of the anoscope, a 4×4-cm gauze pad that has been soaked in ordinary 3% vinegar solution and wrapped around a cotton swab is inserted through the scope for 1 to 2 minutes, with the vinegar providing the equivalent of the acetowhite staining that is used in cervical dysplasia screening. The anoscope is then reinserted for examination. Suspicious lesions, such as those with acetowhitening or areas showing punctation, mosaicism, atypical vessels, or ulcerations, should be biopsied (eg, with baby Tischler forceps). Lugol's iodine can be applied, causing dysplastic lesions to appear mustard or light yellow instead of mahogany brown.

Chin-Hong and Palefsky recently updated screening and treatment recommendations for anal HPV disease. Dr Mathews and colleagues perform high = resolution anoscopy in patients with ASCUS, LSIL, or HSIL. In patients with normal Pap findings, Pap testing may be repeated in 1 year in those with HIV infection and in 2 to 3 years in those without HIV infection. In patients with cytologic abnormalities whose initial high-resolution anoscopy-guided biopsy shows either no lesion or one of lesser severity than the Pap test, repeat high-resolution anoscopy is recommended at approximately 3 months. Patients with LSIL undergo repeat colposcopy at 6 months; those with HSIL or severe dysplasia or those with carcinoma in situ who do not undergo treatment have colposcopy repeated at 3 months.

Current estimates indicate that anal dysplasia screening would be highly

cost-effective. Typically, treatment modalities with a cost of less than $30,000 to $50,000 per year of life saved are considered cost-effective by policy makers. Cervical cytology screening every 3 years in HIV-seronegative women is estimated to have a cost-effectiveness ratio of approximately $180,000 per year of life saved, compared with a ratio of approximately $13,100 per life-year saved with annual screening in HIV-infected women (Goldie et al, *Ann Intern Med*, 1999; Eddy, *Ann Intern Med*, 1990). The cost per life-year saved with anal cytology screening is estimated at approximately $11,000 for HIV-infected men with annual screening and approximately $7800 for HIV-uninfected men with screening every 3 years (Goldie et al, *JAMA,* 1999; Goldie et al, *Am J Med,* 2000).

Does Screening Improve Treatment Outcome?

Unfortunately, there currently is no widely accepted standard of treatment for anal squamous intraepithelial lesions. One approach was recently proposed by Chin-Hong and Palefsky (*Clin Infect Dis,* 2002). Only those patients with HSIL should be routinely recommended for treatment. Treatment options are limited by morbidity and high (50%-85%) recurrence rates. Current options include excision with fulguration; topical treatment with 80% trichloroacetic acid, cryotherapy, imiquimod, podophyllotoxin, or 5-fluorouracil cream; laser ablation; thermocoagulation or infrared coagulation; and intralesional interferon alfa. Immunologic therapies may ultimately offer the best hope of effective treatment.

Investigational Immunologic Therapies

One investigational vaccine, ZYC101a, is derived from a plasmid DNA encoding multiple HLA-A2-restricted cytotoxic T lymphocyte epitopes from the HPV-16 E7 protein. In a small study, 12 men with HPV-16 and the appropriate HLA-A2 restriction received 4 intramuscular injections of the vaccine 3 weeks apart. Enzyme-linked immunospot assay of peripheral blood mononuclear cells from the subjects showed HPV-specific γ-interferon-producing cells in samples from each of the 9 who were evaluable for response (Lathey et al, 41st ICAAC, 2001). Also encouraging have been findings of a study of HspE7, a recombinant fusion product of the heat shock protein 65 and the E7 protein. Of 56 patients with anal HSIL receiving 3 500-µg injections of the vaccine, 40 (71%) had dysplasia downgraded to LSIL at 6 months after immunization. Only 3 of 37 evaluated responders were HPV-16-positive, indicating a broad, non-type-specific response to the vaccine (Palefsky et al, 41st ICAAC, 2001).

Conclusions

Anal HSIL is likely a precursor to anal carcinoma. Anal dysplasia is detectable by Pap screening and colposcopic biopsy, but the relatively low reproducibility of the Pap testing results is a limiting characteristic in screening. Current treatment options for HSIL and carcinoma in situ are relatively ineffective, but monitoring may detect early invasive disease and permit better tolerance and outcome of treatment. There is some promise of better treatment alternatives in the near future. Until treatment improves, some form of screening for anal dysplasia is prudent, including 2 baseline Pap tests, routine digital rectal exam, and high-resolution anoscopy, if available.

Presented by Dr Mathews in November 2002. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Mathews in January 2003.

Financial Disclosure: Dr Mathews has received grant and research support from Abbott, Agouron, and Gilead.

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Perspective

Strategies for Managing Hepatitis C Virus Infection in HIV-Infected Patients

Liver disease associated with hepatitis C virus (HCV) is a significant and increasing cause of death for HIV-infected patients, but limited data exist to guide treatment of coinfection. Increased knowledge of HCV disease and its treatment among HIV care practitioners and adoption of routine care procedures can improve management of coinfected patients. This article discusses HCV screening and diagnosis, counseling and health care maintenance, and evaluation for and supervision of treatment in HIV-seropositive patients who are coinfected with HCV. The experiences of the Oakland, California-based Alameda County Medical Center, which treats more than 200 coinfected patients, are detailed and serve as the basis for suggested management strategies. This article summarizes a presentation given by Kathleen A. Clanon, MD, at the November 2002 International AIDS Society–USA course in San Diego.

Challenges in the Management of HIV/HCV Coinfection

Hepatitis C virus (HCV) infection is a common comorbidity in HIV-infected individuals in the United States, with current estimates indicating that one-fourth to one-third of HIV-seropositive patients are coinfected with HCV. Liver disease associated with HCV, as well as with hepatitis B virus (HBV) and other causes, is a significant and increasing cause of death in the HIV-infected patient population. Current treatment for HCV infection, consisting of an interferon alfa-based therapy (currently pegylated interferon alfa/ribavirin), is of limited effectiveness, difficult to tolerate, expensive, and dangerous in some subsets of patients. Currently, HIV clinicians are struggling with how extensively they can and should treat HCV in coinfected patients.

Some idea of the inadequacy of care extended to HCV-coinfected patients is demonstrated by a chart review performed in 2000 among patients from a consortium of community clinics in Alameda County, Calif (S. O'Brien, MD, unpublished data). This review showed that the majority of the 1021 HIV-infected patients attending these clinics had been screened for HCV and HBV infection and that 271 (27%) had HCV coinfection. In the HIV/HCV-coinfected group, however, counseling about coinfection status was rarely documented clearly, less than half the group had received recommended vaccinations for HBV and hepatitis A virus (HAV), and only 5 patients (1.8%) had received interferon alfa-based treatment for HCV infection. Since the time of this review, however, the clinics have made efforts to improve the routine management of HCV-coinfected patients, as discussed below.

There are a number of barriers to providing optimal treatment for HIV/HCV-coinfected patients. HIV care providers are inexperienced with and skeptical of interferon alfa-based treatment of HCV infection. HCV experts are pessimistic about the outcomes of HCV treatment in HIV-infected patients and reluctant to provide such care. Relevant work-ups, especially liver biopsy, and treatment are expensive and often not funded for the medically indigent. In many cases, mental health care and substance abuse treatment are crucial to optimal HCV treatment but are frequently difficult to access.

Inadequate overall knowledge of HCV infection and treatment among HIV care practitioners also appears to hinder provision of optimal care. A recent survey tested HCV knowledge among 109 HIV care practitioners rating themselves as experts in HIV care (Smith et al, 39th IDSA, 2001). Of the respondents, 64% were physicians and the remainder were nurse practitioners or physician assistants; most had practices with more than 100 HIV-infected patients. Overall, only 23% of the respondents received a passing score of 65% or better.

On the other hand, optimal care for HCV infection appears to be elusive even when physician expertise is not at issue. In a chart review study in an urban gastroenterology specialty clinic, only 83 (28%) of 293 patients evaluated for HCV infection received treatment; the most frequent reason for not providing treatment was patient nonadherence to scheduled visits (37%), followed by medical contraindication (34%), active substance abuse (13%), and patient preference (11%) (Falck-Ytter et al, *Ann Intern Med*, 2002). The authors of this report concluded that most HCV-infected patients will not be able to derive benefit from interferon alfa-based therapy. However, the above findings also suggest opportunities for improving care. In particular, appropriate support in the HCV care clinical setting guided by improved knowledge of HCV disease and treatment might improve management and treatment of coinfected patients.

Indeed, HCV infection should be considered a primary care issue in the HIV-infected population, given the high frequency of coinfection. HIV care practitioners should become knowledgeable about HCV disease and treatment issues and design or adopt protocols for managing coinfected patients and providing direct care or referrals consistent with available resources. The Alameda County Medical Center, for example, has organized management of HIV/HCV coinfection by phases of care, consisting of screening and diagnosis, counseling and health care maintenance, evaluation for

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treatment, and supervision of such treatment. Alameda County Medical Center practitioners also use the treatment decision tree for HIV/HCV coinfection depicted in Figure 1. Published resources that may be of assistance in devising management protocols include Veterans Administration guidelines for HCV testing and prevention counseling (available at www.va.gov/hepatitisc/pdf/ce203_testncoun slguides.pdf) and for providing and monitoring HCV therapy (available at www.va.gov/hepatitisc/pved/trtgdlns00.htm). The National Institutes of Health has also recently released updated consensus guidelines for managing HCV (available at http://consensus.nih.gov/cons/116/116cdc_intro.htm).

Screening and Diagnosis

Screening for and diagnosis of HCV infection are relatively straightforward. All HIV-infected patients should be assessed by enzyme immunosorbent assay for HCV antibody and by standard HCV serology. A small proportion of patients, particularly those with low CD4+ cell counts, may be HCV antibody-negative but exhibit HCV viral load. For example, 3.4% of 474 patients in one series had false-negative antibody results (Boyle and Vaamonde, Dig Dis Week, 2002), and 7 of the more than 200 HIV/HCV-coinfected patients in the Alameda County Medical Center's clinic population have remained HCV antibody-negative. Thus, assessment of HCV viral load should be considered in antibody-negative patients who have risk factors for HCV infection or unexplained persistently elevated alanine aminotransferase or aspartate aminotranferase levels.

Counseling and Health Care Maintenance

Counseling should include discussion of prognosis of coinfection, importance of avoiding alcohol consumption and potentially hepatotoxic medications, avoidance of transmission of HCV, and basic treatment approaches for HCV infection. With regard to prognosis, a number of studies have indicated that coinfection results in increased risk of progression of liver disease, though it remains unclear whether progression of HIV disease is accelerated. For example, one study in a cohort of 134 hemophilia patients (Lesens et al, *J Infect Dis,* 1999) found an odds ratio of 7.4 for progressive liver disease among 81 coinfected patients compared with risk in 53 patients with HCV infection alone. The median survival after diagnosis of progressive liver disease in coinfected patients was 3.2 years.

Needle sharing is the primary mode of HCV transmission. According to the Centers for Disease Control and Prevention, risk also appears to be associated with shared household items, such as toothbrushes and razors (www.cdc.gov/ncidod/diseases/hepatitis/c/faq.htm). Some guidelines recommend against sharing such items. Sex does not appear to be a major route of HCV transmission, but barrier methods are clearly indicated in the coinfected population. Health care maintenance steps include referrals to alcohol and drug treatment programs, needle-exchange programs, and peer support groups and resources; provision of HAV and HBV vaccines to patients without immunity; and intensified monitoring of liver enzymes in patients receiving potent antiretroviral therapy.

> Liver disease associated with HCV, as well as with HBV and other causes, is an increasing cause of death in HIV-infected persons

Evaluation for Treatment

Evaluation for potential interferon alfa-based treatment includes assessment of treatment readiness, ensuring that the patient:

- Understands the difficulty and uncertain benefits of treatment and wishes to go forward with it
- Abstains from alcohol and drugs for more than 6 months or is engaged in a drug treatment program
- Has support resources in place
- Has or can obtain insurance coverage for treatment (in some states, AIDS Drug Assistance Program funding covers HCV treatment in HIV-infected persons)

Medical assessments include HCV genotype, which determines the length of therapy and influences the likelihood of a successful outcome. Liver enzymes, prothrombin time/partial prothrombin time, bilirubin, albumin, and complete blood count should be measured as part of an assessment for preexisting cirrhosis, which does not serve as a contraindication to treatment but increases associated risk of cytopenia. Thyroid-stimulating hormone and antinuclear antibody levels should be measured to detect preexisting thyroid abnormalities and autoimmune hepatitis, since each can occur with interferon alfa-based therapy. Ferritin and alpha-fetoprotein should be assessed to check for concomitant liver disease associated with HCV or other causes. Pregnancy tests should be performed in women with child-bearing potential, since ribavirin is teratogenic. Liver biopsy should be obtained if possible to assess fibrosis and inflammation, with these findings being the primary determinant of whether a patient should begin treatment.

The potential benefits of treatment include delaying progression of liver disease and death in patients with fibrosis stage 3 or 4. It should be noted that although there is evidence of such benefit in patients with HCV infection alone, data are not yet available on outcomes in coinfected patients. Additional benefits may include the potential for eradicating HCV (if HIV disease is stable and CD4+ cell count is >200/µL), making potent antiretroviral therapy safer and more tolerable by reducing liver toxicity, and reducing pain, offering hope, and

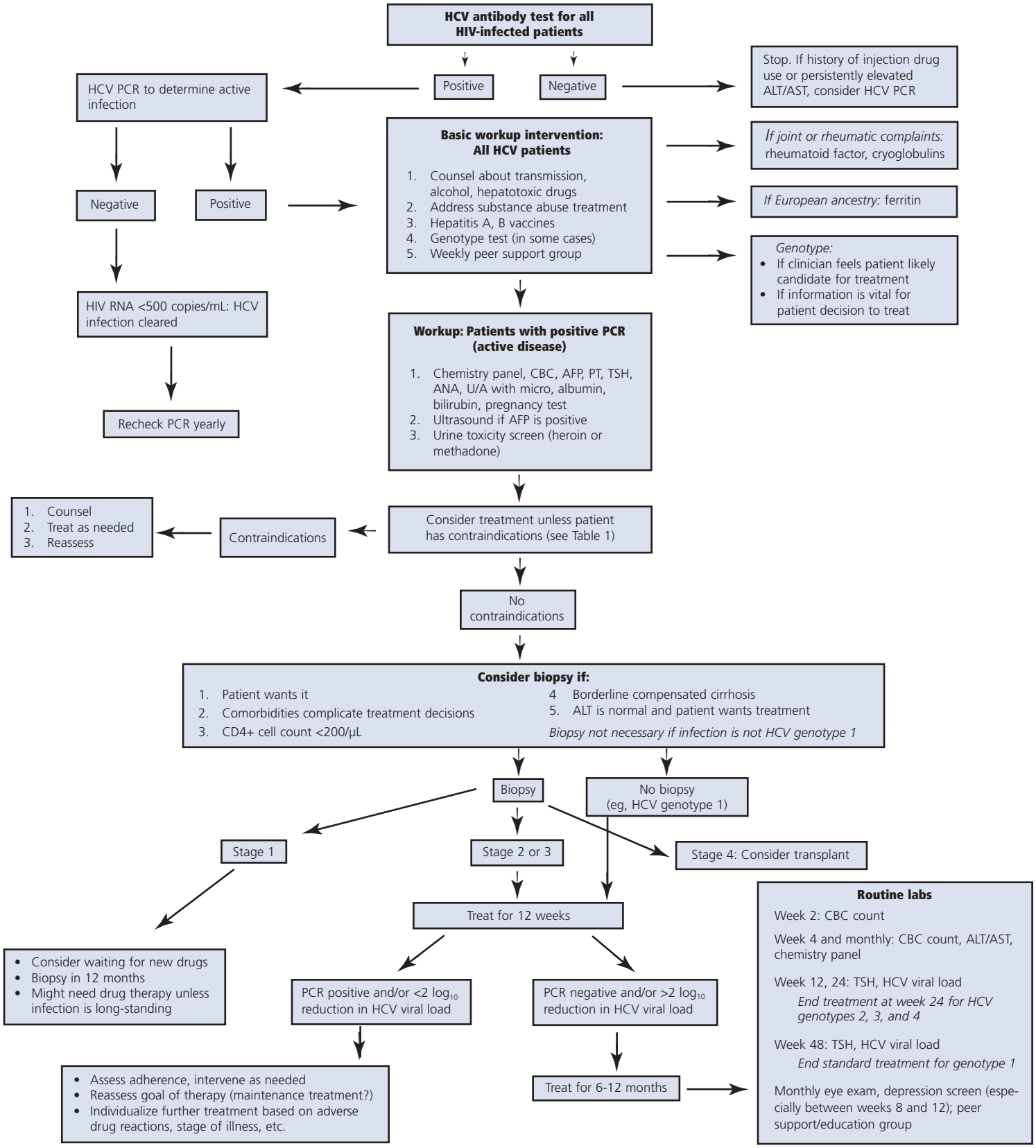

Figure **1.** Alameda County Medical Center treatment decision tree for coinfection with HIV and hepatits C virus (HCV). This decision tree contains expert opinion but is not clinically validated. AFP indicates alpha-fetoprotein; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CBC, complete blood cell; PCR, polymerase chain reaction; PT, prothrombin time; TSH, thyroid-stimulating hormone; U/A, urine analysis.

staving off liver transplantation. None of the studies of interferon alfa/ribavirin therapy performed thus far, however, provides information on whether treatment is successful in inducing regression of liver disease, even in the absence of control of HCV replication.

An idea of the results achieved with interferon alfa/ribavirin therapy in coinfection is provided by the recent RIBAVIC study (Perronne et al, 42nd ICAAC, 2002). In that study, 416 coinfected patients with a mean CD4+ cell count of 515/μL were randomized to pegylated interferon alfa/ribavirin or standard interferon alfa/ribavirin for 48 weeks. Eighty percent of patients were receiving potent antiretroviral therapy and 66% were infected with HCV genotype 1 or 4, the most common HCV genotypes in the United States. End-of-treatment response rates (proportion of patients with HCV viral load below assay detection limits at the end of treatment) at 48 weeks in an intent-to-treat analysis were 38% (59 of 157) in the pegylated interferon alfa/ribavirin group and 24% (39 of 162) in the standard interferon alfa group ($P = .01$). On as-treated analysis, end-of-treatment response rates were 50% (50 of 100) in the pegylated interferon alfa/ribavirin group versus 31% (32 of 105) in the standard interferon alfa/ribavirin group ($P < .01$), including rates of 27% for pegylated interferon alfa/ribavirin and 9% for standard interferon alfa/ribavirin in the group of patients with genotype 1 or 4 HCV.

Sustained virologic response is defined as viral load below limits of assay detection at 6 months after the end of therapy; in patients with HCV monoinfection, such response is predictive of absence of detectable virus at 5 years. Sustained virologic response rates in coinfected patients have been reported in smaller studies of standard interferon alfa-based therapies of 17.9% (Bochet et al, 8th CROI, 2001), 21% (Landau et al, *AIDS,* 2001), 40% (Sauleda et al, *Hepatology,* 2001), and 22% (Perez-Olmeda et al, 9th CROI, 2002). The RIBAVIC study discussed above will also examine post-treatment liver biopsies, which are expected to provide important information on the effects of treatment on liver disease regression and progression. Another ongoing large-scale study in coinfected patients, undertaken by the AIDS Clinical Trials Group, will provide additional data on treatment response in the coinfected population.

On the basis of currently available data, medical factors that provide strong indications and contraindications for initiating interferon alfa-based therapy are listed in Table 1.

Supervising Treatment

Supervising HCV therapy is an intensive process and should be undertaken only if sufficient resources can be devoted to patient monitoring. Pegylated interferon alfa/ribavirin has better efficacy than standard interferon alfa/ribavirin (Fried et al, *N Engl J Med,* 2002). It is administered by once-weekly injection for 48 weeks in the case of HCV genotype 1 infection and for 24 weeks in the case of infection with other genotypes. Treatment efficacy is indicated by normalization of aspartate aminotransferase levels (which generally occurs at 6 weeks to 2 months after the start of successful treatment) and by HCV viral load below limits of assay detection at 24 weeks, end of treatment, and 6 months after treatment. Treatment discontinuation should be considered if there is no virologic response at 24 weeks. Coinfected patients are more likely than patients infected with HCV alone to develop hemolytic anemia and leukopenia within the first few weeks of interferon alfa/ribavirin therapy. Complete blood cell count with differential should be obtained for coinfected patients after the second week of treatment and then every month thereafter. A low threshold for use of epoetin alfa (ie, hemoglobin < 10 g/dL) and granulocyte colony-stimulating factor (ie, neutrophil count < 1000/mL) should be maintained; in fact, all coinfected patients receiving HCV treatment at the Alameda County Medical Center begin epoetin alfa therapy immediately since anemia has been a predictable complication of treatment (Dieterich et al, 53rd Am Assoc Stud Liver Dis, 2002). The ribavirin dose should be decreased by 200 mg if hemoglobin decreases to less than 10 g/dL.

Depression is a very common complication of treatment, and pretreatment with selective serotonin reuptake inhibitor antidepressants should be considered (Schaefer et al, *Hepatology,* 2003); such pretreatment is routinely performed at Alameda County Medical Center. Thyroid-stimulating hormone should be assessed every 6 months. Pregnancy tests should be performed every month during treatment and for 6 months after treatment. Although routine screening of lactate levels is not recommended yet, it is prudent to remain alert for signs of lactic acidosis. A recent report of 265 coinfected patients on potent antiretroviral therapy (mean CD4+ cell count, 505/μL) who received either pegylated or standard interferon alfa/ribavirin for 48 weeks found 10 cases of hyperlactatemia and 4 cases of

Table **1.** Indications and Contraindications for Interferon Alfa-Based Treatment of HCV Infection

Indications

- Portal or bridging fibrosis and moderate inflammation or necrosis on liver biopsy
- Clinical signs of compensated cirrhosis and persistently elevated alanine aminotransferase and detectable HCV RNA levels
- In HIV/HCV-coinfected patients, high CD4+ cell count and not currently on antiretroviral therapy (these patients are better candidates for HCV therapy)

Contraindications

- Signs of decompensated cirrhosis (eg, varices, encephalopathy, ascites)
- Severe anemia or platelets <75,000/mL or white blood cell count <1500/mL
- Current severe or uncontrolled depression
- Pregnancy, breastfeeding, or likelihood of getting another person pregnant
- In HIV/HCV-coinfected patients, unstable HIV disease (eg, recent opportunistic disease)

HCV indicates hepatitis C virus.

pancreatitis in 13 patients. Twelve of these patients were receiving stavudine or didanosine for HIV therapy and 9 were receiving both (Hor et al, 42nd ICAAC, 2002). Suspicion of lactic acidosis or pancreatitis should be heightened in patients receiving either of these nucleoside reverse transcriptase inhibitors, and switching to other antiretroviral drugs should be considered if HCV therapy is to be started.

Treatment Protocols at Alameda County Medical Center

At Alameda County Medical Center, 22 coinfected patients had begun receiving pegylated interferon alfa/ribavirin therapy as of November 2002. For training purposes, clinicians shadow a gastroenterology specialist for 3 days to learn management strategies. Weekly patient peer support groups are important for symptom management, with patients providing invaluable advice to each other on how to handle adverse effects of treatment. Patients are contacted by telephone at a minimum of once daily during the first week of treatment and once weekly thereafter, as daily contact during the first week has been found to be a significant predictor of continuation of treatment into the second week. As the number of coinfected patients being monitored on HCV therapy grew to more than 10, one registered nurse was assigned to work exclusively with these patients, with the time expenditure equaling approximately one-half that of a full-time employee.

In addition to learning that routine early use of epoetin alfa and pretreatment with antidepressant therapy are advisable, Alameda County Medical Center has found that drinking water is the best way for patients to reduce the symptoms of adverse drug effects and recommends intake of 10 to 15 8-oz glasses a day. Patients are also warned that T-cell counts will fall, with CD4+ cell percentage remaining unchanged, during the white blood cell count decrease accompanying interferon alfa/ribavirin therapy. These measures have likely increased adherence to treatment and improved quality of care; however, the treatment dropout rate remains high at about 30%, consistent with what has been reported in the clinical trial literature.

Presented by Dr Clanon in November 2002. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Clanon in January 2003.

Financial Disclosure: Dr Clanon has no affiliations with commercial organizations that may have interests related to the content of this article.

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Top HIV Med. 2003;11(2):50-54

Review

Sex Differences in Adverse Reactions to Antiretroviral Drugs

Ighovwerha Ofotokun, MD, and Claire Pomeroy, MD

Abstract. *There have been recent increases in the number of female participants in HIV clinical trials and the number of studies addressing the influence of sex on HIV infection. The findings of some studies indicate a potential sex difference in the frequency and severity of adverse reactions to antiretroviral drugs. This article reviews the available data on the incidence and characteristics of potential sex differences in adverse reactions to certain nucleoside and nonnucleoside reverse transcriptase inhibitors and protease inhibitors. Adverse effects for which a sex difference has been reported include lactic acidosis, rash, elevation in liver enzymes, dyslipidemia, and insulin resistance. The reasons for these sex differences in adverse drug events are unclear but may include differences between men and women in body mass index and fat composition, hormonal effects on drug metabolism, or the effects of genomic constitutional differences on the levels of various enzymes. These differences warrant further study.*

Introduction

Although the incidence of HIV infection among women is increasing,[1] the proportion of women in clinical trials that evaluate interventions for the treatment of HIV infection and its complications has historically been lower than the proportion of women in the HIV/AIDS patient population. Therefore, most knowledge about the efficacy of antiretroviral drugs and the adverse reactions associated with their use has been derived from studies involving predominantly male subjects.[2,3] A review of female participation in large, multicenter clinical trials found that only 6.7% of the 11,909 AIDS Clinical Trials Group (ACTG) study participants from 1987 through 1990 were women.[4] As a result of the relatively small number of female subjects in earlier HIV clinical trials, little is known about the influence of sex on the natural history of HIV infection and on the incidence and characteristics of adverse drug effects.

Since a 1994 change in the National Institutes of Health policy on the enrollment of human subjects in clinical trials,[5] more women have been involved in HIV-related studies. The proportion of women enrolled in ACTG-funded studies increased from 5.6% in 1987 to 16.9% in 1996.[6] Current estimates are that approximately 20% of participants in ACTG clinical trials are women.[7] However, the proportion of women in these trials still lags behind the proportion (25%) of reported AIDS cases in the United States that occur among women.[8] In addition, several multicenter studies have enrolled exclusively women with or at risk of HIV infection. Examples include the Women's Interagency HIV Study (WIHS), with 2066 HIV-seropositive and 575 HIV-seronegative women[9]; the HIV Epidemiology Research Study (HERS), with 863 HIV-seropositive and 430 HIV-seronegative women[10]; and the Women and Infants Transmission Study (WITS), with 2336 HIV-seropositive women and 1887 infants.[11] Data from several of these studies suggest that sex differences may exist in several aspects of HIV infection and its management, including differences in the tolerability of some antiretroviral drugs.[12-17] This article reviews the incidence and characteristics of sex differences in adverse reactions to antiretroviral drugs used to treat HIV infection.

Nucleoside Reverse Transcriptase Inhibitors

The nucleoside reverse transcriptase inhibitors (nRTIs) were the first antiretroviral drugs introduced into clinical practice and represent the cornerstone of highly active antiretroviral therapy (HAART). These drugs are associated with various adverse effects (Table 1), including myelosuppression, pancreatitis, gastrointestinal (GI) intolerance, peripheral neuropathy, myopathy, and lactic acidosis. Many of these adverse effects are postulated to be mediated through mitochondrial toxicity.[18,19] Some studies have indicated that women are less likely than men to tolerate regimens containing certain nRTIs. In the ACTG 175 trial,[20] monotherapy with zidovudine or didanosine was compared with combination therapy with zidovudine and zalcitabine or with zidovudine and didanosine. Reduction in drug dosage or discontinuation of didanosine-containing regimens because of adverse effects was more common among women than among men. Another study[21] evaluated the incidence of adverse events during nRTI therapy in 1450 subjects with a CD4+ cell count of less than 500/μL. The risk of developing an adverse event related to didanosine was nearly 3 times higher for women than for men (relative risk, 2.7; $P = .03$).

Lactic acidosis is one of the most serious presentations of nRTI-associated mitochondrial toxicity. Although this complication is rare, the associated mortality rate may be as high as 80% when plasma lactate levels exceed 10 mmol/L.[22] The role of sex in the occurrence of this complication has not been directly studied, but a report from the US Food and Drug Admin-

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Table **1.** Clinical Trials on Sex and Nucleoside Reverse Transcriptase Inhibitor-Associated Toxicity

Study	Population	Drugs	Sex Difference in Toxicity
Squires et al: START I and II[12]	78 women, 331 men	Zidovudine or stavudine + lamivudine/indinavir vs stavudine/didanosine/indinavir	Incidence of adverse events higher among women
Currier et al: ACTG 175[20]	438 women, 2029 men	Zidovudine or didanosine or zidovudine/zalcitabine or zidovudine/didanosine	Higher likelihood of reducing dose or discontinuing didanosine-containing regimen among women
Moore et al[21]	392 women, 1058 men	Zidovudine/didanosine/zalcitabine	Nearly 3-fold increase in the risk of an adverse event due to didanosine among women
Boxwell et al[22]	60 patients (50 women, 10 men) with lactic acidosis after treatment with nRTIs	nRTI-containing regimens	83% of cases of lactic acidosis and 85% of the 20 fatal cases occurred in women

ACTG indicates AIDS Clinical Trials Group; nRTI, nucleoside reverse transcriptase inhibitor; START, Selection of Thymidine Analog Regimen Therapy Trials.

istration[23] suggests that women may be at higher risk of lactic acidosis than men. This report found that 83% of 60 lactic acidosis cases in HIV-infected patients treated with an nRTI occurred in women, and 85% of the 20 fatal cases occurred in women. In addition, fatty liver, or hepatic steatosis, occurred in 71% of women, and pancreatitis in 29%.

Nonnucleoside Reverse Transcriptase Inhibitors

The nonnucleoside reverse transcriptase inhibitors (NNRTIs) have become important components of HAART, especially when a protease inhibitor (PI)-sparing regimen is desired. The NNRTI nevirapine is of particular importance to women. This drug is relatively inexpensive and easy to administer and has been shown to significantly reduce the vertical transmission of HIV infection. It is thus an especially attractive option for reducing mother-to-child transmission of HIV, especially in resource-poor countries of the world.[24]

The common adverse effects of NNRTIs are rash and hepatitis (Table 2). Gangar and colleagues[25] were the first to suggest a trend toward a higher frequency of rash among women taking nevirapine than among men taking the drug. Three additional studies provide further support of this sex difference. The first, a multicenter, retrospective cohort study of patients treated with nevirapine,[26] found that 9 of 95 women (9.5%) but only 3 of 263 men (1.14%) experienced a severe rash; the sex difference was statistically significant ($P = .005$). Women had a 7-fold greater risk of severe rash and were 3 to 5 times more likely to discontinue nevirapine therapy than men. A second study[13] assessed the prevalence of skin rash among 280 HIV-infected persons after exposure to nevirapine. The relative risk of rash for women was 11.7 times higher than that for men ($P = .006$). Of the 3 patients who developed Stevens-Johnson syndrome, 2 were women. The third and most recent study[27] reviewed 31 Chinese patients who were taking nevirapine. A nevirapine-associated rash developed in 5 of 8 women (62.5%) but in only 6 of 23 men (26%).

Another concerning adverse effect of NNRTIs is hepatitis, a complication that may be more likely to occur among women taking nevirapine than among men taking the drug. In the FTC-302 study,[28] 468 patients in South Africa were randomly assigned to a regimen of either emtricitabine, an investigational nRTI, or lamivudine, in addition to a background regimen of stavudine and either nevirapine or efavirenz. After 24 weeks of therapy, the incidence of grade 4 elevation in liver enzymes among patients in the nevirapine-containing arm of the study was 9.4%, whereas that among patients in the efavirenz-containing arm was 0%. In the nevirapine-containing arm, the incidence of grade 4 elevation in liver enzymes was 2 times higher for women (12%) than for men (6%; $P = .05$). The 2 patients who died of liver failure were women.

Protease Inhibitors

The introduction of PIs to clinical practice has revolutionized the management of HIV disease. The use of PIs in combination with other antiretroviral agents has led to a substantial reduction in the mortality and morbidity rates associated with HIV infection.[29] The primary toxic effects associated with PIs include GI intolerance, abnormal fat distribution, and metabolic disorders (Table 3).

Several investigators have reported sex differences in the frequency and severity of some of these adverse reactions. In a study[30] of 90 women and 996 men taking ritonavir in combination with reverse transcriptase inhibitors, Currier and colleagues found that men and women experienced similar types of adverse effects. However, the frequency of GI side effects

was higher among women than among men. Nausea, vomiting, and numbness or tingling around the mouth occurred more frequently among women, although diarrhea was more common among men. Another study of ritonavir intolerance in men and women included 93 subjects, 87 of whom were evaluated for adverse events.[31] Ritonavir was associated primarily with GI and neurologic adverse effects. The risk of ritonavir intolerance was significantly higher ($P < .001$) for women (23 of 35; 66%) than for men (14 of 52; 27%).

An analysis of 3 separate trials[32] evaluated the efficacy and tolerability of nelfinavir-containing regimens administered to 78 women and 616 men. The efficacy of nelfinavir in lowering HIV-1 RNA plasma concentrations was similar for men and women. The mean increase in CD4+ cell count was greater among women (116/μL) than among men (84/μL). Although men and women experienced similar types of adverse effects (abdominal pain, diarrhea, pruritus, and skin rash), all of these adverse effects, except for diarrhea, occurred more frequently among women.

Lucas and colleagues also reported a sex difference in the tolerability of PI-containing HAART regimens.[33] This study evaluated the occurrence of treatment failure and adverse drug reactions in HIV-infected persons receiving HAART. No significant difference was found between men and women in plasma HIV-1 suppression: undetectable HIV-1 RNA plasma concentrations were achieved in 37% of the 273 patients. However, the rate of adverse drug reactions was significantly higher ($P = .008$) for women (37%) than for men (25%). The primary adverse effects were GI-related.

Abnormalities in fat distribution and metabolic disorders have been frequently observed in HIV-infected persons treated with HAART. Two prominent clinical features associated with lipodystrophy syndrome are peripheral fat loss and central fat accumulation. Because men and women naturally differ in the amount of body fat and its distribution, it has been speculated that sex differences in these 2 clinical manifestations of lipodystrophy syndrome are likely. A review[14] of 208 HIV-infected patients who experienced lipodystrophy syndrome during HAART found that fat accumulation (in the breast and abdomen) was more common in women and that fat loss (in the limbs and buttocks) was predominant in men. A similar but larger study[34] examined the correlation between sex and morphologic alterations in 2258 HIV-infected persons undergoing antiretroviral therapy. Morphologic alterations (fat loss or fat accumulation) occurred in 33.2% of the subjects but were more common in women than in men, with an adjusted odds ratio of 2.019 ($P = .001$).

Metabolic abnormalities associated with HAART also include hypercholesterolemia, hypertriglyceridemia, insulin resistance, and type 2 diabetes mellitus. In a study[35] designed to examine sex differences in the occurrence of HAART-associated dyslipidemia, 27 men and 13 women who had been taking nelfinavir/didanosine/stavudine for 6 months were tested for lipid abnormalities. A significant increase above baseline ($P < .05$) was found in both sexes for serum concentrations of triglycerides, leptin, and low-density lipoprotein (LDL) cholesterol; these increases were higher among women than among men. Fasting insulin levels and the ratio of LDL to high-density lipoprotein (HDL) cholesterol increased only in female patients ($P < .02$). In contrast, endothelial activation, as measured by circulating E-selectin (cE-selectin) concentrations, showed a larger decrease among men than among women ($P < .02$). As a result, women had higher triglyceride and leptin levels after therapy than did men; in addition, the ratio of LDL to HDL cholesterol and the cE-selectin levels, which had been initially higher among men, were no longer significantly different in men versus women. Although the number of patients in this study was small, the findings suggest that the baseline cardiovascular protection normally enjoyed by women because of a favorable lipid profile may be lost with HAART.

Another adverse event that may be associated with HAART is hypertension, which could be of particular importance for

Table **2.** Clinical Trials on Sex and Nonnucleoside Reverse Transcriptase Inhibitor-Associated Toxicity

Study	Population	Drugs	Sex Difference in Toxicity
Mazhude et al[13]	102 women, 178 men	Nevirapine-containing regimens	11.7-fold increase in risk of skin rash among women; 2 of 3 cases of Stevens-Johnson syndrome occurred in women
Bersoff-Matcha et al[26]	95 women, 263 men	Nevirapine-containing regimens	7-fold increase in risk of rash among women; women were 3-5 times more likely to discontinue nevirapine use
Wong et al[27]	8 women, 23 men	Nevirapine-containing regimens	Higher rate of rash among women
Bartlett J[28]	276 women, 192 men	Emtricitabine or lamivudine + stavudine + efavirenz or nevirapine	2-fold higher incidence of grade 4 elevation in liver enzymes among women than among men on nevirapine-containing regimens

Table **3.** Clinical Trials on Sex and Toxicity Associated with Protease Inhibitors or Highly Active Antiretroviral Therapy

Study	Population	Drugs	Sex Difference in Toxicity
Muurahainen et al[14]	49 women, 159 men	HAART	Women had more fat accumulation; men had more fat loss
Currier et al[30]	90 women, 996 men	Ritonavir + reverse transcriptase inhibitors	Higher rates of nausea, vomiting, and tingling around the mouth but a lower rate of diarrhea among women
Gatti et al[31]	35 women, 52 men	Ritonavir-containing regimens	Greater than 2-fold increase in ritonavir intolerance among women than among men
Gersten et al[32]	78 women, 616 men	Nelfinavir-containing regimens	Women had more abdominal pain and itching; men had more diarrhea
Lucas et al[33]	76 women, 197 men	HAART	Higher rates of adverse drug reactions among women
Galli et al[34]	673 women, 1585 men	HAART	Morphologic alterations more common among women

HAART indicates highly active antiretroviral therapy.

women with HIV infection if further studies confirm that HAART results in a less favorable lipid profile among women than among men. Khalsa and colleagues,[36] in a study of the WIHS cohort, reviewed the incidence and prevalence of hypertension among 2057 HIV-infected women and 569 demographically similar HIV-seronegative women at risk of infection. The baseline prevalence of hypertension was similar among the HIV-seropositive women (14.4%) and the HIV-seronegative women (16.2%; P = not significant). However, multivariate analyses that were controlled for age, ethnicity, and body mass index and that excluded baseline prevalent cases revealed an increase in hypertension after HAART administration for 2 years or more (odds ratio, 1.54; $P < .05$). This increase in hypertension among HAART-treated women was of borderline statistical significance and thus needs to be confirmed in further studies. Nonetheless, the fact that women treated with HAART experience higher rates of dyslipidemia and insulin resistance and may experience a higher rate of hypertension suggests that they may be at greater risk of cardiovascular disease than are men on the same therapy.

Postulated Mechanisms of Sex Differences in Antiretroviral Toxicity

No one knows for certain why sex differences exist in adverse reactions to antiretroviral drugs. Differences in weight and body mass index between men and women may play an important role. Other mechanisms proposed to explain sex differences in the toxicity of drugs in general may also be involved.[37-39] These mechanisms include hormonal changes in women at puberty, during menstrual cycles, and at menopause and the effect of these changes on drug metabolism. Sex differences in fat composition and the impact on drug distribution may also play a role, as may the genomic constitutional difference that exists between men and women and the way in which this difference affects the levels of various enzymes involved in drug metabolism.[40]

Conclusion

The number of women participating in HIV clinical trials and the number of studies designed to address the influence of sex differences on HIV infection are increasing. The results of some of these studies suggest that sex differences may exist in adverse reactions to antiretroviral drugs. More studies are needed to further characterize the specific nature and magnitude of these differences in the toxicity of antiretroviral drugs in women. The mechanisms behind the role of sex in antiretroviral toxicity need to be aggressively evaluated. Finally, the role of therapeutic drug monitoring of antiretroviral drugs needs to be further clarified. Individualized dose regimens based on drug plasma levels may reduce the frequency and severity of some adverse reactions and thus improve the tolerability of antiretroviral drugs for women.

Financial Disclosure: Drs Ofotokun and Pomeroy have no affiliations with commercial organizations that may have interests related to the content of this article.

Acknowledgement: The authors are indebted to Flo Witte for her editorial review of the manuscript.

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Top HIV Med. 2003;11(2):55-59

Highlights of Selected US and International Groups Providing HIV Care and Services in Developing Countries

In recent months, the International AIDS Society–USA (IAS–USA) has seen growing clinician interest in efforts by organizations in developed countries to assist HIV-infected patients in the developing world. Audience questions posed at IAS–USA continuing medical education courses, for example, increasingly seek information about US- or international-led groups working through clinical care, physician training, patient education, or other means to address the epidemic worldwide. Profiles of 8 such organizations, collected through an IAS–USA survey sent to 18 groups, are provided below in alphabetical order. Included is information on how individual practitioners might contribute time or resources to each group's activities.

These 8 organizations primarily focus their efforts in Africa. Services are also provided in Asia, Latin America, and Eastern Europe, but less frequently. On the whole, the groups focus their efforts in developing countries on medical training of local health care practitioners; community education about strategies to prevent HIV transmission, particularly mother-to-child transmission; and care for HIV-seropositive patients, including counseling, prophylaxis and treatment of opportunistic infections, and related services. For several organizations, such care increasingly includes antiretroviral therapy, offered to select patients. At least 2 groups are also conducting organized research into effective methods to provide antiretroviral drugs within resource-limited settings.

The IAS–USA does not endorse the groups included in this article, and information provided comes directly from the organizations. Further, this compilation by no means exhausts the list of organizations working in this sphere, and readers are welcome to submit suggestions for additional profiles, which may be included in a future issue of *Topics in HIV Medicine*. Suggestions may be e-mailed to topics@iasusa.org.

Academic Alliance for AIDS Care and Prevention

A joint effort by US and Ugandan physicians to provide enhanced care, educate clinicians, and conduct research

Overview

The Academic Alliance for AIDS Care and Prevention is led by a group of physicians from the Infectious Diseases Society of America (IDSA) and the Kampala, Uganda-based Makerere University. The project began in June 2001 with an initial grant from Pfizer Inc. for the construction of the Infectious Diseases Institute, an HIV clinic, in Kampala. The alliance is primarily academic in nature, integrated fully into Makerere University Medical School and Kampala's Mulago Hospital. It is also a nongovernmental organization with private-public partnerships, through which it receives additional funding from many donors. The project targets adults and children in Kampala and has outreach efforts throughout Uganda. Primary goals of the project include:

- Provide enhanced care, including antiretroviral drugs and prophylaxis and treatment of opportunistic infections, to HIV-infected patients
- Train African medical practitioners in HIV care through an intensive educational program linked with the IDSA
- Conduct operational and outcomes research to create better guidelines for the care of HIV-infected patients in Africa
- Conduct prevention-based research, focusing on voluntary testing and counseling, reducing mother-to-child transmission of HIV, and reducing the spread of other sexually transmitted diseases
- Implement state-of-the-art laboratory techniques appropriate for the initiation and monitoring of antiretroviral therapy in resource-limited settings

Volunteer Opportunities

Physicians may volunteer through the Academic Alliance to help train African physicians in HIV care. Volunteers must be willing to live in Uganda and serve as trainers for at least 2 years. Round-trip airfare to Kampala, onsite housing, and a per diem for living expenses are provided to volunteers. Further information about the training program and an application form are available through the IDSA Web site at www.idsociety.org/ATP/Background.htm.

Contact Information

Academic Alliance for AIDS Care and Prevention
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AIDS Empowerment and Treatment International

An international network of associations of people living with HIV/AIDS

Overview

AIDS Empowerment and Treatment International (AIDSETI) is an international network of 22 associations of people living with HIV/AIDS in 14 African and Caribbean countries. Incorporated in Uganda and in Delaware as a 501(c)(3) not-for-profit organization, AIDSETI aims in the next several years to implement a cross-country program to test the scalability, quality, and cost-effectiveness of an association-based treatment model for HIV. Through this model, all financial, pharmaceutical, and human resources are controlled by local associations. AIDSETI is led by an independent board of 13 directors, the majority of whom are from developing countries. It also maintains a small administrative staff, based in Washington, DC, whose responsibilities include network management and information dissemination. Once the network is fully operational, services provided to HIV/AIDS patients by AIDSETI associations will include the following:

- Psychosocial and nutritional support
- Education on healthy living and survival skills
- Monitoring of disease progression
- Prophylaxis and treatment of opportunistic infections
- Antiretroviral drugs for patients in more advanced stages of disease

AIDSETI will also help conduct operational research to improve referral systems, carry out clinical trials to adapt treatment to resource-poor settings, and ultimately make available a researchable cross-country treatment database. AIDSETI is seeking funding from the Global Fund to Fight AIDS, Tuberculosis and Malaria to cover the majority of costs over the first 3 years of implementation. The network also expects to receive contributions from associations, patients, and other corporate or organizational donors.

Volunteer Opportunities

A printable form on AIDSETI's Web site allows individuals to propose volunteer opportunities or make financial donations. The form is available at www.aidseti.org/ReturnForm1.htm.

Contact Information

AIDSETI
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Global AIDS Interfaith Alliance

Web: www.idsociety.org/ATP/Background.htm
Using religious organizations in Africa to help those in rural areas develop HIV prevention and care strategies

Overview

The Global AIDS Interfaith Alliance (GAIA) works through religious organizations in rural Africa to develop village-level action plans for HIV prevention and care. GAIA uses Christian, Muslim, and traditional African religious organizations in its efforts, which are funded through gifts from individuals, foundations, and religious congregations in the developed world. The nongovernmental organization trains rural residents to deliver home-based care, health counseling, pastoral counseling, and support services, as well as to make referrals to testing, diagnostic, and treatment centers if available. In addition, GAIA provides small grants to purchase bicycle ambulances, HIV testing kits, blankets, food, and other supplies.

Volunteer Opportunities

Although GAIA does not formally sponsor the work of health care practitioners from developed countries in the developing world, it can refer volunteers to care facilities in those areas. The group has helped one US-based HIV testing, treatment, and counseling center partner with a rural clinic in Central Africa and would be interested in helping other organizations create similar affiliations.

Contact Information

Global AIDS Interfaith Alliance
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Global Strategies for HIV Prevention

Educational efforts to stem HIV transmission in developing countries

Overview

Global Strategies for HIV Prevention is a US-based, 501(c)(3) not-for-profit organization that works to prevent HIV transmission in resource-poor areas of developing countries. The organization's goals include the following:

- Facilitate community programs to prevent mother-to-child HIV transmission
- Sponsor focused workshops and conferences in developing countries on issues relevant to preventing HIV transmission
- Establish programs to prevent HIV infection in women and children who are sexually abused
- Establish prevention programs for health care workers caring for HIV-seropositive patients
- Create mentoring relationships between medical advisors in developed countries and health care workers in developing countries
- Develop and distribute, via all available communication means, HIV information to communities with limited access to educational material

The organization's educational efforts include a CD-ROM entitled "Women, Children and HIV," developed in collaboration with the University of California San Francisco's HIV InSite program. The CD-ROM contains the equivalent of 5000 printed pages of information on categories such as counseling and testing, care of women and children with HIV, prevention, and nutrition. The first edition was distributed to 2000 individuals in 52 countries. The second edition, currently in development, will be distributed to 15,000 individuals and organizations worldwide.

Global Strategies also provides nevirapine to prevent mother-to-child HIV transmission; rapid HIV tests; and antibiotics to treat opportunistic infections. The organization, which is funded through individuals, corporations, foundations, and other grants, has supported programs in more than 20 countries.

Volunteer Opportunities

Global Strategies does not use volunteer physicians to serve patients in the developing world directly. However, volunteers may contribute education, training, and resource information for the educational CD-ROM described above. The organization also welcomes volunteer editors to help confirm the accuracy of such information.

Contact Information

Global Strategies for HIV Prevention
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International Center for Equal Healthcare Access

Volunteer physicians provide health practitioner training in community-based care settings in order to enhance clinical care provided to HIV-infected patients

Overview

The International Center for Equal Healthcare Access (ICEHA) is a US-based, 501(c)(3) not-for-profit organization that represents a network of clinicians from various US medical facilities who donate their time toward improving the quality and expanding the capacity of community-based HIV/AIDS care in developing countries. The organization targets countries where access to antiretroviral drugs is growing. Services provided by ICEHA include medical education and hands-on training for community-based care providers; HIV health literacy and empowerment programs to raise awareness at the village level; and home-based care.

As of November 2002, ICEHA oversaw projects in the following areas:

- *Northern Vietnam:* A medical education and practical training program targets all health care practitioners in Langson province (northern highlands and Chinese border area) in an effort to slow the spread of HIV in the region; if successful, the program may expand nationwide.
- *Côte d'Ivoire:* Medical education is offered to community-based practitioners in the city of Abidjan, who serve roughly 4500 HIV-seropositive patients in a general population of 35,000. An HIV health literacy and health care empowerment program targets 20,000 people in 10 villages in the Bas-Sassandra region.
- *Nigeria:* A program at the rural Ogun-State antenatal clinic to prevent vertical HIV transmission draws on existing antiretroviral services and will serve approximately 3000 pregnant women over a 2-year period.

As of November 2002, ICEHA was considering an additional 5 program proposals. Most projects are scheduled to run 12 to 15

months, although duration varies according to need. ICEHA projects are funded through various sources, including foundations and corporate support.

Volunteer Opportunities

ICEHA is a network of clinicians who donate their time. Current participants practice in the fields of infectious diseases, internal medicine, pediatrics, and obstetrics, among others. Experience levels range from chief residents and fellows to senior-level clinical experts. Medical volunteers work in local clinics, where they provide care while working to train local practitioners by example. A minimum time commitment of 8 weeks is required. Expenses incurred when participating in ICEHA programs may be covered, although reimbursement varies between projects.

Physicians unable to contribute their time may assist ICEHA through financial contributions, distribution of printed materials, and fundraising.

Contact Information

International Center for Equal Healthcare Access
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Médecins Sans Frontières/Doctors Without Borders

Offering HIV prevention, counseling, testing, and antiretroviral treatment through projects worldwide

Overview

Médecins Sans Frontières (MSF) is an international medical aid network that, among its many projects, serves HIV/AIDS patients in developing countries. The organization offers HIV prevention services, especially related to mother-to-child transmission; voluntary counseling and testing; psychosocial support; and prophylaxis and treatment of opportunistic infections. Since 2001, MSF has also provided antiretroviral drugs to HIV-infected patients in Cambodia, Cameroon, Guatemala, Honduras, Kenya, Malawi, South Africa, Thailand, Uganda, and Ukraine. As of December 2002, these programs served almost 2300 patients; in 2003, MSF expects to double the number of countries and patients to which it provides antiretroviral therapy. MSF is a private, not-for-profit organization that receives funding from the public, foundations, corporations, not-for-profit organizations, governments, and international agencies.

Volunteer Opportunities

Approximately 2500 volunteers a year, including physicians, nurses, and other medical personnel, participate in MSF projects around the world. The minimum commitment for a first-time volunteer is 6 months, and commitments of 9 to 12 months are more typical. Volunteer applicants must undergo an in-person interview at an MSF office. Foreign language skills and prior experience in developing or underserved regions are valued.

Volunteer responsibilities vary according to project but generally include a combination of treatment and education.

Contact Information

Médecins Sans Frontières/Doctors Without Borders
Attention: Human Resources Department
6 East 39th Street, 8th Floor, New York, NY 10016
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E-mail: field_volunteers@newyork.msf.org
Web: www.doctorswithoutborders.org

MTCT-Plus Initiative

Adding care and treatment to existing programs to prevent mother-to-child transmission of HIV

Overview

Coordinated by Columbia University's Mailman School of Public Health, the MTCT-Plus Initiative aims to add HIV care and treatment to existing programs to prevent mother-to-child transmission of HIV in developing countries. The project, which launched in December 2001, has identified 12 prevention programs in 8 countries (7 in Africa and 1 in Thailand). Beginning in early 2003, pregnant women enrolled in these programs will be offered a post-delivery package of care and treatment services, including education, counseling, prophylaxis and treatment of HIV complications, and antiretroviral therapy where appropriate. Services are offered to women on a lifetime basis, and are also offered to their HIV-seropositive partners and children. The MTCT-Plus Initiative is supported by a coalition of 9 US-based foundations.

Volunteer Opportunities

MTCT-Plus does not currently use physician volunteers from developed countries, although it may do so in the future.

Contact Information

MTCT-Plus Initiative
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Pangaea Global AIDS Foundation

Working to broaden access to antiretroviral therapy and to support development of an effective HIV vaccine

Overview

The Pangaea Global AIDS Foundation is a US-based affiliate of the San Francisco AIDS Foundation. Launched in May 2000, the nongovernmental organization works in developing countries to broaden access to antiretroviral therapy and other HIV care and to support the development of an effective HIV vaccine. Funding for its efforts comes from private foundations, corporations, individual donors, and the governments of developed countries. Pangaea has projects in Rwanda, South Africa, Uganda, and the Bahamas, where it works in partnership with local medical, academic, and civic organizations to create programs that are sustainable for the long term; culturally relevant and sensitive; locally controlled; and supported by strong management systems, among other considerations. Pangaea's efforts in these 4 countries are described below.

- *Rwanda:* Pangaea's Family HIV Care and Support Project, a joint initiative with the country's Ministry of Health and Office of the First Lady, works with clinics and a hospital in Kigali to provide antiretroviral drugs to HIV-seropositive women and their partners and children.
- *South Africa:* The organization has partnered with hospitals, university medical institutions, and community clinics in the provinces of Kwa-Zulu Natal, Gauteng, and the Western Cape to develop, test, and implement different models of care that include access to antiretroviral drugs.
- *Uganda:* Pangaea has collaborated with Pfizer Inc. and the Academic Alliance for AIDS Care and Prevention in Africa (see above) to create an HIV clinical care and training institute in Kampala. Pangaea is the fiscal agent on an $11 million grant provided by Pfizer for clinic construction.
- *Bahamas:* In partnership with the William Jefferson Clinton Foundation, Pangaea has performed an assessment of the Bahamas' capacity to provide HIV care and developed a plan to provide treatment, including antiretroviral drugs, to local patients beginning in 2003.

Volunteer Opportunities

Pangaea does not currently use physician volunteers from developed countries, although it may do so in the future. Individual physicians can contribute to the organization's efforts by advocating for funding, providing contacts, and assisting in resource solicitation.

Contact Information

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The International AIDS Society–USA publishes *Topics in HIV Medicine* as a resource for physicians and other health care practitioners who are actively involved in HIV and AIDS care. The journal is indexed in *Index Medicus*/MEDLINE and is distributed to approximately 12,000 national and international subscribers.

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[1]International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2001. Available at http://www.icmje.org. Accessed January 24, 2003.

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The next issue of *Topics in HIV Medicine* will feature summaries of new research presented at the 10th Conference on Retroviruses and Opportunistic Infections, held February 10 to 14 in Boston, Mass. These articles will also be available online at www.iasusa.org prior to print publication. Topics covered will include:

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Mario Stevenson, PhD

HIV Pathogenesis and Vaccine Development
R. Paul Johnson, MD, and Amitinder Kaur, MD

Complications of HIV Disease and Therapy
Judith S. Currier, MD, and Diane V. Havlir, MD

Management of Antiretroviral Therapy
Timothy J. Wilkin, MD, MPH, Mary A. Albrecht, MD, Eoin P.G. Coakley, MD, and Scott M. Hammer, MD

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Chairs: Gerald H. Friedland, MD, and Paul A. Volberding, MD

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Chairs: John P. Phair, MD, and Harold A. Kessler, MD

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Chairs: Paul A. Volberding, MD, and Stephen E. Follansbee, MD

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Tuesday, May 20, 2003
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