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Topics in Antiviral Medicine™

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  - **Tuesday, March 31, 2015**
  - New York Marriott Marquis

- **Washington, DC**
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- **Chicago, Illinois**
  - **Tuesday, May 19, 2015**
  - Chicago Marriott Downtown
  - Magnificent Mile

- **Los Angeles, California**
  - **Date and Venue TBD**

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HIV Preexposure Prophylaxis in the Real World

According to evolving guidelines, candidates for HIV preexposure prophylaxis (PrEP) include HIV-uninfected men who have sex with men who engage in condomless anal intercourse, individuals in HIV-serodifferent sexual relationships, those with frequent anogenital sexually transmitted infections, and those who have received repeated nonoccupational postexposure prophylaxis treatment courses. In the real-world setting, indications for PrEP and management of PrEP candidates and patients may be less than clear-cut. Factors to be considered when assessing candidacy for PrEP and maximizing efficacy of treatment are discussed. This article summarizes a presentation by Demetre C. Daskalakis, MD, MPH, at the IAS–USA continuing education program held in Los Angeles, California, in April 2014.

Keywords: HIV, risk behavior, serodiscordant, serodifferent, preexposure prophylaxis, PrEP, tenofovir, emtricitabine

Preexposure prophylaxis (PrEP) for HIV is not intended as a lifelong intervention, but rather a temporary method of increasing the chances of prevention of HIV acquisition during phases of increased high-risk behaviors. Although guidelines vary, potential candidates for PrEP include the following HIV-uninfected individuals: men who have sex with men (MSM) who engage in unprotected anal intercourse; individuals in a sexual relationship with an HIV-infected partner; transgender individuals engaging in high-risk sexual behaviors; individuals engaging in transactional sex; injection drug users engaging in injection-related or sexual risk behaviors; users of stimulant drugs, such as methamphetamine, that are associated with high-risk behaviors; individuals diagnosed with more than 1 anogenital sexually transmitted infection (STI) in the previous year; and individuals who have received nonoccupational postexposure prophylaxis (nPEP) but continue to engage in high-risk behaviors or have received repeated nPEP treatment courses (Table 1).1

Case 1: Continued Exposures

Patient 1 is a 27-year-old man who visits his primary care practitioner to discuss his risk for HIV infection. He states that he engages in behaviors that place him at high risk for acquisition of HIV and other STIs. He confides that he sometimes engages in condomless anal sex with men, often anonymously and in the context of drug use. He has received 3 courses of nPEP in the past year and was diagnosed with rectal lymphogranuloma venereum 2 months ago and rectal gonorrhea a few weeks before that. The patient asks his physician about the possibility of starting PrEP. He has heard in the news that there is a daily pill that could lower his risk for HIV infection. The physician must consider whether this patient is a candidate for PrEP.

Patient 1 meets several PrEP candidacy criteria, including the recent diagnosis of more than 1 anogenital STI. Studies in San Francisco, California, have shown that risk of HIV infection increases 8-fold for MSM with 2 prior rectal chlamydial or gonococcal infections and that the annual incidence of HIV infection was 15 per 100 person-years among MSM with an average of 1 rectal infection per year.2 Studies in New York City indicate an annual HIV infection incidence of 6.7% in MSM diagnosed with rectal STIs compared with 2.5% in MSM who did not have rectal STIs.3

The patient is also a candidate for PrEP on the basis of his having received repeated courses of nPEP, an indicator that his risk behaviors are ongoing. Data from studies in Amsterdam indicate a high frequency of HIV seroconversions following nPEP, owing not

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Table 1. HIV-Uninfected Individuals Meeting Criteria for PrEP

- MSM who engage in unprotected anal sex
- Individuals in HIV-serodifferent sexual relationships
- Transgender individuals who engage in high-risk sexual behaviors
- Individuals who engage in transactional sex (eg, provide sex in exchange for money, drugs, housing, etc)
- IDUs who report:
  - Sharing injection equipment, including to inject hormones
  - Injecting 1 or more times per day
  - Injecting cocaine or methamphetamine
  - Engaging in high-risk sexual behaviors
- Individuals who use stimulant drugs (eg, methamphetamine) associated with high-risk behaviors
- Individuals diagnosed with more than 1 anogenital STI in the past year
- Individuals who have been prescribed nPEP who continue to engage in high-risk behaviors or have taken repeated courses of nPEP

Abbreviations: IDU, injection drug user; MSM, men who have sex with men; nPEP, non-occupational postexposure prophylaxis; PrEP, preexposure prophylaxis; STI, sexually transmitted infection. Adapted from New York State Department of Health.4

Dr Daskalakis is Associate Professor of Medicine at Icahn School of Medicine at Mount Sinai in New York, New York.
to nonadherence or a lack of efficacy but to continuation of risk activity after the nPEP treatment course. One study showed that 8 of 11 seroconversions among nPEP users occurred more than 3 months after they received nPEP. Another study showed 5 seroconversions out of 239 nPEP users, all occurring late in follow-up.

The patient’s physician is unsure about using tenofovir disoproxil fumarate and emtricitabine for PrEP. He has never prescribed this medication and is uncomfortable with the patient’s revelation that he engages in ongoing condomless sex, and he believes that prescribing PrEP would be condoning the patient’s risk behavior. Further, he does not believe that the protective efficacy of PrEP is as great as that of other protective treatments used for other disease states in his practice, such as statins to prevent cardiovascular events. He guides the patient away from considering PrEP but offers to refer him to an HIV specialist for further discussion of the intervention.

Using malaria as an example of an infection for which we have experience providing chemoprophylaxis, 2 models may exist for infection prevention. Unfortunately, the physician in this case was embracing an unhelpful model of infection prevention. In this model, the answer to the question “When traveling to parts of the world where malaria can be contracted, how can this be avoided?” might be something like “Always use bed nets, avoid mosquito exposure, and never leave your hotel.” Extrapolating this to HIV prevention, the answer to “When in a behavioral or epidemiologic environment where HIV infection risk is high, how can this risk be reduced?” might be “Always use condoms, have only 1 sexual partner, and do not have sex with an HIV-infected partner.” A more reasonable and realistic model might answer the first question for malaria with “Use bed nets, avoid mosquitoes as much as possible, and take antimalarial medications as malaria preexposure prophylaxis” and the second question with “Use condoms, but if condoms are not used consistently or at all, talk to a physician about HIV medications that may help to prevent the acquisition of HIV infection.”

The physician should confirm to the patient that PrEP is a reasonable choice and should heavily emphasize the need for strict adherence to a PrEP regimen, because the degree of adherence dictates the degree of efficacy. In the iPrEx (Chemo prophylaxis for HIV Prevention in Men) trial, there was a 44% reduction in HIV acquisition with the use of tenofovir and emtricitabine, in a modified intent-to-treat analysis. However, in a case-control study of the iPrEx population, analysis showed a 92% reduction in risk in patients with detectable intracellular tenofovir diphosphate levels. PrEP, like antiretroviral therapy for chronic HIV infection, works when it is taken. This finding is consistent across PrEP studies, with a higher percentage of patients with blood samples showing detectable levels of tenofovir correlating with higher protective efficacy rates in randomized comparisons—81% and 75%, respectively, in the Partners PrEP study; 79% and 62%, respectively, in the TDF2 study; 51% and 44%, respectively, in the iPrEx study; and only 26% and 6%, respectively, in the FEM-PrEP (Preexposure Prophylaxis Trial for HIV Prevention among African Women) study.

Nonadherence to a PrEP regimen lowers the barrier to acquisition of HIV infection. Physicians should be mindful of this and patients should be reminded of this, particularly in light of the finding that there appears to be no change in risk behaviors in many patients taking PrEP. In the iPrEx study, for example, there was no marked change in condom use between patients who perceived themselves to be taking a placebo and those who perceived themselves to be taking PrEP. Physicians should not expect to see large reductions or increases in risk behaviors among patients taking PrEP. Risk-reduction counseling and risk assessment should be part of every PrEP-related office visit.

Finally, there is the concern of the physician in this case that PrEP does not have the preventive efficacy of other treatments, such as statins, that he routinely prescribes in practice. As shown in Figure 1, the number of patients needed to treat for 1 year to prevent 1 HIV infection is smaller in trials of HIV PrEP than the number needed to treat with statins in primary prevention to prevent 1 cardiovascular event, suggesting that PrEP is indeed an efficient but costly intervention, at $8,000 to $14,000 per year.

The patient in this case visits an HIV specialist, who reviews the patient’s risk and decides that a PrEP regimen of tenofovir and emtricitabine is a potentially good intervention to supplement barriers to HIV infection and STIs, as long as the patient is medically cleared to start PrEP. The patient then reports that he engaged in condomless receptive anal sex 5 weeks ago with a partner whose HIV serostatus is unknown.

Baseline HIV testing is part of the preprescription evaluation of all patients being considered for PrEP. Considerations for preprescription

Figure 1. Number of patients needed to treat for 1 year to prevent 1 case of HIV acquisition in preexposure prophylaxis (PrEP) trials or 1 cardiovascular event with statin use for primary prevention. CAPRISA indicates Center for the AIDS Program of Research in South Africa; FTC, emtricitabine; iPrEx, Chemoprophylaxis for HIV Prevention in Men; TDF, tenofovir disoproxil fumarate. Adapted with permission from Glidden.
**Table 2. Preprescription Considerations for PrEP**

<table>
<thead>
<tr>
<th><strong>Education</strong></th>
<th><strong>Assessment</strong></th>
<th><strong>Laboratory</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Teach how PrEP works</td>
<td>■ Screen for symptoms of acute HIV infection within the past 6 weeks</td>
<td>■ Baseline HIV testing</td>
</tr>
<tr>
<td>■ Define the limits of PrEP</td>
<td>■ Review medication list</td>
<td>■ Third- or fourth-generation HIV test</td>
</tr>
<tr>
<td>□ Adherence</td>
<td>□ Are there any potential interactions or synergistic toxicities?</td>
<td>□ NAAT for HIV in:</td>
</tr>
<tr>
<td>□ Lack of protection against STIs</td>
<td>Assess mental health and substance use</td>
<td>- Patients with symptoms of acute HIV infection</td>
</tr>
<tr>
<td>□ Does not offer 100% protection against HIV</td>
<td>Explore patient knowledge of PrEP and motivation for initiating medication</td>
<td>- Patients whose HIV antibody test results are negative but who have reported engaging in unprotected sex with an HIV-infected partner within the past month</td>
</tr>
<tr>
<td>■ Reinforce daily dosing of PrEP</td>
<td>Evaluate willingness to take PrEP daily</td>
<td>■ Drug-resistant HIV has been observed in patients with undiagnosed HIV infection taking a PrEP regimen of tenofovir and emtricitabine</td>
</tr>
<tr>
<td>■ Review adverse effects</td>
<td>■ The patient connected to primary care?</td>
<td>■ Basic metabolic panel</td>
</tr>
<tr>
<td>■ Discuss the long-term safety of PrEP in HIV-seronegative individuals</td>
<td>■ Is patient involved with HIV-seropositive sexual partners?</td>
<td>□ PrEP should not be initiated for patients with a creatinine clearance &lt;60 mL/min</td>
</tr>
<tr>
<td>■ Confirm a schedule for follow-up and testing, especially HIV testing every 90 days</td>
<td>□ Are any HIV-seropositive sexual partners taking antiretroviral therapy?</td>
<td>■ Urinalysis</td>
</tr>
<tr>
<td>■ Review stopping criteria for PrEP</td>
<td>□ Are resistance data available?</td>
<td>□ Proteinuria can be an early warning sign of tenofovir toxicity</td>
</tr>
<tr>
<td>□ Positive HIV test result</td>
<td>■ Screen for domestic violence</td>
<td>■ Baseline urinalysis should be used to identify any preexisting proteinuria</td>
</tr>
<tr>
<td>□ Renal disease</td>
<td>■ Assess housing status</td>
<td>■ Serologies for hepatitis A, B, and C viruses</td>
</tr>
<tr>
<td>□ Nonadherence</td>
<td>■ Does patient have the means to pay for PrEP?</td>
<td>□ Immunize patients against hepatitis A and B viruses as needed</td>
</tr>
<tr>
<td>□ Change in risk-taking behavior</td>
<td>■ Evaluate fertility goals and contraception use in women who are PrEP candidates</td>
<td>■ STI screening</td>
</tr>
<tr>
<td>■ Teach about symptoms of acute HIV infection</td>
<td>■ For a woman is pregnant when starting PrEP or becomes pregnant while taking PrEP, known risks and benefits should be discussed</td>
<td></td>
</tr>
<tr>
<td>■ Discuss with women:</td>
<td>■ Nucleic acid amplification test; PrEP, preexposure prophylaxis; STI, sexually transmitted infection. Adapted from New York State Department of Health.</td>
<td>■ NAAT for gonococcal and chlamydial infection; 3-site screening (genital, rectal, pharyngeal)</td>
</tr>
<tr>
<td>□ How PrEP can help prevent HIV infection and transmission during pregnancy</td>
<td>■ Rapid plasma reagent test for syphilis</td>
<td></td>
</tr>
<tr>
<td>□ Potential but undemonstrated risk of birth defects</td>
<td>■ Pregnancy testing</td>
<td></td>
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<tr>
<td>■ Fertility goals and potential embryo-fetal toxicity should be discussed with patients when appropriate</td>
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education and evaluation are shown in Table 2. Important components of education include informing patients about the nature and limitations of PrEP, stressing the need for adherence, and ensuring that the patient understands that treatment is part of a larger package that includes HIV testing, with the invitation to visit every 3 months for repeat testing, and STI prevention, testing, and treatment. Potential adverse effects of treatment with tenofovir and emtricitabine, including bone and kidney effects, should be considered. Fertility goals and potential embryo-fetal toxicity should be discussed with patients when appropriate. Clinical evaluation includes screening for symptoms of acute HIV infection, review of current medications for potential drug interactions and augmented toxicity, and assessment of a patient’s motivation for taking PrEP, mental health, substance use status, and status with regard to such psychosocial factors as stable housing and domestic violence. Laboratory evaluation includes assessment of kidney function, urinalysis to identify preexisting proteinuria (proteinuria may be an early sign of tenofovir renal toxicity), STI screening, viral hepatitis serology (including ensuring that patients are up to date with their vaccinations), and pregnancy testing. With regard to HIV testing, current PrEP pre-prescription guidelines state that nucleic acid amplification testing for HIV viral load should be performed in patients with symptoms of acute HIV infection and in those with a negative HIV antibody test who report engaging in unprotected sex with an HIV-infected partner in the past month. It is important for physicians and patients to know that drug-resistant HIV has been found in patients with undiagnosed HIV infection who were taking a PrEP regimen of tenofovir and emtricitabine.

For the patient in this case, the HIV specialist performs HIV viral load testing, which shows no evidence of infection, and attempts to get approval from the patient’s insurance company to initiate PrEP. However, the insurance company denies coverage on the basis of the treatment’s being “not medically necessary.” The insurance company’s statement notes that “as per health plan criteria for tenofovir and emtricitabine, coverage cannot be approved at this time. This drug cannot be approved if recent exposure (less than a month) to the HIV virus is not suspected.” The HIV specialist responds by engaging the insurance company in a discussion and ultimately gaining approval for the treatment. Responses such as this from insurance companies have become somewhat less common in practice. However, it is important for physicians to note that some barriers do exist to obtaining coverage for PrEP and that an aggressive approach may
be necessary in order to incorporate PrEP into a practice.

Cases 2 and 3: “Risk Vacation” or Pregnancy

Patient 2 is a 35-year-old, HIV-seronegative man who uses condoms 100% of the time when home in Los Angeles, California, but once a year he goes on vacation to Palm Springs, California, where he engages in condomless insertive and receptive anal sex. He foresees numerous possible exposures to HIV infection while on vacation. Patient 3 is a 35-year-old, HIV-seronegative woman who wants to have a baby with her HIV-seropositive husband. She does not intend to use any fertility technology to become pregnant. Her husband has undetectable HIV RNA levels, and they use condoms but are planning to stop using them in order to achieve their fertility goal. Both patient 2 and patient 3 want advice on PrEP from their physicians.

From an appropriately nonjudgmental medical point of view, these individuals are likely to have biologically similar exposures to HIV, notwithstanding the difference (pleasure vs fertility) in psychosocial context. Are they candidates for PrEP? If so, how should PrEP be managed in such settings?

Extant data indicate that PrEP works very well for heterosexual serodifferent couples. The Partners PrEP study showed a preventive efficacy rate of 66% among women and 84% among men taking tenofovir and emtricitabine.7 Outside the context of serodifferent couples, PrEP also works well in the setting of heterosexual high-risk individuals and partners of unknown HIV serostatus. Results of the TDF2 trial examining HIV-seronegative individuals in Botswana revealed a 62% protective efficacy rate among men and women (combined) taking regimens of tenofovir and emtricitabine.8

It is important to note that there have also been disappointing results in PrEP studies—notably, in the FEM-PrEP and VOICE (Microbicide Trials Network-003 Vaginal and Oral Interventions to Control the Epidemic) studies of high-risk HIV-seronegative African women. The FEM-PrEP study was stopped early owing to the lack of efficacy of tenofovir and emtricitabine; assessment of tenofovir levels in blood suggested an adherence rate of less than 40%, too low to allow assessment of efficacy.9 The oral tenofovir and vaginal tenofovir gel arms in the VOICE study were also discontinued early owing to a lack of efficacy, and the oral tenofovir and emtricitabine arm showed no protective efficacy. As in the FEM-PrEP study, poor adherence also explained the lack of efficacy observed in the VOICE trial, and no relationship was found between reported adherence and tenofovir levels in blood.

These findings drive home the need for strong support of adherence for patients taking PrEP. In the setting of HIV infection, many clinics have resources and staff specifically devoted to supporting patients’ adherence goals. The same level of resources does not exist in the preventive setting, and it is thus incumbent on physicians and partnerships with community-based organizations to generate and maintain support.

In considering how long before HIV exposure tenofovir and emtricitabine should be started, it is useful to know that protective drug levels do not necessarily depend on achievement of steady state blood levels. It takes between 4 and 7 half-lives for a drug to reach steady state. The intracellular half-life of tenofovir is 150 hours, indicating that achieving steady state takes approximately 25 days.10 The intracellular half-life of emtricitabine is 59 hours, indicating that achieving steady state takes approximately 6 days.11 However, efficacy may be achieved in the absence of steady state conditions if a drug reaches sufficiently high concentrations within a short time and those concentrations are maintained throughout the period of exposure to HIV. After oral administration of a single 300 mg dose of tenofovir, maximum tenofovir concentration is reached in approximately 2 hours.12 Similarly, emtricitabine is rapidly absorbed and reaches maximum concentration in 1 hour to 2 hours.13

Dosing after exposure to HIV is also important, although when to stop tenofovir and emtricitabine dosing after exposure is less clear; guidelines for nPEP indicate that 28 days of treatment are needed for efficacy.14,15

In the absence of definitive data and guidance, a reasonable approach for the individuals in these 2 cases and others in similar settings is to start PrEP at least 1 week before a planned HIV exposure. If it is possible, starting PrEP 1 month before a planned HIV exposure makes sense given the steady state kinetics of PrEP drugs, particularly tenofovir. In extrapolation from the nPEP guidelines, PrEP should be continued for at least 28 days after the last HIV exposure. Further, continuation of PrEP should be discussed with both of these patients, given the potential for unplanned exposures; depending on their actual risk, they may be candidates for longer-term PrEP.

Case 4: Monogamous HIV-Serodifferent Sexual Partners

Patient 4 is an HIV-seronegative man in a monogamous relationship with his HIV-seropositive husband. His husband has a CD4+ cell count of 688/µL and his plasma HIV RNA level has been below 20 copies/mL for several years on antiretroviral therapy. The patient is tired of using condoms for insertive anal sex but uses condoms for all receptive anal sex. He wants to know if he should be taking PrEP.

The issue raised by this case is how PrEP fits into prevention efforts, given the success of treatment as prevention; that is, is PrEP indicated in the setting of a monogamous HIV-serodifferent relationship (same sex or heterosexual) if there is a decreased risk of transmission associated with viral suppression in the HIV-infected partner?

Data showing the efficacy of treatment as prevention come from the HIV Prevention Trials Network 052 trial, in which 1763 HIV-serodifferent couples were randomized to have the HIV-infected partner initiate antiretroviral therapy immediately or, according to then-current guidelines, when their
CD4+ cell count dropped below 250/µL or they developed other indications. Of the 28 linked transmissions of HIV infection observed in the study, only 1 occurred in the immediate treatment arm, a case in which the HIV-infected patient had not been taking antiretroviral therapy for long and still had detectable virus. The reduction in HIV acquisition was 96% with immediate treatment. However, HIV-serodifferent couples of MSM accounted for only 3% of couples in the trial, raising questions about the applicability of the findings to the MSM population.  

The PARTNER study, however, included 16,400 occasions of unprotected sex among 767 couples of MSM. The HIV-infected partner had to be taking antiretroviral therapy and have an HIV RNA level of less than 200 copies/mL. Estimated rates of HIV transmission based on sexual behavior reported by the HIV-uninfected partners were 0 per 100 couple-years of follow-up among women who engaged in heterosexual vaginal sex with ejaculation (total, 192 couple-years); among men who engaged in heterosexual vaginal sex (total, 272 couple-years); and among MSM who engaged in receptive anal sex with ejaculation (total, 93 couple-years), receptive anal sex without ejaculation (total, 157 couple-years), and insertive anal sex (total, 262 couple-years). These data, however, should not be interpreted as indicating an absence of risk. The upper bound of the 95% confidence interval for the point estimates of risk imply that although the incidence of HIV infection was 0, the probability of infection may not be. These bounds were highest for MSM who engaged in receptive anal sex with ejaculation, followed by MSM who engaged in receptive anal sex without ejaculation, women who engaged in heterosexual vaginal sex with ejaculation, and men who engaged in heterosexual vaginal sex or MSM who engaged in insertive anal sex. Although sex with a vireologically suppressed partner is likely low risk, it is not statistically correct to call it zero risk.

It is unclear whether patient 4 requires or should receive PrEP, given the protective effect of antiretroviral therapy in his partner and the patient’s 100% use of condoms for receptive anal sex. Given the current available data, it is possible that PrEP is not necessary in this setting.

**Case 5: PrEP Stigma**

Patient 5 is a 23-year-old African American male who presents to a physician to be treated for syphilis. The patient states that he is heterosexual but sometimes has sex with other heterosexual men. He also states that he does not use condoms when engaging in anal sex because his older partners prefer it that way. The physician attempts to discuss PrEP with the patient, but the patient indicates that he does not think he needs it. He thinks PrEP is only for homosexual men and not for him.

It is clear that there are patient-level barriers to PrEP, including a stigma attached to its use. In addition, there appears to be substantial denial or lack of knowledge in some at-risk individuals’ assessment of their own risk level. Daskalakis and colleagues recently surveyed individuals attending commercial sex venues in New York City (eg, bath houses and sex clubs) regarding whether they believed their risk for HIV infection was high enough to make them candidates for PrEP. Because the study began before there were established guidelines for PrEP, iPrEx trial entry criteria were used to assess candidacy. Of the 511 men surveyed, 377 (73%) met these criteria and were thus PrEP candidates. Of these 377, only 84 (22%) believed HIV infection risk was sufficient to warrant PrEP.

**Conclusion**

Like many innovations in the realm of HIV medicine, technology has outpaced both implementation and social norms. With condoms being the only biomedical intervention available to HIV-uninfected individuals, PrEP has challenged the dogma of HIV prevention. Efficacious if adhered to, PrEP has demonstrated that it deserves a place in the biomedical compartment of the HIV prevention toolbox alongside treatment as prevention, condoms, STI treatment or control, and postexposure prophylaxis. Real-world implementation and a shift in the dialogue of prevention toward risk acknowledgment and mitigation rather than zero tolerance will be the path to fully realizing the power of PrEP.

Presented by Dr Daskalakis in April 2014. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Daskalakis in September 2014.

Financial affiliations in the past 12 months: Dr Daskalakis has no relevant financial affiliations to disclose.

**References**


**Additional Suggested Reading**


**Top Antivir Med.** 2014;22(4):670-675 ©2014, IAS–USA. All rights reserved.

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**Recommendations for Testing, Managing, and Treating Hepatitis C**

*Recommendations for Testing, Managing, and Treating Hepatitis C* is a website sponsored by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society–USA (IAS–USA) to provide the most current guidance for the treatment of hepatitis C virus (HCV).

**Available sections:**

- HCV Testing and Linkage To Care
- When and in Whom to Initiate HCV Therapy
- Initial Treatment of HCV Infection in Patients Starting Treatment
- Retreatment of Persons in Whom Prior Therapy Has Failed
- Monitoring Patients Who Are Starting Hepatitis C Treatment, Are on Treatment, or Have Completed Therapy
- Unique Patient Populations
- Management of Acute HCV Infection

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- Assists practitioners in treating the estimated 3 to 4 million Americans infected with HCV by highlighting the latest information in improved diagnostics and new drug options as they meet FDA approval.
- Offers guidance to practitioners about how to best use the next generation of direct-acting antivirals and other treatment options in the care of their patients.
Perspective

Cardiovascular Disease in HIV: Traditional and Nontraditional Risk Factors

A new paradigm for atherogenesis in HIV infection is emerging, in which viral replication and microbial translocation result in ongoing T-cell and monocyte activation, with persistent inflammation leading to the development of atypical, high-risk morphology plaques. These plaques, characterized by low attenuation and positive remodeling, can be found even among HIV-infected patients who are at low risk for cardiovascular disease based on traditional risk factors. Prevention of cardiovascular events in HIV infection requires modulation of traditional risk factors and is also likely to require effective antiinflammatory treatment strategies. Statins, which are traditionally used to treat dyslipidemia, have also been shown to exert antiinflammatory effects associated with clinical benefit and may be useful to treat and prevent cardiovascular disease in HIV-infected patients. However, large-scale studies of statins in the context of HIV infection must be conducted. This article summarizes a presentation by Steven K. Grinspoon, MD, at the IAS–USA continuing education program held in Chicago, Illinois, in May 2014.

Keywords: cardiovascular disease, CVD, HIV, inflammation, immune activation, plaque, antiinflammatory

The preponderance of evidence from many cohort studies indicates that HIV-infected patients are at a 1.5- to 2-fold greater risk for cardiovascular disease (CVD) than the general population. The traditional paradigm for explaining this increased risk includes the effects of HIV infection itself, the effects of antiretroviral therapy in causing dyslipidemia, ectopic fat accumulation, and diabetes or insulin resistance; and risk factors such as smoking, coinfections, or drug use. In this traditional paradigm, these factors contribute to the formation of calcified coronary plaques and resulting coronary events. However, accumulating evidence strongly indicates that persistent immune activation and inflammation play a major role in CVD risk in the setting of HIV infection, with atherosclerosis characterized by formation of atypical, noncalcified, high-risk plaques.

Traditional and Nontraditional CVD Risk Factors in HIV

HIV-infected patients have increased risk for diabetes, primarily associated with insulin resistance. Representative data from the MACS (Multicenter AIDS Cohort Study) study showed that the prevalence of diabetes was 5% in HIV-uninfected individuals, 7% in HIV-infected individuals who were not taking antiretroviral therapy, and 14% in HIV-infected individuals who were taking potent antiretroviral therapy. Dyslipidemia is common among HIV-infected patients. Representative data show considerably elevated triglyceride and considerably lower high-density lipoprotein (HDL) cholesterol levels in HIV-infected patients than in age-, sex-, and body mass index–matched controls. Low-density lipoprotein (LDL) levels may also increase, but increases are less consistent and LDL levels may often remain normal. Fat redistribution in HIV infection consists primarily of accumulation of abdominal (visceral) fat and loss of subcutaneous fat in the extremities and face. Fat redistribution has implications for survival in HIV infection. The FRAM (The Study of Fat Redistribution and Metabolic Change in HIV Infection) study, for example, showed an increased risk of death when visceral adipose tissue increased and fat in the extremities decreased, after adjustment for other risk factors.

However, traditional risk factors account for only a portion of the excess CVD risk in HIV disease. In a large epidemiologic cohort study reported in 2007 that included 3851 HIV-infected patients and more than 1 million HIV-uninfected patients who received longitudinal care from 1996 to 2004, the relative risk for myocardial infarction (MI) in HIV-infected patients was 1.75 (P < .0001). Of this 75% increase in risk, approximately 25% was attributable to traditional risk factors (ie, diabetes, dyslipidemia, and hypertension), although smoking status was not included in the analysis. HIV infection itself was found to confer MI risk comparable to that conferred by traditional risk factors. In more recent years, persistent inflammation and immune activation have been found to be major contributors to CVD risk among HIV-infected individuals.

Initial studies of CVD risk in the context of HIV disease suggested that the excess risk was mainly attributable to the effects of antiretroviral drugs. However, the results of the SMART (Strategies for the Management of Antiretroviral Therapy) trial, reported in 2006, showed that an intermittent treatment strategy based on CD4+ cell count—hypothesized to reduce CVD risk by reducing drug exposure—was associated with greater MI risk than a continuous treatment strategy. The findings of the trial were pivotal in focusing attention on the role of viral infection and resultant inflammation in CVD risk. Among more recent studies of the relationship between immune markers and CVD is one recently reported by Silverberg and colleagues that showed a substantially increased MI risk based on lower recent CD4+ cell count and lower nadir CD4+ cell count among HIV-infected patients.
Assessment of Nontraditional Risk Factors With Novel Techniques

Computed Tomography Angiography Studies of Plaques

In studies by Lo, Burdo, and colleagues, coronary computed tomography (CT) angiography was used to investigate the presence of plaques and plaque features in young HIV-infected men and matched controls with no dyslipidemia or hypertension, similar Framingham risk scores (FRSs), and similar smoking rates.8,9 The HIV-infected men did not have statistically significantly different Agatson calcium scores than controls or a greater number of calcified segments but did have a statistically significantly higher risk for plaques (59% vs 34%, respectively; P = .02), greater plaque volume (mean 173 μL vs 85 μL, P = .02), more segments with plaque (2.2 vs 1.2, respectively; P = .03), and more noncalcified segments (0.99 vs 0.46, respectively; P < .05), and a low and not statistically significantly greater prevalence of any stenosis greater than 70% (6.5% vs 0%, respectively; P = .06).

Other studies have shown that whereas traditional CVD risk factors are associated with elevated calcium scores and calcium-enriched plaques, noncalcified plaques are associated with monocyte or macrophage activation markers, such as soluble CD163 and sCD14.9 Evidence is thus emerging that immune activation may lead to the development of atypical plaques in HIV disease.

Figure 1 shows the type of coronary lesions commonly found in HIV-infected patients.10,11 These lesions are not the calcified lesions typically associated with coronary disease and generally do not cause critical stenosis. They are atypical, noncalcified, high-risk morphology plaques characterized by low attenuation and positive remodeling. These plaques are characterized by a fatty core and are eccentric, building up under the luminal surface toward the outer wall of the vessel. If the lumen of the affected coronary artery is not compromised during the buildup of eccentric plaque, sufficient blood flow is preserved that collateral circulation may not develop. Further, these atypical lesions feature thin fibroatheroma caps, making rupture more likely. When rupture does occur, a greater portion of the myocardium may be at risk because of the absence of collateral circulation, especially if the lesion is in a proximal segment. In a CT angiography study of 101 HIV-infected and 41 HIV-uninfected patients, Zanni and colleagues found that HIV-infected patients had a higher prevalence of these high-risk morphology plaques—at least 1 low attenuation plaque was present in 22.8% of HIV-infected patients compared with 7.3% of HIV-uninfected patients, and at least 1 positively remodeled plaque was present in 49.5% of HIV-infected patients compared with 31.7% of HIV-uninfected patients.12 Studies of HIV-uninfected patients have shown that event-free survival is statistically significantly lower (P < .01) in those with 2-feature plaques (low attenuation and positive remodeling) than in those with 1 or none of these features.13,14

Assessment of Vascular Inflammation in HIV

18Fluorine-2-deoxy-D-glucose positron emission tomography (18F-FDG-PET) provides a noninvasive method for arterial imaging and detection of arterial inflammation.15 18F-FDG is taken up into metabolic pathways and allows for imaging of metabolically active cells. In atherosclerotic plaques, 18F-FDG is sequestered beneath the fibrous cap in the lipid core area and within activated macrophages.15 Increased vascular 18F-FDG signaling has been shown to be associated with statistically significant reduction in event-free survival (P < .001).16

In a study by Subramanian and colleagues, cardiac 18F-FDG-PET was used to assess 27 HIV-infected patients with no known CVD; 27 age-, sex-, and FRS-matched, HIV-uninfected patients that did not have atherosclerosis; and 27 HIV-uninfected, sex-matched patients with known atherosclerotic disease.17 HIV-infected patients and HIV-uninfected, FRS-matched patients without atherosclerosis were balanced in demographic and clinical characteristics: mean ages were 53 years and 54 years, respectively; mean FRSs were 6.4 and 6.6, respectively, indicative of very low risk; mean LDL cholesterol levels were 115 mg/dL and 118 mg/dL, respectively; and median calcium scores on CT angiography were 24 and 0, respectively. HIV-infected patients had a mean duration of HIV infection of 15.5 years, all were on antiretroviral therapy (mean duration of 12.3 years), and 81% had undetectable HIV RNA levels; mean current CD4+ cell count was 641/μL and mean nadir CD4+ cell count was 99/μL.

This study provided some of the first direct evidence of increased arterial
inflammation among HIV-infected patients. Inflammation—measured as aortic target-to-background ratio (TBR) of \(^{18}\)F-FDG-PET uptake—among HIV-infected patients was statistically significantly greater than among HIV-uninfected controls who did not have atherosclerosis (P < 0.001) and equal to that among HIV-uninfected controls that did have atherosclerosis. Subgroup analysis showed that TBR was statistically significantly higher among HIV-infected patients than HIV-uninfected patients in analyses restricted to those with no measured calcium (P = 0.009), FRSS of less than 10 (P = 0.002), LDL cholesterol levels of less than 100 mg/dL (P = 0.01), those who did not use statins (P = 0.001) or were nonsmokers (P = 0.001), and among HIV-infected patients with undetectable HIV RNA levels (P < 0.001). Increased aortic TBR was associated with increased levels of the monocyte or macrophage activation marker sCD163 (P = 0.04) among HIV-infected patients.

These investigators subsequently showed that increased arterial inflammation, indicated by higher TBR on \(^{18}\)F-FDG-PET imaging, was associated with increased prevalence of high-risk morphology lesions.\(^{18}\) When patients with higher and lower arterial inflammation were compared, 40% and 10%, respectively, (P = 0.02) had at least 1 low attenuation plaque; 85% and 67%, respectively, (P = 0.17) had at least 1 positively remodeled plaque; 90% and 67%, respectively, (P = 0.06) had at least 1 plaque with 1 feature; and 55% and 10%, respectively, (P = 0.04) had at least 1 plaque with 2 features.

**A New Paradigm and New Treatment Strategies**

Taken together, these data suggest a new mechanistic paradigm for atherogenesis in HIV disease, and potential strategies for reducing inflammation and atherosclerosis (Figure 2). In this paradigm, viral replication and microtubular translocation result in ongoing T-cell and monocyte activation, with persistent inflammation leading to the development of atypical, high-risk plaques.

**Figure 2.** Recent data suggest a potential new paradigm for cardiovascular disease risk in HIV disease. Persistent low-grade undetectable viral replication and ongoing microbial translocation, along with hepatitis C virus or other viral coinfection, may lead to increased T-cell activation and ongoing monocyte activation, which may contribute to the development of high-risk plaque morphology and increased arterial inflammation.

Given the evolving understanding of atherogenesis in HIV infection, strategies to reduce CVD risk include minimizing traditional risk factors (ie, smoking cessation, blood pressure control, correction of insulin resistance and dyslipidemia, reduction of excess visceral adipose tissue, and use of less-toxic antiretroviral therapy). Viral burden and latency can be reduced through earlier initiation of antiretroviral therapy and use of intensification strategies. Potential strategies to counter inflammation include modulation of T-cell and monocyte activation, chemokine receptor antagonism, use of proinflammatory cytokine antagonists (eg, anti-interleukin-6 agents), and use of low-dose methotrexate. These strategies remain under investigation.

Statin therapy warrants particular attention, given its pleiotropic effects. Statins have the potential to markedly reduce cardiovascular events among HIV-infected patients. In addition to their traditional ability to lower LDL cholesterol level (generally comparable between HIV-infected and HIV-uninfected patients\(^{19}\)), statins reduce monocyte activation, chemotraction, and vascular inflammation in HIV-infected patients\(^{20}\), and reduce noncalcified plaque volume in HIV-uninfected patients\(^{21}\). Initial data from nonrandomized studies indicate that statin use is associated with reduced mortality among HIV-infected patients (hazard ratio [HR], 0.33; P = 0.009).\(^{22}\) The JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial of rosuvastatin in HIV-uninfected individuals showed that primary prevention treatment with statins reduced cardiovascular events in those with low LDL cholesterol levels and elevated inflammation, indicated by raised C-reactive protein levels (events per 100 person-years were 0.77 with rosuvastatin and 1.36 with placebo; HR, 0.56).\(^{23}\) In this trial, rosuvastatin treatment was associated with an increased risk of diabetes that, although not large, was statistically significant. There has been some study of pitavastatin, a potent statin that lowers LDL cholesterol level, in HIV-infected patients; it has not been associated with diabetes in small studies to date.\(^{24}\)

Statins are associated with a somewhat elevated risk for adverse events among HIV-infected patients (eg, myositis was reported in 1.9% of HIV-infected patients vs 0.5% of HIV-uninfected patients).\(^{19}\) However, the overall risk of adverse events appears to remain generally low. Despite the potential benefits of statin therapy, statin use is uncommon among the HIV-infected population. The AIDS Clinical Trials Group reported that only 19.6% of HIV-infected patients use statins. Large clinical trials are needed to better identify the potential benefits and risks of statin therapy for the HIV-infected population. Indeed, a large randomized study, REPREVE (A Randomised Study to Prevent Vascular Events in HIV), was recently funded by the National Institutes of Health to address this question.

**Summary**

CVD risk is higher in the setting of HIV infection. As of 2014, preventing CVD is an important but unmet goal for
HIV-infected patients. Traditional risk factors (e.g., ectopic fat, insulin resistance, dyslipidemia) and nontraditional risk factors (e.g., immune activation, inflammation) contribute to this increased risk, which manifests in the development of noncalcified, high-risk coronary plaques. Modulation of traditional and nontraditional risk factors is necessary to prevent CVD in HIV-infected patients. Antiinflammatory strategies, including use of statins, may prove effective in reducing CVD risk.

Presented by Steven K. Grinspoon, MD, in May 2014. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Grinspoon in October 2014.

Financial affiliations in the past 12 months: Dr Grinspoon has served as a consultant to AstraZeneca, Navidea, NovoNordisk, and Theratechnologies.

References


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The vast majority of HIV-infected patients experience some type of skin disorder; these may broadly be categorized as infectious, neoplastic, or inflammatory. Additionally, primary pruritus afflicts a considerable percentage of HIV-infected individuals, and an attempt should be made to identify potential underlying triggers. Chronic itch, whether related to an underlying cutaneous, systemic, or psychiatric illness, can have a profound effect on quality of life. Therapy for inflammatory skin disorders may involve initiation of antiretroviral therapy in those who have not yet started such treatment, oral antihistamines, topical corticosteroids, topical antipruritic agents, and skin moisturizers. Because topical corticosteroids are often a necessary component of the therapeutic armamentarium for skin diseases, practitioners are encouraged to become familiar with the appropriate indications, strengths, and formulations of available preparations. In some instances, psychiatric medications or phototherapy may be necessary for the treatment of HIV-associated skin disorders, particularly for patients experiencing refractory itch. Although psoriasis is not more frequent among HIV-infected patients than in the general population, it can be more severe and debilitating for those who are HIV infected. Our understanding of psoriasis in the setting of HIV infection has evolved and new therapies for psoriasis have recently become available. This article summarizes a presentation by Sareeta R. S. Parker, MD, at the IAS–USA continuing education program held in Atlanta, Georgia, in April 2014.

Keywords: HIV, skin, pruritus, psoriasis, antiretroviral therapy, topical steroids, itch, Merkel cell carcinoma, scabies

Approximately 90% of HIV-infected patients develop some type of skin disease. Indeed, skin disease may be the only overt sign of HIV infection and can be a major cause of morbidity despite stable HIV disease. HIV-infected patients have impaired systemic and local immunity and are thus at increased risk for skin infections, malignancies, and worsening of existing dermatoses.

Skin conditions frequently encountered in those with HIV infection are listed in Table 1 and include infections, infestations, neoplasms, and inflammatory conditions. Scabies in those with advanced or poorly controlled HIV disease is notable for possible absence of associated itch; it should be considered when a patient presents with genital skin lesions. Topical steroids are not an effective treatment for scabies. Appropriate scabies treatment may include the topical scabicide permethrin or oral ivermectin.

Among neoplasms, Merkel cell carcinoma (MCC) deserves particular attention because it has been a generally underrecognized entity. MCC, a neuroendocrine-derived neoplasm observed more commonly in immunosuppressed persons, has recently been shown to be associated with polyomavirus infection. It is nodular or nodulocystic in appearance and is more commonly encountered in fair-completed individuals. The biologic behavior of MCC parallels that of melanoma in that both malignancies are potentially lethal; once MCC grows to larger than 2 cm in diameter, the likelihood of survival is approximately 50%. With regard to other conditions encountered in the outpatient setting, drug eruptions occur up to 10 times more frequently among HIV-infected patients than in the general population, even after adjustment for increased drug exposure among HIV-infected patients.

### Table 1. Selected Skin Conditions in HIV Infection

<table>
<thead>
<tr>
<th>Infections</th>
<th>Infestations</th>
<th>Neoplasms</th>
<th>Inflammatory Conditions</th>
<th>Other</th>
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<td>Cutaneous fungal, bacterial</td>
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<td>Seborrheic dermatitis</td>
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<td>- Candida, tinea, staphylococcus</td>
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<td>Prurigo nodularis</td>
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<td>Syphilis</td>
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<td>Herpes simplex virus and varicella-zoster virus</td>
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<td>Human papillomavirus, epidermodysplasia verruciformis–like phenotype</td>
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<td>Molluscum contagiosum</td>
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<td>Scabies</td>
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<td>Drug eruptions</td>
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<td>Immune reconstitution inflammatory syndrome (IRIS)-related flare of skin disease or infection</td>
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Dr Parker is Adjunct Associate Professor of Dermatology at Emory University in Atlanta, Georgia.
Topical steroids are divided into classes based on potency. It is helpful to become familiar with several distinct formulations (eg, ointment, gel, cream, or lotion), as this may affect patient adherence and effectiveness. For example, prescribing an ointment to be applied to a dense hair-bearing area is likely to result in poor adherence and outcome. Adverse effects of topical steroids should be considered; these include glaucoma if used around eyes or eyelids, striae or skin atrophy, acneiform eruptions, and bruising or purpura.

From lower to higher potency, commonly used topical steroids include hydrocortisone 2.5% cream or ointment; alclometasone cream or ointment; triamcinolone 0.1% cream or ointment (available in a 1-lb jar or in smaller quantities); fluocinonide 0.05% cream or ointment; and clobetasol cream, ointment, or solution. Generic formulations of many of these medications are available at lower cost than brand-name formulations.

Because they are the least potent of the topical steroids, hydrocortisone and alclometasone preparations are generally safe for long-term use on the face. For patients with seborrheic dermatitis, for example, it is helpful to supply several refills, enabling the patient to resume application if dermatitis recurs.

Dermatologists frequently prescribe triamcinolone 0.1% for widespread inflammatory skin diseases because it is available in a 1-lb jar. However, smaller quantities are also available and may be more appropriate for patients with limited skin involvement. Caution should be used when prescribing triamcinolone, as the 0.5% formulation is far more potent, and its use should be limited owing to greater potential for adverse effects.

Higher potency topical steroids, such as fluocinonide and clobetasol, are generally not recommended for use on the face, genitals, or body folds. Patients should be advised to limit use to lesional skin only. These stronger agents are useful when lesions are thick, as with psoriatic lesions, or heavily lichenified, as there is less concern of potential atrophy.

Approximately 30 g of cream is required to cover the surface of an average-size body once; this number should be considered when selecting the quantity of topical steroid to prescribe.

**Itch**

Itching is defined as an unpleasant cutaneous sensation that induces the desire to scratch, and it serves as a physiologic self-protective mechanism. The mediators of itch are not entirely known. Histamine is one but not the sole mediator. In recent years, there have been advances in the understanding of the mechanisms of itch. For many years it was thought that itch sensation, similar to pain sensation, was transmitted only or primarily through unmyelinated C fibers. It is now known that several nerve fibers, including thinly myelinated Aβ (fast) and Aδ (slow) fibers, transmit itch. It was also thought that nerve receptors did not penetrate the epidermis, whereas it is now recognized that neurofibrils do reach into the epidermis.

Itching is a serious problem for many HIV-infected individuals. A recent study of 200 HIV-infected patients in the southeast United States showed an itching prevalence of approximately 45%, with more than half of these patients reporting that itching had a statistically significant negative impact on their quality of life.

The evaluation for an HIV-infected patient presenting with itch is fairly straightforward: examine for skin disease, evaluate the patient for systemic disease, and consider any underlying psychiatric conditions. With regard to the latter, itch perception may be amplified for those with psychiatric diseases, and the ability to control the impulse to scratch may be impaired, resulting in severe self-induced skin damage.

A diagnostic approach for chronic pruritus was proposed by Yosipovitch and Bernhard, and an adapted version is presented in Figure 1. The patient should be evaluated for the presence or absence of primary lesions. If primary lesions are present and infestation (ie, scabies) is excluded, the condition can
usually be treated with topical steroids. HIV-associated eosinophilic folliculitis and pruritic papular eruption have been added to the list of dermatologic causes of itch because they are commonly encountered among HIV-infected patients. With regard to nondermatologic causes, most components of the workup for systemic causes of itch are already part of routine evaluation of HIV-infected patients. Of note, both lymphoma and hepatitis C virus infection can be underlying causes of chronic itch.

Examples of primary lesions are shown in Figure 2. The patient shown in Figure 2 has urticarial red papules on his neck and excoriations on the entire back and the anterior aspect of his trunk. This condition is eosinophilic folliculitis, a hallmark of which is the absence of lesions below the nipple line on the chest and the absence of lower-body involvement. The patient shown in Figure 3 has central chest lesions and lesions on the distal arms, and thus does not have eosinophilic folliculitis but rather pruritic papular eruption associated with HIV. Characteristic of this condition, the complete systemic workup for itch revealed nothing aside from HIV infection. Some of the lesions on this patient are primary lesions, while others are lichenified papules; the hemorrhagic, crusted excoriations attest to the severity of the itch associated with this condition. The patient shown in Figure 4 does not have a primary lesion and no papules, pustules, or blisters are evident. Linear excoriations, old scars, and some angular ulcerations in reachable areas are visible. The only identifiable underlying source of this patient’s itch was HIV infection.

Treatment for itch includes oral agents such as the antihistamines diphenhydramine, hydroxyzine (10 mg to 50 mg up to 4 times daily), and doxepin (10 mg to 25 mg up to 4 times daily); the anticonvulsants gabapentin and pregabalin; and the serotonin-norepinephrine reuptake inhibitor mirtazapine (15 mg to 30 mg). Other therapeutic options include psychiatric medications (e.g., the selective serotonin reuptake inhibitors paroxetine and sertraline); behavioral modification; antiretroviral therapy; topical treatments such as corticosteroids or antipruritic agents (e.g., calamine or pramoxine-containing creams); treatment of dry skin with moisturizers and avoidance of harsh soaps; and phototherapy.

Antihistamine dosage can be self-titrated by patients. Doxepin is more potent than hydroxyzine or diphenhydramine, and some antihistamines have anxiolytic effects. For refractory itch, the anticonvulsants gabapentin and pregabalin can be added. Gabapentin and pregabalin produce excellent
melanoma or squamous cell carcinoma. It is, however, not always practical, requiring patients to visit a dermatologist’s office to use a phototherapy unit 3 times a week for up to several months.

**Psoriasis**

Psoriasis, unlike many of the aforementioned conditions, is not more common among HIV-infected patients than HIV-uninfected patients. It is often, however, more severe in the setting of advanced HIV infection.

Numerous studies in the dermatology literature, and now also in the general medical literature, strongly support that psoriasis in and of itself is an independent risk factor for myocardial infarction, and is associated with elevated risk for metabolic syndrome, stroke, and peripheral vascular disease. The risk of cardiovascular disease is especially high in younger patients with psoriasis. HIV-infected patients with psoriasis should be evaluated for cardiovascular disease risk factors.

Psoriasis is an immune-mediated chronic inflammatory disorder that manifests not only in the skin and joints but also as systemic inflammation. It occurs in genetically predisposed individuals and is estimated to affect approximately 3% of the US population. The disorder is mediated by T cells, and therapies that target T cells, such as cyclosporine, are effective in resolving psoriasis.

The classic presentations of psoriasis on the elbow, knee, trunk, hands, and feet are shown in Figure 5. The patient shown in Figure 5 (F and G) has psoriatic arthritis manifesting as inflamed, edematous fingers and near complete obliteration of the nails.

Why psoriasis worsens in the context of HIV disease is unclear. Psoriasis was once thought to be a T helper 1 (Th1) cell-mediated disease, whereas inflammation in advanced HIV disease is characterized by predominance of Th2 cell cytokines. The presence of or exacerbation of psoriasis in advanced HIV infection, when CD4+ helper cells are diminished, would seem paradoxical. In the past several years, however, it has become clear that CD8+ cells are prominently involved in psoriasis. CD8+ cells in psoriatic skin produce inflammatory cytokines such as interleukin 17 (IL-17) and IL-22, and a number of novel IL-17 inhibitors have been found to be highly active in

**Figure 4.** Pruritus with no primary lesions in the context of HIV-related itch; note sparing of the mid back in a region that is difficult for the patient to reach.

**Figure 5.** Classic, pink, psoriatic plaques on the knee (A), trunk (B), bilateral palms (C), and feet (D and E). Psoriatic nail dystrophy and psoriatic arthritis affecting several joints in the hands (F and G).
treating psoriasis. As our understanding of the pathophysiology of psoriasis improves, there is thus hope for safer, more targeted, and more effective psoriasis therapies, including for patients with HIV infection.

Presented by Dr Parker in April 2014. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Parker in September 2014.

Financial affiliations in the past 12 months: Dr Parker has no relevant financial affiliations to disclose.

References


Additional Suggested Reading


Perspective

Cirrhosis in Hepatitis C Virus–Infected Patients: A Review for Practitioners New to Hepatitis C Care

Treatment of hepatitis C virus (HCV)-infected patients with cirrhosis remains challenging. Biopsy to stage liver fibrosis remains the standard for identifying cirrhosis, although the noninvasive technique of transient elastography is promising in this regard. Cirrhosis is categorized as compensated or decompensated, with the latter characterized by ascites, hepatic hydrothorax, bleeding varices, hepatic encephalopathy, and hepatorenal syndrome. In the interferon alfa treatment era, patients with compensated cirrhosis have been candidates for interferon alfa–based treatment, whereas those with decompensated cirrhosis have been treated with caution and only at a tertiary care or transplant center. New interferon alfa–free regimens offer safer treatment alternatives to patients with cirrhosis. Response to interferon alfa–based therapy alone and in combination with the first-generation HCV protease inhibitors boceprevir or telaprevir for the treatment of HCV genotype 1 infection has been poorer in patients with cirrhosis than in those without. With regimens that include newer direct-acting antivirals, response rates are tremendously improved for patients with cirrhosis but still slightly lower than those for patients without cirrhosis. As new regimens enter use outside of clinical trials, optimizing efficacy for patients with cirrhosis will be an important goal. Patients with cirrhosis must be taught to practice liver wellness following HCV cure, to lower the risk of progression of their liver disease. Risk of hepatocellular carcinoma also persists in patients with cirrhosis even if cure of HCV infection is achieved. The risk of these complications is dramatically reduced with cure of HCV infection through antiviral treatment. This article summarizes a presentation by Andrew J. Muir, MD, MHS, at the IAS–USA continuing education program held in Atlanta, Georgia, in September 2013.

Keywords: cirrhosis, compensated, DAAs, decompensated, direct-acting antivirals, fibrosis, HIV, HCV, hepatitis C, interferon alfa, protease inhibitors

According to a generally accepted model of the natural history of hepatitis C virus (HCV) infection, chronic HCV infection develops in approximately 75% to 85% of persons with acute HCV infection and cirrhosis develops in approximately 20% of those with chronic HCV infection, with progression to cirrhosis occurring over a period of 20 years to 50 years. More rapid progression is associated with older age at infection, alcohol use, coinfec­tion with HIV, and periods of immunosuppression following transplantation.

Disease Staging

Disease staging has relied on the use of liver biopsy to evaluate level of fibrosis, with Metavir scoring as the most common method of quantification. In this scoring system, F1 indicates portal fibrosis, F2 portal fibrosis with few septa, F3 septal fibrosis (or bridging), and F4 cirrhosis. In practice, limitations in assessment warrant grouping of F3 and F4 as advanced fibrosis, and overall clinical assessment must be taken into account in staging. For example, a patient in whom staging in the past year indicated F3 fibrosis but who currently has a low platelet count (eg, 70,000/μL) should be considered to have cirrhosis. Although liver biopsy is the current gold standard for staging, it is invasive, associated with morbidity in 3 of 1000 cases and mortality in 1 of 10,000 cases, subject to observer variability and sampling error, and costly.

Alternatives to biopsy include serologic panels and radiographic assessments. However, these noninvasive measurements also have limitations, including the inability to reliably differentiate fibrosis stages (ie, they are best used to distinguish between early and advanced fibrosis only) and risk of indeterminate outcomes. Serologic markers such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) can be affected by inflammation and thus are not always reliable.

One useful and inexpensive noninvasive technique for the assessment of liver fibrosis in HCV infection is the AST-to-platelet ratio index (APRI), calculated as (AST/upper limit of normal of AST) × 100 divided by (platelet count/1000). Thus, a patient with an AST level of 82 U/L, with an upper limit of normal of 45 U/L, and a platelet count of 70,000/μL has an APRI of 2.6, strongly suggestive of cirrhosis. A recent meta-analysis comprising 40 studies found that an APRI threshold of 0.7 was predictive of significant fibrosis with 77% sensitivity and 72% specificity and that a threshold of 1.0 was predictive of cirrhosis with 76% sensitivity and 72% specificity.4 Some recent clinical trials have used an APRI threshold of 2.0 for cirrhosis. Sensitivity and specificity are somewhat poorer in HCV/HIV–coinfected patients because of the lower platelet counts associated with coinfection.

One commercially distributed index incorporates 6 serum biochemical markers—alpha 2 macroglobulin, haptoglobin, gamma globulin, apolipoprotein A1, gamma glutamyltransferase, and total bilirubin—to generate a measurement.

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of liver fibrosis and has been found to have 75% sensitivity and 85% specificity for Metavir fibrosis stages F2 to F4. In practice, high and low scores are generally accurate, but midrange scores are not clinically useful. Other serum marker assays for fibrosis include the European liver fibrosis panel, FIB-4, the Forns index, and the SHASTA index, along with a number of commercially distributed panels.

Among radiographic assessments, conventional ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) studies are not used to stage fibrosis; they are useful to detect complications of advanced disease, such as ascites, obvious varices, or hepatocellular carcinoma (HCC). Transient elastography, a technique using an ultrasonic transducer in which generated shear wave velocity correlates with tissue stiffness, has been available in Europe for years and is now available in the United States. A meta-analysis comprising 50 studies assessed the effectiveness of transient elastography as a diagnostic tool for liver fibrosis and found the mean area under the receiver operating characteristic (AUROC) curve for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis to be 0.84, 0.89, and 0.94, respectively. Thus far, in clinical practice in the United States, transient elastography appears to be reliable in detecting cirrhosis.

Acoustic radiation force imaging (ARFI) is a similar technology that is becoming more widely available, although transient elastography has been more extensively evaluated than ARFI at this point. Magnetic resonance elastography is also available in the United States and has been found to have 94% sensitivity and 95% specificity for Metavir fibrosis stages F2 to F4 and 92% sensitivity and 96% specificity for stages F3 to F4.

Cirrhosis Characteristics

Cirrhosis is categorized as compensated cirrhosis—that is, cirrhosis diagnosed through biopsy but without complications—or as decompensated cirrhosis, which is characterized by ascites, hepatic hydrothorax, bleeding varices, hepatic encephalopathy, and hepatorenal syndrome. Patients with compensated cirrhosis are candidates for interferon alfa-based treatment. Those with decompensated cirrhosis should receive treatment only at a tertiary care or transplant center.

Insight into the natural history of cirrhosis is provided by an Italian study in which 214 patients with Child-Pugh class A cirrhosis who received no antiviral therapy were followed for 114 months. HCC occurred in 32%, ascites in 23%, upper gastrointestinal bleeding in 6%, hepatic encephalopathy in 1%, and death in 35%, with annual incidences of 3.9%, 2.9%, 0.7%, 0.1%, and 4.0%, respectively. During the study period, 154 patients (72%) remained in Child-Pugh class A. Predictors of poor outcome were alcohol use, hepatitis B virus (HBV) coinfection, and iron overload.

There are a number of scoring systems for categorizing severity of cirrhosis in individual patients. The Child-Pugh score incorporates bilirubin, albumin, prothrombin time, and presence or absence and severity of ascites and hepatic encephalopathy. Although no longer used for liver transplant allocation, the Child-Pugh system does provide guidance on surgical mortality risk and overall prognosis, with class B (1- and 2-year survival of 81% and 57%) and class C (1- and 2-year survival of 45% and 35%) being associated with much poorer survival than class A (1- and 2-year survival of 100% and 85%).

The Model for End-Stage Liver Disease (MELD) scoring system has largely replaced the Child-Pugh system in clinical use and incorporates total bilirubin, serum creatinine, and prothrombin time. The American Association for the Study of Liver Diseases (AASLD) criteria for referral for liver transplantation specify evidence of hepatic dysfunction with a Child-Pugh score greater than 7, a MELD score greater than 10 or the onset of ascites, variceal bleeding, or encephalopathy as a first major complication. Patients with HCC with 1 lesion less than 5 cm or 3 lesions each less than 3 cm in diameter are also candidates for liver transplantation.

Patients with cirrhosis who are not receiving antiviral treatment should generally be seen by their practitioner every 6 months if they have compensated disease and every 3 months if they have decompensated disease. Assessments should include MELD laboratory evaluations, HCC surveillance, and regular endoscopies to screen for gastroesophageal varices. The risk of developing HCC appears to be 3% to 5% per year in patients with cirrhosis, and the risk persists even if HCV infection is subsequently cured, with cases seen in cirrhosis patients up to 8 years after sustained virologic response (SVR) has been achieved.

AASLD recommendations for HCC surveillance include ultrasound every 6 months. Ultrasound in obese individuals remains challenging. Data on CT and MRI surveillance for HCC are limited but should be considered for obese patients or any patient with an inadequate ultrasound. Alpha-fetoprotein measurement is not sufficiently sensitive or specific to recommend it as a screening tool for HCC in patients with cirrhosis, but it remains part of the diagnostic approach for patients with a liver mass. AASLD guidelines for screening for gastroesophageal varices include an upper endoscopy at diagnosis of cirrhosis and a repeat endoscopy every 3 years in patients with compensated cirrhosis and no varices and annually in those with decompensated disease and no varices.

Variceal bleeding carries a mortality risk of 30%. In those with varices, beta blockers and banding ligation are potential treatment options.

Selection of Patients for Treatment

Until 2013, standard treatment for all patients with HCV infection involved a backbone of peginterferon alfa. Because of the risks associated with peginterferon alfa use and the lower response rates of patients with cirrhosis, few patients with decompensated cirrhosis received treatment with this drug.

The first-generation HCV protease inhibitors (PIs) boceprevir and telaprevir
offered great promise for patients with cirrhosis and did lead to improved response rates, but these drugs also increased the risks associated with treatment. Although data from phase III trials of these drugs suggest that they are well tolerated in patients with cirrhosis, outcomes have proved different in clinical practice.

In the French cohort study CUPIC (Compassionate Use of Protease Inhibitors in Cirrhotics), patients with HCV genotype 1 infection and cirrhosis were given early access to triple therapy including boceprevir or telaprevir. Outcomes included serious adverse events in more than half of patients, severe anemia, numerous deaths, grade 5 or 4 infections, and a 5% risk of hepatic decompensation.

Patients with cirrhosis and HCV genotype 2 or 3 infection may be treated with a currently available, effective, interferon alfa–free regimen of sofosbuvir and ribavirin. However, most HCV-infected Americans have genotype 1, and interferon alfa–free regimens for the treatment of HCV genotype 1 infection are expected to be available by the end of 2014. Although treatment is quickly moving to an interferon alfa–free approach, selected patients may still need to consider interferon alfa–based regimens.

If treatment with an interferon alfa–based regimen is being considered in patients with cirrhosis, there should be a discussion about the risks and benefits, documentation of the discussion, and consideration of transplant referral or treatment at a tertiary care center for patients with a MELD score greater than 10, portal hypertension, or thrombocytopenia. Management strategies should be discussed with patients, including the use of dose reduction versus erythropoiesis-stimulating agents in case of anemia. Leukopenia usually poses less of a problem in this setting. The potential use of thrombopoietin agonists should also be addressed. Although effective in increasing platelet count to permit initiation and tolerance of therapy, thrombopoietin agonists pose the risk of portal vein thrombosis that can further compromise liver function and affect candidacy for transplantation.

**Treatment of Patients with Cirrhosis**

**HCV Genotype 1**

At the time of this update, patients with HCV genotype 1 cirrhosis have the option of treatment with peginterferon alfa, ribavirin, and the polymerase inhibitor sofosbuvir for 12 weeks; sofosbuvir and ribavirin for 24 weeks; or simprevir plus sofosbuvir, with or without ribavirin, for 12 weeks. In the single-arm, open-label NEUTRINO study of sofosbuvir plus peginterferon alfa and ribavirin in treatment-naïve patients with HCV genotype 1, 4, 5, or 6 infection, SVR was achieved in 92% (252 of 273) of patients without cirrhosis and 80% (43 of 54) of patients with cirrhosis. With the caveat that this was a clinical trial, and thus did not include the sicker patients who are and will continue to be encountered in the clinic, treatment was well tolerated. Treatment was discontinued in 2% of patients and serious adverse events were reported in 1%. The combination of sofosbuvir and ribavirin was studied in the SPARE and PHOTON-1 trials and produced SVR rates of 68% and 76%, respectively. This regimen has been evaluated in patients with advanced cirrhosis and liver cancer, prior to transplantation, and was found to prevent HCV infection recurrence after transplant.

Although not an approved indication by the US Food and Drug Administration (FDA), the use of a combination of the second-generation PI simprevir with sofosbuvir has been endorsed by the AASLD/Infectious Diseases Society of America (IDSA)/IAS–USA HCV treatment Guidance and has been well received by patients and clinicians. This regimen was studied for 12 weeks to 24 weeks, with or without ribavirin, in the COSMOS (A Study of TMC435 in Combination with PSI-7977 [GS7977] in Chronic Hepatitis C Genotype 1 -Infected Prior Null Responders to Peginterferon/Ribavirin Therapy or HCV Treatment-Naïve Patients) trial. The 87 patients in the second cohort included those who were treatment naïve and those with a null response, and 47% had cirrhosis. The regimen was very well tolerated and led to SVR in 94% of patients overall. No clear differences were seen based on treatment duration or ribavirin use. Owing to the increased exposure, simprevir has not been extensively studied and must be used with caution in patients with Child-Pugh class B or C cirrhosis.

Two other interferon alfa–free regimens are expected to be available in late 2014 for patients with HCV genotype 1 infection. One regimen is the investigational combination of the ritonavir-boosted PI ABT-450, the nonstructural protein 5A (NS5A) inhibitor ombitasvir (formerly ABT-267), the nonnucleoside polymerase inhibitor dasabuvir (formerly ABT-333), and ribavirin. A recently reported phase III trial enrolled treatment-naïve and -experienced patients, and all 380 patients had Child-Pugh class A cirrhosis. The SVR rates were 91.8% in the 12-week arm and 95.9% in the 24-week arm. Anemia, defined as a hemoglobin level less than 10 g/dL, occurred in 7.2% of the 12-week arm and 11.0% of the 24-week arm. Overall, treatment was very well tolerated in these patients with compensated cirrhosis.

Another well-tolerated treatment, expected to be available in the fall of 2014, is the combination of sofosbuvir and the investigational NS5A inhibitor ledipasvir. The phase III ION-1 study of treatment-naïve patients and the ION-2 study of treatment-experienced patients included patients with cirrhosis (15%-20% of patients in each treatment arm) and examined 12 weeks versus 24 weeks of treatment and the role of ribavirin. In the ION-1 study, all study arms achieved SVR rates greater than 95%, with no obvious impact from the presence of cirrhosis. In the ION-2 study, the SVR rates were 94% and 96% in the 12-week arms, respectively, and 99% in each of the 24-week arms. In the 12-week arms, the presence of cirrhosis did appear to impact outcome. The SVR rates in the 12-week arms were 86% with sofosbuvir plus ledipasvir and 82% with sofosbuvir, ledipasvir, and ribavirin, compared with 100% in the 24-week arms. Further recommendations on treatment duration...
with these regimens are expected at the time of regulatory approval. In any event, these regimens offer patients with compensated cirrhosis excellent efficacy outcomes with well-tolerated regimens. These regimens will require further study to determine if they are appropriate for patients with decompensated cirrhosis.

**HCV Genotypes 2 and 3**

The interferon alfa–free regimen of sofosbuvir and ribavirin is FDA approved and available for patients with HCV genotype 2 or 3 infection. For patients with HCV genotype 2, sofosbuvir and ribavirin for 12 weeks is a highly effective regimen. In the FISSION trial of treatment-naive patients, the overall SVR rate for those with HCV genotype 2 infection was 92% (85 of 92) for patients without cirrhosis and 94% (16 of 17) for patients with cirrhosis. In the FUSION trial of treatment-experienced patients, the SVR rate was 90% (26 of 29) for patients without cirrhosis and 60% (6 of 10) in patients with cirrhosis. The FUSION study examined 16 weeks of treatment and reported an SVR rate of 78% (7 of 9) in patients with HCV genotype 2 infection and cirrhosis. Although a small number, the lower response rate at 12 weeks led the AASLD/IDSA/IAS–USA HCV Guidance to recommend consideration of a 16-week treatment duration for treatment-experienced, HCV genotype 2–infected patients with cirrhosis. For patients with HCV genotype 3 infection, the FISSION and FUSION trials demonstrated that outcomes with 12 weeks of sofosbuvir and ribavirin were inadequate. Outcomes were especially poor for patients with HCV genotype 3 who had cirrhosis, with SVR rates of 34% for treatment-naive patients and 19% for treatment-experienced patients.

Longer treatment duration was explored in the VALENCE trial of treatment-naive and -experienced patients. The study was amended to extend treatment from 12 weeks to 24 weeks for patients with HCV genotype 3 infection. For treatment-naive HCV genotype 3–infected patients, SVR rates were 95% (86 of 92) for those without cirrhosis and 92% (12 of 13) for those with cirrhosis. For treatment-experienced HCV genotype 3–infected patients, SVR rates were 87% (87 of 100) for those without cirrhosis and 62% (28 of 45) for those with cirrhosis.

Two recent studies have examined the role of peginterferon alfa in combination with sofosbuvir and ribavirin for 12 weeks in the LONESTAR-2 trial, 85% (10 of 12) of treatment-experienced HCV genotype 3–infected patients achieved SVR with this regimen. In another study, of HCV genotype 2– and 3–infected patients whose previous treatment with sofosbuvir had failed, subjects were randomized to receive peginterferon alfa in combination with sofosbuvir and ribavirin for 12 weeks or only sofosbuvir and ribavirin for 24 weeks. Among HCV genotype 3–infected patients with cirrhosis, 88% (7 of 8) achieved SVR with a peginterferon alfa–containing regimen compared with 47% (7 of 15) in the group that received sofosbuvir plus ribavirin alone. This collection of results, especially among treatment-experienced patients with cirrhosis, highlights the need for further developments in treatment of HCV genotype 3 infection. Currently, 24 weeks of ribavirin is a very reasonable and safe treatment option for HCV genotype 3–infected patients with cirrhosis, and clinicians may consider the role of peginterferon alfa after examining its risks and benefits. Regularly updated recommendations for testing, managing, and treating HCV infection can be found at [http://www.hcvguidelines.org](http://www.hcvguidelines.org).

**Conclusion**

Patients at risk for cirrhosis must be monitored closely, including for complications of portal hypertension, indicators of HCC, and support of overall liver health, alcohol abstinence, maintenance of healthy weight, and getting appropriate vaccinations. Well-tolerated and effective interferon alfa–free regimens are available now for patients with HCV genotype 2 or 3 infection and are expected to be available, by the end of 2014, for those with HCV genotype 1 infection. Selected patients may consider the addition of peginterferon alfa to these regimens after potential risks have been evaluated. Patients with cirrhosis should be urged to seek evaluation for antiviral treatment, to prevent progression of their liver disease.


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**References**


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Michelle Zukusoka, MD, MHS, Wendy S. Post, MD, MS, and Todd T. Brown, MD, PhD
CME Credit Available: **1.50 AMA PRA Category 1 Credits™** Level: **Advanced**

Given the prevalence of traditional risk factors, the aging of HIV-infected individuals, and the potential cardiovascular consequences of HIV disease and antiretroviral therapy, more attention should be focused on efforts to decrease the morbidity and mortality associated with atherosclerotic cardiovascular disease (ASCVD) and HIV infection. The key to success in CVD prevention is education of the clinician and the patient.

**Geriatrics and HIV**
Harjot K. Singh, MD, ScM, and Eugenia Siegler, MD
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The percentage of HIV-infected patients older than 50 years is expected to increase to more than 50% by 2020, based on modeling. Treatment with single-tablet regimens can lead to durable viral suppression. However, viral suppression comes at the price of lifelong treatment and is further complicated by the expected challenges associated with aging itself.

**Hepatitis C Viral Targets**
Stuart C. Ray, MD, Justin R. Bailey, MD, PhD
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A 2008 study by Limketkai and colleagues showed that in patients with HIV/HCV coinfection, hepatic fibrosis stage was independently associated with risk of progression to end-stage liver disease, hepatocellular carcinoma, and death, and that sustained virologic response after treatment of HCV infection was associated with survival. These findings highlight the importance of staging of liver disease and, whenever possible, treating HCV in HIV/HCV-coinfected individuals.

**Initiating Antiretroviral Therapy in Resource-Limited Settings**
Habib Ramadhani Omary, MD, MPH, MHS, and John A. Bartlett, MD
CME Credit Available: **1.50 AMA PRA Category 1 Credits™** Level: **Advanced**

Antiretroviral therapy has been tremendously successful in reducing morbidity and mortality among HIV-infected persons, and an estimated 10,000,000 people globally are now receiving it. Stigma and the need for strict medication adherence are commonly encountered throughout the world. In resource-limited contexts, there is an additional challenge of maintaining a continuous drug supply and having the ability to properly monitor treatment. Early treatment initiation is essential to preserve immunity, prevent the emergence of AIDS-defining illnesses, and decrease HIV transmission.

**Novel HIV-1 Resistance and Tropism Testing**
Jonathan Li, MD
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The remarkable diversity of HIV stems from a high replication rate and the error-prone reverse transcriptase enzyme used to translate HIV RNA into DNA. Up to 5 mutations may arise with each new HIV virus produced; more than a billion new virions may be produced daily in a chronically infected patient. This diversity and rapid evolution allow HIV drug resistance to emerge in patients who are on antiretroviral therapy that is not adequately suppressive or who are not fully adherent to their antiretroviral regimen. When available, HIV drug–resistance testing should be used to guide the selection of an optimal antiretroviral regimen.

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