

# Special Issues in HIV Care

BREAKFAST SEMINAR

**9:00 AM - 12:00 NOON: Seminar**  
**Continental Breakfast at 8:30 AM**  
**Location: Catalina Room, Wyndham**  
**Palm Springs, California**  
**Chairman: Orlando H. Pile, MD**

## Program Agenda

### **Hepatitis C and HIV Coinfection:** *Treatment Challenges and Emerging Therapies*

**LAVEEZA BHATTI, MD, PhD**

Clinical Instructor, Department of Medicine  
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### **Women and HIV:**

#### *Approaches to Improve Clinical Outcomes*

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Assistant Professor of Clinical Obstetrics and Gynecology  
Director of Perinatal Services, Maternal, Child and  
Adolescent HIV Program  
Faculty, Pacific AIDS Education and Training Center (PAETC)  
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### **Opportunities and Challenges of HIV Care in Correctional Settings**

**ORLANDO H. PILE, MD**

Chief of Communicable Diseases  
Los Angeles County Sheriff's Department  
Twin Tower Correctional Facility  
Los Angeles, California

### **Crystal Methamphetamine:**

#### *An Epidemic with Serious Impact on HIV*

**WILLIAM D. KING, MD, JD**

Private Practice  
Los Angeles, California

### **New Antiretroviral Agents:**

#### *Current Clinical Data*

**W. DAVID HARDY, MD**

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## Program Description

Whether due to economic issues, access to care, socio-cultural values and beliefs, or communication barriers, eliminating disparities in HIV/AIDS care among minority populations and certain groups remains an important goal for health-care providers, policy makers, and treatment advocates.

While individuals with HIV share many of the key issues and challenges of living with HIV/AIDS, effective HIV prevention and care obligates the recognition and thorough understanding of specific issues that are unique to a group.

To that end, this seminar will explore the specific health-care needs of several groups and will outline disease-, epidemiology-, and population-specific treatment strategies to optimize patient outcomes as well as review the role of new therapeutic agents.

## Objectives

At the completion of this seminar, participants should be able to:

- Anticipate potential barriers and challenges to the care of HIV-infected women, inmates, and those coinfecting with the hepatitis C virus and outline interventions to prevent or limit the impact of such barriers to effective HIV care
- Evaluate various treatment regimens for both initial and maintenance HIV therapy based on population-specific issues related to both drug choice and drug-specific adverse effects
- Describe strategies for managing difficult patients or complications within the framework of diverse populations
- Discuss the optimal management of patients coinfecting with hepatitis C
- Review the clinical data on new classes of antiretroviral agents and discern their role in the treatment of HIV



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# Special Issues in HIV Care:

## New Agents, Hepatitis C, Women, Methamphetamine, Inmates

### Abstract

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Highly active antiretroviral therapy, or HAART, which combines different classes of anti-HIV medications since the mid 1990s, has made major advances in the treatment of human immunodeficiency virus (HIV) infection. Yet there is a continued need for new therapeutic agents because of toxicity and tolerability issues, as well as viral resistance, associated with current agents. While individuals with HIV infection share many of the key issues and challenges of living with HIV/AIDS, there are unique issues that affect special populations of patients, such as pregnant women, incarcerated individuals, and those with hepatitis C coinfection. In these special populations, many barriers to care exist, including economic status, sociocultural values and beliefs, and communication challenges. Despite this, the main goal of therapy remains the same: to maintain and improve the health of the individual patients and to educate to decrease the spread of HIV. The main objectives of this article are to discuss the new classes of antiretroviral agents and treatment regimens and review the optimal management of HIV-infected women, inmates, injection drug users, and those coinfecting with hepatitis C.

### Introduction

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According to the latest report of the Joint United Nations Programme on HIV/AIDS (UNAIDS), the global prevalence of human immunodeficiency virus (HIV) has leveled off, and the incidence of new infections has fallen.<sup>1</sup> Yet the disease burden remains high as the numbers of people living with HIV/AIDS increases, due to longer survival times, over a continuously growing general population.

In 2007, approximately 33.2 million people around the world were estimated to be living with HIV, a vast majority from sub-Saharan Africa and increasingly from Asia.<sup>1</sup> While about 2.1 million people died of AIDS, approximately 2.5 million became newly infected.<sup>1</sup> Globally, 20% of individuals with advanced HIV infection (country range: 1%–100%) and only 9% of HIV-positive pregnant women receive antiretroviral therapy.

Improved surveillance methods, along with educational efforts and better understanding of the disease process and the availability of antiretroviral therapies, have dramatically changed the course of the disease and contributed to the leveling of the worldwide prevalence and decrease in number of deaths. However, the toxicity and tolerability issues associated with many drugs, alone and in combination, as well as viral resistance to current therapeutic agents, present a treatment challenge for many individuals living with HIV. In addition, in certain populations—such as women, inmates, and those with coinfections—effective treatment of HIV is further complicated by concomitant conditions or other issues. Finally, many barriers to effective care still exist, including socioeconomic status, sociocultural values and beliefs, and communication challenges. Individuals with HIV infection share many of the key issues and challenges of living with HIV/AIDS; therefore, effective HIV care and prevention necessitate the recognition and thorough understanding of the unique issues in special populations. The information presented here reviews the new classes of therapeutic agents available for the management of HIV and explores the specific health care needs of special populations.

## New Antiretroviral Agents: Current Clinical Data

W. David Hardy, MD

Treatment for HIV infection has progressed dramatically over the past decade. Currently, there are 24 unique antiretroviral agents approved by the US Food and Drug Administration (FDA) for the treatment of HIV infection.<sup>2</sup> A minimum of 3 or 4 of these are used in combination to construct a highly active antiretroviral therapy (HAART) regimen. In addition, there are 5 FDA-approved coformulated preparations that contain 2 or 3 antiretroviral agents in single-pill form.

Antiretroviral agents are grouped into 6 different drug classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 antagonists, and integrase inhibitors.<sup>2,3</sup> These agents in these 6 drug classes inhibit different steps in the HIV replication cycle to halt infection of uninfected T-cells and disrupt the formation of new infectious HIV particles. Until recently, there were only 3 classes of antiretroviral drugs—the NRTIs, NNRTIs, and PIs—but over the past 5 years at least one new drug in 3 new classes has been approved: enfuvirtide (a fusion protein, approved in March 2003), maraviroc (a CCR5 antagonist, approved in August 2007), and raltegravir (an integrase inhibitor, approved in October 2007).

The early days of HIV treatment were characterized by the use of monotherapy with a single agent belonging to one of the available drug classes.<sup>3</sup> Subsequent research demonstrated that more potent and sustained efficacy was achieved with administration of 3 or more agents from different classes. This “cocktail” approach to HIV—HAART—has become the standard treatment approach for HIV-infected individuals. Despite dramatic improvements since the advent of HAART, a number of challenges remain, primarily related to viral resistance to these drugs, toxicity and intolerance associated with them, and patient adherence. There are also questions about when to initiate treatment.

### Current trends in HIV infection, testing, and treatment

In the United States, the Centers for Disease Control and Prevention (CDC) revised its guidelines for HIV testing in

2006, recommending that all persons 13 to 64 years of age should be tested for HIV at least once and then regularly based on potential exposure risks such as having unprotected vaginal or anal sex or shared drug-use paraphernalia. It has been estimated that 250 000 to 300 000 individuals in the United States are not aware that they are HIV positive.<sup>4</sup> Universal HIV testing would help to identify more HIV-positive persons and enable them to receive counseling and treatment.

Testing for HIV in the United States appears to be becoming more acceptable, less marginalized, less exceptionalized, and more a part of routine medical care in today’s world. In May 2006, the San Francisco Department of Public Health eliminated the need for written informed consent prior to testing, and the number of individuals opting for testing increased from 13.5 to 17.9 HIV tests per 1000 patient-visits after the change in policy.<sup>5</sup> In addition, the number of positive tests per month increased significantly from 20.6 to 30.6 ( $P = .006$ ). A similar trend was seen in Cook County, Chicago, when HIV screening with rapid tests was offered to patients in emergency departments regardless of risks or symptoms.<sup>6</sup> Of eligible patients, 58% accepted the offer and were tested.<sup>6</sup> Of the screened patients, 1.2% were HIV positive, 77% of whom entered HIV care. This suggests that a substantial number of persons with HIV would have been missed and would have failed to receive proper care if testing had been available or offered to individuals based only on identified risk factors. This fact further supports the CDC recommendations for regular universal testing of all persons in the US.

Recent clinical trial results suggest that the care of patients infected with HIV may be improved by initiation of treatment earlier than is currently recommended. The most recent version of the US Department of Health and Human Services (DHHS) guidelines, updated on December 1, 2007, and again on January 29, 2008, recommend that antiretroviral therapy be initiated in all asymptomatic HIV+ individuals with or without a history of an AIDS-defining disease when their CD4+ T-cell counts are  $<350$  cells/mm<sup>3</sup>.<sup>7</sup> In addition, these guidelines recommend that antiretroviral therapy (ART) be initiated in all HIV+ persons who have HIV-related kidney disease,

females who are pregnant, and those who are coinfecting with hepatitis B, which requires treatment. These new recommendations are based on results from recent studies that suggest that therapeutic intervention early in the course of the disease is better than waiting for a greater degree of immunodeficiency. For example, the SMART (Strategies for Management of Antiretroviral Therapy) study assessed the impact of immediate versus deferred ART in patients who were treatment naïve or not on ART at randomization. The study showed that the risk of the composite endpoint of opportunistic infection, death, or a serious non-AIDS event was significantly higher in the deferred ART group (hazard ratio = 5.08; 95% confidence interval [CI]: 1.91-13.5;  $P = .001$ ).<sup>8</sup> Similarly, in the CASCADE (Concerted Action on SeroConversion to AIDS and Death in Europe) study, there was less death and fewer opportunistic infections when individuals with higher CD4+ T-cell counts were started on therapy sooner rather than later.<sup>9</sup> In the current environment, the pendulum appears to be swinging back to the idea of encouraging therapy at an earlier point after infection. The fact that current therapies are more efficacious, easier to take, and less toxic is also supportive of earlier therapy.

### Recent studies with NRTIs, NNRTIs, or PIs

**Studies in treatment-naïve patients**—In July 2006, the FDA approved the first once-daily 3-drug combination tablet for treatment of HIV-1 infection, called Atripla<sup>®</sup> (efavirenz, emtricitabine, and tenofovir). A 3-year study compared triple therapy with efavirenz 300 mg/day, emtricitabine 200 mg/day, and tenofovir 600 mg/day (the components of Atripla) with triple therapy consisting of zidovudine/lamivudine 300/150 mg twice daily plus efavirenz 600 mg/day in treatment-naïve HIV patients with viral load <10 000 copies/mL.<sup>10</sup>

The efficacy results from this study showed a significantly higher percentage of patients in the efavirenz/emtricitabine/tenofovir group versus the zidovudine/lamivudine/efavirenz group with HIV RNA levels <400 copies/mL at week 144 (71% vs 58%,  $P = .004$ ).<sup>10</sup> Also noted with efavirenz/emtricitabine/tenofovir were nonsignificant trends for greater increase in CD4+ T-cell counts (312 vs 271 cells/mm<sup>3</sup>,  $P = .09$ ) and a higher proportion of patients with HIV RNA

levels <50 copies/mL (64% vs 56%,  $P = .08$ ). In addition, the development of the M184V mutation was less with efavirenz/emtricitabine/tenofovir. There were no significant differences between the two treatment regimens in terms of renal toxicity. Triple therapy with the once-daily regimen of efavirenz/emtricitabine/tenofovir was associated with significantly less lipoatrophy, or fat wasting, at weeks 48 ( $P = .035$ ), 96 ( $P < .001$ ), and 144 ( $P < .001$ ) and significantly lower plasma levels of total cholesterol ( $P = .005$ ) and triglycerides ( $P = .047$ ) at week 144.<sup>10</sup> The study is planned for another 2 years of follow-up.

A growing collection of recent studies is clearly demonstrating that the currently available protease inhibitors provide similar effects when boosted with low-dose ritonavir. The recent KLEAN (Kaletra versus Lexiva with Eпивir and Abacavir in ART-Naïve patients) study compared fosamprenavir/ritonavir with coformulation of lopinavir/ritonavir (Kaletra<sup>®</sup>)—both in combination with a coformulation of NRTIs (abacavir/lamivudine)—as initial HIV-1 treatment.<sup>11</sup> KLEAN was an open-label, 48-week, noninferiority study that comprised 878 antiretroviral-naïve patients infected with HIV-1. The 48-week data showed that fosamprenavir/ritonavir was noninferior to lopinavir/ritonavir for proportion of patients with HIV RNA levels <400 copies/mL (73% vs 71%), a primary study endpoint, as well as for proportion of patients with HIV RNA levels <50 copies/mL (66% vs 65%). Similar proportions of patients in the two treatment groups discontinued treatment due to adverse events (12% with fosamprenavir/ritonavir vs 10% with lopinavir/ritonavir). The results from KLEAN suggest that fosamprenavir/ritonavir is as effective as lopinavir/ritonavir when used in combination with abacavir/lamivudine as first-line therapy in patients with HIV-1 infection.

The GEMINI study is a 48-week, open-label study comparing saquinavir plus ritonavir with lopinavir/ritonavir in treatment-naïve HIV-infected patients. All patients also received treatment with the NRTI combination of emtricitabine/tenofovir. Preliminary results at the 24-week (as well as the 48-week) analysis revealed that the two protease inhibitor combinations were essentially identical in terms of proportion of patients with HIV RNA <50 copies/mL (69.9% vs 69.0%) and <400 copies/mL (81.3% vs 81.3%).<sup>12</sup> The distinguishing differences between the two boosted PIs were seen in

significantly lower elevations in triglycerides with saquinavir/ritonavir versus lopinavir/ritonavir.

The ARTEMIS (Antiretroviral Therapy with TMC114 Examined in Naïve Subjects) trial compared the newest member of the protease inhibitor class, darunavir, with lopinavir, both used in combination with low-dose ritonavir and emtricitabine/tenofovir in treatment-naïve HIV patients. Study participants had a median CD4+ T-cell count  $<250/\text{mm}^3$  and median HIV RNA copies  $>60\,000/\text{mL}$ .<sup>13</sup> Darunavir/ritonavir was administered as 800/100 mg once daily, and lopinavir/ritonavir as either 400/100 mg twice daily or 800/200 mg once daily. This dosing of darunavir was unique in that it is typically administered as 600 mg twice daily rather than 800 mg once daily as used here; the dose of ritonavir was also reduced from 100 mg twice daily to 100 mg once daily. The efficacy data at 48 weeks after initiating treatment showed generally similar proportions of patients with HIV RNA  $<50$  copies/mL in the two treatment groups (DRV/r<sub>tv</sub> – 84% vs LPV/r<sub>tv</sub> – 78%). However, the incidence of grades 2-4 diarrhea was greater in the lopinavir/ritonavir than in the darunavir/ritonavir group (10% vs 4%). There was also a greater increase in plasma triglyceride levels with lopinavir/ritonavir, although change in the low-density-lipoprotein cholesterol/high-density-lipoprotein cholesterol (LDL-C/HDL-C) ratio was not significantly different between groups.

The most notable finding from ARTEMIS was that darunavir/ritonavir treatment demonstrated better efficacy than lopinavir/ritonavir did in the subgroup of patients with the highest viral loads ( $>100\,000$  copies/mL) and lowest levels of CD4+ T-cells ( $<50$  cells/ $\text{mm}^3$ ). Significantly more patients in the darunavir/ritonavir arm (79%) compared with lopinavir/ritonavir (67%) achieved a viral load  $<50$  copies/mL ( $P < .05$ ), suggesting that darunavir/ritonavir is the better option for patients starting HAART with high viral loads and low T-cell counts.

*Studies in treatment-experienced patients*—Clinicians know how difficult it can be to treat HIV-infected patients who have been on multiple prior regimens and have significant antiretroviral drug resistance. The DHHS clinical practice guidelines identify the resuppression of HIV RNA levels to  $<50$  copies/mL and prevention of further selection of resistance mutations as treatment goals in these patients.<sup>7</sup> Fortunately today, effective medications are

available for patients with extensive prior antiretroviral drug experience and high-level resistance. As the 2006 International AIDS Society guidelines for the treatment of adult HIV treatment noted, “Trials with newer antiretroviral agents have shown that it is possible to achieve plasma HIV-1 RNA levels below 50 copies/mL even in highly treatment-experienced patients.”<sup>14</sup> Since the publication of those guidelines, 2 new classes of antiretrovirals, each with a novel mechanism of action, have been approved, as has a new and probably next-generation NNRTI, expanding the options for treatment-experienced patients with HIV who are resistant to other antiretroviral drugs.

A number of recent studies have explored new treatment regimens in treatment-experienced HIV patients. For example, the TITAN phase 3 trial compared darunavir/ritonavir 600/100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily in treatment-experienced, lopinavir-naïve patients with HIV-1 RNA  $>1000$  copies/mL ( $n = 595$ ).<sup>15</sup> Patients in both groups also received treatment with an optimized background regimen. The 48-week efficacy results demonstrated that darunavir/ritonavir was both noninferior and superior to lopinavir/ritonavir based on the proportion of patients achieving HIV RNA  $<400$  copies/mL (77% vs 67%,  $P = .0001$ ) as well as  $<50$  copies/mL (71% vs 60%,  $P = .005$ ). The incidence of treatment-emergent adverse events appeared to be similar between the two treatment groups, although diarrhea was higher in the lopinavir/ritonavir group (41.8% vs 31.9%), and rash was higher in the darunavir/ritonavir group (16.1% vs 6.7%).

Two large, international, phase 3 studies, DUET-1 and -2, compared the next-generation NNRTI, etravirine, dosed at 200 mg twice daily with placebo in HIV-infected patients with virologic failure on their current HAART regimen, current or a history of  $\geq 1$  NNRTI resistance mutations,  $\geq 3$  major protease inhibitor mutations, and HIV-1 RNA  $>5000$  copies/mL ( $n = 1,203$ ).<sup>16-18</sup> Both treatment groups also received treatment with darunavir/ritonavir 600/100 mg/mL plus  $\geq 2$  NRTIs with or without the fusion inhibitor, enfuvirtide. The 48-week results showed that a significantly greater proportion of patients in the etravirine versus placebo group achieved HIV RNA  $<50$  copies/mL in both DUET-1 (56% vs 39%,  $P = .005$ ) and DUET-2 (62% vs 44%,  $P = .0003$ ). Hence, the addition of etravirine to a darunavir/ritonavir-based regimen was associated with an approximately 20%

improvement in virologic response despite prior failure of first-generation NNRTIs. Based on these and other data, the FDA approved etravirine in January 2008 as part of a HAART regimen for treatment-experienced adults with HIV infection who have virus with resistance to current classes of antiretroviral agents.

### Recent studies with new antiretroviral drug classes

As discussed earlier, 2 drugs from 2 new classes of antiretroviral agents— maraviroc, a CCR5 inhibitor, and raltegravir, an integrase inhibitor—were approved by the FDA in the second half of 2007. Both drugs received accelerated approval and are indicated for use in combination with other antiretroviral agents in adults with HIV-1 infection and evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.<sup>19,20</sup>

Maraviroc is related to fusion inhibitors such as enfuvirtide in that both are considered entry inhibitors, but each works at a different step of the HIV entry process. Unlike enfuvirtide, which inhibits fusion between the HIV outer envelope and the host CD4+ T-cell's plasma membrane by binding with the HIV glycoprotein 41 (gp41), maraviroc selectively binds to, and alters the shape of, the CCR5 chemokine coreceptor, the protein on the surface of human CD4+ T-cells to which HIV must bind in order to gain entry into the cell. Specifically, maraviroc prevents the HIV glycoprotein 120 (gp120) from binding to the CCR5 co-receptor.<sup>2,19</sup> Maraviroc is indicated specifically for treatment of treatment-experienced HIV+ patients with CCR5-tropic HIV. Maraviroc was granted FDA approval based on the 24-week interim data from 2 ongoing trials: MOTIVATE I and MOTIVATE II.<sup>21,22</sup>

In MOTIVATE I and II, 1049 patients with CCR5-tropic HIV infection and HIV RNA  $\geq 5000$  copies/mL were randomized in 1:2:2 ratio to receive placebo, maraviroc 1 once daily, or maraviroc twice daily, plus optimized background therapy (OBT; 3-6 antiretroviral drugs, not counting pharmacokinetic boosting doses of ritonavir). Patients receiving a boosted protease inhibitor (except tipranavir, which was used in <15% of patients) as part of their OBT received the maraviroc 150 mg dosed once or twice a day, while in all other patients maraviroc was dosed at 300 mg once or twice a day. This was due to the

approximate doubling of the area under the curve (AUC) of maraviroc versus most boosted PIs. Of note, due to incomplete pharmacokinetic interaction data, darunavir/ritonavir was not allowed to be used as part of OBTs in these studies.

The 48-week results from MOTIVATE I and II were recently presented and showed that a significantly greater proportion of patients in both maraviroc dosing groups achieved HIV-1 RNA <400 copies/mL (56.1% and 51.7% with twice daily or once daily, respectively, vs 22.5% with placebo;  $P < .0001$ ) as well as <50 copies/mL (45.5% and 43.2% with twice daily or once daily, respectively, vs 16.7% with placebo;  $P < .0001$ ).<sup>23</sup> These results were essentially the same as those observed at the 24-week interim analysis: achievement of these targets with maraviroc was essentially stable over this time period, although the proportions decreased in the placebo group (from 27.8% to 22.5% for HIV RNA <400 copies/mL and from 22.0% to 16.7% for HIV RNA <50 copies/mL).

Similarly, median change from baseline in CD4+ T-cell counts was significantly greater with both maraviroc-treated groups compared with placebo at the 48-week analysis [+124 (twice daily) and +116 (once daily) cells/mm<sup>3</sup> vs +61 (placebo) cell/mm<sup>3</sup>]. These numbers demonstrated a continued rise in cells for the maraviroc-treated groups, compared to little change in the placebo group, to those observed at the 24-week interim analysis. Similar percentages of persons in all three treatment groups experienced adverse events, discontinued due to adverse events or death, or had grade 3, grade 4, or serious adverse events.<sup>23</sup>

The MERIT study was designed to compare maraviroc 300 mg twice daily (n = 360) with efavirenz 600 mg once daily (n = 361), both used in combination with zidovudine/lamivudine, in antiretroviral-naïve patients infected with CCR5-tropic HIV-1 and HIV-1 RNA  $\geq 2,000$  copies/mL. Efficacy results for the 48-week analysis demonstrated noninferiority of maraviroc to efavirenz for viral response for HIV RNA <400 copies/mL but did not demonstrate noninferiority for the <50 copies/mL comparison. Overall tolerability and safety were similar between the two arms of the study, but there were more grades 3 and 4 adverse events and class C CDC events seen in the efavirenz arm.<sup>24</sup> Maraviroc is not currently indicated for the first-line treatment of patients with HIV infection.

Raltegravir, the other new antiretroviral drug approved in 2007, is the first member of the new integrase inhibitor class of antiretroviral drugs. Once HIV has infected the host cell—its RNA reverse transcribed into DNA and then transported into the host nucleus—it needs to be inserted into the host DNA in order for the viral genes to be transcribed and translated into protein.<sup>2</sup> Integrase is the viral enzyme that plays a key role in this integration process; raltegravir disrupts this process by inhibiting the catalytic activity of HIV-1 integrase.<sup>20</sup> Raltegravir is metabolized mainly via hepatic glucuronidation, and it is not a potent inhibitor or inducer of CYP3A4; therefore, it does not require boosting with ritonavir. In vitro studies suggest it is active against multidrug-resistant HIV and both CCR5 and CXCR4 HIV-1.<sup>25</sup> The approval of raltegravir for use in treatment-experienced adults infected with HIV was based largely on a 24-week analysis of results from a clinical trial of raltegravir plus optimized background therapy.<sup>26</sup> In this study, 61% to 63% of the patients achieved HIV RNA <50 copies/mL with raltegravir and an optimized background regimen after failing therapy with triple-class-resistant virus.

BENCHMRK-1<sup>27</sup> and BENCHMRK-2<sup>28</sup> are further exploring the efficacy and safety of raltegravir versus placebo, plus optimized background therapy, in highly treatment-experienced patients. Forty-eight-week data demonstrate that significantly greater proportion of patients in the raltegravir versus placebo group achieved virologic suppression (65% vs 31% and 62% vs 34%, respectively;  $P < .001$ ).

Encouraging results with raltegravir-based therapy in treatment-naïve, HIV+ patients have also recently been reported. A multicenter, double-blind, randomized, controlled phase II study compared raltegravir (100, 200, 400, or 600 mg twice daily) with efavirenz 600 mg once

daily, all in combination with tenofovir/lamivudine, in antiretroviral-naïve patients with HIV-1 RNA  $\geq 5000$  copies/mL and CD4+ T-cell counts  $\geq 100$  cells/mm<sup>3</sup>.<sup>29</sup> A greater percentage of patients on raltegravir than on efavirenz achieved HIV-1 RNA <50 copies/mL in weeks 2, 4, and 8 of the study, indicating rapid first-phase viral decay. Analyses after 24 and 48 weeks showed that similar proportions of patients in all treatment groups (above 80% for all groups) had achieved HIV-1 RNA <50 copies/mL.

These results are remarkable because efavirenz-based HAART regimens have been considered the antiretroviral regimens associated with fastest suppression of viral loads; however, in this study, raltegravir achieved more rapid suppression of HIV-1 RNA to <50 copies/mL than efavirenz did. Both raltegravir and efavirenz were associated with durable virologic responses in a similarly high proportion of patients.<sup>29</sup> The other noteworthy finding from this study was that raltegravir was associated with fewer patient-reported, drug-related adverse events than efavirenz was—particularly, neuropsychiatric adverse events. In addition, whereas efavirenz was associated with increased serum levels of total cholesterol, LDL-C, and triglycerides after 24 and 48 weeks of treatment, raltegravir had no effect on these lipid levels.

The use of antiretroviral therapy will continue to grow, in both treatment-naïve and treatment-experienced patients who go on to salvage therapy. It is conceivable that the term salvage will no longer be used in the near future, because the outcomes with new therapeutic options will be much improved. There has been an explosion of new medications for treatment-experienced patients, for whom we can now offer effective long-term viral suppression with dramatically reduced side effects.

# Hepatitis C Virus and HIV Coinfection: Treatment Challenges and Emerging Therapies

Laveeza Bhatti, MD, PhD

Of those infected with HIV in the United States, 15% to 25% are coinfecting with hepatitis C virus (HCV).<sup>30,31</sup> The prevalence of coinfection varies by HIV patient subgroup, ranging in one study from 9.8% in patients with male homosexual contact to 14.3% in those with heterosexual contact, and 85.1% in intravenous drug users.<sup>31</sup> Both HIV and HCV can be transmitted by percutaneous exposure to blood, through sexual contact, or perinatally from mother to child, but the efficiency of transmission varies for the different routes. HCV is more readily transmitted via percutaneous exposure to small blood volumes (eg, needlesticks) than HIV is, while HIV is more easily transmitted from mother to infant and through sexual contact.<sup>30</sup>

## Impact of HIV on progression of HCV infection

In approximately 70% to 85% of patients, HCV infection progresses from an acute to chronic phase and further progresses to liver cirrhosis in 20% of patients with chronic infection.<sup>32</sup> Disease progression is rapid in about one fourth of patients with cirrhosis of the liver due to chronic HCV infection and ultimately ends in hepatocellular cancer, end-stage liver disease, or death. Coinfection with HIV adversely affects each step in the natural history of HCV infection. For example, in 15% to 30% of monoinfected individuals, HCV infection resolves spontaneously, whereas only 5% to 10% of patients coinfecting with HIV exhibit spontaneous resolution of HCV infection.<sup>30</sup> Moreover, higher HCV viral levels and a more rapid progression of HCV disease—including cirrhosis, liver failure, and hepatocellular cancer—are seen in coinfecting patients.<sup>33-35</sup> In addition, the virologic response to HCV therapy is lower in patients with HCV/HIV coinfection compared with the response in those with HCV infection alone.<sup>36,37</sup>

Consistent with these findings, HCV status has been

shown to have a significant adverse effect on hospitalization rates in a prospective, longitudinal, cohort study of HIV patients.<sup>38</sup> While hospitalization rates significantly decreased from 1995 to 2000 for HCV-negative patients, they significantly increased for HCV-positive patients. In multivariate analysis, HCV infection status along with female gender, African-American ethnicity, and CD4+ cell count <50 cells/mm<sup>3</sup> was a strong independent predictor of hospitalization.<sup>38</sup> Of note, end-stage liver disease is now considered a leading cause of mortality in hospitalized HIV-positive patients and is often associated with HCV coinfection. For example, a 2001 retrospective study reported that 94% of hospitalized HIV patients who died due to end-stage liver disease in 1998 had detectable antibodies to HCV.<sup>39</sup> Moreover, 55% of the patients had CD4+ cell counts <200 cells/mm<sup>3</sup> or nondetectable HIV RNA levels, suggesting that HCV infection leads to an increased risk of death in HCV/HIV coinfecting individuals, even when HIV is relatively well controlled.

The impact of HIV on HCV disease progression appears to be greatest in older individuals.<sup>40</sup> Only 15% of HCV/HIV coinfecting patients aged ≤30 years who had elevated alanine aminotransferase levels had a baseline liver fibrosis score of F3 or F4 (ie, severe disease) compared with 36% of patients aged 31 to 46 years and 46% of patients >41 years.<sup>41</sup> These results suggest that the severity of liver fibrosis or HCV disease progression increases significantly with age in coinfecting patients. These results also underscore the importance of early treatment of both HIV and HCV in coinfecting patients. Coinfecting individuals often underestimate the importance of controlling HCV. While recognizing the need to take antiretroviral drugs to lower HIV levels and maintain high T-cell counts, they often do not fully appreciate the importance of controlling HCV in order to minimize liver damage. In addition, many patients are under the misconception that low HIV levels correlate with low HCV levels.

### Does HCV coinfection have a negative impact on progression of HIV infection?

In addition to the negative impact of HIV coinfection on the course of HCV infection, there is some suggestion that coinfection with HCV may also have a negative impact on the course of HIV infection. Results from the Swiss HIV Cohort Study suggested that HIV/HCV coinfecting patients (most of whom had a history of intravenous drug use) had more rapid clinical progression, lower survival, and poorer immune recovery during antiretroviral therapy than HCV-negative patients did.<sup>42</sup> More specifically, in multivariate analysis, HCV seropositivity was independently associated with the probability of progression to a new AIDS-defining clinical event or to death. In addition, HCV/HIV coinfecting patients exhibited a relatively suppressed CD4+ lymphocyte response compared with recovery in HCV-negative HIV patients. Deaths from liver disease were 3-fold higher in HCV-positive than HCV-negative patients, although the virologic response to antiretroviral therapy was not associated with HCV serostatus.<sup>42</sup>

Despite these findings, a number of other studies have failed to demonstrate a statistical relationship between HCV serostatus and progression to AIDS or death,<sup>43-46</sup> although significant relationships between elevated transaminase levels and increased rate of death or AIDS<sup>44,46</sup> and between cirrhosis and AIDS<sup>46</sup> have been reported. Given these data, one possible management approach is that HCV treatment should be initiated as early as possible in coinfecting patients in order to reduce liver damage and lower adverse outcomes associated with this damage.

### Treatment-related issues in HCV/HIV coinfecting patients

Coinfection of HIV patients with HCV may cause difficulties with antiretroviral treatment. A number of studies have identified HCV coinfection or seropositivity as risk factors for antiretroviral therapy-related hepatotoxicity.<sup>47,48</sup> While the mechanism underlying the association of HCV and antiretroviral therapy-related hepatotoxicity is not completely understood, this association once again highlights the complex relationships that exist between HCV and HIV in

coinfecting patients and the treatment challenges with their dual presence.

For example, the incidences of flu-like adverse events (fatigue, diarrhea, nausea) associated with peginterferon alfa-2a/ribavirin combination HCV therapy were generally higher in HIV coinfecting patients with CD4+ counts <200 cells/mm<sup>3</sup> presumably due to the greater severity of HIV and liver disease in this group.<sup>49</sup> This suggests that the higher the T-cell count when anti-HCV treatment is started, the better the patient will be able to tolerate therapy.

More generally, evidence indicates that liver histology or function is improved with anti-HCV treatment in patients coinfecting with HIV. For example, in a small (n = 22) retrospective analysis of HCV/HIV patients with bridging fibrosis/cirrhosis, peginterferon alfa-2a/ribavirin therapy was associated with histologic response in 68% of patients, suggesting that most coinfecting patients who receive anti-HCV treatment can expect an improvement in liver health/function or at least stabilization of disease—even those with advanced HCV.<sup>50</sup>

Long-term effects of interferon therapy in patients mono infected with HCV support the positive impact of treatment on liver histology. For example, the mean fibrosis score regressed in patients with a sustained virologic response to interferon treatment and exhibited limited progression in patients with an unsustained response (ie, without full virus eradication), suggesting that interferon has antifibrogenic and hepatoprotective properties that impart benefits even in the absence of viral response<sup>51</sup> and therefore may be a part of the complete disease management program.

It is important that patients and clinicians be aware that initiation of interferon alfa or peginterferon alfa-2a, with or without ribavirin, causes a significant drop in CD4+ T-cell counts.<sup>52</sup> Although T-cell counts typically return to normal as soon as the 48-week treatment regimen ends, and the benefits of therapy outweigh the risks, in patients who already have low T-cell counts, the likelihood of opportunistic infections warrants careful monitoring.

### Viral kinetics and new HCV drug targets

Advances in anti-HCV treatment have lagged behind those in anti-HIV or antiretroviral treatment. Currently

approved agents in the United States include interferon alfa, peginterferon alfa-2a or -2b, and ribavirin. The current standard of care is combination therapy with peginterferon alfa and ribavirin.<sup>53</sup> In monoinfected patients, peginterferon alfa/ribavirin treatment produces sustained virologic response in 54% to 56% of patients, including 42% to 46% of patients infected with HCV genotype 1 and approximately 80% of those infected with HCV genotype 2. Corresponding rates of sustained virologic response with peginterferon alfa/ribavirin combination in patients with HCV/HIV coinfection are 40% overall and 29% and 62% for patients infected with genotype 1 and genotype 2 or 3, respectively.<sup>52</sup>

A number of new compounds are being investigated as potential future treatment for HCV. In the disease process, HCV infects hepatocytes, and when these cells die, they release HCV into the blood, which then infects previously uninfected hepatocytes. Therapies can be targeted to prevent reinfection or new infection of previously uninfected hepatocytes. Knowledge of the molecular structure of HCV proteins has also enabled the development of compounds that disrupt HCV replication.<sup>54</sup> VX-950 (telaprevir) and SCH503034 are HCV protease inhibitors being investigated in clinical trials, and valopicitabine (NM-283) is an HCV

polymerase inhibitor currently in development. Other potential future treatment strategies focus on the use of vaccines or other immune modifiers to boost the body's immune response to provide viral control. Additional drugs in development include a peginterferon with longer half-life (albuferon-alpha or albumin-interferon-alpha), a prodrug of ribavirin associated with reduced anemia risk (viramidine), and various toll-like receptor agonists.

There are many unmet needs and future challenges in HCV treatment, particularly in patients coinfecting with HIV: prevention of chronicity following acute infection, prevention of disease progression, reduction in treatment duration, second-chance therapies in nonresponders, improvement in hard-to-treat patients, improved sustained virologic response in HCV/HIV coinfection, prevention of recurrent HCV posttransplant, prevention of resistance to newer therapies, reduction in side effects, and reduction in costs. The introduction of new antivirals with innovative mechanisms of action may help to meet these needs—either alone or in combination with peginterferon with or without ribavirin or in combination with other new antivirals with different targets. Now is the opportunity to develop pipeline therapies toward these many unmet needs.

## Women and HIV: Approaches to Improve Clinical Outcomes

Alice M. Stek, MD

**G**lobally, HIV can almost be classified as a women's issue: Approximately 47% of HIV-infected adults are women.<sup>1</sup> In sub-Saharan Africa, which has the highest rate of HIV infection, more than half (about 60%) of HIV-infected adults are women.<sup>1</sup> Worldwide each year approximately 600 000 children become infected, and in >90% of these cases, the mother transmits HIV to the infant during pregnancy, delivery, or breastfeeding.<sup>55-57</sup> Although the statistics are much more favorable in the United States, HIV incidence among women is still high, constituting 26% of all new infections, 75% of which are among Hispanic and African-American women. In the United States, AIDS still is one of the leading causes of death in younger women.<sup>58</sup>

Several factors contribute to the high HIV prevalence among women. While the relative contribution of each factor varies among regions or countries, the overall patterns are remarkably similar. Biologically, women are more likely to contract HIV from unprotected vaginal intercourse than men are, due to substantial mucosal tissue exposed to seminal fluids.<sup>59,60</sup> While the majority of new HIV infections in women occur in long-term relationships with primary partners, sexual attacks against women and other forms of nonconsensual sex also contribute. In both resource-poor and wealthy countries, women's lower socioeconomic status, gender power inequities, and sociocultural norms contribute to the risk of HIV infection in women,<sup>61</sup> particularly in younger women. For example, in Zambia and South Africa, 18% to 21% of women become infected within a year of becoming sexually active. In all countries, lack of education, ignorance of one's body and of the disease, and limited access to care also exacerbate the problem.

### Mother-to-child transmission: Testing and treatment

In the absence of any intervention, data from various

studies show that about 15% to 30% of babies born to HIV-positive mothers are infected with HIV.<sup>62,63</sup> There are numerous studies, often confusing, regarding maternal risk factors associated with perinatal transmission. Several interventions—including better identification of women at risk, providing antiretroviral medications, good perinatal care, cesarean delivery in selected cases, and avoidance of breastfeeding—have been shown to contribute to the decrease in mother-to-child transmission (MTCT).

One of the earliest studies to show the dramatic effect of maternal treatment on MTCT was the AIDS Clinical Trials Group (ACTG) protocol 076, in which zidovudine (ZDV or AZT) treatment of the mother significantly reduced the risk of perinatal transmission regardless of her viral load or CD4+ T-cell count.<sup>64</sup> ZDV given orally to HIV+ women starting at 14 to 34 weeks' gestation, then given intravenously during labor, and then as a syrup to the newborn for 6 weeks resulted in a significant, 67% reduction in transmission (placebo 25.5% vs ZDV 8.3%;  $P = .00006$ ).

Since this landmark study, similar dramatic reductions in vertical transmission have been reported, which has led to public health recommendations since 1995 that all pregnant women be offered counseling and voluntary HIV testing and treatment if positive.<sup>65-70</sup> In its most recent guidelines, the CDC advises that all pregnant women be notified that HIV screening is recommended and will be done as part of the routine prenatal tests unless they decline (ie, opt out). Women at higher risk due to behavior, high-risk partners, or geographic location should be retested during the third trimester, preferably before 36 weeks of gestation; consideration should be given to retesting of all pregnant women during late pregnancy.<sup>68</sup> For women in labor whose HIV test results are undocumented, screening with a rapid HIV test in labor and delivery is recommended. If all HIV-infected pregnant women are identified and receive HAART, the chances of

transmitting HIV to the baby will be decreased to <2%. In my own clinic, our last case of transmission was in December 1996; since then, we have delivered approximately 500 babies with zero transmission.

While the benefits of antiretroviral therapy must be weighed against the risks of adverse effects in the mother and baby, such as drug toxicities and teratogenic effects, it is now recommended that all HIV+ women be treated with antiretroviral therapy. Ideally, antiretroviral drug resistance testing should be performed in all pregnant women before starting antiretroviral therapy or prophylaxis. However, if an HIV-positive woman presents for care in the latter half of the second trimester or in the third trimester, therapy can be initiated—and modified later based on the results of resistance testing. Combination drug regimens, rather than monotherapy, are the current standard of care for the treatment of HIV infection and for prevention of perinatal HIV transmission regardless of maternal CD4+ cell count.<sup>70,71</sup> In women with HIV RNA >1000 copies/mL, triple combination therapy should be instituted and should be considered in women with viral load <1000. The choice of specific antiretroviral agents is based on the treatment history of the mother and her unique circumstances, including the results of antiretroviral resistance testing.

Despite the effectiveness of perinatal antiretroviral therapy, many women may not receive this treatment, because they are unaware of their HIV status<sup>72</sup> and/or they are not targeted by their health care providers for testing and treatment. For example, knowledge of MTCT and acceptance of guidelines for universal testing of pregnant women by physicians do not always translate into clinical action.<sup>73,74</sup> The lack of a timely HIV diagnosis in pregnant women is a large contributor to perinatal transmission, yet with the availability of rapid testing,<sup>75</sup> at-risk infants can be identified, and preventive measures such as neonatal antiretroviral prophylaxis and formula feeding can be initiated immediately after delivery.

The standard adult HIV test identifies HIV immunoglobulin G (IgG) antibody, which may not be useful in infants under 18 months of age. All infants born to HIV+ mothers are themselves HIV IgG antibody positive because of maternal antibodies that cross the placenta and persist in the neonatal circulation for 12 to 18 months after birth. Therefore, direct viral testing using DNA or RNA polymerase chain reaction should be

used in infants under 18 months of age.<sup>76</sup> Diagnosis is usually made within 2 months of testing if there is no additional exposure after delivery.

### Mother-to-child transmission: Labor and delivery

Elective cesarean deliveries, especially in women with plasma viral loads of >1000 copies/mL, also decrease the MTCT rate by reducing the exposure of the infant to transplacental transmission HIV and to HIV in the genital tract during labor. Elective cesareans can be options in settings where antiretroviral treatment was not used.<sup>77, 78</sup> In a meta-analysis of 15 cohort studies, including 8533 mother-child pairs, elective cesarean delivery was associated with a nearly 50% reduction in vertical transmission compared with other modes of delivery regardless of ZDV use.<sup>78</sup> Note that this study examined the pre-HAART era and that women were on no antiretrovirals and no ZDV monotherapy. Although elective cesareans are recommended for women with high viral loads or who did not take antiretrovirals, for pregnant women who have been receiving combination antiretroviral therapy during pregnancy and with plasma HIV RNA levels <1000 copies/mL near the time of delivery, elective cesareans do not confer any additional benefits in the prevention of perinatal transmission.<sup>70,71</sup> A cesarean delivery is not a panacea: it has associated complications; and furthermore, in resource-limited settings, in areas where postpartum care is suboptimal, or in women with repeat pregnancies, multiple cesarean deliveries are generally not the safest or the most desirable alternatives.

### Preconception counseling

Preconception counseling is recommended for HIV-positive women of childbearing age. Safe and effective contraception to prevent unintended pregnancy is essential. Clinicians should be aware of potential drug interactions that might decrease the efficacy of hormonal contraception. In addition to issues relevant to all women who desire pregnancy, for HIV+ women on treatment, counseling should include an evaluation for potentially teratogenic or otherwise harmful medications

and a recommendation to attain maximally suppressed viral load prior to conception.

### Mother-to-child transmission: Breastfeeding

Postpartum transmission of HIV from mother to infant is substantially greater in breastfed than formula-fed infants.<sup>79,80</sup> In regions where safe and nutritionally acceptable alternatives to breastfeeding exist, a shift to formula feeding has been associated with a further decrease in MTCT. However, this may not be possible in resource-limited settings where clean water or adequate supplies of nutritionally balanced infant formula are not readily available or where the societal norms and customs are not permissive of formula feeding.<sup>81</sup> In cases where replacement feeding is not

safe, acceptable, feasible, or affordable, exclusive breastfeeding for the first few months confers less risk than mixed feeding.<sup>82</sup> Multiple studies of maternal and/or infant antiretroviral treatment during breastfeeding are currently in progress. Not surprisingly, preliminary results indicate that treatment decreases the risk of transmission to the infant during breastfeeding.

The goal of HIV management in pregnancy encompasses the physical well-being of the mother and the fetus in addition to the prevention of transmission. HIV-infected women need ongoing medical care, education, and support so they are empowered to make informed decisions regarding their health and that of their baby. While much has been done to increase awareness regarding the global burden of HIV/AIDS, substantially more needs to be invested in resource-poor settings and in the people most affected by this epidemic.

## Crystal Methamphetamine: An Epidemic with Serious Impact on HIV

*William D. King, MD*

With more than 35 million users worldwide, methamphetamine has become the second-most-abused drug, after marijuana. The availability of its main ingredients and the relative ease with which it can be manufactured into the final product have led to the widespread availability of methamphetamine. In the United States, about 3.9 million people use methamphetamine.<sup>83</sup> There is a growing trend of methamphetamine abuse among youths, which is a serious health concern in terms of the shift of HIV infection from high-risk to traditionally low-risk populations. In a recent survey, among 14,322 respondents aged 18 to 26 years, nearly 3% indicated crystal methamphetamine use in the previous year.<sup>84</sup> Similarly, in a secondary analysis of the 2003 Youth Risk Behavior Survey (n = 15 240) among a nationally representative sample of US high school students in grades 9 through 12, a substantial proportion (7.6%) indicated having used methamphetamine at least once, which was associated with approximately 2 to 11 times the likelihood of engaging in sexual-risk behaviors.<sup>85</sup> In general, the prevalence of methamphetamine use was slightly higher among males than females (8.3% vs 6.8%) and increased as males progressed in grade, whereas it decreased among females as they progressed in grade. Prevalence was more than twice as high for white (8.1%) and Hispanic (8.2%) as for black students (3.1%). The tendency to engage in high-risk sexual behaviors increased with increasing frequency of methamphetamine use such that heavy users were significantly more likely to report higher numbers of sexual partners ( $\geq 4$ ), having had sexual intercourse before age 13, and having gotten someone pregnant once or more compared with lower-frequency users.<sup>85</sup>

Because methamphetamine use is associated with high-risk behaviors leading to HIV infection, the growing methamphetamine epidemic has become a concern for those focused on limiting the spread of HIV.

A derivative of phenylethylamine, methamphetamine

can also be synthesized from L-ephedrine, commonly found in Sudafed or in antihistamines, yielding the D-methamphetamine form, which is more potent than the L-form and which has a more euphoric effect.<sup>86</sup> Methamphetamine is a powerful central nervous system stimulant that acts by preventing the natural reuptake of dopamine in brain regions that control emotions, including sensations of euphoria. Although similar to cocaine in its effects, dopamine release with methamphetamine is more powerful, resulting in a longer half-life. Methamphetamine is sought after because of its long half-life and its short-term effects, including increased alertness and energy, heightened sex drive, and euphoria. Physiologic effects of methamphetamine include tachycardia; increases in perspiration, arterial pressure, and respiration rate; decreases in appetite and sleep, and slower reaction time.<sup>87</sup> Chronic use contributes to physical conditions such as malnutrition, eating disorders, and periodontal disease with loss of teeth as well as mental disorders such as anxiety, depression, hallucinations, and psychosis. Acute and chronic use can result in heart disease, stroke, renal failure, and even death.<sup>88,89</sup>

Methamphetamine use has become a new challenge in the treatment and prevention of HIV infection because methamphetamine leads to heightened sexual arousal and disinhibition, therefore contributing to unsafe and risky sex behaviors among heterosexual persons and among men who have sex with men (MSM).<sup>90-93</sup> These individuals are at high risk of contracting HIV, as indicated by a positive correlation between methamphetamine use and HIV infection.<sup>94</sup> In one study of MSM seeking treatment for methamphetamine use, long-term usage was associated with higher HIV prevalence. The lowest HIV prevalence rate (23%) was in those who reported recent methamphetamine use, followed by those who used at least once a month for 6 months (42%), followed by those (61%) seeking intensive outpatient treatment. The highest rate (86%) was observed among MSM

seeking residential treatment for methamphetamine dependence.<sup>94</sup> In another study, however, even intermittent, recreational methamphetamine use was associated with risky sexual practices, such as unprotected anal intercourse with an HIV-positive or unknown-status partner.<sup>95</sup>

Treatment for methamphetamine use is also complicated by neurocognitive decline. The neurophysiologic mechanism responsible for the desired effects of methamphetamine also leads to neurocognitive deficits. Methamphetamine has been shown to induce damage to dopamine (DA) terminals in laboratory animals.<sup>96</sup> In humans, a significant loss of DA transporters—the markers of DA terminals—has been shown in the brains of methamphetamine abusers.<sup>97-99</sup> For example, compared with nonusers, significantly lower DA transporter levels were measured in the caudate (27.8% difference) and in the putamen (21.1% difference) of methamphetamine abusers ( $P < .0001$ ), which was further correlated with significantly reduced motor speed ( $P < .05$ ) and impaired verbal learning and memory ( $P < .01$ ).<sup>98</sup> While DA transporter levels may increase with abstinence, full functional recovery has not been demonstrated.<sup>99,100</sup>

The clinical implication of this relates to medication adherence. By itself, illicit-drug use has been correlated with medication noncompliance. For example, medication adherence among HIV-infected individuals tracked over a 6-month period using an electronic monitoring device revealed significantly worse medication adherence among illicit-drug users than drug-negative participants (63% vs 79%, respectively).<sup>101</sup> When coupled with neurocognitive decline, how much of the verbal instructions or the content of the patient information pamphlets do these methamphetamine-using patients understand or remember? If an HIV patient is chronically using methamphetamine or is detoxing, is the patient able to understand educational materials or adhere to treatment regimens? Therefore, it is important that the clinical staff members be alert to the potential for medication nonadherence and that they include behavioral interventions in overall HIV management. A simple way to approach this topic is by the 5 A's: ask, advise, assess, assist, arrange. This process should be repeated often—preferably at every visit—and should be reinforced by all team members: the physician, nurse, case manager, and others.

Treatment options are limited. Recent studies have focused on pharmacotherapy, behavioral interventions, or both in combination. Bupropion pharmacotherapy for treatment for methamphetamine has shown some efficacy in light users.<sup>102</sup> In a double-blind, placebo-controlled study of 151 methamphetamine-dependent individuals seeking treatment, compared with placebo, sustained-release bupropion 150 mg twice daily was significantly more effective in increasing the number of weeks of abstinence in participants with low-to-moderate methamphetamine dependence at baseline ( $P < .0001$ ).<sup>102</sup> Modafinil, which is used in the management of the symptoms of narcolepsy, is another agent being evaluated for use in the management of methamphetamine dependence. This drug promotes increases in energy and decreases in the levels of depression and fatigue<sup>103,104</sup> and is currently in clinical trials.

A number of behavioral interventions are used to combat methamphetamine addiction. The efficacy of 4 behavioral approaches in reducing methamphetamine use and sexual risk behaviors was assessed in a randomized controlled trial in 162 methamphetamine-dependent gay and bisexual men in Los Angeles County.<sup>105</sup> Participants were randomly assigned to 1 of 4 treatment conditions for 16 weeks: standard cognitive behavioral therapy (CBT), contingency management (CM), combined cognitive behavioral therapy and contingency management (CBT+CM), and a culturally tailored cognitive behavioral therapy (GCBT). At 6- and 12-month follow-up assessments, there were significant reductions in methamphetamine use and sexual risk behaviors in all intervention groups; however, the CM and CBT+CM conditions were better than standard CBT.<sup>105</sup>

Although more work is needed to illustrate the relative superiority of one method over another, some key concepts that bring about change are (1) encouraging and reinforcing behavior change in patients, (2) promoting the recognition and avoidance of high-risk situations, (3) acquiring the skills to cope with conditioned triggers, (4) understanding and dealing with cravings, (5) establishing behavioral planning, and (6) getting back on the wagon should relapses occur.

In summary, methamphetamine use—and its potential association with high-risk sexual behaviors—have become emerging health problems for both the heterosexual and MSM communities, and they need to be considered as part of the HIV treatment paradigm.

## Opportunities and Challenges of HIV Care in Correctional Settings

Orlando H. Pile, MD

The burden of HIV/AIDS and other infectious diseases is much greater in correctional systems than in the general population.<sup>106</sup> In any given year since 2001, more than 1.3 million adults are incarcerated in state and federal prisons, and another 600 000 plus in local jails.<sup>107-109</sup> According to the US Department of Justice Bureau of Statistics, in 2005 a total of 20 888 state prison inmates and 1592 federal prison inmates were infected with HIV or had confirmed AIDS, representing 1.8% of state and 1.0% of federal prisoners, or 1.7% of the total prison population.<sup>107</sup> In 1997, 20% to 26% of all individuals living with HIV in the United States had passed through a correctional facility,<sup>106</sup> even though incarcerated individuals constitute only approximately 0.8% of the total US population.<sup>110</sup> A recent report from the CDC stated that the estimated prevalence of HIV in the United States is nearly 5 times higher among the incarcerated versus general population.<sup>111</sup>

### Opportunities

Incarceration poses unique challenges but also opportunities for the treatment of HIV. Correctional institutions are important targets for intervention because HIV-infected individuals frequently are diagnosed and initiate antiretroviral therapy in prison. In a study of the incarcerated population in Rhode Island, where routine HIV testing is offered to all inmates at entry, approximately one third of all persons who test positive in the state were identified in a correctional facility.<sup>112</sup> This study reported that incarcerated males (35%), African Americans (42%), and injection drug users (43%) were particularly likely to be first diagnosed in a state correctional setting.<sup>112</sup> A study of women in a Connecticut correctional facility showed that 67% of inmates diagnosed with HIV infection were first offered antiretroviral agents while in prison.<sup>113</sup> For many individuals engaging in high-risk behaviors, incarceration

in a correctional institution offers the first real opportunity to be tested and receive care for HIV infection.<sup>114</sup> Unlike the general population, incarcerated individuals have a recognized constitutional right to health care, since the US Supreme Court has determined that deliberate indifference to serious medical needs of prisoners is a violation of the 8th amendment.<sup>115-117</sup>

Hence, the large reservoir of individuals with HIV in correctional facilities—together with a structured environment, including universal access to health care—identifies correctional facilities as important sites for the diagnosis and subsequent treatment of HIV-infected individuals.<sup>114</sup> The structured environment also provides an opportunity for educational initiatives focused on reducing high-risk behaviors associated with HIV infection and AIDS and on the importance of antiretroviral treatment for HIV infection.<sup>118</sup> However, some studies have reported inconsistent access to HIV prevention and education services in the corrections setting.<sup>119</sup> From a wider societal perspective, it is important to identify incarcerated individuals with HIV and to provide care to reduce high-risk behaviors, because most of these individuals will be released back into the wider community, where they become potential sources for HIV transmission. As the United Nations publication *HIV/AIDS Prevention, Care, Treatment and Support in Prison Settings* states, good prison health is good public health, given that the vast majority of persons committed to prison eventually return to wider society.<sup>120</sup> More than 600 000 inmates are released to the community each year in the United States, with a significant percentage carrying HIV.

In addition, although the rate of HIV transmission within correctional institutions is relatively low, with most HIV-positive incarcerated individuals contracting the virus while on the outside, the transmission rate within correctional institutions is not negligible.<sup>106,111,114</sup> A number of studies indicate that the prevalence of high-risk behaviors remains high among incarcerated

individuals.<sup>106,118,121</sup> Efforts should be focused on reducing high-risk behaviors while inside the institution as well as in the transition back to society. Furthermore, while individuals in state or federal prisons will be there for extended periods of time, jails are used as housing facilities for arrestees or for individuals serving 1 year or less of time.<sup>114</sup> This means there may be limited time for efforts focused on identifying infected individuals, initiating treatment, and providing education about high-risk behaviors.

### Challenges

There are several challenges to providing adequate HIV care in correctional facilities. These include lack of HIV specialists, integrated delivery systems, and community standard practices; the remote locations of prisons, limiting health-care access; continuity of care post-release or after transfer to another facility; mistrust and stigma that limit effective and honest communication; language or cultural barriers; restricted formularies; and issues related to confidentiality and privacy. In addition, it is important to recognize that many adults or juveniles with HIV in correctional facilities are also infected with HCV or have other comorbidities that need to be effectively managed and that may complicate HIV treatment, including substance abuse disorder or other mental illnesses, tuberculosis, and sexually transmitted diseases.<sup>122-125</sup>

At the Los Angeles County Jail, which is the largest jail in the United States and where I work, there is an average daily population of approximately 20 000 and 52% of these individuals are Hispanic, many of whom do not speak English well or at all. The average length of stay at the jail is 54 days, and more than 1 million prescriptions are filled annually. If quality health care is to be provided to these patients, as is required by law, staff members need to be able to communicate with these prisoners. Many other non-English-speaking individuals also are in prison in Los Angeles and throughout the nation. How can we provide adequate health care and communicate to or educate them about the need to reduce high-risk behaviors and about the importance of adherence to antiretroviral therapy if there are no staff members within the corrections system who speak their language?

The mistrust and stigma of being HIV positive in a correctional environment can be tremendous. Some inmates who are HIV positive when incarcerated do not reveal their HIV status when they are booked. However, as time passes, these prisoners get concerned, or they may begin to experience symptoms, but by this time, valuable time has been lost.

Individuals entering a correctional facility may also resist being tested for HIV because of confidentiality or privacy concerns, especially if they are found to be positive.<sup>109</sup> Prison staff members also need to maintain privacy and confidentiality about HIV-positive prisoners in order to avoid potential backlash from other prisoners upon inadvertently learning about the individual with HIV. Privacy is especially important because drug adherence has been strongly correlated with inmate trust in the correctional facility's health-care system to protect the inmate's confidentiality and privacy.<sup>114,118</sup>

The position of the National Commission on Correctional Health Care (NCCCHC) is that all medications approved for HIV treatment should be on the formulary of the correctional facility and that all intake facilities should have a system to assure continuity of HIV medications.<sup>126</sup> The commission emphasizes that successful HIV therapy requires a lack of interruption in antiretroviral therapy, and that correctional facilities can assure this continuity by establishing mechanisms for continuous availability of antiretroviral therapy, including having a comparable formulary to that in existence outside health-care institutions, so that inmates can continue their treatment without interruption. However, correctional system formularies are often very restricted and lag behind those outside this system.<sup>114</sup> At the Los Angeles County Jail, our goal is to have the same availability that the formulary at Los Angeles County Medical Center has. However, this is a problem if the inmate has been receiving a research or investigational agent. In this case, we are typically unable to continue the inmate's precise antiretroviral therapy within the facility. In addition, the frequent transfer or movement of inmates within or between correctional facilities, or when inmates leave the facility for court appearances, provides a challenge to continuity of care. Again, mechanisms need to be put in place to assure the HIV-positive inmate continues to receive quality care, without interruption. These

potential discontinuities need to be anticipated and planned. From the outset, there should be discussions including the inmate about continuity of care. Since the individuals are in a structured setting with equal access to care, their incarceration provides an opportunity to educate them about HIV, antiretroviral therapy, and the importance of adherence without interruption. However, there is little purpose to trying to provide education or talking about adherence to an inmate with a substance abuse problem currently undergoing withdrawal or detoxification. These individuals should complete their detoxification before beginning the HIV education about treatment adherence as well as the need to reduce high-risk behaviors. Recognizing that HIV-positive inmates often experience an interruption in therapy for a variety of reasons, the HIV & Hepatitis Education Prison Project (HEPP) has developed a decision tree for initiating and restarting antiretroviral therapy for inmates in correctional facilities.<sup>116</sup>

In addition, although inmates are the only segment of the US population with a recognized constitutional right to health care, there is at least anecdotal evidence that racial discrimination sometimes results in unequal care even within correctional systems.<sup>109</sup> For example, there are anecdotal reports that African-American inmates receive less favorable responses to sick-call requests than their white counterparts do.<sup>109</sup> The United Nations publication *HIV/AIDS Prevention, Care, Treatment and Support in Prison Settings* emphasizes that prisoners are entitled, without discrimination, to a standard of health care equivalent to that available in the outside community, including preventive measures.<sup>120</sup>

Optimal treatment of the HIV-positive inmate is also challenged by the frequent comorbidities in this population.<sup>122-125</sup> For example, the treatments of multiple coexistent conditions may complicate treatment and

increase risk of nonadherence. Fortunately, antiretroviral treatment of HIV infection has significantly advanced over the past decade, including the availability of combination pills where previously, multiple pills were required. This allows for simplified regimens, often without food restrictions, both of which facilitate treatment adherence. In terms of frequency of dosing, the aim should be once or twice a day, never three or more times daily. In addition, the coexistence of mental disorder in an HIV-positive inmate can also be a factor leading to patient nonadherence with therapy, and as discussed, many adult and juvenile inmates are burdened by mental illness as well as HIV infection.<sup>122-125</sup> The NCCHC highlights the need for correctional administrators to ensure the availability of mental health services for inmates with HIV.<sup>126</sup>

There are a number of other considerations when initiating antiretroviral therapy in a correctional setting that would not come into play in the same way when treating individuals in larger society, including the need for adequate length of stay to assess initial tolerability and response, availability of therapy at intake, timely renewal of medications, organization of medication dispensation, adequate discharge medications when leaving or transferring from the institution, and linkage to community providers. It is important that inmates with HIV have access to staff trained in HIV care and be provided with additional support mechanisms both while in the correctional setting and after their release.

In summary, despite the significant challenges to providing optimal HIV care in correctional facilities, a large number of HIV-positive individuals pass through the prison system each year, and these institutions provide an important opportunity to detect, educate, and treat a large number of HIV-infected persons both for their benefit and for the benefit of society at large.<sup>106</sup>

## Conclusion

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This review outlines many obstacles present in today's society with respect to HIV therapy. For example, HCV and HIV coinfecting patients are nonresponders unless they undergo treatment for hepatitis C. Once the HCV RNA levels have been lowered, then HAART can be used to increase CD4+ levels and lower HIV levels, emphasizing the importance of addressing both HCV and HIV in coinfecting individuals. Proper diagnosis and antiretroviral treatment in HIV-infected pregnant women are needed to decrease the likelihood of HIV transmission from mother to infant. The goal is to inform the woman that individualized treatment including HAART during pregnancy, antiretroviral prophylaxis of the neonate, and avoiding breastfeeding will dramatically decrease the likelihood of the infant's becoming infected with HIV to <2%. The review also outlined promising anti-HIV drugs currently being tested in clinical trials. These may be used to better treat HIV patients with high viral RNA levels and low CD4+ cell counts. Investigational drugs also hold the promise of fewer side effects compared with currently available treatments.

The epidemic of crystal methamphetamine abuse threatens to propel further increases in HIV transmission, as users of methamphetamine are prone to engage in high-risk behaviors promoting infection with and transmission of HIV. Controlling the HIV/AIDS epidemic also involves controlling the growing methamphetamine epidemic. The last article in the review highlights the elevated prevalence of HIV in inmates in correctional systems in the United States. These structured settings offer the opportunity for HIV testing, treatment, and education, although they also pose numerous challenges to quality care. In general, a critical goal of health-care organizations is to educate the general public about the importance of getting tested, getting HIV+ people into care to maintain their health, and controlling the spread of this disease.

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