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New antiretroviral agents

As the HIV epidemic matures and the prevalence of the infection rises, an increasing number of HIV-infected patients will receive antiretroviral HIV therapy. Unfortunately, many will harbor or develop a virus with antiretroviral drug resistance. HIV-infected men and women cycling in and out of prisons and jails may be particularly vulnerable to the development of drug resistant HIV as they may initiate, interrupt and re-initiate care during and between incarcerations. Infected inmates may also face a number of challenges to adherence with their HIV therapies including mental illness and substance abuse.

Results from a number of important clinical trials of new antiretroviral drugs were presented at CROI 2007 and offer hope for patients infected with multidrug resistant HIV. We report on two new antiretroviral agents that are relatively advanced in their clinical development, are currently available via expanded access programs, and may be of immediate clinical interest. These drugs represent two novel antiretroviral classes and have the potential to positively impact treatment outcomes as well as change the prevailing
LETTER FROM THE EDITOR

Dear Correctional Colleagues,

One of the most exciting but challenging aspects of providing HIV care is the dizzying speed with which new developments in the field are reported and then incorporated into clinical practice. New drugs are developed, studied and fast-tracked for approval; meanwhile, clinical trial results are made public and before you can say 'press release' are influencing treatment decisions in the clinic.

To keep up, clinicians caring for HIV-infected individuals must look to a number of sources of information. One such resource you are holding in your hands (to those of you online, my apologies). In addition, there are an array of conferences showcasing the latest data in advance of publication.

You would not know it from its longwinded and anachronistic name but the Conference on Retroviruses and Opportunistic Infections (CROI) is the top U.S. HIV conference in this country. Held annually, CROI is jam-packed with information on treatment, complications and prevention. It is a tough meeting to cover. There are so many important presentations that it is difficult to distill the most significant into a single summary. But, in this issue we do just that. Our team of correctional experts was in Los Angeles and together have written a concise review of the meeting mindful of the types of information that would interest a readership of correctional health care providers. We supplement our conference coverage with actual clinical case studies that incorporate data presented at CROI. For more information about the conference and the data that were presented there, check out our Resource section for links to the conference and other sites containing conference summaries and analyses.

An old AIDS activist battle cry was, "Knowledge = Power." Many of those activists may be gone but with more to know, their words were never truer. We at IDCR are proud to be able to provide this kind of reviews to our colleagues working along side us in our prisons and jails. We hope you value the newsletter as an objective source of information from clinicians who 'walk the walk' of correctional health care. If you do, please let our sponsors’ representatives know that their support is a worthwhile investment. Of course, also feel free to share your appreciation of IDCR with representatives of those who, as of yet, have not chosen to support our modest publication. It can’t hurt.

Sincerely,

David A. Wohl, MD
Associate Professor of Medicine
AIDS Clinical Research Unit
The University of North Carolina - Chapel Hill

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treatment paradigm of combining two nucleosides with a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor as the cornerstone of highly active antiretroviral therapy (HAART).

Maraviroc

To gain entry into CD4 cells, HIV must interact with not only the CD4 receptor but with other co-receptors as well. Maraviroc (MVC) is an entry inhibitor that is a CCR5 (R5) antagonist with in vitro activity against virus that is tropic for cells that express the R5 receptor but not cells that use CXCR4 (X4) receptors or that use both types of receptors (i.e. dual tropic HIV-1). Interim 24-week analyses of two parallel ongoing phase IIb/III double-blind, placebo-controlled studies of MVC in antiretroviral treatment-experienced, HIV-infected adults, MOTIVATE (Maraviroc Plus Optimized Background Therapy in Viremic ART-Experienced Patients) 1 and 2, were presented 1,2. These studies were identical in design and were conducted in the U.S. and abroad. Eligible participants were triple antiretroviral class-experienced with viremia of > 5000 copies/mL and any R5 tropic virus on baseline tropism screening, and were randomized 1:2:2 to receive placebo, twice daily MVC 300 mg or once daily MVC 300 mg. An optimized background therapy (OBT) was required of the treating physicians to accompany the study treatment. The dose of MVC was reduced to 150 mg if the OBT contained protease inhibitors (except tipranavir) or delavirdine. Participants were further stratified by eligibility for enfuvirtide use or by HIV-1 RNA value above or below 100,000 copies/ml (see Table 1).

At 24 weeks, MVC plus OBT provided superior virologic and immunologic outcomes compared to placebo plus OBT. Overall, similar results were noted for MVC once daily and twice daily dosing regimens. However, a larger proportion of patients who were found on antiretroviral resistance testing to have active drug in OBT achieved HIV-1 RNA below 50 copies/ml in the two MVC BID arms compared to MVC QD or placebo arms in combined analysis (18% vs. 3% respectively in an analysis combining the results of the two trials).

No differences in the reduction in HIV-1 RNA were noted when regimens were stratified by receipt of enfuvirtide or by baseline HIV-1 RNA values. Adverse events were similar in all arms. Specifically, no increased risk of lymphoma or other malignancies was observed in the MVC arms compared to the placebo arm. In the subset of patients that failed treatment, patients receiving MVC were much more likely to have had shifts to X4 or dual tropic virus than those receiving placebo (see Table 1).

MVC is scheduled in April for review by the FDA for accelerated approval. It represents a welcomed addition to our antiretroviral armamentarium but its optimal role in antiretroviral therapy remains to be defined. Chemokine receptor inhibitors are the first antiretroviral drugs that target host proteins rather than viral targets. While the apparent absence of any significant sequela among individuals with congenital deficiencies in chemokine receptors (e.g., CCR5-32 homozygotes) provides some reassurance that the therapeutic use of chemokine receptor inhibitors will be well tolerated, and that the term safety of CCR5 inhibition is yet to be proven. Recent reports that homozygous CCR3 x32 is a strong host genetic risk factor for symptomatic laboratory-confirmed West Nile Virus infection supports safety concerns.3 Similarly, initial concerns regarding the emergence of X4 virus during treatment with an R5 antagonist remain. Additionally, the clinical use of MVC, in particular in treatment-experienced patients, appears to require pretreatment screening with a tropism assay because the drug will not be effective in those infected with an X4 or dual tropic virus. The expense of such assays may strain already stretched financial resources. Finally, resistance to R5 antagonists is incompletely understood.

Raltegravir

Raltegravir, previously known as MK-0518, is an integrase inhibitor that has previously been shown to confer significant virologic benefit to HIV-infected patients, as well as heavily treatment-experienced patients with HIV resistant to agents in each of the three original antiretroviral drug classes. The integrase enzyme is responsible for incorporating viral DNA into the host genome where, once integrated, it encodes for the production of viral proteins. As such it has been an attractive but elusive antiretroviral target. Sixteen-week data from two identical, parallel, phase III double-blind, placebo-controlled studies, designated BENCHMRK-1 and -2, were presented at CROI 2007.4,5 Eligible participants were those failing antiretroviral therapy with triple antiretroviral class resistance and were randomized 2:1 to raltegravir 400 mg twice daily or placebo. OBT was selected by the treating physicians. Selected drugs that were investigational at the time the study was conducted (e.g. darunavir) were permitted to be part of OBT (see Table 2).

Raltegravir demonstrated superior virologic and immunologic efficacy at 16 weeks over placebo. Similar to raltegravir, adherence to the raltegravir arm was maintained regardless of baseline CD4 count, HIV-1 RNA values as well as predicated resistance to agents in the OBT by resistance testing. Adverse events were similar between groups (see Table 2).

Raltegravir has shown impressive efficacy in both antiretroviral naive and treatment-experienced patients. While its approval by the FDA is eagerly anticipated, its optimal role in the sequence of antiretroviral therapy remains to be well defined.

Current antiretrovirals

Once daily versus twice a day lopinavir/ritonavir and the role of directly observed therapy (DOT)

Once daily antiretroviral regimens have become de rigueur for reasons that are obvious to anyone who must take medications chronically. It is hoped that simplification of HIV therapy will improve adherence; however few studies have examined the relative efficacy of once daily and twice daily administration of the same antiretroviral agents. Once daily HIV therapy regimens also make direct observation of dosing more feasible. Certainly, no one has more experience administering antiretrovirals via directly observed therapy (DOT) than correctional facilities. Yet, again, there are limited data available regarding the role for DOT in HIV care.

AIDS Clinical Trials Group (ACTG) study A5073 aimed to compare the safety and virologic efficacy of lopinavir/ritonavir dosed at 800/200 mg once a day (n=159) versus 400/100 mg twice a day (n=161) in treatment naive patients.6 The drug was combined with emtricitabine (FTC) plus either tenofovir (used in ~ 40% of subjects) or stavudine-XR. In addition, a third arm of the study administered the once daily regimen under DOT for 24 weeks (n=82). In this study DOT consisted of the observation of ingestion of the lopinavir/ritonavir five days of the week by a health professional (e.g. doctor, nurse, pharmacist).

By 48 weeks after study entry, there was no overall difference in time to virologic failure between the self-administered once daily versus twice daily study arms with about 30% of patients in each experiencing failure by this time point. However, when stratifying response by baseline viral load, those with a HIV-1 RNA level > 100,000 copies/mL, virologic failure was more common with self-administered once daily lopinavir/ritonavir compared to self-administered twice a day lopinavir/ritonavir.

Seventy-four percent of those assigned to DOT of once daily lopinavir/ritonavir complet- ed the 24 week DOT program. There was 86% adherence with the DOT visits among these participants. There was a trend favoring DOT at the end of the 24 weeks in comparing the self administered once daily lopinavir/ritonavir arm to the DOT once daily lopinavir/ritonavir arm. This did not achieve statistical significance. By week 48 (24 weeks after DOT ceased) there was no difference in the probability of virologic failure between the DOT and self-administered once daily therapy arms. Over the 48 weeks of study, there was a trend toward fewer new AIDS diagnoses and deaths among those getting their treatment via DOT, but there were too few events to make firm conclusions regarding this finding.

This trial found that once daily lopinavir/ritonavir can be safely administered to patients with a pre-therapy viral load of less than 100,000 copies/mL. The unexpected finding of increased risk of virologic failure among those with higher viral loads assigned to once a day lopinavir/ritonavir is concerning and requires further study. Modified DOT (i.e. observation of some but not all doses) was not found to provide significant advantages over self-administered therapy in this community-based study, although there were intriguing trends in better virologic responses and clinical outcomes among those getting their treatment under DOT.

These trends will likely spur increased efforts to study community-based DOT for HIV treatment.
COVERAGE OF THE 14TH CONFERENCE...
(continued from page 3)

Early failure of tenofovir, lamivudine (3TC) and nevirapine

HIV health care providers frequently must be creative in crafting antiretroviral regimens. While published guidelines assist clinicians in choosing appropriate therapy for patients starting HIV treatment, patients may have adverse reactions to recommended agents or other contraindications that require consideration of alternative combinations.

Investigators in France conducted a trial comparing tenofovir, lamivudine (3TC) and nevirapine versus zidovudine (ZDV), 3TC and nevirapine among treatment naïve patients.7 The study was designed to enroll 250 people, but was halted after 71 were randomized as there was an excess of virologic failures in the tenofovir, 3TC and nevirapine arm. Nine of 36 participants assigned to that arm, compared to only one of 35 receiving ZDV, 3TC and nevirapine, failed. Only one of the ten patients who failed therapy had baseline resistance. Nevirapine levels were measured and found to be adequate in all failure patients. Mutations conferring resistance to nevirapine were the most commonly detected mutations observed followed by the K65R mutation, associated with tenofovir resistance and the M184V 3TC mutation.

This study serves as a cautionary tale regarding the use of untested antiretroviral regimens, particularly in treatment naïve patients who are able to take more standard combinations. The reason for the early failure of tenofovir, 3TC and nevirapine remains unclear and is unexpected given the proven potency of tenofovir, 3TC and efavirenz. Further examination of these data and this regimen are needed. Until then, avoiding this particular regimen seems prudent.

Safely dosing H2 blockers with atazanavir/ritonavir

Atazanavir is a protease inhibitor that requires gastric acid to be adequately absorbed. Therefore, co-administration of proton pump inhibitors and atazanavir is contraindicated. Previous data demonstrate that H2 blockers, specifically famotidine, can be used during atazanavir therapy. According to the package insert, in treatment-naïve patients atazanavir at a dose of 300 mg with ritonavir 100 mg once daily can be taken with food, without the need for separation of the dose from the H2-receptor antagonist. In treatment-experienced patients it is recommended that atazanavir/ritonavir 300/100 mg once daily be taken with food at least 2 hours before and at least 10 hours after the H2-receptor antagonist.

In a study of HIV-uninfected volunteers, atazanavir/ritonavir in standard doses along with tenofovir was administered with famotidine either simultaneously or temporally separated (10 h before and 4 h after).3 Tenofovir is commonly prescribed with ritonavir boosted atazanavir even though this nucleotide analogue reduces atazanavir levels - an effect that is largely overcome with ritonavir boosting. In this study, atazanavir levels were measured and found to be adequate in all failure patients. Mutations conferring resistance to nevirapine were the most commonly detected mutations observed followed by the K65R, and the M184V mutations.

Continued on page 5
were adequate when famotidine 20 mg BID was given with or without ATV+RTV dose. Likewise, atazanavir levels were adequate when famotidine at a dose of 40 mg daily was given separate from the protease inhibitors. However, atazanavir levels were significantly reduced when famotidine at 40 mg BID was given, even when administered separately from the protease inhibitors. Therefore, twice daily dosing of this H2 blocker at the higher dose should not be administered on atazanavir and should be used cautiously with this boosted protease inhibitor even at lower doses.

Metabolic complications

There were several important presentations regarding metabolic complications of HIV and its therapies. Most notable were the metabolic results of ACTG trial A5142, a large study comparing efavirenz plus two nucleoside analogues, b) lopinavir/ritonavir plus two nucleoside analogues and c) efavirenz and lopinavir/ritonavir without nucleosides. The virologic and immunologic results of the trial were presented at the International AIDS Conference last summer (see IDCR September 2006). At CROI 2007, the relative effects of each of the three study arms on limb fat and lipids were presented and were surprising to many. Foremost, over 96 weeks, those patients assigned to efavirenz plus two nucleoside experience an initial increase in total limb fat of approximately 8% by 48 weeks but this declined precipitously to just a 1.4% gain over baseline at 96 weeks. This is in stark contrast to those randomized to lopinavir/ritonavir who experienced an increase in limb fat of almost 10% by week 48, which persisted at 96 weeks. The nucleoside-sparing regimen produced progressive limb fat gains during the study reaching 18% at week 96.

Importantly, the nucleoside agents used in the two arms containing class of antiretrovirals was balanced between the arms with about 30% of patients randomized to efavirenz plus lopinavir/ritonavir and the remaining choosing stavudine-XR. Even among those taking tenofovir, a drug not thought to contribute to fat wasting, there was more lipolathrophy (>20% limb fat loss from baseline) among those assigned to take efavirenz (12%) than lopinavir/ritonavir (6%). The rise and fall of limb fat seen in the efavirenz plus two nucleoside group was similar to the initial increase seen in the ZDV+3TC+efavirenz arm of another study presented at CROI 2007 - a trial of this combination versus lopinavir/ritonavir monotherapy after withdrawal of ZDV+3TC once viral suppression was achieved. In that study, as in A5142, the ZDV+3TC+efavirenz arm experienced an early increase in limb fat followed by a progressive decline over time. In this case, there was a net loss of fat compared to baseline in this group.

Defying predictions, increases in total cholesterol during A5142 were no different in the lopinavir/ritonavir and the efavirenz arms, rising approximately 30 mg/dL in each group. In contrast, the nucleoside sparing arm had a statistically significant greater increase of 57 mg/dL at week 96. Triglycerides rose higher after the initiation of therapy in the lopinavir/ritonavir plus two nucleoside arm (46 mg/dL) compared to the efavirenz arm (19 mg/dL). Again, the efavirenz plus lopinavir/ritonavir group saw the greatest increase (62 mg/dL).

This important trial reveals that combinations of antiretrovirals can act together to produce peripheral fat wasting. In addition, the perception that metabolic toxicities belong solely within the province of protease inhibitors is demonstrated to be incorrect. Indeed, in this trial of hepatic fat, differences seen between the study arms in changes of trunk fat - an adverse effect that is typically ascribed to protease inhibitors.

HCV therapy

Lessons from clinical trials of HIV/HCV co-infected patients

In correctional settings, we have traditionally thought of HCV as being primarily a blood-borne infection. Data from CROI, however, challenge this notion and may have important implications for more routine testing for HIV in populations not previously thought to be at highest risk. In one study of 7223 men who have sex with men (MSM) in the U.K., increased risk for HCV infection included unprotected sex, multiple sexual partners and the use of injected substances, such as gonorrhea and syphilis. HCV transmission among this cohort appeared to increase among HIV-infected individuals, perhaps due to the higher levels of HIV viremia and impaired immunological responses. Correctional inmates before, during or after release engage in many of the risks identified in this study and merit increased screening and risk behavior counseling.

In a plenary session by David Thomas, MD, from Johns Hopkins University, the pros and cons of liver biopsy in HIV/HCV co-infected patients were thoroughly discussed. Unlike the case for HIV where surrogate markers such as viral load and CD4 cell count are the best predictors of disease progression, the extent of hepatic fibrosis is the best prognostic factor for progression of liver disease in HCV-infected patients. Liver biopsy has been the primary tool for assessing hepatic fibrosis, yet is subject to several important limitations including: 1) its invasive nature with potential for significant complications; 2) the possibility of sampling error due to a relatively small biopsy size (150,000th of the liver); 3) the fragmentation of examined tissues and/or the inherent heterogeneity of hepatic fibrosis; 4) low acceptance by many patients; 4) cost considerations; and 5) lack of availability. While liver biopsy has the advantage of providing additional information on other relevant histologic findings, such as necroinflammation and steatosis, some argue that its use in patients with HIV co-infection has less merit given the accelerated rate of fibrosis and its low rate of liver disease-related morbidity and mortality. Nonetheless, development of noninvasive tools for staging hepatic fibrosis has been urgently needed.

Assessing liver fibrosis using non-invasive procedures has been divided into two distinct categories: 1) imaging techniques, such as elastometry (e.g., FibroScan), and serum biochemical marker tests (e.g., Fibrotest, APRI, SHASTA, FIB-4, Forns, serum hyaluronic acid). These tools are generally accurate in discriminating between a lack of fibrosis and advanced fibrosis, but they are less precise at distinguishing between intermediate fibrosis stages. The predictive value of these tests is particularly good for advanced hepatic fibrosis and cirrhosis. Liver fibrosis staging using elastometry seems to be particularly reliable. Assessed within 10 minutes, it is relatively low cost, can be repeated frequently without risk to the patient. It also has a positive predictive value greater than 90% for advanced fibrosis.

Despite these advances, waiting until a patient has advanced fibrosis for treatment is less than optimal in HCV/HIV co-infected patients. Instead, Thomas recommends that when chronic HCV infection is clear by the presence of HIV viremia alone, in the absence of other clinical indicators that would preclude treatment (e.g., Childs Pugh B or C cirrhosis, suggestion of autoimmune hepatitis, advanced and uncontrolled HIV infection or presence of significant side effect profile such as drug interactions) is sufficient to warrant treatment. The relatively high response to pegylated interferon plus weight-based ribavirin, the faster progression of HCV-related liver disease in the HCV/HIV co-infected and the opportunity for assessing the HCV response at earlier time points to identify who will and will not respond to therapy all favor initiating anti-HCV therapy without the need for a liver biopsy in most cases.

In the following plenary session, Raymond Chung, MD, from Harvard University, reviewed that current HCV treatment in HIV co-infected patients. In addition to reviewing the three large prospective trials treating HCV among HIV/HCV co-infected patients, where sub-therapeutic ribavirin dosing was used (APRICOT, ACTG 5071, and RIBA21), updated data from the PRESCO trial using weight-based ribavirin doses of 1000 to 1200 mg per day presented at CROI 2007 were also reviewed.

The PRESCO trial demonstrated increased sustained virologic response rates (SVR, undetectable HCV viral load six months after treatment completion) (49.6%) compared to other studies. The PRESCO trial also confirmed low rates of premature discontinuation (8.2%) - similar to trials of weight-based ribavirin and pegylated interferon in HCV mono-infected patients. The PRESCO trial answered additional questions. First, the SVR among genotype 1 was 35.6% and 72.4% in genotypes 2 and 3. The study was also designed to address the issue of treatment selection (short versus extended treatment). Patients with genotypes 2 or 3 were randomized to receive 24 weeks (short) versus 48 weeks (extended) of treatment and patients with genotypes 1 or 4 received 48 weeks (short) versus 72 weeks (extended) of treatment. SVR rates were higher among patients assigned to received extended versus standard durations of therapy. For genotypes 2 or 3, SVR was 52% with 48 weeks versus 67% with 24 weeks. For genotypes 1 or 4, 53% had SVR with 72 weeks versus 31% with 48 weeks. Extended treatment duration did not, however, decrease the likelihood of relapse in patients with genotype 1 (33%) or genotypes 2 or 3 (17%), but did...
reduce relapse rates from 21% to 0% in patients with genotype 4. Extended treatment was associated with increased toxicity and drop-out.\textsuperscript{23}

Further data from CROI suggested that improved outcomes can be achieved if HIV infection is optimally managed (e.g., excluding individuals receiving zidovudine or didanosine or patients with low CD4 cell counts and uncontrolled HIV RNA levels).\textsuperscript{24}

In addition to this data on extended duration of treatment for HCV/HIV co-infection, a number of additional clinical pearls were gleaned from other presentations that should assist with optimizing HCV treatment. A sub-study of the RIBAVIC trial demonstrated reduced SVR among patients concomitantly receiving abacavir and ribavirin, suggesting a potential drug interaction between the two guanosine analogues.\textsuperscript{25} Though not clinically available to clinicians now, the use of transcription-mediated amplification (TMA), a very sensitive tool that has a lower limit of HCV RNA detection of 5 IU/mL, for detecting serum HCV RNA at the end of a course of HCV treatment has positive and negative predictive values exceeding 80% for relapse.\textsuperscript{26} Tools similar to this one, rather than extended treatment courses, will help individualize treatment duration.

More data supportive for dispensing with transaminase elevations as a guide for treatment evaluation were presented. Matched HCV/HIV co-infected patients with persistently normal versus elevated transaminase levels were compared. Among patients with advanced liver fibrosis (Metavir scores of F3 or F4) nearly 15% of co-infected patients had persistently normal transaminases; this finding was more frequent among women and those with genotype.\textsuperscript{4} Thus, co-infected patients with normal liver enzyme levels should not be excluded from anti-HCV therapy, as liver disease progression may occur in a significant proportion of these patients in a silent manner.

**Who gets treated and who does not**

HCV therapy is becoming increasingly available in correctional facilities. A study from Johns Hopkins University looked at eligibility of HIV/HCV co-infected and HCV mono-infected injection drug users (IDUs) for HCV therapy.\textsuperscript{27} Patients studied included 180 HCV mono-infected individuals participating in a community-based Hopkins-run addiction treatment program and 183 HIV/HCV co-infected patients of the hospital’s HCV clinic. All were offered free HCV therapy (see Table 3).

Eleven percent of the co-infected patients had a negative HCV RNA as did 22% of the mono-infected. More of the HIV-infected patients (40%) were deemed ineligible for HCV treatment due to having a life expectancy less than two years, active depression or suicidal ideation, allergic reaction to interferon or ribavirin, severe hepatic abnormalities, renal insufficiency, pregnancy, or unwillingness to use birth control than the HIV-uninfected (26%). However, a similar proportion of patients (66-67%) did not start HCV therapy (see Table 3).

Therefore, HIV co-infected patients were less likely to be eligible for HCV therapy - largely as a consequence of poor life expectancy and anemia - but the eligible mono-infected patients were less likely to actually start HCV treatment. In both groups, the vast majority of HCV eligible patients never initiated HCV treatment. The investigators also reported that most patients (79% in the mono-infected group and 67% among the co-infected) had no or minimal fibrosis seen on liver biopsy - perhaps suggesting that disease staging had an influence on the uptake of HCV treatment (see Table 3).

**Conclusions**

As usual, there were a number of presentations at CROI of great interest to the HIV clinician. The results of phase III trials of two new HIV therapies belonging to novel classes of antiretrovirals produced palpable excitement at the conference as clinicians recognized that a critical mass of new therapies for the patient with multi-drug resistant virus was at hand. However, for correctional clinicians unresolved issues related to the need to assess viral tropism prior to therapy initiation may temper enthusiasm for MVC. These assays are likely to carry a significant price tag and it may take weeks for a result to return. During that time as many as 8% of patients may experience a shift in viral tropism from R5 to dual/mixed virus. It is only a matter of time (measured in months) before the first correctional physicians will be prescribing these new agents and these issues will need to be addressed by the manufacturer of this important new agent.

Other clinical trial data refined our understanding of current management of HIV and HCV infections - helping us to better tailor therapy to the individual patient. Thus, while no presentation focused specifically on the HIV epidemic in corrections, there was plenty here for correctional clinicians to learn and use.

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**Table 3. Low Rates of HCV Therapy among Treatment-eligible injection Drug Users with and without HIV Co-infection**

<table>
<thead>
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<td>Tx ineligible</td>
<td>N=58 (40%)</td>
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<td>HCV</td>
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<td>Tx ineligible</td>
<td>N=34 (26%)</td>
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<td>Tx Eligible</td>
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<tr>
<td>No Start Tx</td>
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The right test? Program and abstracts of the 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, California. Abstract 105aLB.


7. Fisher M, Richardson D, Sabin C. Acute hepatitis C in MSM is not confined to those infected with HIV, and their number continues to increase. Program and abstracts of the 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, California. Abstract 130.


11. Fisher M, Richardson D, Sabin C. Acute hepatitis C in MSM is not confined to those infected with HIV, and their number continues to increase. Program and abstracts of the 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, California. Abstract 130.


Case 1: D.T. is a 43-year-old male inmate diagnosed with HIV infection in 1994 who has a history of AIDs (by CD4 cell count), distal peripheral neuropathy, hypertiglyceridemia and major depression. He presents for a routine infectious diseases clinic appointment two months after being incarcerated with a complaint of extreme fatigue. He recently had routine laboratories performed and these were normal except for a platelet count of 118 thousand. His hepatitis B surface antibody is positive but his hepatitis C antibody is negative. He is serving a four-year prison sentence.

He has a history of less than perfect adherence in years past, partially due to depression and lack of ability to tolerate medications. His nadir (lowest ever) CD4 cell count was 60/mm3 in August of 2002. At his last visit six weeks prior his HIV RNA PCR (viral load) was 17,000 copies/mL and the CD4 cell count was 726/mm3 (25%). Four months prior outside records indicate his viral load was 1,200 copies/mL.

His current medications included lopinavir/ritonavir, saquinavir, lamivudine, gemfribrozil, fish oil and fluoxetine.

His past antiretroviral history includes treatment with each of the following: zidovudine, zalcitabine, didanosine, lamivudine, tenofovir, stavudine, abacavir, efavirenz, indinavir and amprenavir.

A genotype was obtained on his current medication and revealed the following mutations:

- NRTI: 67N, 184V, (other mutations detected: K219S)
- NNRTI: None
- PI: mutations: 10I, 24I, 33F, 46L, 63P, 71V, 82A, 84V

Prior genotypes outside of prison reveal:

- NRTI: 41L, 67N, 210W, 215Y, 184V
- NNRTI: 103N, 181C
- PI: 10I, 24I, 33F, 46L, 54V, 71V, 82A, 84V

Question: Taking into consideration the genotype results, medication history and past issues with adherence, what would be your next antiretroviral regimen?

Discussion: This patient has an extensive past antiretroviral experience. In addition, he has had mental health and substance abuse problems that have negatively impacted his ability to adhere to his HIV therapies. Since his incarceration he has been seen by mental health and is responding well to his antidepressant. After a 40-minute discussion regarding his commitment to HIV therapy during which he pledged to be adherent to HIV and mental health care it was decided to craft a new regimen. This was comprised of darunavir and ritonavir, and fixed dose emtricitabine/tenofovir and zidovudine were selected.

Darunavir was selected despite the presence of a few mutations associated with reduced susceptibility to this protease inhibitor including the 33F and 84V mutations. Data from the darunavir package insert suggest that as many as 40% of treatment experienced patients with two major mutations associated with reduced darunavir susceptibility can achieve reductions in viral load below 50 copies/mL at 24 weeks. The patient harbors virus that is resistant to all the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and even though these mutations are not evident on his latest genotype resistance test, they persist and will reemerge if NNRTIs are used. Therefore, no currently approved NNRTIs will work against his virus. He also has developed resistance to drugs in the nucleoside reverse transcriptase inhibitor (NRTI) class. It is possible that his virus does retain some susceptibility to tenofovir, so this drug is being added to his regimen. In addition, there are some data to suggest that maintenance of drug resistance.

The clinician and patient also discussed the addition of enfuvirtide, an injected fusion inhibitor. This agent would be expected to provide additional antiretroviral activity and work well with his new combination of medications. However, the patient was opposed to twice-daily dosing and preferred to reserve this drug in case of suboptimal response to his new regimen or for a subsequent regimen.

Prior to receipt of his medications, the patient was counseled regarding potential toxicities of the drugs. He was encouraged to give the medications a chance and told that his body would most likely adjust should he have early problems such as gastrointestinal discomfort.

After approximately 3 weeks, the patient underwent laboratory testing. The viral had decreased by 2 logs to 936 copies/mL and the patient was tolerating the medications. He reported 100% adherence with the new regimen and this was supported by nursing records as his medications were administered under direct observation. He reports not fatigue, despite addition of zidovudine. Routine laboratory results were remarkable. Six weeks after initiating his regimen the viral load was less than 50 copies/mL and the CD4 cell count was 810/mm3. A fasting lipid panel revealed a triglyceride level of 165 mg/dL, LDL cholesterol of 102 mg/dL, and cholesterol of 44 mg/dL on gemfibrozil and fish oil capsules. A return clinic visit at three months after therapy initiation is scheduled to document continued viral suppression, to assess for adverse effects and adherence and provide continued adherence counseling and encouragement.

Case 2: B.D. is a 45-year-old woman with AIDS (CD4 nadir = 21/mm3), genital herpes simplex and history of venous stasis disease. She was diagnosed with HIV in 1994 and has been treated with a variety of antiretrovirals as listed below. Early in her treatment she suffered from intolerance to most of her HIV medications and often was non-adherent. However, over the years she has been able to tolerate her HIV therapy and has become dependent on the antiretroviral regimens. Her current medications (since about 12/03) are lopinavir/ritonavir, lamivudine/zidovudine and tenofovir.

Three months ago her CD4 cell count was 184/mm3 and her viral load was 38,000 copies/mL. A genotype resistance test was performed and revealed an extensive number of resistance mutations in each of the three classes of antiretroviral drugs (see 101). A repeat viral load is drawn and reveals a viral load of 29,000 copies/mL but no significant change in her CD4 cell count.

Her past antiretroviral history includes treatment with each of the following agents: stavudine, didanosine, efavirenz, indinavir, nevirapine, saquinavir and amprenavir.

Question: What would be her best next step in treating her HIV infection?

Discussion: First, the patient should be placed on appropriate prophylaxis for pneumocystis jiroveci pneumonia (formerly, pneumocystis carinii) then attention can turn to her antiretroviral options. Unfortunately, she now has multi-drug resistant HIV and few of the currently available antiretrovirals would be predicted to suppress the replication of her virus. The many resistance mutations her HIV has developed are likely a consequence of her inability to adhere to her medications, especially when she was prescribed early in her HIV care. Unfortunately, she now has multi-drug resistant HIV and few of the currently available antiretrovirals would be predicted to suppress the replication of her virus. The many resistance mutations her HIV has developed are likely a consequence of her inability to adhere to her medications, especially when she was prescribed early in her HIV care. Unfortunately, she now has multi-drug resistant HIV and few of the currently available antiretrovirals would be predicted to suppress the replication of her virus. The many resistance mutations her HIV has developed are likely a consequence of her inability to adhere to her medications, especially when she was prescribed early in her HIV care. Unfortunately, she now has multi-drug resistant HIV and few of the currently available antiretrovirals would be predicted to suppress the replication of her virus. The many resistance mutations her HIV has developed are likely a consequence of her inability to adhere to her medications, especially when she was prescribed early in her HIV care.
three such mutations, some activity of the protease inhibitor agents can be expected. Additionally, she is naïve to enfuvirtide and she is willing to receive twice daily subcutaneous injections, if necessary.

While we have the option of enfuvirtide we do not have a critical mass of agents to add to this drug to provide a regimen that could be expected to reduce her viral load to undetectable levels and keep it there. Either darunavir or tipranavir can be useful but the resistance present may truncate their antiretroviral effect. The addition of at least one other new agent anticipated to be active against this virus would increase confidence in her ‘salvage’ regimen.

Based on the data presented at CROI 2007, we could expect the integrase inhibitor raltegravir, to be effective against this patient’s virus (see main article). Participants in the Benchmrk studies were, like our patient, resistant to or experienced with drugs in all three original classes of antiretroviral. In these studies those patients who received raltegravir and either darunavir or enfuvirtide (and were naïve to these two agents) had the best outcomes. Among those who took all three agents, 98% achieved viral loads less than 50 copies/mL at 16 weeks.

TMC-125 would be another agent that may provide some antiretroviral activity. The activity of TMC-125 is diminished as NNRTI mutations accumulate, therefore, if she harbors additional mutations - acquired during her treatment with efavirenz but not sufficiently present now to be detected - this drug may be less useful.

Therefore, it is decided to maintain her current therapy with the plan to start raltegravir, darunavir/ritonavir, enfuvirtide and tenofovir/emtricitabine once the integrase inhibitor becomes available, anticipated to be within the next six months. The risks of maintaining the current regimen including the cultivation of additional resistance mutations versus discontinuing her regimen and experiencing an even greater rise in viremia and attendant reduction in CD4 cell count are explained to the patient. She voices understanding of the considerations and opts to continue on her present therapy until the raltegravir becomes available and the new combination can be started.

**HIV Resistance Testing 101: Genotype**

[Table of mutations and predicted responses to therapy]

Go to www.AAHIVM.org to learn about membership, continuing education and the new partnership with IDCR. Visit IDCR online at www.IDCRonline.org.
SAVE THE DATES

Updates in Correctional Health Care
Orlando, FL
May 5-8, 2007
Visit:www.ncchc.org/education/index.html

The 34th Annual International Conference on Global Health
May 29 - June 1, 2007
Washington, D.C.
Visit:www.globalhealth.org/2007_conference/

The American Conference for the Treatment of HIV (ACTHIV)
May 31 - June 3, 2007
Dallas, TX
Visit:www.acthiv.org

Medication Assisted Therapy (MAT): Interventions for Drug Users in Correctional Settings
American Correctional Health Services Association (ACHSA) 2007
Multidisciplinary Professional Development Conference
June 4, 2007
Reno, NV
Visit:http://www.achsa.org/display-common.cfm?f=1&subarticlenbr=49

Dual Focus on Correctional Health: Legal and Ethical Considerations and Emerging Issues
American Correctional Health Services Association (ACHSA) 2007
Multidisciplinary Professional Development Conference
June 5-7, 2007
Reno, NV
Visit:http://www.achsa.org/display-common.cfm?an=4

Correctional Mental Health Seminar
Las Vegas, NV
July 15-16, 2007
Visit:www.ncchc.org/education/MH200/7lavegas.html

IAS 2007: 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention
Sydney, Australia
July 22-27, 2007

National Conference on Correctional Health Care
Nashville, TN
October 13-17

NEWS AND LITERATURE REVIEWS

Antibiotic Resistance Prompts Changes in CDC’s Treatment Guidelines for Gonorrhea

In the April 13th issue of MMWR, the CDC released an updated recommendation of the Sexually Transmitted Diseases Treatment Guidelines, 2006, which no longer recommends treating gonorrhea with fluoroquinolones; antibiotics such as Cipro, Floxin, and Levaquin. Instead of fluoroquinolones, the CDC recommends the cephalosporin class of antibiotics. The CDC has recommended fluoroquinolones as a gonorrhea treatment option since 1993. At first the use of fluoroquinolones was strongly supported but fluoroquinolone-resistant gonorrhea has increased in recent years -- first in Hawaii, then California, and then nationwide among men who have sex with men. As a result, the CDC recommended in 2000 and 2002 that fluoroquinolones not be used to treat gonorrhea infections acquired only in Hawaii and California. In 2004, they recommend that fluoroquinolones no longer be used to treat gonorrhea in men who have sex with men across the U.S. The CDC recommends the use of cephalosporins for treatment of all gonorrhea cases. The CDC based its recommendations on preliminary 2006 data showing that fluoroquinolone-resistant gonorrhea is present nationwide and is continuing to rise among heterosexual men and among men who have sex with men. For more information on the updated treatment recommendations including drug regimens visit: http://www.cdc.gov/STD/treatment/2006/updated-regimens.htm


Limited Spending: An Analysis of Correctional Expenditures on Antiretrovirals for HIV-Infected Prisoners

A substantial proportion of persons with HIV infection are incarcerated. As such, jails and prisons are important venues for the provision of HIV therapy. In an effort to determine whether HIV therapy is being adequately provided to inmates, reseach from Brown Medical School performed an analysis comparing national correctional system antiretroviral expenditures to the projected cost of such treatment based on the number of inmates who are HIV-infected. By utilizing known HIV prevalence estimates from the U.S. Bureau of Justice Statistics (BJS), average HIV treatment costs, and national data on pharmaceutical sales to correctional institutions, the authors were able present real correctional expenditures as a percentage of estimated total expenditures to determine the unmet need within the incarcerated population.

The results, published in Public Health Reports, indicate that there is a substantial unmet need for antiretrovirals in correctional health care, as total antiretroviral sales represented only 29% of the funds estimated to be required to treat all inmates eligible for such treatment. By end of 2003, there were just over 23,600 state and federal prisoners with known HIV infection - 1.9% of the incarcerated population. Based on Centers for Disease Control and Prevention (CDC) data on antiretroviral therapy usage among HIV-infected patients, 86% of inmates should be receiving such therapy. Multiplying the number of inmates expected to be on antiretrovirals with the estimated cost of HIV therapy, the authors arrived at a total anticipated correctional antiretroviral expenditure of over $454 million. However, prisons only spent $52.5 million on antiretroviral medications.

In assessing the many limitations of the study, the investigators note their reliance on BJS HIV prevalence data, which is drawn from only 19 prisons that routinely test for HIV entry upon entry into the facility and reports only those inmates with known HIV infection. Additionally, differing protocols regarding initiation of HIV therapy and the use of drugs other than antiretrovirals may have contributed to an inaccurate estimate of the percentage of positive HIV individuals eligible for HIV therapy. Despite the many barriers to care, the authors underscore the need for treatment of HIV-infected prisoners, emphasizing the reduced costs associated with HIV-related complications and linkage to HIV care in the community.


Substance Use and Sexual Behavior During Incarceration Among 18- to 29-Year-Old Men: Prevalence and Correlates

In this study, a supplement to a larger multi-site intervention trial, investigators conducted an audio-computer assisted self-interviewing (ACASI) survey of 197 men with a history of incarceration, ages 18-29 years, in order to assess substance abuse and sexual behavior during incarceration. The findings support the need to ask about substance use or have sex during incarceration if they reported having a male partner while incarcerated. In a supplemental separate analysis, the authors noted that men were more likely to use illegal substances during incarceration if they reported hard drug use prior to incarceration. Limitations of the study include a reliance on self-reported behavior from a small convenience sample of men and recall bias. Nonetheless, the authors assert that these findings emphasize the need for future longitudinal research to explore the extent to which men's experiences pre-to-post incarceration are directly linked, not only to examine the ways that pre-incarceration experience influences behavior during incarceration, but also to study the ways that incarceration experiences affect behavior in the community following release from a correctional facility. Such research, the authors suggest, might inform the development of novel or improved risk reduction interventions.

Substance Use and Sexual Behavior During Incarceration Among 18- to 29-Year-Old Men: Prevalence and Correlates. Seal, DW et al. AIDS Behavior. 2007 March 8

Compiled by Ross Boyce MS1 And Elizabeth Closson
SELF-ASSESSMENT TEST FOR CONTINUING MEDICAL EDUCATION CREDIT

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for continuing Medical Education through the joint sponsorship of Medical Education Collaborative, Inc. (MEC) and IDCR. MEC is accredited by the ACCME to provide continuing medical education for physicians.

Medical Education Collaborative designates this educational activity for a maximum of 1.25 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity. Statements of credit will be mailed within 6 to 8 weeks following the program.

Objectives:
- The learner will become familiar with the new research and clinical trials presented at CROI pertaining to Maraviroc, Reltegravir, and current antiretrovirals.
- The learner will become familiar with the clinical trials and research of HIV/HCV infected patients presented at CROI.
- The learner will be able to analyze a genotype chart for HIV resistance testing.

1. True or False? The clinical use of Maraviroc (MVC) with treatment-naïve patients appears to require pretreatment screening with a tropism assay because the drug will not be effective in those infected with a x4 or dual tropic virus.

TRUE or FALSE?

2. According to the AIDS Clinical Trials Group (ACTG) study A5073, the unexpected finding of increased risk of virologic failure among those with higher viral loads assigned to once a day _________ is concerning and requires further study.

A. Lamivudine (3TC)  
B. Lopinavir/ritonavir  
C. Tenofovir  
D. Atazanavir/ritonavir

3. The following is commonly prescribed with ritonavir boosted atazanavir even though this nucleotide analogue reduces atazanavir levels.

A. Tenofovir  
B. Efavirenz  
C. Raltegravir  
D. None of the above

4. In a study from Johns Hopkins on the eligibility of HIV/HCV co-infected and HCV mono-infected injection drug users (IDUs) for HCV therapy, HIV co-infected patients were less likely to be eligible for HCV therapy.

TRUE or FALSE?

In order to receive credit, participants must score at least a 70% on the post test and submit it along with the credit application and evaluation form to the address/fax number indicated. Statements of credit will be mailed within 6-8 weeks following the program.

Instructions:
- Applications for credit will be accepted until April 31, 2008.
- Late applications will not be accepted.
- Please anticipate 6-8 weeks to receive your certificate.

Please print clearly as illegible applications will result in a delay.

Name: _________________________________________________  Profession: _____________________________________
License #: _________________________________________  State of License: __________________________________________
Address: ____________________________________________________________________________________________
City: ________________________ State: ________ Zip: ________________________ Telephone: ___________________

Please check which credit you are requesting ___ ACCME  or  ___ Non Physicians

I certify that I participated in IDCR monograph - April 2007 Issue

Please fill in the number of actual hours that you attended this activity.

Date of participation: ________________________
Number of Hours (max. 1): ________________________
Signature: _______________________________________

Please Submit Completed Application to:

Medical Education Collaborative
651 Corporate Circle, Suite 104, Golden CO 80401
Phone: 303-420-3252 FAX: 303-420-3259
For questions regarding the accreditation of this activity, please call 303-420-3252
## Course Evaluation

### I. Please evaluate this educational activity by checking the appropriate box:

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<th>Activity Evaluation</th>
<th>Excellent</th>
<th>Very Good</th>
<th>Good</th>
<th>Fair</th>
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<td>How well did this activity avoid commercial bias and present content that was fair and balanced?</td>
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<td>What is the likelihood you will change the way you practice based on what you learned in this activity?</td>
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### II. Course Objectives

Were the following overall course objectives met? At the conclusion of this presentation, are you able to:

- The learner will become familiar with the new research and clinical trials presented at CROI pertaining to Maraviroc, Raltegravir, and current antiretrovirals.  
  - YES  
  - NO  
  - SOMEWHAT

- The learner will become familiar with the clinical trials and research of HIV/HCV infected patients presented at CROI.  
  - YES  
  - NO  
  - SOMEWHAT

- The learner will be able to analyze a genotype chart for HIV resistance testing.  
  - YES  
  - NO  
  - SOMEWHAT

### III. Additional Questions

a. Suggested topics and/or speakers you would like for future activities.

b. Additional Comments