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HEPP NEWS

May 2002 Vol. 5, Issue 5

HIV & HEPATITIS
EDUCATION
PRISON
PROJECT

SPONSORED BY THE BROWN MEDICAL SCHOOL OFFICE OF CONTINUING MEDICAL EDUCATION.

ABOUT HEPP

HEPP News, a forum for correctional problem solving, targets correctional administrators and HIV/AIDS and hepatitis care providers including physicians, nurses, outreach workers, and case managers. Continuing Medical Education credits are provided by the Brown University Office of Continuing Medical Education to physicians who accurately respond to the questions on the last page of the newsletter.

CHIEF EDITOR

Anne S. De Groot, M.D.

Director, TB/HIV Research Lab,
Brown Medical School

DEPUTY EDITORS

Frederick L. Altice, M.D.

Director, HIV in Prisons Program,
Yale University AIDS Program

Joseph Bick, M.D.

Director, HIV Treatment Services,
California Medical Facility,
California Department of Corrections

David P. Paar, M.D.

Director, AIDS Care and Clinical
Research Program,
University of Texas, Medical Branch

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HIV TREATMENT UPDATE FOR PRISON AND JAILS: 2002

Anne De Groot, M.D.*, Brown Medical School and Rick Altice, M.D.**, Yale HIV in Prisons Program

SAFE STEERING AND THE GLOBAL AIDS CRISIS

Bill Gates, founder of Microsoft, opened the 9th Conference on Retroviruses and Opportunistic Infections (9th CROI) as keynote speaker by comparing the AIDS epidemic in Africa to the sinking of the Titanic. This analogy is extremely apt, for not only is it proving difficult to gauge the severity of the epidemic by examining the tips of the icebergs (those known to be infected), but it also appears that the number of lifeboats on board (available treatments) is inadequate to ensure the safety of all the passengers. Although Bill Gates did not elaborate further, he clearly implied that passengers in steerage may not be aware of existing disparities between their chances of survival compared to passengers holding a higher class of ticket. He invoked philanthropy as one potential solution to the global AIDS crisis, and asked every conference participant to view those afflicted by HIV/AIDS as their neighbors in the world village and to engage in the battle against AIDS on pure humanitarian grounds.

This article will review aspects of the 9th CROI relevant to the management of HIV and hepatitis in correctional settings. The impact of research reported at the CROI on the current management of HIV infection, as summarized in HHS guidelines (last updated Feb. 4, 2002), will also be presented.

STARTING CONTROVERSY

In only a few short years, recommendations on initial antiretroviral treatment in the treatment-naïve individual have completely changed course. In 1996, the "hit early, hit hard" approach to HIV management was unveiled by David Ho and colleagues at the World AIDS conference in Vancouver. Their recommendation for early, intense therapy was based on the results of mathematical models that predicted that HIV infection could be eradicated from infected cells in a matter of years if viral replication were completely suppressed.¹ Unfortunately, these early models of HIV replication were flawed because it was not known at the time that HIV could persist for decades in resting T cells, macrophages, and other "sanctuary" sites. It is now recognized that this persistent virus is a source for renewed viral replication and infection of other cells when HAART is discontinued.²

Gradually, optimistic sessions on "HIV Eradication" at the annual CROI meeting have given way to sessions focusing on optimizing the durability of therapeutic response and limiting drug toxicity using strategic treatment interruption (STI), immunotherapy, and other strategies which reduce exposure to or even obviate the need for antiretroviral therapy.³ This year, initial hopes for interrupted therapy were dashed as STI was put to "R.I.P." (rest in peace) by Bernard Hirschel, who summarized data from the Swiss Spanish Intermittent Therapy Trial (SSITT).⁴ Reports on the long term side effects associated with HAART also became more numerous (Adverse Events will be covered in Update Part Two in the June/July issue of HEPP News; Volume 5, Issue 6/7).

In the "Controversies" session of the CROI conference, Richard Chaisson, M.D., of Johns Hopkins University raised another note of caution and proposed that we temper our enthusiasm for early treatment by considering the potential for treatment-related adverse events along with new data on patient outcomes when deciding when to initiate treatment.⁵ This more cautious approach to the initiation of HAART is also reflected in the most recent version of the HHS Guidelines for the management of HIV infection in Adults and Adolescents⁶ (Table 1): "While randomized clinical trials provide strong evidence for treating patients with <200 CD4+ T cells/mm³, the optimal time to initiate antiretroviral therapy among asymptomatic patients with CD4+ T cell counts >200 cells/mm³ is not known. For individuals with >200 CD4+ T cells/mm³, the strength of the recommendation for therapy must balance the readiness of the patient for treatment, consideration of the prognosis for disease-free survival as determined by baseline CD4+ T cell count and viral load levels, and assessment of the risks and potential benefits associated with initiating antiretroviral therapy."⁶

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HIV TREATMENT UPDATE...
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An important new concept that was discussed at the meeting was the "AUC" or "area under the curve" for HIV viral load. There appears to be a good correlation, as expected, between viral load AUC and clinical outcomes. It should come as no surprise that lower viral load AUC (fewer detectable viral loads or lower viral loads measured at several time points during therapy) were directly correlated with patient adherence and combination therapy potency. This relationship between adherence and outcomes is emphasized in the HHS guidelines: "patient readiness" is to be used as a key determinant for initiating therapy.⁶

STARTING AT <200 CD4

Due in part to the ability of HAART to lower viral loads for prolonged periods of time, new data from longitudinal cohort studies appears to demonstrate that delaying HAART may not be detrimental in the context of the current standard of HIV care in developed countries (in Europe, the US or Australia, where the cohort studies were located). One study by a group in Europe⁷ showed that virologic suppression can be achieved even when starting HAART at CD4+ T cell <200, and that the level of virologic suppression achieved was equivalent to starting HAART at >350. At first glance, this appeared to contrast with another report by Sterling et al., which indicated that starting HAART at higher CD4+ T cell appeared to be associated with improved clinical outcomes.^{8,9} However, Richard Chaisson, one of the investigators, pointed out that even in this study, the beneficial effects of early treatment were eliminated when controlling for the viral load AUC.^{5,8} In other words, patients who achieved similarly low viral loads did equally well whether they were started at <200 or <350.⁸ Dr. Chaisson was emphatic, stating "Patients started on antiretroviral therapy with CD4+ T cell counts >350 are likely to experience considerable toxicity as well as emergence of drug-resistant virus in the absence of a compelling clinical benefit. Initiation of therapy should be based on CD4+ T cell count and the patient's ability to comply with complex and potentially toxic regimens."⁵

STARTING AT >350 CD4

In contrast, several clinical studies presented at the 9th CROI appeared to demonstrate that earlier HAART initiation (at CD4+ T cells >350) might be advantageous. David Cooper, from the Sydney (Australia) AIDS group¹⁰ showed that immune function could be restored in patients who started HAART later, but the durability of the restoration might be decreased. In that study, as in the EUROSIDA study, baseline CD4+ T cell

TABLE 1 : Indications for Initiating HAART in HIV-1 Infected Patients

Clinical Category	CD4+ T Cell Count	Plasma HIV RNA	Recommendation
Symptomatic (AIDS, severe symptoms)	Any value	Any value	Treat
Asymptomatic, AIDS	<200/mm ³	Any value	Treat
Asymptomatic	>200/mm ³ but <350 mm ³	Any value	Treatment should generally be offered, though controversy exists. [^]
Asymptomatic	>350/mm ³	>55,000 (by bDNA or RT-PCR)	Some experts would recommend initiating therapy, recognizing that the 3-year risk of developing AIDS in untreated patients is >30% and some would defer therapy and monitor CD4+ T cell counts more frequently.
Asymptomatic	>350/mm ³	<55,000 (by bDNA or RT-PCR)	Many experts would defer therapy and observe, recognizing that the 3-year risk of developing AIDS in untreated patients is 15%.

[^]Clinical benefit has been demonstrated in controlled trials only for patients with CD4+ T cells <200/mm³. However, most experts would offer therapy at a CD4+ T cell threshold <350/mm³. A recent evaluation of data from the MACS cohort of 231 individuals with CD4+ T cell counts >200 and <350 cells/mm³ demonstrated that of 40 (17%) individuals with plasma HIV RNA <10,000 copies/ml, none progressed to AIDS by 3 years (Alvaro Munoz, personal communication). Of 28 individuals (29%) with plasma viremia of 10,000-20,000 copies/mL, 4% and 11% progressed to AIDS at 2 and 3 years respectively. Plasma HIV RNA was calculated as RT-PCR values from measured bDNA values. For further information, see the full HHS guidelines. Adapted from HHS guidelines, updated February 4, 2002, p.37⁶

count at initiation of therapy determined which patients would achieve CD4+ T cell counts above 500 cells/mm³ with HAART.¹¹ Another study by the Hopkins group (Palella et al.) showed that initiation of HAART at CD4+ T cell 201-350/mm³ was associated with reduction in mortality in comparison with patients for whom HAART was delayed until they reached a lower CD4+ T cell count.¹² Thus, individual clinicians will need to continue to use their discretion when considering when to start therapy. Perhaps all of these studies are best interpreted as indicating that patients who are highly motivated (and expected to achieve lower viral load AUC) might choose to initiate therapy at lower CD4+ T cell counts (<200) and still achieve excellent virologic response. Delaying therapy may have other important effects on the overall epidemic: (1) HIV is more easily transmitted by persons who are HIV infected and not on treatment and (2) delayed treatment may impair the reconstitution of anti-HIV immune responses - which may become more important as therapeutic HIV vaccines advance to Phase III trials. The bottom line is that the whole patient (medical status, psychosocial context, motivation, etc.) must be considered.

Despite these revisions to the guidelines, not all HIV treaters are convinced that delayed treatment is the optimal strategy. As Brigitte Autran (Pitié-Salpêtrière, Paris, France) explained in her opening day ple-

nary talk, HIV immunopathogenesis data seems to indicate that starting HAART earlier may preserve T cell responses that are specifically directed against HIV, which are associated with better control of chronic infection.¹³ In her plenary talk on immune restoration, Autran postulates that the early recovery of anti-opportunistic infection (OI) CD4+ T cell response is due to the presence of chronic OI. She provided data showing that Tetanus, CMV, and Candida responses return after HAART, but not with anti HIV-specific help: the CD4+ T cells specific for HIV that had been erased soon after primary infection do not reconstitute, while the preexisting CD8+ T cells decrease in direct proportion with the viral load.¹³ Such data, as well as information presented at the 9th CROI on once-a-day regimens and 2nd generation ART drugs with fewer side effects, may eventually re-shift treatment recommendations towards earlier (>350 CD4+ T cells/mm³) treatment in the future.

IMPACT OF CLINICAL CARE

In what now appears to be an annual update on the impact of access to specialty care in HIV morbidity and mortality, Kitahata and colleagues reported that the risk of HIV disease progression and death was determined by whether or not patients received HAART within 12 months of their initial clinic visit (this study cohort consisted of 238 patients receiving care at a university-affiliated HIV clinic). CD4+ T cell counts

LETTER FROM THE EDITOR

Dear Colleagues:

The two themes that run through this issue of HEPP News are the changing standards of HIV care and women's issues.

Most of us are wary of changes of any sort because change may result in confusion, suspicion, and extra work. With regard to HIV care, the standard for initiating antiretroviral therapy in asymptomatic individuals has changed from relatively early intervention (CD4 count < 500 cells per cc of blood or viral load greater than 20,000 copies per cc of blood) to delayed therapy (CD4 < 350 cells/cc and VL > 55,000). The main article provides a summary of the latest HIV research that was presented at the 9th Conference on Retroviruses and Opportunistic Infections (February 24 - 28, 2002, Seattle, Washington) and also highlights the changes in the HHS treatment guidelines. The results of clinical trials and other research provide us, the clinicians, with the evidence upon which to base our medical treatment. Within the prison, adherence to these new guidelines will probably result in fewer patients on antiretroviral therapy. While this may please administrators who oversee the budget for medical care, it may also arouse suspicion in inmates who suspect we are skimping on their care. So clinicians will have to work extra hard to educate themselves and their patients about the pros and cons of early versus delayed therapy. Testing in correctional settings also continues to be a high priority, given the large number of people who do not know they are infected. You can expect to see more changes in future guidelines as the latest research results are incorporated into evidence-based medicine, the most rational way of treating medical conditions.

Because Mother's Day occurs in May, HEPP News has, according to our tradition, included a spotlight on women and HIV. Unfortunately, as this spotlight indicates, there is still a relative dearth of research on women's issues. Nonetheless some encouraging information has been reported: low-grade cervical lesions in HIV-positive women may have a lower than expected frequency of progression to neoplasia and mother-to-child transmission of HIV can almost be eliminated if the mother receives antiretroviral therapy to reduce the VL to undetectable levels.

After reading this issue, providers should understand the changes in the HHS guidelines, be familiar with the Black Box Warnings and the new research on women and HIV, and have an idea of how to treat the HIV/HCV coinfecting patient.

We hope you enjoy this issue of HEPP NEWS. Please provide us with your feedback and comments so that we can continue to provide you with useful information for treating incarcerated patients with HIV and/or HCV.

Sincerely yours,



David P. Paar

Published monthly and distributed by fax, HEPP News provides up-to-the-moment information on HIV and hepatitis treatment, efficient approaches to administering treatment in the correctional environment, national and international news related to HIV and hepatitis in prisons and jails, and changes in correctional care that impact HIV and hepatitis treatment.

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Univ. of Washington Division of Infectious Disease, Seattle HIVNET

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University of North Carolina

Managers

Craig Grein
Brown University

Michelle Gaseau
The Corrections Connection

Layout

Kimberly Backlund-Lewis
The Corrections Connection

Distribution

Screened Images Multimedia

Managing Editor

Rebecca Nerenberg
HIV/Hepatitis Education Prison Project

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HIV TREATMENT UPDATE... (continued from page 2)

were also an independent risk factor for disease progression. Patients with CD4+ T cell counts < 200 cells/mm³ were at significantly greater risk of disease progression than patients with higher CD4+ T cell counts, even if antiretroviral therapy was started. These data again suggest that starting therapy sooner rather than later may be beneficial regardless of the CD4+ T cell count.¹⁴

ADVERSE EFFECT ACCUMULATION

Part of the dampening of enthusiasm for early treatment at the 9th CROI is due to accumulation of data on adverse events associated with HAART. The list of adverse events associated with HAART now includes: lactic acidosis/ hepatic steatosis, HAART-associated hepatotoxicity, fat maldistribution or lipodystrophy, hyperlipidemia, osteopenia, skin rash, and new additions to the HHS guidelines: hyperglycemia, osteonecrosis, and osteoporosis. And, as shown in the HIV 101, the list of serious side effects (issued as "black box" warnings by the FDA) is growing, with the recent addition of NNRTI-associated hepatitis (nevirapine) and NRTI-associated lactic acidosis in association with Guillain-Barré-like neurotoxicity following severe lactic acidosis (as reported at the 9th CROI). Skin rash has now become a class-related adverse event (associated with NNRTIs).

EMERGING RESISTANCE

Reports at the 9th CROI also raised concern about the impact of drug resistance on future HAART therapy. This concern is reflected in the new emphasis in the HHS guidelines on genotyping at initiation of HAART for individuals in whom acute HIV infection is diagnosed. For example, Bennett and colleagues studied 923 recently diagnosed people in 10 US cities (1998-2000) and noted that resistance to 1 or more antiretroviral from any class increased from 3.8% to 9.0% during the study period.¹⁵ Grant and colleagues evaluated viral genotypes in 225 recently infected individuals in San Francisco, California and found that resistance to any class of drug increased from 16.7% to 27.6% between July 1996 and 2001.¹⁶ In contrast, investigators in Sydney, Australia, failed to observe such an increase.¹⁷ The new HHS guidelines reflect concerns about the impact of drug resistance on response to initiation of treatment: *"Transmission of drug-resistant strains of HIV has been documented, and may be associated with a suboptimal virologic response to initial antiretroviral therapy. If the decision is made to initiate therapy in a individual with acute HIV infection, optimization of the initial antiretroviral regimen through the use of resistance testing is a reasonable, albeit untested, strategy.*

*Because of its more rapid turnaround time, the use of a genotypic assay may be preferred in this setting."*⁶

INTERRUPTED THERAPY AND IMMUNITY

As is well known, in the course of chronic infection, HIV specific T cells are extremely activated and active, located in proximity to dendritic cells (DCs) that not only present HIV specific epitopes (which activate them) but also have live virions on their surface. Therefore the DCs simultaneously activate and infect CD4+ T helper cells - which then, in turn, become the target of HIV-specific CD8+ cytotoxic T cells (CTL). This leads to the preferential depletion of CD4+ T cells specific for HIV, as has been described by a number of expert HIV immunologists including B. Autran and Bruce Walker. The process is termed "depletion of HIV-specific T helper cells" and is a critical issue at the heart of controversies related to initiation of HAART, STI, and therapeutic vaccination.

What happens to the HIV specific CD4+ T cells? After interruption of HAART (as with STI), Autran, speaking in the plenary session, saw increases in HIV specific CD4+ T cells that were associated with the rebound in viremia. The CD4+ T cells rebounded even before the virus was detectable, and, alarmingly, usually disappear before the treatment was re-introduced. She postulated that these HIV-specific CD4+ T cells are immediately eliminated (either by HIV-specific CD8+ T cells or by the direct destruction of the cell due to viral replication). Thus, Autran says that STI may actually be problematic - because as each wave of CD4+ T cells is re-introduced, they are wiped out by the HIV-specific CD8+ T cells. This observation has major implications for patients who undergo periods of "Unstructured Treatment Interruption" such as those individuals who cycle through correctional facilities. Furthermore, given this information, STI is bound to fail.

A related report at the 9th CROI demonstrated the co-evolution of antibody responses and viral escape, in waves, during infection. Using a novel HIV entry assay, Richman and colleagues evaluated the co-evolution of HIV envelope and neutralizing antibody from plasma following primary HIV-1 infection. Most patients (12/14) rapidly generated strong neutralizing antibody responses to autologous virus. However, each sequentially replicating generation of viruses consistently and rapidly escaped the concurrent neutralizing antibody response by developing mutations in the RNA sequences that code for the neutralizing epitopes. The rate of viral neutralization escape was remarkable and indicated that neutralizing antibody can exert a previously unappreciated level of selective pressure on viral

evolution. These data have important implications for natural history and vaccine development.¹⁸

STOPPING THERAPY

In a report from CROI that was very relevant to HIV care in corrections, the EUROSIDA group evaluated the impact of stopping antiretroviral therapy. They evaluated the clinical outcome of 565 patients in the EUROSIDA study who interrupted HAART on their own. Of the 565, 49% have restarted therapy, and 290 developed a new AIDS Related Event (ARE) or died. Twenty-eight of these events occurred after being off therapy for at least 3 months (28/140 person-years = 0.20 per person-year). The relative hazard of a new ARE or death associated with having been off therapy for at least 3 months was 2.4 (95% CI 1.6-3.6; p=0.0001) after adjustment for the latest CD4+ T cell count and viral load. These data indicate that risk of AIDS and death increases more than two fold upon therapy interruption or stopping. The absolute risk remains closely linked to the latest CD4+ T cell count and was highest among patients with a latest CD4+ T cell count below 200/mm³.¹⁹

DETECTING HIV

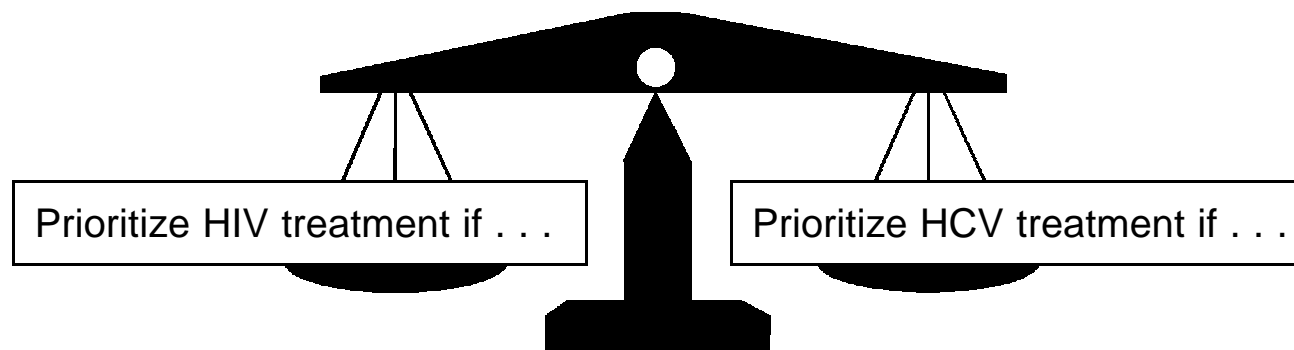
Perhaps the most important role that corrections plays in the global AIDS crisis is the role of testing and educating HIV-infected individuals. At the 9th CROI, Fleming and colleagues from the Centers for Disease Control and Prevention (CDC) reported on the continued spread of HIV in the United States. They estimated that in 2000, between 850,000 and 900,000 people in the United States were living with HIV infection, and 40,800 people acquired infection. A substantial number of people with HIV infection (between 180,000 and 280,000) are unaware of this fact, further increasing the risk for transmission.²⁰

Perhaps more importantly, it is still clear that many HIV-infected subjects do not know their status. The goal of the CDC's Project SAFE (Serostatus Approach to Fighting the Epidemic) is to bring people into care and counseling earlier.²¹ Unfortunately, it now appears that treatment of HIV-infected individuals is to be delayed until they achieve lower CD4+ T cell counts, leading to the inevitable question from the patient: Why get tested? Clearly, because there are so many individuals who are unaware of their infection, it is important to continue to test individuals for HIV. This is particularly true in corrections, a setting with which many people at high risk for HIV infection come into contact. While the patient may not see the benefit of getting tested for HIV, the correctional health care provider must continue to encourage testing of individuals at risk for infection. Returning to the image of the Titanic proposed by Bill Gates, reports pre-

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HEPPIGRAM

Correctional Physicians Dilemma: Which to Treat First in the Co-infected (HIV/HCV) Patient?



- | | |
|--|--|
| <ul style="list-style-type: none"> ◆ HIV is advanced ◆ HCV is stable ◆ EtOH/drug use still an issue (must be totally controlled first) ◆ Controlling HIV may lower HCV VL and improve immune response to HCV | <ul style="list-style-type: none"> ◆ Early HIV infection, treatment not needed yet ◆ HCV more advanced ◆ Increased liver damage on biopsy ◆ HCV infection complicating HIV treatment |
|--|--|

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HIV TREATMENT UPDATE... (continued from page 4)

sented at the 9th CROI leave us lost at sea, surrounded by dangers that are half-perceived. The best advice for correctional health care providers may be to stay tuned in for more changes in course as our understanding of HIV continues to evolve.

DISCLOSURES:

*Consultant & Speaker's Bureau: Abbott, Agouron Pharmaceuticals, Merck, Roche, Boehringer-Ingelheim, Schering Plough

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SPOTLIGHT: An Update on HIV Care for Women

by Rick Altice, M.D.*, Yale HIV in Prisons Program

The topic of HIV management in women received hardly any attention at the 9th CROI, despite recent findings on the gender differences in CD4+ T cell counts and viral loads at the time of AIDS diagnosis (Table 1). The significance of these differences remains to be determined. Overall, the women appear to progress to AIDS at the same rate as men, given equivalent access to care¹, and the CD4 T cell counts are more similar than they are different². Until large cohort comparisons are performed, it is not clear whether we should be starting women on treatment using different viral load thresholds or T cell measurements than are used for men.

Despite the relative lack of focus on women's issues, a few important insights on the management of HIV+ women emerged. As presented in one late breaker session that has relevance to the management of HIV infection in incarcerated women³, HIV seropositive and HIV seronegative women with biopsy-proven Squamous Intraepithelial Lesions (SIL) of the cervix were randomized to two distinct interventions, based on whether they had low (LGSIL) or high (HGSIL) grade cervical lesions. Women with LGSIL were randomized into observation or cryotherapy; those with HGSIL received either cryotherapy, LEEP or surgical cone therapy. At one year, HIV seropositives with LGSIL were less likely to have a normal pap smear than HIV seronegatives (24% vs. 61% for those being observed without intervention and 56% vs. 95% among those having received cryotherapy). Only 4% of HIV seropositive women with LGSIL who were either observed or who received cryotherapy developed HGSIL at one year. Among HIV seropositives with severe cervical disease (HGSIL), all treatment modalities resulted in a much poorer response rate than for HIV seronegatives. The proportion with a normal pap smear was 29%, 42% and 45% for those receiving cryotherapy, LEEP or cone treatment, respectively (these differences were not statistically significant). Thus, no single treatment modality was preferred.

The take home message for correctional providers is that HIV seropositive women with SIL do not respond to standard cervical therapies as well as HIV seronegatives. However, those HIV seropositive women with LGSIL may not need immediate interventions as was once thought because the rate of progression is not fast. Among HIV seropositive women with HGSIL, therapy is indicated; however there does not appear to be any preferred treatment modality. Correctional providers should also recognize that if treatment is delayed and the patient leaves the correctional facility, the careful follow-up available in the correctional system may be lost and the disease may progress without further care, resulting in increased morbidity and mortality in the community. Until data points to the contrary, Pap smear abnormalities should continue to be followed up and treated in a timely fashion.

Mother-to-child transmission (MTCT) of HIV was another topic pertinent to both women and children that was reviewed at the 9th CROI. Judith Currier⁴ summarized recent findings from PACTG (Pediatric AIDS Clinical Trials Group) 316 (use of single-dose nevirapine to mother and infant in addition to other maternal antiretrovirals during pregnancy)⁵ which demonstrated that it is possible to reduce MTCT rates from the 8% observed in the famous 076 study (AZT monotherapy) to 1.6% with the use of potent combination

TABLE 1: Differences Between Men and Women in HIV Disease

	CD4 Count at AIDS	CD4 Count at Death	Baseline RNA (b-DNA)	Follow-Up RNA (RT-PCR)
Women	146	44	3365	45,416
Men	49	22	8907	93,130

antiretroviral therapy. Lower viral loads had a dramatic effect on the transmission of HIV: among women with HIV-1 RNA <1000 copies/mL throughout pregnancy, transmission rates were 1.8% with a single antiretroviral agent and 0.8% when multiple agents were used. In addition, for women whose last measure of virus load during pregnancy was <1000 copies/mL, transmission rates were <1%.⁶

Data were presented from 2,087 pregnancies of HIV-infected women since January 1998 in a review of PACTG 367. Given excellent care (97% received prenatal care, and 60% were on protease inhibitors) there were no significant differences between vaginal delivery and elective C-section delivery; however, when only intrapartum transmissions were considered, the transmission rates during vaginal deliveries and elective C-sections were 3.4% and 1.7%, respectively, a difference that approached statistical significance.

Due to concern about serious adverse events related to lactic acidosis, warnings on the use of d4T and ddI during pregnancy have been issued (FDA, package inserts). According to one report (AERS), 8 pregnant women developed pancreatitis and/or lactic acidosis at 32 weeks gestation. In 7/8 (88%) cases, the patient was taking the combination of ddI and d4T. The eighth patient was taking d4T and 3TC. Among the 7 women taking ddI and d4T, 3 died. Fetal death was documented in 3 of these cases, including the woman taking d4T and 3TC. These researchers found that the combination use of d4T and ddI during pregnancy increased the risk of development of lactic acidosis and/or pancreatitis, that the risk appears to be greatest in the third trimester and with longer duration of ddI/d4T therapy. Based on these findings, ddI/d4T therapy should be given only to those pregnant women in whom the potential benefits clearly outweigh the risks.⁷

DISCLOSURES:

*Consultant and Speaker's Bureau: Abbott Laboratories, Boehringer Ingelheim, Roche, Agouron, Bristol Myers Squibb, GlaxoSmithKline, Gilead Sciences, Ortho Biotech and Merck Pharmaceuticals.

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Correction: In the April 2002 issue of HEPP News, in the section titled "HIV/HCV Response to Therapy," there are references to studies demonstrating the efficacy of pegylated interferon/ribavirin combination therapy in coinfecting patients. The pegylated interferon used in these studies was pegylated interferon alpha 2a (Pegasys, Roche), NOT the pegylated interferon alpha 2b (PEG-Intron, Schering) that had been discussed earlier in the article. Furthermore, in the HIV101, it was not made clear that dosing ribavirin by weight, used with standard interferons, has not been FDA approved for use with pegylated interferon alpha 2b (PEG-Intron), although some experts believe that the data can be extrapolated. This is based on a retrospective analysis of a study in which some lighter weight patients received only 800 mg ribavirin. PEG-intron is currently only FDA approved for use with 800 mg daily ribavirin.

"Black Box Warnings" For Antiretroviral Medications

Certain medications are associated with adverse events. Those adverse events that may lead to death or serious injury are often required (by the FDA) to be placed in a prominent box, known as the "black box" on the product insert. Presented here are antiretroviral medications along with their "black box warnings". Note that there may be other toxicities associated with these medications that are listed in the current HHS guidelines, available at http://www.hivatis.org/guidelines/adult/Feb04_02/AdultGdl.pdf.

Antiretroviral Drug Generic Name (Abbr., Brand name, Mfr.)	Black Box Warnings
NRTIs (Nucleoside Reverse Transcriptase Inhibitors)	
Abacavir (ABC, Ziagen, GlaxoSmithKline [GSK]) or as Trizivir** See HEPP News January 2002, HEPPigram, p. 5	<ul style="list-style-type: none"> ➤ Fatal hypersensitivity reactions: <ul style="list-style-type: none"> ◆ Signs/Symptoms: fever, skin rash, fatigue, GI and respiratory symptoms ◆ ABC should be discontinued as soon as hypersensitivity is suspected ◆ ABC SHOULD NOT be restarted; If restarted, more severe symptoms will recur within hours and may include life-threatening hypotension and death ◆ ABC sensitivity syndrome should be noted on the patient's chart Note that Trizivir contains ABC and sensitivity to Trizivir should be noted as well ➤ Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination
Didanosine (ddl, Videx, Videx-EC, Bristol Myers-Squibb [BMS])	<ul style="list-style-type: none"> ➤ Fatal and nonfatal pancreatitis have occurred with ddl alone or in combination with other antiretroviral agents <ul style="list-style-type: none"> ◆ ddl should be held if pancreatitis is suspected and should be discontinued if pancreatitis is confirmed ➤ See fatal lactic acidosis above (in abacavir box) ➤ Fatal lactic acidosis has been reported in pregnant women who received a combination of ddl and d4T along with other antiretroviral combinations, therefore, ddl and d4T combination should only be used during pregnancy if the potential benefits clearly outweigh the potential risks
Lamivudine (3TC, Epivir, GSK) or as Combivir* or Trizivir**	<ul style="list-style-type: none"> ➤ See lactic acidosis above (in abacavir box)
Stavudine (d4T, Zerit, BMS)	<ul style="list-style-type: none"> ➤ See lactic acidosis above (in abacavir box) ➤ See fatal lactic acidosis above (in didanosine box) ➤ Fatal and non-fatal pancreatitis have occurred when d4T was part of a combination regimen with ddl with or without hydroxyurea ➤ Potentially fatal neuromuscular reaction mimicking Guillain-Barre syndrome has been reported
Zidovudine (AZT, Retrovir, GSK) or as Combivir* or Trizivir**	<ul style="list-style-type: none"> ➤ AZT may be associated with hematologic toxicities, including granulocytopenia and severe anemia, particularly in advanced HIV patients ➤ Prolonged AZT use has been associated with symptomatic myopathy ➤ See lactic acidosis above (in abacavir box)
Nucleotide Reverse Transcriptase Inhibitor	
Tenofovir (TDF, Viread, Gilead)	<ul style="list-style-type: none"> ➤ See lactic acidosis above (in abacavir box)
NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors)	
Nevirapine (NVP, Viramune, Boehringer-Ingelheim)	<ul style="list-style-type: none"> ➤ Severe, life-threatening hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure. Patients should be advised to seek medical evaluation immediately should signs and symptoms of hepatitis occur. ➤ Severe, life-threatening, and even fatal skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction have occurred with NVP treatment ➤ Patients should be monitored intensively during the first 12 weeks of NVP therapy to detect potentially life-threatening hepatotoxicity or skin reactions. ➤ A 14-day lead-in period with NVP 200mg daily must be strictly followed. ➤ NVP should not be restarted after severe hepatic, skin, or hypersensitivity reactions
PIs (Protease Inhibitors)	
Amprenavir Oral Solution (APV, Agenerase, GSK)	<ul style="list-style-type: none"> ➤ Because of potential risk of toxicity from large amounts of the excipient propylene glycol in APV Oral Solution, it is contraindicated in: children < 4 years old; pregnant women; patients with renal or hepatic failure; patients treated with disulfiram or metronidazole ➤ Oral solution should be used only when APV capsules or other PIs cannot be used
Ritonavir (RTV, Norvir, Abbott Laboratories)	<ul style="list-style-type: none"> ➤ Co-administration of RTV with certain medications may result in potentially serious and/or life-threatening adverse events due to effects of RTV on hepatic metabolism of certain drugs

Special note: Providers need to note the following combination therapies as dangerous reactions that apply to any of the drugs in the combination form apply to the combination therapy as well: * Combivir, GSK = Lamivudine + Zidovudine; ** Trizivir, GSK = Lamivudine + Zidovudine + Abacavir

The following antiretrovirals have no "black box warnings" (see guidelines for full information on other toxicities): Delavirdine (Rescriptor, Pharmacia & Upjohn); Efavirenz (Sustiva, BMS); Indinavir (Crixivan, Merck & Co.); Lopinavir/Ritonavir (Kaletra, Abbott Labs); Nelfinavir (Viracept, Agouron); Saquinavir (Invirase, Fortovase, Hoffman-LaRoche).

Adapted from: HHS Adult and Adolescent Guidelines, Table 16 (p.49-50).

SAVE THE DATES

Sixth Annual HIV Update: Contemporary Issues in Management

June 6-8, 2002

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cme@hms.harvard.edu

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Conference can be viewed via the

Internet at <http://videocast.nih.gov>

Call: 301.592.3320

Fax: 301.593.9433

Email: hepc@prospectassoc.com

10th National Roundtable for Women in Prison

June 20-23, 2002

New York, New York

Fee: After May 15: \$175

Visit: www.wpaonline.org

Email: rnelson@wpaonline.org or

tkingsley@wpaonline.org

XIV International AIDS Conference

July 7-12, 2002

Barcelona, Spain

Fee: After May 1: \$1050 (special

rates and scholarships available)

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congrex.se

6th Annual United States Conference on AIDS (USCA)

September 19-22, 2002

Anaheim, California

Fee: Before June 14th -

\$330 members/

\$400 non-members;

before August 23- \$375/\$450

Visit: www.nmac.org/usca2002/

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INSIDE NEWS

HCV

New Data Shows High SVR For Genotype 1 Patients on Pegylated Interferon (Pegasys)

hivandhepatitis.com, 4/18/02, www.easl.ch

At the European Association for the Study of the Liver (EASL) meeting in April, Roche presented data from prospective trials with its new pegylated interferon, Pegasys. Overall (including results from all HCV genotypes), the data showed a sustained virologic response (SVR; see HEPP News, April 2002) rate of 61%; for patients with genotype 1 HCV, (the most common and the hardest to treat) the SVR rate was 51%, the highest SVR for genotype 1 patients seen thus far. These patients received 180 micrograms of Pegasys once per week along with 1000mg (if <75kg) or 1200mg (if ≥75 kg) of ribavirin per day for 48 weeks. Patients with genotype 2 or 3 who received 180mg of Pegasys once per week along with the lower 800 mg of ribavirin for 24 weeks achieved an SVR of 78%. Roche expects FDA approval of Pegasys later this year.

HIV

Tenofovir Increases DDI Levels in Blood

Bristol-Meyers Squibb Letter to Health Care Professionals, 5/02

A new study on the pharmacokinetics of ddl (Videx, BMS) and tenofovir (Viread, Gilead) has shown that administration of ddl, in the extended formulation or in the capsular form, one hour before tenofovir DF 300 mg QD (both in the fasting state) results in roughly a 40% increase in didanosine exposure relative to the administration of ddl (EC or tablets) 400 mg alone in the fasted state. Furthermore, if the two drugs are co-administered with a light meal, there is an even greater (50 to 60% increase in ddl exposure, tablet and EC, respectively) relative to ddl given alone in the fasting state. The impact of this increase is not clear, but ddl side effects may become more pronounced when ddl is used with tenofovir. Providers are encouraged to monitor patients taking standard doses of ddl and tenofovir for adverse events related to these drugs (see HIV101 for Black Box Warnings).

Mandatory Testing Before Release?

Miami Herald, 4/23/02

A bill passed by the Florida State legislature and senate would make HIV testing mandatory for all

inmates 60 days prior to release. According to the legislation, inmates who test positive for HIV will be provided with a 30-day supply of medications upon release. Some corrections experts believe the legislature has not truly comprehended the price tag for this proposed legislation, as the legislature appropriated slightly more than half of the funds the Department of Corrections requested to cover the cost of the program.

HIV Seroprevalence of New York State DOC Inmates Drops Over the Past 12 Years

Abstract 767-W, 9th CROI

A study examining HIV infection in New York State correctional facilities found that the seroprevalence among female inmates dropped from 18.8% in 1988 to 13.9% in 2000. Among male inmates, the HIV seroprevalence dropped from 17.6% to 4.7% in the same time period. Injection drug use also decreased from 1988 to 2000, dropping from about 28% for both male and female inmates to 5.8% for male inmates and 14.5% for female inmates. Experts recommend that more prevention services be offered to parolees and jail inmates.

Valganciclovir Effective as Induction Therapy for CMV

NEJM 2002; 346 (15): 1119-1126.

A new study has shown that oral valganciclovir (Valcyte, Roche) is as effective in induction therapy for cytomegalovirus (CMV) as the intravenous ganciclovir traditionally used. Valganciclovir, in its oral form, is more convenient for most patients than an intravenous drug.

TB

HEPP TB Article: CDC Communication

According to the CDC, total numbers of TB cases in the United States have declined 39% since 1992. The decline of TB in corrections has been even greater: there were 588 cases of TB in corrections in 2000, compared with 1065 cases in 1994, a decline of 45%. Furthermore, the case rate of TB in corrections stated on p.2 of the March 2002 issue of HEPP may be overstated as the "% of Population Incarcerated" in Table 1 (p.1) did not take into account those persons incarcerated in local and county facilities, thereby understating the percent of the state population that is incarcerated.

RESOURCES & WEBSITES

9th Annual Conferences on Retroviruses and Opportunistic Infections

<http://www.retroconference.org/2002/>

New Bureau of Justice Statistics Report: Prison and Jail Inmates at Midyear 2001

<http://www.ojp.usdoj.gov/bjs/pub/pdf/pjim01.pdf>

Correctional Health Care: Guidelines for the Management of an Adequate Delivery System, 2001 Update

<http://www.nicic.org/pubs/2001/017521.htm>

Three Part Report: "Corrections, Inc."

American Radio Works report explores aspects of

the correctional industry, listen or read at <http://www.americanradioworks.org/features/corrections/index.html>

amFAR HIV/AIDS Treatment Directory, 2002 Winter Edition

Free (incl. shipping); Large quantities available for clinic settings.

Contact Gretchen.Schmelz@amfar.org or call 212.806.1762

Updated HHS Guidelines for the Use of Antiretrovirals in Pregnant Women

http://www.hivatis.org/guidelines/perinatal/Feb4_02/Perin.pdf

SELF-ASSESSMENT TEST FOR CONTINUING MEDICAL EDUCATION CREDIT

Brown Medical School designates this educational activity for 1 hour in category 1 credit toward the AMA Physician's Recognition Award. To be eligible for CME credit, answer the questions below by circling the letter next to the correct answer to each of the questions. A minimum of 70% of the questions must be answered correctly. This activity is eligible for CME credit through December 31, 2002. The estimated time for completion of this activity is one hour and there is no fee for participation.

1. For an HIV-positive, asymptomatic patient with a CD4+ T cell count of 500 cells/mm³ and a viral load of 15,000 copies, what do the majority of experts say should be done?
 - a) Treat the patient aggressively and immediately
 - b) Wait to treat the patient until the CD4+ T cell count falls below 400 cells/mm³, regardless of viral load
 - c) Defer therapy and observe the patient
 - d) Defer therapy until the patient is symptomatic
 - e) None of the above

2. Which of the following adverse events has been associated with HAART?
 - a) lactic acidosis/hepatic steatosis
 - b) osteoporosis
 - c) skin rash
 - d) NNRTI-associated hepatitis
 - e) All of the above

3. The CDC estimates that between 20% and 30% of HIV-positive people in the United States do not know they are infected.
 - a) True
 - b) False

4. "Lactic acidosis and sever hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination." To which class(es) of antiretroviral drugs does this statement apply?
 - a) NNRTIs
 - b) NRTIs
 - c) PIs
 - d) NRTIs and Nucleotide Reverse Transcriptase Inhibitors
 - e) NRTIs, NNRTIs, and PIs

5. New information presented at the 9th CROI discussed which of the following findings related to SIL?
 - a) HIV-positive women with LGSIL were less likely to have a normal Pap Smear than HIV-negatives at one year of follow-up
 - b) HIV seropositives with HGSIL had much poorer responses to treatments than HIV seronegatives
 - c) No single treatment modality (i.e. cryotherapy, LEEP or cone treatment) was preferred for HIV-seropositive women with HGSIL
 - d) HIV-positive women do not respond to cervical therapies as well as HIV-negative women
 - e) all of the above

6. A patient is coinfectd with both HIV and HCV. A biopsy was done and showed moderate cirrhosis of the liver. The patient's ALTs and LFTs are outside the normal range. The HIV has been recently diagnosed, and the patient has a CD4+ T cell count of 500 cells/mL and a viral load of 35,000 copies/mL. Which infection should the provider consider treating first?
 - a) HIV
 - b) HCV
 - c) treat both infections simultaneously
 - d) neither
 - e) begin HIV treatment first; when viral load is undetectable, then begin treating the HCV

HEPP NEWS EVALUATION

5 Excellent 4 Very Good 3 Fair 2 Poor 1 Very Poor

1. Please evaluate the following sections with respect to:

	educational value	clarity
Main Article	5 4 3 2 1	5 4 3 2 1
HEPPigram	5 4 3 2 1	5 4 3 2 1
HIV 101	5 4 3 2 1	5 4 3 2 1
Save the Dates	5 4 3 2 1	5 4 3 2 1

2. Do you feel that HEPP News helps you in your work? Why or why not?

3. What future topics should HEPP News address?

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5. Do you have specific comments on this issue?

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