2-2001

HEPP News, Vol. 4 No. 2

HIV Education Prison Project

HEPP NEWS

HIV EDUCATION PRISON PROJECT

February 2001 Vol. 4, Issue 2

Sponsored by the Brown Medical School Office of Continuing Medical Education and the Brown University AIDS Program.

ABOUT HEPP

HEPP News, a forum for correctional problem solving, targets correctional administrators and HIV/AIDS care providers including physicians, nurses, outreach workers, and case managers. Published monthly and distributed by fax, HEPP News provides up-to-the-moment information on HIV treatment, efficient approaches to administering HIV treatment in the correctional environment, national and international news related to HIV in prisons and jails, and changes in correctional care that impact HIV treatment. 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.

Faculty Disclosure

In accordance with the Accreditation Council for Continuing Medical Education Standards for Commercial Support, the faculty for this activity have been asked to complete Conflict of Interest Disclosure forms. Disclosures are listed at the end of articles. All of the individual medications discussed in this newsletter are approved for treatment of HIV unless otherwise indicated. For the treatment of HIV infection, many physicians opt to use combination antiretroviral therapy which is not addressed by the FDA.

HEPP News is grateful for the support of Abbott Laboratories, Agouron Pharmaceuticals, Boehringer-Ingelheim/ Roxane Laboratories, Dupont, Merck & Co. and Roche Pharmaceuticals through unrestricted educational grants.

Treatment Update for Correctional HIV providers: News from Chicago

Anne S. De Groot, M.D.*, *Brown Medical School, Editor, HEPP News*

HIV experts unanimously agreed on three aspects of HIV management during the 8th national Conference on Retroviruses and Opportunistic Infections (8th CROI), held in Chicago during Feb 3-5 of this year. The three points of agreement were: promoting voluntary testing, improving access to care, and the need for new approaches to eradicating latent HIV after initiating treatment with HAART.

This article reviews presentations at the conference that were relevant to the management of HIV in corrections, including (1) viral eradication; (2) new aspects of the HHS guidelines for HIV management including management of drug resistance and the application of genotyping in clinical practice, (3) new drugs in the HIV treatment pipeline, and (4) structured treatment interruption.

Viral Eradication: The Elusive Holy Grail?

Bob Siliciano of Johns Hopkins University reviewed the status of HIV eradication in the Monday opening plenary. It is well known that Highly Active Antiretroviral Therapy (HAART) effectively interrupts replication of the virus in activated T cells in the blood, reducing viral loads but not completely eradicating the virus. The identity of the reservoir of latent virus has been debated. Dr. Silicano focused his talk on the population of memory T cells that harbor latent virus in a form that is directly integrated into the T cell DNA. When these cells divide, as they do at a low rate approximately every 6 months, the viral genes are transferred to daughter T memory cells. Current antiretroviral medications do not have any impact on the perpetuation of this viral reservoir, due to their action on viral proteins (not host and viral gene replication). Thus, no amount of HAART will ever eradicate the virus from the T memory cell reservoir. Newer treatments that attack integrated viral DNA are needed if viral eradication is to be achieved.

There was one bright note in this discussion: new evidence from Dr. Silicano's laboratory appears to confirm that effective HAART can reduce viral replication to zero. Patients with a history of having been adherent to HAART over several years continued to harbor virus that was resistant to previously used drugs, but no new mutations occurred. This data suggests that fully suppressive treatment of HIV creates a viral reservoir that remains "frozen in time", with no genetic evidence for new cycles of virus replication.[1]

New evidence appears to confirm that effective HAART can reduce viral replication to zero.

This finding was relevant in the context of other discussions about drug toxicities and management of patients with HAART at the conference. Several speakers discussed the concept of "substitution" - substituting triple NRTI or NRTI + NNRTI regimens for the more potent NRTI + PI regimen when patients achieve non-detectable viral loads.[2] This observation leads to the next most obvious study: what would be the impact of attacking HIV with highly active drugs (three and four drug regimens including PIs), reducing the replication to zero, and then substituting a new, more tolerable, regimen? This concept was not addressed at the 8th CROI, but studies are sure to follow.

The New Guidelines: Use Tools and Consult Experts

Updated US HHS guidelines[3] were made available on the web during the CROI conference; they are now available at: http://www.hivatis.org. A yellow-shaded version of the guidelines is also available at this site, highlighting changes from the last document. The most important change in the guide-

Continued on page 2

WHAT'S INSIDE

Treatment Update...

(continued from page 1)

lines is to delay the initiation of HIV treatment until absolute CD4 T cell counts are 350 or lower and/or HIV RNA viral loads are 55,000 or higher (Refer to HEPPigram Table 2 page 8). Some experts disagreed with this decision, which appears to de-emphasize well-known data on the risk of progression to AIDS at higher viral loads (see Table 1). Treatment should be initiated by an HIV treatment expert who takes into consideration the 'willingness' of the individual to begin therapy, the degree of existing immunodeficiency as determined the CD4 T cell count, the risk of disease progression as determined by the CD4 T cell count and the plasma viral RNA, the potential benefits and risks of therapy, and the likelihood of adherence.

Clinical experts at the CROI meeting cautioned against oversimplification in the rush to delay treatment. Three key components of the guidelines deserve emphasis here: (1) treatment should not be terminated in patients who have already begun treatment based on guidelines distributed prior to this year; (2) careful monitoring of CD4 T cell count and viral load are critical components of HIV treatment and most experts would advise checking these parameters at least every three months because patients often experience sudden declines; (3) use of experts to prescribe and adjust HIV treatment is increasingly important.

CD4 T Cell Count and Viral Load: Tools for HIV Management

The CD4 T cell count (CD4) and the viral load (VL) are the two most important tools in the HIV specialist's armamentarium. RNA-PCR (Roche) is the only FDA approved viral load monitoring tool. These two lab tests provide information on the HIV stage of disease and the likelihood of progression. As can be seen from Table 1, the chance of progressing to AIDS at a CD4 of 350 and VL of 50,000 is 36.4% after three years. Both the CD4 T cell count and the VL should be measured (at least twice, to establish a firm baseline) prior to initiating therapy; the VL should be repeated between two to eight weeks after initiation of therapy so as to establish the rate of decline in response to therapy. There should be a one-log decrease in VL at this point to indicate response to therapy (this emphasis is new). At eight weeks, if the VL is detectable (defined using the ultrasensitive assay as a VL less than 50 copies per ml), adherence should be checked, and the need to intensify or change therapy should be considered.

VL and CD4 are also used to monitor the success of therapy; these tests should be repeated every three to four months.

Table 1. Risk of Progression to AIDS Defining Illness in Treatment Naïve Patients*

IN PATIENTS WITH CD4 201-350 AND PLASMA VIRAL LOAD (copies/ml) OF:	% AIDS (AIDS-defining complication)	
RT-PCR	**3 Years**	**6 Years**
1501-7000	0	20
7001-20,000	6.9	44.4
20,001-55,000	36.4	72.2
> 55,000	64.4	89.3

**Data from the Multi-Center AIDS Cohort Study (MACS), adapted from Mellors JW, Rinaldo CR, Gupta P, et al. Prognosis in HIV-1 Infection predicted by the quantity of virus in plasma. Science. 1996; 272:1167-1170, for inclusion in US Dept of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Washington, DC: US Dept of Health and Human Services; February 2001. P37. Online at http://www.hivatis.org.*

Table 2. Test Plasma HIV RNA When the Following Clinical Indications are Present:

- Syndrome consistent with acute HIV infection
- Initial evaluation of newly diagnosed HIV infection
- Every 3-4 months in patients not on therapy
- 2-8 weeks after initiation of antiretroviral therapy
- 3-4 months after start of therapy
- Every 3-4 months in patients on therapy
- Significant decline in CD4+ T cells

Successful therapy is indicated by VL less than 50 (note the new emphasis on ultrasensitive viral load testing). A VL increase of three-fold or one log and CD4 T cell decline in absolute numbers more than 30% percent (or more than 3% change in CD4 T cell percentage) should be confirmed, adherence ascertained, and a change of therapy should be considered (see HEPPigram page 7).

Drug-Resistant Viruses Fuel Need for HIV Drug Sequencing

Viral resistance testing (either genotyping or phenotyping) is a new recommendation included the HHS guidelines this year (see Table 2). Genotyping detects mutations in the virus that are linked to changes in drug sensitivity. Genotyping is more rapid than phenotyping, but phenotyping is more precise (some mutations are more or less relevant in vivo). There was no recommendation to use one over the other. Furthermore, expert advice on the interpretation of genotyping results, and a careful history of prior ART exposure are both recommended. In view of reports at the CROI that up to 26% of patients who are recently diagnosed harbor resistant virus, genotyping prior to initiation of therapy may become commonplace, particularly in cases where the patient may have been exposed to a heavily pretreated patient. The value of baseline genotyping in chronically infected treatment naïve patients is less clear, as resistant strains tend to fall to undetectable levels in untreated patients. Interested clinicians should read the HHS guidelines carefully or review the HEPP News on resistance testing (online at http://www.hivcorrections.org/archives/sept00). In short, resistance mutations can be archived and the patient's history of prior exposure to ART, their current ART regimen, and cross-resistance within classes may have an influence on the outcome and interpretation of resistance tests.

Acute HIV Infection

Between 10 and 50% of patients with acute HIV infection present to clinicians with symptoms. Less than 20% of these individuals are correctly identified as having acute HIV. Data presented by Bruce Walker (see STI section, page 4) suggests that early treatment may lower the "setpoint" of HIV infection, possibly prolonging life and potentially permitting the patient to stop therapy. The duration of therapy of acute HIV infection is completely unknown at this time. Expert consultation should be obtained.

New approaches and Re-evaluations of existing approaches

Results from 144 weeks of the DPC 006 and DMP 006 studies were presented, showing that the mean time to failure on dual NRTI and NNRTI regimens will be about 6 years. These results supported the inclusion of efavirenz (Sustiva) in the list of "first line" treatments in the new HHS guidelines. Results of studies using Lopinavir/Ritonavir (Kaletra) as initial therapy were also presented at the CROI, showing excellent responses. Ritonavir-boosted PI treatments Lopinavir/Ritonavir and Indinavir/Ritonavir were two new additions to the "recommended therapy" list this year (see HEPPigram Table 1, page 7).

Continued on page 4

Letter from the Editor

Dear Colleagues,

The 8th Conference on Retroviruses and Opportunistic Infections (8th CROI) had little to say about our patients in the correctional system, but provided a startling picture of the global HIV/AIDS epidemic, of which our patients are an integral part.

"Just saying no" to sex has the same impact on HIV transmission anywhere in the world, but differences between the HIV prevalence rates distinguish the impact of "just saying yes" in North Dakota and the Congo, according to Dr. Kevin DeCock of the Center for Disease Control.[1] In areas of the world where most individuals are unaware of their HIV status until they are dying from AIDS, these individuals are highly likely to transmit the virus to their sexual partners, who then transmit to others, including their children. The impact of "just saying yes" without knowledge of HIV infection on sub-Saharan Africa has been catastrophic: AIDS is decimating the ranks of productive adult workers (including health care workers), impoverishing families and dramatically increasing the number of children orphaned by AIDS. While DeCock decried international response to this human emergency of enormous scale, he did not mention in his speech problems closer to home - such as the impact of HIV/AIDS on selected sectors of US populations including African Americans, women, and incarcerated populations, even though there were many parallels.

This issue of HEPP News brings you commentary and news from the 8th CROI that is relevant to clinical practice in the correctional setting. After reviewing this issue, readers should be able to describe the new changes in the HHS guidelines regarding HIV treatment and resistance testing, how fusion inhibitors may become part of HIV antiretroviral therapy, and explain why strategic treatment interruption is not recommended. Our next issue will cover tuberculosis and HIV infection.

We apologize for the tardiness of this issue, but we have a good excuse! Our layout editor delivered her first child, a baby boy, on Valentine's Day. HEPP News welcomes the new addition to the staff.

Thank you for your continued support and comments. Be sure to visit us online at www.HIVcorrections.org!

Sincerely,

Anne S. De Groot, MD *Joseph Bick, MD*

[1] *DeCock K. Keynote Lecture - Heterogeneity and public health in the global HIV/AIDS epidemic. 8th CROI; February 4-8, 2001; Chicago, Illinois. Abstract L2.*

Subscribe to HEPP News

Fax to **617.770.3339** for any of the following: *(please print clearly or type)*

____ Yes, I would like to add/update/correct (circle one) my contact information for my complimentary subscription of HEPP News fax/email newsletter.

____ Yes, I would like to sign up the following colleague to receive a complimentary subscription of HEPP News fax/email newsletter.

____ Yes, I would like to have the following back issues emailed to me (please include volume/issue/date).

____ Yes, I would like my HEPP News to be delivered in the future as an attached PDF file in an email (rather than have a fax).

NAME: _____

FACILITY: _____ (Optional) # of HIV-Infected Inmates: _____

CHECK ONE: ○ Physician ○ Physician Assistant ○ Nurse Practitioner ○ Nurse/Nurse Administrator ○ Pharmacist ○ Medical Director/Administrator ○ HIV Case Worker/Counselor ○ Other

ADDRESS: _____

CITY: _____ STATE: _____ ZIP: _____

FAX: _____ PHONE: _____ EMAIL: _____

SIGNATURE: _____ DATE: _____

Treatment Update...

(continued from page 2)

Improved formulations of ART medications are permitting researchers to address the topic of once-daily therapy, an innovation in treatment that may improve adherence in correctional settings and methadone programs. Italian researchers and French researchers showed outcomes from treatment with once-daily didanosine (Videx, 300 mg), lamivudine (3TC, Epivir, 300 mg), and efavirenz (Sustiva, 600 mg) in 75 patients naive to antiretroviral therapy.[4] There is a growing list of ART drugs that can be considered for once-daily therapy, including DDI, 3TC (and newer derivatives), efavirenz, nevirapine (Viramune), abacavir (Ziagen) and amprenavir/ritonavir. This writer believes that these newer, more tolerable regimens will result in yet another revision of the guidelines next year.

New "entry blocking" Treatments

Viral entry into the host cell is a new target for HIV drugs. However, compounds that are developed to block entry of virus will be ineffective against virus that spreads by syncitia formation (cell-to-cell) and will not have any effect on non-replicating virus. It is likely that entry blockers will be used in combination with existing antiretroviral agents. Two classes of entry inhibitor are in development - fusion inhibitors and chemokine receptor blockers. These drugs are probably most effective when used in combination.

Fusion Inhibitors

T-20 (made by Trimeris) is the first member of the fusion inhibitor class. T-20 is a very short (39 amino acid) peptide that binds to one of the two helical domains of gp41. Gp41 is a spring-loaded HIV-1 protein that is activated when CD4 binds to HIV gp-120. The fusion action of gp41 is inhibited if its two helical domains cannot fold together. T20 binds to gp41, effectively keeping the protein from functioning. Unfortunately, this drug is a peptide, so it cannot be given orally. It is given as an injection, and more than 10% of patients develop reactions at the injection site. Previous studies of T20 without HAART showed that resistance is rapid to develop. However, when used in combination with other ART, the drug appears to be effective. In a "late breaker report", Lalezari reported on a Phase I (dose finding) study of 71 patients receiving combination HAART and T20. By week 16, patients participating in the T-20 arms of the study had 0.5 log lower HIV RNA levels than patients in the non T-20 arms.[5] In the future, due to the need for injections, T20 will probably be used only in the setting of extensive resistance. Trimeris is also developing variant of this drug, called T-1249.

STI are viewed by patients as a welcome respite to therapy - this is probably one of the main motivators for research in this area.

CCR5 Blockers

Another key protein involved in HIV entry is CCR5 (chemokine receptor 5). This protein is ubiquitous on immune cell membranes. Blocking this receptor is believed to be safe, and important, since individuals who have homozygous deletion of this gene appear not to have any increased susceptibility to infections and are almost completely resistant to HIV infection. The CCR5 blocking-compound furthest along in development is a Shering Plough drug, SCH-C.[6]

Un-Successful and Un-Structured Treatment Interruptions (STI)

Structured treatment interruptions (STI) were addressed by a number of the speakers at the 8th CROI. The rationale for STI is that CD4 T cell replication is achieved in effective HAART, so providers were interested in whether patients could contain virus (they cannot) and whether "autovaccination" might improve immune responses to the virus (they do not). Furthermore, there is a hope that virus will revert to wild type (it does not, as resistance mutation are archived in latently infected T cells). Finally, STI are viewed by patients as a welcome respite to therapy - this is probably one of the main motivators for research in this area.

STI may have a role in EARLY (before seroconversion) treatment of HIV, as reported by Bruce Walker.[7] However, based on the results reported at the 8th CROI, it is too early to know whether STI is viable options, and treatment of acute HIV infection should be supervised by an HIV specialist. At present, no guidelines exist as to whether treatment may be stopped after initial therapy or whether it should be continued indefinitely (which would run counter to the HHS guidelines stating treatment should be delayed until later in the course of disease).

Therapy-Related Adverse Events

Adverse events were one of the major reasons for changes in the HHS guidelines. Details on mitochondrial toxicity and hepatic steatosis, fat maldistribution, rash, and diabetes/pancreatitis are given in the new guidelines. These topic and neuropathy were also covered at the 8th CROI. In short, concern about side effects resulted in changes in the guidelines for the use of antiretroviral therapy this year (see HEPPigram Table 1, page 7 and the upcoming HEPP News issue in April on neuropathy).

There's Always More...

A special feature for this month, the *Rapid Report* on page 6 has further news from the conference. In the upcoming issues we will cover more topics from the 8th CROI such as neuropathy and the CDC's new program on National HIV Prevention. In the meantime, visit the conference website http://www.retroconference.org/2001 or Medscape at http://www.medscape.com.

Funding for this conference coverage was provided by educational grants from Agouron Pharmaceuticals, DuPont Pharmaceuticals Company, Hoffman La Roche, and Boehringer-Ingelheim/Roxane Laboratories.

** Consultant & Speaker's Bureau: Agouron Pharmaceuticals, Dupont, Merck, Roche, Boehringer-Ingelheim/Roxane Laboratories*

REFERENCES:

1. Robert Siliciano Viral Reservoirs and Ongoing Virus Replication in Patients on HAART: Implications for Clinical Management. 8th CROI. Abstract L5

2. Becker S, Rachlis A, Gill J, et al. Successful substitution of protease inhibitors with efavirenz (EFV) in patients with undetectable viral loads -- a prospective, randomized, multicenter, open-label study (DMP-049). 8th CROI. Abstract 20.

3. US Dept of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Washington, DC: US Dept of Health and Human Services; February 2001. Published online at: http://hivatis.org/trtgdlns.html.

4. Maggiolo F, Migliorino M, Maserati R, et al. Once-a-day treatment for HIV infection: final 48-week results. 8th CRO. Abstract 320.

5. J. Lalezari, J. Drucker, R. Demasi, S. Hopkins, and M. SalgoA Controlled Phase II Trial Assessing Three Doses of T-20 in Combination with Abacavir, Amprenavir, Low Dose Ritonavir and Efavirenz in Non-Nucleoside Naïve Protease Inhibitor Experienced HIV-1 Infected Adults . 8th CROI. Abstract LB5

6. Reyes G. Development of CCR5 Antagonists as a New Class of Anti-HIV Therapeutic. 8th CROI. Abstract L11.

7. Rosenberg ES, Altfeld M, Poon SH, et al. Immune control of HIV-1 after early treatment of acute infection. Nature. 2000; 407:523-526. 407:523-526., reported by Bruce Walker in his talk: Structured treatment interruption: novel strategy or oxymoron? State-of-the-art lecture and summary. 8th CROI. Abstract 266.

SPOTLIGHT: Directly Observed Therapy for HIV Therapy in Corrections: Ready or Not?

A point and counterpoint discussion of the use of Directly Observed Therapy for HIV treatment in the correctional setting.

Dr. Margaret Fischl, director of the Miami AIDS Clinical Research Unit, presented at the CROI (Feb. 7, 2001) her comparison of the outcomes of treatment naïve ACTG subjects enrolled in antiretroviral treatment trials conducted both at the Miami AIDS Clinical Research Unit and the Florida state prison (CROI Abstract 528). Within the prison system, inmate-patients are administered antiretrovirals under direct observation (DOT). Fischl examined the viral load responses to study regimens among 50 prisoners receiving their study medications via DOT and 50 AIDS Clinical Research Unit outpatients receiving study medication in the conventional, unobserved way. The two groups were different demographically, with more of the incarcerated patients likely to be African American, Latino, male and to have a history of injection drug use. Further, the patients in prison had lower CD4 cell counts and higher viral loads. After 24 weeks, 90% of the prisoners had viral loads that were below 50 copies/mL while 77% of the free subjects achieved this goal at this time point. These differences in response rates remained out to 90 weeks of follow-up and were highly statistically significant. In general, simpler regimens of three drugs had better response rates than more complex four-agent combinations.

POINT

By David A. Wohl, M.D.*, *Director, Central Prison Infectious Disease Service, UNC Central Prison Hospital, North Carolina Department of Corrections*

Reprinted with permission from the National AIDS Treatment Advocacy Project.

While on the face of it, these results seem to be a resounding endorsement for DOT, several questions lurk. Although all the incarcerated subjects received DOT, it is not clear this was responsible for their excellent responses (above the enviable rates seen among the free patients). There are many confounding factors that could have contributed to the inmates' success including the regimented structure of prison life, the influence of correctional medical staff or just simply having 'three hots and a cot' and (relatively) limited access to crack cocaine. The differences between the two groups of patients extend beyond the presence or absence of DOT and, therefore, DOT alone cannot be regarded as the crucial determinant of the observed results. In the North Carolina Department of Corrections, we have found DOT adds nothing to self-administration of antiretrovirals (Wohl DA, Stephenson B, et al. Adherence to Directly Observed Therapy (DOT) of Antiretrovirals in a State Prison System [357]. Infectious Disease Society of America, New Orleans, 2000). In fact, many inmates complain that DOT renders them conspicuous as being HIV-infected as they stand in line for medication and therefore, opt not to present for DOT. Under such conditions, DOT may present an obstacle rather than a path to adherence. Before DOT is used as an intervention to enhance adherence, some prospective investigation on both sides of the barbed wire is warranted beyond this interesting first step.

COUNTERPOINT

By David Thomas, M.D.**, *Director of Health Services, Florida Department of Corrections*

As a co-author of this presentation and the person responsible for all of the Health Services in the Florida Department of Corrections, let me respond to Dr. Wohl's concerns. We strongly agree that medical therapy in isolation (e.g. DOT) may be only one of the contributing factors, and may have reduced opportunities for better diets and illicit drug use. The authors strongly feel that the adherence to medical pharmacotherapeutic regimen is the key reason for improvement. To test this hypothesis, another study is planned of two groups, both of which are incarcerated. In systems that do not use DOT, but have the other realities of prison life, rates of viral load improvement match the community setting. Clearly, there are some situations and conditions where DOT can lead to aversive elements, so the initiation must be done with care and sensitivity. In Florida, we have been using DOT for a long time, and our staff and inmates report they are comfortable with it. Of the 2,700 inmates with HIV, the vast majority are on treatment (2,250). Of the remainder, the overwhelming majority are not captured by the guidelines (and we still use the more aggressive 5-10,000 viral load cut-off for treatment). It is only a small minority who refuse because of direct observed therapy. Most cite other reasons.

HEPP Editor's Note: *Clearly, there is a use for DOT in some settings, but its success will vary between facilities. There is an acute need for further study.*

**Speaker's Bureau: Abbott Laboratories, GlaxoSmithKline and Merck & Co.*
***Consultant & Speaker's Bureau: Agouron Pharmaceuticals, Bristol- Myers Squibb , GlaxoSmithKline, Boehringer-Ingelheim/Roxane Laboratories, Roche Pharmaceuticals, Merck & Co.*

CME is Now Available Online at www.hivcorrections.org:

HEPP readers are now able to take HEPP News' continuing medical education (CME) tests online at http://www.HIVcorrections.org. Any internet browser will enable you to take the HEPP News CME tests every month. Your test results will be registered with the Brown Medical School Office for Continuing Medical Education. When you pass the test, you can either download your CME certificate from the website or request Brown to send the certificate in the mail. Try it out this week!

Rapid Report: The Latest News From the 8th Conference on Retroviruses and Opportunistic Infections

By Joseph Bick, M.D.*, *Director, HIV Treatment Services, California Medical Facility -Vacaville, California Department of Corrections*

ANTIRETROVIRAL CHEMOTHERAPY

Although promising data was presented on new NNRTIs and PIs that are more potent and demonstrate improved resistance profiles, none of them are likely to be available for widespread use within the coming year. Likewise, fusion inhibitors and IL-2 require further study before entering clinical practice. What follows are comments on a few abstracts that deal with simplified preparations or pharmacokinetic (PK) enhancement of existing agents, which are more immediately applicable to clinical care. Full texts of all conference abstracts are available at http://www.retroconference.org/2001.

Abstracts 315 and 316 demonstrated Trizivir's equivalent activity to its components, AZT, 3TC, and abacavir. For selected patients, this offers the simplicity of one pill twice daily .

Abstracts 318 and 319 supported the efficacy of the new extended release formulation of ddI EC as compared to either standard ddI or to other HAART regimens. Enteric-coated Didanosine is easier to take and leads to less drug-drug interactions than standard ddI tablets.

Abstracts 332, 405, and 739 evaluated various dosing regimens for the ritonavir (RTV) enhancement of amprenavir (AMP). Combining data from these studies, the following regimens all appear to have similar efficacy to the standard dosing of AMP 1200 mg bid: AMP 600/RTV 100 bid, AMP 450/RTV 200 bid, and AMP 1200/RTV 200 or 400 qd. All of the alternative regimens decrease pill burden, increase C min (less opportunity for resistance), decrease C max (less toxicity) and lead to similar AUC. The 450/200 option appears to have the best overall PK parameters, and also obviates the need for dose modification when used with NNRTIs.

Abstracts 334, 335, and 336 studied the PKs of ritonavir enhancement of indinavir (IDV). Pooling data from these three studies, the standard dosing of IDV 800 mg tid had similar PK to IDV 800/RTV 100 bid, IDV 400/RTV 400 bid, and IDV 1200/RTV 200 qd. The bid and qd regimens provided less frequent dosing and eliminated the necessity for dosing on an empty stomach. Overall, the 400/400 option appeared to have the best PK parameters with the least side effects.

Abstracts 18 and 321 provided additional data on the once daily use of emtricitibine (FTC), a NRTI with greater potency and prolonged half-life as compared to 3TC.

In conclusion, virtually every HAART regimen can now be delivered in two daily doses, and there are an increasing number of options for once daily therapies. In the correctional setting, this will increase adherence and simplify directly observed therapy for those systems that chose to use it.

EPIDEMIOLOGY

The following four abstracts demonstrate the overwhelming ongoing need for inmate peer education for all prisoners- whether known to be infected or not.

- Abstracts 211 (NYC) and 212 (6 U.S. cities) both studied young men who have sex with men (MSM) and found an alarming rate of unprotected anal sex within the past six months (~50% of those interviewed). Both studies also found rates of HIV seropositivity among African American men of approximately 30%--over twice as high as those from all other racial/ethnic backgrounds.
- Abstract 213 from Los Angeles found that those MSM who had confidence that HAART decreases the risk of HIV transmission were more likely to have had recent unprotected anal sex.
- Abstract 261 from Amsterdam found a marked increased rate of syphilis and gonorrhea (GC) among MSM. Among HIV seropositive MSM, those who experienced a HAART induced rise in CD-4 and drop in viral load were found to then increase their rate of unprotected sex with casual partners.

TRANSMISSION

A number of studies have shown that HAART induced drops in HIV viral load decrease the rate of transmission to seronegative partners. Abstract 221 from Thailand corroborated such prior studies by finding no cases of transmission when the HIV viral load was <1094.

Prior studies have shown that the presence of ulcerative genital disease increases the transmission rate of HIV. Abstract 222 demonstrated that the presence of GC urethritis also markedly increases HIV transmission, reminding us of the unique opportunity that we have in correctional medicine to impact the spread of disease by diagnosing and treating STDs.

Lastly, an important study from the Kaiser HMO system in California (219) evaluated 416 individuals recently diagnosed with HIV. At the time of diagnosis, 44% already had CD-4 <200, with 19% <50. Since HAART is most effective when instituted earlier in the course of the disease (see abstracts 341 and 342), many patients are being diagnosed too late for optimal benefit. Furthermore, 40% of these newly diagnosed individuals had presented with known HIV risk factors at least 12 months before they were eventually tested- reflecting missed opportunities for earlier diagnosis and treatment. Risk factors included oral infection, pneumonia, unexplained fever >100, herpes zoster, seborrheic dermatitis, night sweats, and unexplained weight loss. Undiagnosed persons not only go untreated, but they also unknowingly pass the virus to others. How often in our own correctional practices have we missed opportunities for earlier diagnosis?

HCV ACCELERATES HIV AND VICE VERSA

The impact of HIV on HCV and vice versa has been the subject of much debate. CROI reports contributed to the confusion. In a population of hemophiliacs, Dr Eric Daar found a close linear relationship between HCV RNA level and abnormal liver function tests (SGOT or ALT). The HCV viral load level (by branched-chain DNA) appeared to independently predict an increased risk of HIV clinical progression (abstract 35). This observation was confirmed in a Swiss cohort, described in the Lancet (Greub G, et al. Lancet, 2000;356:1800-1805. However, a report by Sulkowski at CROI contraindicated these findings, suggesting that risk of progression was more linked to lack of access to medical care (for HIV) in his cohort of African American patients who had HIV and HCV coinfection (abstract 34).

**No affiliations to disclose.*

HEPPIGRAM: Treatment for HIV Infection

Table 1. Initial Treatment for Established HIV Infection

This table provides a guide to the use of available treatment regimens for patients with limited or no prior experience on HIV therapy. In accordance with the established goals of HIV therapy, priority is given to regimens for which clinical trials data suggest the following: sustained suppression of HIV plasma RNA (particularly in patients with high baseline viral load) and sustained increase in CD4+ T cell count (in most cases over 48 weeks), and favorable clinical outcome (i.e. delayed progression to AIDS and death). Particular emphasis is given to regimens that have been compared directly with other regimens that perform sufficiently well with regard to these parameters to be included in the "Strongly Recommended" category. Additional consideration is given to the regimen's pill burden, dosing frequency, food requirements, convenience, toxicity, and drug interaction profile compared with other regimens.

It is important to note that all antiretroviral agents, including those in the "Strongly Recommended" category, have potentially serious toxic and adverse events associated with their use. The reader is strongly encouraged to consult the HHS HIV Treatment Guidelines (available at www.hivatis.org) while formulating an antiretroviral regimen.

Antiretroviral drug regiments are comprised of one choice each from columns A and B. Drugs are listed in alphabetical, not priority, order.

Strongly Recommended	Column A Efavirenz (Sustiva, EFV) Indinavir (Crixivan, IDV) Nelfinavir (Viracept, NFV) **Ritonavir (Norvir, RTV)+ Indinavir[ab] **Ritonavir/Lopinavir (Kaletra)[a] Ritonavir + Saquinavir[a] (SGC[c] or HGC)	Column B Stavudine (Zerit, d4T)+ Didanosine (Videx, ddI, ddi EC)[d] Stavudine + Lamivudine (Epivir, 3TC) Zidovudine (Retrovir, ZDV) + Didanosine Zidovudine + Lamivudine (Combivir)
Recommended as Alternatives	Column A Abacavir (Ziagen, ABC) Amprenavir (Agenerase, AMP) Delavirdine (Rescriptor, DLV) Nelfinavir + Saquinavir Nevirapine (Viramune, NVP) Ritonavir Saquinavir-SGC Trizivir (Abacavir, Lamivudine, Zidovudine)	Column B Didanosine + Lamivudine Zidovudine + Zalcitabine (Hivid, ddC)
No Recommendation: Insufficient Data[e]	Hydroxyurea in combination with antiretroviral drugs **Ritonavir + Amprenavir[a] Ritonavir + Nelfinavir[a]	
Not Recommended: Should Not Be Offered	All monotherapies, whether from Column A or B[f] Column A Saquinavir-HGC[g]	Column B Stavudine + Zidovudine Zalcitabine + Didanosine Zalcitabine + Lamivudine Zalcitabine + Stavudine

*[a] See Guidelines page 16 for more information on optimizing protease inhibitor exposure with ritonavir.***
*[b] Based on expert Opinion***
*[c] Saquinavir-SGC, soft-gel capsule (Fortovase); Saquinavir-HGC. Hard-gel capsule (Invirase).***
[d] Pregnant women may be at increased risk for lactic acidosis and liver damage when treated with the combination of stavudine and didanosine. This combination should be used in pregnant women only when the potential benefit clearly outweighs the potential risk.
*[e] This category includes drugs or combinations for which information is too limed to allow a recommendation for or against use.***
[f] Zidovudine monotherapy may be considered for prophylactic use in pregnant women with low viral load and high CD4+ T cell counts to prevent perinatal transmission, as discussed under "Considerations in the Pregnant Woman" in the Guidelines.
[g] Use of Saquinavir-HGC (Invirase) is not recommended, except in combination with ritonavir.

***Changes from last year's guidelines are starred.*

(HEPPigram continued on page 8)

Save the Dates

American Correctional Health Services Multidisciplinary Training Conference
March 15-18, 2001
Atlanta, Georgia
Call: 877.918.1842
Visit: www.corrections.com/achsa/conferences.html

Implementing HIV Treatment Guidelines in Corrections
Panel organized by HEPP at the National AIDS Update Conference (March 20-23)
March 21, 2001
11:00am-12:30pm
San Francisco, California
Conference sponsored by amfAR
For information on the panel,
Call: 401.863.2180
Email: bstubb@Brown.edu
For information on the conference,
Call: 514.874.1998
Visit: http://www.nauc.org

United States Conference on AIDS (USCA)
September 13-16, 2001
Fort Lauderdale, Florida
Abstract Deadline: April 2, 2001
Call: 202.483.6622
Email: info@nmac.org
Visit: www.usca.org

Clinical Updates in Correctional Health Care: 6th Semi-Annual Spring Educational Conference
May 5-8, 2001
Las Vegas, Nevada
Sponsored by: NCCHC and ACHP
Call: 773/880.1460
Fax: 773/880.2424
Visit: http://www.ncchc.org/conference/clinical.html

Other News . . .
We have a new sign-up number, so tell your colleagues to sign up for HEPP News by calling 1.800.748.4336.
(You can also sign up on the website at www. hivcorrections.org or by faxing 1.617.770.3339 or emailing hepp@corrections.net.)

HEPPigram *(Continued from page 7)*

Table 2. Indications for the Initiation of Antiretroviral Therapy in the Chronically HIV-1 Infected Patient

Clinical Category	CD4+ T Cell Count	Plasma HIV RNA	Recommendation
Symptomatic	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	>30,000 (bDNA) or >55,000 (RT-PCR)	Some experts would recommend initiating therapy, recognizing that the 3-year risk of developing AIDS in untreated patients is >30%. In the absence of very high levels of plasma HIV RNA, some would defer therapy and monitor the CD4+ T cell count and level of plasma HIV RNA more frequently. Clinical outcomes data after initiating therapy are lacking.
Asymptomatic	>350/mm^3	<30,000 (bDNA) or <55,000 (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/ mm^3. However, most experts would offer therapy at a CD4+ T cell threshold <350/mm^3. All decisions to initiate therapy should be based on prognosis for disease-free survival in the absence of treatment, as determined by the CD4+ T cell count and level of plasma HIV RNA shown in Table 5, the potential benefits and risks of therapy shown in Table 4, and the willingness of the patient to accept therapy. For further information, see "Considerations for Initiating Therapy in the Patient with Asymptomatic HIV Infection," page 6 of the HHS Guidelines.*

These tables were taken from US Dept of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Washington, DC: US Dept of Health and Human Services; February 2001. P44 and 38. Online at http://www.hivatis.org.

Resources

Websites:

***Updated DHHS HIV/AIDS Treatment Guidelines**
http://www.hivatis.org

8th Conference on Retroviruses and Opportunistic Infections
http://www.retroconference.org/2001

Medscape Coverage of the 8th CROI
http://www.medscape.com/conferences/Retrovirus2001

Medscape HIV/AIDS Online
http://www.medscape.com/Home/Topics/AIDS/AIDS.html

HIV Treatment Websites:

HIV/AIDS Treatment Information Service
http://www.hivatis.org

HIV Insite
http://hivinsite.ucsf.edu/

AEGiS: the largest HIV/AIDS resource on the internet
http://www.aegis.com

The Body: An AIDS and HIV information Resource
http://www.thebody.com

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 Feb. 28, 2002. The estimated time for completion of this activity is one hour and there is no fee for participation.

CME is now available ONLINE at www.hivcorrections.org

1. Which of the following statements is false?
   a) T memory cells act as a long-lived reservoir for HIV infection.
   b) HAART can dramatically interrupt the replication of HIV in activated T cells
   c) Patients who have been started on ART should stop treatment if their CD4 T cell count is above 350.
   d) Adherence to HAART can "freeze" HIV in time, preventing the evolution of new resistance mutations.
   e) The decision to modify HIV treatment guidelines was based on evidence of long-term drug toxicity

2. When should plasma RNA be measured?
   a) Patient presents with syndrome consistent with acute HIV infection.
   b) As part of initial evaluation of newly diagnosed HIV infection.
   c) 2-8 weeks after initiation of antiretroviral therapy.
   d) 3-4 months after initiation of antiretroviral therapy.
   e) Patient presents with clinical evidence or significant decline in CD4+ T cell count.
   f) All of the above
   g) None of the above

3. The new guidelines indicate that physicians should delay the initiation of HIV treatment until absolute CD4 T cell counts are _____ and/or HIV RNA viral loads are _____.
   a) CD4 T cell count <500 and/or HIV RNA viral load >5000.
   b) CD4 T cell count <450 and/or HIV RNA viral load >30,000.
   c) CD4 T cell counts <350 and/or HIV RNA viral load >55,000.
   d) CD4 T cell count >350 and/or HIV RNA viral load >55,000.

4. Which of the following are true?
   a) Response to therapy should be indicated by a one-log reduction in viral load.
   b) Viral resistance testing should be included in HIV treatment management.
   c) Ultrasensitive viral load testing should be included in HIV treatment management.
   d) All of the above.
   e) None of the above.

5. When presented with an asymptomatic patient with AIDS, CD4+ T cell <200/mm3 and plasma RNA of 50,000, you should:
   a) Treat.
   b) Consult an expert and consider treatment.
   c) Obtain a genotype.
   d) Defer treatment.

6. CD4+ T cell count and viral load should be monitored every ___ months because patients often experience sudden declines.
   a) 2
   b) 3
   c) 6
   d) 12

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
Spotlight	5 4 3 2 1	5 4 3 2 1
HEPPigram	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?

4. How can HEPP News be made more useful to you?

5. Do you have specific comments on this issue?

Brown Medical School • Office of Continuing Medical Education • Box G-A2 • Providence, RI 02912
The Brown Medical School is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education activities for physicians.

For Continuing Medical Education credit please complete the following and mail or fax to 401.863.2660 or register online at www.hivcorrections.org. Be sure to print clearly so that we have the correct information for you.

Name _____ Degree _____

Address _____

_____

City _____ State _____ Zip _____

Telephone _____ Fax _____