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HIV Education Prison Project HEPP NEWS

October 1999 • Volume 2, Issue 9

Brown University School of Medicine Providence, RI 02912
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ICAAC Highlights, Part I: HAART Trial Reports

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.

The editorial board and contributors to HEPP News include national and regional correctional professionals, selected on the basis of their experience with HIV care in the correctional setting and their familiarity with current HIV treatment. We encourage submissions, feedback, and correspondence from our readership. The goal of HEPP News is to provide our readers with reports of effective and cost-conscious HIV care that can truly be implemented with the correctional environment. We hope our newsletter achieves that goal.

EDITORS

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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 beneath the authors' names.

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 primary support of Agouron Pharmaceuticals through an unrestricted educational grant and the additional support of Roche Pharmaceuticals.

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HIV Treatment

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The 39th annual Interscience Conference on Anti-microbial Agents in Chemotherapy (ICAAC) was held in San Francisco September 25-29, 1999. From the correctional perspective, some of the most relevant HIV related topics that were discussed include: longer term follow-up of some previously reported highly active antiretroviral (HAART) trials, genotypic and phenotypic resistance testing, discontinuation of opportunistic infection (OI) prophylaxis, further elucidation of host factors involved in the immune response to HIV, and troubling information regarding side effects of HAART.

One common theme was that the most important predictor of achieving an undetectable HIV viral load (VL) is patient adherence to therapy. In spite of glowing reports from some clinical trials, the fact remains that approximately 40% of previously treatment naïve patients receiving HAART will experience virologic failure within one year. Nationwide, about one third of patients on ≥ 3 agents have HIV VL $>20,000$. The proportion of patients who will maintain an HIV VL of < 400 drops precipitously when adherence falls below 95% (i.e. missing 1-2 doses per month).

Understanding that a major predictor of a patient's adherence to therapy is trust in his or her clinician, it is crucial to implement approaches in correctional settings that allow effective patient education and foster trusting relationships with clinicians. Correctional providers should take the time to carefully review treatment options with their patients, since the initiation of HAART is rarely an emergency, and the second regimen rarely works as well as the first.

This month's report from ICAAC will review HAART trial reports and HIV resistance testing. Next month's report will discuss updates concerning opportunistic infection side effects and host factors.

Longer-term Data on Multiple Clinical Trials

Longer-term data on multiple clinical trials was presented and demonstrated a clear role for non-

protease inhibitor (PI) containing regimens in the initial treatment of ART naïve patients. Brief synopses follow:

- CNA 3005: 48 week data was presented from this study which compared zidovudine(AZT) / lamivudine(3TC) / indinavir(IDV) vs. AZT/3TC/abacavir(ABC). In terms of achieving an HIV VL of <400 , the triple nucleoside class sparing combination performed as well as the PI containing regimen. In the subset of patients who began therapy with a VL of $>100,000$, the PI containing arm was more successful.

- DUPONT 006: 72 week data was presented from this study comparing AZT/3TC/efavirenz (EFV) vs AZT/3TC/IDV vs EFV/IDV. In an intent to treat analysis (see glossary), the AZT/3TC/EFV arm performed significantly better than the AZT/3TC/IDV arm in achieving a VL of <400 and <50 . Not only did the PI sparing regimen perform better, it was better tolerated.

- DUPONT 006 (AZT/3TC/EFV)
- DUPONT 043 (d4T/3TC/EFV)
- DUPONT 049 (ddl/d4T/EFV)

A comparison of these three PI sparing regimens which each utilized 1NNRTI + 2NRTIs revealed similar outcomes. This information provides further flexibility in terms of which nucleoside agents to utilize in an EFV containing PI sparing regimen.

- VIRGO: 52 week data of a regimen composed of once daily nevirapine (NVP) and didanosine (ddl) with twice daily stavudine (d4T) demonstrated sustained efficacy with roughly 2/3 of patients having VL <50 .

Continued on page 2

What's Inside

Resources	pg 3
Expert Opinion.....	pg 4
HEPPigram	pg 6
HIV 101	pg 8
Self-Assessment Test	pg 10

ICAAC Highlights, Part I: HAART Trial Reports

Continued from page 1

- Atlantic Study: 48 week data was presented on this study which involved three arms. Each included ddI, d4t, and either IDV, NVP, or 3TC. All three arms were similarly successful in achieving an HIV VL of <400. The triple nucleoside arm of ddI/d4T/3TC was less efficacious in those who started out with HIV VL of >100,000, and was also less effective in achieving a VL of <50.

When considered together, the above studies provide strong evidence for the efficacy of PI sparing regimens utilizing either 3 NRTIs or 2 NRTIs plus 1NNRTI in ART naïve patients. This data suggests, however, that triple nucleoside regimens perform less well in those with baseline HIV VL's of >100,000 (see also our Expert Opinion on intensification, by HEPP editor Rick Altice - on page 4). Non PI containing-regimens involve fewer pills, fewer doses, and often less side effects - all factors which can help improve adherence. Data also revealed that EFV/dual nucleoside regimens are as effective as those containing PIs in reducing HIV replication in sanctuary sites such as lymph nodes.

Dosing news:

- "TID BID": This study provides data that 1600 mg of saquinivir (SQV) bid or 1200 mg SQV bid with 1250 mg bid NFV are as effective in combination therapy as 1200 mg SQV tid.

Other ART Agents

- Adefovir: a nucleotide reverse transcriptase inhibitor (RTI), dosed qd. Adefovir currently has investigational new drug status, showing 0.3-0.4 log decline in HIV VL in those with prior treatment failure. Adefovir is not active against AZT resistant virus, but activity is enhanced in the presence of the 184 resistance mutation. Renal toxicity can be significant, but may be decreased if dosing is reduced from 120 mg/d to 60 mg/d. Additionally, probenecid may decrease nephrotoxicity.
- Tenofovir: (also known as PMPA pro-drug): Also a nucleotide RTI, administered once daily. Less toxic than adefovir, and more efficacious (decrease HIV VL 1 log). Activity is enhanced by the 184 mutation and not diminished by the 151 multi-drug resistance mutation.
- T20 fusion inhibitor: An amino acid that blocks gp41 fusion. No cross resistance noted with other ART, and has shown some promise in patients with multiple drug resistant virus at doses of 50 mg subcutaneously bid.
- ABT-378/ritonavir (RTV) An investigational second generation PI which utilizes low doses of RTV to markedly improve pharmacokinetics. In vitro data demonstrates activity against RTV and IDV resistant isolates. Week 36 data from studies involving both naïve patients and those who had failed one PI demonstrated excellent tolerability and potency.
- Hydroxyurea (HU): HU functions as an inhibitor of ribonucleotide reductase, which leads to decreased intra cellular concentrations of nucleosides and therefore a competitive advantage for ddI. A pooled evaluation of 4 trials involving >500 patients, most of whom were asymptomatic and naïve, revealed an additional 0.4-0.6 log reduction in HIV VL when HU was included in a ddI containing regimen. Toxicity was limited, including fatigue, neuropathy and <1% severe anemia. CD4 increases were blunted in HIV regimens, but CD4% were not affected. In conclusion, it appears that efficacy of HU has been demonstrated in the first line treatment of asymptomatic individuals.

Salvage Therapy

Much less hopeful information was presented on salvage regimens for those failing multiple other treatment combinations. Follow-up data on "Mega HAART" (>5 drugs) guided by genotypic analysis revealed response rates (VL<400) in about 1/3 of patients over the short term. Mega

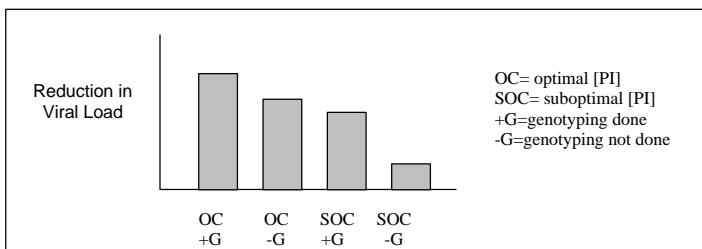
HAART is associated with a high rate of side effects and requires a very motivated patient. Response rates to salvage therapy were related to patient adherence, pre-treatment VL and the use of a new drug class.

HIV Resistance Testing

A major focus at ICAAC was the role of HIV resistance testing in clinical practice. In spite of significant limitations of the current methodologies, it is clear that resistance testing will soon be considered standard of care.

Genotypic analysis attempts to identify the viral mutations known to be most important in predicting resistance to ART. Phenotypic analysis is analogous to antimicrobial resistance testing, where "resistant" is generally defined as ten times the IC 90 of the virus. Both methods are expensive and time consuming. It is likely that over the next year, costs and turn around times will fall, making testing more accessible.

Two studies were discussed which attributed improved patient outcomes (as measured by HIV VL) to the use of resistance testing. A 12-week analysis of the GART study revealed a benefit to genotypic analysis coupled with expert opinion as opposed to standard care. The latest analysis of the VIRADEPT study demonstrated ongoing clinical benefit to the use of resistance testing at 12 months of follow-up (See following figure).



VIRADEPT also analyzed serum PI levels and found that they correlated with virologic outcomes. This data raises the question of whether drug levels will eventually become an important part of our treatment strategies.

There was considerable discussion concerning the substantial variability in reliability of resistance testing from one lab to another. Other data demonstrated that patients who experience virologic failure to HAART are often resistant to only one drug in their regimen. In this setting, resistance testing would help prevent the "discarding" of agents that retain efficacy.

Finally, a number of abstracts pointed out the significant baseline levels of genotypic and phenotypic resistance in untreated (naïve) patients. As with tuberculosis, it may become important to know the prevalence of resistant virus circulating in your patient population prior to selection of an initial regimen.

Glossary

PI sparing stands for protease inhibitor sparing, or antiretroviral combinations that do not include a protease inhibitor.

Intent to Treat (ITT) Analysis versus As Treated (AT) Analysis

When evaluating the results of a clinical trial, in the ITT analysis, if a patient starts on one combination and then quits (for any reason) they are counted as a treatment failure. In the AT analysis, the data is evaluated based upon the success of what the patient is actually taking. For example, consider two different treatments. One works in 100% of the people but is so dreadful that only 10% of patients can stay on it. A second treatment works in only 80% of the people, but is much more tolerable. If the two treatments were compared, the type of analysis used would lead to different interpretations.

In the as treated analysis, the therapy that only 10% of the people could stay on would look better because those who stayed on it all did well. In the intent to treat analysis, the therapy that worked 80% of the time but was much more tolerable would be graded better.

LETTER FROM THE EDITOR

Dear colleagues,

We're thrilled to announce that this issue marks the first anniversary of HEPP News. Over the past year we've worked extremely hard to bring you HIV treatment information, news, and resources that are relevant to prison and jail HIV care, written by HIV experts who work in corrections. We provide HEPP News to you in fax format so that you can have it right at work, and we provide access to the newsletter in downloadable formats at www.HIVcorrections.org, where back issues are also archived. As of January 2000, we'll be able to email the newsletter directly to you in PDF format as it rolls off the press. Furthermore, we're working on integrating this newsletter with another resource, HIV Inside, a quarterly publication providing more basic HIV education for correctional care providers that are not yet HIV specialists (see subscription forms for both resources on the last page). We certainly hope our readership is pleased with the HIV care resources that are now available in a range of formats.

Indeed, the year has been full of outstanding events for those of us who are involved with HIV care in correctional settings. There's been a flurry of interest in our topic - first from the Correctional Black Caucus, then by Donna Shalala's office (HHS). Correctional HIV care also created a stir at the National HIV Prevention Conference in Atlanta where Ted Hammett (Abt Associates) reported that prison inmates are five times more likely than non-inmates to have AIDS and 10 times more likely to have HIV. It's now public knowledge that the number of HIV infected individuals we care for in correctional settings represents almost 20% of the total number of HIV infected patients who are in treatment in the US.

HIV in corrections is also attracting the attention of public opinion makers and policy makers. Reverend Jesse Jackson joined forces with public health officials and correctional experts at a meeting held in Chicago (the October 2-3, 1999 Public Health / Corrections Collaborations meeting - a second meeting on this topic will be held at the NCCHC conference in November, see Dates for more information). He pointed out that people living with HIV are "all under one big tent," whether they're getting their care in the prison or in the community" and urged policy makers to focus on linking health care and disease prevention in correctional facilities with health care "outside" corrections. He urged greater collaboration between corrections and public health, stating that policy makers must address the epidemic of HIV in minority communities or become "dream busters."

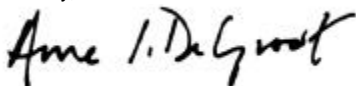
Another event that received a great deal of press coverage was the conference on Clinical Trials in Correctional Settings sponsored by HIV Education/Prison Project (HEPP at Brown University), the Yale HIV in Prison Project, and the Center for Interdisciplinary Research on AIDS (CIRA, Yale University). Correctional HIV experts, lawyers, prisoner advocates and ethicists gathered in Providence to discuss current HIV/AIDS studies that are being conducted in correctional settings and to develop more detailed guidelines for the conduct of such trials than currently exist. A list of the conference participants is provided on our website, and a full report on the conference will be published in HEPP News, next month.

This anniversary issue of HEPP News brings you an update on HIV treatment from the Interscience Conference on Anti-microbial Agents in Chemotherapy (ICAAC) and an expert opinion on intensification. Intensification is a newer approach to HIV management made possible by viral load monitoring. This approach, as outlined by HEPP editor Rick Altice may permit correctional HIV care providers to avoid having to salvage patients with new regimens of HAART until absolutely necessary. A wise HIV care provider can thereby "save" ART options for the future, and avoid exposing the patient to frequent medication changes which can be expensive and may be associated with additional side effects.

After reading this issue of HEPP News, readers should be able to describe the benefits and drawbacks of intensification versus salvage therapy, list possible drug interactions with individual antiretrovirals, and understand the latest updates on HAART trials HIV resistance testing.

Thank you for your continued support of HEPP News. We look forward to hearing from you!

Sincerely,



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HEPP Editor

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R e s o u r c e s

WEBSITES

Quick Reference Guide to Antiretrovirals and New Antoretrovirals
<http://hiv.medscape.com/Medscape/HIV/TreatmentUpdate/1998/tu01/public/toc-eng.tu01.html>

University of Penn. AIDS Service Websites
<http://www.med.upenn.edu/~pennactu/service/sites/>

HIV and Its Treatment: What You Should Know

<http://hivatis.org/atishnew.html>
This consumer brochure includes information from the Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents and uses a question and answer format to make the information easier to understand by people without a technical background. It also includes a section on adherence to treatment plans.

The Journal of the American Medical Association HIV/AIDS Information Center Antiretroviral Therapy for HIV Infection Page
<http://www.ama-assn.org/special/hiv/treatmnt/guide/guidtr.htm>

HEPP News
<http://www.hivcorrections.org>
The Corrections Connection
<http://www.corrections.com>

Expert Opinion

Modifying HAART: Strategies for Avoiding Salvage Therapy for HIV

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Speaker's Bureau: BMS, DuPont, Glaxo Wellcome, Agouron, Abbott, Roche, Merck

Grant Research Support: Abbott, Roche

Consultant: BMS, DuPont, Glaxo Wellcome, Agouron

HIV treatment is getting more complex as treatment options multiply and information on viral resistance becomes more readily available. Correctional HIV providers need to learn to consider intensification as an option for their patients if their initial HIV regimen appears to be failing. This article will give you an "inside view" of this new approach to HIV management.

Current guidelines for the use of antiretroviral therapy for the management of HIV disease include the use of at least three antiretrovirals for initial therapy. Across many studies of individuals receiving recommended combination therapy, the proportion achieving a virologic response of an HIV-1 RNA level less than 500 copies is around 70%-80%. However, the proportion of patients achieving the more desirable viral load of less than 50 copies is only approximately 40%-50%.

Patients who fail to achieve a non-detectable viral load (less than 50 copies) are more likely to have virologic progression and develop resistance to antiretroviral medications than those who do not achieve virologic success. Low level replication is bound to lead to resistance. Therefore, though a virologic failure may not immediately lead to immunologic failure (lower CD4 T cell counts), the implication of low level viral replication in the presence of antiretroviral therapy for future antiretroviral options could be serious for the patient and even more expensive, in the long run.

Future options for a patient experiencing viral replication in the face of HAART may be difficult to tolerate and to design, especially if a second (or third) regimen requires five, six or seven antiretrovirals to overcome multi-drug resistant strains. Thus, it remains a major priority to initiate appropriate and potent antiretroviral therapy with the initial regimen and monitor response to the regimen very closely. The mantra of HIV therapy has now been modified to: start early, start hard, and start smart.

Predictors of Virological Failure

Clinicians who understand the causes of virological failure can make informed decisions about how to prevent it. Four major factors predict virological failure:

- the presence of HIV-1 resistant strains to individual or multiple antiretrovirals at the time of initiation of therapy (baseline resistance);
- HIV-1 RNA more than 100,000 copies/mL at the time of initiation (baseline high viral load);
- CD4 less than 200 cells/mL (baseline immunological compromise); and
- non-adherence with antiretroviral therapy.

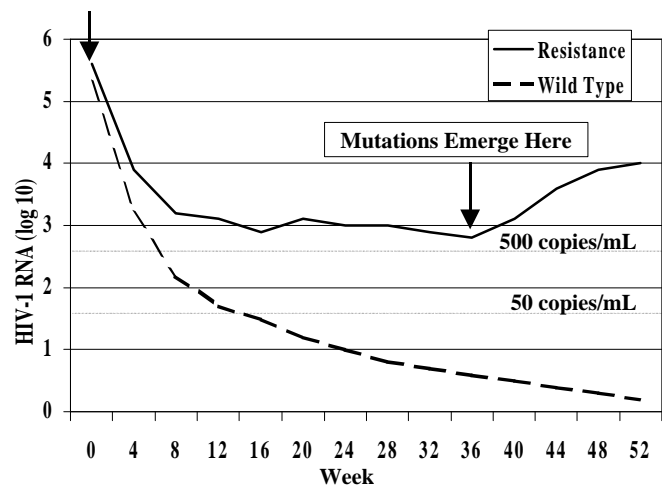
Possible approaches to the management of each of these causes of treatment failure are discussed in the next few paragraphs.

Baseline HIV Resistance

Prevalence of baseline resistance to one or more antiretrovirals has been reported at previous meetings (see HEPP News report on the

6th Retrovirus meeting, March 1999, archived at <http://www.HIVcorrections.org>). As a result, many clinicians are choosing to obtain genotypic or phenotypic resistance testing before initiating therapy. Even though this approach is not yet considered to be standard clinical practice, the rationale is that if baseline resistance is detected, an alternative antiretroviral regimen could be selected to assure that all of the agents in the initial regimen will have an effect on the virus. If, for example, an individual demonstrated resistance to one of the NRTIs at baseline, selecting an alternate NRTI may put more effective pressure on the virus and improved response to treatment.

If, in contrast, an individual were not known to be resistant to one antiretroviral, and was started on that agent along with two others in the initial regimen, the combination would be equivalent to treatment with only two agents, rather than three, and would be more likely lead to treatment failure and the development of multi-drug resistance. These two scenarios are described in Figure 1 below. Note the divergence in the reduction of HIV-1 RNA levels between two patients. At baseline, one patient is infected with a genotypic wild-type strain (non resistant) and the other patient is infected with a strain that has resistance to one nucleoside RTI (resulting in a regimen that contains only two active agents out of the three that were prescribed). In this setting, as illustrated, incomplete viral suppression results in the later emergence of new mutations, resulting in an increase in HIV-1 RNA levels.



Unfortunately, existing HIV genotypic assays are not able to evaluate all quasi-species of HIV in each patient. Thus, the patient may be infected with resistant quasi species that are not detected by the test. Furthermore, the selective pressure of any initial regimen may permit the selection of resistant quasi-species soon after initiation. Patients who develop resistance early are likely to have clinical indicators of their failing regimen soon after therapy is initiated. A vigilant HIV provider would be able to detect this failure early on, and would then modify therapy before multi-drug resistant strains develop.

Baseline HIV-1 RNA More Than 100,000

The major reason patients with high viral loads do not achieve complete viral suppression is that many three-drug antiretroviral combinations may not be potent enough to reduce the burden of virus in the body. Simply put, the larger the difference between baseline viral load and non-detectable viral load, the more potent the antiretroviral combination must be in order to suppress the virus.

Continued on page 5

Modifying HAART: Strategies for Avoiding Salvage Therapy for HIV

Continued from page 4

For example, a patient with a baseline HIV-1 RNA level of 500,000 copies/mL (log = 5.7) would have to decrease their viral load by more than log 4.0 (more than 10,000 fold) to achieve a viral load of less than 50 copies/mL. Unfortunately, most three-drug regimens achieve a mean of 2.5 to 3.0 log reductions. The range for viral load reduction is obviously quite variable. In addition, other co-factors such as baseline CD4 lymphocyte count and baseline resistance contribute to the magnitude in viral load reduction.

Baseline CD4 Less Than 200

CD4 lymphocyte responses remain a critical component in the host's response to controlling HIV replication. When this system of defense is compromised, lymphocyte killing of HIV is diminished, even in the setting of potent antiretroviral therapy. Patients with low CD4 lymphocyte counts are less likely to have an effective cell-mediated response to HIV compared to those individuals with higher CD4 counts. Therefore, it is no surprise that individuals with a low CD4 lymphocyte count commonly have an extremely high HIV-1 RNA level, though the correlation is not perfect. Thus, low CD4 and high HIV-1 RNA, can each contribute to failing standard combination therapy.

Preventing Treatment Failure

Four-drug initial therapy is one possible intervention for patients who have high initial viral loads or low initial CD4 T cell counts. However, patients with advanced disease are also more likely to experience adverse side effects from antiretroviral therapy compared to those with less-advanced disease. Thus, many clinicians may wish to avoid the use of four (or more) antiretrovirals when initiating therapy, realizing that they may not achieve virologic success. The question is, then, what are the options for better treatment in this setting?

Intensification vs. Salvage

Intensification refers to the strategy of adding an additional agent or agents when the initial regimen appears to need a 'boost' to improve its effectiveness. Intensification is implemented when the initial regimen is continuing to reduce HIV-1 RNA levels (i.e. no increase in HIV-1 RNA), but the regimen does not appear to be likely to achieve virological success by the end of six months (the time when all initial antiretroviral regimens should achieve maximal HIV-1 suppression). In this setting, intensification may be used, because HIV-1 levels are continuing to decline, and the development of resistant strains is unlikely.

Salvage therapy, on the other hand, is used when an initial antiretroviral combination has achieved an initial response (with or without achieving maximum virological suppression), followed by an increase in HIV-1 RNA levels. Of course, the astute clinician will want to rule out non-adherence to the medications before modifying the regimen. In the face of adherence, an increase in HIV-1 levels suggests the emergence of antiretroviral resistant strains.

Thus, intensification allows the clinician to add a new medication to a regimen that is succeeding but needs a little help while salvage implements a new or markedly modified regimen in the setting of developing resistance. The clinician must carefully exclude non-adherence and early resistance as other possible explanations for the viral load increase, and only then intensify therapy.

Early Signs of Treatment Failure

- Three early predictors of failing an initial antiretroviral com-

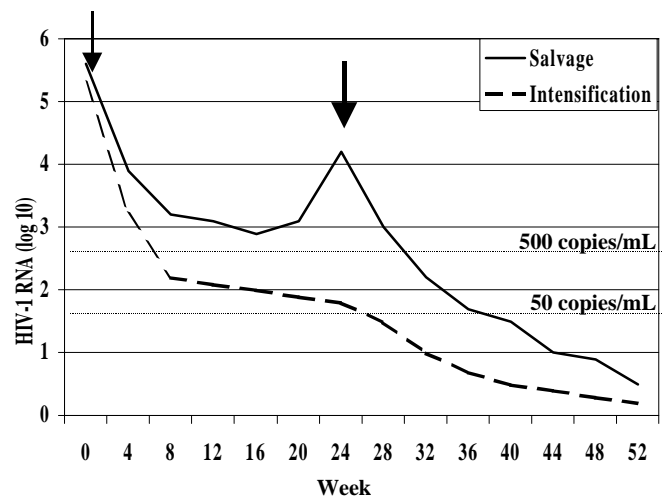
bination have been identified: HIV-1 RNA level = 1,000 at Week four;

- HIV-1 RNA level = 400 copies at Week twelve; and
- HIV-1 RNA = 50 copies at Week 24.

Viral Load Monitoring

To consider intensification therapy in a correctional setting, an HIV specialist must have access to regular viral load testing. The costs for viral load testing are infinitely less than the cost of changing a failing regimen. In order to assess the efficacy of therapy, viral load determinations should be obtained at least four, twelve, and twenty-four weeks after an antiretroviral combination is initiated. If the HIV clinician is concerned that a patient may fail, monitoring viral load frequently (i.e. monthly) may be necessary. Increases in viral load are an indicator that intervention may be required.

Figure 2 below schematically illustrates the difference between patients who initiate unsuccessful combination antiretroviral therapy and whose regimens are either intensified or salvaged at Week 24. Both patients depicted in this graph have a baseline HIV-1 RNA of around 350,000 copies/mL (high risk for virologic failure) and respond with an initial brisk reduction in HIV-1 RNA levels.



Earlier Salvage

The patient with the solid line had a viral load reduction of about 2.5 log by Week 12 (but only to a level of around 2,000 copies) where the viral load level initially stabilizes. By Week 24, however, the HIV-1 RNA level has increased by about 1.0 log in the setting of perfect adherence. Pathophysiologically, from Week 12 through Week 20, viral replication of the wild type was maximally suppressed and the development of resistant strains had begun. This led to emergence of resistant strains by Week 24 when an entirely new antiretroviral combination (salvage therapy) was initiated with a prompt reduction in HIV-1 RNA levels.

Even though salvage was clearly indicated at this point, the patient might have benefited if his regimen had been modified earlier rather than waiting until week 24 to completely replace the regimen. The success of salvage therapy is moderated by how early therapy is changed after viral replication has increased. The best success when using a salvage regimen is a change in therapy when the viral load remains low (theoretically when there are less genotypic mutations conferring resistance).

HEPPigram

A feature of HEPP News providing concise solutions to correctional HIV-related problems.

Strategies to Improve Adherence

Adapted from Altice FL, Buitrago MI. (1998). Adherence to antiretroviral therapy in correctional settings. *J Correctional Health Care*. 5:2. 179-200, as well as *The Living Document: Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*, May 5, 1999, available at www.hivatis.org

Medications-Related

- Inform patient, anticipate, and treat side effects
- Simplify food requirements
- Avoid adverse drug interactions (see HIV-101)
- If possible, reduce dose frequency and number of pills
- Adapt schedule to patient's schedule

Doctor Related

- Establish trust
- Either serve as educator, source of information, ongoing support and monitoring, or provide access to a trusted individual such as a nurse case manager who can perform the above.
- Provide access between visits for questions
- Monitor ongoing adherence; intensify management in periods of low adherence (i.e. more frequent visits and deployment of other team members. In systems which use directly observed therapy (DOT) or modified DOT, check the medication logs to verify.)
- Consider impact of new diagnoses on adherence, e.g. depression, liver disease, wasting, recurrent chemical dependency, and include adherence intervention in management
- Schedule frequent follow up visits soon after initiating or changing treatment plan

Patient Related

- Ask patient to keep a 1-2 week diary of activities before starting therapy to identify key facilitators or barriers to adherence.
- Describe and agree on a treatment plan
- Check that the patient understands the plan
- Ask the patient to adhere to the plan
- Take time, multiple encounters to educate and explain goals of therapy and need for adherence
- Develop concrete plan for specific regimen, relation to meals, daily schedule, side effects
- Provide written schedule and pictures of medications and other medical aids to adherence
- All HIV infected persons should be screened, and if indicated, should be treated for co-morbid mental illnesses

System Related

- Confidentiality is essential within the units of the correctional system, with special attention to the patient's safety and security
- Develop adherence support groups, or add adherence issue to regular agenda of support groups
- Continuous healthcare intervention should be provided, including follow up without a break in care upon transfer or discharge from a correctional facility
- Timely and appropriate access/accommodation to care is needed that is comparable to that available in the community
- Establish an HIV care team

SAVE THE DATES

The Eighth Annual UCLA AIDS Institute Scientific Symposium "Global Challenges"

November 19, 1999

The Anderson School at UCLA, Korn Convocation Hall
Los Angeles, CA

Keynote Speaker: Dr. Helene Gayle, Director of CDC's National Center for HIV, STD and TB Prevention. For further information call 310.794.5335

<http://www.medsch.ucla.edu/aidsinst/about/Conferences.htm>

6th National AIDS Treatment Forum

December 11-14, 1999

Miami, Florida

The purpose of the conference is to develop HIV treatment educators and case managers. Sponsored by NATAF.

Contact: National Minority AIDS Council at 202.483.NMAC (6622). Register by November 15, 1999

Retroconference 2000 - 7th Conference

January 30-February 2, 2000

San Francisco, CA

Registration opens for abstract authors: November 12, 1999

Registration opens for other researchers and clinicians: November 30, 1999

Late breaker abstract deadline: January 5, 2000

The Call for Abstracts will be posted at the following site:

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

10th Annual Clinical Care Options for HIV Symposium

May 4-7, 2000

Hyatt Gainey Ranch,

Scottsdale, Arizona

http://hiv.medscape.com/Medscape/public/symposia/AIDS2000/form_symp2000.html

Modifying HAART: Strategies for Avoiding Salvage Therapy for HIV

Continued from page 5

Appropriate Intensification

The patient depicted by the dashed line is an example of an anti-retroviral intensification strategy. Similar to the patient with the solid line, the baseline viral load is around 350,000 copies/mL and rapidly decreases soon after initiation of a three-drug antiretroviral combination. From Week 12 to Week 24, the HIV-1 RNA is continuing to decrease, albeit slowly. This is in contradistinction to the other patient. Here, the patient had not achieved a non-detectable viral load by Week 24 and the viral load had not risen, therefore a fourth antiretroviral agent could be added to the regimen to maximize viral suppression. Note that in this setting a single drug is being added to a succeeding regimen, not a failing regimen. When a regimen is failing, the appropriate intervention is salvage therapy instead of intensification.

How to Intensify?

Studies of antiretroviral intensification are currently underway. Unfortunately, no clinical trials have been performed as yet that indicate which antiretrovirals are appropriate for intensification of therapy. The following recommendations are issued, therefore, with the caveat: intensification therapy is currently based on scientific principles and not on health outcomes research.

The table below lists potential intensification options for patients initiating antiretroviral therapy. A decision to intensify should be made based on viral load at one of the three time points: week 4; week 12; or week 24.

It is important to note that intensification never applies to two drug regimens, which are only recommended in highly controlled circumstances. Therefore intensification should NEVER include starting with two antiretrovirals and adding a third after six months when viral suppression is not achieved, as two drug regimens have all proven to be inferior to three-drug combinations.

Summary and Key Points

Optimal initial antiretroviral therapy includes the use of at least three potent antiretrovirals, a regimen that has been shown to allow a majority of patients to achieve and sustain a non-detectable viral load. For those patients who do not reach this goal, there are several clinical predictors which can guide clinicians to optimize therapy before virological failure occurs and less-optimal salvage therapy must be initiated. One such strategy to avoid salvage therapy includes antiretroviral intensification. This approach may avoid the development of antiretroviral resistance, and the associated toxicities of four or more antiretrovirals during initial therapy and may ultimately be more cost-effective than salvage therapy regimens. The strategy is unproven as of yet, although it is gaining favor in community HIV practices and holds promise for the future. Successful implementation of intensification strategies is dependent upon the availability of frequent viral load testing. Appropriate use of intensification may, in the long run, reduce correctional HIV costs. While we anticipate more information on outcomes studies, we may judiciously implement this approach in our management of correctional HIV patients.

Initial Antiretroviral Combination	Intensification Antiretroviral
3 NRTIs	+ PI or + NNRTI
2 NRTIs + NNRTI	+ NRTI or + PI
2 NRTIs + PI	+ NRTI or + NNRTI
3 NRTIs*	+ Hydroxyurea (HU)
2 NRTIs* + NNRTI	+ Hydroxyurea (HU)
2 NRTIs* + PI	+ Hydroxyurea (HU)

* Since HU works with DDI, One NRTI should be didanosine if hydroxyurea is considered.

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HIV 101

*See next month's issue for interactions between retroviral agents.

Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents
Table 1: Drugs that Should Not be Used With Antiretrovirals

(Adapted from HIVATIS webpage: www.thebody.com/hivatis/agents/agents01.html)

Drug Category	Indinavir	Ritonavir	Saquinavir	Nelfinavir	Amprenavir	Nevirapine	Delavirdine	Efavirenz
Analgesics	None	Mepiridine, Piroxicam, Propoxyphene	None	None	None	None	None	None
Ca++ Channel Blocker	None	Bepridil	None	None	None	None	None	None
Cardiac	None	Amioderone, Encainide, Flecainide, Propafenone, Quinidine	None	None	None	None	None	None
Lipid Lowering Agents	Simvastatin, Lovastatin	Simvastatin, Lovastatin	Simvastatin, Lovastatin	Simvastatin, Lovastatin	Simvastatin, Lovastatin	None	Simvastatin, Lovastatin	None
Anti-mycobacterial	Rifampin	None	Rifampin, Rifabutin	Rifampin	Rifampin	None	Rifampin, Rifabutin	None
Antihistamine	Astemizole, Terfenadine	Astemizole, Terfenadine	Astemizole, Terfenadine	Astemizole, Terfenadine	Astemizole, Terfenadine	None	Astemizole, Terfenadine	Astemizole, Terfenadine
Gastro-intestinal Drugs	Cisapride	Cisapride	Cisapride	Cisapride	Cisapride	None	Cisapride, H-2 Blockers, Proton pump inhibitors	Cisapride
Anti-depressant	None	Bupropion	None	None	None	None	None	None
Neuroleptic	None	Clozapine, Pimozide	None	None	None	None	None	None
Psychotropic	Midazolam, Triazolam	Clorazepate, Diazepam, Estazolam, Flurazepam, Midazolam, Triazolam, Zolpidem	Midazolam, Triazolam	Midazolam, Triazolam	Midazolam, Triazolam	None	Midazolam, Triazolam	Midazolam, Triazolam
Ergot Alkaloids (vaso-constrictor)	Dihydro-ergotamine (D.H.E. 45) ergotamine* * (various forms)	Dihydro-ergotamine (D.H.E. 45) ergotamine* * (various forms)	Dihydro-ergotamine (D.H.E. 45) ergotamine* * (various forms)	Dihydro-ergotamine (D.H.E. 45) ergotamine* * (various forms)	Dihydro-ergotamine (D.H.E. 45) ergotamine** (various forms)	None	Dihydro-ergotamine (D.H.E. 45) ergotamine* * (various forms)	Dihydro-ergotamine (D.H.E. 45) ergotamine* * (various forms)

* The contraindicated drugs listed are based on theoretical considerations. Thus, drugs with low therapeutic indices yet with suspected major metabolic contribution from cytochrome P450 3A, CYP2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

** This is likely a class effect.

Suggested Alternatives:

Simvastatin, Lovastatin, Atorvastatin, Pravastatin, Fluvastatin, Cerivastatin (alternatives should be used with caution)

Rifabutin: Clarithromycin, Azithromycin, (MAI Prophylaxis); Clarithromycin, ethambutol (MAI Treatment)

Astemizole, Terfenadine: Loratidine

Midazolam, Triazolam: Temazepam, Lorazepam

HIV/AIDS Behind Bars, 1999: Public Health/Corrections Collaborations

Pre-Conference Colloquium on Saturday, November 6 from 1pm to 5pm
 23rd National Conference on Correctional Health Care, Fort Lauderdale, FL

The Conference:

The goal of this year's colloquium is to describe the rationale for engaging in collaborations between public health and correctional health. Representatives of the CDC and HRSA will discuss funding mechanisms for this type of collaboration. Examples of successful projects will be presented. Register with the registration for the NCCHC conference. CME available.

Travel Fellowships:

Travel fellowships are for persons wishing to learn more about how to improve HIV diagnosis, management and continuity of care by creating collaborations with public health agencies. First priority will go to persons who are not currently involved in public health/corrections collaborations but would like to learn more about such opportunities.

For more information, contact Matthew Stark at: tel: 401.863.2180 or fax: 401.863.1243 or e-mail: heppnews@brown.edu

For more information on the 23rd NCCHC conference, call 773.880.1460 or go to <http://www.ncchc.org>

News Flashes

CDC Announces \$7 Million for HIV and STD Prevention in Prisons

As correctional health officials met in Chicago last month to create guidelines to curb the HIV infection rate among prison inmates, the CDC announced a \$7 million grant to battle AIDS, STDs and substance abuse among minority prisoners in seven states, which together house 83% of the nation's inmates. Each state -- California, Florida, Georgia, Illinois, Massachusetts, New Jersey and New York - will receive between \$900,000 and \$1.1 million. The funding is part of the \$39 million the Congressional Black Caucus obtained to address "a public health emergency" among minorities, as reflected in the following statistics: one out of four black men passes through the correctional system where the HIV infection rate is 5% and AIDS has become the leading cause of death for black men ages 25-44. Dr. Helene Gayle, director of the CDC's National Center for HIV, STD and TB Prevention said, "Prison and jails provide a critical opportunity to provide lifesaving HIV prevention services to a population that might otherwise be missed. Many of these individuals pass through these facilities only briefly before returning to the community. If we fail them, we fail our communities." (Associated Press, 10/4).

NIJ/BJS Study Provides New Numbers for a Familiar Problem: High AIDS Rates in U.S. Prisons

Prison inmates are 5-10 times more likely than non-inmates to have AIDS or HIV, indicating an AIDS prevalence rate 5 times higher than the total population, and an HIV prevalence rate 8-10 times higher than the total population. A study presented at the National HIV Prevention Conference (Atlanta, GA, August 29-September 1) estimated that 39,000 people, or approximately 17 percent of the 229,000 people with AIDS in 1996, had been released from a correctional facility that year. The percentages were even higher for HIV infection, hepatitis C and tuberculosis.

Testing and treating persons passing through correctional systems could greatly reduce HIV/AIDS transmission within the community. A

survey conducted for the CDC in 1996 and 1997 found that only 10 percent of state and federal prison systems and only 5 percent of city and county jail systems offered comprehensive HIV prevention programs for inmates. (Hammett T, Maruschak L. 1996-1996 Update: HIV/AIDS, STDS, and TB in Correctional Facilities. USDOJ/OJP/NIJ. NCJ 176344. July 1999.)

Updated Antiretroviral HIV Drug Approvals and Pediatric Labeling Information

As of April 16, 1999 there are 16 drug products (14 drug substances) approved by the Food and Drug Administration (FDA) for the treatment of HIV infection. Eight drug products have pediatric information in the approved product labeling. The reason for the difference in numbers is two of the products are related to previously approved products. Combivir is a combination formulation of two previously approved products, zidovudine and lamivudine. Fortovase is a new formulation for saquinavir. <http://www.fda.gov/oashi/aids/pedlbl.html>

Outreach for HIV Coaxes Difficult Clients into Drug Treatment

People at risk for HIV/AIDS because of their drug use behaviors can be successfully engaged in substance abuse treatment programs through carefully designed public health outreach efforts. A special issue of the journal, *Evaluation and Program Planning* reported this key finding from demonstration projects supported by the Substance Abuse and Mental Health Services Administration's (SAMHSA) Center for Substance Abuse Treatment (CSAT). The results of the study indicate that hard-to-reach populations are more likely to enter treatment for substance abuse through participation in HIV outreach programs than would clients recruited specifically for treatment. (Evaluation and Program Planning, September 16, 1999; special issue.)

Study Indicates Feasible STD Testing for Women Entering Correctional Facilities

According to a study published in the CDC's *Morbidity and Mortality Weekly Report*, routinely testing women for chlamydia and gonorrhea

infections as they enter corrections facilities is "feasible" and would increase the number of women undergoing treatment, as a high percentage of women in corrections facilities who have STDs go undiagnosed. The entire article is available at: <http://www2.cdc.gov/mmwr/>

HIV-1 Drug Resistance in Newly Infected Individuals

A September article in JAMA reported that 16.3% of 67 newly infected patients had a variant of HIV-1 that was resistant to any antiretroviral drug. Twenty-seven percent were at least threefold resistant to at least one antiretroviral drug. These findings indicate the need to increase resistance testing among patients infected with HIV-1. Further research is necessary to examine both the genotype and phenotype of transmitted viruses. (Boden et al. JAMA 9/22/99-09/29/99; 282(12): 1135).

Good News: Perinatal HIV/AIDS Trend in the US

The CDC reported that the decline in perinatal AIDS incidence and the increase in perinatal zidovudine use indicate that there has been success in implementing PHS guidelines. Cases of perinatal AIDS peaked in 1992 and then dropped 67 percent through 1997 (Lindegren, M et al. JAMA 8/11/99; Vol. 282, No. 6, P. 531). Two other recent reports also address perinatal transmission: L Mofenson, et al. NEJM 341(6):385-93 (1999); and P Garcia, et al. NEJM 341(6):394-402 (1999).

Single Dose Prophylaxis Reduces Perinatal HIV Transmission

American and Ugandan researchers found that a single \$4 dose of nevirapine cuts transmission nearly in half, surpassing the current therapy of choice, a short and expensive course of AZT. In the Uganda study, four months after birth, 13% of the infants receiving nevirapine tested positive for HIV, compared with 25% of infants receiving AZT. This simpler intervention might prevent up to 400,000 new infections annually in developing countries. While the study does show promise, further study is needed before the treatment is introduced on a greater scale (New York Times, 7/15/99).

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Brown University School of Medicine 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 November 30, 1999. The estimated time for completion of this activity is one hour and there is no fee for participation in this activity.

1. A decision to intensify antiretrovirals should be based on viral load taken at:

- a) week 4, week 8, week 16
- b) week 3, week 9, week 12
- c) week 4, week 10, week 18
- d) week 4, week 12, week 24

2. Which of these two cases should be treated with salvage therapy?

	Baseline HIV-1 RNA	Week 12 HIV-1 RNA	Week 24 HIV-1 RNA
Case A	350,000 copies/mL	2.5 log reduction	1.0 log increase
Case B	350,000 copies/mL	2.5 log reduction	additional 0.1 log reduction

a) Case A b) Case B c) Neither; each should be intensified, not salvaged.

3. Indicate which of the following statements are true:

- a) Clinical Trials of antiretroviral intensification have shown clinicians which antiretrovirals are appropriate for intensification.
- b) The cost for regular viral load testing is infinitely less than the cost of changing a false regimen.
- c) Multiple encounters with the clinician do not directly improve a patient's adherence to ART.
- d) Improved patient outcomes cannot be traced to the use of resistance testing.

4. Indicate which of the following statements are false:

- a) Intensification can be applied to both three-drug and two-drug regimens.
- b) One study has shown that HU taken with a ddI-containing regimen may reduce HIV viral load by an additional 0.4-0.6 log.
- c) T20 fusion inhibitor has shown cross resistance with other ART

5. Which of the statements below accurately describe a new finding about the following regimen? 1600mg of SQV bid or 1200mg SQV with 1250 mg NFV bid:

- a) This regimen is cross resistant with other ART
- b) This regimen is as effective in combination therapy as 1200mg SQV tid.
- c) This regimen may reduce HIV viral load by an additional 0.8 to 1.2 logs.
- d) This regimen is more effective in combination therapy than 1200 mg SQV tid.

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