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HEPP NEWS

February 2000 Vol. 3, Issue 2

HIV
EDUCATION
PRISON
PROJECT

Sponsored by the Brown University School of Medicine 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.

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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.

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HIV MANAGEMENT GUIDELINES: NEWS AND TRENDS

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Existing HIV treatment guidelines are updated every two years by the International AIDS Society¹ and published in the Journal of the American Medical Association. Consensus from the Kaiser Foundation and Health and Human Services on new agents are inserted on the Guidelines Website as they become available (www.hivaits.org; last update 5/99).

Correctional clinicians must carefully weigh the benefits of ART against the implications of long term therapy.

A new version of the guidelines was recently published in the *Journal of the American Medical Association*.² This article will review the new guidelines and highlight important changes since the last version was published 18 months ago (1998).

The July 1998 guidelines marked the codification of "highly active antiretroviral therapy" (HAART), a move that was supported by accumulating data from clinical and pathogenesis studies. At the time, there were a number of possible combination regimens available and an expanding number of choices for initial regimens.

In updates published since 1998, Efavirenz (Sustiva), Abacavir (Ziagen) and Amprenavir (Agenerase) have been added to the list of possible treatment options. Now a total of 15 antiretroviral agents are available in the United States (see Table 1). This underscores a guidelines recommendation that treatment of HIV-infected patients should be directed by a physician with extensive experience in the care of these patients.

The most significant difference between recommendations from 1998 and the "state of ART" in 2000 should come as no surprise to correctional HIV providers who have experience treating HIV patients. The concept that we should "hit hard, hit early" is evolving into "think hard, get the patient involved, then hit hard as early as possible." There are two reasons for the new hesitancy: (1) side effects and (2) adherence. Indeed, when

the guidelines were written in 1998, protease inhibitors were having a miraculous effect on patients, and it appeared as if a cure for HIV was at hand. Since then, an array of side effects associated with HAART has been noted, and concerns about the long-term durability of the new drugs have been raised.

Correctional clinicians must carefully weigh the benefits of ART against the implications of long term therapy. For our patients who commonly experience destabilizing "life events," it becomes increasingly important to identify factors that can assist with stabilizing a patients' life before initiating treatment. Thus, rehabilitation, education, and careful discharge planning are increasingly important components of expert HIV management in corrections.

REVISITING "HIT EARLY, HIT HARD"
Initial theoretical modeling that HIV might be eradicated after about three years of complete viral suppression,³ have been withdrawn or radically amended, as reports of viral rebound after lengthy viral suppression accumulate.⁴ Unfortunately, the early speculative calculations did not take into account the existence of a small but critical pool of resting memory CD4+ lymphocytes that may contribute to persistence of replication-competent HIV in persons in spite of maximal viral suppression.^{5,6,7}

The good news is that there are few reports of emergence of resistance when viral loads are suppressed to 20 to 50 copies/mL, even though most HIV researchers believe that viral replication is ongoing at low levels in reservoir sites. Furthermore, long-term suppression correlates with durability of virologic response to potent regimens.^{8,9,10}

ADHERENCE IN THE REAL WORLD
Even though patients are aware that close drug

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HIV MANAGEMENT...

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adherence is essential in preventing viral resistance, current regimens can be difficult for patients to adhere to. Recognizing this, the 1998 guidelines stated that adherence, short-term and long-term adverse effects, impact on quality of life, and evolution of resistance must be addressed with each person considering treatment. The 2000 guidelines discern advantages and disadvantages of each type of triple drug regimen, highlighting regimens that are easier to adhere to (see HIV 101, pg. 8).

LONG TERM ADVERSE DRUG EFFECTS

Over the past few years, HIV care providers have been more concerned about the potential for long-term adverse drug effects. Lipodystrophy continues to be a significant side effect associated with protease inhibitors, and new studies appear to indicate that this condition may not be linked to any particular drug, rather it may be linked to the duration of therapy, to baseline body mass index, and to the quantity of fat in the patients' diet (for more on these recent findings, see next month's HEPP News for a report on the 7th Retrovirus conference). Reports of mitochondrial toxicity (manifested by fatigue, nausea, vomiting, abdominal pain, weight loss, dyspnea and low serum bicarbonate levels) have been associated with the use of NRTIs (particularly D4T and 3TC in one study of 106 cases by Boxwell and Styrt, who reported the FDA experience with mitochondrial toxicity at the 1999 ICAAC meeting, Abstract 1284). However, physicians who follow large numbers of incarcerated HIV-infected patients on HAART have failed to identify cases of severe mitochondrial toxicity to date, even though low serum "bicarbonate" is a frequent finding associated with treatment.

WHEN TO INITIATE THERAPY:

PLAN A/PLAN B

The last time the guidelines were published, there was growing recognition that early treatment initiation was associated with virologic, immunologic, and clinical benefits. Based on that perception, the International AIDS Society-USA panel recommends antiretroviral therapy for any patient with established HIV infection and a confirmed plasma HIV-1 RNA level 5,000-30,000 copies/mL or T-cell count 350-500 copies/ μ L who "is committed to the complex, long-term therapy" (see Table 2).

However, since the first therapeutic intervention (Plan A) is the one with the greatest chance of success, careful discussion of the regimen with the patient is recommended. The patient and physician should have another plan (Plan B) in mind for future treatment options, as well as some supplemental interventions (intensification) for the current regimen in case the initial regimen begins to falter.

In addition to drug failure secondary to poor adherence and suboptimal regimens, new data has accumulated over the past year that poor initial response may be due to pre-existing resistance to one or more of the selected agents.^{11,12} Genotyping at the time of treatment

initiation is gaining favor (see section "Monitoring resistance" and Table 2, pg. 7).

Many would also consider therapy for patients who have detectable viral loads at any level and evidence of T-cell decline over time, however, there is a great deal of variation among experienced practitioners. (See HIV 101 pg. 8 for a discussion of the options available at the initiation of therapy.)

HHS/IAS guidelines (Table 2) currently recommend:

1. For asymptomatic patients with low plasma HIV RNA level (e.g., <5000/mL) and high

CD4+ cell count (e.g., >350-500/ μ L) deferral of therapy with close follow-up may be recommended given treatment complexities, risk of adverse effects, consequences of resistance, and the possibility that such persons may fall into the category broadly described as long-term nonprogressor.

2. For those with moderately high HIV RNA levels (e.g., 5,000-30,000 copies/mL) and low CD4+ cell count (e.g. <350/ μ L) therapy initiation is recommended, given independent prognostic significance of CD4+ cell count and clinical trial data support.

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TABLE 1. Current HIV Antiretrovirals and Dosages.*

DRUG (Trade Name & Manufacturer)	DOSAGE	FORMULATIONS	COMMENTS
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)			
Zidovudine(AZT, ZDV) (Retrovir) Glaxo Wellcome	300mg BID or 200mg TID	100mg capsules	Can cause anemia, neutropenia, nausea, lethargy/confusion/agitation and myositis.
Didanosine (ddl) (Videx) Bristol-Myers Squibb	200mg BID or 400 QD	100mg tablets	Take on empty stomach. ¹ Toxicities include pancreatitis, peripheral neuropathy.
Zalcitabine (ddC) (Hivid) Roche	0.75mg TID	0.75mg tablets	Peripheral neuropathy most common toxicity; also pancreatitis
Lamivudine (3TC) (EpiVir) Glaxo Wellcome	150mg BID	150mg tablets	Minimal toxicity; rapid resistance.
Stavudine (d4T)(Zerit) Bristol-Myers Squibb	20 or 40mg BID	40mg capsules	Can cause peripheral neuropathy
Combivir (lamivudine + zidovudine) Glaxo Wellcome	1 tablet BID	1 tablet	See comments under individual drugs
Abacavir (Ziagen) Glaxo Wellcome	300mg BID	300mg tablets	Rash, upper respiratory symptoms, muscle aches: flu-like syndrome that must be carefully diagnosed - rechallenge may lead to anaphylaxis and death.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Nevirapine (Viramune) Boehringer/Roxane	200mg BID see comments	200mg tablet	Rapid resistance; good tissue penetration; rash is common. Start with 200QDx14 days then 200mg BID
Delavirdine (Rescriptor) Pharmacia/Upjohn	400mg TID	100mg tablets	Less experience; raises level of some protease inhibitors; rash less common than with nevirapine: most would use in combination with other drugs as a "booster"
Efavirenz (Sustiva) Dupont Pharmaceuticals	600mg QD	200mg capsules	Vivid dreams, rash, diarrhea, headache
Protease Inhibitors (PIs)			
Saquinavir (Inverase, Fortovase) Roche	Invirase: 3x200mg TID	200mg hard gelatin capsules	Poorly absorbed; should not be used as the only PI. Mild gastrointestinal disturbances common
	Fortovase: 6x200mg TID	200mg hard gelatin capsules	Better absorbed than invirase, mild gastrointestinal disturbances common.
Ritonavir (Norvir) Abbott	600mg BID	100mg capsules	Gastrointestinal side effects common
Indinavir (Crixivan) Merck	800mg TID (q8h)	400mg capsules	TID dosing; take on empty stomach. ¹ Nephrolithiasis common; can be reduced with adequate rehydration
Nelfinavir (Viracept) Agouron	750mg TID or 1250 mg BID	250mg tablets	May cause diarrhea; may induce less cross-resistance
Amprenavir (Agenerase) Glaxo Wellcome	1200mg BID	150mg capsules	Most common side effects include nausea, vomiting, diarrhea, rash, and tingling sensation around the mouth.

*Antiviral drug dosages are frequently updated. Consult the MMWR (Morbidity and Mortality Weekly Report) for the most updated dosages (www.cdc.gov/mmwr).

¹30 minutes before or two hours after a meal.

Adapted from Merigan T, Bartlett J, Bolognesi D. *Textbook of AIDS Medicine*. Second ed. Williams and Wilkins, Baltimore MD. 1999. And *HIV AIDS Treatment and Information Services: www.hivatis.org*.

LETTER FROM THE EDITOR

Dear Colleagues,

Welcome to the February issue of HEPP News. You'll note a number of important changes in this issue. First, we are pleased to announce that Joe Bick of the California Department of Corrections Medical Facility at Vacaville is joining Rick Altice and Anne De Groot as a main editor. Lester Wright, Medical Director at the New York State Department of Correctional Services, Joseph Paris, Medical Director of the Georgia Department of Corrections, Khurram Rana, pharmacist at Roger Williams Hospital in Rhode Island, and Ralf Jürgens of the Canadian AIDS Society have also joined the HEPP Advisory Board. David Paar is now a Senior Advisor instead of an Associate Editor. All of us at HEPP would like to thank Steve Szebenyi and Roderic Gottula, who are stepping down from the Advisory Board, for all of their help and support this past year.

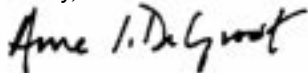
Second, we have received the results of our reader survey and we sincerely appreciate your feedback. We are encouraged by the number of positive responses we received; according to you, we meet your needs for HIV information that is corrections specific. In response to your requests, we'll be providing more "Ask the Expert" cases, alternating these cases with "Spotlights" on correctional HIV personalities or special programs.

Third, we hope you like the new "look" that our layout experts Michelle Gaseau and Kim Backlund-Lewis of The Corrections Connection have provided.

After reviewing this issue, readers should be able to chose the appropriate antiretroviral regimens for either initiating or restarting therapy, identify which course of action to take given a recidivist patient who had discontinued therapy, and describe the advantages and disadvantages of different antiretroviral therapy. In next month's issue we will bring you news from the 7th Conference on Retroviruses and Opportunistic Infections, as well as an update on the treatment of tuberculosis in the correctional setting, edited by Joe Bick.

Give us your feedback! We like hearing from you.

Sincerely,



Anne S. De Groot, M.D.

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, feed-back, and correspondence from our readership.

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HIV MANAGEMENT...

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THERAPEUTIC CAVEATS

It is important to note that dual NRTI and dual PI regimens (without a third drug) are still not considered acceptable forms of ART. Dual NRTI regimens are not considered acceptable except when encountering patients currently succeeding on such a regimen. In those cases, most HIV practitioners would not "rock the boat" and would elect to keep the patient on the dual NRTI treatment.

An increasing concern has been whether disease stage should dictate the approach to treatment, since response rates decrease as HIV disease advances. Many experienced providers would consider using four drugs instead of three for patients who were starting therapy in later stage HIV/AIDS.

HOW TO START

The most important factors to consider when first initiating a regimen include the following: (1) the patient's status (CD4+ T-cell count, viral load); (2) the potency of the regimen; and (3) the willingness and ability of the patient to adhere to the regimen. Additional considerations include the potential for drug interactions with other necessary medications, the potential for exacerbation of underlying medical conditions (e.g., neuropathy), the potential for long-term adverse effects, and the preservation of future treatment options. The latter point is worth keeping firmly in mind when discussing the initial regimen with the patient. A well-designed Plan A (initial regimen) keeps an equally effective and tolerable Plan B in reserve.

MONITORING THERAPY RESPONSE

Beginning in 1998, the guidelines also featured a recommendation that quantitative viral load assays be used to monitor therapeutic response. The assays were considered "an essential parameter" by the 1998 guidelines panel and have become routine adjuncts to the HIV management portfolio, even in correctional settings. CD4+ T-cell counts have been de-emphasized as a result, and now should be followed at less frequent intervals (every three to six months) after the initiation of therapy.

A major advance in HIV treatment has been the development of plasma HIV RNA assays of increased sensitivity. These assays now achieve a range of about 20-50 to about 50,000 copies/mL of plasma. Most physicians obtain "Version 1" viral load measurements (sensitive to about 400 copies/mL) about six weeks to eight weeks after initiating therapy (sooner if failure is considered possible) as the first follow up indicator of response to a new regimen. If a response is seen, this is followed by an "ultrasensitive" assay about two to four weeks later. The expected response to an effective regimen is reduction of viral load by one log at eight weeks and no detectable virus at four to six months after initiation. The more rapid the reduction, the more effective the therapy is believed to be. The ultra sensitive assay confirms suppression of virus to the

TABLE 2. Ranges of CD4+ T-cell Count & Viral Load Levels for Therapy Initiation

CD4+ T-cells, 3x10 ⁶ /L	Plasma HIV RNA Level, Copies/mL		
	<5,000	5,000-30,000	>30,000
<350	Recommend Therapy	Recommend Therapy	Recommend Therapy
350-500	Consider Therapy**	Recommend Therapy	Recommend Therapy
>500	Defer Therapy	Consider Therapy	Recommend Therapy

**Opinions vary. Aggressive clinicians would treat patients at this level. Some choose to defer treatment. Adapted from JAMA 1/19/00; 283(3): 382.

lowest detectable level and provides a benchmark for monitoring future response to therapy.

The rationale for tighter monitoring of viral loads is that evolution of resistance is restricted in patients who have viral load levels less than 50 copies/mL, even though low levels of viral replication probably still persist. Evidence of failing regimen includes: a decrease in CD4+ T-cell count of greater than 30% from baseline, and a greater than 0.5 log (or three-fold) increase in viral load. As intercurrent infections and vaccinations can affect viral loads, measurements should be repeated before instituting changes in therapy.

MONITORING RESISTANCE AND DRUG LEVELS

In 1998, both Genotyping and Therapeutic Drug Level monitoring were thought to be interesting but unproven; data now exists that these tools are useful in some clinical settings when implemented by fairly experienced HIV providers. Note that drug resistance testing is extremely costly. Resistance testing is best used in combination with a careful drug history to choose new regimens, since absence of genotypic or phenotypic evidence of resistance does not imply that a drug is guaranteed to be active. Drug level monitoring is available in some settings but will see limited use in correctional settings due to cost and the absence of good data showing better outcomes.

TREATMENT FAILURE:

IMPLEMENTING PLAN B

The strictest definition of treatment failure is that of confirmed detectable plasma HIV RNA (i.e., >50 copies/mL) in an adherent patient who had achieved a viral load level below the detection limit and has not experienced a recent acute infectious illness or vaccination. Indications for change include the following:

1. Less than a 0.5 to 0.75 log reduction of plasma HIV RNA by four weeks following initiation of therapy or less than a 1 log reduction at eight weeks (intensification might be the best option; see article by Rick Altice, MD in the October 1999 issue of HEPP News);
2. Failure to suppress plasma HIV RNA to undetectable levels within four to six months of initiating therapy (except when the patient starts from a very high e.g. 106 viral load).
3. Repeated detection of virus after initial suppression, suggesting viral resistance;

4. Any reproducible increase in the viral load defined as three fold or greater that is not due to acute intercurrent infectious illness or vaccination;

5. Dual nucleoside therapy (if viral load not undetectable). Note recommendation that all patients be on at least triple drug regimens, and note also that some clinicians would not "rock the boat" as discussed above;

6. Persistently declining CD4+ T-cell numbers as measured on at least two separate occasions;

7. Clinical deterioration (bearing in mind that some patients experience "reactivation" of opportunistic infection, or "immune reconstitution syndrome" as their immune system recovers with HAART).^{13, 14}

For patients with their second or third regimen failure, the decreasing number of options remaining for the patient may dictate a more conservative stance, with deferral of treatment changes until evidence of further increases in HIV RNA level or decreases in CD4+ T-cell count. Despite viral load increases, patients continue to benefit from potent regimens even after rebound viremia; for them, stopping therapy may result in further viral load increase, rendering re-establishment of adequate viral suppression more difficult.¹⁵

VIRAL LOAD/CD4 "DISCONNECT"

Sometimes patients exhibit a discordant CD4+ decline in the face of continued viral load suppression. In these cases, it is important to examine the regimen for evidence of myelotoxic drugs (AZT, Hydroxyurea) and to continue to monitor. The pathogenic causes for discordant responses are uncertain. For those with a confirmed CD4 cell decrease or confirmed rapid decrease, treatment changes may be useful.

OTHER REGIMEN MODIFICATIONS

"Induction/maintenance" regimens are not useful in the setting of HIV infection. Furthermore, studies of patients who have discontinued therapy after prolonged adherence to HAART and undetectable viral loads have now repeatedly shown viral rebound, in some cases to levels above the original set point.

INTENSIFICATION

The practice of adding to, or intensifying an existing regimen (reviewed by Dr. Rick Altice in the October 1999 issue of HEPP News) is a

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ASK THE EXPERT

Case: A 28 year-old female offender returns to your facility having discontinued medication during her period of release. She was diagnosed as HIV positive during her previous incarceration. She had been on ddI, D4T and efavirenz with no problems through her date of release. Her old chart shows that she responded to the medication with a lower viral load from 15,000 to <50 copies/mL after eight weeks of therapy and increased T-cell counts from 228 to 344. Her viral load is now 75,000 and her CD4 is dramatically lower (from 380 at release to 180 now). What are your considerations when deciding how to proceed, and what treatment do you recommend now?

Expert Response: Dr. Stephen Tabet, MD, MPH,* University of Washington Division of Infectious Disease, Seattle HIVNET

When patients who have previously been on antiretrovirals enter the prison system off their regimen, it is important to first determine why the patient is no longer taking their medications. Generally, the reasons incarcerated patients are off medications can be grouped into four overlapping categories:

1. Non-adherence. Try to determine the reasons for poor adherence and provide support to help the patient be more successful. One of the biggest reasons that patients don't take their medications once they leave the correctional environment is because they don't have linkages to care in the community; they simply stop taking their medications once they run out. Drug and alcohol use is clearly a strong component in non-adherence. During incarceration, drugs and alcohol and other competing outside interests are often less of an issue. A more structured environment allows some patients to be more adherent.

2. Drug intolerance. The patient may have stopped taking antiretrovirals because of such common side effects as nausea or diarrhea that were not treated.

3. Situation out of the patient's control. When individuals are arrested, they rarely have medications with them. Many jails do not allow others to bring patients their medications, or incarcerated persons may not have access to someone who can bring in the medication and so they are discontinued on their regimen at the initial point of incarceration.

4. Patient makes a conscious decision to temporarily stop taking medications. Whether it is due to life circumstances outside the correctional system or the stress associated with reincarceration, some individuals choose to hold off on medications until they are in a more stable setting.

The next step is to determine whether the patient was on a failing antiretroviral regimen. When possible, patients on a failing regimen should be started on an entirely new one as outlined in Table XVI of the DHHS/Kaiser Guidelines (www.hivatis.org). Also see HEPPigram on pg. 7). In actuality, it is often difficult to restart therapy, given prior treatment failures and drug toxicities. Patients with few good treatment options can either be kept on their previous regimen, use a 'recycled' regimen with previous medications, or even be placed on mega-HAART regimens.

In this specific patient, I would initially start her on *Pneumocystis carinii* pneumonia prophylaxis given that the CD4+ T-cells are below 200 cells/mL. Next, I would try to determine why the patient stopped her medications. If the patient is going to be incarcerated for a short period (days) then I would likely recommend holding off on antiretrovirals until she establishes care or returns to care in the community. I would make sure she has medical and case management appointments arranged prior to her leaving the institution. If the patient were going to be incarcerated for the long-term, I would strongly recommend antiretrovirals since she has a low CD4 count.

The next step is to determine the antiretroviral regimen. This individual, at least initially, tolerated the d4T, ddI, and efavirenz. If the patient had tolerated her regimen and stopped all three antiretrovirals at once, I would re-start the same regimen. I would follow her viral load closely (one month and three month post-therapy to start) given that her virus may already be resistant, especially to efavirenz. Otherwise, I would discuss other regimens with her, avoid NNRTIs altogether, and offer her two new NRTIs and at least one protease inhibitor.

*Grant Research/Support: Bristol-Myers Squibb and Merck Immune Response Corp

HIV MANAGEMENT...

(continued from page 4)

viable option in cases where the initial suppression of viral load after the initiation of therapy is less than adequate. For regimens achieving satisfactory early HIV RNA declines, but not below the limits of the most sensitive assay available, addition of drug(s) to intensify the regimen may maximize long-term treatment benefit. New drugs must be added before viral rebound occurs; otherwise, addition of a single new drug can be viewed as incremental therapy, which may promote resistance.

PLAN B: WHAT TO CHANGE TO

When the decision is made to change therapy, the approach should be guided by the reason for the change. For adverse effects, intolerance, or suboptimal adherence to an otherwise successful regimen (i.e., HIV RNA level below detection limits), selective substitution of individual, identifiable offending components is reasonable. When a change in therapy is indicated due to drug failure, the same principles and considerations apply as described previously. Efforts should be made

to change the regimen in its entirety, using drugs with least potential for cross-resistance to current drugs. (See Table 4 in the 2000 guidelines). We will address this issue at greater length in a future issue of HEPP News.

INTERMITTENT THERAPY

New findings show that intermittent interruption of anti-retroviral therapy appears to have been beneficial. Some exposure to HIV primes the immune response and may, in the long run, be beneficial. Further studies¹⁶ of intermittent interruption are underway. However, some researchers feel that there are other means of achieving immune stimulation in the absence of viral replication. Therapeutic vaccination is one such strategy (see HEPP News, March 2000, Retrovirus Conference update).

BUDGET IMPACT

While ART has been good news for patients and their providers, one area of concern for correctional budgeters has been the cost of long-term therapy. Over the past few years, researchers have published data that showed that the use of potent therapy has resulted in remarkable declines in hospitalization rates, morbidity, and mortality where the drugs are

available.¹⁷⁻²² In community settings, protease inhibitor (PI)-containing regimens were shown to be cost-effective.^{23, 24}

WHEN TO STOP THERAPY

Eradication of HIV with maximally suppressive therapy alone is unlikely given the present understanding of HIV pathogenesis; thus, therapy should be continued indefinitely. Even with virologic failure, many patients maintain clinical and immunologic benefit.²⁵ After attempts to adjust the drug regimen to suppress replication are made, therapy should be continued in the face of virologic failure, if evidence of clinical and immunologic stability exists. In contrast, stopping all antiretroviral therapy is reasonable when the patient, after discussion with the physician, still believes that the adverse effects outweigh potential benefits of therapy.

Primary infection, post exposure prophylaxis, and "Mega HAART" are also addressed by the 2000 guidelines, but will not be addressed here. (For more information see www.jama.org where the guidelines will be accessible until the end of March, 2000).

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HIV MANAGEMENT...

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In short, HIV management has transformed dramatically over the past 20 years of the epidemic. We're now entering an age where we have many therapeutic options available to patients, and where careful choice, and even more careful adherence to a regimen, will determine the outcome of a disease that should, in most cases, resemble a chronic disease. See the March HEPP News for additional updates from the San Francisco Retrovirus meeting.

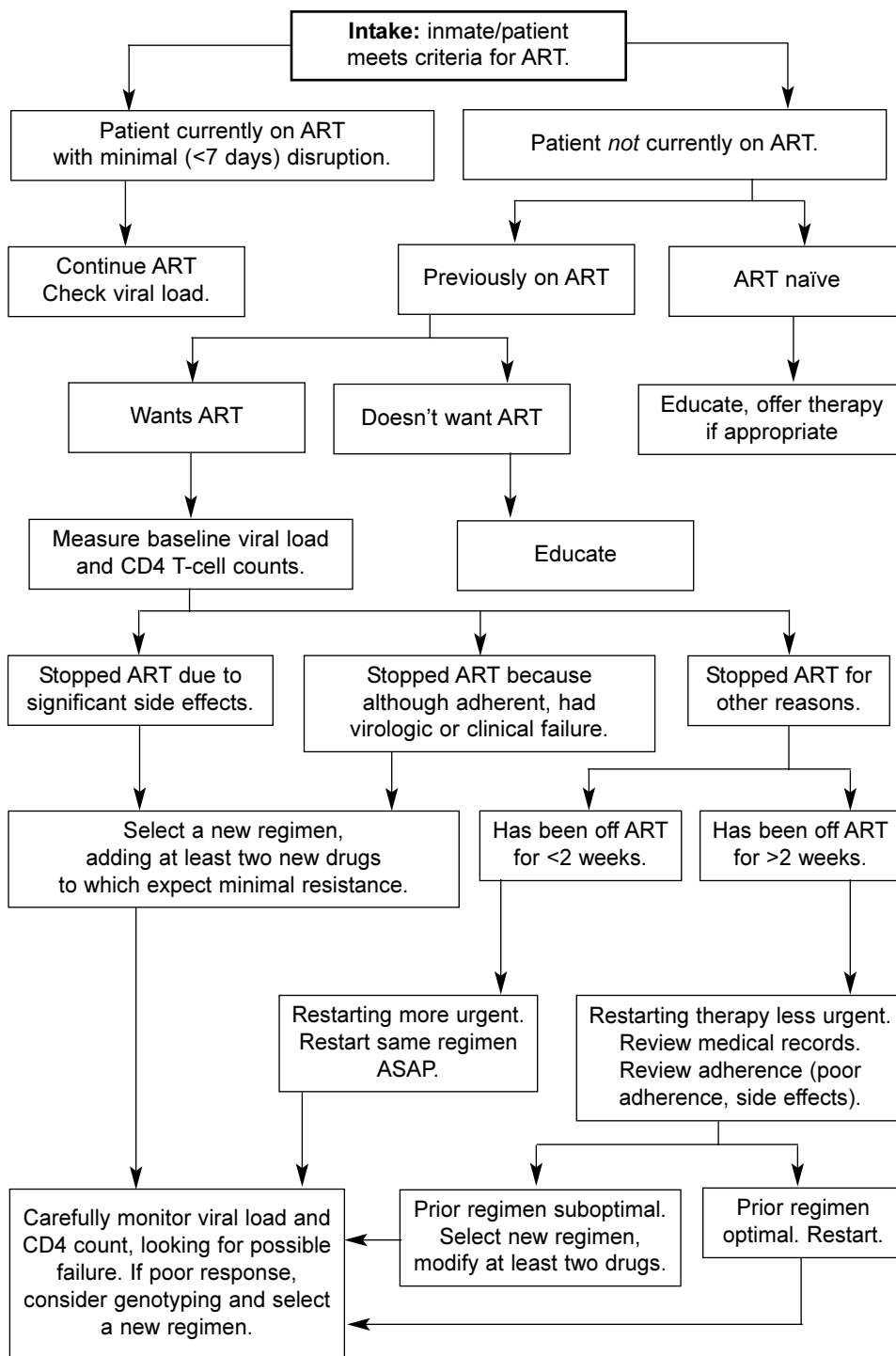
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HEPPIGRAM

Proposed Decision Tree for Initiating or Restarting Antiretroviral Therapy



This decision tree was developed by HEPP Editors in order to describe how we restart treatment for an HIV infected inmate who enters our facility off medications. The purpose of the tree is to provide a framework for discussion. Actual decisions regarding ART are very complex and involve talking with patient and thoroughly discussing the treatment options. If readers have any suggestions as to how this tree might be modified, please send your comments to Betsy Stubblefield at heppnews@brown.edu or fax 401.863.1243.

SAVE THE DATES

The 2000 National Conference on African-Americans and AIDS

February 24-25, 2000

Renaissance Hotel, Washington DC
Call: 410.955.2959
Fax: 410.955.0807
E-mail: cmenet@jhmi.edu
Visit: www.med.jhu.edu/cme

The Science and Treatment of HIV: An Advanced CME Course for Clinicians

March 25-29, 2000

Snowmass Village, CO
Call: 415.561.6725
Fax: 415.561.6740

E-mail: cme@iasusa.org
Visit: www.iasusa.org

Sponsor: International AIDS Society

HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management

February 26, Los Angeles, CA

March 8, Boston, MA

March 22, New York, NY

May date TBA, Dallas, TX

Call: 415.561.6725

Fax: 415.561.6740

E-mail: cme@iasusa.org

Visit: www.iasusa.org

Sponsor: International AIDS Society

National HIV/AIDS Update Conference

HIV/AIDS at the Crossroads:

Confronting Critical Issues

March 14-17, 2000

San Francisco, CA

Call: 514.874.1998

Fax: 514.874.1580

E-mail nauc@total.net

Visit: www.nauc.org

Sponsor: AmFar

American Society of Clinical Pathologists Teleconference

Update on Occupational Bloodborne Disease Exposure: New Tests, New Approaches to Prevention & Treatment

March 21, 2000 1pm CST

Call: 800.621.4142

Email: info@ascp.org

CME credit available.

National Conference on Pharmaceutical Care to Underserved Populations

April 3-4, 2000

Chapel Hill, NC

Call: 919.966.8138

Email: steve_moore@unc.edu

Sponsors: School of Pharmacy and

Cecil Sheps Center for Health

Services Research, UNC at Chapel

Hill, HRSA, NC Assn of Pharmacists

CME available

HIV Prevention with Incarcerated Persons

A Public Health Training Network Satellite Broadcast

April 27, 2000 1:00-3:00 PM EST

Call: 800.458.5231 or

TTY 800.243.7012

Visit: www.cdcpin.org/broadcast

Sponsor: CDC's National

Prevention Information Network

NEWS FLASHES

Drug Warning for Abacavir Sulfate (Ziagen)

A revised warning concerning abacavir sulfate (Ziagen) has been issued. Since its approval in December 1998, the labeling for abacavir sulfate has included a warning and description of fatal hypersensitivity reactions to the drug. The new warning emphasizes the importance of careful consideration of abacavir sulfate patients who have respiratory symptoms. Fatalities in patients treated with abacavir sulfate who developed hypersensitivity reactions including respiratory symptoms of dyspnea, cough, or pharyngitis have been reported. A delay in diagnosis of hypersensitivity can result in abacavir sulfate being continued or re-introduced, leading to more severe hypersensitivity reactions, such as life-threatening hypotension and death. (See HEPPigram, April 1999 HEPP News). Cases of hypersensitivity reaction should be reported to the Abacavir Hypersensitivity Reaction Registry at Glaxo Wellcome at 800-270-0425 or to the FDA MedWatch program at 800-FDA-1088.

Study Recommends Influenza Vaccine for HIV- Infected Persons

Previous differing findings on the immunologic and virologic effects of vaccination have caused disparity in recommendations for influenza vaccination. More recent studies involving HAART treated persons document good antibody responses in greater proportions of patients, although the responses generally remain poor in individuals with the lowest CD4+ cell counts. A study by Salvato, et al., found that patients who responded to antiretroviral therapy also responded well to influenza vaccine. Because of its cost effectiveness, the authors recommend that influenza should be part of routine prophylaxis for HIV-positive persons. (Salvato, P. et al., AIDS Reader, 12/99; 9(9):634-6291).

HAART May Reduce Genital Warts Despite HPV

In the December issue of the AIDS Reader, Heard, et al., summarized their findings concerning HAART and HPV. Cervical lesions respond poorly to standard treatment and exhibit a high recurrence rate in HIV-infected women. Despite the persistence of HPV in women with advanced HIV disease, HAART may provide a reduced prevalence of cervical squamous intraepithelial lesions. (Heard et al., AIDS Reader, 12/99; 9(9):630-635).

HIV Medication Still Compatible with Hepatitis B or C

Hepatotoxicity, caused by the use of antiretroviral drugs in treating HIV, prompted researchers to evaluate the effects of the drugs in people with Hepatitis B or C virus and attempt to determine which drug combinations were more likely to cause liver problems. The study included 298 patients who started new antiretroviral therapy between January 1996 and January 1998, with 71 percent receiving protease inhibitors. The other patients received dual NRTI regimens, the standard at that time. Overall, severe hepatotoxicity was seen in about 10 percent of the patients. The risk was greater for patients taking ritonavir; 30% of patients on ritonavir experienced hepatotoxicity versus only 8.1% of patients on other PIs. The risks for nelfinavir, indinavir, and NRTI regimens were similar and no deaths were associated with the toxicity. The authors conclude that antiretroviral therapies should be given to HIV-infected people who are infected with Hepatitis B or C. (Sulkowski MS. JAMA 1/05/00; 283 (1) 74.)

Supreme Court Denies Appeal of HIV Case

Last month the Supreme Court let stand a ruling that allows Alabama prisons to segregate HIV-positive inmates from the general prison population during educational, vocational, recreational and religious activities. The court, without comment, rejected an appeal filed on behalf of hundreds of HIV-positive Alabama inmates that argued the state's policy violates federal laws protecting the disabled. By rejecting the appeal, the high court leaves intact an 11th U.S. Circuit Court of Appeals ruling from last year that said the policy is valid "because HIV-positive inmates pose a 'significant risk' to others." (New York Times, 1/18/00).

FDA Denies Accelerated Approval of Adefovir

Adefovir (Preveon), the first nucleotide analogue to be clinically evaluated for the treatment of HIV, has been denied accelerated approval by the Food and Drug Administration (FDA). This reverse transcriptase inhibitor has been demonstrated to be a potent antiretroviral in patients who have failed zidovudine (ZDV) and lamivudine (3TC) therapy. Despite its antiretroviral efficacy at 120 mg per day, adefovir has significant nephrotoxicity (61%). Though trials using 60 mg per day are under evaluation, the FDA was unable to determine adequate efficacy and safety using this dose. At the present time, adefovir is no longer available through its expanded access program. (For more information, call 800-GILEAD-5 x1).

ACHSA 2000 Conference

The ACHSA 2000 Multidisciplinary Training Conference was held in conjunction with ACA in Phoenix, Arizona, and January 8-12, 2000. A number of presentations were made concerning HIV in corrections. In her presentation, Anne Spaulding, MD suggested that HIV and HCV coinfecting patients should be considered candidates for therapy and not disqualified as in the past. Joseph Paris, MD emphasized the dilemma presented to correctional managers: too many denials of care may result in undertreatment, inmate morbidity, and litigation. A weekly utilization management system will ultimately fail because of excessive health care costs. In a different presentation, Dr. Paris discussed the use of all nucleoside regimens and the new non-nucleoside antiretrovirals that complement the previously available protease inhibitors in the correction setting. Robert Greifinger, MD, presented a paper describing efforts to lobby the Legislature towards implementation of minimum correctional health care standards. (For more information on the conference, go to www.corrections.com/aca). Contributed by: Joseph E. Paris, MD, SCP President.

COMING NEXT MONTH . . .

March HEPP News

Main Article: by Elsa Villarino, MD

Discusses TB treatment in the correctional setting.

HIV 101: TB and HIV medications interactions

HEPPigram: PPD Testing Flow sheet

Ask the Expert: Discussion of TB and HIV coinfection

Plus updates from the 7th Conference on Retroviruses and Opportunistic Infections.

REGIMENS FOR INITIATING ANTIRETROVIRAL THERAPY: ADVANTAGES AND DISADVANTAGES

REGIMEN	ADVANTAGES	DISADVANTAGES
2 NRTIs* + PI*	Good to high potency Clinical data Combination with longest experience 2 different "points of attack"	Complexity and high pill burden May compromise future protease inhibitor regimens Long-term toxicity Some dietary restrictions Potential for many P450 drug interactions
2 NRTIs + NNRTI*	Good to high potency Defers protease inhibitor Low pill burden Acceptable to first line treatment Less dietary restrictions	Limited long-term data May compromise future NNRTI regimens Potential P450 drug interactions (due to NNRTI)
2 NRTIs + 2 PIs	High potency Convenient dosing Less dietary restrictions	High pill burden with some regimens Long-term toxicities unknown Potential P450 drug interactions (due to PI) Limited data as initial regimen
Regimens Under Evaluation		
3 NRTIs	Defers exposure to protease inhibitor and NNRTI Low pill burden Low potential for drug interactions	Efficacy in patients with higher viral loads and lower CD4 not yet determined Limited long-term data Compromises future NRTI regimens
NRTI + NNRTI + PI	High potency 3 "points of attack"	Complexity Compromises future regimens Multiple-drug toxicity Potential P450 drug interactions (due to PI)

Table adapted from JAMA 1/19/00; 283(3): 384 by Khurram Rana, Pharm D.

*NRTIs are nucleoside reverse transcriptase inhibitors. NNRTIs are nonnucleoside reverse transcriptase inhibitors. PIs are protease inhibitors.

Examples of combinations in current use for initial therapy include the following: (1) 1 PI and 2 NRTIs; (2) 1 NNRTI and 2 NRTIs; (3) 2 PIs with 2 NRTIs; (4) 1 PI and 1 NNRTI with 1 or 2 NRTIs; and (5) 3 NRTIs. Regimen #4 is considered the least favorable option, because of concerns about employing representatives of each of the 3 drug classes in an initial regimen; there is potential for multi-drug-class resistance should the initial regimen fail.

Recently, regimen #1 (PI containing) and regimen #2 (PI sparing, NNRTI) were compared and found to be equivalent for the combinations Indinavir/AZT/3TC and Efavirenz/AZT/3TC (see January HEPP Newsflash). Additional studies may be required before this regimen is implemented as first line treatment for patients with VL >100,000. Similarly, regimen #5 is a new option for those with baseline viral load <500,000 that has done well in initial studies (Abacavir/AZT/3TC vs. Indinavir/AZT/3TC, see Newsflash in January HEPP News, vol. 3 (1)).

RESOURCES

Ryan White Title IV: Grants for Coordinated HIV Services and Access to Research for Youth, Women, and Families

The Health Resources and Services Administration's HIV/AIDS Bureau (HRSA/HAB), announces the availability of funds for fiscal year (FY) 2000 for discretionary grants to coordinate services and provide medical care, support services and access to research for HIV-infected and affected children, youth, women and families. To obtain a full copy of this announcement, please go to <http://www.hrsa.gov/grantsf.htm>

Application due date: March 1, 2000

Call: 877.477.2123

Fax: 877.477.2345

E-mail: hvsagac@hrsa.gov

WEBSITES:

The Journal of the American Medical Association

<http://www.jama.org>

National Center for HIV, STD and TB Prevention, Divisions of HIV/AIDS Prevention

<http://www.cdcnpi.org/hiv/start.htm>

7th Conference on Retroviruses and Opportunistic Infections

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

AEGIS-AIDS Education Global Information System

<http://www.aegis.com>

HIV Info Web, an on-line library containing HIV and AIDS-related information, maintained online by the Massachusetts DPH AIDS Bureau

<http://www.infoweb.org>

The Body: daily updated information on HIV/AIDS

<http://www.thebody.com>

The Corrections Connection

<http://www.corrections.com>

TREATMENT RELATED WEBSITES:

CDC National Prevention Information Network

<http://www.cdcnpi.org>

The HIV/AIDS Treatment Information Service (ATIS)

<http://www.hivatis.org>

HIV/AIDS Treatment Directory

<http://www.amfar.org/td>

Doctor's Guide to the Internet: a straightforward guide to internet medical resources

<http://www.docguide.com>

SELF-ASSESSMENT TEST FOR CONTINUING MEDICAL EDUCATION CREDIT

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 March 31, 2000. The estimated time for completion of this activity is one hour and there is no fee for participation.

1. Which of the following parameters are relevant when initiating anti-retroviral treatment?
 - a) Readiness to start
 - b) Stable life situation
 - c) CD4 T-cell count below 500
 - d) CD4 T-cell count rapidly declining
 - e) Viral load above 5000.
 - f) a and b
 - g) b and c
 - h) All of the above

2. Which regimen is preferred for a treatment-naïve patient with a viral load of 100,000 and a CD4 T-cell count of 250?
 - a) Two PIs and an NNRTI
 - b) One NNRTI, one NRTI, and one PI
 - c) Two NRTIs and one PI
 - d) Two NNRTIs and one NRTI
 - e) Two NRTIs and one NNRTI

3. Which regimen is preferred for a treatment-naïve patient with a viral load above 10,000 and a CD4 T-cell count of 450?
 - a) Two PIs and an NNRTI
 - b) One NNRTI, one NRTI, and one PI
 - c) Two NRTIs and one PI
 - d) Two NNRTIs and one NRTI
 - e) Two NRTIs and one NNRTI

4. Which of the following regimens have the lowest pill and dose burden? (*More than one regimen may be correct.*)
 - a) AZT/3TC (Combivir) and abacavir
 - b) AZT/3TC (Combivir) and nelfinavir
 - c) AZT/3TC (Combivir) and efavirenz
 - d) DDI/D4T and efavirenz
 - e) DDI/D4T and indinavir
 - f) D4T/3TC and saquinavir

5. Indicate the advantage(s) of using a regimen of 2 NRTIs and a protease inhibitor instead of 2 NRTIs and an NNRTI.
 - a) The NNRTI containing regimen has a lower pill burden.
 - b) The protease inhibitor-containing regimen has a lower pill burden.
 - c) The NNRTI containing regimen has potential for many P450-drug interactions.
 - d) The protease inhibitor-containing regimen has less association with lipodystrophy.

6. At intake, a patient reports a history of ART, but he currently does not take any medications. He would like to restart. What is the next step?
 - a) Review viral load history.
 - b) Evaluate last regimen for adherence or access issues.
 - c) Take a careful medication history to find out how and when the medications were discontinued.
 - d) Try the former regimen and take a viral load and CD4 count at four weeks.
 - e) Check viral load.

HEPP NEWS EVALUATION

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

1. Please evaluate the following sections with respect to:
 educational value clarity

Main Article	5	4	3	2	1	5	4	3	2	1
HEPPigram	5	4	3	2	1	5	4	3	2	1
HIV 101	5	4	3	2	1	5	4	3	2	1
Updates	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?

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