



IDCR

INFECTIOUS DISEASES IN CORRECTIONS REPORT

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

FORMERLY HEPP Report

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ABOUT IDCR

IDCR, a forum for correctional problem solving, targets correctional physicians, nurses, administrators, outreach workers, and case managers. Published monthly and distributed by email and fax, IDCR provides up-to-the moment information on HIV/AIDS, hepatitis, and other infectious diseases, as well as efficient ways to administer treatment in the correctional environment. Continuing Medical Education credits are provided by the Brown University Office of Continuing Medical Education. IDCR is distributed to all members of the Society of Correctional Physicians (SCP) within the SCP publication, CorrDocs (www.corrdocs.org).

IDCR MISSION STATEMENT

We changed our name from HEPP Report to IDCR (Infectious Diseases in Corrections Report) to encompass all infectious diseases that impact the correctional setting. IDCR's goal is to educate correctional health care providers about the appropriate medical management of prisoners infected with HIV, hepatitis, TB, and other infectious diseases; to encourage these providers to improve their networks with correctional, academic or community-based infectious disease experts; and to promote a level of infectious disease care in correctional facilities that is equivalent to the "community standard."

ADULT AND ADOLESCENT ANTIRETROVIRAL THERAPY UPDATE

David Paar*, MD, Director, HIV Care for University of Texas Medical Branch at Galveston

The United States Department of Health and Human Services (DHHS) first published Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents on April 24th, 1998. Commonly referred to as the DHHS Guidelines or simply The Guidelines, they represent the consensus opinion of the Panel on Clinical Practices for Treatment of HIV. The Panel, which is referred to many times in this article, is appointed and convened by the DHHS and is composed of basic and clinical researchers as well as clinicians, participants from the DHHS, and nonvoting observers. The panel has monthly conference calls and meets in person at least twice per year to review publications and information from scientific meetings and to issue updates as new information regarding the treatment of HIV emerges. Not only do these guidelines provide the most up-to-date information regarding HIV care, they have also helped to set an acceptable standard of care for the treatment of HIV in the United States, which would also apply to the care of persons incarcerated in jails and prisons. The most recent update of the guidelines was published on October 29th, 2004 and is available at <http://www.hhs.gov>. This article will serve to summarize those modifications of the guidelines that are relevant to correctional health care providers.

changed from a "preferred" to an "alternative" agent; and tenofovir and lamivudine (or emtricitabine) are now recommended as preferred or alternative nucleoside (or nucleotide) backbones in protease inhibitor (PI) as well as non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens.

Additions to The Guidelines include a section on special populations; a discussion on discontinuation or interruption of ART, and several new tables showing data about the probability of progressing to AIDS, data from 48-week treatment trials, and revised tables on ART associated adverse events.

Any mention of hydroxyurea has been deleted from The Guidelines since the Panel feels it should limit its commentary to FDA-approved agents with indications for the treatment of HIV infection.

These changes and additions will be discussed in the general context of the primary care of HIV infected patients outlined in this update.

EXPERTISE IN THE TREATMENT OF HIV INFECTION

The guidelines continue to emphasize the importance of HIV expertise in "clinical care" since multiple studies have shown better outcomes when HIV-experienced treaters care for HIV infected patients. The Panel recommends HIV primary care by a clinician with at least 20,

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WHAT IS NEW IN THIS VERSION OF THE GUIDELINES

Changes in recommendations in this latest revision have to do with the initiation of antiretroviral therapy (ART) in ART-naïve patients. These include an increase in the viral load recommendation to defer or consider therapy from 55,000 copies/mm³ to 100,000 copies/mm³ in asymptomatic patients with a CD4 cell count greater than 350 cells/mm³. Stavudine has been

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but preferably 50 HIV-infected patients and the guidelines also suggest that these HIV providers fulfill CME requirements on HIV-related topics.

PRETREATMENT EVALUATION

The basic pretreatment "intake" evaluation for HIV care is aimed at confirming HIV infection and whether it is acute, identifying co-infections, and assessing the overall health of the patient. A complete history and physical examination should be performed. Factors that are known to affect adherence to therapy, including substance abuse, economic factors, need for social support, psychiatric illness, and other comorbidities should be identified and if present, managed with available resources. The initial laboratory evaluation should include HIV antibody testing if confirmation of infection is not available, CD4 cell count, plasma HIV RNA, CBC, chemistry profile, transaminase levels, BUN and creatinine, urinalysis, serologic testing for syphilis, tuberculin skin testing, fasting blood glucose, serum lipids levels and serologies to measure antibodies to *Toxoplasma gondii*, Hepatitis A, B, and C. Women should have a PAP test. Testing for infection with *Chlamydia trachomatis* and *Neisseria gonorrhoea* is optional and a chest radiograph should be performed if clinically indicated.

CD4 CELL COUNT AND VIRAL LOAD

The CD4 cell count and the plasma HIV RNA to measure HIV viral load (VL) remain the two key serologic markers that are routinely used to determine when to initiate ART and to monitor ongoing efficacy of treatment. In general, VL and CD4 should be monitored every three to four months with more frequent assessments of the VL occurring when ART is initiated or changed.

The Panel recommends that VL be measured immediately before instituting or changing treatment and again two to eight weeks after treatment initiation or change. The results of this test help guide treatment and therefore limitations on VL testing that may be imposed in correctional settings (such as once every three months) would not apply in this situation. The primary goal of therapy remains a reduction in VL below the limits of detection and this can be achieved within 16-24 weeks of initiation of therapy.

The Food and Drug Administration has approved three VL assays, any of which can be used (most correctional systems will have selected one for use by all of their practitioners). Since VL testing can be used to evaluate control of HIV, "ultrasensitive" tests (that measure VL down to the lowest number of copies/mm³) should be used when changing therapy or evaluating the effectiveness of therapy. Available VL assays are summarized in *Table 1*.

Table 1. U.S. FDA Approved VL Assays

TEST	Manufacturer	Lower limit of detection
HIV 1 reverse transcriptase polymerase chain reaction assay (Amplicor HIV-1 Monitor Test, version 1.5)	Roche Diagnostics	<50 copies per ml
Nucleic acid amplification test for HIV RNA (NucliSens HIV -1 QT)	Organon Teknika	<80 copies per ml
Signal amplification nucleic acid probe assay (VERSANT HIV 1 RNA 3.0 assay)	Bayer	<75 copies per ml

Table 2. Recommendations for Initiating ART

Clinical Category	CD4 Cell Count	Plasma HIV RNA	Recommendation
AIDS-defining illness or severe symptoms*	Any value	Any value	Treat
Asymptomatic	CD4 <200 cells/mm ³	Any value	Treat
Asymptomatic	CD4 >200 cells/mm ³ , but <350 cells/mm ³	Any value	Treatment should be offered following full discussion of the advantages and disadvantages of treatment
Asymptomatic	CD4 >350 cells/mm ³	>100,000 copies/mm ³	Most clinicians recommend deferring therapy, but some clinicians will treat
Asymptomatic	CD4 >350 cells/mm ³	<100,000 copies/mm ³	Defer therapy

*severe symptoms include unexplained fever or diarrhea for >two-four weeks, oral candidiasis, or >10% unexplained weight loss.

WHEN TO TREAT

Table 2 summarizes Panel recommendations for initiation of ART. The primary change in these recommendations is the increase in VL from 55,000 to 100,000 copies/mm³ as a cutoff for when to consider initiation of therapy. This trend towards delaying therapy based on VL determination is supported by data demonstrating that the risk for progression to AIDS within six months is greatest in those with a VL higher than 100,000 copies/mm³ whose CD4 cell count is less than 200 cells/mm³. Conversely, in most individuals who have VL less than 100,000 copies/mm³ and a CD4 cell count greater than 350 cells/mm³, the risk of progression to AIDS within six months is less than 2%.

In patients who are in care and having regular monitoring of VL, CD4 cell count, and clinical status, deferring therapy can provide extra time for addressing issues of substance use, psychiatric illness, other co-morbidities and extra time for education and preparing the patient to accept potent combination therapy aimed at suppressing VL to undetectable levels. The guidelines were changed in the hope that deferring therapy will decrease the long-term complications of ART by decreasing total expo-

sure time to ART drugs. The correctional clinician should schedule regular follow up visits to monitor the patients' readiness for therapy. These visits provide an additional opportunity for education about the risks and benefits of ART.

INITIAL COMBINATION REGIMENS FOR THE ANTIRETROVIRAL -NAÏVE PATIENT

There are currently 20 different drugs belonging to four different classes that can be used to create combination regimens that are potent enough to suppress plasma viremia to nondetectable levels. These four classes are nucleoside/ nucleotide reverse transcriptase inhibitors (NRTI), nonnucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI) and fusion inhibitors (FI). The Panel prefers to call these combinations "potent combination ART" rather than Highly Active Antiretroviral Therapy (HAART). Current recommendations for treatment combinations are organized based on the three types of regimens for which there is information from clinical trials and clinical experience. These three combinations are NNRTI-based (1 NNRTI +2 NRTI), PI-based (1-2 PI + 2 NRTI), and triple NRTI-

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based regimens.

The panel defines a "preferred" regimen as one where clinical trial data have demonstrated efficacy and durability with acceptable tolerability and ease of use. An "alternative" regimen is defined by the Panel as a regimen that is efficacious, but has disadvantages compared to preferred regimens in terms of antiviral activity, durability, tolerability, or ease of use.

Efavirenz (Sustiva) and lopinavir/ritonavir fixed dose combination (Kaletra) remain the preferred NNRTI and PI for initial therapy. With regard to the NRTI backbone, stavudine has been moved from the preferred to the alternative list due to increasing evidence of adverse events. Tenofovir (Viread) and lamivudine (3TC) (or emtricitabine [FTC]) is recommended as a preferred and alternative NRTI backbone for both NNRTI- and PI-based regimens. This is the first time that emtricitabine has appeared as either a preferred or alternative agent in the guidelines.

MANAGEMENT OF THE TREATMENT-EXPERIENCED PATIENT

A full discussion of the management of treatment-experienced patients is beyond the scope of this article. However, the Panel recommends that resistance testing and expert advice should be part of this management. For more information, see the December 2004 issue of IDCR, article by Dr. Ian Frank "Use of HIV Resistance Testing in Antiretroviral Therapy Decision Making" (www.idcronline.org). A summary of the Panel's recommendations for experienced patients follows:

- ♦ Although most patients experience benefits from taking antiretroviral regimens, adherence, intolerance/toxicity and pharmacokinetic issues may complicate therapy and virologic failure or treatment-limiting toxicity occur commonly.
- ♦ Evaluation of ART failure should include assessing the severity of HIV disease of the patient; the antiretroviral treatment history, including the duration, drugs used, antiretroviral potency, adherence history, and drug intolerance/toxicity; and the results of current and prior drug resistance testing.
- ♦ Virologic failure on treatment can be defined as a confirmed HIV RNA level >400 copies/mm³ after 24 weeks, >50 copies/mm³ after 48 weeks, or repeated HIV RNA level >400 copies/mm³ after prior suppression of viremia to <400 copies/mm³.
- ♦ In managing virologic failure, the provider should make a distinction between limited, intermediate, and extensive prior treatment exposure and resistance.
- ♦ The goal of treatment in those with limited or intermediate prior drug exposure and whose viral isolates demonstrate limited or intermediate drug resistance is to re-establish maximal virologic suppression.

Table 3. Preferred and Alternative Regimens

	REGIMENS	# of pills
Preferred Regimens		
NNRTI-based	♦ Efavirenz* + (lamivudine or emtricitabine) + (zidovudine or tenofovir)	2-3
PI-based	♦ Lopinavir/ritonavir (Kaletra) + (lamivudine or emtricitabine) + zidovudine	8-9
Alternative Regimens		
NNRTI-based	♦ Efavirenz + (lamivudine or emtricitabine) + (abacavir or didanosine or stavudine)	2-4
	♦ Nevirapine + (lamivudine or emtricitabine) + (zidovudine or stavudine or didanosine or abacavir or tenofovir)	3-6
PI-based	♦ Atazanavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or didanosine) or (tenofovir + ritonavir 100 mg)	3-6
	♦ Fosamprenavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)	5-8
	♦ Fosamprenavir/ritonavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)	5-8
	♦ Indinavir/ritonavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)	7-12
	♦ Lopinavir/ritonavir + (lamivudine or emtricitabine) + (stavudine or abacavir or tenofovir or didanosine)	7-10
	♦ Nelfinavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)	5-8
3 NRTI-based	♦ Saquinavir/ritonavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)	13-16
	♦ Abacavir + Zidovudine + lamivudine - only when a preferred or an alternative NNRTI- or PI-based regimen cannot or should not be used	2

*efavirenz is not recommended for use in 1st trimester of pregnancy or in women with high pregnancy potential (women who want to conceive or who are not using birth control).

lish maximal virologic suppression.

- ♦ The goal of treatment in those with extensive prior drug exposure and whose viral isolates demonstrate extensive drug resistance where viral suppression is difficult or impossible to achieve with currently available drugs is preservation of immune function and prevention of clinical progression.
- ♦ Assessing and managing a patient with extensive prior antiretroviral experience and drug resistance who is experiencing treatment failure is complex and expert advice is critical.

TREATMENT INTERRUPTION AND REINSTITUTION BASED ON CD4 CELL COUNT (CD4 Guided Therapy)

The new guidelines briefly discuss the option of discontinuing successful ART in patients whose treatment was started when the CD4 cell count was >350 cells/mm³ and who might not meet recommendations for initiating ART by today's guidelines. Although no large, long term studies have examined this strategy, several small studies and case reports seem to indicate that there is little risk of resistance following a single episode of treatment interruption.

When this strategy is employed, a target CD4 count at which to resume therapy should be discussed with the patient ahead of time. The patient needs to know that there will be an increase in VL that may be associated with an increased risk of transmission to sexual and needle-sharing partners.

SPECIAL POPULATIONS SECTION

This newly added section presents discussion on considerations for ART in HIV-infected adolescents, injection drug users, HBV and HCV co-infected patients and HIV infected patients with tuberculosis. Although these sections address some of the special issues faced in correctional HIV care, other issues faced in corrections such as method of pill distribution, educational needs of the correctional population, and continuity of care upon discharge are not addressed.

SUMMARY

The new guidelines that were released in October 2004 push back the criteria for initiation of treatment and describe new rec-

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HIV 101: Psychiatric and HIV Medication Interactions

Category	NNRTIs	NRTIs	PIs
SSRIs	Prozac increases levels of Rescriptor 50%	NPD*	Prozac may lead to increased effects of Norvir, but no dose adjustment of Norvir is needed when used in combination. Norvir increases levels of Prozac, Luvox, Paxil, and Zoloft.
TCAs	NPD	NPD	Norvir decreases Norpramin clearance by 50%, causing higher than anticipated blood levels; may increase levels of Elavil, Sinequan, Tofranil, Depakote. When used in combination with Norvir, caution is required. It is recommended to use lower doses, and regularly monitor EKG and serum TCA levels.
Other: Wellbutrin	Sustiva may increase wellbutrin levels.	NPD	Viracept and Norvir may increase wellbutrin levels, increasing risk of drug-induced seizures.
Other: Serzone	NPD	NPD	Caution advised; combination of PIs and Serzone may increase levels of both drugs.
SNRIs	NPD	NPD	Effexor may decrease Crixivan levels.
Other: Desyrel	NPD	NPD	Potential for drug interactions when Desyrel is co-administered. Adverse effects including nausea, hypotension, and syncope were observed when Norvir and Desyrel were co-administered. It is likely that Nizoral, Crixivan, and other CYP34A inhibitors may lead to increases in Desyrel plasma concentrations with potential for adverse effects. If Desyrel is used with a potent CYP34A inhibitor, a lower dose of Desyrel should be considered.
Benzodiazepines	NPD	NPD	Kaletra and Halcion may have possible interactions; Halcion and other antipsychotics from this class are contraindicated in combination with PIs due to the potential for serious and life-threatening reactions such as prolonged or severe sedation or respiratory depression. Xanax, Dalmane, Klonopin, and Valium should be used in caution with PIs due to the potential for serious reactions such as prolonged or severe sedation or respiratory depression. Ativan, Restoril, and Tranxene are free of the serious interactions with PIs found with other benzodiazepines.
Non-Benzodiazepine sedative/hypnotics	NPD	NPD	Ambien and Sonata should be used with caution in combination with PIs due to the potential for serious reactions such as prolonged or severe sedation or respiratory depression.
Lithium carbonate	NPD	NPD	NPD
Anticonvulsants	Tegretol and Dilantin may decrease levels of PIs and NNRTIs.	Long term clinical implications not known; monitor for Retrovir toxicity.	Tegretol may decrease levels of PIs and NNRTIs. Known to decrease Crixivan levels with loss of viral suppression. Tegretol levels increased by Norvir. Dilantin: co-administered with Kaletra results in decreased concentrations of both Dilantin and Kaletra.
First Generation - Typical	NPD	NPD	Orap is contraindicated in combination with PIs due to potential for serious and life-threatening reactions, such as cardiac arrhythmia. Norvir may increase levels of antipsychotics.
Second Generation - Atypical	NPD	NPD	PIs may increase plasma levels of Clozaril and increase the risk for seizures and orthostatic hypotension. Geodon: caution is indicated when Geodon is co-administered with Norvir.
Third Generation	NPD	NPD	NPD
St. John's Wort	May reduce blood levels of NNRTIs. Induces metabolism of Viramune; increased clearance ~35%.	NPD	May reduce blood levels of PIs. <i>These tables have been adapted from "Psychiatric Medications and HIV Antiretrovirals: A Guide to Interactions for Clinicians." NY/NJ AIDS Education and Training Center</i>

*No Published Data about drug interactions specific to this combination.

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ommendations for the initiation of treatment. It is important for the correctional provider to understand that the guidelines are a "living document" and can be expected to be modified on a yearly basis or more frequently as further research is conducted. Important changes to the guidelines will be noted in IDCR, and are also available at the DHHS website (www.hhs.gov). The document provides a wealth of information and should be required reading for all correctional HIV providers. If perusing the greater than 100 page documents seems overwhelming, one might opt for a more thorough reading of the

black boxes in the text of the document that summarize the recommendations of the Panel and a review of the tables (these start on page 41). And finally, these guidelines provide a framework for treatment, which must involve a partnership with the patient. Most correctional HIV patients present with co-morbidities that complicate treatment - these will be addressed in future issues of IDCR.

DISCLOSURES: *Consultant: Ortho Biotech, Grant/Research; Support: GlaxoSmithKline, Agouron, Merck, DCHD, Serono, Gilead, Chiron Corp, Boehringer-Ingelheim, Abbott Labs, Bristol-Myers Squibb; Speaker's Bureau: Roche, Bristol-Myers Squibb, Ortho Biotech

LETTER FROM THE EDITOR

In the early days of the AIDS epidemic, much of the basic pathogenesis and epidemiology of HIV had not yet been clarified. Not enough was known about how the virus was transmitted, how it could be prevented, how it caused immune deterioration, what infections and cancers infected persons were at risk for, and how these opportunistic infections could be prevented. As a result, the management of those with HIV infection was relegated to infectious disease specialists and to a small cadre of dedicated pioneers drawn from a variety of medical fields.

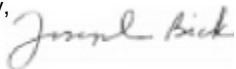
By the end of the 1980s, much of the basic details concerning HIV had been elucidated. Soon, the number of cases of HIV in this country overwhelmed the available specialists. Because of the simplicity of the limited treatment options (essentially PCP prophylaxis and AZT) most primary care clinicians were able to manage the treatment of those infected with HIV.

The 1990s witnessed a dramatic increase in treatment options for HIV and related illnesses. Along with these new treatments have come severe, potentially fatal side effects and a myriad of complex pharmacokinetic interactions. Outcome based studies have demonstrated that patients who do not receive care from clinicians who specialize in the management of HIV are at a greater risk for HIV related morbidity. Furthermore, the life expectancy of those who are HIV-infected is directly related to the experience of their physician. Clearly, we have come full circle, in that only those clinicians who make it a priority are able to master the complexities of the care of the HIV-infected. We can all hope that in the future the HIV specialist will be obsolete... until that time, we have a responsibility to ensure that those inmates entrusted to our care have access to clinicians who specialize in the management of HIV.

This month, Dr. David Paar provides an update on guidelines for the treatment of HIV. Dr. Bethany Weaver presents a case that discusses some of the challenges of using efavirenz in those who have a major mental illness, and our HIV 101 details some of the pharmacokinetic interactions that can occur between antiretroviral agents and psychotropics. At the conclusion of this issue, readers will be more familiar with the new HIV treatment guidelines, be aware of potential for drug interactions between HAART and psychotropics, and know more about the potential side effects of efavirenz.

Beginning next month, Dr. David Thomas will assume the role of co-chief editor managing content for IDCR. We welcome Dr. Thomas to this new role, and we also welcome three new members to our editorial board: Dr. William Cassidy, Associate Professor of Medicine at Louisiana State University Health Sciences Center, Dr. Neil Fisher, Medical Director and Chief Health Officer of Martin Correctional Institute; and Barry Zack, MPH, Executive Director of Centerforce. Thank you for your continued readership of IDCR, and we encourage your suggestions concerning future topics.

Sincerely,



Joseph Bick, MD

Faculty Disclosure

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

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ASK THE EXPERT: Case Study - Acute Psychosis in a Patient with AIDS

By Bethany Weaver*, D.O., M.P.H., Acting Instructor of Medicine, University of Washington Center for AIDS & STD Research (CFAR) and Northwest Correctional Medicine Education Program. DISCLOSURES: *Pfizer: Stockholder

CASE: A 33 year-old male inmate presents with untreated C3 HIV/AIDS in need of treatment. His CD4 cell count and HIV-1 viral load two months ago were 100 cells (13%) and 100,000 copies/ml, respectively. He is taking trimethoprim/sulfamethoxazole and azithromycin for PCP and MAC prophylaxis and has been off antiretroviral medications for six months due to intolerance and virologic failure, known because he had genotype resistance assays in his record documenting high level resistance to all available protease inhibitors. He has never taken efavirenz (sustiva) or nevirapine (viramune). He is an injecting drug user with a history of bipolar disorder for which he receives lithium by directly observed therapy (DOT). He has no history of suicide attempts and has been hospitalized twice with mania after cocaine use. He weighs 145 pounds and has an unremarkable physical exam. He has two years remaining in his sentence. He tells you that he would like to resume antiretroviral medications as soon as possible due to increasing fatigue and worsening memory but is concerned about his ability to remain adherent if the regimen is too complicated. You recommend he start tenofovir, lamivudine, and efavirenz.

Q: What potential adverse effects should you warn him about?

A: He should be warned about the potential for hallucinations, precipitation of mania, insomnia, depression, and nightmares on efavirenz, particularly in the first 10-14 days on the drug. You tell him that you are hesitant about placing him on the drug because of the potential for these symptoms, particularly with his history of bipolar disorder. However, you realize he has limited protease inhibitor treatment options. You rationalize that if he is going to develop adverse effects on efavirenz, at least they will occur in a supervised, safe setting while he is incarcerated. You also recommend that he see psychiatry more regularly (e.g. every two weeks) for the first few months on this regimen.

He returns for follow-up two weeks later and appears anxious with pressured speech. He reports some mild insomnia but is feeling "better than I've felt in years". Also, he loves taking the efavirenz because it is only one pill at bedtime, which he feels improves his adherence.

Q: Do you have any concerns at this time? What other questions should you ask him? When should you see him again in clinic?

A: Yes, you should be concerned about precipitation of mania with potential for it to progress over the next few weeks. You should ask him when he is taking efavirenz since it was prescribed as "keep on person", making it difficult to be sure what time he is taking it every day. If he is taking the drug within an hour or so of a high fat meal, the absorption will be increased with higher risk for side effects. Since efavirenz is cleared in the liver via the cytochrome P450 system, a review of his other medications is warranted to be sure there are no significant drug-drug interactions, and checking a lithium level, liver function tests and evaluating for hepatitis B and C and undetected cirrhosis would be reasonable. Finally, you recommend he see you again in two weeks so you can re-evaluate his tolerability of the new regimen.

Q: Are there any other tests to consider at this time?

A: A plasma efavirenz level (trough) can be performed with a blood draw and is probably best drawn eight-15 hours after the dose is taken, which is typically in the morning since most patients take the drug in the evening to minimize side effects. This test is performed at reference laboratories and may take two-four weeks for a result to be received. If the level is above 4000mg/l, CNS toxicity may be three times more likely than if the level is below this cutoff. Virologic failure is more often seen when the level is below 1000mg/l. It is speculated that a level somewhere between 1000 and 4000mg/l is best for optimal efficacy and tolerability. Unfortunately, because of the long return time for the efavirenz level, it is difficult to use the results of this test as a clinical tool in the management of the patient and is not likely cost-effective for

this reason. Decisions in response to a drug level above 4000 mg/ml may be difficult as there are no published guidelines for dose reduction needed with an elevated efavirenz level.

The inmate returns to see you two weeks later. Over the last two weeks, he has received three infractions due to violent outbursts, is paranoid and delusional, and was sent to segregation, then the mental health unit due to concern for his safety and the safety of others. He is still reluctant to stop the new regimen since he "feels great" and his CD4 count is now 160 cells/ml (15%) with HIV-1 viral load of 5,000 copies/ml after three weeks on the drugs. His lithium level and LFTs were normal, and he had no evidence of chronic active hepatitis B or C.

Discussion

Though efavirenz is an attractive HIV treatment option because of its long half-life (only dosed once a day) and high tolerability after the first two weeks, it presents some challenges for use in the incarcerated setting. First, the meals in the correctional setting are typically high in fat and difficult to control, and this may contribute to risk of CNS toxicity. If the drug is taken two-three or more hours after dinner, this problem should be minimized. However, the bedtime pill line in corrections is often shortly after dinner, rather than at 9 or 10 p.m. If the inmate keeps the drug on person, the inmate could then take the dose at 10 p.m. with only a light snack or on an empty stomach. Second, though the risk for severe neurotoxicity in the general population appears low (only discontinued in approximately 4% of patients due to severity or persistence of adverse effects), it is likely higher among incarcerated individuals since they often have a history of significant prior mental illness as well as underlying significant liver disease from hepatitis C and/or alcohol. Third, when psychosis does occur in the incarcerated setting, it can be quite detrimental to the inmate. The patient in this case received numerous infractions for his behavior with an extended sentence, was placed on the mental health unit for observation, and required intensive psychiatric monitoring. The drug was discontinued as his mania and psychosis were not manageable despite intensive psychiatric care and addition of antipsychotics, and the effects lasted for several weeks, even after discontinuing the medication.

In patients who require salvage therapy and have risk factors for CNS toxicity, it is reasonable to consider use of efavirenz in a supervised setting, such as the correctional setting. The potential for problems should be weighed against potential benefits, particularly in patients who have advanced HIV/AIDS. It is important to counsel the patient and the staff about the potential complications. The role of therapeutic drug monitoring is still unclear. Optimal use requires dose adjustment on the basis of a drug level. More research on this topic is needed in order for this practice to be cost-effective and clinically meaningful for the patient.

SAVE THE DATES

Conference on Retroviruses and Opportunistic Infections

February 22-25, 2005

Boston, MA

Visit:

www.retroconference.org/2005

IUALTD Challenges to TB Control

February 23-26, 2005

Vancouver, British Columbia, Canada

Call: 604.732.5864

Email: biagtan@bc.lung.ca

Improving the Management of HIV Disease Regional CME Courses

Atlanta, GA:

Friday, March 11, 2005

New York, NY:

Thursday, March 17, 2005

Los Angeles, CA:

Saturday, April 16, 2005

Chicago, IL :

Monday, May 2, 2005

Washington, DC: May 2005

San Francisco: May or June 2005:

Registration for this course will open soon.

Visit: www.iasusa.org/registration/index.html

Management of HIV/AIDS in the Correctional Setting: A Live Satellite Videoconference Series "The Triply Diagnosed Patient: HIV, Mental Health & Substance Use"

March 9, 2005

12:30-2:30 p.m. EST

Call: 518.262.4674

E-mail: ybarraj@mail.amc.edu

Visit: www.amc.edu/patient/hiv/hivconf/index.htm

ACHSA Diminishing Resources: The New Reality

March 31-April 3, 2005

Oakland, CA

Visit: www.achsa.org

RESOURCES

The Department of Health and Human Services

www.dhhs.gov

NY/NJ AIDS Education and Training Center

www.nynjaetc.org

NATAP www.natap.org

IN THE NEWS

Hepatitis A Vaccine Safe in HIV Patients

Hepatitis A virus (HAV) is common among persons who are at highest risk for HIV infection. One hundred eighty subjects, 90 of whom were HIV-infected were given an inactivated HAV vaccine to determine the safety and efficacy in HIV-infected patients. The HIV-infected subjects were stratified into two groups: one group with CD4 cell counts <300cells/mm³ and one group with CD4 cell counts >300cells/mm³. Vaccine or placebo was administered at zero and 24 weeks. At week 28, seroconversion rates among HIV-infected and HIV-uninfected subjects were 94% and 100%, respectively. Additionally, HIV-infected subjects with CD4 cell counts <300 cells/mm³ had a seroconversion rate of 87%, while HIV-infected subjects with CD4 cell counts >300 cells/mm³ had a seroconversion rate of 100%. Conclusions drawn from this study are that HAV vaccine is immunogenic and safe among HIV-infected persons, and should be part of their preventative care.

Clin Infect Dis 2004; 39:1207-13.

Combination Therapy for HBV

Thirty treatment naïve, hepatitis B virus (HBV) e antigen positive (HBeAg+) patients were randomized to receive adefovir dipivoxil (ADV) plus emtricitabine (FTC) or ADV plus placebo for 48 weeks. The study aims were to compare the efficacy of a new combination therapy of ADV plus FTC versus ADV monotherapy. At baseline, median HBV DNA was 7.6 log copies/ml in the ADV plus FTC arm and 8.5 log copies/ml in the ADV arm. The median log change from baseline HBV DNA was -3.95 for the ADV plus FTC arm and -2.44 for the ADV arm. HBeAg seroconversion occurred in three patients total; two in the combination arm and one in the ADV arm. Additionally, 80% of HbeAg positive patients taking ADV plus FTC had undetectable HBV DNA, versus 20% taking ADV alone at 48 weeks. Combination therapy with ADV plus FTC may be superior to ADV alone, at least in the short term.

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Risk of Early Virologic Failure with ddI+TDF+NNRTI

Two studies reported at the 2004 ICAAC meeting found that regimens combining the nucleoside/nucleotide analogs didanosine (ddI) and tenofovir disoproxil fumarate (TDF), plus either efavirenz (EFV) or nevirapine (NVP) can cause early virologic failure in treatment-naïve persons, particularly in those persons commencing treatment with a high viral load. Podzamczar et. al. found that 43% of people taking TDF/ddI/efavirenz had virologic failure, defined as less than a two log drop in viral load by month three of their study. None of the subjects taking TDF/ddI/efavirenz plus lopinavir/ritonavir had virologic failure. In a larger study conducted by Moyle et al, 44 subjects were randomized to start TDF/ddI/efavirenz and 36 were randomized to start 3TC/ddI/efavirenz. While adherence exceeded 99% in both groups, virologic failure in the TDF/ddI/efavirenz group and 3TC/ddI/efavirenz group were 12% and 0%, respectively. All people with a virologic failure had

a pretreatment CD4 count below 200 cells/uL and a viral load greater than 100,000 copies/mL. The mechanism of early virologic failure in these patients is unclear. Clinicians should use caution when coadministering ddI/TDF and either EFV or NVP in treatment-naïve patients with high baseline viral loads.

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Tenofovir for the Treatment of Lamivudine-Resistant Hepatitis B Virus (HBV)

Adefovir dipivoxil, which was recently approved for the treatment of wild-type and lamivudine-resistant HBV infection, and tenofovir disoproxil fumarate (TDF) were compared in a study of 53 subjects to measure the decline of HBV DNA levels in lamivudine-resistant HBV infection. Thirty-five subjects received TDF 300 mg/day for 72-130 weeks, while 18 subjects received adefovir 10mg/day for 60-80 weeks. The TDF-treated group was further divided into three groups: HBV-infected subjects, HIV/HBV coinfecting subjects who had received TDF as a part of antiretroviral therapy, and immunosuppressed HBV-infected subjects following kidney transplantation. None of the adefovir subjects had these comorbidity features. Subjects were matched for age, sex, ALT levels, hepatitis B e antigen (HBeAg) status, and HBV DNA level at baseline. All TDF-treated subjects showed a strong and early suppression of HBV DNA within a few weeks, including the HIV coinfecting subjects. At week 48, 100% of the TDF-treated subjects had HBV DNA levels below 105 copies/mL, in contrast to only 44% of those subjects treated with adefovir. While tenofovir has not been approved for the treatment of HBV, this study shows that it may become an effective alternative for the treatment of patients with lamivudine-resistant HBV infection.

Hepatology; 2004: 40:6

Barriers to Care of HCV for Drug Users

Five hundred fifty-seven HIV-seropositive and HIV-seronegative current and former injection drug users were enrolled in a prospective study to gauge the natural history of hepatitis C virus (HCV) infection. The 228 subjects with chronic HCV infection were offered referral for HCV evaluation and treatment; only 56% accepted referrals. Reasons study participants gave for declining referrals included self-reported clinical care elsewhere (62%), not interested or too busy (16%), or not ready (9%). Additional reasons included fear of biopsy or treatment, unable to keep appointments, and end-stage liver disease. Of the 56% of subjects who did accept referrals, only 43% arrived for evaluation, which was located two city blocks from the research site. Additionally, of those who did arrive for evaluation, only 22% had a liver biopsy, and only 7% were treated. Despite counseling about HCV infection and the need for medical evaluation, only a small percentage of subjects actually followed through to treatment. This study suggests that there must be other barriers, besides access to care, that inhibit HCV infected injection drug users from seeking and receiving treatment.

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Brown Medical School designates this educational activity for one hour in category one 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 June 30, 2005. The estimated time for completion of this activity is one hour and there is no fee for participation.

1. Based upon the most recent guidelines for the treatment of adults with HIV, the following individuals should be offered anti-retroviral therapy:
 - a. All those with CD4 counts less than 500
 - b. All those with HIV viral loads greater than 55,000
 - c. All those who have an HIV related opportunistic infection
 - d. All those who are co-infected with hepatitis C

2. Which of the following statements is false:
 - a. Efavirenz and kaletra are preferred agents in the new HIV treatment guidelines
 - b. Didanosine, emtricitabine, lamivudine, and tenofovir can be dosed once daily
 - c. Stavudine has been linked to a lower risk for lipoatrophy
 - d. Ritonavir can cause an increase in triglycerides

3. The following protease inhibitors cannot be used in once daily regimens:
 - a. Nelfinavir
 - b. Amprenavir
 - c. Atazanavir
 - d. Saquinavir

4. The following antiretroviral combinations should be avoided:
 - a. Tenofovir plus didanosine
 - b. Emtricitabine plus lamivudine
 - c. Azidothymidine plus stavudine
 - d. Didanosine plus stavudine
 - e. Efavirenz plus nevirapine
 - f. All of the above

5. Which of the following statements is false:
 - a. When used in combination with ritonavir, the dose of amprenavir should be increased
 - b. When used in combination with efavirenz, the dose of kaletra should be increased
 - c. When used in antiretroviral experienced patients, atazanavir should be boosted with ritonavir
 - d. When used in patients who are receiving ritonavir, the dose of fuzeon need not be changed

IDCR EVALUATION

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