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HIV Education Prison Project

HEPP NEWS

HIV EDUCATION PRISON PROJECT

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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.

Faculty Disclosure

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

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Antiretroviral Resistance Testing Here and Now

David Paar, MD*, *Director, AIDS Care and Clinical Research Program, University of Texas Medical Branch at Galveston*
Frederick L. Altice, MD**, *Editor, HEPP News*

Only a few short years ago, viral load (HIV-1 RNA) testing was introduced as a new tool for HIV management. Many physicians, inside corrections as well as outside, delayed implementing the test. Though most of the arguments against its use included lack of standardization, inability to process specimens and shortage of specialists to interpret and utilize results in HIV management, the major unspoken obstacle was cost. In 2000, we now face a similar situation with antiretroviral resistance testing. Despite national guidelines for their use as the community standard of care in the US and favorable retrospective and prospective data, few correctional systems have embraced genotypic or phenotypic testing. This article will address specific issues in the use of resistance testing and provide an overview of clinical studies and potential application for their use.

Defining Resistance: The Causes of Viral Rebound

The presence of antiretroviral resistance to HIV medications may be signaled clinically by the observation of viral rebound. Viral rebound can be defined as any reproducible increase in the viral load determined to be threefold or greater that is not due to acute intercurrent infectious illness or vaccination. It is important to note that not all rebound phenomena are related to drug resistance. In fact, the most common cause of rebound is poor adherence. In studies of virologic rebound occurring in patients receiving a triple combination including a protease inhibitor, the largest percentage demonstrate no mutations at all, followed by mutations to the nucleoside reverse transcriptase inhibitor and then to the protease inhibitor.

Resistance is the result of two major characteristics of HIV: 1) its rapid turnover rate; and 2) its error prone RNA replication process. HIV lacks a proofreading function that corrects the mistakes in viral replication that result in mutations. Within a given patient, HIV exists as a combination of multiple strains (quasispecies) that diverge from the original wild-type or unmutated virus. The quasispecies differ based on acquired mutations that are passed onto daughter viruses.

The most common cause of viral rebound is poor adherence.

Most mutations that occur naturally in the course of viral replication result in no effect on viral susceptibility to ART, while others lead to death of the virus. In order to cause clinically important resistance, a mutation must: 1) decrease the viral sensitivity to the drug, 2) become the dominant quasispecies because of increased viral fitness in the setting of selective drug pressure, and 3) provide a competitive advantage over the wild-type of the virus and maintain viral replication by preserving enzyme function. If one of several quasispecies has a mutation that results in resistance to a specific drug, then exposure to that drug acts as a selective pressure that allows the resistant quasispecies to replicate freely while the other quasispecies and wild-type virus that lack the resistance mutation are suppressed. The resistant quasispecies then becomes the predominant replicating strain. Clinically, the patient's viral load increases and treatment fails. The patterns and types of mutations associated with NRTIs, NNRTIs and PIs are described in the HIV 101, page 5.

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WHAT'S INSIDE

Antiretroviral Resistance Testing...

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The key to understanding the limitations of resistance testing is understanding that resistant quasispecies become the dominant strain when HAART is being used, while other forms of the virus are suppressed, including those that might be resistant to other drugs. That is, resistance to a given drug may not be detected if the patient is not taking that drug at the time that a resistance test is given. Since the selective pressure that favors replication of the resistant quasispecies over the susceptible strains has been removed, there may not be enough of the resistant quasispecies present to be detected by current resistance assays. Yet the resistant strain will rapidly re-emerge if the selective pressure (the drug) is re-instituted. Thus, knowledge of prior antiretroviral treatment may steer a clinician away from a drug that might appear effective when the results of resistance assays are interpreted without knowledge of prior treatment history.

Resistance to drugs may decrease the ability of the virus to replicate, as has been reported by a number of investigators. Drug resistance is associated with impaired protease and reverse transcriptase (RT) function and reduced replication capacity. In one report, Nelfinavir resistant viruses exhibited many protease cleavage defects and 70% of Nelfinavir-resistant viruses showed large reductions in viral replication (1). In addition, some viruses exhibit hypersensitivity to selected drugs after developing mutations (2).

Genotyping versus phenotyping

Resistance is measured by two methods: genotyping and phenotyping. Commercial assays using both of these methods are available. For example, TruGene (Visible Genetics) and ViroSequ (PE Applied Biosystems) provide genotyping information, and AntiVirogram (Virco) and PhenoSense (ViroLogic) provide phenotyping information. Genotypic assays provide information on mutations in the genes coding for reverse transcriptase and protease that confer drug. Phenotypic resistance is a direct measure of sensitivity and is similar to our current antibiotic sensitivity testing practices. Phenotypic assays rely on changes in the IC50, the minimum inhibitory concentration of the drug required to decrease viral replication by 50% in the particular cellular system used. The emergence of resistance is signaled by a significant increase in IC50 over baseline (3, 4).

Table 1. Studies of the Value of Resistance Testing in Creating Successful ART

STUDY	N	PRIMARY ENDPOINT	OUTCOME
GENOTYPING STUDIES			
GART	153	Change in viral RNA (at wk. 8)	Decline in viral RNA Group A: -1.12 log Group B: -0.52 log
VIRADAPT	108	Change in viral RNA(at wk. 24)	Decline in viral RNA Group A: -1.15 log Group B: -0.67 log
PHENOTYPING STUDIES			
VIRA 3001	221	Achieving VL <400 copies/mL (at wk. 16)	Observed Data: 59% of Group A had VL<400, 42% Group B had <400.
Melnick et al.	115	Decline in viral RNA (at wk. 4, 16)	At 4 wks, decline in viral RNA: Group A: -1.0 log Group B: -0.5 log (at wk. 16, no significant difference)
GENOTYPING, PHENOTYPING AND SOC STUDIES			
NARVAL	541	HIV RNA <200 (at wk. 24)	No significant difference

All studies compared regimens based on resistance testing (Group A) versus standard of care (Group B).

Both genotyping and phenotyping are complex technologies that utilize the polymerase chain reaction and other molecular techniques. They require specialized facilities staffed by well-trained laboratory personnel. Commercial assays using both methodologies are available, and the turnaround times for results are 1-2 weeks for genotyping and 2-4 weeks for phenotyping.

It is important to note that a plasma HIV RNA level above 1,000 copies/mL is necessary for either method to produce reliable results. Furthermore, neither method can routinely detect minority quasispecies; therefore, some resistant strains of virus may be missed. Although both types of assays are reproducible, both intra- and interlaboratory variability may be greater with genotypic assays. With regard to interpretation of results, complex mutational patterns detected by genotyping frequently require the interpretation of an expert whereas the results of phenotypic assays may be more easily interpreted by treating physicians. Phenotypic assays generally cost more than genotypic (3).

Interpreting Genotypic and Phenotypic Resistance Assays

Interpretation of genotypic assays requires not only knowledge of the individual mutations, which confer resistance and cross-resistance to drugs within the same class, but also an understanding of the interactions of multiple resistance mutations. For example, a single mutation in the protease gene may confer high-level resistance for one PI, yet for another, it may require multiple mutations to confer resistance. However, the phenotypic expression of a combination of genotypically detected mutations cannot always be predicted (3). To address this issue, Virco (Mechelen, Belgium), a manufacturer of one commercially available genotypic assay, has used a relational database of over 10,000 clinical isolates of HIV for which genotypic and phenotypic results are known, to assign a "virtual phenotype" to viral isolates based on mutational patterns. How this virtual phenotype correlates with response to antiretroviral therapy must be explored with appropriately designed clinical trials (5).

Interpretation of phenotypic assay results suffers from a lack of clinical information regarding correlation of fold increase in resistance to in vivo activity of the various antiretroviral drugs. For example, a small fold increase in resistance to a protease inhibitor may be overcome by increasing serum levels of the protease inhibitor (3).

Using Resistance Testing in Clinical Practice

The DHHS/Kaiser Guidelines (4) for using antiretroviral agents recommend that resistance assays be used to modify antiretroviral therapy in the setting of virologic failure during ongoing HAART and in the case of suboptimal viral suppression after initiating a new regimen. Resistance testing should also be considered in antiretroviral naïve

Continued on page 4

Letter from the Editor

Dear Colleagues,

Hello Alaska! Hello Arkansas! Hello North Dakota! I have just reviewed our list of subscribers, and I was amazed and humbled by the breadth and depth of the list. We reach more than 2,300 of you in all 50 states and several countries. You are physicians, nurse practitioners, pharmacists, and AIDS educators, who work on the front line of HIV care and interface with the HIV-infected inmate. I am thrilled that so many correctional providers want to be updated on HIV and Hepatitis and I am honored by your trust in this educational newsletter. This publication reaches a great network of correctional healthcare providers, binds us, and weaves us together in a web of influence. Together, we are making change in correctional HIV care.

Collectively, we care for almost one-fifth of the nations' HIV-infected individuals in correctional clinic settings. We take care of one-third of the nations' Hepatitis C-infected patients. We see more STDs, TB, and mental illness than community providers could ever imagine. We do this within the confines of prison and jail walls, usually at a distance from academic medical centers, and even farther from easy access to medical technology. Because of our isolation from the community, we must often rely on our clinical skills to treat and triage patients.

In the 12 years that I've been working as an HIV provider in correctional settings, I've seen - and heard about - a great deal of change. Correctional HIV care in the U.S. is moving toward, and in some cases beyond, the community standard. Certain institutions provide an exemplary level of care. More important, links between prisons and jails and the community are growing. From the medical perspective, the walls of correctional facilities are becoming more porous; meaning that medical education and treatment advances are reaching inside, and - perhaps more importantly - information about the work we do and our patients in need is reaching the outside world.

This issue marks our second anniversary at HEPP News! In our third year of publication, we pledge to continue to bring you the latest in HIV and Hepatitis management, written by correctional professionals with hands-on experience providing patient care in correctional facilities.

After reviewing this issue of HEPP News, readers should understand how to incorporate resistance testing into HIV care, identify when resistant strains of HIV are signaled clinically, list the newest treatment strategies for Molluscum contagiosum, and describe the latest news on antiretrovirals.

Last but not least, be sure to update your subscriber information - if you'd like to receive the newsletter by email, in pdf format (can be read on all types of computers), please let us know. We can fax you AND email you the newsletter if you prefer both formats. Don't forget to visit us for online archives of HEPP News at www.hivcorrections.org.

We love to hear from you and we accept written contributions. Please write, email, fax, or call!

Sincerely,

Anne S. De Groot, M.D.

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Antiretroviral Resistance Testing...

(continued from page 2)

patients with acute HIV infection for whom treatment is planned. Suppression of viral replication during acute HIV infection may favorably alter the long-term course of HIV infection by allowing the immune system to develop antiviral responses that are otherwise impaired by unchecked viral replication during acute infection. This accounts for the recommendation of resistance testing for naïve patients with acute HIV infection, but not for naïve patients with established, chronic infection.

Studies Reveal Effectiveness of Resistance Testing

Several prospective studies provide information on the clinical utility of using HIV-1 resistance assays to direct therapy in patients who are failing an antiretroviral regimen. See Table 1 pg.2 for a summary. The GART (6) and VIRADAPT (7) studies used genotypic resistance assays. In the GART study, at eight weeks, the mean decline in HIV RNA was significantly greater in the group whose regimens were based on resistance testing than in the SOC group (-1.12 log vs. -0.52 log). Fifty-five percent of those in the resistance testing-based group had a viral load <500 copies/ml versus 25% in the SOC group. In the VIRADAPT study, at six months, the resistance testing group had a significantly greater decline in viral load than the SOC group (-1.15 log v. -0.67 log).

The VIRA 3001 Study (8) and a study reported by Melnick, et al. (9) used phenotypic resistance assays to direct a change in antiretroviral therapy. Using intent-to-treat analysis in which patients lost to follow up were counted as failures, the VIRA 3001 Study found no significant difference between the groups in the primary endpoint. In an alternative analysis using observed data, there was a significant difference in the groups (59% of those in the resistance-testing group had a viral load <400 copies/mL v. 42% in the SOC group, Melnick et al.) At four weeks, there was a statistically greater decline in viral RNA in the resistance-testing group than in the SOC group, but the difference was not sustained at 16 weeks. These two studies were conducted with participants who were more highly treatment-experienced than those in GART and VIRADAPT. Therefore, the number of available active agents was limited, particularly in the study reported by Melnick et al. in which even those on resistance-testing-based-regimens were on an average of less than three active drugs. This fact must be taken into account when interpreting these studies.

In the NARVAL study, 541 (10) highly treatment-experienced patients failing a 3 drug protease inhibitor containing regimen were randomized to therapy based either on genotyping, phenotyping, or SOC. At week 24, a greater percentage of participants in the genotyping-based group had HIV-1 RNA levels less than 200 copies/mL, but the difference was not statistically significant.

Although short in duration, GART and VIRADAPT clearly support the use of resistance assays to help direct antiretroviral therapy. VIRA 3001 and the study reported by Melnick, et al. are equivocal, while NARVAL does not support resistance testing. Because participants in these last three studies had greater prior treatment experience than in GART and VIRADAPT, one interpretation of these data is that resistance testing is less useful in highly treatment-experienced patients with few treatment options. Thus, one clear indication for use of resistance testing is after the first regimen fails.

Conclusion

In summary, the use of both genotypic and phenotypic resistance assays is expanding in clinical practice. Although specialized facilities and personnel are necessary to conduct these tests, commercially available kits have made the results reproducible, available in a timely fashion, and relatively affordable. Resistance testing to guide modifications in ongoing therapy is recommended in the setting of antiretroviral failure when a new regimen is anticipated and also in the setting of incomplete suppression of viral replication by a new regimen. It should also be considered when the decision is made to treat acute HIV infection. Several prospective clinical trials have demonstrated better suppression of viral replication in patients whose antiretroviral regimen has been guided by resistance testing, particularly in patients whose exposure to prior antiretroviral therapy has been limited, i.e. after the first regimen fails. Despite this benefit, resistance testing information must be combined with a complete medical history that details prior regimens, side effects to medications, and adherence with treatment. Such information is essential in selecting a regimen that is not only effective in suppressing viral replication but also acceptable to the individual patient.

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**Speaker's Bureau: Roche Pharmaceuticals*
***Speaker's Bureau: Agouron Pharmaceuticals, Bristol-Myers Squibb, DuPont, Glaxo Wellcome, Merck, Roche.*

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HIV 101

HIV Medications and Gene Mutations

Primary mutations are those that are associated with high-level resistance to an ART. Secondary mutations include those that alter conformation such that viral fitness is modified but not high-level resistance. For patients who are sustained on partially suppressive therapy for prolonged time periods, additional compensatory mutations may develop. This list of primary and secondary mutations for each available ART is listed below. This chart will be updated in future issues as new information is described.

ANTIRETROVIRAL	1° MUTATIONS	2° MUTATIONS
ALL NRTIS	69, 151	
Zidovudine (AZT, ZDV)	70, 215	41, 67, 210, 219
Didanosine (DDI)	74	65, 184
Zalcitibine (DDC)	74	65,69,184
Stavudine (D4T)	75	-
Lamivudine (3TC)	184	-
Abacavir (ABC)	184	65, 74, 115
NNRTIS		
Nevirapine (NVP)	103, 181,190	106,108,188
Delavirdine (DLV)	103, 181	236
Efavirenz (EFV)	103	100,108, 188, 190
PROTEASE INHIBITORS		
Saquinavir (SQV)	48,90	10,54,63,71,73,82,84
Indinavir (IDV)	46,82	10,20,24,32,54,63,71,73,84,90
Ritonavir (RTV)	82	20,32,33,36,46,54,63,71,84,90
Nelfinavir (NLF)	30	36,46,63,71,77,84,88,90
Amprenavir (APV)	50	10,46,47,84

Amino acid changes in the viral enzyme system are the result of a mutation. Such changes may be in the form of substitutions, insertions or deletions. Mutations are also classified as primary and secondary. Primary mutations typically arise first in response to therapy with a particular antiretroviral agent. Primary mutations are drug specific and typically interfere with the binding of the drug to the viral enzyme. The extent to which the mutation alters the binding of the drug to the enzyme directly influences the reduction in IC50. Secondary mutations accumulate during continued therapy with a given drug and usually potentiate the effect that the primary mutation had on drug binding. Secondary mutations have a less dramatic effect on increasing the IC50, however may significantly affect cross-resistance. For instance, if a patient remains on a non-suppressive, PI-containing regimen for considerable time in the setting of a high viral load, the number of secondary mutations increases and may adversely affect the ability to use another PI in salvage therapy.

The occurrence of cross-resistance has resulted in many clinicians adhering to the concept that the first regimen will be the most effective regimen or the first shot is the best shot. Therefore clinicians, when possible, should select regimens with a high genetic barrier for developing resistance. This must be tempered by selecting regimens that are simple and have few side effects. These competing paradigms often require clinicians to frequently monitor viral load and change regimens quickly after viral rebound to avoid the development of cross resistance. Resistance testing may aid in the decision for altering an antiretroviral regimen in such settings.

Web Resources

Updated HIV Drug Resistance Testing Guidelines, published by the International AIDS Society, USA Part II.
http://jama.ama-assn.org/issues/v283n18/full/jst90018.htm

The AIDS Gateway to the Internet
http://www.aids.org

AIDS Medications Information
http://www.aidsmeds.com

UK National AIDS Manual/ British HIV Association
http://www.aidsmap.com

Physicians Research Network
http://www.pnr.org

7th Conference on Retroviruses and Opportunistic Infections
http://www.retroconference.org

Treatment Updates

XIIIth International AIDS Conference Continued: The Difficulty of Deep Salvage

The International Conference on AIDS is the premier venue for presentation of HIV-related research from all over the world. The last issue of HEPP News covered the prison-related data, and some of the medical reports. This article will review the important data regarding the care of individuals with access to potent HIV therapies.

An increasingly frequent conundrum confronting clinicians is the management of the highly treatment-experienced patient.

In areas where combination antiretroviral agents have been available, there are still persistent questions regarding the care of the treatment naïve patient as well as the patient whose treatment meets virologic failure. New data related to each of these areas could be found at the conference and, while unexpected or spectacular headline-making results were not announced, several instructive lessons for providers and patients were presented.

As discussed in the main article, an increasingly frequent conundrum confronting clinicians is the management of the highly treatment experienced patient. Most studies to date have demonstrated that successful virologic suppression of such patients is difficult to achieve regardless of the choice of agents employed. Aggressive attempts to regain control of viral replication by using multiple antiretrovirals in combination, so called 'megaHAART', have had some better results. Follow-up data from one of the few mavens of megaHAART, Julio Montaner, were presented at Durban. Overall, using combinations of up to 8 antiretroviral agents in heavily treatment experienced patients in Vancouver, approximate-

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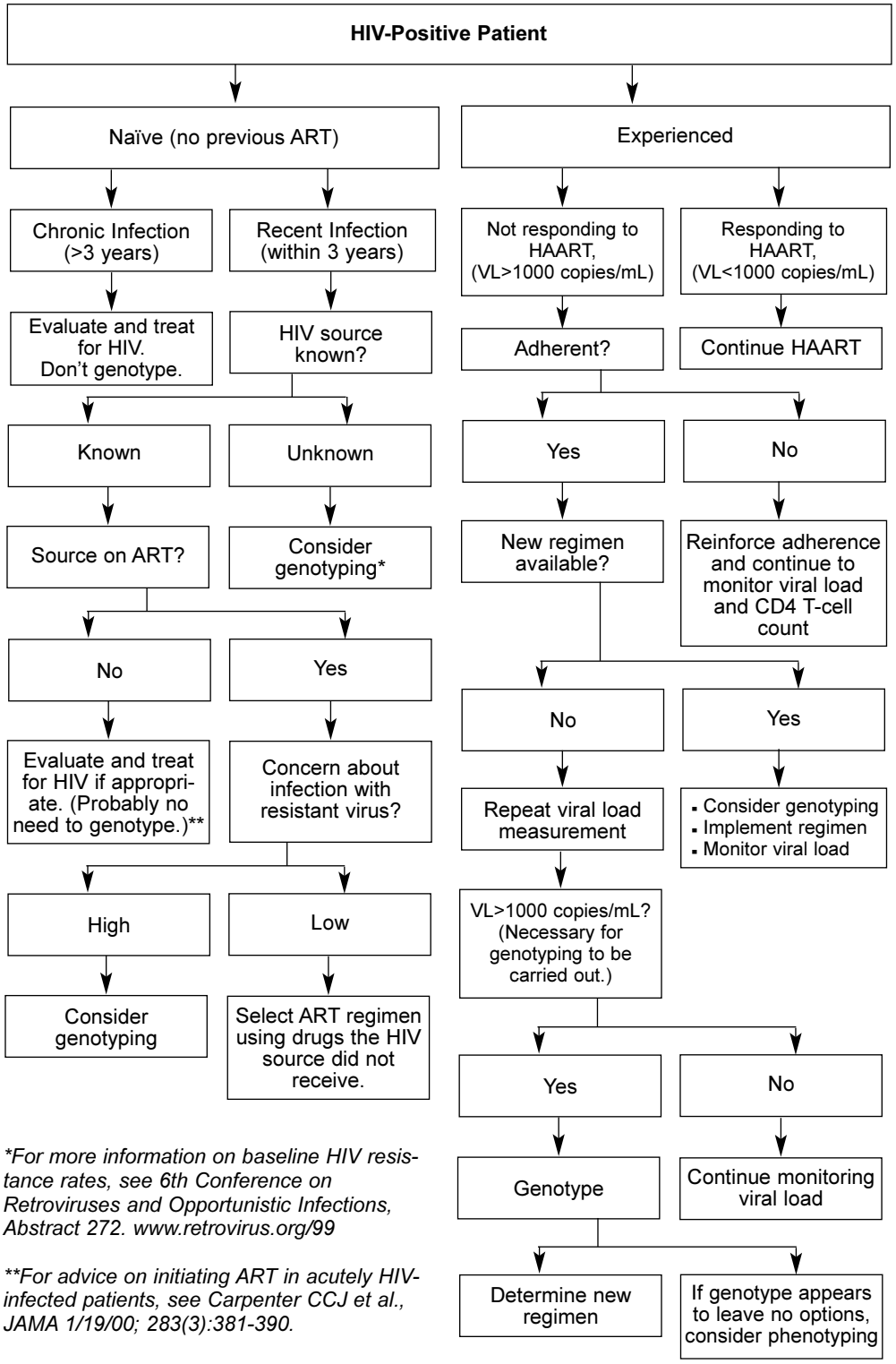
HEPPigram

When to Genotype in the Management of Drug Resistance Among HIV-infected Inmates



**For more information on baseline HIV resistance rates, see 6th Conference on Retroviruses and Opportunistic Infections, Abstract 272. www.retrovirus.org/99*

***For advice on initiating ART in acutely HIV-infected patients, see Carpenter CCJ et al., JAMA 1/19/00; 283(3):381-390.*

Important Correction from July/August 2000 issue: in the HEPPigram, VCG IgG antibody positive patients are immune, contrary to what we printed. VCG IgG antibody negative patients should follow the remaining path in the flow sheet.

Treatment Updates...

(continued from page 6)

ly 40% of subjects who could tolerate these intensive regimens had HIV RNA levels below 400 copies/mL at one year. As expected, intolerance and toxicity were high and resistance testing predicted success. MegaHAART remains an option for select patients for whom treatment cannot wait until the release of new drugs. However, extreme caution must be used when combining these agents to minimize drug interactions and serious toxicity.

For many patients with multiple antiretroviral experience and resistance, new drugs offer the only hope to regain virologic control.

For many patients with multiple antiretroviral experience and resistance, new drugs offer the only hope to regain virologic control. One of the most talked about drugs on the horizon is ABT-378/r or lopinavir - recently christened with the trade name Kaletra. This drug is actually a combination of two protease inhibitors, ABT-378 400 mg plus 100 mg of ritonavir - the latter, included to increase plasma concentrations of the former. Several posters reported on the potency of this agent including treatment of multiple drug experienced patients (TuPeB3196, TuPeB3197, TuPeB3198). In one study by Clumek et al. of 57 subjects with extensive NRTI and PI experience but who were all NNRTI naïve, EFV and a NRTI chosen by the investigator plus one of two doses of lopinavir/ritonavir (400/100 versus 533/133) were studied. In an intent to treat analysis, 69% of the lower dose arm and 80% of the higher dose arm achieved viral loads below 400 copies/mL (TuPeB3196). Additionally, the drug appears to be effective despite predicted resistance by genotype and phenotype testing. Diarrhea and nausea are the major toxicities associated with lopinavir. The ritonavir component may present problems for maintenance of normal blood lipids.

Other new agents discussed at the conference, which appear promising include: T-20, an injectable HIV fusion inhibitor that continues to maintain good responses out to 48 weeks of study follow-up and DAPD another guanosine analog (like ABC) that may actually have activity against multi-nucleoside resistant virus. (For more information on the conference and abstracts, visit www.aids2000.org).

Ask the Expert

Dr. Feller, of Miriam Hospital and Clinical Professor of Medicine at Brown University, Providence, contributed the following case. Dr. Feller is a hepatologist who provides expert consultation to HIV practitioners who wish to treat their HIV and HCV co-infected patients for Hepatitis C.

HEPP News Expert Case: *A 34-year-old male intravenous drug user with well-controlled AIDS and abnormal alanine transferase is seen in Infectious Disease clinic at the prison. His T cell count is 250, and he has had several consecutive undetectable viral loads (<50) by RNA PCR over the past 6 months. His HIV is controlled with DDI, D4T, Efavirenz; he takes his DDI on his own in the morning (two concentrated formulation 200 mg tablets) and receives the other two medications by DOT at the medline window.*

The ID consultant obtains an HCV antibody test, which is positive. After discussion, it is clear that the patient will be remaining in prison until his maximum sentencing date two years hence. He is currently enrolled in a drug "recovery" program at the prison, and he willingly states that he is committed to a life without drugs and alcohol. He has a history of depression, and was on serotonin-uptake inhibitors in the past, but he claims that this is "under control" right now and doesn't want to take any "mood altering drugs" while he's in the drug recovery program.

A liver biopsy is ordered and approved by the URC after careful review. The biopsy reveals moderate fibrosis. Combination treatment for HCV with interferon/ribavirin is initiated. What concerns would you have, as the HCV expert, about his course of treatment?

Dr. Feller: In Rhode Island, as in other state correctional systems, we've observed a high prevalence of HCV and HIV co-infection in incarcerated populations. With highlly active antiretroviral therapy (HAART) and a subsequent decline in mortality from opportunistic infections in HIV, hepatic failure is likely to increase as a leading cause of death in incarcerated patients. Co-infection with HIV raises particular treatment issues.

For example, we've observed that co-infected patients on combination therapy tend to have more problems with ribavirin-associated hemolytic anemia and interferon-related thrombocytopenia than patients who are not co-infected. Monitoring will detect which patients develop anemia (hemoglobin <10-11 grams %), that can be treated with erythropoiten at dose of 40,000 units weekly.

Although patients have slightly more difficulty tolerating therapy, HCV treatment does clear HCV RNA from serum in a portion of patients who have HIV co-infection, similar to non co-infected patients.

Occasionally, patients will experience hepatotoxicity when an HIV regimen is instituted. Treating HCV first to suppress viral activity may permit the introduction of HIV drugs with less hepatotoxicity.

Certain HIV treatments are more toxic when used in combination with HCV. For example, the protease inhibitor ritonavir is most hepatotoxic, followed by indinavir. Sacquinavir and nelfinavir are generally better tolerated. HIV treatment is generally introduced first because HIV may be more rapidly progressive. At times, severe hepatic disease may necessitate early HCV therapy, allowing subsequent introductions of HIV drugs with decreased hepatotoxicity.

Q: What types of HCV treatment-related issues arise with HIV-infected patients that are not different from other patients?

Dr. Feller: Interferon-related depression is real and can be fatal. Should depression reoccur here, the ID consultant should select serotonin re-uptake inhibitors, monitor mental status, and not withhold anti-HCV therapy for well-controlled depression.

Q: What findings do you consider "new" and important for our audience, that might also be relevant to this case?

Dr. Feller: This patient has moderate fibrosis. He may not completely recover from HCV infection, however there is recent evidence that some patients who do not clear HCV-RNA from serum may have interferon-related improvement in liver fibrosis. Some research has suggested that even if interferon does not clear the virus, maintenance therapy may decrease or stabilize hepatic fibrosis and prevent end-stage cirrhosis. (See News Flashes on page 8.)

Q: What other concerns exist in the treatment of HCV in HIV-infected patients?

Dr. Feller: Be wary in initiating anti-retroviral therapy of "immune reactivation" flare up (HCV patients started on anti-HIV therapy may get hepatomegaly, upper abdominal pain, deterioration of liver function). Also watch for drug hepatotoxicity, and immune system reconstitution.

For more information on the management of Hepatitis C, see HEPP News Vol. 3, Issue 6, June 2000 at http://www.HIVcorrections.org.

Save the Dates

United States Conference on AIDS
October 1-4, 2000
Atlanta, GA
Contact: Oscar Medrano, Conference Registrar, National Minority AIDS Council, 1931 13th St NW, Washington DC 20009-4432
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October 3, 2000
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Contact: Sande Gracia Jones
958 Whitehall Ln.,
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National STD Prevention Conference
December 4-7, 2000
Milwaukee, WI
Contact: Glenda Vaughn, Centers for Disease Control and Prevention
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E-mail: ghv1@cdc.gov

Medical Management of AIDS: A Comprehensive Review of HIV Management - Winter Symposium
December 7-9, 2000
San Francisco, CA
Contact: Cliff Brock
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News Flashes

Treating STDs Could Reduce HIV Transmission by 27 Percent

Dr. Richard Rothenberg of the Ad Hoc STD/HIV Transmission Group found that identifying and treating people who have both HIV and another sexually transmitted disease (STD) could reduce the risk of HIV transmission to an uninfected person by 27 percent. Data from eight clinics across the United States on more than 4,500 HIV- and STD-infected individuals showed that the decrease in possible HIV transmission ranged from 10 percent in Los Angeles to 38.1 percent in Colorado Springs. (STD, August 2000;27:411-416).

Success Against Molluscum Contagiosum Virus (MCV) Noted

Recently, doctors at the National Cancer Institute in Bethesda, MD, reported some success against MCV (Molluscum contagiosum virus) lesions using the antiviral drug cidofovir (Vistide). MCV can cause disfiguring lesions on the face, neck and genitals of people with HIV/AIDS. There is no therapy specifically licensed by the FDA for the treatment of MCV lesions, but doctors have used, with varying degrees of success, the immune boosters Aldara (imiquimod) and DNCB, liquid nitrogen, electric "zapping" of lesions and Retin-A. A recent study reviewed the cases of two young HIV-infected boys: one 4-year-old (CD4+ count of 168 and viral load of 430,000 copies), and one 8-year-old (CD4+ count of 329 and viral load of >700,000). Despite the fact that both boys had been receiving HAART for two years, hundreds of MC lesions had developed on their bodies. Using a skin treatment consisting of 15 grams of cidofovir with 22.5 grams of Dermovan ointment, the doctors treated the skin lesions once daily for five consecutive days each week, for eight weeks. After two months of cidofovir therapy the MC lesions cleared and have not returned after 18 months of monitoring. (Archives of Dermatology 2000;136:983-985).

Two Important Follow-Ups on HCV Liver Fibrosis

At the 4th International Workshop on HIV Drug Resistance and Treatment Strategies, N. Shulman of Stanford University reported on "Histologic improvements of liver despite virologic failure of interferon (IFN)+ribavirin therapy in 3 HIV+/HCV+ patients." Following up from our Hepatitis C issue in June, this was a reference we could not locate showing the link between treatment and improved post treatment liver biopsy regardless of stage of disease. In an ongoing treatment trial of IFN alpha, 3 million units TIW + ribavirin 800mg/d , 3 patients with virologic failure at 6 months received pre- and post-therapy liver biopsies. As has been shown in HIV- HCV+ patients, treatment of HCV with interferon-based therapy can lead to histologic benefits despite lack of HCV clearance or ALT normalization. Biopsy outcomes should be an important part of future therapeutic trials for these patients.

M Putoi from University of Brescia, Italy, presented "Liver Fibrosis progression is related to CD4+ cells depletion in patients with Hepatitis C and Human Immunodeficiency Virus Coinfection." The relationship between the stage of liver fibrosis and CD4 levels was analyzed taking into account the variables known or suspected to influence liver fibrosis progression by using polytomous logistic regression. The authors concluded that CD4 cells depletion is independently associated with the severity of liver fibrosis in chronic Hepatitis C. Antiretroviral combination therapy aiming at keeping high CD4 counts should be regarded as a priority in the care of HIV and HCV coinfected patients. (Reports from the 4th International Workshop on HIV Drug Resistance and Treatment Strategies, Sitges, Spain, June 12-16, 2000).

Resources & Opportunities

Inmate Adherence Videotape Series: A Strategy to Increase HIV/AIDS Medication Adherence in Correctional Settings

Comprised of five videotapes, this series aims to increase HIV-infected inmates' awareness of their disease and treatment with the ultimate goal of reducing the progression of HIV observed in correctional medical units. Additionally, these tapes may encourage cost of savings for correctional facilities by reducing the expenses associated with treating preventable complications of HIV. $40.00. Contact Albany Medical College at 518/ 262. 6864 or santosm@mail.amc.edu

Pocket Guide to HIV/AIDS Treatment is available from the Hopkins HIV Report. The guide was created for the AIDS Education and Treatment Center's National Resource Center, a project sponsored by HRSA. To obtain a copy, contact your regional AETC, or visit http://www.aids-ed.org.

A New Treatment Directory through the National Institutes of Health Clinical Center of Pharmacology is available at: http://www.cc.nih.gov/phar

Free CME materials are available through the Healthcare Consortium http://www.hivcme.org

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

1. The 184 mutation confers resistance to which antiretroviral drug?
   a) Stavudine (D4T)
   b) Zidovudine (ZDV, AZT)
   c) Lamivudine (3TC)
   d) Nevirapine (NVP)

2. Which of the following HIV antiretrovirals are reported to be well-tolerated in the presence of HCV treatment?
   a) ritonavir
   b) indinavir
   c) saquinavir
   d) Abacavir

3. In which of the following situtations is resistance testing recommended?
   a) For ART naïve patients with established, chronic infection
   b) For ART naïve patients with acute HIV infection
   c) In the case of suboptimal viral suppression after initiating a new regimen
   d) a and b
   e) b and c
   f) None of the above

4. Not all viral mutations cause clinically important resistance to ART. Which of the following mutations cause clinically significant resistance?
   a) Mutations that become the dominant quasispecies because of increased viral fitness in the setting of selective drug pressure
   b) Mutations that provide a competitive advantage over the wild-type of the virus and maintain viral replication by pre serving enzyme function.
   c) Mutations that increase viral sensitivity to the drug
   d) a and b
   e) all of the above

5. How is the presence of antiretroviral resistance to HIV medications signaled clinically?
   a) reduction in CD4 count
   b) any reproducable three fold or greater increase in viral load in any patient who is adherent
   c) Significant increase (VL>50mL) in viral rebound in any patient who is adherent
   d) Significant fluctuation of CD4 count

6. According to a recent report, which of the following treatments are FDA approved for use against Molluscum contagiosum?
   a) immune boosters Aldara (imiquimod)
   b) DNCB
   c) electric "zapping" of lesions
   d) Retin-A
   e) the antiviral drug cidofovir (Vistide)
   f) none of the above
   g) all of the above

HEPP News Evaluation

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

1. Please evaluate the following sections with respect to:

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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
Treatment 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?

5. Do you have specific comments on this issue?

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