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HIV & Hepatitis Education Prison Project

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ABOUT HEPP

HEPP News, a forum for correctional problem solving, targets correctional administrators and HIV/AIDS and hepatitis care providers including physicians, nurses, outreach workers, and case managers. 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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UPDATE ON HIV RESISTANCE TESTING

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INTRODUCTION

Since the publication of a review of Antiretroviral Resistance Testing in the September 2000 *HEPP News*,[1] resistance testing has become an important component of standard care for HIV - infected patients. This is largely due to the widespread availability of genotypic testing, as well as increased access to both the virtual and standard phenotype tests. Additionally, the increasing presence of resistance in both antiretroviral (ARV) experienced and ARV naïve individuals, combined with the availability of newer ARV agents capable of overcoming drug resistance, has fueled the need to assess for drug resistance in patients being treated for HIV infection. This article will provide an update on new developments in the area of HIV resistance and provide a guide to the implementation of resistance testing in correctional settings.

PREVALENCE OF RESISTANCE

HIV resistance is increasing in the U.S. Richman, *et al.*[2] reported in a study in late 2001 on the prevalence of resistance in the United States. In using the HIV Cost and Service Utilization Study database, 1,906 patients who were on treatment (receiving antiretroviral therapy) between 1996 and 1999 were identified. A phenotypic resistance assay was done on 1,209 patients whose viral load was >500 copies/mm^3. Seventy eight percent (78%) had resistance to at least one ARV agent, 50% had resistance present in two classes of ARV agents, and 14% had three-class, or multi-drug resistant HIV (MDR-HIV). The majority of resistance was found in the nucleoside reverse transcriptase inhibitor (NRTI) class with lesser degrees in the protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) classes, which may have been related to the date of the study (PIs and NRTIs were new when the study started). This degree of resistance likely reflects incomplete adherence to therapy (see Figure 1).

Equally disturbing is the increasing prevalence of ARV resistance in drug-naïve people who are recently HIV infected as first described by Little *et al.* and subsequently confirmed by others. Little *et al.* showed that 15% of acutely infected (naïve) patients had genotypic mutations at the time of their diagnosis. More importantly, these mutations in the reverse transcriptase and protease genomes persisted up to 303 days in the absence of ARV therapy[3]. Bennett *et al*. described the prevalence of genotypic resistance in a cohort of patients newly infected with HIV between 1998 and 2000[4]. Ten percent of patients had NRTI resistance mutations, 4% had PI mutations, and 3% had NNRTI mutations; and 4% had resistance mutations in two classes of agents.

FIGURE 1: Relationship Between Drug Pressure and Amount of Drug-Resistant HIV

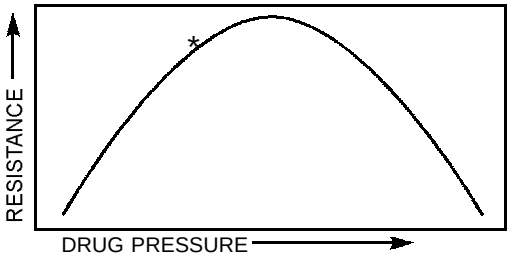

Figure 1 represents the relationship between the amount of drug pressure applied to HIV versus the viral drug-resistance that develops. At the extreme left of the curve, there is absolutely no drug pressure applied to the virus, and thus the amount of viral mutation that occurs and results in drug-resistant virus is very low. As drug pressure increases, however, the virus must mutate and become drug-resistant if it is to continue to "survive," or replicate. Drug-resistant virus is most likely to occur when there is enough drug pressure to select for drug-resistant virus, but not enough to significantly suppress viral replication (the star on the left side of the graph illustrates such a situation, for example, when patients are not adherent to their medications). At the far end of the graph, there is again little drug-resistant virus present because there is enough drug pressure to significantly inhibit viral replication. This makes the likelihood of a drug-resistant mutation small, as there are so few copies of the virus being made at any given time (this often occurs when a patient is on successful ARV treatment).

WHEN TO USE RESISTANCE ASSAYS

Use of genotypic or phenotypic resistance assays has been shown to improve response to

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WHAT'S INSIDE

Update on HIV Resistance Testing... *(continued from page 1)*

rescue therapy in patients failing therapy.[5,6] Combined with the above data, the current recommendation that resistance testing be performed in patients failing therapy or with incomplete viral suppression is warranted. And, although not yet generally recommended, the epidemiological data described above support the use of genotypic testing in recently infected patients for up to a year after their infection. However, clinical studies assessing this strategy have not been done (see HEPPigram, page 7 for guidance).

Defining Resistance

Resistance is best defined as reduced susceptibility of HIV to a specific ARV agent. As a result, resistance is not an all or none phenomenon. This relative reduction in susceptibility is best displayed through the use of phenotypic testing. The phenotypic assay reports the fold-increase in drug concentration needed to inhibit 50% of viral replication (IC_{50}). The threshold defining reduced susceptibility for the nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs) is drug-specific. For example, a greater than 1.6-fold increase in the IC_{50} for stavudine confers resistance, whereas for tenofovir a 3.8-fold increase is necessary to confer resistance.

For non-ritonavir enhanced protease inhibitors (PIs), a greater than 2.5 - 4 fold increase in the IC_{50} (depending on the assay used) usually signifies an intermediate reduction in susceptibility, whereas a greater than 10-fold increase is required to confer complete resistance. With the introduction of co-formulated lopinavir/ritonavir (Kaletra), the standard PI thresholds no longer apply. The small amount of ritonavir in Kaletra leads to a large increase in lopinavir drug levels. Specifically, the lopinavir trough concentration (C_{min}) greatly exceeds the IC_{50} in both wild-type and drug resistant HIV strains. Therefore the so-called inhibitory quotient (C_{min}/ IC_{50}) for lopinavir is quite large.[7] Patients who failed three or more prior PI-containing regimens still responded to rescue therapy containing lopinavir/ritonavir as long as the fold-change in the IC_{50} was less than 40. Specific thresholds have not yet been defined for other ritonavir-enhanced regimens such as ritonavir plus indinavir, amprenavir, or saquinavir.

One last concept specific to phenotypic resistance testing is hypersusceptibility. Hypersusceptibility exists when there is a decrease in the amount of drug needed to inhibit viral replication. This is most commonly seen with the NNRTIs in the setting of significant prior NRTI use, but has also been seen with amprenavir. Clinically, Shulman et al has shown an enhanced anti-viral response in the presence of hypersusceptibility to efavirenz.[8]

Table 1: Advantages and Disadvantages of Genotypic and Phenotypic Testing[17]

ADVANTAGES	DISADVANTAGES
Genotypic Assays	
◆ Less expensive ($300 to $480/test) ◆ Short turn-around (1-2 weeks) ◆ May detect presence of resistance mutations before they have affected phenotypic resistance	◆ Detect resistance only in dominant species of virus (>20% of patient's isolates) ◆ Interpretation requires understanding and knowledge of mutational changes (i.e. expertise) ◆ Technician experience may influence results ◆ May show discrepancy with phenotype ◆ Require viral load> 1000 copies/mL
Phenotypic Assays	
◆ Interpretation more analogous to resistance testing of bacteria ◆ Asseses 3-dimensional molecule, including mutations and mutational interactions ◆ Reproducibility is good ◆ Advantage over genotype when multiple mutations exist	◆ More expensive ($800-$1000) ◆ Longer delay in reporting (2-3 weeks) ◆ Thresholds to define susceptibility to drug are arbitrary and non-standardized; do not always reflect achievable drug concentrations ◆ Detect resistance only in dominant species (>20% of patient's isolates) ◆ Require viral load >500-1000 copies/mL

In contrast to phenotypic testing, genotypic testing defines resistance based on the number of known resistance-conferring mutations present at the time of testing. The threshold differs for each drug because resistance is conferred by different mutational patterns. Each genotypic resistance-testing manufacturer sets up their own rules by which they interpret whether the mutations present are likely to confer reduced susceptibility. This can lead to significant differences in interpretations between testing kits, as well as confusion amongst clinicians inexperienced in interpreting genotypic resistance test results.[9] Therefore, it is recommended that HIV experts assist with interpreting genotypic testing (see Table 1 for a comparison of genotypic and phenotypic testing).

Genotypic testing has led to the recently appreciated concept of NRTI class cross-resistance. Although the infrequently (1-3%) seen Q151M and T69S insertion mutations have been known to confer resistance across most of the NRTI class, work done by Whitcomb *et al.* at Virologic has shown that mutations previously associated with just zidovudine resistance actually confer resistance to all the NRTIs.[10] These specific codon mutations-41, 67, 70, 210, 215, and 219-referred to as thymidine or nucleoside analogue mutations (TAMs or NAMs) cause varying degrees of resistance to all the nucleoside and nucleotide analogues (see HIV101, page 5). The more mutations present, the broader the resistance.

Despite all the data that may be derived about a patient's virus from the use of resistance assays, additional intricacies may limit their utility. First, discordance between genotypic and phenotypic testing exists. Parkin, *et al.* evaluated 200 patient samples with both testing modalities and found one-drug discordance in 75% and four-drug discordance in 22% of samples.[11] Additionally, these *in vitro* assays may not translate into *in vivo* response. The reasons for this are multifactorial and include non-adherence, interpatient variability in absorption and metabolism of the agents (variability in therapeutic drug levels, see TDM below), and adverse drug-drug interactions. Finally, it should be understood that resistance test results reflect the pressure exerted by the current regimen on the virus. So if a patient who had previously developed the M184V (amino acid M replaced by amino acid V at position 184) mutation while on lamivudine is not taking it at the time resistance testing is repeated, this mutation may not be prevalent in adequate amounts to be detected (it may be present in an "archived" form in resting T cells). However if the patient is then started on a lamivudine-containing regimen that is not fully suppressive, the mutation will reappear and lead to virologic failure. Therefore, clinicians must utilize all available resistance test results and information about prior ARV therapy when planning rescue therapy.

Evolving Resistance in the Face of Low-Level Viremia

Several years ago, Deeks *et al.* in San Francisco described their cohort of patients who had previously been undetectable on PI-based ARV therapy but subsequently had viral breakthrough. In this group, despite persistent viremia while on their failing regimen, most remained immunologically and clinically stable for many years.[12] This study led many clinicians to maintain patients on their failing regimens. Coakley

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Letter from the Editor

Dear Colleagues:

As I begin my tenth year providing healthcare to the incarcerated, I've taken some time to reflect on the past decade and the successes and failures I've experienced in our efforts to provide quality treatment to those living behind bars with HIV, hepatitis, and other serious medical conditions.

Like all perfectionists, I tend to dwell on the deficiencies…staffing problems, budgetary woes, and all of my yet-to-be accomplished goals in correctional healthcare. Sometimes I need to be reminded of how far we have come in improving the life expectancies and quality of life of our HIV-infected patients.

In April of this year I joined three other physicians on a medical mission to Benin City in Edo state, Nigeria. Our goals included providing an intensive HIV educational program for healthcare providers, and attempting to lay the foundation for an HIV treatment program. We met some intensely dedicated individuals struggling against all odds to provide basic healthcare in the absence of running water, reliable electricity, medications, gloves, basic supplies, and, oft times, even a salary.

I returned saddened by what I saw, but also inspired by my Nigerian colleagues and reminded of how blessed we are to have the basic tools to provide our patients treatment for what is in many parts of the world still an untreatable disease.

This month, Dr. Peter Piliero updates us on the use of HIV genotype and phenotype analysis. This month's HEPPigram provides an approach to the application of HIV resistance testing. After reading this issue providers should be familiar with the issues of HIV resistance and genotype and phenotype analysis.

My kudos to all of you who continue to struggle to improve the quality of healthcare for the incarcerated. You all contribute mightily, not only to your patients but also to this nation's public health.

Sincerely,

Joseph Bick

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Published monthly and distributed by fax, HEPP News provides up-to-the-moment information on HIV and hepatitis treatment, efficient approaches to administering treatment in the correctional environment, national and international news related to HIV and hepatitis in prisons and jails, and changes in correctional care that impact HIV and hepatitis treatment.

Update on HIV Resistance Testing... *(continued from page 2)*

et al. recently reported on a cohort of patients who were receiving similar ARV therapy and who had rebounded with a viral load less than 1000 copies/mm^3.[13] These patients had detectable viremia for a mean of 22 months during which their CD4 count rose 97 cells/mm^3 and viral load rose 61 copies/mm^3. Forty patients had a genotype obtained which revealed that 90% had resistance to one or more of the ARVs they were taking. Six of seven patients whose viral load rose above 1000 copies/mm^3 had resistance to all three agents compared with only nine of 33 whose viral load remained less than 1000 copies/mm^3. Therefore, despite the lack of clinical and immunologic damage during low level viremia, viral evolution is ongoing and is likely to be clinically significant when rescue therapy is attempted. Thus, maintaining patients on failing regimens may be detrimental.

Combining Resistance Testing with Other Modalities

Newer testing modalities such as therapeutic drug monitoring (TDM) and viral fitness assays are not yet widely available, but are being studied in patients taking ARV therapy. When available, these will most likely be utilized in patients failing treatment and will therefore be combined with resistance assay results to further assist in the management of this expanding population.

Therapeutic Drug Monitoring (TDM)

TDM involves measuring plasma drug concentrations. The trough (or C_{min}) is the concentration of drug just prior to administration of the next dose. Protease inhibitor trough levels have been linked to efficacy.[14] This data, in conjunction with the unpredictable pharmacokinetic profile of the protease inhibitors, has led to clinical studies examining the role of TDM. Burger, *et al.* looked at the use of TDM with nelfinavir based regimens and found that use of TDM led to increasing the nelfinavir dose to achieve a better C_{min} and virologic outcome.[15] As mentioned earlier, ritonavir-boosted PIs achieve higher C_{min} values and when TDM is readily available it will likely be combined with phenotypic data to adjust dosing in individuals to overcome resistance.

Viral Fitness

Viral fitness is the ability of the virus to replicate, infect, and kill T cells. Fitness varies between wild type and resistant strains. The acquisition of resistance mutations often leads to a period of decreased fitness, which in turn has been associated with prolonged immunologic stability in the setting of virologic failure.[16] A fitness assay might be utilized to determine which patterns of resistance are less damaging. Clinicians can now begin receiving this type of information with a new replication assay, Replication Capacity (Virologic), that is now provided with Virologic's phenotype assays.

Clinical Application of Resistance Testing

The use of resistance testing is illustrated by the following clinical case. A 38 year-old African-American inmate presented for HIV specialty care in March 2000. He had a history of HIV infection since 1996 but was asymptomatic and had a history of hepatitis C. In March 2000 he had a CD4 count of 375 cells/mm^3 (15%) and a viral load of 736 copies. He was taking stavudine, lamivudine, and efavirenz since July 1999 but notably each drug had been started sequentially over a 2-year period. He had also received zidovudine, indinavir, and nelfinavir in the past. The decision at this time was to continue his current ARV given his overall stability.

He remained clinically stable on this regimen for the next 16 months and his CD4 count and viral load ranged from 324-414 cells/mm^3 and <400-1571 copies/mm^3 respectively. In August 2001 his viral load peaked at 3,080 copies/mm^3 with a concurrent CD4 count of 399 (18%). A genotype was ordered and showed mutations at the following positions: 1) NRTI: 184, 2) NNRTI: 103, and 3) PI: 30, 63, 77, and 88 (see HIV101, page 5). These mutations were interpreted as conferring resistance to lamivudine, all the NNRTIs, and nelfinavir.

Due to the increase in his viral load and clear accumulation of resistance mutations, a change in ARV to lopinavir/ritonavir (Kaletra), stavudine (D4T or Zerit), didanosine (ddI, Videx), and abacavir (ABC, Ziagen) was made. Viral load two and six months later were 703 and <400 copies/mm^3 respectively, and his CD4 remained stable at 336 (18%). He was subsequently paroled on stable ARV.

This case illustrates several important clinical issues regarding HIV resistance. First, sequential changes in ARV agents rather than changing the entire regimen when failing therapy will lead to incomplete suppression. This patient's current ARV regimen was not started simultaneously and the addition of agents with a low genetic barrier to resistance (due to the low number of mutations required to develop resistance, see HIV 101), ie. lamivudine and efavirenz, while there is incomplete suppression will lead to the development of resistance to these agents. Second, despite clinical and immunologic stability, viral evolution and accumulation of mutations will occur in the setting of incomplete viral suppression as was shown by Coakley *et al*. Any replication, even at low levels as in this patient, will allow the virus to evolve and develop mutations that sabotage the success of the regimen. Finally, resistance testing in the setting of virologic failure provides important information that leads to a greater likelihood of successful rescue therapy. As has been exhibited in several prospective studies, use of resistance assays allows clinicians to choose an ARV regimen with more active agents and therefore have a higher chance of suppressing viral replication.

Conclusion

Because of the significant prevalence of drug-resistant virus in both treatment-experienced and treatment-naïve patients, resistance testing has become an important component of the care of HIV-infected patients. It is important to keep in mind that patients with persistent low-level viremia continue to evolve drug-resistant viruses. Genotype and phenotype testing have been shown to increase patient response to rescue therapies in treatment-experienced individuals. The benefits of genotyping and phenotyping increase when the test results are used in conjunction with the consultation of an HIV expert to develop a treatment plan. Therapeutic drug-monitoring may play a greater role in the future, especially with drugs that have a low trough (C_{min}) level.

Glossary of Terms[17]

Genotypic analysis involves: 1) amplication of the reverse transcriptase (RT) gene, protease (Pr) gene, or both by RT PCR; 2) DNA sequencing of amplicons generated for the dominant species (mutations are limited to those present in >20% of plasma virions); 3) reporting of mutations for each gene using a letter-number-letter standard, in which the first letter indicates the amino acid at the designated codon with wild type virus, the number is the codon, and the second letter indicates the amino acid substituted in the mutation (See HIV101, page 5 for a list of amino acid single letter abbreviations). Updated information on resistance testing can be obtained at http://hiv-web.lanl.gov. Genotypic assays include GeneSeq (Virologic), Truegene (Visible Genetics) and GenoSURE (LabCorp).

Phenotypic analysis involves insertion of the RT and protease genes from the patient's strain into a backbone laboratory clone by cloning or recombination. Replication is monitored at various drug concentrations and compared to a reference wild type virus. This assay is comparable to conventional in vitro tests of antimicrobial sensitivity, in which the microbe is grown in serial dilutions of antiviral agents. Results are reported as the IC_{50} for the test strain relative to that of a reference or wild type strain. The interpretation was previously based on a fixed ratio such as 4x to define resistance,

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HIV 101

Understanding HIV Drug-Resistance Mutations

Drug-resistance mutations are named according to a certain formula: the first letter represents the amino acid present in the wild type virus (see Table 1). This is followed by a number that indicates the position of the amino acid that has mutated. The last letter indicates the new amino acid present at that position. For example, M184V, a common reverse transcriptase mutation, means that the methionine at position 184 in the wild type virus has been replaced by a valine at position 184 in the mutated virus.

Sample Patient Genotype Results

HIV, Genotype
06/03/02 Mutations detected on reverse transcriptase gene: A98S, K103N, M184V
Mutations detected on protease gene: L63P

TABLE 1. Common Drug-Resistance Mutations[1]

ANTIRETROVIRAL DRUG	POSITIONS OF CODON MUTATIONS	COMMENT
Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Nucleotide RTIs		
Zidovudine (AZT)	41,67,70,210,215,219	Mutations are "TAMs*"- reduce susceptibility to AZT, d4T, ABC
Lamivudine (3TC)	184	184- high level 3TC resistance, increases activity of d4T, AZT, and tenofovir
Zalcitabine (ddC)	65,69,184	
Stavudine (d4T)	75	D4T selects for TAMs, which reduce sensitivity to d4T, AZT, ABC. The 75 mutation is rarely seen in vivo. Instead, mutations listed for AZT should probably be viewed as primary and secondary d4T mutations, as well.
Abacavir (ABC)	41,65,67,70,74,115, 184,210,215,219	Resistance depends on the number of TAMs. Virus with M184V and 3 or more TAMs is generally resistant to ABC. ABC selects for mutations that may confer cross-resistance to 3TC and ddI.
Multinucleoside resistance- A	62,75,77,116,151	Occurs with or without TAMs. Confers resistance to all NRTIs, but NOT tenofovir
Multinuceloside resistance-B	41,62,67,69 (insertion),70,210,215, 219	Requires TAMs. Confers resistance to all NRTIs AND tenofovir, but NOT DAPD.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Nevirapine (NVP)	100,103,106,108,181, 188,190,230	Y181C is favored mutation with NVP, unless combined with AZT, then K103N is favored
Efavirenz (EFV)	100,103,108,188L,190, 225,230	Sensitive in vitro to 181 mutants; resistance with 188L but not 188C or 188H

Table 1 continued on page 6

Single-Letter Codes Used for Amino Acids

A	Alanine	G	Glycine	M	Methionine	S	Serine
C	Cytosine	H	Histidine	N	Asparagine	T	Threonine
D	Aspartic acid	I	Isoleucine	P	Proline	V	Valine
E	Glutamic acid	K	Lysine	Q	Glutamine	W	Tryptophan
F	Phenylalanine	L	Leucine	R	Arginine	Y	Tyrosine

HIV 101 Continued on page 6

HIV 101

Understanding HIV Drug-Resistance Mutations *(cont. from page 5)*

TABLE 1. Common Drug-Resistance Mutations[1] *(cont. from page 5)*

PIs (Protease Inhibitors)			
DRUG	**PRIMARY^**	**SECONDARY^^**	**COMMENTS**
Indinavir (IDV)	46, 82	10,20,24,46, 63,64,82,84, 90	At least 3 mutations required for resistance (>4x decrease in susceptibility)
Nelfinavir (NFV)	30, 90	35,36,46,71, 88	D30N most common mutation: no PI cross-resistance. L90M occurs in some, leading to greater PI cross-resistance
Ritonavir (RTV)	82	8,10,20,33, 36,46,54,63, 71,84,90	Cross-resistance with IDV common
Saquinivir (SQV)	48, 90	10,24,30,46, 54,63,64,71, 73,77,81,84, 88	90 develops first, then 48; codon 48 mutation unique but L90M confers PI cross-resistance
Amprenavir (APV)	50, 84	10,32,46,47, 54	50 not associated with cross-resistance
Lopinavir (LPV)/RTV (Kaletra)	____	10,20,24,46,53,63,71,82,84, 90	Resistance correlated with number mutations. Minimal data available on PI mutations following LPV/RTV failure.

*Evolving data suggest cross-resistance between AZT and d4T and ABC ascribed to thymidine analog mutations (TAMs) introduced by exposure to AZT or d4T.

The distinction between primary and secondary mutations has been eliminated for NRTIs and NNRTIs by the International AIDS Society Expert Committee; the distinction has been retained for PIs.
^Primary mutations: usually develop first, and are associated with decreased drug binding;
^^Secondary mutations: also contribute to drug resistance and may affect drug binding in vitro less than primary mutations.

[1] Table from Bartlett JG, Gallant JE, et al. 2001-2002 Medical Management of HIV Infection. Johns Hopkins University, Division of Infectious Diseases; 2001 (p.20). On the web at http://hopkins-aids.edu.

UPDATE ON HIV RESISTANCE TESTING...

(continued from page 4)

meaning resistance is four-fold greater than that of the reference strain. The newer method individualizes by drug. For the Virco assay, the fold changes that define resistance are: zidovudine (AZT) - 4.0, lamivudine (3TC) - 4.5, didanosine (ddI) - 3.5, zalcitabine (ddC) - 3.5, stavudine (d4T) - 3.0, abacavir (ABC) - 3.0, nevirapine (NVP) - 8.0, efavirenz (EFV) - 6.0, indinavir (IDV) - 3.0, ritonavir (RTV) - 3.5, nelfinavir (NFV) - 4.0, saquinavir (SQV) - 2.5, amprenavir (APV) -2.5.

Virtual phenotype is a prediction of the phenotype of the test strain based on genotypic analysis. The mutational pattern of the test strain is compared with results of phenotypic assay results with strains showing similar mutations from a databank of >55,000 HIV isolates.
Phenotypic assays include Phenosense and Phenosense GT (genotype and phenotype in one) (Virologic), Antivirogram and Virtual Phenotype (Virco).

DISCLOSURES:
** Speaker's Bureau & Research Support: Bristol-Myers Squibb, Chiron, GlaxoSmithKline, Merck, Roche; Speaker's Bureau: Abbott, Agouron, Gilead*
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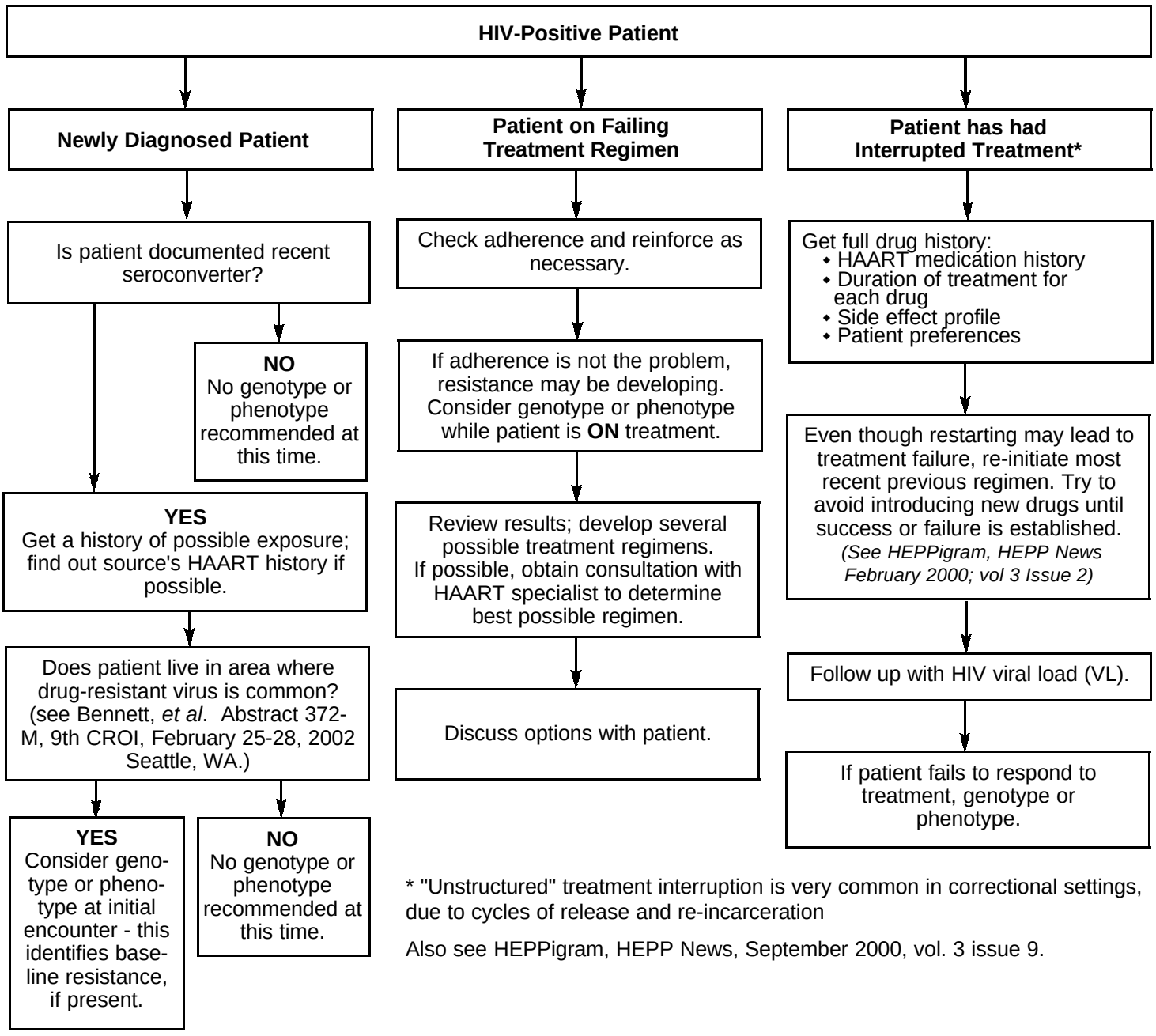
HEPPIGRAM: When to Genotype and/or Phenotype



* "Unstructured" treatment interruption is very common in correctional settings, due to cycles of release and re-incarceration

Also see HEPPigram, HEPP News, September 2000, vol. 3 issue 9.

Resources & Websites

Resistance Resources:

International AIDS Society-USA
http://www.iasusa.org/resistance_mutations/index.html
http://www.iasusa.org/resistance_mutations/revisedmutafigures-11.30.01.pdf

HIV/Hepatitis Resources:

NIH Hepatitis Consensus meeting
Updates at http://consensus.nih.gov

Canadian HIV/AIDS Policy and Law Review (Latest issue)
Reviews: HIV/AIDS in prison, mother-to-child transmission, and compulsory testing after occupational exposure http://www.aidslaw.ca/Maincontent/otherdocs/Newsletter/newsletter.htm#ci

Hopkins HIV Report May 2002: Women and HIV
http://hopkins-aids.edu/publications/report/ may02_1.html

The Women's Caucus
http://www.thebody.com/bp/janfeb02/womens_caucus.html

Big Shot: Passion, Politics, and the Struggle for an AIDS Vaccine
By Patricia Thomas, Review at
http://bmj.com/cgi/content/full/324/7339/743

amfAR HIV/AIDS Treatment Directory, 2002 Winter Edition
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Save the Dates

XIV International AIDS Conference
July 7-12, 2002
Barcelona, Spain
Fee: After May 1: $1050
(special rates and scholarships available)
Visit: www.aids2002.com
Email: aids2002.registration@congrex.se
HEPP News staff will be in attendance.

6th Annual United States Conference on AIDS (USCA)
September 19-22, 2002
Anaheim, California
Fee: before 8/23- $375/$450
Visit: http://www.nmac.org/usca2002/
Call: Paul Woods, 202.483.6622 ext. 343
Email: pwoods@nmac.org

Management of HIV/AIDS in the Correctional Setting: "Occupational Exposure to Viruses"
Satellite Videoconference
October 15, 2002; 12:30-3:30 EST
CME & Nursing Credits Available
Visit: http://www.amc.edu/Patient/HIV/hivconf.htm
Call: 518.262.4674
E-mail: ybarraj@mail.amc.edu

26th National Conference on Correctional Health Care
October 19-23, 2002
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Call: 773.880.1460
Email: ncchc@ncchc.org

North American AIDS Treatment Action Forum
December 8-11, 2002
New Orleans, Louisiana
Visit: http://www.nmac.org/nataf/2002/
Call: 202.483.6622

Inside News

HIV

High Prevalence of HIV/AIDS Risk Behaviors Among Incarcerated Women
Am J Public Health 2002;92:818-825
A new study of the Cook County Department of Corrections system reveals that urban women jailed for relatively minor infringements of the law have a high prevalence of HIV/AIDS risk behaviors. Inmates with the highest risk behaviors include Caucasian women, older women, those with previous arrests, and those with severe mental illness. Additionally, sexual and drug use risk scores were higher for women who had previously been arrested for prostitution, drug possession, or theft than women who were arrested for the first time. This study provides further support to the recommendation to provide HIV testing to all inmates.

Preliminary Results Show Tenofovir Comparable to Stavudine in Treatment Naïve
Press Release, 5/7/02
Preliminary data from Gilead Science's 903 study has shown that tenofovir (TDF, Viread) and stavudine (d4T, Zerit, Bristol Myers Squibb) have comparable efficacy in treatment-naïve HIV-positive patients. All 600 patients in this placebo-controlled, double-blinded study are on three-drug cocktails of either tenofovir/lamivudine (3TC)/efavirenz or stavudine/lamivudine/efavirenz. The data released from the 48-week time point shows that 87% of patients in each group achieved suppression of HIV viral load below 400 copies/mL; 82% of patients in the tenofovir arm of the study achieved viral load suppression below 50 copies/mL compared with 81% of the patients in the stavudine arm of the study. This preliminary data shows that tenofovir is effective in treatment-naïve patients.

New Protease Inhibitor in Development Pipeline Now Available to Some Patients
www.natap.org, 5/21/02
Bristol-Myers Squibb has announced an early access program (EAP) to provide atazanavir, a new, experimental protease inhibitor to patients who meet specified entry criteria. For more information, call 1.877.7BMSEAP (1.877.726.7327).

60% of Monthly Releasees from South Africa Prisons are HIV Positive
Agence France-Presse, 5/21/02
According to Judge Johannes Fagan, approximately 60% of the 10,000 inmates released from South African prisons each month are HIV-positive, based on a sample of 100 inmates. In his presentation to the parliamentary correctional services committee, Fagan also addressed the overcrowding in the prisons, citing that overcrowding is not conducive to the health of HIV-positive inmates and contributes to the spread of tuberculosis.

Results from Phase III Trial of T-20 Fusion Inhibitor
Wall Street Journal, 4/19/02
T-20, a fusion inhibitor that works by blocking HIV from fusing with and entering uninfected cells, has shown encouraging results in its first Phase III clinical trial. T-20 must be injected twice a day. Roche and Trimeris, who manufacture the drug, plan to apply for FDA approval later this year.

Viral Fitness Assay Now Available
Virologic Press Release, 6/3/02
Virologic has announced the availability of a new assay that will measure the viral fitness, or replication capacity, of HIV. This Replication Capacity (RC) assay measures the ability of a patient¹s virus to make copies of itself and may be useful in guiding HIC treatment strategy. The RC assay will be included in combination with the company's Phenosense HIV and Phenosense GT assays that measure HIV-drug resistance (see Main Article for a discussion of drug-resistance).

HEPATITIS

NIH Consensus Panel Addresses HCV in Corrections
http://www.nih.gov/news/pr/jun2002/od-12.htm
Hepatitis treatment guidelines were addressed at the NIH Hepatitis Consensus Meeting June 10-12, 2002. The NIH Hepatitis Consensus Panel states: "Because a large number of HCV-infected persons in the United States are incarcerated, strategies should be developed to better prevent, diagnose, and treat these individuals." The full text of the panel's statement will be available in draft form at http://consensus.nih.gov. A summary of the hepatitis C evidence report prepared by the Johns Hopkins University School of Medicine is available at http://www.ahrq.gov/clinic/epcix.htm. Copies are also available by calling 1-800-358-9295.

Common Household Items May Transmit HCV
Reuters Health, 5/22/02
A new study presented at Digestive Disease Week, common household items, including toothbrushes, may present an avenue of HCV transmission.The study looked at 30 HCV-infected patients, and examined their saliva and their toothbrushes for the presence of HCV infection. Approximately 40% of the toothbrushes tested positive for HCV, along with 30% of saliva samples collected before tooth-brushing and 38% of samples collected after tooth-brushing. These results did not seem to be tied to oral hygiene or disease severity. Although it is not known whether the virus found on the toothbrushes could be used to infect another individual, experts say this is "not impossible." Study authors urge HCV-positive individuals not to share these sorts of household items.

Chowchilla Prison Suit Settled Pre-Trial
Fresno Bee, 6/14/02
A lawsuit alleging medical neglect that led to the death of an inmate at California's Chowchilla women's facility has been settled out of court for $225,000. The inmate died in 1999 and was infected with hepatitis C. According to accounts of the case, the inmate had told medical personnel in the prison that she was infected with HCV, but was placed in an aggressive TB treatment program and given medications that are known to be toxic to people with liver disease. The inmate did not have access to a liver disease expert until a few days prior to her death.

Self-Assessment Test for Continuing Medical Education Credit

Brown Medical School designates this educational activity for 1 hour in category 1 credit toward the AMA Physician's Recognition Award. To be eligible for CME credit, answer the questions below by circling the letter next to the correct answer to each of the questions. A minimum of 70% of the questions must be answered correctly. This activity is eligible for CME credit through January 31, 2003. The estimated time for completion of this activity is one hour and there is no fee for participation.

1. In the Richman, et al. study, what percentage of patients on treatment with viral loads >500 copies/mL had resistance to at least one antiretroviral (ARV) agent?
   a) 14%
   b) 23%
   c) 56%
   d) 78%
   e) 92%

2. Resistance is not an all or none phenomenon.
   a) True
   b) False

3. A patient was on lamivudine as part of her HAART regimen and developed resistance to the drug. Her drug regimen was therefore changed completely. Two years later, the same patient undergoes resistance testing. The new data does not show a resistance to lamivudine. If the patient is restarted on lamivudine, would you expect viral replication to be suppressed? Why or Why not?
   a) Yes; the patient is no longer harboring lamivudine-resistant virus
   b) Yes; the patient has not "seen" the drug in two years
   c) No; the patient is still harboring lamivudine-resistant virus, but not in large enough amounts to be picked up by the resistance testing
   d) No; once a patient is taken off a drug for any reason, s/he will not be able to respond to it again
   e) It is impossible to hypothesize

4. Resistance test results shows a G190A mutations in the reverse transcriptase gene. What does G190A mean, and which drugs might it confer resistance to?
   a) A glutamine at position 190 in wild-type reverse transcriptase has mutated to an alanine; virus might be resistant to nevirapine
   b) A glutamic acid at position 190 in wild-type reverse transcriptase has mutated to an arginine; virus might be resistant to nevirapine and efavirenz
   c) An alanine at position 190 in wild-type reverse transcriptase has mutated to an glycine; virus might be resistant to nevirapine and efavirenz
   d) A glycine at position 190 in wild-type reverse transcriptase has mutated to an alanine; virus might be resistant to nevirapine and efavirenz
   e) A glycine at position 190 in wild-type protease has mutated to an aspartic acid; virus might be resistant to efavirenz

5. Which of the following statements is (are) true?
   a) Sequential changes in antiretroviral agents (rather than changing the entire regime at once) will lead to incomplete suppression.
   b) Viral evolution and mutation accumulation will occur in the setting of incomplete viral suppression (even with clinical and immunologic stability)
   c) In order to interpret genotypic test results, a certain level of knowledge and expertise of drug-resistance mutations is required
   d) a and c
   e) a, b, and c

6. If a patient seems to be failing his drug regimen, and it is determined that the patients needs to be genotyped or phenotyped, when should the test occur?
   a) While the patient is still adhering to his current HAART regimen
   b) After the patient has been off HAART therapy for two weeks
   c) After the patient has been off of HAART therapy for 1 month
   d) Two weeks after the patient begins a new HAART regimen
   e) The test should only be done if the patient has been on the same HAART regimen for longer than 1 year

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

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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