

# THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

## DHHS Issues Adult Guideline Revisions *By John G. Bartlett, M.D.*

Another revision of the DHHS "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents" was published, in draft form for public comment, on November 10, 2003. This represents a new style for the Guideline Panel, intended to address relevant issues in a more timely fashion and to permit "audience participation". This reflects the velocity of changes that take place in this field, which was forced, in part, by the introduction of 4 new antiretroviral agents in 2003. The decision to invite public comment is based, to a large extent, on the substantial precedent with other guidelines. The following is a summary of the more recent changes accompanied by a comment:

### Regimens for Treatment-Naïve Patients

A distinction is now made between "preferred" and "alternative" regimens. The preferred are: (1) efavirenz/lamivudine/(zidovudine or tenofovir or stavudine), or (2) lopinavir/ritonavir/lamivudine/(zidovudine or stavudine). The alternative regimens consist of eleven other combinations, including abacavir/lamivudine/(zidovudine or stavudine). The preferred regimens are selected based on clinical trial data that suggests "...optimal efficacy and durability with acceptable tolerability and ease of use."

**Comment:** It needs to be emphasized that the alternative regimens may be preferred in some patients. With regard to the classification, to my knowledge, this and the WHO guidelines are the only guidelines that make specific recommendations rather than the generic "PI or boosted PI combined with two nucleosides." The rationale for this specificity is, at least in part, the data from multiple clinical trials that make generic recommendations less useful, given variation among regimens in efficacy, toxicity, convenience, or potential for drug interactions. Thus, the emphasis is on the specific regimens that have been used in clinical trials with demonstrated efficacy and durability

### New Drugs

The new drugs approved in 2003 are enfuvirtide, atazanavir, emtricitabine and

fosamprenavir. Emtricitabine and atazanavir are included as components of alternative regimens, and enfuvirtide is discussed in terms of salvage therapy.

**Comment:** It should be noted that atazanavir is recommended without ritonavir boosting, in large part reflecting the fact that studies in treatment-naïve patients were completed with unboosted atazanavir. Fosamprenavir was approved very recently and is, therefore, not mentioned in this version of the guidelines.

### Triple NRTI Regimens to Avoid

The combinations of tenofovir + lamivudine + either abacavir or didanosine are now listed as combinations to avoid.

**Comment:** This admonition is based on the therapeutic trial showing virologic failure in 49% of patients given TDF/ABC/3TC compared to 5% in those given EFV/ABC/3TC [Gallant JE, et al. ICAAC, Sept, 2003, Abstract H-1722a].

Similarly, there was a 91% failure rate in another trial with TDF/ddI/3TC ["Dear Health Care Professional Letter" from Gilead Sciences, Inc., 10/14/03].

### Preferred Dual NRTI combinations with a PI or NNRTI

The preferred combination is 3TC/(AZT or d4T) and the combination of tenofovir/3TC is also included when combined with efavirenz. Alternatives with efavirenz are lamivudine + tenofovir. Emtricitabine (FTC) is listed as an alternative to lamivudine and the combination of ddI and 3TC or FTC is also classified as an alternative dual-NRTI regimen in combination with efavirenz or nevirapine.

**Comment:** Lamivudine + either AZT or d4T are recommended in virtually all of the preferred and alternative regimens based on the fact that they have shown "durable virologic potency for over five years" when combined with



"Winter, Yorkville, Toronto, Ontario" photograph by Joel Meneses

other agents. Nevertheless, the provider is warned that commonly noted side effects include bone marrow suppression with AZT, and prolonged use of d4T has been associated with high rates of lipoatrophy, peripheral neuropathy and/or lactic acidosis. The combination of tenofovir + 3TC is recommended with efavirenz based on data from the Gilead 903 trial. The combination of d4T and ddI is not generally recommended due to high rates of peripheral neuropathy, pancreatitis and hyperlactatemia. Other dual nucleoside combinations in the "not recommended" category are ddC + either d4T or ddI (additive for peripheral neuropathy) and AZT/d4T (pharmacologic antagonism). Hydroxyurea is simply not recommended. FTC is listed as an alternative to 3TC rather than a preferred agent because of its recent approval with less long-term data. The combination of ABC/3TC is not currently mentioned in the guidelines, although there are increasing data supporting its use.

*continued on page 5*

## Inside This Issue

From the IDSA Meeting – Important New Findings in HIV Treatment and Pathogenesis, 2003 . . . . . 2

New Guidelines for Management of Dyslipidemia from IDSA and the ACTG . . . 4  
Adherence and HIV Drug Resistance . . . . . 6



## From the Infectious Diseases Society of America (IDSA) Meeting - Important New Findings in HIV Treatment and Pathogenesis, 2003

By John G. Bartlett, M.D.

Paul A. Volberding, M.D., University of California at San Francisco and William G. Powderly, M.D., Washington University conducted a review of literature and conference presentations on the important new findings in HIV. The review was presented as part of "Symposium: What's Hot: Review of Recent HIV and ID Literature" at the 41<sup>st</sup> IDSA meeting held in San Diego this fall and is summarized in this article.

### Treatment Interruption in Patients Failing Therapy

A recent study demonstrated that for patients who have multidrug-resistant HIV and who are about to start a salvage regimen, treatment interruption prior to salvage therapy is clearly inferior to an immediate switch to the new regimen [*N Engl J Med* 2003;349:837-46].

However, there may be potential settings in which STI makes sense. Katlama and co-workers recently presented some data showing that there may be some benefit in terms of viral load and CD4 count with treatment interruption of shorter duration and more aggressive therapy post-STI.

### New Drugs

The most promising new drug this year is enfuvirtide, or ENF. The TORO-1 [*N Engl J Med* 348:2186-95, 2003] and TORO-2 [*N Engl J Med* 348:2175-85, 2003] studies published recently showed significant benefits of ENF at 24 weeks when added to an optimized background antiretroviral regimen, and these benefits appear to hold at 48 weeks. [Abstract LB02, IAS 2003, Paris] The percentage of patients receiving ENF who achieved a 1 log<sub>10</sub> reduction in viral load at 24 and 48 weeks was 47% and 37% respectively. Good prognostic factors included a baseline CD4 count >100 cells/mm<sup>3</sup>, viral load <100,000 c/mL, previous exposure to ≤10 antiretroviral drugs, and ≥2 active drugs in the "optimized background" regimen. The response rate in the ENF arm was only 15% if none of these factors was present, compared to 80% if all 4 factors were present.

### Continuation of RTIs in Failing PI-Based Regimens

Steve Deeks presented some interesting preliminary data from a small, uncontrolled, non-randomized study at the CROI meeting this year [Abstract 640, 11<sup>th</sup> CROI 2003, Boston]. As we know from clinical experience, patients sometimes seem to do relatively well on antiretroviral therapy

despite ongoing viremia and extensive mutations that would predict virologic failure. This study attempted to identify the utility of selected individual drug therapy in patients who were failing protease inhibitor (PI)-based regimens by either discontinuing the PI or the nucleoside analog reverse transcriptase inhibitor (NRTI). Patients in whom the PI was discontinued did relatively well, with a trivial decrease in CD4 and increase in viral load. On the other hand, patients in whom the NRTIs were discontinued did poorly, with a rapid decline in CD4 count and rise in viral load. Although these data are very preliminary, and if confirmed in larger, controlled studies, they would suggest that at least in some patients failing PI-based regimens, the NRTI are still partially active and should be continued.

### Boosted Atazanavir

At the IAS meeting, preliminary data on atazanavir (ATV) with and without ritonavir (RTV) boosting was presented. At 24 weeks boosted atazanavir appeared to be as potent, less lipotoxic, and more convenient in PI-experienced patients compared to lopinavir/ritonavir.

### Reduced Potency of Tenofovir/Abacavir Combination

At the 2003 ICAAC meeting, data demonstrating the reduced potency of the combination regimen consisting of tenofovir, 3TC, and abacavir was presented [Gallant JE, et al. Abstract H-1722a 43<sup>rd</sup> ICAAC 2003, Chicago]. This regimen has been shown to lead to early virologic failure compared to efavirenz, 3TC, and abacavir. However, the reason for the inferior potency of the triple nucleoside regimen is not known, since there are no data to suggest a drug-drug interaction (there is no apparent effect of tenofovir on serum abacavir levels), or intracellular interaction. Patients who received the triple nucleoside regimen were tested 12 weeks after initiation of therapy for drug resistance. Sixty-four percent (64%) of those who failed and had genotype data available had both M184V and K65R; 34% had only M184V. This suggests that this regimen may have a low genetic resistance barrier.

### Maternal-Fetal Transmission of HIV

An important study appearing in the *Lancet*

this year was the 18 month follow-up demonstrating the superiority of single dose intrapartum nevirapine to a short course of intrapartum/neonatal zidovudine for prevention of maternal-fetal transmission of HIV [*Lancet* 2003; 362:859-68], in which nevirapine was shown to be superior to zidovudine in decreasing fetal HIV transmission. In addition to assignment to the zidovudine arm, predictors of increased neonatal transmission in this study included low maternal CD4 count and high maternal HIV RNA. Unfortunately, NNRTI-associated resistance mutations were eventually detected in up to 75% of patients receiving nevirapine.

### Markers Predicting Response to HAART

Another study published in the *Lancet* looked at the effect of starting HAART on prognostic markers of HIV infection [*Lancet* 2003; 362:679-86]. Previous data emphasized the importance of baseline CD4 and viral load on predicting long-term clinical outcomes, but this study concluded that once HAART was initiated, baseline CD4 and viral load were not as predictive of clinical outcome as was virologic response to HAART at 6 months.

### HAART and Heart Disease

A study looked at the risk of developing cardiac disease on HAART [*N Engl J Med* 2003;348:702-10]. This was a very large study of 36,799 patients followed at VA hospitals between 1991 and 1999, which found that the risk of cardiovascular events, including strokes, decreased over that time period. There was no evidence of an increase in cardiac-related admissions with use of antiretroviral therapy (whether this was PI-based or not). These results are in contradistinction to an earlier and smaller study that demonstrated a relatively low, but increased risk of myocardial infarction (MI) associated with use of PIs (as well as with hypertension, tobacco use, male sex, age >50 years, dyslipidemia, and diabetes mellitus). The DAD study, a multivariate analysis of 13 studies that was presented at this year's CROI, revealed an increasing risk of MI with longer duration of combination antiretroviral therapy [Friis-Møller, et al. Abstract 130, 11<sup>th</sup> CROI 2003, Boston]. Other independent risk factors included age, male sex, tobacco use, and cholesterol level. Unpublished data show that cholesterol levels



## From the Infectious Diseases Society of America (IDSA) Meeting - Important New Findings in HIV Treatment and Pathogenesis, 2003

actually fall after HIV seroconversion prior to initiation of HAART and then rise after HAART therapy. From all these data, however, it appears that the overall risk of cardiovascular disease remains relatively low and certainly does not justify not treating HIV if treatment is indicated.

Clinical situations in which resistance testing is recommended include:

- Acute infection
- HIV infection <1 year
- Suboptimal HIV RNA response after 8-12 weeks of HAART
- Pregnancy, if mother has detectable HIV RNA
- Before initiation of ART in established HIV infection ( $\leq 2$  years, possibly longer) after first or multiple regimen failures.

The CATCH study demonstrated that the

prevalence of drug resistance in patients infected with HIV <1 year is ~11%, vs ~8% in those with chronic HIV (>1 year).

### Viral Infectivity Factor

Viral infectivity factor (VIF) is an HIV-1 accessory protein, that neutralizes a potent antiviral pathway in human T lymphocytes and is required for the production of infectious virions by CD4 lymphocytes. The cellular target of VIF was recently described in a series of papers [*Nature* 2003;424:99-103; *Nature* 2003;424:94-8]. VIF appears to counter the effect of APOBEC, a host cell cytidine deaminase nucleic acid-editing enzyme that inhibits retroviral replication by inducing hypermutation in the viral genome [*Cell* 2003;114:21-31]. ▲

## Coming Soon

### HHR Subscription List Confirmation

In an effort to reduce postage costs, the HHR staff are planning to correct and update our mailing list. This activity is very important and your participation is critical.

Within the next few weeks long term subscribers (those with subscriptions numbers lower than 90400) will be sent a communication with a postage paid return postcard.

Your subscription number is located above your name and mailing address on the address label.

This address update card will need to be returned in order to maintain you name on the subscription list. Please look for and return the HHR Subscription List Confirmation card. ▲

# THE HOPKINS HIV REPORT

## EDITORIAL BOARD

### John G. Bartlett, M.D.

*Professor of Medicine; Director, Division of Infectious Diseases; Director, Johns Hopkins University AIDS Service*

### Joel N. Blankson, M.D.

*Assistant Professor, Medicine*

### Emily J. Erbdelding, M.D., M.P.H.

*Assistant Professor of Medicine, Epidemiology, and Pediatrics*

### Joel E. Gallant, M.D., M.P.H.

*Associate Director, Johns Hopkins University AIDS Service*

### Kelly A. Gebo, M.D., M.P.H.

*Assistant Professor of Medicine and Epidemiology*

### Jeanne Keruly, M.S., C.R.N.P.

*Instructor, Medicine*

### Gregory M. Lucas, M.D.

*Assistant Professor of Medicine*

## CONTRIBUTING EDITORS

### Jean R. Anderson, M.D.

*Associate Professor of Obstetrics, Gynecology, and Medicine*

### Richard E. Chaisson, M.D.

*Professor of Medicine, Epidemiology, and International Health*

### Joseph Cofrancesco, Jr., M.D., M.P.H.

*Assistant Professor of Medicine*

### James P. Dunn, M.D.

*Associate Professor of Ophthalmology*

### Charles W. Flexner, M.D.

*Associate Professor of Medicine, Pharmacology and Molecular Science, and International Health; Associate Director of Graduate Training Program in Clinical Investigation*

### Rajesh T. Gandhi, M.D.

*Instructor in Medicine, Partners AIDS Research Center Massachusetts General Hospital Boston, MA*

### Douglas A. Jabs, M.D.

*Professor of Ophthalmology and Medicine*

### Brooks Jackson, M.D.

*Professor of Pathology; Deputy Director for Clinical Affairs, Department of Pathology*

### Ciro R. Martins, M.D.

*Assistant Professor of Dermatology*

### Justin C. McArthur, M.B., B.S., M.P.H.

*Professor of Neurology and Epidemiology*

### Richard D. Moore, M.D.

*Professor of Medicine and Epidemiology*

### Thomas C. Quinn, M.D.

*Professor of Medicine, International Health, Molecular Microbiology and Immunology*

### Robert Siliciano, M.D., Ph.D.

*Professor of Medicine, Molecular Biology and Genetics*

### Timothy R. Sterling, M.D.

*Associate Professor of Medicine, Vanderbilt University Medical Center*

### Glenn J. Treisman, M.D., Ph.D.

*Associate Professor of Psychiatry and Medicine*

## NEWSLETTER STAFF

### Richard Dunning, M.H.S.

*Managing Editor*

### Lisa Darrah, B.A.

*Design and Production*

### Sharon M. McAvinue

*Business Development*

Visit The Johns Hopkins AIDS Service Website:

<http://www.hopkins-aids.edu>

## SUPPORT

The Hopkins HIV Report is published six times per year by The Johns Hopkins University AIDS Service, Division of Infectious Diseases. Publication of this newsletter is underwritten by a generous grant from GlaxoSmithKline; we gratefully acknowledge their support.

©2004 The Johns Hopkins University AIDS Service, Division of Infectious Diseases. Permission to use and reproduce portions of this newsletter is hereby granted, provided that author and publication are fully credited and both the copyright and permission notice appear. All other rights reserved.

Canada Post Publications Sales Agreement  
# 40683044



# New Guidelines for Management of Dyslipidemia from IDSA and the ACTG

By John G. Bartlett, M.D.

The IDSA and the ACTG recently updated their guidelines for management of dyslipidemia, which were published as "Guidelines for the Evaluation and Management of Dyslipidemia in Human Immunodeficiency Virus (HIV)-Infected Adults Receiving Antiretroviral Therapy: Recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group" [Dube MP, et al. *Clin Infect Dis* 2003;37:613] Hyperlipidemia is now recognized as a relatively common complication of HAART. The ACTG Cardiovascular Disease Focus Group addressed this issue with preliminary guidelines for evaluation and management of dyslipidemia in 2000 [Dube MP, et al. *Clin Infect Dis* 2000;31:1216]. Since that

time there has been substantial progress in the field as well as new guidelines from the National Cholesterol Education Program (NCEP) [Expert Panel, *JAMA*, 2001;285:2486]. The following represents a summary of the updated guidelines from the Cardiovascular Disease Focus Group.

The major risk factors (exclusive of low density lipoprotein-cholesterol [LDL-C]) that modify LDL-C goals are:

- **Cigarette smoking**
- **Hypertension:** BP >140 or antihypertensive treatment)
- **Low high density lipoprotein cholesterol (HDL-C):** <40 mg/dL
- **Family history:** Male first degree relative <55 years or female first degree <65 years
- **Age:** Men >45 years, women >55 years

### Goal of Therapy

The major target is LDL-C based on the more recent NCEP guidelines. LDL-C goals and recommendation for when to initiate intervention are summarized below. These recommendations are based on associated conditions that confer independent risks derived from the Framingham Heart Study.

### Screening

Patients should be tested for total cholesterol, HDL-C and triglyceride levels after a ≥8 (preferably 12) hour fast at baseline, at 3-6

months after initiation of therapy, and then annually. The LDL-C and non-HDL-C levels are calculated using these results. Non-HDL-C is calculated as total cholesterol minus HDL-C, and is an alternative measure of "bad" cholesterol. The non-HDL-C goals are 30 mg/dL higher than the LDC-C levels in the table above. Levels should be measured more frequently if they are elevated or if drug therapy is initiated.

### Therapy

- **Non-drug therapy:** lifestyle changes including dietary change, smoking cessation, and exercise. Treatment of high blood pressure and diabetes are also the first line of therapy.
- If life style changes are ineffective in modifying dyslipidemia, initiation of drug therapy is recommended (see "Drug Therapy for Modifying Dyslipidemia" table below).
- **Sequencing:** Initiate non-drug therapy first unless there are extreme elevations (e.g. LDL-C >220 mg/dL and/or triglyceride >2000 mg/dL or >1000 mg/dL plus a history of pancreatitis).
- Switching antiretroviral therapy. The following changes may be considered
  - PI- NVP or ABC:** Improves total cholesterol and triglyceride
  - PI- EFV:** is less effective than switching to NVP or ABC
  - d4T- ABC:** the effect upon lipids is inconclusive

### EDITORIAL POLICY & DISCLAIMER

Organizations providing financial support do not participate in the editorial process or otherwise influence editorial decisions. The information presented in *The Hopkins HIV Report* represents the standards of care of the Johns Hopkins University AIDS Service. Every effort is made to ensure the timeliness and accuracy of information presented in this newsletter, but standards of care change rapidly; therefore, the authors, editors, and publisher will not in any way be held liable for the timeliness of information or for errors, omissions, or inaccuracies in this publication. Readers should review carefully the product information contained in manufacturers' package inserts for any drug mentioned in this publication; mention of products does not constitute endorsement.

### THE HOPKINS HIV REPORT (HHR) IS FREE IN PRINT AND ONLINE

- **View** the current and archived newsletters online at <http://hopkins-aids.edu/publications.html>
  - **Subscribe online** to receive the print version of *The Hopkins HIV Report*.
  - **Change of address?** Complete the online form using the website address above *or* let us know by sending a postcard with your old (very important) and new address, plus the subscription number (located above your name and address on the HHR mailing label) to:
    - The Hopkins HIV Report*, Change of Address
    - P.O. Box 651266
    - Potomac Falls, VA 20165-1266
  - **All other correspondence:** Email [hivreport@PMR-printing.com](mailto:hivreport@PMR-printing.com) *or* write:
    - The Hopkins HIV Report*
    - JHU ID @ Lighthouse Point
    - 2700 Lighthouse Point East, STE 220
    - Baltimore, MD 21224
- Please note:** The HHR is published every *other* month- January, March, May, July, September, and November.

### LDL-C Goals

Risk	LDL Goal (mg/dL)	Lifestyle Changes	Drug Therapy
CHD or equivalent	<100	>100	>130
>2 risks* plus:			
10 years risk 10% to 20%	<130	>130	>130
10 years risk <10%	<130	>130	>160
0-1 risk factors	<160	>130	>190

\* Based on multiple variables (see <http://hin.nhlbi.nih.gov/atp/iii/calculator.asp>).

### Drug Therapy for Modifying Dyslipidemia

Abnormality	Preferred	Alternative	Agent & Starting Dose	
Increased LDL-C or non-HDL-C	Statin	Fibrate	Pravastatin	20-40 mg/d
			Atorvastatin	10 mg/d
			Fluvastatin	20-40 mg/d
Triglyceride >500 mg/dL	Fibrate	Niacin Fish oils	Gemfibrozil	600 mg bid
			Fenofibrate	54-160 mg bid



## New Guidelines for Management of Dyslipidemia from IDSA and the ACTG

continued from page 4

### Drug Interactions

Drug	PI	NVP	EFV
Simvastatin	↑↑ statin levels—contraindicated	Probably none (statin levels may ↓)*	Unknown
Lovastatin	↑↑ statin levels—contraindicated	Probably none (statin levels may ↓)*	Unknown
Atorvastatin	↑ statin levels— use caution	Probably none (statin levels may ↓)*	Probably none
Pravastatin	Probably none except possible— statin levels with RTV/SQV (and possibly with NFV)	Probably none	Probably none
Fluvastatin	Probably none except possible_ statin levels with RTV & NFV	Probably none	Probably none
Cerivastatin†	Probably none	Probably none	Probably none
Rosuvastatin†	Probably none	Probably none	Probably none

\* Author opinion

†Added by author

Additional references for drug interactions:

- Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047 [Fichtenbaum CJ, et al. *AIDS* 2002 Mar 8;16(4):569-77]
- Pravastatin 40 mg qd Does Not Alter Protease Inhibitor (PI) Exposure or Virological Efficacy Over 24 Weeks Therapy [Moyle GJ, et al. Abstract 446W 9<sup>th</sup> CROI 2002]

### Comment on the Guidelines

Many of the recommendations are based on the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults [*JAMA* 2001;285:2486].

This particularly applies to risk assessment, the goals for LDL-cholesterol levels and the approach to drug therapy. Factors that are somewhat unique to persons with HIV infection are the influence of HAART on lipids, the recommendations for screening in patients receiving this therapy, several issues regarding therapeutic intervention, and drug interactions between statins and protease inhibitors. With regard to the recommended drugs, the statins that are favored for concurrent use with PIs

include pravastatin, atorvastatin and fluvastatin. Unfortunately, their recommendations appear to have preceded the FDA approval of rosuvastatin, which is of particular interest because of its potency and lack of effect on the cytochrome P450 metabolic pathway. The recommendations also preceded the approval of atazanavir, which does not increase lipid levels. ▲

### Nevirapine Warning

By John G. Bartlett, M.D.

Extensive analysis of the Boeringer-Ingelheim database by the company has indicated a high risk of hepatotoxicity in women with CD4 counts >250 cells/mm<sup>3</sup> who have been treated with nevirapine. It is the manufacturer's recommendation that nevirapine either not be used in women with CD4 counts >250 cells/mm<sup>3</sup> or that treatment be undertaken with careful monitoring. ▲

## DHHS Adult Guideline Revisions

continued from page 1

### Drug Interactions

Following are the most significant changes:

- **Atorvastatin:** The recommendation for use in combination with all PIs, including atazanavir, is to use the lowest starting dose (10 mg qd) and monitor carefully.
- **Vardenafil:** Data are available showing increased levels with indinavir (16 fold increase in vardenafil AUC) and ritonavir (49 fold increase) but are not available for other PIs. The recommendation with all PIs is to start with 2.5 mg and do not exceed that dose for 24 hours, or for 72 hours when given with ritonavir.
- **Atazanavir:** The major concerns are use of this drug with tenofovir or efavirenz because of reduction in atazanavir levels. The recommendation is to avoid concomitant use unless ATV is combined with ritonavir (300 mg ATV/100 mg RTV qd); other drug interactions with ATV include buffered ddI (take two hours before or one hour after buffered ddI or use ddI-EC); clarithromycin due to 94% increase in clarithromycin AUC with possible QTc prolongation (reduce clarithromycin dose by 50% or use alternative agent); other drugs that may increase QTc (use with caution or avoid); rifabutin dose is 150 mg qod or 3 times/week; drugs to avoid with concomitant use include proton pump inhibitors, bepridil, rifampin, simvastatin, lovastatin, and indinavir.
- **Voriconazole:** There are no data for interactions with any PI or NNRTI, but the concern is a "potential for bi-directional inhibition, monitor for toxicities and/or voriconazole effectiveness".

### PI Combinations

New additions are: (1) indinavir in the 400 mg bid regimen with ritonavir (100-400 mg bid) is accompanied by a caution for renal toxicity; (2) amprenavir/*Kaletra* in combination should be APV 600-750 mg bid + LPV/r standard or 533/133 mg (4 tabs) bid; (3) Atazanavir with ritonavir should be 300/100 mg qd.

It should be noted that the above summary hits the highlights. There are many other changes that are not included because they are considered less important. It is emphasized that this is a "draft document" with invited comments that may prompt changes prior to the official version. This mechanism for public comment is now expected with each revision. ▲



Since its availability in 1996, the use of highly active antiretroviral therapy (HAART) to treat HIV-infection has led to declines in U.S. AIDS mortality rates and increases in the number of persons living with HIV. For HIV-infected individuals, drug resistance is a major concern, but it is unknown whether resistance is an inevitable consequence of long-term HAART use. HAART can be inherently complex if it involves taking many pills at specific times or with food restrictions, or if it is associated with side effects.

Non-adherence is recognized as one of the main causes of treatment failure. The association between non-adherence to antiretroviral therapy (ART) and HIV drug resistance was first shown in patients receiving protease inhibitor (PI) monotherapy [Vanhove, et al. *JAMA* 1996; 276:1955]. Studies have also demonstrated that incomplete adherence to HAART is associated with drug resistance. In 1998, Montaner and colleagues showed in a clinical trial that incomplete adherence to HAART was also associated with HIV drug resistance [*JAMA* 1998; 279:930]. In 2000, two separate studies demonstrated that patients who experienced virologic failure did not necessarily have resistance to all drugs in their regimen [Descamps, et al. *JAMA* 2000; 283:205; Havlir, et al. *JAMA* 2000; 283:229]. This finding provided a rationale for resistance testing in patients failing therapy, which was subsequently recommended by an International AIDS Society-USA Panel [Hirsch, et al. *JAMA* 2000 283:2417] and by a panel from the Department of Health and Human Services [January 28, 2000 version; <http://aidsinfo.nih.gov>].

### Bell-shaped Relationship

Paterson and colleagues showed that at least 95% adherence was needed to maximally suppress viral replication in patients receiving HAART [Paterson, et al. *Ann Intern Med* 2000;133:21]. However, while the relationship between adherence and risk of virologic failure appears to be more or less linear, the relationship between adherence and the risk of drug resistance is not. Friedland and Williams proposed that there are two clinical scenarios resulting in minimal development of resistance: 1) extremely high levels of adherence leading to maximal suppression of viral replication; and 2) very poor

adherence, resulting in no inhibition of viral replication [*AIDS* 1999; 13 Suppl 1: S61]. In the first scenario, resistance is unlikely to develop because there is little or no viral replication. In the second scenario, viral replication takes place in the absence of antiretroviral drug exposure sufficient to result in selective pressure favoring resistant virus. Between these two extremes lies a middle zone in which viral replication occurs in the face of drug pressure, leading to a risk of drug resistance (see Figure 1A). Several studies have attempted to confirm this hypothetical "bell-shaped" relationship between adherence and resistance and to determine the level of adherence to HAART associated with the maximum risk of development of HIV drug resistance.

### Data Review

In 2001, Gallego and colleagues examined patterns of drug resistance mutations among HIV-infected patients who were failing their first HAART regimen that included indinavir at 3 different hospitals in Spain [*AIDS* 2001; 15:1701]. Genotypic resistance was examined at the time of first virologic failure (>50 c/mL) among 51 patients reporting at least 90% adherence to their regimen and 14 patients reporting <90% adherence. They found that among patients taking >90% of their medication, 51% had resistance to nucleosides and 27% had resistance to protease inhibitors. None of the subjects with <90% adherence were found to have mutations associated with HIV drug resistance. Since patients had to have maintained viral suppression for 6 months to be eligible for the study, the researchers could be assured that resistance detected at the time of failure was incident rather than prevalent. However, low sample size prevented the investigators from examining the relationship between adherence and resistance more thoroughly. The cross-sectional nature of the study was also a limitation, as the effect of long-term non-adherence on resistance development could not be assessed.

In 2002, Walsh and colleagues also showed that lower adherence was associated with lower detection of HIV drug resistance [*J Acquir Immune Defic Syndr* 2002; 30:278]. The investigators examined adherence assessed by various methods among 68 HIV-infected adults receiving their first PI-containing HAART regimen for at least 6 months at a London HIV

clinic. Among the 32 patients who experienced virologic failure and the 36 who did not, mean adherence was 84% and 95% of pills taken in the previous 3 days, respectively. Subjects who had experienced virologic failure were tested for resistance, which revealed that subjects whose virus had a sensitive phenotype had significantly lower average adherence (69%) than those with either intermediate (93%) or resistant phenotype (99%). Since they demonstrated a significant positive linear relationship between adherence and HIV resistance, the researchers suggested that if there is a "bell-shaped" relationship between adherence and resistance, and that the association is probably skewed to the left, such that the greatest risk of drug resistance results from only marginally sub-optimal adherence. The investigators acknowledged that since their study was cross-sectional, it was not possible to determine if adherence measured during the study was reflective of past adherence and if resistance detected during the study was due to past non-adherence.

In a recently published prospective study of HIV-infected urban poor individuals in the Research on Access to Care in the Homeless (REACH) cohort in San Francisco, Bangsberg and colleagues examined the relationship between adherence, viral suppression, and HIV drug resistance among 148 participants who received at least one month of HAART [*AIDS* 2003;17:1925]. Adherence was assessed by unannounced pill counts at the participants' place of residence and measured at every 3 to 6 weeks for one year. Higher adherence was correlated with longer time on treatment ( $p < 0.0001$ ) and viral suppression defined as viral load <50 c/mL. Over the 12-month period, mean adherence was 82% for those with a mean viral load <50 c/mL and 58% for those with a mean viral load >50 c/mL. Based on model estimations from 22 (15%) participants who developed new drug resistance mutations and 37 (25%) participants who maintained viral suppression during the period of observation, the investigators suggested that 23% of drug resistance mutations occur in individuals with 92-100% adherence, 30% with 79-91% adherence, 15% with 58-78% adherence, 20% with 42-57% adherence, and 12% with 0-41% adherence (see Figure 1B). The authors concluded that high levels of resistance correlate with increasing rates of viral suppression,



## Adherence and HIV Drug Resistance

but also that high levels of adherence correlate with drug resistance.

Another recently published prospective study conducted employed a rigorous study design to determine the level of non-adherence to HAART that was associated with the greatest risk of HIV drug resistance [Sethi, et al. *Clin Infect Dis* 2003; 37:1112]. The researchers followed 195 patients who had maintained viral suppression while receiving HAART at the Johns Hopkins Moore Clinic for one year. Adherence in the past 3-days was assessed by questionnaire and collected each time patients had an appointment with their HIV clinician. The investigators found that cumulative adherence of 70 to 89% prior to the development of resistance was associated with more than a 3-fold greater risk of resistance compared to those with <70% and >90% adherence. Overall incidence of resistance was 14.5 per 100 person-years and was 9.6, 13.6, 36.6, 44.9, and 12.3 per 100 person-years for patients whose cumulative adherence was 100%, 90-99%, 80-89%, 70-79%, and <70%, respectively (see Figure 1C). It was also found that missing a scheduled clinic visit in the past month was independently associated with more than a 2-fold increase in the risk of developing drug resistance. The researchers concluded that high-level adherence was needed to avoid the development of resistance. The limitation of this study was the use of self-reported adherence, which is generally higher than objective adherence measures.

The relationship between adherence and resistance also depends on the regimen potency. In a sub-analysis of the Abbott 863 trial, a phase 3 study of antiretroviral-naïve patients receiving d4T, 3TC, and either lopinavir/ritonavir (N=326) or nelfinavir (N=327), King and colleagues examined adherence as measured by pill count and the development of resistance [2<sup>nd</sup> IAS conference on Pathogenesis and Treatment 2003, Paris, France, Abstract 798]. Overall, a bell-shaped relationship between adherence and resistance was observed, with highest probability of resistance observed among those with 80-85% adherence. When examined by regimen type, individuals with perfect adherence to the nelfinavir-based regimen were over 3 times more likely to develop resistance than those with perfect adherence to the more potent lopinavir/ritonavir-based regimen.

### Clinical Implications

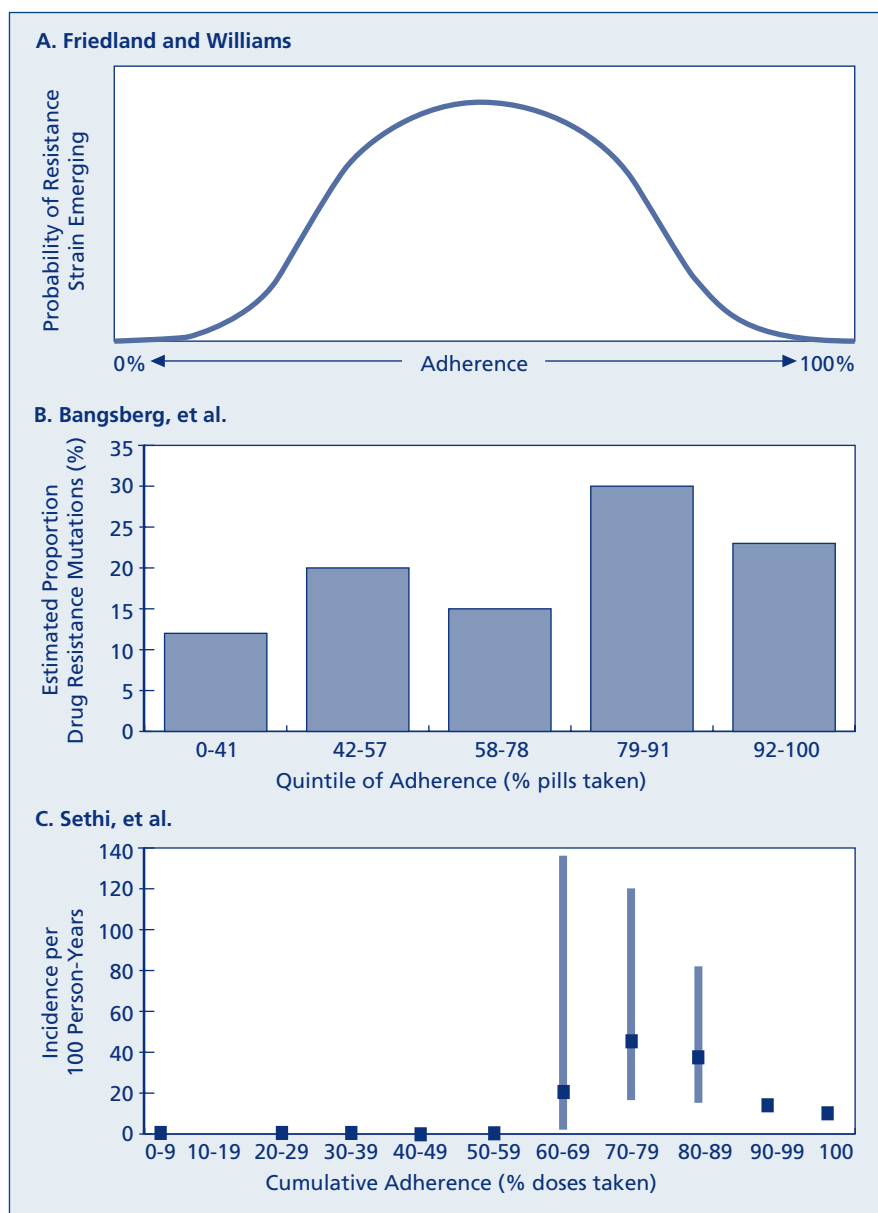
In summary, there is growing evidence to support the hypothesis that the relationship between adherence and drug resistance is in fact bell-shaped. This becomes a dilemma for HIV clinicians and patients, who must decide whether their adherence is high enough to prevent resistance. For patients who are poorly adherent, adherence-promoting interventions may actually increase the risk of resistance if they promote

adherence that falls short of the high levels necessary to maximally suppress viral replication.

Although very poor adherence appears to be associated with a decreased risk of resistance, there is evidence that even minimal adherence can lead to resistance since drug-resistant HIV has been detected after just a single-dose of nevirapine to prevent mother-to-child

*continued on page 8*

Figure 1: Association Between Adherence and HIV Drug Resistance: A. Hypothetical Relationship Proposed by Friedland and Williams (1999); B. Data from Bangsberg, et al. (2003); C. Data from Sethi, et al. (2003).





## Adherence and HIV Drug Resistance

*continued from page 7*

transmission [Jackson, et al. *AIDS* 2000; 14: F111]. Moreover, non-adherence is associated with virologic failure, immunologic failure, and clinical disease progression. In some cases, complete interruption of therapy might be preferable to continued therapy with poor adherence, with reinitiation after the reasons for non-adherence are addressed. This reinforces the need for HIV clinicians to counsel patients about the risks and consequences of non-adherence prior to beginning HAART and on an ongoing basis once HAART has been initiated.

Unfortunately, even perfect adherence may not prevent resistance, especially in those treated with less potent regimens and those who have acquired or were infected with drug-resistant virus. High-level adherence to regimens containing agents with a low genetic barrier to resistance (one mutation causes resistance) is also necessary. Routine monitoring and documentation of patient adherence is critical, along with ongoing assessment of potential barriers to maintaining long-term adherence. Adherence to clinic visits is also important, as it is associated with medication adherence. Clinic staff must continually assess the underlying reasons for missed appointments and attempt to improve show rates.

HIV-infected individuals who are nonadherent to HAART will likely develop drug resistance. To avoid the development of resistance, regimens must be highly potent and near-perfect adherence appears to be necessary. Unfortunately, for many patients, adherence can be difficult. A collective effort on the parts of HIV clinicians, clinic staff, and patients is required to assure long-term high-level adherence. ▲

## The Moore Clinic Celebrates Its 20<sup>th</sup> Anniversary

*By Richard W. Dunning, M.H.S.*

This year marks the 20<sup>th</sup> anniversary of the Moore Clinic and the beginning of the Johns Hopkins AIDS Service. The Moore Clinic had its origins in 1915 as a clinic for the treatment of syphilis. Over the ensuing years the Moore Clinic served people with a variety of chronic and hereditary disorders. In January 1984, Dr. Frank Polk and Dr. John G. Bartlett set aside one half day a week in the Clinic to take care of a small group of gay men with AIDS. This was at a time when the viral origin of AIDS was only hypothesized and there was little medical intervention except treatment of opportunistic infections. Since then, the Clinic expanded and became "HIV dedicated" in response to the growing epidemic in Baltimore and central Maryland. In the last year, the 150 providers in the AIDS Service cared for 3,200 patients and provided more than 20,000 ambulatory visits. The direction and development of the AIDS Service can be credited to several individuals, but Dr. John G. Bartlett and Dr. Richard E. Chaisson were the two instrumental leaders of the Service after the untimely death of Dr. Frank Polk in 1988. Dr. Joel E. Gallant has also been instrumental in his role as former medical director and now Associate Director of the AIDS Service, and has become recognized for his clinical expertise in the field. Current leadership of the Moore clinic includes Dr. William Ruby and Ms. Heather Campbell.

Over the years the AIDS Service developed programs that not only include ambulatory care in the Moore Clinic, but also several programs that provide regional care for HIV consumers in the surrounding counties of Baltimore, more distant counties on the Eastern Shore and Western Maryland, telemedicine linkages with the Maryland Division of Corrections and the Federal Prison system, access to clinical trials, inpatient services, and a dedicated outpatient pharmacy for the AIDS Service. The clinical care programs are supported by a number of specialty programs for women and psychiatric health, outreach, patient advocacy, and support programs for patients including two newsletters: *Moore News Quarterly* and *Patient Advocate*. *The Hopkins HIV Report* and a website are also important educational components of the Service.

The AIDS Service has experienced a number of firsts, including a collaborative program to establish longitudinal HIV care in the Baltimore City Health Department's STD clinics in 1989, the AIDS-Hemophilia Program (and the only clinic with combined hemophilia and HIV specialty services in Maryland) in 1994, and a clinic for treatment of HIV/hepatitis C-coinfected patients in 1997, a dedicated treatment adherence program in 1997, and an anal dysplasia clinic in 1999. ▲

## THE HOPKINS HIV REPORT

The Johns Hopkins University AIDS Service  
*The Hopkins HIV Report* Distribution  
P.O. Box 651266  
Potomac Falls, VA 20165-1266

**ADDRESS SERVICE REQUESTED**

Non-Profit Org.  
U.S. Postage  
**PAID**  
Dulles, VA  
Permit No. 056