



## HIV JournalView

by David Alain Wohl, M.D.

University of North Carolina, AIDS Research and Treatment Unit



David Wohl, M.D.

from The Body Pro

May/June 2006

### Table of Contents

- [Quantifying the Benefits of HIV Care and Treatment](#)
- [New Data Help Predict When Ritonavir-Boosted Atazanavir and Lopinavir Won't Work](#)
- [Increasing Prevalence of Transmitted Drug Resistant HIV in NYC: A Case for Baseline Genotype Testing](#)
- [Conspiracy Theories on Origins of HIV Prevalent: It Is not Just a "Black Thing"](#)
- [Adherence and Sexual Risk Reduction: What Works?](#)
- [Another Salvo in the Great Body Shape Debate](#)
- [References](#)

## Quantifying the Benefits of HIV Care and Treatment

### A review of:

*The survival benefits of AIDS treatment in the United States.* Rochelle P. Walensky, A. David Paltiel, Elena Losina, Lauren M. Mercincavage, Bruce R. Schackman, Paul E. Sax, Milton C. Weinstein, Kenneth A. Freedberg. *The Journal of Infectious Diseases.* July 1, 2006;194 (1):11-19.

The benefits of HIV therapy are obvious: Improved immune function, HIV suppression, weight gain, freedom from opportunistic conditions and improved quality of life can each be expected from current therapeutic regimens. But when it comes to the actual *survival* benefit of HIV care, it is difficult to quantify just how much time therapy adds to the lives of people living with HIV infection.

On the 10th anniversary of the approval of the first protease inhibitor (PI), a dream team of investigators and health care economists attempted to quantify the years of life saved by HIV/AIDS care as delivered in the United States. By feeding into a computer simulation model published data on the number of individuals diagnosed with HIV and entering care, the team was able to calculate the years of life gained

### STUDY SNAPSHOT

<b>Design:</b>	Computer simulation model.
<b>Population:</b>	Theoretical population of HIV-infected individuals receiving care in the United States.

subsequent to major milestones in HIV management during 1989 to 2003, starting with the use of prophylaxis for *pneumocystis* pneumonia (PCP) and ending with the current palette of antiretrovirals for initial and salvage therapy.

**The results suggest that incremental advances in HIV care have led to substantial**

**increases in per person survival. More than 2.8 million years of life have been saved and 2,900 cases of pediatric HIV infection averted. According to the model, a typical person living with HIV infection who receives potent combination antiretrovirals can expect to live at least 13 years longer than if no therapy has been taken.** In comparison, similar analyses have found that chemotherapy for non-small cell lung cancer yields an average survival benefit of only seven months, while bone marrow transplantation for relapsing non-Hodgkin's lymphoma yields a benefit of 92 months.

**Main Results:**

HIV care -- starting with opportunistic infection prophylaxis and concluding with the current state of antiretroviral strategies -- and the prevention of pediatric HIV infection has led to at least three million years of life saved. Care presently available can be expected to provide over 13 years of additional life compared to the absence of care.

**Significance:**

Compelling quantification of the benefits of HIV care in terms of years of additional life lived that will be of interest to patients, clinicians and policy-makers.

Including the years of life saved by preventing pediatric HIV infection adds over 137,000 additional years of benefit to yield an overall total of at least three million years of added survival.

**The Bottom Line**

These results are important for several reasons. First, they provide a *numerical* value to compliment the success stories HIV clinicians witness in their clinics every day. Second, clinicians can use these estimates to reassure patients that, in very general terms, many can expect over a decade of added survival during which there surely will be further advances that will likely *extend* the benefits of care. Third, for those of us who must lock horns with those who oversee funding of HIV care, three million lives saved and 13 years of added survival are meaningful terms that can be used to justify the price tag of HIV care.

Lastly, the extrapolation of these findings to HIV-infected people who remain *undiagnosed* produces an inverted picture of the years of life lost among these individuals and supports the need to expand HIV testing, which should include routine HIV testing in clinical settings. However, these data on the benefits of current care need to be used creatively to help increase HIV testing in a way that does not engender a cavalier attitude among the at-risk that HIV is no longer a big deal.

These findings clearly demonstrate the vast promise of HIV care if made available globally. When applied to the world, this model suggests that hundreds of millions of years of life will not be lived if we do not work harder to share these advances.

**New Data Help Predict When Ritonavir-Boosted Atazanavir and Lopinavir Won't Work**

**A review of:**

*Effect of baseline protease genotype and phenotype on HIV response to atazanavir/ritonavir in treatment-experienced patients.* Lisa K. Naeger, Kimberly A. Struble. *AIDS*. April 4, 2006;20(6):847-853.

For the same reasons you would not try to complete a jigsaw puzzle in the dark, you would not attempt to craft an antiretroviral salvage regimen without the benefit of a drug resistance test. Knowing which mutations a patient's virus has produced permits the clinician to avoid the use of antiretrovirals that, according to in vitro and clinical data, can be expected to have significantly diminished activity against resistant strains.

Of course, resistance tests are only as good as our understanding of the associations between the changes that HIV undergoes after treatment exposure and the continued efficacy of a given antiretroviral. As new resistance data emerge, they are included in the databases that kick out

those nifty resistance test reports, as well as printed on the handy resistance mutation cards we post in our clinics.

Clinical trial results have become an increasingly important source of information on resistance interpretation. For instance, researchers from the U.S. Food and Drug Administration (FDA) recently examined the patterns of drug resistance that predict response to the ritonavir (RTV, Norvir)-boosted PIs atazanavir (ATV, Reyataz) and lopinavir (LPV). To do so, the investigators analyzed data from BMS A1424-045, a pivotal study of ritonavir-boosted atazanavir that was submitted to support the FDA New Drug Application for this PI. (Atazanavir was approved by the FDA in 2003.)

In this trial, 358 highly treatment-experienced patients -- all of whom had failed two prior rounds of combination HIV therapy and had a plasma HIV-RNA level of 1,000 copies/mL or more -- were randomized to switch to either:

1. ritonavir-boosted atazanavir + tenofovir (TDF, Viread) + a second nucleoside; or
2. ritonavir-boosted lopinavir + tenofovir + a second nucleoside.

(A third arm was randomized to receive atazanavir + saquinavir (SQV, Invirase) + tenofovir + a second nucleoside, but this assignment was found to perform poorly.)

As has been published, response rates between the two ritonavir-boosted PI arms were similar at 48 weeks. The proportion of patients with less than 50 copies/mL HIV RNA at 48 weeks was 38% for atazanavir and 45% for lopinavir (95% CI, -21.5, 7.3). At study entry, most patients had more than one PI mutation (median = 3 mutations).<sup>1</sup>

In the present study, the FDA researchers looked at the differential responses to atazanavir and lopinavir after taking into account 1) the type of mutations detected by genotypic resistance testing done at study entry, 2) the number of such mutations and 3) the results of phenotypic testing.

The researchers found that certain resistance mutations at baseline were associated with diminished responses to both these agents. Specifically, **less than 30% of the 110 patients receiving boosted atazanavir who had a substitution at M46, G73, I84 or L90 responded to therapy. In contrast, the response rate of the 113 patients on boosted lopinavir was less than 30% if mutations at M46, I54 or I84 were present.**

Interestingly, when looking specifically at the L90M mutation -- which is broadly associated with reduced susceptibility to PIs -- **only 23% of patients on atazanavir harboring L90M responded, compared to 50% of patients on lopinavir.** However, the L90M mutation only

## STUDY SNAPSHOT

<b>Design:</b>	Post-hoc analysis to determine the effect of baseline PI resistance on response to ritonavir-boosted atazanavir vs. ritonavir-boosted lopinavir.
<b>Population:</b>	358 treatment-experienced patients with HIV RNA > 1,000 copies/mL randomized to tenofovir plus another NRTI and either ritonavir-boosted atazanavir or ritonavir-boosted lopinavir.
<b>Main Results:</b>	The presence of M46, G73, I84 or L90 predicted poor response to atazanavir while M46, I54 or I84 was associated with lopinavir failure. L90M was only able to hamper atazanavir response in the presence of two or more other protease mutations but had less effect on response to lopinavir. Response rates to both drugs were similar if zero to four mutations were present, but if five or more mutations were present at baseline, none of the atazanavir-assigned patients responded compared to 28% of those randomized to lopinavir. Similar differences in responses were associated with a five-fold or greater change in susceptibility based on phenotype.
<b>Significance:</b>	Key mutations can hamstring both atazanavir and lopinavir; however, responses to lopinavir were less impacted by the number of mutations present and the degree of change in viral susceptibility.

seemed to impact atazanavir responses when it was accompanied by *at least two other major mutations in the protease region*. Lopinavir appeared to be much more tolerant of L90M, even when additional PI resistance mutations were present.

Additionally, the D30N mutation -- which is associated with prior nelfinavir (NFV, Viracept) exposure -- and the M36I/V, V77I and N88S/D mutations were *not* found to affect response to either atazanavir or lopinavir. No trial participant had an I50L atazanavir signature resistance mutation detected at baseline.

The authors also compared patients' responses to each drug depending on the number of PI mutations present at study entry. Here again, there was little differentiation between atazanavir and lopinavir when there were less than two mutations present: When this was the case, about 75% of participants responded to therapy. As expected, in both arms, additional mutations led to diminished virologic success. However, **when five or more mutations were present, none (0/8) of the patients in the atazanavir group had a virologic response, compared to 28% (5/18) of those assigned lopinavir.**

Fold changes in viral susceptibility to the study drugs were assessed by phenotypic resistance testing. Mirroring the pattern seen with genotypic testing, responses to atazanavir and lopinavir became divergent when greater drug resistance was present, with patients faring worse on atazanavir than lopinavir.

### The Bottom Line

This analysis demonstrates that, in terms of virologic response, *ritonavir-boosted atazanavir was not as capable as ritonavir-boosted lopinavir* of weathering the onslaught of heavy drug resistance -- at least when "heavy resistance" is defined as the presence of: 1) five or more major resistance mutations on genotypic testing or 2) five-fold reduced susceptibility on phenotypic resistance testing.

In addition, this study provides insights into the ways that baseline resistance influences a patient's response to atazanavir relative to lopinavir. Both agents can produce substantial rates of viral suppression *despite* the presence of resistance; however, key mutations can be devastating, particularly when coupled with other major substitutions.

Finally, the sheer fact that these findings have been published by the FDA is, in and of itself, significant. With this paper, the authors have clarified the details of their review of the New Drug Application for atazanavir and expanded upon their initial findings. Further, they have focused attention on the increasingly important need for information on drug resistance and cross resistance *at the time of drug approval*. All too often, registrational studies of experimental HIV medications include only the minimum number of participants, all of whom are selected based on their likelihood of having the best responses. This precludes observation of more realistic outcomes such as virologic failure and drug resistance development. Resistance data are particularly important when new salvage drugs (e.g., tipranavir [TPV, Aptivus] and TMC114 [darunavir, Prezista]) and novel agents (e.g., CCR5 antagonists, integrase inhibitors and maturation inhibitors) are approved and launched.

As recent history demonstrates, clinicians are left fairly clueless about what mutations evolve during treatment with these new agents, as well as the significance of these mutations (especially in combination) and their downstream effect on subsequent regimens. For example, both tipranavir and darunavir are now available for clinical use but important questions regarding specific mutations and resistance patterns that could attenuate the effectiveness of these agents were frustratingly unanswered at the time of their approval. Such resistance data does eventually become available during post-approval investigations -- but not until after all the hoopla of the drug's launch subsides, and hundreds, if not thousands, of patients have already received the medication. Recognizing this problem, the FDA now requests more information regarding resistance when evaluating new antiretrovirals; such data are now included in the package insert.

In publishing these details from the data it received as part of the New Drug Application for atazanavir's approval, the FDA is following through on its pledge to have resistance data available for clinicians. There are limitations to this study, however: As is pointed out in an accompanying editorial by Veronica Miller of George Washington University, the data are from a restricted group of patients, and other studies have identified different mutational patterns associated with response to atazanavir.<sup>2</sup> Additionally, with greater use of the drug in regular clinical practice, additional information on resistance patterns will likely emerge.

## Increasing Prevalence of Transmitted Drug Resistant HIV in NYC: A Case for Baseline Genotype Testing

### A review of:

*Tracking the prevalence of transmitted antiretroviral drug-resistant HIV-1: a decade of experience.*  
**Anita Shet, Leslie Berry, Hiroshi Mohri, Saurabh Mehandru, Chris Chung, Alexandria Kim, Patrick Jean-Pierre, Christine Hogan, Viviana Simon, Daniel Boden, Martin Markowitz.**  
*Journal of Acquired Immune Deficiency Syndromes.* April 1, 2006;41(4):439-446.

For several years HIV literature has been peppered with reports of transmitted antiretroviral resistant virus. Most studies from urban centers in the United States and Europe have found that 10%-16% of persons acquiring HIV are infected with drug resistant strains.<sup>3</sup> Concern regarding the effect of acquired drug resistant HIV on response to HIV therapy has prompted many clinicians to order genotypic resistance tests on those about to initiate antiretrovirals. Indeed, recently, the U.S. Department of Health and Human Services (DHHS) has, in its guidelines on the treatment of HIV in adults and adolescents, updated its recommendation regarding baseline genotype testing to B(III) -- (moderately strong recommendation).<sup>4</sup> It now recommends genotypic resistance testing before initiating treatment in patients with acute or chronic HIV infection, and notes that resistance testing may be considered in all patients entering care whether they are in need of treatment or not.

Whether the prevalence of transmitted resistance is changing has been a subject of some debate. Some reports have observed a drop in cases of transmitted drug resistance -- potentially a result of the enhanced potency of HIV therapies and the relatively poor transmissibility of certain types of mutant virus.<sup>5,6</sup> However, other data suggest that this is not the case and that the spread of resistant virus may be increasing.<sup>7-10</sup>

As most drug resistant viruses do not persist in numbers sufficient to be detected by routine resistance testing, the early period following

HIV infection provides the best opportunity to detect these mutations. To assess trends in the prevalence of transmitted drug resistant virus, investigators at the Aaron Diamond AIDS Research Center in Manhattan analyzed genotypic resistance test results collected from a cohort of individuals with acute and recent (within 12 months based on prior negative HIV antibody testing or a negative detuned assay) HIV infection.

A total of 361 participants were recruited from mid-1995 until the end of 2004; all were antiretroviral treatment naive at the time of the initial evaluation. Among those enrolled during 2003 and 2004, 112 had sufficient virus for genotypic analyses. These participants were mostly male (98%) and white (71%) and underwent resistance testing an estimated 58 days post-infection. Only 10% were deemed to be in the acute phase of infection, while 70% appeared to be infected within the prior six months and the remainder within the past year.

Resistance (defined using the current [IAS-USA Consensus Guidelines](#)) was detected in 24.1% of those enrolled in 2003-2004 compared to 16.7% of the 102 who entered in 2001-2002, 19.7% of the 71 who were followed since 1999-2000 and 13.2% of the 76 who first enrolled in 1995-1998 ( $P = .11$ ) (see [Table 1](#)). Therefore, **there was no statistical trend in the change in the prevalence of overall drug resistance; however, the finding of most interest was that resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) was observed to**

### STUDY SNAPSHOT

<b>Design:</b>	Retrospective study of prevalence of transmitted antiretroviral therapy resistant HIV.
<b>Population:</b>	361 individuals with acute or recent HIV infection in NYC.
<b>Main Results:</b>	Transmitted drug resistant strains of HIV are detectable in 13%-25% of persons with newly acquired infection. The overall prevalence of resistance was not found to be significantly changed from 1995 to 2004; however, there was a significant rise in NNRTI resistance during this period.
<b>Significance:</b>	The high prevalence of drug resistance detected in this cohort highlights the importance of baseline genotype resistance testing. Resistance mutations were found to persist during follow-up.

increase over time, shifting from 2.6% in the mid-1990s to 13.4% in those infected during 2003-2004 ( $P = .0007$ ). There was a trend toward increasing PI resistance, although this did not achieve statistical significance. Transmission of multidrug resistant virus was, fortunately, rare. Only five cases were detected since 1995; however, three of these were observed in patients enrolled between 2003 and 2004.

When comparing the clinical outcomes of the 112 most recently infected participants who were receiving HIV therapy (on regimens based on their genotype results), there were no significant differences in the time to virologic suppression, rate of HIV RNA decay or CD4+ cell count rise between those who had resistance detected and those who did not. This suggests that genotype-guided HIV therapy can lead to treatment success *despite* these pre-existing mutations.

**Table 1. Resistance Detected in Acute and Recently HIV-Infected Individuals in NYC, 1995 to 2004**

	1995-1998 n=76	1999-2000 n=71	2001-2002 n=102	2003-2004 n=112	P for Trend
<b>Any resistance</b>	13.2%	19.7%	16.7%	24.1%	0.11
<b>Any NRTI</b>	11.8%	15.5%	8.8%	16.1%	0.67
<b>Any NNRTI</b>	2.6%	5.5%	7.8%	13.4%	0.007
<b>Any PI</b>	1.3%	5.6%	4.9%	7.1%	0.10
<b>Resistance to 2+ ART classes</b>	2.6%	5.6%	3.9%	9.8%	0.007
<b>Resistance to 3+ ART classes</b>	0%	1.4%	1.0%	2.7%	0.17

### The Bottom Line

Though transmitted drug resistance was not observed to be increasing in this cohort of mostly men who have sex with men (MSM) in New York City, it is clear that a substantial proportion (13%-25%) of those recently infected with HIV had drug resistant strains and that these mutations were detectable months after infection. The most important message to take home from this report is the need to perform genotype resistance testing on patients who are naive to HIV therapy -- as is now recommended by the DHHS in their most recent update to the guidelines regarding initial antiretroviral treatment. Even if HIV therapy is not indicated at that time, the documentation of evidence of resistance will inform the construction of a future initial regimen.

The rise of NNRTI resistant mutations is of particular concern. The popularity of this class of antiretrovirals, its relatively low genetic barrier to resistance, the stability of NNRTI mutations and the potential abuse of efavirenz (Sustiva, Stocrin) as a "club drug" may explain this rise. It is also notable that the knowledge of baseline resistance was applied successfully to create effective HIV treatment regimens that avoided drugs to which the virus was less susceptible. The data on the ability to use baseline resistance data to craft effective antiretroviral regimens further support the value of baseline testing.

### Conspiracy Theories on Origins of HIV Prevalent: It Is not Just a "Black Thing"

#### **A review of:**

*Conspiracy beliefs about the origin of HIV/AIDS in four racial/ethnic groups. Michael W. Ross, E. James Essien, Isabel Torres. Journal of Acquired Immune Deficiency Syndromes. March 2006;41(3):342-344.*

A few weeks ago, a server at the restaurant where an HIV continuing education event was being held approached the speaker at the end of the evening and asked whether it was true that the government had a cure for HIV but was holding it back to maximize pharmaceutical industry profits. At a recent question and answer session during a health day fair conducted by a community church, a parishioner prefaced his question on HIV screening with the statement, "We all know the government created HIV to kill black people and gays." The same week, a newly diagnosed patient asked her provider whether HIV was created in a government lab.

Once it became clear that AIDS was caused by an infectious agent, theories regarding its origins turned to the conspiratorial. That the epidemic first centered on MSM and then injection drug users and later racial and ethnic minorities has been taken by some as a smoking gun implicating a nefarious U.S. government bent on purging the most marginalized populations in the country. Following investigations that convincingly link HIV to simian viruses found in Africa,<sup>11</sup> a new theory emerged and suggested that HIV was spread through mid-20th

century vaccine programs in that continent -- a hypothesis that has subsequently been debunked. Yet, cynicism regarding the origins of the HIV epidemic persists.

Studies examining the prevalence of conspiracy theories regarding the origins of HIV have focused on populations that are perceived by the investigators to harbor such beliefs and, generally, do not include racially/ethnically diverse samples. Therefore, several investigations have detected widespread belief in theories that HIV was designed by the government among African Americans;<sup>12,13</sup> however, just how pervasive such beliefs are in other groups remains unclear.

Michael W. Ross et al in Houston, Texas, assessed the prevalence of conspiracy beliefs on the origins of HIV in a diverse cohort. They did this by examining the responses to two questions included in an anonymous community-based survey designed to determine knowledge, misconceptions and sources of information regarding HIV that was administered to English-speaking adults recruited at public parks, mass transit locations and malls in downtown Houston. The survey included the fairly provocative statement, "AIDS is an agent of genocide created by the U.S. government to kill off minority populations (true, false, don't know)" and later asked about condom use with the awkward and ambiguous query, "What percentage of your partners use condoms during sexual contact (none, 25%, 50%, 75%, 100%)?"

Importantly, although published last March, this study was conducted between 1997 and 1998 (an explanation for the prolonged delay is not provided by the authors, which suggests it was likely due to a shortage of at least one of two precious resources: time and/or money). Of those approached to participate, about 40% declined, mostly because they were too busy. Despite this, almost 1,500 individuals were enrolled in the study, including 441 African Americans (53% women), 456 Latinos (45% women), 300 Asians (51% women) and 297 whites (33% women) -- a quite diverse group.

Regarding the HIV-as-an-agent-of-genocide question, among African Americans 27% of men and 31% of women said they thought this was true, compared to 21% of Latino men and 24% of Latino women and 20% of white men and 22% of white women. Asian participants were much less likely to buy this, with 11% of men and 7% of women finding the statement valid. A multinomial regression model, which included 1) the response to the conspiracy question, 2) gender, 3) age and 4) education found that *being African American or Latino was significantly associated with finding the genocide statement not false* (i.e., answered it was true or did not know).

Further, there was a significant relationship between the conspiracy belief response and reported condom use -- i.e., indicating less condom use ( $P = .03$ ) -- among only those African-American men who did not find the conspiracy statement to be false. No significant association between the two was found among the other male or female racial/ethnic groups. However, in a multiple regression model, race/ethnicity, gender, age and education were each found to be independent predictors of condom use.

## STUDY SNAPSHOT

<b>Design:</b>	Prospective cohort study.
<b>Population:</b>	Persons frequenting public locations in Houston surveyed.
<b>Main Results:</b>	20%-31% of those surveyed believed that HIV was created by the government as an agent of genocide. This belief was held by similar proportions of individuals in different racial/ethnic groups -- among African-American men this belief was associated with reduced condom use.
<b>Significance:</b>	Conspiracy theories on the origin of HIV may be prevalent across race and ethnic lines. The association with reduced condom usage among African-American men indicates a need to address these beliefs when launching prevention initiatives.

## The Bottom Line

This study, although clearly plagued by limitations, not the least of which is the relevance of its findings almost 10 years after the study was conducted, is nonetheless interesting in that it found conspiracy beliefs to *not* be restricted to African Americans. Latinos and whites in surprisingly high numbers (and this was in Texas!!) also expressed a belief in a malevolent origin for HIV. Most HIV clinicians today, even outside the Lone Star state, would likely agree that these beliefs persist. In fact, one can posit that such cynical views on the HIV epidemic may have only increased since 1998 with the spread of HIV to populations already suspicious of the federal government, and dissatisfaction among many African Americans regarding the outcome of the 2000 presidential election and the government's response to Hurricane Katrina.

Since this study was conducted, evidence that HIV originated as a zoonotic infection in central Africa has been made public; yet, few of those now living with HIV/AIDS may be aware of these data or find them reliable.

That there may be an association between belief in a government role in the HIV epidemic and condom use is of great importance and signals the need for such beliefs to be addressed as part of HIV prevention efforts, including safer sex programs and vaccine studies. Clinicians also need to be aware of the pervasiveness of such conspiracy theories and, using the trust they cultivate with their patients, serve as a source of sound information to help minimize the role of skepticism in thwarting prevention and treatment benefits. Setting the waitress straight might also help.

## Adherence and Sexual Risk Reduction: What Works?

### **A review of:**

*Sexual risk reduction for persons living with HIV: research synthesis of randomized controlled trials, 1993 to 2004.* Blair T. Johnson, Michael P. Carey, Stephenie R. Chaudoir, Allecia E. Reid. *Journal of Acquired Immune Deficiency Syndromes.* April 15, 2006;41(5):642-650.

and

*Efficacy of antiretroviral therapy adherence interventions: a research synthesis of trials, 1996 to 2004.* K. Rivet Amico, Jennifer J. Harman, Blair T. Johnson. *Journal of Acquired Immune Deficiency Syndromes.* March 2006;41(3):285-297.

Human behavior is hard to change -- a truism well known to health care providers who expend considerable amounts of exhaled breath trying to convince smokers to put aside their cigarettes, the obese to cut out the cookies and all of us to exercise, schedule our colonoscopies, wear our seat belts and, for crying out loud, put on some sunscreen. In addition to this list of dos and don'ts, those living with HIV infection are also asked to take their antiretrovirals religiously and to practice safe sex.

There have been scores of interventions developed and tested to achieve each of these aims. However, what really works is not completely clear. Two separate reviews led by researchers from the University of Connecticut and published a month apart in *JAIDS* provide an invaluable service in synthesizing the published, and even unpublished, data in order to make heads and tails of adherence and prevention interventions.

Each review took

### STUDY SNAPSHOT

<b>Design:</b>	Two meta-analyses of interventions targeting antiretroviral adherence and HIV risk behavior reduction among persons with HIV infection.
<b>Main Results:</b>	Adherence interventions worked best when applied to those who have or are deemed at risk for non-adherence. Prevention interventions increase condom use when informational, motivational and behavioral components are each included. Younger individuals were most likely to respond to prevention interventions compared to older participants. Prevention interventions had much less effect on condom use by MSM than non-MSM.

advantage of online databases (e.g., Medline) to identify relevant intervention studies.

Further, the researchers,

innovatively, contacted the original study investigators directly (in the case of the prevention review, they searched the National Institutes of Health database of awardees of grants). Lastly, they used what has proved to be the most powerful tool in medical education since the advent of the medical journal -- Google -- to identify additional studies.

#### Significance:

These reviews inform which types of interventions are likely to be effective in the field and the design of future interventions.

### Adherence Meta-Analysis

In their meta-analysis of adherence investigations, the authors included only studies that contained an intervention targeting antiretroviral therapy adherence, compared the intervention to a control or baseline assessment, were published in a peer-reviewed journal and provided sufficient information (sample size, pre- and post-adherence values) to calculate an effect size. They included studies from 1996 to the end of 2004.

Out of a pool of 828 articles, book chapters and dissertations (!), only 24 met their criteria and were included in the meta-analysis. Of these, most had a primary outcome measure of self-reported adherence, although four employed electronic medication monitoring devices (i.e., medication event monitoring system, or MEMS, caps). Overall, adherence improved with the interventions studied, which included various types and intensities of counseling provided by individuals across the spectrum of training. Some studies also added devices to remind patients to take their medications, support groups and skills building components.

There was, however, considerable variability in the degree of success across the trials. The authors tried to identify participant, study and intervention characteristics that could account for this variability. Yet, demographics, intervention intensity or duration, use of MEMS caps, and the articulation of a theoretical basis for an intervention -- each of which could be thought (especially by grant reviewers) as key to the success of an adherence intervention -- were *not* found to be associated with success of the adherence interventions studied. **The sole factor linked to a greater effect of the adherence intervention was the recruitment of participants with known or anticipated difficulties with treatment adherence.** In contrast, studies enrolling patients *without* known problems adhering to their HIV medications had a small effect size. **Therefore, interventions that targeted patients considered at risk for or experiencing poor adherence had the greatest effect on adherence.**

### Prevention Meta-Analysis

Turning to HIV prevention studies, the authors focused on randomized controlled trials in which risk reduction interventions were used to prevent transmission from HIV-infected persons. To be included, studies had to assess; condom use or number of sexual partners; and report sufficient data to permit the calculation of an effect size. From amongst the 699 studies appearing between 1993 and 2004 that contained the correct search terms, 15 studies met the above criteria and were included in this review.

Each study provided HIV/AIDS information to participants, 13 provided motivational components and 12 provided behavioral skills training such as in condom use. All but one study evaluated condom use and two looked at only the number of partners; five used both. **Overall, there was an increase in condom use relative to controls. However, there was no change in partner number compared to controls in studies examining this variable. Interventions were more successful at increasing condom use when younger participants were enrolled, when the sample did not include MSM and when both motivational and behavioral skills were part of the intervention.**

### The Bottom Line

These reviews perform a great service in distilling the results of disparate studies so that predictors of the effectiveness of adherence and risk reduction interventions can emerge. In addition to informing clinicians and educators, the findings of these meta-analyses can also be of value to researchers planning their own intervention studies.

That adherence interventions were most effective among those with demonstrated or suspected poor adherence to HIV medications is a key finding and suggests broadly applied adherence interventions will yield diminishing returns. Similarly, the almost complete absence of an effect of

interventions on condom use among HIV-infected MSM highlights the need for additional study to address this critical problem. Lastly, it is of major importance that a combination of approaches, including informational, motivational and behavioral, was found to be most effective in increasing condom use, and thus supporting a multidisciplinary approach to behavioral change, although partner number was more impervious to any intervention when combined.

## Another Salvo in the Great Body Shape Debate

### A review of:

*Mixed patterns of changes in central and peripheral fat following initiation of antiretroviral therapy in a randomized trial. Kathleen Mulligan, Robert A. Parker, Lauren Komarow, Steven K. Grinspoon, Pablo Tebas, Gregory K. Robbins, Ronenn Roubenoff, Michael P. Dube, for the ACTG 384 and A5005s Study Teams. Journal of Acquired Immune Deficiency Syndromes. April 15, 2006;41(5):590-597.*

Several studies have convincingly demonstrated a relationship between HIV therapy containing thymidine analogs and the loss of fat from the limbs and the subcutaneous abdomen. More contentious is whether fat accumulation in the visceral abdomen and dorsocervical fat pad (known colloquially as "buffalo hump") are a manifestation of certain HIV therapies. Although many clinicians and certainly most patients deeply believe that antiretroviral agents, and PIs in particular, can lead to fat accumulation, the data supporting such a relationship are fairly sparse. Papers have been published that have shown an increase in visceral adipose volume and/or waist circumference during HIV therapy;<sup>14-16</sup> however, it is not clear from these studies whether this fat gain is a return of fat that was previously lost during advancing HIV disease.

Importantly, data from the FRAM (Fat Redistribution and Metabolic Change in HIV Infection) study,<sup>17</sup> a cross-sectional investigation of HIV-infected patients and control subjects, found no significant differences in visceral fat volume between men with HIV and the controls. The prevalence of dorsocervical fat pad enlargement was also similar between the groups, at least in men, but was markedly larger in the HIV-infected group. It was fat wasting of the limbs and subcutaneous abdomen

that really distinguished the HIV-infected from the control population; the combination of a fat belly and skinny arms that was considered to be a dominant feature of highly active antiretroviral therapy (HAART)-induced body shape change did not exist.

The FRAM results caused the equivalent of a food fight among members of the HIV metabolic complications community. On the one side are those who lob criticisms of the cross-sectional FRAM study such as it was unable to detect changes in fat during treatment and that the controls used may not have been appropriate. Across the table are those who toss back the problem of insufficient data to support a phenotype of combined fat accumulation and atrophy.

Then along came AIDS Clinical Trials Group (ACTG) study A5005s.<sup>18</sup> This metabolic sub-study of a large antiretroviral trial that enrolled 334 treatment-naive patients used standardized anthropometrics (tape measures and calipers) and dual energy X-ray absorptiometry (DEXA) scans to longitudinally measure body shape changes in trial participants initiating PI and/or NNRTI-based regimens. At last, a prospective study that could rigorously assess changes over time following exposure to different types of HAART. The major results of this study were published last year<sup>18</sup> and were notable for the observed increases in trunk fat seen in each treatment group and

### STUDY SNAPSHOT

<b>Design:</b>	Prospective observational sub-study of a large randomized trial of six different initial antiretroviral regimens.
<b>Population:</b>	Treatment-naive patients.
<b>Main Results:</b>	Changes in limb and trunk fat during therapy occurred in the same direction in over two thirds of patients. In 26% a loss of limb fat was accompanied by a gain in trunk fat.
<b>Significance:</b>	This study is the largest and most rigorous to prospectively assess changes in fat depots across a variety of antiretroviral therapy regimens. The finds help validate clinical observations and expand on the findings of cross-sectional body shape analyses.

the general loss of limb fat seen, especially among those assigned to stavudine (d4T, Zerit) and didanosine (ddI, Videx).

In this latest analysis, the authors get to the heart of the fat belly/skinny limbs controversy by looking at the combinations of fat gain or loss in the limbs and trunk. **Changes in limb and trunk fat were directionally concordant in most participants over 64 weeks of therapy, with increases in both limb and trunk fat detected in 36% of participants and decreases in both limb and trunk fat detected in 32% of participants. One third of patients had discordant results, with 26% of the cohort having a decrease in limb fat accompanied by a gain in trunk fat.**

Further, the investigators found that 1) DEXA and anthropometrics were decently concordant and that 2) waist-to-hip ratios need to be interpreted with caution because in half of the patients the ratio increased due to an increase in the size of the waist alone while in the other half a decline in hip, with or without a rise in waist circumference, occurred.

### The Bottom Line

This study provides the best prospective, longitudinal data we have on changes in adipose depots during HIV therapy. Like FRAM, ACTG 5005s found that peripheral fat loss and central fat gain were not linked in most patients; however, these changes can indeed co-exist in as many as a quarter of patients -- accounting for clinical observations of the combined changes. In addition, trunk fat did increase in this study following treatment, making it clear this is a treatment associated phenomenon and that isolated lipoatrophy is not the dominant body shape complication of therapy. These are important findings that most metabolic minded HIV researchers can live with.

### References

1. Johnson M, Grinsztejn B, Rodriguez C, et al. [Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures](#). *AIDS*. April 29, 2005;19(7):685-694.
2. Miller V. [Defining clinically relevant HIV drug resistance -- from drug development to clinical reality](#). *AIDS*. April 4, 2006;20(6):929-931.
3. Novak RM, Chen L, MacArthur RD, et al, and the Terry Beinr Community Programs for Clinical Research on AIDS 058 Study Team. [Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy](#). *Clin Infect Dis*. February 1, 2005;40(3):468-474.
4. Panel on Clinical Practices for Treatment of HIV Infection. [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#). U.S. Dept of Health and Human Services; May 4, 2006.
5. Bezemer D, Jurriaans S, Prins M, et al. [Declining trend in transmission of drug-resistant HIV-1 in Amsterdam](#). *AIDS*. July 23, 2004;18(11):1571-1577.
6. Routy J-P, Machouf N, Edwardes MD, et al. [Factors associated with a decrease in the prevalence of drug resistance in newly HIV-1-infected individuals in Montreal](#). In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, Calif. Abstract 678.
7. Little SJ, Holte S, Routy J-P, et al. [Antiretroviral-drug resistance among patients recently infected with HIV](#). *N Engl J Med*. August 8, 2002;347(6):385-394.
8. Grant RM, Hecht FM, Warmerdam M, et al. [Time trends in primary HIV-1 drug resistance among recently infected persons](#). *JAMA*. July 10, 2002;288(2):181-188.
9. Simon V, Vanderhoeven J, Hurley A, et al. [Evolving patterns of HIV-1 resistance to](#)

[antiretroviral agents in newly infected individuals](#). *AIDS*. July 26, 2002;16(11):1511-1519.

10. Boden D, Hurley A, Zhang L, et al. [HIV-1 drug resistance in newly infected individuals](#). *JAMA*. September 22, 1999;282(12):1135-1141.
11. Gao F, Bailes E, Robertson DL, et al. [Origin of HIV-1 in the chimpanzee \*Pan troglodytes troglodytes\*](#). *Nature*. February 4, 1999;397(6718):436-441.
12. Klonoff EA, Landrine H. [Do blacks believe that HIV/AIDS is a government conspiracy against them?](#) *Pre Med*. May 1999;28(5):451-457.
13. Bogart LM, Thorburn S. [Are HIV/AIDS conspiracy beliefs a barrier to HIV prevention among African Americans?](#) *J Acquir Immune Defic Syndr*. February 1, 2005;38(2):213-218.
14. Saint-Marc T, Partisani M, Poizot-Martin I, et al. [Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study](#). *AIDS*. January 7, 2000;14(1):37-49.
15. Dubé MP, Parker RA, Tebas P, et al. [Glucose metabolism, lipid, and body fat changes in antiretroviral-naive subjects randomized to nelfinavir or efavirenz plus dual nucleosides](#). *AIDS*. November 4, 2005;19(16):1807-1818.
16. Mallon PW, Miller J, Cooper DA, Carr A. [Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy](#). *AIDS*. May 2, 2003;17(7):971-979.
17. Bacchetti P, Gripshover B, Grunfeld C, et al, from the Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). [Fat distribution in men with HIV infection](#). *J Acquir Immune Defic Syndr*. October 1, 2005;40(2):121-131.
18. Dube MP, Parker RA, Tebas P, et al. [Glucose metabolism, lipid, and body fat changes in antiretroviral-naive subjects randomized to nelfinavir or efavirenz plus dual nucleosides](#). *AIDS*. November 4, 2005;19(16):1807-1818.

*Please fill out this quick survey and tell us what you think of this HIV JournalView article!*

---

For a complete index of The Body Pro's HIV JournalViews, click [here](#).

---

**Please note:** Knowledge about HIV changes rapidly. Note the date of this article, and before treating patients or employing any therapies described in these materials, verify all information independently. If you are a patient, please consult a doctor or other medical professional before acting on any of the information presented in this article.

© 2006 Body Health Resources Corporation