The Body Pro
Top 10 Research Publications in HIV Care -- 2005
A Special, Year-End Issue of *HIV JournalView*

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- Top Published Research of 2005:

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   Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda
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2. A Novel -- and Essential -- Method for Spotting Acute HIV Infections
   Detection of acute infections during HIV testing in North Carolina
   By Christopher D. Pilcher, et al, *The New England Journal of Medicine*, May 5, 2005

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   By Ginger Lehrman, et al, *The Lancet*, August 13, 2005
   and
   Effect of treatment, during primary infection, on establishment and clearance of cellular reservoirs of HIV-1
   By Matthew C. Strain, et al, *The Journal of Infectious Diseases*, May 1, 2005

4. Expanded Screening for HIV Infection Saves Money and Reduces the Spread of HIV
   Expanded screening for HIV in the United States -- an analysis of cost-effectiveness
   By A. David Paltiel, et al, *The New England Journal of Medicine*, February 10, 2005
   and

Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy
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5. Tenofovir + Didanosine: The Downfall of a Lovely Combination
   Early virologic failure in HIV-1 infected subjects on didanosine/tenofovir/efavirenz: 12-week results from a randomized trial
   By Desmond Maitland, et al, *AIDS*, July 22, 2005
   and
   High virological failure rate in HIV patients after switching to a regimen with two nucleoside reverse transcriptase inhibitors plus tenofovir
   By Maria J. Perez-Elias, et al, *AIDS*, April 29, 2005
   and
   Paradoxical CD4+ T-cell decline in HIV-infected patients with complete virus suppression taking tenofovir and didanosine
   By Ana Barrios, et al, *AIDS*, April 8, 2005

6. Metabolic Complications and HAART: Some New Answers and Many More Questions
   Glucose metabolism, lipid, and body fat changes in antiretroviral-naive subjects randomized to nelfinavir or efavirenz plus dual nucleosides
   By Michael P. Dube, et al, *AIDS*, November 4, 2005
   and
   Fat distribution in men with HIV infection
   By Peter Bacchetti, et al, *Journal of Acquired Immune Deficiency Syndromes*, October 1, 2005

7. A Supersized Epidemic: The Twin Problems of Obesity and HIV
   A tale of 2 epidemics: the intersection between obesity and HIV infection in Philadelphia
   By Valerianna Amorosa, et al, *Journal of Acquired Immune Deficiency Syndromes*, August 15, 2005

8. Low-Level Viremia May Slowly Breed Resistance, but Watch Out for NNRTIs
   HIV-1 drug resistance evolution among patients on potent combination antiretroviral therapy with detectable viremia
   By Sonia Napravnik, et al, *Journal of Acquired Immune Deficiency Syndromes*, September 1, 2005

9. Risk of Tenofovir Nephrotoxicity May Be Real, Though Murky
   Changes in renal function associated with tenofovir disoproxil treatment, compared with nucleoside reverse transcriptase inhibitor treatment
   By Joel E. Gallant, et al, *Clinical Infectious Diseases*, April 15, 2005

10. Efavirenz Has No Significant, Lasting Impact on Neuropsychological Performance
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Introduction

One year is a long time in the world of HIV research. It's not simply that new developments in HIV evolve at an extraordinary pace; it's that some of these developments have the potential to dramatically affect the way in which we do our jobs as healthcare professionals -- and, as a result, to alter the lives of the patients we serve. While most of us have no trouble staying abreast of the more dramatic research news, many smaller findings that have the potential to have a big impact can easily escape the notice of many people -- at least those of us who were not able to skim through the more than 12,000 articles on HIV that were published in 2005. For the rest of us there are year-end reviews, such as this one.

To identify 2005's most significant HIV-related papers and present a diverse range of clinical perspectives, I consulted several experts from across the United States who are working in HIV research, care and prevention. I asked them to nominate the published research they felt had the greatest impact on their work over the past year. My only criterion was that the selections have relevance to clinical practice or importance to those combating HIV.

The result was an interesting mix. While the selections you are about to read are not free of my own biases, I can say that I have chosen those I considered most likely to interest you, the reader. Although this is not meant to be an exhaustive list, it should give the harried healthcare professional a comprehensive sense of the year's most significant developments in our understanding of HIV transmission, diagnosis, pathogenesis, complications and treatment.

My thanks to my colleagues for their excellent suggestions, and to you for taking the time to read this review.

HIV Transmission Highest During Acute Infection and End Stage Disease

***Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda*. Maria J. Wawer, Ronald H. Gray, Nelson K. Sewankambo, David Serwadda, Xianbin Li, Oliver Laeyendecker, Noah Kiwanuka, Godfrey Kigozi, Mohammed Kiddugavu, Thomas Lutalo, Fred Nalugoda, Fred Wabwire-Mangen, Mary P. Meehan, and Thomas C. Quinn. The Journal of Infectious Diseases; May 1, 2005;191(9):1403-1409.**

It's one of the most frequently asked questions on AIDS hotlines across the United States: "What is my risk of getting HIV during sex?" A number of different epidemiological investigations have been conducted in an attempt to answer this question. They collectively

suggest that the risk of HIV infection per sexual encounter between an individual who is HIV infected and an uninfected partner is in the neighborhood of 1 in 1,000.[1]

But this figure seems low, given the rapid and expansive spread of HIV during the past 20 to 30 years -- even accounting for factors that influence sexual transmission, such as plasma and genital HIV viral load, HIV clade, and ulcerative and inflammatory sexually transmitted diseases (STDs).

STUDY SNAPSHOT	
Design:	Post-hoc analysis of large clinical trial to determine risk of heterosexual transmission of HIV per coital act.
Population:	235 HIV serostatus discordant heterosexual couples in Uganda.
Main Results:	68 intra-couple transmissions of HIV. Risk of transmission was higher among those with very early HIV infection and those with late stage disease versus those with chronic infection.
Significance:	First population study to demonstrate actual increased risk of HIV transmission during early HIV infection.

As we've expanded our understanding of the dynamics of HIV viremia, it has been postulated that the greatest likelihood of HIV transmission is during specific periods of time, specifically during the earliest and latest phases of HIV infection, when viremia tends to be highest. Indeed, mathematical models have predicted that HIV transmission is more likely during *early* infection, when the viral load in the blood (and probably genital secretions) is in the millions/mL -- the highest it will ever be in that individual -- and the behaviors that led to infection are likely to be repeated.[1,2] However, these predictions have been based on computer simulations rather than any observation in real populations.

In Rakai, Uganda, Maria Wawer and colleagues have been working to identify the determinants of HIV transmission among monogamous, HIV sero-discordant heterosexual couples. They analyzed the data from a large, clinical trial they conducted in the late 1990s.

The original randomized study was an ambitious effort involving more than 15,000 participants in 56 villages. The goal was to determine the efficacy of intermittent treatment of STDs on the reduction of HIV transmission.[3-5] Although the intervention was not found to reduce the incidence of HIV infection, the investigators collected a wealth of data, including behavioral data and biological specimens from the participants. Previously, they had demonstrated that HIV transmission was strongly correlated with viral load and the incidence of genital ulcer disease.[6]

In this analysis, the investigators retrospectively identified 235 discordant couples among whom the HIV-uninfected partner reported being monogamous. Importantly, in 23 of these couples, both partners were HIV-uninfected at study enrollment. The authors refer to the partner who infected the HIV-uninfected partner of the couple as the *index partner*. The index partner could be a *prevalent index partner* (had HIV infection at study entry) or an *incident index partner* (acquired HIV infection during study followup). Molecular techniques were employed to determine the relatedness of viral isolates among many of the partners to confirm intra-couple transmission.

Based on self-report, the median number of coital acts per couple was 8.3 per month. This

number was the same for couples who were sero-discordant at baseline and couples in which both partners were uninfected at baseline.

Not surprisingly, plasma viral load increased after the seroconversion of the incident index partner and then decreased over time. Among the prevalent index partners, viremia tended to increase during follow-up. Index partners with advanced HIV disease had a high median viral load, suggesting even greater increases in HIV viremia during late stage disease.

A total of 68 of the 235 index partners transmitted HIV to their initially uninfected partner. Strikingly, almost *half* of the index partners acquiring HIV during the study (i.e., incident index partners) transmitted the virus to their partner during *acute HIV infection*. Specifically, 10 of the 23 incident index partners transmitted HIV during approximately the first 2.5 months after their seroconversion.

Three additional incident index partners transmitted the virus within 35 months of their own infection. Prevalent index partners transmitted HIV to their partners at a lower rate of 8.4% per year. Of the index partners with late stage HIV disease, 37.3% infected their partner within approximately 6 to 35 months prior to their death.

The authors calculate that the risk of HIV transmission was 0.0082 per coital act among acutely infected index partners, falling to 0.0015 per coital act following the acute infection period -- which was not significantly different than the rate observed among couples with a prevalent index partner (0.0007 per coital act).

The researchers estimate that if the observation period had been reduced to the first 30 days rather than 2.5 months following the acute HIV infection of the index partner, the rate could be as high as 0.02 per coital act (i.e., 1 in 50).

There was an increase in transmission risk (0.0036 per coital act) in partners with advanced, late-stage HIV disease during the months preceding their death -- a significantly greater risk of transmission than observed among prevalent index partners in earlier stages of the disease.

Only 29% of the couples in this study reported any condom use and none used them consistently (despite the counseling that was provided on safe sex). The risk factors that were identified with HIV transmission in an adjusted model included early- and late-stage HIV infection, high viral load, genital ulcer disease and young age of the index partner.

The Bottom Line

These important data confirm the validity of earlier modeling that predicted the greatest period of danger for viral transmission is during the period of acute HIV infection[1,2] and strongly suggest that those with early HIV infection are the leading edge in the spread of the epidemic.

This provocative finding in actual people has tremendous implications for public health policy. It underscores an urgent need to develop techniques to identify people experiencing acute HIV infection so we can intervene to reduce their risk of transmitting the virus to others.

Although late-stage HIV disease was also associated with an increased transmission potential, the patients with more advanced illness report fewer coital acts, have few partners and more commonly have partners who are *not* serodiscordant.

Although the study was conducted in Africa, where there is a higher prevalence of non-B clade virus and a higher prevalence of STDs, the factors that account for increased sexual HIV transmission during acute infection are also operative in other regions.

Therefore, if we are to derail the continued spread of the HIV pandemic, we *must* stop HIV transmission when it is most likely to occur -- *soon after infection* -- rather than concentrate only on teaching prevention to positives or expect antiretroviral therapy to render later-stage patients less infectious. A huge flaw in our HIV prevention efforts is ignoring those still undiagnosed.

The challenges are obvious:

- Many with acute HIV infection are asymptomatic or have symptoms that can be mistaken for other illnesses.
- There is currently limited capacity to screen patients who are at greater risk of having acute HIV infection (e.g., STD clinic patients, those presenting to emergency rooms with viral syndrome, individuals getting tested for HIV).
- The cost and turn around time of individual viral load testing is a disincentive for testing for acute HIV infection.
- Many clinicians are unfamiliar with the signs and symptoms of acute HIV infection and the laboratory testing needed to detect such infections.

Overcoming these obstacles will require the efforts of many people, including clinicians, public health officials, AIDS community groups, AIDS organizations and governmental leaders. As a start, screening for acute and recent HIV infection must become a greater part of medical education. No student graduating from medical school in the United States should be able to plead ignorance when it comes to the diagnosis of acute HIV infection.

Strategies to test those at greatest risk of HIV infection need to be further developed (see Pilcher et al, in the next summary) *and* widely implemented. Screening at high-risk sites, such as STD centers, will certainly yield acutely infected individuals. To delay such testing is to waste an opportunity to prevent downstream infections. Interruption of transmission saves lives and breaks a cycle that has served to perpetuate the epidemic. The benefits are as obvious as the challenges.

A Novel -- and Essential -- Method for Spotting Acute HIV Infections

Detection of acute infections during HIV testing in North Carolina*. Christopher D. Pilcher, Susan A. Fiscus, Trang Q. Nguyen, Evelyn Foust, Leslie Wolf, Del Williams, Rhonda Ashby, Judy Owen O'Dowd, J. Todd McPherson, Brandt Stalzer, Lisa Hightow, William C. Miller, Joseph J. Eron Jr., Myron S. Cohen and Peter A. Leone. The New England Journal of Medicine; May 5, 2005;352(18):1873-83.

At present, the detection of acute HIV infection relies immensely on clinical suspicion and is therefore rarely recognized. Given how critical the detection of acute HIV infection is to halting the continued spread of HIV infection -- as described in detail in the previous summary -- strategies that can more reliably detect acute infection are needed.

In detecting HIV infection early, timing is everything. Standard antibody testing, such as ELISA and Western Blot, can be negative for up to six weeks after infection. In contrast, viral load tests, such as PCR and other amplification techniques, can detect the presence of virus within *days* of infection.

Another technique that has been used in some studies to identify recent HIV infection is the "detuned" assay, a modified ELISA that is intentionally made to be less sensitive relative to

the standard ELISA test.[7,8] Detection of antibodies by the standard ELISA but not the detuned ELISA suggests that infection occurred within the prior 170 days. However, a drawback of the detuned assay is that it does not detect acute HIV infection.

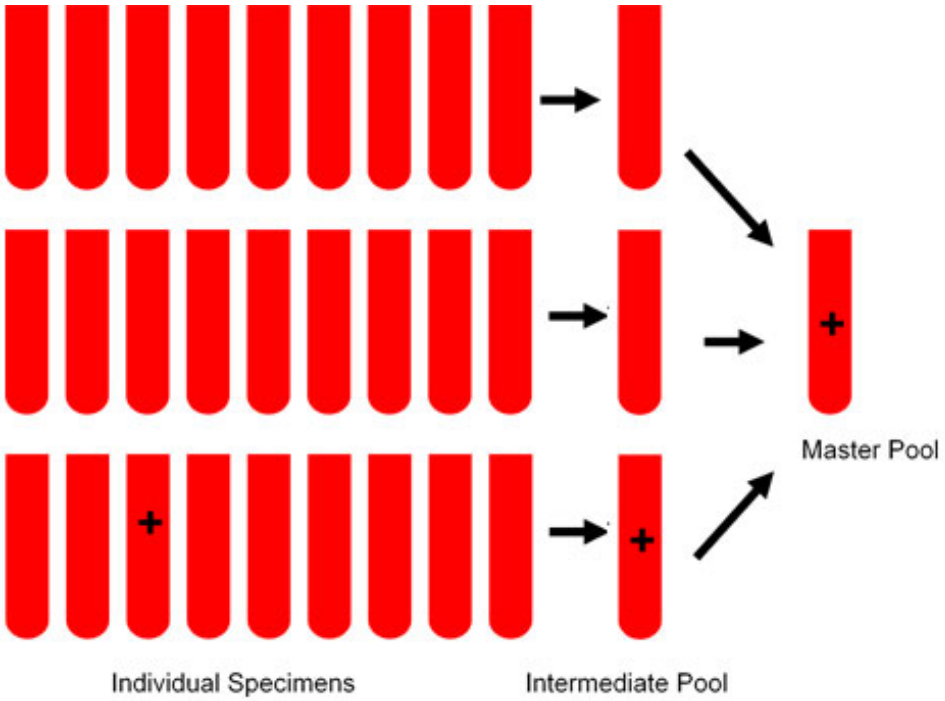
STUDY SNAPSHOT	
Design:	Retrospective analysis of state HIV testing algorithm designed to identify acute and recent HIV infection.
Population:	109,250 individuals presenting for voluntary HIV testing.
Main Results:	606 were found to be HIV-infected: 476 with chronic HIV, 107 with recent HIV and 23 with acute HIV.
Significance:	3.8% of those HIV infected were acutely infected and would have been missed by usual testing.

In a unique approach to the problem of identifying acutely infected individuals, the state of North Carolina has developed a screening program for acute infection among people visiting publicly funded testing sites for voluntary, confidential HIV testing.

To accomplish this, blood is tested for HIV antibodies using the standard ELISA and Western Blot assays. Specimens that are positive by both are then subjected to the detuned assay in order to determine whether individuals were recently infected. Those that test negative or indeterminate for the standard ELISA and Western Blot are pooled using a novel technique to reduce cost and false-positive rates (see figure below).[9] Pools of 10 consecutive specimens are mixed; from nine of these, aliquots are taken to create a larger pool representing specimens from 90 individuals.

This final master pool is tested with nucleic acid amplification for HIV-1 RNA. When the amplification test is negative, it is very likely that *none* of the 90 individuals are HIV infected. If the assay detects virus in the master pool, nucleic acid amplification testing is done on the pools of 10 and when one of these is positive, all 10 specimens in that pool are individually tested with the assay. Any individual positive specimens are retested with the ELISA and an HIV-RNA PCR assay. Positive results are cases of possible acute infection.

A central element of the program is the rapid notification of any acutely infected individual by public health specialists who assist with referrals to appropriate care and who initiate contact tracing.



Christopher Pilcher, from the University of North Carolina at Chapel Hill, and colleagues reported on the track record of this system. From November 2002 to October 2003, 110,890 persons sought HIV testing at one of the 110 publicly funded testing sites in North Carolina. Of these, 1,427 had insufficient data collected to be included in the analysis and 213 were known to be HIV infected prior to their testing and thus were excluded.

Of the remaining 109,250 individuals tested, 583 had positive ELISA and Western Blot results. Of these, 107 had recent infection by the detuned assay. Among the 108,667 individuals with a negative or indeterminate ELISA and Western Blot, 25 had HIV RNA detected by nucleic acid amplification testing, two of whom were determined to be false positives using repeat antibody and viral load testing. The remaining 23 individuals were documented to have acute HIV infections -- including a woman who was pregnant. (Following counseling and treatment, she delivered an uninfected infant.) Therefore, **606 new infections were detected, 3.795% of whom had acute HIV infection that would not have been detected if the screening program were not in place.**

Acute and recent infections (as determined by nucleic acid amplification and the detuned assay, respectively, both in combination with standard antibody testing) were found to be more prevalent among African Americans, men, persons over age 24 years, men who have sex with men and those with another STD. Importantly, only half of the 23 acute cases had symptoms consistent with acute retroviral syndrome.

All patients with acute infection were notified by a public health specialist; 17 were notified within 72 hours after their test result became known. All results were known within two weeks after the blood draw.

Forty-eight sexual partners of the acute cases received counseling, and 18 (38%) of them had HIV infection -- 13 knew they were HIV infected and five were newly detected. Eleven partners were considered likely to have transmitted the infection to the acutely infected partner and only three had disclosed their HIV status. Three possible transmitters had been named in surveillance records as a potential source of infection in at least three other cases, suggesting these individuals were core transmitters.

Eleven of the 15 acutely infected male patients named a male sex partner. Recent prison

release, sex work, multiple anonymous sex partners and heavy alcohol or drug abuse were associated with acute infection. Four patients were college students, which then led to a separate investigation that revealed an outbreak among young African-American male students who had sex with men.

The Bottom Line

The creative strategy employed in North Carolina will *not* detect all cases of acute infection and relies on an individual's presentation for HIV testing. However, 23 people (3.8% of all those who tested HIV positive) who under normal conditions would have been told they were HIV uninfected -- and possibly would have continued to practice unsafe behaviors at a time they were most likely to transmit their virus -- were identified and counseled instead.

Further, 70% of the people experiencing acute HIV infection were tested at STD clinics, indicating such sites are primed with people who have been recently infected with HIV. Other sites, such as emergency rooms and urgent care centers may also be expected to yield individuals with acute HIV, based on previous data.[10-12] The potential impact of this kind of system in countries that have a high prevalence of HIV infection is even greater and can be envisioned as an important element, along with increased behavioral interventions and antiretroviral access, of efforts to stem HIV's spread in these regions.

At a minimum, expansion of this testing algorithm beyond North Carolina is warranted. For states that have anonymous HIV testing, this screening strategy will require modification, as immediate notification of the individual is not possible and some individuals with acute infection may not return for their results. Yet, even in these states, additional cases will be detected under such a screening procedure and individuals informed of their acute infection. Surveillance data on acute infections will surely be of value to public health authorities in these states.

The advent of rapid HIV tests presents a challenge to the diagnosis of acute HIV infection, as these tests are not designed to detect those who were infected within the prior six weeks. The inability of rapid tests to detect acute HIV infection is a critical shortcoming that must be considered when choosing to use them.

If cost is an issue, it will come as a surprise that the cost of the North Carolina screening strategy is negligible: about $3.63 added to the cost of a routine test. Thus cost is certainly not an excuse to avoid implementation of this or similar techniques to detect the many cases of acute HIV infection that are missed every year across the country.

Reducing Latent HIV Reservoirs

***Depletion of latent HIV-1 infection in vivo: a proof-of-concept study*. By Ginger Lehrman, Ian B. Hogue, Sarah Palmer, Cheryl Jennings, Celsa A. Spina, Ann Wiegand, Alan L. Landay, Robert W. Coombs, Douglas D. Richman, John W. Mellors, John M. Coffin, Ronald J. Bosch, David M. Margolis. The Lancet. August 13, 2005;366 (9485):549-55.**

And

***Effect of treatment, during primary infection, on establishment and clearance of cellular reservoirs of HIV-1*. Matthew C. Strain, Susan J. Little, Eric S. Daar, Diane V. Havlir, Huldrych F. G¸nthard, Ruby Y. Lam, Otto A. Daly, Juin Nguyen, Caroline C. Ignacio, Celsa A. Spina, Douglas D. Richman, Joseph K. Wong. The Journal of Infectious**

Diseases; May 1, 2005;191(9):1410-8.

Based solely on the publicity it has generated, this paper by Ginger Lehrman and colleagues deserves mention. Their proof-of-concept study garnered attention with its conclusion that the eradication of HIV is possible. However, the study is notable for at least two reasons beyond its "promise of a cure" punch line. First is the novel application of a commonly used and inexpensive anticonvulsant to deplete HIV from resting CD4+ cells. Second is the novel quantification of resting pools of HIV-infected cells that the investigators performed using leucopheresis.

STUDY SNAPSHOT	
Design:	Single arm pilot study of valproic acid and T-20 to reduce latently infected CD4+ cell pool.
Population:	4 individuals with <50 copies/mL plasma HIV-RNA levels on HAART.
Main Results:	Significant reductions in latent reservoir in three of four patients.
Significance:	Demonstration of reduction in latent pool opens door for future efforts aimed at eradicating HIV from the body.

The goal of this study was to make a dent in the population of latently HIV-infected memory CD4+ cells. These resting cells harbor integrated viral genome and produce virus only when activated. Their long life permits the presence of a stable reservoir of virus, despite prolonged exposure to potent HIV therapy and suppressed viremia. It is the greatest obstacle to the eradication of HIV from the body -- i.e., what would be called a cure.

Lehrman and colleagues aimed to determine the effect of valproic acid (Depakote, Depakene, Depacon) on the clearance of HIV from resting CD4+ cells. This anticonvulsant also happens to be an inhibitor of histone deacetylase 1 (HDAC1), a protein that represses HIV gene expression and production of virion. Inhibition of HDAC1 had been previously observed to induce HIV expression from resting CD4+ cells in patients without detectable plasma HIV RNA while on highly active antiretroviral therapy (HAART).[13]

Lehrman's study enrolled four patients who are receiving HAART and had plasma HIV-RNA levels less than 50 copies/mL for at least two years. Each underwent leucopheresis to harvest infected resting CD4+ cells.

All four participants had their HAART intensified with enfuvirtide (T-20, Fuzeon) for four to six weeks in order to prevent the potential dissemination of HIV in the presence of valproic acid. Then valproic acid (500-750 mg) was administered twice a day for three months, with drug levels monitored to permit dose titration. Leucopheresis was repeated after 16-18 weeks to reassess the HIV-infected CD4+ cell population.

During the study, CD4+ cell count remained stable and plasma HIV-RNA PCR remained undetectable in all patients, except for a single blip to 75 copies/mL in one patient during an upper respiratory illness. A super-sensitive assay used to detect a single copy of HIV RNA per mL of plasma found that in three of the four patients, single-digit viral levels were detected at baseline and did not change during the study.

Following the administration of valproic acid and enfuvirtide, three of the four participants experienced a decline of 68% to 84% in their latently infected CD4+ cell pool. The other patient experienced a 29% reduction in infected resting cells, which is

within the range observed with HAART alone. Anemia was seen in one patient who was also on zidovudine (AZT, Retrovir); valproic acid increases the bioavailability of this antiretroviral and inhibits its metabolism.

The results of this study are provocative and have undoubtedly spawned a number of follow-up investigations, including studies that will attempt to isolate the contribution of valproic acid independent of intensification with enfuvirtide.

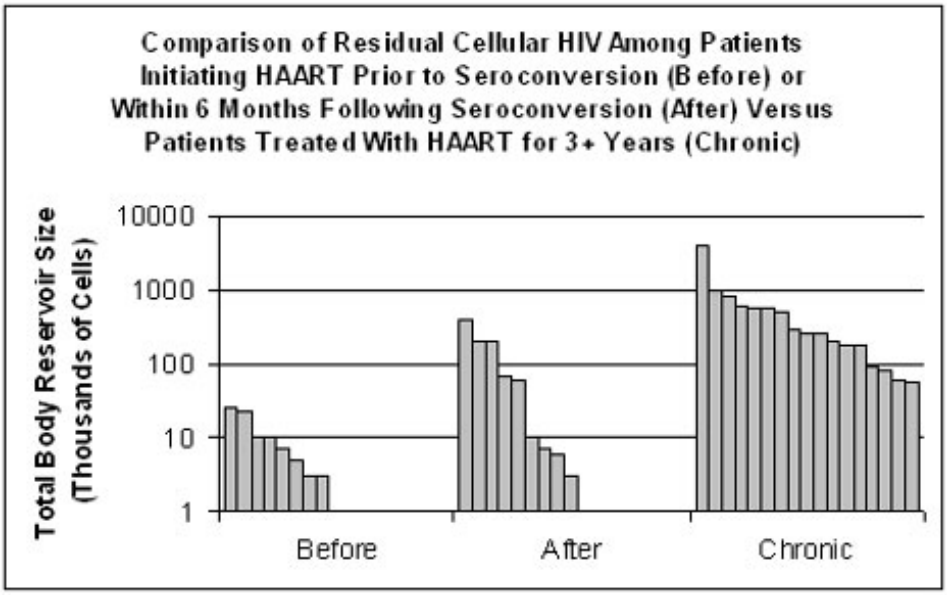
One obvious application of any approach to reducing the pool of latently infected CD4+ cells is to target patients in whom this pool may not be fully established -- those with early HIV infection (it keeps coming back to acute HIV!).

The papers by Lehrman and Pilcher gain some added significance when viewed alongside a recent paper published in the *Journal of Infectious Diseases* and written by Matthew Strain of University of California-San Diego and colleagues. They found that treatment with antiretroviral therapy soon after infection prevented the complete establishment of a reservoir of latently infected cells.

Strain et al studied 27 patients who were treated with HAART early in the course of their HIV infection. Thirteen of the patients had acute infection and had initiated HAART prior to full seroconversion. The other 14 started therapy after seroconversion, although it was determined using a detuned assay that they had recent infection (as opposed to acute infection).

Strain's major finding was that among the patients with acute infection who consented to large volume blood draws, *none* had virus that could be stimulated from their harvested CD4+ cells after more than a year of therapy.

Of those who had initiated HAART soon after seroconversion, six out of eight also had undetectable cell-associated virus. In contrast, in a control group of 17 patients who started HAART during *chronic* HIV infection and had long-standing, undetectable plasma HIV-RNA levels (mean six years), *all* had virus retrieved by the same activation protocol. Estimates of the size of the residual cell reservoirs in each subpopulation is shown in the figure below.



These data suggest that early treatment limits the size of the pool of latently infected CD4+

cells. A smaller pool of latently infected cells could arguably afford some benefits to patients (i.e., reduced storage of drug-resistant virus), but more significantly, it would be expected to be more amenable to elimination, since there is less virus to either coax from cells or destroy.

Strain's paper also makes a good case for early treatment of HIV infection, although data on early treatment have been mixed and additional studies are needed before such treatment can be established as a standard of care. Patients with acute or recent HIV infection are a precious group and should be referred to a clinical trial of early HIV therapy when possible.

The Bottom Line

Together, these two papers raise the ante on the need to identify acutely infected individuals, as well as the need to develop novel therapies directed at eliminating this reservoir. Strain suggests that early HIV infection may be a prime time to target the pool of latently infected cells, and Lehrman has introduced the possibility that this pool cannot only be reduced, but with augmentation of HAART, it may even be eliminated (i.e., cure HIV).

Expanded Screening for HIV Infection Saves Money and Reduces the Spread of HIV

Expanded screening for HIV in the United States -- an analysis of cost-effectiveness*. *A. David Paltiel, Milton C. Weinstein, April D. Kimmel, George R. Seage III, Elena Losina, Hong Zhang, Kenneth A. Freedberg and Rochelle P. Walensky. The New England Journal of Medicine; February 10, 2005;352(6):586-95.

And

Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy*. *By Gillian D. Sanders, Ahmed M. Bayoumi, Vandana Sundaram, S. Pinar Bilir, Christopher P. Neukermans, Chara E. Rydzak, Lena R. Douglass, Laura C. Lazzeroni, Mark Holodniy and Douglas K. Owens. The New England Journal of Medicine; February 10, 2005;352(6):570-85.

It is estimated that 800,000 to one million people in the United States are HIV infected. With a population of approximately 300 million, close to one in every 300 people in this country are infected. According to the U.S. Centers for Disease Control and Prevention (CDC), as many as 28% of those who are infected are unaware that they have HIV.[14]

STUDY SNAPSHOT	
Design:	Computer simulations of the effect of HIV testing at varying frequencies in populations with a prevalence of HIV infection that is 1% or higher.
Main Results:	Expanded screening for HIV infection is cost effective when performed where prevalence is 1% or higher. In general population costs are higher but may be offset by prevention of secondary infections.

Clearly, the importance of detecting HIV infection is not completely limited to people who have been recently infected. The identification of HIV-infected individuals with chronic infection allows for treatment initiation

Significance:	Expanded screening is controversial and in the absence of actual population studies, these different models arrive at similar conclusions supporting more widespread screening.

(including opportunistic infection prophylaxis), mental health care, substance abuse treatment and HIV prevention counseling. Ignorance of infection is a major reason why a substantial proportion of those newly diagnosed with HIV already have advanced HIV disease, with a CD4+ cell count less than 200.[15]

A pair of papers used different models to simulate the effectiveness of routine screening for HIV infection in settings with varying HIV prevalence. They arrived at similar conclusions regarding the cost effectiveness of expanded HIV testing.

According to a paper published in the *New England Journal of Medicine* and written by David Paltiel, of the Yale School of Medicine, and colleagues, adoption of widespread, onetime HIV screening would result in an increase in CD4+ cell count at the time of diagnosis from 154 to 210 cells/mm^3 -- with further increases seen when the model included repeat testing (e.g., every three years and every five years). In addition, expanded screening is believed to increase the life expectancy of those diagnosed with HIV infection by at least one year.

The price tag for this expanded HIV screening depends on the frequency of testing and the population. In a setting where one in 100 patients are HIV infected, one-time testing would cost $38,000 per quality-adjusted life-year saved. Screening every five and three years would save $71,000 and $85,000 per quality-adjusted life-year saved, respectively. $50,000 per quality-adjusted life-year saved is considered a bargain by health economists.[15]

In the general population, onetime screening would cost $113,000 per quality-adjusted life-year saved, an expense that is higher than many widely accepted screening tests, but which does not account for the benefits of (and savings associated with) prevention of secondary cases.

In a population assumed to have an HIV prevalence rate of 1%, Gillian Sanders, of Duke University, and colleagues, in a paper published in the *New England Journal of Medicine*, found similar effects from expanded screening on life expectancy at comparable expense -- and with similar predictions of reduced transmission of HIV.

The Bottom Line

Expanded screening for HIV infection makes sense in all but the lowest-risk populations. However, beyond the models, there are limited hard data to prove that the benefits of routine HIV testing outweigh the potential harms -- mostly the emotional effect of a false-positive result. The absence of such data has led the U.S. Preventive Services Task Force to make no recommendation (known as a grade C recommendation) regarding HIV screening for individuals not known to be at risk for HIV. This unfortunate decision is in contrast to their strong recommendation (grade A) that all pregnant women be tested for HIV.

The case for expanded HIV screening has been well articulated by Curt Beckwith and colleagues in an article published in the *Annals of Internal Medicine*.[16] In rebuttal to the task force recommendation, they wrote that:

- The incidence of HIV infection has been largely unchanged over the past decade,

and data suggest that those diagnosed with HIV infection often adopt prevention behaviors.[17-19]
- Heightened screening of pregnant women has led to dramatic decreases in vertical transmission.
- Clinician determination of HIV risk is faulty, and as many as one quarter of HIV-infected patients report *no* risk factors.

Perhaps, the biggest challenge to routine testing is *time* -- time to perform pre- and post-test counseling (including counseling of false positives), follow up on results and find those who do not return for their results. Such demands can strain clinics and pull staff from other responsibilities. But HIV screening systems can be devised so they are integrated into routine practice and still conducted in a way that is voluntary, protects confidentiality and provides appropriate referral to supportive services to those testing positive. All it takes is will.

Recognition of the problem is a critical first step. Public campaigns to encourage HIV testing can help facilitate acceptance of testing and may actually lead to patients asking to be tested (pharmaceutical industry representatives, are you listening?). In the absence of firm recommendations from authorities, it may take grassroots efforts to get more people to find out whether they are HIV infected. Meanwhile, under the status quo, another 45,000 or so people in the United States were infected in 2005. Many of these infections could surely have been stopped if we had expanded HIV testing and people who felt they were not at risk were tested while receiving routine medical care.

Tenofovir + Didanosine: The Downfall of a Lovely Combination

Early virologic failure in HIV-1 infected subjects on didanosine/tenofovir/efavirenz: 12-week results from a randomized trial. By Desmond Maitland, Graeme Moyle, James Hand, Sundhiya Mandalia, Marta Boffito, Mark Nelson, and Brian Gazzard. AIDS. July 22, 2005;19(11):1183-8.

And

High virological failure rate in HIV patients after switching to a regimen with two nucleoside reverse transcriptase inhibitors plus tenofovir. By Maria Jesus Perez-Elias, Santiago Moreno, Carolina Gutierrez, Dolores Lopez, Victor Abraira, Ana Moreno, Fernando Dronda, Jose Luis Casado, Antonio Antela, and Miguel Angel Rodriguez. AIDS. April 29, 2005;19(7):695-8.

And

Paradoxical CD4+ T-cell decline in HIV-infected patients with complete virus suppression taking tenofovir and didanosine. By Ana Barrios, Ana Rendon, Eugenia Negredo, Pablo Barreiro, Teresa Garcia-Benayas, Pablo Labarga, Jesús Santos, Pere Domingo, Matilde Sánchez-Conde, Ivana Maida, Luz Martún-Carbonero, Marina Nuñez, Francisco Blanco, Bonaventura Clotet, Maria Antonia Sambeat, Paloma Gil, Juan Gonzalez-Lahoz, David Cooper and Vincent Soriano. AIDS. April 8, 2005;19 (6):569-75.

It happened so quickly. One day we were lauding the benefits of twice-a-day antiretroviral regimens and the next we were learning how to write "daily" rather than "QD." At present, at least 11 antiretroviral agents can be taken once daily, not including nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) co-formulations. The temptation to combine these to craft potent combinations that are more convenient and more likely to be adhered to is

overwhelming.

STUDY SNAPSHOT	
Design:	Randomized controlled trial of TDF+ddI +EFV vs. 3TC+ddI+EFV.
Population:	77 treatment-naive patients.
Main Results:	Study stopped early due to reduced viral suppression and higher rates of virologic failure and resistance among the TDF+ddI-assigned patients.
Significance:	Reveals that TDF+ddI+EFV (and probably any NNRTI) is suboptimal and is not to be used. Other data point to paradoxical CD4+ decline with TDF+ddI despite dose reduction of ddI.

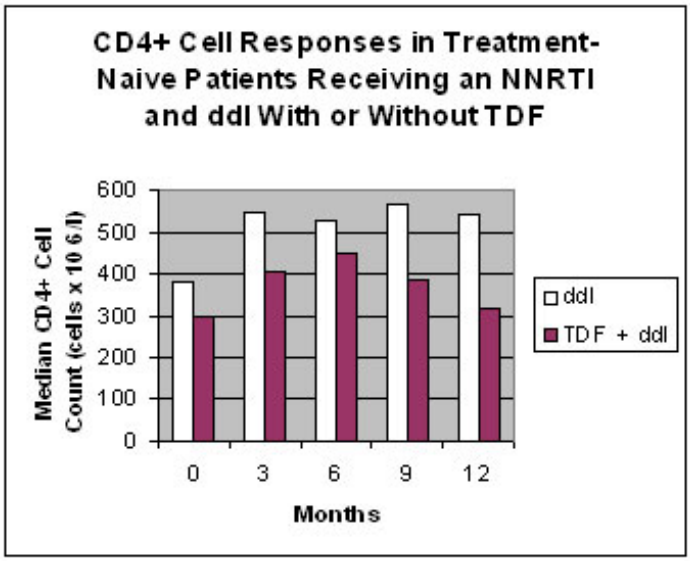
The combination of tenofovir (TDF, Viread) + didanosine (ddI, Videx) was particularly attractive, either as a compact initial regimen or along with a boosted protease inhibitor (PI) in patients failing a first-line regimen, such as zidovudine/ lamivudine (AZT/3TC, Combivir) + efavirenz (EFV, Sustiva, Stocrin). This past year, however, converging data have demonstrated that the pairing of these two adenosine analogs can be troublesome.

First, Desmond Maitland and colleagues reported that among 77 patients enrolled in a randomized clinical trial comparing tenofovir + didanosine + efavirenz with lamivudine (3TC, Epivir) + didanosine + efavirenz, an interim analysis showed there was significantly less viral suppression among those receiving tenofovir + didanosine (HIV RNA at week 12: 1.83 $\log_{10}$ copies/mL in lamivudine + didanosine arm versus 2.28 $\log_{10}$ copies/mL in tenofovir + didanosine arm, $P = .013$). **By week 12, more than 12% of the tenofovir + didanosine-assigned trial participants experienced virologic failure, compared to none of those in the lamivudine + didanosine arm ($P < .05$).** All those failing tenofovir + didanosine had a CD4+ cell count less than 200 x 10^6 cells/L and an HIVRNA level of more than 100,000 copies/mL at study entry, and had no evidence of baseline drug resistance on genotype testing. All had non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations detected subsequent to drug failure, with a smattering of NRTI resistance seen in most. These findings led to the early closure of this study to further recruitment.

A subsequent retrospective study by Maria PÈrez-ElÌas from the Hospital Ramon y Cajal, Madrid, and colleagues found that even among patients with an undetectable HIV-RNA level on first-line therapy who, for reasons of convenience or toxicity, were switched to tenofovir + didanosine plus a third NRTI (not an NNRTI or protease inhibitor [PI]), experienced a high rate of virologic failure compared to patients who switched to tenofovir plus two other non-didanosine NRTIs. **Only one of 21 patients treated with tenofovir + didanosine maintained viral suppression, while 16 of 34 patients on non-didanosine, tenofovir-containing regimens remained undetectable ($P < .001$).**

On the heels of these results came other reports that fairly conclusively demonstrate that **the combination of tenofovir + didanosine leads to a paradoxical decline in CD4+ cell count --** which is perhaps the next-worst thing for a regimen after being virologically inferior. A study by Ana Barrios (to whom I am grateful for introducing me to the word "posology," which means the pharmacological determination of appropriate doses of drugs and medicines), from the Instituto de Salud Carlos III in Madrid, and colleagues found that among 570 patients on their first (or first successful simplified) PI-sparing regimen with

undetectable viremia, those receiving tenofovir + didanosine (n = 298) had a significant decline in CD4+ cell count relative to all other combinations, including those that included either drug separately. A decline or relatively smaller gain in CD4+ cell count was observed in the tenofovir + didanosine-treated patients regardless of the third drug used, or whether they were on an initial or simplified first regimen (see figure below).



Interestingly, over 90% of the tenofovir + didanosine patients were initially treated without the recommended dose reduction in didanosine (i.e., that the dose of didanosine be reduced when combined with tenofovir to 250 mg daily if the patient's weight is 60 kg or more, and to 200 mg if less than 60 kg). Duration of higher-dose didanosine, along with low weight and higher CD4+ cell count at baseline, were associated with CD4+ cell count decline in a multivariable analysis. Importantly, the CD4+ cell count decline may follow an initial rise, take several months to develop and is accompanied by declines in CD4+ percentage. These results were supported by an analysis of the TORO (T-20 versus Optimized Regimen Only) studies of salvage therapy with enfuvirtide, which found little CD4+ cell accrual among those on tenofovir + didanosine relative to those on one or none of these agents.[20]

The Bottom Line

This year we learned that a match we thought had been made in heaven can, like all too many hopeful couplings, end in disaster. Tenofovir + didanosine plus any NNRTI should not be used. The reason for the poor antiviral showing of tenofovir + didanosine + NNRTI is unclear, but may be due to hard-to-measure intracellular interactions between tenofovir and didanosine -- both of which target the same nucleotide. This or other interactions may also account for the pair's effect on CD4+ cell counts. These reports are extremely useful to clinicians, who should become well-versed in their findings and also remain cautious of new, unstudied regimens *before* applying broadly in clinical practice.

Metabolic Complications and HAART: Some New Answers and Many More Questions

***Glucose metabolism, lipid, and body fat changes in antiretroviral-naive subjects randomized to nelfinavir or efavirenz plus dual nucleosides*. By Michael P. Dubé, Robert A. Parker, Pablo Tebas, Steven K. Grinspoon, Robert A. Zackin, Gregory K. Robbins,**

Ronenn Roubenoff, Robert W. Shafer, David A. Wininger, William A. Meyer III, Sally W. Snyder, and Kathleen Mulligan. AIDS. November 4, 2005;4;19(16):1807-18.

And

Fat distribution in men with HIV infection. By Peter Bacchetti, Barbara Gripshover, Carl Grunfeld, Steven Heymsfield, Heather McCreath, Dennis Osmond, Michael Saag, Rebecca Scherzer, Michael Shlipak, and Phyllis Tien. Journal of Acquired Immune Deficiency Syndromes; October 1, 2005;40(2):121-31.

For all that has been written and presented regarding metabolic complications of HIV and HIV therapies, it is remarkable that, until recently, there had been *no* large-scale, longitudinal studies on body shape or other metabolic disorders that employ rigorous objective evaluations among patients before and after initiating antiretroviral therapy. Such studies provide the best perspective from which to assess the relationship between these complications and host, viral, immunologic and therapeutic factors.

STUDY SNAPSHOT	
Design:	Prospective substudy of a randomized, controlled trial of NFV, EFV or both combined with either d4T+ddI or AZT+3TC.
Population:	334 treatment-naive patients.
Main Results:	d4T+ddI was associated with limb-fat wasting, increased trunk fat and increased lipids; NFV and EFV both increased trunk fat and raised lipids, although EFV was associated with higher HDL cholesterol gains.
Significance:	First large, prospective study to demonstrate relationship between treatment and metabolic complication.

A major question is: What is the contribution of specific antiretrovirals to alterations in fat distribution, dyslipidemia and glucose metabolism disorders? The steady trickle of observational and cross-sectional data that have been published since the mid-1990s, coupled with clinician and patient anecdotes, have led to the development of belief systems that assume links where none have been demonstrated.

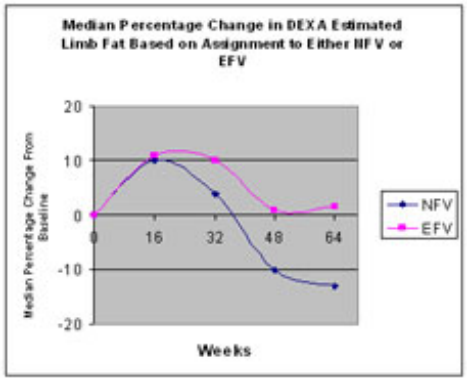
AIDS Clinical Trials Group (ACTG) Study 384, a large, randomized comparison of six regimens for initial HIV treatment, provided a unique opportunity to evaluate the relationship between disparate antiretrovirals and metabolic complications. Peter Bacchetti and colleagues lobbied hard and successfully to create a sub-study to thoroughly evaluate metabolic and body-shape parameters longitudinally in a subset of the main study participants.[21,22] Evaluations included whole body dual energy X-ray absorptiometry (DEXA) scans and fasting lipid, glucose and insulin levels. Patients were randomized to nelfinavir (NFV, Viracept), efavirenz or both with either zidovudine (AZT, Retrovir) + lamivudine or stavudine (d4T, Zerit) + didanosine. For the purposes of the substudy, comparisons were made between the PI and NNRTI and between the NRTI pairs (see table below for design and sample size).

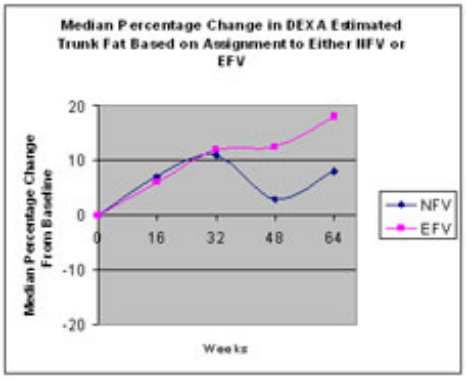
Study Treatment Assignments and Groups Compared for the Primary Outcomes

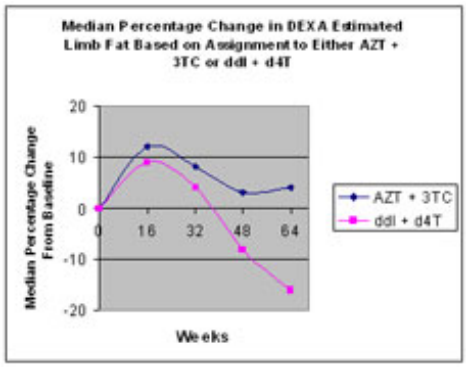
		PI vs. NNRTI Comparison			
		NFV	**EFV**	**NFV + EFV**	**Total**
NRTI Comparison	AZT + 3TC	44	50	60	154
	ddl + d4T	55	60	65	180
	Total	99	110		

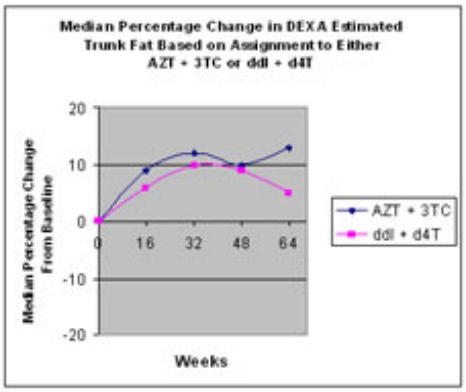
The primary analyses were intent-to-treat; however, there was considerable switching from the original treatment assignment due to virologic failure and adverse events. Secondary analyses did consider on-treatment analyses.

The major finding was the association of stavudine + didanosine with reduced limb fat compared to zidovudine + lamivudine. In the case of nelfinavir, in the intent-to-treat analysis, nelfinavir assignment was also associated with limb fat loss compared to a modest net gain in peripheral fat in the efavirenz-assigned group. However, in the on-treatment analysis this difference was no longer statistically significant; during the study, 43% of those on nelfinavir switched to efavirenz, and 18% made the reverse switch.









The most interesting aspect of the body-shape results was the general increase in limb and trunk fat seen during the 32 weeks of treatment in *all* groups. This may represent a "return to health" or "re-feeding phenomenon" early in antiretroviral therapy. However, with exposure to stavudine + didanosine, this period is followed by a profound and progressive decrease in limb fat, leading to a net loss relative to baseline.

Smaller reductions in limb fat following the initial increase were also seen in the zidovudine + lamivudine assigned patients. Trunk fat generally rose in all groups whether they received efavirenz, nelfinavir, stavudine + didanosine or zidovudine + lamivudine and tended to remain elevated compared to baseline -- rehabilitating, at least for nelfinavir, a reputation for causing paunchiness.

As far as lipids go, all groups experienced increases in total, non-high-density lipoprotein (HDL) and HDL cholesterol and triglycerides. As expected, the only significant differences between the groups were a greater HDL cholesterol rise in the patients receiving efavirenz compared to the nelfinavir group, and significant increases in all the lipid parameters in the stavudine + didanosine groups compared to those treated with zidovudine + lamivudine.

There was a modest increase in estimated insulin resistance in the study cohort, without any observed differences between treatment assignments.

The Bottom Line

This study, which is the largest and most rigorous longitudinal study of metabolic complications performed to date, is instructive *despite* its limitations (e.g., frequent changes in study-assigned regimens and the study of a PI that is no longer widely used). Most significantly, the PI studied was *not* associated with undue increases in lipids or insulin resistance compared to efavirenz, nor was it the exclusive cause of an increase in trunk fat. If anything, nelfinavir was suspected of contributing to peripheral fat *loss*, although this was difficult to demonstrate conclusively given the on-treatment results. That nelfinavir was about as metabolically offensive as efavirenz suggests we need to adjust our assumptions regarding this PI (and perhaps others), or better appreciate the role of efavirenz in changes in lipids and body shape.

The longitudinal results of this ACTG study are interesting to compare to another major study of body shape change in persons with HIV infection published in 2005, the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) Study. This large, cross-sectional, multicenter study compared the body shape of a representative sample of HIV-infected men and women attending outpatient HIV clinics to a control group of individuals not known to be HIV infected and who were enrolled in a study of cardiovascular risk assessment. Peter Bacchetti and colleagues report the findings in the *Journal of Acquired Immune Deficiency Syndromes* regarding the males enrolled in this study (results from a study of the female participants are expected shortly).

Self-reported body shape, physical examination and whole body magnetic resonance imaging (MRI) were performed on the 425 HIV-infected men and the 152 male controls. **Only peripheral lipoatrophy distinguished the two groups.** Visceral (central) fat accumulation was *not* more common in the HIV-infected men -- in fact, it was less frequent. Further, among the HIV-infected men, those with peripheral lipoatrophy had less visceral fat than HIV-infected men *without* peripheral lipoatrophy -- debunking the concept of a mixed peripheral lipoatrophy-central lipohypertrophy picture. Stavudine was associated with less limb fat, as was indinavir.

By contrast, an analysis of the ACTG study presented at the 12th Conference on Retroviruses and Opportunistic Infections emphasized that isolated lipoatrophy was *not* the dominant body shape change experienced in the cohort, and demonstrated that a quarter had a mixed picture of limb fat loss and central fat gain as measured by DEXA scan.[23]

Clearly, the differences between the findings of the ACTG and FRAM studies have *everything* to do with who was studied, when they were studied and who they were compared to. The ACTG study was able to evaluate changes in body shape over a period of

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64 weeks following the initiation of therapy. Comparisons were made between patients exposed to differing antiretroviral combinations, and relative differences from baseline to end-of-study follow-up could be assessed. However, it is difficult to determine whether the changes in body shape that were observed represent an abnormality versus a return to a habitus associated with improved health. In contrast, in FRAM, the one-time look at body shape was unable to yield longitudinal effects of therapy, but it was able to permit a comparison to uninfected controls.

Neither study is the final word. Both point to a complex picture that defies simplified generalizations, and both leave us hanging. Is there visceral fat accumulation? Most HIV clinicians endowed with sight would say so. Will use of zidovudine lead over time to a net loss of limb fat in the ACTG study, and will the FRAM folks develop more of a paunch? Only time will tell as further data from each study is expected.

Meanwhile, the clinician looking for the answer of how to prevent lipoatrophy should know well enough by now that stavudine is bad news and that, based on other studies, zidovudine can also cause some peripheral fat wasting.[24-26] For fat accumulation (if you are a believer), there is less to hang a hat on, but blaming PIs no longer works.

In addition to data from the planned followup to the ACTG study and FRAM, further insight will come from the 2005-6 version of ACTG 384: ACTG 5202, a large clinical trial comparing ritonavir-boosted atazanavir versus efavirenz when either is combined with tenofovir/emtricitabine (FTC, Emtriva) or abacavir/lamivudine. Additionally, important information will surely arrive from the metabolic substudy of ACTG 5095 -- a study of protease inhibitor-sparing regimens. All will be more metabolic fodder for future year-end reviews.

A Supersized Epidemic: The Twin Problems of Obesity and HIV

A tale of 2 epidemics: The intersection between obesity and HIV infection in Philadelphia. Valerianna Amorosa, Marie Synnestvedt, Robert Gross, Harvey Friedman, Rob Roy MacGregor, Debie Gudonis, Ian Frank, and Pablo Tebas. Journal of Acquired Immune Deficiency Syndromes. August 15, 2005;39(5):557-61.

In the 1980s it was wasting syndrome; during the 1990s, lipoatrophy. But the body shape disorder for people currently living with HIV infection in the United States is obesity, according to an interesting study by Valerianna Amorosa and colleagues at the University of Pennsylvania.

STUDY SNAPSHOT	
Design:	Retrospective study of HIV-infected patients. Data from urban survey of obesity used for comparison.
Population:	1,689 HIV-infected outpatients.
Main Results:	Being overweight or obese was common among HIV-infected patients, and both were more common than wasting. Women, especially those who are African American, had the highest rates of obesity.

In the United States, the home of the brave and land of the supersized Happy Meal, more than 20% of adults are estimated to be obese (Body Mass Index [BMI] $\geq$ 30 kg/m^2) and about half are considered to be overweight (BMI $\geq$ 25 kg/m^2).[27-30] Besides its obvious effects

on appearance and self-esteem, obesity has serious health implications.

Significance:	Identifies the alarming problem of obesity in HIV-infected individuals, given its links to cardiovascular disease and other disorders.

Obesity is a feature of metabolic syndrome and a risk factor for cardiovascular disease, diabetes mellitus, hypertension and certain malignancies, including breast, colon, prostate, endometrial, kidney and gallbladder cancers.[31]

As more people living with HIV infection benefit from HAART and are rendered essentially asymptomatic, they too become vulnerable to excessive caloric intake. To determine the prevalence of obesity among HIV-infected patients, the researchers examined the BMI data of almost 1,700 HIV-infected patients in Philadelphia, Pa. Most of the HIV-infected patients (78%) were men, 60% were African American, 18% were injection drug users and all but 9% were antiretroviral experienced.

Of the men, 55% were African American, as were 78% of the women. A CD4+ cell count of less than 200 cells/mm^3 was recorded in 22% of the cohort and almost half had a viral load below 400 copies/mL. The mean BMI among men was 24.9 kg/m^2; for women, it was 27.5 kg/m^2. The prevalence of obesity and being overweight by subgroup is detailed in the table below.

Prevalance of Obesity and Overweight Among HIV-Infected Patients		
	Obese	**Overweight**
Men	10.7%	31.6%
Women	28.3%	29.9%
African-American Men	13.4%	29.7%
African-American Women	30%	31.4%
Non-African-American Men	7.5%	33.9%
Non-African-American Women	22.5%	25%

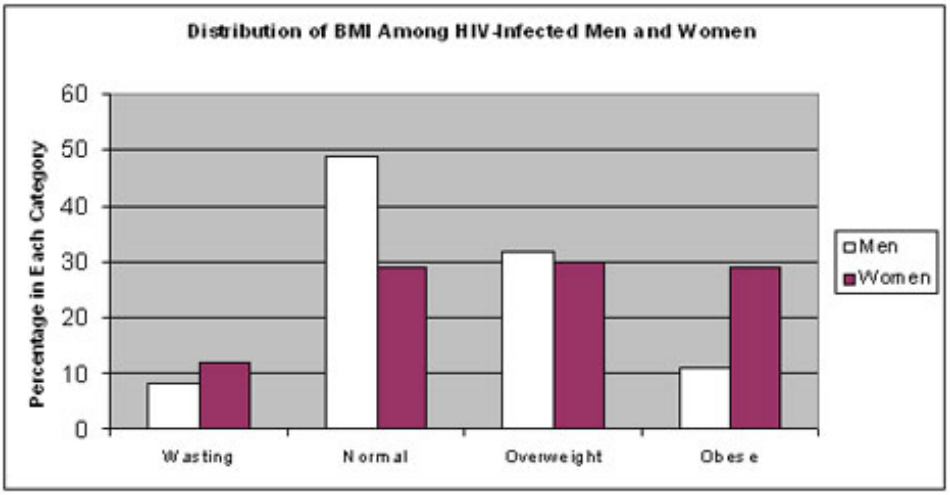
In a multivariable analysis, among women, being African American and having a CD4+ cell count of 200 cells/mm^3 or greater was associated with being overweight or obese. For men, only a CD4+ cell count of 200 cells/mm^3 or greater was associated with being overweight or obese, while cigarette smoking was found to be protective (a finding not observed among the women). Neither HIV therapy in general nor the use of PI-based therapy was associated with being overweight or obese.

To gain a sense of the magnitude of the problem of obesity in this cohort, the authors compared their results with previously collected obesity prevalence data on residents of Philadelphia. What is striking is the incredibly high prevalence of obesity in this city.

Almost 70% of African-American men in the city that brought us the cheese steak (calories per serving >1,000!) are either overweight or obese, as are more than 60% of non-African-American men, more than 70% of African-American women and about 45% of non-African-American women.

Against this (big) backdrop, HIV-infected patients indeed had a lower prevalence of

obesity, although among non-African-American women, the rates were almost equal. However, being overweight or obese was more common than fat wasting among HIV-infected individuals.



The Bottom Line

This is the first of what will certainly be additional studies on the problem of obesity among the HIV-infected. The obesity epidemic is fueled by the consumption of often too-large helpings of energy-rich, nutrient-poor foods packed with sugar and saturated fats (e.g., fast food), coupled with an increasingly sedentary lifestyle. People with HIV infection, now largely free from the catabolic effects of advanced HIV disease, are not immune to the effects of the ready availability of cheap fast food and other societal factors that have resulted in the fattening of America.

This study from Philadelphia demonstrates an extremely high prevalence of obesity in that city, which is reflected among its HIV-infected residents. While this cohort was urban and largely African American, so too is the HIV epidemic. Therefore, it is likely that similar results will be found in other areas that share this epidemiology of HIV infection.

Although both generalized and fat wasting have been a cause of significant concern among HIV-infected patients and clinicians, wasting syndrome was detected in only 9% of the HIV-infected cohort participants; by contrast, 14% were obese and 31% were overweight.

Clearly, we need to rethink what metabolic issues are likely to be the most important to our patients in the coming years. The association between obesity and cardiovascular disease strongly indicates a need for the development of interventions to reduce excessive weight gain in the setting of HIV infection. At present there is no evidence to suggest that weight reduction interventions for HIV-infected people should differ from interventions found to be effective in other populations, but this needs to be better evaluated. Decreased energy intake, particularly of simple sugars and fat; increased exercise; and avoidance of fad diets that do not lead to sustained weight loss, should be recommended. Rather than be considered a relatively more desirable problem for individuals living with HIV infection than the wasting syndrome of yesteryear, obesity must be recognized for the threat that it is and treated seriously.

Low-Level Viremia May Slowly Breed Resistance, but Watch Out for NNRTIs

HIV-1 drug resistance evolution among patients on potent combination antiretroviral therapy with detectable viremia. By Sonia Napravnik, David Edwards, Paul Stewart, Brant Stalzer, Elizabeth Matteson, and Joseph J. Eron, Jr. Journal of Acquired Immune Deficiency Syndromes. September 1, 2005;40(1):34-40.

In the Olympic Games, not everyone gets a gold medal. So it is in the clinic, where silvers and bronzes go to patients who do not quite achieve an undetectable level of HIV viremia despite multiple-$\log_{10}$ declines from their original viral load level.

STUDY SNAPSHOT	
Design:	Retrospective database analysis.
Population:	98 HIV-infected patients with persistent viremia on stable HAART and two genotype resistance tests at least 30 days apart.
Main Results:	Viral load increased modestly during nine-month interval between resistance tests, but on average, patients developed only one new primary resistance mutation. Being on an NNRTI-based regimen, fewer baseline mutations and the slope of viral load change predicted new mutations.
Significance:	Allows stratification of risk for new mutations among those with persistent viremia on HAART. Continued therapy in those on NNRTIs is particularly risky.

To the purists, detectable equals failure. According to this hard-line position, continued detectable viremia means replication in the face of drugs, which could result in crippling resistance and, ultimately, the failure of a regimen.

Pragmatists, on the other hand, recognize this risk, but they also understand the problems that attend the chasing of the virus through the rabbit hole to the lower limits of assay detection. New drugs risk new side effects and also drug resistance. Further, it is still unclear what the downsides to continued therapy are in cases where the virus is present at a low level, but the patient's CD4+ cell count has steadily increased.

Lastly, when told their viral load result is suboptimal, patients may feel like *they* failed when it is *the drugs* that are failing to achieve the goal -- a goal that merely reflects whatever is the current laboratory threshold for detecting virus. Even the language we use seems to make that assumption: We typically say, "The patient has failed the regimen."

Clinicians confronted with a patient who has persistent low-level viremia can either "hold em or fold em" -- that is, maintain the patient's current regimen or trade it for a new set of drugs. (Intensification is also an option, but one I have rarely found to be successful.) This decision would be made easier if there were some way to predict which patients were likely to do well on their current regimen and which were more likely to develop resistance.

Such data has been provided by Sonia Napravnik, from the University of North Carolina, and colleagues, using an HIV clinic database of more than 1,600 patients to identify those with persistent viremia and examine determinants of success and failure.

The researchers found 98 patients who had two genotype test results at least 30 days apart and who had not changed their antiretroviral therapy within 30 days prior to the first genotype or between genotypes. Of the 98 patients, almost a third were women (29%), two thirds were African American (64%) and one quarter (26%) were men who have sex with

men.

These patients had a median of three prior regimens, which consisted of a median of six antiretroviral agents. Only 15% of the patients were taking their initial regimen; more than half (55%) were on their fourth regimen or greater. At some point in their treatment, almost all had received an NRTI, 88% a PI and 63% an NNRTI.

At the time of their first genotype, the median time patients had been on their current therapy was nine months. Over half of the patients (55%) were on a PI-based therapy, 14% were on an NNRTI-based therapy, 14% were on both a PI and an NNRTI, and 16% were on NRTIs alone.

The median time between the patients' first and second genotype was 9.3 months. The changes in CD4+ cell count, HIV-RNA level and the proportion of patients who had existing and new resistance mutations during the time spanning the first and second genotype are found in the table below.

Immunologic, Virologic and Antiretroviral Drug Resistance Characteristics at Baseline and Follow-Up			
Characteristic	**Baseline**	**Follow-Up**	***P* Value**
Median (IQR) CD4+ cell count (cells/µL)	246 (113-472)	242 (98-410)	.59
Median (IQR) HIV-RNA level (log10 copies/mL)	3.9 (3.1-4.6)	4.3 (3.5-4.9)	.02
Number (%) with ≥1 mutation			
To any antiretroviral (n = 98)	86 (87.8)	91 (92.9)	.23
To NRTIs (n = 96)*	66 (68.8)	74 (77.1)	.19
To PIs (major and minor mutations) (n = 68)*	54 (79.4)	57 (83.8)	.51
To PIs (major mutations only) (n = 68)*	25 (36.8)	32 (47.1)	.22
To NNRTIs (n = 28)*	16 (57.1)	24 (85.7)	<.001
* Denominator includes only patients receiving specific antiretroviral drug class. IQR = Interquartile Range.			

No change was seen in patients' median CD4+ cell count between the first and second genotype tests; however, viral load did increase significantly, albeit modestly. At the time of the first genotype, 88% of the patients had at least one mutation recognized that reduced susceptibility to antiretrovirals (median number of mutations = 3).

During the period of continued viremia, a significant change was not seen in the proportion of patients with one or more mutations. However, when viewed from the vantage point of the patients' *baseline* antiretroviral regimen, a significant increase

was seen in the proportion of patients receiving NNRTIs who developed NNRTI mutations. In contrast, *no* significant increase in the cultivation of PI or NRTI mutations was seen among those who were taking either of these therapies.

Importantly, 60% of the patients acquired a new detectable resistance mutation. These resistance cases were fairly predictable, however, being driven by the development of mutations to drugs that have a relatively low genetic barrier to resistance. For instance, M184V developed in patients who were receiving lamivudine and did not have this mutation at baseline, while NNRTI mutations were acquired among patients who were on NNRTI therapy.

The *overall* incidence rate of new mutations was 1.61 mutations per person-year at risk (95%, CI 1.36, 1.90). When minor PI mutations were excluded, the overall incidence rate dropped to 1.08 per person-year at risk (95%, CI 0.87, 1.32). Therefore, on average, one new mutation developed during nine months of continued low-level viremia -- a number that is much lower than many would have guessed, given the presence of ongoing viremia.

In a multivariable analysis, there were three predictors of new mutation acquisition:

1. the number of baseline mutations,
2. the mean HIVRNA levels and
3. the slope of the change in HIV RNA during the intra-genotype period.

Patients who had little or no resistance mutations at baseline were found to be at greatest risk for developing new mutations. (This makes sense for the simple reason that those with a greater number of mutations at baseline had fewer new potential mutations to acquire.) Patients with a decreasing or stable viral load had a lower risk of new mutations compared to those with increasing HIV-RNA levels.

Interestingly, patients with a moderate viral load level (3-4 $\log_{10}$ copies/mL) were *more* likely to have new mutations detected than those who had a low (below 3 $\log_{10}$ copies/mL) or high (more than 4 $\log_{10}$ copies/mL) viral load.

How can we make sense of this? A moderate viral load represents a partial, though suboptimal, antiretroviral effect, whereas a *low* viral load signifies greater treatment efficacy and perhaps better adherence. A high viral load is evidence of nonadherence and minimal drug exposure, and thus minimal selective pressure for resistance (i.e., *no* drug = *no* resistance).

Using genotypic rules-based drug susceptibility interpretation, there were no significant changes in the number of PIs and NRTIs predicted by the assay algorithms to retain activity from baseline to second genotype. Again, among the patients who were receiving NNRTIs, there were fewer agents predicted to be active in this class during the follow-up genotype.

The Bottom Line

This investigation provides an excellent assessment of the risks of continuing a patient's antiretroviral therapy during low-level viremia (i.e., less than 1,000 copies/mL) -- an all-too-common situation. Many providers have zero tolerance for detectable viremia and hold that *any* persistently detectable viral load is cause for treatment change. For those of us who are not as "trigger happy" when it comes to low levels of detectable HIV RNA in our patients, the results of this study are somewhat reassuring. They suggest that there is a relatively slow rate of resistance evolution in patients with low-level viremia who maintain their current HIV therapy. Even though 60% of the patients in this study developed new

mutations, the average number of such mutations was only one, and drug susceptibility to NRTIs and PIs remained largely unchanged.

Of note, this study may *overestimate* resistance among low-level viremic patients, since there are many patients with low-level viremia who have insufficient quantities of circulating virus for genotypic testing. These patients are not considered in such studies, but given the results reported here, they may be at very low risk for acquisition of new resistance mutations.

The authors valuably identify patients for whom continuing therapy is clearly a bad idea. In clarifying the relative risks of virologic failure in this cohort, they allow us to make wiser choices regarding whether to maintain or switch therapy in such patients. They note that patients who have minimal baseline mutations and a viral load of more than 1,000 copies/mL were found to be at an *increased* risk for developing resistance during therapy continuation.

Further, maintaining therapy in the face of continued viremia among patients who are taking NNRTIs was found to be disastrous and should be discouraged, given the high rate of crippling resistance seen in these patients. Not all persistent low-level viremic patients face the same risk of virologic rebound with maintained therapy, and this study makes clear that we can stratify risk based on certain identified factors. These are important data for every clinician who is prescribing HIV therapy.

Risk of Tenofovir Nephrotoxicity May Be Real, Though Murky

Changes in renal function associated with tenofovir disoproxil treatment, compared with nucleoside reverse transcriptase inhibitor treatment. By Joel E. Gallant, Michelle A. Parish, Jeanne C. Keruly, and Richard D. Moore. Clinical Infectious Diseases. April 15, 2005;40(8):1194-8.

Tenofovir is a popular nucleotide analog considered in the U.S. Department of Health and Human Services' antiretroviral treatment guidelines as one of the preferred agents for initial therapy of HIV infection.

Tenofovir also has a potential for nephrotoxicity, which is evidenced by cases of renal impairment when administered at higher-than-recommended doses and when taken by patients receiving other nephrotoxic agents. Although tenofovir has not been linked to renal dysfunction in clinical trials, these studies were largely restricted to patients with good

STUDY SNAPSHOT	
Design:	Retrospective database analysis. Baseline and maximal serum creatinine compared between those on TDF or alternative NRTI.
Population:	658 HIV-infected patients treated with TDF or an NRTI.
Main Results:	TDF not associated with higher median serum creatinine or lower median CrCl. Those on TDF had a statistically significant small increase in creatinine and a decline in CrCl.

baseline renal function.

Significance:	Best data we have on TDF's effects on renal function in a clinic-based population. Changes in renal function were statistically significant but were apparently deemed trivial by clinicians.

Therefore, despite clinical experience showing that tenofovir is a rare cause of nephrotoxicity when dosed according to the manufacturer's prescribing information, there has been concern among some providers regarding the drug's long-term renal effects.

In a study that garnered much attention when first reported, Joel Gallant and colleagues from the Johns Hopkins School of Medicine performed a retrospective database analysis to longitudinally compare renal function among patients who were receiving tenofovir to those taking an alternative drug in the NRTI class.

The researchers identified 344 patients who were prescribed tenofovir and 314 others who were administered a non-tenofovir, NRTI-containing regimen. To assess renal function, the investigators looked at absolute levels of, and the change in, serum creatinine and creatinine clearance (CrCl), calculated using the Crockcroft-Gault formula. For each creatinine value, the averages of two determinations around the time therapy was started and at the point when the serum creatinine peaked after therapy initiation were used in the analysis.

At the start of the analysis, the tenofovir and alternative NRTI groups differed significantly ($P < .05$) in the proportion of patients who were on initial therapy (13.5% in the tenofovir group and 38.5% in the other group) and receiving lopinavir/ritonavir (LPV/r, Kaletra) (29.9% in the tenofovir group and 14.0% in the other group). It is unclear how many patients had a CrCl of less than 50 mL/min -- a trigger for dose reduction of tenofovir -- but the authors state only two such patients on tenofovir had their dose modified.

As is shown in the table below, during more than 300 days of therapy, **there were no significant differences between the two groups in median absolute serum creatinine level at baseline or in the median maximum level detected during clinical follow-up.**

Likewise, when examining median CrCl, there were *no* significant differences at the start of treatment or at the time of maximal serum creatinine.There was a significantly greater median increase in serum creatinine among those prescribed tenofovir (+0.15 versus +0.10, *P* = .01 -- see the table below for confidence intervals). Similarly, both the median change in CrCl (-13.3 versus -7.5, *P* = .005) and the median percentage change in CrCl (-10% versus -6%, *P* = .007) were significantly greater in the tenofovir group.

Comparison of Change in Renal Function Between Patients Who Received Tenofovir vs. Alternative NRTIs			
Variable median value (1st, 3rd quartiles)	**NRTI Group n = 314**	**TDF Group n = 344**	***P***
Serum creatinine level at start of treatment, mg/dL	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	.56
CrCl at start of treatment, mL/min	118 (92, 177)	117 (95, 148)	.69
Treatment period, days	336 (175, 365)	303 (169, 365)	.19

Maximum serum creatinine level, mg/dL	0.9 (0.8, 1.1)	1.0 (0.8, 1.2)	.17
Absolute change in serum creatinine level, mg/dL	+0.10 (0.0, +0.25)	+0.15 (+0.05, +0.30)	.01
Calculated minimum CrCl, mL/min	102 (79, 129)	98 (71, 125)	.43
Absolute change in CrCl, mL/min	-7.5 (-20.5, +6.5)	-13.3 (-24.0, 0)	.005
Percent change in CrCl, %	-6 (-17, +6)	-10 (-22, 0)	.007
Patients with decline in CrCl, no. (%)			
>50% decline	6 (1.9)	15 (4.4)	.14[a]
25%-50% decline	34 (10.8)	46 (13.4)	
1%-25% decline	141 (44.9)	158 (45.9)	
≤0% decline[b]	133 (42.3)	125 (36.3)	

CrCl, creatinine clearance.

a. P for trend.

b. CrCl same or improved.

In a multivariable analysis, tenofovir use and a CD4+ cell count of less than 50 cells/mm^3 were associated with a CrCl decline. The exclusion of patients on tenofovir who should have had, but did not have, a dose adjustment for a CrCl < 50 mL/min did *not* alter this result. There were trends indicating an independent effect from diabetes mellitus and a lower baseline CrCl, although these did not reach statistical significance.

The Bottom Line

This important retrospective study suggests that patients with greater treatment exposure who receive tenofovir do experience small changes in CrCl relative to patients with less treatment experience who are receiving other NRTIs. The role of treatment history in renal function is unclear, but a greater number of prior regimens serves as a marker for antiretroviral therapy duration and possibly length of time living with HIV infection -- both of which could influence CrCl.

While tenofovir did not lead to a significantly higher maximal serum creatinine during therapy or even to a significantly lower CrCl at the time the maximal serum creatinine was recorded, *changes* in both parameters were greater in the tenofovir-treated patients. This finding raises the very real possibility that these changes were a result of tenofovir exposure.

Many providers, recalling the insidious toxicities that emerged with stavudine, are justifiably sensitive to the potential adverse effects of "darling drugs" and have a healthy skepticism of efforts to downplay the negative baggage that comes with all medications.

But tenofovir is clearly not stavudine. This study by Gallant and colleagues, coupled with other reports of renal impairment during tenofovir therapy, point to a potential problem that requires continued attention, but also helpfully demonstrate that the changes seen were subtle. The median increase in serum creatinine over about a year was 0.15 mg/dL, while CrCl fell by 10% -- changes that would be unlikely to motivate clinicians to modify a successful and otherwise well-tolerated regimen. Further, no patient in this study discontinued therapy secondary to renal issues, and in plotting CrCl over time, the decline in CrCl was hardly steep.

The NRTI wars conducted by the marketing arms of the pharmaceutical industry have led to some intransigence among some clinicians regarding their NRTI allegiances. However, the noise these battles have generated should not deafen us to accepting the existence of problems with any of these drugs, or to the magnitude of these problems. Certainly, further study of tenofovir in a variety of patient populations is warranted to assess the clinical significance of any changes in renal function observed during treatment, and to identify patients who may be at greater risk for such effects.

Meanwhile, as a clinician who, it should be disclosed, serves as a paid speaker for the manufacturer of tenofovir and who was also a major in the drum beat against stavudine, I continue to prescribe this useful antiretroviral. I also make ample use of calculators to estimate CrCl to determine the proper dosage of tenofovir and believe that CrCl should be estimated for almost all patients regardless of serum creatinine, especially as the latter can be misleading, particularly in women and older patients.

Efavirenz Has No Significant, Lasting Impact on Neuropsychological Performance

Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. By David B. Clifford, Scott Evans, Yijun Yang, Edward P. Acosta, Karl Goodkin, Karen Tashima, David Simpson, David Dorfman, Heather Ribaudo, and Roy M. Gulick, for the A5097s Study Team. Annals of Internal Medicine. November 15, 2005;143(10):714-21.

Speaking of popular HIV drugs, it is hard to get more popular than efavirenz. Potent, time tested, convenient and once-daily, this antiretroviral has become a mainstay of initial HIV therapy. It has been approved in the United States for the treatment of HIV infection for seven years now.

We all know what familiarity breeds: contempt. The adverse effects, particularly the neuropsychiatric effects, of efavirenz have become well-appreciated by both clinicians and patients. For some, a fear of mood changes, dizziness, sleep problems and other toxicities ascribed to

STUDY SNAPSHOT	
Design:	Prospective observational study of neuropsych evals in a cohort enrolled in a randomized, placebo-controlled trial.
Population:	303 treatment-naive patients randomized to one of three study regimens, two of which contained EFV.

efavirenz have made it an *antiretroviral non grata*.

Main Results:	Dream-related and vestibular symptoms more common in EFV group at week 1, but no difference between groups thereafter. EFV was not associated with impaired neuropsych function -- which improved in EFV and non-EFV groups -- or depression, anxiety and sleep quality.
Significance:	Rigorously performed placebo-controlled study that demonstrates transient symptoms of EFV and absence of detectable effect on neuropsych parameters, depression or anxiety. EFV should not be withheld solely because of depression or anxiety.

However, there has been some debate regarding just what efavirenz can do and how often it does it, especially when it comes to triggering or worsening depression. By some estimates, over 50% of HIV-infected outpatients suffer from mental illnesses, the majority of which are mood disorders.[32] Therefore, the tolerability of one of the most effective antiretrovirals, especially in relation to prompting or exacerbating mental illness, is of tremendous importance to providers and their patients.

David Clifford, from the Washington University School of Medicine in St. Louis, and colleagues prospectively studied a subset of participants from ACTG study 5095 to evaluate the effect of efavirenz on neuropsychological performance. Although existing literature has already demonstrated the better-known effects of efavirenz on sleep and dreams, it is fairly limited when it comes to efavirenz and depression, which is why Clifford's evaluation included depression scales.

The parent study was a large, double-blind, placebo-controlled clinical trial that enrolled more than 1,100 treatment-naive HIV-infected men and women.[33] Patients were randomized to one of three study arms:

1. zidovudine + lamivudine + efavirenz,
2. abacavir (ABC, Ziagen) + zidovudine + lamivudine + efavirenz or
3. abacavir + zidovudine + lamivudine

Of this cohort, 303 participated in the substudy and completed a battery of neuropsychological tests that assessed functioning in areas of motor persistence, sustained attention, response speed, visual motor coordination, and conceptual shifting and tracking. In addition, symptoms including those known (and not known) to be associated with efavirenz were sought, and surveys of sleep quality, anxiety and depression (CES-D) were administered. All evaluations were performed at baseline (prior to study drug administration) and at weeks 1, 4, 12 and 24.

In general, during the 24-week study follow-up, neuropsychological scores *improved* in those who were receiving efavirenz as well as those who were not. There were *no* significant differences observed at any time point in either group.

An analysis of the correlation between efavirenz plasma levels and testing results did find a significant, but small, negative correlation wherein higher levels of efavirenz were associated with poorer neuropsychological performance at weeks 4 and 12. As expected, **symptoms related to efavirenz were significantly more common among those receiving this drug, but only at week 1 and *not* at other time points. Trial participants taking efavirenz had a greater frequency of bad dreams after one week of therapy, but, interestingly, patients who were *not* taking efavirenz experienced poorer sleep quality**

at week 4 compared to the patients receiving efavirenz.

Based on responses to the anxiety surveys, anxiety was common in this cohort at baseline (more than 80%) and increased during the study. At week 1 there was less anxiety recorded in the efavirenz group, but at later time points *no* significant difference was detected between groups in terms of anxiety changes. **Depression was *not* correlated with efavirenz treatment, although 12 (6%) participants taking efavirenz modified their regimen due to central nervous system (CNS) or mood disorders, compared to none of those not taking efavirenz (*P* = .01).** Plasma levels of efavirenz correlated with depression scores at week 4 alone.

Overall, 21% of patients in the efavirenz group modified therapy, versus 17% of those not receiving efavirenz (*P* = .44). Patients not tolerating efavirenz were permitted to change to nevirapine (NVP, Viramune) and, in a back-of-the-envelope calculation, it appears that 14 efavirenz-assigned patients did so. But this was not found to significantly alter the results.

The Bottom Line

This is the largest and most rigorously conducted study of the effect of efavirenz on neuropsychological functioning. Experts can quibble about the choice of the specific evaluations performed, but the results indicate that a regimen containing efavirenz did *not* impact major neuropsychological domains relative to a regimen that did not contain efavirenz.

Symptoms related to efavirenz -- such as vestibular disturbance, unusual dreams, a feeling of being hungover, etc. -- were more common in the efavirenz group after one week of therapy, but dissipated subsequently to a level that was indistinguishable from the non-efavirenz group. Importantly, there was no effect of efavirenz on either depression or anxiety, both of which were prevalent at baseline. This is a significant finding, as many clinicians have been reluctant to prescribe efavirenz to patients who have depression, anxiety or other mental illnesses because of the drug's CNS effects early in the course of treatment. Further, as in most every study of efavirenz, treatment discontinuation related to toxicity was low -- only 6% of those on efavirenz switched to nevirapine in ACTG 5095.[33]

This placebo-controlled, blinded study did not demonstrate incident depression or worsening of prior depression associated with efavirenz exposure. This confirms data from a study published in *JAIDS* by Hans-Jürgen von Giesen and colleagues.[34] They found no difference in the neuropsychiatric disorders between 414 patients receiving efavirenz and 320 patients taking nevirapine. Based on these combined data, efavirenz should not be withheld from those with depression or anxiety.

Another key finding in von Giesen's study was that drug levels did *not* correlate well with the results of neuropsychiatric evaluations. A prior, smaller study had found that drug levels of efavirenz were associated with CNS side effects[35]; however, this study included fewer neuropsychiatric evaluations. In the Clifford study, only at week 1 were higher drug levels and increased prevalence of efavirenz-related symptoms associated. Therefore, attempts to alter the dose of efavirenz to ameliorate these adverse effects are unlikely to be fruitful.

This pivotal and thorough investigation is what clinical research is all about. Well-executed studies help us to separate belief from reality. In this case, the very real CNS effects of efavirenz became exaggerated in street lore -- fed by anecdotes from patients and clinicians alike. The findings by Clifford and his team bring us back to earth, and are reassuring to those who are prescribed (or prescribing) this important antiretroviral.

Honorable Mentions

No "top 10" summary can truly hope to encompass all of the critical HIV research in a given year -- even if one tries to combine several studies under a single umbrella, as I did in this article. There were a number of other noteworthy reports (both published and unpublished) and developments in HIV that made waves in 2005 and are worthy of mention; they include:

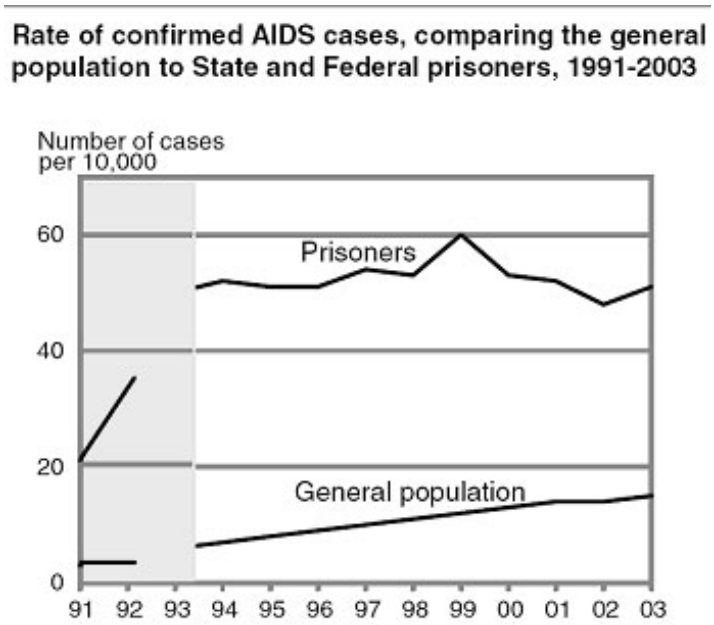
3 x 5 Initiative Misses the Mark

Perhaps the biggest story of the year was the one that did *not* happen. The World Health Organization (WHO) had vowed that the end of 2005 would mark the availability of HIV therapy for three million people living with HIV in developing countries -- the socalled "3 x 5 Initiative," which was launched in 2003. However, by the end of 2005, only approximately *one* million people in developing nations had received HIV treatment. In its June 2005 report,[36] the WHO mentions "bottlenecks" to expanded access to HIV care, in particular inadequate funding. While acknowledging the likelihood that it would fail to reach its target, the WHO diplomatically recommended steps that would at least help it achieve the "3" part of the 3 x 5 Initiative, including increased political effort, standardized treatment approaches, harmonized efforts between different entities, the linking of treatment with prevention, and increased financial support for the initiative.

There is no doubt that an increasing number of people are receiving HIV therapies, albeit slowly. But even had the WHO managed to reach three million, it would still be well short of the universal access that should be the stated goal of this project. To the optimist, the glass is a third full, but the rest of us can only shake our head and ask, "Is this the best the world can do?"

High HIV Rates Found in U.S. Prisons, Particularly Among Women

At least 2% of all state prison inmates in the United States are HIV infected, according to a September 2005 report issued by the Bureau of Justice Statistics of the National Institute of Justice.[37] This is more than six times the prevalence rate of the general unincarcerated population (0.3%) -- and is likely an underestimate, since HIV testing of inmates is not mandatory in all states. The 2% prevalence rate puts the United States' incarcerated population on par with the general populations of the Dominican Republic, Mali and Thailand.[38] The report, using data from 2003, found a slight decline (less than 1%) in the overall number of inmates with HIV infection (which now totals more than 23,000), despite a 1.6% increase in the prison population as a whole. The prevalence of AIDS in prisons from 1991 to 2003 compared to the general population is shown in the figure below.



Although fewer women are incarcerated compared to men, the prevalence of HIV infection among female inmates is approximately 2.8%, versus 1.9% among male inmates. There is only one state (New York) in which more than 5% of male inmates are known to be HIV infected; by contrast, more than 5% of incarcerated women are HIV infected in *six* states. In addition, HIV seroprevalence rates for women are above *10%* in two states: Maryland and New York.

These data should serve to remind us that a substantial proportion of people living with HIV infection are incarcerated. Previous data estimate that one in five persons with HIV infection pass through a prison or jail each year.[39] Any attempt to manage the HIV epidemic *must* include strategies to enhance the provision of care and prevention services to incarcerated people who are living with, or who are at risk for, HIV infection.

Tipranavir Approved, TMC114 on the Way: New PIs for Treatment-Experienced Patients

It has been a decade since the first PI was approved in the United States, and since then, tens of thousands of HIV-infected patients have benefited from combination therapy. Unfortunately, a steadily growing number of patients have developed multi-drug resistance and are now on suboptimal regimens while they await the development of new agents. Thankfully, 2005 brought an important new addition to our antiretroviral armament: the PI tipranavir (TPV, Aptivus). Following the completion of the RESIST-1 and RESIST-2 trials, tipranavir was approved in the United States in June 2005 and in Europe four months later. Tipranavir, which is administered with 200 mg of ritonavir (RTV, Norvir) twice a day, can be effective against virus that is resistant to other PIs. It is especially effective when combined with the fusion inhibitor enfuvirtide in patients who have not previously been treated with enfuvirtide.

Another drug in the PI class, TMC114, is on track to becoming the next to receive approval. Data presented at the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment and the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy were encouraging regarding the efficacy of TMC114 in treatment-experienced patients. Two clinical trials of TMC114 (POWER-1 and POWER-2) are ongoing, and the drug is currently available to multidrug-resistant U.S. patients through an expanded access program.

Fighting HIV With Medications *and* Prevention

Combating the spread of the HIV pandemic will be best accomplished using a model that combines treatment and prevention efforts, according to an analysis by Joshua Salomon and colleagues published in the January 2005 issue of *PLoS Medicine*.[40] In their report, they investigate a range of potential scenarios to reduce mortality and transmission of HIV. They found that under a treatment-centered strategy, mortality would decrease, but new infections might only modestly decrease, and might even increase. Conversely, a prevention-based strategy would reduce new infections but have less effect on mortality.

With HIV treatment-enhanced prevention efforts, the authors estimate that 29 million infections would be averted during the next 15 years, along with 10 million deaths. The synergy of the combined approach means that fewer people would need to be treated in order to obtain the greatest benefit, Salomon et al assert. These fascinating data provide the broad strokes for an approach to the control of HIV infection that makes goals many of us have considered "optimistic" actually seem realistic.

Dosing Adjustment Likely Needed for Statins Taken With NNRTIs

The association of HIV infection and antiretroviral use with hyperlipidemia, as well as the growing epidemic of hyperlipidemia among the U.S. population in general, has led more and more patients to take lipid-lowering medications such as statins. However, there are well-appreciated interactions between statins and PIs wherein the plasma levels of the statin are generally increased. The potential for dramatic increases in statin levels and serious adverse effects has led to the recommendation that certain statins not be co-administered with PIs, and that others be started at a lower dose. But what about NNRTIs? An important ACTG study by John Gerber and colleagues at the University of Colorado Health Sciences Center examined the interaction between statins and this antiretroviral class.[41]

Gerber and colleagues studied the effects of efavirenz on statin levels among 52 HIV-uninfected volunteers and found that efavirenz significantly lowers the levels of several statins: simvastatin (Vytorin, Zocor), pravastatin (Pravachol, Pravigard) and atorvastatin (Caduet, Lipitor). Similar results are expected with nevirapine. The researchers suggest that higher doses of these lipid-lowering agents may be needed to ensure efficacy when they are used by patients receiving an NNRTI.

The Rise of Generic Antiretrovirals -- in *Developed* Countries

Generic formulations of both didanosine and zidovudine have been approved by the U.S. Food and Drug Administration during the last year and a half. Many in the United States and other developed nations have long awaited generic versions of antiretrovirals, and their approval is a milestone in HIV therapeutics. However, low-cost versions of these two NRTIs have not yet made a big impact on the accessibility of HIV therapies for low-income individuals. This is probably because the use of zidovudine outside of coformulations such as Combivir and Trizivir is unusual, and thus generic zidovudine is not helpful for most people. But patients taking Videx EC, the brand-name formulation of didanosine, certainly could switch to the cheaper generic formulation.

Generic formulations can be of tremendous benefit to the many persons with HIV infection in the United States who do not have adequate medication insurance coverage and do not qualify for AIDS Drug Assistance Programs or pharmaceutical support programs. In particular, the working poor who make enough to exclude them from such assistance but

who must struggle to come up with a proportion of the cost of their medications will greatly benefit from these generics.

Conclusion

It was only 10 years ago -- at the 1996 International AIDS Conference in Vancouver -- that we collectively shared the exhilaration of finally having HIV treatment regimens that worked. Now, as we prepare to head to Canada again this summer for another International AIDS Conference, much has changed. We now prescribe tried-and-true HAART regimens that we know can keep our patients alive and healthy. We continue to develop new drugs that provide less-toxic, more-potent options for treatment-naive and treatment-experienced patients alike. And we continue to establish a greater understanding of the long-term potential adverse effects of our therapies, and how they can be avoided or treated.

In a sense, clinicians in wealthy nations are privileged enough to have moved from the spectacular clinical responses of the early HAART era into a period of therapy *optimization*, during which treatment is fine-tuned to extend its benefits and minimize its toxicity. However, this reality only makes it all the more painful that we have failed to reach millions of HIV-infected people in the developing world -- people for whom effective treatment remains little more than a dream.

At the same time, we have recognized that preventing the spread of HIV infection is a goal that is obtainable, although it will require the same diligence and substantial effort that led to the past decade's dramatic treatment advances. In fact, as Joshua Salomon and colleagues asserted in 2005 in *PLoS Medicine*,[40] potent HIV therapies *must* play a critical role in strategies to contain HIV transmission. Perhaps this marriage of treatment and prevention will be recognized at the International AIDS Conference in Toronto this summer, thus ushering in a new age in which HIV *prevention* becomes the central theme.

The articles selected for this year-end review reflect both the HIV healthcare profession's preoccupation with advancing the treatment of HIV infection and the reality that the virus continues to spread. A cynic might say that we are making therapies better for all the new patients who will need them. However, for those who are already living with the virus, we are obligated to work to improve therapy on all fronts.

Unfortunately, when it comes to HIV prevention, there has yet to be a HAART equivalent -- no revolutionarily new and effective developments to "hang our hat" on. Vaccines, microbicides and even the prophylactic use of antiretrovirals such as tenofovir remain matters for academic study, not widespread clinical use. 2005 has made one thing clear: There is still much work to be done.

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