


THE BODY PRO
The HIV/AIDS Resource for Healthcare Professionals

[E-mail a colleague](#)
SEARCH:

HIV JournalView

Top 10 Research Reports of 2004

Year-end issue

 by [David Alain Wohl, M.D.](#)

University of North Carolina, AIDS Research and Treatment Unit



David Wohl, M.D.

from The Body Pro

January 2005
 [View PDF](#)

Table of Contents

- [Introduction](#)
- [AIDS Epidemic Update: December 2004, UNAIDS/WHO](#)
- [Lopinavir/Ritonavir Monotherapy in Treatment-Naive Patients](#)
- [Atazanavir -- The Little PI That Could](#)
- [A5095 and the Triple-Nucleoside Saga](#)
- [The Risk of NNRTI Resistance Following Perinatal Nevirapine and Ramifications for Subsequent Antiretroviral Therapy Success](#)
- [The Genomics of Efavirenz Toxicity](#)
- [Stable Viral Load but Evolving Drug Resistance](#)
- [How Stable Is Stable Low-Level Viremia?](#)
- [The Down Low](#)
- [HCV Therapy in Coinfected Patients](#)
- [Summary](#)
- [References](#)

Introduction

For over 25 years the deadliest infectious disease epidemic in history has raged across this planet. During these 2.5 decades, advances in our ability to respond to the HIV epidemic have come in fits and starts. The last 10 years, in particular, have witnessed a virtual renaissance in HIV research and care that has allowed us to consider HIV infection a manageable, even chronic, disease.

More recently, however, we have reached a plateau, with major clinical breakthroughs becoming rarer and less dramatic. For example, in 2004 no major developments in HIV care were announced nor were any new antiretrovirals approved. However, there were a number of significant contributions that helped refine our understanding of how to use the HIV therapies we have at hand. Some of these developments have already reached the clinic and have led to improvements in HIV therapeutics, while the full effects of others have yet to be realized.

In addition, there were ample data released in 2004 noting the dangers and challenges we continue to face in our effort to combat the epidemic. Collectively, these data indicate we are hardly anywhere near being out of the woods yet.

Ten of the most noteworthy research reports, at least in this author's opinion, are detailed below.

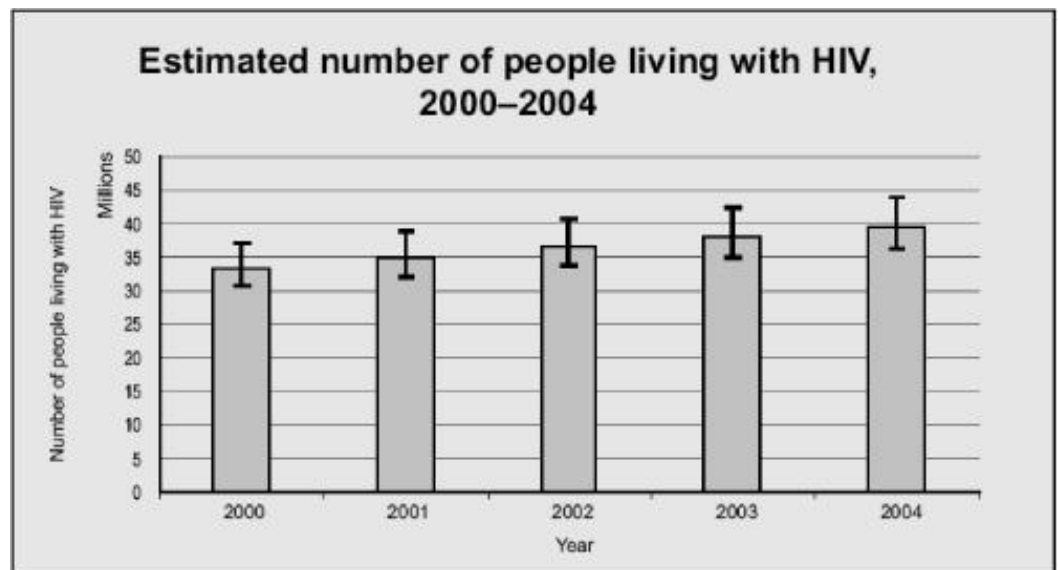
AIDS Epidemic Update: December 2004, UNAIDS/WHO

UNAIDS/WHO. AIDS Epidemic Update: December 2004. UNAIDS; December 2004.

UNAIDS and the World Health Organization (WHO) periodically issue a report card on the world's response to the HIV/AIDS epidemic. The 2004 update, released in December, made for quite sober reading. The number of people living with HIV infection on our planet increased to an all-time high: Approximately *40 million* men, women and children are now HIV infected. A whopping *5 million* of these individuals acquired the virus in 2004 alone (see [table](#)). Higher rates of infection were seen in every region, but this was particularly true in Eastern Europe and East Asia. In these areas, the prevalence of HIV this past year increased 40-50%, fueled by the malignant spread of HIV specifically in Russia, the Ukraine and China. (For a detailed report on the response of the world's most populous nation to HIV, see Cohen J. [HIV/AIDS in China: Poised for Takeoff?](#) *Science*. June 4, 2004; 304(5676): 1430-1439.)

All indicators suggest that HIV incidence is rising globally, especially among women and girls -- a finding that can only be interpreted as evidence of a failure of the world's leaders to seize HIV prevention opportunities. Stigmatization of those infected with HIV, collective denial of the scope of the HIV threat, general ignorance and the bleeding of limited resources to finance military priorities have yielded countless infections that could have been prevented.

But there is no monopoly on ignorance. Even in the United States, where HIV literacy is relatively high, we watched as the candidates for vice president uncomfortably demonstrated, during their televised election debate, an embarrassing lack of awareness of the growing HIV incidence among African-American women.



In addition to the record increases in the number of HIV cases, 2004 also witnessed the greatest amount of funding pledged and allocated to combat the epidemic. Global funding has risen from US\$2 billion to over US\$6 billion in the past 4 years. This has permitted broader access to prevention programs, voluntary testing and treatment.

Yet, to date, the results have been modest. Despite a 56% increase in the number of patients receiving HIV therapy in the developing world and valiant pledges to have 3 million people on therapy by end-of-year 2005 via WHO's [3 by 5 initiative](#), only 440,000 are currently being treated worldwide. This, according to WHO, means that 9 out of 10 people with HIV who need therapy are not receiving it.

The UNAIDS/WHO report forces us to ask the question, "Where is the war on HIV?" Imagine the misery behind the numbers and then ask yourself where, in this world of glistening wealth and multi-million-dollar weapon systems, is the large-scale, well-financed and focused effort to halt the spread of an infectious disease that killed 3.1 million adults and children in this past year alone?

Much has been made during the U.S. presidential election of a yearning for morality and values

among the electorate. But where else can moral value be found, if not in delivering treatment to people who are enduring the suffering that is the hallmark of this disease?

A 2001 poll sponsored by the University of Maryland showed that most Americans think the United States spends about 24% of its annual budget on foreign aid. In reality, less than 1% of the U.S. budget is spent on foreign aid.^{1,2} A separate survey also performed by the University of Maryland suggests Americans want to increase foreign assistance.

As we clinicians ponder issues such as what the next generation of antiretrovirals will be, or whether our patients have enough testosterone, G-CSF or erythropoietin, we must also consider our own response to these latest figures. Can we emerge from our small corner of this unprecedented, global epidemic to demand that the next UNAIDS/WHO report be the very last to tally our sad failures?

Lopinavir/Ritonavir Monotherapy in Treatment-Naive Patients

Gathe JC Jr, Washington MY, Mayberry C, Piot D, Nemecek J. IMANI-1 TC3WP single drug HAART -- proof of concept study. Pilot study of the safety and efficacy of Kaletra (LPV/r) as single drug HAART in HIV+ ARV-naive patients -- interim analysis of subjects completing final 48 week data. In: Program and abstracts of the XV International AIDS Conference; July 11-16, 2004; Bangkok, Thailand. Abstract MoOrB1057.

Perhaps the Yiddish word most commonly borrowed by speakers of other languages is the word *chutzpah*, which basically means to have unmitigated gall. In the past, major advances in HIV management were made by people with *chutzpah*. "Give pregnant women with HIV AZT? Are you crazy?" was the typical response when the AIDS Clinical Trials Group (ACTG) Study 076 was proposed in the early 1990s. Likewise, inserting an implant of ganciclovir (Cytovene) into the orbit of an AIDS patient's eye seemed far-fetched -- until someone did it in the mid 1990s, and it worked.

Today, does anyone have more *chutzpah* than Joe Gathe and colleagues in Houston, Texas, who are treating antiretroviral-naive patients -- disadvantaged patients at that -- with a single, boosted protease inhibitor (PI)? To the surprise of many, Gathe et al reported good results. Their findings have ushered in new thinking regarding what constitutes highly active antiretroviral therapy (HAART).

Their report details the experience of 30 patients who were treated with the co-formulation lopinavir/ritonavir (LPV/r, Kaletra) at either 400/100 mg twice daily (if they weighed less than 70 kg) or 533/133 mg twice daily (if they weighed 70 kg or more). The patients were reported to have had limited access to HIV therapy due to financial constraints, but were able to receive lopinavir/ritonavir. The participants had a mean CD4+ cell count and plasma HIV-RNA level of 170 cells/ μ L and 262,000 copies/mL, respectively. More than half the patients had a baseline viral load above 100,000 copies/mL and 43% had a CD4+ cell count below 50 cells/ μ L.

After 48 weeks, 20 (67%) of the patients saw their viral load drop to less than 400 copies/mL and 60% had a viral load below 50 copies/mL. The mean CD4+ cell count rise among these 20 patients was 317 cells/ μ L.

Of the 10 patients who did not reach week 48, 2 had pure virologic failure, 2 had gastrointestinal adverse events, 2 were deemed non-adherent, 2 were lost to follow-up, 1 was deported and 1 was diagnosed with hepatitis B virus infection. No evidence of drug resistance was reported in any patient.

These results have obvious implications for HIV therapeutics. The cost savings, improved tolerability and potentially enhanced adherence gained by the use of a single agent would make this an attractive approach, if the findings are duplicated and found to be durable. Other studies^{3,4} have switched patients treated with triple-drug therapy to lopinavir/ritonavir monotherapy, also with good result, which supports Gathe's premise.

It will also be important to explore monotherapy with other boosted PIs. The ACTG is [currently recruiting](#) patients for a simplification study that uses boosted atazanavir (ATV, Reyataz). Simply for their *chutzpah* -- for doing what most of us would never dare to do -- Gathe et al deserve credit. They should also be acknowledged for their outside-the-box thinking, which may lead to a whole new HIV treatment approach.

Atazanavir -- The Little PI That Could

Squires K, Lazzarin A, Gatell JM, et al. *Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. J Acquir Immune Defic Syndr. August 15, 2004;36(5):1011-1019.*

Atazanavir may have been approved in 2003, but 2004 was a good year for this PI. Prior to its approval, clinicians and patients had to face some unsavory choices when reaching for a PI. Pill count, dosing frequency and side effects all conspired to make prescribing, let alone taking, these agents depressing. With the introduction of once-daily atazanavir, prescribing a PI became palatable -- even when boosted with ritonavir (RTV, Norvir), as prescribed by most clinicians.

The study that made the U.S. Food and Drug Administration say "yea" to atazanavir was this quirky international, randomized, double-blind, 2-arm, comparative study in treatment-naive patients. One study arm received 600 mg of efavirenz (EFV, Sustiva, Stocrin). The other study arm received 400 mg of atazanavir given orally once a day. Both arms also received fixed-dose zidovudine/lamivudine (AZT/3TC, Combivir), given orally, twice daily for 48 weeks. The primary endpoint was the number of treated patients who achieved a plasma viral load below 400 copies/mL at 48 weeks. The secondary endpoint was the number of patients who achieved a plasma viral load below 50 copies/mL at 48 weeks.

Patients were stratified 1:1 by baseline viral load (<30,000 vs. \geq 30,000 copies/mL). Safety, tolerability and toxicity were also monitored throughout the study. Of the 810 randomized patients, 805 began therapy (404 atazanavir, 401 efavirenz) and 144 discontinued therapy before week 48 (20% of the efavirenz arm and 16% of the atazanavir arm).

Viral load responses were not significantly different between arms (64% vs. 70% in the efavirenz and atazanavir arms, respectively, achieved <400 copies/mL, and 37% vs. 32% in the efavirenz and atazanavir arms, respectively, achieved <50 copies/mL). The rate of adverse effects were similar across the study arms and were low. Not surprisingly, there was more hyperbilirubinemia among those receiving atazanavir, although this was rarely treatment-limiting. Lipid elevations were more common among the efavirenz-assigned subjects, with an 18-23% rise in lipid parameters over 48 weeks in this arm versus no change in cholesterol values and a 9% decline in triglyceride levels in the atazanavir group.

From this data, it looks like the arms are potent. The only question is: Why did such a surprisingly small number of patients, from both arms, achieve a viral load below 50 copies/mL at 48 weeks?

Previous studies of efavirenz^{5,6} have demonstrated dramatically different numbers. The apparent explanation, which took some investigation, was that the blood taken from study participants had been collected in 2 different types of tubes: plasma preparation tubes (PPT) and standard EDTA Vacutainer blood collection tubes.

The patients' original viral load results were produced from blood plasma that had been collected in PPT tubes. Reanalysis of the data from standard EDTA tubes revealed consistently lower viral loads than those from PPT tubes: 89% of the blood plasma collected with EDTA tubes, compared to 55% of the PPT samples, had viral loads that were below 50 copies/mL.

The researchers theorize that part of this difference may be the result of different centrifugation parameters (time and g-force) used in the processing of each kind of tube type. EDTA tubes are spun twice as long (20 minutes) as PPT tubes and g-force can vary between 800 and 1,600 g. PPT tubes are spun for 10 minutes at 1,100 g. These factors can alter the amount of cellular debris and platelet-associated virus contained in presumably cell-free plasma, and could affect viral load quantitation. Therefore, an additional important finding emerging from this study and a cautionary tale for HIV clinical researchers is that the tube type can affect HIV viral load results and mess with data.

Aside from the tube issue, this study established the bona fides of an important new agent. These results, combined with data from the study of treatment-experienced patients,⁷ demonstrate atazanavir's potency when boosted with ritonavir, the drug's ability to be combined with other once-daily antiretrovirals, its low pill burden and its benign metabolic effects -- all of which have made atazanavir an attractive agent in many clinics.

Atazanavir's major downside -- even when boosted with ritonavir -- is its negative interaction with

therapies that increase gastric pH, such as proton pump inhibitors and H2 blockers. This is a bummer for the dyspeptic HIV-infected patient in need of a PI. Because many patients with HIV use these medications, which are now obtainable over the counter, clinicians must be careful to educate their patients about the profound effects these acid reducers have on the body's ability to absorb atazanavir. To a lesser extent, hyperbilirubinemia is another adverse event that may present problems for the drug, but as suggested in this trial, few patients stop therapy due to elevated bilirubin.

This was a big year for atazanavir and it started with this study. As we get to know this drug, we will come to better appreciate its strengths and limitations. How to position atazanavir in the sequencing of antiretroviral regimens continues to be explored, as are the patterns of resistance to this PI. Also necessary is further work detailing the effects of this agent, when boosted with ritonavir, on metabolic parameters including body shape. Again, answers may come from ACTG, which is on the verge of launching a comparative trial of ritonavir boosted atazanavir versus efavirenz in treatment-naive patients. This large study will include an intensive metabolic substudy. This is a study you will be hearing a lot about in the future.

A5095 and the Triple-Nucleoside Saga

Gulick RM, Ribaldo HJ, Shikuma CM, et al, for the AIDS Clinical Trials Group Study A5095 Team. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med.* April 29, 2004;350(18):1850-1861.

There may be some rule in The Body Pro's writers' guide about citing a study as one of the year's top 10 for 2 consecutive years, but if so, I have not seen it. While preliminary results from ACTG Study A5095 were presented in 2003, the actual results from this important trial were only published in 2004. Further, the results, although well known, are even more remarkable now when one considers recent data from other trials of triple nucleoside-only regimens -- all of which have demonstrated far greater failure rates than observed in this trial with the triple-nuke zidovudine/lamivudine/abacavir (AZT/3TC/ABC, Trizivir). Therefore, it has become evident that, like movies starring Hugh Grant, not all nucleoside combinations are equally bad.

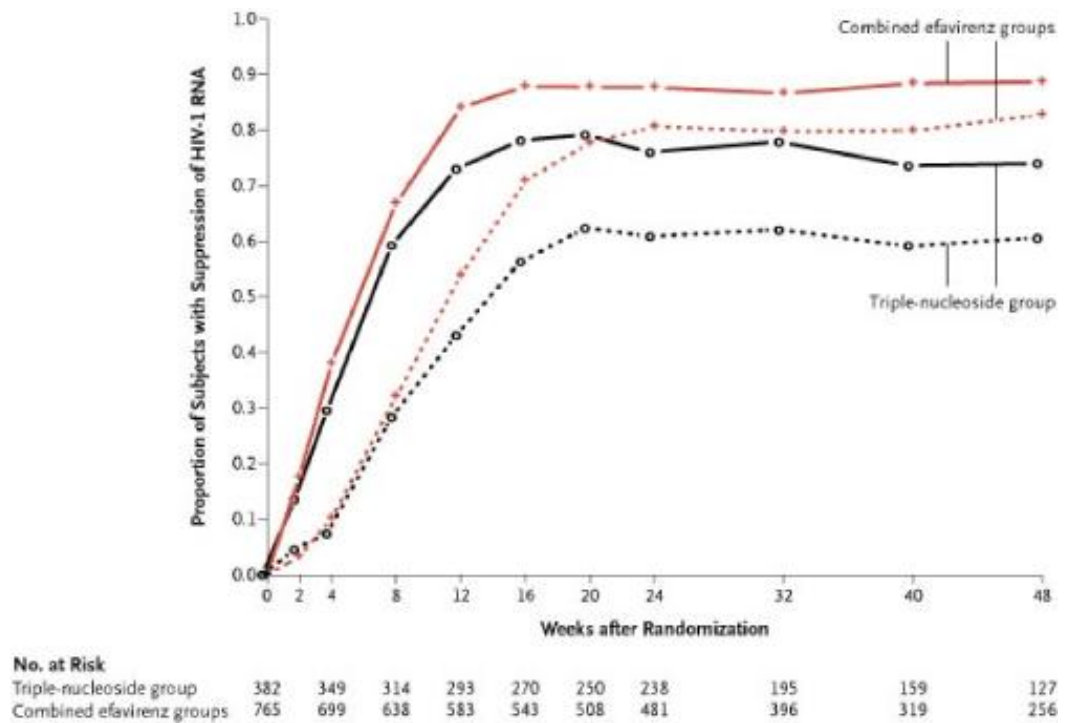
In A5095, zidovudine/lamivudine/abacavir was found to be virologically inferior when compared to zidovudine/lamivudine/abacavir plus efavirenz or zidovudine/lamivudine plus efavirenz. (The comparison between the 2 efavirenz-containing arms awaits trial completion.)

However, while zidovudine/lamivudine/abacavir fared poorly in this trial when compared to the other study arms, it helps to keep in mind that it was not quite an absolute failure. After a median follow-up of 32 weeks, 82 of the 382 (21%) participants in the triple-nucleoside group and 85 of the 765 (11%) of those in the combined efavirenz groups had virologic failure.

After 48 weeks, 74% of the participants in the triple-nucleoside group had an HIV-1 RNA level below 200 copies/mL, and 61% had a viral load below 50 copies/mL. At the same time point, however, the corresponding percentages in the combined efavirenz groups were 89% and 83%.

A post-hoc analysis was done to examine the durability of viral suppression in the subgroup of 923 participants, with at least one HIV-1 RNA value below 200 copies/mL during therapy. It demonstrated that the time to virologic failure was *shorter* in the triple-nucleoside group than in the combined efavirenz groups ($P < .001$).

In an analysis that included the 780 subjects who had at least one HIV-1 RNA value below 50 copies/mL, a similar difference was suggested, although it was not statistically significant ($P = .08$).



The difference in virologic outcome between the triple-nucleoside arm and the combined efavirenz arms persisted regardless of the participant's viral load (above or below 100,000 copies/mL) or CD4+ cell count (above or below 200 cells/ μ L). Genotypic resistance testing results were also reported from participants failing the triple-nucleoside arm. Of the 82 patients in this arm with virologic failure, 18 had wild-type virus at the time of failure. However, 28 of these patients had the M184V mutation alone, 9 had M184V plus another nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) mutation and 2 had an NRTI mutation without M184V. Twenty-two participants did not have their virus sequenced, since their viral load was below 500 copies/mL and sequencing was not able to be done in 3 participants.

It is important to note that zidovudine/lamivudine/abacavir did not do so poorly -- the data simply indicates that it was not as effective as the efavirenz-containing regimens. The relatively poorer durability of this triple nucleoside also should strike a cautionary note among those with patients on zidovudine/lamivudine/abacavir and still doing well. In this study, a significant proportion of patients assigned the triple-nuke regimen experienced virologic failure *after* achieving suppression of their HIV viremia for a period of time. Thus, early success with zidovudine/lamivudine/abacavir does *not* signify that longer term success is assured.

An additional distinction needs to be made between the performance of zidovudine/lamivudine/abacavir in A5095 and other studies as well as the results of several recent trials of other triple-nucleoside combinations (e.g., tenofovir [TDF, Viread] + didanosine [ddI, Videx] + lamivudine [3TC, Epivir] and tenofovir + abacavir [ABC, Ziagen] + lamivudine) that had near-universal failure rates.⁸⁻¹⁰ In trials of these other triple nucleosides, *three quarters or more* of the subjects failed virologically as opposed to what was seen with zidovudine/lamivudine/abacavir here (i.e., the inverse). Although the reasons for the difference in the performance of these triple-nucleoside combinations is still being debated, they include drug penetration within cells as well as vulnerability to resistance. At this point, it seems that triple-nucleoside combinations that include a thymidine analogue fare much better than other triple-nucleoside combinations. It is likely that this is at least partly due to the salutary effects of thymidine analogues such as zidovudine (AZT, Retrovir) on the development of lamivudine resistance, thus minimizing a weak link in a combination such as abacavir plus lamivudine plus tenofovir. The critical role played by thymidine analogues in nucleoside-only regimens is well illustrated by a recent retrospective study by Mauss et al¹¹ who examined the outcomes of 40 patients who were switched from a prior antiretroviral regimen to tenofovir plus lamivudine plus zidovudine. After 6 months, HIV-RNA levels were less than 50 copies/mL in 23 out of 27 patients who were switched with an undetectable viral load and in 8 of the 13 patients with a detectable viral load at the time of the switch.

The bottom line, then, is that zidovudine/lamivudine/abacavir is not as potent or durable as the efavirenz combinations studied, but it is markedly better than triple-nucleoside regimens that do not contain a thymidine analogue. This finding is important because it instructs us that zidovudine/lamivudine/abacavir can no longer be considered a first line option in the treatment of HIV

infection and it demonstrates that certain combinations of nucleosides are better than others.

As an aside, it is the vulnerabilities of certain nucleoside pairings that make it also worthwhile to mention two other related studies. Graeme Moyle et al recently reported results from a trial in which the combination of tenofovir and didanosine was found to be less effective than didanosine plus lamivudine when each of these nucleoside pairs was used with efavirenz.¹² A week-12 interim analysis of this 77-patient study (the original design called for 100) found that *none* of the didanosine plus lamivudine-assigned subjects experienced virologic failure, while 12% ($P < .5$) of the didanosine plus tenofovir-randomized subjects did. All the failures occurred in patients who had a baseline viral load of greater than 100,000 copies/mL and a CD4+ cell count of less than 200 cells/ μ L.

These results endorse the findings of Podzamczar et al. In a planned clinical trial comparing tenofovir plus didanosine plus efavirenz, with and without lopinavir/ritonavir, the team was forced to also stop its trial early, with only 33 patients enrolled, when 6 of 14 participants in the 3-drug arm experienced virologic failure, compared to none of the 19 receiving lopinavir/ritonavir.¹³ These results led to the issuing of a "Dear Doctor" letter by Bristol-Myers Squibb Company, the maker of didanosine, warning about the combination of tenofovir plus didanosine with a non-nucleotide reverse transcriptase inhibitor (NNRTI). The mechanism of the suboptimal performance of this combination is still uncertain, although it may be due to mutational interactions that when combined can facilitate resistance to one or more of these agents. Whether didanosine and tenofovir can be used with an agent other than a non-nucleoside (i.e., a boosted PI) is unclear and needs to be examined.

These studies of nucleosides are intriguing and involve combinations of agents many clinicians were creatively employing. The demise of triple nucleosides and possibly didanosine plus tenofovir caution us against using untested combinations of antiretrovirals. Already, some clinicians are exploring quadruple-nucleoside regimens and relatively small studies have provided encouraging results.^{14, 15} However, large and longer term studies are required to demonstrate such regimens are effective and safe.

The Risk of NNRTI Resistance Following Perinatal Nevirapine and Ramifications for Subsequent Antiretroviral Therapy Success

Jourdain G, Ngo-Giang-Huong N, Tungyai P, et al, and the Perinatal HIV Prevention Trial Group. *Exposure to intrapartum single-dose nevirapine and subsequent maternal 6-month response to NNRTI-based regimens. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, Calif. Abstract 41LB.*

Martinson N, Morris L, Gray G, et al. *HIV resistance and transmission following single-dose nevirapine in a PMTCT cohort. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, Calif. Abstract 38.*

Dual reports about the use of nevirapine (NVP, Viramune) to prevent mother-to-child transmission (MTCT) of HIV demonstrate the ability of nevirapine to reduce MTCT; however, high levels of NNRTI resistance among the mothers were observed. Further, it appears that acquired resistance has implications for transmission of HIV to the infant as well as for the mother's response to subsequent antiretroviral therapy.

In one study, conducted in South Africa with more than 600 HIV-infected women, Martinson et al detected NNRTI resistance at 6 weeks postpartum in 39% of mothers who had taken a single dose of nevirapine and 42% of the few HIV-infected infants born to these women. It should be noted that the transmission rate in this study was a mere 8.6%.

In a separate study, which was performed in Thailand by Jourdain and colleagues, resistance to nevirapine and response to HIV therapy were assessed among participants. The trial compared zidovudine given alone versus zidovudine given with a single dose of nevirapine to HIV-infected women in the third trimester of pregnancy.

The use of both drugs was found to be more effective at reducing MTCT than zidovudine alone (1% versus 6%). However, NNRTI resistance developed in almost a third of the women who

received the nevirapine.

Further, the detection of NNRTI resistance was associated with a reduced likelihood of responding to antiretroviral therapy that contained an NNRTI. At 3 months, 80% of the 66 women who had at least 1 mutation, 87% of the 112 single-dose nevirapine exposed women with no mutation and 88% of the 41 women not exposed to nevirapine had a viral load ≤ 400 copies/mL (viral load ≤ 50 : 45%, 46% and 54%, respectively). At 6 months, 68% of the 50 women with at least 1 mutation, 80% of the 92 exposed women without a mutation and 85% of the 27 non-exposed women had a viral load ≤ 400 (P for trend = .057) (viral load ≤ 50 : 38%, 50% and 74%, respectively; (P for trend = .0034).

The good news, therefore, is that nevirapine reduced the risk of MTCT; the bad news, however, is that a significant minority of the mothers, as well as the infants who were infected despite the prophylaxis, developed resistance to one of the most accessible antiretroviral classes in the world: the NNRTIs.

Clearly, and it's worth emphasizing, nevirapine has saved tens of thousands of children from acquiring HIV and should certainly continue to be made available for prevention of MTCT. This is an important point, especially given the controversy surrounding HIVNET 012, a trial of single-dose nevirapine conducted in Uganda in the late 1990s. A summary of the controversy can be found at www.thebodypro.com/atn/nevirapine_controversy.html. Suffice it to say that despite the problems with HIVNET 012 and the recognized shortcomings of nevirapine, the drug is extremely easy to administer and is effective at preventing HIV transmission from mother to child. However, the studies described above indicate there is room for improvement.

Spurred by this work, several groups are looking at ways to reduce the risk of nevirapine resistance. The long half life of NNRTIs, a characteristic that is exploited in this setting and allows for single dosing, may be the problem since NNRTI levels slowly decrease to sub-therapeutic levels. Covering the nevirapine "tail" with other antiretrovirals is being studied. This is a tremendous issue that requires a quick solution, especially now that single-dose nevirapine has become the recommended standard for prevention of MTCT in areas where other agents are simply not available.

The Genomics of Efavirenz Toxicity

Haas DW, Ribaldo HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: An Adult AIDS Clinical Trials Group study. *AIDS*. December 3, 2004;18 (18):2391-2400.

In the film "The Graduate," there is a fabulous and well-known scene in which Dustin Hoffman in the title role returns home aimless from college. Pool-side, a family friend provides him with one word career advice, "plastics." Perhaps that was the word for the 1960s when that film was released. In our time, the buzz word that supposedly points the way to medicine's future frontier is "genomics."

The sequencing of the human genome has been heralded as a new age that will bestow untold benefits. Yet, for all the promise, there has not been much that genomics has done to change current clinical practice. However there are many areas within medicine, including HIV therapeutics, in which understanding human genetics may prove extremely useful. One such area is pharmacogenetics -- the study of how genes influence the effect of drugs.

Elucidation of the genetic factors that influence drug metabolism, treatment response and adverse effects has obvious implications for HIV management and may explain some of the variability we see among patients, such as plasma PI concentrations and adverse events, as well as differential treatment effects across ethnic and racial groups.

Jumping right into the genomics pool, Haas et al were interested in examining the relationship between the genetic variability in the cytochrome P450 enzymes which are primarily responsible for the metabolism of efavirenz, an NNRTI that previous data^{16,17} suggested could be differentially cleared among ethnic and racial minorities.

The investigators focused their attention on polymorphisms in genes coding for CYP2B6, CYP3A4, CYP3A5 and MDR1. They took advantage of the cohort enrolled in ACTG Study A5095 (see [above](#)), a clinical trial in which roughly two thirds of the subjects were receiving efavirenz. In this study,

detailed examination of efavirenz's neurological adverse effects were collected in a substudy. A total of 157 subjects were evaluated and this group had a nice racial/ethnic mix: 57% were European American, 32% African American and 10% Hispanic.

The bottom line of this investigation was that the African Americans enrolled in this study were found to more likely have a polymorphism at CYP2B6 (T/T genotype at position G516T) than European Americans (20% versus 3%). Carrying this gene was associated with greater plasma concentrations of efavirenz and central nervous system side effects during the first 6 months of therapy.

These findings may explain the racial differences in the pharmacokinetics of efavirenz and differential clinical outcomes that have been suggested,¹⁸ perhaps secondary to greater intolerance of efavirenz among African Americans.

Importantly, this polymorphism may also influence the metabolism of other CYP2B6 substrates, including nevirapine (potentially contributing to the long half life of the drug -- see discussion of [single-dose nevirapine](#) above), methadone, diazepam (Valium, Valrelease) as well as the street drug Ecstasy.

This important paper provides a rationale for the continued development of therapeutic approaches that consider host genotype. The screening of patients for clinically significant polymorphisms and the tailoring of therapy based on the genetic profile of the patient are conceivable outcomes that await further study. If this is what the future holds, we have this paper to thank for it.

Stable Viral Load but Evolving Drug Resistance

Kantor R, Shafer RW, Follansbee S, et al. *Evolution of resistance to drugs in HIV-1-infected patients failing antiretroviral therapy. AIDS. July 23, 2004;18(11)1503-1511.*

Not every patient on potent antiretroviral therapy achieves an undetectable viral load. Therefore, despite our best efforts, some HIV-infected patients have reduced but detectable plasma HIV-RNA levels while on therapy. Emerging data suggest that some of these patients with stable, even low-level, viremia accumulate new antiretroviral therapy resistance.

To evaluate the risk of resistance cultivation in patients with detectable viral loads, researchers at Stanford University in California searched their database for patients who had known treatment histories, 2 genotypic resistance tests performed at least 2 months apart and no change in antiretroviral therapy during the period between the 2 genotypic resistance tests.

Their search yielded 106 patients. The researchers found that the median duration of the antiretroviral therapy regimen prior to the patients' first genotypic resistance test was 29 months. The median time between genotypic resistance tests was 14 months.

When the first genotypic resistance test was given, patients' median viral load and CD4+ cell count were 3.7 log₁₀ copies/mL and 336 cells/mm³, respectively. At the time of the second genotypic resistance test, these were 4.0 log₁₀ copies/mL and 339 cells/mm³, respectively, which was statistically significant only for the change in viral load.

In the period of time between the 2 genotypic resistance tests, 75% of the patients had developed a new drug resistance mutation. There were PI mutations in 62% of those on PIs, NRTI mutations in 42% of those on drugs of this class and NNRTI mutations in 29% of those on efavirenz or nevirapine. Among patients with a viral load of less than 5,000 copies/mL at first test, 37% developed new drug resistance, as did 12 of the 13 patients who maintained a viral load of 50-999 copies/mL. The total number of drugs predicted by resistance testing to be "resistant" increased from a median of 8 to 10.

These results are cause for concern. While, reassuringly, CD4+ cell counts and viral loads changed little while antiretroviral therapy was continued and viremia remained detectable, drug resistance nonetheless increased in the large majority of patients.

This finding is not a complete surprise when one recognizes that ongoing viral replication in the face of drug exposure always poses a risk for the generation of drug resistance mutations. In this

case, replication is low level and thus, resistance emerges, albeit slowly. This observation supports those made by others including, most recently Lafeuille and colleagues.¹⁹ Reassuringly, available data suggest that despite this risk of resistance development, patients with low-level viremia (viral load 400-20,000 copies/mL) over the short run (~4 years) do not experience progression of their HIV disease at rates that exceed those of patients with an undetectable HIV-RNA level.²⁰

However, it is still unclear what to do about this risk of viral resistance in such patients. The studies performed in this area are limited by the ability of today's resistance tests to detect resistance mutations in patients who have extremely low viral loads. What would be ideal would be a set of predictors of resistance in the setting of low-level viremia. If we knew, for example, that people with certain antiretroviral therapy histories, baseline viral load levels, slope of plasma HIV-RNA decays and/or baseline mutations were more at risk of accumulating more resistance during low-level viremia, we could then make educated guesses about which patients to keep on their regimen and whom to switch. Certainly, for the patient with little or no therapeutic options remaining (i.e., deep salvage) such predictors may be less useful but could still indicate who would need to be monitored more closely for virologic failure.

How Stable Is Stable Low-Level Viremia?

Re VL III, Gasink L, Kostman JR, Leonard D, Gross R. *Natural history of patients with low-level HIV viremia on antiretroviral therapy. AIDS Patient Care and STDs. August 2004;18(8):436-442.*

The issue of how to manage a patient with persistent low-level viremia extends beyond whether such patients are at risk for cultivating drug resistance, but importantly also raises the question of how long can these low levels be maintained before clear virologic failure ensues.

In this study, researchers followed patients who were on a stable antiretroviral regimen and had a viral load between 50-500 copies/mL for at least 3 months prior to and at study entry. The main outcome of this study was the proportion of patients whose viral load increased to over 1,000 copies/mL.

Although 79 participants were originally included in the study, 5 people changed antiretroviral regimens during the course of the study. The median patient age was 47 years, 56% were African American and 84% were male. The median viral load and CD4+ cell count at entry were 139 copies/mL and 455 cells/mm³, respectively. The median follow-up was 693 days.

A virologic increase of more than 1,000 copies/mL was seen in 29/79 (37%) of the patients at a median of just under a year (357 days). An additional 30/79 (38%) were undetectable (<50 copies/mL) at their last follow-up visit. After 3 years of follow-up, approximately 40% of the patients with a detectable viral load had still not reached a viral load of more than 1000 copies/mL. To determine the risk factors associated with virologic rebound, Cox proportional hazard models were used and determined that the only factors associated with rebound were, inexplicably, white race and higher viral load level at study entry.

This study is small comfort to those clinicians who are angst-ridden by patients experiencing low-level viremia -- an increasingly expanding group of patients. Some of these people seem to maintain their low viral loads, but others do not. As in the Stanford University study on viral resistance during low-level viremia discussed above, we still do not understand exactly what factors differentiate patients who develop resistance and rebound and those who don't. Certainly, as stated previously, it is comforting to know that, clinically, patients with undetectable versus patients with low-level viremia do not seem to experience major differences in their rate of opportunistic infection development or death in the short run. However, a better question is: Will these groups separate over the long haul? My guess is, they will.

So, for those of us who tend to maintain patients with low-level viremia on their regimens, this study and the one above it help us to appreciate the risk our patients face when we decide to "stand there and do nothing." This study suggests that a third of such patients will rebound and similarly, according to the previous study (Kantor et al) about this proportion with a viral load less than 5,000 copies/mL will develop new resistance mutations. These are the odds as we understand them today. Do you feel lucky?

The Down Low

Centers for Disease Control and Prevention. *HIV transmission among black college student and non-student men who have sex with men -- North Carolina, 2003. MMWR. August 20, 2004;53(32)731-734.*

Men who have sex with men (MSM) but do not identify themselves as gay, what is now referred to as living on the "down low" (or DL), are not a new phenomena. However, a perfect storm of events over the past few years has led to a surge of interest in the down low, particularly as it relates to African-American men.

The finding of high rates of HIV infection among African-American MSM in U.S. cities, followed by updated statistics that show that large numbers of African-American women are being infected with HIV, set up a story that has grown legs of its own and has found its way to the Oprah Winfrey television show and back.

For all the hype and misunderstanding, there is genuine concern that some proportion of the spread of HIV in African-American communities may be related to the down low and the stigmatization and secrecy associated with it. However, in addition to the hype, there are also data.

In November 2002, in North Carolina, a unique program was designed to identify acute HIV infection among those presenting for HIV antibody testing. The researchers identified 2 male, African-American college students with acute HIV. A retrospective review of all men between 18 to 30 years of age with HIV diagnosed during January 2000 to May 2003 in that area indicated an increase in HIV case reports among male college students, from 2 cases in 2000 to 56 cases during January 2001 to May 2003. Of these 56 men, a total of 49 of the cases (88%) were in African Americans, and nearly all were MSM, including some men who had sex with both men and women.

In follow-up, a case control study was initiated to identify behavioral risk factors for HIV infection in young, black MSM. The cases were of black, HIV-infected, MSM college students, age 18 to 30 years, diagnosed during 2001 to 2003. All were North Carolina residents. These cases were compared to 2 groups of HIV-uninfected controls: college students and non-students, all of whom were also black MSM, aged 18 to 30 years, who lived in North Carolina. The study recruited 17 (35%) of the 49 African-American men who were college students and identified by the state surveillance system as being HIV infected. The 2 groups of HIV-uninfected controls: 19 HIV-uninfected college students and 15 HIV-uninfected non-students were recruited during HIV pre- or post-test counseling activities at local health departments (n = 5), gay nightclubs (n = 26) and the North Carolina Pride Festival (n = 3).

The general characteristics of the 3 groups (HIV-infected MSM college students, HIV-uninfected MSM college students and HIV-uninfected MSM non-college students) were similar; however, there were lower rates of sexually transmitted diseases among the HIV-uninfected students compared to the HIV-infected group. The mean number of steady male partners during the preceding 12 months was similar for the 3 groups and the frequency of unprotected receptive anal intercourse with steady partners ranged from 38% among non-students to 56% among HIV-infected students. More non-students tended to have casual male sex partners than students. While one third of both HIV-infected and HIV-uninfected college students met sex partners on college campuses, most met their sex partners at gay nightclubs or over the Internet. Compared to non-college students, fewer college students identified themselves as gay or disclosed their sexual identity. Importantly, approximately 20% of all the study participants had a female sex partner during the preceding 12 months and this did not differ between the groups.

There is much more work that needs to be done to understand the contribution of the down low to the HIV epidemic in the United States. However, it is equally important that this work not be misinterpreted and risk further heightening the stigmatization of MSM, particularly those who are African American. Obviously, as has been noted long ago, homophobia plays a critical role in fueling the spread of HIV/AIDS. It is conceivable, if not likely, that the continually negative pressures that MSM often face from society and their communities, families and religious institutions drive them to secrecy. Reducing or eliminating these pressures, in essence, allowing gay men to be gay, could go a long way to making the down low a historic footnote in the long history of the HIV epidemic.

The grim statistics strongly support vastly improved efforts to make safer sex a reality for both African-American men and women at risk. Identification and counseling of HIV-infected individuals, combined with encouragement of condom use are key elements of this effort but further innovation will be needed. Add that to the "to do" list for 2005.

HCV Therapy in Coinfected Patients

Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al, for the APRICOT Study Group.
Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients.
N Engl J Med. July 29, 2004;**351(5):438-450.**

Hepatitis C virus (HCV) infection is a leading cause of death among HIV-infected persons in many regions.²¹⁻²³ Yet, this infection is probably under-treated. Certainly, the obstacles to treatment are hardly trivial. The expense of therapy, the adverse effects associated with treatment and the preference for the rather invasive liver biopsy for diagnosis (with its own rare but significant associated risks) all can make this a difficult proposition. Added to that is the relatively low rate of success of therapy, particularly for genotype 1 HCV virus. However, recent clinical trials demonstrate that efficacy can be improved with the use of pegylated interferon plus ribavirin (Copegus, Rebetol, Virazole).

In the AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT), a large (n = 868) study enrolling in 19 countries, patients were randomized to 1 of 3 regimens: peginterferon alfa-2a (Pegasys) (180 µg per week) plus ribavirin (800 mg per day), peginterferon alfa-2a plus placebo or interferon alfa-2a (Roferon-A) (3 million IU three times a week) plus ribavirin.

Patients were treated for 48 weeks and followed for an additional 24 weeks. The primary end point was a sustained virologic response (defined as a serum HCV-RNA level below 50 IU per milliliter at the end of follow-up, at week 72).

The overall rate of sustained virologic response was significantly higher among the recipients of peginterferon alfa-2a plus ribavirin than among those assigned to interferon alfa-2a plus ribavirin (40% vs. 12%, $P < .001$), or peginterferon alfa-2a plus placebo (40% vs. 20%, $P < .001$). Among patients infected with HCV genotype 1, the most common genotype in the United States, the rates of sustained virologic response were lower: 29% with peginterferon alfa-2a plus ribavirin, 14% with peginterferon alfa-2a plus placebo and 7% with interferon alfa-2a plus ribavirin.

Other studies reported in 2004 also support the use of pegylated interferon plus ribavirin in coinfecting patients, although lower response rates were reported in most (i.e., in the ACTG Study A5071: there was 14% sustained response rate among genotype 1 subjects).^{24,25} The intolerability of therapy (with side effects such as depression, anemia, neutropenia and fatigue) continues to plague HCV therapy in the setting of HIV; however, these can be minimized with the involvement of experienced clinicians who have the infrastructure to provide extended support to patients during their HCV treatment course. Collectively, the data support offering HCV therapy to our HIV-infected patients. At present, the "cure" rates for HCV in coinfecting patients are 14% to 30%. Although these rates are not high they are higher than the cure rate for HIV (which, of course, is still 0%).

Summary

In my opinion, the best studies are those that improve our understanding of disease and practice of medicine. The papers described above are, at the very least, thought-provoking. Some are instructive, advising how to prescribe certain therapies, while others are a call to action to prevent new infections here and abroad.

We are at an interesting juncture in the history of HIV therapy. For those of us in resource-rich nations, we have become well acquainted with HAART and, while we tinker with it, we continue to look for that "next best thing." For patients and clinicians with limited access to HIV therapies, procuring therapy has become the goal. I am confident this will happen, albeit at a rate most will agree is tectonic relative to the need. But, even those in Africa and Asia stand to benefit from some of the lessons we in the United States, Europe and Australia have learned getting to this point.

The start of a new year is a fine time to chronicle HIV medical achievements, and it also provides an opportunity to list our shortcomings and resolve to address these in the coming year. In 2005 we can work to capitalize on our gains and make the benefits of what we have achieved available to everyone living with HIV worldwide. At the same time, we must continue to search for the breakthroughs that will advance our fight against this epidemic and ultimately make our list of top 10 HIV/AIDS articles obsolete.

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

References

1. Program on International Policy Attitudes. [Americans on Foreign Aid and World Hunger: A Study of U.S. Public Attitudes](#). University of Maryland; February 2, 2001.
2. Program on International Policy Attitudes. [Americans on Defense Spending and the War on Terrorism](#). University of Maryland; August 2, 2002.
3. Ruane P, Luber A, Gaultier C, et al. [Maintenance therapy using lopinavir/ritonavir \(LPV/r\) alone with well-controlled HIV infection](#). In: Program and abstracts of the XV International AIDS Conference; July 11-16, 2004; Bangkok, Thailand. Abstract TuPeB4577.
4. Pierone G, Mieras J, Fontaine L, et al. [Simplification to lopinavir/ritonavir monotherapy from NNRTI-based HAART in HIV-infected patients with complete viral suppression](#). In: Program and abstracts of the XV International AIDS Conference; July 11-16, 2004; Bangkok, Thailand. Abstract TuPeB4595.
5. Gallant JE, Staszewski S, Pozniak AL, et al, for the 903 Study Group. [Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: A 3-year randomized trial](#). JAMA. July 14, 2004;292(2):191-201.
6. Staszewski S, Morales-Ramirez J, Tashima KT, et al, for the Study 006 Team. [Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults](#). N Engl J Med. December 16, 1999;341(25):1865-1873.
7. DeJesus E, Grinsztejn B, Rodriguez C, et al. [Efficacy and safety of atazanavir with ritonavir or saquinavir vs lopinavir/ritonavir in patients who have experienced virologic failure on multiple HAART regimens: 48-week results from BMS A1424-045](#). In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, Calif. Abstract 547.
8. Gallant JE, Rodriguez AE, Weinberg W, et al. [Early non-response to tenofovir DF \(TDF\) + abacavir \(ABC\) and lamivudine \(3TC\) in a randomized trial compared to efavirenz \(EFV\) + ABC and 3TC: ESS30009 unplanned interim analysis](#). In: Program and abstracts of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy; September 14-17, 2003; Chicago, Ill. Abstract H-1722a.
9. Gerstoft J, Kirk O, Obel N, et al. [Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine](#). AIDS. September 26, 2003;17(14):2045-2052.
10. Jemsek J, Hutcherson P, Harper E. [Poor virologic responses and early emergence of resistance in treatment naive, HIV-infected patients receiving a once daily triple nucleoside regimen of didanosine, lamivudine, and tenofovir DF](#). In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, Calif. Abstract 51.
11. Mauss S, Milinkovic A, Hoffmann C, et al. [Low rate of treatment failure on antiretroviral therapy with tenofovir, lamivudine and zidovudine](#). AIDS. January 3, 2005;19(1):101-103.
12. Moyle G, Maitland D, Hand J, Mandalia S, Nelson M, Gazzard B. [Early virological failure in persons with viral loads >100,000 cps/mL and CD4 counts <200/mm³ receiving ddI/tenofovir/efavirenz as initial therapy: Results from a randomized comparative trial](#). In: Program and abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy; October 30 - November 2, 2004; Washington, DC. Abstract H-566.
13. Podzamczar D, Ferrer E, Gatell JM, et al. [Early virological failure and occurrence of](#)

- resistance in naive patients receiving tenofovir, didanosine and efavirenz. *Antivir Ther.* 2004; 9:S172.
14. Moyle G, Nelson M, Higgs C, et al. [A randomised open label comparative study of Combivir + efavirenz \(2 class triple therapy\) versus Trizivir + tenofovir \(single class quadruple therapy\) in initial therapy for HIV-1 infection.](#) In: Program and abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy; October 30 - November 2, 2004; Washington, D.C. Abstract H-1131.
 15. Elion R, Cohen C, DeJesus E, et al, and the COL40263 Study Team. [COL40263: Resistance and efficacy of once-daily Trizivir and tenofovir DF in antiretroviral naive subjects.](#) In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, Calif. Abstract 53.
 16. Barrett JS, Joshi AS, Chai M, Ludden TM, Fiske WD, Pieniaszek HJ Jr. [Population pharmacokinetic meta-analysis with efavirenz.](#) *Int J Clin Pharmacol Ther.* November 2002; 40(11):507-519.
 17. Pfister M, Labbe L, Hammer SM, et al, and the AIDS Clinical Trial Group Protocol 398 Investigators. [Population pharmacokinetics and pharmacodynamics of efavirenz, nelfinavir, and indinavir: Adult AIDS Clinical Trial Group Study 398.](#) *Antimicrob Agents Chemother.* January 2003; 47(1):130-137.
 18. Wegner S, Vahey M, Dolan M, et al. [Racial differences in clinical efficacy of efavirenz-based antiretroviral therapy.](#) In: Program and abstracts of the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Wash. Abstract 428-W.
 19. Lafeuillade A, Hittinger G, Delbeke E, Poggi C. [Resistance selection in patients with stable low levels of HIV-1 viremia.](#) In: Program and abstracts of the XV International AIDS Conference; July 11-16, 2004; Bangkok, Thailand. Abstract WeOrB1293.
 20. Raffanti SP, Fusco JS, Sherrill BH, et al. [Effect of persistent moderate viremia on disease progression during HIV therapy.](#) *J Acquir Immune Defic Syndr.* September 1, 2004; 37(1):1147-1154.
 21. Gupta AK, et al. Increasing incidence of hepatitis C (HCV) and human immunodeficiency virus (HIV)-HCV co-infection -- significance for the future. In: Program and abstracts of the 37th Annual Meeting of the Infectious Diseases Society of America; November 18-21, 1999; Philadelphia, Pa. Abstract 708.
 22. McGovern BH, et al. Increasing mortality from end-stage liver disease secondary to hepatitis C in patients with human immunodeficiency virus infection. In: Program and abstracts of the 37th Annual Meeting of the Infectious Diseases Society of America; November 18-21, 1999; Philadelphia, Pa. Abstract 235.
 23. Jain MK, Skiest DJ, Cloud JW, Jain CL, Burns D, Berggren RE. [Changes in mortality related to human immunodeficiency virus infection: Comparative analysis of inpatient deaths in 1995 and in 1999-2000.](#) *Clin Infect Dis.* April 15, 2003; 36(8): 1030-1038.
 24. Chung R, Andersen J, Volberding P, et al. [A randomized, controlled trial of PEG-interferon-alfa-2a plus ribavirin vs interferon-alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-co-infected persons: Follow-up results of ACTG A5071.](#) In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, Calif. Abstract 110.
 25. Perronne C, Carrat F, Bani-Sadr F, et al. [Final results of ANRS HC02-RIBAVIC: A randomized controlled trial of pegylated-interferon-alfa-2b plus ribavirin vs. interferon-alfa-2b plus ribavirin for the initial treatment of chronic hepatitis C in HIV co-infected patients.](#) In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, Calif. Abstract 117LB.

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

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

© 2005 Body Health Resources Corporation