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Top Ten Research Reports of 2003

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February 2004

Table of Contents

- [Introduction](#)
- 1. [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#)
- 2. [ACTG 5095: A Comparative Study of Three Protease Inhibitor-Sparing Antiretroviral Regimens for the Initial Treatment of HIV Infection](#)
- 3. [ACTG 5097s: Impact of Efavirenz \(EFV\) on Neuropsychological Performance, Mood and Sleep Behavior in HIV-Positive Individuals](#)
- 4. [Combination Antiretroviral Therapy and the Risk of Myocardial Infarction](#)
- 5. [Impact of HIV Infection and HAART on Serum Lipids in Men](#)
- 6. [Efficacy and Safety of Atazanavir With Ritonavir or Saquinavir Versus Lopinavir/Ritonavir in Combination With Tenofovir and One NRTI in Patients Who Have Experienced Virologic Failure to Multiple HAART Regimens: 24-Week Results From BMS AI424-045](#)
- 7. [Continued Reverse Transcriptase Inhibitor Therapy Is Sufficient to Maintain Short-Term Partial Suppression of Multi-Drug Resistant Viremia](#)
- 8. [Analysis From More Than 1,600 Newly Diagnosed Patients](#)

- [With HIV From 17 European Countries Shows That 10% of the Patients Carry Primary Drug Resistance: The CATCH Study](#)
9. [Enfuvirtide, an HIV-1 Fusion Inhibitor, for Drug-Resistant HIV Infection in North and South America](#)
 10. [Prognostic Importance of Initial Response in HIV-1 Infected Patients Starting Potent Antiretroviral Therapy: Analysis of Prospective Studies](#)
 - [Conclusion: Achievements and Limitations](#)
 - [Chart Outlining the Clinical Impact of 2003's Top Reports](#)
 - [References](#)

Introduction

At the close of one year and the beginning of the next, a deep-seated human gene is expressed compelling us to list the top 10 of all things great and small during the past 12 months. The year-end top 10 phenomenon has also found its way into medical education, where experts report what they consider to be the most important developments in their fields. Such lists are, naturally, quite subjective, reflecting the interests of the list-maker, but to a great extent they can also be somewhat redundant as the big news-making studies deservedly find a place on every such list.

What follows is the view of one U.S.-based clinical researcher/clinician on what new information led to a change in the way we practice HIV care -- or, at the very least, made us stop and think long and hard about what we are doing. The accompanying [table](#) provides a quick overview of the take-home message from each item on the list, describes how the selected data influenced and advanced our understanding of HIV medicine and, finally, details what remains to be learned.

1. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS). [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#). 2003 Nov 10.

Background

Although not a research paper per se, the U.S. Department of Health and Human Services (DHHS) guidelines and their now-frequent updates are extremely influential and informative. However, as is the case for presidential biographies and tell-all memoirs, most people who like to talk about the guidelines have not actually read them. But they are worth a close reading. The guidelines were developed by the Panel on Clinical Practices for Treatment of HIV Infection convened by the DHHS, and the concise and carefully worded text describes the data supporting the panel's recommendations. The 2003 updates were most notable for their recommendations regarding when to initiate therapy and detailed lists of which therapies to use.

What Is New Here?

While many clinicians and persons living with HIV infection are understandably fixated on the new drug pipeline and when the hottest new antiretrovirals will become available, it still remains less than perfectly clear at what point in the course of HIV infection it is optimal to initiate HIV treatment. The complexity of this issue has been reflected in the varying recommendations throughout the many versions of the DHHS guidelines (as well as the International AIDS Society guidelines) and, most critically, in the clinical practices of physicians across the United States.

It was not long ago when the DHHS recommended that all HIV-positive patients with a CD4 cell count below 500 cells/uL should be prescribed antiretroviral therapy. Paradoxically, in the interim, HIV therapies have become more potent, yet their limitations (toxicity, cross resistance, cost) have prompted greater caution regarding their use. While most clinicians are delaying the start of therapy until after a patient's CD4 cell count has dropped well below 500 cells/uL, a stalemate has emerged between the "hit early" versus "hit late" camps. This has led to the creation of a gray area between 200 and 350 cells/uL in which the merits of therapy remain debated.

In the 2003 edition of the treatment guidelines, the focus is still on the importance of using a patient's CD4 cell count to decide when therapy should begin. As in earlier versions, the new guidelines state that

serious consideration to initiate treatment should begin when a patient's CD4 cell count falls below 350 cells/uL or, of course, if symptoms of HIV develop.

The striking difference in the July update to the guidelines was the addition of the new designations of "preferred" and "alternative" to certain antiretroviral regimens and the bold positions that were taken regarding the superiority of certain agents and regimens over others.

The guidelines designated as "preferred" regimens for initial therapy those combinations containing two NRTIs plus either efavirenz (EFV, Sustiva, Stocrin) or lopinavir/ritonavir (LPV/r, Kaletra). The guidelines did not mince words; efavirenz or lopinavir/ritonavir were determined to be superior to all other agents in their respective classes based on available evidence. "Alternative" regimens included commonly used combinations.

Based on recent clinical trial results, including results from AIDS Clinical Trials Group (ACTG) 5095 (see [next report](#)), it was recommended that triple-NRTI regimens should be considered only if an NNRTI- or protease inhibitor (PI)-anchored regimen is not possible. The important caveat was the specification that only ZDV (zidovudine, Retrovir) + 3TC (lamivudine, Epivir) + abacavir (ABC, Ziagen) be used and *not* other triple NRTI regimens, such as tenofovir (TDF, Viread) + 3TC + abacavir or tenofovir + 3TC + ddI (didanosine, Videx) -- regimens that have shown extremely high rates of failure in recent studies.

The Bottom Line

The DHHS guidelines are an evolving document that reflects, as much as it dictates, how clinicians approach the management of HIV. The new recommendations certainly reflect what clinicians across the United States already have been doing, but they also add nuanced arguments that challenge some of our assumptions -- e.g., though many clinicians believe that efavirenz and nevirapine (NVP, Viramune) are as similar as Coke and Pepsi, the guidelines state a clear preference for efavirenz. The ascendance of lopinavir/ritonavir to the same throne as efavirenz also surprised some clinicians and signals a shift back to PI-based therapy as initial HIV treatment.

It is for Vegas odds-makers and panel watchers to predict future changes to the guidelines. In the short term, the rise of ritonavir-boosted atazanavir as an initial treatment -- which seems to be the newest practice among clinicians -- may lead this drug to a coveted berth, particularly if more data supporting this approach emerge. In the long run, how the guidelines evolve will be interesting to see. In the 2003 changes the panel responsible for the guidelines seemed to have become more willing to make recommendations that may be seen as controversial. An example of this is the current version's rationale for the preference of efavirenz over nevirapine as a first-line agent.

I think that the latest changes increase the relevance of the recommendations, particularly for seasoned HIV treaters. For clinicians with few HIV-infected patients, the guidelines have always been an indispensable resource. However, the guidelines tended to be less useful to veteran HIV providers whose practice the guidelines mirror. In my practice, I find that the guidelines validate my choice of medications, reassure my patients that my recommendations are not the ravings of a mad, scruffy clinical scientist and, I admit it, they actually influence my clinical decisions. Whether you agree with the recommendations or not, and increasingly many do, it is a compelling read.

2. ACTG 5095: A Comparative Study of Three Protease Inhibitor-Sparing Antiretroviral Regimens for the Initial Treatment of HIV Infection

Gulick R. M., Ribaldo H. J., Shikuma C. M. et al. [ACTG 5095: A Comparative Study of Three Protease Inhibitor-Sparing Antiretroviral Regimens for the Initial Treatment of HIV Infection](#). Presented at: 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment; July 13-16, 2003; Paris, France. Abstract 41.

Background

Triple-NRTI therapy as HAART was ushered into common usage with the introduction of Trizivir -- the single tablet formulation of ZDV/3TC/abacavir. Early studies comparing these three nucleoside analogues to PI-based therapies had mixed results. The open-label trials demonstrated similar efficacy, but the blinded studies indicated better virologic outcomes with PI-containing regimens.^{[1-3](#)}

Many people looked at this data and believed that the convenience of a regimen that consisted of only one pill dosed twice a day compensated for Trizivir's relative deficiency in potency. This helps explain the popularity of Trizivir despite these doubts and the equipoise of the available data before A5095.

What Is New Here?

No single clinical trial result presented in the past year has had as dramatic an impact on how U.S. HIV specialists treat their patients as the ACTG 5095 study. As described in my summary of the [U.S. DHHS treatment guidelines](#), the interim results have prompted considerable modification to the initial treatment of HIV infection. This study was the most significant of several events that spelled the beginning of the end of our love affair with triple-nucleoside therapy.

This blinded study was originally designed to compare three combinations: ZDV + 3TC + abacavir versus ZDV + 3TC + efavirenz versus ZDV + 3TC + abacavir + efavirenz. A scheduled interim analysis after a mean of 32 weeks on-treatment revealed a higher rate of virologic failure (HIV RNA PCR > 200 copies/mL after 16 weeks following entry) among those subjects assigned to the triple-NRTI arm compared to those on the pooled efavirenz-containing arms (21% vs. 10%, respectively, $p < 0.001$).

For subjects who had 48-week data, the proportion with a viral load <200 copies/mL was lower in the triple-NRTI arm (74%) compared to the pooled NNRTI arms (89%). Significantly, the differences between the triple-NRTI arm and the remaining two arms were *not* influenced much by baseline viral load. In fact, the triple-NRTI combination fared worse even among patients with an HIV RNA level below 100,000 copies/mL.

Further, although at baseline 95% of the 82 subjects who failed ZDV + 3TC + abacavir had wild-type virus by genotypic resistance testing, at the time of failure, 65% of those patients with a genotype available had a 3TC-associated M184V mutation (a quarter of whom also had another NRTI mutation). Notably, there was evidence of increasing cross-resistance over time following the failure of this triple-NRTI combination. More than half of the subjects who had genotype data a

year following failure had M184V *plus* at least one thymidine-analogue-associated mutation (TAM).

The development of the 3TC-signature mutation as well as a TAM, significantly hampers the use of NRTIs in subsequent salvage regimens. These resistance data, along with the relatively greater rate of virologic failure of the triple nucleoside, are the reasons for the newfound allergy many clinicians now have to Trizivir.

The Bottom Line

The ACTG 5095 data seem to validate earlier blinded studies that cast shadows across the claims of equipotence of ZDV + 3TC + abacavir and PI-based regimens. They also raise concern that although this triple-NRTI combination may perform well at the onset, late failures with crippling mutations can occur.

On the heels of these results, a series of presentations on other triple-NRTI regimens were publicized, each of which had horrendous rates of failure and resistance development. A once-a-day regimen of tenofovir + 3TC + abacavir, when compared to ZDV + 3TC + efavirenz, performed much worse than ZDV + 3TC + abacavir did in A5095. All subjects failing this regimen had a M184V mutation, usually along with a K65R tenofovir- and abacavir-associated mutation. A smaller, single-arm study of ddI-EC (enteric-coated formulation) + 3TC + tenofovir had an astounding 91% rate of virologic failure by week 12 of the study, again with almost universal 3TC resistance at the time of failure.⁴

The focus of much discussion among clinicians and investigators during the latter half of 2003 has been regarding what to make of these remarkable results. Perhaps lost to a casual observer is that these triple NRTIs did not appear to be equally bad. A 74% proportion of subjects on ZDV + 3TC + abacavir did reach an undetectable HIV RNA at 48 weeks.⁴⁻⁵ While this is clearly not as good as its efavirenz-powered competitors, it is not altogether unrespectable and is in a different league from the miserable performance of the other triple-NRTI results that have followed.

Why the difference? Some speculate that the presence of the thymidine analogue ZDV in this combination is the key. ZDV provides pressure

preventing the emergence of the M184V mutation, which is a weak-link mutation that both destroys 3TC's antiviral activity and reduces viral susceptibility to abacavir once it develops. Another potential benefit of having ZDV in the mix is that M184V mutants are generally hypersusceptible to ZDV. Therefore, it helps to keep in mind that although not all triple NRTIs are created equally, they should all be avoided.

This 1,100-subject study is still ongoing. Look for the details of the ACTG 5095 study in an upcoming issue of the *New England Journal of Medicine*.

3. ACTG 5097s: Impact of Efavirenz on Neuropsychological Performance, Mood and Sleep Behavior in HIV-Positive Individuals

Clifford D. B., Evans S., Yang Y. et al. [ACTG 5097s: Impact of Efavirenz \(EFV\) on Neuropsychological Performance, Mood and Sleep Behavior in HIV-Positive Individuals](#). Presented at: 2nd IAS Conference on HIV Pathogenesis and Treatment; July 13-16, 2003; Paris, France. Abstract 54.

Background

There seem to be two types of U.S. HIV care providers, at least in areas in which potent combination antiretroviral agents are available: those who like efavirenz and those who don't. The latter often predicate their distaste for the current king of antiretrovirals based on the neuropsychiatric toxicities associated with it. Dizziness, sleep disturbance, depression and dissociation have been ascribed to efavirenz, something which has prompted most patients to take this drug prior to going to sleep (despite the additional adverse event of vivid dreams). Although these central nervous system (CNS) adverse effects are reported by the manufacturer to be short-lived, subsiding after a few weeks, there are few data supporting this claim and many providers remain unconvinced, believing the drug has longer-lasting toxicity.

As a substudy of [A5095](#) (described earlier) the neuropsychological effects of efavirenz were carefully evaluated with a battery of tests in a

subset of 303 participants.

What Is New Here?

A concentrated evaluation of the CNS effects of efavirenz has not previously been done in a large number of patients. The blinded nature of the study offered added opportunities to dissect efavirenz's impact on patients' thinking and functioning and, in so doing, separate fact from the myth regarding this popular agent.

Of the 303 subjects enrolled, 200 were taking efavirenz. All the patients were tested at baseline and then again at weeks one, four, 12 and 24 of therapy. Looking strictly at neuropsychological function, there were no statistically or clinically significant differences at the time points between patients who were and those who were not assigned efavirenz. Some efavirenz-specific symptoms, such as bad dreams, were more common in those receiving this drug, but only at the week one evaluation. Interestingly, sleep quality was recorded as *better* in the efavirenz arms at week four, but subsequently there were differences. Depression and anxiety scales also found no differences between the groups.

The Bottom Line

Efavirenz clearly led to some of the adverse effects it has become well known for, especially dream disturbance, but these side effects vanished by week four. Other neuropsychological adverse effects were not seen to be different from those taking ZDV + 3TC + abacavir. These data are important and help explain the relatively low treatment discontinuation rates (5-10%) observed in the clinical trials of efavirenz. Given the reliance on efavirenz as a preferred anchor of initial antiretroviral therapy and the concerns expressed regarding the CNS effects of this drug (sometimes by competitors), this study is reassuring and finally settles some popularly held beliefs with some real facts.

4. Combination Antiretroviral Therapy and the Risk of Myocardial Infarction

Friis-Møller N., Sabin C. A., Weber R. et al. [Combination](#)

[Antiretroviral Therapy and the Risk of Myocardial Infarction](#). New England Journal of Medicine, 2003 Nov 20; 349(21):1993-2003.

Friis-Møller N., Weber R., Reiss P. et al. [Cardiovascular Disease Risk Factors in HIV Patients -- Association With Antiretroviral Therapy: Results From the D:A:D Study](#). AIDS. 2003 May 23; 17(8):1179-93.

Background

Lipid abnormalities [have long been proven](#) to accompany both HIV infection and HAART.⁶ As individuals with HIV enjoy longer survival, concern has justifiably been focused on the risk these patients face for cardiovascular disease (CVD). In what until now was the largest study focusing on CVD and HIV, *no* increase in the rate of CVD-related hospital admissions or death was demonstrated among 36,766 patients of Veteran's Administration (VA) hospitals in the five years prior to and following the introduction of combination antiretroviral therapy.⁷ Notably, in this study, overall death rates *declined* dramatically, mirroring the decline in AIDS-related mortality seen nationwide.

Other, smaller studies, however, have suggested increases in CVD among antiretroviral-treated patients, although the overall number of events was small. This has left many wondering what is really going on. So where are we right now? Unfortunately, we still have a lot of inconclusive results.

What Is New Here?

In a multinational prospective study called the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, the incidence of myocardial infarction (MI) was examined. The majority of the more than 23,000 patients in this study were receiving combination antiretroviral therapy. During 36,199 patient years of follow-up, 126 probable or verified MIs were recorded, about a third of which were fatal. Each year of antiretroviral-therapy exposure was associated with a 26% increased risk of MI. Other contributing factors independently predicting the incidence of MI were age, smoking and a history of previous CVD. An elevated baseline LDL cholesterol, but not hypertriglyceridemia, was also associated with MI incidence. Counterintuitively, clinician-defined lipodystrophy was associated with

a *reduced* risk of MI.

The Bottom Line

The D:A:D study serves as an important counterpoint to the VA study. D:A:D is a prospective study while the VA study was retrospective, which may help explain the divergent results. Importantly, D:A:D is continuing to monitor the study participants, providing an extended look at a condition that, outside the setting of HIV, usually takes years and even decades to manifest as clinically evident disease.

It is essential to keep in mind that the rate of MI seen in this study was very low, which demonstrates that at this point, CVD is not at all widespread among antiretroviral-treated patients. This is important to emphasize -- particularly to patients, who, because of the wide press coverage of this study, often perceive the risk of CVD to be much greater.

It's equally crucial not to lose sight of the benefits antiretroviral therapy conferred both in the VA and D:A:D studies vis-à-vis mortality. Given the lipid profiles associated with both HIV and its treatment, few researchers expect that there will not be additional risk of CVD among persons living with HIV; i.e., HIV is unlikely to be a cardioprotective virus. The development of medications such as atazanavir (Reyataz), which have limited dyslipidemic properties, will likely help avoid excess CVD morbidity and mortality.

Other mutable factors seem to be just as critical to CVD risk, though. These include smoking, diet and exercise -- just as for the HIV-uninfected. Meanwhile, it is essential for clinicians to consider cardiovascular risk when crafting antiretroviral regimens. Lipids and other CVD risk factors should be assessed prior to the start of new regimens and they should be regularly followed while someone is on therapy. The [National Cholesterol Education Program](#) (NCEP) guidelines describe how to estimate CVD risk and the indications for lipid-lowering therapy.⁸ HIV-specific guidelines to dyslipidemias have also been published.⁹

Until D:A:D and other observational cohorts can elucidate the risk conferred by individual drugs among patients with significant risk for CVD, avoidance, when possible, of the antiretrovirals that can raise

lipids, such as indinavir (IDV, Crixivan), nelfinavir (NFV, Viracept), lopinavir/ritonavir (LPV/r, Kaletra) and stavudine (d4T, Zerit), is prudent.

5. Impact of HIV Infection and HAART on Serum Lipids in Men

Riddler S. A., Smit E., Cole S. R. et al. [Impact of HIV Infection and HAART on Serum Lipids in Men](#). JAMA. 2003 June 11; 289(22):2978-82.

Background

Much of the dyslipidemia observed in HIV-infected people has been pinned on HIV therapies. Yet lipid abnormalities -- specifically elevated triglyceride and low HDL cholesterol levels -- are well documented in HIV-infected patients who have never received antiretrovirals. Teasing apart the relative contributions of antiretrovirals and HIV infection itself has been challenging. The ideal way to analyze exactly the part each plays in creating lipid abnormalities would be a longitudinal follow-up of HIV-negative people who become infected and then, after some time, start antiretrovirals. That is exactly what Riddler and colleagues did.

What Is New Here?

The power of the Multi-Center AIDS Cohort Study (MACS) never ceases to amaze. This prescient, observational study enrolled HIV-infected and HIV-uninfected gay and bisexual men at the beginning of the epidemic and has been following many of these men ever since. Fifty of the 517 participants in the MACS cohort who seroconverted during the study had pre-infection, post-infection and post-antiretroviral therapy initiation non-fasting serum for cholesterol levels available.

What was observed in this study was fascinating. Prior to HIV infection, the men had fairly typical cholesterol profiles. Subsequent to acquisition of HIV, their total cholesterol, LDL cholesterol and HDL cholesterol all dropped (triglycerides were not measured). After the initiation of antiretroviral therapy -- predominantly with PI-based

regimens -- their total cholesterol and LDL cholesterol rose above the pre-HIV infection baseline but to levels that would be predicted with age adjustment. Interestingly, antiretroviral therapy did not reverse the decline in HDL cholesterol observed following HIV infection.

The Bottom Line

The study provided a unique vantage point from which to look at the effect of antiretrovirals on lipids, and its findings are provocative. There is no argument that many agents affect lipids, creating a profile that in HIV-uninfected populations is associated with atherosclerosis development. We even know that 500 mg of ritonavir twice a day in HIV-uninfected volunteers raises cholesterol and triglycerides.¹⁰ However, the finding that total cholesterol and LDL cholesterol rise to levels consistent with those that exist prior to HIV infection challenges the contention that antiretrovirals alone raise lipids to pathologic levels. Rather, it appears that HIV therapy actually *reverses* much of the lipid-suppressive effect of HIV itself. Why this reversal seems to happen with some antiretrovirals and not others is unclear. At present, this remains a fascinating observation that may help put the dyslipidemias we are seeing in perspective.

It is likewise unclear why a patient's HDL cholesterol level remains low following HIV infection. With increased use of NNRTIs, which tend to increase HDL cholesterol, this may change. Additionally, whether the results seen here will also be the case among more diverse populations -- such as African Americans and women -- than those in the mostly white, male MACS study is not known and may not be known anytime soon given the unique circumstances of this study. Regardless, lipid elevations during antiretroviral therapy should continue to be considered seriously and treated when appropriate.

6. Efficacy and Safety of Atazanavir With Ritonavir or Saquinavir Versus Lopinavir/Ritonavir in Combination With Tenofovir and One NRTI in Patients Who Have Experienced Virologic Failure to Multiple HAART Regimens: 24-Week Results From BMS AI424-045

Badaro R., DeJesus E., Lazzarin A. et al. [Efficacy and Safety of](#)

[Atazanavir With Ritonavir or Saquinavir Versus Lopinavir/Ritonavir in Combination With Tenofovir and One NRTI in Patients Who Have Experienced Virologic Failure to Multiple HAART Regimens: 24-Week Results From BMS AI424-045](#). Presented at: 2nd IAS Conference on HIV Pathogenesis and Treatment; July 13-16, 2003; Paris, France. Abstract 118.

Background

The protease inhibitor field is a crowded one. At the beginning of 2003, there were half a dozen agents vying to be the one and only PI. To break into this pack, an agent must demonstrate some advantage compared to its competitors. Me-too drugs don't go very far and can be a drag on formularies (to say nothing about the poor drug reps who have to detail the stuff). The early buzz on atazanavir, one of the two PIs approved during this past year, was not always encouraging.

Atazanavir is administered once daily, although in clinical trials¹¹ it had potency that appeared to be on par with nelfinavir (which is one of the weakest PIs, not necessarily something to boast about when positioning yourself against lopinavir/ritonavir). In addition, atazanavir caused hyperbilirubinemia in enough study subjects to lead some to recommend that atazanavir be renamed to "turns-you-yellow-avir."

The situation was not helped much by the results of a quirky study Kate Squires, M.D., and others presented at ICAAC that on the one hand showed atazanavir to be equivalent to efavirenz when combined with two nucleosides, but on the other hand demonstrated that both agents had surprisingly low (<40%) rates of virologic success as measured by a viral load <50 copies/mL at 48 weeks.¹²

Yet, something surprising has happened. Since its release, atazanavir has been embraced. This is largely due to its once-a-day administration and its lipid- and glucose-friendly side-effect profile. However, these advantages alone may not have sufficed if it were not for this trial presented by Dr. Badaro at last summer's IAS conference. It indicates that atazanavir's potency, when coupled with a single, 100-mg dose of ritonavir, is similar to that of lopinavir/ritonavir.

What Is New Here?

In Badaro's study, 358 subjects who had failed two combination antiretroviral regimens -- which included drugs from each of the three treatment classes -- were randomized to tenofovir plus any NRTI and either one of three possible arms: A.) atazanavir 300 mg/ritonavir 100 mg QD versus B.) atazanavir 400 mg/saquinavir 1,200 mg QD versus C.) lopinavir/ritonavir at the standard dose BID.

Surprisingly, the atazanavir/ritonavir combination did very well, with 39% of patients on this regimen achieving a viral load <50 copies/mL at week 24, compared to 42% on lopinavir/ritonavir and only 23% on atazanavir/saquinavir. Importantly, the addition of low-dose ritonavir did not considerably abrogate the lipid-neutral effects of atazanavir.

The Bottom Line

It is extremely impressive that ritonavir-boosted atazanavir can hold its own against lopinavir/ritonavir, arguably the most potent antiretroviral around, and it has many clinicians and patients looking at the drug in a new light. Longer-term data will emerge from this ongoing study, but for those of us treating patients, the addition of a powerful once-daily protease inhibitor to our bag of RXs -- one that can also be readily combined with other once-a-day antiretrovirals -- is tremendously welcome.

7. Continued Reverse Transcriptase Inhibitor Therapy Is Sufficient to Maintain Short-Term Partial Suppression of Multi-Drug Resistant Viremia

Deeks S. G., Martin J. N., Hoh R. et al. [Continued Reverse Transcriptase Inhibitor Therapy Is Sufficient to Maintain Short-Term Partial Suppression of Multi-Drug Resistant Viremia](#). Presented at: 10th Conference on Retroviruses and Opportunistic Infections; February 10-14, 2003; Boston, Mass. Abstract 640.

Background

Just when we thought we understood the fundamentals of HIV drug resistance, along comes a study that teaches us how much we still have

to learn. We do know for a fact that it is not uncommon to observe patients on treatment who have viral loads well below their pre-therapy levels and CD4 cell counts that remain improved, yet who have low-level viremia and mutations to their current regimen.

A possible explanation for this common phenomenon is that the mutations the virus has developed have come at a cost to viral pathogenicity (i.e., the virus becomes less fit and therefore less able to replicate). This also explains why, when an antiretroviral regimen is discontinued in such patients, their viral load typically shoots up, their CD4 cell count plummets and resistant virus is supplanted by more pathogenic, wild-type virus -- Darwinian evolution over the course of a few weeks.

What Is New Here?

In a study presented at CROI 2003, Steven Deeks and colleagues closely observed what occurred when 20 patients with persistent, detectable, multi-drug-resistant viremia, while on stable antiretroviral therapy with a protease inhibitor and nucleosides for at least one year, either stopped their PI (n=15) or their nucleosides (n=5). The choice of which therapy was to be discontinued was based on the toxicity a patient was experiencing at the time of study entry.

What happened next will explain why this is one of 2003's most critical studies: 13 of the 15 patients who stopped their PI had both stable viral loads and CD4 cell counts after 16 weeks. Their toxicities improved, as did their lipids. PI mutations were no longer seen on genotype testing, since the selective pressure from the PI was gone and the risk of accumulation of new PI-associated resistance was reduced. In contrast, the five subjects who discontinued their NRTIs experienced a significant rise in their viral loads and an average 97-cell drop in their CD4 cell counts.

The Bottom Line

This study overturns many of our assumptions about resistance. Few would have accurately predicted the outcome observed by the investigators. The implication here is that the nucleosides may be doing more than we have ever recognized, even when resistance to these drugs is present. Practically speaking, these data suggest that for similar

patients, the removal of a protease inhibitor and the maintenance of the nucleosides may be an option to prevent the cultivation of further PI resistance and limit toxicity. Periodic PI administration may help keep viral loads down and inevitable nucleoside failure at bay. In addition, continuation of "failing" nucleosides, as is commonly done with 3TC, may be a prudent approach to salvage therapy.

On a theoretical level, these preliminary data help us appreciate that resistance is *not* black and white, that partial antiviral effects may persist and that the impact of resistance on viral fitness may increasingly play a role in our treatment decision making.

8. Analysis From More Than 1,600 Newly Diagnosed Patients With HIV From 17 European Countries Shows That 10% of the Patients Carry Primary Drug Resistance: The CATCH Study

Wensing A. M. J., van de Vijver D. A. M. C., Asjo B. et al. [Analysis From More Than 1,600 Newly Diagnosed Patients With HIV From 17 European Countries Shows That 10% of the Patients Carry Primary Drug Resistance: The CATCH Study](#). Presented at: 2nd IAS Conference on Pathogenesis and Treatment; July 13-16, 2003; Paris, France. Abstract LB1.

Background

Viral resistance is not limited to those who have received HIV therapy. Data¹³ from U.S. investigators studying recently infected patients have found evidence of increasing antiretroviral-drug resistance, particularly to those drugs that have been available the longest. The CATCH Study was conducted in 17 countries in Europe and examined the incidence of genotypic resistance among persons newly diagnosed with HIV.

What Is New Here?

The study is a comprehensive examination of transmitted resistance that included people more than a year out from their acquisition of the virus. The investigators found that almost 10% of these treatment-naive

participants had evidence of at least one major antiretroviral mutation. The prevalence of resistance to nucleosides was 6.9%, to non-nucleosides was 2.6%, to PIs was 2.2% and to more than two classes of agents was 1.7%.

Interestingly, the prevalence of primary resistance among patients with seroconversion in the previous year was 10.9% versus 7.5% in patients who had been infected for over a year ($p=0.06$). Further, the prevalence of resistance was significantly higher in patients with subtype B (11.3%) than in patients with non-B subtypes (3.3%), the latter likely representing people infected outside of Europe, in areas where access to antiretroviral therapy is limited.

The Bottom Line

These are dramatic results. That one in 10 people in Europe with newly diagnosed HIV infection harbors antiretroviral-resistant virus casts any argument against the use of resistance testing prior to therapy initiation in a new light. This study was unique in that it demonstrated that contrary to popular perception, the mutations were detectable in the majority of these treatment-naive patients who initially showed resistance *even more than a year after infection*.

The full implication of these resistance mutations for response to subsequent therapy is not yet known, but they are unlikely to be a good thing and, until evidence supports the contrary, they should be respected when initial regimens are being crafted. While resistance testing at initial evaluation is not always within the capacity or budget of many clinics, this study supports such testing when it is possible. In addition, efforts to reduce HIV transmission risk behavior among HIV-infected people must increase to limit the spread of the virus, resistant or otherwise.

9. Enfuvirtide, an HIV-1 Fusion Inhibitor, for Drug-Resistant HIV Infection in North and South America

Lalezari J.P., Henry K., O'Hearn M. et al. [Enfuvirtide, an HIV-1 Fusion Inhibitor, for Drug-Resistant HIV Infection in North and South America](#). New England Journal of Medicine. 2003 May 29; 348 (22):2175-85.

Lazzarin A., Clotet B., Cooper D. et al. [Efficacy of Enfuvirtide in Patients Infected With Drug-Resistant HIV-1 in Europe and Australia.](#) *New England Journal of Medicine*. 2003 May 29; 348(22):2186-95.

Background

Any clinician who has received a genotype with more red ink on it than any other color is well aware that there is a need for the HIV drug pipeline to keep pumping. One of the best hopes to come along for patients with highly resistant HIV is enfuvirtide (T-20, Fuzeon). Certainly, there are problems with this first approved drug of the fusion inhibitor class -- including limited access, twice-a-day injections, injection site reactions, cost -- but enfuvirtide is a powerful agent that has given many patients a second (well, for many people, its more like a third, fourth or fifth) chance. The efficacy and safety of this agent in treatment-experienced patients was examined in two similar studies known as TORO1 and TORO2, which were published in the *New England Journal of Medicine*.

What Is New Here?

These are the first controlled studies of enfuvirtide. Together, they enrolled more than 1,000 subjects with triple-antiretroviral-class experience and/or resistance to agents in each of these classes and a viral load above 5,000 copies/mL. Two thirds of the subjects were randomized to optimize their therapy and add enfuvirtide; the remaining third optimized therapy without the addition of enfuvirtide.

After six months, the average decrease in the HIV-1 RNA level was 1.7 and 1.4 copies/mL in the TORO1 and TORO2 enfuvirtide groups, respectively, versus a drop of 0.8 and 0.6 log₁₀ copies/mL in the control groups. The percentage of patients with an HIV-1 RNA level below 50 copies/mL and the percentage with a decrease of more than 1.0 log₁₀ copies/mL were both significantly greater in the enfuvirtide arms than in the control groups. Not surprisingly, CD4 cell counts increased more among those on enfuvirtide.

Enfuvirtide is not without toxicity. Injection site reactions are inevitable and are characterized by painful nodules that can persist. Tellingly, however, few subjects discontinued therapy because of injection site

reactions (<3%). Massaging the site after the injection and applying ice when reactions develop can help. For unknown reasons, pneumonia was experienced in the subjects receiving enfuvirtide at a rate eight times that seen in the controls. In addition, two patients had a serious, systemic hypersensitivity reaction to enfuvirtide, which on re-challenge, reoccurred.

The Bottom Line

Enfuvirtide is a potent new agent that can benefit some of the patients who need the most help in controlling their virus. This potential is hindered by the requirement for twice-daily injections. Looming even larger is the cost of the drug, currently around \$20,000 annually. This is an incredible sum that, when coupled with the other medications candidate patients are taking, exceeds \$30,000 a year. (The recent increase in the price of ritonavir pushes this figure even higher.) Also, the supply of the drug has been limited due to manufacturing issues.

For patients with access to it, enfuvirtide is an excellent rescue option for a motivated patient. Its role will likely expand if access improves, familiarity with the drug grows and its price enters the realm of reason.

10. Prognostic Importance of Initial Response in HIV-1 Infected Patients Starting Potent Antiretroviral Therapy: Analysis of Prospective Studies

Egger M., Chere B., Sterne J. A. et al. [Prognostic Importance of Initial Response in HIV-1 Infected Patients Starting Potent Antiretroviral Therapy: Analysis of Prospective Studies](#). Lancet. 2003 Aug. 30; 362 (9385):679-86.

Background

Baseline CD4 and HIV viral load have been reported to predict HIV disease progression among patients initiating HIV therapy.¹⁴

However, these parameters can change rather quickly within weeks of the start of antiretroviral treatment. The question of whether this initial

response to therapy provides more information regarding a patient's prognosis was examined among patients being followed in 13 different cohorts in Europe and North America.

What Is New Here?

The strength of this investigation is that it includes a large enough group of patients that sufficient clinical events occurred to permit analyses of predictive factors. More than 9,300 patients initiating potent HIV therapy were included in the analysis. The patients had the typical profiles of those starting antiretroviral therapy: a mean CD4 cell count of 250/uL and mean viral load of 76,000. Most started on PI-based regimens.

The majority of patients did very well on therapy, with over 70% achieving a six-month viral load below 500 copies/mL. During follow-up, however, 263 people developed at least one AIDS event, 152 died and 374 developed AIDS or died.

The striking finding was that once the baseline viral load and CD4 cell count were controlled for a six-month response, the baseline levels were no longer predictive of a patient's disease progression. Instead the inverse was true: The *six-month* viral load and CD4 cell count became predictive after controlling for the baseline values.

The Bottom Line

This study suggests that we are misguided in thinking that it is the baseline values that predict what will happen after therapy starts. Rather, *it is how well therapy works six months after treatment is initiated that is prognostic for advancement to AIDS and death.* Said in another way, it is *not* the initial *change* in a patient's levels but where they land six months hence. The authors provide the example of a patient who experienced an increase in CD4 cell count from 175 cells/uL to 225 cells/uL six months after starting therapy. This person has a better outlook than another person whose counts rose from 25 cells/uL to 100 cells/uL, but a worse outlook than a patient with a jump from 325 cells/uL to 375 cells/uL.

This has important implications for both clinicians and patients. A patient's suboptimal response to therapy should prompt more aggressive

measures by providers. For patients, an understanding that *it is the response to therapy that counts* may be an additional motivator for stricter adherence to therapy.

Unfortunately, even the most aggressive interventions may not help raise reluctant CD4 cell counts of patients who start therapy with basement-level counts. However, these data signal that clinicians need to pay close attention to a patient's response to treatment months into therapy.

Conclusion: Achievements and Limitations

The year that was 2003 saw many reports that in small ways moved us closer to the prize we all eye: relief from the suffering caused by HIV. I included work that I feel all clinicians need to be familiar with, but I am also aware the list neglects what may be an even greater story: the long-overdue beginning of antiretroviral use in Africa, China, India and other places where AIDS rages unopposed. Last year, many more people in resource-poor nations received HIV treatment than the year before, although this relief still only found a small fraction of those in need. This is just the first step toward making advances in HIV care available to everyone. We can hope that in 2004 we will see more people living with HIV get the treatments they, as human beings, deserve. In fact, we can demand it.

While the list offered here highlights achievements in understanding that readily translate into improved care, more often than not, it illustrates areas where answers are scarce and more work is required. How we face the challenge of answering these questions over the next year will be judged, and around this time in 2005 another top 10 will be listed. It seems we just can't help it!

Quick Overview of the Top 2003 Research Reports

What We Used to Think	What We Think Now	What We Hope to Find in the Future

<p>Initial therapy with NNRTI- and PI-based regimens, as well as triple NRTIs, could provide reasonably similar results.</p>	<p>Lopinavir/ritonavir- and efavirenz-based regimens have emerged as leading choices as the anchor of a first regimen.</p> <p>Clinical trials have indicated that triple-NRTI therapy is not as effective as efavirenz-containing regimens. Triple-NRTI combinations that do not include a thymidine analogue appear to be dramatically less effective than ZDV/3TC/ABC.</p>	<p>The specific role of atazanavir (particularly when boosted with ritonavir) as first-line therapy.</p> <p>Will novel triple-NRTI combinations perform better than ZDV/3TC/ABC? Or is the issue the use of drugs from a single ART class?</p> <p>An ongoing ACTG study comparing efavirenz and lopinavir/ritonavir will likely clarify the merits and pitfalls of each of these preferred regimens.</p>
<p>"Hit hard and early" should succumb to a more cautious "hit hard and later" approach.</p>	<p>There is increasing comfort with initiation of HIV therapy at a CD4 cell count of 350/uL. Some data suggest there are advantages to starting treatment at 350 and higher.</p>	<p>As HIV therapies become less toxic, will the benefits of ART at CD4 cell counts above 350/uL become more apparent, leading to a shift back toward early therapy?</p>

<p>Efavirenz CNS toxicity is a major limiting factor in use of this drug.</p>	<p>Close monitoring of subjects receiving efavirenz demonstrates that the side effects are short lived (less than four weeks) and limited to the known adverse effects ascribed to the drug. In clinical trials, treatment discontinuation rates are low.</p>	<p>Longer term follow-up may provide further insights on cumulative toxicity, if any exists.</p>
<p>The lipid changes associated with HIV therapy may increase risk of cardiovascular disease, but the extent of the risk is not known.</p>	<p>Several studies demonstrate that the risk appears, at this point, to be very low.</p> <p>However, some studies do indicate increasing rates of cardiovascular disease among antiretroviral-receiving patients. Overall the benefits of therapy far outweigh this risk.</p>	<p>Longitudinal follow-up of large cohorts will continue to generate information concerning risk.</p>
<p>Protease inhibitors cause a rise in lipids that increase the risk of cardiovascular disease.</p>	<p>HIV therapy alone is not the sole cause of lipid disorders. HIV infection itself perturbs lipid levels. This effect is partially reversed by antiretroviral therapy, which raises lipids to levels consistent with those that existed prior to HIV infection.</p>	<p>How will aggressive lipid management, increasingly being adopted into standard HIV practice, impact future cardiovascular disease risk?</p> <p>Is the reversal of HIV infection-induced changes in lipids by ART seen</p>

		also in women, African Americans and other populations?
Atazanavir is a protease inhibitor with a lipid- and glucose-friendly profile but is less potent than other agents in the class.	The combination of atazanavir with low-dose ritonavir has been shown to increase the potency of this agent without significant cost to its favorable effect on metabolic parameters.	Further study of the use of ritonavir-boosted atazanavir, particularly its durability and salvage potential, are needed.
Once resistance develops to an antiretroviral it loses its effectiveness.	Resistance mutations do confer reduced viral susceptibility to an agent, but in the case of NRTIs some antiviral effect may remain. The subsequent impact of resistance on viral fitness may be protective against rapid CD4 cell decline and full viral rebound.	Can reductions in viral fitness accompanying NRTI resistance be exploited as a management strategy?
Antiretroviral resistance may be transmitted to others. Evidence of resistance fades over time making it difficult to detect years later.	Resistance <i>is</i> transmittable. One out of 10 newly diagnosed individuals have evidence of major ART mutations. Even after being infected for more than a year, patients show evidence of resistance.	Will resistance testing prior to starting therapy prove to be a clinically effective and cost-effective approach?

<p>Fusion inhibitors would be nice.</p>	<p>The first fusion inhibitor has been approved, but stand in line and have your cash ready. Enfuvirtide works and is better tolerated than expected.</p>	<p>Can enough enfuvirtide be made to satisfy the need? Will the drug find a role beyond salvage (early therapy, post exposure prophylaxis)? Does enfuvirtide lead to immunologic changes that predispose someone to pneumonia?</p>
<p>Baseline CD4 cell count and viral load predict HIV disease progression.</p>	<p>Disease progression may actually be best predicted by the change in CD4 and viral load months after therapy starts.</p>	<p>Does a patient's six-month response need to be evaluated with the aim of manipulating therapy to optimize effect? Is this feasible given limitations of currently available ARTs?</p>
<p>Once-daily therapy would be nice.</p>	<p>Once-daily therapy <i>is</i> nice. More options for once-a-day dosing exist. Most believe this will increase antiretroviral adherence.</p>	<p>Is adherence to and efficacy of once-daily therapy improved? For whom is once-daily therapy <i>not</i> advisable?</p>

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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.

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