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Research Focus

Antiretroviral Treatment Update From the 17th International AIDS Conference

By

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The 17th International AIDS Conference was held in Mexico City from August 3 to 8, 2008. This conference attracted more than 20,000 participants and provided some significant new insights into HIV therapeutics.

TREATMENT AS PREVENTION

One of the themes of this conference was antiretroviral treatment as prevention. Since the last AIDS Conference in Toronto, 2 million people have started antiretroviral treatment, but 5 million people have become newly infected with HIV. These data strongly indicate a need to implement better preventive measures. There are currently 4 opportunities for intervention, some of which have only been marginally successful when used independently¹:

1. Behavioral modifications, including, among others, abstinence, monogamy, and the use of barrier protection (eg, condoms, clean needles, and circumcision).
2. Vaccination and antiretroviral preexposure prophylaxis, including microbicides.
3. Postexposure treatment prophylaxis, which has already proved to be very effective in preventing maternal-fetal transmission.

4. Active treatment of HIV-infected viremic patients to decrease their rate of infectivity.

There are currently 36 to 39 million people infected with HIV, but only 2.5 million are receiving active antiretroviral treatment, leaving millions of persons who may be viremic and able to infect others. The infectivity rate of each infected person is a dynamic factor of many variables, which includes the number and type of exposures and the size of the inoculum. It is the inoculum's size that can be favorably changed with active antiretroviral treatment to minimize infectivity and decrease transmission.

Low plasma HIV RNA levels have been correlated with low HIV RNA levels in genital secretions, which, in turn, reduces the probability of sexual transmission. Several studies have documented a very low rate of HIV transmission among serodiscordant couples in which the infected partner's HIV RNA level is fully suppressed (ie, less than 50 copies/mL) while he or she is receiving antiretroviral therapy. However, this is not fully protective in all cases at all times, and so caution must be exercised in overemphasizing the safety of this approach to prevent disease transmission. Accordingly, an appropriate strategy for HIV prevention should marry multiple, proven HIV prevention strategies with the use of antiretroviral therapy for HIV-positive persons.

At this year's International AIDS Conference, data were presented that indicated that such a strategy might be highly effective in reducing HIV infection rates. Montaner and colleagues² from the BC Centre for Excellence in HIV/AIDS, Vancouver, British Columbia, presented an analysis in which they assessed plasma HIV RNA levels within a prospective cohort of HIV-infected injection drug users (IDUs) whom they had followed up semi-annually between May 1996 and December 2004. These data were matched to the incidence of HIV infection in a sister cohort of HIV-negative IDUs in the same community and during the same period. The median semiannual plasma HIV RNA level and the semiannual HIV infection incidence were statistically correlated, and the results showed that a longitudinal measure of community plasma HIV RNA levels correlated with the community HIV infection incidence and strongly predicted HIV infection incidence independently of unsafe sexual behaviors and the reuse of syringes. These data indicate that by lowering the viral load—whether on an individual or community level—the incidence of HIV infection may be significantly lowered. The lead author concluded, "It's a lot easier to understand that at a population level, if we lower the population viral load through the use of antiretroviral therapy, we could act as an added second sort of layer of protection, and therefore see decreases in HIV transmission."²

STUDIES OF PREFERRED NRTI COMBINATIONS

NRTI Efficacy in Persons With High HIV Viral Load

[Abacavir](#) ([Drug information on abacavir](#)) plus [lamivudine](#) ([Drug information on lamivudine](#)) and tenofovir plus emtricitabine are both preferred NRTI combinations for initial treatment of HIV infection but, before this year's conference, have only once before been directly compared. However, multiple studies that compared the clinical efficacy and safety of these 2 NRTI backbones were presented at the conference.

The AIDS Clinical Trials Group (ACTG) 5202 study was a large, prospective, placebo-controlled study that compared the efficacy of the 2 above-mentioned NRTI backbones, each as a fixed-dose combination, when given with a third drug: either efavirenz or ritonavir-boosted [atazanavir](#) ([Drug information on atazanavir](#)) (ATV/r).³ Four initial treatment strategies were evaluated:

- Abacavir/lamivudine + [efavirenz](#) ([Drug information on efavirenz](#)).
- Tenofovir/emtricitabine + efavirenz.
- Abacavir/lamivudine + ATV/r.
- Tenofovir/emtricitabine + ATV/r.

The NRTI components of the study were administered in a double-blind fashion, while the "third drug" comparison was given open label. The study enrolled 1858 patients from September 2005 through November 2007 regardless of CD4⁺ cell count, with a planned follow-up 96 weeks after the last patient was enrolled. The 3 primary end points of the ACTG 5202 study were as follows:

- Efficacy:** Time to virological failure, defined as "early failure" if there was a confirmed HIV RNA level above 1000 copies/mL between weeks 16 and 24 or "later failure" if there was a confirmed HIV RNA level above 200 copies/mL at week 24 or after.
- Safety:** Time to the first grade 3 or 4 sign, symptom, or laboratory test result abnormality and at least one grade higher than at baseline.
- Tolerability:** Time to modification of the initial randomized regimen.

At the first efficacy review in January 2008 by the Data Safety and Monitoring Board (DSMB) for the trial, excess virological failures were observed in the abac-avir/lamivudine arms, and the DSMB recommended that the similar NRTI treatment arms be combined and that the 2 NRTI combinations be analyzed. In this additional analysis, the excess virological failures occurred in the group of patients with a screening HIV RNA level above 100,000 copies/mL, and unblinding of this stratum was recommended; the results presented here are those from this analysis, which consisted of 797 patients.

At baseline, the participants were well matched, with a mean HIV RNA level of 5.1 log₁₀ copies/mL and a mean CD4⁺ cell count of 181/μL. At study entry, 43% of the patients underwent resistance testing, which was only required if HIV infection was acquired recently or if testing was part of a study site's standard-of-care. Patients with a known resistance mutation to any of the drug classes in the study were excluded.

For the primary efficacy end point, abacavir/lamivudine treatment was associated with a shorter time to virological failure, with 57 (14%) of abacavir/lamivudine-treated patients and 26 (7%) of the tenofovir/emtricitabine-treated patients experiencing this virological end point ($P = .0003$) (Figure 1). Virological failures occurred in greater numbers in the abacavir/lamivudine arm using both the early and late failure criteria. Virological failure did not appear to be related to suspected abacavir hypersensitivity, which occurred in 7% of each treatment arm. (No HLA-B*5701 testing was required in this study.)

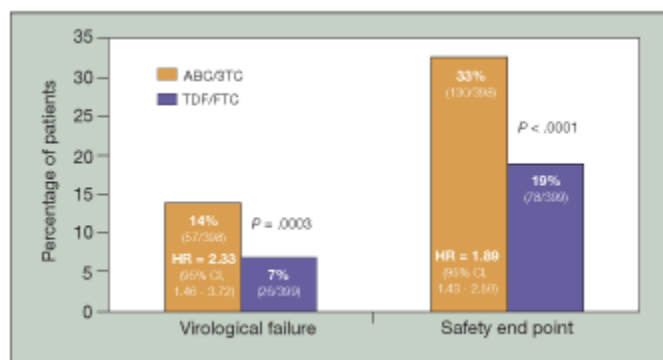


Figure 1. Virological and safety outcomes of the AIDS Clinical Trials Group 5202 study. (ABC/3TC, abacavir/lamivudine; TDF/FTC, tenofovir/emtricitabine; HR, hazard ratio; CI, confidence interval.) (Adapted from Sax P et al. 2008.³)

Using a combined end point of virological failure or modification of the NRTI backbone, the results showed that 114 of abacavir/lamivudine-treated patients and 68 of tenofovir/emtricitabine persons met these failure criteria ($P < .0001$ for time to reach the combined end point). A secondary intention-to-treat analysis, which included patients who experienced virological failure or switched NRTIs, found that 75% of abacavir/lamivudine- and 80% of tenofovir/emtricitabine-treated patients had HIV RNA levels below 50 copies/mL at week 48 ($P = .20$), although nearly twice as many abacavir/lamivudine-treated patients as tenofovir/emtricitabine-treated patients had switched therapy.

In addition, abacavir/lamivudine-treated patients had a shorter time to a grade 3 or 4 sign, symptom, or laboratory test result abnormality one grade higher than baseline than those receiving tenofovir/emtricitabine ($P < .0001$); most of these safety events were increases in lipid levels and nonspecific body aches (Figure 1). Although statistically significant, the lipid changes were small in magnitude, and the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol did not differ between the two arms. There was no difference in the incidence of myocardial infarction (MI) between study arms; one person in the abacavir/lamivudine arm died, possibly as a result of abacavir hypersensitivity after rechallenge. The analysis of baseline and treatment-emergent resistance was ongoing at the time the results were presented.

Importantly, several efficacy evaluations of the ACTG 5202 study are continuing, including the comparison between abacavir/lamivudine and tenofovir/emtricitabine NRTI combinations at HIV RNA levels below 100,000 copies/mL and between efavirenz and ATV/r. None-the-less, these results so far strongly suggest that tenofovir/emtricitabine would be preferred over abacavir/lamivudine in patients with HIV RNA levels of 100,000 copies/mL or higher.

In response to the initial ACTG 5202 study results, which were made public in February 2008, the manufacturer of the abacavir/lamivudine combination, GlaxoSmithKline (GSK), conducted a retrospective analysis of their abacavir clinical trial database using the ACTG 5202 definitions of treatment failure and regimen toxicity.⁴ A total of 2940 patients who had been enrolled in 6 clinical trials were included. Contrary to the results of the ACTG 5202 study, the GSK database review found that abacavir-treated patients who had baseline HIV RNA levels above 100,000 copies/mL did not have a lower virological response rate or higher toxicity than those who had lower HIV RNA levels.

The results for one of the studies included in the GSK analysis, the Head-to-Head Epzicom Truvada (HEAT) study, were updated for the 96-week data at the conference.⁵ The results of this study, which enrolled 688 persons, of whom about 43% had an HIV RNA level of 100,000 copies/mL or higher, indicated that when given with once-daily [ritonavir \(Drug information on ritonavir\)](#)-boosted [lopinavir \(Drug information on lopinavir\)](#) (LPV/r), abacavir/lamivudine was noninferior to tenofovir/emtricitabine, with relatively equal numbers of patients with high and low viral loads reaching an HIV RNA level under 50 copies/mL.

How might these apparently conflicting results be explained? The larger sample size of the ACTG 5202 study relative to that of the HEAT study may have allowed the ACTG investigators to observe differences between study arms with greater precision. In addition, the "third drug" used in the two studies differed: efavirenz or ATV/r in the 5202 study and once-daily LPV/r in the HEAT study. In addition, most of the studies summarized in the GSK review did not directly compare abacavir/lamivudine and tenofovir/emtricitabine. Finally, end points and analysis strategies differed among the studies.

Cardiovascular Risk Associated With Abacavir Exposure

Results from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study have indicated that recent use of abacavir or [didanosine \(Drug information on didanosine\)](#) is associated with an increased risk of MI, which persists as long as the patient remains exposed to one of those drugs.⁶ In an effort to evaluate whether these results could be replicated in a data set where the use of NRTIs was different from that in the DAD study and to explore possible biological mechanisms responsible for this association, the Strategies for Management of Anti-Retroviral Therapy (SMART) investigators evaluated abacavir, didanosine, and the other NRTIs.⁷ The study design included 3 groups: patients receiving an antiretroviral regimen containing abacavir but not didanosine ($n = 1019$), patients receiving any didanosine-containing regimen ($n = 643$), and those receiving an NRTI-containing regimen but not

including abacavir or didanosine ($n = 2882$). Patients in the 3 study groups were similar with regard to age, gender, HIV disease status, antiretroviral treatment history, prior cardiovascular disease, presence of an ischemic abnormality, tobacco use, diabetes, and use of lipid-lowering and antihypertensive agents. There were 3 clinical end points:

- Major cardiovascular disease, including stroke and MI.
- Major cardiovascular disease expanded to include other serious cardiovascular disease, such as peripheral vascular disease and congestive heart failure.
- Minor cardiovascular disease, which included peripheral vascular disease, congestive heart failure, or coronary artery disease requiring treatment.

After adjusting for cardiovascular disease risk factors, the SMART investigators found that abacavir was associated with a significantly increased risk of MI (hazard ratio [HR], 4.3), major cardiovascular disease with the expanded definition (HR, 1.9), and minor cardiovascular disease (HR, 2.7). There was no association found regarding didanosine or any other NRTI, including tenofovir, although the data presented on tenofovir were preliminary. The cardiovascular disease risk associated with abacavir appeared to be greatest among patients who were at relatively high risk for cardiovascular disease or who had ischemic abnormalities on an ECG. In addition, a possible inflammatory mechanism for this effect is possible, since the abacavir-treated patients were found to have higher levels of certain inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP) ($P = .07$), interleukin-6 (IL-6) ($P = .07$), and amyloid P ($P = .02$).

In response to these data, GSK presented an analysis of 54 GSK trials containing abacavir, which included 9639 persons who received abacavir (7845 person-years of abacavir exposure), and found no increase in frequency of MI events.⁸ There was a variable time of observation in these trials, ranging from 24 weeks to less than 2 years. A 96-week subanalysis of the HEAT study, which was GSK-sponsored, found that although hs-CRP levels were numerically higher in abacavir-treated patients, there were no significant differences regarding hs-CRP or IL-6 levels among those patients who received or did not receive abacavir.⁵ While these data sets may seem contradictory, one possibility may be that the cardiovascular disease risk seen in both the DAD and SMART studies is easier to identify for persons at higher risk for cardiovascular disease, and the GSK database may reflect a different population with different risk profiles followed up for relatively shorter time periods. The corroboration of biomarkers is an ongoing area of research that we hope may guide us in the understanding of current antiretroviral regimens and more appropriate individualization of treatment.

Tenofovir Renal Safety

Several studies presented at the International AIDS Conference evaluated the long-term renal effects of tenofovir. A pooled analysis evaluated renal parameters at 144 weeks in 1111 patients enrolled in 2 trials comparing a regimen of efavirenz and tenofovir plus [emtricitabine](#) (Drug information on emtricitabine) or lamivudine with a regimen of efavirenz and lamivudine plus [zidovudine](#) (Drug information on zidovudine) or [stavudine](#) (Drug information on stavudine).⁹ There were no significant differences between the 2 pooled groups with respect to proteinuria, changes in glomerular filtration rate (GFR), or increases in creatinine clearance. In 2 other studies, 70 patients receiving a regimen of tenofovir, lamivudine, and efavirenz were followed up for 7 years and demonstrated no significant changes in GFR, whether estimated using the Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault (CG) equation (Figure 2),¹⁰ and 74 patients were followed up for 4 years on the same drug regimen and showed no significant difference in GFR using the MDRD calculation but a decline in GFR using the CG equation (123 mL/min at baseline vs 115 mL/min at 4 years; $P < .001$).¹¹



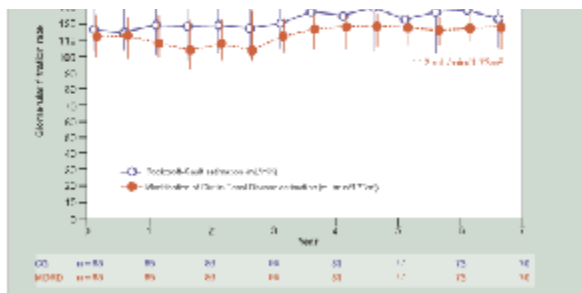


Figure 2. Renal function in patients receiving tenofovir in the GS 903E study. (CG, Cockcroft-Gault; MDRD, Modification of Diet in Renal Disease.) (Adapted from Madruga J et al. 2008.¹⁰)

There were 2 trials that reported results after 96 weeks of follow-up. The 96-week data from the HEAT study showed declines in GFR of 5% in both arms and a low incidence of renal failure (none in the abacavir arm and 2 in the tenofovir arm) among the 688 participants.⁵ The ACTG 5202 study also reported low rates of renal complications, with a 1% incidence of renal failure in the treatment arms with tenofovir and without tenofovir.³

A retrospective cohort study assessed the incidence of and risk factors for renal toxicity associated with tenofovir use in 1574 HIV-infected patients (55% African American) of whom 744 (47%) were receiving a tenofovir-containing regimen.¹² Renal toxicity was defined as either a decrease in GFR of more than 50% or a drop in creatinine clearance of 25 mL/min or more. Notably, there was no significant increase in nephrotoxicity in tenofovir-treated patients (4.7% vs 4.2% in those not receiving tenofovir). Among those patients who received tenofovir, the significant risk factors for renal toxicity were the following: concomitant use of nephrotoxic drugs (eg, amphotericin B (Drug information on amphotericin b), aminoglycosides), other medical comorbidities (eg, diabetes, heart failure), hypertension, chronic pain (associated with NSAID use), concurrent or past use of a protease inhibitor (PI), and a history of an opportunistic infection. Use of tenofovir with an NNRTI was associated with a decreased incidence of renal toxicity (odds ratio, 0.36).

Another study evaluated 323 patients (61% African American) for approximately 3 years and found only hypertension, body weight, and age to be predictive for declines in GFR of 25% or more from baseline without an association with a specific antiretroviral regimen.¹³ Finally, a study that evaluated 500 patients over 2 years found that while there were significant differences in renal function seen in the first 3 months between the tenofovir and control arms, there was no significant change in renal function after the initial year of treatment.¹⁴

UPDATES ON NEWER, FDA-APPROVED ANTIRETROVIRALS

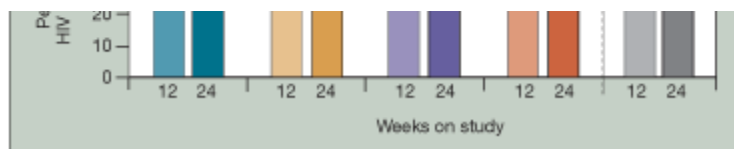
Etravirine (Drug information on etravirine): A New NNRTI

The etravirine expanded access program (EAP) provided access to the NNRTI etravirine for 2212 patients who were viremic, were triple-class-experienced and/or –resistant, and had prior exposure to at least 2 PIs.¹⁵ The median baseline HIV RNA level was 4.3 log₁₀ copies/mL and the CD4⁺ cell count was 152/μL. There were few limitations regarding the other antiretrovirals that could be used, noting that while several boosted PIs can be used with etravirine, tipranavir (Drug information on tipranavir) was specifically excluded because of an unfavorable drug-drug interaction. Overall, 15% also received enfuvirtide. By week 24, about 65% of patients had an HIV RNA level below 75 copies/mL (Figure 3).



Figure 3. Virological outcomes in the etravirine expanded access program. (ETR, etravirine; DRV/r, ritonavir-boosted darunavir; RAL, raltegravir; BR, background therapy.) (Adapted from Towner W et al. 2008.¹⁵)

There were similar rates of virological



suppression with a wide variety of etravirine-containing regimens—for example, regimens that included ritonavir-boosted darunavir (DRV/r) or other boosted and unboosted PIs, regimens

with raltegravir with and without darunavir, and even PI-sparing regimens. These etravirine regimens were also very well tolerated; only 1.9% of patients discontinued their regimen because of an adverse event. These data demonstrate the efficacy of a variety of etravirine-containing regimens in highly treatment-experienced patients.

Raltegravir: The First Integrase Inhibitor

Updated and new information on the integrase inhibitor raltegravir in treatment-naïve and -experienced patients was presented at the conference. Markowitz and colleagues¹⁶ presented the 96-week data from a phase 2 study comparing raltegravir and efavirenz, each together with tenofovir and lamivudine in treatment-naïve patients. A preliminary analysis of the study had been presented at the previous International AIDS Conference in 2006, and the 48-week data has since been published.¹⁷ At week 48, the proportion of persons with an HIV RNA level below 50 copies/mL was 85% in the efavirenz group and 83% to 88% in each of the 4 raltegravir groups in this study (100, 200, 400, and 600 mg, each given twice daily), although the time to HIV RNA suppression to below 50 copies/mL was shorter for each of the raltegravir groups than for the efavirenz group.

After week 48, the doses of all raltegravir recipients were switched to 400 mg twice daily, and at week 96, 83% of persons in the raltegravir group and 84% in the efa-virenz group had HIV RNA levels below 50 copies/mL. Since both regimens' long-term virological suppression rates were similar, this may indicate that the more rapid reduction in viral load seen with raltegravir did not translate into better long-term virological outcomes. Virological failure was uncommon, but raltegravir resistance was seen in 3 of 6 patients receiving raltegravir—all of whom started treatment at the 100- or 200-mg twice-daily dosage—and NNRTI resistance was seen in the 2 patients whose efavirenz-containing regimen had failed. Therefore, the barrier to raltegravir resistance is not likely to be high, but results may differ in patients in whom the FDA-approved dose of 400 mg twice daily fails.

Clinical adverse events were more common in the efavirenz group, largely because of efavirenz-associated CNS toxicities. Grade 3 or 4 laboratory adverse events were uncommon, although increases in the creatinine kinase level (10 times or higher than the upper limit of normal) occurred in 6.3% of persons who received raltegravir versus 2.6% of those who received efavirenz; and lipid level changes were slightly better in the raltegravir group: the ratio of total cholesterol to HDL cholesterol decreased to a similar extent in both groups, but triglyceride levels decreased with raltegravir treatment and increased with efavirenz treatment. In summary, the slight advantage raltegravir appears to have with respect to adverse events and lipid profiles probably does not overcome the convenience of once-daily efavirenz, and therefore this study does not make a compelling case to start raltegravir therapy in antiretroviral-naïve patients. Larger studies of raltegravir in treatment-naïve patients are planned.

With respect to treatment-experienced patients, 2 reports described virological outcomes after a switch from enfuvirtide to raltegravir in highly antiretroviral-experienced patients but with undetectable viral loads.^{18,19} Out of a combined total of 69 patients, all had viral loads below detectable levels following the switch, with a minimum follow-up of 12 weeks. A third research group reported on 3 cases of hepatic toxicity following a switch from enfuvirtide to raltegravir, although all patients were also receiving ritonavir-boosted tipranavir.²⁰ Therefore, the switch from enfuvirtide to raltegravir appears to

preserve virological suppression, but laboratory tests for safety monitoring should probably be performed shortly after the switch, rather than delaying such tests, for example, until a 3-month follow-up appointment.

Maraviroc: The First Coreceptor Inhibitor

At the conference, retrospective analyses were presented on use of the CCR5-coreceptor inhibitor maraviroc that provide some additional perspectives regarding the outcomes in the MOTIVATE (Maraviroc Plus Optimized Therapy in Viremic Antiretroviral Treatment Experienced Patients) and MERIT studies, the phase 2b/3 trials of maraviroc in treatment-experienced and -naive patients, respectively, with pure R5 virus (at screening).

In an analysis of the MOTIVATE data, outcomes in persons with and persons without triple-class resistance were compared.²¹ Persons with triple-class resistance had a median phenotypic susceptibility score (PSS) to PIs of 1, while those without triple-class resistance had a PSS to PIs of 3. Among maraviroc recipients, 42.9% of persons with baseline triple-class resistance and 49.7% of persons without triple-class resistance achieved an HIV RNA level below 50 copies/mL at week 48, compared with 10.0% and 25.8% of placebo recipients, respectively. Focusing on just those persons with triple-class resistance, declines in HIV RNA levels were $-1.7 \log_{10}$ copies/mL in the maraviroc group and $-0.4 \log_{10}$ copies/mL in the placebo group. When considering persons who had 2 active drugs in their optimized background, 53.4% of persons who received maraviroc had an HIV RNA level less than 50 copies/mL, compared with 8.5% of placebo recipients. These data indicate that maraviroc provided considerable activity in this study, but the resistance scoring system likely overestimated the activity of the NRTIs and PIs that were used in the optimized background combination.

Persons in the MERIT study received maraviroc or efavirenz in combination with zidovudine and lamivudine. In this analysis, a model was developed to identify factors that contributed to a person achieving an HIV RNA level below 50 copies/mL at week 48.²² The following factors, all significantly associated with achieving an undetectable viral load, are listed in decreasing order of importance: baseline coreceptor tropism average maraviroc concentration, baseline HIV RNA level, age, time since HIV diagnosis, and baseline CD4 count. Persons with an average maraviroc concentration of 75 ng/mL or higher were very likely to have an undetectable viral load. This finding is interesting and suggests that monitoring drug concentrations could help predict successful treatment outcomes, but at present, clinicians are not likely to be able to calculate average drug concentrations in their patients.

TRIO Study: Combining Raltegravir, Darunavir, and Etravirine

When the BENCHMRK (Blocking integrase in treatment Experienced patients with a Novel Compound against HIV: MeRcK, MK-0518) study results were presented over 1 year ago,²³ it was impressive to many that a regimen that included raltegravir, DRV/r, and enfuvirtide led to very high rates of virological suppression in highly treatment-experienced patients. These data spurred an interest in combining multiple active agents in order to maximize virological suppression in treatment-experienced patients; however, it has been clear for years that while enfuvirtide is an important drug in a novel class, and therefore fully active for many patients, it has limited acceptance because of the practical challenges of self-injection. As a result, it is not surprising that at this conference, the results from 2 data sets that combined raltegravir, DRV/r, and etravirine as the basis of a new regimen were presented.

One study, the ANRS 139 TRIO study, was conducted in several sites in France. The study enrolled 103 patients who had not previously been exposed to any of the 3 drugs and had a median HIV RNA level of $4 \log_{10}$ copies/mL and baseline CD4⁺ cell count of 255/ μ L.²⁴ The cohort was defined as one in need of a new regimen but likely to respond to the new regimen: the patients had documented virological failure while they were receiving an NNRTI-containing regimen but no more than 3 NNRTI mutations,

documentation of at least 3 primary PI mutations but 3 or fewer darunavir mutations, and 3 or more NRTI mutations. In addition to the 3 new drugs, the regimen could include NRTIs and enfuvirtide. In all, 83% of the patients also had NRTIs in their regimens, while 12 patients used enfuvirtide for the first time in this study. At weeks 12 and 24, 88% and 90% of patients, respectively, achieved an HIV RNA level below 50 copies/mL (Figure 4), and the median increase in CD4⁺ cell count was 99/ μ L at 24 weeks. There was only one discontinuation because of rash. These data, while not surprising, are reassuring about what can be achieved with the targeted use of 3 of the newest and most active oral antiretroviral agents.

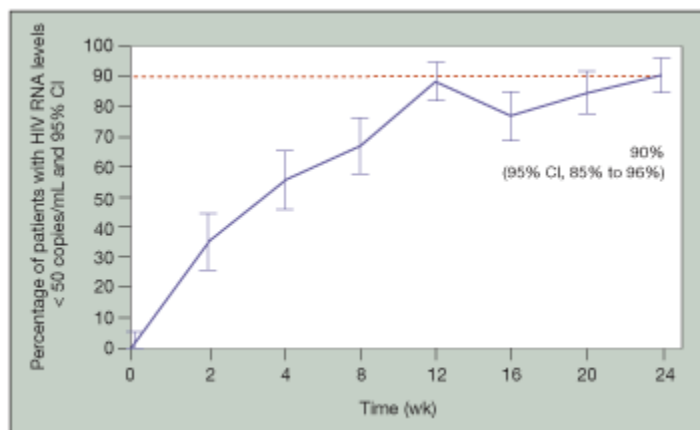


Figure 4. Virological results in the ANRS 139 TRIO study. (CI, confidence interval.) (Adapted from Yazdanpanah Y et al. 2008.²⁴)

The difference between 65% response rates seen in the etravirine EAP (see above) versus the higher rates in the TRIO study are easily attributed to multiple causes, including enrolling patients in the TRIO study with favorable baseline characteristics compared with those in the EAP, in which any patient, including those with challenging resistance mutation patterns, can be enrolled.

Nevertheless, these studies together clarify the impact that these newer drugs, when given in multiple appropriate combinations, are already having as a result of the treatment advances of the past year.

UPDATES ON NEW ANTIRETROVIRALS IN DEVELOPMENT

Investigational NRTIs

Elvucitabine. This drug is a cytosine analogue similar to lamivudine and emtricitabine and active against viral variants harboring the M184V/I mutation. In a phase 2a pilot study, elvucitabine (10 mg once daily) was compared with lamivudine (300 mg once daily), both in combination with efavirenz and tenofovir, in 77 antiretroviral-naïve patients.²⁵ The study was double-blind for the first 12 weeks, and then patients continued with open-label treatment. The virological efficacy results at 24 weeks are shown in the Table.

Table. Results of a Phase 2a Trial Comparing Elvucitabine With Lamivudine at 24 Weeks

	Elvucitabine	Lamivudine
Change in HIV RNA level from baseline (intention-to-treat analysis), log ₁₀ copies/mL	-2.78	-3.02
Proportion of patients achieving HIV RNA level < 50 copies/mL		
Intention-to-treat analysis	70.3%	83.8%
As-treated analysis	100%	93.3%

Note: No between-group difference was statistically significant ($P > .05$).

There were 7 serious adverse events reported in 6 patients, all in the elvucitabine arm, and 2 of the events led to study discontinuation; however, none were deemed by the investigator to be related to the study drug. These data support continued research of elvucitabine, and larger studies are planned.

Apricitabine. This drug is a novel cytidine nucleoside analogue that also maintains activity in the presence of the M184V mutation. At this conference, safety data were reported from a 24-week, ongoing trial of 51 treatment-experienced patients with the M184V mutation who were randomized to

receive apricitabine (600 or 800 mg twice daily) or lamivudine (150 mg twice daily) in combination with other antiretrovirals.²⁶ The results were impressive because there were no serious adverse events and no discontinuations deemed to be related to apricitabine. This is another compound moving along in development with promising activity against M184V mutation.

Investigational NNRTIs

Rilpivirine. The 96-week data from a dose-ranging study comparing rilpivirine (formerly TMC 278) with efavirenz in treatment-naïve patients were presented at the conference.²⁷ Key baseline characteristics included a median HIV RNA level of 4.8 log₁₀ copies/mL and CD4⁺ cell count of about 200/μL. At week 96, 71% to 76% of patients had an HIV RNA level below 50 copies/mL, with no differences in efficacy between efavirenz and the 3 doses of rilpivirine studied (25, 75, and 150 mg once daily). Focusing on durability, there were very few new virological failures after week 48 across all of the study arms and no evidence that the lower dose of rilpivirine was less active than the higher doses studied. In all 4 arms, virological failure with resistance mutations occurred for about 6% to 7% of patients, and there were no differences observed in the likelihood of NNRTI resistance development between the two drugs.

The proportions of patients who experienced any adverse event were similar among the treatment arms, including those events that led to discontinuation (9% efavirenz, 12% rilpivirine). However, it was noted that the typical efavirenz adverse effects were significantly less likely with rilpivirine; that is, significantly fewer patients had abnormal dreams, dizziness, and somnolence. Finally, it was noted that QTc prolongation was more likely at the higher doses; since there was the lowest likelihood of this abnormality with the 25-mg dose, this provided the justification for moving ahead with that dose in the phase 3 studies. In addition, QTc prolongation was more common for those who received zidovudine/lamivudine rather than tenofovir/emtricitabine. Efficacy of rilpivirine is similar to that of efavirenz, but rilpivirine has a different safety profile with some potential advantages. In phase 3 trials, efavirenz will be compared with rilpivirine 25 mg once daily combined with 2 NRTIs in treatment-naïve persons.

RDEA806. This antiretroviral agent is a novel NNRTI structure and is active against a wide range of single- and double-mutant NNRTI-resistant virus, including the K103N mutation. Also reported at the conference were data from a 7-day dose-finding monotherapy activity study that included 4 dose groups of 8 RDEA806-treated patients and 2 patients per group receiving placebo.²⁸ Two of the dose groups included 400 mg twice daily and 600 mg once daily using a capsule formulation and the other 2 included 800 and 1000 mg once daily using an enteric-coated formulation. The results showed potent antiviral activity at all doses. On day 8, changes in HIV RNA level from baseline, given as log₁₀ copies/mL, were as follows: placebo, +0.2; 400 mg twice daily, -1.8; 600 mg once daily, -1.5; 800 mg once daily, -1.8; and 1000 mg once daily, -1.8. All patients in the 400-mg twice-daily and the 800- and 1000-mg once-daily groups achieved at least a 1-log decline in their HIV RNA level. No person discontinued because of adverse events. Adverse events were seen at similar frequency and intensity in the RDEA806 and placebo arms. Phase 2b studies are now planned.

IDX899. This drug is a novel NNRTI with some structural relation to rilpivirine. Preclinical data indicate activity against NNRTI-resistant virus, including strains with the K103N mutation. The results of a 7-day dose-finding monotherapy activity study were reported.²⁹ There were 3 dosing cohorts of 10 patients each; in each cohort 8 received IDX899 (800, 400, and 200 mg once daily) and 2 received placebo. The day 8 viral load responses from baseline, given as log₁₀ HIV RNA copies/mL, were as follows: 800 mg once daily, -1.78; 400 mg once daily, -1.78; 200 mg once daily, -1.83; and placebo, +0.05. No clear pharmacokinetic/pharmacodynamic relationship was demonstrated. There were no treatment-emergent adverse events or premature discontinuations and no discernible patterns in adverse

events among the treatment groups. After completion of this study and relevant drug interaction studies, IDX899 is anticipated to advance to phase 2b development.

CONCLUSION

One of the themes of this year's International AIDS Conference was treatment as prevention. The data presented by Montaner and colleagues² as well as other research teams indicate that by providing treatment to all HIV-infected patients who need it, the rates of HIV transmission may be significantly reduced. Concerns have arisen about the use of abacavir with lamivudine as an NRTI backbone, with the ACTG 5202 study results indicating that this NRTI combination is less effective than tenofovir plus emtricitabine in patients with an HIV RNA level of 100,000 copies/mL or higher and with the DAD and SMART trials indicating that abacavir is associated with a higher cardiovascular risk than are other NRTIs in patients with cardiovascular risk factors at baseline. However, in general, as demonstrated by the clinical studies summarized in this article, antiretroviral therapy is highly effective and safe. Further, the data on the newer approved antiretrovirals, and the new antiretrovirals in development, indicate that patients will have many antiretroviral choices in the future to achieve full virological suppression, even if they are antiretroviral-experienced.

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References

1. Cohen M. Prevention of the sexual transmission of HIV-1: a view from early in the 21st century. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract TUPL0101.
2. Montaner J, Kerr T, Li K, et al. Longitudinal community plasma HIV RNA level and HIV incidence among injection drug users. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract LBPE1160.
3. Sax P, Tierney C, Collier A, et al. ACTG 5202: shorter time to virologic failure (VF) with abacavir/lamivudine (ABC/3TC) than tenofovir/emtricitabine (TDF/FTC) as part of combination

- therapy in treatment-naïve persons with screening HIV RNA \leq 100,000 c/mL. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract THAB0303.
4. Pappa K, Hernandez J, Ha B, et al. Abacavir/lamivudine (ABC/3TC) shows robust virologic responses in ART-naïve patients for baseline (BL) viral loads (VL) of \leq 100,000 c/mL and $<$ 100,000 c/mL by endpoint used in ACTG5202. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract THAB0304.
 5. Smith K, Fine D, Patel P, et al. Similarity in efficacy and safety of abacavir/lamivudine (ABC/3TC) compared to tenofovir/emtricitabine (TDF/FTC) in combination with QD lopinavir/ritonavir (LPV/r) over 96 weeks in the HEAT Study. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract LBPE1138.
 6. D:A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration [published correction appears in *Lancet*. 2008;372:292]. *Lancet*. 2008;371:1417-1426.
 7. Lundgren J, Neuhaus J, Babiker A, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the SMART study. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract THAB0305.
 8. Cutrell A, Hernandez J, Yeo J, et al. Is abacavir (ABC)-containing combination antiretroviral therapy (CART) associated with myocardial infarction (MI)? No association identified in pooled summary of 54 clinical trials. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract WEAB0106.
 9. Gallant J, Pozniak A, DeJesus E, et al. Renal safety profile of tenofovir DF (TDF)-containing vs thymidine analog containing regimens through 144 weeks in antiretroviral-naïve patients. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract THPE0186.
 10. Madruga J, Casetti I, Suleiman J, et al. The safety and efficacy of switching stavudine to tenofovir DF in combination with lamivudine and efavirenz in HIV-1-infected patients: a four-year follow-up. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract TUPE0054.
 11. Casetti I, Madruga J, Etzel A, et al. The safety and efficacy of tenofovir DF (TDF) in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral-naïve patients through seven years. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract TUPE0057.
 12. Castellano C, Williams W, Kepler T, et al. Clinical predictors of tenofovir associated nephrotoxicity in HIV-1-infected patients. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract WEAB104.
 13. Rawlings K, Klein J, Klingler E, et al. Impact of drug therapy and comorbidities on the development of renal impairment in HIV-infected patients: results of a large retrospective database study. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract THPE0182.
 14. Short W, Solari P, Kaplan B. Comparison of renal function in a cohort of patients on tenofovir (TDF) versus non-tenofovir containing regimens. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract THPE0202.
 15. Towner W, Haigney Z, Sension M, et al. Efficacy, safety and tolerability of etravirine with and without darunavir and/or raltegravir in treatment experienced patients: preliminary analysis of TMC125-C214 Early Access Programme (EAP). 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract TUPE0066.
 16. Markowitz M, Nguyen B, Gotuzzo E, et al. Sustained antiretroviral efficacy of raltegravir as part of combination ART in treatment-naïve HIV-1 infected patients: 96-week data. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract TUAB0102.
 17. Markowitz M, Nguyen BY, Gotuzzo E, et al; Protocol 004 Part II Study Team. Rapid and durable antiretroviral effect of the HIV-1 integrase inhibitor raltegravir as part of combination therapy in treatment-naïve patients with HIV-1 infection: results of a 48-week controlled study. *J Acquir Immune Defic Syndr*. 2007;46:125-133.
 18. Talbot A, Machouf N, Thomas R, et al. Retrospective analysis of a switch from enfuvirtide to raltegravir in patients with undetectable viral load: efficacy and safety at 12 weeks in a Montreal cohort.

17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract TUPE0112.

19. Towner W, Klein D, Follansbee S, et al. Pilot study of switching enfuvirtide to raltegravir in HIV-1 positive patients well controlled on an enfuvirtide based regimen. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract TUPE0115.

20. Khanlou H, Allavena C, Billaud E, et al. Development of hepatic cytolysis after switching from enfuvirtide to raltegravir in virologically suppressed patients treated with tipranavir/ritonavir. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract TUPE0087.

21. Nelson M, Fisher M, Gonzalez-Garcia J, et al. Impact of baseline antiretroviral resistance status on efficacy outcomes among patients receiving maraviroc (MVC) plus an optimized background therapy (OBT) versus placebo (PBO) plus OBT in the MOTIVATE 1 and 2 trials. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract TUPE0119.

22. McFadyen L, Jacqmin P, Wade J, Weatherley B. Maraviroc exposure-efficacy (< 50 copies/mL) analysis in HIV-1-infected treatment-naïve subjectsITT population (MERIT study). 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract TUPE0053.

23. Steigbigel RT, Cooper DA, Kumar PN, et al; BENCHMRK Study Teams. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med.* 2008;359:339-354.

24. Yazdanpanah Y, Fagard C, Descamps D, et al. High rate of virologic success with raltegravir plus etravirine and darunavir/ritonavir in treatment-experienced patients with multidrug-resistant virus: results of the ANRS 139 TRIO trial. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract THAB0406.

25. DeJesus E; ACH443-015 Study Team. Elvucitabine phase II 24 week interim results show safety and efficacy profiles similar to lamivudine in naïve HIV-1 infected patients. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract TUPE0010.

26. Cox S, Moore S, Southby J, Alsumde A. Safety profile of apricitabine, a novel NRTI, during 24-week dosing in experienced HIV-1 infected patients. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract TUAB0106.

27. Santoscoy M, Cahn P, Gonzalez C, et al. TMC278 (rilpivirine), a next-generation NNRTI, demonstrates long-term efficacy and tolerability in ARV-naïve patients: 96-week results of study C204. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract TUAB0103.

28. Moyle G, Boffito M, Manhard K, et al. Antiviral activity of RDEA806, a novel HIV non-nucleoside reverse transcriptase inhibitor, in treatment of naïve HIV patients. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract THAB0403.

29. Zala C, Murphy R, Zhou X, et al. IDX899, a novel HIV-1 NNRTI with high barrier to resistance, provides suppression of HIV viral load in treatment-naïve HIV-1-infected subjects. 17th International AIDS Conference; August 3-8, 2008; Mexico City. Abstract THAB0402.