

Perspective

Antiretroviral Therapy: New Drugs, Formulations, Ideas, and Strategies

There is a continuing need for new antiretroviral drugs and formulations and updated strategies for using new and established drugs. Strategies being investigated for expanding initial treatment options include use of rilpivirine, raltegravir, or maraviroc as an alternative to efavirenz, use of pharmacokinetics enhancers without anti-HIV activity as an alternative to ritonavir as a boosting agent, and use of regimens sparing nucleoside analogue reverse transcriptase inhibitors, including ritonavir-boosted (/r) lopinavir plus raltegravir; darunavir/r plus raltegravir; vicriviroc plus atazanavir/r; and unboosted atazanavir plus raltegravir. For patients receiving fully suppressive regimens, strategies such as switching from lopinavir/r to raltegravir and from enfuvirtide to raltegravir have been examined. In highly treatment-experienced patients, use of 3 new active drugs has been found to be successful in suppressing virus. This article summarizes a presentation made by Joseph J. Eron, Jr, MD, at the International AIDS Society–USA continuing medical education program in Chicago in May 2009. The original presentation is available as a Webcast at www.iasusa.org.

New antiretroviral drugs and formulations and new strategies for using available drugs are continually needed. Because no new drugs are expected to be available in the near future from new classes of antiretroviral drugs, advances in treatment will come from strategies using new or available drugs in established classes. For treatment-naive patients, the need is for well-tolerated, highly active, and convenient antiretroviral therapy for all individuals requiring treatment, including women of child-bearing potential, individuals with tuberculosis or other complex medical or psychiatric conditions, and patients with transmitted drug-resistant virus, among others. Expanded treatment options will also become increasingly important as more is learned about long-term toxic effects of existing drugs and regimens. For treatment-experienced patients, new drugs and strategies are needed to expand treatment choices, avoid complex regimens and drugs with substantial toxic effects, and improve the ability to achieve full

suppression of HIV replication in highly treatment-experienced patients and others with drug-resistant virus.

Strategies in Treatment-Naive Patients

For initial treatment, options may be expanded by identifying alternatives to the fixed-dose combination of efavirenz/tenofovir/emtricitabine, to the use of ritonavir to boost protease inhibitors (PIs), and to the use of nucleoside analogue reverse transcriptase inhibitors (nRTIs). Among drugs used in initial or second-line treatment, ritonavir and efavirenz are 2 sources of difficulty in terms of tolerability, drug-drug interactions or limitations in certain patient groups (eg, for efavirenz, women of child-bearing potential who are considering pregnancy). The nRTIs remain a mainstay in initial regimens, but options have dwindled as the long-term toxic effects of these drugs have become more apparent.

Alternatives to Efavirenz

Rilpivirine. A recent phase IIb trial compared the second-generation investigational nonnucleoside analogue

reverse transcriptase inhibitor (NNRTI) rilpivirine (TMC278) with efavirenz, each plus 2 nRTIs in treatment-naive patients with plasma HIV RNA levels of at least 5000 copies/mL (Santoso et al, IAC, 2008). At 96 weeks, rates of virologic response (plasma HIV RNA level < 50 copies/mL) were 71% to 76% with rilpivirine 25 mg daily (n = 93), 75 mg daily (n = 95), or 150 mg daily (n = 91) and 71% with efavirenz (n = 89).

The overall incidence of adverse events was similar in the rilpivirine and efavirenz groups, with efavirenz associated with a higher incidence of rash (21% vs 9%, respectively; $P < .01$), nervous system disorders (48% vs 31%; $P < .01$), and neuropsychiatric disorders (21% vs 16%). The corrected QT interval (QTc) increased in all study groups through week 48 and then plateaued. QTc prolongation was smallest with the rilpivirine 25 mg daily dose, the dose selected for study in phase III trials. NNRTI resistance-associated mutations emerged at similar rates with rilpivirine and efavirenz, though the most common resistance mutations that emerge during rilpivirine therapy have not yet been described.

Rilpivirine 25 mg daily is being evaluated in 2 parallel, 48-week phase III trials: the ECHO (Efficacy Comparison in Treatment-Naive HIV-Infected Subjects of TMC278 and Efavirenz) trial, comparing rilpivirine versus efavirenz with tenofovir/emtricitabine; and the THRIVE (TMC278 Against HIV, in a Once-Daily Regimen Versus Efavirenz) trial, comparing rilpivirine versus efavirenz with investigator-chosen tenofovir/emtricitabine, abacavir/lamivudine, or zidovudine/lamivudine. Both trials have a target population of 680 patients and are fully enrolled.

Raltegravir. In the STARTMRK trial comparing the integrase inhibitor raltegravir with efavirenz, each plus tenofovir/emtricitabine, virologic response

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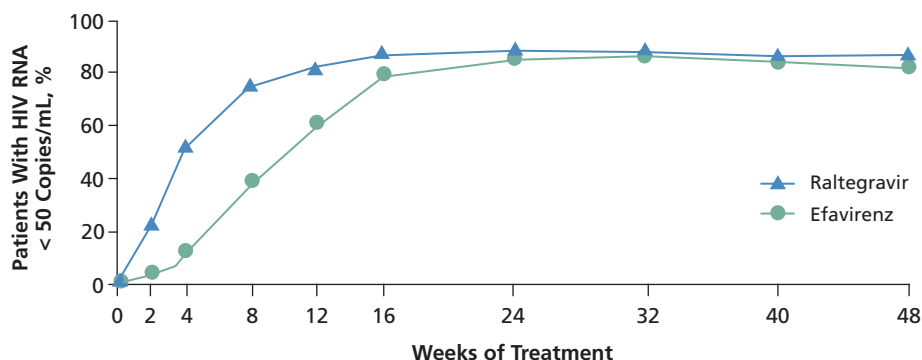


Figure 1. Proportions of patients achieving plasma HIV RNA level below 50 copies/mL in STARTMRK trial comparing raltegravir twice daily versus efavirenz plus tenofovir/emtricitabine. Adapted from Lennox et al, *Lancet*, 2009.

(plasma HIV RNA level < 50 copies/mL) occurred in 86% of raltegravir patients and 82% of efavirenz patients, with the difference satisfying the criterion for noninferiority of raltegravir ($P < .001$; Figure 1; Lennox et al, *Lancet*, 2009). Raltegravir treatment was associated with a statistically significantly shorter time to virologic response ($P < .001$) and a greater CD4+ count increase (189 vs 163 cells/ μ L, respectively) than efavirenz. Similar responses with raltegravir were observed in analyses by sex, race, and high and low viral load. Resistance mutations appeared to emerge at a similar rate with both study drugs.

A drawback of raltegravir is that it currently is given twice daily, and it is not yet available in fixed-dose combination forms with other drugs. However, once-daily raltegravir currently is being investigated. The drug has intriguing pharmacokinetic and pharmacodynamic characteristics, with no clear relationship between drug concentration and antiviral effect and minimum concentrations of the drug varying by nearly 1000-fold between patients. A phase III trial has been undertaken to compare raltegravir 800 mg daily with raltegravir 400 mg twice daily, each plus tenofovir/emtricitabine. The trial enrolled a fraction of the total number of subjects initially, and enrollment was placed on hold until the initial virologic response could be evaluated in this lead group. Enrollment to the trial has resumed, suggesting there were no substantial

concerns in this lead cohort.

Maraviroc. Patients are more likely to have CC chemokine receptor 5 (CCR5)-tropic virus in early infection. The MERIT (Maraviroc Versus Efavirenz Regimens as Initial Therapy) trial compared the CCR5 inhibitor maraviroc with efavirenz, each with zidovudine/lamivudine, in patients with CCR5-tropic HIV. Maraviroc twice daily was associated with a poorer virologic response rate than efavirenz. At the time of the trial, minority variants in patients' viral population could be detected only down to a threshold of approximately 10%. A new phenotypic tropism assay now permits detection of CXC chemokine receptor 4 (CXCR4)-using HIV down to approximately 0.3% of a viral population, representing a 30-fold improvement in ability to detect CXCR5 or dual/mixed viral phenotypes (Trinh et al, ICAAC/IDSA, 2008).

Reanalysis of samples from the MERIT trial using the new assay resulted in identification of dual/mixed virus in 15% of patients. When these patients were excluded from the efficacy analysis, the rate of virologic response (plasma HIV RNA level < 50 copies/mL) at 48 weeks with maraviroc met the noninferiority criterion compared with the response rate with efavirenz (overall, 68.5% vs 68.3%, respectively). On this reanalysis, response rates with maraviroc and efavirenz were also similar according to analysis by baseline HIV RNA levels with similar responses in the

2 arms in the subgroups with baseline HIV RNA level of 100,000 copies/mL or below and with baseline HIV RNA level above 100,000 copies/mL (Saag et al, ICAAC/IDSA, 2008). Another comparative trial using the enhanced tropism assay may be needed to clarify the efficacy of maraviroc versus efavirenz in this setting.

Alternatives to Ritonavir

Pharmacokinetic enhancers without anti-HIV activity. Several drugs that can enhance the pharmacokinetics of antiretroviral drugs without exerting anti-HIV effects are currently being developed. As noted, ritonavir use as a PI booster is associated with poor tolerability in some patients, extensive drug-drug interactions, and substantial effects on lipid metabolism. Ritonavir has been used primarily to boost other PIs, but it can also boost drugs in other classes such as the investigational agents elvitegravir (an integrase inhibitor) and vicriviroc (a CCR5 inhibitor). In clinical studies other than short-term proof-of-principle studies, regulatory agencies have preferred that low-dose ritonavir be used in regimens that contain a PI even if elvitegravir, for example, is also being used and boosted. The logic behind this preference is to avoid low-dose PI exposure (with ritonavir) in a non-PI-based regimen. Further, although ritonavir exerts its boosting activity by inhibiting the cytochrome P450 (CYP) 3A4 enzyme, it also inhibits other CYP isoenzymes and is an inducer of several liver enzymes, yielding complicated pharmacokinetic interactions with other drugs.

Among the pharmacokinetic enhancers currently under development is GS-9350, a drug with no anti-HIV activity that is being investigated in combination with the integrase inhibitor elvitegravir and with the PI atazanavir. GS-9350 exhibits potent inhibition of CYP3A similar in magnitude to that observed with ritonavir, has minimal inductive effects on CYP3A, and has less effect on other CYP enzymes than ritonavir. It also appears to have a lower potential for causing lipid abnor-

malities than ritonavir, showing markedly reduced inhibition of normal lipid accumulation and inhibition of glucose uptake in adipocyte function assays. GS-9350 also has improved aqueous solubility at normal pH, allowing it to be developed in tablet form.

In pharmacokinetic and pharmacodynamic studies, GS-9350 exhibited time- and dose-dependent pharmacokinetics and produced near-maximal inhibition of CYP3A activity (measured as inhibition of midazolam clearance) at doses of 100 mg or higher (reductions from pretreatment of 92% at 50 mg and 95% at 200 mg, compared with 95% with ritonavir); Mathias et al, CROI, 2009). Assessment of fixed-dose combinations of 100 mg and 150 mg GS-9350 with elvitegravir showed boosting of elvitegravir similar to that with ritonavir 100 mg (Table 1). The 150-mg GS-9350 dose resulted in higher trough concentrations of elvitegravir (11-fold higher than the protein-binding adjusted elvitegravir 95% inhibitory concentration), with low within-subject variability (15% coefficient of variation). A phase II study called the Quad study currently is evaluating a fixed-dose combination of GS-9350-boosted elvitegravir/tenofovir/emtricitabine compared with fixed-dose efavirenz/tenofovir/emtricitabine, and studies comparing ritonavir-boosted atazanavir with GS-9350-boosted atazanavir are ongoing.

SPI-452 is another investigational pharmacokinetic enhancer without anti-HIV activity. A proof-of-clinical-concept study showed that SPI-452 given at 25 mg, 50 mg, or 200 mg in-

creased exposure to darunavir and to atazanavir after 2 weeks of coadministration (Gulnik et al, CROI, 2009).

Alternatives to Nucleoside Analogue Reverse Transcriptase Inhibitors

A number of alternatives to nRTIs in initial regimens are being examined. An open-label study comparing lopinavir/r plus raltegravir versus lopinavir/r plus tenofovir/emtricitabine is under way. The combination of darunavir/r plus raltegravir as an alternative to nRTI-containing regimens for initial therapy is being examined in an ACTG (AIDS Clinical Trials Group) single-arm pilot study and a small comparative trial; a large-scale study is being planned in Europe. The combination of the CCR5 inhibitor vicriviroc 30 mg daily plus atazanavir/r 300 mg/100 mg daily is being compared with atazanavir/r plus tenofovir/emtricitabine in a phase II randomized, open-label trial in treatment-naïve patients with CCR5-tropic virus and a CD4+ count of at least 200 cells/ μ L.

Other studies are examining use of twice-daily, unboosted atazanavir plus raltegravir. In a pharmacokinetic study in healthy volunteers, coadministration of atazanavir 300 mg twice daily and raltegravir 400 mg twice daily reduced atazanavir exposure and increased raltegravir exposure (Zhu et al, CROI, 2009). For atazanavir (based on geometric mean values), maximum concentration (C_{max}) was reduced by 11%, area under the concentration-time curve for 0 hours to 12 hours (AUC_{0-12h}) was reduced

by 17%, and minimum concentration (C_{min}) was reduced by 29%. For raltegravir, increases were 39% for C_{max} , 54% for AUC_{0-12h} , and 48% for C_{min} (Zhu et al, CROI, 2009). The atazanavir C_{min} value (817 ng/mL) with twice-daily dosing of the combination was similar to the trough atazanavir concentration observed with atazanavir/r (300 mg/100 mg) once daily in HIV patients (although healthy volunteers do achieve higher atazanavir levels than HIV patients). The combination of atazanavir 300 mg plus raltegravir 400 mg, given twice daily, currently is being compared with atazanavir/r plus tenofovir/emtricitabine in a phase II randomized, open-label study in treatment-naïve patients.

Switching Therapy in Suppressed Patients

Goals for switching therapy in patients with viral suppression include simplifying regimens, reducing toxic effects, and improving tolerability; reducing cost would be good, too.

Switching from Lopinavir/Ritonavir to Raltegravir

The SWITCHMRK 1 (protocol 032) and 2 (protocol 033) studies were identical randomized, double-blind studies, conducted in different areas of the world (patients from North America and Australia were included in both studies). These studies examined the lipid effects, virologic effects, and safety and tolerability profiles associated with switching from lopinavir/r to raltegravir in patients on stable treatment with a lopinavir/r twice-daily regimen plus at least 2 nRTIs and no additional PIs for at least 3 months. In both trials, patients were randomly assigned to switch to raltegravir ($n = 174$ in protocol 032; $n = 176$ in protocol 033) or continue treatment with lopinavir/r ($n = 174$ in protocol 032; $n = 178$ in protocol 033) while maintaining background therapy. Patients were required to have had a plasma HIV RNA level below 50 copies/mL by polymerase chain reaction assay or 75 copies/mL by branch DNA assay and no lipid-lowering therapy for at least 12 weeks before study entry.

Table 1. Pharmacokinetic Effects of GS-9350 and Ritonavir on Elvitegravir Exposure in 42 Patients

Variable (units)	Mean Elvitegravir Exposure With:		
	GS-9350, 100 mg Mean (%)	GS-9350, 150 mg Mean (%)	Ritonavir, 100 mg Mean (%)
AUC_{tau} (ng·h/mL)	21,100 (25.4)	27,000 (29.4)	22,500 (23.4)
C_{max} (ng/mL)	2250 (26.3)	2660 (27.6)	2500 (32.1)
C_{tau} (ng/mL)	282 (60.4)	490 (52.9)	409 (40.5)

Adapted from data presented by Mathias et al, CROI, 2009.

AUC_{tau} indicates area under concentration curve at end of dosing interval (1 dose in 24 h);

C_{max} , maximum concentration; C_{tau} , minimum concentration after 24h.

Study participants were not required to be intolerant of lopinavir/r; those with prior virologic failure with other antiretroviral regimens were not excluded; and there was no limit on the number of prior regimens (Eron et al, CROI, 2009).

Primary endpoints included changes in lipid levels at 12 weeks and proportions of patients with a viral load below 50 copies/mL at 24 weeks. More than 80% of patients in each group in both studies had been taking lopinavir/r for more than 1 year. The median durations of prior antiretroviral therapy were 3.3 years to 4.6 years across the 4 treatment groups. Minimum durations of treatment ranged from 0.3 years to 0.6 years and maximum from 16.3 years to 22.3 years; median numbers of prior antiretroviral drugs taken were 5 or 6, with maximum numbers of 13 to 16. This wide heterogeneity in prior exposure to treatment makes findings on the virologic effect of switching to raltegravir from stable lopinavir/r somewhat difficult to interpret.

As shown in Figure 2, switching to raltegravir was associated with a pronounced reduction in triglyceride levels (median, 41% to 43% reduction from baseline) at 12 weeks, along with statistically significant reductions in levels of total cholesterol and non-high-density lipoprotein cholesterol compared with continued treatment with lopinavir/r. At 24 weeks, however, virologic response rates (noncompleter = failure analysis) were lower in the raltegravir groups in both protocol 032 (81% vs 87%, respectively) and protocol 033 (88% vs 94%, respectively). Confirmed virologic failure (requiring confirmation of viral rebound by measurements taken at least 1 week apart, with plasma HIV RNA level above 400 copies/mL) occurred in 3 raltegravir patients versus 2 lopinavir/r patients in protocol 032 and in 9 versus 2 patients,

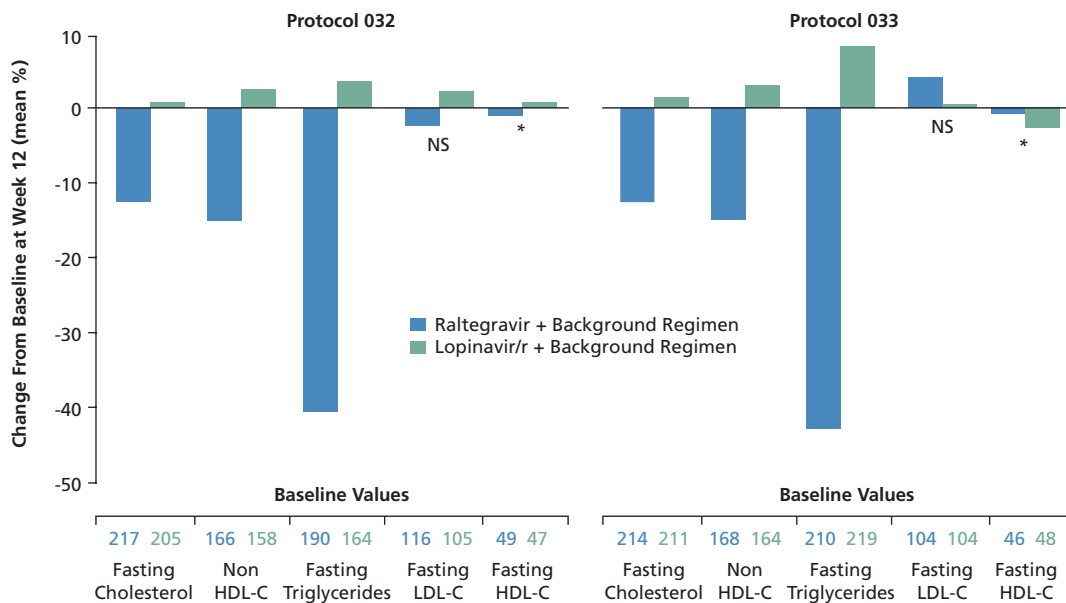


Figure 2. Lipid changes at 12 weeks in patients in SWITCHMRK 1 (protocol 032) and 2 (protocol 033) who were switched to raltegravir or continued treatment with lopinavir/ritonavir (lopinavir/r). Values are median mg/dL for triglycerides and mean mg/dL for all other lipid measures. C indicates cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Differences between lopinavir and raltegravir are statistically significant ($P < .001$) unless noted as not statistically significant (NS). Asterisk indicates that a statistical comparison was not prespecified in the analysis. Adapted from Eron et al, CROI, 2009, with permission. Original slide copyright© 2009 Merck Sharp & Dohme Corp; all rights reserved.

respectively, in protocol 033, with failure at greater than 50 copies/mL occurring in 13 versus 10 patients, respectively, and 19 versus 7 patients, respectively.

A post hoc analysis showed that the regimen at entry to the study was not the first antiretroviral regimen in 27 (84%) of the 32 raltegravir patients with virologic failure; among these 27 patients, 18 (66%) reported a history of virologic failure with a prior regimen. Study of resistance mutations in 9 raltegravir patients with virologic failure to greater than 400 copies/mL in protocol 033 showed raltegravir resistance mutations in 7. Analysis of the findings in the SWITCHMRK studies is ongoing; despite the lipid benefits observed with the switch, there is clearly concern over the loss of virologic control in a substantial subgroup of patients switched to raltegravir and the emergence of resistance mutations in cases of virologic failure.

Switching from Enfuvirtide to Raltegravir

Use of the fusion inhibitor enfuvirtide requires twice-daily subcutaneous injection. The EASIER (Efficacy and Tolerance of the Switch From Enfuvirtide to Raltegravir in Antiretroviral Therapy Regimen in Patients With Undetectable Viral Load; ANRS 138) trial compared the substitution of raltegravir ($n = 85$) with remaining on enfuvirtide ($n = 85$) in patients with triple-class-resistant virus or enfuvirtide intolerance who had a plasma HIV RNA level below 400 copies/mL for at least 3 months on a stable enfuvirtide-containing regimen. After the primary analysis at week 24, patients in the enfuvirtide group were switched to raltegravir for the remainder of the 48-week study. The mean duration of enfuvirtide use was 2.3 years.

The findings at 24 weeks indicate that switching does not result in loss of virologic control. At baseline, HIV RNA level was less than 50 copies/mL in 88% of the enfuvirtide group and 85% of the raltegravir group; at week 24, suppression to less than 50 copies/mL was achieved in 89% and 88%, respec-

tively (De Castro et al, CROI, 2009). Low frequencies of grade 3 or grade 4 laboratory abnormalities and adverse events occurred in both groups.

Three-Active-Drug Postfailure Regimens

The phase II TRIO (Efficacy of Darunavir/Ritonavir, Etravirine, and Raltegravir in HIV Patients With Resistance Viruses; ANRS 139) study provided evidence that a regimen of 3 active drugs could suppress virus in highly treatment-experienced patients. The combination of darunavir/r, etravirine, and raltegravir was given to 103 patients with 3 or fewer darunavir resistance-associated mutations and 3 or fewer etravirine resistance-associated mutations; 59% of patients had no active drugs in optimized background therapy on genotypic analysis. Enfuvirtide or nRTIs could be used at physician discretion. At week 24, 90% of patients (95% confidence interval, 85% to 96%) had HIV RNA levels below 50 copies/mL, and the median increase in CD4+ cell count was 99/ μ L (interquartile range, 32 to 147/ μ L) (Yazdanpanah et al, IAC, 2008). Of 10 patients with detectable virus at week 24, only 3 had HIV RNA levels above 400 copies/mL. Two possibly drug-related grade 4 adverse events were reported, with 1 leading to treatment discontinuation.

Presented by Dr Eron in May 2009. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Eron in November 2009.

Financial Disclosure: Dr Eron received research grants to University of North Carolina from Boehringer Ingelheim Pharmaceuticals, Inc, GlaxoSmithKline, and Merck & Co, Inc. He served as a consultant to Avexa Ltd, Bristol-Myers Squibb, Chimerix Inc, GlaxoSmithKline, Merck & Co, Inc, Pfizer Inc, Tibotec Therapeutics, Tobira Therapeutics Inc, and Virco Lab, Inc. He was on the speakers' bureaus of Bristol-Myers Squibb, Merck & Co, Inc, Roche, Tibotec Therapeutics, and Virco Lab, Inc.

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Top HIV Med. 2009;17(5):146-150

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