**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/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 (Santoscoy 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
suggesting there were no substantial
Enrollment to the trial has resumed,
hold until the initial virologic response
initially, and enrollment was placed on
vir/emtricitabine. The trial enrolled a
400 mg twice daily, each plus tenofo-
raltegravir 800 mg daily with raltegravir
trial has been undertaken to compare
1000-fold between patients. A phase III
antiviral effect and minimum concen-
tration between drug concentration and
pharmacokinetic and pharmacodynam-
investigated. The drug has intriguing
once-daily raltegravir currently is being
not yet available in fixed-dose combina-
tions by sex, race, and high and low viral
load. Resistance mutations appeared to
erge at a similar rate with both study
drugs.
A drawback of raltegravir is that it
currently given twice daily, and it is
not yet available in fixed-dose combina-
tions with other drugs. However, once-daily raltegravir currently is being
investigated. The drug has intriguing
pharmacokinetic and pharmacodynamic
characteristics, with no clear relation-
ship between drug concentration and antiviral effect and minimum concen-
trations 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 tenofo-
vir/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 com-
pared the CCR5 inhibitor maraviroc
with efavirenz, each with zidovudine/
lamivudine, in patients with CCR5-trop-
ic HIV. Maraviroc twice daily was asso-
ciated with a poorer virologic response
rate than efavirenz. At the time of the
trial, minority variants in patients’ vi-
ral population could be detected only
down to a threshold of approximately
10%. A new phenotypic tropism assay
now permits detection of CXC che-
mokine receptor 4 (CXCR4)-using HIV
down to approximately 0.3% of a viral
population, representing a 50-fold im-
provement 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 result-
ed in identification of dual/mixed virus
in 15% of patients. When these patients
assigned the efficacy criterion compared with the
response rate with efavirenz (overall,
68.5% vs 68.3%, respectively). On this
reanalysis, response rates with mara-
viroc 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 compara-
tive trial using the enhanced tropism
assay may be needed to clarify the ef-
cacy 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, exten-
sive drug-drug interactions, and sub-
stantial 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 in-
vestigational agents elvitegravir (an
integrate inhibitor) and vicriviroc (a
CCR5 inhibitor). In clinical studies oth-
er than short-term proof-of-principle
studies, regulatory agencies have pre-
ferred 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 sever-
er liver enzymes, yielding com-
plicated pharmacokinetic interactions
with other drugs.

Among the pharmacokinetic enha-
cers currently under development is
GS-9350, a drug with no anti-HIV
activity that is being investigated in
combination with the integrase inhibi-
tor elvitegravir and with the PI ataza-
navir. GS-9350 exhibits potent inhibi-
tion of CYP3A similar in magnitude to
that observed with ritonavir, has mini-
mal 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-
mally 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 increased 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 500 mg/100 mg daily is being compared with atazanavir/r plus tenofovir/emtricitabine in a phase II randomized, open-label trial in treatment-naive patients with CCR5-tropic virus and a CD4+ count of at least 200 cells/µL.

Other studies are examining use of twice-daily, unboosted atazanavir plus raltegravir. In a pharmacokinetic study in healthy volunteers, coadministration of atazanavir 500 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 (Cmax) was reduced by 11%, area under the concentration-time curve for 48 hours (Cauc) was reduced by 17%, and minimum concentration (Cmin) was reduced by 29%. For raltegravir, increases were 59% for Cmax, 54% for AUC0-12h, and 48% for Cmin (Zhu et al, CROI, 2009). The atazanavir Cmin 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-naive 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

<table>
<thead>
<tr>
<th>Variable (units)</th>
<th>Mean Elvitegravir Exposure With:</th>
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<tbody>
<tr>
<td></td>
<td>GS-9350, 100 mg</td>
</tr>
<tr>
<td>AUC0-12h (ng·h/mL)</td>
<td>21,100 (25.4)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>2250 (26.3)</td>
</tr>
<tr>
<td>Cmin (ng/mL)</td>
<td>282 (60.4)</td>
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Adapted from data presented by Mathias et al, CROI, 2009. AUC0-12h indicates area under concentration curve at end of dosing interval (1 dose in 24 h); Cmax, maximum concentration; Cmin, 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, 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/µL (interquartile range, 32 to 147/µL) (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.

*Suggested Reading*


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**Suggested Reading**


