INVITED ARTICLE REVIEWS OF ANTI-INFECTIVE AGENTS

Louis D. Saravolatz

RALTEGRAVIR: THE FIRST HIV TYPE 1 INTEGRASE INHIBITOR

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Raltegravir is the first approved human immunodeficiency virus type 1 (HIV-1) integrase inhibitor; it targets the strand transfer step of HIV-1 integration. Clinical trials have demonstrated that raltegravir-containing regimens have potent antiretroviral activity and are well tolerated in HIV-1–infected individuals. In antiretroviral treatment–experienced persons with drug-resistant HIV infection, raltegravir-containing treatment with an optimized background regimen was superior to an optimized background regimen alone. In treatment-naive persons, raltegravir was not inferior to efavirenz when the drugs were administered with tenofovir and lamivudine or emtricitabine. Raltegravir is metabolized by glucuronidation, not hepatically; thus, the potential for drug-drug interactions is decreased. Drug resistance, conferred by substitutions in the gene coding for the HIV-1 integrase enzyme, develops relatively frequently after virologic failure. As an antiretroviral drug with a novel mechanism of action, raltegravir is an important advancement in HIV-1 treatment options.

More than 20 years into the era of antiretroviral therapy, the need for new antiretroviral agents continues to be substantial. The development of drugs targeting critical steps in the life cycle of HIV-1 has been central to treatment success; such drug classes include HIV-1 reverse-transcriptase inhibitors (both nucleoside analogues and nonnucleoside inhibitors), HIV-1 protease inhibitors, and HIV-1 entry inhibitors (fusion inhibitors and CCR5 antagonists). Raltegravir is the first approved drug to successfully inhibit the HIV-1 integrase enzyme [1]. It is currently approved by the US Food and Drug Administration “in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents” [2, p. 1].

BACKGROUND

The HIV-1 integrase enzyme is responsible for transfer of virally encoded DNA into the host chromosome—a necessary event in retrovirus replication. The process of HIV-1 integration occurs through 3 essential steps: formation of the preintegration viral DNA complex, 3’ processing, and strand transfer [1, 3–6]. Formation of the preintegration complex permits passage of HIV-1 viral DNA into the nucleus, where DNA strand transfer occurs. The integrase enzyme binds to the virally encoded DNA, joining it with host chromosomal DNA, after which cellular repair activities seal the viral DNA in the chromosome. A key element of the enzyme essential to binding is located in a highly conserved region known as the catalytic core. It is thought that divalent cations in the catalytic core enable integrase to form covalent bonds with the phosphodiester backbone of DNA. Raltegravir, the first approved drug to prevent strand transfer, works by preventing formation of these covalent bonds with host DNA (figure 1).

IN VITRO ACTIVITY

Raltegravir has potent in vitro activity against HIV-1, with a 95% inhibitory concentration (IC95; ± SD) in human T lymphoid cell cultures of 31 ± 20 nmol/L [2]. The drug is ~83% bound to human plasma proteins [2]. It is active against a wide range of wild-type and drug-resistant HIV-1 isolates, including both CCR5 coreceptor–using strains and CXCR4 coreceptor–using strains [1]. Raltegravir was also active against HIV-2 when the drug was tested in CEMx174 cells, with an IC50 of 6 nmol/L. Additive to synergistic activity was observed when human T lymphoid cell culture samples infected with the H9IIB variant of HIV-1 were incubated with raltegravir and a panel of available nucleoside analogue reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors, and protease inhibitors. In vitro data are not currently available for darunavir,
half-life of a biphasic decrease in drug concentrations, with an initial-phase time to maximum concentration of 0.5–1.3 h [7]. There was volunteers showed raltegravir to be rapidly absorbed with a median dose study (10–1600 mg) involving 47 HIV-1–uninfected vol-
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INTERACTIONS
CLINICAL PHARMACOLOGY AND DRUG INTERACTIONS
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dose study (10–1600 mg) involving 47 HIV-1–uninfected vol-
unteers showed raltegravir to be rapidly absorbed with a median
time to maximum concentration of 0.5–1.3 h [7]. There was a biphasic decrease in drug concentrations, with an initial-phase half-life of ∼1 h and a terminal-phase half-life of 7–12 h. These characteristics were not affected by food with moderate-to-high fat content. A subsequent 10-day multiple dosing study in-
volving 40 HIV-1–uninfected male patients revealed that steady-state drug concentrations were achieved within 2 days. Significant drug accumulation was not observed.

The first study of raltegravir in HIV-1–infected persons (004 study) was a multicenter, double-blind, randomized, dose-
escalation, placebo-controlled trial involving antiretroviral ther-
apy–naive persons. In this study, raltegravir monotherapy was administered for 10 days at dosages of 100, 200, 400, or 600 mg every 12 h [8]. Participants subsequently received raltegravir or efavirenz with the nucleoside analogue reverse-transcriptase inhibitors tenofovir and lamivudine. During the monotherapy stage, pharmacokinetic characteristics were assessed on day 10. The geometric mean values for maximum concentration and area under the curve at 12 h increased with dose up to the dosage of 400 mg twice daily. The maximum concentration was 2.1 μmol/L (with the 100-mg dose), 3.5 μmol/L (with the 200-
mg dose), 4.5 μmol/L (with the 400-mg dose), and 3.8 μmol/
L (with the 600-mg dose). The area under the curve at 12 h was 5.7 μmol/L/h (with the 100-mg dose), 9.2 μmol/L/h (with
the 200-mg dose), 14.2 μmol/L/h (with the 400-mg dose), and 14.6 μmol/L/h (with the 600-mg dose). On the basis of these data, the dosage selected for development (and that was sub-
sequently approved) was 400 mg twice daily.

Raltegravir metabolism occurs primarily through glucuron-
iddation [9]. Drugs that are strong inducers of the glucurononi-
dation enzyme, UGT1A1, significantly reduce raltegravir con-
centrations and should not be used; for example, rifampin decreases raltegravir concentrations by 38%–61% [2]. Other drugs that induce UGT1A1 less strongly (e.g., phenytoin and phenobarbital) may also reduce concentrations of raltegravir, but this has not been well characterized. Weak UGT1A1 in-
ducers (e.g., St. John’s Wort, efavirenz, nevirapine, and rifabutin) are not expected to have a clinically significant impact, and no change in raltegravir dosing is warranted [2]. No dose adjustments are recommended for severe renal impairment or mild-to-moderate hepatic impairment [2].

A study of human liver microsomes demonstrated that ral-
tegravir exhibited weak inhibitory effects on hepatic cyto-
chrome P450 activity. Raltegravir did not induce CYP3A4 RNA expression or CYP3A4-dependent testosterone 6-β-hydroxylase activity [10]. The lack of a clinically relevant effect was verified in vivo in a study of 10 HIV-1–uninfected volunteers [10]. There were no statistically significant changes in midazolam area-under-the-curve concentrations, maximum plasma concentrations, time to maximum concentration, or apparent plasma half-life after 2 weeks of raltegravir therapy, demon-
strating that raltegravir is neither an inducer nor an inhibitor of cytochrome P450 enzymes, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2G19, CYP3D6, and CYP3A. In ad-
dition, raltegravir does not inhibit P-glycoprotein–mediated drug transportation [2]. As a consequence, raltegravir likely does not affect the pharmacokinetics of methadone, opioids, statins, azole antifungals, proton pump inhibitors, oral contra-
ceptives, erectile dysfunction therapies, or most other antiret-
roviral drugs.

However, a multiple-dose study of atazanavir (with or without ritonavir boosting) and raltegravir demonstrated modest increases in raltegravir concentrations (of 24%–95%, depend-
ing on the parameter measured) [11]. This appears to be attribut-
able to an inhibitory effect of atazanavir on UGT1A1 and is not believed to be clinically significant. A study of 10 HIV-
uninfected volunteers revealed that co-administration of ralte-
gravir with tenofovir decreases raltegravir concentrations by 49%–64% and tenofovir concentrations by 10%–13% (neither decreases were thought to be clinically significant) [12]. Other studies of antiretroviral agents have shown no more than mod-
erate decreases in raltegravir concentrations during co-admin-
istration with efavirenz (decreases of 21%–36%), etravirine (de-
creases of 10%–34%), ritonavir (no effect), or tipranavir plus ritonavir (decreases of 18%–55%) [13–15]. None of these re-
ductions are thought to be clinically significant. Finally, data from a single patient showed that tipranavir trough concen-

Figure 1. HIV-1 integrase mechanism of action [1]. *Cellular function. LTR, long terminal repeats; PIC, preintegration complex.
trations more than doubled after initiation of raltegravir. Table 1 summarizes data on raltegravir interactions with selected antiretroviral medications.

**CLINICAL TRIALS**

**Treatment-naive patients.** The aforementioned 004 phase I study assessed the safety and efficacy of raltegravir in HIV-1–infected, treatment-naive individuals [8]. Thirty-five participants with HIV-1 RNA levels >5000 copies/mL and CD4 cell counts >100 cells/µL were randomized to receive 1 of 4 doses of raltegravir or placebo (table 2). On day 10, mean decreases in viral load were 1.9 log_{10} copies/mL in the 100-mg dose group, 2.0 log_{10} copies/mL in the 200-mg dose group, 1.7 log_{10} copies/mL in the 400-mg dose group, 2.2 log_{10} copies/mL in the 600-mg dose group, and 0.2 log_{10} copies/mL in the placebo group (P < .001, for pairwise comparisons of each raltegravir dose vs. placebo). Part II of this protocol was a similarly designed randomized study in which HIV-infected, antiretroviral therapy–naive persons received tenofovir and lamivudine (300 mg of each daily) combined with either raltegravir (100, 200, 400, or 600 mg twice daily) or standard-dose efavirenz for 48 weeks [17, 18]. A total of 201 participants (30 from part I and 171 new participants) with a mean baseline viral load of 4.7–4.8 log_{10} copies/mL (34% had a baseline viral load >100,000 copies/mL) and a mean baseline CD4 cell count of 280–305 cells/µL were randomized; 198 received study therapy. After week 48, all participants in the raltegravir arms were given 400 mg twice daily. At week 96, the HIV-1 RNA level was <50 copies/mL in 83% of raltegravir recipients and in 84% of efavirenz recipients.

Of interest, there was a significantly shorter time to achievement of an HIV-1 RNA level <50 copies/mL in the raltegravir groups, compared with the efavirenz group (P < .05), with more persons in each raltegravir group achieving viral suppression at weeks 2, 4, and 8. Other investigators reviewed these data and determined that plasma HIV-1 RNA levels were 70% lower at the initiation of second-phase viral decay for individuals who received raltegravir, compared with individuals who received efavirenz [24]. However, the clinical significance of the more rapid decrease in HIV-1 RNA level associated with raltegravir is unknown, particularly in light of the fact that similar proportions of treated patients experienced HIV-1 suppression at weeks 24, 48, and 96.

Initial data from a randomized, blinded phase III study (STARTMRK) were reported that compared the safety and efficacy of raltegravir-based treatment with the safety and efficacy of efavirenz-based treatment (both given with tenofovir and emtricitabine) in 563 treatment-naive persons [19]. The median baseline viral load was >100,000 copies/mL, and almost one-half of the persons enrolled had CD4 cell counts <200 cells/µL. At 48 weeks, the median HIV-1 RNA level was <50 copies/mL in 86% of patients who received raltegravir-based treatment and in 82% of patients who received efavirenz-based treatment (in an intention-to-treat analysis in which patients who did not complete the regimen were considered to have experienced treatment failure); this demonstrated noninferiority of raltegravir, compared with efavirenz. Time to virologic response was significantly shorter and increases in CD4 cell count were significantly greater in the raltegravir arm, compared with the efavirenz arm (increase of 189 cells/µL vs. increase of 163 cells/µL; difference, 26 cells/µL; 95% CI, 4–47 cells/µL). Clinical adverse events, drug-related clinical adverse events, and early CNS symptoms were significantly more common in the efavirenz arm than in the raltegravir arm.

**Treatment-experienced patients.** In a phase II blinded study, treatment-experienced participants infected with HIV with documented resistance to at least 1 nucleoside analogue reverse-transcriptase inhibitor, 1 nonnucleoside reverse-transcriptase inhibitor, and 1 protease inhibitor were randomized.

**Table 1. Raltegravir (RAL) interactions with selected antiretroviral drugs.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction with RAL</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI: Tenofovir</td>
<td>Increased RAL C_{min} by 64% and AUC by 49%; RAL C_{max} unchanged; decreased tenofovir AUC by 10% and C_{min} by 13%</td>
<td>[12]</td>
</tr>
<tr>
<td>NNRTI Efavirenz</td>
<td>RAL C_{12hr} geometric mean ratio, 0.79; AUC geometric mean ratio, 0.64</td>
<td>[13]</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Decreased RAL C_{max} by 11%, C_{min} by 34%, and AUC by 10%</td>
<td>[14]</td>
</tr>
<tr>
<td>Protease inhibitor</td>
<td>Atazanavir Increased RAL C_{max} by 53%, C_{min} by 95%, and AUC by 75%</td>
<td>[11]</td>
</tr>
<tr>
<td></td>
<td>Atazanavir plus ritonavir Increased RAL C_{max} by 41%, C_{min} by 24%, and AUC by 75%</td>
<td>[11]</td>
</tr>
<tr>
<td></td>
<td>Ritonavir No effect on RAL parameters</td>
<td>[12]</td>
</tr>
<tr>
<td></td>
<td>Tipranavir plus ritonavir Decreased RAL C_{max} by 18%, C_{min} by 55%, and AUC by 24%; increased tipranavir plus ritonavir C_{min} by 2.3-fold in 1 patient</td>
<td>[15, 16]</td>
</tr>
</tbody>
</table>

**NOTE.** On the basis of current data, no drug dosage changes are recommended for any antiretroviral agents administered with raltegravir. AUC, area under the curve; C_{max}, maximum concentration; C_{min}, minimum concentration; C_{12hr}, concentration 12 h after receipt of a dose; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor.
Table 2. Clinical studies of raltegravir (RAL).

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>No. of participants</th>
<th>Study population</th>
<th>Study regimen</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>004</td>
<td></td>
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<tr>
<td>Part 1</td>
<td>I</td>
<td>35</td>
<td>HIV-1–infected, treatment-naive; HIV-1 RNA level (&gt;5000) copies/mL; CD4 cell count (&gt;100) cells/(\mu L)</td>
<td>RAL (100, 200, 400, or 600 mg), or placebo twice daily</td>
<td>On day 10 HIV-1 RNA level had decreased by 1.9 (RAL; 100 mg), 2.0 (RAL; 200 mg), 1.7 (RAL; 400 mg), 2.2 (RAL; 600 mg), and 0.2 log(_10) copies/mL (placebo)</td>
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<tr>
<td>Part 2</td>
<td>II</td>
<td>201</td>
<td>HIV-1–infected, treatment-naive; HIV-1 RNA level (&gt;5000) copies/mL; CD4 cell count (&gt;100) cells/(\mu L)</td>
<td>TDF plus 3TC and RAL (100, 200, 400, or 600 mg) twice daily or EFV</td>
<td>At week 48, the proportions of patients with an HIV-1 RNA level (&lt;50) copies/mL were 85% (RAL; 100 mg), 83% (RAL; 200 mg), 88% (RAL; 400 mg and 600 mg), and 87% (EFV)</td>
</tr>
<tr>
<td>Extension</td>
<td>II</td>
<td>198</td>
<td>Same as above</td>
<td>TDF plus 3TC and RAL (400 mg twice daily; beginning at week 48) or EFV</td>
<td>At week 96, the proportions of patients with an HIV-1 RNA level (&lt;50) copies/mL were 83% (RAL) and 84% (EFV)</td>
</tr>
<tr>
<td>STARTMRK</td>
<td>III</td>
<td>563</td>
<td>HIV-1–infected, treatment-naive; HIV-1 RNA level (&gt;5000) copies/mL</td>
<td>TDF, FTC, and RAL (400 mg) twice daily or EFV</td>
<td>At week 48, the proportions of patients with an HIV-1 RNA level (&lt;50) copies/mL were 96% (RAL) and 82% (EFV)</td>
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<tr>
<td>Main</td>
<td>II</td>
<td>178</td>
<td>HIV-1–infected, treatment-experienced; HIV-1 RNA level (&gt;5000) copies/mL; CD4 cell count (&gt;50) cells/(\mu L)</td>
<td>OBT and RAL (200, 400, or 600 mg) or placebo twice daily</td>
<td>At week 24, the proportions of patients with an HIV-1 RNA level (&lt;50) copies/mL were 65% (RAL; 200 mg), 56% (RAL; 400 mg), 67% (RAL; 600 mg), and 13% (placebo)</td>
</tr>
<tr>
<td>Extension</td>
<td>II</td>
<td>178</td>
<td>Same as above</td>
<td>OBT and RAL (400 mg; beginning at week 24) or placebo twice daily</td>
<td>At week 48, the proportions of patients with an HIV-1 RNA level (&lt;50) copies/mL were 64% (RAL; 200 mg), 46% (RAL; 400 mg), 53% (RAL; 600 mg), and 9% (placebo)</td>
</tr>
<tr>
<td>BENCHMRK</td>
<td>III</td>
<td>350</td>
<td>HIV-1–infected, treatment-experienced; HIV-1 RNA level (&gt;1000) copies/mL; any CD4 cell count</td>
<td>OBT and RAL (400 mg) or placebo twice daily (randomized 2:1)</td>
<td>At week 48, the proportions of patients with an HIV-1 RNA level (&lt;50) copies/mL were 65% (RAL) and 31% (placebo)</td>
</tr>
</tbody>
</table>

**NOTE.** EFV, efavirenz; OBT, optimized background antiretroviral therapy; TDF, tenofovir; 3TC, lamivudine.

to receive raltegravir (200, 400, or 600 mg) or placebo twice daily, together with an antiretroviral regimen selected on the basis of treatment history and drug susceptibility testing [20]. Of note, neither tipranavir, darunavir, nor other newer agents were available for use in this study; enfuvirtide was available. At week 24, the proportions of persons with an HIV-1 RNA level \(<50\) copies/mL were 65% in the 200-mg dose arm, 56% in the 400-mg dose arm, 67% in the 600-mg dose arm, and...
13% in the placebo arm ($P < .001$, for pairwise comparisons with placebo). After 24 weeks, all participants received raltegravir (400 mg twice daily) [21]. At week 48, the HIV-1 RNA level remained suppressed at $< 50$ copies/mL in 54% of patients who were receiving the raltegravir-based regimen.

The BENCHMRK trials were 2 international, parallel, randomized, placebo-controlled 48-week studies of raltegravir in 699 treatment-experienced participants infected with HIV with documented resistance to nucleoside analogue reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors, and protease inhibitors [22, 23]. Eligible persons were randomized at a 2:1 ratio to receive raltegravir (400 mg) or placebo twice daily, each in combination with an optimized background antiretroviral regimen. The mean baseline HIV-1 RNA level was 4.5–4.7 log$_{10}$ copies/mL, and the median CD4 cell count was 102–140 cells/µL. At week 48, 62% of patients in the raltegravir arm and 33% of patients in the placebo arm had an HIV-1 RNA level $< 50$ copies/mL (in an intention-to-treat analysis in which patients who did not complete the regimen were considered to have experienced treatment failure; $P < .001$). CD4 cell counts increased to 109 cells/µL in the raltegravir arm, compared with 45 cells/µL in the placebo arm ($P < .001$). Patients with more active agents in the background regimen (including newer agents, such as enfuvirtide and/or darunavir) had better virologic suppression rates [22]. Response rates based on the number of active agents in the background regimen, as determined by the genotypic susceptibility score, were 45% (genotypic susceptibility score, 0), 67% (genotypic susceptibility score, 1), and 77% (genotypic susceptibility score, 2). These results led to approval of raltegravir for antiretroviral treatment–experienced persons by the US Food and Drug Administration in October 2007.

In a pilot study of 35 HIV-1–infected enfuvirtide–treated persons with HIV-1 RNA levels $< 50$ copies/mL who experienced treatment-limiting injection site reactions, raltegravir was substituted for enfuvirtide in the antiretroviral regimens [25]. With a median duration of follow-up of 7 months (range, 1–13 months), 34 patients continued to have virologic suppression. Two studies of similar design enrolled an additional 77 persons and reported 12–24 weeks of follow-up after raltegravir substitution; 73 of 77 patients maintained viral suppression (HIV-1 RNA level, $< 50$ copies/mL), 2 participants had an HIV RNA level $> 50$ copies/mL, 1 withdrew from the study, and 1 died [26, 27]. A small case series of persons receiving tipranavir plus ritonavir noted significant increases in hepatic transaminase levels in 3 persons after a switch from enfuvirtide to raltegravir; these increases resolved after darunavir was substituted for tipranavir [16]. Although available data are clearly limited, the strategy of substituting raltegravir for enfuvirtide appears to be promising.

**SAFETY AND TOXICITY**

**Treatment-naive patients.** In 3 phase I studies involving HIV-1–uninfected individuals, raltegravir, given as single doses of 10–1600 mg or as multiple doses of 100–800 mg every 12 h for 10 days, was well tolerated (table 3). The most common adverse events were transient mild-to-moderate headache and fatigue [7]. There were no consistent treatment-related changes in laboratory, vital signs, or electrocardiogram parameters.

In the phase I study of 10 days of raltegravir monotherapy given to HIV-1–infected, treatment-naive individuals, there were no apparent dose-related toxicities; the adverse event profile was similar to that for placebo [8]. In the follow-up 96-week phase II study that compared raltegravir with efavirenz (each in combination with tenofovir and lamivudine), the incidence of serious adverse events was similar between the groups (6%), and no event was considered to be drug related or led to treatment discontinuation [17, 18]. Over 96 weeks, there was a higher percentage of grade 3 and 4 creatine phosphokinase elevations in the raltegravir arm than in the efavirenz arm (6.3% vs. 2.6%), and there was 1 case of rhabdomyolysis. Changes in lipid levels were less significant in the raltegravir arm than in the efavirenz arm (total cholesterol level, increase of 1 mg/dL vs. increase of 24 mg/dL; low-density lipoprotein cholesterol level, decrease of 6 mg/dL vs. increase of 4 mg/dL; high-density lipoprotein cholesterol level, increase of 7 mg/dL vs. increase of 13 mg/dL; triglyceride level, decrease of 11 mg/dL vs. increase of 13 mg/dL).

In the phase III study involving treatment-naive persons treated with tenofovir and emtricitabine and either raltegravir or efavirenz, clinical and drug-related adverse events were significantly less common among those receiving raltegravir [19]. Moreover, decreases from baseline in total cholesterol, low-density lipoprotein cholesterol level, decrease of 6 mg/dL vs. increase of 4 mg/dL; high-density lipoprotein cholesterol level, increase of 7 mg/dL vs. increase of 13 mg/dL; triglyceride level, decrease of 11 mg/dL vs. increase of 13 mg/dL.

**Treatment-experienced patients.** In the phase II study that compared raltegravir with placebo in treatment-experienced persons, the safety profile in the study arms was similar, with no reported dose-related toxicities [20, 21]. In the large phase III studies that compared raltegravir with placebo in highly treatment-experienced persons, raltegravir was well tolerated, and the adverse event profile was similar to that for placebo, with comparable numbers of drug-related adverse events, study drug discontinuation because of an adverse event, and deaths [22, 23].

In an initial combined analysis of the double-blind parts of raltegravir phase II and III studies, 10 patients (1.3%) who were receiving raltegravir, compared with 1 patient (0.3%) in the control arm, developed malignancies [28]. This apparent imbalance prompted an updated assessment with use of both...
Table 3. Frequency of treatment-related adverse events and laboratory abnormalities in phase II and III clinical trials involving treatment-experienced patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raltegravir (400 mg twice daily) plus OBT (n = 507)</td>
</tr>
<tr>
<td>Adverse event</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.7</td>
</tr>
<tr>
<td>Headache</td>
<td>2.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.2</td>
</tr>
<tr>
<td>Discontinuation of treatment because of adverse events</td>
<td>2.0</td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td></td>
</tr>
<tr>
<td>Grade 2 (750–999 cells/μL)</td>
<td>3.7</td>
</tr>
<tr>
<td>Grade 3 (500–749 cells/μL)</td>
<td>2.4</td>
</tr>
<tr>
<td>Hemoglobin level: grade 2 (7.5–8.4 g/dL)</td>
<td>1.0</td>
</tr>
<tr>
<td>Platelet level: grade 2 (50–90,000 × 10^3 cells/μL</td>
<td>3.7</td>
</tr>
<tr>
<td>Fasting glucose level: grade 2 (126–250 mg/dL)</td>
<td>9.3</td>
</tr>
<tr>
<td>Bilirubin level: grade 2 (1.6–2.5 × ULN)</td>
<td>5.3</td>
</tr>
<tr>
<td>Aspartate aminotransferase level</td>
<td></td>
</tr>
<tr>
<td>Grade 2 (2.6–5 × ULN)</td>
<td>9.1</td>
</tr>
<tr>
<td>Grade 3 (5.1–10 × ULN)</td>
<td>2.2</td>
</tr>
<tr>
<td>Alanine aminotransferase level</td>
<td></td>
</tr>
<tr>
<td>Grade 2 (2.6–5 × ULN)</td>
<td>6.9</td>
</tr>
<tr>
<td>Grade 3 (5.1–10 × ULN)</td>
<td>3.0</td>
</tr>
<tr>
<td>Alkaline phosphatase level: grade 2 (2.6–5 × ULN)</td>
<td>2.0</td>
</tr>
<tr>
<td>Pancreatic amylase level: grade 3 (2.1–5 × ULN)</td>
<td>3.6</td>
</tr>
<tr>
<td>Lipase level: grade 2 (1.6–3 × ULN)</td>
<td>3.4</td>
</tr>
<tr>
<td>Creatine phosphokinase level</td>
<td></td>
</tr>
<tr>
<td>Grade 2 (6–9.9 × ULN)</td>
<td>2.2</td>
</tr>
<tr>
<td>Grade 3 (10–19.9 × ULN)</td>
<td>2.4</td>
</tr>
<tr>
<td>Grade 4 (&gt;20 × ULN)</td>
<td>2.2</td>
</tr>
</tbody>
</table>

NOTE. Moderate-to-severe adverse events occurred in ≥2% of patients [6]. OBT, optimized background therapy; ULN, upper limit of normal.

blinded and open-label data from phase II and III studies, as well as data from the expanded access program. This update found malignancies in 19 (2.5%) of 820 patients receiving raltegravir, compared with 5 (1.9%) of 261 control subjects, showing a diminished difference between the groups [28]. In contrast, data from the phase III STARTMRK trial found more malignancies among those randomized to receive efavirenz (9 [3.2%] of 281 patients) than among those who received raltegravir (1 [0.4%] of 281 patients) [19]. Recent reports have expanded information on other possible raltegravir-associated adverse events, including case reports of rhabdomyolysis and exacerbation of depression [19, 29, 30].

**DRUG RESISTANCE**

Clinical experience with integrase inhibitor treatment failure and resistance is relatively limited (table 4). In vitro data suggest that significant resistance to raltegravir is usually a consequence of multiple integrase gene substitutions [31]. This has been confirmed by data from early treatment trials and from the BENCHMRK studies, which demonstrated 3 main drug-resistance pathways associated with treatment failure and confirmed the association with multiple integrase gene substitutions [23, 32, 33] By week 48 in the BENCHMRK studies, 105 (23%) of 462 raltegravir recipients experienced virologic failure; 94 (90%) of 105 had genotypic data available, and 64 (68%) of 94 had genotypic evidence of integrase resistance. Most (75%) had multiple mutations, including either Y143, Q148, or N155. Drug resistance was more common in patients with high baseline viral loads and in those with low genotypic or phenotypic susceptibility scores.

Resistance to the investigational integrase inhibitor elvitegravir has also been described. Early in vitro results suggested...
that some pathways to resistance did not cause cross-resistance to raltegravir; however, others did cause cross-resistance [34]. Clinical data on cross-resistance in this context are limited, but the development of either the Q148R or N155H pathways produces high-level phenotypic resistance to both compounds. Two persons who experienced elvitegravir treatment failure were subsequently treated with raltegravir and showed no virologic response; mutations Q148R and N155H were present [35]. In vitro data from patient samples obtained in a phase II study of elvitegravir further suggested the likelihood of significant cross-resistance between the 2 compounds [36].

### CLINICAL USE

On the basis of phase II and III studies, the US Food and Drug Administration approved the use of raltegravir in combination with other antiretroviral drugs in treatment-experienced adults with ongoing viral replication and multidrug-resistant viral strains [20–23]. Better virologic responses with raltegravir-based regimens were seen in patients whose background therapy included more active antiretroviral agents, although some patients responded even when the background regimen had no fully active agents, presumably because of partial virologic activity of some of the drugs [23]. Raltegravir resistance commonly developed among patients who experienced virologic failure. These observations support current antiretroviral treatment guidelines that recommend a regimen with ≥2 fully active drugs for treatment-experienced patients [37]. For a patient without prior integrase inhibitor experience, raltegravir certainly constitutes a fully active drug. Although data are limited, it is probably reasonable to substitute raltegravir for enfuvirtide in patients who are not tolerating the latter agent [25–27]. Such a strategy is only possible for persons without prior exposure to integrase inhibitors, and close monitoring is essential after the switch is made. Recent data suggest that substitution of raltegravir for other agents (particularly protease inhibitors) is not appropriate, even in patients who have fully suppressed viral replication [38].

Phase II and III studies involving treatment-naive persons demonstrated that raltegravir was at least as effective as efavirenz when it was used with tenofovir and emtricitabine (or lamivudine). Raltegravir treatment had less effect on lipid levels and was associated with fewer overall adverse events (particularly CNS events), compared with efavirenz. On the basis of these data, raltegravir could be an option for patients initiating their first antiretroviral treatment regimen. Clinical trials involving HIV-infected persons are exploring novel combinations that pair raltegravir with an initial protease inhibitor. Other populations of interest include children, adolescents, and pregnant women. Additional scenarios to be studied include the use of raltegravir as add-on therapy for selected persons with viral loads <50 copies/mL and the use of raltegravir as post-exposure prophylaxis.

### CONCLUSIONS

HIV-1 integrase is a unique target for antiretroviral therapy. Raltegravir is an HIV strand transfer integrase inhibitor currently approved for HIV-1–infected, treatment-experienced adults with ongoing viremia and virus resistant to multiple other antiretroviral drugs. Studies are ongoing for treatment of HIV-1–infected treatment-naive patients and other populations to determine the role of raltegravir in other contexts. Because of the new mechanism of action, demonstrated virologic activity, and tolerability of raltegravir, it is an important advance in HIV-1 therapeutics.

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