REVIEW

Raltegravir: The evidence of its therapeutic value in HIV-1 infection

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Introduction: The antiretroviral treatment paradigm for human immunodeficiency virus-1 (HIV-1) infection has undergone a significant change with the addition of a new class of therapeutic agents targeting HIV-1 integrase (IN). IN inhibitors prevent the integration of viral DNA into the human genome and terminate the viral life cycle. As the first member of this new class of anti-HIV drugs, raltegravir has shown promising results in the clinic.

Aims: To review the emerging evidence for the use of the IN inhibitor raltegravir in the treatment of HIV-1 infection.

Evidence review: Strong evidence shows that raltegravir is effective in reducing the viral load to less than 50 copies/mL and increasing CD4 cell count in treatment-experienced patients with triple-drug class-resistant HIV-1 infection. Substantial evidence also indicates that while raltegravir is able to achieve treatment response in patients with drug-resistant HIV-1, it is susceptible to development of resistance. Raltegravir should be used with at least one other active drug. In addition to its use in salvage therapy upon failure of first-line antiretroviral treatment, a raltegravir-based treatment regimen may also be effective as initial therapy. Substantial evidence also shows that raltegravir-based treatment regimen is well tolerated with minimal clinically severe adverse events and toxicities. Modeling studies suggest a cost-effectiveness of US\$21,339 per quality-adjusted life year gained with raltegravir use, though further direct evidence on quality of life and cost-effectiveness is needed.

Place in therapy: Raltegravir shows significant and sustained virologic and immunologic response in combination with other antiretrovirals in treatment-experienced HIV-1 infected patients who show evidence of viral replication or multidrug-resistant HIV-1 strains, without any significant tolerability issues.

Keywords: raltegravir, isentress, MK-0518, integrase inhibitor, HIV-1, clinical evidence

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Core evidence place in therapy summary for raltegravir as an antiretroviral drug in HIV-1 patients

Outcome measure	Evidence	Implications
Disease-oriented evidence Reduction in viral load to less than 50 copies/mL	Clear	Sustained virologic response can be achieved in treatment-experienced and multidrug-resistant HIV-1 patients. Effective alternative for salvage therapy.
Increase in CD4 cell count	Clear	Increase in CD4 immune cell count with addition of raltegravir in triple-class drug-resistant HIV-1 patients. Effective alternative for salvage therapy.

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Outcome measure	Evidence	Implications
Virologic failure	Substantial	Low genetic barrier for developing integrase mutations. Raltegravir should be used with at least one other active drug.
Reduction in incidence of AIDS-related infections	Limited	No reduction in risk of AIDS-related infections with raltegravir use.
Patient-oriented evidence		
Decrease in adverse events	Substantial	No statistically significant difference in the incidence of adverse events with raltegravir use.
Reduction in toxicity	Substantial	No statistically significant difference in the incidence of adverse events with raltegravir use.
Reduction in drug–drug and drug–food interactions	Clear	No clinically significant interactions. No dosage adjustments recommended, except for coadministration with rifampin.
Reduction in mortality	Limited	No incremental improvement in survival with raltegravir use.
Improvement in quality of life	No evidence	
Improvement in patient compliance	No evidence	
Economic evidence		
Cost-effectiveness as an antiretroviral agent in HIV-1 patients	Limited	US$21,339 per quality-adjusted life year gained with raltegravir use.

Scope, aims, and objectives

Raltegravir (MK-0518, Isentress®; Merck & Co., Whitehouse Station, NJ) was approved by the US Food and Drug Administration (FDA) in October, 2007 and granted European approval in January, 2008 as the first human immunodeficiency virus-1 (HIV-1) integrase (IN) inhibitor for the treatment of HIV-1 infection in treatment-experienced patients. It differs from other currently available antiretrovirals in that it targets a distinct step in the viral life cycle namely, integration into the human genome. Raltegravir has demonstrated clinical efficacy in treatment-experienced patients, who showed evidence of viral replication or multidrug-resistant HIV-1 strains, and has resulted in sustained suppression of virologic load. Studies in animals and healthy volunteers have shown minimal clinically significant drug interactions. This has generated great optimism of overcoming the challenges with current antiretroviral treatment.

This article reviews the evidence for the use of raltegravir for the treatment of HIV-1 infection in treatment-experienced patients, provides an assessment of the benefits and challenges with the use of raltegravir, and considers its implications for IN inhibitors next in line. Use in pediatric patients is excluded as the safety and efficacy of raltegravir in this population have not been established.

Methods

Relevant publications including peer-reviewed articles, letters and case reports were identified by searching the following electronic databases. Initial search was performed in October, 2008 and updated in February, 2009. The search strategy included the following keywords: 'Raltegravir' OR 'MK-0581' OR 'Isentress'. In addition to literature on clinical findings, relevant publications regarding the pharmacology of raltegravir were also reviewed.

- Pubmed, http://www.ncbi.nlm.nih.gov/sites/entrez. Search strategy: "MK 0518"[Substance Name] OR "MK 0518"[All Fields] OR "raltegravir"[All Fields] and limited to English-language results.

- Ovid MEDLINE(R), http://ovidsp.tx.ovid.com/spa/ovidweb.cgi. Search limited to English-language results.
- National Library of Medicine (NLM) Gateway, http://gateway.nlm.nih.gov/gw/Cmd.
- Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials, http://www.cochrane.org/.
- EBM Reviews – NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects and Health Technology Assessment, http://ovidsp.tx.ovid.com/spa/ovidweb.cgi.
- NIHR Health Technology Assessment programme, http://www.ncchta.org/.
- National Guideline Clearing House, http://www.guideline.gov/.
- Essential Evidence Plus, http://www.essentialevidenceplus.com/.
- Clinical Evidence (BMJ), http://clinicalevidence.bmj.com/.
- International Pharmaceutical Abstracts, http://ovidsp.tx.ovid.com/spa/ovidweb.cgi.

A total of 156 relevant records were retrieved from Pubmed/Medline/NLM gateway. Eleven records were retrieved from Cochrane Central Register of Controlled Trials. Six related guidelines were identified from the National Guideline Clearinghouse. No matches were found in the other database searches. Records were manually reviewed, and a total of 138 records including duplicate records, nonsystematic reviews, animal studies and *in vitro* studies were excluded (Table 1).

Scientific abstracts from relevant meetings and conferences were identified by searching the following websites:

- BIOSIS Previews, http://www.isiknowledge.com/.
- Conference on Retroviruses and Opportunistic Infections, http://www.retroconference.org/ (1997–2009).
- Interscience Conference on Antimicrobial Agents and Chemotherapy, http://www.icaac.org/.
- International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention and International AIDS Conference, http://www.iasociety.org/ (2001–2008).

This retrieved a total of 101 records. After excluding records on animal studies, *in vitro* studies, duplicate publications presented in full papers and studies that did not investigate the clinical use of raltegravir, a total of 19 records were included for discussion. In the absence of level 1 evidence specifically evaluating the therapeutic efficacy of raltegravir, outcomes from original level 2 or 3 studies were included for discussion for clinical evidence.

Disease overview

HIV is the causative pathogen of the global pandemic, acquired immunodeficiency syndrome (AIDS). There were an estimated 33 million people living with HIV worldwide in 2007, with approximately one million in the United States. The estimated number of deaths among adults and children due to AIDS globally was approximately two million in 2007.[1] In the recent years, there has been major progress in terms of developing newer antiretrovirals and expanding access to treatment. This has resulted in a better prognosis for patients with AIDS despite the high disease incidence levels.

HIV is perhaps one of the most adaptive and evasive pathogens. Upon exposure, the retrovirus binds to the human T lymphocytes. HIV fuses into the host and releases its genetic material in the form of RNA. This step is called fusion. Viral RNA is then converted into proviral DNA by reverse transcription catalyzed by the enzyme reverse transcriptase (RT). This is followed by insertion of the proviral DNA into the host genome by IN–integration step. The viral genome is transcribed using host machinery, and viral proteins are processed by viral protease enzyme. Newly assembled particles are released from the cell by budding. Ultimately, viral replication causes depletion of the human immune system, leaving the infected individual susceptible to opportunistic infections such as pulmonary infection, gastrointestinal infection, neurological conditions, and tumors and malignancies.

Treatment with antiretroviral agents can provide virologic suppression, immunologic response, and other disease-related

Table 1 Evidence base included in the review

Category	Number of records	
	Full papers	**Abstracts**
Initial search	167	101
Records excluded	138	82
Records included	29	19
Level 1 clinical evidence	0	0
Level 2 clinical evidence	14	6
Level ≥ 3 clinical evidence	15	11
Trials other than RCT	13	11
Case studies	2	0
Economic evidence	0	2

Abbreviation: RCT, randomized, controlled trials.

benefits. Recent guidelines recommend antiretroviral therapy for individuals with symptomatic HIV disease. For asymptomatic individuals, treatment with antiretroviral agents should be initiated before the CD4 cell count decreases to less than 350 per μL. For asymptomatic individuals with CD4 cell count more than 350 per μL, individualized therapy depending on comorbities and risk of disease progression is recommended.[2] There is no clear evidence to support treatment initiation in primary HIV-1 infection.

Current therapy options

The current standard of treatment, the highly active antiretroviral treatment (HAART), consists of a cocktail of antiretroviral drugs, which includes nucleoside RT inhibitors, nonnucleoside RT inhibitors, protease inhibitors, and/or a fusion inhibitor. These antiretroviral agents target various stages in the viral life cycle. The goal of antiretroviral therapy is to reduce and maintain an HIV-1 RNA level of less than 50 copies/mL, regardless of previous treatment experience.[2] A randomized multicenter, open-label trial study by the AIDS clinical trials group compared three treatment regimens: efavirenz, a nonnucleoside RT inhibitor, plus two nucleoside RT inhibitors; ritonavir boosted lopinavir plus two nucleoside RT inhibitors; and efavirenz plus lopinavir/ ritonavir without nucleoside RT inhibitors.[3] Nonnucleoside RT inhibitor-based treatment regimens showed durable virologic suppression to less than 50 copies/mL with longer time to treatment failure at 96 weeks. On the other hand, increase in basleine CD4 cell count was greater in patients taking lopinavir/ritonavir plus two nucleoside RT inhibitors. Other protease inhibitor-based regimens have also demonstrated similar outcomes to lopinavir/ritonavir treatment. The current recommendations for initial therapy are two nucleoside RT inhibitors plus efavirenz or a protease inhibitor boosted with ritonavir. Efavirenz is not recommended for women in early pregnancy. Nevirapine is another alternative for a nonnucleoside RT inhibitor-based regimen. Recommended ritonavir boosted protease inhibitors include lopinavir, atazanavir, fosamprenavir, darunavir or saquinavir. Tenofovir/emtricitabine or abacavir/lamivudine are the recommended nucleoside RT inhibitor combinations for initial therapy. The choice of the treatment regimen is influenced by various factors such as pill burden, toxicity, and adverse effects, drug interactions, comorbid illness, and presence of primary drug resistance.

Three new antiretrovirals have been recently approved. These newer drugs are active against drug-resistant HIV-1 viral strains and approved for use as salvage therapy in treatment-experienced patients with treatment failure

and/or multidrug resistance. Raltegravir is an IN inhibitor. Maraviroc (Selzentry™; Pfizer, New York, NY) is a CCR5 co-receptor antagonist. It is indicated for use only in patients with CCR5-tropic virus. It does not show efficacy in mixed or dual tropism viruses and requires a tropism assay before prescribing maraviroc treatment. Maraviroc is metabolized by cytochrome P450 enzymes and, therefore, its dosing depends on the effect of coadministered drugs on these enzymes.[4] Etravirine (Intelence™; Tibotec, Bridgewater, NJ) is a nonnucleoside RT inhibitor. It is recommended for use in patients who are resistant to currently-used nonnucleoside RT inhibitors. Etravirine is also metabolized by the cytochrome P450 enzymes and suffers from potential drug interactions, especially with certain protease inhibitors.[5,6] Raltegravir is recommended for use in combination therapy upon failure of first-line treatment regimen with nonnucleoside RT inhibitor or protease inhibitor or in the case of multidrug resistance. Initial therapy with raltegravir should be considered only under rare circumstances. With the use of raltegravir and the other newer antiretrovirals maraviroc and etravirine, viral load suppression to less than 50 copies/mL can be achieved even in patients with virologic failure and multidrug resistance. Raltegravir offers the additional advantages of improved tolerability and safety profiles.

Unmet needs

Despite the availability of effective antiretroviral agents, therapeutic needs for effective disease management are still unmet. The limitations of existing antiretrovirals include severe drug toxicities and interactions, adverse events, the emergence of multidrug resistance strains and eventual treatment failure.[7] Long-term treatment with antiretrovirals can result in toxicitites such as nephrotoxicity, hepatotoxicity and cardiovascular effects. In addition to drug toxicities, antiretroviral therapy can have a wide range of adverse effects. Mild adverse events include nausea, diarrhea, fatigue, and headache, while more serious adverse effects include peripheral neuropathy, hepatotoxicity, lipodystrophy, hypersensitivity, and skin rashes.[8]

Treatment of HIV infection involves a combination of various antiretroviral agents. In addition, concomitant medications for opportunistic infections and other comorbid conditions are also often included in this cocktail. Several of the existing antiretrovirals inhibit or induce various drug-metabolizing enzymes. This can affect the pharmacokinetics and plasma concentrations of concomitantly administered drugs in an advantageous or undesirable way.[9] Choice of treatment should therefore consider all possibilities

of drug interactions in order to minimize suboptimal therapy and toxic effects.

Another area of growing concern is the emergence of multidrug-resistant viral strains. Due to the inherent genetic adaptability of the retrovirus, drug-resistant viral strains rapidly emerge, leading to treatment failure. In addition to treatment-experienced patients who are drug-resistant and unresponsive, there is also an increase among treatment-naïve patients who are infected with multidrug-resistant viral strains.[10] Antiretroviral therapy therefore must include at least two fully active drugs against the multidrug-resistant viral strains.

Treatment adherence is also another critical factor that determines the success of antiretroviral therapy. Drug-related factors that influence patient compliance include tolerability of medication, dosing frequency, dietary restrictions, pill burden, and cost.[11] Improving regimen convenience will contribute to greater adherence to therapy and lesser likelihood of drug resistance.[12,13] It is hoped that these unmet needs would be addressed by newer classes of antiretrovirals such as the IN inhibitors.

Pharmacology of raltegravir

Raltegravir inhibits the strand transfer function of HIV-1 IN with potency in the low nanomolar range. An apparent half-maximal inhibitory concentration (IC_{50}) of 2–7 nM for strand transfer inhibition was determined by *in vitro* experiments using purified IN enzyme. The compound blocks the stable insertion of the viral DNA into the human genome and hence sustained viral replication and infectivity. Consequently, raltegravir also exhibits potent antiviral activity in cell-based assays. In a multicycle replication assay, it blocked HIV-1 replication with an IC_{95} value of 19 ± 14 nM and 33 ± 23 nM when tested in the presence of 10% fetal bovine serum and 50% normal human serum, respectively.[14,15] Raltegravir is effective against a panel of 15 primary HIV-1 isolates of 6 subtypes. It also exhibits potent *in vitro* activity against multidrug-resistant HIV-1 clinical isolates, HIV-2 and simian immunodeficiency virus.[14,16] Quantitative polymerase chain reaction (PCR) studies revealed that HIV infected cells treated with raltegravir showed an increase in two-long terminal repeat circular DNA, while HIV cDNA synthesis was unaffected. Formation of circular DNA is a result of accumulation of viral cDNA and is indicative of a defective HIV integration into host genome. Studies regarding the effect of higher doses of raltegravir on the rate of decay of latent viral reservoirs are ongoing.

Raltegravir shows greater than 1,000-fold selectivity for HIV-1 IN over several related Mg^{2+}-dependent enzymes such as hepatitis C virus (HCV) polymerase, HIV RT, HIV RNase-H, and human α-, β- and γ-polymerases (IC_{50} values > 50 μM). It is also inactive at concentrations of less than 10 μM against various enzymes, channels and receptors.[15] Raltegravir does not inhibit any of the major cytochrome P450 enzymes such as CYP1A2, CYP2C9, CYP2D6 or CYP3A4 with IC_{50} values > 50 μM. Binding affinity to hERG channels was greater than 50 μM. This suggests minimal off-target effects.

Pharmacokinetics and metabolism

The pharmacokinetic profile and metabolism of raltegravir were studied in three preclinical species: Sprague–Dawley rats, dogs, and rhesus monkeys. Raltegravir was dosed orally as different salt forms using 1% methyl cellulose as vehicle. Better bioavailability with a linear dose-proportional area under the curve (AUC) was obtained with the potassium salt of raltegravir. It exhibited moderate to high binding to plasma proteins. Raltegravir is stable in liver microsomes. It is primarily metabolized via the glucuronidation pathway by the enzyme, uridine diphosphate (UDP)-glucuronosyl transferase isoenzyme 1A1 (UGT1A1). *In vivo* metabolism studies using radiolabeled raltegravir also confirmed glucuronidation as the major route of metabolism.

The safety, tolerability and pharmacokinetics of raltegravir in humans were evaluated in three phase I studies. Single-dose escalation studies over a dose range of 10–1200 mg of raltegravir demonstrated approximately dose-proportional increases in AUC and plasma concentrations.[17] Raltegravir was rapidly absorbed, and time to peak plasma concentrations were between 0.5 to 1.3 h. A biphasic decline in plasma concentrations was observed with an apparent half-life of initial phase of 1 h and a terminal phase half-life of 7–12 h. Raltegravir dose of 200 mg or higher achieved $C_{12 h}$ concentrations greater than the protein-adjusted IC_{95} value of 33 nM. Key pharmacokinetic parameters of raltegravir at 200 and 400 mg doses are summarized in Table 2. The fraction unbound to plasma proteins as determined by *in vitro* studies is 17%.[15] Multiple dosing studies showed little to modest accumulation of raltegravir. The accumulation ratios for maximum concentration (C_{max}) and $AUC_{0-12 h}$ ranged between 0.7 and 1.2, while that for $C_{12 h}$ ranged between 1.2 and 1.6. Overall exposure profile was similar between male and female subjects, though comparatively lower $C_{12 h}$ values and longer apparent terminal elimination half-lives were observed in female subjects.

Substantial amounts of radioactivity were recovered from urine (32%) and feces (51%) after a single oral dose

Table 2 Clinical pharmacokinetic profile of raltegravir in healthy volunteers following fasted administration of oral dose

Parameter	Dose (mg)		Multiple-dose escalation study (q12 h)
	Single-dose escalation study		
	400	800	400
$C_{12 h}$ (nM)	81.3	206.9	200.6
$AUC_{0-12 h}$ (μM.h)	24.61	63.11	28.68
C_{max} (μM)	10.63	24.67	11.18
T_{max} (h)	1.0	1.3	1.0
$T_{1/2}-\alpha$ (h)	1.07	1.01	1.07
$T_{1/2}-\beta$ (h)	6.9	12.4	10.7
Fraction eliminated unchanged in urine	9.95	9.77	11.4
Renal clearance (mL/min)	60.88	48.52	60.5

Abbreviations: AUC, area under the curve; C_{max}, maximum concentration.

of 200 mg of [^{14}C]-raltegravir in healthy male volunteers[18] Raltegravir was eliminated rapidly, and the majority of the administered dose was recovered within 24 h. Metabolite profiling identified raltegravir as the unchanged drug (9%) and its glucuronide form (23%) as the major components in the urinary fraction. Raltegravir is eliminated via the fecal route as the parent unchanged compound, likely derived from the hydrolysis of its glucuronide form secreted into bile. Raltegravir was also identified as the major circulating form in the plasma (70%). Raltegravir was stable in liver microsomes and was not metabolized. Using cDNA expressed UGTs and specific enzyme inhibitors, UGT1A1 isoform was identified as the major metabolizing enzyme of raltegravir.

Clinical evidence with raltegravir

Clinical efficacy of raltegravir has been demonstrated in treatment-naïve as well as treatment-experienced patient populations. Evidence regarding disease-oriented outcomes such as virologic response, immunologic response, emergence of resistance, treatment failure and incidence of AIDS-related events, as well as patient-oriented outcomes such as drug toxicity, adverse events, and drug interactions are presented here.

Virologic response in HIV-1-infected treatment-naïve patients

The short-term antiretroviral activity and safety of raltegravir has been explored in a multicentered, double-blinded, randomized, placebo-controlled study.[19] Four different doses of raltegravir (100, 200, 400, and 600 mg) given twice daily for 10 days as monotherapy were compared with placebo.

After 10 days of treatment, raltegravir showed significant virologic response with a decrease in baseline HIV-1 RNA level of 2 $\log_{10}$ copies/mL at all four doses, compared to a decrease of 0.2 $\log_{10}$ copies/mL with placebo treatment. At least 50% of the patients treated with raltegravir as a single agent achieved HIV-1 RNA levels less than 400 copies/mL. No serious adverse events were observed. Though monotherapy with raltegravir proved effective in reducing viral loads, there was a higher risk for development of resistance. Therefore, the efficacy of raltegravir was compared against that of efavirenz as part of combination therapy with tenofovir and lamivudine in treatment-naïve patients.[20] Raltegravir, at all four doses, along with the combination therapy resulted in sustained reduction in HIV-1 RNA levels. By week 4 and week 8, HIV-1 RNA levels were rapidly reduced to less than 50 copies/mL in a significant proportion of patients treated with raltegravir compared to those taking efavirenz. These reductions in viral load were maintained through 48 weeks (Figure 1). However, virologic failure occurred in 3% of patients with the emergence of resistance mutations. The adverse events observed during the study were similar in patients receiving either treatment. This study demonstrated rapid and sustained suppression of plasma viremia. The overall antiviral efficacy of raltegravir at 24 and 48 weeks was similar to that of efavirenz, although raltegravir achieved more rapid reduction in viral load.

Recent data on the efficacy of raltegravir after 96 weeks of combination therapy in treatment-naïve patients shows sustained antiviral effects similar to the 48-week data. No new resistance mutations emerged after 48 weeks of treatment. Though 100 and 200 mg raltegravir twice daily were successful in achieving viral suppression through
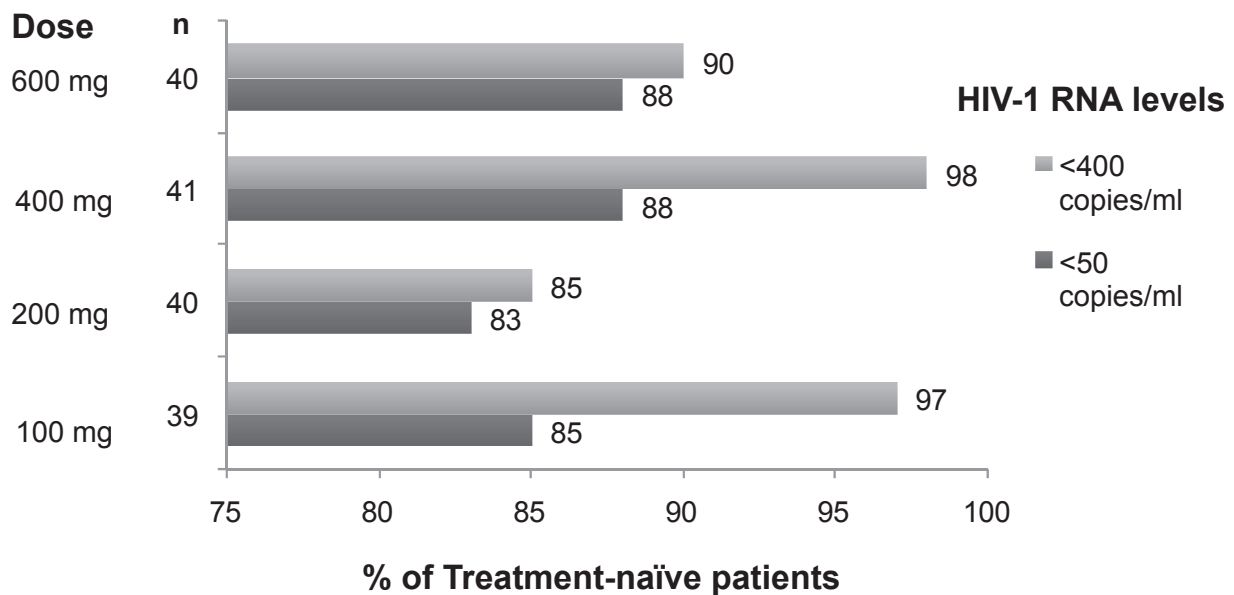
Figure 1 Efficacy of raltegravir as part of combination therapy in treatment-naïve patients at week 48 of treatment.

48 weeks, 400 mg dose was administered to all patients after 48 weeks. In general, raltegravir appeared well tolerated with no serious side effects at 96 weeks of combination therapy.[21]

In a large, randomized phase III study STARTMRK, the safety and efficacy of raltegravir-based regimens were compared against efavirenz-based treatment regimens in treatment-naïve patients.[22,23] The optimized background therapy (OBT) in both treatment groups included tenofovir and emtricitabine. At week 48, raltegravir-based treatment demonstrated noninferior antiretroviral activity, with 86% of patients taking raltegravir achieving a viral load of less than 50 copies/mL compared to 82% of patients on efavirenz. Raltegravir treatment also increased CD4 cell count more than efavirenz treatment with significantly fewer adverse effects. Further subgroup analysis demonstrated consistent virologic and immunologic response with raltegravir treatment across various demographic and baseline prognostic factors such as baseline HIV-1 RNA level and baseline CD4 cell count.

Virologic response in treatment-experienced HIV-1-infected patients

Efficacy of raltegravir in combination with OBT in treatment-experienced patients was evaluated in a multicenter, dose-ranging, randomized, placebo-controlled phase II study.[24] Treatment-experienced patients included in the study had advanced HIV-1 infection with treatment failure, with triple-class drug-resistant virus, and with a limited number of effective treatment options. Raltegravir in combination

with OBT, at doses of 200, 400, or 600 mg twice daily, was compared with placebo. As observed in treatment-naïve patients, raltegravir treatment resulted in a decrease of 2 $\log_{10}$ copies/mL in HIV-1 RNA levels from baseline viral load within two weeks of initiation of treatment. By week 24, a reduction in HIV-1 RNA levels to less than 50 copies/mL was achieved in 70%, 64.5%, and 62.5% of patients in the treatment groups with 200, 400, and 600 mg of raltegravir, respectively.

Identical, randomized phase-III international trials – BENCHMRK-I and BENCHMRK-II – conducted in different geographic regions also demonstrated efficacy of raltegravir compared against placebo in combination with OBT. The goal of these studies was to evaluate the safety and efficacy of raltegravir at a dose of 400 mg in a larger population of HIV-1 infected patients, with triple-class resistance mutations in whom previous antiretroviral therapy had failed.[25] In the BENCHMRK-I trial, considering lack of efficacy as treatment failure, HIV-1 RNA levels below 50 copies/mL were achieved in 79.5% of patients who received raltegravir compared with 42.5% of placebo recipients. Similar results were obtained in the BENCHMRK-II trial; HIV-1 RNA levels below 50 copies/mL were achieved in 79.7% of raltegravir recipients compared with 43.6% of placebo recipients. In the combined analysis of the two trials, HIV-1 RNA levels at week 48 were reduced below 50 copies/mL in 62.1% of raltegravir recipients compared with 32.9% of placebo recipients, considering noncompletion as treatment failure (Figure 2).
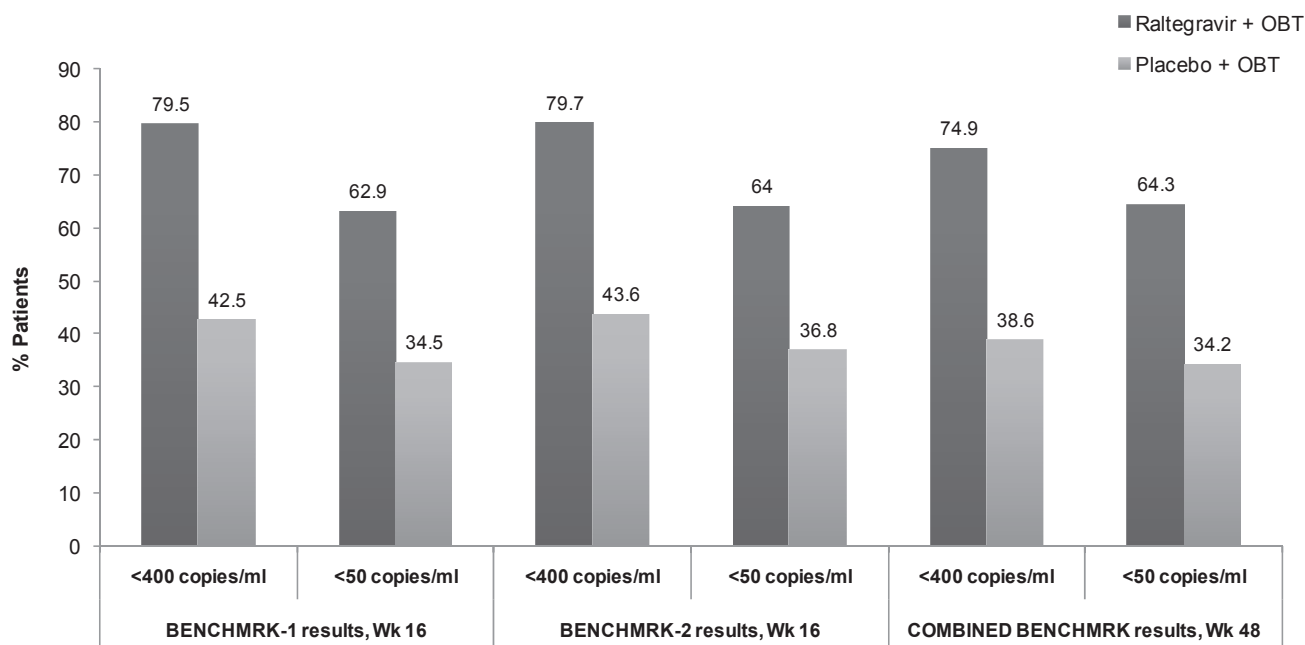
Figure 2 Efficacy of raltegravir in treatment-experienced patients with triple-class drug resistance.
Notes: p < 0.001 between the treatment groups for all the studies.
Abbreviation: OBT, optimized background therapy.

These studies have provided sufficient evidence that raltegravir in combination with OBT provides better viral suppression than OBT alone in triple-class drug-resistant HIV-1-infected patients. Recent 96-week results from the BENCHMRK 1&2 phase III trials further demonstrate sustained and superior antiretroviral and immunological response with raltegravir plus OBT compared to OBT alone in triple-class drug-resistant HIV-1 patients. 58% of raltegravir recipients compared with 26% of placebo recipients had HIV-1 RNA less than 50 copies/mL.[26]

The effect of raltegravir on the dynamics of viral production is rather surprising. Monotherapy with raltegravir decreases the first-phase viral production arising from infected CD4 T cells. In combination with other antiretroviral agents, it resulted in rapid and extended first-phase decay and reduced the viral load at which the second-phase of viral production commenced.[27] The second-phase of viral production is thought to be influenced by long-lived infected cells and dissociating viruses from dendritic cells. Since raltegravir targets the integration step, it is not expected to act on the second-phase of viral production. The rapid decay dynamics observed with raltegravir treatment in all the clinical studies are thought to be a consequence of the stage in the viral life cycle it inhibits and not necessarily due to its greater efficacy.[28] Using mathematical models to analyze viral decay dynamics, it has been proposed that more rapid decay in viremia is achieved by inhibitors that act late in the viral life cycle.

Virologic response in multidrug resistant HIV-1 infected patients

Patients infected with multidrug-resistant viral strains are currently treated with an enfuvirtide-based treatment regimen. Owing to its ease of administration and improved long-term tolerability over the injectable enfuvirtide, raltegravir is being considered as an alternative in salvage therapy. A cohort of patients who were treated with enfuvirtide for a median of 25 months and who had plasma HIV-1 RNA levels less than 50 copies/mL switched to raltegravir.[29] Concomitant antiretrovirals which included nucleoside RT inhibitors and protease inhibitors in all patients, and nonnucleoside RT inhibitors in few patients, were left unchanged. After a median follow-up time of seven months, all but one patient had HIV-1 RNA levels less than 50 copies/mL. Only mild and no severe adverse events were observed. In another randomized, noninferiority trial, patients with triple-class resistant HIV-1 infection were randomized between enfuvirtide-based regimen and enfuvirtide-based regimen followed by switch to raltegravir-based regimen. At week 24, 89% of patients in both treatment groups had plasma RNA levels less 50 copies/mL, suggesting a noninferior antiviral activity of raltegravir compared to enfuvirtide.[30]

Changing from enfuvirtide to raltegravir in a salvage therapy regimen was well tolerated, and effective virologic suppression was sustained. In addition, raltegravir offers the advantages of improved patient compliance to treatment regimen and economic viability. Randomized, multicenter, controlled noninferiority trials SWITCHMRK 1&2 evaluated the outcome of switching to raltegravir-based regimen in HIV-1 patients who had undetectable viral loads on a lopinavir/ritonavir-based treatment regimen. Raltegravir treatment was well tolerated and resulted in improved lipid parameters. However, switching from stable lopinavir/ritonavir-based treatment regimen to raltegravir-based regimen did not demonstrate noninferior outcome at week 24.[31] This study included patients who had failed prior therapies who may have accumulated high level resistance to the other antiretrovirals used in the treatment regimen. In such conditions, switching from an active boosted protease inhibitor with a high genetic barrier to a drug with low genetic barrier did not yield a superior therapeutic outcome.

Efficacy of raltegravir in HIV-2-infected patients

Raltegravir inhibited replication of HIV-2 isolates in CEMx174 cells with an IC_{95} value of 6.3 nM in the presence of 10% fetal bovine serum.[16] Sequence analysis revealed naturally occurring polymorphisms in 38% of HIV-2 IN residues. Interestingly, polymorphisms in HIV-2, at residues implicated in HIV-1 resistance to raltegravir, did not affect its phenotypic susceptibility to IN inhibitors. Also, the key primary mutations that confer high level resistance to raltegravir were absent in HIV-2, though secondary mutations were found.[32]

A short-term virologic efficacy study in a HIV-2 infected patient demonstrated response with raltegravir treatment. Two months of treatment with raltegravir in combination with abacavir, azidovudine and darunavir/ritonavir in the heavily pretreated drug-resistant HIV-2 patient resulted in over 500-fold reduction in viral load. However, resistance mutations (N155H) emerged rapidly.[33] HIV-2 differs substantially from HIV-1 in its structure and sequence. It is less susceptible to antiretroviral agents and hence, patients infected with HIV-2 have limited therapeutic options. In the light of these findings, raltegravir and the class of IN inhibitors represent a novel therapeutic option for adjuvant therapy in HIV-2 infected patients.

Immunologic response

In the BENCHMRK trials, results at week 48 also demonstrated significant increase in baseline CD4 cell count with raltegravir-based treatment regimen (109 cells/mm³) in comparison to the control group (45 cells/mm³).[25] Even at 96 weeks of treatment, the results were consistent with a sustained and superior immunologic response with mean increase in baseline CD4 cell count being 123 cells/mm³ in raltegravir recipients versus 49 cells/mm³ in control group.[26]

In addition to the increase in CD4 immune cell count, occurrence of immune reconstitution syndrome has also been reported. During initial treatment with raltegravir, rapid reduction of viral load and increase in CD4 cell count could result in immune reconstitution syndrome in some patients. This is an inflammatory response to residual opportunistic infections, and monitoring and treatment may be necessary. Frequency of rash of mild to moderate intensity was slightly higher in raltegravir treatment group. Other less common immune-related adverse reaction was hypersensitivity in less than 2% of raltegravir recepients.

Resistance and treatment failure

The low genetic barrier of HIV-1 IN compromises the susceptibility of viruses to raltegravir. Rapid development of resistance has been observed in both *in vitro* and clinical studies. Resistance to raltegravir arises due to a combination of few primary mutations and several additional secondary mutations. Several IN residues implicated in the development of drug resistance have been identified through resistance passage studies, and the resistance profile of raltegravir has been studied using HIV-1 containing these IN mutations.[15] Mutations at residues N155 and Q148 lead to greater than 10-fold shift in raltegravir sensitivity in single-infectivity assays. Several other single mutations contribute to raltegravir resistance, but to a lesser extent. Combination of a key mutation with other secondary mutations results in high level resistance. Double mutants such as Q148H/R/G140S resulted in greater than 400-fold decrease in susceptibility to raltegravir. Similarly, N155H/E92Q results in a 13- to 64-fold drug resistance. A novel mutation, L68V is found to be specifically associated with E92Q mutation in clinical isolates. L68V/Q148R mutant was 53-fold resistant to raltegravir.[34] A summary of the raltegravir resistance profile due to various key and minor mutations is shown in Figure 3.

Subgroup analysis of the data from BENCHMRK studies found that at 48 weeks of treatment with raltegravir in combination with OBT, 23% of the drug recipients suffered virologic failure.[35] IN genotyping done at baseline and after treatment failure revealed the presence of mutations in the IN gene. Mutations at one of the three residues – N155, Q148, or
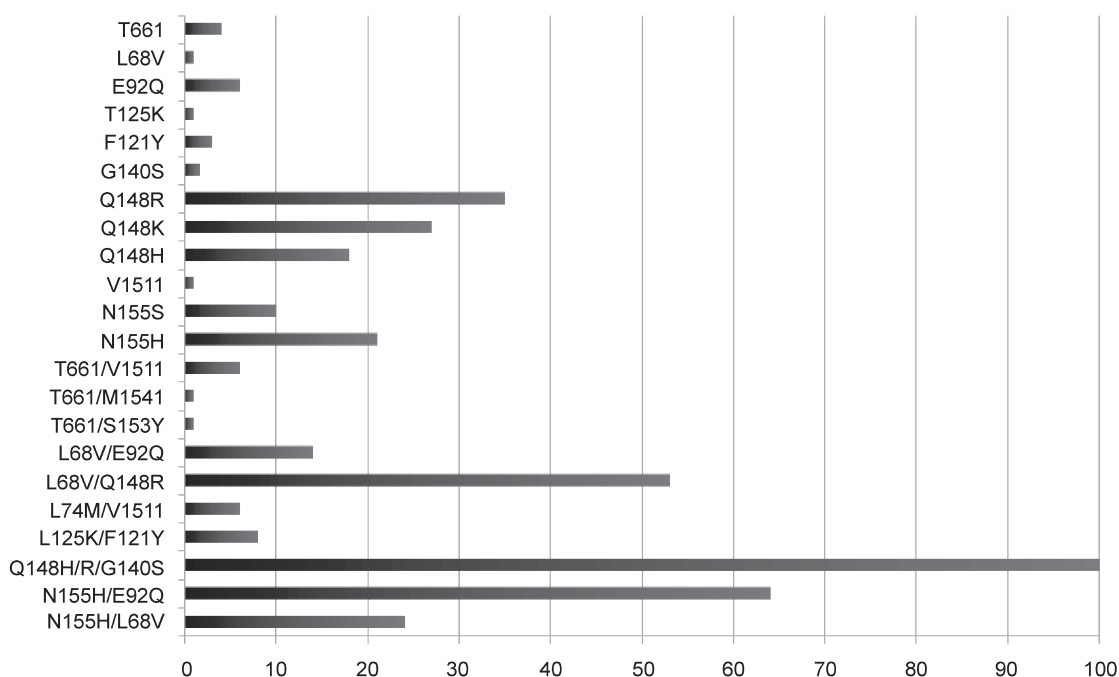
Figure 3 Relative fold change in susceptibility to raltegravir.

Y143 – resulted in high level resistance. Additional secondary mutations at residues T66, L74, and E92 have also been found. Similar results were obtained in another cohort of multidrug-resistant HIV-1-infected patients, who suffered from virologic failure, after treatment with raltegravir.[36] HIV-1 IN sequence analysis of these resistant strains revealed the appearance of an identical pattern of nonpolymorphic mutations. N155H mutant was 14-fold less sensitive to raltegravir, while the sensitivity of E92Q and G140S/Q148H mutants was reduced by 7- to 8-fold. An important observation from these studies is that the risk of mutations and treatment failure with raltegravir seems to be increased in patients with a higher baseline HIV-1 RNA levels and lower CD4 cell counts. An earlier study had reported similar findings wherein sustained viral suppression was achieved in rhesus monkeys infected with simian-HIV, when treatment with IN inhibitor was initiated before CD4 cell depletion.[37] Cellular immunity and initial viral load were thought to facilitate the therapeutic efficacy of the IN inhibitor. Such an association between raltegravir response rate, the baseline viral load and the CD4 count warrants further analysis.

Naturally occurring sequence variations in IN such as L74I, A91V, E92G are thought to be associated with the risk of drug resistance. While some of the secondary mutations associated with raltegravir resistance are found in inhibitor-naïve populations, the major mutations (N155H, Q148K/H/R and E92Q) leading to high level resistance are infrequent.[38,39]

No association between clade and frequency of occurrence of polymorphisms has been found. There was also only a minimal effect of clade-specific polymorphisms on raltegravir susceptibility.[40]

A better characterization of resistance development upon long-term clinical use of raltegravir is important. Time to viral suppression versus time to virologic failure due to emergence of resistance upon long-term treatment needs to be analyzed. In addition, many of the resistance mutations impair the catalytic activities of IN and affect the viral replication. Therefore, long-term efficacy data of raltegravir used in combination with other active antiretrovirals is required to evaluate the effect of such mutations on overall viral infectivity and to understand their impact on raltegravir efficacy. The efficacy of other IN inhibitors, which share a similar mechanism of action as raltegravir, would be affected because of cross-resistance.[41] However, the choice of the resistance pathway depends on the viral strain and the inhibitor. A recent study has suggested the use of a combination of IN strand transfer inhibitors to overcome the development of cross-resistance.[42] Raltegravir acts by a distinct mechanism, different from that of other antiretrovirals, and it is likely to show no cross-resistance with other antiretrovirals in the treatment regimen. This would mean that HIV-1 viral strains resistant to raltegravir should still be susceptible to other classes of antiretrovirals and hopefully, to mechanistically different IN inhibitors.

Drug interactions with antiretrovirals

The current treatment paradigm involves coadministration of raltegravir along with other anti-HIV agents. The effects of coadministered drugs on raltegravir pharmacokinetics are summarized in Table 3. Raltegravir is primarily metabolized by UGT1A1. Atazanavir, a protease inhibitor, inhibits UGT1A1. Hence, coadministration with atazanavir can be expected to affect the drug levels of raltegravir. Pharmacokinetic data obtained from healthy volunteers indicate a moderate increase in plasma levels of raltegravir administered with atazanavir alone or in combination with ritonavir.[43] Though coadministration with atazanavir resulted in increased plasma concentrations of raltegravir, no serious adverse effects or toxicities were reported in the study. Instead, this interaction could be favorable as it results in increased raltegravir trough concentrations. Another clinical study explored two-way pharmacokinetic interaction between atazanavir 300 mg, twice daily given along with raltegravir 400 mg, twice daily. Coadministration with raltegravir decreased the plasma drug levels of atazanavir. Raltegravir drug levels were also increased. Incidence of adverse events was similar in both treatment groups. Similar results were obtained for tenofovir disoproxil fumarate, another protease inhibitor that is also known to inhibit UGT1A1.[44]

Coadministration of other antiretrovirals such as ritonavir, lopinavir, tenofovir, etravirine, and efavirenz showed weak to moderate influence on the plasma concentrations and pharmacokinetic profile of raltegravir. None of these interactions were considered clinically significant. There has been a recent report of a potential interaction between raltegravir and tipranavir. Patients who switched from enfuvirtide to raltegravir, while also taking tipranavir/ritonavir, developed hepatic cytolysis two weeks after initiating raltegravir treatment.[45] By replacing tipranavir/ritonavir with darunavir/ritonavir, their elevated liver function was restored to normal levels. The increase in tipranavir trough concentrations after raltegravir dosing has been attributed to a potential drug interaction.

Drug interactions with concomitant medications

Raltegravir does not induce or inhibit any of the cytochrome P450 enzymes. It had only a weak inhibitory effect on the seven different cytochrome enzymes, even at concentrations greater than 100 μM. It also did not induce cytochrome P450 3A4 at concentrations up to 10 μM. Coadministration of raltegravir with midazolam, a sensitive cytochrome P450 3A4 substrate, did not significantly affect the plasma pharmacokinetics of midazolam.[46] On the other hand, strong inducers of UGT1A1 such as rifampin can be expected to reduce the plasma levels of raltegravir. Coadministration with rifampin decreased drug levels and peak concentrations significantly.[47] A dose adjustment is recommended. Coadministration of raltegravir with oral contraceptives such as Ortho Tri-Cyclen (ethinyl estradiol/ norgestimate) did not have any clinically significant pharmacokinetic interactions.[48] Pharmacokinetics of raltegravir were found to be affected by omeprazole coadministration in healthy subjects in a phase I study.[49] The plasma concentrations of raltegravir were increased with a 3–4-fold increase in AUC and C_{max}. A possible mechanism for this observation involves an increase in gastric pH by omeprazole, causing increased solubility and absorption of raltegravir. This interaction however did not seem to have a clinically significant effect in HIV-1-infected patients. Therefore, no dose adjustments have been recommended for coadministration of raltegravir with omeprazole.

Serum lipids/dyslipidemia

The most common laboratory abnormalities in the raltegravir treatment group in treatment-experienced patients were increased serum cholesterol and triglyceride levels. These drug-related increases in serum cholesterol and triglyceride levels were not associated with any lipid abnormalities.[50] In comparison to efavirenz, raltegravir was found to be more lipid neutral.

Creatine kinase

Raltegravir also caused transient increases in serum creatine kinase, which were not considered significantly large. Patients at risk of muscle problems and renal failure have been recommended against using raltegravir. A case of severe rhabdomyolysis and acute worsening of renal insufficiency was reported in a 46-year-old patient initiated on raltegravir.[51] Further studies on raltegravir-associated rhabdomyolysis are warranted.

Cardiovascular effects

A double-blind, randomized, single-dose crossover study was conducted to assess the potential for a supratherapeutic dose of raltegravir to prolong the ventricular repolarization or QT/QTc interval. Administration of the supratherapeutic dose of 1600 mg of raltegravir was well tolerated and had no cardiac effects, such as prolongation of QT interval.[52]

Adverse events and tolerability

The safety and tolerability of raltegravir was assessed in the BENCHMRK trials. Overall, treatment with raltegravir

Table 3 Interactions with concomitant medications

Drug	Mechanism of interaction	Raltegravir/coadministered drug dose	Effect on raltegravir pharmacokinetics	Recommendations	Reference
Atazanavir	UGT1A1 inhibitor	100 mg/400 mg	$C_{12\,hr}$ ↑ by 1.95 fold C_{max} ↑ by 1.53 fold $AUC_{0-12\,hr}$ ↑ by 49%	No dose adjustment required	(Iwamoto et al)[43]
Ritonavir	Induces glucuronosyltransferases	400 mg/100 mg	$AUC_{12\,hr}$ ↓ by 16% C_{max} ↓ by 24%	No dose adjustment required	(Iwamoto et al)[64]
Lopinavir/Ritonavir	P-gp induction?	–	$C_{12\,hr}$ ↓	No dose adjustment required	(Rhame et al)[65]
Tipranavir/Ritonavir	Induces UGT1A1, Induces/inhibits P-gp	–	$C_{12\,hr}$ ↓ by 55% $AUC_{12\,hr}$ ↓ by 24%	Dose adjustment may be required	(Wenning et al)[66]
Efavirenz	Induces metabolizing enzymes	40 mg/600 mg	$C_{12\,hr}$ ↓ by 21 % C_{max} ↓ by 36% $AUC_{0-1\,hr}$ ↓ by 36%	No dose adjustment required	(Iwamoto et al)[64]
Etravirine	Effect on glucuronidation unknown	400 mg/200 mg	$C_{12\,hr}$ ↓ by 34% C_{max} ↓ by 10 % $AUC_{0-12\,hr}$ ↓ by 10%	No dose adjustment required	(Anderson et al)[67]
Tenofovir	UGT1A1 inhibitor	400 mg/300 mg	$AUC_{0-12\,hr}$ ↑ by 49% C_{max} ↑ by 64%	No dose adjustment required	(Wenning et al)[44]
Rifampin	Induces UGT1A1	–	$C_{12\,hr}$ ↓ by 61% AUC ↓ by 40% C_{max} ↓ by 38%	Dose adjustment may be required	(Hazuda et al)[47]

Abbreviations: AUC, area under the curve; C_{max}, maximum concentration.

was well tolerated. The adverse events and their frequencies were comparable with the placebo-treated groups. The most common drug-related adverse events were diarrhea, nausea, headaches, and fatigue.[25,53]

Depression

A case report of exacerbation of pre-existing depression related with the initiation of raltegravir therapy in treatment-experienced patients has been described.[54] In addition to raltegravir and other antiretrovirals, these patients were also receiving treatment with antidepressants. Further studies are required to understand if this is a drug interaction with antidepressants, or a raltegravir-related effect.

Incidence of malignancies and mortalities

An increase in the number of malignancies was observed in patients receiving raltegravir as compared to placebo recipients in the clinical trials. A relative risk of 4.26 for occurrence of cancer with raltegravir treatment versus comparator treatment has been reported. It is unclear whether this increased occurrence of cancer is drug-related or due to anticipated complications in such a patient population. Nine fatalities were reported in the BENCHMRK studies. These deaths were related to severe opportunistic infection and/or malignancy and were not drug-related. A comprehensive analysis of cancer rates in the five different randomized trials and an expanded access program has been reported.[55] With up to 48 weeks follow-up in clinical trials, cancer rates were found to be slightly lower for raltegravir. In open and expanded access settings with 24 weeks follow-up time, similar results for cancer rates were found. Overall, there seems to be no difference in risk for occurrence of cancer in HIV-1 patients receiving raltegravir or other antiretroviral agents.

Economic evidence

The wholesale acquisition cost of raltegravir (400 mg, twice daily, oral) is approximately US$27 per day or US$1,012.50 for a 30-day supply. This is similar to or less than the acquisition costs of other recently approved antiretrovirals. Darunavir boosted with ritonavir (600 mg/100 mg, twice daily, oral) costs US$31 per day. Enfuvirtide (90 mg, twice daily, subcutaneous injection) costs US$81 per day.[56]

The cost-effectiveness of raltegravir in treatment-experienced HIV-1 patients in Switzerland has been analyzed using a cohort-state transition model.[57] The model classified patients according to their HIV-1 RNA level, CD4 cell count and presence of opportunistic infections combined with inputs from clinical trials and published reports. The model estimated an increase in discounted life expectancy by 3.5 years with raltegravir plus OBT treatment versus OBT alone. The incremental cost-effectiveness ratio for raltegravir plus OBT compared with OBT alone was US$2,1339 and US$45,077 per quality-adjusted life year gained for one- and five-year duration of raltegravir use, respectively. According to this study, addition of raltegravir to OBT results in substantial survival benefits and also proves to be a cost-effective option. In another cost–utility study conducted by Merck, the cost-effectiveness of raltegravir plus OBT was compared against OBT alone in patients with triple-class failure HIV-1 infection. Raltegravir plus OBT was associated with an incremental cost-effectiveness ratio of US$32,227 per quality-adjusted life year. In a secondary analysis, substituting raltegravir for tenofovir was associated with an incremental cost-effectiveness ratio of US$5,800 per quality-adjusted life year.[56]

There is only limited economic evidence regarding the cost-effectiveness of raltegravir compared to its comparators. The relative costs of raltegravir and etravirine in treating treatment-experienced HIV-1 patients have been compared in a cost-minimization analysis.[58] Since no head-to-head comparison between raltegravir and etravirine exists, an indirect comparison at week 24 was made from the clinical outcomes of the DUET 1&2 trials for etravirine and BENCHMRK 1&2 trials for raltegravir. Differences in OBT in these studies were accounted for. The efficacy and acquisition costs for each therapy to achieve viral load suppression to less than 50 copies/mL were analyzed. Both treatments demonstrated similar efficacy. The mean odd ratio versus placebo was 2.08 for etravirine and 1.92 for raltegravir. Annual drug acquisition costs were US$7,957 for etravirine and US$9,855 for raltegravir.

Extensive pharmacoeconomic studies in clinical practice are required to evaluate the cost-effectiveness of raltegravir treatment regimen in HIV-1 infected patients. There is no evidence to evaluate the potential impact of raltegravir use on health resource utilization.

Patient group/population

Raltegravir is currently approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who show evidence of viral replication and multidrug-resistant HIV-1 viral strains. First-line treatment with raltegravir is not currently recommended.[2]

The following treatment guidelines have been provided regarding the use of raltegravir in HIV-1-infected patient population:

- In treatment-naïve patients, safety and efficacy of raltegravir have not been established, and such use is currently not recommended.[59,60]
- In pediatric patients and patients aged less than 16 years, safety and efficacy of raltegravir have not been established, and such use is currently not recommended.[59,60]
- In HIV-1-infected patients misusing barbiturates, doubling the raltegravir dose has been recommended.[61]
- In HIV-1 infected patients with tuberculosis, coadministration of rifampin reduces plasma concentrations of raltegravir. Recently, the Isentress® product label and package insert have been updated following its traditional approval by the US FDA. Increasing raltegravir dose to 800 mg twice daily during coadministration with rifampin has been recommended[62] Limited pharmacokinetic data is available regarding concomitant administration of rifabutin with raltegravir, and no such dose adjustments have been recommended.

Patients with hepatic impairment

An open-label, single dose, phase I study found no clinically important effect of moderate hepatic impairment on raltegravir pharmacokinetics.[63] In this study, eight patients with chronic moderate hepatic impairment as defined by a Child–Pugh score of 7 to 9 and eight healthy, matched control subjects each received a single 400 mg dose of raltegravir. No clinically important differences in the pharmacokinetic parameters between the hepatic impaired group and healthy control group were observed. Results of this study indicate a low risk for reduced efficacy and reduced tolerability in patients with hepatic impairment. No dose adjustment is necessary for patients with mild to moderate hepatic impairment. No evidence is available on the pharmacokinetics of raltegravir in patients with severe hepatic impairment.

Patients with renal insufficiency

The effect of renal impairment on the pharmacokinetics of raltegravir was investigated in an open-label, single 400 mg dose, phase I study in 10 patients with severe renal insufficiency defined as a creatinine clearance of <30 mL/min per 1.73 m² and 10 healthy, matched control subjects. No clinically important differences in the pharmacokinetic parameters between the two groups were observed, though percent dose excreted in urine and renal clearance were considerably lower for patients with severe renal insufficiency. Also, since renal elimination of raltegravir is only modest, the results of this study can be extrapolated to patients with mild or moderate renal insufficiency including patients on dialysis. However, additional studies in patients undergoing dialysis may be required.[63]

Patients with hepatitis B or C virus co-infection

10%–20% of patients enrolled in the BENCHMRK 1&2 studies were co-infected with hepatitis B or C virus.[23] In patients with hepatitis B or C virus co-infection, the safety profile of raltegravir was similar to that in patients without co-infection. The rate of laboratory abnormalities from baseline alanine aminotransferase (ALT) and aspartate aminotransferase (AST), or total bilirubin was higher in patients with hepatitis B or C virus co-infected in raltegravir as well as placebo treatment groups.

Patients with risk of myopathy and rhabdomyolysis

Adverse events such as myopathy and rhabdomyolysis have been reported with use of raltegravir. In patients at increased risk of myopathy and rhabdomyolysis such as patients receiving concomitant medications known to cause these conditions, raltegravir must be used with caution.

Dosage, administration, and formulations

Raltegravir (Isentress®), in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and drug-resistant HIV-1 viral strains. It is formulated as its potassium salt and is available as film-coated tablets containing 434.4 mg of raltegravir potassium or 400 mg equivalent of raltegravir. The current prescribed dosing is 400 mg taken orally, twice daily without any dietary restrictions. Boosting with ritonavir is not required. Raltegravir is not metabolized by cytochrome P450 enzymes and does not have significant drug interactions. Hence, no dose adjustment has been recommended when coadministered with other antiretroviral agents. However, during coadministration with rifampin, 800 mg raltegravir twice daily is recommended.[62]

Place in therapy

As the first member of the new class, raltegravir has established the clinical potential of IN inhibitors in the treatment of HIV-1 infection. Raltegravir has demonstrated substantial clinical efficacy in treatment-experienced HIV-1 patients. Key evidence relating to disease-oriented and patient-oriented outcomes are summarized in the evidence summary table. There is strong evidence that raltegravir can achieve significant and sustained suppression of viral RNA levels to less than 50 copies/mL and substantial

immune response in drug-resistant HIV-1 patients. This offers the much needed alternative salvage therapy to HIV-1 infected patients faced with drug resistance and failure of first-line antiretroviral regimen. Treatment with raltegravir has been found to be well tolerated with good safety and minimal toxicity. Drug interactions with most other antiretroviral agents and concomitant medications did not have clinical significance. Dose-adjustment has been recommended during concomitant use with rifampin. There is insufficient data regarding other patient-oriented outcomes, such as improvement in quality of life, improvement in patient compliance and adherence to treatment, improvement in morbidity and mortality.

Since raltegravir acts selectively on HIV IN, there is no risk of developing cross-resistance against other classes of antiretrovirals. However, the high propensity for development of resistance mutations may undermine the therapeutic benefit of raltegravir. Hence, raltegravir should be used in combination with at least one other active drug. There is also high probability of cross-resistance against other mechanistically similar IN inhibitors. Future efforts on developing second generation IN inhibitors should be directed against overcoming the challenge of therapeutic resistance.

There is limited economic evidence regarding the use of raltegravir. However, preliminary analysis of the acquisition cost and cost-effectiveness estimate an incremental cost-effectiveness ratio for raltegravir at $US21339 per quality-adjusted life year gained. Direct evidence from studies evaluating the cost-effectiveness in a combination therapy is needed to confirm the economic benefits of raltegravir.

In summary, there is strong evidence that treatment with raltegravir in treatment-experienced patients results in sustained suppression of viremia to less than 50 HIV-1 RNA copies per milliliter accompanied with improvement in immunologic response. Substantial evidence also show that raltegravir has no significant interactions with other antiretrovirals and concomitant medications and has a good safety and tolerability profile.

Disclosure

The authors report no conflicts of interest in this work.

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