# The place of raltegravir in the clinical management of HIV-1 infection

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## Practice Points

- Lifetime mandatory continuous antiretroviral therapy is associated with toxicity, such as the development of bone, renal and cardiovascular disorders. Hence, alternative strategies, balancing toxicity and viral efficacy are needed.
- Raltegravir (RAL) is the first member of the new class of HIV-1 integrase strand transfer inhibitors (INSTIs), initially approved for the salvage therapy of multiexperienced continuous antiretroviral therapy adult patients, based on the results of the pivotal BENCHMRK 1 and 2 trials.
- Due to the potent virologic efficacy, leading to rapid viral suppression, and the good tolerance profile, RAL is currently part of the preferred first-line triple therapy regimens in antiretroviral-naive patients.
- Metabolization by the glucuronidation pathway resulting in limited drug–drug interactions and the lack of metabolic toxicity make RAL an important option in aging HIV patients, with multiple comorbidities, and in special populations, such as HIV–hepatitis C virus co-infected patients.
- Possible drawbacks concern the twice-daily dosing, cost and the need of a fully-active background regimen as RAL monotherapy is hazardous in terms of resistance.

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**SUMMARY** Raltegravir (RAL) is the first licensed drug of the new class of HIV-1 integrase strand transfer inhibitors. Developed to target multiresistant HIV, RAL acts by preventing the integration of HIV DNA into cells and is now widely used in both naive and experienced patients. The high viral potency of the drug (ensuring a rapid viral decrease), the excellent safety profile with a good immediate tolerability and a favorable long-term metabolic profile, have placed RAL, the first approved integrase strand transfer inhibitor, in a key position within the HIV armamentarium. This article provides a brief overview of data on RAL efficacy, safety and tolerability, and on its use in special populations.

Despite reducing morbidity, mortality and transmission, the most potent continuous antiretroviral therapy (cART) is currently inefficient at eradicating HIV, implying mandatory lifetime-therapy and optimal treatment adherence in order to avoid development of drug resistance. Indeed cART discontinuation leads to increased mortality [1]. Even though currently used drugs are much more acceptable in terms of tolerance and ease of use, long-term administration leads to toxicity, spanning from lipodystrophy, dyslipidemia, renal and neurotoxicity, increased inflammation and immunosenescence [2,3]. Hence, the optimal regimen needs to balance viral efficacy, resistance risk and toxicity, while ensuring the premises for optimal adherence.

Developed by Merck & Co., Raltegravir (RAL; also known as MK-0518 and Isentress®) is the first member of a new class of antiretrovirals called integrase strand transfer inhibitors (INSTIs), intended to respond to the urgent need for active drugs in heavily pretreated HIV-infected patients. Currently, the INSTI elvitegravir (EVG) combined with tenofovir (TDF), emtricitabine (FTC) and the pharmacokinetic (PK) enhancer cobicistat, as a single-tablet regimen, is approved by the US FDA and another INSTI, dolutegravir (DTG), active on most RAL-resistant strains, is in advanced stages of development. This article explores the role of RAL in the clinical management of HIV-1-infected patients, reviewing data on efficacy, safety and tolerability, and on its use in special populations.

## Mechanism of action

RAL prevents the formation of functional integrated proviral DNA [4] by blocking the binding of the HIV preintegration complex to host cell DNA. The approximately 27 h-long binding period to the integration complex exceeds the half-life of the preintegration complex in the cells [5,6]. RAL is active on both HIV-1 and HIV-2, independent of viral tropism [7,8]. It was initially approved by the FDA in 2007 for the salvage therapy of multiexperienced cART patients, because of its activity on multiresistant HIV-1 [4,9,10]. Initiated in 2009, RAL use was extended for the first-line treatment of cART-naive patients [4].

## Pharmacology

### Pharmacokinetics & pharmacodynamics

RAL is only available for oral administration, at the standard recommended dose of 400 mg twice daily. It is rapidly absorbed, with a maximum concentration reached after 3 h in the fasted state [4]. Although the changes in exposure to RAL may vary depending on food intake, these differences were not associated with either reduced efficacy or increased incidence of adverse events and, thus, meals do not influence the drug administration [4,11,12]. At doses between 100–800 mg, the area under the curve (AUC) and the 12 h through concentration ($C_{12}$) increase linearly, AUC ranges between 6.53 and 45.27 µM/(l.h) and $C_{12}$ between 70.6 and 300.8 nM [13]. Protein-binding is 83%, steady state is achieved after 48-h and 95% inhibitory concentration ($IC_{95}$) values in 50% human serum cell-cultures is 33 nmol/l corresponding to a target $C_{12}$ of approximately 16 µg/ml [11,13,14].

RAL is metabolized through glucuronidation by uridine 5′-diphosphoglucuronosyltransferase 1A1. The elimination half-life is 9 h, half being excreted in feces and 9% of the dose excreted in urine as unchanged parent compound; the rest is excreted as the metabolite [13]. RAL plasma concentrations are modestly higher in individuals carrying the UGT1A1*28/*28 polymorphism. This increase is not clinically significant, and therefore no dose adjustment is required in these patients [15].

Despite a considerable intra- and inter-individual variability [11,16,17], RAL has a large therapeutic window and data suggest that overall variability does not preclude safety or efficacy. Gender, race/ethnicity, age, BMI, moderate renal or hepatic insufficiency do not significantly affect RAL PK [16]. To date, there is no identified through concentration ($C_{trough}$) proven to be correlated with reduced efficacy [9,16,18,19]. Burger *et al.* recently suggested that cumulative AUC exposure assessment may be more informative than single time point measurements [20]. However, two recent PK/pharmacodynamics papers, including one focusing on QDMRK, a Phase III clinical trial of RAL given once daily (800-mg dose) versus twice daily (400 mg per dose), each in combination with once-daily coformulated TDF/FTC, in treatment-naive HIV-infected patients, clearly suggest an association between $C_{trough}$ and efficacy [21,22].

RAL penetrates well into compartments, achieving therapeutic levels in genital fluids, with concentrations similar or superior to those in blood [23–25]. In gut-associated lymphoid tissue, RAL demonstrated levels 1.5–7-times higher than in plasma [26]. RAL has been shown to exceed 50% inhibitory concentration ($IC_{50}$) in cerebrospinal fluid for wild-type HIV-1 by a median of 4.5-fold [27], reaching $IC_{95}$ in approximately half of cases [28].

## Drug interactions

Metabolism by the low-affinity, high-capacity glucuronidation pathway results in limited drug–drug interactions (DDIs) and a lack of interference with the hepatic cytochrome P450-3A4, which represents an advantage compared with the non-nucleosidic reverse transcriptase inhibitors and protease inhibitors (PIs) currently in use [16,17]. Indeed HIV-infected patients frequently have concomitant therapies at risk to induce DDIs. **Table 1** summarizes the most important RAL interactions that occur when it is administered with potent UGTA1-inducers (e.g., rifampicine) or inhibitors

**Table 1. The main drug–drug interactions of raltegravir.**

| Co-medication | Effect of co-medication on RAL AUC (%) | Effect of co-medication on RAL $C_{12}$ (%) | Dosing recommendation | Ref. |
|---|---|---|---|---|
| **NRTIs** | | | | |
| Tenofovir | +49 | +3 | Maintain standard dosing | [82] |
| **NNRTIs** | | | | |
| Efavirenz | -36 | -21 | Maintain standard dosing | [83] |
| Etravirine | -10 | -34 | Maintain standard dosing | [84] |
| Rilpivirine | NS | NS | – | [85] |
| **PIs** | | | | |
| Atazanavir/r | +41 | +77 | Maintain standard dosing | [86] |
| Darunavir/r | -29 | +38 | Maintain standard dosing | [87] |
| Lopinavir/r | +3 | -30 | Maintain standard dosing | [88] |
| Tipranavir/r | -24 | -55 | Maintain standard dosing | [89] |
| **CCR5 antagonist** | | | | |
| Maraviroc (300 mg b.i.d.) | -37 | -28 | Maintain standard dosing | [90] |
| **TB agents** | | | | |
| Rifampicine | -40 | -61 | Increase RAL dose to 800 mg b.i.d. | [78] |
| Rifabutine | +19 | -20 | Maintain standard dosing | [91] |
| **First-generation hepatitis C PIs** | | | | |
| Boceprevir | NS | NS | Maintain standard dosing | [92] |
| Telaprevir | +31 | +78 | Maintain standard dosing | [93] |
| **Other agents** | | | | |
| Omeprazole | +212 | +46 | Maintain standard dosing | [94] |

/r: Boosted by ritonavir; AUC: Area under the curve; b.i.d.: Twice daily; $C_{12}$: 12-h trough concentration; NNRTI: Non-nucleoside reverse-transcriptase inhibitor: NRTI: Nucleoside reverse-transcriptase inhibitor; NS: Not significant; PI: Protease inhibitor; RAL: Raltegravir.

(e.g., atazanavir). Globally, RAL displays a profile of low and nonclinically significant interactions with agents such as immunosupressants, psychoactive agents (e.g., methadone), statins, oral contraceptives or anti-hepatitis C virus (HCV) agents, making it a molecule of choice in various patient settings [11]. The only dose adjustment currently recommended is the doubling of RAL dosage when coadministered with rifampicine [29,30,101]. However, the enzyme induction of RAL metabolism seems less important than in healthy volunteers when administered with rifampicine. The safety and efficacy of RAL 400 mg twice a day (b.i.d.) and RAL 800 mg b.i.d. in combination with TDF and lamivudine in HIV–TB co-infected patients has recently been demonstrated up to 48 weeks [31,32].

## Resistance

RAL has a moderately low genetic barrier to resistance and continued activity is dependent upon the presence of a supportive background regimen [33,34]. Resistant strains could emerge as early as 1 month after treatment initiation in RAL-naive patients [35]. The main pathways involved are mutations at positions N155H, Q148H/R/K and Y143R/C/H [36,37]. Single mutations in the integrase gene are sufficient to confer high-level phenotypic resistance to both RAL and elvitegravir [34]. The presence of Q148H and G140S simultaneously leads to emergence of highly resistant strains [38]. The involvement of the N155/Q148 pathways leads to a lack of residual antiviral activity [34,39].

As RAL has been recently introduced, primary-resistance is still low [40], but could become a growing concern due to the extensive use of this drug [19]. RAL and EVG present extensive crossresistance, with mutations at codon 143 affecting RAL more than EVG. DTG is a second-generation INSTI fully active against N155H ± E92Q or Y143CR (± T97A) strains [34,41,42]. DTG imminent approval will provide treatment options for patients that have previously acquired these mutations after virologic failure under a RAL-containing regimen. However, Q148 pathway involvement causes a greater decrease of susceptibility to DTG, which can be reduced by 10–20-fold in certain combinations with mutations at codons (L74, E138 and G140) [34]. Overall, key messages regarding RAL resistance are the crucial role of an efficacious optimized background therapy (OBT) [43] and the need for a prompt reassessment of a RAL-based treatment regimen in the event of viral replication, in order to preserve future INSTI response [44].

## Clinical experience

### ■ Studies in antiretroviral-experienced patients

RAL was developed to respond to the need for active molecules in multiresistant HIV patients. It was initially approved for the salvage therapy of multiexperienced cART adult patients, based on the results of the pivotal double-blind, randomized, Phase III BENCHMRK 1 and 2 trials [45]. A total of 699 patients were randomly assigned to receive RAL 400 mg twice daily or placebo in a 2:1 ratio, with an OBT. Patients had documented three-class resistance at inclusion. RAL demonstrated a potent and superior antiretroviral effect, compared with OBT alone. At 48 and 96 weeks, respectively, 62.1 and 57% of patients in the RAL-arm versus 32.9 and 26% in the placebo-arm ($p < 0.001$ at both time points) achieved a viral load <50 copies/ml. Efficacy was high regardless of baseline viral load or CD4 cell count, with no differences between the arms. In this trial, more than 50% of patients had a high viral load ≥100,000 copies/ml at baseline. Virologic failure occurred by week 96 in 150 out of 462 (33%) of RAL-recipients. Genotypic resistance test results showed the development of integrase resistance in 73 out of 112 (65%) patients and 30 out of 94 subjects (32%) did not show RAL resistance mutations at failure with viral load >400 copies/ml. Final 5-year analysis showed that 42% of RAL recipients had HIV RNA <50 copies/ml, compared with just 16% of placebo recipients. Results were similar (45 vs 17%, respectively) for viral load <400 copies/ml [46].

Thus, long-term data show that RAL offers a valuable treatment option for patients infected with multidrug-resistant HIV, provided the chosen OBT presents with sufficient antiviral potency. This reinforces the key ART principle of building strategies with sufficient antiviral potency (e.g., comprising at least two fully-active drugs).

### ■ Studies in antiretroviral-naive patients

#### Pivotal studies

Due to potent virologic efficacy and a good tolerance profile, RAL has rapidly appeared as an attractive first-line therapy. Based on

the results of pivotal Phase II and III trials [47–50], RAL combined with TDF/FTC, is currently part of the preferred first-line triple therapy regimens in HIV-1 antiretroviral-naive patients [30,101].

Approval in treatment-naive patients was founded on the results of the Phase III multinational STARTMRK study, demonstrating that RAL was noninferior to efavirenz when used in combination with TDF/FTC through 156 weeks of therapy [49]. Counting noncompleters as failures, at week 156, 75.4% (212 out of 281) versus 68.1% (192 out of 282) had viral load (VL) <50 copies/ml in the RAL and efavirenz groups, respectively (noninferiority $p < 0.001$). Key features were the more rapid viral supression in the RAL arm ($p < 0.0001$), more modest lipid elevations ($p < 0.005$) and lower frequency of serious drug-related events ($p < 0.001$). The STARTMRK trial is the first Phase III trial comparing two different classes of drugs (INSTI versus non-nucleosidic reverse transcriptase inhibitors in combination with TDF/FTC) in naive patients and the only double-blind trial maintained during the 5 years of the study. Prespecified sensitivity analyses at week 240 confirmed the noninferiority of RAL to efavirenz, and were consistent with superiority of the RAL regimen over the efavirenz regimen demonstrated by the primary noncompleters as failures approach [51]. After 240 weeks of follow-up, analysis showed a low level of resistance. Only seven patients in the RAL group possessed resistance mutations. Among 55 out of 281 naive patients with virological failure in the RAL arm, only one patient had resistance to RAL alone, three patients to RAL and nucleoside reverse transcriptase inhibitor (NRTI) and three to NRTI only.

Furthermore, the efficacy of another dual NRTIs/RAL combination was demonstrated by the noncomparative pilot SHIELD trial [52]. After 96 weeks, RAL plus abacavir/lamivudine displayed potent viral suppression, with 77% (27 out of 35) of subjects achieving undetectable VL <50 copies/ml. The discontinuation rate was larger than expected between weeks 48 and 96 ($n = 5$), but only one patient discontinued because of a lack of efficacy and subjects discontinuing for administrative reasons were from a single site. Conclusions of this study are limited mainly because of the small sample size.

## Once-daily dosing studies

Given the potential benefits in terms of adherence, once-daily (800 mg) dosing of RAL was investigated. An international, double-blind, randomized, Phase III noninferiority study, known as QDMRK, failed to prove the noninferiority of a once-daily dose of 800 mg plus TDF/FTC compared with the approved dose in the same combination, as first-line treatment of HIV infection [53]. Indeed virological failure was more common with once-daily dosing, especially in patients with baseline VL >100,000 copies/ml and more patients in the once-daily group developed resistance to both RAL and FTC at the time of virological failure [53]. Once-daily simplification strategy was also evaluated by the ODIS randomized trial. After switch in virologically controlled patients from PIs to RAL either 400 mg twice daily or 800 mg once daily, viral suppression was maintained as long as prior NRTI resistance had not been selected [54]. However, the trial was halted prematurely at week 24 because of unfavorable antiviral efficacy in the once-daily versus the twice-daily arm (6.4 vs 2.9%, respectively), hampering definitive conclusions.

## Nucleoside analog-sparing strategies

Several studies have investigated the role of RAL combined with newer PIs as part of innovative nucleoside-sparing initiation regimens. The ACTG A5262 study, enrolled 112 antiretroviral-naive subjects receiving darunavir 800 mg once daily/ritonavir 100 mg once daily plus RAL 400 mg twice daily [55]. At 48 weeks, 61% (69 out of 113) of subjects achieved VL <50 copies/ml, with a high rate of virologic failure among patients with a baseline VL >100,000 cp/ml. One potential explanation could reside in potential DDIs between RAL and darunavir (DRV), resulting in overall lower DRV AUC [56], even though measured DRV $C_{trough}$ were within the range reported in an intensive pharmacokinetic study using the same dosage [57]. Further arguments are awaited from the ANRS 143/NEAT 001 study [102], an ongoing randomized trial assessing the nucleoside-sparing regimen of RAL and darunavir/ritonavir, expected to enrol 800 subjects and to present its first results by 2014.

Another strategy evaluated a regimen of lopinavir/r 400/100 mg twice daily in combination with either RAL or TDF/FTC once

daily in naive patients (PROGRESS trial) [58]. At 48 weeks, the RAL-based bitherapy displayed noninferiority to the three-drug regimen, and at 96 weeks both arms displayed similar rates of virologic suppression (p = 0.767). These results were in line with another study investigating dual RAL/lopinavir as initiation therapy [59], but should be interpreted with caution due to the small sample size.

Finally, in the SPARTAN study, the safety and efficacy of RAL 400 mg twice daily plus atazanavir 300 mg twice daily was assessed in naive subjects [60]. The proportion of patients with HIV VL <50 copies/ml at week 24 was 74.6% (47 out of 63) in the atazanavir (ATV) + RAL arm and 63.3% (19 out of 30) in the ATV/r + TDF/FTC arm. However, the overall profile did not appear optimal for further clinical development given its development of resistance to RAL and higher rates of hyperbilirubinemia with twice-daily ATV compared with ATV/r.

### Switch studies

Given the life-long treatment and known cART toxicity, such as bone and renal disorders related to TDF and increased cardiovascular risk with PIs, alternative strategies to standardize regimens are needed. RAL has become an attractive option in aging HIV-infected patients accumulating toxicity under current cART. Several switch studies have evaluated the place of RAL as a switch agent, given its high efficacy and its tolerability profile **(Table 2)**.

In terms of virologic safety, based mostly on the results of the SWITCHMRK 1 and 2 studies [43], current guidelines recommend caution when switching an antiretroviral-experienced patient from a boosted-PI regimen to RAL, underlining the importance of a fully active OBT, as functional RAL monotherapy has been shown to be associated with higher rates of virologic failure and resistance.

In terms of toxicity and tolerance, switch studies demonstrated the benefits after RAL initiation [43,61–63]. Metabolic modifications have been the focus of several substudies of the SPIRAL trial. In one substudy, endothelial dysfunction as an early event in the development of atherosclerosis, was prospectively evaluated through flow-mediated dilatation at baseline, at weeks 24 and 48 [64]. Total cholesterol, low-density lipoprotein cholesterol and triglyceride levels decreased at weeks 16 and 32 in the RAL-switch arm, while no changes were observed in the PI/r arm, but switch to RAL did not seem to have an impact on endothelial function after a 1-year follow-up. However, another substudy [61] demonstrated that a shift from LDL phenotype B to the less atherogenic phenotype A was observed only in the RAL arm ($p < 0.001$) by 48 weeks. Improvement in several biomarkers, such as hsCRP, osteoprotegerin, IL-6, TNF-α, insulin and D-dimer have also been shown [62]. Finally, the SPIRAL-LIP substudy evaluated changes in body fat distribution and bone mineral density between patients switching from a PI/r to RAL and patients continuing with PI/r [65]. Although there were no significant changes in body fat between the groups, maintaining the PI/r was associated with a significant increase in visceral and truncal adipose tissue, while switching to RAL led to a significant increase in femoral neck bone mineral density.

### Eradication studies

The advent of a new class of drugs, such as integrase inhibitors, has revived the scientific interest in intensification strategies, using RAL in order to evaluate whether the HIV reservoir could be reduced. To date, there is a consensus that ART intensification with RAL is not capable of durably modifying residual viremia or HIV DNA provirus in PBMC [66–68], despite some results suggesting a potential benefit [69], along with a reduction of $CD8^+$ T-cell activation [66], and of the level of cell-associated HIV RNA in $CD4^+$ T cells in the terminal ileum [70].

### Tolerance

An overall favorable tolerance profile of RAL has been confirmed by 5 years of use in clinical practice. The most common adverse events (2–10% incidence) associated with RAL are gastrointestinal symptoms, headache, insomnia and dizziness, which are generally transient and mild-to-moderate in severity [4,71,72]. There is no clear association between the dose and the frequency of adverse events. Nervous system events were reported to have a similar incidence to the placebo arm in the BENCHMRK studies [45], but psychiatric events were significantly lower when compared with the efavirenz arm in the STARTMRK studies [50]. Even though rare, 5–13% grade 3–4 creatine kinase increases have been observed in treatment-naive prospective

**Table 2. Raltegravir switch studies.**

| Study (year) | Number of patients | Study design | Outcome | Ref. |
|---|---|---|---|---|
| Towner *et al.* (CHEER; 2009) | 52 | Multicenter, nonrandomized, open-label trial in patients switching from OBT + enfuvirtide to OBT + RAL | 24 weeks: 94.2% (49 out of 52) of patients had HIV-1 RNA level <50 or 75 copies/ml, depending on the assay used | [95] |
| Gallien *et al.* (EASIER-ANRS 138; 2011) | 170 | Multicenter, randomized, prospective, open-label trial in multidrug-resistant HIV patients under an enfuvirtide-based regimen, switching to OBT + RAL at day 0 (immediate switch) or at week 24 (deferred switch) | 48 weeks: 90% of patients in both the immediate and deferred groups had plasma HIV-1 RNA levels <50 copies/ml | [63] |
| Eron *et al.* (SWITCHMRK 1 and 2; 2010) | 707 | Multicenter, randomized, double-blind, double-dummy, noninferiority trials in patients switching from OBT + LPV/r to OBT + RAL vs continuing OBT + LPV/r | 24 weeks (halted prematurely): 84.4% (293 out of 347) patients in the RAL group and 90.6% (319 out of 352) in the LPV/r group had plasma HIV-1 RNA levels <50 copies/ml; noninferiority not proven | [43] |
| Martinez *et al.* (SPIRAL; 2010) | 282 | Multicenter, randomized, open-label noninferiority trial in patients switching from OBT + PI/r to OBT + RAL vs continuing OBT + PI/r | 48 weeks: 96.9% (124 out of 128) patients in the RAL group and 95.1% (116 out of 122) in the PI/r group had plasma HIV-1 RNA levels <50 copies/ml; difference: 1.8%; 95% CI: -3.5–7.5 – noninferiority demonstrated | [96] |
| Ofotokun *et al.* (KITE; 2012) | 60 | Single-center, randomized, open-label pilot in patients switching to LPV/r + RAL or continuing baseline ART | 48 weeks: 92% of the LPV-r/RAL arm and 88% baseline ART arm had plasma HIV-1 RNA levels <50 copies/ml | [97] |
| Nguyen *et al.* (SWITCH-ER; 2011) | 57 | Multicenter, randomized, double-blind, crossover study comparing RAL as replacement agent for EFV, with primary end point patient preference for the first or the second regimen, assessed after 4 weeks | 2 weeks: half of patients previously on a stable EFV preferred to switch to RAL, after double-blind exposure to RAL for 2 weeks. Significant difference in anxiety and stress scores favoring RAL ($p = 0.04$ and 0.03, respectively) | [98] |
| Lake *et al.* (2012) | 39 | Multicenter, randomized, open-label trial in women under 2NRTI + PI/r or NNRTI, switching to 2NRTI + RAL or continuing baseline regimen, with primary end point the between-group change in CT-quantified visceral AT volume | 24 weeks: compared with continued PI or NNRTI, switch to RAL was associated with statistically significant 24-week improvements in total and LDL cholesterol but not AT volumes | [99] |
| Calin *et al.* (2012) | 18 | Single-center, observational study in patients switching to dual RAL/etravirine therapy | 48 weeks: ITT 83.3% (15 out of 18) and PP 100% (15 out of 15) patients had plasma HIV-1 RNA levels <50 copies/ml | [100] |

/r: Boosted by ritonavir; ART: antiretroviral therapy; AT: Adipose tissue; CT: Computed tomography; EFV: Efavirenz; ITT: Intent to treat; LDL: Low-density lipoprotein; LPV: Lopinavir; NNRTI: Non-nucleoside reverse-transcriptase inhibitor; NRTI: Nucleoside reverse-transcriptase inhibitor; OBT: Optimized background treatment; PI: Protease inhibitor; PP: Per protocol; RAL: Raltegravir.

studies and 11% in treatment-experienced prospective studies [72]. Myopathy and several cases of rhabdomyolysis have been reported, with an increased risk when statins were concomitantly used [72], and the FDA advised that RAL should be used with caution in patients at risk of developing a myopathy. Severe, life-threatening cases of Stevens–Johnson syndrome and toxic epidermal necrolysis have also been reported, warning for caution in patients with hypersensitivity reactions. In 2011, the RAL package insert was updated with an FDA warning concerning potentially life-threatening and fatal skin reactions. Hence, RAL and other suspect agents should be immediately discontinued if signs or symptoms of severe skin reactions or hypersensitivity reactions develop. Reports of immune reconstitution inflammatory syndrome in patients receiving RAL are comparable with other classes. There is no dose adjustment recommended in case of renal or hepatic failure [4]. Overall, the favorable toxicity profile makes RAL an option in patients intolerant to other classes.

## Special populations

### ■ HCV/HBV co-infection & solid-organ transplant

The limited DDIs with molecules metabolized by the liver cytochrome P450 system have made RAL a key agent in the comanagement of HCV therapy in HIV/HCV coinfected

patients. RAL-based cART was safe in HIV/HCV-cirrhotic patients receiving Peg-IFN/ribavirine plus telaprevir or boceprevir and did not affect the 12-week efficacy of direct-acting antiviral-based anti-HCV therapy [73]. Similarly, in solid-organ transplant recipients, the use of RAL spares DDIs with immunosuppressants metabolized by cytochrome P450, thus proving a treatment alternative for these patients [74,75].

### Pre- & post-exposure prophylaxis

Given its rapid efficacy and tolerability profile, RAL appears to be a good option in clinical practice in the management of HIV postexposure prophylaxis, even though it is not yet part of the current guidelines. Recently, Mayer *et al.* showed that a regimen composed of RAL/TDF/FTC demonstrated safety and tolerability as PEP in 100 HIV-infected individuals [76].

RAL has also been regarded as a potential pre-exposure prophylaxis (PreP) agent. However, despite good concentrations and demonstrated efficacy as PreP in animal model, RAL may require twice-daily dosing and has a low genetic barrier [77]. Hence, no current clinical studies of RAL as PreP are foreseen.

### HIV/TB co-infection

Combined treatment of HIV and TB remains a challenge because of DDIs, overlapping toxicity, high pill-burden and development of resistance. Given its very rapid efficacy on viral replication, RAL is a key drug particularly in patients with low CD4 cell counts. However rifampicin decreases RAL drug concentration [78]. The recent ANRS 12 180 REFLATE study has compared the standard daily dose of RAL 400 mg b.i.d. to the double dose of RAL 800 mg and to the standard efavirenz-containing regimen in naive HIV/TB co-infected patients [79]. Antiviral efficacy results at week 24 (the primary end point) showed similar rates of virologic success with RAL 400 mg b.i.d. (76%), RAL 800 mg b.i.d. (78%) and EFV 600 mg once a day (63%) [79]. Success rates at week 48 were 63% (95% CI: 49–76%), 76% (95% CI: 65–88%) and 67% (95% CI: 54–80%) in the RAL 800, RAL 400 and EFV arms [32]. There was an important variability of RAL pharmacokinetic parameters and a trend toward lower concentrations when RAL 400 mg b.i.d. was combined with RIF which was compensated by the 800 mg b.i.d. dosing [31]. These data support current guidelines that recommend a dose of 800 mg twice daily to be used in patients receiving rifampicin [29,30,101].

### Pregnancy

Despite the fact that there is no evidence of teratogenicity in animal studies, RAL is currently not a recommended drug during pregnancy. However given its capacity to rapidly decrease the HIV viral load, the good penetration into the cervix and the high transfer across the placenta barrier, RAL would potentially be a valuable molecule especially in women presenting with HIV in late pregnancy [80]. Preliminary results from the PANNA pharmacology network show that in a small cohort (n = 6) exposure to RAL was not lower during pregnancy than postpartum [81]. This is in contrast to a number of other antiretroviral agents, especially PIs. These results need to be confirmed in a larger group of patients.

## Conclusion

RAL, as the original and first licensed drug in the class of INSTIs, is a key compound in the HIV armamentarium. Prominent features such as rapidity of the virologic response, high efficacy, lower risk of drug–drug interactions and favorable toxicity profile, prompt many clinicians to use RAL in the long-term management of both naive and heavily-pretreated patients, especially in well-developed settings. The attractiveness of this molecule could potentially be hindered by the twice-daily dosing, its cost and the need of a fully-active background agent, as functional RAL monotherapy has proven hazardous in terms of resistance. The expanding class of INSTIs will undisputedly play a major role in the future management of HIV-infected patients.

### Financial & competing interests disclosure

*C Katlama received travel grants and honoraria from presentations at workshops and consultancy honoraria from Abbott, Schering-Plough, GlaxoSmithKline, Janssen Cilag, Merck & Co., Tibotec, Bristol-Myers Squibb, Gilead, Roche and Boehringer Ingelheim. R Calin received travel and congress participation grants from Merck & Co. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

*No writing assistance was utilized in the production of this manuscript.*

## References


1 El-Sadr WM, Lundgren J, Neaton JD *et al.* CD4$^+$ count-guided interruption of antiretroviral treatment. *N. Engl. J. Med.* 355, 2283–2296 (2006).

2 Izzedine H, Harris M, Perazella MA. The nephrotoxic effects of HAART. *Nat. Rev. Nephrol.* 5, 563–573 (2009).

3 Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu. Rev. Med.* 62, 141–155 (2011).

4 Isentress® (Raltegravir). Product Information. Merck & Co. Inc., NJ, USA (2011).

5 Grobler J, McKenna PM, Ly S. Functionally irreversible inhibition of integration by slowly dissociating strand transfer inhibitor. In: *10th International Workshop on Clinical Pharmacology of HIV Therapy*. Amsterdam, The Netherlands, 15–17 April 2009 (Abstract O-10).

6 McSharry J, Weng Q, Zager K, Soldani K, Kulawy R, Drusano G. Pharmacodynamics of raltegravir, an HIV integrase inhibitor in an *in vitro* hollow fiber infection model system. Presented at: *48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy*. Washington, DC, USA, 25–28 October 2008 (Abstract A-960).

7 Roquebert B, Damond F, Collin G *et al.* HIV-2 integrase gene polymorphism and phenotypic susceptibility of HIV-2 clinical isolates to the integrase inhibitors raltegravir and elvitegravir *in vitro*. *J. Antimicrob. Chemother.* 62, 914–920 (2008).

8 Garrett N, Xu L, Smit E *et al.* Raltegravir treatment response in an HIV-2 infected patient: a case report. *AIDS* 22, 1091–1092 (2008).

9 Grinsztejn B, Nguyen BY, Katlama C *et al.* Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a Phase II randomised controlled trial. *Lancet* 369, 1261–1269 (2007).

10 Gatell JM, Katlama C, Grinsztejn B *et al.* Long-term efficacy and safety of the HIV integrase inhibitor raltegravir in patients with limited treatment options in a Phase II study. *J. Acquir. Immune Defic. Syndr.* 53, 456–463 (2010).

11 Burger DM. Raltegravir: a review of its pharmacokinetics, pharmacology and clinical studies. *Expert Opin. Drug Metab. Toxicol.* 6, 1151–1160 (2010).

12 Brainard DM, Friedman EJ, Jin B *et al.* Effect of low-, moderate-, and high-fat meals on raltegravir pharmacokinetics. *J. Clin. Pharmacol.* 51, 422–427 (2011).

13 Iwamoto M, Wenning LA, Petry AS *et al.* Safety, tolerability, and pharmacokinetics of raltegravir after single and multiple doses in healthy subjects. *Clin. Pharmacol. Ther.* 83, 293–299 (2008).

14 Markowitz M, Morales-Ramirez JO, Nguyen BY *et al.* Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals. *J. Acquir. Immune Defic. Syndr.* 43, 509–515 (2006).

15 Wenning LA, Petry AS, Kost JT *et al.* Pharmacokinetics of raltegravir in individuals with UGT1A1 polymorphisms. *Clin. Pharmacol. Ther.* 85, 623–627 (2009).

16 Brainard DM, Wenning LA, Stone JA *et al.* Clinical pharmacology profile of raltegravir, an HIV-1 integrase strand transfer inhibitor. *J. Clin. Pharmacol.* 51, 1376–1402 (2011).

17 Adams JL, Greener BN, Kashuba AD. Pharmacology of HIV integrase inhibitors. *Curr. Opin. HIV AIDS* 7, 390–400 (2012).

18 Wenning L, Hwang E, Nguyen BY *et al.* Pharmacokinetic/pharmacodynamic (PK/PD) analyses for raltegravir (RAL) in Phase III studies in treatment experienced HIV-infected patients following 48 weeks treatment. Presented at: *48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy/46th Infectious Diseases Society of America Meeting*. Washington, DC, USA, 25–28 October 2008.

19 Rokas KE, Bookstaver PB, Shamroe CL *et al.* Role of raltegravir in HIV-1 management. *Ann. Pharmacother.* 46, 578–589 (2012).

20 Burger D, Colbers EPH, van Luin M *et al.* AUCO-3h of raltegravir is correlated with AUCO-12: a novel approach for therapeutic drug monitoring of raltegravir. Presented at: *11th International Workshop on Clinical Pharmacology of HIV Therapy*. Sorrento, Italy, 7–9 April 2010.

21 Rizk ML, Hang Y, Luo WL *et al.* Pharmacokinetics and pharmacodynamics of once-daily versus twice-daily raltegravir in treatment-naive HIV-infected patients. *Antimicrob. Agents Chemother.* 56, 3101–3106 (2012).

22 Ananworanich J, Gorowara M, Avihingsanon A *et al.* Pharmacokinetics of and short-term virologic response to low-dose 400-milligram once-daily raltegravir maintenance therapy. *Antimicrob. Agents Chemother.* 56, 1892–1898 (2012).

23 Clavel C, Peytavin G, Tubiana R *et al.* Raltegravir concentrations in the genital tract of HIV-1-infected women treated with a raltegravir-containing regimen (DIVA 01 study). *Antimicrob. Agents Chemother.* 55, 3018–3021 (2011).

24 Jones A, Talameh JA, Patterson KB *et al.* First dose and steady-state pharmacokinetics of raltegravir in the genital tract of HIV negative women. Presented at: *10th International Workshop on Clinical Pharmacology on HIV Therapy*. Amsterdam, The Netherlands, 15 April–1 May 2009 (Abstract O-06).

25 Bonora S, D'Avolio A, Simele M *et al.* Steady-state raltegravir penetration in seminal plasma of healthy volunteers. Presented at: *17th Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA, USA, 16–19 February 2010 (Abstract 609).

26 Patterson K, Stevens T, Prince H *et al.* Antiretroviral for prevention: pharmacokinetics of raltegravir in gut-associated lymphoid tissue (GALT) of healthy male volunteers. Presented at: *13th International Workshop on Clinical Pharmacology of HIV Therapy*. Barcelona, Spain, 16–18 April 2012 (Abstract O_11).

27 Croteau D, Letendre S, Best BM *et al.* Total raltegravir concentrations in cerebrospinal fluid exceed the 50-percent inhibitory concentration for wild-type HIV-1. *Antimicrob. Agents Chemother.* 54, 5156–5160 (2010).

28 Yilmaz A, Gisslen M, Spudich S *et al.* Raltegravir cerebrospinal fluid concentrations in HIV-1 infection. *PLoS ONE* 4, e6877 (2009).

29 Thompson MA, Aberg JA, Hoy JF *et al.* Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. *JAMA* 308, 387–402 (2012).

30 *European AIDS Clinical Society Guidelines Version 6.1, November 2012.* European AIDS Clinical Society, Brussels, Belgium (2012).

31 Sauvageon H, Grinsztejn B, Arnold V *et al.* Pharmacokinetics of two doses of Raltegravir in combination with Rifampin in HIV-TB co-infected patients, an ANRS 12 180 Reflate TB sub-study. Presented at: *20th Conference on Retroviruses and Opportunistic Infections*. Atlanta, GA, USA, 3–6 March 2013 (Abstract 539).

32 Grinsztejn B, De Castro N, Arnold V *et al.* Efficacy and safety of raltegravir vs efavirenz for the treatment of HIV/TB patients: 48-week results of the ANRS 12 180 Reflate TB trial. Presented at: *20th Conference on Retroviruses and Opportunistic Infections*. Atlanta, GA, USA, 3–6 March 2013 (Abstract 853).

33 Blanco JL, Varghese V, Rhee SY *et al.* HIV-1 integrase inhibitor resistance and its clinical implications. *J. Infect. Dis.* 203, 1204–1214 (2011).

34 Geretti AM, Armenia D, Ceccherini-Silberstein F. Emerging patterns and implications of HIV-1 integrase inhibitor resistance. *Curr. Opin. Infect. Dis.* 25, 677–686 (2012).

35 Baldanti F, Paolucci S, Gulminetti R *et al.* Early emergence of raltegravir resistance mutations in patients receiving HAART salvage regimens. *J. Med. Virol.* 82, 116–122 (2010).

36 Metifiot M, Marchand C, Maddali K *et al.* Resistance to integrase inhibitors. *Viruses* 2, 1347–1366 (2010).

37 Fransen S, Gupta S, Danovich R *et al.* Loss of raltegravir susceptibility by human immunodeficiency virus type 1 is conferred via multiple nonoverlapping genetic pathways. *J. Virol.* 83, 11440–11446 (2009).

38 Delelis O, Malet I, Na L *et al.* The G140S mutation in HIV integrases from raltegravir-resistant patients rescues catalytic defect due to the resistance Q148H mutation. *Nucleic Acids Res.* 37, 1193–1201 (2009).

39 Wirden M, Simon A, Schneider L *et al.* Raltegravir has no residual antiviral activity *in vivo* against HIV-1 with resistance-associated mutations to this drug. *J. Antimicrob. Chemother.* 64, 1087–1090 (2009).

40 Ceccherini-Silberstein F, Malet I, Fabeni L *et al.* Specific HIV-1 integrase polymorphisms change their prevalence in untreated versus antiretroviral-treated HIV-1-infected patients, all naive to integrase inhibitors. *J. Antimicrob. Chemother.* 65, 2305–2318 (2010).

41 Kobayashi M, Yoshinaga T, Seki T *et al.* *In vitro* antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. *Antimicrob. Agents Chemother.* 55, 813–821 (2011).

42 Canducci F, Ceresola ER, Boeri E *et al.* Cross-resistance profile of the novel integrase inhibitor Dolutegravir (S/GSK1349572) using clonal viral variants selected in patients failing raltegravir. *J. Infect. Dis.* 204, 1811–1815 (2011).

43 Eron JJ, Young B, Cooper DA *et al.* Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. *Lancet* 375, 396–407 (2010).

44 Malet I, Fourati S, Morand-Joubert L *et al.* Risk factors for raltegravir resistance development in clinical practice. *J. Antimicrob. Chemother.* 67, 2494–2500 (2012).

45 Steigbigel RT, Cooper DA, Teppler H *et al.* Long-term efficacy and safety of Raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 Phase III trials. *Clin. Infect. Dis.* 50, 605–612 (2010).

46 Eron J, Cooper D, Steigbigel R *et al.* (BENCHMRK-1 and 2 Study Groups). Final five-year results of the BENCHMRK studies: sustained antiretroviral effect of raltegravir and exploratory analysis of late outcomes based on early virologic response. Presented at: *AIDS 2012 XIX International AIDS Conference.* Washington, DC, USA, 22–27 July 2012 (Poster TUPE025).

47 Markowitz M, Nguyen BY, Gotuzzo E *et al.* Rapid and durable antiretroviral effect of the HIV-1 integrase inhibitor raltegravir as part of combination therapy in treatment-naive patients with HIV-1 infection: results of a 48-week controlled study. *J. Acquir. Immune Defic. Syndr.* 46, 125–133 (2007).

48 Gotuzzo E, Markowitz M, Ratanasuwan W *et al.* Sustained efficacy and safety of raltegravir after 5 years of combination antiretroviral therapy as initial treatment of HIV-1 infection: final results of a randomized, controlled, Phase II study (Protocol 004). *J. Acquir. Immune Defic. Syndr.* 61, 73–77 (2012).

49 Rockstroh JK, Lennox JL, Dejesus E *et al.* Long-term treatment with raltegravir or efavirenz combined with tenofovir/emtricitabine for treatment-naive human immunodeficiency virus-1-infected patients: 156-week results from STARTMRK. *Clin. Infect. Dis.* 53, 807–816 (2011).

50 Lennox JL, DeJesus E, Lazzarin A *et al.* Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* 374, 796–806 (2009).

51 Rockstroh JK, Dejesus E, Lennox JL *et al.* Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1 infected patients: final five-year results from STARTMRK. *J. Acquir. Immune Defic. Syndr.* 63(1), 77–85 (2013).

52 Young SD, Hlavka Z, Modiba P *et al.* HIV-related stigma, social norms, and HIV testing in Soweto and Vulindlela, South Africa: National Institutes of Mental Health Project Accept (HPTN 043). *J. Acquir. Immune Defic. Syndr.* 55, 620–624 (2010).

53 Eron JJ Jr, Rockstroh JK, Reynes J *et al.* Raltegravir once daily or twice daily in previously untreated patients with HIV-1: a randomised, active-controlled, Phase 3 non-inferiority trial. *Lancet Infect. Dis.* 11, 907–915 (2011).

54 Vispo E, Barreiro P, Maida I *et al.* Simplification from protease inhibitors to once- or twice-daily raltegravir: the ODIS trial. *HIV Clin. Trials* 11, 197–204 (2010).

55 Taiwo B, Zheng L, Gallien S *et al.* Efficacy of a nucleoside-sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naive HIV-1-infected patients (ACTG A5262). *AIDS* 25, 2113–2122 (2011).

56 Gervasoni C, Cattaneo D. Pharmacokinetic concerns related to the AIDS Clinical Trial Group (ACTG) A5262 trial. *AIDS* 26, 398–400; author reply 397–398 (2012).

57 Boffito M, Moyle M, Hill A, Sekar V, Lefebvre E, De Pauw M. The pharmacokinetic profile of darunavir with low-dose ritonavir (DRV/r) in various multiple-dose regimens over 120 h. Presented at: *9th International Workshop on Clinical Pharmacology of HIV Therapy*. New Orleans, Louisiana, USA, 7–9 April 2008 (Abstract P-31).

58 Reynes J, Trinh R, Pulido F *et al.* Lopinavir/ritonavir combined with raltegravir or tenofovir/emtricitabine in antiretroviral-naive subjects: 96-week results of the PROGRESS Study. *AIDS Res. Hum. Retroviruses* 29(2), 256–265 (2012).

59 Bowman V, Rieg G, Jain S *et al.* 48 week results of a pilot randomized study of a nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimen of raltegravir (RAL) + lopinavir/ritonavir (LPV/r) versus efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) in antiretroviral naive patients. Presented at: *International AIDS Conference*. Vienna, Austria, 18–23 July 2010 (Abstract CDB 336).

60 Kozal MJ, Lupo S, DeJesus E *et al.* A nucleoside- and ritonavir-sparing regimen containing atazanavir plus raltegravir in antiretroviral treatment-naive HIV-infected patients: SPARTAN study results. *HIV Clin. Trials* 13, 119–130 (2012).

61 Saumoy M, Sanchez-Quesada JL, Martinez E *et al.* LDL subclasses and lipoprotein-phospholipase A2 activity in suppressed

HIV-infected patients switching to raltegravir: spiral substudy. *Atherosclerosis* 225, 200–207 (2012).

62 Martinez E, D'Albuquerque PM, Llibre JM *et al.* Changes in cardiovascular biomarkers in HIV-infected patients switching from ritonavir-boosted protease inhibitors to raltegravir. *AIDS* 26, 2315–2326 (2012).

63 Gallien S, Braun J, Delaugerre C *et al.* Efficacy and safety of raltegravir in treatment-experienced HIV-1-infected patients switching from enfuvirtide-based regimens: 48 week results of the randomized EASIER ANRS 138 trial. *J. Antimicrob. Chemother.* 66, 2099–2106 (2011).

64 Masia M, Martinez E, Padilla S *et al.* Endothelial function in HIV-infected patients switching from a boosted protease inhibitor-based regimen to raltegravir: a substudy of the SPIRAL study. *J. Antimicrob. Chemother.* 68(2), 409–413 (2012).

65 Curran A, Martinez E, Saumoy M *et al.* Body composition changes after switching from protease inhibitors to raltegravir: SPIRAL-LIP substudy. *AIDS* 26, 475–481 (2012).

66 Gandhi RT, Zheng L, Bosch RJ *et al.* The effect of raltegravir intensification on low-level residual viremia in HIV-infected patients on antiretroviral therapy: a randomized controlled trial. *PLoS Med.* 7(8), pii: e1000321 (2010).

67 Hatano H, Hayes TL, Dahl V *et al.* A randomized, controlled trial of raltegravir intensification in antiretroviral-treated, HIV-infected patients with a suboptimal $CD4^+$ T cell response. *J. Infect. Dis.* 203, 960–968 (2011).

68 McMahon D, Jones J, Wiegand A *et al.* Short-course raltegravir intensification does not reduce persistent low-level viremia in patients with HIV-1 suppression during receipt of combination antiretroviral therapy. *Clin. Infect. Dis.* 50, 912–919 (2010).

69 Buzon MJ, Massanella M, Llibre JM *et al.* HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects. *Nat. Med.* 16, 460–465 (2010).

70 Yukl SA, Shergill AK, McQuaid K *et al.* Effect of raltegravir-containing intensification on HIV burden and T-cell activation in multiple gut sites of HIV-positive adults on suppressive antiretroviral therapy. *AIDS* 24, 2451–2460 (2010).

71 Teppler H, Brown DD, Leavitt RY *et al.* Long-term safety from the raltegravir clinical development program. *Curr. HIV Res.* 9, 40–53 (2011).

72 Lee FJ, Carr A. Tolerability of HIV integrase inhibitors. *Curr. Opin. HIV AIDS* 7, 422–428 (2012).

73 Moreno A, Quereda C, Montes M *et al.* Safe coadministration of raltegravir-based HAART in HIV-infected patients with HCV-cirrhosis receiving triple therapy with telaprevir or boceprevir. *J. Acquir. Immune. Defic. Syndr.* 61, e47–e49 (2012).

74 Miro JM, Ricart MJ, Trullas JC *et al.* Simultaneous pancreas-kidney transplantation in HIV-infected patients: a case report and literature review. *Transplant. Proc.* 42, 3887–3891 (2010).

75 Tricot L, Teicher E, Peytavin G *et al.* Safety and efficacy of raltegravir in HIV-infected transplant patients cotreated with immunosuppressive drugs. *Am. J. Transplant.* 9, 1946–1952 (2009).

76 Mayer KH, Mimiaga MJ, Gelman M *et al.* Raltegravir, tenofovir DF, and emtricitabine for postexposure prophylaxis to prevent the sexual transmission of HIV: safety, tolerability, and adherence. *J. Acquir. Immune Defic. Syndr.* 59, 354–359 (2012).

77 Abraham BK, Gulick R. Next-generation oral preexposure prophylaxis: beyond tenofovir. *Curr. Opin. HIV AIDS* 7, 600–606 (2012).

78 Wenning LA, Hanley WD, Brainard DM *et al.* Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. *Antimicrob. Agents Chemother.* 53, 2852–2856 (2009).

79 Grinsztejn B, De Castro N, Arnold V *et al.* A randomized multicentre open-label trial to estimate the efficacy and safety of two doses of raltegravir (RAL) to efavirenz (EFV) for the treatment of HIV-TB co-infected patients: results of the ANRS 12 180 Reflate TB trial. Presented at: *19th International AIDS Conference.* Washington, DC, USA, 22–27 July 2012 (Abstract THLBB01).

80 Westling K, Pettersson K, Kaldma A *et al.* Rapid decline in HIV viral load when introducing raltegravir-containing antiretroviral treatment late in pregnancy. *AIDS Patient Care STDS* 26, 714–717 (2012).

81 Colbers A, Moltó J, Ivanovic J *et al.* A comparison of the pharmacokinetics of raltegravir during pregnancy and post-partum. Presented at: *12th International Workshop on Clinical Pharmacology of HIV Therapy.* Miami, Florida, USA, 13–15 April 2011 (Poster 18).

82 Wenning LA, Friedman EJ, Kost JT *et al.* Lack of a significant drug interaction between raltegravir and tenofovir. *Antimicrob. Agents Chemother.* 52, 3253–3258 (2008).

83 Iwamoto M, Wenning LA, Petry AS *et al.* Minimal effects of ritonavir and efavirenz on the pharmacokinetics of raltegravir. *Antimicrob. Agents Chemother.* 52, 4338–4343 (2008).

84 Anderson MS, Kakuda TN, Hanley W *et al.* Minimal pharmacokinetic interaction between the human immunodeficiency virus nonnucleoside reverse transcriptase inhibitor etravirine and the integrase inhibitor raltegravir in healthy subjects. *Antimicrob. Agents Chemother.* 52, 4228–4232 (2008).

85 Crauwels H, Stevens M, De La Rosa G, Boven K. Absence of pharmacokinetic interaction between the NNRTI rilpivirine (TMC278) and the integrase inhibitor raltegravir. Presented at: *19th Conference on Retroviruses and Opportunistic Infections*. Seattle, WA, USA, 5–8 March 2012 (Abstract 617).

86 Iwamoto M, Wenning LA, Mistry GC *et al.* Atazanavir modestly increases plasma levels of raltegravir in healthy subjects. *Clin. Infect. Dis.* 47, 137–140 (2008).

87 Anderson M, Sekar V, Tomaka F. Pharmacokinetic evaluation of darunavir/ritonavir and raltegravir in healthy subjects. Presented at: *48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy/46th Infectious Diseases Society of America Meeting.* Washington, DC, USA, 25–28 October 2008 (Abstract A-962).

88 Rhame F, Long M, Acosta E. RAL-KAL: pharmacokinetics (PK) of coadministered raltegravir (RAL) and lopinavir-ritonavir (KAL) in healthy adults. Presented at: *AIDS 2008 XVII International AIDS Conference.* Mexico City, Mexico, 3–8 August 2008 (Abstract TUPE0075).

89 Hanley WD, Wenning LA, Moreau A *et al.* Effect of tipranavir-ritonavir on pharmacokinetics of raltegravir. *Antimicrob. Agents Chemother.* 53, 2752–2755 (2009).

90 Andrews E, Glue P, Fang J, Crownover P, Tressler R, Damle B. A pharmacokinetic study to evaluate an interaction between maraviroc and raltegravir in healthy adults. Presented at: *48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy/46th Infectious Diseases Society of America Meeting.* Washington, DC, USA, October 2008 (Abstract H-4055).

91 Brainard DM, Kassahun K, Wenning LA *et al.* Lack of a clinically meaningful pharmacokinetic effect of rifabutin on raltegravir: *in vitro*/*in vivo* correlation. *J. Clin. Pharmacol.* 51, 943–950 (2011).

92 de Kanter CT, Blonk MI, Colbers AP *et al.* Lack of a clinically significant drug–drug

interaction in healthy volunteers between the hepatitis C virus protease inhibitor boceprevir and the HIV integrase inhibitor raltegravir. *Clin. Infect. Dis.* 56, 300–306 (2013).

93 van Heeswijk R, Garg V, Boogaerts G *et al.* The pharmacokinetic interaction between telaprevir and raltegravir in healthy volunteers. LB A1-1738a. Presented at: *51st Interscience Conference on Antimicrobial Agents and Chemotherapy*. Chicago, IL, USA, 17–20 September 2012.

94 Iwamoto M, Wenning LA, Nguyen BY *et al.* Effects of omeprazole on plasma levels of raltegravir. *Clin. Infect. Dis.* 48, 489–492 (2009).

95 Towner W, Klein D, Kerrigan HL *et al.* Virologic outcomes of changing enfuvirtide to raltegravir in HIV-1 patients well controlled on an enfuvirtide based regimen: 24-week results of the CHEER study. *J. Acquir. Immune. Defic. Syndr.* 51, 367–373 (2009).

96 Martinez E, Larrousse M, Llibre JM *et al.* Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. *AIDS* 24, 1697–1707 (2010).

97 Ofotokun I, Sheth AN, Sanford SE *et al.* A switch in therapy to a reverse transcriptase inhibitor sparing combination of lopinavir/ritonavir and raltegravir in virologically suppressed HIV-infected patients: a pilot randomized trial to assess efficacy and safety profile: the KITE study. *AIDS Res. Hum. Retroviruses* 28, 1196–1206 (2012).

98 Nguyen A, Calmy A, Delhumeau C *et al.* A randomized cross-over study to compare raltegravir and efavirenz (SWITCH-ER study). *AIDS* 25, 1481–1487 (2011).

99 Lake JE, McComsey GA, Hulgan TM *et al.* A randomized trial of Raltegravir replacement for protease inhibitor or non-nucleoside reverse transcriptase inhibitor in HIV-infected women with lipohypertrophy. *AIDS Patient Care STDS* 26, 532–540 (2012).

100 Calin R, Paris L, Simon A *et al.* Dual raltegravir/etravirine combination in virologically suppressed HIV-1-infected patients on antiretroviral therapy. *Antivir. Ther.* 17, 1601–1604 (2012).

## Websites

101 Adolescents. PoAGfAa. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

102 Study of darunavir/r + tenofovir/emtricitabine vs. darunavir/r + raltegravir in HIV-infected antiretroviral naive subjects (ANRS 143). http://clinicaltrials.gov/show/NCT01066962