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

Ruxandra Calin¹ & Christine Katlama*¹,²,³

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-naïve 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
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 (C12) increase linearly, AUC ranges between 6.53 and 45.27 µM/(l.h) and C12 between 70.6 and 300.8 nM [13]. Protein-binding is 83%, steady state is achieved after 48-h and 95% inhibitory concentration (IC95) values in 50% human serum cell-cultures is 33 nmol/l corresponding to a target C12 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-naïve 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 UGT1A1-inducers (e.g., rifampicine) or inhibitors

<table>
<thead>
<tr>
<th>Table 1. The main drug–drug interactions of raltegravir.</th>
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<tr>
<td><strong>Co-medication</strong></td>
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<td>NRTIs</td>
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<td>Tenofovir</td>
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<td>Efavirenz</td>
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<td>Atazanavir/r</td>
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<td>Lopinavir/r</td>
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<td>Tipranavir/r</td>
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<td>CCR5 antagonist</td>
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<td>Maraviroc (300 mg b.i.d.)</td>
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<td>TB agents</td>
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<td>Rifampicine</td>
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<td>Rifabutine</td>
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<td>First-generation hepatitis C PIs</td>
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<td>Boceprevir</td>
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<td>Telaprevir</td>
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<td>Other agents</td>
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<td>Omeprazole</td>
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</table>

* /: 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 immunosuppressants, 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 609 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...
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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 naïve 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 naïve 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-naïve prospective
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

### Table 2. Raltegravir switch studies.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Number of patients</th>
<th>Study design</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
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<tbody>
<tr>
<td>Towner et al. (CHEER; 2009)</td>
<td>52</td>
<td>Multicenter, nonrandomized, open-label trial in patients switching from OBT + enfuvirtide to OBT + RAL</td>
<td>24 weeks: 94.2% (49 out of 52) of patients had HIV-1 RNA level &lt;50 or 75 copies/ml, depending on the assay used</td>
<td>[95]</td>
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<tr>
<td>Gallien et al. (EASIER-ANRS 138; 2011)</td>
<td>170</td>
<td>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)</td>
<td>48 weeks: 90% of patients in both the immediate and deferred groups had plasma HIV-1 RNA levels &lt;50 copies/ml</td>
<td>[63]</td>
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<tr>
<td>Eron et al. (SWITCHERK 1 and 2; 2010)</td>
<td>707</td>
<td>Multicenter, randomized, double-blind, double-dummy, noninferiority trials in patients switching from OBT + LPV/r to OBT + RAL vs continuing OBT + LPV/r</td>
<td>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 &lt;50 copies/ml; noninferiority not proven</td>
<td>[43]</td>
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<tr>
<td>Martinez et al. (SPIRAL; 2010)</td>
<td>282</td>
<td>Multicenter, randomized, open-label noninferiority trial in patients switching from OBT + PI/r to OBT + RAL vs continuing OBT + PI/r</td>
<td>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 &lt;50 copies/ml; difference: 1.8%; 95% CI: -3.5–7.5 – noninferiority demonstrated</td>
<td>[96]</td>
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<tr>
<td>Ofotokun et al. (KITE; 2012)</td>
<td>60</td>
<td>Single-center, randomized, open-label pilot in patients switching to LPV/r + RAL or continuing baseline ART</td>
<td>48 weeks: 92% of the LPV-r/RAL arm and 88% baseline ART arm had plasma HIV-1 RNA levels &lt;50 copies/ml</td>
<td>[97]</td>
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<tr>
<td>Nguyen et al. (SWITCH-ER; 2011)</td>
<td>57</td>
<td>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</td>
<td>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)</td>
<td>[98]</td>
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<tr>
<td>Lake et al. (2012)</td>
<td>39</td>
<td>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</td>
<td>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</td>
<td>[99]</td>
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<tr>
<td>Calin et al. (2012)</td>
<td>18</td>
<td>Single-center, observational study in patients switching to dual RAL/etravirine therapy</td>
<td>48 weeks: ITT 83.3% (15 out of 18) and PP 100% (15 out of 15) patients had plasma HIV-1 RNA levels &lt;50 copies/ml</td>
<td>[100]</td>
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Notes: 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.
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 naïve 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 naïve 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.

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