Research Review
PRODUCT REVIEW

Raltegravir (Isentress®)

About the Reviewer

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Rupert Handy is a New Zealand trained Infectious Diseases Physician. After undergraduate training at the University of Otago Medical School, he completed post-graduate training in Medicine and Infectious Diseases in Auckland. He also worked in the United Kingdom prior to his appointment as a Consultant Physician at Auckland City Hospital in 2006. His current practice interests include HIV medicine, infections of the immunocompromised host and antimicrobial stewardship. He is a member of the Australasian Society for Infectious Diseases, The Australasian Society for HIV Medicine and the HIV Medicine Association.

The Infectious Diseases Unit and Community HIV Team at Auckland City Hospital (staffed by 6 specialist physicians, 4 specialist nurses and a dedicated social worker) works closely with Auckland Sexual Health Services, Starship Childrens' Health and Womens' Health to deliver multidisciplinary holistic healthcare to all people living with HIV in Auckland and The North.

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Research Review publications are intended for New Zealand medical professionals.

This review discusses the evidence in support of the use of raltegravir (Isentress®), an integrase strand transfer inhibitor (INSTI) that has increased treatment options for the management of both treatment-experienced adult patients with multidrug-resistant HIV-1 strains and treatment-naïve patients.

Access to care and antiretroviral therapy

More than 34 million people worldwide were living with HIV at the end of 2010, an estimated 15 million in low- and middle-income countries and needing treatment.[1] Access to treatment has improved over recent years; 1.2 million people received HIV antiretroviral therapy (ART) regimens for the first time in 2009 alone – an increase in the number of people receiving treatment of 30% in a single year.[1] Globally, the number of people receiving ART regimens has increased 13-fold since 2004 to more than 5 million people in low- and middle-income countries.[1] This expansion in treatment access has contributed to a 19% decline in deaths among people living with HIV between 2004 and 2009.[1] However, despite these dramatic gains in treatment access, 10 million people with HIV who were eligible for treatment under the new WHO guidelines were not receiving it, as of December 2010.[1]

In June 2010, the UNAIDS Secretariat and WHO launched *Treatment 2.0*, an initiative designed to achieve and sustain universal access and maximise the preventive benefits of ART.[2] *Treatment 2.0* recognises and recommends ART as a prevention tool. The document includes five key recommendations for invigorating the global HIV/AIDS response:

1. Optimise drug regimens
2. Provide access to point-of-care diagnostics
3. Reduce costs
4. Strengthen delivery systems
5. Mobilise communities.

UNAIDS suggests that if countries provide ART regimens to all people living with HIV who need treatment, following revised WHO treatment guidelines, the *Treatment 2.0* strategy could prevent up to one million new HIV infections each year and as many as 10 million AIDS-related deaths by 2025.[2] ART regimens have significantly reduced the morbidity and mortality associated with HIV infections. However, drug resistance commonly emerges with suboptimal adherence to ART regimens or exposure to inadequately potent (e.g., single- or two-drug) ART regimens.[3] In addition, transmission of drug-resistant HIV strains is well documented and associated with suboptimal virologic response to initial ART.[3] Evidence from the USA and Europe indicates that between 6% and 16% of transmitted virus will be resistant to at least one antiretroviral agent,[4-8] and that between 3% and 5% of transmitted viruses exhibit resistance to drugs from more than one class.[7] Among viraemic treatment-experienced patients in the USA, as many as 70% have been estimated to be infected with drug-resistant virus and more than 13% of these patients are believed to be resistant to at least 3 classes of antiretrovirals.[9] Of great concern, a clear pattern of increasing resistance to ART regimens has been observed in low-income settings, which potentially threatens the success of the worldwide HIV-control agenda.[3] Access to care and effective ART regimens are urgently needed to have maximum impact on preventing progression to disease and death, as well as HIV transmission.

HIV/AIDS in New Zealand

The latest figures from AIDS New Zealand* report that:

- 149 people were diagnosed with HIV in New Zealand in 2010, through antibody testing.
- 90 were men infected through sex with other men, 35 (17 men and 18 women) through heterosexual contact, and one child through mother-to-child transmission. The means of infection has not yet been established for the remaining people.
- A further 36 people were reported with HIV infection through viral load testing. These were mostly people who had been previously diagnosed overseas.
- 39 people were notified with AIDS in 2010 because of progression to AIDS-defining illnesses.

The current number of people with HIV under care in New Zealand is estimated to be over 1,500, of whom around 1,400 were receiving fully funded cART, based on PHARMAC data at the end of 2010. A significant number of people living with HIV in New Zealand have yet to be diagnosed.

* Ministry of Health. AIDS New Zealand Newsletter. Issue 67, February 2011.

Raltegravir: novel mechanism of action

A key step in HIV-1 viral replication is the integration of viral complementary DNA into host cell genome using the viral integrase and represents a novel, clinically validated target to block HIV-1 replication.[10] The integrase strand transfer inhibitor (INSTI), raltegravir (RAL), is the first of a new class of HIV-1 therapies to be approved for use in the treatment of HIV-1 infection and, as a result of a different mechanism to other ART agents, has good activity against HIV-1 strains that exhibit resistance to conventional ART agents. Notably, *in vitro* and *in vivo* studies have demonstrated that RAL has no inductive or inhibitory potential against a number of cytochrome P450 (CYP) enzymes (including CYP3A), major uridine diphosphate glucuronosyltransferase (UGT) isozymes and P-glycoprotein, in contrast to most of the currently marketed non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs).[11] Consequently, specific contraindications have been issued in regard to inducers and inhibitors of CYP enzymes, which limits co-administration of ART or supportive agents. No such restrictions are associated with RAL, making it an attractive choice of ART agent for clinicians when considering treatment regimens for their patients.

RAL was initially approved by the US FDA in October 2007 for use in treatment-experienced adult patients who have HIV-1 strains resistant to multiple antiretroviral agents. In July 2009, the FDA granted expanded approval for use of RAL in patients who have not yet been treated for HIV infection. Large phase 3 studies of RAL in treatment-naive[12-16] and treatment-experienced patients[17-19] have demonstrated rapid suppression by RAL-based combination regimens of HIV RNA viral loads below the limit of detection in most patients.

Advantages of raltegravir

Raltegravir, an integrase inhibitor, has good activity against HIV-1 strains that exhibit resistance to conventional ART agents. Raltegravir-based combination regimens have demonstrated rapid suppression of HIV RNA viral loads below the limit of detection in treatment-experienced and treatment-naïve patients.[12-19]

Pharmacological properties of raltegravir

- RAL is an HIV integrase strand transfer inhibitor active against viral HIV-1.[20]
- RAL has potent *in vitro* activity against a variety of HIV-1 clinical isolates.[20]
- RAL shows additive-to-synergistic *in vitro* antiretroviral activity in combination with nucleoside analogue reverse transcriptase inhibitors (NRTIs), NNRTIs, PIs and a fusion inhibitor.[20]
- HIV viruses with mutations at any of the signature domains Q148 H, K, R or N155H have reduced susceptibility to RAL.
- RAL had no effect on the QTc interval in healthy volunteers in a placebo-controlled, crossover study.[20]
- Bioavailability of RAL has not been adequately described; it is rapidly absorbed with a T_{max} of approximately 3 hours post-dose in the fasted state.[20] The half-life ranges from 1 to 9 hours.[20]
- Twice-daily dosing rapidly achieves steady-state raltegravir concentrations, within approximately the first 2 days of dosing.[20] There is little to no accumulation in AUC and C_{max} and evidence of slight accumulation in C_{12}.[20]
- RAL can be taken independently of food.[20]
- Protein binding approximates 80% over the concentration range of 2–10 µmol/L.[20]
- RAL is cleared by UGT1A1 glucuronidation and was eliminated predominantly in the faeces (51%) and urine (32%) of healthy volunteers following an oral dose of radiolabelled RAL.[20]
- No clinically important pharmacokinetic differences were observed in evaluations of the effects of gender, age, race, body mass index (BMI), body weight, mild to moderate hepatic insufficiency and severe renal insufficiency; dosage adjustments are not necessary in these patient groups.[20]
- UGT1A1 polymorphisms do not alter PK in a clinically meaningful way, but co-prescription of UGT1A1 inducers or inhibitors (such as rifampicin) may result in undesired alteration of PK.[20]
- **The favourable clinical pharmacology, adverse effect and drug interaction profile of RAL make it suitable for widely diverse patient populations, when co-administered with other antiretrovirals and supportive medications, without restrictions or dose adjustment.**

Therapeutic efficacy of raltegravir

The therapeutic efficacy of RAL in combination with other antiretroviral agents has been evaluated in treatment-naïve patients with HIV-1 infection[12-16] and in treatment-experienced patients with multidrug antiretroviral resistance.[17-19]

RAL in antiretroviral-naïve patients

Results from the phase 3 STARTMRK trial established the non-inferiority of RAL to efavirenz (EFV) (each administered in combination with fixed-dose tenofovir/emtricitabine [TDF/FTC]) in treatment-naïve patients with HIV-1 infection.[12] After 48 weeks' treatment, 86.1% of the RAL group and 81.9% of the EFV group had a RNA viral load of <50 copies/mL. RAL-treated patients had a modestly, but statistically significant, better CD4 count response and faster viral suppression, as well as a more favourable safety profile with minimal lipid effects and fewer CNS adverse events, compared with EFV-treated patients, although both treatments were well tolerated.

An additional, detailed 48-week analysis on subsets of STARTMRK participants determined the association between virologic and immunologic outcomes and several baseline demographic and prognostic factors.[12] For every baseline characteristic examined (HIV-1 RNA viral load, CD4 count, history of AIDS diagnosis, hepatitis status, age, sex, race, region, and viral subtype), the RAL and EFV arms demonstrated consistent and very similar virologic and immunologic activity. In some of these subsets, CD4 count changes favoured RAL, although differences were modest and significant only in subgroups with a larger sample size. In patients with very low pretreatment CD4 counts (≤50 cells/µL), both regimens performed slightly less well than in patients with higher CD4 counts, but without any significant difference between the arms.

96-, 156-week (3-year) and 192-week follow-up data from the STARTMRK trial consistently demonstrated a sustained antiviral efficacy and safety profile of RAL.[13-15] The rates of sustained virologic response and immune restoration observed with RAL was at least equivalent to EFV through 156 weeks of therapy. Patients in both treatment arms experienced similar changes in body fat composition. In addition, although both regimens were well tolerated, RAL was associated with fewer drug-related clinical adverse events and smaller elevations in lipid levels.

The phase 2 Protocol 004 study compared RAL with EFV (both with tenofovir/lamivudine [TDF/3TC]) in treatment-naïve patients and demonstrated sustained efficacy and good tolerability through 240 weeks (5 years) of treatment.[16] At 240 weeks, 68.8% of RAL-treated patients and 63.2% of EFV-treated patients had HIV RNA <50 copies/mL. CD4 counts continued to increase through 5 years in both groups. The safety profile of RAL at week 240 was similar to that at week 144 (3 years) and week 192 (4 years). Drug-related adverse events were less frequent with RAL than with EFV. In addition, RAL was associated with minimal effects on LDL cholesterol and triglyceride levels.

RAL in antiretroviral-experienced patients

The recently released combined analysis at week 192 of the identically-designed phase 3 BENCHMRK-1 and BENCHMRK-2 trials confirmed persistent, potent antiviral effects of orally administered RAL 400 mg twice daily in combination with optimised background therapy (OBT) in treatment-experienced patients with HIV-1 infection, evidence of viral replication and HIV-1 strains resistant to multiple ART agents.[19] RAL was associated with superior virologic responses and greater CD4 increases than placebo: 45% and 16% of patients achieved viral RNA <50 copies/mL, 49% and 18% viral RNA <400 copies/mL, and CD4 increases of 164 and 55 cells/uL, respectively. An exploratory analysis that assessed late viral RNA and CD4 responses in patients originally randomised to RAL categorised patients into one of 3 groups by viral RNA between weeks 16 and 48: 1) continuous suppression (CS; <50 copies/mL always); 2) low level viraemia (LLV; <400 copies/mL throughout and >50 copies/mL at least once); 3) not suppressed (NS; >400 copies/mL at least once). In this analysis, baseline CD4 count was higher and viral RNA lower for the CS group compared to the LLV group. At week 192, 79%, 70% and 26% of patients in the CS, LLV and NS groups, respectively, had viral RNA <50 copies/mL. Changes from baseline in CD4 cell count were 222, 239 and 98 for the CS, LLV and NS groups, respectively. The RAL-containing regimen was generally well tolerated, with few patients discontinuing because of adverse events.

Switching to raltegravir

The Easier-ANRS 138 study was designed to determine the efficacy and safety of switching from enfuvirtide (T-20) to RAL in 170 virologically suppressed (HIV-1 RNA <400 copies/mL), multidrug-resistant patients who were receiving a stable T-20-containing regimen for an average of 2.5 years.[21] They were randomised in a 48-week prospective, open-label study to continue T-20 or switch to RAL at standard doses (immediate group), while other agents in the regimen remained unchanged. At week 24, patients in the maintenance arm also switched to RAL (deferred group). The on-treatment analysis at week 48 revealed that only one patient in the immediate group, with a baseline genotypic susceptibility score (GSS) of 0, had developed virologic failure (a confirmed RNA viral load ≥400 copies/mL up to week 48). At week 48, 90% of patients in both the immediate and deferred groups had RNA viral levels <50 copies/mL. Median CD4 counts remained stable during follow-up. A total of 12 of 66 (18.2%) patients receiving a regimen combining RAL and ritonavir-boosted tipranavir (TPV/r) experienced ALT elevations, which led to a switch from TPV to darunavir (DRV) in 8 cases, without discontinuation of RAL. From week 24 to 48, the incidence of grade 3 or 4 laboratory abnormalities was 12% and the incidence of grade 3 or 4 clinical adverse events was 7%.

Two identical phase 3 studies, SWITCHMRK 1 and 2, randomised patients aged ≥18 years on a stable, virologically suppressive lopinavir/ritonavir (LPV/r) regimen to continue LPV/r or switch to RAL while maintaining background NRTIs.[22] At week 12, improvements in lipid parameters from baseline were significantly greater in the RAL group than in the LPV/r group in each study, but the study was discontinued at week 24; 84.4% of patients in the RAL group had an HIV viral load of <50 copies/mL compared with 90.6% of patients in the LPV/r group, demonstrating that the trial failed to meet the prespecified virologic endpoint for noninferiority. Clinical and laboratory adverse events occurred at similar frequencies in the treatment groups. No serious drug-related adverse events or deaths occurred.

The SPIRAL trial investigated the efficacy of switching patients with sustained virologic suppression on ritonavir-boosted PI-based therapy to RAL.[23] At 48 weeks, 89.2% (RAL-based therapy) and 86.6% (ritonavir-boosted PI-based therapy) of the patients remained free of treatment failure; corresponding values for patients who remained free of virologic failure were 96.9% and 95.1%, respectively. Switching to RAL was associated with significant decreases in plasma lipids and total-to-HDL cholesterol ratio compared with continuing ritonavir-boosted PI. Severe adverse events and study drug discontinuations due to any adverse event occurred in 4% and 2% of the patients in each group.

Important limitations of RAL therapy

The phase 3 QDMRK trial evaluated the efficacy and safety of once-daily (QD) RAL versus the approved twice-daily (BID) dose, each combined with TDF/FTC.[24] Patients were antiretroviral treatment-naïve with HIV-1 RNA 5,000 copies/mL at baseline and without baseline resistance to TDF or FTC. At week 48, RAL QD did not meet the prespecified non-inferiority boundary relative to RAL BID for a difference in proportion of patients with HIV-1 RNA <50 copies/mL. Compared with RAL BID, the RAL QD regimen was associated with a significantly shorter time to loss of virologic response and a higher rate of virologic failure. Resistance to RAL and FTC was also more frequent among patients with virologic failure in the RAL QD arm versus the RAL BID arm. In a pharmacokinetic subset analysis, RAL trough concentrations (C_{trough}) were lower with QD than with BID dosing, while RAL AUC and C_{max} concentrations were higher with QD than with BID dosing. There was a decreased virologic efficacy in the lowest C_{trough} quartile in the RAL QD arm; this was not observed with the RAL BID arm.

The ACTG A5262 trial investigated the virologic efficacy of DVR/r plus RAL, with the expectation that this combination of potent, well-tolerated antiretrovirals would be very effective.[25] At baseline, the patients had no DRV or RAL resistance-associated mutations. The treatment regimen was associated with a substantial virologic failure rate at weeks 24 and 48: only 79% and 71% of patients, respectively, had HIV RNA levels of <50 copies/mL. By week 48, a total of 28 subjects had confirmed virologic failure. Of 15 patients who underwent resistance testing, 5 demonstrated integrase resistance. Virologic failure was associated with higher baseline HIV RNA and with lower CD4 counts. In addition, all those with emergent integrase resistance had HIV RNA of >100,000 copies/mL at baseline.

EFFICACY AND SAFETY OF RALTEGRAVIR IN MAJOR CLINICAL TRIALS

Raltegravir (RAL)-based therapy demonstrates superior virologic suppression and immunologic response compared with efavirenz (EFV)-based therapy, with a favorable metabolic profile through 4 years in treatment-naïve patients: 192 week results from STARTMRK[15]

Summary: STARTMRK randomised 563 previously untreated patients with HIV-1 RNA levels >5000 copies/mL and without baseline resistance to EFV, TDF, or FTC to receive RAL 400 mg twice daily or EFV 600 mg once daily, each in combination with fixed-dose TDF/FTC and placebo. At week 192 counting noncompleters as failures, significantly more patients in the RAL arm than in the EFV arm had RNA viral levels <50 copies/mL (76.2% vs 67.0%; p<0.001). Mean changes from baseline CD4 count were 361 and 301 cells/mm^3 in the RAL and EFV arms, respectively (p<0.001). RAL was associated with significantly fewer drug-related clinical adverse events, compared to EFV (50.2% vs 80.1%, respectively; p<0.001), with discontinuations due to adverse events in 5.0% and 8.2% of patients, respectively, although this difference was not significant. RAL was also associated with smaller elevations in fasting lipids compared with those in the EFV group; the change from baseline in the total cholesterol:HDL cholesterol ratio was –0.17 for the RAL arm and 0.02 for the EFV arm (p=0.177).

Comment from Rupert Handy: These data, presented as a poster at IDSA 2011 and awaiting publication, provide intriguing insight into the long-term efficacy of RAL. Sustained virologic suppression and CD4 responses in the EFV group did not meet the prespecified criteria for non-inferiority to the RAL group. It seems likely that both tolerability and barriers to resistance are important to the better virologic response seen with RAL, but there may be other factors contributing to the effect on CD4 count. The study is planned to run for 5 years.

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[26]

Summary: The parallel phase 3 BENCHMRK-1&2 studies randomised HIV-infected patients with triple-class resistance (genotypic or phenotypic resistance to ≥1 PI, NRTI, and NNRTI) and HIV-1 RNA >1,000 copies/mL to receive RAL 400 mg twice daily or placebo, each combined with OBT. At week 96, virologic and immunologic responses were consistent between the BENCHMRK studies. In a combined analysis of efficacy outcomes, 57% of RAL-treated patients achieved viral suppression to <50 copies/mL at week 96, compared with 26% of patients in the placebo group (p<0.001); 61% and 28%, respectively, achieved RNA viral levels <400 copies/mL (p<0.001). Mean changes from baseline in $\log_{10}$ RNA levels and CD4 counts were significantly greater at week 96 in the RAL group than in the placebo group (RNA level: –1.5 $\log_{10}$ copies/mL vs –0.6 $\log_{10}$ copies/mL; CD4 count: 123 cells/mm^3 vs 49 cells/mm^3; p<0.001 for both comparisons).

Efficacy analyses by baseline prognostic factors demonstrated a consistent treatment advantage of RAL over placebo, even in patients with high baseline RNA viral levels, low baseline CD4 counts, and those with low genotypic and phenotypic sensitivity scores. Among patients receiving multiple drugs in their OBT, such as those with genotypic and phenotypic sensitivity scores of ≥2, RAL was associated with a trend toward modestly higher numerical response rates, compared with placebo. Additional efficacy analyses, by viral subtype, age, sex, and race, demonstrated consistently greater response rates in the RAL group than in the placebo group.

RAL was well tolerated in these trials. Frequencies and exposure-adjusted rates of clinical adverse events and grade 3 and 4 laboratory abnormalities were similar in the RAL and placebo groups, with few discontinuations of treatment because of adverse events. In addition, the development of cancer was comparable between the RAL and placebo groups; exposure-adjusted rates for new, recurrent, or progressive cancer during the double-blind phase were 3.0 cases per 100 person-years in the RAL group and 2.6 cases per 100 person-years in the placebo group (RR 1.1; 95% CI, 0.5 to 3.1).

Comment from Rupert Handy: The late follow-up data from the pivotal RAL registration studies in highly treatment-experienced patients confirmed efficacy and safety compared to OBT alone after 96 weeks' treatment with 57% v. 26% achieving virologic suppression overall. But more importantly for me, for the patient subgroups also receiving DRV/r and T-20 or with a GSS ≥1, the results were 79% and 72%, respectively, setting a new benchmark for salvage therapy comparable to previously untreated patients. The study was not powered to investigate mortality but there was a trend to reduced AIDS-Defining Conditions or death as shown by an RR of 0.49 (95% CI, 0.22 to 1.12).

Switch from enfuvirtide to raltegravir in highly treatment experienced HIV-1 infected patients: a randomized open-label non-inferiority trial, Easier-ARNS138[21]

Summary: This trial examined the efficacy and safety of substituting RAL for T-20 in virologically suppressed, multidrug-resistant patients with HIV-1 infection. The trial enrolled 170 patients with triple-class failure or intolerance (PIs, NRTIs, and NNRTIs) who had been receiving a suppressive T-20-based regimen for ≥3 months and had achieved HIV-1 RNA <400 copies/mL for ≥3 months. None of the patients had previous experience of integrase inhibitor use. In the on-treatment analysis at week 48, only one patient in the immediate arm, with a baseline GSS of 0, developed virologic failure at week 8, without emergence of RAL-associated resistance mutations. Following treatment changes, this patient achieved a viral RNA level <50 copies/mL at week 48 on a RAL-based regimen. The overall rate of virologic failure (viral RNA level ≥400 copies/mL at 48 weeks) was 0.6%. In the intent-to-treat analysis, the rate of virologic failure in the immediate arm was 1.2%. A total of 90% of patients overall had viral RNA levels <50 copies/mL at 48 weeks. While receiving the RAL-based regimen, 30.4% of patients experienced at least one transient viraemia >50 copies/mL, but only 1.8% (3 patients), including the patient with virologic failure, developed viral RNA levels ≥400 copies/mL. No AIDS-defining events or deaths occurred during the study. From week 24 to 48, while all patients were receiving a RAL-based regimen, the incidence of grade 3 or 4 laboratory abnormalities was 12% and the incidence of grade 3 or 4 clinical adverse events was 7%. These rates did not differ significantly from those observed in the first 24 weeks of the trial among patients in the immediate arm. Of the 12 patients who experienced ALT elevations while receiving RAL and TPV up to week 48, 9 had grade 3 or 4 ALT elevations, which led to a switch from TPV to DRV in 8, while maintaining RAL in all.

Comment from Rupert Handy: This study provides supportive efficacy data for simplifying ART by switching T-20 to RAL, with only 1 virologic failure occurring in a patient with a low GSS. But it is important to also recognise the contribution of OBT to success – use of a boosted PI was nearly universal and the majority (86%) of patients had a GSS ≥1.

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[22]

Summary: The SWITCHMRK 1 and 2 phase 3 trials compared substitution of RAL for LPV/r with continuation of LPV/r in HIV-infected patients with stable viral suppression on LPV/r-based combination therapy. A total of 707 patients aged ≥18 years with documented HIV viral loads below the limit of assay quantification for ≥3 months while on a LPV/r-based regimen were randomised to switch from LPV/r to RAL (400 mg twice daily) or to remain on LPV/r (two 200 mg/50 mg tablets twice daily), while continuing background therapy consisting of ≥2 nucleoside inhibitors or NRTIs. Primary endpoints were the mean percentage change in serum lipid levels from baseline to week 12, and the proportion of patients with viral loads <50 copies/mL at week 24. At week 12, percentage changes from baseline in lipid levels were significantly greater (p<0.0001) in the RAL group than in the LPV/r group in each study, yielding combined results for total cholesterol –12.6% vs 1.0%, non-HDL cholesterol –15.0% vs 2.6%, and triglycerides –42.2% vs 6.2%, respectively. At week 24, 84.4% of patients in the RAL group and 90.6% of patients in the LPV/r group had viral loads <50 copies/mL. Clinical and laboratory adverse events occurred at similar frequencies in the treatment groups. There were no serious drug-related adverse events or deaths. The only drug-related clinical adverse event of moderate to severe intensity reported in ≥1% of either treatment group was diarrhoea, which occurred in 10 patients in the LPV/r group (3%) and no patients in the RAL group.

Comment from Rupert Handy: Switching away from the ritonavir-boosted protease lopinavir to RAL resulted in a clinically useful improvement in lipid profiles, which may benefit patients with metabolic complications or vascular disease. However, the study was terminated after the 24-week analysis because of lower than expected efficacy of RAL for the endpoints of virologic failure and time to virologic failure. Subgroup analyisis indicated that failure after switch to RAL was more likely for patients with a history of virologic failure or treatment experience. In this group of patients RAL may not be a suitable alternative to a boosted protease.

Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study[23]

Summary: The 48-week SPIRAL trial involved 273 adults with plasma HIV RNA <50 copies/mL for ≥6 months on ritonavir-boosted PI-based therapy, who were randomised to switch from the ritonavir-boosted PI to RAL or to continue on ritonavir-boosted PI-based therapy. At 48 weeks, 89.2% (RAL-based therapy) and 86.6% (ritonavir-boosted PI-based therapy) of the patients remained free of treatment failure; corresponding values for patients who remained free of virologic failure were 96.9% and 95.1%, respectively. Switching to RAL was associated with significant decreases in plasma lipids and the total-to-HDL cholesterol ratio, compared with continuing ritonavir-boosted PI therapy. Severe adverse events and study drug discontinuations due to any adverse event occurred in 4% and 2% of the patients in each group.

Comment from Rupert Handy: In contrast to SWITCHMRK, this smaller randomised open-label study with a longer follow-up period confirmed improvements in lipid profiles after switching from a range of boosted proteases to RAL, but found no difference in virologic efficacy for the entire cohort or subgroups with prior treatment experience or virologic failure. Methodological and population differences may account for the result.

Raltegravir once daily or twice daily in previously untreated patients with HIV-1: a randomised, active-controlled, phase 3 non-inferiority trial[24]

Summary: QDMRK evaluated the safety and efficacy of once-daily RAL (800 mg QD) and twice-daily RAL (400 mg BID) regimens in treatment-naive patients with HIV RNA levels >5,000 copies/mL and no resistance to TDF or FTC. Each RAL arm was administered with TDF/FTC. Of 382 once-daily and 388 twice-daily RAL-treated patients, 40% and 39% had baseline HIV RNA >100,000 copies/mL, respectively. At week 48, 13.9% of patients in the once-daily arm versus 9.0% of the twice-daily arm experienced virologic failures (non-response or rebound). Of patients with available resistance data, there were 9 vs 2 patients from the once-daily and twice-daily groups, respectively, with integrase- (and FTC)-resistant virus. Higher C_{trough} and C_{all} (geometric mean of all sparse pharmacokinetics for an individual) were associated with a greater probability of a successful treatment outcome. Serious clinical adverse events and discontinuations occurred at a similar and infrequent rate in both arms.

Comment from Rupert Handy: QD-dosed RAL was inferior to BD dosing for the prespecified MIT 48-week endpoint of virologic failure, and time to virologic response was longer and time to virologic failure shorter, for the QD group. Interpretation of the PK substudy suggests that the explanation is unfavourable pharmacodynamics for QD dosing – which is not recommended. However, BD dosing resulted in a remarkable 91% virologic response, confirming the efficacy of RAL as first-line treatment.

Results from a single arm study of darunavir/ritonavir plus raltegravir in treatment-naïve HIV-1-infected patients (ACTG A5262)[25]

Summary: This phase 2b study enrolled 112 antiretroviral-naïve patients with HIV-1 infection, none of whom had DRV or RAL resistance-associated mutations at study entry. All received once-daily darunavir/ritonavir (DRV/r) 800/100 mg plus twice-daily RAL 400 mg combination therapy. Virologic failure was defined as confirmed plasma HIV-1 RNA ≥1,000 copies/mL at week 12 or a >0.5 $\log_{10}$ copies/mL increase from week 4 to 12, or >50 copies/mL at or after week 24. In an intention-to-treat analysis that ignored missing data or off-study patients, 79% had undetectable HIV RNA at week 24, falling to 71% by week 48. The virologic failure rate was 16% by week 24 (11 patients failed to suppress and 6 rebounded), rising to 26% by week 48 (11 additional rebounds). Viral load at virologic failure was 51–200 copies/mL in 17/28 failures. Adjusting for age and sex, virologic failure was associated with baseline viral load >100,000 copies/mL (HR 3.76; p=0.004) and lower CD4 count (0.77 per 100 cells/mm^3 increase; p=0.037). When trough RAL concentrations were included as a time-varying covariate in the analysis, virologic failure remained associated with baseline viral load >100,000 copies/mL (HR 4.67; p<0.001) while RAL concentrations below detection limit in plasma at one or more previous visits was associated with increased hazard (HR 3.42; p=0.006). Five of 25 patients who underwent resistance testing demonstrated integrase resistance, all 5 patients had baseline viral load of >100,000 copies/mL at baseline; none developed DRV-associated mutations.

Comment from Rupert Handy: Class-sparing dual therapy has conceptual advantages for treatment simplification or when adherence and drug intolerances are important considerations. In this phase 2 study, the combination of RAL and DRV/r had a poor virologic response and high rate of failure after 48 weeks in treatment-naïve patients, especially in the high viral load strata, with detection of integrase resistance in 20% of those tested. Dual therapy is not recommended in this setting.

Guidelines on the use of raltegravir

In the most recent recommendations of the International AIDS Society-USA Panel, RAL is listed as a recommended key third agent for use with a dual NRTI component in an initial ART regimen and is considered a suitable third agent for patients with high cardiovascular risk or chronic kidney disease.[27]

In the most recent recommendations issued by the US Department of Health and Human Services, the Panel lists RAL plus TDF/FTC as one of the preferred initial combination regimens for antiretroviral-naïve patients, with reference to clinical trial data on RAL-based regimens that have resulted in suppression of HIV RNA levels and CD4 count increases in a large majority of patients.[11]

In regard to results from clinical trials that have investigated replacing a boosted PI with RAL in virologically suppressed patients, the Panel suggests that in ART-experienced patients, RAL should be used with caution as a substitute for a boosted PI. The Panel adds that this strategy should be avoided in patients with documented NRTI resistance unless there are other fully active drugs in the regimen.

CONCLUSION (Rupert Handy)

As the first-in-class INSTI, raltegravir has been part of a recent revolution in ART heralding hope with effective and durable new options for treatment-experienced patients with multiply-resistant HIV. It is now realistic to achieve the same goals for these patients as for those who are treatment-naïve. Safety and efficacy has now been observed in practice for nearly five years. It has also proved to be an excellent first-line option in conjunction with tenofovir and emtricitabine – but for most clinicians it is especially useful when co-morbidity, co-prescribing, drug intolerance or resistance are issues of concern. Recent data provide further valuable insight for clinical practice; raltegravir is suitable when simplification of an injectable regimen is required, or for mitigation of metabolic adverse effects. But the importance of twice-daily dosing and careful optimisation of the backbone in order to maintain a high barrier to resistance and achieve the best results has been clarified.

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