Optimal use of raltegravir (Isentress®) in the treatment of HIV-infected adults – Canadian consensus guidelines

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BACKGROUND AND OBJECTIVES: A meeting of a Canadian group with significant experience and knowledge in HIV management, consisting of five physicians, a pharmacist and an AIDS researcher, was convened. Their goal was to develop guidance for Canadian HIV-treating physicians on the appropriate use of raltegravir (MK-0518, Isentress®, Merck Frosst Canada Inc) in HIV-infected adults.

METHODS: Evidence from the published literature and conference presentations, as well as expert opinions of the group members, was considered and evaluated to develop the recommendations. Feedback on the draft recommendations was obtained from this core group, as well as from five other physicians and scientists across Canada with expertise in HIV treatment and antiretroviral drug resistance, and experience in the use of raltegravir. The final recommendations represent the core group's consensus agreement once all feedback was considered.

RESULTS/CONCLUSIONS: Recommendations were developed to guide physicians in the optimal use of raltegravir. The issues considered included raltegravir's role in overall treatment strategy, efficacy, durability of effect, rate of viral load reduction, resistance, safety/toxicity, pharmacokinetics and drug interactions.

Key Words: HIV; Integrase inhibitors; Raltegravir; Recommendations; Resistance; Treatment

Treatment of HIV infection has evolved considerably over time. For most patients in developed countries, HIV infection has become a chronic disease that is treated with antiretroviral medications on an ongoing basis. Life expectancy in individuals on combination antiretroviral therapy in high-income countries has increased such that their average life expectancy at age 20 is 49.4 years, two-thirds of that in the general population (1). Recently updated guidelines recommend initiation of therapy for asymptomatic patients with higher CD4 cell counts than previously indicated (up to 350 cells/mm³) (2-4), in part because of evidence that delayed initiation of antiretroviral therapy until CD4 cell count falls below 250 cells/mm³ was associated with serious morbidities

L'utilisation optimale de raltégravir (Isentress®) pour le traitement d'adultes infectés par le VIH : Lignes directrices consensuelles canadiennes

HISTORIQUE ET OBJECTIFS : On a organisé la rencontre d'un groupe canadien possédant une grande expérience et des connaissances importantes en matière de prise en charge du VIH, composé de cinq médecins, d'un pharmacien et d'un chercheur sur le sida. Ce groupe visait à préparer des lignes directrices à l'intention des médecins canadiens traitant le VIH quant à l'utilisation convenable du raltégravir (MK-0518, Isentress®, Merck Frosst Canada Inc.) chez des adultes infectés par le VIH.

MÉTHODOLOGIE : On a tenu compte des données probantes tirées de publications et de présentations dans le cadre de congrès et conférences ainsi que de l'opinion d'expert des membres du groupe et on les a évaluées pour élaborer les recommandations. On a obtenu les commentaires de ce groupe au sujet de la première version des recommandations, de même que ceux de cinq autres médecins et scientifiques du Canada possédant des compétences dans le traitement du VIH et de la résistance antirétrovirale ainsi que de l'expérience dans l'utilisation du raltégravir. Les recommandations définitives représentent le consensus du groupe principal après l'évaluation de tous les commentaires.

RÉSULTATS ET CONCLUSIONS : On a préparé des recommandations pour orienter les médecins quant à l'utilisation optimale du raltégravir. Les enjeux examinés incluaient le rôle du raltégravir dans la stratégie globale de traitement, l'efficacité, la durabilité de l'effet, le taux de réduction de la charge virale, la résistance, l'innocuité et la toxicité, la pharmacocinétique et les interactions entre les médicaments.

and death (5). Therefore, antiretroviral drugs are likely to be started earlier and used longer than in the past.

Antiretroviral drug selection

In patients who require treatment for HIV infection, combination antiretroviral therapy is necessary to achieve the goal of sustained virological suppression (viral load less than 50 copies/mL). However, factors related to the individual, the virus, and/or the available drugs may interfere with implementation of the most effective regimen to achieve this goal.

The therapy needs and challenges for treatment-naïve and treatment-experienced patients differ somewhat to achieve the goal of sustained virological suppression. For treatment-naïve

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patients, current guidelines recommend the combination of one non-nucleoside reverse transcriptase inhibitor (NNRTI) with two nucleoside reverse transcriptase inhibitors (NRTI), or a protease inhibitor (PI) (preferably ritonavir-boosted) with two NRTIs as initial therapy (3,4). In these patients, issues such as tolerability can limit treatment choices (6,7) by affecting adherence, and therefore can lead to treatment failure and/or drug resistance.

Studies have shown that it is now possible to achieve the goal of viral suppression (viral load less than 50 copies/mL) in highly treatment-experienced patients, even in the presence of multiple resistance mutations (8-11). Current guidelines for treatment-experienced patients recommend the combination of active agents from the NRTI, PI and NNRTI classes of drugs along with the newer classes, specifically fusion inhibitors, integrase inhibitors, and CCR5 receptor antagonists (3,4). These guidelines reflect clinical data supporting the use of three or more fully active agents from at least two antiretroviral drug classes (8-11). Issues of drug safety and tolerability that affect treatment choices in treatment-naïve patients may also limit options in treatment-experienced patients. For example, even newer PIs (darunavir/ritonavir, tipranavir/ritonavir) are associated with toxicities that have serious implications, such as hepatotoxicity and dyslipidemia (12-15). The entry inhibitor enfuvirtide is associated with bothersome injection site reactions and injection fatigue, both leading to decreased adherence to therapy (16,17).

Another limitation, viral tropism, is specific to the use of CCR5 antagonists; maraviroc is only effective in patients with CCR5 tropic virus, and tropism testing is required to identify these patients (18-20).

Drug interactions are another potential hindrance to use of an agent or class: for example, the ritonavir component of boosted PIs is associated with multiple clinically significant drug interactions (21).

Once resistance of virus to an antiretroviral drug develops, it may limit the use of other agents in the same class. Resistance may arise due to previous nonsuppressive mono- or dual therapy; inadequate drug levels due to gastrointestinal pathology, pharmacokinetics, or drug interactions; and especially due to inconsistent adherence (22,23). Persistent viral replication in the presence of suboptimal drug levels has been associated with poor outcomes (24,25). The issue of resistance is not limited to treatment-experienced patients: primary drug resistance is also an issue in treatment-naïve patients. The prevalence of antiretroviral resistance among treatment-naïve patients is estimated to be between 7% and 24% in the United States (US) and Europe (26-29). In Canada, the prevalence of primary drug resistance to at least one antiretroviral drug is estimated to be 9% (29). Of particular concern is the increasing level of primary resistance to NNRTIs (27,28,30).

Given the benefits of combination antiretroviral regimens and the potential issues that may interfere with achieving the goal of viral suppression, the continued development and appropriate use of safe and efficacious antiretroviral agents with unique mechanisms of action are critically important in the effective long-term management of HIV-infected patients.

Integrase inhibitors

Inhibitors of the virus-encoded integrase enzyme are a relatively new class of antiretroviral agents. Integrase is required

for HIV replication (31). It catalyzes insertion of viral DNA into the genome of infected cells in several steps (Figure 1) (6,7,31,32):

- cleavage of two nucleotides from the 3' ends of viral DNA following reverse transcription;
- importation into the nucleus of the pre-integration complex (PIC) consisting of HIV-1 integrase, viral DNA, and other viral and cellular proteins; and
- strand transfer to host DNA, a step in which host DNA is cleaved and viral DNA is covalently linked to host DNA.

Strand transfer is the step that is targeted by the diketo aryl/ β -diketo acid (DKA) and DKA-like integrase inhibitors, which are integrase specific. Blockade of the strand transfer step results in circular complexes of HIV DNA that are unable to bind to host DNA, thereby preventing viral replication (6,33).

Raltegravir

Raltegravir (MK-0518, Isentress®; Merck Frosst Canada Inc), a DKA integrase inhibitor, was approved by Health Canada in November 2007. It has been shown to be effective in the treatment of HIV-1 infection in both treatment-naïve and treatment-experienced patients, and well tolerated in studies to date (34-36). Raltegravir has a rapid onset of action following oral administration and a durable effect. No cases of transmitted resistance to raltegravir have been reported to date. Raltegravir also seems to be active against HIV-2, like PIs and NRTIs, and unlike NNRTIs (37,38). Though additional study is needed to further characterize its long-term efficacy and safety, raltegravir is a useful addition to regimens for treatment of patients with HIV infection.

Raltegravir has been approved for use in Canada in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adults who have evidence of viral replication and have HIV-1 strains resistant to multiple antiretroviral agents.

GUIDELINES OBJECTIVE AND METHODS

These guidelines are intended to provide recommendations to Canadian health care providers regarding the optimal use of raltegravir in adults with HIV-1 infection. These guidelines are not a substitute for the judgement of a physician experienced in treating HIV-infected patients.

Development of the guidelines began with a meeting in June 2008 of seven clinicians/scientists with significant HIV experience: five infectious disease specialists/family physicians, one pharmacist with expertise in pharmacokinetics, and one researcher with particular expertise in HIV resistance. Before this meeting, group members reviewed the relevant literature for their predetermined area of focus. A summary of their findings in each area was presented at the meeting for discussion.

The consensus recommendations were based on scientific evidence and expert opinion. The strength of recommendation and quality of evidence were rated using the US Department of Health and Human Services (DHHS) guidelines scheme (Table 1) (3).

The final consensus guidelines were developed by a process of review and comment on drafts by the original core group of seven, as well as by five additional physicians and scientists

Figure 1 Mechanism of action of integrase inhibitors. Based on the findings of Hazuda et al 2000 (33). LTR Long terminal repeat (sequences found at ends of viral DNA)

across Canada with HIV expertise and/or clinical experience with raltegravir. The recommendations reflect the core group's consensus agreement, after considering comments from the additional reviewers.

RALTEGRAVIR EFFICACY

Treatment-experienced HIV-infected adults

The effectiveness of raltegravir in treatment-experienced HIV-infected adults has been demonstrated in several trials, including the phase III BENCHMRK studies (36).

A phase II, randomized, double-blind, placebo-controlled, dose-ranging study (study 005) was conducted in 178 adults (35). Subjects were infected with HIV strains resistant to at least one NNRTI, one NRTI, and one PI, and had plasma HIV-1 RNA greater than 5000 copies/mL and CD4 cell count greater than 50/mm³. Treatment consisted of placebo twice daily (bid), or one of three doses of raltegravir (200 mg, 400 mg or 600 mg bid), in addition to an optimized background regimen selected by the investigator for each patient, for 24 weeks. This study was ongoing when 400 mg bid was selected as the phase III study dose, so subsequently, patients could receive open-label raltegravir 400 mg bid after at least 24 weeks of treatment (39). Randomization was stratified by enfuvirtide use (yes/no) and by degree of PI resistance (resistant to one PI versus more than one PI) at baseline (35). The study was initially divided into two substudies: because prestudy pharmacokinetic data suggested that atazanavir might affect raltegravir plasma concentrations (40), one substudy included subjects with atazanavir in their optimized background regimen and the other substudy included subjects without atazanavir in their background regimen (35). Subjects with virological failure (viral load reduction less than 1.0 log₁₀ copies/mL from baseline) after week 16 could switch to open-label treatment with raltegravir plus optimized background therapy.

At baseline, mean plasma viral loads for the treatment groups were 49,842 cells/mm³ (range 44,643 copies/mL to 59,108 copies/mL) and mean CD4 counts ranged from 220 cells/mm³ to 274 cells/mm³ (35). Treatment effects on viral load and CD4 cell count were comparable in the with/without atazanavir substudies, and so the data were combined (Table 2). At the end of the 24-week double-blind period, the mean decrease in viral load ranged from 1.80 log₁₀ copies/mL to 1.87 log₁₀ copies/mL in the raltegravir dose groups versus 0.35 log₁₀ copies/mL in

TABLE 1
Rating scheme for recommendations

Strength of recommendation	Quality of evidence for recommendation
A: Strong	I: At least one randomized trial with clinical outcomes and/or validated laboratory end points
B: Moderate	II: At least one well-designed, nonrandomized trial or observational cohort study with long-term clinical outcomes
C: Optional	III: Expert opinion

Adapted from reference 3

the placebo group ($p < 0.0001$ for all), and decreases were noted as early as two weeks after start of treatment. The proportion of subjects who achieved viral loads less than 50 copies/mL ranged from 55.6% to 66.7% in the raltegravir dose groups versus 13.3% in the placebo group ($p < 0.0001$ for all). This effect was observed as early as week 4 and was maintained through week 24 in all raltegravir groups. Increases in CD4 cell counts were greater in the raltegravir groups versus the placebo group (62.9 cells/mm³ to 112.8 cells/mm³ in the raltegravir groups versus 5.4 cells/mm³ in the placebo group, $p < 0.0001$ for all). These treatment differences were consistent across all levels of HIV drug resistance, as assessed by phenotypic sensitivity scores (PSS) and genotypic sensitivity scores (GSS).

The median number of agents in the optimized background regimen was four (35). With the exception of enfuvirtide, no effective antiretroviral agents were in the optimized background for 72% of treated subjects based on genotypic resistance testing and in 48% based on phenotypic testing. Neither darunavir nor tipranavir was included in the background regimen for any patient. The use of enfuvirtide in the background regimen resulted in improved virological outcomes in all treatment groups.

The BENCHMRK studies are two randomized, double-blind, placebo-controlled phase III trials with identical designs (36). These studies are currently ongoing, with a planned total duration of at least 156 weeks of study therapy. Enrolled subjects were aged 16 years and older, had documented phenotypic or genotypic resistance to at least one drug in each of the NRTI, NNRTI, and PI classes, and had a viral load of greater than 1000 copies/mL. Subjects were randomized 2:1 to treatment with either raltegravir 400 mg bid or placebo bid, plus an optimized background regimen selected by the investigator. Darunavir and tipranavir (both investigational at the time of enrolment) were allowed in the optimized background. Etravirine and maraviroc were not available as options for the background regimen. Randomization was stratified by enfuvirtide use (yes/no) and degree of resistance to PIs (resistance to one PI versus more than one PI).

The combined analyses of BENCHMRK-1 and BENCHMRK-2 data at 48 weeks found significantly greater efficacy of raltegravir versus placebo (Table 2) (36). Mean viral load reductions were 1.7 log₁₀ copies/mL in the raltegravir groups versus 0.8 log₁₀ copies/mL in the placebo groups ($p < 0.001$). The mean increases in CD4 counts from baseline to 48 weeks were 109 cells/mm³ in the raltegravir groups versus 45 cells/mm³ in the placebo groups ($p < 0.001$).

In the 350 subjects treated in BENCHMRK-1, viral load at 48 weeks was significantly different from baseline for both

TABLE 2
Summary of raltegravir efficacy

Study/treatment duration	Parameter	Raltegravir plus TDF/3TC	Efavirenz plus TDF/3TC	P-value
Treatment-naïve				
004 Study (part 2)/48 weeks	N	160	38	
	Viral load change from baseline (log ₁₀ copies/mL)	–	–	–
	Viral load <50 copies/mL (%)	83–88*	87	–
	CD4 count increase from baseline (cells/mm ³)	144–221*	170	–
		Raltegravir plus TDF/FTC	Efavirenz plus TDF/FTC	P-value†
STARTMRK/48 weeks	N	280	281	
	Viral load <50 copies/mL (%)	86	82	<0.001
	N	258	251	
	CD4 count increase from baseline (cells/mm ³)	189	163	95% CI for difference between arms: 4–47
Study / treatment duration	Parameter	Raltegravir plus background	Placebo plus background	P-value
Treatment-experienced				
005 Study/24 weeks	N	133	45	
	Viral load change from baseline (log ₁₀ copies/mL)	–1.80 to –1.87‡	–0.35	<0.0001
	Viral load <50 copies/mL (%)	55.6–66.7‡	13.3	<0.0001
	CD4 count increase from baseline (cells/mm ³)	62.9–112.8‡	5.4	<0.0001
BENCHMRK-1/48 weeks	N	232	118	
	Viral load change from baseline (log ₁₀ copies/mL)	–1.7	–0.7	<0.001
	Viral load <50 copies/mL (%)	65	31	<0.001
	CD4 count increase from baseline (cells/mm ³)	120	49	<0.001
BENCHMRK-2/48 weeks	N	230	119	
	Viral load change from baseline (log ₁₀ copies/mL)	–1.8	–0.9	<0.001
	Viral load <50 copies/mL (%)	60	34	<0.001
	CD4 count increase from baseline (cells/mm ³)	98	40	<0.001

Data from references 35,41,42,54,56. *Dose ranging study: raltegravir 100 mg twice daily (bid), 200 mg bid, 400 mg bid and 600 mg bid. †P-value for test of noninferiority of raltegravir + tenofovir/emtricitabine (TDF/FTC) versus efavirenz + TDF/FTC; ‡Dose ranging study: raltegravir 200 mg bid, 400 mg bid and 600 mg bid. Data were combined to include both atazanavir substudies (with/without) because treatment effects on viral load and CD4 cell count were comparable. 3TC Lamivudine

TABLE 3
Summary of key efficacy results by subgroup: % subjects with virological suppression (<50 copies/mL) – pooled 48-week data for BENCHMRK studies

% of subjects with viral load <50 copies/mL	Raltegravir plus		Placebo plus	
	N	background	N	background
Overall	443	62	228	33
Baseline viral load ≤100,000 copies/mL	287	73	152	43
Baseline viral load >100,000 copies/mL	156	48	76	16
Baseline CD4 cells/mm ³ ≤50	139	50	75	20
Baseline CD4 cells/mm ³ >50 and ≤200	167	67	82	39
Baseline CD4 cells/mm ³ >200	136	76	71	44
GSS 0	112	45	65	3
GSS 1	166	67	92	37
GSS 2	109	77	47	62
GSS ≥3	49	71	21	52
Optimized background includes:				
Enfuvirtide and darunavir	44	89	22	68
Enfuvirtide	45	80	23	57
Darunavir	75	69	47	47
Neither enfuvirtide nor darunavir	191	60	90	20

Data from references 36,41–43. GSS Genotypic susceptibility score

treatment groups (41). The proportion of subjects with viral suppression (less than 50 copies/mL) was significantly greater

in the raltegravir group versus the placebo group. No effective antiretroviral agents were in the optimized background for 30% of raltegravir-treated subjects based on genotypic resistance testing and in 19% based on phenotypic testing. Similar results for proportion of subjects with viral suppression were obtained in the 349 subjects treated in BENCHMRK-2 (Table 2) (42). No effective antiretroviral agents were in the optimized background for 20% of raltegravir-treated subjects based on genotypic resistance testing and in 10% based on phenotypic testing. For both studies, enfuvirtide and darunavir were each counted as one active agent in subjects naïve to either drug.

In subgroup analyses, virological suppression (less than 50 copies/mL) was achieved in a higher proportion of subjects with baseline viral loads of 100,000 copies/mL or less (versus greater than 100,000 copies/mL), subjects with baseline CD4 cell counts greater than 200 cells/mm³ (versus 200 cells/mm³ or less), and in more subjects treated with raltegravir (versus placebo) (Table 3) (43).

As in other studies of novel agents (DUET: etravirine; POWER: darunavir; TORO: enfuvirtide; RESIST: tipranavir) (8–11), the BENCHMRK trials showed that virological suppression was improved with an increasing number of active agents (GSS 2 or greater) in the background regimen. The BENCHMRK data analysis further indicated that for GSS of 3 or greater, this improvement in virological suppression with increasing numbers of active agents tapers off (43).

The BENCHMRK trials showed that greater efficacy was achieved with the inclusion of raltegravir in the regimen (Table 3) (41-43). The results were similar at PSS levels from 0 to 2, confirming raltegravir's contribution to the efficacy of the treatment regimen regardless of the activity of the background regimen.

Overall efficacy in the BENCHMRK studies was unaffected by HIV clade (subtype): in the raltegravir groups, virological response rates were 64% for clade B versus 67% for other clades (43-45). Increases in CD4 cell counts from baseline were 105 cells/mm³ and 150 cells/mm³ for clades B and non-B, respectively, at week 48 (45). Caution should be used in drawing any conclusions from these data, because the number of subjects with non-B clade subtypes was small (n=38 in the raltegravir groups) (43,45).

A number of nonrandomized studies have reported on the virological and immunological efficacy of raltegravir for treatment-experienced subjects (46-49), including in combination with efavirenz and darunavir (50-52). These primarily clinic-based studies further confirm the benefits observed in randomized clinical trials of raltegravir as a component of combination therapy for treatment experienced patients.

Treatment-naïve HIV-infected adults

A multicentre, double-blind, randomized, placebo-controlled two-part study of raltegravir (study 004) was conducted in treatment-naïve adults (53-54). In part 1 of the study, 35 subjects were randomly assigned to either placebo or one of four doses of raltegravir for 10 days of monotherapy. In part 2 of the study, 201 subjects either continued at the same dose of raltegravir, or received efavirenz 600 mg once daily in place of placebo, all in combination with tenofovir/lamivudine (both 300 mg once daily), for 48 weeks of treatment. If new to the study, subjects were randomly assigned to one of four raltegravir doses (100 mg bid, 200 mg bid, 400 mg bid or 600 mg bid) or efavirenz 600 mg once daily. After 48 weeks, all patients in the raltegravir groups received raltegravir 400 mg bid (55). To enter the study, subjects had to have plasma HIV-1 RNA of 5000 copies/mL or greater, and CD4 cell counts of 100 cells/mm³ or greater. Subjects were stratified for HIV RNA levels of 50,000 copies/mL or less, or greater than 50,000 copies/mL. No prior antiretroviral therapy of greater than seven days was allowed. To enter part 2, subjects also had to have HIV susceptible to efavirenz, tenofovir, and lamivudine as determined by genotypic resistance testing. Subjects with active hepatitis B or C were excluded from both parts of the study.

In part 1 (10 day monotherapy), all four raltegravir dose groups (combined n=28) had mean viral load reductions from baseline that were significantly greater than placebo (n=7) at day 10 ($p<0.001$) (53). No differences in viral load reductions among raltegravir dose groups were found. Similar proportions of subjects in the raltegravir groups had HIV RNA levels less than 400 copies/mL at day 10 (50-57%), whereas none of the placebo recipients achieved this level. Viral suppression (less than 50 copies/mL) was achieved by day 10 for at least one subject in each raltegravir dose group (n=6 to n=8 in each group). Viral decay rates (rate of viral load reduction) were similar in all raltegravir treatment groups, either overall or stratified by baseline HIV RNA level (less than versus greater than 50,000 copies/mL), and all were greater than in the placebo arm. CD4 count changes from baseline to day 10 were not significant in any group.

In part 2 (96 weeks combination therapy), rapid and sustained reductions in viral load were observed in all raltegravir dose groups: the proportion of subjects with viral load less than 50 copies/mL was greater in each of the raltegravir groups versus the efavirenz group at weeks 2, 4, and 8 (54). By time-to-event analysis up to 48 weeks, patients receiving any dose of raltegravir achieved HIV-1 RNA below 50 copies/mL earlier than patients receiving efavirenz ($p<0.050$). By week 24, the raltegravir and efavirenz groups were similar in terms of viral load reduction, and 85% to 95% of subjects in all treatment groups had viral loads of less than 50 copies/mL. These viral load reductions continued through week 96 (83% to 84% in each group) (55). Results were similar in the subjects who continued from part 1 and the subjects enrolled directly into part 2 of the study (54). CD4 count increased comparably in all treatment groups (mean change from baseline 70 cells/mm³ to 104 cells/mm³ at week 2, and 221 cells/mm³ to 232 cells/mm³ at week 96) (54,55). Antiretroviral efficacy was demonstrated to be similar regardless of baseline HIV-1 RNA (stratifications of less than or equal to versus greater than 50,000 copies/mL, and less than or equal to versus greater than 100,000 copies/mL) (54).

In study 004, the efficacy of raltegravir did not appear to be affected by viral clade: viral suppression at 96 weeks was achieved by 91% and 100% of subjects with clade B versus non-B virus, respectively, but it should be noted that only 23 subjects with non-B virus received raltegravir (45). Raltegravir-treated patients had similar CD4 cell count increases from baseline at 96 weeks: 216 cells/mm³ and 250 cells/mm³ for clades B and non-B, respectively.

A phase III, double-blind, randomized study, STARTMRK, is ongoing and includes treatment-naïve subjects with baseline HIV RNA levels of greater than 5000 copies/mL and susceptibility to efavirenz, tenofovir, and emtricitabine (56). The study is investigating the noninferiority of raltegravir 400 mg bid versus efavirenz 600 mg once daily, both plus tenofovir and emtricitabine, in the suppression of viral load (less than 50 copies/mL). At baseline, geometric mean viral loads were 103,205 copies/mL to 106,215 copies/mL and mean CD4 cell counts were 217 cells/mm³ to 219 cells/mm³.

Noninferiority of the raltegravir arm was proven versus the efavirenz arm at 48 weeks in the proportion of subjects with viral load of less than 50 copies/mL (86% versus 82%, respectively; $p<0.001$) (Table 2) (56). Subjects who did not complete the study were considered to be treatment failures. The changes in CD4 cell counts from baseline were greater in the raltegravir arm (189 cells/mm³ versus 163 cells/mm³, 95% CI 4 to 47). In a subgroup analysis, both arms had comparable efficacy regardless of baseline viral load (greater than 100,000 copies/mL versus 100,000 copies/mL or less) (57). The relative virological and immunological efficacies of the raltegravir arm were unaffected by demographic and baseline characteristics (age, sex, region, race), hepatitis B or C coinfection, and viral subtype (although interpretation of the latter should be cautious as the number of non-clade B subjects was relatively small [n=54] versus clade B [n=208]).

Durability of raltegravir efficacy

Studies of treatment-experienced subjects (study 005, BENCHMRK) gave evidence of the durability of raltegravir's effect in this population. In the phase II 005 study, analyses of

time points after the end of the double-blind period at week 24 combined both the double-blind and open label phases. The viral load reductions and CD4 count increases that continued to week 48 confirm maintenance of the difference between raltegravir- versus placebo-treated subjects (39). In the BENCHMRK trials, viral load reductions and CD4 count increases in raltegravir-treated subjects relative to placebo-treated subjects persisted from the primary endpoint at week 16 (58,59) to week 96 (60).

Durability of response to raltegravir over 48 weeks was also demonstrated in treatment-naïve subjects in the double-blind, randomized study of raltegravir versus efavirenz, both in combination with tenofovir and lamivudine (54), as well as in the STARTMRK study (56).

Rapid reduction of viral load with raltegravir

In the phase III STARTMRK study of treatment-naïve subjects, the time to virological response (viral load of less than 50 copies/mL) was significantly shorter for the raltegravir group versus the efavirenz group (log-rank $p < 0.001$) (56). In the phase II study of treatment-naïve subjects (study 004), plasma HIV-1 RNA levels were significantly lower for the combined raltegravir groups versus the efavirenz group at all time points up to day 168 (61). A higher proportion of raltegravir-treated subjects, regardless of dose, had HIV-1 RNA less than 50 copies/mL from day 15 to day 57 versus efavirenz-treated subjects ($p \leq 0.047$). Viral suppression occurred significantly earlier with raltegravir-containing regimens than with efavirenz-containing regimens.

Further study has led to the conclusion that the rapid viral load reduction seen with raltegravir treatment reflects raltegravir's specific locus of action in the viral life cycle and the associated timing and efficiency of the integration process, and is not necessarily an indicator of superior viral inhibition by raltegravir (62). The clinical significance of these findings and their impact on long-term antiviral efficacy require further investigation.

Pediatric patients

Little data are currently available regarding the efficacy of raltegravir in children and adolescents younger than 16 years of age. In both a preliminary analysis of the IMPAACT study of 36 adolescents aged 12 to 18 years and an expanded access study of 23 adolescents aged 12 to 17 years, raltegravir appeared to be efficacious and was well tolerated (63,64). However, due to the scarcity of data, no recommendations regarding use of raltegravir in pediatric patients can be made at this time.

RALTEGRAVIR SAFETY

Based on clinical trial data in 507 treatment-experienced subjects who received raltegravir 400 mg bid, raltegravir was well tolerated with a safety profile similar to that of placebo ($n=282$) (34-36,60). Most events were mild to moderate in severity (35). Treatment discontinuations due to adverse events occurred in 2.0% of treatment-experienced subjects receiving raltegravir and 1.4% of subjects receiving placebo (34).

The safety profile for raltegravir in treatment-naïve subjects is similar to that in treatment-experienced subjects, with no dose-related toxicities. Previously naïve subjects treated with raltegravir had fewer serious adverse events and fewer drug-

related laboratory abnormalities overall than efavirenz-treated subjects (54,56). In the 004 study, no adverse event was more common with raltegravir treatment than with efavirenz treatment, except for increased alanine transaminase (ALT) in one raltegravir dose group (10.0% in the 200 mg group versus 5.3% in the efavirenz group). This finding is of doubtful clinical significance, as all other raltegravir dose groups had incidences lower than the efavirenz group: range 0% to 5.0%. Furthermore, at 96 weeks, grade 3/4 ALT abnormalities were less common in the raltegravir group than the efavirenz group (1.3% versus 5.3%) (55). The phase III STARTMRK study of treatment-naïve subjects did not identify any clinical or laboratory adverse events that were more common with raltegravir-based versus efavirenz-based therapy (56).

AIDS-defining conditions

The incidence of AIDS-defining conditions in the BENCHMRK studies of treatment-experienced subjects was lower in the raltegravir arm at week 48: exposure-adjusted rates were 3.7 per 100 patient-years in the raltegravir arm versus 6.2 per 100 patient-years in the placebo arm (relative risk [RR] 0.6; 95% CI 0.3 to 1.4) (65). A similar finding was noted at 96 weeks (60). The median time to onset of AIDS-defining conditions was shorter in the raltegravir arm (64 days versus 105 days in the placebo arm). Esophageal candidiasis was the most common AIDS-defining condition reported. Subjects who had an AIDS-defining condition or who died had higher baseline viral load, lower baseline CD4 cell counts, and more frequent histories of previous AIDS-defining conditions, and also had lower virological and immunological responses to study treatment.

Laboratory events

Grade 3/4 laboratory abnormalities were uncommon in subjects treated with raltegravir in clinical trials. Serum lipid levels were generally not adversely affected by raltegravir, and beneficial effects were seen in one study. In BENCHMRK-1, grade 3 fasting total cholesterol levels (greater than 7.76 mmol/L [300 mg/dL]) occurred more frequently in the raltegravir group than in the placebo group (11.6% versus 4.2%, respectively) at 48 weeks, but no such difference was found in BENCHMRK-2 (41,42). The reason for this difference between treatments in BENCHMRK-1 is difficult to evaluate in a treatment-experienced population, as previous therapies may have had an impact. No substantial difference in grade 3 fasting cholesterol was seen at 96 weeks in the combined analysis of the BENCHMRK studies (5.7% in the raltegravir group versus 4.8% in the placebo group) (60). In treatment-naïve subjects (004 study), the effects of raltegravir on changes from baseline to 48 weeks in total cholesterol (+0.03 mmol/L [+1.1 mg/dL]), low-density lipoprotein cholesterol (LDL-C) (-0.15 mmol/L [-5.8 g/dL]), and triglycerides (-0.12 mmol/L [-10.8 mg/dL]) were considered to be neutral and not clinically significant (54,55). Effects of raltegravir on serum lipids were also minimal after 48 weeks in the STARTMRK study (56). In the SWITCHMRK studies, significantly greater reductions in total cholesterol, fasting triglycerides, and non-high density lipoprotein cholesterol (HDL-C) were seen after 12 weeks in subjects who switched to a raltegravir-based regimen versus those who remained on a lopinavir/ritonavir (LPV/r)-based regimen (66).

Liver enzyme test abnormalities were also uncommon in raltegravir-treated subjects in all studies: grade 4 abnormalities

were infrequent (less than 3% of subjects) in any trial, and grade 3/4 aspartate transaminase (AST) and ALT abnormalities were low in incidence (0.8% to 2.1% in raltegravir groups) (35,41,42,56). It should be noted that no data specific to subjects with decompensated liver disease have been reported. Grade 2-4 abnormalities of creatine kinase were reported in clinical trials in subjects treated with raltegravir (34). Grade 4 creatine kinase occurred more frequently in raltegravir-treated treatment-experienced subjects (2.2% versus 0.7% in placebo-treated subjects). Furthermore, myopathy and rhabdomyolysis have been reported in studies of raltegravir (34). A single case report (67) has been published of severe rhabdomyolysis in a patient receiving raltegravir, which subsided on drug discontinuation and treatment by hydration. A causal relationship between raltegravir and rhabdomyolysis cannot be established or excluded on the basis of this single case report.

Neuropsychiatric events

Neuropsychiatric events in raltegravir-treated subjects occurred at rates similar to placebo-treated subjects and less than efavirenz-treated subjects in clinical trials (34,55,56). Although no treatment-related changes in the incidences of psychiatric events or depression associated with raltegravir have been noted in clinical trials, a recent report from one clinic raises the question of exacerbation of depression in four treatment-experienced patients (68). In these patients, depression symptoms improved over time without modification of raltegravir treatment. The mechanism by which raltegravir may have played a role in this observation is unclear.

Malignancies

Malignancies were reported in treatment-experienced subjects who received raltegravir, and some were recurrences (34). The types and rates of cancer were similar to those expected for a highly immunodeficient population in which most had prior AIDS diagnoses. Most subjects also had other risk factors for cancer including tobacco use, human papillomavirus infection, and active hepatitis B infection. In a risk assessment that included all double-blind data from five phase II and III trials with follow-up up to 120 weeks, malignancy rates were 1.7/100 patient-years of exposure to raltegravir versus 2.2/100 patient-years of exposure to comparators (relative risk 0.8 [95% CI 0.4 to 1.5]) (69). These data include malignancy recurrences, non-melanoma skin cancers, and carcinoma in situ. Similar trends with lower malignancy rates were noted when these three categories were excluded. Rates were similar in the expanded access setting. As the relationship of raltegravir to these cancer diagnoses is currently unknown, the possibility of an association will continue to be reevaluated as more and longer-term data for raltegravir are reported.

QTc interval

A double-blind, randomized, placebo-controlled, double-dummy, three-period single crossover study of a single supratherapeutic dose of raltegravir (1600 mg) in healthy volunteers was conducted to assess its effect on the QTcF interval (QTc interval corrected for heart rate using Fridericia's formula) (70). No QTcF values greater than 450 msec nor change from baseline greater than 30 msec were found in either the raltegravir or placebo groups, indicating no prolongation of the QTcF interval by raltegravir.

Hypersensitivity

Serious drug-related reactions in treatment-experienced subjects included two cases of hypersensitivity: treatment with raltegravir was interrupted and upon rechallenge, subjects had no further effects and were able to resume therapy. Stevens-Johnson syndrome (SJS) has occurred in one or more patients taking raltegravir, based on postmarketing reports. The relationship of SJS to raltegravir is unknown, as these reports are made without regard to causality (data on file, Merck Frosst Canada Inc).

Safety in pregnancy and breastfeeding

Based on toxicity studies in animals to date at exposures three to four times above those at the recommended human dose, raltegravir does not appear to have teratogenic or postpartum effects other than treatment-related increases in supernumerary ribs in a rat study (34). The drug has been assigned a Pregnancy Category C by the United States Food and Drug Administration (FDA), meaning that animal studies have revealed an adverse effect on the fetus, but benefits in humans may be acceptable despite potential risks. No adequate and well-controlled studies of raltegravir in pregnant women have been completed. A study of the pharmacokinetic disposition of raltegravir in pregnant HIV-1-infected women was ongoing at the time of writing (clinicaltrials.gov identifier NCT00689910).

No human data are available regarding raltegravir and breastfeeding. However, in animal studies, raltegravir was found to be secreted in the milk of lactating rats (34). Drug concentrations in milk were approximately threefold higher than in plasma.

Safety in other patient populations: Hepatitis coinfection, renal and hepatic insufficiency, and the elderly

In phase III studies of treatment-experienced subjects, concomitant hepatitis B and/or C coinfection (16.2% of subjects) did not alter the safety profile of raltegravir (34). However, as expected, AST and ALT abnormalities were more common in the coinfecting subgroups of both raltegravir- and placebo-treated subjects.

Because no clinically important differences in the pharmacokinetics of raltegravir were found between patients with moderate hepatic insufficiency or severe renal insufficiency and healthy subjects, no dose adjustment is necessary in patients with these conditions (34).

The number of subjects 65 years of age and older in clinical trials was insufficient to determine whether they respond differently to raltegravir than younger subjects.

SWITCHING TO RALTEGRAVIR

To test switching to a raltegravir-based regimen, two identical, randomized, multicentre, double-blind studies (SWITCHMRK 1 and 2) were conducted in subjects who were well controlled on a stable LPV/r regimen in combination with at least two NRTIs (and no other active PI) for three or more months (66). There was no limit on exposure to prior ARV regimens. At 24 weeks after switching to a raltegravir-based regimen, the raltegravir arm was not noninferior to the LPV/r arm (difference between groups in subjects with viral load of less than 50 copies/mL: 6.6% and 5.8% in the two studies). Most subjects who failed therapy in the raltegravir arm had RTI, PI, and/or integrase inhibitor resistance mutations at failure.

Switching from enfuvirtide to raltegravir was tested in a randomized, multicentre, open label study of 169 subjects with triple class resistant HIV-1 infection and viral load of less than 400 copies/mL for at least three months while receiving enfuvirtide (71). Subjects' treatment was randomized to either maintain an enfuvirtide-based regimen, or switch to a raltegravir-based regimen. At 24 weeks, 89% of subjects who switched to a raltegravir-based regimen had viral loads of less than 50 copies/mL (versus 88% in the enfuvirtide group). Virological failure rates were low (1.2% in both groups). No significant changes in CD4 cell count occurred in either group.

Several nonrandomized/cohort studies of switching treatment from enfuvirtide to raltegravir also showed this strategy to be successful with minimal disruption to patients. In an ongoing nonrandomized study of 35 adults with well-controlled multidrug-resistant HIV infection (plasma HIV-RNA levels less than 50 copies/mL, median duration 24 months), enfuvirtide was replaced with raltegravir 400 mg bid, and the rest of their regimen remained unaltered (72). These subjects had ongoing tolerability issues (injection site reactions) or injection fatigue with an enfuvirtide-containing regimen. In January 2008, 34 of 35 patients still had virological suppression (less than 50 copies/mL). The 35th patient had viral loads of 60 copies/mL after five months of raltegravir treatment; he had previously experienced transient viral load increases while taking enfuvirtide, and his viral load subsequently decreased to less than 50 copies/mL while taking raltegravir (M Harris, personal communication). The switch from enfuvirtide to raltegravir in these patients was therefore effective, well-tolerated, and highly acceptable to patients. As of December 2008, all patients continued to take raltegravir (M Harris, personal communication).

A number of other cohort studies have indicated similar maintenance of virological suppression and good tolerability following substitution of raltegravir for enfuvirtide with 12 to 24 weeks of follow-up (73-76). However, one study reported three cases of hepatic toxicity within 2 to 4 weeks following this treatment switch strategy (77). All patients in this study were receiving concomitant tipranavir/ritonavir, but 32% of subjects (8 of 25) in another study (74) received tipranavir/ritonavir concomitantly with no evidence of hepatic toxicity. The relationship of raltegravir with hepatic toxicity in the context of switching from enfuvirtide is therefore currently unclear.

RALTEGRAVIR RESISTANCE

It is unclear how much of a genetic barrier raltegravir has to the development of resistance mutations, though it seems to be low to medium (78). In the BENCHMRK studies, good virological responses were obtained even with a GSS of zero for the background regimen (36), suggesting a relatively high barrier to the development of resistance. Recent *in vitro* data suggest that a "post-antibiotic effect" due to the long off-rate for raltegravir of HIV pre-integration complexes may be contributing to these results (79).

In clinical trials of treatment-experienced subjects, virological failure in those who received raltegravir was associated with integrase gene mutations that primarily occurred along one of two genetic pathways (43,78). These pathways were defined by two or more mutations that included a major

mutation at Y143C/H/R, Q148R/H/K, or N155H; and one or more additional mutations that seem unique to each pathway (43,60,78,80-82). The N155H pathway appears to be independent and exclusive from the Q148R/H and Y143C/R pathways (83,84). For the Q148 pathway, the most common mutational profile was Q148H/G140S (78). The Q148H/G140S mutation pattern was associated with the greatest loss of drug susceptibility.

These results were confirmed by clonal analysis of isolates from raltegravir treated patients (85). This analysis found no virus population with mutations at both Q148 and N155H. G140A was also identified as a mutation in the N155H pathway. In a longitudinal analysis of samples from BENCHMRK subjects, N155 mutations decreased with treatment and the Q148 pathway was preferred (79).

It is important to understand that each of the Y143, Q148, and N155H mutations seems to be first required to establish a minimal level of resistance against raltegravir. However, each of these mutations also has a severe adverse impact on viral replicative fitness. It is the addition of the secondary mutations in each pathway that simultaneously increases both levels of resistance against raltegravir and viral replicative fitness. This finding helps to explain the fact that clinical isolates of HIV that are resistant to raltegravir almost invariably contain at least two mutations, since those viruses that only contain a single mutation are likely to be relatively unfit and therefore difficult to detect by population-based genotyping.

Data from clinical isolates found similar, although not identical, mutation patterns as those described in clinical trials. In clinical isolates of nine patients in France who received salvage therapy that included raltegravir and who subsequently had virological failure, the N155H mutation was associated with the greatest decrease in susceptibility to raltegravir *in vitro*, followed by the E92Q and G140S/Q148H profiles (86).

A longitudinal analysis of resistance in the subjects with triple class resistant virus who failed raltegravir therapy in the 005 study showed a preference for the Q148 pathway (87). The Q148 variants were relatively stable, while the viruses with N155H mutations often switched to G140S/Q148H. In subjects for whom the N155H viruses remained the majority population, additional mutations developed over time. Viral fitness was greatest for the Q148H/G140S mutations.

Data from the BENCHMRK studies indicate that more than one integrase mutation is usually found in virus resistant to raltegravir (43). In the 005 study, the highest levels of resistance were observed in the presence of three or more mutations (88). Single mutations were rare, and no single mutation had a significant impact on resistance or virological response.

In the 004 study, raltegravir-associated mutations were found in isolates from only two subjects who received the raltegravir combination regimen and had virological failure, the first report of acquired resistance to raltegravir in a previously treatment-naïve subject (54). Virus from both subjects had the N155H mutation. One subject tested at week 24 had resistance-conferring mutations for all three components of his/her regimen (raltegravir, tenofovir, and lamivudine). This subject continued treatment with raltegravir and had a greater than 1.0 log₁₀ reduction in viral load at week 48. Although the N155H mutation results in a 15-fold increase in raltegravir resistance, these data suggest that raltegravir may retain some

activity in the presence of the treatment-emergent N155H mutation alone. No new raltegravir-associated mutations were identified at 96 weeks (55). Among the 12 raltegravir-treated subjects with treatment failure in the STARTMRK study of treatment-naïve subjects, only four had raltegravir resistance mutations, with patterns that matched those reported in treatment-experienced subjects (56). Primary raltegravir resistance mutations were rare in the STARTMRK subjects, although secondary raltegravir resistance mutations were detected more frequently (less than 0.5% of the viral population) (89). Raltegravir resistance mutations present at baseline generally did not correlate with virological failure (82,89).

Current evidence indicates that cross-resistance between raltegravir and an investigational integrase inhibitor, elvitegravir, is substantial. A report of two treatment-experienced patients who failed on elvitegravir-containing regimens indicated no reduction in viral load when raltegravir was substituted for elvitegravir/ritonavir (90). Cross-resistance between raltegravir and elvitegravir was found to be considerable in isolates from highly treatment-experienced patients and in clonal analyses (81,91). However, levels of resistance associated with treatment failure after elvitegravir use may be higher than those associated with raltegravir (91). In another study, varying levels of resistance to integrase inhibitors, each with different mutations, indicated the potential for very different resistance profiles within this class of agents (92). Second generation integrase inhibitors (MK-2048, MK-0536) had less cross resistance than elvitegravir to virus with raltegravir resistance mutations *in vitro* (81). Future clinical trials will be necessary to determine whether the cross-resistance seen between raltegravir and elvitegravir extends to other members of this class.

Resistance reporting

Drug resistance analysis in Canada is often performed using the Virco Lab Inc (USA) virco® TYPE HIV-1 genotypic drug resistance test. Virco does not currently offer genotyping reports for raltegravir, but may eventually make this interpretation available. An alternative is to have resistance tests for integrase inhibitors carried out by drug resistance testing laboratories located in Quebec and British Columbia, or by laboratories in the United States, with expert interpretation.

RALTEGRAVIR PHARMACOKINETICS AND DRUG-DRUG INTERACTIONS

Raltegravir pharmacokinetics support bid dosing: the time of peak plasma concentration (T_{max}) was observed to be approximately 3 h (fasted), the terminal half-life ($t_{1/2}$) was 7 h to 12 h, and slight accumulation in clearance was seen at 12 h with multiple doses (93,94). An *in vitro* pharmacodynamic analysis suggested that once-daily dosing may be possible (95). This possibility is currently under investigation. Raltegravir pharmacokinetics were consistent regardless of sex, race, age (in adults and adolescents), HIV infection status, hepatic and renal function, and body mass index, although it should be noted that limited patient numbers were available for these analyses (93,94,96).

Raltegravir is a substrate for uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) (97). Drugs that induce or inhibit this enzyme may therefore affect the pharmacokinetics

of raltegravir. Raltegravir is neither a substrate for, nor an inducer of, cytochrome P450 (CYP) enzymes, and does not inhibit P-glycoprotein-mediated transport or UGT enzymes (UGT1A1, UGT1A4/2B7) (34,98). Therefore, raltegravir is unlikely to significantly affect the pharmacokinetics of drugs that are substrates of these enzymes or of P-glycoprotein.

A study compared the pharmacokinetics of raltegravir in individuals with decreased UGT1A1 activity (UGT1A1*28/*28 genotype) versus those with normal UGT1A1 activity (UGT1A1*1/*1) (99). Modestly higher raltegravir plasma concentrations were found in these subjects versus the normal activity genotype, but the difference was not clinically significant and dose adjustments are not required in these individuals.

Other ARVs tested to date do not significantly affect the pharmacokinetics of raltegravir, and therefore no dose adjustments are necessary when coadministered with raltegravir (34,35,40,100-108). A strong effect on UGT1A1 seems to be necessary for a significant drug interaction with raltegravir to be evident. Though atazanavir inhibits UGT1A1, and ritonavir, efavirenz and tipranavir induce UGT1A1, none had a significant effect on raltegravir pharmacokinetics and therefore no dose adjustments are required when these agents are coadministered with raltegravir (34,35,40,101,103,104,106,109).

Other pharmacokinetic data for raltegravir coadministered with antiretrovirals are available, but the implications are less clear due to the presence of multiple agents. In the 004 study of treatment-naïve subjects, the raltegravir pharmacokinetic parameters, area under the plasma concentration curve from 0h to 12 hours (AUC_{0-12h}), T_{max} , and C_{12h} , when coadministered with tenofovir and lamivudine were somewhat higher than with raltegravir alone, but findings were generally consistent with the drug interaction study of raltegravir coadministered with tenofovir in healthy volunteers (54,105). These effects were not considered to be significant enough to warrant dose adjustment of raltegravir (103,105).

Pharmacokinetic studies have not been performed on the interactions of raltegravir and all antiretroviral agents, but based on results with less potent inducers of UGT1A1, no clinically significant interactions are expected with other antiretroviral agents that are not potent inducers or inhibitors of UGT1A1.

With respect to potential interactions with investigational antiretroviral agents, the integrase inhibitor elvitegravir is metabolized primarily by CYP3A4 (110), and therefore would be unlikely to interact with raltegravir if they were coadministered. Elvitegravir is unlikely to be used with raltegravir as it does not offer a new drug class to the antiretroviral regimen. Interactions between raltegravir and the CCR5 receptor antagonist vicriviroc have not been assessed to date.

For other agents commonly used in the treatment of patients with HIV infection, pharmacokinetic data are currently only available for coadministration with rifampin and omeprazole. Rifampin coadministration resulted in a 40% reduction in the AUC of raltegravir (34). However, doubling the raltegravir dose to 800 mg bid when coadministered with rifampin failed to increase raltegravir trough concentrations in healthy subjects, so caution should be used in combining these agents until data in HIV-infected patients are available (111). Omeprazole coadministration increased raltegravir AUC by

210% (112). However, no dose adjustment of raltegravir is needed, since population pharmacokinetic data in HIV infected subjects indicate no changes in raltegravir levels when coadministered with gastric pH-altering agents. Gastric pH differences between healthy and HIV-infected subjects may explain this finding (113). A single case report of coadministration of raltegravir and sirolimus in an HIV-infected patient with renal impairment suggests a lack of interaction (114).

Despite reports of *in vitro* glucuronidation of statins and resulting concerns about the potential for drug-drug interactions, statin interactions with raltegravir are unlikely, as most statins are cleared primarily by CYP enzymes or non-metabolic routes (115).

Drug interactions are summarized in the manufacturer's product monograph. Based on the pharmacokinetic data, the manufacturer's only current recommendation for caution is for rifampin when coadministered with raltegravir (34).

ROLE OF RALTEGRAVIR IN ANTIVIRAL THERAPY

In the BENCHMRK studies of treatment-experienced subjects, raltegravir-treated subjects had virological responses (defined as viral load of less than 50 copies/mL) that were superior to placebo regardless of baseline viral load or baseline CD4 count (43). However, better responses were observed in both treatment groups when subjects had lower baseline viral loads or higher baseline CD4 counts (Table 3). In treatment-naïve subjects, raltegravir-containing treatment was shown to be non-inferior to efavirenz-containing treatment in terms of viral suppression (STARTMRK) (56).

Raltegravir is active and results in significant viral load reduction even when no other fully active agents are available (ie, GSS=0) (43). Although this attribute makes raltegravir a viable option for patients with few treatment options, it should be combined with an optimized combination regimen that includes other drugs with full or partial antiretroviral activity. Treatment response to raltegravir is improved by increasing the number of other active antiretroviral agents in the regimen, a finding not unique to raltegravir.

Substituting raltegravir for enfuvirtide in virologically suppressed patients is supported by several cohort studies and one randomized clinical trial.

Wholesale switching from LPV/r to raltegravir in all patients with virological suppression on LPV/r plus two nucleosides is not supported by randomized trials (SWITCHMRK 1 and 2).

Though additional study is needed to further characterize its long-term effects, raltegravir has been shown to be effective in combination with two or more active agents for treatment of patients with HIV infection. Other strategies for the use of raltegravir such as substitution for a PI or NNRTI in suppressed patients without resistance mutations to any components of their regimen and in combination with a PI in a nucleoside sparing regimen has not been validated in randomized clinical trials.

RECOMMENDATIONS

- Raltegravir is recommended for treatment-experienced patients with triple class resistant HIV in combination with two other active agents (AI):

- Under special circumstances, raltegravir and one other active agent may be appropriate; consult a physician expert in treating HIV before proceeding in these cases.
- Raltegravir is recommended when resistance, toxicity, or drug interactions prevent the use of agents from other classes, to construct a regimen of at least three active agents (BIII).
- Switching from enfuvirtide to raltegravir is a viable option in treatment-experienced patients with virological suppression (AI).
- In treatment-naïve patients, raltegravir may be considered as the third agent in addition to two NRTIs (AII).
- Resistance testing for integrase mutations is not currently recommended before raltegravir treatment. Resistance testing of integrase is recommended for all patients who have experienced virological failure after treatment with raltegravir, to determine whether raltegravir retains any antiviral effect in future regimens (AIII).
- Drug interactions should be taken into account when selecting agent and dose for therapy concomitant with raltegravir (AII). The manufacturer's recommendations in the package insert or product monograph should be consulted, as well as a pharmacist expert in HIV treatment, if available (BIII).
- The safety profile of raltegravir to date indicates that its use is not precluded in most patient populations due to safety issues, except for hypersensitivity to components of its formulation (AII).
- Until more data become available, raltegravir should not be used in pediatric patients younger than 16 years of age, or in pregnant or breastfeeding women unless the potential benefits outweigh the risks (BIII).

CONCLUSIONS

Raltegravir is the first of the integrase inhibitor class of agents to be available for use in HIV-infected patients. It offers durable efficacy, a rapid onset of response, and a good safety profile, based on up to 48 weeks of treatment. Longer-term efficacy and safety are currently under investigation, but data will be available in the near term. Raltegravir offers clinicians a new treatment option for patients with HIV infection. These guidelines have been developed to assist physicians in the optimal use of this new agent.

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