Research Review
PRODUCT REVIEW

Dolutegravir (Tivicay®) in the Treatment of HIV Infection

About the Reviewer

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This review is a summary of the pharmacological and clinical characteristics of dolutegravir (Tivicay®), which is an orally-administered integrase strand transfer inhibitor (INSTI) approved for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and children aged >12 years and weighing ≥40kg. Expert commentary on the use of dolutegravir from a clinical practice perspective is provided by Dr Rupert Handy (ADHB). This review is sponsored by GlaxoSmithKline (NZ) Ltd.

Burden of HIV

The number of people with HIV in the New Zealand general population has been estimated at 2800 people.[1] This equates to a prevalence 62 per 100,000 total population, which is considered to be low.[1]

The main risk for acquiring HIV infection remains sexual contact between men. Although New Zealand has a relatively low prevalence of HIV infection among men who have sex with men (MSM) by global standards, recently estimated to be 6.5%,[2] the number of MSM with diagnosed HIV infection is increasing.[3] In addition, while the number of heterosexual men and women infected with HIV in New Zealand is low, the number has increased gradually since the mid-1990s.[1]

In terms of the financial burden of HIV infection, the domestic spend on prevention and antiretroviral agents was $NZ12-14 million and $NZ38.8 million, respectively, for the 2-year period 2012-2013.[1]

Treatment of HIV infection

The medical interventions for HIV infection, especially antiretroviral therapy (ART), have a profound effect in reducing the burden of disease. According to one estimate, ART has saved 5.7 million years of life in developed countries since 1996.[4]

The aim of treatment is to prevent HIV replication. The ART regimen chosen should take into account factors of patient convenience and tolerance to facilitate adherence to therapy. The development of drug resistance is reduced by using a combination of drugs. These combinations should have synergistic or additive activity while avoiding additive toxicity. Viral susceptibility to antiretroviral drugs should be established before starting treatment or before switching drugs if not responding.

Medical treatment of people with HIV in New Zealand is generally considered to be of a high standard,[1] and a range of different antiretroviral agents are registered (as of November 2016) for treating HIV infection (**Table 1**).[1,5] The annual number of deaths from AIDS in New Zealand is now consistently lower than the number notified with AIDS, which reflects the longer survival of people who are diagnosed with AIDS.[1]

NRTIs/NtRTIs	NNRTIs	PIs	INSTIs	Fusion inhibitors	Co-formulated options
stavudine **zidovudine** **didanosine** **lamivudine** **abacavir** **emtricitabine** **tenofovir**	**nevirapine** **efavirenz** **etravirine** rilpivirine	**ritonavir** **indinavir** **atazanavir** **darunavir**	**raltegravir** **dolutegravir**	**enfuviritde**	*Single class:* **zidovudine/lamivudine** **abacavir/lamivudine** **emtricitabine/tenofovir** **lopinavir/ritonavir** *Mixed class:* abacavir/dolutegravir/lamivudine **efavirenz/emtricitabine/tenofovir** emtricitabine/rilpivirine/tenofovir elvitegravir/cobicistat/emtricitabine/efavirenz

Table 1. List of HIV medicines registered in New Zealand, with those in bold font being funded by Pharmac (as of November 2016).[5]
Abbreviations: INSTIs = integrase strand transfer inhibitors; NNRTIs = non-nucleoside reverse transcriptase inhibitors; NRTIs/NtRTIs = nucleoside/nucleotide reverse transcriptase inhibitors; PIs = protease inhibitors

The Australian Society for HIV Medicine (ASHM) Antiretroviral Guidelines (i.e. the US Department of Health and Human Services (DHHS) Guidelines with Australian commentary) recommend that the optimal ART regimen for a treatment-*naïve* patient should consist of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third antiretroviral drug from one of three drug classes: a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI) boosted with ritonavir, or an integrase inhibitor (INSTI).[6,7]

Following its approval in the US in 2013 and subsequently in Australia in 2014, dolutegravir was added to the INSTIs already recommended in the ASHM Antiretroviral Guidelines, elvitegravir and raltegravir.[6] In both the DHHS and ASHM guidelines, INSTI and PI treatment regimens (including those containing dolutegravir) are recommended treatment options in appropriate patients.[6,7] The 2016 International Antiviral Society-USA (IAS-USA) Recommendations on Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults recommend an INSTI as a component of initial regimens with two NRTIs.[8]

The clinical potential of new antiretroviral drugs, such as dolutegravir, should be considered in the real-world scenario of a need for simplified efficacious regimens that provide a smaller pill burden, reduced dose frequency, and a more favourable safety profile, as well as a need for a higher genetic barrier against viral resistance.[9]

Overview of pharmacology

The following is a summary of important aspects of the pharmacology of dolutegravir. The dolutegravir Data Sheet should be consulted for full details of its pharmacology, potential drug interactions, contraindications and precautions, and use in special populations.

Mechanism of action

Dolutegravir has a mechanism of action similar to that of other drugs in the INSTI class of antiretroviral agents. It binds to the integrase site of HIV-1 and prevents the retroviral HIV genome from integrating into the DNA of host cells, thereby inhibiting the replication of HIV-1.[9-11] Because dolutegravir fits loosely into the intasome binding pocket it is able to retain its binding ability despite conformational changes in the pocket structure. The ability of dolutegravir to readjust its binding position is thought to enhance the genetic barrier to antiretroviral drug-resistance.[12,13]

Pharmacokinetics

Dolutegravir is rapidly absorbed after oral administration; its median time to reach peak plasma concentration (C_{max}) being 2-3 hours post dose.[11]

The bioavailability of dolutegravir depends on meal content. Dolutegravir exposure increases between 34% and 66% if a dose is taken with food, depending on fat content, but the increases are only clinically significant for treatment-experienced patients and dolutegravir can usually be administered regardless of food.[11] The absolute bioavailability of dolutegravir has not been established.[11]

Dolutegravir is highly bound (approximately 99.3%) to human plasma proteins. The apparent volume of distribution is estimated at 12.5L.[11]

Dolutegravir is mainly metabolised and eliminated by the liver, with the major and minor metabolic pathways for dolutegravir being UDP glucuronosyltransferase (UGT)1A1 and cytochrome P450 (CYP)3A4, respectively. Renal elimination of dolutegravir as unchanged drug is <1% of the dose with 31% of the dose being excreted in the urine as metabolites.[11] The terminal half-life of dolutegravir is approximately 14 hours and it has an apparent clearance of 0.56 L/hr.[11]

In vitro studies suggest that dolutegravir reversibly inhibits the organic cation transporter 2 (OCT2), which mediates the tubular secretion of creatinine.[11] This observation appears to explain the small increases in serum creatinine observed in clinical studies of dolutegravir (see section on Overview of Efficacy and Safety).

Dosing

Dolutegravir has a long serum half-life of approximately 14 hours, allowing it to be administered once-daily in patients without pre-existing INSTI resistance.[11] Twice-daily administration is recommended in patients with known or suspected resistance mutations to first-generation INSTIs.[11]

A pharmacokinetic booster is not required (e.g. with concomitant ritonavir), thus minimising the potential for drug-drug interactions.[9,10] Dosage adjustment is not required in cases of mild to moderate hepatic impairment, although patients with severe hepatic impairment have yet to be treated with dolutegravir in clinical studies.[11]

Drug interactions

In terms of drug interactions, dolutegravir neither inhibits nor induces CYP isoenzymes, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporter polypeptides to a clinically-significant degree.[11] This lack of an effect on CYP isoenzymes, P-gp, BCRP, and drug transporters is of value for HIV-infected individuals who may require poly-pharmacy.[7] However, because dolutegravir is a substrate of UGT1A3, UGT1A9, BCRP, and P-gp, dolutegravir dosage modification may be required in patients using medications that induce or inhibit these enzymes.[11]

The following are selected important drug interactions:

- Cationic antacids (e.g. aluminium or magnesium salts) significantly decrease dolutegravir concentrations. Dolutegravir should be administered two hours before or six hours after cation-containing antacids.
- Co-administration of dolutegravir with etravirine is not recommended unless the patient is also receiving concomitant atazanavir/ritonavir, lopinavir/ritonavir, or darunavir/ritonavir.
- When co-administered with efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin, the recommended dose of dolutegravir is 50mg twice daily.
- Because metformin concentrations may be increased by the co-administration of dolutegravir, diabetes control should be monitored during initiation of therapy and a dose adjustment of metformin may be required.
- Rifampicin reduces dolutegravir plasma concentration; hence, the recommended dose of dolutegravir is 50mg twice daily when co-administered with rifampicin.
- Co-administration with carbamazepine, a metabolic inducer, has been shown to reduce dolutegravir plasma concentrations. Although not yet studied, the effect of co-administration with the metabolic inducers, phenytoin, phenobarbital, and St John's wort, on dolutegravir is likely to be similar to that with carbamazepine. Therefore, the recommended dose of dolutegravir is 50mg twice daily when co-administered with carbamazepine or these other metabolic inducers. Where possible, alternative combinations that do not include carbamazepine or these other metabolic inducers should be used in INSTI-resistant patients.[11]

Dolutegravir does not interact significantly with methadone or oral contraceptives and hence there is no need for dose adjustment when co-prescribed with these drugs.[11]

Special patient groups

Pharmacokinetic data indicate that dolutegravir exposure in HIV-infected children and adolescents was comparable to that in adults after dolutegravir 50mg once daily. However, the safety and efficacy of dolutegravir has not yet been established in children.[11]

There are no adequate and well-controlled studies of dolutegravir in pregnant women and the effect of dolutegravir on human pregnancy is unknown. Therefore, dolutegravir should only be used during pregnancy if the expected benefit justifies the potential risk to the foetus.[11]

Pharmacokinetic data on the use of dolutegravir in patients aged ≥65 years are limited; however, there is no evidence that elderly HIV-infected patients require a different dose than younger adult patients.[11]

Resistance

Drug resistance mutations have evolved against all of the currently marketed anti-HIV agents, including the first generation INSTIs raltegravir and elvitegravir.[9] INSTI resistance arises from single-point mutations within the integrase gene. Dolutegravir appears to have a high genetic barrier to the development of resistance and limited cross resistance, which may account for its effectiveness against strains of HIV-1 that are resistant to raltegravir and elvitegravir.[9,10] For example, in one of the largest studies to characterise INSTI resistance in patients experiencing virological failure on raltegravir, a high proportion of viruses (64%) were shown to remain susceptible to dolutegravir.[14]

The results of an *in vitro* resistance profiling study in which dolutegravir exhibited significantly slower (5- to 40-fold slower) dissociation from the integrase enzyme than raltegravir and elvitegravir in both wild-type viruses and viruses containing single-point mutations suggest that dolutegravir has a higher genetic barrier to resistance than raltegravir and elvitegravir.[15] Dolutegravir also appears to undergo positional and conformational changes at the active site allowing it to overcome the physical barrier created by single-point mutations,[12,13] thus suggesting limited cross-resistance to raltegravir and elvitegravir. In addition, the results of a more recent *in vitro* resistance profiling study, which used wild-type HIV-1 and mutants with the E92Q, Y143C, Y143R, Q148H, Q148K, Q148R, and N155H substitutions, suggest that dolutegravir has a high barrier to the development of resistance in the presence of raltegravir or elvitegravir signature mutations other than Q148.[16]

In vitro susceptibility studies have yet to identify major resistance mutations against dolutegravir and have demonstrated dolutegravir to be effective against strains of HIV resistant to raltegravir and elvitegravir.[9] Moreover, clinical evidence that dolutegravir possesses activity against raltegravir- and elvitegravir-resistant

strains is indicted by the virological efficacy of dolutegravir in raltegravir-treated patients demonstrated in the VIKING studies[17,18] and the significantly lower rate of virological failure with dolutegravir versus raltegravir observed in treatment-experienced patients in the SAILING study.[19]

Summary

Dolutegravir offers the potential for improved adherence and therapeutic response to ART and suitability for use in single tablet regimens by virtue of requiring only once-daily administration (as first-line therapy), not needing pharmacokinetic boosting, being able to be taken with or without food, having a reduced potential for adverse drug interactions, and demonstrating a high genetic barrier to resistance.

Overview of efficacy and safety

Dolutegravir has been developed as an unboosted once-daily therapy for use in combination with other antiretroviral agents for the treatment of both treatment-*naïve* and treatment-experienced patients with HIV-1 infection.

Phase III trials of dolutegravir 50mg once daily have demonstrated its non-inferiority in treatment-*naïve* patients with HIV infection compared with the standard of care, efavirenz-based and raltegravir-based regimens, in terms of both virological and immunological efficacy.[9,10,12] Phase III trials in treatment-experienced patients have also demonstrated that the antiviral activity of dolutegravir is retained in the presence of antiretroviral drug resistance.[9,10,12]

A favourable tolerability and safety profile for dolutegravir has been consistently demonstrated in clinical studies for all dosage regimens.[9,10,12] Nausea, headache, diarrhoea, and sleep disturbances were among the most commonly reported adverse events. Less commonly occurring, but notable, adverse effects included hypersensitivity reactions, liver injury (especially in cases of unrecognised hepatitis B or C), immune reconstitution syndrome, and body fat redistribution. The majority of treatment-emergent adverse events were of mild or moderate severity, with a low rate of discontinuation due to adverse events being evident. The frequencies of laboratory abnormalities, which included elevated cholesterol, liver enzyme, and creatine kinase levels were generally similar across all dolutegravir treatment and comparator arms. Dolutegravir is associated with small increases in serum creatinine during the first 4 weeks of treatment that persist but are stable over time and not considered to be clinically relevant.[9,10,12]

Clinical findings with dolutegravir should be considered in the context of the relatively short duration of follow up and post-marketing surveillance.

Pivotal Clinical Trials

The following are individual summaries of pivotal phase III studies of dolutegravir in the treatment of antiretroviral-*naïve* HIV-infected patients and a generalised summary of phase III studies in antiretroviral-experienced patients with HIV infection. Expert commentary describing the clinical practice relevance of these studies is provided by Rupert Handy.

TREATMENT-*NAÏVE* PATIENTS

SINGLE study

Dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-*naïve* patients: week 96 and week 144 results from the SINGLE randomized clinical trial[20]

Authors: Walmsley S et al.

Summary: SINGLE is an ongoing, phase III, multicentre, randomised, double-blind, non-inferiority study designed to assess the safety and efficacy of dolutegravir 50mg plus a fixed-dose combination of abacavir 600mg/lamivudine 300mg once daily (DTG+ABC/3TC) compared with fixed-dose efavirenz 600mg/tenofovir disoproxil fumarate 300mg/emtricitabine 200mg once daily (EFV/TDF/FTC) in treatment-*naïve* HIV-infected patients. A total of 833 patients were randomised (1:1) and received at ≥1 dose of study medication: DTG+ABC/3TC (n=414); EFV/TDF/FTC (n=419). In the primary analysis, more patients in the DTG+ABC/3TC group (88%) responded with an HIV-1 RNA level of <50 copies/mL than in the EFV/TDF/FTC group (81%) through to week 48 (difference: 7.4%; 95% CI: 2.5-12.3%; p=0.003).[20] The trial continued double-blinded with a secondary analysis at week 96 and then open-label from week 96 to 144. More patients in the DTG+ABC/3TC group than in the EFV/TDF/FTC group maintained HIV-1 RNA level of <50 copies/mL at week 96 (80% vs 72%; p=0.006) and this difference was maintained at week 144 (71% vs 63%; p=0.01; **Figure 1**). Change from baseline in CD4+ cell counts was consistently greater in the DTG+ABC/3TC group than in the EFV/TDF/FTC group (**Figure 1**). Nine (2%) drug-related serious adverse events occurred in the EFV/TDF/FTC group versus two (<1%) in the DTG+ABC/3TC through to week 144. No treatment-emergent integrase or nucleoside resistance was observed in DTG+ABC/3TC recipients through to week 144.

Comment: SINGLE[21] demonstrated superiority of DTG+ABC/3TC compared to EFV/TDF/3TC for the first-line treatment of HIV infection at 48 weeks. The difference was maintained at the 96-week analysis and also the 144-week analysis conducted after an open-label extension.[19] The superiority of DTG was driven mostly by discontinuations of the comparator (usually for tolerability reasons, as opposed to differences in efficacy) and notably, after unblinding, during the open-label phase data was lacking for 30% of subjects receiving EFV/TDF/FTC compared to 18% of subjects receiving DTG+ABC/3TC.

The impressive results require clinical interpretation; applicability of the findings is compromised by the small numbers of females, non-Caucasians, and subjects with CD4 counts <200 cells. Reassuringly, non-inferiority was not seen in subgroups analyses of women, patients older than 50 years, with CD4 counts <200 cells or with HIV viral loads >100,000 copies/mL. There were no signals regarding suboptimal safety or potency of the ABC/3TC backbone, even in high viral load strata. DTG resistance was not observed and DTG+ABC/3TC was better tolerated with fewer discontinuations due to rash or neuropsychiatric side effects. DTG+ABC/3TC did result in a clinically insignificant mean increase in serum creatinine of 10.2-13.4 μmol/L but this was stable during 144 weeks of follow up.

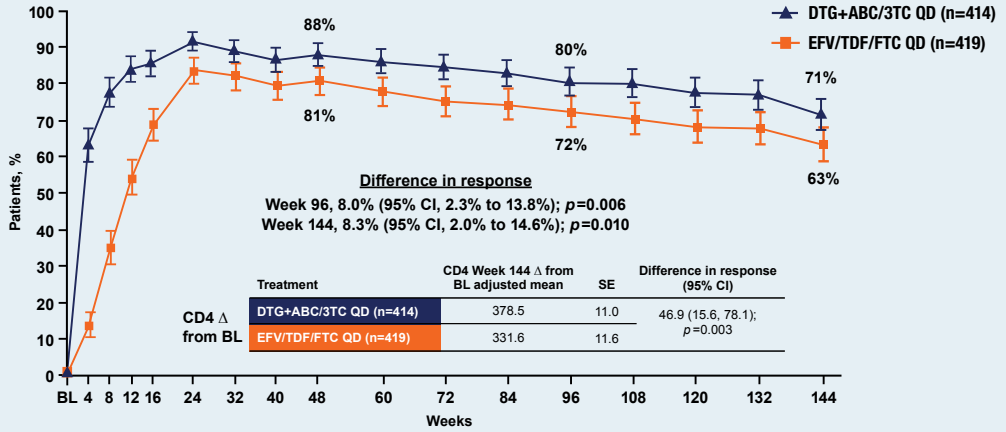

Figure 1. Percentage of patients with HIV-1 RNA levels of <50 copies/mL and change in CD4 count (x 10^6/L cells) from baseline during 144 weeks of treatment with dolutegravir plus abacavir/lamivudine once daily (DTG+ABC/3TC; n=414) versus efavirenz/tenofovir disoproxil fumarate/emtricitabine once daily (EFV/TDF/FTC; n=419) in the SINGLE study.[20]

Abbreviations:
BL=baseline; CI=confidence interval; QD=once daily; SE=standard error.

SPRING-2 study

Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-*naïve* adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial[22]

Authors: Raffi F et al.

Summary: This 96-week, randomised, double-blind, non-inferiority study involved 100 sites in Canada, USA, Australia, and Europe. Treatment-*naïve* adults with HIV-1 infection and HIV-1 RNA levels of ≥1000 copies/mL received at least one dose of either dolutegravir 50mg once daily (n=411) or raltegravir 400mg twice daily (n=411). Study drugs were given with co-formulated tenofovir/emtricitabine or abacavir/lamivudine. At 48 weeks, 361 (88%) patients in the dolutegravir group achieved an HIV-1 RNA value of <50 copies/mL compared with 351 (85%) in the raltegravir group. The same non-inferiority conclusion was also reached at week 96 (81% vs 76% virological success). Adverse events were similar between treatment groups. Few patients had drug-related serious adverse events (3 dolutegravir [<1%] vs 5 raltegravir patients [1%]) and few had adverse events leading to discontinuation (10 [2%] vs 7 [2%]). Small increases in mean serum creatinine (evident by week 2 and remaining stable through to week 96) were noted for both treatments, although the increase was smaller for raltegravir (**Figure 2**). CD4 cell counts increased from baseline to week 48 in both treatment groups by a median of 230 cells/μL. No evidence of treatment-emergent resistance in patients with virological failure on dolutegravir was noted. In patients with virological failure on raltegravir, one (6%) had integrase treatment-emergent resistance and four (21%) had NRTI treatment-emergent resistance.

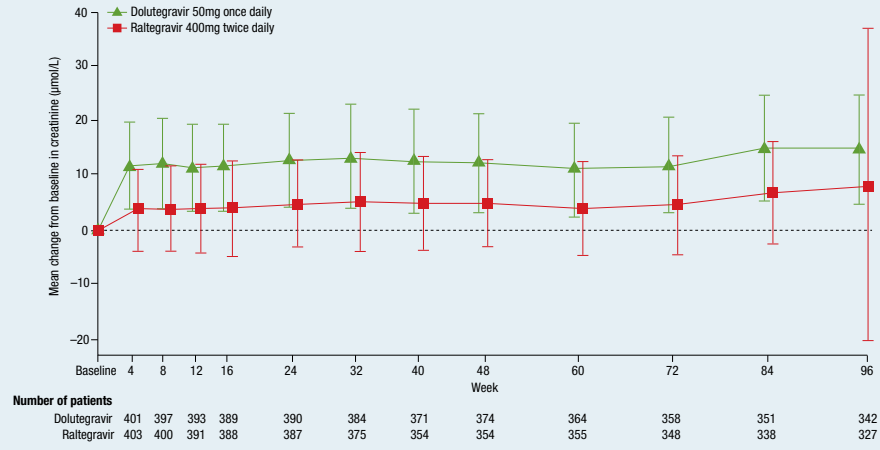

Figure 2. Mean change in serum creatinine during 96 weeks of treatment with dolutegravir 50mg once daily (n=411) versus raltegravir 400mg twice daily (n=411) in the SPRING-2 study.[21] Error bars indicate standard deviations.

Comment: In SPRING-2, dolutegravir compares favourably to the first-in-class INSTI raltegravir. Non-inferiority was demonstrated at 48 and 96 weeks and also in subgroups with CD4 <200 cells and viral loads >100,000 copies/mL and appeared independent of backbone. Clinically insignificant increases in creatinine were seen with in both arms; after 96 weeks the mean increase in serum creatinine was 14.6 μmol/L for dolutegravir versus 8.2 μmol/L for raltegravir. Both regimens were similarly tolerable, with most treatment discontinuations being for administrative reasons. No dolutegravir resistance was detected. Adherence was not reported, but the double-blind, double-dummy study design precluded any effect from the once-daily dosing schedule, which, with the high barrier to resistance, is the major advantage of dolutegravir.

FLAMINGO study

Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-*naïve* adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase IIIb study[23]

Authors: Clotet B, et al.

Summary: In this multicentre, randomised, open-label, non-inferiority study, HIV-1-infected treatment-*naïve* adult patients with HIV-1 RNA levels of ≥1000 copies/mL and no resistance at screening received either dolutegravir 50mg once daily (n=242) or darunavir 800mg plus ritonavir 100mg once daily (n=242), with investigator-selected tenofovir-emtricitabine or abacavir-lamivudine. At week 48, 217 (90%) patients receiving dolutegravir and 200 (83%) patients receiving darunavir plus ritonavir had HIV-1 RNA <50 copies/mL. The adjusted treatment difference between groups met non-inferiority and on pre-specified secondary analysis dolutegravir was superior (p=0.025). Confirmed virological failure occurred in two (<1%) patients in each group but no treatment-emergent resistance was detected in either group. Both groups had similar types and rates of adverse events, although discontinuation due to adverse events or stopping criteria was less frequent for dolutegravir (4 [2%] patients) than for darunavir plus ritonavir (10 [4%] patients) and contributed to the difference in response rates.

Once-daily dolutegravir versus darunavir plus ritonavir for treatment-*naïve* adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase IIIb study[24]

Authors: Molina J-M et al.

Summary: This article presents longer-term secondary efficacy and safety results from the Flamingo study. At 96 weeks, 194/242 patients (80%) in the dolutegravir group had HIV-1 RNA <50 copies/mL (adjusted difference 12.4, 95% CI 4.7–20.2; p=0.002) versus 164/242 patients (68%) in the ritonavir-boosted darunavir group, with the greatest difference being in patients that had high viral load at baseline (50/61 [82%] vs 32/61 [52%], homogeneity test p=0.014). Six participants (three since 48 weeks) in the dolutegravir group and 13 (four) in the darunavir plus ritonavir group discontinued because of adverse events. Diarrhoea (23/242 [10%]

in the dolutegravir group vs 57/242 [24%] in the darunavir plus ritonavir group), nausea (31/242 [13%] vs 34/242 [14%]), and headache (17/242 [7%] vs 12/242 [5%]) were the most common drug-related adverse events.

Comment: In FLAMINGO, dolutegravir was proven superior to a guideline-preferred boosted protease regimen at 48 and 96 weeks of follow up. The effect was independent of baseline viral load or backbone assignment. Dolutegravir resistance was not detected in any study subjects. There were fewer discontinuations in the dolutegravir arm, which contributed to the superiority of dolutegravir in virologic success. However, bias may have been introduced by the open-label study design if patient preference for the single tablet regimen influenced darunavir discontinuations. Applicability of the findings may also be limited because study subjects included few females, or patients with hepatitis co-infection or with CD4 <200 cells. Overall, taken in concert with the results of SINGLE and SPRING-2, dolutegravir is a very well-tolerated and effective option for treatment-*naïve* HIV-infected patients with a variety of nucleoside backbones.

TREATMENT-EXPERIENCED PATIENTS (SALVAGE THERAPY)

SAILING and VIKING-3 study

Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-*naïve* adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study[19]

Authors: Cahn P et al.

Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study[17]

Authors: Castanga A et al.

Summary: SAILING and VIKING-3, two pivotal phase III studies, demonstrated the efficacy of dolutegravir in the treatment of HIV-infected patients who had failed prior ART, retaining partial to full activity in patients with integrase resistance.[15,17] Dolutegravir 50mg once daily, on top of an optimised background regimen, exerted a greater virological effect than raltegravir 400mg twice daily in antiretroviral-experienced, integrase-inhibitor-*naïve* adults with HIV-1 in the randomised, double-blind SAILING study.[17] The recommended dosage for dolutegravir as salvage therapy is 50mg twice daily, however, as established in the phase IIb VIKING pilot study in which dolutegravir 50mg twice daily was well tolerated and provided greater and more durable antiviral benefit than the once-daily regimen in patients with HIV-1 infection resistant to raltegravir.[16] These results were subsequently confirmed in the non-blinded VIKING-3 study in which dolutegravir 50mg twice daily was effective and well tolerated in highly treatment-experienced patients with advanced HIV disease and evidence of resistance to raltegravir and elvitegravir.[15]

Comment: Dolutegravir is expected to have a utility in salvage therapy for treatment-experienced patients but the optimum role is not yet certain. Within class, dolutegravir cross resistance has been well described but dolutegravir retains useful activity, although this decreases with accrual of Q148 position mutations which are the characteristic signature of dolutegravir resistance. For this reason, failing raltegravir-, elvitegravir- and dolutegravir-containing regimens should ideally be detected and discontinued at the earliest opportunity to facilitate sequencing options with dolutegravir. However, an INSTI-sequencing strategy has not been subject to randomised controlled trials and in most cases an orthodox approach is recommended when constructing a salvage regimen, such that the new regimen contains new active agents from at least two classes in addition to optimised background therapy for best outcomes.

EXPERT'S CONCLUDING REMARKS

Dolutegravir is a potent and durable treatment for treatment-*naïve* and -experienced HIV-infected patients. Well designed and conducted randomised controlled trials have demonstrated non-inferiority or superiority versus guideline-recommended first-line regimens from the NNRTI, INSTI and PI classes. This efficacy has been driven by the superior tolerability profile of the agent. It will likely be a popular choice with patients because of this and the once-daily dosing schedule, especially if available as a single tablet regimen.

The pharmacokinetics and pharmacodynamics are relatively forgiving, but there is an important enhancing effect of food on bioavailability which is important in treatment-experienced patients. Drug-drug interactions are uncommon, but there are important interactions with rifampicin and other antiretrovirals, including the NNRTIs efavirenz and etravirine and the PIs tipranavir and fosamprenavir, that require a compensatory twice-daily dose increase and should be carefully considered when prescribing salvage regimens. There are no significant interactions with NRTIs and dolutegravir performs equally well with ABC/3TC or TDF/FTC backbones in first-line therapy. When HLA-B*57:01 screening is available, ABC/3TC may be the preferred backbone in view of renal safety or if a single tablet regimen is preferred.

Prescribers do need to be familiar with the unique renal profile of dolutegravir, and it should be used with care in patients with chronic renal diseases, or significant comorbidities such as diabetes and/or hypertension, or prescribed other medication that may adversely affect renal function to ensure that any important changes in renal function are recognised.

In the future, dolutegravir may have a role in the treatment of special populations, such as children. The favourable pharmacodynamics, tolerability and high barrier to resistance also offer prospects for novel approaches to ART including class-sparing regimens and treatment simplification strategies such as dual- or even mono-therapy.

Dolutegravir is now a recommended first-line INSTI regimen with ABC/3TC or TDF/FTC in the IAS-USA, DHHS and ASHM guidelines but the optimum role in national treatment programmes requires debate and expert consensus. In an era of effective well-tolerated generic ART, cost-effectiveness must be also be taken into consideration. In resource-constrained settings, universal access to cost-effective ART should be the overriding public health priority. Dolutegravir can also have an important role; for example, dolutegravir is a logical first-line choice for patients with transmitted NNRTI resistance or a psychiatric contraindication to EFV, or as a component of a second-line regimen if intolerant of NNRTI. However, for many treatment-*naïve* patients dolutegravir may not have realisable advantages over currently available treatments, which will remain appropriate and effective.

TAKE-HOME MESSAGES

- Dolutegravir is a second-generation integrase inhibitor that is indicated for the treatment of HIV-1 infection in adults and adolescents.
- The pharmacological profile of dolutegravir allows for once daily dosing, reduced potential for drug interactions and less potential for drug resistance (**Table 2**).
- Dolutegravir has demonstrated statistical superiority in terms of efficacy and safety when compared with other first-line regimens, such as those containing efavirenz or darunavir/ritonavir in treatment-*naïve* patients.
- Dolutegravir, in the treatment of *naïve* patients, has demonstrated a high barrier to resistance comparable with protease inhibitors.
- Dolutegravir has a favourable safety and tolerability profile.
- Dolutegravir causes an increase in the observed serum creatinine level but does not affect renal function.
- Treatment guidelines recommend dolutegravir as a preferred agent in combination with NRTIs for treatment-*naïve* HIV-infected patients.

	Recommended dose	Metabolism	Advantages	Disadvantages
dolutegravir	50mg once daily in treatment-*naïve* patients 50mg twice daily in INSTI-resistant patients	Primary pathway: UGT1A1-mediated glucuronidation Secondary pathway: CYP3A4	Low potential for drug–drug interactions No food restrictions Once-daily administration Does not require pharmacokinetic boosting High genetic barrier Suitability for use in STR	Inhibits tubular secretion of creatinine May cause headache or insomnia
elvitegravir †	150mg once daily + booster (ritonavir 100mg or COBI)	Primary pathway: CYP3A4 Secondary pathways: UGT1A1/3-mediated glucuronidation and oxidative metabolism	Fewer CNS adverse effects and rash, and better lipid profile than efavirenz Non-inferior to raltegravir in treatment-experienced patients Once-daily administration with COBI in STR	Not recommended for patients with eGFR <70 mL/min Must be taken with food Low genetic barrier Many booster-related drug-drug interactions
raltegravir	400mg twice daily	UGT1A1-mediated glucuronidation	Lowest potential for drug–drug interactions No food restrictions Does not require pharmacokinetic boosting Longest clinical experience	No STR available Inferior to dolutegravir in treatment-experienced patients Low genetic barrier Twice daily administration

Table 2. Overview of the main pharmacological and clinical characteristics of dolutegravir, raltegravir, and elvitegravir [8]. †Only registered in New Zealand as the combination agent elvitegravir/cobicistat/emtricitabine/tenofovir (as of September 2016). Abbreviations: COBI = cobicistat; CYP3A4 = cytochrome P450 3A4; eGFR = estimated glomerular filtration rate; INSTI = integrase strand transfer inhibitor; STR = single tablet regimen; UGT = uridine diphosphate glucuronosyltransferase

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Please consult the full Dolutegravir Data Sheet at www.medsafe.govt.nz before prescribing. Treatment decisions based on these data are the full responsibility of the prescribing physician.