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in HIV/AIDS

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Dear Doctor:

Dolutegravir, a second-generation integrase strand transfer inhibitor (INSTI) is now available through the BC Centre for Excellence in HIV/AIDS (BC-CfE) Drug Treatment Program and is considered 'Extended Therapy'.

Dolutegravir has been studied in treatment-naïve and experienced individuals. In brief, clinical trials in antiretroviral-naïve patients demonstrated non-inferiority of virologic suppression with dolutegravir compared to raltegravir[1,2] and superiority when compared to efavirenz (88% vs 81% suppression)[3] driven primarily by differences in discontinuations due to adverse events. When compared to darunavir**,** at week 48, 90% of those receiving dolutegravir achieved viral suppression vs. 83% in the darunavir arm (difference 7.1%; 95% CI 0.9% to 13.2%), meeting both non-inferiority and superiority criteria.[4] The superiority difference was again driven by differences in discontinuations due to adverse events/other reasons (4% vs. 10%). No emergent resistance mutations related to treatment were seen in either arm. In treatment-experienced but INSTI-naïve patients dolutegravir was superior to raltegravir at week 48, with 71% of those receiving dolutegravir achieving pVL < 50 copies/mL compared to 64% in those receiving raltegravir (difference 7.4%; 95% CI 0.7 to 14.2%).[5]

Dolutegravir has excellent bio-absorption with maximum concentrations achieved within two hours of dosing. Dolutegravir is well absorbed in both fasting and non-fasting states and can be administered with or without food.[6,7]

Dolutegravir is given 50mg once daily in INSTI-naïve individuals[8] or 50mg twice daily in treatment-experienced patients with certain INSTI resistance mutations or suspected resistance. The 50mg twice daily dose should be used in INSTI-naive patients taking strong UGT1A/CYP3A inducers.

Dolutegravir is metabolized by UGT1A1 with some contribution of CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4 and membrane transporters P-gp and BCRP *in vitro.*[9] No known dose reductions are required for mild to moderate hepatic dysfunction, but there are limited data for use in individuals with severe hepatic dysfunction. Drugs that

induce these enzymes or transporters may reduce plasma levels or dolutegravir and its therapeutic effect and drugs that inhibit these enzymes or transporters may increase plasma levels of dolutegravir.

Dolutegravir twice daily dosing should be used with concomitant efavirenz, fosamprenavir and tipranavir. Use of etravirine or nevirapine with dolutegravir is not recommended due to a significant reduction in dolutegravir exposure. However, etravirine and dolutegravir may be used with concomitant ritonavir-boosted darunavir, lopinavir or atazanavir as this effect was mitigated.[9,10] Dolutegravir does not have significant interactions with methadone, oral contraceptives, or prednisone.[11,12,13] Rifampin, but not rifabutin, affects dolutegravir concentration, requiring dolutegravir twice daily dosing. [6]

Due to effects on dolutegravir absorption, dolutegravir should be taken at least 2 hours before or 6 hours after taking medications containing polyvalent cations (e.g. magnesium, aluminum, iron or calcium)[9] including sucralfate, oral iron or calcium supplements, buffered medications and cation-containing antacids or laxatives. Gastric acid lowering medications such as H2 antagonists or proton pump inhibitors may be co-administered with dolutegravir (limited data).

Dolutegravir inhibits the renal organic cationic transporter-2 (OCT-2), resulting in an early but stable increase in serum creatinine of approximately 10-12 μmol/L.[14,15] This observed increase in serum creatinine (and resultant decrease in eGFR) is artefactual,[16] similar to that seen with trimethoprim, cimetidine, cobicistat, and rilpivirine. There is no evidence that dolutegravir has an adverse effect on actual renal function. Severe renal impairment (i.e. creatinine clearance <30mL/min) is associated with decreased dolutegravir levels. No dolutegravir dose adjustment is required in individuals with mild to moderate renal impairment; however, caution is warranted in INSTI-experienced individuals with suspected INSTI resistance or certain INSTI-associated mutations with severe renal impairment due to potential decreased therapeutic effect. Standard dolutegravir dose adjustments, however, are not advised. [17] Dolutegravir has not been studied in patients requiring hemodialysis.[9]

Dolutegravir has been well tolerated in clinical trials; however, side effects reported in ≥2% of clinical trial participants include diarrhea, headache, and insomnia. Blood work monitoring should include hepatic transaminases, bilirubin, serum creatinine and creatine phosphokinase.

Dolutegravir has a higher barrier to development of resistance compared to raltegravir and elvitegravir. However, baseline INSTI mutations at positions N155 and Q148 with the presence of additional secondary INSTI mutations has been shown to result in decreased dolutegravir susceptibility in treatment-experienced patients, notably the combination of Q148H and G140S mutations.[13,18] Prolonged exposure to a failing INSTI-based regimen should be avoided to minimize accumulation of INSTI resistance mutations.

Safety and efficacy of dolutegravir has not yet been established in children younger than 12 years or weighing less than <40kg, or in pregnant or breastfeeding women.

Guidelines for use

1. Dolutegravir 50mg daily can be considered an alternate option for antiretroviral therapy, combined with either abacavir/lamivudine or tenofovir/emtricitabine in those individuals unable to tolerate other regimens or when other first line options are not optimal.
2. Dolutegravir 50mg daily dosing can be considered for use in treatment-experienced patients without prior INSTI exposure or resistance.
3. Dolutegravir should not be combined with etravirine without the presence of boosted darunavir, lopinavir or atazanavir. Dolutegravir should be given twice daily in patients also taking efavirenz, fosamprenavir, tipranavir, or rifampin.
4. Baseline INSTI resistance mutations must be evaluated when using dolutegravir in patients with a history of virologic failure while receiving raltegravir or elvitegravir, and 50mg twice daily dosing is recommended.
5. Dolutegravir can be dosed without regard to food but should be taken at least 2 hours before or 6 hours after medications containing polyvalent cations (e.g. oral calcium or iron supplements, sucralfate, cation-containing antacids or laxatives, and buffered medications) due to effects on dolutegravir absorption.
6. An increase in serum creatinine of approximately 10-12 µmol/L may be expected during the first 2 weeks of treatment with dolutegravir (whether dosed once or twice daily), with stabilization thereafter. Further investigation and consideration of nephrology referral is recommended if the increase in serum creatinine is > 20 µmol/L, if the serum creatinine continues to increase after 4 weeks on therapy, or if other signs of kidney disease (e.g. new onset proteinuria) are present.

Yours sincerely,

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