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Dolutegravir: its use in adult patients

The second generation integrase inhibitor dolutegravir was recently registered by the Medicines Control Council, together with the fixed-dose combination tablet of abacavir/lamivudine/dolutegravir. The standard dose of dolutegravir is 50mg once-daily; for the abacavir/lamivudine/dolutegravir fixed-dose combination tablet it is one tablet daily.

Dolutegravir in first-line ART: Three randomised trials of dolutegravir in ART-naïve patients have been conducted. The SINGLE trial compared dolutegravir/abacavir/lamivudine versus efavirenz/tenofovir/emtricitabine in ART-naïve adults (n=833). At week 48, the dolutegravir arm was superior to the efavirenz arm: the proportion of participants with an HIV viral load < 50 copies/ml was 88% in the dolutegravir arm versus 81% in the efavirenz arm (p=0.003). This difference was driven by the superior tolerability of the dolutegravir arm: 2% versus 10% had an adverse event leading to discontinuation of study drug and such discontinuations were then counted as failures in the viral suppression analysis [Walmsley]. In the two other trials, a dolutegravir regimen was found to be superior to a darunavir/ritonavir-based first-line regimen [Molina] and non-inferior to a raltegravir-based first-line regimen [Raffi].

AfA does not currently recommend routine inclusion of dolutegravir in the first-line ART regimen. The reasons for this are its cost and to retain alignment with the public sector ART programme. Many patients transition between the private and public sectors, and alignment of the drug classes used in 1st, 2nd and 3rd line ART regimens to date has allowed for uncomplicated transition of patients between these sectors. Also, dolutegravir still needs to be adequately evaluated in patients on treatment for TB (there is an ongoing trial: the INSPIRING study). We recommend use of dolutegravir in first-line regimens for patients who develop a severe hypersensitivity reaction to an NNRTI (rash or hepatitis) contra-indicating further use of that class.

While dolutegravir was superior to efavirenz in the SINGLE trial this was because more patients needed to be switched from efavirenz to an alternative, usually because of CNS side effects. After this was accounted for there was no difference in terms of virological suppression between the arms. In patients who develop severe or persistent CNS side effects on efavirenz we recommend switching to rilpivirine, which has a much lower incidence of CNS side effects.

Dolutegravir in second-line ART: The SAILING study compared raltegravir versus dolutegravir in adult patients who were ART-experienced, but integrase inhibitor-naïve with at least two class resistance (n = 715). At week 48, analysis of viral efficacy (viral load <50 copies/mL) showed that dolutegravir was superior to raltegravir (71% vs 64% suppression; p=0.03). Importantly in this trial background regimens were individually optimised using resistance test results and treatment history, and had to contain 1 or 2 fully active drugs based on the resistance test.

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There is an ongoing trial comparing dolutegravir plus NRTIs versus lopinavir/ritonavir plus NRTIs in patients who have failed a first-line of 2 NRTIs and an NNRTI. In this trial too patients have a resistance test before being enrolled and must receive at least one fully active agent within the NRTI background regimen. (<https://clinicaltrials.gov/ct2/show/NCT02227238>).

Thus we do not currently know whether the combination of 2 NRTIs + dolutegravir will perform as well as the current standard second-line regimen of 2 NRTIs + boosted PI regimen, particularly in situations where resistance testing at first-line failure has not been done and thus it is not known whether there is susceptibility to the 2 NRTIs in the backbone. We know from the EARNEST trial [Paton] and the ACTG 5273 trial (<http://www.croiconference.org/sessions/actg-5273-randomized-trial-second-line-art-supports-who-guidance>) that a 2NRTI + lopinavir/ritonavir regimen achieves high rates of viral suppression despite there being resistance to the 2NRTIs in the regimen; we do not have similar data for dolutegravir currently. Until we have comparative data, AfA does not recommend the use of 2 NRTIs + dolutegravir as a second line regimen either initially or to switch to this combination.

Dolutegravir in third-line ART: To date for third-line ART regimens, AfA has usually recommended darunavir/ritonavir plus raltegravir combined with other drugs based on the resistance test result. Raltegravir has a considerably lower barrier to resistance compared to dolutegravir, as it requires only a single mutation for significant resistance to develop. We, therefore, now recommend that if an integrase inhibitor is required in third-line ART it should be dolutegravir and not raltegravir. In a patient who is established on third-line ART containing raltegravir we recommend switching to dolutegravir. If their HIV viral load is < 50 copies/ml then a straight switch to dolutegravir 50mg daily can be made. If their viral load is not suppressed then the case should be discussed with AfA first.

Dolutegravir and its high genetic barrier to resistance: In all 3 of the first-line trials discussed above, dolutegravir resistance was not observed in patients failing the dolutegravir regimen. The high genetic barrier to resistance for dolutegravir relates to the specific mutations it selects. The most common mutation selected by dolutegravir *in vitro* and in trials of ART-experienced patients is R263K. When present as a single primary mutation, this mutation results in impaired DNA binding and integration, ultimately reducing viral fitness [Quashie]. A secondary mutation (H51Y) may follow; H51Y further compromises viral fitness [Mesplede 2013]. The combination of these two mutations carry a severe fitness cost with relatively low level resistance thereby crippling viral replication and preventing the emergence of additional compensatory mutations [Mesplede 2014]. This likely explains why it is difficult to develop resistance to dolutegravir in patients naïve to integrase inhibitors. In contrast, in patients who have failed a raltegravir regimen, certain of the mutations that accumulate that cause raltegravir resistance can cause cross-resistance to dolutegravir.

Dolutegravir and side effects: Dolutegravir is generally well tolerated. It has CNS side effects, but these are observed less frequently than with efavirenz apart from insomnia (which is more common than with efavirenz). It may also cause abdominal symptoms and derangements in liver function tests.

Dolutegravir with TB treatment: Rifampicin induces UGT-1A1 (the major metabolizing enzyme for dolutegravir) and cytochrome 3A4 (which also contributes to dolutegravir metabolism) and thereby increases clearance of dolutegravir. Twice daily dosing (dolutegravir 50mg 12-hourly) has been shown to overcome this induction in healthy volunteers [Dooley] and this strategy is currently being evaluated in TB patients (INSPIRING study).

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Dolutegravir: its use in paediatric patients

Integrase inhibitors (INSTI)s are an increasingly important option for children. Currently, raltegravir is a useful option for 3rd line antiretroviral therapy (ART) and for intolerance to key antiretrovirals in South Africa. Dolutegravir, a next generation INSTI, has a higher threshold for resistance than raltegravir, is dosed once daily (versus twice daily for raltegravir), and is a more potent molecule, requiring a lower dose making it more suitable than raltegravir for fixed dose combinations. ViiV Healthcare, the developer of dolutegravir, has agreed to register dolutegravir with the Medicines Patent Pool in 2014 to permit generic formulations in low- and middle-income countries.

IMPAACT 1093, an ongoing open-label pharmacokinetic, safety and efficacy study of dolutegravir plus optimised background regimen in children and adolescents, presented data at the Conference on Retroviruses and Opportunistic Infections, 2016 in Boston. Children 6 to 12 years of age who were failing a current ART regimen were recruited in a multi-centre study. The median age was 10 years, CD4 count was 645 cells/mm³, and viral load was 100,000 copies/mL. Eighteen of 23 (78%) children responded to a dolutegravir-based regimen with virological suppression to < 400 HIV RNA copies/mL after 48 weeks on study.¹ There were no dolutegravir-related adverse events. ViiV Healthcare filed two reduced strength tablets (10 mg and 25 mg) for the 6-12 years age group with the FDA in 2015. An ongoing study (P1093) is enrolling infants from 4 weeks of age until 6 years of age and is evaluating granules and dispersible tablet formulations.²

Dolutegravir is a promising new antiretroviral for children. However, a worrying 'real-life' report from Holland found that 62 of 387 adults (16%) stopped dolutegravir due to intolerance, mainly sleep disorders, gastrointestinal upset and psychiatric conditions.³ With any new medication, vigilance is essential.

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Drug-drug interactions between antiretrovirals and itraconazole

Itraconazole is the azole of choice in patients with disseminated histoplasmosis (after an initial treatment phase with intravenous amphotericin B). However, there are important drug-drug interactions between itraconazole and many antiretrovirals, shown in the following table (nucleoside reverse transcriptase inhibitors do not interact so they are not included in the table):

Antiretroviral	Effect on itraconazole	Recommendation for itraconazole dose
Efavirenz	40% reduction in AUC	Increase itraconazole dose 50%
Etravirine	No data – reduction likely	Avoid co-administration
Nevirapine	60% reduction in AUC	Avoid co-administration
Rilpivirine	No data – interaction unlikely (rilpivirine concentrations will likely be increased)	No change
Raltegravir/dolutegravir	No effect	No change
Ritonavir-boosted PI	3-fold increase in AUC	Maximal itraconazole dose 200 mg/day

AUC = area under the concentration-time curve

In summary, antiretrovirals that are enzyme inducers (e.g. efavirenz, etravirine & nevirapine) will reduce the concentrations of itraconazole. A dose increase of itraconazole may overcome this with efavirenz, but AfA does not recommend this approach as there is considerable variability in itraconazole exposure, unless therapeutic drug monitoring can be done. Antiretrovirals that are enzyme inhibitors (e.g. ritonavir) cause a marked increase in itraconazole concentrations. Itraconazole has been reported to cause serious dose-related toxicity, including cardiac failure and adrenal suppression, so it is imperative that the dose of itraconazole not exceed 200 mg/day when co-administered with a ritonavir-boosted protease inhibitor. An integrase inhibitor-based regimen is recommended for people who need itraconazole.

The 11th edition of the AfA Clinical Guidelines will be available in July 2016. Please send us an email (afa@afadm.co.za) with your postal address or phone 0860 100 646 if you would like us to send you a free copy. Alternatively, the updated guidelines will soon be available to download from the AfA website (www.aidforaids.co.za)



Zika and HIV

Like its counterparts, dengue and chikungunya, Zika virus causes a syndrome of fever, rash, arthritis and conjunctivitis, within 1 week of transmission from mosquitoes of the *Aedes* species. First discovered in 1947 in primates from the Zika Forest of Uganda, the first human cases were recorded in 1952. Since then, Zika outbreaks and cases have been documented in other African countries, Southeast Asia and South America and the Caribbean.



Countries and territories reporting active mosquito transmission of Zika virus

Symptoms usually last for up to a week and chronic sequelae are slowly becoming evident. In addition to the well-publicised causation of microcephaly in the babies of women who become infected in pregnancy, a link between Zika and Guillain-Barré is also being investigated. Treatment of Zika is symptomatic, and there is currently no vaccine available.

HIV-infected persons are not known to be at increased risk of acquisition of Zika virus, nor of having more severe disease once infected. However, the Zika clinical spectrum continues to unfold, and it is known that HIV infection does predispose to more severe infection with Zika's counterpart, dengue.

Persons with HIV who are travelling to a Zika-endemic country, such as to Brazil for the Rio Olympics in July, are encouraged to seek a consultation with their travel medicine provider, to ensure that all routine vaccines are up to date, and that Yellow Fever vaccination is discussed if applicable. Mosquito bite avoidance is the primary measure, using repellants containing at least 20% DEET, and protective clothing which may be impregnated with permethrin. *Aedes* species are diurnal biters, peak activity being at dawn and dusk, but also at other times of the day. Sexual transmission of Zika has been documented, so safe sex using condoms is advised for all travellers.