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Why you should switch patients doing well on efavirenz to dolutegravir

“If it ain’t broke, don’t fix it” is a common attitude among clinicians treating patients on chronic medicines. If a patient is doing well on an antiretroviral therapy (ART) regimen, switching could cause harm by introducing different drugs with new side effects. Many patients are virologically suppressed on their first-line ART regimen of efavirenz, typically combined with tenofovir and emtricitabine/lamivudine. Efavirenz is generally well tolerated; it commonly causes neuropsychiatric toxicity, but tolerance rapidly develops after the first few weeks in most patients. Long term efavirenz toxicity can occur but is uncommon.

Why then do WHO and South African guidelines recommend switching patients who are virologically suppressed on a first-line efavirenz regimen to a dolutegravir regimen? The reason for this policy is the far greater durability of dolutegravir-based first-line ART. Efavirenz has a low genetic barrier to resistance, meaning that a single mutation can confer high level resistance to efavirenz and other non-nucleoside reverse transcriptase inhibitors (NNRTI), often together with resistance to lamivudine and emtricitabine, both of which also have a low genetic barrier to resistance and share the same resistance mutation. A short period of poor adherence or a treatment interruption on efavirenz-based first-line ART can result in resistance, which can be transmitted to people not yet on ART. A systematic review found that NNRTI resistance in southern Africa was present in 3.8% of ART-naïve patients and 31.5% in patients recommencing ART.¹ By contrast, dolutegravir has a high genetic barrier to resistance; several resistance mutations are required before the antiviral activity of dolutegravir is compromised. Dolutegravir resistance has only very rarely been described in patients on first-line ART consisting of dolutegravir and two nucleoside reverse transcriptase inhibitors. Therefore, first-line dolutegravir-based ART will be much more durable than efavirenz-based ART.

Dolutegravir is better tolerated than efavirenz in randomised controlled trials in people starting ART. More weight gain has been associated with dolutegravir than efavirenz but this has been shown to be due to a toxic effect of efavirenz impairing weight gain in people who are genetic slow metabolisers of efavirenz (about a fifth of South Africans).² Severe long term toxicity (e.g. encephalopathy, suicidal ideation, drug-induced liver injury) occurs more commonly in genetic slow metabolisers of efavirenz. Therefore, switching people back to efavirenz if they gain weight on dolutegravir could increase the risk of drug-related toxicity.

References:

1. Gupta RK, Gregson J, Parkin N et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. *Lancet Infect Dis* 2017;18:346–55.
2. <https://www.afa.co.za/wp-content/uploads/2022/01/nletdec20.pdf>

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