HIV-1 diversity and the implementation of integrase strand-transfer inhibitors as part of combination antiretroviral therapy

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To the Editor: The integrase (IN) strand-transfer inhibitor (InSTI) dolutegravir (DTG) is now recommended by the World Health Organization as part of salvage and/or first-line combination antiretroviral therapy (cART).[1] DTG has a high genetic barrier against developing resistance and is effective against all strains that previously exhibited resistance-associated mutations (RAMs) against other cART regimens.[2] Recommendations to use DTG were delayed owing to preliminary findings from Botswana that indicated potential safety concerns in pregnancy, with a small increased risk of neural tube defects.[3] Studies that investigated the safety and efficacy of DTG now support its use in all populations, including pregnant women and those of childbearing potential.[4,5]

HIV-1 genetic diversity continues to make it difficult to control the pandemic. New subtypes are still being identified, with HIV-1 subtype L only being described and characterised in 2019.[6] It is well known that HIV-1 diversity remains a key challenge pertaining to a wide spectrum of fields, such as serological diagnoses, virological follow-up, vaccine development and therapeutic monitoring. Although HIV-1 subtype C is prevalent in southern Africa, the majority of the HIV-1 groups and subtypes, including circulating recombinant forms (CRFs), can be found in Africa.[7] Some mutation pathways clearly differ by subtype variation. For example, a study by Doyle *et al.*[8] comparing major IN RAMs in raltegravir (RAL) recipients at positions 148 and 140 of IN between subtype B and non-B clades found that these mutations were exclusively present in subtype B sequences. The G118R InSTI mutation was only found among individuals infected with HIV-1 subtype C and CRF02_AG. This mutation is rarely present in HIV-1 subtype B.[9] It has been postulated that G118R could be an alternative pathway for DTG resistance in non-subtype B viruses, whereas R263K is the preferred pathway for subtype B viruses.[10] Of note, the majority of group O viruses are naturally resistant to non-nucleoside reverse transcriptase inhibitors owing to the presence of the C181Y mutation in the reverse transcriptase gene.[9] In our studies, we observed low-level RAMs against InSTIs.[7,11,12] The effect of these mutations is yet to be fully understood. Through our structural modelling and docking studies, we observed differences of InSTIs drug-binding interactions to different HIV-1 IN subtypes, but we did not observe any significant differences in binding affinity for each InSTI.[13-15] This finding implies no significant alteration to the binding site in the wild-type IN, which may consequently prevent InSTI drug binding. By using triple therapy, the impact of developing clinical resistance should be limited if patients remain fully adherent. In cases where it is suspected that cART failure is due to resistance development, resistance testing should be done before patients are switched to a new regimen. We do support the full-scale use of DTG in African settings where diverse subtypes are prevalent. Continued close monitoring strategies to ensure a successful switch of regimens is warranted in patients with virological failure and who have developed resistance to their cART regimens.

Sello Given Mikasi
Division of Medical Virology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
mikasi@sun.ac.za

George Mondinde Ikomey
Centre for the Study and Control of Communicable Diseases, University of Yaoundé 1, Cameroon

Adetayo Emmanuel Obasa
Division of Medical Virology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

Ruben Cloete
South African Medical Research Council Bioinformatics Unit, South African National Bioinformatics Institute, University of the Western Cape, Cape Town, South Africa

Graeme Brendon Jacobs
Division of Medical Virology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
graeme@sun.ac.za

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