

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

Item Type	Article
Authors	Mikasi, S.G.;Ikomey, G.M.;Obasa, A.E.;Cloete, R.;Jacobs, G.B.
Citation	Mikasi SG, Ikomey GM, Obasa AE, Cloete R, Jacobs GB. HIV-1 diversity and the implementation of integrase strand-transfer inhibitors as part of combination antiretroviral therapy. S Afr Med J. 2020 Aug 31;110(9):13071. doi:10.7196/SAMJ.2020.v110i9.14848.
DOI	10.7196/SAMJ.2020.v110i9.14848
Publisher	South African Medical Journal
Journal	South African Medical Journal
Rights	Attribution 3.0 United States
Download date	2024-07-22 10:25:35
Item License	http://creativecommons.org/licenses/by/3.0/us/
Link to Item	http://www.samj.org.za/index.php/samj/article/view/13071



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

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

1. World Health Organization. Policy brief: Update of recommendations on first- and second-line antiretroviral regimens (WHO/CDS/HIV/19.15). 2019. <https://apps.who.int/iris/handle/10665/325892> (accessed 10 August 2020).
2. Messiaen P, Wensing AMJ, Fun A, Nijhuis M, Brusselselaers N, Vandekerckhove L. Clinical use of HIV integrase inhibitors: A systematic review and meta-analysis. *PLoS ONE* 2013;8(1):e52562. <https://doi.org/10.1371/journal.pone.0052562>
3. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. *N Engl J Med* 2018;379(10):979-981. <https://doi.org/10.1056/NEJMc1807653>
4. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med* 2019;381(9):827-840. <https://doi.org/10.1056/NEJMoa1905230>
5. Pereira G, Kim A, Jalil E, et al. National Cohort Study of Dolutegravir and Pregnancy Outcomes in Brazil. No occurrences of neural tube defects among 382 women on dolutegravir at pregnancy conception in Brazil. Presented at IAS 2019, Mexico City, 21 - 24 July 2019. <http://programme.ias2019.org/Abstract/Abstract/4991> (accessed 23 April 2020).
6. Yamaguchi J, McArthur C, Vallari A, et al. Complete genome sequence of CG-0018a-01 establishes HIV-1 subtype L. *J Acquir Immune Defic Syndr* 2020;83(3):319-322. <https://doi.org/10.1097/QAI.0000000000002246>
7. Mikasi SG, Gichana JO, van der Walt C, et al. HIV-1 integrase diversity and resistance-associated mutations and polymorphisms among integrase strand transfer inhibitor-naïve HIV-1 patients from Cameroon. *AIDS Res Hum Retroviruses* 2020;36(5):450-455. <https://doi.org/10.1089/AID.2019.0264>
8. Doyle T, Dunn D, Ceccherini-Silberstein F, et al. Integrase inhibitor (INI) genotypic resistance in treatment-naïve and raltegravir-experienced patients infected with diverse HIV-1 clades. *J Antimicrob Chemother* 2015;70(11):3080-3086. <https://doi.org/10.1093/jac/dkv243>
9. Quashie PK, Oliveira M, Veres T, et al. Differential effects of the G118R, H51Y, and E138K resistance substitutions in different subtypes of HIV integrase. *J Virol* 2015;89(6):3163-3175. <https://doi.org/10.1128/JVI.03353-14>
10. Trono D, van Lint C, Rouzioux C, et al. HIV persistence and the prospect of longterm drug-free remissions for HIV-infected individuals. *Science* 2010;329(5988):174-180. <https://doi.org/10.1126/science.1191047>
11. Obasa AE, Mikasi SG, Brado D, et al. Drug resistance mutations against protease, reverse transcriptase and integrase inhibitors in people living with HIV-1 receiving boosted protease inhibitors in South Africa. *Front Microbiol* 2020;11:438. <https://doi.org/10.3389/fmicb.2020.00438>
12. Mikasi SG, Isaacs D, Ikomey GM, et al. HIV-1 drug resistance mutation analyses of Cameroon derived integrase sequences. *AIDS Res Hum Retroviruses* 2020 (epub 10 August 2020). <https://doi.org/10.1089/aid.2020.0022>
13. Brado D, Obasa AE, Ikomey GM, et al. Analyses of HIV-1 integrase sequences prior to South African national HIV-treatment program and availability of integrase inhibitors in Cape Town, South Africa. *Sci Rep* 2018;8:4709. <https://doi.org/10.1038/s41598-018-22914-5>
14. Chitongo R, Obasa AE, Mikasi SG, Jacobs GB, Cloete R. Correction: Molecular dynamic simulations to investigate the structural impact of known drug resistance mutations on HIV-1C integrase-dolutegravir binding. *PLoS ONE* 2020;15(6):e0234581. <https://doi.org/10.1371/journal.pone.0234581>
15. Isaacs D, Mikasi SG, Obasa AE, Ikomey GM. Structural comparison of diverse HIV-1 subtypes using molecular modelling and docking analyses of integrase inhibitors. Preprints 2020 (epub 5 February 2020). <https://doi.org/10.20944/preprints202002.0062.v1>

S Afr Med J 2020;110(9):827. <https://doi.org/10.7196/SAMJ.2020.v110i9.14848>