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Increasing level of pretreatment HIV drug resistance: a real menace or minor detail?

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Dear editor,

In a randomized study in Kenya, Chung and colleagues [1] report a lower impact of pretreatment drug resistance (PDR) to non-nucleoside reverse transcriptase inhibitor (NNRTI) on virological outcomes of antiretroviral therapy (ART) than previously reported. [2–6] Given the increasing levels of NNRTI-PDR in many low- and middle-income countries (LMICs) [7], this conclusion may lead to complacency in addressing the PDR impact. In our view, the study findings need to be interpreted in light of the following considerations:

First, several other studies have shown significant effect of PDR on virological failure (VF) for efavirenz-containing ART.[2–6] Moreover, despite the overall lower impact of PDR in the study by Chung et al, the authors also observed that among participants with NNRTI-associated PDR, those receiving protease inhibitor-based ART had lower odds of VF than did those who received first-line NNRTI-based ART (OR 0.32; $p=0.036$), supporting the argument that the use of NNRTIs in patients with NNRTI-PDR should be avoided.

Second, the comparator regimen to efavirenz-based ART was based on lopinavir/ritonavir, which yielded a slightly lower suppression rate (92.0% versus 93.6%) among those with no PDR. The use of a more efficacious comparator drug, such as dolutegravir, could have led to a larger difference in effectiveness between patients treated with NNRTIs compared to those in the (non-NNRTIs) intervention group, leading to a larger population-level impact of the intervention. This may explain the discrepant observation in the modelling study by Philips et al, which showcased superiority of dolutegravir with respect of reduced mortality,

morbidity, HIV incidence and cost vs EFV-based ART, and predicted a substantial increase in the beneficial effect of dolutegravir with increasing levels of NNRTI-PDR prevalence in LMIC. [8]

Lastly, the decision to act upon high levels of PDR may best be advised by estimating the magnitude of VF that can be attributed to PDR at the population-level, i.e. the population attributable fraction.[9] Using the study's crude odds ratio data from the NNRTI study arm and the reported PDR prevalence (9.4%), PDR may explain up to 28.4% of the VF cases. Notably, at contemporary NNRTI-PDR estimates of 10-20% observed in many LMICs, the contribution of PDR on VF would be expected to be even higher [10].

To achieve HIV epidemic control, more effective and less costly first-line regimens, such as dolutegravir-based ART, should be scaled up, and this transition is particularly urgent in settings with high NNRTI-PDR levels, as per WHO recommendations.[11]

References

- 1 Chung MH, McGrath CJ, Beck IA, Levine M, Milne RS, So I, *et al.* Evaluation of the management of pretreatment HIV drug resistance by oligonucleotide ligation assay: a randomised controlled trial. *Lancet HIV* Published Online First: December 2019. doi:10.1016/S2352-3018(19)30337-6
- 2 Ávila-Ríos S, García-Morales C, Matías-Florentino M, Romero-Mora KA, Tapia-Trejo D, Quiroz-Morales VS, *et al.* Pretreatment HIV-drug resistance in Mexico and its impact on the effectiveness of first-line antiretroviral therapy: a nationally representative 2015 WHO survey. *Lancet HIV* 2016; 3:e579–e591.
- 3 Borroto-Esoda K, Waters JM, Bae AS, Harris JL, Hinkle JE, Quinn JB, *et al.* Baseline genotype as a predictor of virological failure to emtricitabine or stavudine in combination with didanosine and efavirenz. *AIDS Res Hum Retroviruses* 2007; 23:988–995.
- 4 Kantor R, Smeaton L, Vardhanabhuti S, Hudelson SE, Wallis CL, Tripathy S, *et al.* Pretreatment HIV Drug Resistance and HIV-1 Subtype C Are Independently Associated With Virologic Failure: Results From the Multinational PEARLS (ACTG A5175) Clinical Trial. *Clin Infect Dis* 2015; 60:1541–1549.

- 5 Kuritzkes DR, Lalama CM, Ribaud HJ, Marcial M, Meyer WA 3rd, Shikuma C, *et al.* Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naïve HIV-1-infected subjects. *J Infect Dis* 2008; 197:867–870.
- 6 Kouanfack C, Mpoudi-Etame M, Omgba Bassega P, Eymard-Duvernay S, Leroy S, Boyer S, *et al.* Dolutegravir-Based or Low-Dose Efavirenz-Based Regimen for the Treatment of HIV-1. *N Engl J Med* 2019; 381:816–826.
- 7 World Health Organization. HIV drug resistance report. ; 2019.
<https://www.who.int/hiv/pub/drugresistance/hivdr-report-2019/en/>
- 8 Phillips AN, Cambiano V, Nakagawa F, Revill P, Jordan MR, Hallett TB, *et al.* Cost-effectiveness of public-health policy options in the presence of pretreatment NNRTI drug resistance in sub-Saharan Africa: A modelling study. *Lancet HIV*. 2017.
doi:10.1016/S2352-3018(17)30190-X
- 9 Northridge ME. Public health methods--attributable risk as a link between causality and public health action. *Am J Public Health* 1995; 85:1202–1204.
- 10 Inzaule SC, Bertagnolio S, Kityo CM, Siwale M, Akanmu AS, Wellington M, *et al.* The etiology of viremic episodes during antiretroviral therapy in sub-Saharan Africa: HIV drug resistance, non-adherence and low-level viremia. In: *XXVIII International workshop on HIV drug resistance and treatment strategies.*; 2019.
- 11 World Health Organization. Update of recommendations on first- and second-line antiretroviral regimens Policy brief.
<https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf?ua=1> (accessed January 17, 2020)