Population-Based Longitudinal Dynamics of HIV Drug Resistance During Dolutegravir Roll-Out in Uganda

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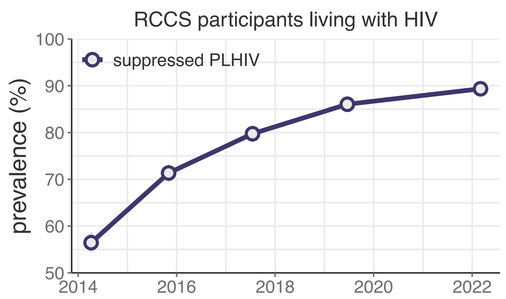
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BACKGROUND

In 2018 the World Health Organization recommended dolutegravir (DTG, an integrase strand transfer inhibitor, INSTI) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) as the preferred first-line regimen for PLHIV. Evidence from clinical trials and from people living HIV (PLIV) who attend clinics indicates that DTG uptake increases rates of viral load suppression with minimal risk of resistance. However, **population-based studies of resistance trends throughout the DTG roll-out in sub-Saharan Africa are extremely limited.**

METHODS

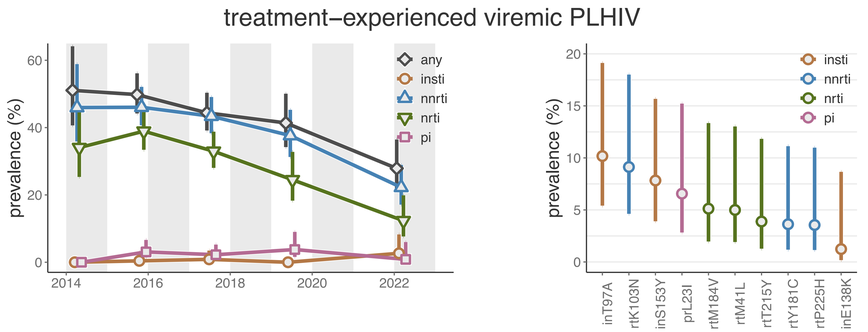
- During five survey rounds between 2012 and 2022, we performed a population-based census of **all people living in communities in southern Uganda**. Residents aged 15-49 were invited to participate in the Rakai Community Cohort Study.
- Consenting survey participants provided samples for HIV testing, viral load quantification, and viral deep-sequencing
- Sequence data from viremic samples (≥1000 copies/mL) was used to predict intermediate/high-level resistance and identify resistance mutations.
- Prevalence estimates were generated using robust Poisson regressions with general estimating equations to account for repeated measures



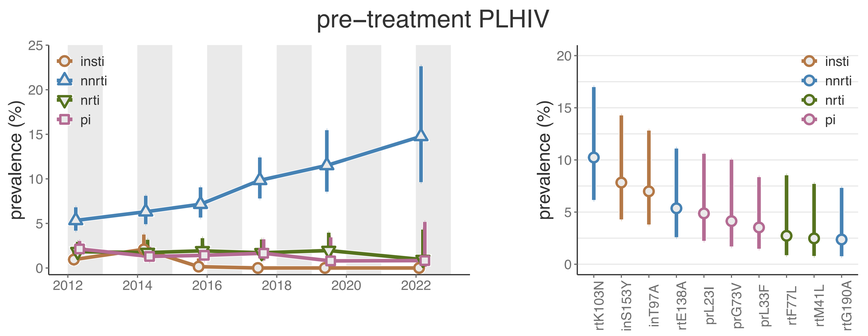
Between 2014 and 2022, viral load suppression among RCCS participants living with HIV increased 1.58-fold to **90% (95% CI 88% - 90%) by the end of the study period.**

Concurrent with the scale-up of DTG, we observe a striking decrease in the prevalence of NNRTI and NRTI resistance among viremic PLHIV and continued increase in NNRTI resistance among pre-treatment PLHIV

RESULTS

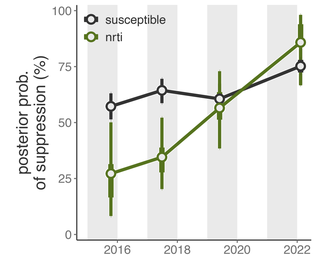


Among treatment-experienced PLHIV who remain viremic, the prevalence of resistance to any class of antiretroviral therapy **decreased 1.64-fold, from 47% (38% - 59%) to 29% (22% - 37%)** between the 2014 and 2022 survey rounds. The majority of remaining resistance among these individuals is attributable to inT97A, rtK103N, and inS153Y. **Only 2/108 (1.85%) of 2022 treatment-experienced viremic PLHIV harbored intermediate/high-level DTG resistance.**

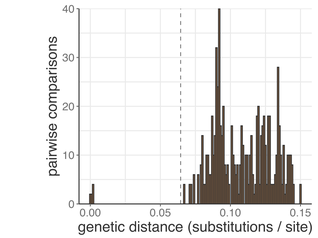


Among pre-treatment PLHIV, the prevalence of resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) **increased 2.7-fold from 5% (4% - 7%) to 14% (9% - 21%)** between the 2012 and 2022 survey rounds, largely due to rtK103N and rtE138A.

RESULTS (CONT.)



In a Bayesian mixed-effects model, the estimated probability of suppression among viremic PLHIV does not vary by NRTI (and NNRTI, not shown) resistance-status in the 2022 survey.



A total of 23/307 (7%) of viremic PLHIV in Rakai communities sampled after 2021 harbor the inS153Y mutation. **Five of these individuals are genetically linked to another PLHIV with inS153Y.**

CONCLUSIONS

- The scale-up of DTG, along with concurrent efforts to increase access and adherence to treatment regimens has resulted in a significant decrease in resistance among treatment-experienced viremic PLHIV. **The majority of treatment-experienced PLHIV who remain viremic have fully susceptible virus.**
- The DTG transition has not yet slowed the increase in NNRTI resistance among pre-treatment PLHIV. **Pre-treatment rtE138A resistance requires monitoring in light of CAB/RPV long-lasting regimens.**
- While DTG-resistance in this cohort remains extremely rare, we see a concerning increase in the inS153Y mutation, which confers two-fold DTG resistance, in the 2022 survey round. **Preliminary evidence is consistent with transmission among genetically-linked PLHIV.**

ACKNOWLEDGEMENTS

We thank all participants of the Rakai Community Cohort study for making this research possible.

NIH · Bill & Melinda Gates foundation · PANGEA HIV · Rakai Health Sciences Program · Center for AIDS Research, Johns Hopkins University · HPTN HIV Prevention Trials Network