Genetically Inferred Patterns of Transmitted HIV Pre-Treatment Resistance in Southern Uganda

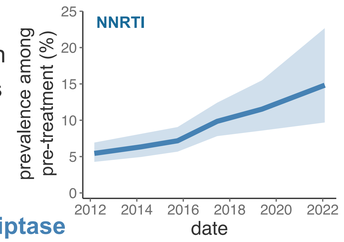
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Michael A. Martin[1,2], Seungwon Kim[1,3], Ronald Moses Galiwango[4], Sikhulile Moyo[5,6], Lucie Abeler-Dörner[7], Christophe Fraser[7], Oliver Ratmann[8,9], David Serwadda[4], Gertrude Nakigozi[4], David Bonsall[10], Steven James Reynolds[4,11,12], M. Kate Grabowski[1,2,4], on behalf of the Rakai Health Sciences Program

[1]Department of Pathology, Johns Hopkins School of Medicine, Baltimore, MD, USA, [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, NC, USA, [4]Rakai Health Sciences Program, Kalisizo, Uganda, [5]Botswana Harvard AIDS Institute Partnership, Botswana Harvard HIV Reference Laboratory, Gaborone, Botswana, [6]Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA, [7]Pandemic Sciences Institute, University of Oxford, Oxford, UK, [8]Department of Mathematics, Imperial College London, London, UK, 9Imperial-X, Imperial College London, London, UK, [10]Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK, [11]Division of Infectious Disease, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA, [12]Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

BACKGROUND

During scale-up of antiretroviral therapy (ART) in sub-Saharan Africa there has been a **striking increase** in the prevalence of pre-treatment resistance to **non-nucleoside reverse transcriptase inhibitors (NNRTIs)**. Our goal was to **quantify the transmission dynamics** giving rise to **pre-treatment ART resistance** using population-based HIV genetic data.



METHODS

We used **2,734 HIV *pol* sequences** and paired viral load data from pre-treatment people with HIV who participated in the population-based **Rakai Community Cohort Study** to identify ART resistance-conferring mutations and assess patterns of genetic clustering to identify **chains of transmitted resistance**.

VIRAL LOAD MODEL

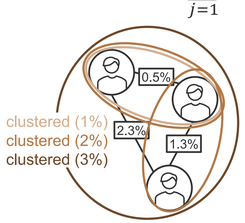
We utilized a Bayesian mixed-effects model to quantify the relationship between the presence of resistance mutations and pre-treatment viral load, which is associated with transmission potential.

$$\log_{10}(v_i) \sim N(\mu_i, \sigma)$$

$$\mu_i = \beta_{\text{sex}} x_i^{\text{sex}} + \beta_{\text{age}} x_i^{\text{age}} + \beta_{\text{subtype}} x_i^{\text{subtype}} + \sum_{j=1}^{n} \beta_j x_i^j$$

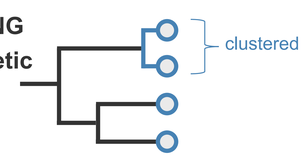
GENETIC CLUSTERING

We calculated the probability that each individual with a resistance conferring mutation was clustered with others with that same mutation across a **range of clustering thresholds** based on **Kimura 2-Parameter** distances.



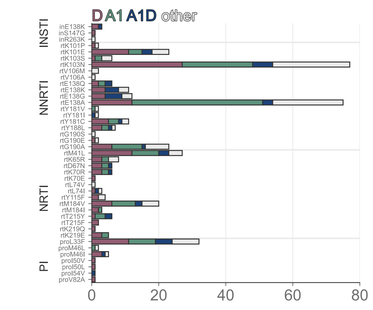
PHYLOGENETIC CLUSTERING

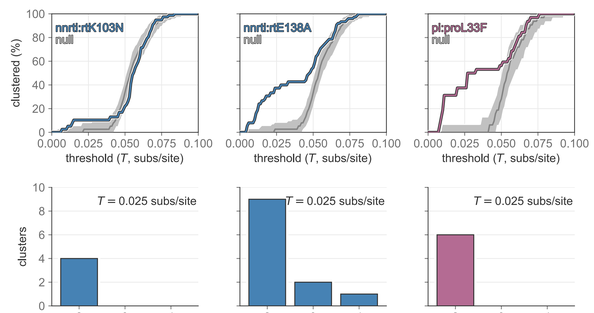
We used **Bayesian phylogenetic reconstruction** for subtype A1 and D viruses with discrete trait analysis to identify chains of transmitted resistance.



We observe **divergent genetic clustering patterns** of resistant mutations among pre-treatment individuals, including **no significant clustering** of **rtK103N** and **sustained pre-treatment transmission** of **rtE138A**

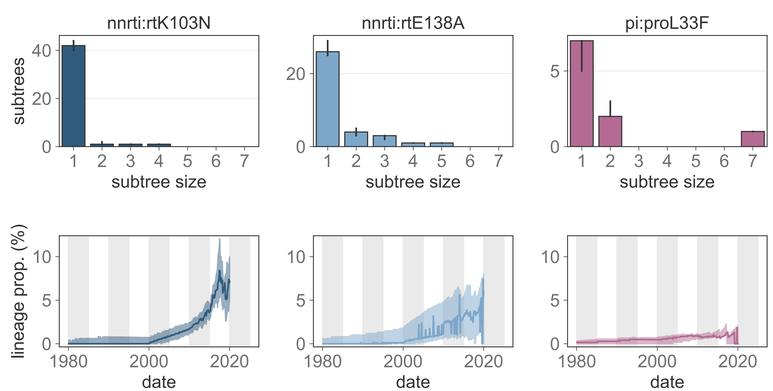
RESULTS





We observe **elevated rates** of genetic clustering of **rtE138A** (**NNRTI**, adj *p*-value <0.033) and **proL33F** (**protease inhibitor, PI**, resistance, adj *p*-value <0.033), but not of **rtK103N** (**NNRTI**, *p*-value = 0.33), the most prominent pre-treatment mutation among study participants.

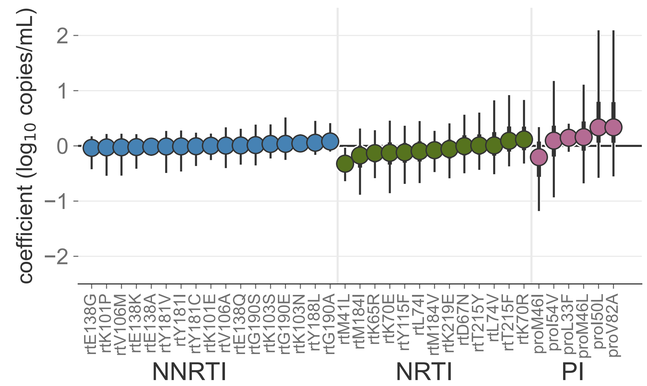
At 0.025 substitutions/site threshold (21 years of evolution at 1.2×10^{-3} substitutions/site/year), there are clusters with 3 and 4 participants with **rtE138A** (*n* = 2,1), suggesting **sustained pre-treatment transmission**.



Bayesian phylogenetics recapitulates **elevated clustering** of **rtE138A** (26% [26-29%] clustered) and **proL33F** (30% [30-50%] clustered), particularly as compared to **rtK103N** (7% [7-11%] clustered). We observe one subtree of **five pre-treatment individuals** with **rtE138A** and one of **seven individuals** with **proL33F**, consistent with sustained pre-treatment transmission.

The proportion of phylogenetic lineages attributed to **rtK103N** **increased rapidly** between 2000 and 2020 concurrent with the **scale-up of ART treatment** programs in this setting.

RESULTS (CONTINUED)



Only **rtM41L** (**nucleoside reverse transcriptase inhibitor, NRTI**) had a statistically significant impact on pre-treatment viral load and was associated with **a 0.32 (95% HPD 0.04-0.60) log10 copies/mL reduction** in pre-treatment viral load. This suggests that other common pre-treatment resistance mutations may be **as transmissible** as wild-type virus in real-world settings.

CONCLUSIONS

No significant **rtK103N** clustering suggests a predominance of acquisition from people failing therapy and **limited sustained pre-treatment transmission**. Our results suggest **sustained pre-treatment transmission** of the naturally occurring **rtE138A**, which is concerning in light of efforts to roll-out long-acting injectables in this setting as **rtE138A** is associated with **CAB/RPV regimen failure**.

ACKNOWLEDGEMENTS

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