HIV-1 SUBTYPE VARIATION IN INTEGRASE STRAND TRANSFER INHIBITOR RESISTANCE IN UGANDA

Germander Soothill[1,2,*], Heather E Grant[2], Deogratius Ssemwanga[3], Pontiano Kaleebu[3], PANGEA-HIV consortium, Andrew Leigh Brown[2], Katherine E Atkins[1,4]

[1]Centre for Global Health, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK; [2]Institute of Evolutionary Biology, University of Edinburgh, Edinburgh, UK; [3]Medical Research Council (MRC)/Uganda Virus Research Institute (UVRI) and London School of Hygiene and Tropical Medicine (LSHTM) Uganda Research Unit, Entebbe, Uganda, [4]Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London, UK; *corresponding author: **gsoothil@ed.ac.uk**

THE UNIVERSITY of EDINBURGH | usher institute

Background

- Success of HIV-1 antiretroviral therapy was threatened by non-nucleoside reverse-transcriptase inhibitor (NNRTI) resistance prevalence reaching 10-15% of pre-treatment HIV-1 cases in many countries.[1]

→ The WHO changed the first-line regimen to tenofovir / lamivudine / dolutegravir (TLD) in 2019.

- Dolutegravir is an integrase strand transfer inhibitor (INSTI) and has a high genetic barrier to resistance.[2]
- HIV-1 subtypes A_1 and D predominate in Uganda. Less is known about the background prevalence of INSTI mutations in these subtypes compared to subtype B which predominates in Europe and USA. Understanding the pattern of mutation prevalence will help predict the trajectory of population dolutegravir resistance.

RESEARCH QUESTIONS

What is the baseline prevalence of HIV-1 INSTI mutations in the subtypes found in Uganda?
What is prevalence of ART resistance in Uganda which could compromise the TLD regimen?

Methods

- 1106 HIV-1 *pol* gene sequences analysed. Samples collected 2007-2017 by the PANGEA consortium[3,4] (Figure 1) plus 60 samples from 1986.[5] 668 near-full length integrase sequences included in gene-specific analysis.
- MAFFT alignment and sequence editing in Geneious Prime 2023.1.2. Subtyping using Context-based Modeling for Expeditious Typing[6], REGA HIV-1 Subtyping Tool – Version 3.0[7] and Subtype Classification Using Evolutionary Algorithms (SCUEAL)[8]. SCUEAL used for recombination breakpoints.
- Resistance testing using the Stanford University HIV Drug Resistance Database HIVdb Algorithm version 9.4.1.[9] Drug resistance mutations classified as major (alone reduce susceptibility to ≥ 1 drug) or accessory.

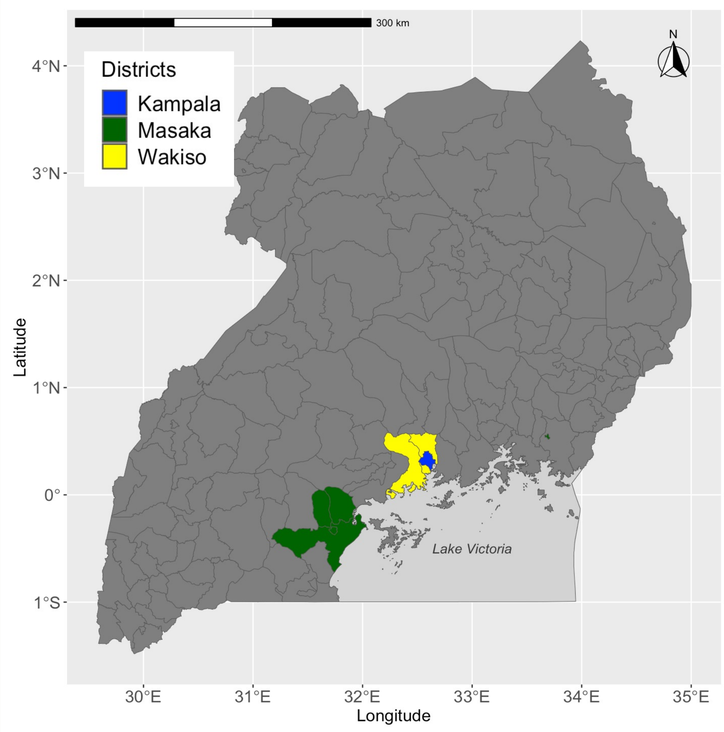

Figure 1: Map of Uganda showing location of sampling.

Results

1. Increasing prevalence of NNRTI resistance

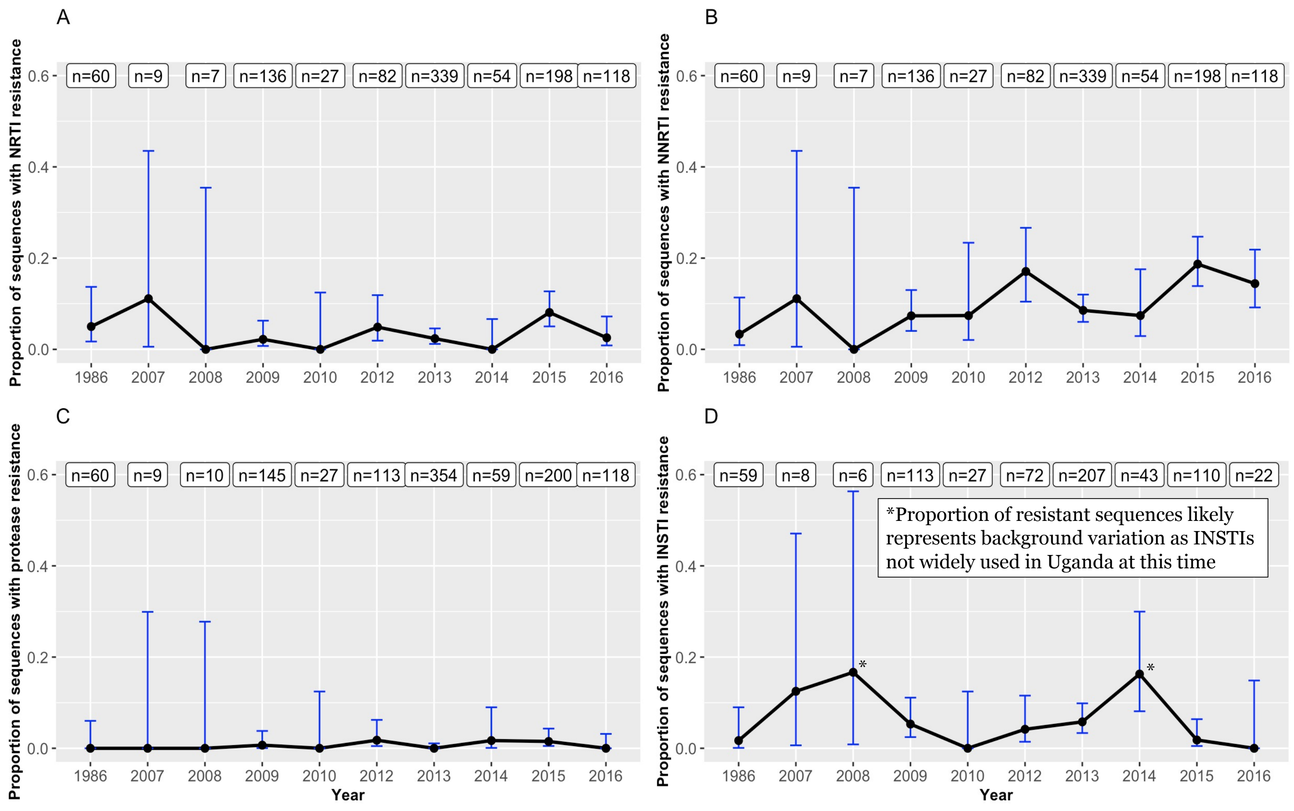

Figure 2: Trend in proportion of sequences with ≥ 1 drug resistance mutation stratified by drug class. NNRTI resistance shown in panel B and INSTI resistance in panel D. Confidence intervals shown in blue.
Nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), integrase strand transfer inhibitor (INSTI) .

2. 15.4% sequences had an INSTI mutation

	All sequences (n=668)		Subtype A1 (n=251)		Subtype D (n=245)		Recombinant (n=63)	
Mutation	N	%	N	%	N	%	N	%
Major								
E138K	3	0.4	1	0.4	1	0.4	1	1.6
E92G	26	3.9	9	3.6	9	3.7	2	3.2
N155S/T	2	0.3	0	0.0	1	0.4	0	0.0
Accessory								
A128T	1	0.1	0	0.0	0	0.0	1	1.6
D232N	1	0.1	0	0.0	1	0.4	0	0.0
E157Q	9	1.3	2	0.8	6	2.4	0	0.0
G163R/K	3	0.4	0	0.0	3	1.2	0	0.0
L74M	3	0.4	1	0.4	2	0.8	0	0.0
S153A	2	0.3	0	0.0	2	0.8	0	0.0
T97A	48	7.2	33	13.1	7	2.9	2	3.2
Double								
E92G, T97A	2	0.3	1	0.4	1	0.4	0	0.0
T97A, A128T	1	0.1	1	0.4	0	0.0	0	0.0
T97A, E157Q	1	0.1	1	0.4	0	0.0	0	0.0
T97A, G163R/K	1	0.1	0	0.0	0	0.0	0	0.0
T97A, L74M	5	0.7	2	0.8	1	0.4	1	1.6
T97A, S153A	1	0.1	1	0.4	0	0.0	0	0.0

Table 1: Number and proportion of sequences with INSTI mutations stratified by subtype (A_1, D, and A_1/D recombinants).

Major mutations

E138K: reduces susceptibility to all INSTIs including dolutegravir and causes altered viral fitness in combination with other mutations. Subtype dependent effects.[11]

E92G: most common major mutation identified. Believed to be rare nonpolymorphic mutation that reduces elvitegravir susceptibility only.[10]

N155S/T: reduces raltegravir and elvitegravir susceptibility. Unlike **N155H** not thought to contribute to reduced dolutegravir susceptibility.

Accessory mutations

E157Q: compensatory polymorphism which can partially restore the decrease in integrase enzyme activity associated with the **R263K** mutation implicated in dolutegravir resistance.[12]

T97A: synergistic polymorphism which in combination with other mutations can reduce susceptibility to all INSTIs.[13]

3. Some INSTI mutations varied with subtype

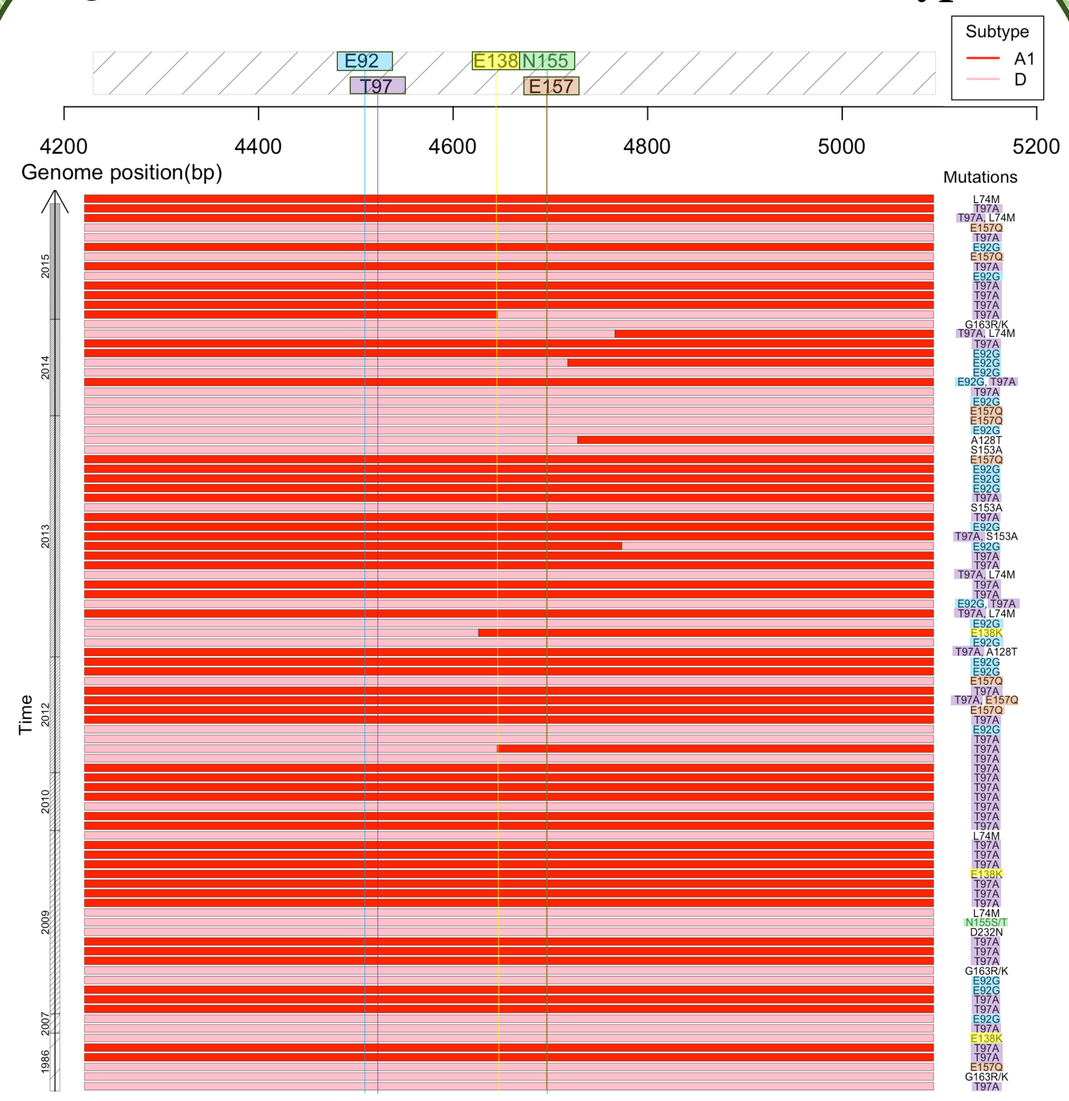

Figure 3: Schematic of 93 sequences with an INSTI mutation. Sequences arranged chronologically on the y-axis. Genome position on the x-axis with location of mutations indicated in the top panel. Each row represents a separate sequence. The colour indicates the subtype at that point on the genome. Mutations in the right hand column.

E157Q: 0.8% subtype A_1 vs 2.4% subtype D p-value*= 0.27
T97A: 13.1% subtype A_1 vs 2.9% subtype D p-value*= 5.3×10^{-5}

*2-sample test for equality of proportions with continuity correction

Conclusions

1. Increase in NNRTI resistance to 10-20% highlights the importance of moving away from NNRTI based regimens in Uganda.
2. Difference in background INSTI mutations in subtype A_1 and D HIV-1 compared to subtype B might lead to different patterns of dolutegravir resistance in Uganda compared to the global North where most use has been until recently.
3. It is important to closely monitor INSTI resistance in Uganda following the role out of dolutegravir as first-line therapy.

FUTURE QUESTIONS

Will dolutegravir resistance evolution vary with subtype?
What will be the trajectory in an era of increased usage?

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