Noncanonical Resistance Mutations in TLD-Treated Individuals with Unexplained Virological Failure

553

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BACKGROUND

Dolutegravir (DTG) based regimens, particularly tenofovir, lamivudine and DTG as fixed-dose combination (TLD) achieve high rates of viral suppression, and integrase (IN) resistance mutations are rarely detected in treatment-naïve individuals. Nevertheless virological failure (VF) despite good adherence and in the absence of IN resistance mutations, is sometimes reported, suggesting alternative resistance pathways including non-canonical mutations within HIV-1 envelope (Env) and gag nucleocapsid (Gag-NC)

METHODS

- HIV-1 Gag-NC and polymerase (Pol) mutations were investigated in 17 participants with VF (>400 copies/mL) of 155 participants from the UTRA study
- Objective adherence was assessed by tenofovir diphosphate (TFV-DP) concentrations in dried blood spots (DBS)
- Longitudinal Gag-NC analysis was performed on 7 participants at baseline and ≥12-month follow-up
- Env single genome sequencing (SGS) performed in a participant with emergent non-polymorphic Gag-NC mutations

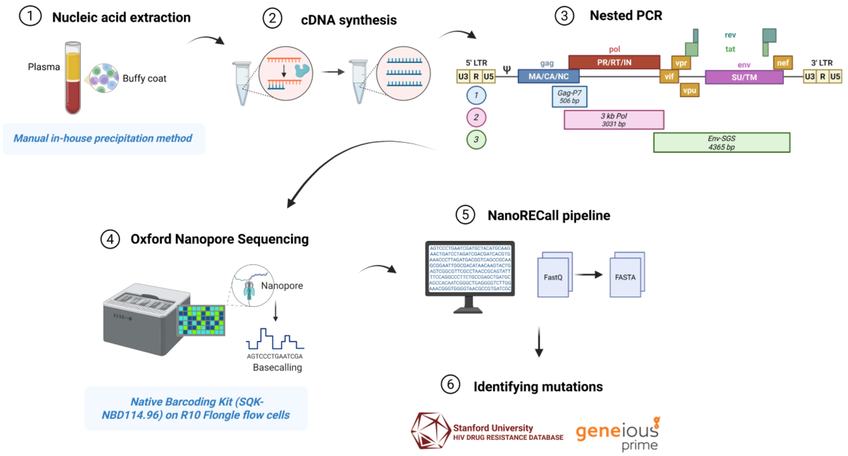


Figure 1: Overview of the methodology

The emergence of Gag-NC and Envelope mutations during TLD treatment

RESULTS

Table 1: Gag-NC mutations detected at baseline and follow-up among participants in a study of people with HIV (PWH) with adherence challenges (UTRA) in South Africa with VF

PID	Viral load at follow-up (copies/mL)	TFV-DP (fmol/3mm)	Baseline Gag-NC Mutation(s)	Follow-up Gag-NC Mutation(s)	Comment
P005	94 306	349	K41R	K41R	K41R polymorphic mutation
P119	621	433	K41R	K41R	
P126	982	680	8S; K41R	8G; K41R	8G conserved in Subtype C
P129	960	90	8S; K41Q	8G; K41Q	
P130	187 046	625	K41R	**N27S**; K41R; **M46L**	**N27S** and **M46L** non-polymorphic mutations; low-level resistance mutations
P155	8 983	494	V13P	V13P	V13P polymorphic mutation
P203	22 006	203	K41Q	K41Q	K41Q polymorphic mutation

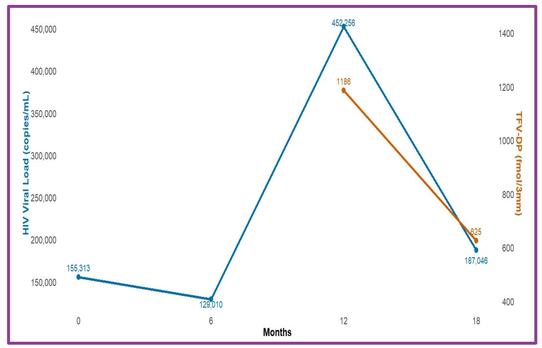
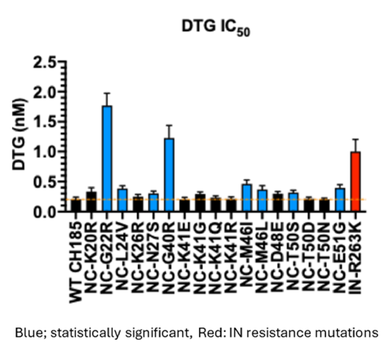


Figure 2: HIV viral load and TFV-DP for participant P130



Blue; statistically significant, Red: IN resistance mutations

Figure 3: The relative IC50 values of various Gag-NC mutations

Table 2: Mutations in the HIV-1 Pol gene for UTRA participant P130

PI Major	PI Accessory	NRTI	NNRTI	INSTI Major	INSTI Accessory	INSTI Other
V82L	L89T	K70KQ,M184V	K103N,Y318F	None	None	**E157V**

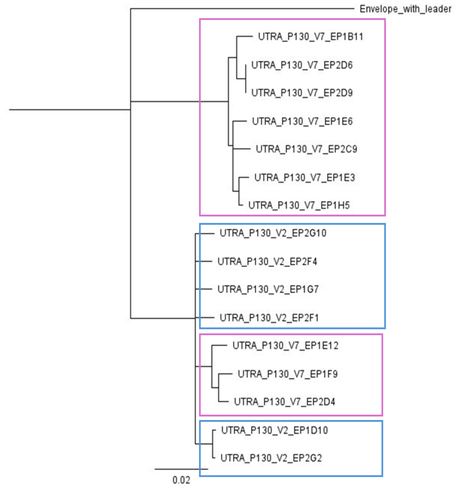


Figure 4: Phylogenetic tree of Env sequences

HIV-1 Env SGS revealed the emergence of mutation **T641I** in 10/10 at follow-up compared to 0/6 at baseline

- Associated with low-level integrase strand transfer inhibitor (INSTI) resistance in HIV subtype C

CONCLUSION

Our study shows non-canonical pathways, including mutations in Gag-NC and Env, may contribute to DTG failure in the absence of IN resistance mutations. Further studies are needed to define their phenotypic impact and clinical relevance, and to assess whether these mutations should be considered in resistance interpretation algorithms

ACKNOWLEDGEMENTS

NIH and SAMRC, U.S.-South Africa Program for Collaborative Biomedical Research, R01AI152119. The content and findings reported herein are the sole deduction, view and responsibility of the researchers and do not reflect the official position and sentiments of the NIH and SAMRC

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