Plasma Dolutegravir Exposure as a Triaging Tool for HIV Drug Resistance Testing by ONT Sequencing

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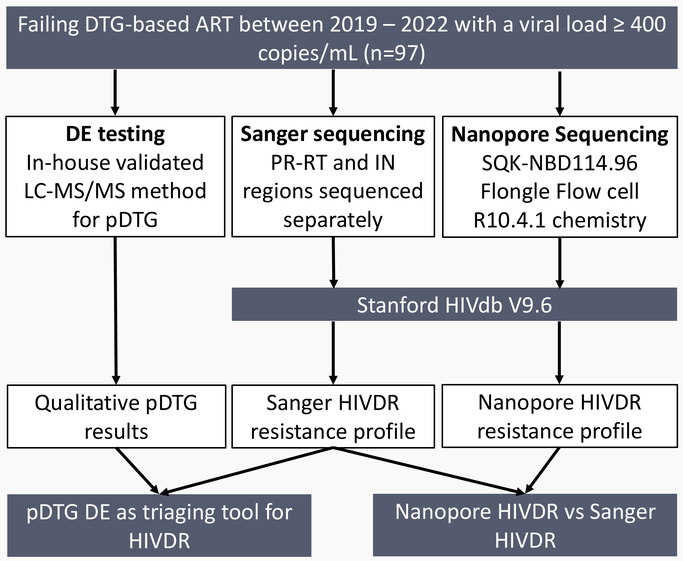
BACKGROUND

South African Antiretroviral Therapy (ART) guidelines recommend the use of Dolutegravir (DTG) based treatment due to sufficient data supporting its safety and efficacy, especially at a time when increasing pretreatment resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) was observed in low to middle income countries (LMICs). (26,28) While DTG resistance remains relatively rare, proactive identification of individuals at an elevated risk of resistance may allow for timely clinical intervention and optimising treatment outcomes.

We assessed the use of plasma DTG (pDTG) drug-exposure (DE) testing as a triaging tool to identify individuals at the highest risk for DTG resistance.

Furthermore, we assessed the use of Oxford Nanopore Technologies (ONT) sequencing for HIV drug resistance (HIVDR) testing. This platform might provide a scalable, cost-effective, and more sensitive approach to monitoring resistance patterns and guiding treatment strategies.

METHODS



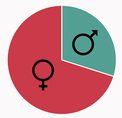
Plasma DTG exposure can be used to triage those in need of HIVDR testing.

Nanopore sequencing shows excellent concordance with Sanger sequencing for HIV drug resistance testing.

RESULTS

Population

Sex distribution	
Males	29.9%
Females	70.1%
Population age (years)	35 (IQR: 20-44)
Viral load (Log_{10} copies/mL)	4.8 (IQR: 3.2-5.7)
Time on DTG (months)	13.8 (IQR: 6.1-26.3)
DTG resistance (Stanford level ≥ 3)	19.5% (n = 19)



pDTG DE as triaging tool for HIVDR

Detectable pDTG	
Positive pDTG	45.3%
Negative pDTG	54.7%



- *Individuals with detectable pDTG levels were more likely to have DTG resistance:*

		95% Confidence interval
Odds Ratio:	9.54 (p=0.001)	2.49 - 36.53

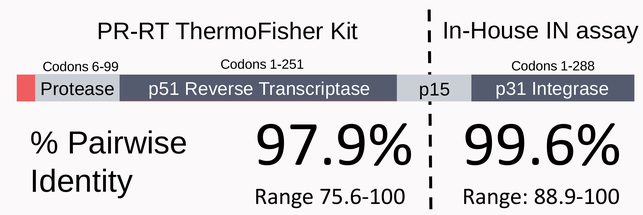
- *Undetectable pDTG predicted the absence of DTG resistance:*

		95% Confidence interval
Negative Predictive Value	94.2%	85.1% - 97.9%
Sensitivity	82.4%	56.7% - 96.2%
Specificity	67.1%	54.9% - 77.9%

Nanopore HIVDR suitability in public health

Testing Parameters

- NanoRecall required a minimum coverage of 400X for valid nanopore sequencing and a 25% mixture threshold
- Similarity assessment criteria were set at 97% for PR-RT and 93% for IN, based on in-house validation.



% Pairwise Identity	97.9% (Range 75.6-100)	99.6% (Range: 88.9-100)

Two IN samples failed similarity assessment (88.9%) due to Nanopore detecting R263K in one and missing the E138AK mixture in another. Six PR-RT samples failed similarity assessment due to detected mixtures.

CONCLUSIONS

We demonstrated that pDTG DE testing can accurately predict the absence of DTG resistance and can be considered an adequate screening method to identify individuals who do not require HIVDR testing. This can ultimately decrease the financial burden associated with HIVDR testing. Additionally, nanopore sequencing may be a suitable alternative to conventional HIVDR testing with excellent concordance between mutation detection by both technologies.

ADDITIONAL KEY INFORMATION

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References:

1) NDoH. 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates (2023)
2) WHO. Update of recommendations on first- and second-line antiretroviral regimens (2019)