HIV virological failure and drug resistance among hospital inpatients in Malawi

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Introduction

- Virological failure and HIV drug resistance (HIVDR) remain barriers to controlling the HIV epidemic
- Antiretroviral therapy (ART) scale-up has led to increasing HIV drug resistance in sub-Saharan Africa (SSA)[1]
- Most patients admitted to hospital in SSA are now taking ART, but the prevalence of virological failure or HIVDR is unknown

- **We sought to describe the proportion of adult inpatients established on ART with virological failure (viral load [VL] ≥1000 copies/ml), and HIVDR**

Methods

- The study was an **observational cohort study** nested in a large TB screening trial (the STAMP trial)[2]
- Patients already established on ART for ≥6 months at hospital admission had frozen plasma samples tested for HIV-1 RNA by real time qPCR
- Those with HIV-1 RNA ≥1000 copies/ml had **drug resistance testing by ultra-deep sequencing** (Illumina MiSeq platform)
- Interpretation of HIVDR mutations used the Stanford HIVDR Algorithm
- Drug resistance was defined as having intermediate or high-level resistance to specific drugs
- Vital status was established at 2-months after admission.

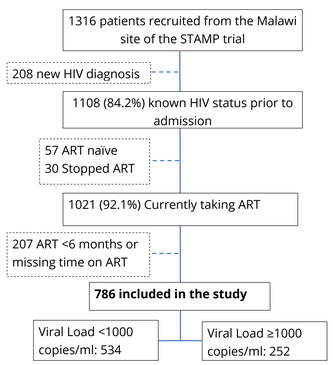

***Figure 1*: Study flow diagram for inclusion into this study**

		Overall	HIV viral load <1000 copies/ml	HIV viral load ≥1000 copies/ml
		n=786	n=534	n=252
Age (years)	mean (SD)	41.5 (11.4)	43.1 (11.8)	38.2 (9.8)
Sex	Male	258 (32.8%)	161 (30.1%)	97 (38.5%)
	Female	528 (67.2%)	373 (69.9%)	155 (61.5%)
Time on ART	median (IQR)	4.7 (2.0, 8.1)	4.6 (1.9, 8.1)	5.0 (2.5, 8.1)
ART regimen	1st Line	770 (98.0%)	524 (98.1%)	246 (97.6%)
	2nd line	16 (2.0%)	10 (1.9%)	6 (2.4%)
CD4 count (cells/μL)	median (IQR)	277 (97, 496)	383 (234, 562)	60 (17, 156)
HIV viral load (copies/ml)	median (IQR)	0 (0, 14782)	0 (0, 0)	125,603 (18,399, 361,423)
Haemoglobin (g/l)	mean (SD)	102.1 (31.0)	107.4 (31.5)	90.7 (26.8)

***Table 1*: Patient characteristics at baseline and outcomes, stratified by virological failure**
ART Antiretroviral therapy; WHO World Health Organization; SD standard deviation; IQR interquartile range

Prevalence of ***virological failure*** and ***HIV drug resistance*** was high in HIV-positive patients admitted to hospital.

Targeted interventions to diagnose and manage ART failure and drug resistance ***may reduce mortality***

Results

- 814/1316 (61.9%) patients recruited between Oct 2015 and Sept 2017 were on ART for ≥6 months (*Figure 1*)
- **252/786 (32.1%) patients had viral load ≥1000 copies/ml (virological failure)**. See *Table 1* for baseline characteristics

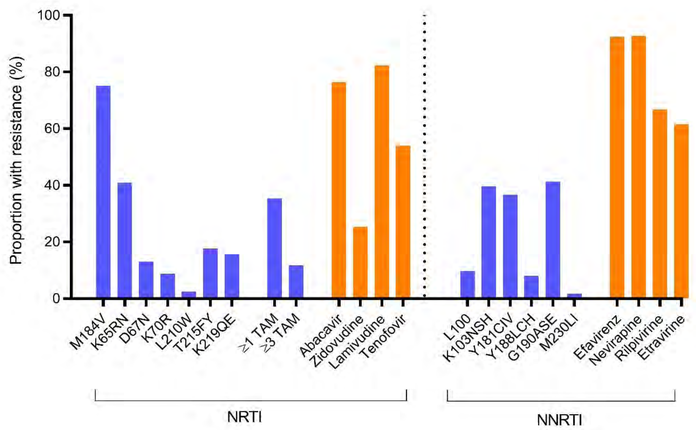

***Figure 2*: Proportion of patients with virological failure who have HIV drug resistance mutations and intermediate or high level resistance to first-line ART drugs**
N=237. ART antiretroviral therapy; NRTI nucleoside reverse transcription inhibitor; NNRRTI non-nucleoside reverse transcription inhibitor; TAM Thymidine analogue mutation.

- 237/252 (94.0%) had HIV drug resistance results available
- 82.3% (n=195) of samples carried resistance to lamivudine, 54.0% (n=128) to tenofovir and 92.4% (n=219) to efavirenz (*Figure 2*)
- In **82.7% (n=196) resistance to at least 2 drugs** was present
- Protease and integrase inhibitor resistance was rare (1/233 and 2/225 had major mutations respectively)
- **2-month mortality was higher in patients with HIVDR to ≥2 drugs** (28.1%) compared to ≤1 drugs (9.8%), unadjusted hazard ratio 1.7, 95% CI 1.2-2.3, p=0.002

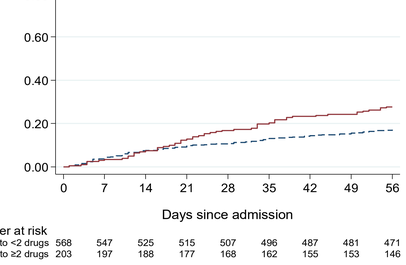

***Figure 3*: Kaplan Meier curve showing probability of death stratified by drug resistance**
Kaplan Meier curve shows time to death stratified by resistance to <2 first-line ART drugs, or resistance to or ≥2 first-line ART drugs (unadjusted HR 1.7, 95% CI 1.2-2.3, p=0.002). Patients with viral loads <1000 copies/ml were assumed to have no resistance, 15 patients without HIV drug resistance data are excluded (n=771).

Conclusions

- These data **support testing hospital inpatients for ART failure**, ideally using a **rapid or point-of-care HIV-1 viral load assay**
- There was **high prevalence of resistance** to multiple drugs and **association with early mortality**
- A **point of care test to identify multidrug resistant HIV** is needed
- Patients **could benefit from switching to second-line ART**
- **Other interventions** may also be warranted, for example differentiated HIV clinic care and adherence support

The Screening for TB to Reduce AIDS Related Mortality in Hospitalised Patients (STAMP) trial was funded by the Joint Global Health Trials Scheme of the UK Department of Health and Social Care, the Department for International Development, the Global Challenges Research Fund, the Medical Research Council and Wellcome Trust (number MR/M007375/1).

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2. Gupta-Wright A, Corbett EL, van Oosterhout JJ, et al. Rapid urine-based screening for tuberculosis in HIV-positive patients admitted to hospital in Africa (STAMP): a pragmatic, multicentre, parallel-group, double-blind, randomised controlled trial. *Lancet* 2018; **392**: 292–301.