Evolution of HIV-1 drug resistance in patients failing a standard thymidine analogue-based first-line ART: implications for the activity of next-line regimens from a longitudinal study in Mozambique

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Background

- Virological monitoring of ART is being implemented in LMIC.
- Recommended 1st-line ART is NNRTI-based.
- After virological failure patients are switched to boosted PI-based 2nd-line.
- 2nd-line more expensive and few/no next-line regimens
- Correct time of switching needs to be accurately established by
  - probability of accumulating resistance to the subsequent treatment lines at a given time of virological failure

Aims

In patients with virological failure after 1 year of first-line ART not switching to second-line ART for one additional year:

- to describe the accumulation of HIV-1 drug resistance
- To analyze its effects on the predicted activity of next-line therapy components

Methods

- Retrospectively selected patients from 3 sites in Maputo, Mozambique:
  a) were on a first-line ART
  b) had an HIV RNA >1,000 copies/mL after 1 year (**t1**) and after 2 years (**t2**) of ART without switching to a second-line ART
  c) had a stored plasma sample at **t1** and **t2**.

- Genotyping (TRUGENE) of RT and PR at **t1** and **t2**.
- Calculated proportion of subjects with major RAM (IAS-USA 2014) and at least low level resistance to each drug (Stanford's HIVdb 7.0)
- Also: **t2^**: 2 years after ART initiation considering historical genotype
- **t3***: projection of RAM at 3 years (2 years after first documented VL >1,000 cp/mL), assuming linear accumulation and historical genotype
- Adherence measured by % on time pharmacy appointment keeping (delay tolerability 10 days)

Baseline characteristics of the 48 patients	
Male gender	24 (50%)
Age (years) (median IQR)	35 (28.5-37.7)
CD4 count (cells/µl)	165 (77.5-269.5)
HIV RNA $\log_{10}$ (copies/ml)	4.69 (4.1-5)
HIV subtype	C (95.8%); G (4.2%)
Calendar year	2010 (2010-2011)

First-line ART drugs	
3TC	48 (100%)
AZT	41 (85.4%)
D4T	5 (10.4%)
TDF	2 (4.2%)
ABC	3 (6.3%)
NVP	40 (83.3%)
EFV	5 (10.4%)

Figure 1. Proportion of patients with major resistance mutations at t1 and t2 and the projection at 3 years

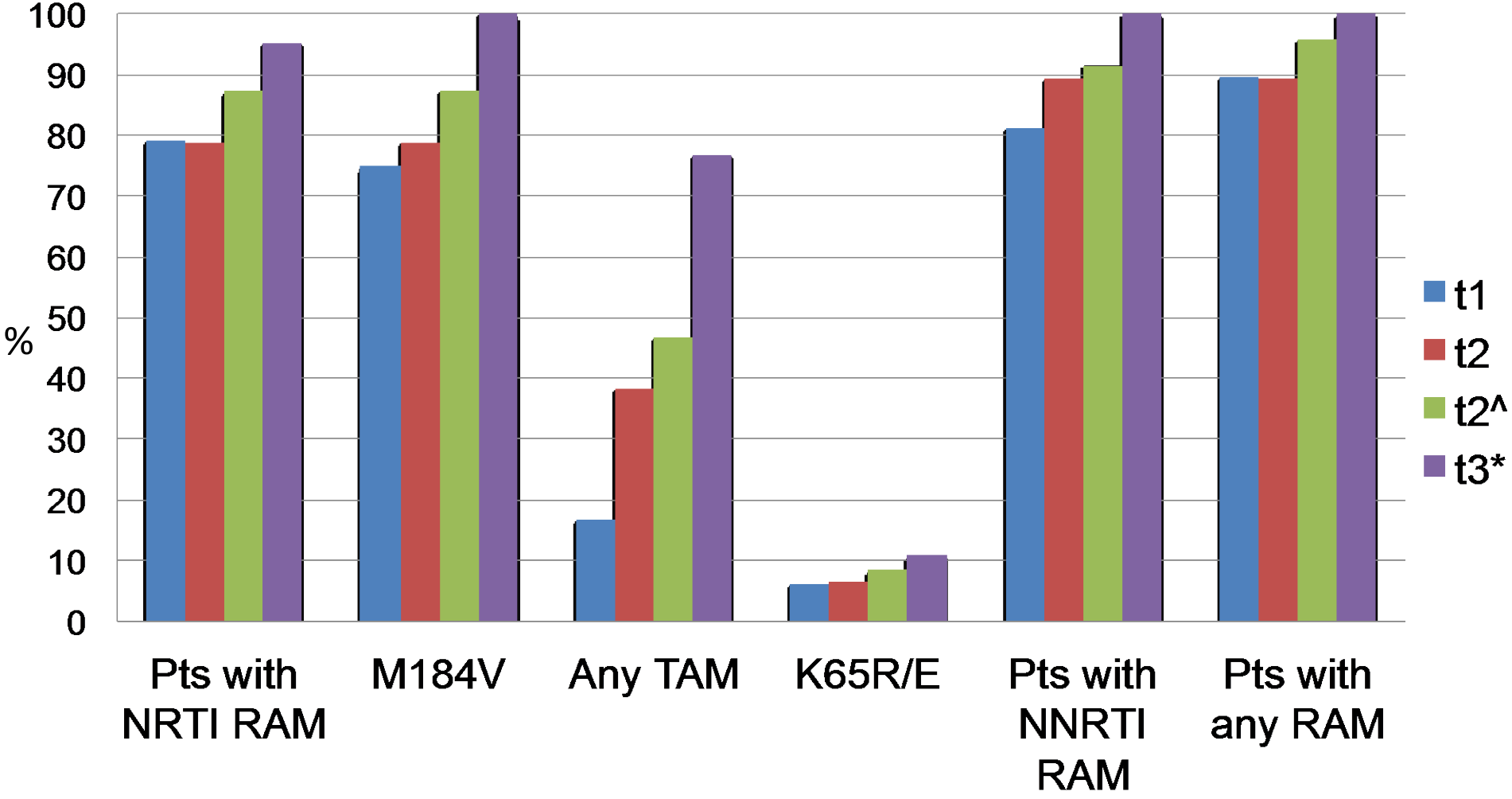
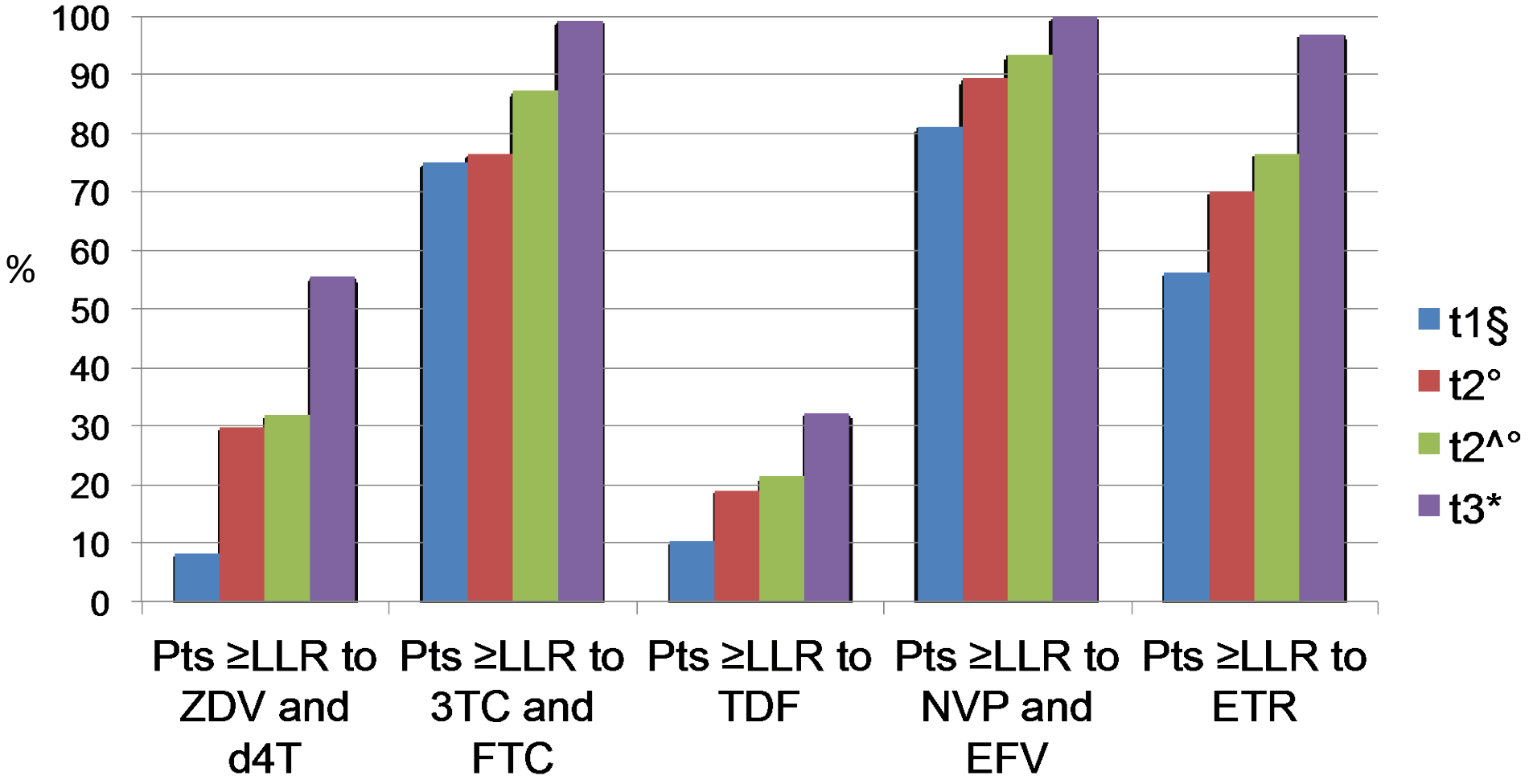


Figure 2. Proportion of patients with predicted resistance to individual drugs at t1 and t2 and the projection at 3 years



Influence of adherence to pharmacy appointments on the prevalence of RAM at different time points

Figure 3. Proportion of patients with RAM at t1 based on adherence

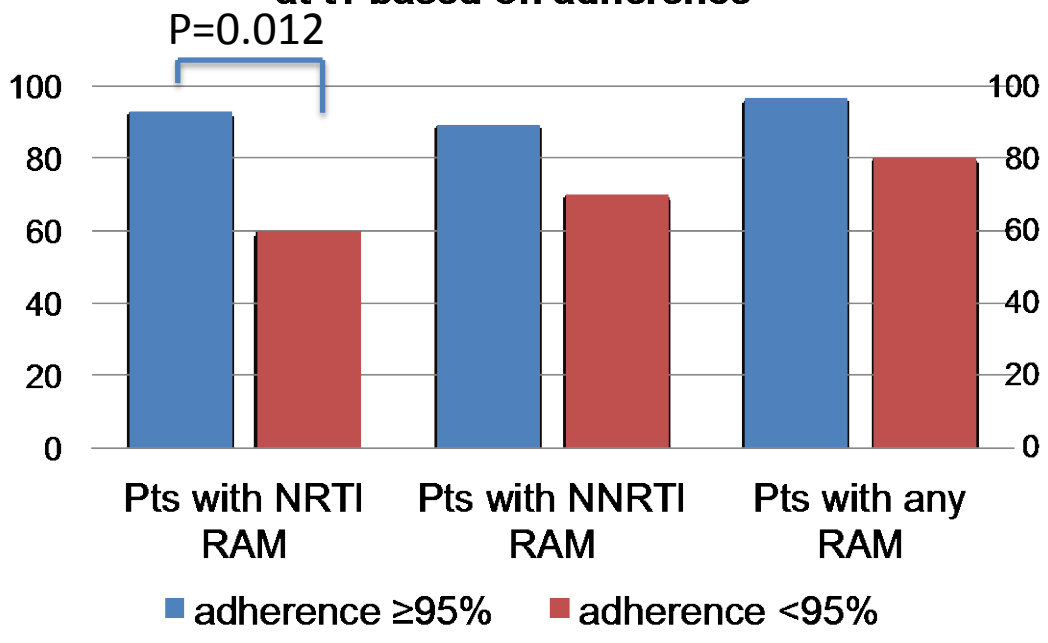
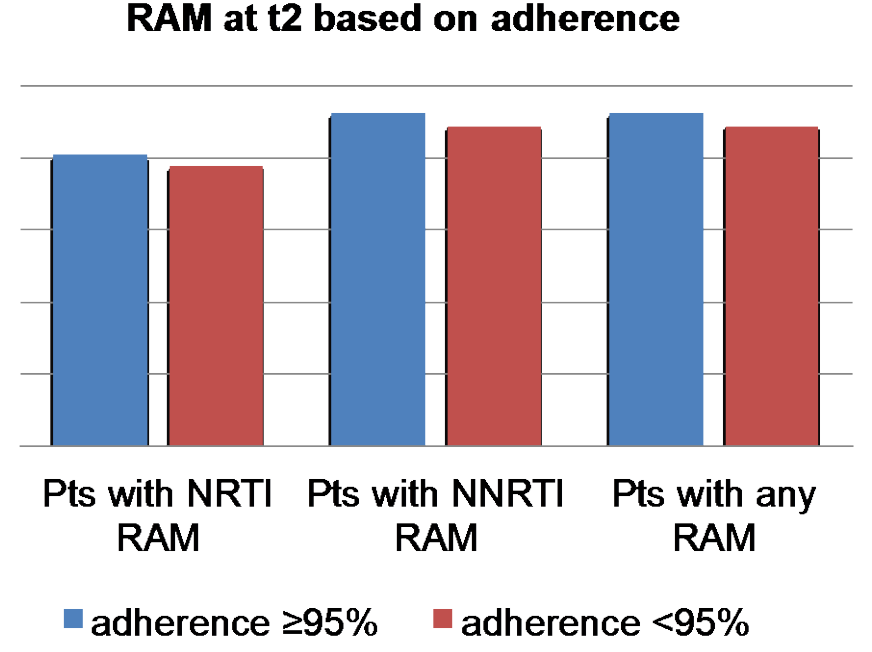
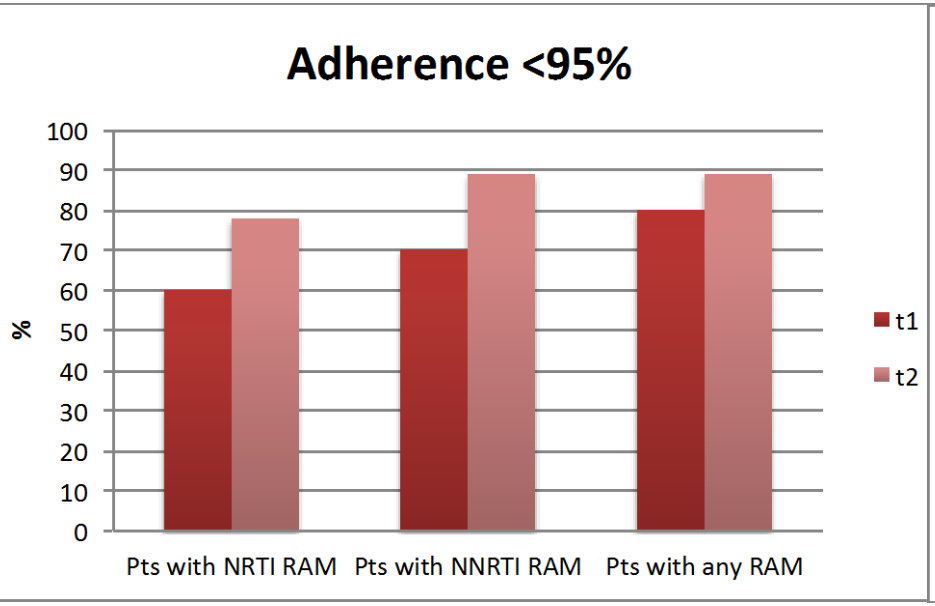
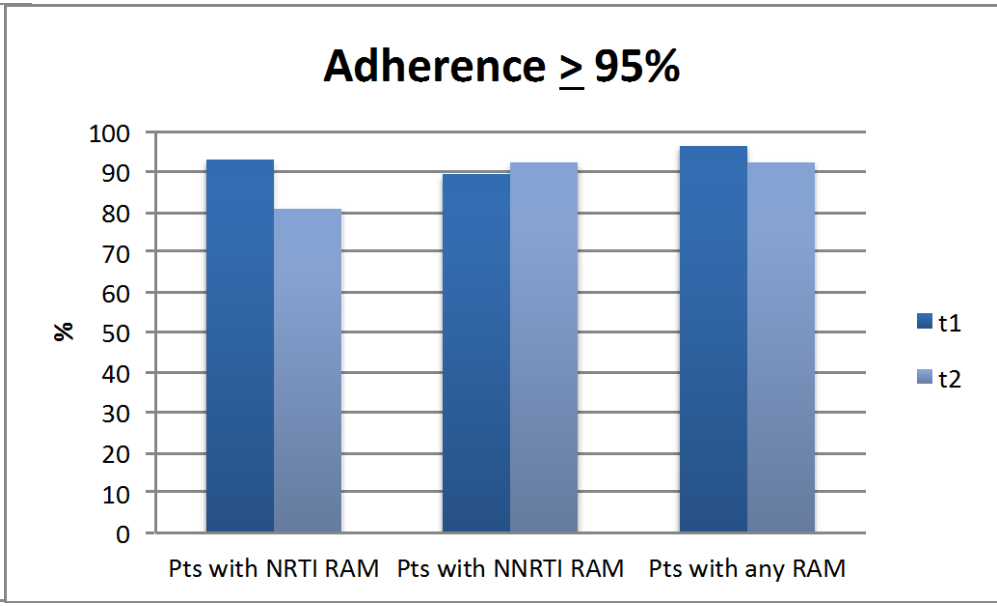


Figure 4. Proportion of patients with RAM at t2 based on adherence



Influence of adherence to pharmacy appointments on the longitudinal prevalence of RAM





Summary

- Activity of NNRTIs is compromised early during failure
- TDF and ZDV activity begin to be reduced after 1 year of documented virological failure of TA-based first-line ART
- *particularly when the historical genotype is considered*
- Less adherent patients have less resistance at year 1 but accumulate more resistance during the second year of continuous viral replication

Conclusions

- In subjects failing 1st-line NNRTI-based ART, drug resistance accumulates over time, but the activity of different agents of the 1st- and next-line ART is affected at different time points and is influenced by medication adherence
- The present observation may inform decisions on when to switch to a 2nd line therapy after virological failure in LMIC settings

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