



Phenotypic data to guide selection of reverse transcriptase inhibitors in second-line therapy following extended virological failure in Uganda

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INTRODUCTION

- Quantitative phenotypic resistance information interpreted via clinical cut-offs can facilitate optimization of combination antiretroviral therapy.
- Resistance to etravirine (TMC125), a new non-nucleoside reverse transcriptase inhibitor (NNRTI), develops through the accumulation of multiple NNRTI resistance associated mutations (RAMs).
- Associated factors and frequency of etravirine cross-resistance among patients infected with non-subtype B HIV-1 failing Combivir[™]/abacavir and Combivir[™]/nevirapine based regimens requires examination.
- Viral load and resistance testing to guide individual patient management is rarely available in resource-limited settings, where switch to second-line therapies are often triggered by clinical failure alone.
- WHO guidelines recommend a change in the entire regimen to one with minimal (expected) cross-resistance with first-line drugs. However, data for cross resistance patterns emerging in those treated without viral load monitoring is still accumulating, and phenotypic data are scarce.

BACKGROUND

NORA was a randomised double-blind trial conducted in two clinical centres in Uganda as a nested substudy within the DART trial.

600 previously untreated symptomatic HIV-infected adults initiating ART with CD4<200 cells/mm³ were randomly allocated to Combivir[™] (fixed dose combination of lamivudine (3TC) 150mg + zidovudine (ZDV) 300mg BID) plus either abacavir (ABC) (300 mg bd) or nevirapine (NVP) (200 mg bd).

After 24 weeks, participants were unblinded and continued their allocated regimen with open-label drug.

AIM

- to determine drug susceptibility (fold resistance for specific NRTI and NNRTI) in both the ABC and NVP arms of NORA at wk0 and wk96 (in samples with VL>1000c/mL and excluding those going on to a STI after wk48).

METHODS

Plasma samples taken at weeks 0, 48 and 96 were retrospectively assayed for HIV-1 RNA. The analysis included samples where

- HIV-1 RNA exceeded 1000 copies/ml
- phenotypic resistance testing results were available (Antivirogram ver2.5.01, Virco BVBA)
- patients remained on first-line therapy at week 96
- no genotypic baseline resistance was detected

Samples at week 96 were classified as phenotypically sensitive/resistant using biological* cut-offs for

- candidate second-line RTI drugs proposed in WHO 2006 guidelines (Table 1).
- etravirine, a second-generation NNRTI

Fold-change values greater than 30 are displayed as 30 exactly in Figure 1 for nevirapine, efavirenz and etravirine.

RESULTS

- Phenotypic results were available for 73 patients at baseline and 55 patients at week 96 - 17 NVP, 38 ABC.
- Of these, the majority of patients (13 NVP, 20 ABC) had VL>1000 at week 48.
- Median (IQR) viral load at week 96 was 41,000 (8,000-77,000) and 33,000 (9,000-98,000) for nevirapine and abacavir groups, respectively.
- The distribution of fold-change values for each drug are shown in Figure 1. The percentage of samples which are phenotypically sensitive are given in Table 2.
- All baseline samples were sensitive to 3TC; at week 96 resistance was present in 34/38 ABC and 16/147 NVP samples.

Table 1: Detailed recommendations for switching to second-line ARV regimens in adults and adolescents*

First-line regimen	Second-line regimen	
	Rti component	PI component
Standard strategy	AZT or d4T + 3TC + NVP or EFV	ddi + ABC or TDF + ABC or TDF + 3TC (± AZT)
	TDF + 3TC + NVP or EFV	ddi + ABC or ddi + 3TC (± AZT)
	ABC + 3TC + NVP or EFV	ddi + 3TC (± AZT) or TDF + 3TC (± AZT)
Alternative strategy	AZT or d4T + 3TC + TDF or ABC	EFV or NVP ± ddi

* taken from Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach. WHO 2006

Figure 1: Distribution of Fold-Change at Baseline and at Week 96 by Randomised Group, for each ARV Drug.

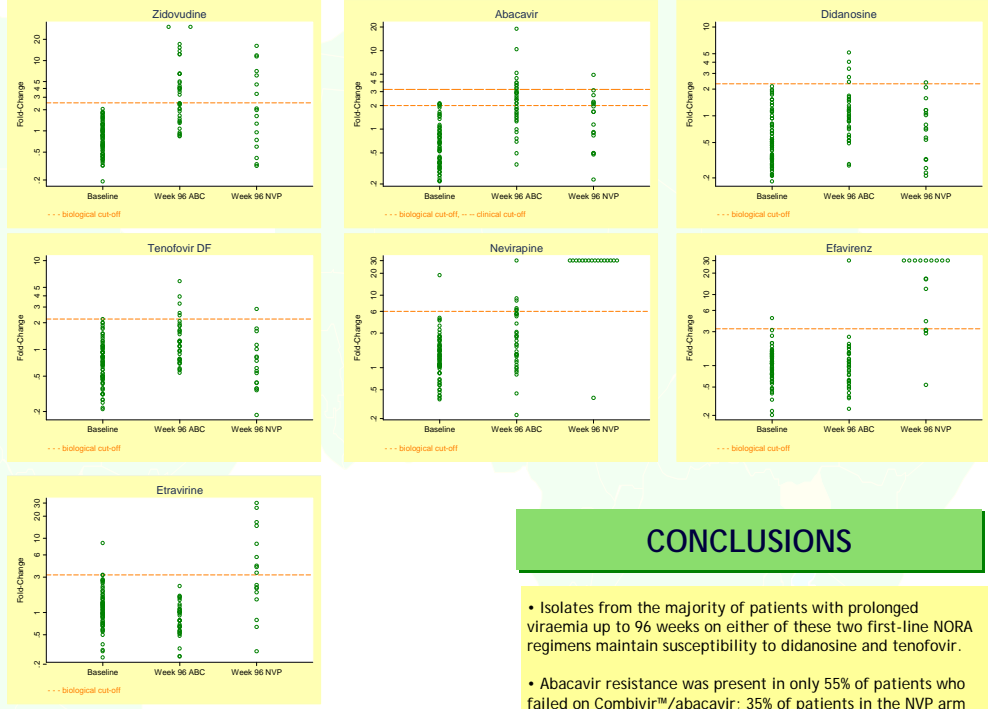


Table 2: Number phenotypically sensitive using biological cut-offs

ARV Drug	NVP (n=17)	ABC (n=38)
Abacavir	11 (65%)	17 (45%)
Didanosine	16 (94%)	33 (87%)
Tenofovir DF	16 (94%)	33 (87%)
Nevirapine	1 (6%)	31 (82%)
Efavirenz	4 (24%)	36 (95%)
Etravirine	8 (47%)	37 (97%)

WHO candidate second-line regimens

CONCLUSIONS

- Isolates from the majority of patients with prolonged viraemia up to 96 weeks on either of these two first-line NORA regimens maintain susceptibility to didanosine and tenofovir.
- Abacavir resistance was present in only 55% of patients who failed on Combivir[™]/abacavir; 35% of patients in the NVP arm also developed abacavir resistance.
- Nevirapine, efavirenz and etravirine are all predicted to have significant activity in patients failing in the ABC arm, who received triple NRTI (class sparing) first line ART.
- Etravirine is predicted to have significant activity in approximately half of the NORA participants with prolonged virological non-suppression on Combivir[™]/nevirapine.
- These values may be conservative estimates as they are based on biological (i.e. based on the distribution for untreated patients) rather than clinical cut-offs.
- These findings should help inform selection of second-line regimens in resource-limited settings.

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