Estimation of virological residual activity on a regimen of abacavir/zidovudine/lamivudine

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INTRODUCTION

Quantifying the virological residual activity (**VRA**) of antiretroviral combinations, in the context of resistant virus, is important both to guide management of highly drug experienced patients and where therapy options are limited, as in many resource-limited settings.

The few quantitative data available on this measure are mainly derived from partial treatment interruption studies, which are no longer undertaken. As part of a detailed study of evolution of resistance to first-line therapy in the absence of virological monitoring, we derive estimates of the residual activity of the triple nucleoside/nucleotide regimen of abacavir/zidovudine/lamivudine (ABC/AZT/3TC).

STUDY

300 antiretroviral-naive HIV-infected Ugandan adults were allocated to receive ABC/AZT/3TC within NORA, a substudy of the DART trial (Lancet 2010,375:123-31). Plasma samples at weeks 0, 48 and 96 were retrospectively assayed for HIV-1 RNA (Roche Amplicor v1.5) and genotypic and phenotypic resistance testing (Antivirogram ver2.5.01, Virco BVBA) performed if HIV-1 RNA exceeded 1000 copies/ml.

METHODS

VRA was defined as the reduction in $\log_{10}$(HIV RNA) at week 48/96 compared to week 0.

The analysis was limited to observations where:

1. The patient remained on their original treatment allocation
2. HIV RNA >1000 copies/ml at week 48/96.
3. Genotypic resistance testing revealed ≥1 major resistance mutations.

Multivariate linear regression modelling was used to relate VRA to $\log_{10}$ fold change (FC) in IC_{50} for AZT and ABC, accounting for

1. baseline HIV RNA
2. statistical non-independence of subjects with data at weeks 48 and 96
3. right-censoring of HIV RNA values.

RESULTS

A total of 59 observations (30 at week 48, 28 at week 96, 9 patients with observations at both time-points) were included.

Mean (SD) baseline HIV RNA was 5.67 (0.57) $\log_{10}$ copies/ml.

All samples (at each time point) had the M184V mutation and high level phenotypic resistance to 3TC (median >58 FC, range 11 to >147).

RESULTS (contd.)

60% (18/30) samples had one or more TAMs at 48 weeks, compared with 90% (26/29) samples at 96 weeks. Only one sample had an ABC-associated mutation (K65R at week 96).

Median (IQR) fold-change for ABC was 2.1 (1.5, 3.0) and 2.4 (1.4, 3.3) at weeks 48 and 96 respectively; corresponding values for AZT were 1.5 (1.0, 3.9) and 3.6 (1.6, 5.0).

VRA was strongly inversely related to the level of phenotypic resistance to both ABC and AZT (Figure 1a/b). (The effect of 3TC FC was not evaluable due to ubiquitous high level resistance.)

The regression model predicted a decrease in VRA of 0.30 (SE 0.15) $\log_{10}$ copies/ml per 2-fold increase in ABC FC (P=0.04) and 0.18 (SE 0.07) $\log_{10}$ copies/ml per 2-fold increase in AZT FC (P=0.013).

A contour plot of VRA as a function of ABC FC and AZT FC showed (Figure 2):

- strong positive correlation between ABC FC and AZT FC (r=0.65), although with evidence of a plateau in ABC FC;
- VRA between 0.5-1.0 in the presence of high level ABC and AZT resistance;
- VRA between 1.5-2.0 in the presence of low level ABC and AZT resistance.

FIGURES

Fig 1a. VRA vs. ABC FC

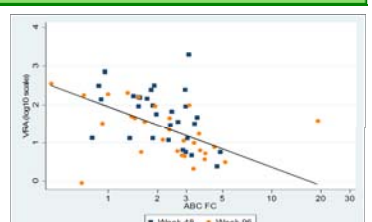


Fig 1b. VRA vs. AZT FC

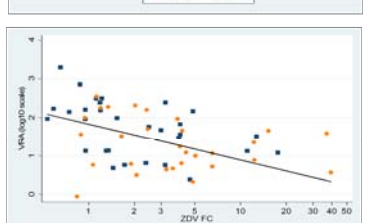
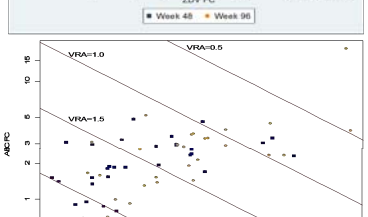


Fig 2. AZT FC vs. ABC FC



SUMMARY

Virological residual activity (VRA) - as defined here - represents the continued antiviral effect of the regimen in the context of the resistance mutations present in the virus isolate, under the assumption that the baseline level of HIV RNA can be validly extrapolated forward in time.

There was a modest virological benefit (0.5-1.0 $\log_{10}$ reduction in HIV RNA) in the presence of high level resistance to all three drugs in the regimen.

Our analysis underscores that VRA is not an absolute phenomenon but depends on the extent of resistance within a particular viral isolate.

We note that viral resistance was measured selectively in samples with HIV RNA >1000 copies/ml. VRA will have been underestimated if there were samples with HIV RNA <1000 copies/ml that harboured resistance mutations.

Further work is required to develop similar VRA scores for other ART combinations, particularly those proposed for resource-limited settings.

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