Reverse Transcriptase Drug Resistance Mutations Amongst a Treatment Experienced Cohort in a Subtype C Epidemic

Colleen Whitelaw[1], Michael Hislop[1], Leon Regensberg[1] and Graeme Meintjes[1,2,3]

Aid for AIDS, Cape Town, South Africa[1] ~ University of Cape Town, South Africa[2] ~ GF Jooste Hospital, Cape Town, South Africa[3]

Background:

Aid for AIDS (AfA) is a private sector disease management programme operating in Southern Africa, contracting services to medical aid funds and companies. The epidemic in Southern Africa is predominantly subtype C. Genotyping (GT) is available to patients enrolled in the programme, but due to cost was until recently restricted to patients who were failing second line antiretroviral therapy (ART) and beyond. This study assessed patterns of reverse transcriptase drug resistance mutations in this patient population.

Methodology:

All GT results from patients > 18 years that were available on the AfA database between May 2000 and September 2005 were analysed. Resistance tests were performed at various private laboratories in South Africa. Data regarding demographics, CD4 counts, viral loads, drug exposure history and outcomes were also extracted. Drug exposure history was in the form of records of ART regimens authorised by the programme.

Table 1: Patient characteristics.

Gender	37 female (45%)
Age at GT	Median 39 years (IQR 34 - 46)
Subtype (known in 30 patients)	29/30 subtype C (97%)
Baseline CD4 (known in 62 patients)	Median 103 cells/mm^3 (IQR 35 - 205)
Baseline viral load (known in 57 patients)	Median 234 000 copies/ml (IQR 74 817 – 519 500)
Number of regimens exposed to at GT	Median 2 (Median 1 mono/dual therapy regimen and median 1 HAART regimen)
Cumulative months of NRTI exposure at GT	Median 36 (IQR 21 - 52)
Cumulative months of NRTI exposure as part of mono/dual therapy at GT	Median 14 (IQR 5 - 21)
Cumulative months of NRTI exposure as part of HAART at GT	Median 19.5 (IQR 10 - 39)

Results:

85 GT results were available for 82 patients. Of the GTs done while patients were on NRTIs, 49 of 65 demonstrated thymidine analogue mutations (TAMs). The median number of TAMs was 2 in these 65 GTs. 11 GTs demonstrated both the M41L and L210W mutation. No K65R, one Q151M and two T69 insertion mutations were detected. Among 24 patients on 3TC at the time of GT, 20 demonstrated the M184V mutation, 2 did not and in 2 this was not specifically reported. Non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations were detected in 45 of 49 GTs of patients on an NNRTI at the time of GT. The median number of NNRTI mutations in these 49 GTs was 2. The most common NNRTI mutations detected were K103N (29), G190A/S (15) and Y181C/I (14).

Figure 1: Duration on NRTIs in months at time of GT versus number of TAMS.

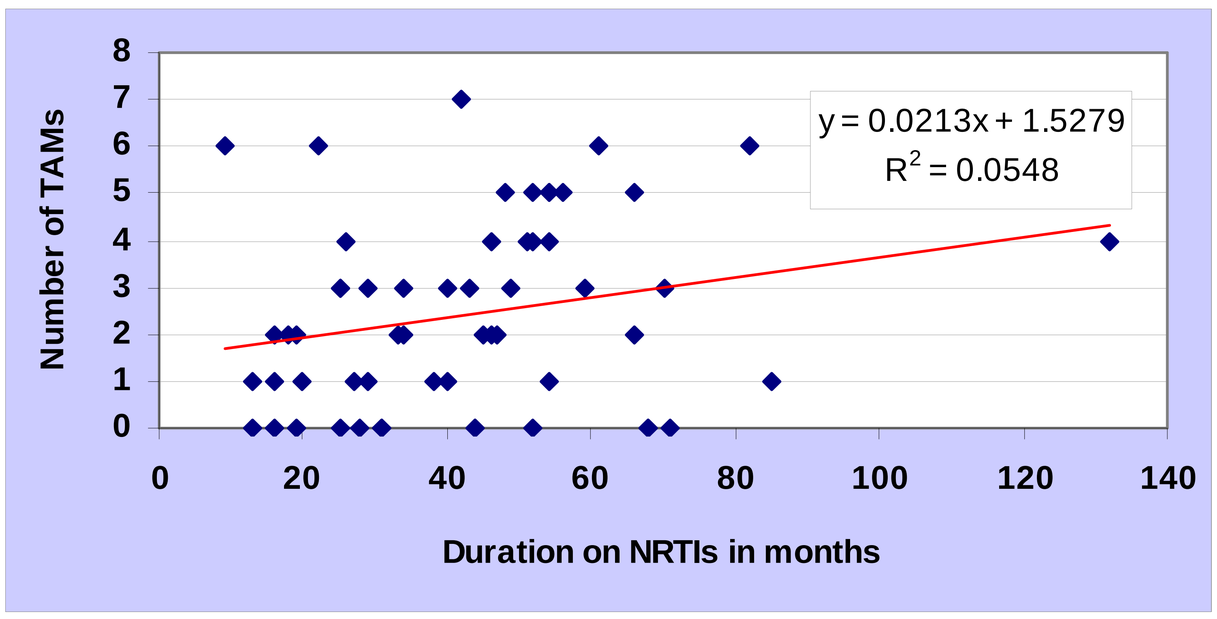

Table 2: Number of TAMs detected in 65 GTs of patients who were on NRTIs at time of GT.

TAM	Frequency	Percent
M41L	29	45%
E44D	5	8%
D67N	31	48%
K70R	21	32%
V118I	7	11%
L210W	12	18%
T215Y/F	36	55%
K219Q/E	15	23%

Conclusions:

In this cohort of patients with a median of 3 years NRTI exposure, the most frequent TAMs detected were T215Y/F, D67N and M41L. No patients developed K65R and 11 developed both M41L and L210W. This has implications for the use of tenofovir in this patient population as M41L, L210W (both of which are TAMs) and K65R are mutations that are known to particularly reduce susceptibility to tenofovir in subsequent regimens (Barrios et al, J. Clin. Microbiol. 2003;41:4421-3). Our results suggest that the majority of patients in this cohort were still susceptible to tenofovir. No correlation between duration on NRTIs and number of TAMs was observed. Unfortunately, we did not have sufficient viral load data to determine whether there was a correlation between duration patients were virologically failing NRTI regimens and number of TAMs.

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Corresponding authors:
Colleen Whitelaw (colleenw@afadm.co.za)
Graeme Meintjes (graemein@mweb.co.za)