

The effect of transmitted HIV drug resistance on pre-therapy viral load

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Background

- Estimates of HIV transmitted drug resistance (TDR) prevalence have varied widely, averaging ~10%
- *In vitro* studies indicate that most drug resistance mutations reduce replication capacity of HIV
- Patients with TDR might be expected to have lower HIV RNA viral load (VL) than patients infected with wild-type virus
- Epidemiological studies to date have been inconclusive (patients with TDR: n=9-77)

Methods

- Extracted *pol* gene sequences from UK HIV Drug Resistance Database, previously linked to demographic and clinical data (UK CHIC study)
- Eligible adult patients had
 - (a) resistance test performed while ART-naïve
 - (b) VL and CD4 count measurements within 6 months of the first test and before starting ART
- Analysed first test per patient
- TDR defined using WHO list (2007) of surveillance drug resistance mutations

Baseline characteristics (n=7,994)

- Calendar year of test: 1997-9 (12%), 2000-4 (36%), 2005-7 (52%)
- Exposure group: MSM (62%), Heterosexual men (10%), Heterosexual women (16%), Other (12%)
- Ethnicity: White (62%), Black (22%), Other (16%)
- Viral subtype: B (68%), C (13%), A (4%), AG (4%), Other (11%)
- Mean (SD) CD4 count: 361 (233) cells/mm³
- Mean (SD) viral load: 4.60 (0.82) log₁₀ copies/ml

Viral load by TDR

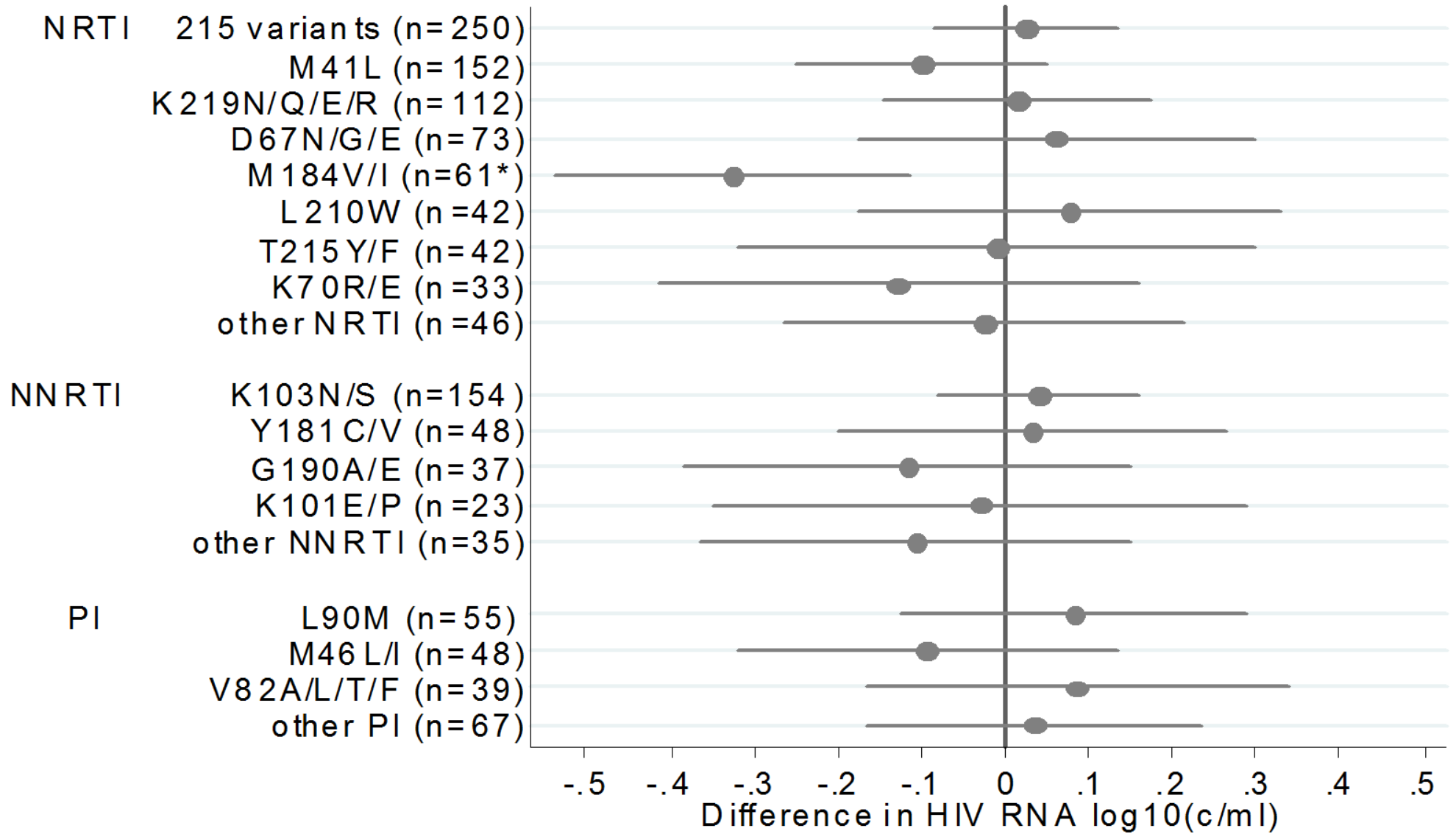
Group	No. (%)	Mean log ₁₀ VL (SD)	Adjusted* difference	P
No TDR	7285 (91)	4.60 (0.82)	REF	
Any TDR	709 (9)	4.58 (0.83)	-0.04	0.12

Adjusted for: CD4 count, viral subtype, ethnicity, exposure group, sex, age, calendar year, clinical centre, VL assay

Viral load by class of TDR

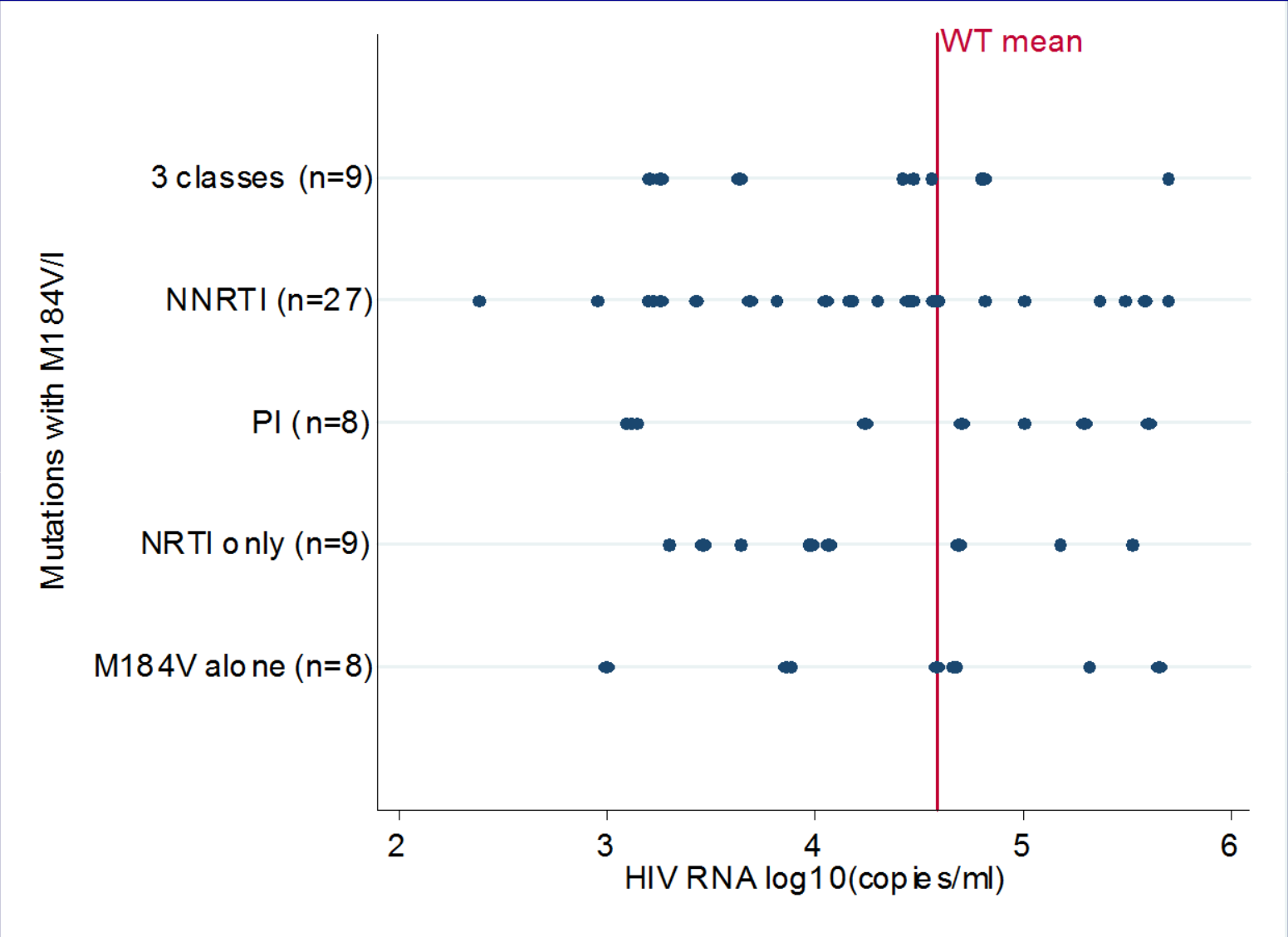
Group	No. (%)	Mean log ₁₀ VL (SD)	Adjusted* difference	P
No TDR	7285 (91)	4.60 (0.82)	REF	
Any TDR	709 (9)	4.58 (0.83)	-0.04	0.12
NRTI only	350 (4)	4.60 (0.85)	-0.05	0.21
NNRTI only	164 (2)	4.59 (0.86)	0.00	0.96
PI only	90 (1)	4.71 (0.75)	0.09	0.27
≥2 classes	105 (1)	4.44 (0.86)	-0.21	0.004

Adjusted for: CD4 count, viral subtype, ethnicity, exposure group, sex, age, calendar year, clinical centre, VL assay

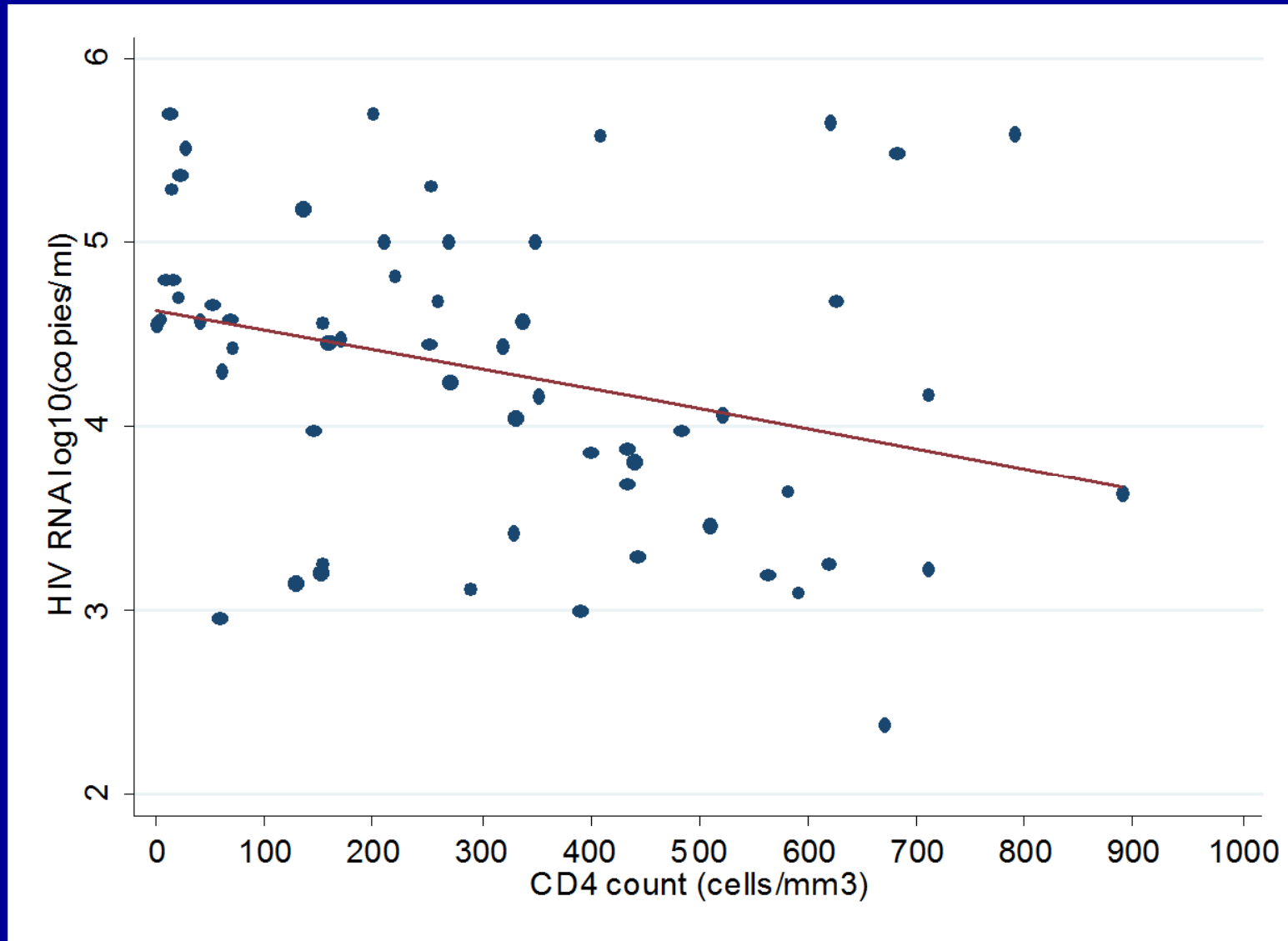


*55V, 4I, 2V/I mixture

Mutations co-expressed with M184V/I



Viral load vs. CD4 count (M184V/I cases)



Conclusions (1)

- We have shown an *in vivo* fitness cost of M184V/I independent of any drug effect
- No effect on viral load observed for any other mutation
 - caveat that most patients likely had an established infection and may have been infected by a resistant virus that reverted to wild type prior to testing

Conclusions (2)

- Has been suggested that TDR may have beneficial clinical effect by reducing risk of HIV transmission or rate of CD4 decline
- Our data suggest any such population-level effect is likely to be small
 - M184V/I only mutation implicated with prevalence of only 0.8%

UK HIV DRUG RESISTANCE DATABASE

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- Reduction in VL from 4.60 to 4.30 copies/ml is predicted to
 - reduce incidence of AIDS (in absence of ART) by $\sim 31\%$ ¹
 - reduce risk of heterosexual HIV transmission by $\sim 24\%$ ²

1. CASCADE Collaboration (AIDS, 2004).

2. Rakai Project Study Group (NEJM, 2000)