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Influence of Transmitted Drug Resistance on CD4 Decline among ART Naïve HIV Patients

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Introduction

- Transmitted drug resistance mutations (TDRM) may lead to an altered progression of HIV disease before the start of antiretroviral therapy (ART).
- Existing research into the effect of the effect of TDRM on the natural history of HIV have found conflicting results.

Aim:

- To investigate the effect of TDRM on CD4 count changes before the start of ART.

Methods

Data and Study population

Data from several European HIV clinics (ViroLAB, EuResist and EuroSIDA contributing clinics; Royal Free and St Mary's Hospital, London; University of Bari) were merged. Individuals were included if they:

- Were older than 18 years old.
- Had at least 1 CD4 count available.
- Had at least 1 genotypic resistance test before starting ART (first date any ART drug was initiated).
- Had data available for the viral set point to be estimated.

FU lasted until the last CD4 measurement before ART. Baseline was defined as the date of the first available CD4 count. TDRM were identified using the WHO 2009 surveillance list[1]. We presumed that mutations detected at any point during follow-up had been present since baseline, and for those with more than one pre-ART resistance test available resistance was considered in a cumulative manner. The set-point was defined as the median of all pre-ART viral load measurements.

Statistical methods

Linear mixed models with a random intercept and slope were used to estimate the effect of TDRM on CD4 slopes. The 10 most commonly detected mutations were tested for their effect on CD4 slopes; for these comparisons we used a Bonferroni corrected p-value threshold of 0.005 to indicate statistical significance.

Sensitivity analyses:

A. The analyses were repeated stratified by subtype B and non-B.
B. The analyses were repeated using the minimum available date for each person as the baseline date, restricting the analyses to those who had this information available (N=1285).

Results

Baseline characteristics

6180 individuals contributing a median of 5 (IQR= 2-9) CD4 measurements over a median of 1 (IQR=0.2-2.7 years) years were included. The baseline characteristics according to the prevalence of TDRM can be seen in **Table 1**. The majority of the individuals were infected with a Subtype B virus (64%).

The median baseline CD4 count was 420 cells/mm3, and the median viral set point was 4.5 $\log_{10}$ cp/ml. Among individuals with TDRM, the median CD4 count was 433 cells/mm^3, and among those with wild-type viruses it was 420 cells/m^3. The viral set point was 4.4 $\log_{10}$ cp/ml among those with TDRM, and 4.5 $\log_{10}$ cp/ml among those without TDRM (**Table 1**). We found no marked changes in CD4 and VL set point according to the class of resistance present (data not shown).

Table 1.

Baseline characteristics of the study population, according to TDRM presence

		Total N (%)	Any TDRM N (%)	Wild-type N (%)	P
Gender	*Male*	4560 (77.3)	476 (83.1)	4084 (76.7)	<.001
	Female	1339 (22.7)	97 (16.9)	1242 (23.3)	
Age, years	*Median, IQR*	36 (30, 42)	37 (30, 43)	35 (30, 42)	0.029
Risk Group	*MSM*	2689 (45.9)	308 (53.6)	2381 (45.1)	<.001
	PWID	635 (10.8)	58 (10.1)	577 (10.9)	
	Heterosexual	1911 (32.6)	139 (24.2)	1772 (33.5)	
	Other	623 (10.6)	70 (12.2)	553 (10.5)	
HIV subgroup	*B*	3976 (64.3)	459 (76.4)	3517 (63.0)	<.001
	Non-B	1471 (23.8)	65 (10.8)	1406 (25.2)	
	Unknown	733 (11.9)	77 (12.8)	656 (11.8)	
Laboratory	*CD4 counts (Median, Range)[1]*	420 (289, 583)	433 (290, 620)	420 (289, 580)	0.071
	Viral set point (Median, Range)[2]	4.5 (4.0, 5.0)	4.4 (3.9, 5.0)	4.5 (4.0, 5.0)	0.161

1. The unit is cells/mm3
2. The unit is $\log_{10}$ cp/ml

Figure 1. Prevalence of Transmitted Drug Resistance

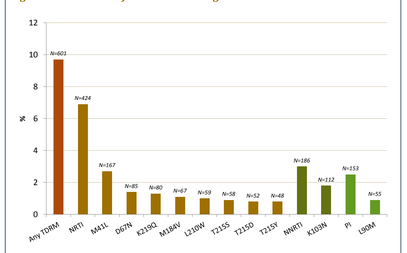
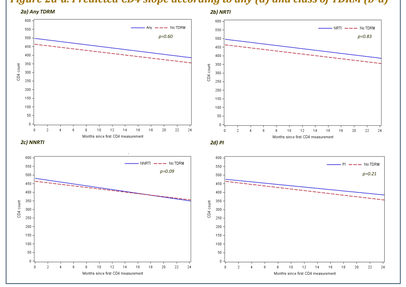


Figure 2a-d. Predicted CD4 slope according to any (a) and class of TDRM (b-d)



Resistance Prevalence

Resistance was detected in 9.7% of individuals; 6.9% had NRTI resistance, 3% NNRTI resistance and 2.5% PI resistance. The 10 most commonly detected mutations and their prevalence can be seen in **Figure 1.**

The effect of TDRM on CD4 count changes before the start of ART

The overall estimated CD4 decline was -54 cells/mm^3/year (95%CI = -56, -52). In univariable analyses, we found no evidence that CD4 decline differed according to the presence of any TDRM compared to wild-type (**Figure 2a-d).** There was also no evidence that CD4 count decline differed among individuals with NRTI or PI resistance as compared to those with wild-type viruses. There was some weak evidence suggesting that CD4 counts declined more steeply among individuals with detected NNRTI resistance (difference compared to wild-type= -12 (95%CI=-25,+2) cells/mm^3/year; p=0.08). These conclusions did not change upon adjustment for covariates including viral load set point (**Table 2**).

Associations between individual TDRM and CD4 count changes before the start of ART

The associations between individual TDRM and CD4 slopes can be seen in **Table 3**. There was some suggestion that CD4 slopes were less marked among individuals who had the T215Y mutation (difference compared to wild-type= +35 (95%CI=+15, +56) cells/mm^3/year) but more marked among individuals who had the revertant T215D mutation (difference compared to wild-type= -39 (95%CI= -63, -15) cells/mm^3/year); however, this was not the case for T215S. There was no evidence of an association between the M184V and CD4 count declines (difference compared to wild-type= +0.3 (-19, +20) cells/mm^3/year).

Sensitivity analyses

The results from sensitivity analyses can be seen in **Table 4a-b.** When restricting the analysis to individuals with subtype B viruses only, there was still no evidence to suggest that the presence of any TDRM was associated with differences in CD4 decline (p=0.76). Using the minimum date available as the baseline date did not change the overall conclusions.

Limitations

-Date of Seroconversion: Due to data availability, we could not use the date of seroconversion as the baseline date. CD4 count trends may differ according to time since seroconversion.
-Generalizability: Individuals with a resistance test before starting treatment may differ from individuals not tested. In addition, the natural history of HIV can vary according to the subtype of the virus. These factors could limit the generalisability of our results.
-Power: The prevalence of TDRM, and in particular the prevalence of individual mutations, is relatively low. Despite the large dataset our analysis may have suffered from a lack of power.

Conclusions and Future Work

- We were not able to find convincing evidence supporting the hypothesis that the rate of CD4 decline in the absence of ART is different between patients with and without TDRM.
- This could reflect the fact that mutations with less impact on fitness are preferentially transmitted.
- We cannot rule out the fact that TDRM may influence the rate of CD4 decline differently in different time-periods since seroconversion.
- Future work will focus on characterising viral load changes over time, describing associations between TDRM and viral load changes and evaluating our assumption that mutations persisted throughout FU in sensitivity analyses.

Table 2.

CD4 slope according to TDRM presence (any and class)

		Adjusted slope[1,2] (95%CI)	Difference (95%CI)	P-value[3] (difference)
Any	Wild-type	-53.75 (-56.12, -51.38)		
	Yes	-56.69 (-63.74, -49.65)	-2.94 (-10.37, +4.49)	0.44
NRTI	Wild-type	-53.83 (-56.21, -51.44)		
	Yes	-55.44 (-63.54, -47.34)	-1.61 (-10.05, +6.83)	0.71
NNRTI	Wild-type	-53.67 (-56.00, -51.34)		
	Yes	-65.61 (-78.92, -52.30)	-11.94 (-25.46, +1.57)	0.08
PI	Wild-type	-53.65 (-55.98, -51.32)		
	Yes	-46.70 (-60.19, -33.21)	+6.95 (-6.74, +20.65)	0.32

1. *Adjusted for risk group, subtype, calendar year of resistance test, cohort, and viral set point.*
2. *Data points with missing data for risk group (N=322) were excluded from the analysis.*
3. *The p-value is for the difference between the two slopes (interaction term from the mixed model), and tests the null hypothesis that the CD4 slopes in both categories of the specified exposure are the same.*

Table 3.

CD4 slope according to TDRM presence (individual mutations)

		Adjusted slope[1] (95%CI)	Difference (95%CI)	P-value (difference)
M41L	Wild-type	-53.60 (-55.95, -51.26)		
	Yes	-43.30 (-56.03, -30.57)	+10.30 (-2.64, +23.25)	0.12
K103N	Wild-type	-53.60 (-55.91, -51.28)		
	Yes	-68.17 (-85.85, -50.49)	-14.58 (-32.41, +3.26)	0.11
D67N	Wild-type	-53.44 (-55.76, -51.13)		
	Yes	-53.46 (-70.08, -36.83)	-0.01 (-16.80, +16.77)	0.99
K219Q	Wild-type	-53.62 (-55.94, -51.29)		
	Yes	-63.54 (-81.61, -45.47)	-9.93 (-28.14, +8.29)	0.27
M184V	Wild-type	-53.84 (-56.20, -51.48)		
	Yes	-53.48 (-73.18, -33.79)	+0.35 (-19.48, +20.18)	0.97
T215S	Wild-type	-53.76 (-56.10, -51.41)		
	Yes	-54.41 (-77.30, -31.51)	-0.65 (-23.67, +22.37)	0.96
L210W	Wild-type	-53.41 (-55.71, -51.10)		
	Yes	-50.11 (-71.04, -29.17)	+3.30 (-17.76, +24.36)	0.76
L90M	Wild-type	-53.66 (-55.98, -51.33)		
	Yes	-28.87 (-50.98, -6.77)	+24.78 (+2.55, +47.01)	0.03
T215D	Wild-type	-53.60 (-55.92, -51.28)		
	Yes	-92.36 (-116.2, -68.47)	-38.76 (-62.76, -14.77)	0.002
T215Y	Wild-type	-53.43 (-55.74, -51.12)		
	Yes	-18.00 (-38.18, +2.18)	+35.43 (+15.12, +55.74)	<.001

1. *Adjusted for risk group, subtype, calendar year of resistance test, cohort, and viral set point.*

Table 4a-b.

Sensitivity A: CD4 slope according to TDRM presence among those with Subtype B virus

		Adjusted slope[1] (95%CI)	Difference (95%CI)	P-value (difference)
Any	Wild-type	-55.59 (-58.53, -52.65)		
	Yes	-56.90 (-64.93, -48.88)	-1.32 (-9.87, 7.24)	0.76
NRTI	Wild-type	-55.69 (-58.65, -52.73)		
	Yes	-55.75 (-64.90, -46.59)	-0.06 (-9.68, 9.56)	0.99
NNRTI	Wild-type	-55.36 (-58.22, -52.50)		
	Yes	-70.35 (-85.91, -54.79)	-14.99 (-30.81, 0.82)	0.06
PI	Wild-type	-55.39 (-58.26, -52.52)		
	Yes	-40.51 (-55.69, -25.33)	14.88 (-0.57, 30.33)	0.06

Sensitivity B: CD4 slope according to TDRM presence using the minimum date as baseline

		Adjusted slope[1] (95%CI)	Difference (95%CI)	P-value (difference)
Any	Wild-type	-55.06 (-59.67, -50.44)		
	Yes	-55.41 (-68.35, -42.46)	-0.35 (-14.09, 13.39)	0.96
NRTI	Wild-type	-54.97 (-59.62, -50.32)		
	Yes	-51.71 (-67.53, -35.90)	3.26 (-13.22, 19.74)	0.70
NNRTI	Wild-type	-54.94 (-59.58, -50.29)		
	Yes	-54.82 (-78.56, -31.08)	0.12 (-24.07, 24.31)	0.99
PI	Wild-type	-54.91 (-59.55, -50.27)		
	Yes	-59.15 (-82.81, -35.50)	-4.24 (-28.35, 19.86)	0.73

1. *Adjusted for risk group, subtype, calendar year of resistance test, cohort, and viral set point.*

References: 1. Bennett DE, Camacho RJ, Otelea D, Kuritzkes DR, Fleury H, Kiuchi M, et al.. PloS One. 2009;4(3):e4724;

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