Rapid Increase in the Frequency of Wild-type HIV-1 Drug Resistance Reports among ART-experienced Patients in the UK

David Dolling[1], Mark Nelson[2], Achim Schwenk[3], Duncan Churchill[4], Deenan Pillay[5], and David Dunn[1]
on behalf of the UK HIV Drug Resistance Database and the UK Collaborative Cohort Study
[1]MRC Clinical Trials Unit, London, UK; [2]Chelsea and Westminster Hospital, London, UK; [3]North Middlesex University Hospital NHS Trust, London, UK;
[4] Royal Sussex County Hospital, Brighton, UK; [5]University College London, London, UK

Contact for further information:
Mr David Dolling
Email: did@ctu.mrc.ac.uk
Tel: +44 20 7670 4933
http://www.hivrdb.org.uk/
http://www.ukchic.org.uk/

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Introduction

- HIV-1 drug resistance tests conducted on ART-experienced patients are increasingly finding no drug resistant mutations and are purely wild-type (WT) virus
- This could reflect a trend where poor ART adherence is the predominant cause of virological failure
- Current UK guidelines recommend that patients experiencing failure on first line ART with a WT virus switch to a PI/r combination ART regimen if on a regimen with a low genetic barrier to resistance.
- We investigated:
  - Trends in WT test results
  - Predictors of WT test results
  - Short-term clinical outcomes following a WT test

Methods

Resistance Data:
The UK HIV Drug Resistance Database collects information on the majority of genotypic resistance tests conducted in the UK as part of routine clinical care. Bulk sequenced resistance tests of the *pol* gene encoding the protease gene and the first 234 codons of the reverse transcriptase gene were analysed.

Clinical Data:
Demographic and clinical information was acquired by linkage to the UK Collaborative HIV Cohort Study (UK CHIC).

Resistance Tests Included:
The first resistance test for all ART-experienced patients aged >16, between 2000 and 2010 were analysed.

Wild-type:
Resistance tests were classified as wild-type if there were no major resistance mutations, as defined by the IAS-USA 2011 mutation list (Johnson et al, 2011).

Decision to switch:
Treatment switch was defined as the addition of one new drug, either new or recycled. We described the competing risk of either treatment switch or viral suppression (defined as a viral load <400 copies/mL) without a treatment switch.

Statistical Methods:

- **Multiple Imputation**

43% of individuals had at least one prognostic factor missing. To avoid a loss in efficiency missing values for age, exposure group, ethnicity, viral load at resistance test, CD4 at resistance test, previous suppression <400 copies/mL, and cumulative viral load were imputed using multiple imputation by chained equations.

- **Logistic Regression**

Predictive variables for a wild-type test result were evaluated using logistic regression.

UK HIV Drug Resistance Database Steering Committee: http://tinyurl.com/a7j38zq
UK Collaborative HIV Cohort Steering Committee: http://tinyurl.com/b6lu4xj

Results

1. Trends in wild-type test results

- 6,870 resistance tests were analysed, 3373 (49%) were wild-type
- Figure 1 shows a strong increasing trend over time

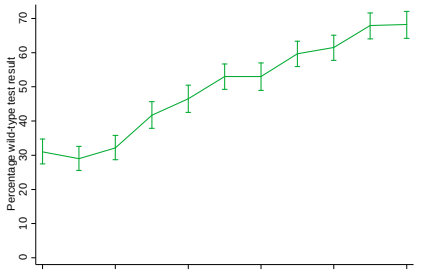

Figure 1: Trends (Proportion; 95% CI) in wild-type test results

# of tests	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Wild-type	198	225	280	376	444	606	629	824	1,039	1,103	1,083
Resistant	470	631	711	705	732	663	674	632	678	639	579

2. Predictors of a wild-type test result

The results for both the univariate and multivariate logistic regression models are shown in Table 1.

Findings:

- Viral load coefficients have a U-shaped relationship.
  - Genotypes performed at VLs<1,000 may represent blips or tests where we are unable to pick up early mutation development with population sequencing
  - VLs>1,000 and <100,000 demonstrate levels of adherence where resistant mutations are more likely to be selected
  - VLs≥100,000 probably reflect suboptimal adherence such that drug levels aren't sufficiently high to select for resistance mutations
- Resistance tests conducted during a treatment break are likely to be wild-type. This reflects resistant mutations being outgrown by wild-type virus once therapy is discontinued
- Genotypes performed in individuals on PI-containing regimens were more likely to be wild-type - this reflects the existing body of evidence that such regimens have a higher genetic barrier to resistance
- Calendar time remained highly significant in the multivariate model after adjustment

Table 1: Baseline characteristics

Variable	Total N	Total %	Wild-type N	Wild-type %
Exposure Group				
MSM	3,155	49.7	1,614	51.2
Male Het	997	15.7	382	38.3
Other Male	212	3.3	110	51.9
Female Het	1,854	29.2	1,035	55.8
Other Female	132	2.1	64	48.5
Ethnicity				
White	3,284	52.8	1,642	50.0
Black	2,420	38.9	1,227	50.7
Other	516	8.3	272	52.7
Viral load at test (copies/mL)				
<1,000	1,257	20.5	719	57.2
1,000-10,000	1,945	31.6	771	39.6
10,000-50,000	1,358	22.1	612	45.1
50,000-100,000	553	9.0	308	55.7
≥100,000	1,034	16.7	648	62.7
Treatment regimen				
NRTI & NNRTI	2,302	33.5	890	38.7
NRTI only	602	8.8	166	27.6
NRTI & boosted PI	1,367	19.9	775	56.7
NRTI & unboosted PI	536	7.8	166	31.0
Boosted PI only	116	1.7	87	75.0
Triple class	190	2.8	46	24.2
Treatment break	1,653	24.1	1,204	72.8
Other	104	1.5	39	37.5
Previously suppressed (≤400 copies/mL)				
No	2,357	35.1	1,181	50.1
Yes	4,354	64.9	2,110	48.5
Days since starting regimen				
>180 days	5,676	82.7	2,626	46.3
≤180 days	503	7.3	281	55.9
≤90 days	691	10.1	467	67.6
Viremia copy years (log10 copies × year on ART/mL)				
≤3	1,237	20.6	688	55.6
3-4	1,345	22.4	500	37.2
4-5	1,816	30.3	867	47.7
>5	1,596	26.6	780	48.9
Regimen Line				
1	3,885	56.6	2,131	54.9
2	1,746	25.4	831	47.6
3+	1,239	18.0	411	33.2
Previous regimens failed				
0	687	10.0	490	71.3
1	4,105	59.8	2,084	50.8
2+	2,078	30.3	799	38.5
Subtype				
Subtype B	3,432	55.3	1,743	50.8
Subtype C	1,055	17.0	500	47.4
Other Subtype	1,718	27.7	909	52.9
	Median		**IQR**	
Age (Decades)	3.86		3.35 - 4.42	
CD4 at test (100 cells/μL)	2.85		1.70 - 4.40	
Years of ART	2.96		0.88 - 5.95	
Year of test	2005		2002 - 2008	

Table 2: Logistic regression model of WT test result

Variable	OR	95% CI	AOR	95% CI	P
Exposure Group					
MSM	Ref	-	Ref	-	<0.001
Male Het	0.60	0.52 - 0.69	0.53	0.42 - 0.67	
Other Male	1.02	0.77 - 1.36	1.23	0.89 - 1.70	
Female Het	1.21	1.08 - 1.35	1.00	0.80 - 1.25	
Other Female	0.89	0.63 - 1.27	0.95	0.63 - 1.42	
Ethnicity					
White	Ref	-	Ref	-	0.974
Black	1.03	0.93 - 1.14	1.02	0.83 - 1.26	
Other	1.11	0.92 - 1.34	1.02	0.82 - 1.28	
Viral load at test (copies/mL)					
<1,000	Ref	-	Ref	-	<0.001
1,000-10,000	0.52	0.45 - 0.60	0.71	0.60 - 0.84	
10,000-50,000	0.64	0.55 - 0.75	0.85	0.70 - 1.04	
50,000-100,000	0.96	0.79 - 1.17	1.11	0.86 - 1.44	
≥100,000	1.26	1.07 - 1.49	1.38	1.09 - 1.74	
Treatment regimen					
NRTI & NNRTI	Ref	-	Ref	-	<0.001
NRTI only	0.60	0.50 - 0.74	0.91	0.74 - 1.13	
NRTI & boosted PI	2.08	1.81 - 2.38	2.18	1.87 - 2.55	
NRTI & unboosted PI	0.71	0.58 - 0.87	1.27	1.01 - 1.59	
Boosted PI only	4.76	3.10 - 7.30	4.74	3.00 - 7.49	
Triple class	0.51	0.36 - 0.71	1.02	0.70 - 1.48	
Treatment break	4.25	3.71 - 4.88	5.52	4.72 - 6.46	
Other	0.95	0.63 - 1.43	0.96	0.61 - 1.51	
Previously suppressed (≤400 copies/mL)					
No	Ref	-	Ref	-	<0.001
Yes	0.92	0.84 - 1.02	1.53	1.31 - 1.77	
Days since starting regimen					
>180 days	Ref	-	Ref	-	<0.001
≤180 days	1.47	1.22 - 1.77	1.36	1.07 - 1.73	
≤90 days	2.42	2.05 - 2.87	3.03	2.35 - 3.90	
Viremia copy years (log10 copies × year on ART/mL)					
≤3	Ref	-	Ref	-	<0.001
3-4	0.45	0.38 - 0.52	0.67	0.55 - 0.82	
4-5	0.64	0.56 - 0.73	0.94	0.76 - 1.17	
>5	0.66	0.57 - 0.76	1.12	0.87 - 1.45	
Regimen Line					
1	Ref	-	Ref	-	<0.001
2	0.75	0.68 - 0.84	1.00	0.85 - 1.17	
3+	0.41	0.36 - 0.47	0.68	0.54 - 0.85	
Previous regimens failed					
0	Ref	-	Ref	-	<0.001
1	0.49	0.41 - 0.57	0.63	0.51 - 0.78	
2+	0.29	0.24 - 0.34	0.49	0.38 - 0.63	
Subtype					
Subtype B	Ref	-	Ref	-	0.014
Subtype C	1.08	0.94 - 1.24	0.89	0.70 - 1.14	
Other Subtype	1.23	1.06 - 1.44	1.16	0.94 - 1.43	
Age (Decades)	0.91	0.86 - 0.96	0.98	0.92 - 1.05	0.616
CD4 at test (100 cells/μL)	1.03	1.00 - 1.05	1.03	1.00 - 1.07	0.026
Years of ART	0.95	0.94 - 0.96	0.96	0.94 - 0.98	<0.001
Year of test	1.20	1.18 - 1.22	1.15	1.13 - 1.18	<0.001

3. Decision to switch

Table 2: Number (%) on treatment with first short-term event

	First event type within a year: Suppression (VL<400 cps/mL)	Treatment switch (≥1 drug)	Neither (VL>400 cps/mL without switch)
Resistant	591 (19.5%)	1,790 (59.1%)	646 (21.3%)
Wild-type	1,095 (50.7%)	654 (30.3%)	411 (19.0%)

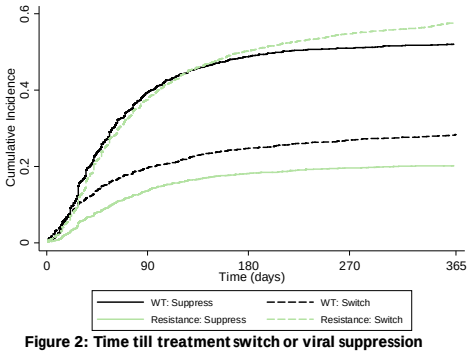

Figure 2: Time till treatment switch or viral suppression

Figure 2 shows that many patients with wild-type virus suppressed their viral load, typically within 180 days.

For WT patients on treatment, treatment switches were typically to:

- NRTI + boosted PI (n=326; 49.9%) regimens from NRTI + boosted PI (n=140; 42.9%), NRTI + unboosted PI (n=27; 8.3%) and NRTI + NNRTI (n=95; 29.1%) regimens.
- NRTI + NNRTI (n=165; 25.2%) regimens from NRTI + boosted PI (n=33; 20.0%), NRTI + unboosted PI (n=19; 11.5%) and NRTI + NNRTI (n=80; 48.5%) regimens.

Regimens added either one (n=216; 33.0%), two (n=211; 32.3%), three (n=127; 19.4%) or four or more (76; 11.6%) new or recycled drugs.

Summary and Conclusions

- Wild-type resistance tests are becoming increasingly common in ART-experienced patients
- Resistance tests continue to be conducted during ART breaks, despite guidelines recommending tests only be conducted during therapy, these are more likely to find purely wild-type virus so aren't likely to be useful
- Very high viral loads, especially those with a boosted PI, likely reflect adherence below that required to select for drug resistant mutations so resistance tests should be used more selectively in these patients and may not always be cost-effective
- Patients with wild-type resistance tests often suppress virus without switching treatment. Clinicians may be using resistance tests to confirm resistance has not developed during periods of non-adherence and to promote better subsequent adherence. Nonetheless many patients do switch treatment, often to NRTI+PI based regimens, as UK guidelines now suggest