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HIV-1 Transmitted Drug Resistance (TDR) in Paired Plasma and Seminal Fluid:

Persistence in Semen and Little Evidence of Differential Evolution

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Background

- In HIV-1 infection, transmitted drug resistance (TDR) is associated with decreased susceptibility to antiretroviral therapy (ART)
- With acquired ART resistance, resistant HIV-1 virus is replaced with wild-type in the absence of ART¹
- In TDR the mutations usually persist but may slowly revert to wild-type²

Background

- Evolution of TDR may not be the same in the blood and the male genital tract
- The importance of TDR minority species (<1%) in each compartment in this context is unclear- is there a threshold that matters?
- To date only one study³ comparing plasma and seminal fluid HIV TDR:
 - Small numbers ($n=5$)
 - Didn't observe the effect of initiating ART
 - No minority species data

Objectives

- To compare the TDR profile in the plasma & genital secretions of HIV-1 infected men
- To investigate the effect of initiating ART on plasma and genital HIV-1 TDR mutations

Inclusion criteria

- HIV-1 infected males
- TDR mutation on baseline resistance test (RT)
- No exposure to ART
- Informed consent

HIV-1 RT and Protease Mutations For Drug Resistance Surveillance								
NRTI			NNRTI			PI		
Pos	Mut		Pos	Mut		Pos	Mut	
M41	L		L100	I		L23	I	
K65	R		K101	E, P		L24	I	
D67	N, G, E		K103	N, S		D30	N	
T69	D, Ins		V106	M, A		V32	I	
K70	R, E		V179	F		M46	I, L	
L74	V, I		Y181	C, I, V		I47	V, A	
V75	M, T, A, S		Y188	L, H, C		G48	V, M	
F77	L		G190	A, S, E		I50	V, L	
Y115	F		P225	H		F53	L, Y	
F116	Y		M230	L		I54	V, L, M, A, T, S	
Q151	M					G73	S, T, C, A	
M184	V, I					L76	V	
L210	W					V82	A, T, F, S, C, M, L	
T215	Y, F, I, S, C, D, V, E					N83	D	
K219	Q, E, N, R					I84	V, A, C	
						I85	V	
						N88	D, S	
						L90	M	

New mutations from the 2007 list are in bold.

Shafer list (2007)

Methods

- Paired semen and blood samples were collected at each study visit:
 - Stable naïve subjects were sampled at 8 monthly intervals
 - Patients initiating ART were sampled at baseline then 4 weekly intervals until undetectable

Methods

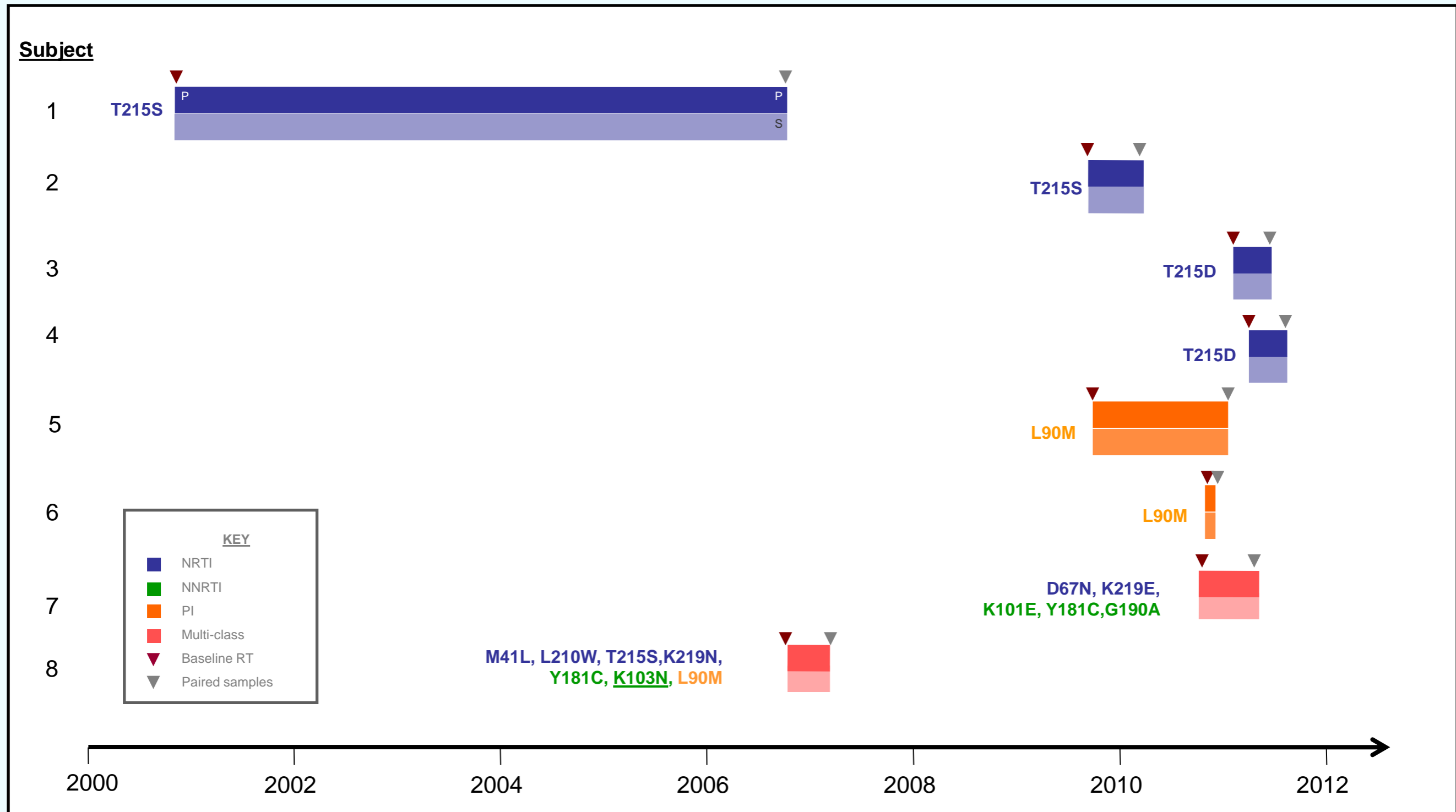
- Analyses performed at HPA Colindale:
 - Population-based sequencing ('standard' RT)⁴
 - Allele-specific PCR sequencing (103, 181, 184)⁵
 - Incidence testing (Anti-HIV Incidence Qn)
- Urine NAAT sampling to exclude STIs
 - *N. gonorrhoea* and *C. trachomatis*

Results

Sample size	15
Route of acquisition	MSM
Median age (range)	37 years (27-51 years)
Median baseline HIV-1 VL (IQR) (copies/mL)	13 756 (7 477-71 960)
Single paired samples	8
Multiple paired samples	7
Positive CT or GC NAAT	0

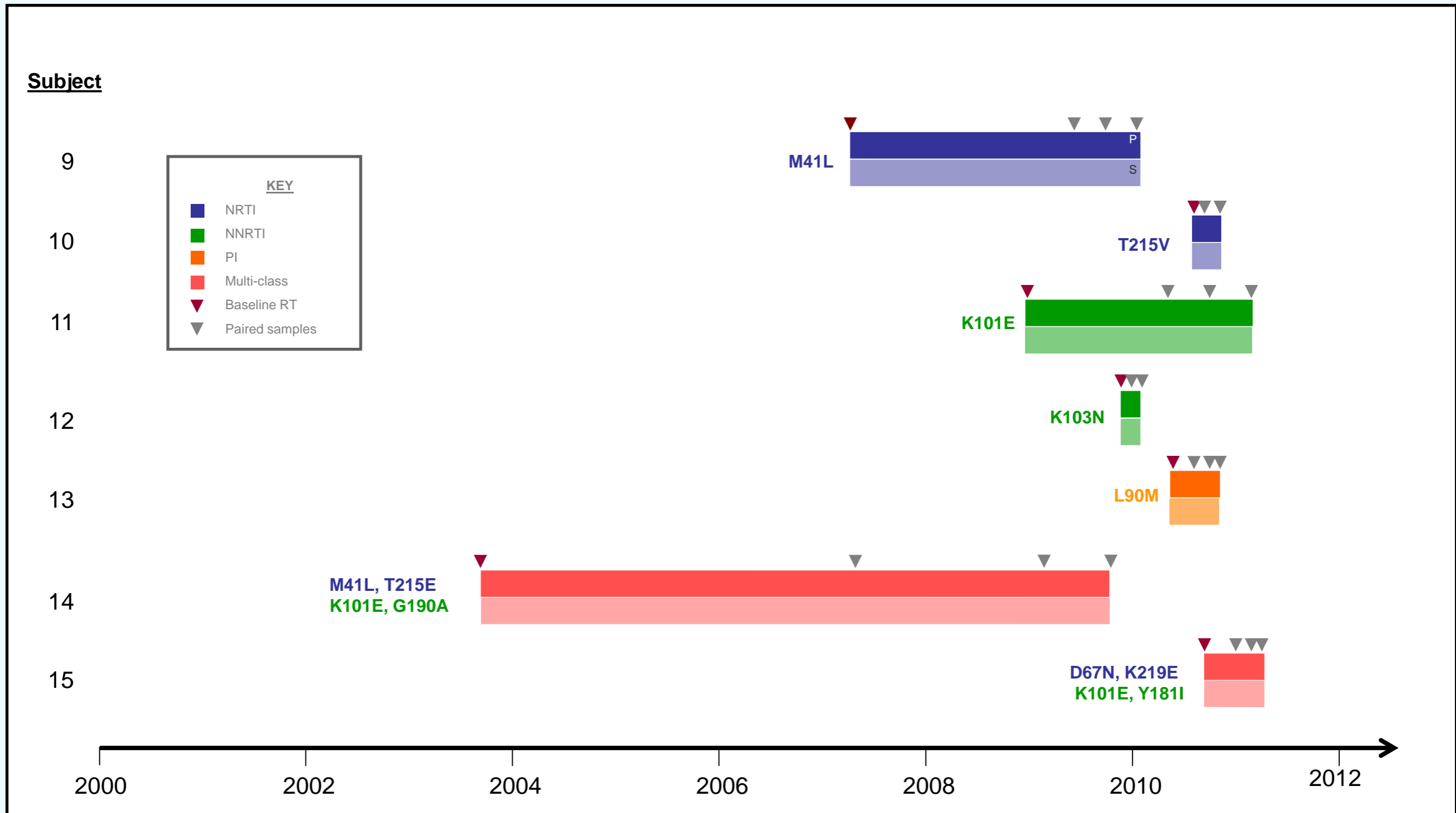
Results

Figure 1: TDR mutations in single paired semen and plasma samples while ART naive



Results

Figure 2: TDR mutations in multiple paired semen and blood samples while ART naive



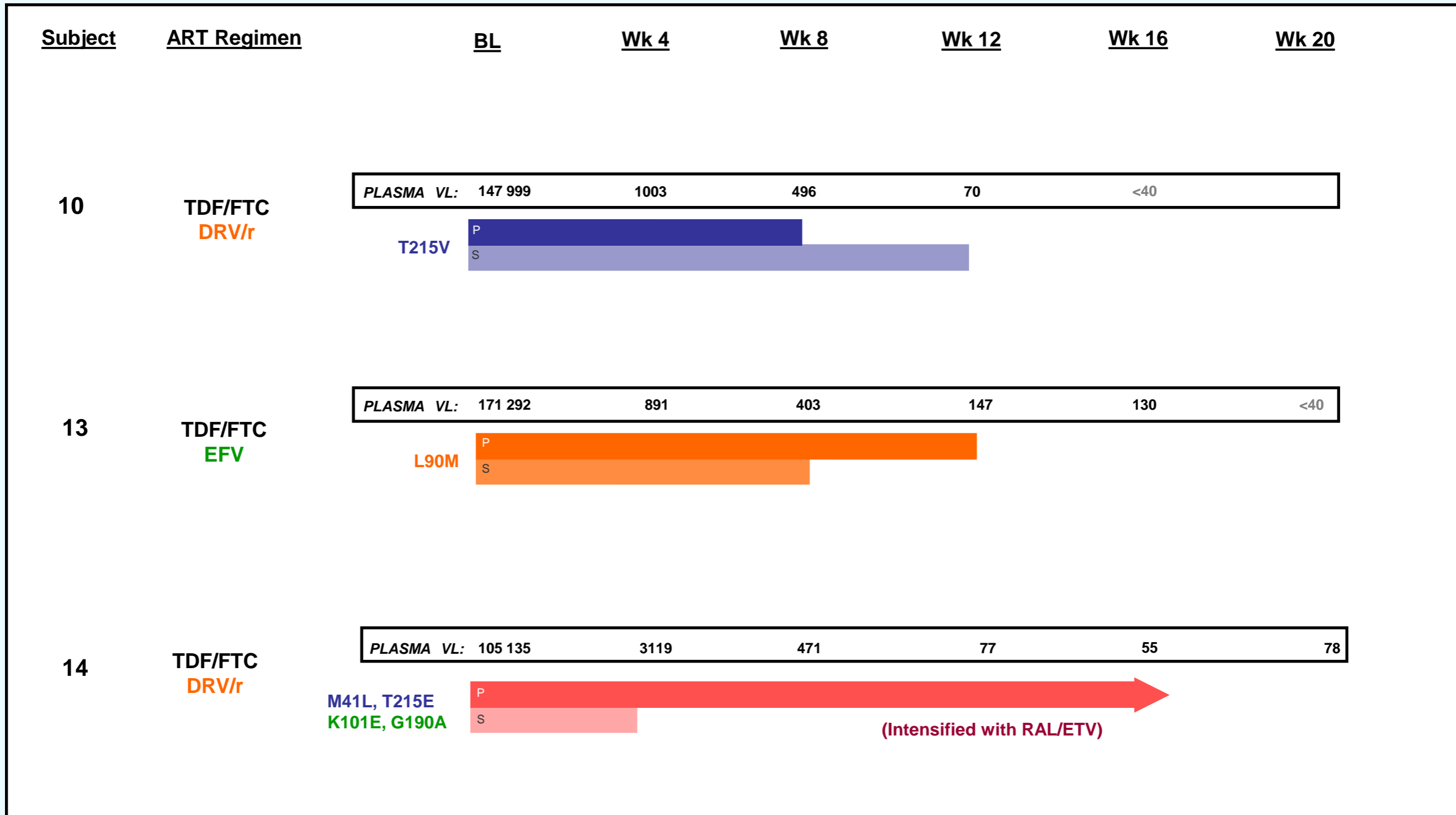
Results

Figure 3: TDR mutations in multiple paired semen and plasma samples while starting ART



Results

Figure 3: TDR mutations in multiple paired semen and blood samples while starting ART



Results

Figure 4: TDR minority species in multiple paired semen and blood samples

Subject	Population sequencing mutations	Allele-specific mutations					
		Plasma			Semen		
		K	Y	M	K	Y	M
		1	1	1	1	1	1
		0	8	8	0	8	8
		3	1	4	3	1	4
1	T215S	-	-	-	-	-	-
2	T215S	■					
3	T215D						
4	T215D	■	■	■	■	■	■
5	L90M	■	■	■	■	■	■
6	D67N, K219E, K101E, Y181C, G190A						
7	M41L, L210W, T215S, K219N, Y181C, K103N, L90M	-	-	-	-	-	-
8	L90M						
9	M41L						
10	T215V	■		■			
11	K101E		■	■			
12	K103N			■			
13	L90M	■	■	■	■	■	
14	M41L, T215E, K101E, G190A	■					
15	D67N, K219E, K101E, Y181I	-	-	-	-	-	-

9 patients had minority species TDR in plasma

3 of these also had minority species TDR in paired semen samples

3 have not been analysed

Limitations

- Underestimates length of TDR persistence
(most were non-incident at baseline)
- Seminal fluid HIV-1 VL not possible
- Minority species data not available for a subset of subjects
- Integrase mutations not characterised

Discussion

- TDR mutation patterns in the plasma and seminal fluids is *very* similar with little evidence of differential evolution
- TDR mutations in both compartments persisted for long time periods (in two cases for over six years)
- 4/15 had multi-class TDR and these mutations persisted for long time periods

Discussion

- On starting ART, TDR persisted in both compartments while HIV-1 remained detectable
- Supports the ***potential for onward transmission*** of TDR (including multi-drug TDR) from drug-naïve/undiagnosed individuals
- Analysis of blood samples alone may be sufficient to describe resistance in patients with TDR

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Questions?
