

**377-M.**

**Replicative Fitness of MDR  
Viruses in Primary HIV-1  
Infection**

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**Background:** Persistence of dual and triple class multidrug (MDR) resistant viruses acquired during primary HIV infection (PHI) may affect virological and treatment outcomes. This study compares the genotypic evolution and fitness of MDR and wild-type viruses present in PHI

**Methods:** Longitudinal sequence analysis was performed on plasma or PBMC samples obtained from PHI patients with WT, single-class, or MDR infections. Changes in genotype and viremia were assessed in relation to relative viral fitness.

**Results:** MDR infections persisted over the entire study period ranging from 1 to 5 years in the absence of antiretroviral (ARV) therapy similar to that observed in PHI with WT virus. This was unlike MDR infections in source partners where the typical pattern of WT outgrowth was observed within 12 weeks of treatment interruption. Viral isolates were obtained and expanded from PHI patients with WT or MDR infections. As expected, MDR viruses were replicatively unfit with severely compromised reverse transcriptase (RT) activity and were consistently out-competed by WT virus in dual infection experiments. Nevertheless, despite their replicative disadvantage, MDR viruses maintained levels of infectivity (TCID<sub>50</sub>), comparable to WT virus. Reintroduction of selective antiretroviral (ARV) drug pressure allows for minor MDR variants to re-emerge, overtaking WT virus. In some cases, MDR viruses were associated with low viremia.

**Conclusions:** These results indicate that MDR viruses expressed following PHI can establish persistent infections despite their impaired replicative competence. In this context, genotypic analysis at the time of initial patient presentation will be an important consideration for optimization of ARV therapy.

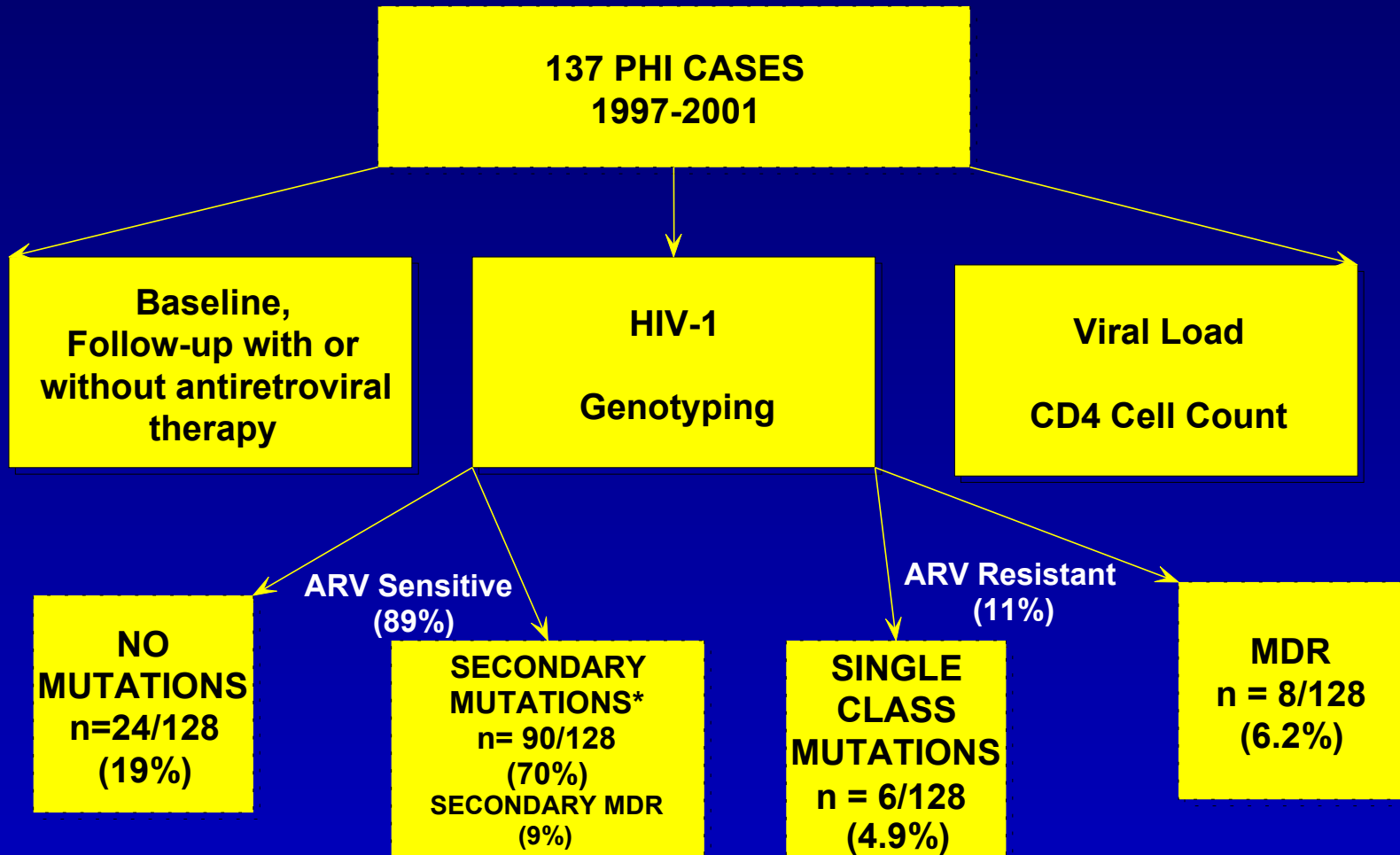
# Study Objectives

- Prevalence of Drug Resistance in PHI
- Genotypic evolution of MDR Infections over time.
- Impact of MDR infection on viremia and CD4 cell count
- Viral fitness of MDR viruses relative to WT virus

**TABLE 1. Transmission of MDR in primary HIV-1 infection**

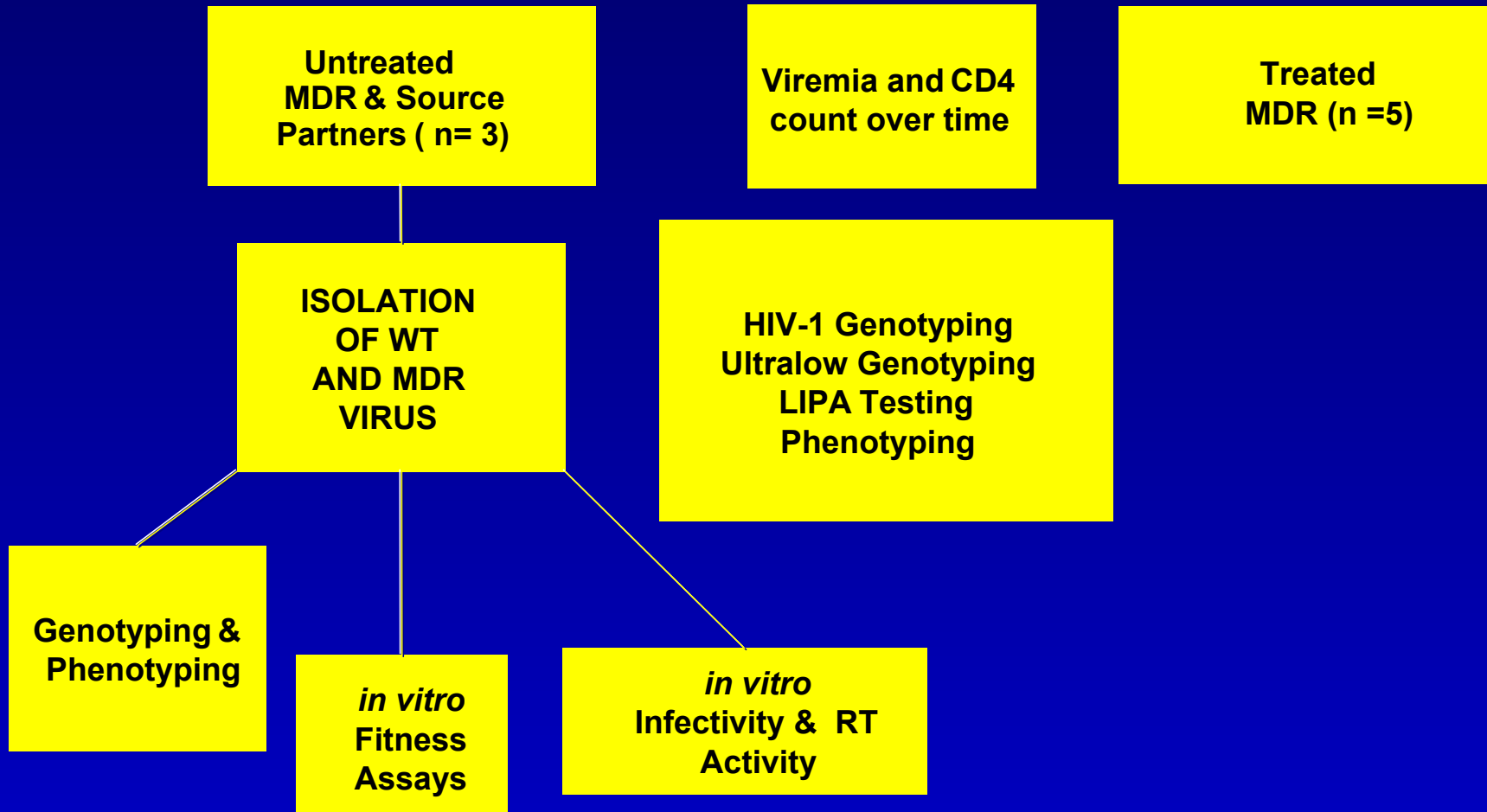
<b>Patient</b>	<b>Codon substitutions associated with drug resistance</b>		
	<b>NRTI mutations</b>	<b>NNRTI mutations</b>	<b>PI mutations</b>
<b>1</b>	<b>41L; 67N; 69N; 70R; 74V; 184V; 215F; 219Q</b>	<b>100I; 103N</b>	<b>10I; 36I; 54V; 63P; 71V; 73S; 82V; 90M</b>
<b>2</b>	<b>41L; 184V; 215Y</b>	<b>103N, 179E</b>	<b>48V; 63P; 71V; 73S; 77I; 82A; 90M</b>
<b>3</b>	<b>None</b>	<b>103N</b>	<b>10I; 54V; 63P; 71V; 82T; 84V; 90M</b>
<b>4</b>	<b>184V; 215Y</b>	<b>103N</b>	<b>77I</b>
<b>5</b>	<b>184V</b>	<b>108I</b>	<b>20R, 77I</b>
<b>6</b>	<b>41L; 67N; 210W; 215Y</b>	<b>None</b>	<b>63P; 71V; 73S; 90M</b>
<b>7</b>	<b>41L; 215Y</b>	<b>101E</b>	<b>None</b>
<b>8</b>	<b>41L; 215Y</b>	<b>101E</b>	<b>None</b>

# MONTREAL PRIMARY HIV -1 (PHI) COHORT STUDY



\*Secondary resistance mutations do not confer phenotypic resistance on their own

# ONE TO FOUR YEAR FOLLOW-UP OF THE 8 CASES WITH MDR INFECTIONS



## Genotype of viral quasispecies over time in untreated PHI patient 1

Week post-PHI	Viral source	Codon substitutions associated with drug resistance		
		NRTI mutations	NNRTI mutations	PI mutations
PHI patient 1				
16*	Plasma & PBMC	41L; 67N; 69N; 70R; 74V; 184V; 215F; 219Q	100I; 103N	10I; 36I; 54V; 63P; 71V; 73S; 82V; 90M
24	Plasma	41L; 67N; 69N; 74V; 70R; 184V; 215F; 219Q	100I; 103N	10I; 63P, 71V, 73S; 90M
30	Plasma	41L; 67N; 69N; 74V; 70R; 184V; 215F; 219Q	100I; 103N	10I; 63P, 71V, 73S; 90M
42	Plasma	70K/R; 184V	None	10I; 63P, 71V, 73S; 90M
44	Plasma	184V	None	10I; 63P, 71V, 73S; 90M
52	Plasma	184 M/V	None	10I; 63P, 71V, 73S; 90M
52	PBMC	None	None	10I; 63P, 71V, 73S; 90M
Source Partner 1				
16 *	Plasma & PBMC	41L; 67N; 69N; 70R; 74V; 184V; 215F; 219Q	100I; 103N	10I; 36I; 54V; 63P, 71V, 73S; 82I/V; 90M
TI	Plasma & PBMC	None	None	None

\*Initial time of presentation

Virus was also isolated from Source Partner 1 following treatment interruption (TI)

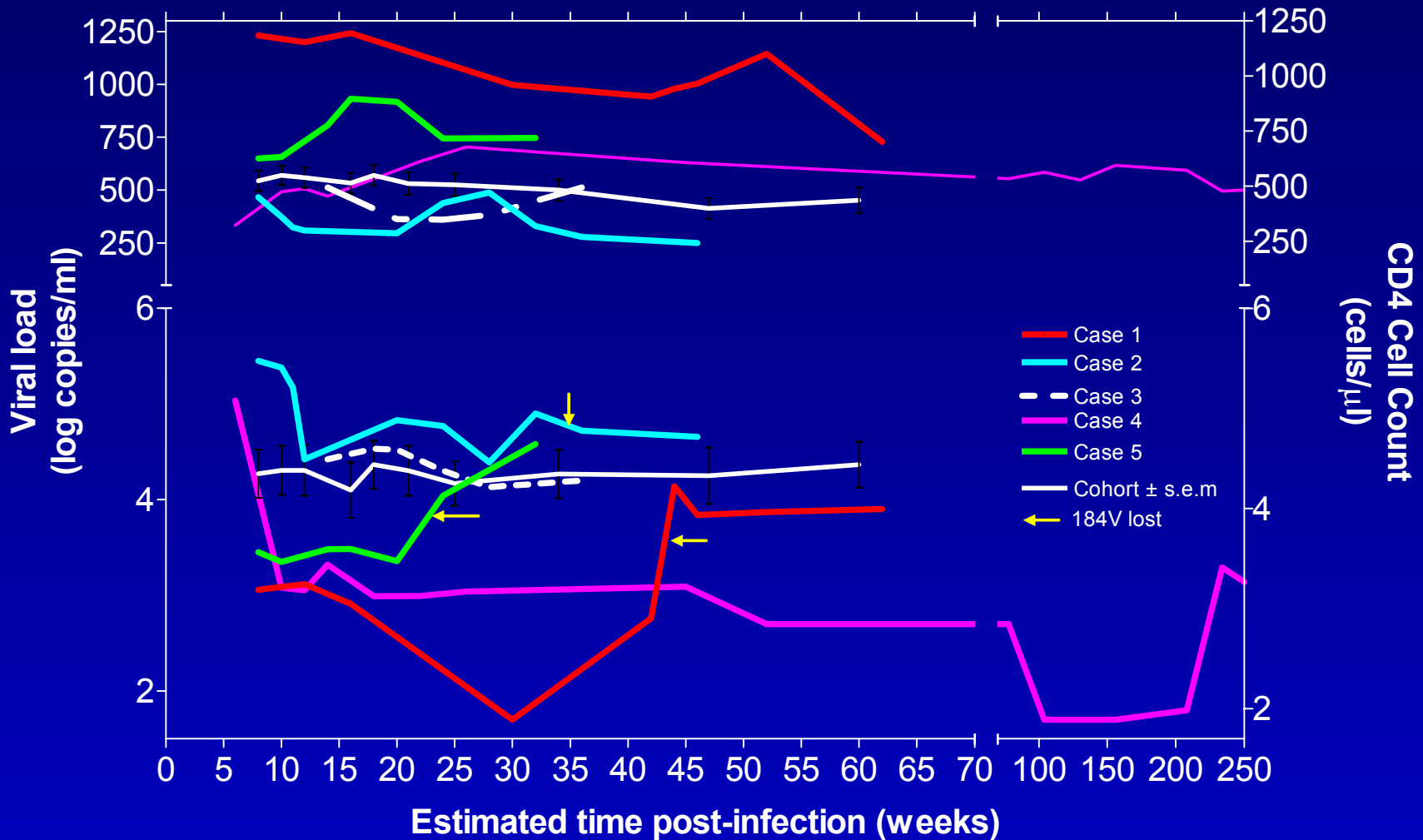
## Genotype of viral quasispecies over time in untreated PHI patient 2

Week post-PHI	Viral source	Codon substitutions associated with drug resistance		
		NRTI mutations	NNRTI mutations	PI mutations
<b>PHI patient 2</b>				
8*	Plasma	41L; 184V; 215Y	103N, 179E	48V; 63P; 71V; 73S; 77I; 82A; 90M
12	Plasma	41L; 184V; 215Y	103N, 179E	48G/V; 63P; 71V; 77I; 82A; 90M
24, 28	Plasma	41L; 184V; 215Y	103N, 179E	63P; 71V; 77I; 82A; 90M
32	Plasma	41L; 184V/M; 215Y	103N, 179E	63P; 71V; 77I; 82A; 90M
36	Plasma	41L; 215Y	103N, 179E	63P; 71V; 77I; 82A; 90M
47	Plasma	41L; 215C	103N, 179E	63P; 71V; 77I; 82A; 90M
47	PBMC	41L; 215C	103N, 179E	63P; 71V; 77I; 82A; 90M
<b>Source partner 2</b>				
8*	Plasma	41L; 184V; 215Y	103N; 179E	48V; 63P; 71V; V77I; 73S; 82A; 90M

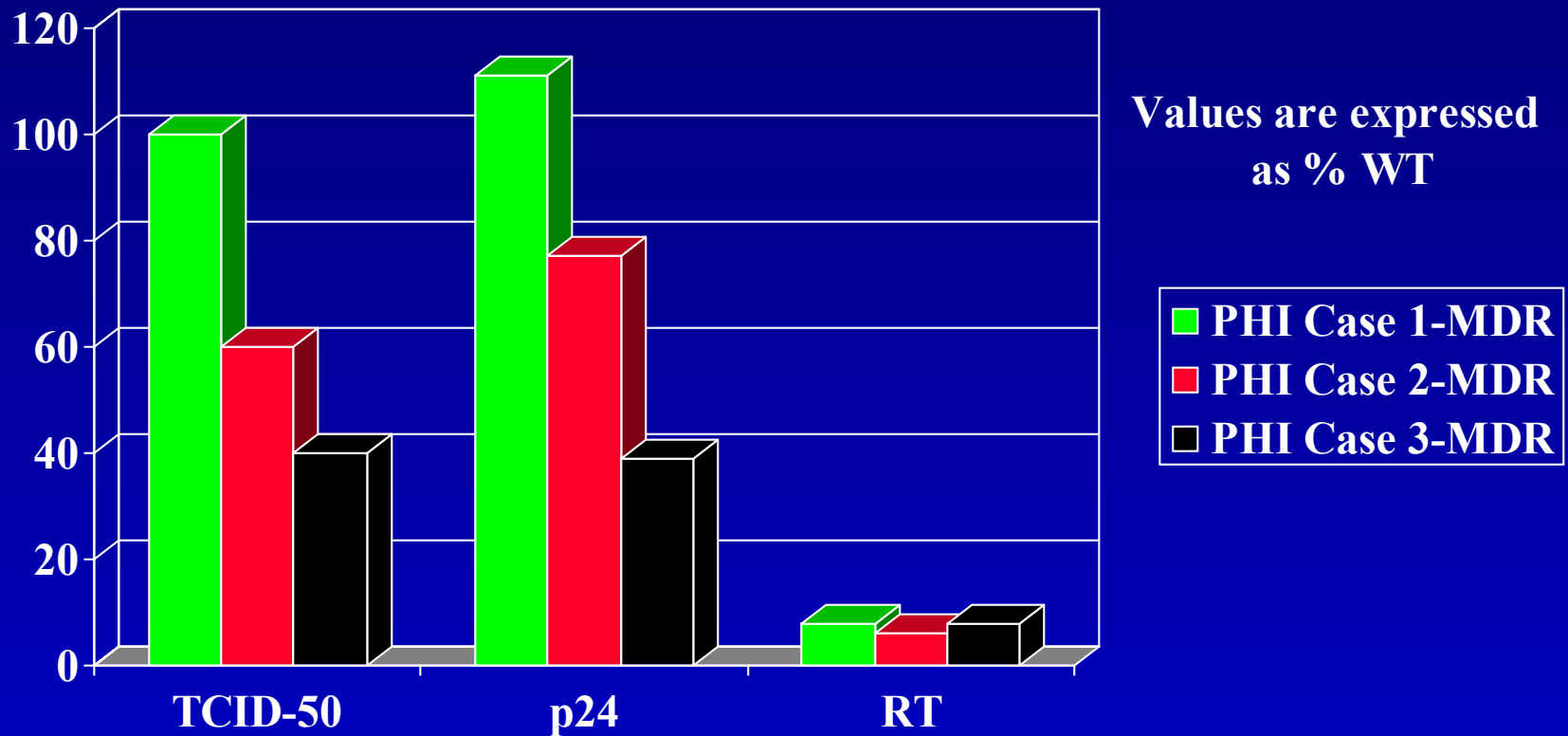
\*designates time of first presentation

**Genotype of viral quasispecies over time in PHI case 3 who acquired MDR from source partner 3 who underwent treatment interruption (TI)**

Week Post-PHI	Sample	Codon substitutions associated with drug resistance		
		NRTI mutations	NNRTI mutations	PI mutations
<b>PHI patient 3</b>				
14*	Plasma	None	103N	10I; 54V; 63P; 71V; 82T; 84V; 90M
14*	PBMC	None	103N	10I; 54V; 63P; 71V; 82T; 84V; 90M
18, 20, 24, 28	Plasma	None	103N	10I; 54V; 63P; 71V; 82T; 84V; 90M
32	Plasma	None	103N	10I; 54V; 63P; 71V; 82T; 90M
36	Plasma	None	103N	10I; 54V; 63P; 71V; 82T; 90M
<b>Source partner 3</b>				
14*	Plasma & PBMC	None	181C/Y; 103N	10I; 46I; 54V; 63P; 71V; 82T; 84V; 90M
Post-TI (3 years)	Plasma & PBMC	None	None	63P



# MDR Viruses have Impaired Replicative Fitness Relative to WT Virus



# Dual competitive infections in vitro with MDR and WT viruses

MDR:WT Ratio	Duration of Infection	NRTI	NNRTI	Primary PI
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## Single Infections

WT	1-10	WT	WT	WT
MDR	1-10	MDR	MDR	MDR

## Dual Infections

10:90	1-10	WT	WT	WT
20:80	1-10	WT	WT	WT
30:70	1-10	WT	WT	WT
40:60	1-10	WT	WT	WT

50:50	1	WT/MDR	WT/MDR	WT/MDR
	2-10	WT	WT	WT

70:30	1-3	WT/MDR	WT/MDR	WT/MDR
	4-10	WT	WT	WT

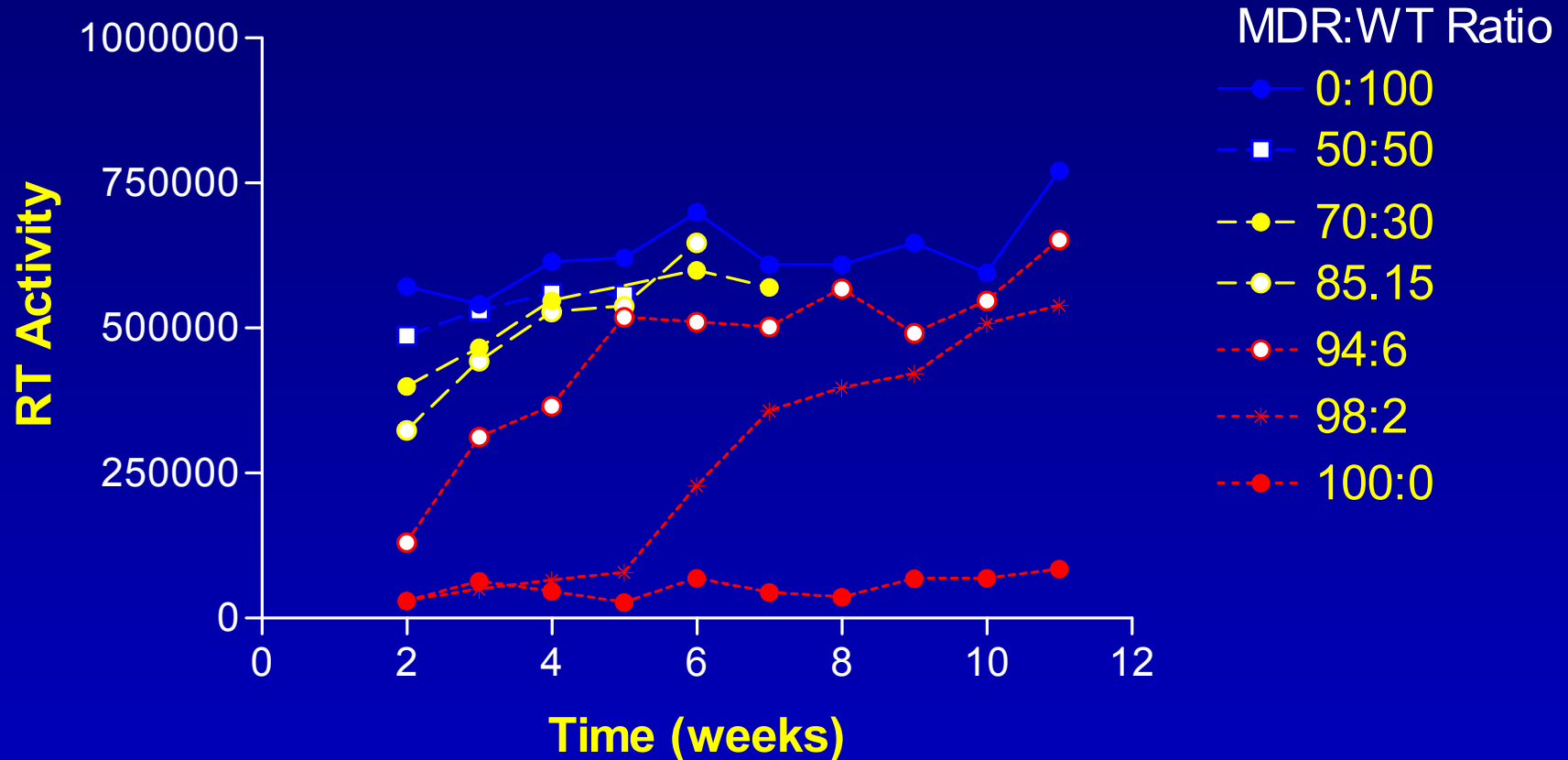
85:15	1	MDR	MDR	MDR
	2-3	WT/MDR	WT/MDR	WT/MDR
	4-10	WT	WT	WT

90:10 or 94: 6	1-2	MDR	MDR	MDR
	3-5	WT/MDR	WT/MDR	WT/MDR
	6-10	WT	WT	WT

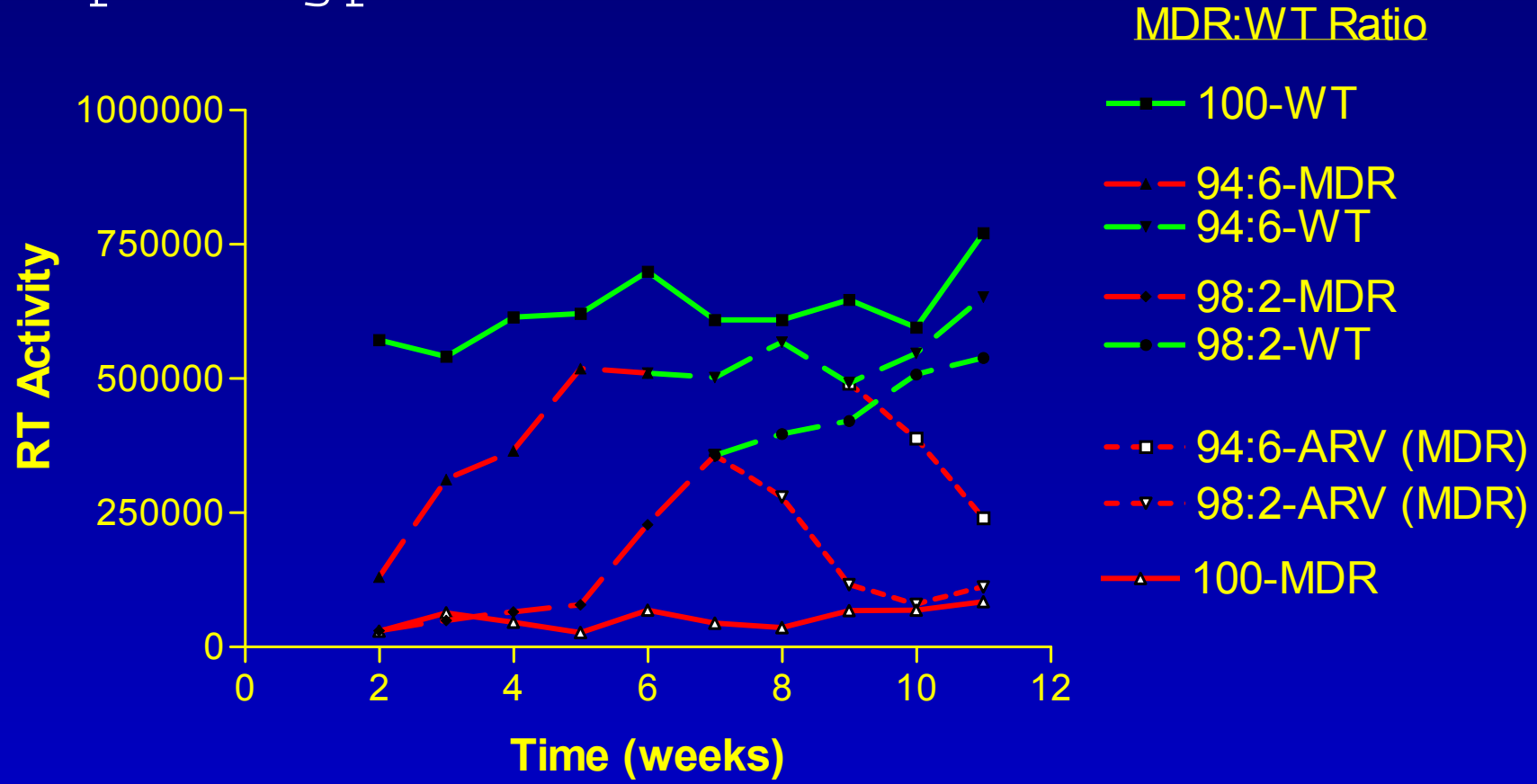
98:2	1-5	MDR	MDR	MDR
	6-8	WT/MDR	WT/MDR	WT/MDR
	>9-10	WT	WT	WT

Infections were followed in tissue culture, sequencing for WT, MDR, or WT/MDR mixtures

# MDR infections sustain lower RT activity as compared to WT



Re-selection of MDR viruses harboring 18 mutations with 3TC and Nevirapine drug pressure



# Conclusions

- 6.2% of PHI cases have MDR infections
- These MDR infections persist over time
- MDR infections can be associated with low viremia
- MDR infections are replicatively unfit

# Investigators and Collaborators

## Quebec Primary HIV-1 infection

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