Emergence of High Level Resistance to Dolutegravir with T97A Mutation in Integrase in Treatment Experienced Patients with Baseline Partial Sensitivity to Dolutegravir

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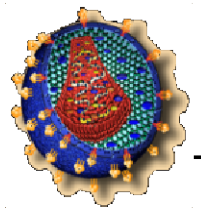

HIV Dynamics and Replication Program

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Background

- T97A is a HIV-1 integrase polymorphism infrequently present in INSTI naive individuals.
- Associated with emergent INSTI resistance primarily in patients experiencing virologic failure on EVG or RAL
- Selected by DTG in heavily treatment experienced patients with pre-existing EVG/RAL resistance associated mutations
- Reported to emerge with additional drug resistance mutations (DRMs) including Q148 and G140
- *Contribution of the sole emergence of T97A to DTG resistance is not well described*

1. Abram ME, et al. PLoS ONE 2017; 12 (2).
2. Eron JJ, et al. J Infect Dis. 2013; 207(5):740–8.
3. Hardy I, et al. J Antimicrob Chemother. 2015; 70(2):405–11
4. Naeger LK et al. Antivir Ther 2016;21(6):481-488

Objective

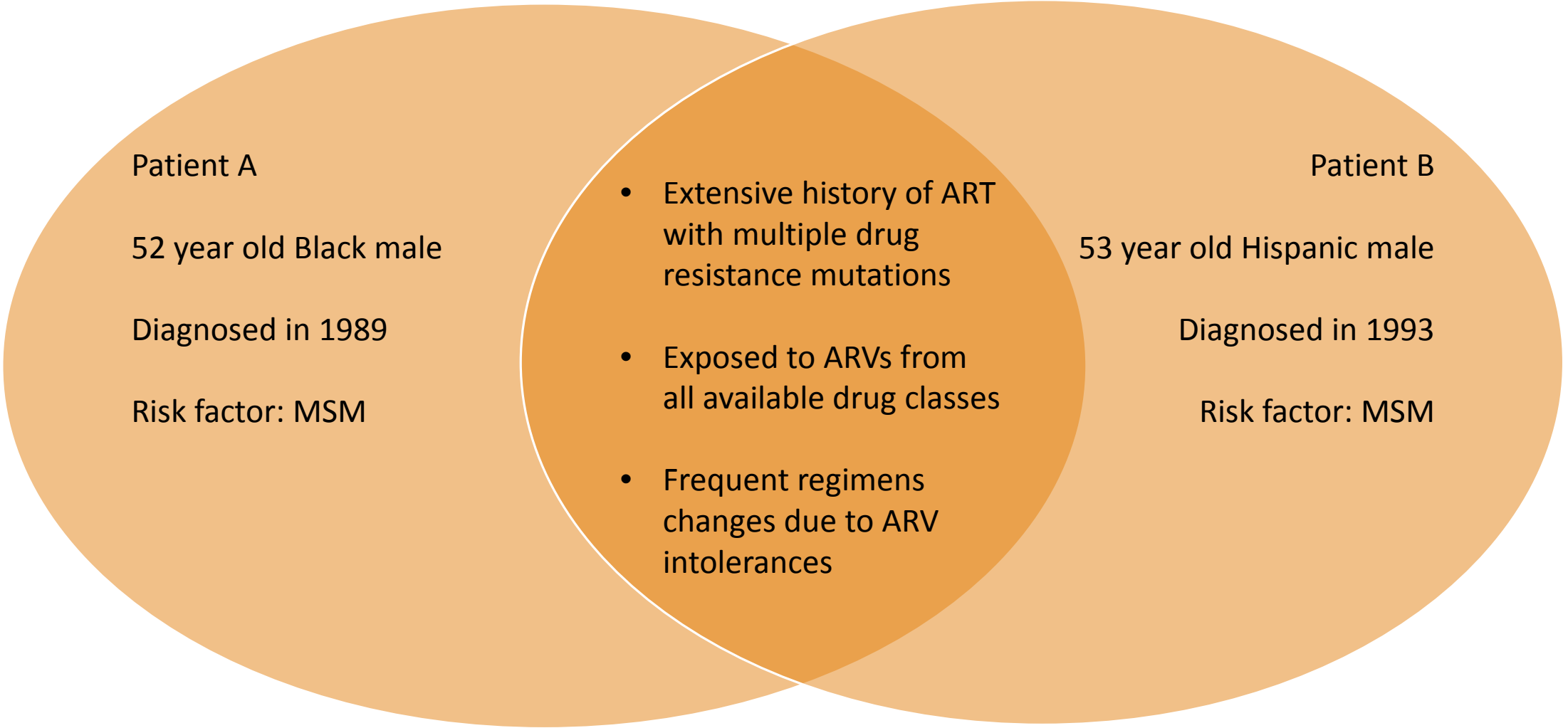
- To describe the role of T97A in INSTI resistance, we studied virologic parameters in 2 highly treatment experienced individuals with HIV while receiving DTG as part of salvage therapy.

Methods

- Patients were enrolled in a clinical study at the NIH Clinical Center to evaluate antiretroviral treatment failure (ClinicalTrials.gov identifier NCT 01976715).
- Plasma samples were analyzed using the following assays:
  - Phenotyping (Monogram Biosciences)
  - Genotyping (TRUGENE)
  - In-house population based genotyping
- Selected samples were subjected to next generation sequencing (NGS, Illumina detection limit c. 1%)
- HIV sequences were analyzed using:
  - Stanford/ANRS algorithms
  - Phenotyping analyses (Phenosense Integrase™, PhenoSense GT® plus Integrase)
- Coreceptor tropicity were performed (Monogram Biosciences)

Patient Cases

Patient Case Comparison



Antiretroviral History

Patient A

Date	Antiretroviral History
1989 – 2004 (Unknown timeframes)	EFV, NVP, IDV, SQV AZT, ddI, ddC, d4T
2004 – 2004	LPV/r, APV, ABC, AZT, 3TC, TDF
2004 – 2005	LPV/r, ATV, ABC, AZT, 3TC, TDF
2005 – 2012	DRV/r, RAL, ABC, TDF, FTCs
2012 – 2014	LPV/r, ATV, TDF, FTC
2014 – 2015	DRV/r, DTG, MVC, TDF, FTC
2015 – 2016	DRV/r, MVC, TDF, FTC,
2016 – present	DRV/r, TAF, FTC,

Patient B

Date	Antiretroviral History
1993 – 1995	AZT
1995 – 1996	AZT, ddC
1996 – 1997	DLV, IDV, NFV
1997 – 1998	NFV, ddI, d4T
1998 – 1999	ABC, EFV, ddI
1999 – 2000	EFV, ABC, ddI, (+ hydroxyurea)
2000 – 2001	EFV, APV, ABC
2001 – 2002	LPV/r, FTC, ddI,
2002 – 2003	LPV/r, TDF, FTC, ddI,
2003 – 2003	LPV/r, TDF, FTC
2003 – 2003	LPV/r, AZT, 3TC
2003 – 2005	TPV/r, T-20, d4T
2005 – 2006	TPV/r, T-20, FTC
2006 – 2008	DRV/r, T-20, FTC
2008 – 2010	ETV, DRV/r, RAL, FTC
2010 – 2015	ETV, TPV/r, RAL, FTC
2015 – 2016	TPV/r, RAL, TDF, FTC
2016 – 2016	DTG, ABC, 3TC, TDF
2016 – 2016	TDF, FTC
2016 – 2017	DTG, ABC, 3TC, TDF
2017 – present	DRV/r, TAF, FTC, ETV

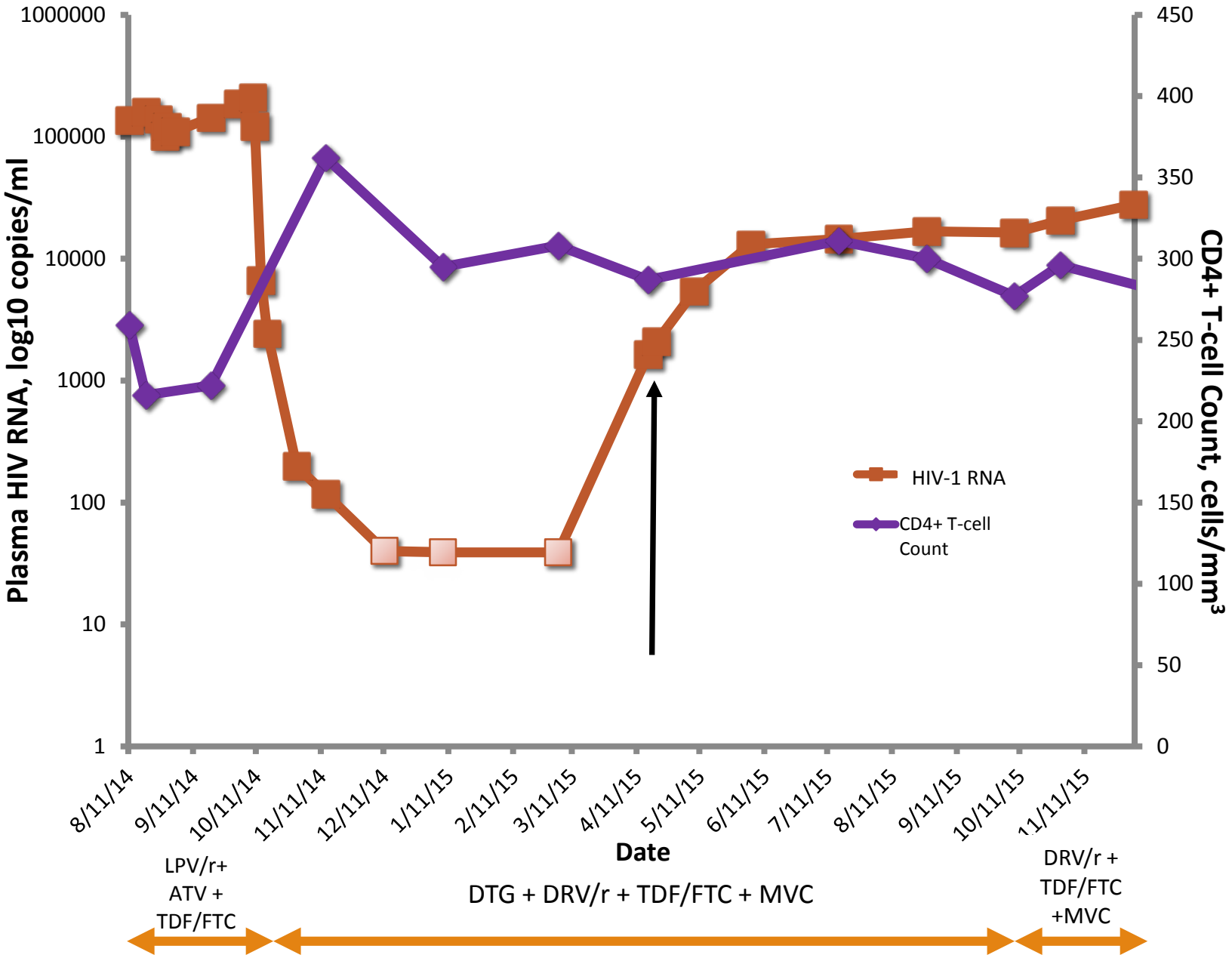
Patient A

PATIENT A

Prior to study enrollment, he was receiving LPV/r + ATV + TDF/FTC:

- CD4 259 cells/mm^3 and
- HIV-1 RNA 136,476 copies/ml

	DRMs Pre-DTG (Commercial Genotype) (cumulative)
N(t)RTI	M41L, A62V, D67E, T69insert, M184V, T215D
NNRTI	A98G, K101E, Y181C, G190A
PI	K20T, V32I, L33F, E35G, K43T, M46L, I54L, I84V, L89V, L90M
INSTI	G140S, Q148H
CCR5 Inhibitor	R5 tropic

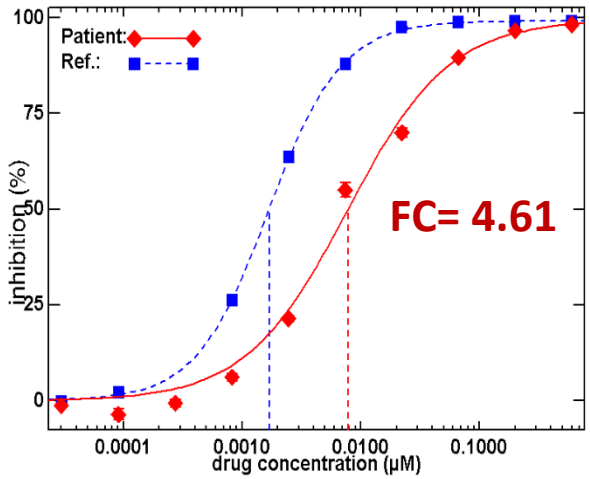


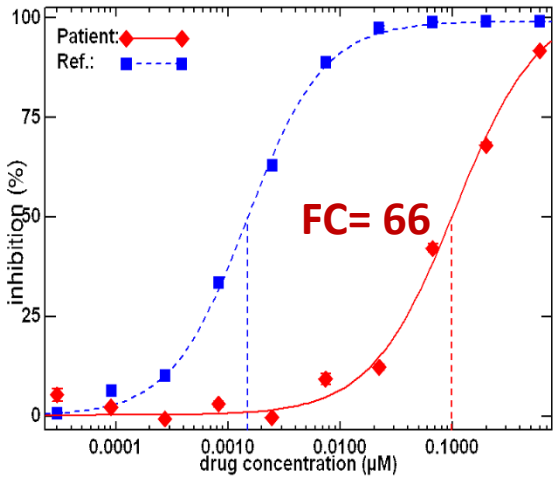
PATIENT A

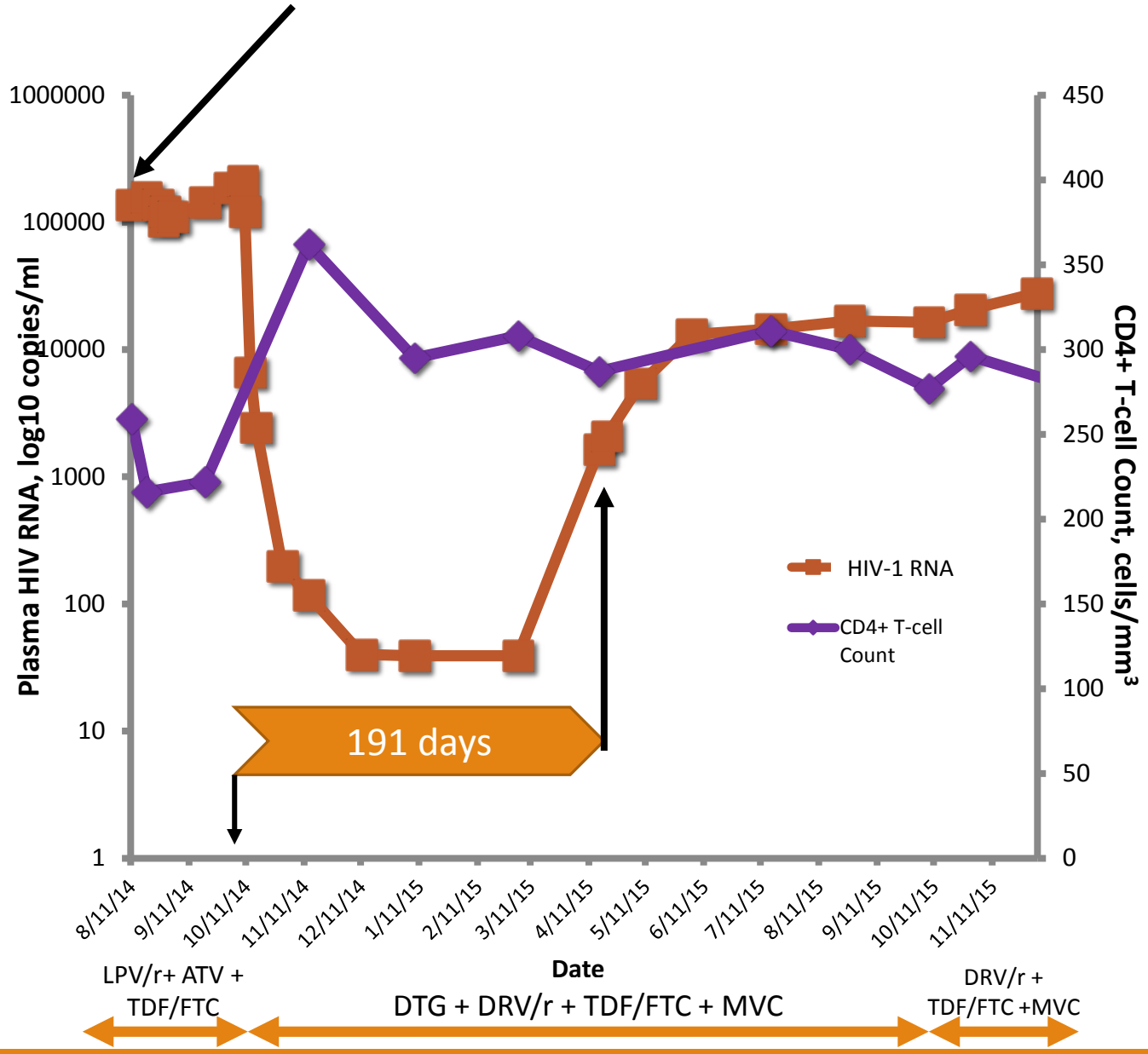
Timeline and Description of Commercial Genotypic and Phenotypic DTG Analyses

August 2014	
INSTI Mutations	G140S, Q148H
Genotype Interpretation	Intermediate Resistance
Phenotype Interpretation	Partially sensitive

April 2015	
INSTI Mutations	G140S, Q148H, **T97A**
Genotype Interpretation	High Level Resistance
Phenotype Interpretation	Resistant







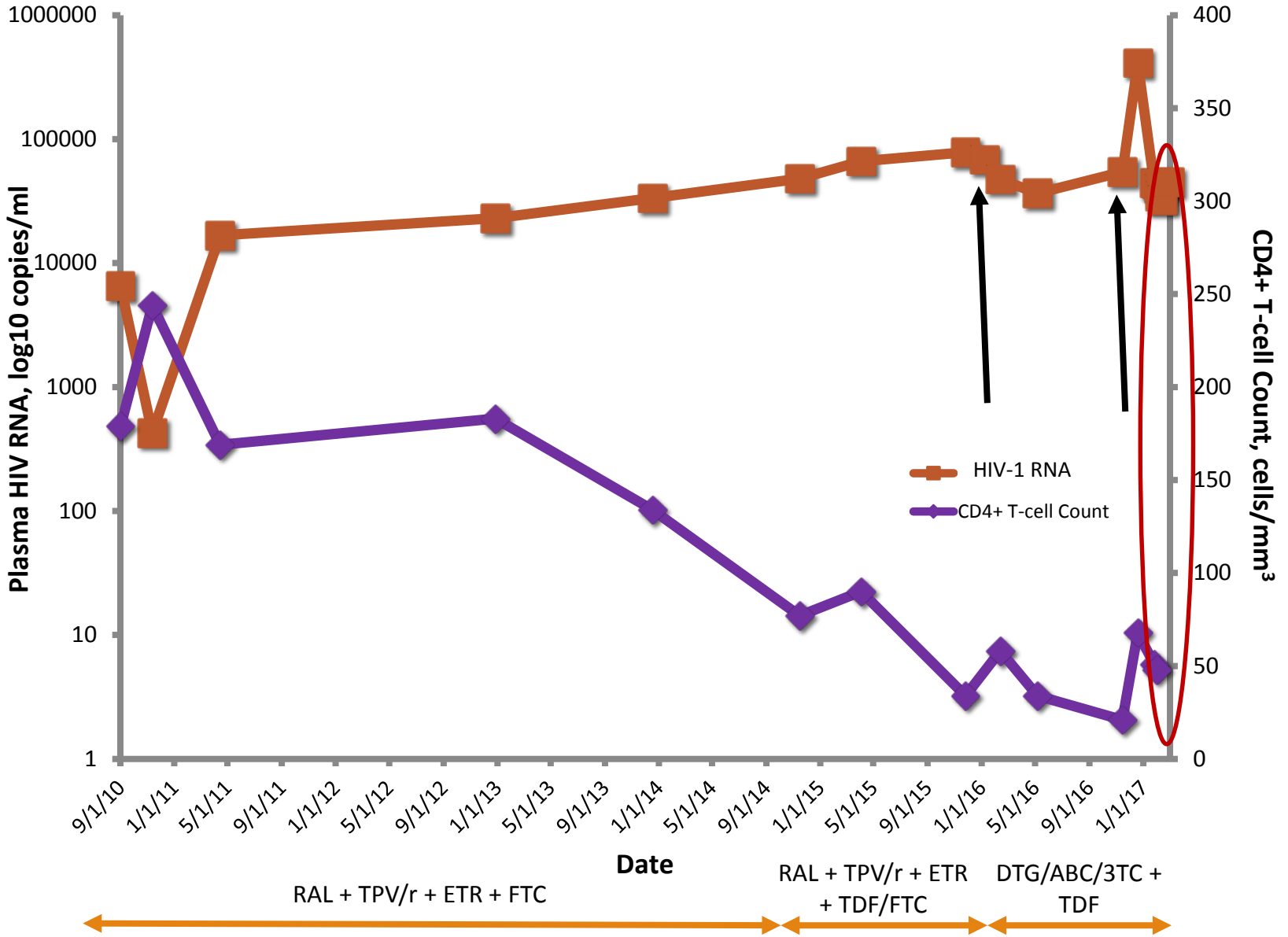
Patient B

PATIENT B

Immediately prior to study enrollment, he was receiving DTG/ABC/3TC + TDF:

- CD4 51 cells/mm^3 and
- HIV-1 RNA 44186 copies/mL

	DRMs Pre-DTG (Commercial Genotype) (cumulative)
N(t)RTI	M41L, D67N, E44D/E, T69D, V75M, M184V, L210W, T215Y, K219N, V118I
NNRTI	V90I, L100I, K103N, E138A, V179L
PI	V32I, I54L, I84V, L90M, L10F/I/V, L33F, Q58E, I13V, K20R, E35D, M36I, A71L, L89M, V82A, M46L
INSTI	E138T, G140S, Q148H
CCR5 Inhibitor	D/M tropic

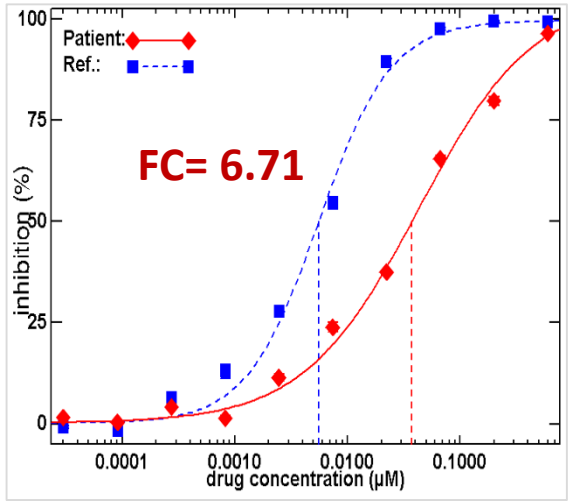


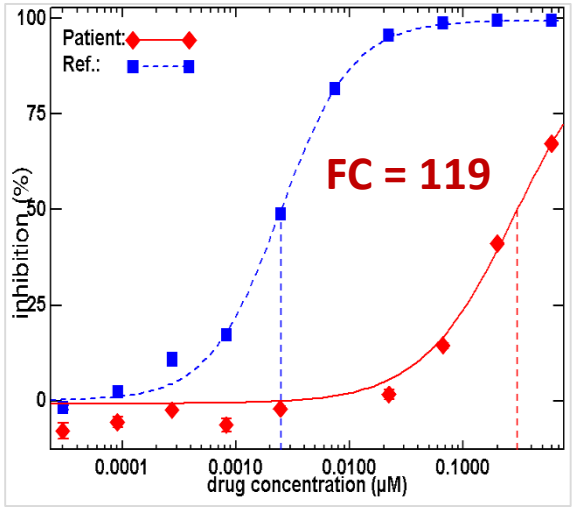
PATIENT B

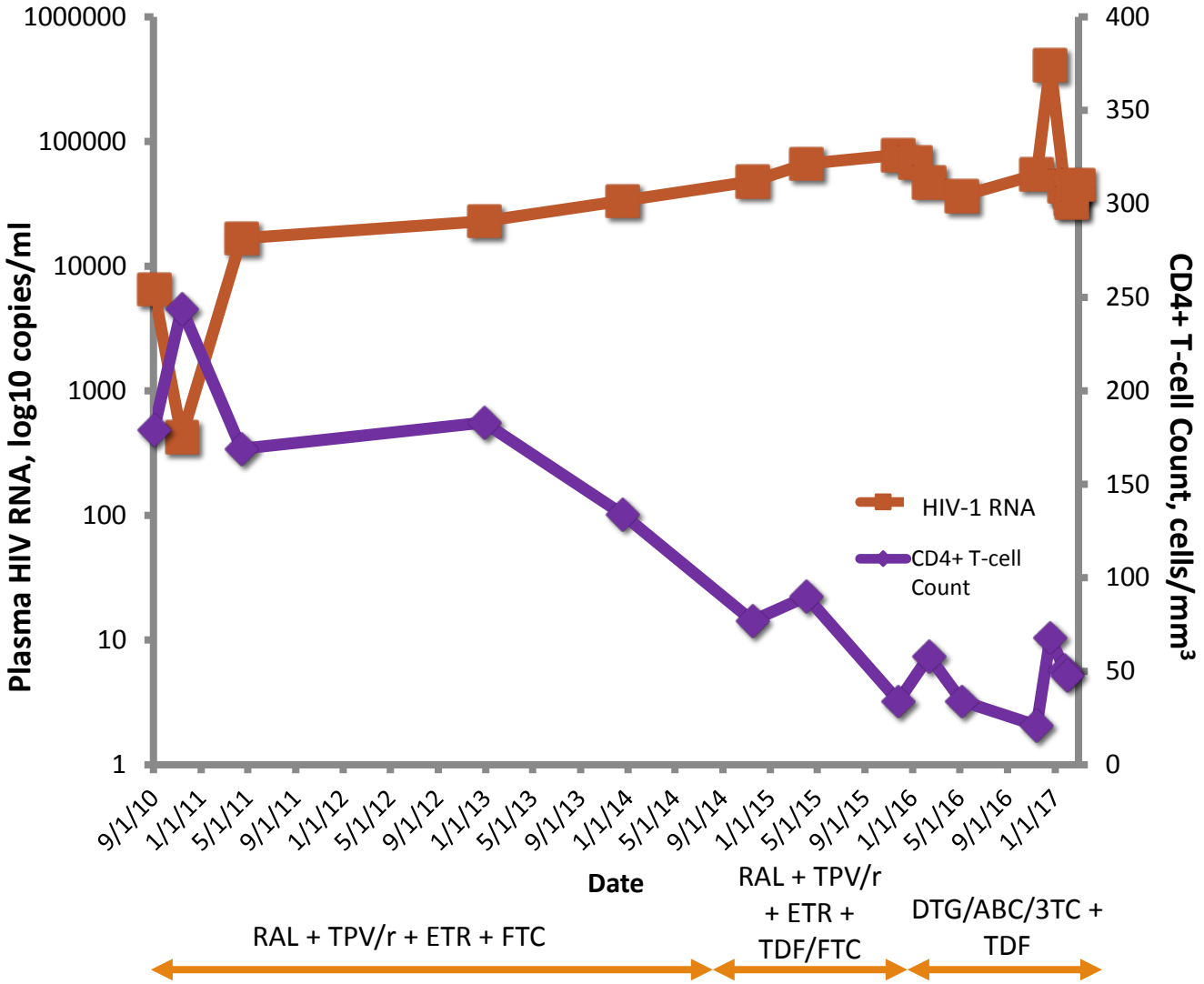
Timeline and Description of Commercial Genotypic and Phenotypic DTG Analyses

Nov 2014	
INSTI Mutations	E138T, G140S, Q148H
Genotype Interpretation	Partially Sensitive
Phenotype Interpretation	Partially Sensitive

Jan 2017	
INSTI Mutations	E138T, G140S, Q148H, **T97A**
Genotype Interpretation	High Level Resistance
Phenotype Interpretation	Resistant







Conclusions

- Sole emergence of T97A played a significant role in the development of high level resistance to DTG
- Greater than 10 fold increases in DTG IC_{50} resulted with the emergence of T97A alone
- Emergence of T97A in HIV with pre-existing major INSTI DRMs led to a profound reduction in the antiviral activity of DTG.
- Presence of T97A should prompt clinicians to monitor patients closely while receiving INSTI based therapy

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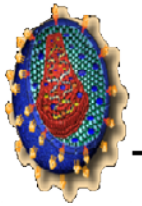
- Cliff Lane MD, NIAID
- Monogram BioSciences



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