

Antiviral Activity of Tenofovir Alafenamide against HIV-1 with Thymidine Analog Mutation(s) and M184V

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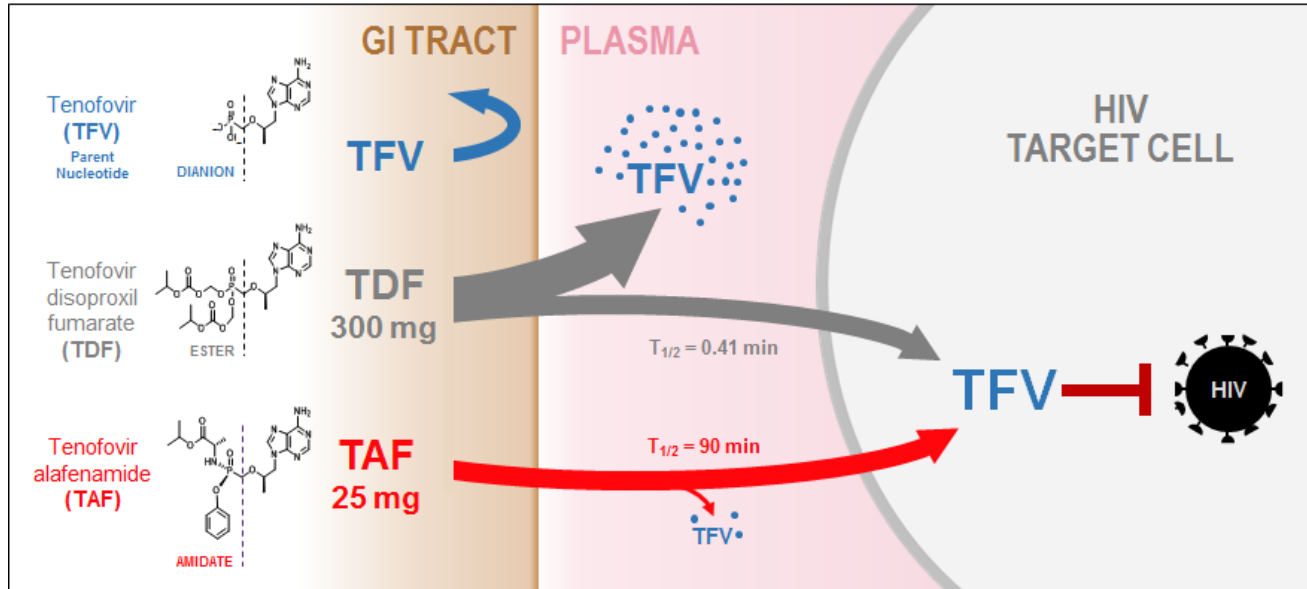
HIV DART AND EMERGING VIRUSES

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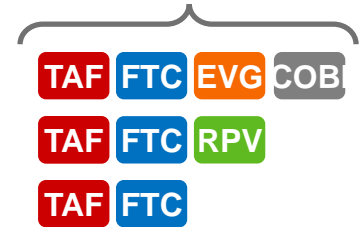
Abstract #0_05

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Tenofovir Alafenamide (TAF)



TAF co-formulation with other ARVs (approved)



TAF:

- HIV-1 NRTI: novel tenofovir prodrug - greater plasma stability (vs. TDF)
- improves the delivery of intracellular TFV - reduces circulating TFV (vs. TDF)
- requires a significantly lower dose for same or higher efficacy (vs. TDF)

TFV Cutoffs

- TFV clinical cutoffs for TDF:
 - established by commercial phenotyping assays
 - 1.4- to 4-fold (for reduced and unlikely clinical response)
- TFV clinical cutoffs for TAF:
 - not established
 - projected to be higher than TDF based on higher intracellular[TFV-DP] in vivo (4X)
- Some HIV-1 isolates with RAMs previously defined as TDF-resistant:
 - may benefit from higher intracellular[TFV-DP] delivered by TAF (such as K65R, TAMs)
 - M184V may increase susceptibility to TFV during TAF-based therapy

TAMs: Thymidine Analog Mutations



Stanford University

HIV DRUG RESISTANCE DATABASE

A curated public database to represent, store and analyze HIV drug resistance data.

HOME GENOTYPE-RX GENOTYPE-PHENO GENOTYPE-CLINICAL HIVdb PROGRAM ABOUT HIVdb

NRTI Resistance Notes (PI · NNRTI · INSTI)

HIVdb version 8.1.1 (last updated 2016-09-23)

Resistance Notes Resistance Mutation Comments Resistance Mutation Scores Mutation Pattern Scores

Major Nucleoside RT Inhibitor (NRTI) Resistance Mutations

	Discriminatory Mutations				
<i>Consensus</i>	184	65	70	74	115
	M	K	K	L	Y
3TC	VI	R			
FTC	VI	R			
ABC	VI	R	E	VI	F
DDI	VI	R	E	VI	
TDF	***	R	E		F
D4T	***	R	E		
ZDV	***	***	*	*	

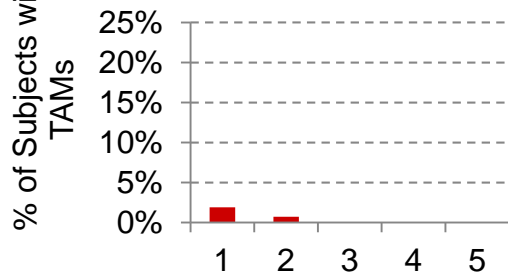
Thymidine Analog Mutations (TAMs)					
41	67	70	210	215	219
M	D	K	T	T	K
L			W	FY	
L			W	FY	
L		R	W	FY	
L	N	R	W	FY	QE
L	N	R	W	FY	QE

MDR Mutations	
69	151
T	Q
Ins	M
Ins	M
Ins	M
Ins	M
Ins	M
Ins	M

TAMs in Treatment-Naive and -Experienced Subjects

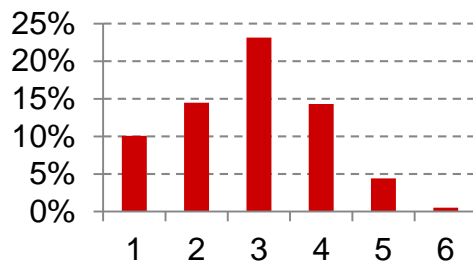
2000 to 2013

Naïve Studies
TAMs at Screening
(n=6704)



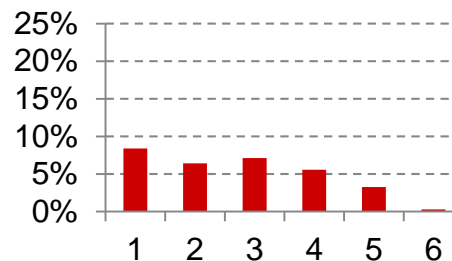
1999

Studies 902/907:
TAMs at Entry
(n=566)



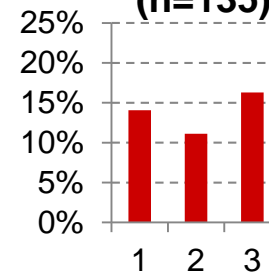
2008

Study 183-0145:
TAMs at Entry
(n=702)



2015

Study 292-0119:
TAMs at Entry
(n=135)



- 1999: 67% TE subjects had TAMs at enrollment (Gilead studies 902 & 907)
- 2008: 31% TE subjects had TAMs at enrollment (Gilead study 183-0145)
- 2015: 42% TE subjects had TAMs at enrollment (Gilead study 292-0119)

TAF Activity for Viruses with 4 TAMs

SDMs in Single Cycle Assay

						- M184V				+ M184V			
M41L	D67N	K70R	L210W	T215Y	K219Q	HIVDB	ANRS	REGA	AVG TAF FC EC ₅₀	HIVDB	ANRS	REGA	AVG TAF FC EC ₅₀
4 TAMs													
M41L	D67N		L210W	T215Y		R	I	I	8.0	I	I	I	3.7
M41L		K70R	L210W	T215Y		R	I	I	4.0	I	I	I	2.5
M41L			L210W	T215Y	K219Q	R	I	I	5.7	I	I	I	2.3
M41L	D67N	K70R		T215Y		I	I	I	7.3	I	I	I	3.1
	D67N	K70R	L210W	T215Y		I	I	I	7.4	I	I	I	3.5
	D67N		L210W	T215Y	K219Q	I	I	I	6.0	I	I	I	2.9
	D67N	K70R		T215Y	K219Q	I	S	I	5.3	I	S	I	2.8

Sensitivity score	
R	resistant
I	intermediate
S	sensitive

- TAF fold-change EC₅₀ ranged from 4.0 to 8.0 (median FC = 6.0) without M184V
- TAF fold-change EC₅₀ ranged from 2.3 to 3.7 (median FC = 2.9) with M184V

TAF Activity for Viruses with 3 TAMs

SDMs in Single Cycle Assay

M41L	D67N	K70R	L210W	T215Y	K219Q	- M184V				+ M184V			
						HIVDB	ANRS	REGA	AVG TAF FC EC ₅₀	HIVDB	ANRS	REGA	AVG TAF FC EC ₅₀
3 TAMs													
M41L			L210W	T215Y		I	I	S	3.7	I	I	I	1.6
M41L	D67N		L210W			I	I	S	1.0	I	I	S	1.0
	D67N		L210W	T215Y		I	I	S	3.8	I	I	S	1.2
M41L	D67N	K70R				I	S	S	1.5	S	S	S	1.1
M41L		K70R	L210W			I	S	S	0.9	I	S	S	0.9
M41L			L210W		K219Q	I	S	S	1.0	I	S	S	0.8
	D67N	K70R	L210W			I	S	S	1.8	S	S	S	2.9
	D67N	K70R		T215Y		I	S	S	4.1	I	S	S	1.4
	D67N	K70R			K219Q	I	S	S	2.5	I	S	S	1.1
	D67N			T215Y	K219Q	I	S	S	2.5	I	S	S	1.2
		K70R	L210W	T215Y		I	S	S	2.1	I	S	S	2.0
			L210W	T215Y	K219Q	I	S	S	2.5	I	S	S	2.0

Sensitivity score	
R	resistant
I	intermediate
S	sensitive

- TAF fold-change EC₅₀ ranged from 0.9 to 4.1 (median FC = 2.3) without M184V
- TAF fold-change EC₅₀ ranged from 0.8 to 2.9 (median FC = 1.2) with M184V

TAF Activity for Viruses with 2 TAMs

SDMs in Single Cycle Assay

						- M184V				+ M184V			
M41L	D67N	K70R	L210W	T215Y	K219Q	HIVDB	ANRS	REGA	AVG TAF FC EC ₅₀	HIVDB	ANRS	REGA	AVG TAF FC EC ₅₀
2 TAMs													
M41L	D67N					I	S	S	1.3	S	S	S	1.4
M41L		K70R				I	S	S	0.8	S	S	S	1.3
M41L			L210W			I	S	S	1.0	I	S	S	1.6
M41L				T215Y		I	S	S	3.1	I	S	S	1.0
M41L					K219Q	I	S	S	0.9	S	S	S	1.5
	D67N	K70R				I	S	S	2.1	S	S	S	1.1
	D67N		L210W			I	S	S	1.6	S	S	S	1.8
	D67N			T215Y		I	S	S	3.6	S	S	S	1.0
	D67N				K219Q	I	S	S	NA	S	S	S	NA
		K70R	L210W			I	S	S	0.9	S	S	S	1.5
		K70R		T215Y		I	S	S	2.3	S	S	S	0.7
		K70R			K219Q	I	S	S	1.3	S	S	S	1.7
			L210W	T215Y		I	S	S	2.3	I	S	S	2.3
			L210W		K219Q	I	S	S	1.6	S	S	S	1.8
				T215Y	K219Q	I	S	S	2.4	S	S	S	2.3

Sensitivity score	
R	resistant
I	intermediate
S	sensitive

- TAF fold-change EC₅₀ ranged from 0.8 to 3.6 (median FC = 1.6) without M184V
- TAF fold-change EC₅₀ ranged from 0.7 to 2.3 (median FC = 1.5) with M184V

TAF Activity for Viruses with 1 TAM

SDMs in Single Cycle Assay

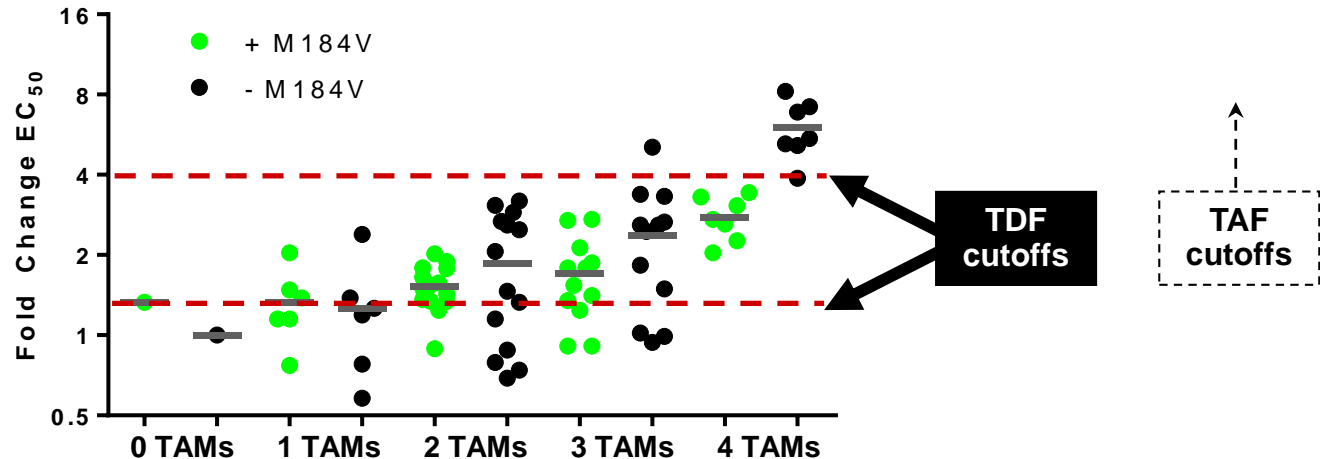
						- M184V				+ M184V			
M41L	D67N	K70R	L210W	T215Y	K219Q	HIVDB	ANRS	REGA	AVG TAF FC EC ₅₀	HIVDB	ANRS	REGA	AVG TAF FC EC ₅₀
1 TAM													
M41L						S	S	S	0.8	S	S	S	0.6
	D67N					S	S	S	1.7	S	S	S	1.5
		K70R				S	S	S	0.9	S	S	S	1.2
			L210W			S	S	S	1.3	S	S	S	1.3
				T215Y		I	S	S	2.1	S	S	S	2.2
					K219Q	S	S	S	1.3	S	S	S	1.5

Sensitivity score	
R	resistant
I	intermediate
S	sensitive

- TAF fold-change EC₅₀ ranged from 0.8 to 2.1 (median FC = 1.3) without M184V
- TAF fold-change EC₅₀ ranged from 0.6 to 2.2 (median FC = 1.4) with M184V

TAF Fold Change for Viruses with up to 4 TAMs +/- M184V

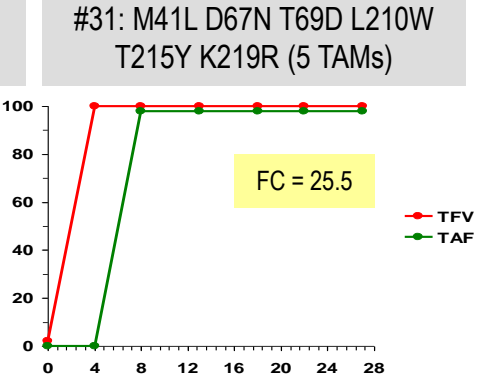
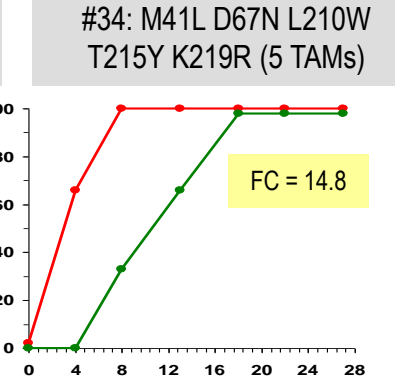
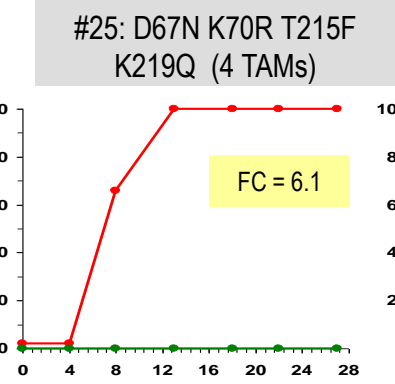
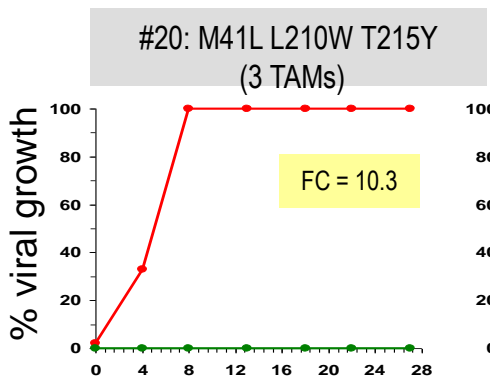
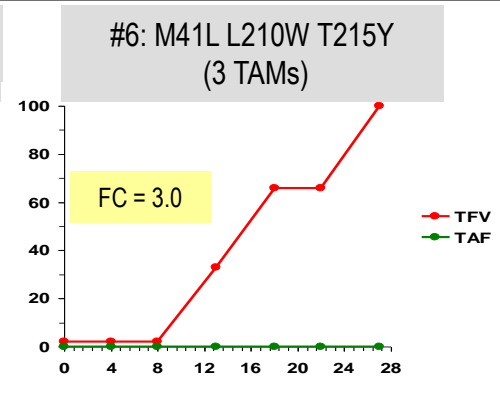
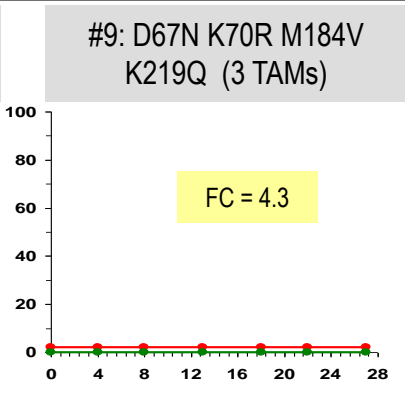
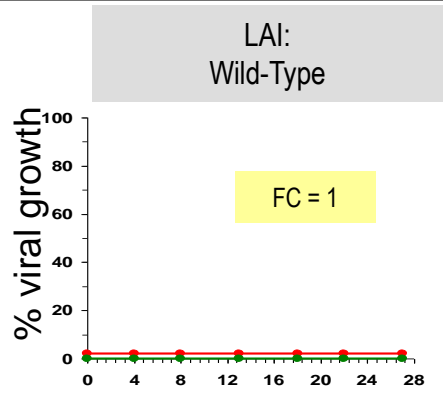
Summary



- Addition of specific TAMs further reduced TAF susceptibility
- Most TAM-containing viruses with M184V exhibited increased susceptibility to TAF

Viral Breakthrough: TAF vs. TFV

TFV 50 μ M
TAF 1 μ M



Days post-infection

Viral Breakthrough: TAF vs. TFV - Summary

Virus	Mutant Category	FC	RT Mutation Details	Time to Viral Breakthrough (days)	
				TAF	TFV
LAI	WT	1	-	>28	>28
#9	3TAMs	4.3	D67N K70R M184V K219Q	>28	>28
#6	3TAMs	3.0	M41L L210W T215Y	>28	13
#25	4TAMs	6.1	D67N K70R T215F K219Q	>28	8
#20	3TAMs	10.3	M41L L210W T215Y	>28	4
#31	5TAMs	25.5	M41L D67N T69D L210W T215Y K219R	8	4
#34	5TAMs	14.8	M41L D67N L210W T215Y K219R	8	4

- Only one HIV isolate with RAMs (3 TAMs) and low FC was inhibited by TFV
- Viruses with up to 4 TAMs (FC up to 10) were inhibited by TAF, but not by TFV (4:1 ratio)
- More evaluation ongoing with all TAMs combinations

Clinical Studies Evaluating TAF in TE Patients w/ RAMs

- **GS-US-292-0119:**
 - Patients with K65R or 1-3 TAMs (most with M184V)
 - Suppressed - Switch to E/C/F/TAF + DRV: completed

- **GS-US-292-0117:**
 - Patients with K65R or 1-3 TAMs (multi-class resistant)
 - Not suppressed – 1) TAF add-on therapy; 2) switch to E/C/F/TAF + ATV: ongoing

- **GS-US-292-1824:**
 - Patients with M184V; then patients with M184V + 1-3 TAMs
 - Suppressed – switch to E/C/F/TAF: ongoing

Conclusions

- Multiple TAMs decrease TFV activity in vitro and reduce TDF potency in vivo
- TAF achieves higher intracellular[TFV-DP] levels in PBMCs (vs.TDF)
- TAF expected be clinically active against many TDF-resistant isolates

- Increase of TAMs further reduced susceptibility to TAF
- Most TAMs with M184V exhibited increased susceptibility to TAF

- Viral breakthrough:
 - mimic in vivo differences in intracellular[TFV-DP]
 - full inhibition of viruses with 3TAMs

- TAF is currently in clinical development for TE population with TAMs

Acknowledgments

Many thanks:

- Clinical Studies Participants, their partners and families, and investigators
- TAF project team members
- Stanford, ANRS and REGA for access to their HIV resistance databases