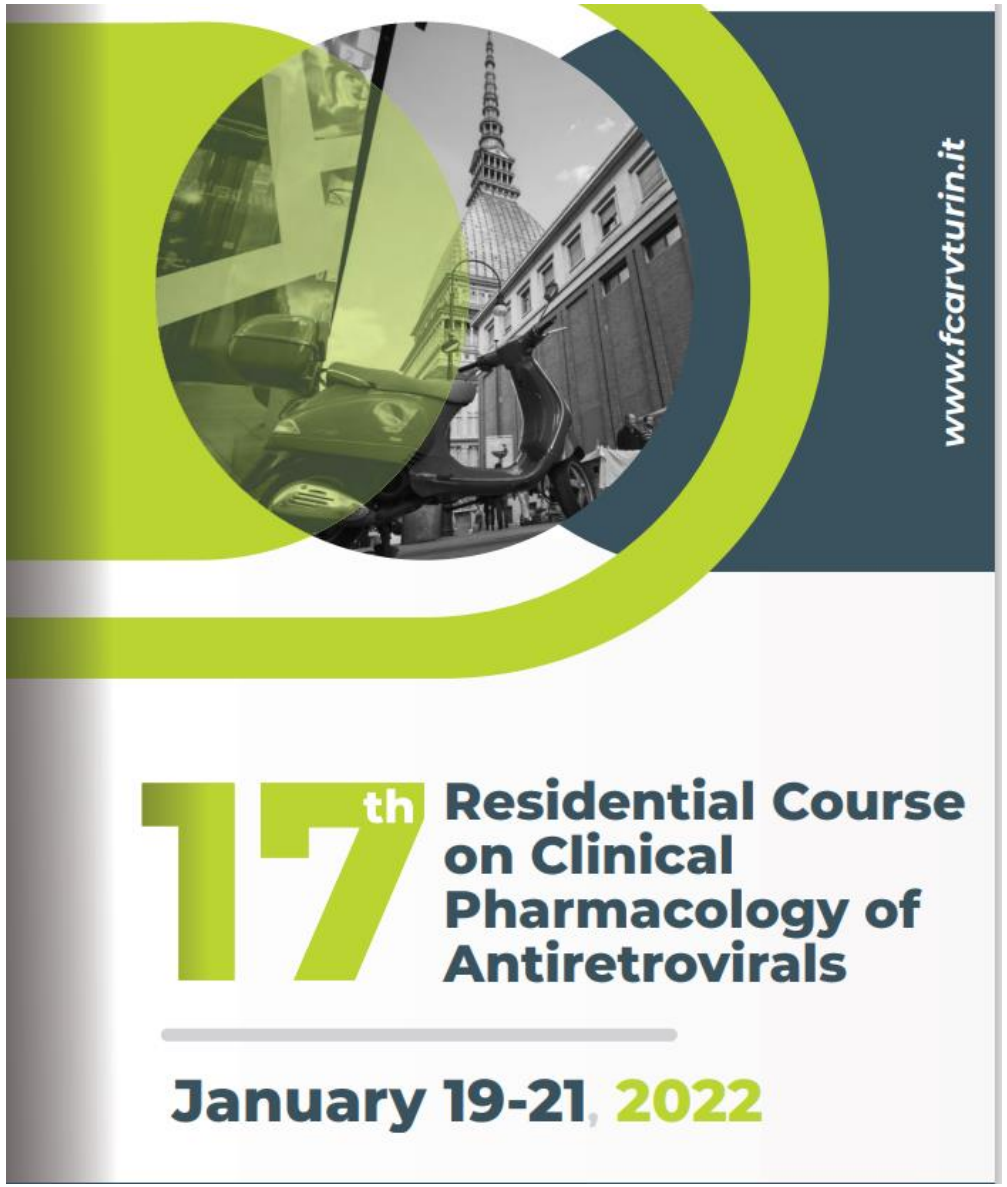
Clinical pharmacology of tenofovir in antiretroviral regimens

Stefano Bonora
Department of Medical Sciences
University of Torino



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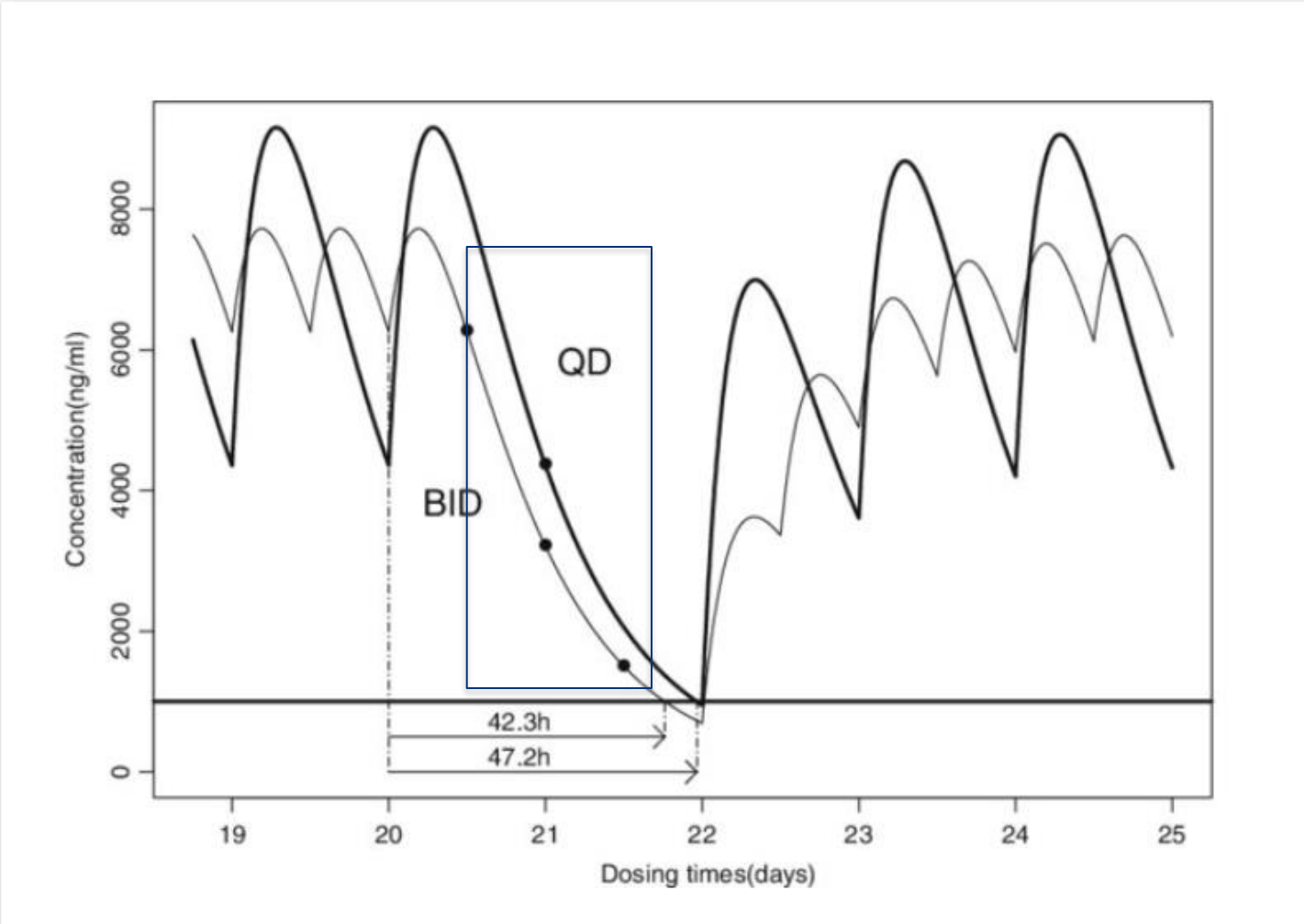
- Abbvie
- BMS
- GS
- MSD
- Janssen
- ViiV

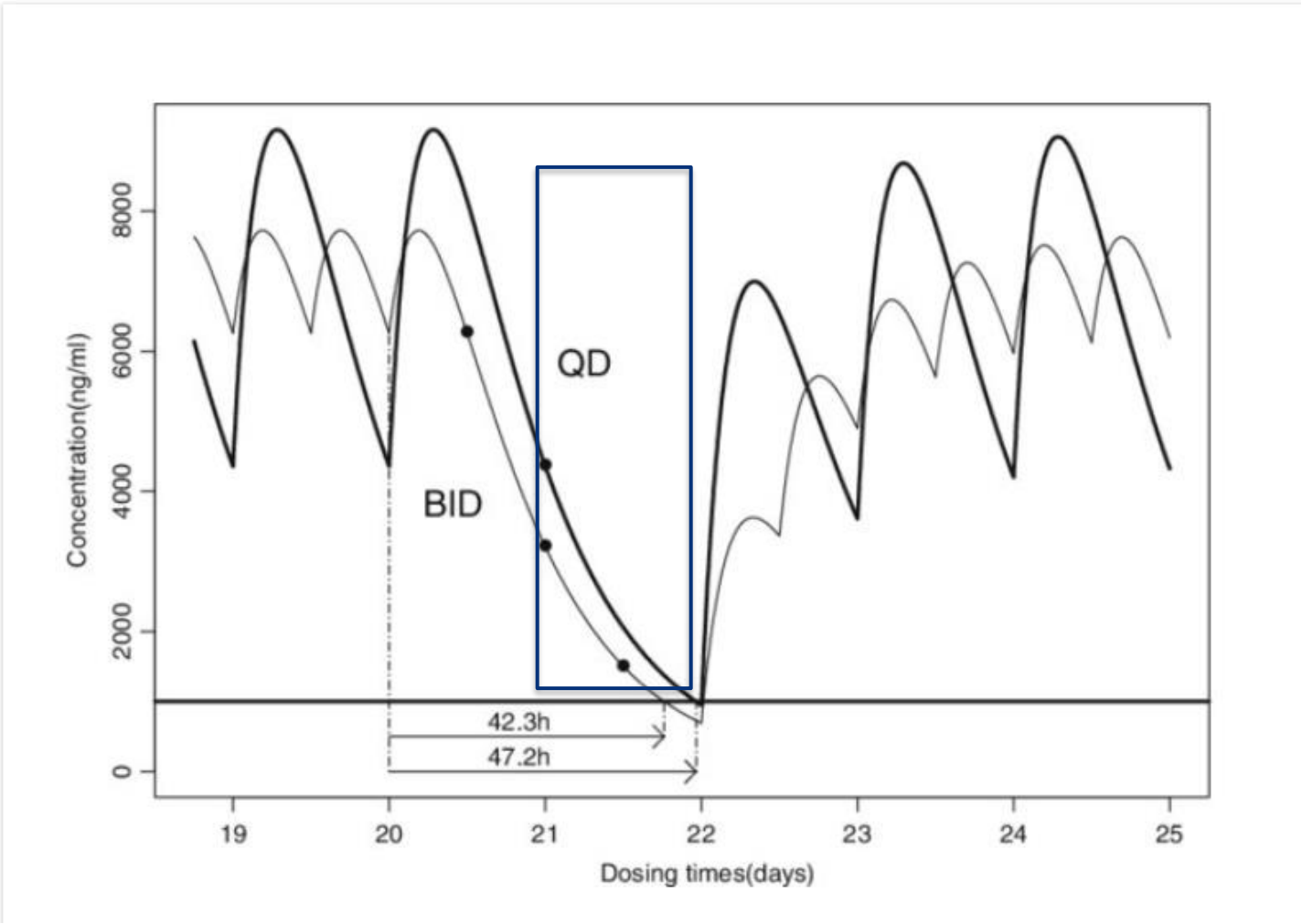
Forgiveness

- Suboptimal adherence may lead to inadequate ARV exposure, virological failure, and drug resistance
- Pharmacokinetic forgiveness is the difference between the duration of beneficial action after dosing and the prescribed dosing interval.
- ARV forgiveness relates to the number of doses that can be missed without causing viral relapse.
- Forgiveness in the context of missed doses is possible when either the elimination half-life of a drug or its inhibitory effect exceeds the recommended dosing interval.

Boffito et al, AIDS Res and Human Retroviruses 2019



Pharmacokinetic of representative patients during a QD or BID dosing regimen . The consequences of missing one QD or three BID doses are illustrated



Forgiveness is a piece of puzzle of virological success with

- potency,
- adherence,
- genetic barrier.

Pharmacokinetic of representative patients during a QD or BID dosing regimen . The consequences of missing one QD or three BID doses are illustrated

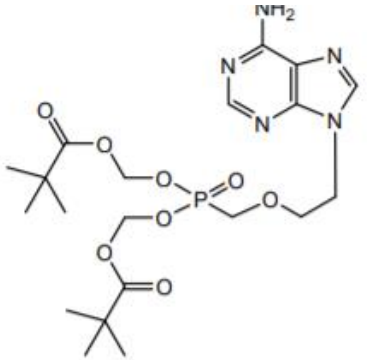
viruses

MDPI

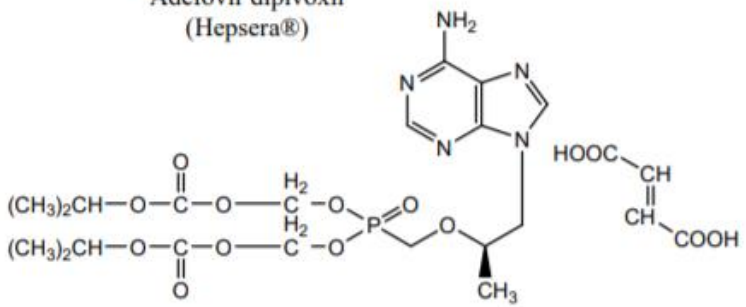
Review

Tribute to John C. Martin at the Twentieth Anniversary of the Breakthrough of Tenofovir in the Treatment of HIV Infections

Erik De Clercq



Adefovir dipivoxil
(Hepsera®)



Tenofovir disoproxil fumarate (TDF)
(Viread®)

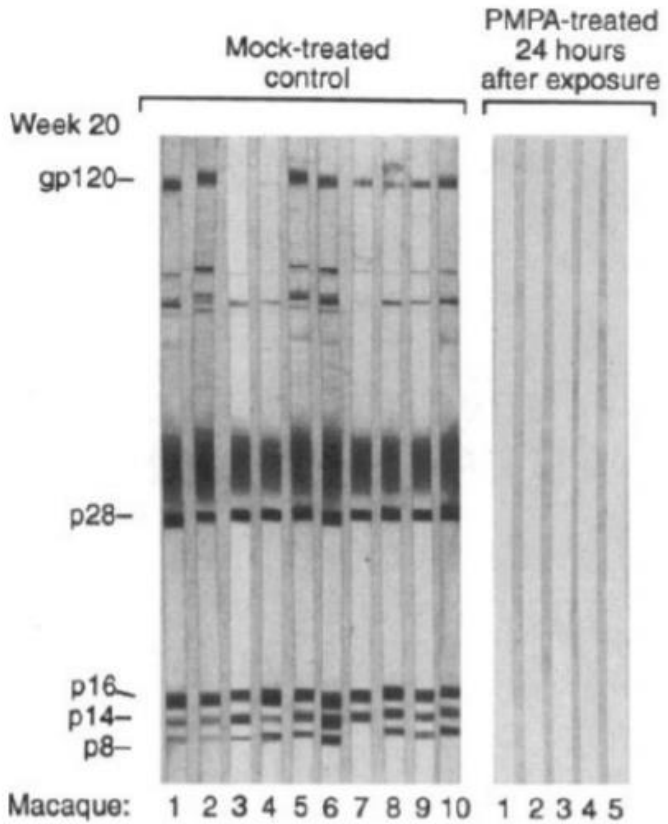
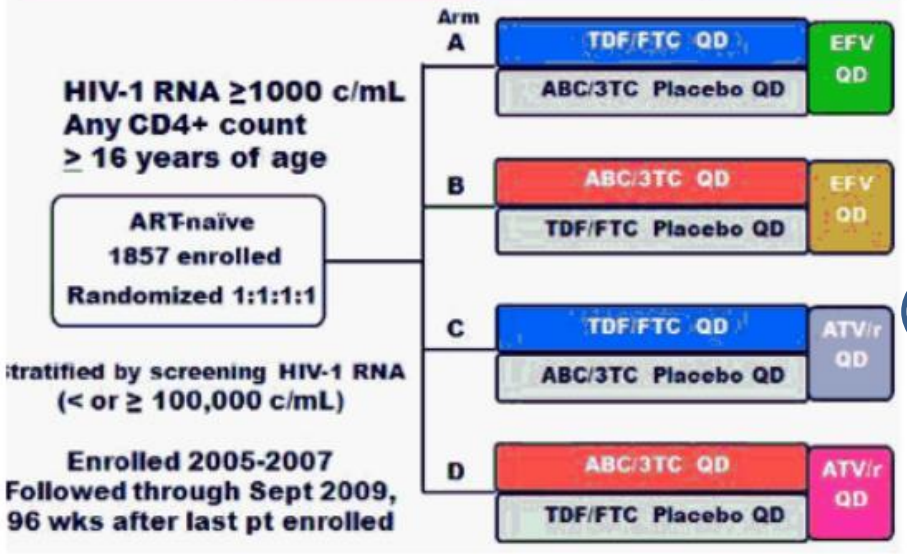


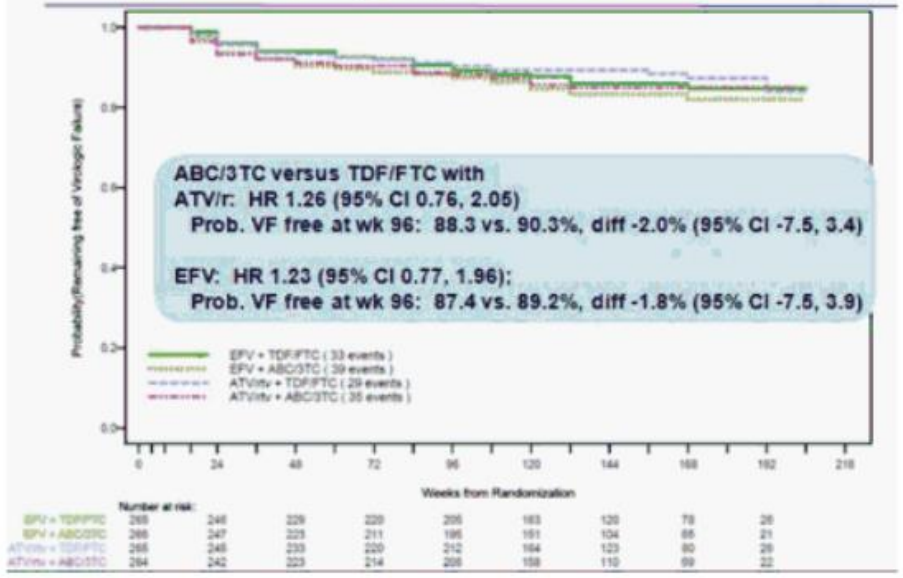
Figure 3. Activity of (*R*)-PMPA when injected shortly before or after SIV infection in rhesus
first prediction that tenofovir may be effective in therapy and prophylaxis of HIV infection i
(figure taken from Tsai et al. [34]).

2021

A5202: Study Design



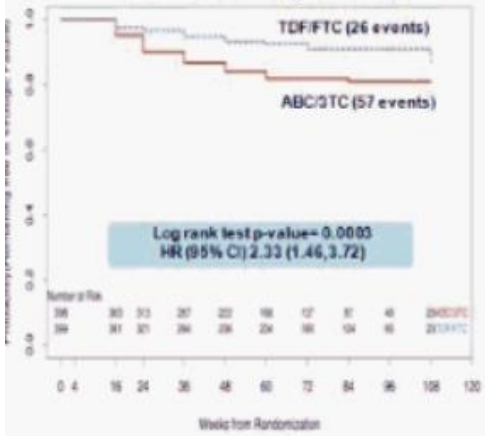
ABC/3TC vs. TDF/FTC
Time to Virologic Failure
(End of Study: Low Viral Load Stratum)



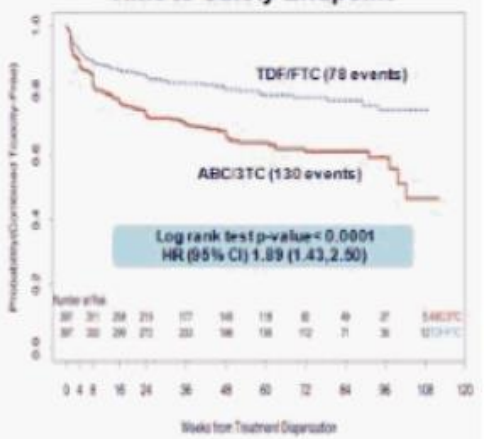
ABC/3TC vs. TDF/FTC
Primary Virologic and Safety Endpoints
(High Viral Load Stratum at DSMB Action)

N=797; median (25th, 75th) follow-up = 60 weeks (28, 84)

Time to Virologic Failure

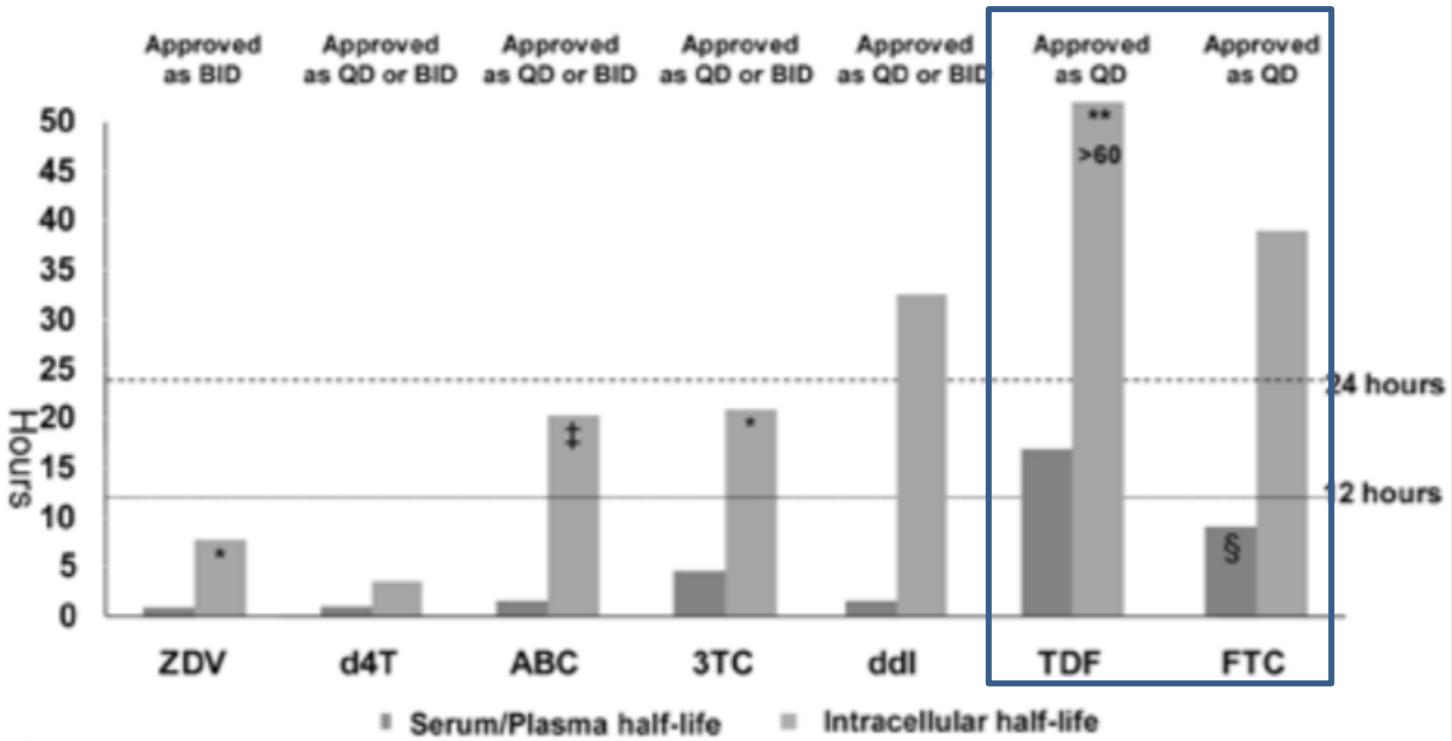


Time to Safety Endpoint



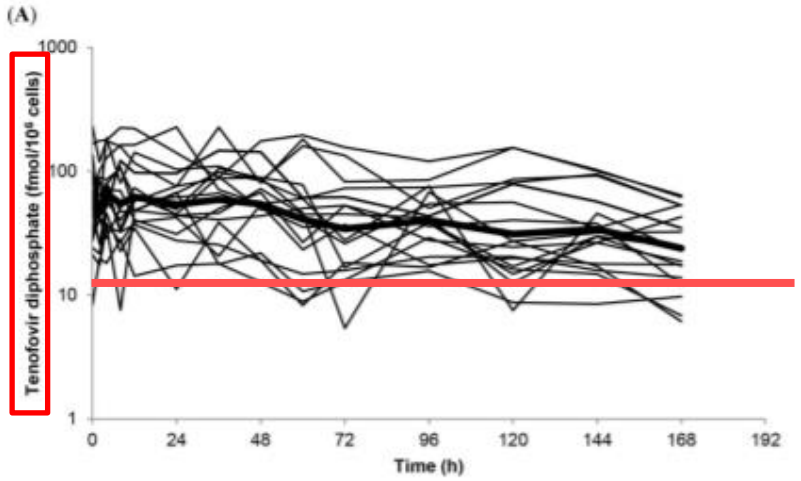
Sax PE, et al. NEJM 2009; 361:2230-2240

Cross Study Comparison
Pharmacokinetics of NRTIs



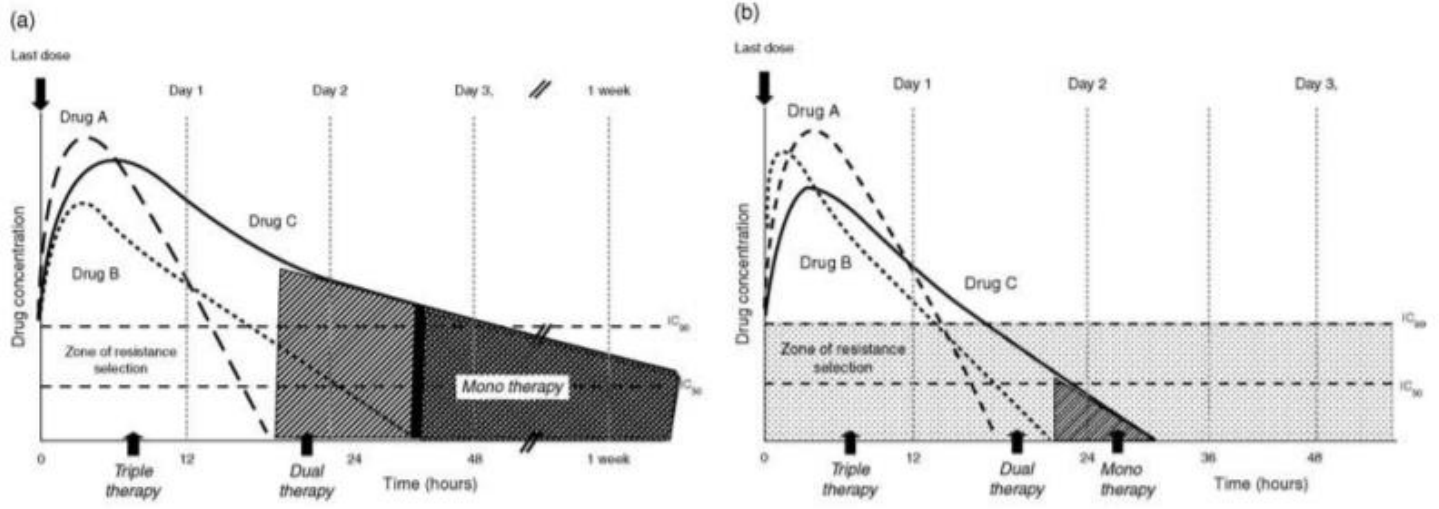
†Data from Centers for Disease Control and Prevention. *MMWR Recomm Rep.* 2002;51(RR-7):1-64 unless otherwise noted
*Anderson et al. AIDS 2003; 17(15):2159-2168. ‡Piliero et al. ICAAC 2003.
**Hawkins et al. 5th IWCPHT 2004 §Wang et al. IAC 2002; #4546.

Plasma Tenofovir, Emtricitabine, and Rilpivirine and Intracellular
Tenofovir Diphosphate and Emtricitabine Triphosphate
Pharmacokinetics following Drug Intake Cessation



Predicted TFV-DP concentrations from the present study were above 16 fmol/10_6 cells **in 94% and 72%** of volunteers at **2 and 7 days** after stopping drug intake

Dickinson et al. AAC 2015



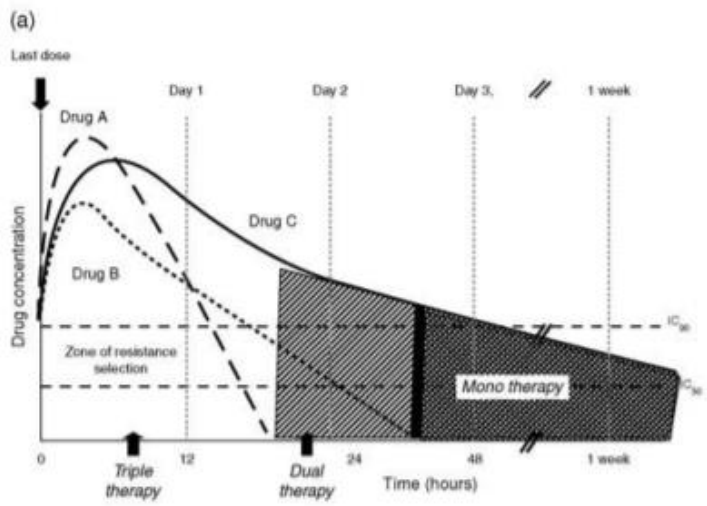
Example
Drugs A: **short half-life NRTI** (AZT, d4t, ddI…)
Drug B: 3TC
Drug C: EFV or NVP

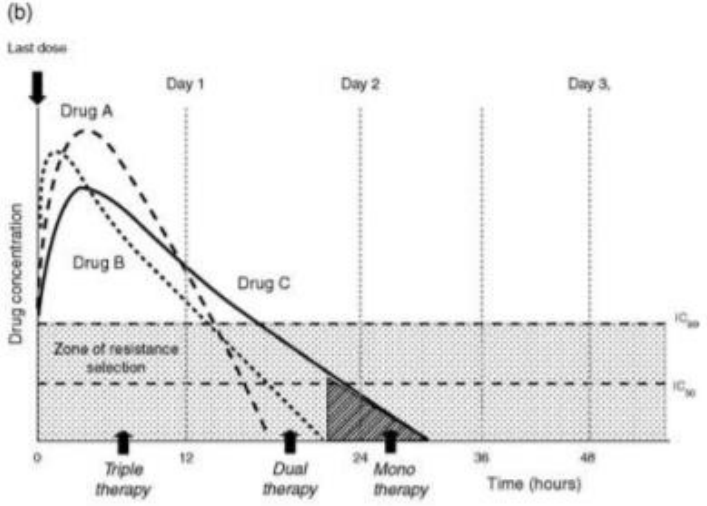
Failure with selection of NNRTI mutatons +/- M184V

Example
Drugs A: **short half-life NRTI** (AZT, d4t, ddI…)
Drug B: 3TC
Drug C: boosted PI

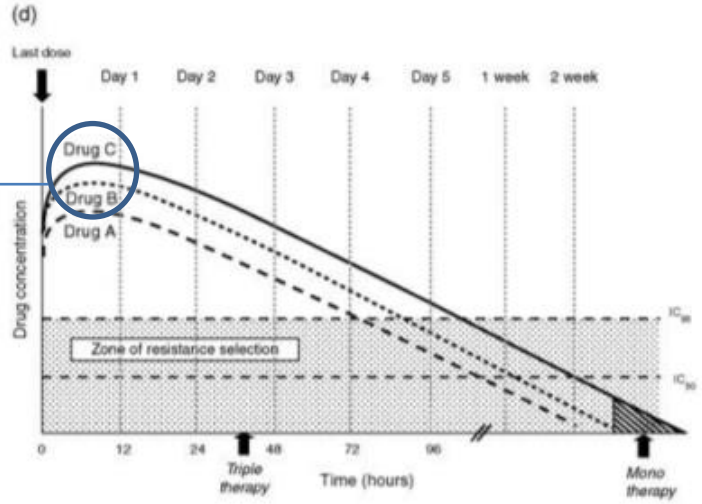
Failure without mutations

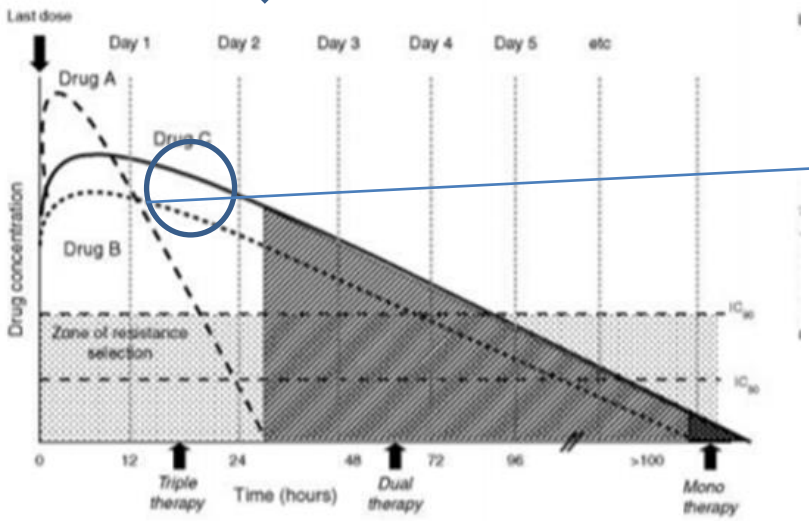
Taylor S, AIDS 2007





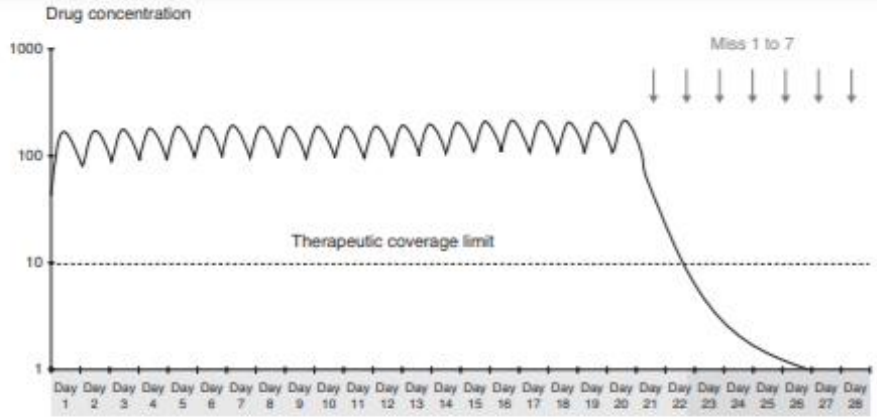
TDF/FTC



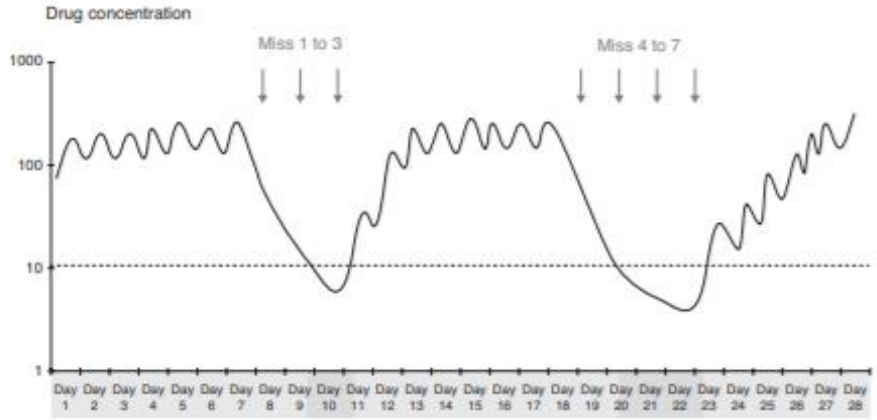


TDF/FTC

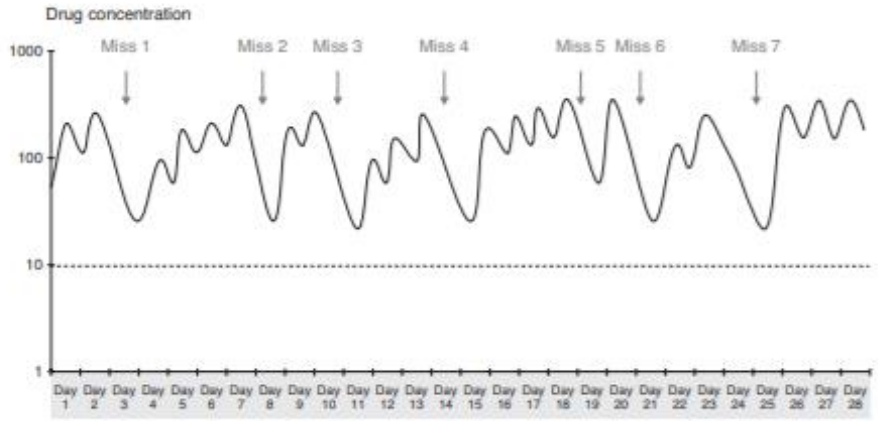
Taylor S, AIDS 2007



Non-persistence



Clustered missed doses



Number of missed doses: why 1 × 7 does not make 7 × 1?

Jean-Jacques Parienti[a,b,c] and David L. Paterson[d]

AIDS 2012, **26**:1437–1440

- Adherence has two metrics*: average adherence* and *longer treatment interruption*
- *Average adherence* is mostly used but *longer treatment interruption* significantly outperform average adherence in predicting HIVRNA replication
- Different patterns of missing the same number of doses could have a different impact on the therapeutic coverage ratio, depending on how many doses are missed.
- Drugs with a longer half-life could allow to cover longer treatment interruptions without reaching the red zone of subtherapeutic concentrations

..but to what extent forgiveness is important in real life?

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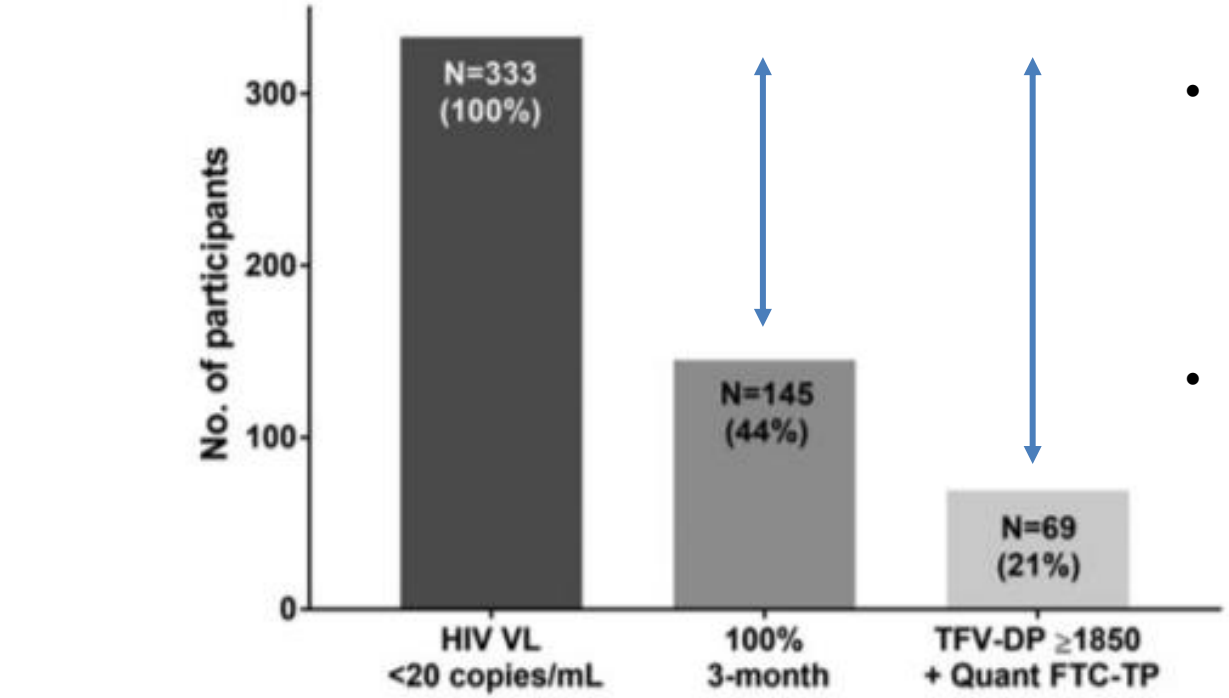
Short Communication: Cascade of Antiretroviral Therapy Adherence in Virologically Suppressed Persons Living with HIV

Jose R. Castillo-Mancilla,[1] Ryan P. Coyle,[1] Stacey S. Coleman,[2] Mary Morrow,[3] Edward M. Gardner,[1] Jia-Hua Zheng,[4] Lucas Ellison,[4] Lane R. Bushman,[4] Jennifer J. Kiser,[4] Samantha MaWhinney,[3] and Peter L. Anderson[4]



TFV-DP (fmol/punch) Median (IQR)	1731 (1269, 2377)	1814 (1393, 2582)	2601 (2199, 3054)

Drug concentrations of phosphorylated antiretroviral anabolites in dried blood spots (DBS) have been used to assess adherence

- **TFV-DP in DBS** is a measure of cumulative TFV adherence and exposure, given its long half-life of 17 days in red blood cells, informing about TDF intake over **the preceding 8 weeks**

- **FTC-TP in DBS** is informative of **recent dosing** due to its shorter half-life of 35 h in red blood cells

Strategies for improving compliance

…therefore, which is nowadays the adherence threshold for virological success?

Forgiveness of Dolutegravir-Based Triple Therapy Compared With Older Antiretroviral Regimens: A Prospective Multicenter Cohort of Adherence Patterns and HIV-RNA Replication

Parienti et al., Open Forum Infectious Diseases 2021

- 399 experienced PWH
- DOLUTECAPS study, international multicenter prospective cohort from May 2015 and December 2018
- Electronic drug monitoring (EDM)

- Inclusion PWH at risk of suboptimal adherence was encouraged
- Exclusion: people using pillbox organizers and PWH not responsible for taking pills

- 3 groups: STARTING group, FAILING group, SWITCHING group

Table 2. Factors Associated With Virological Replication (>50 Copies/mL) at Month 6 in the Overall Cohort (n = 399)

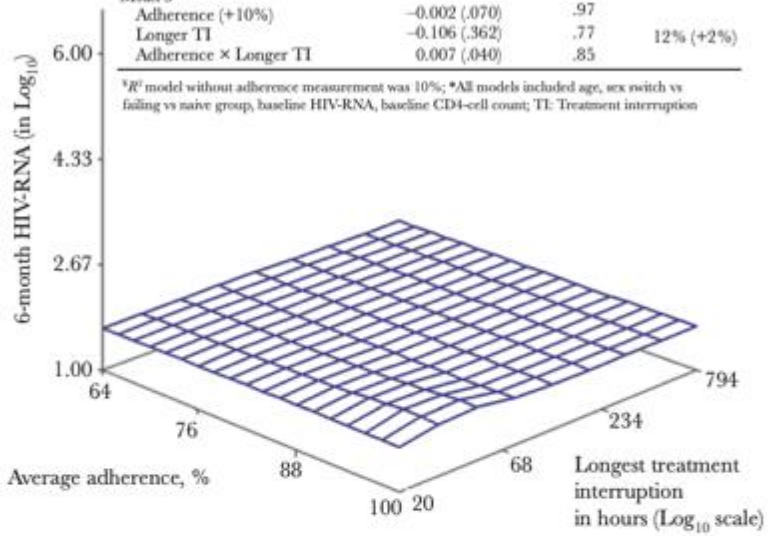
	Univariate Analysis			Multivariate Analysis	
Variables	No VR (n = 335)	VR (n = 64)	*P* Value	aOR [95% CI]	*P* Value
Age, mean (SD), y	44.5 (11.8)	41.6 (11.3)	.07	0.88 [0.63–1.22]	.44
Male	259 (77.3)	53 (82.8)	.41	1.36 [0.6–3.2]	.48
CD4 cells, mean (SD)	494 (256)	402 (250)	.009	0.97 [0.86–1.14]	.92
Log HIV-RNA, mean (SD), cp/mL	2.44 (1.23)	2.90 (1.37)	.008	1.61 [0.97–2.68]	.07
Third antiretroviral agent			.005		
Dolutegravir-based	94 (28.1)	8 (12.5)		Ref.	
Raltegravir-based	72 (21.5)	18 (28.1)		7.7 [2.4–25.2]	.0007
bPI-based	81 (24.2)	26 (40.6)		1.9 [0.6–6.0]	.29
NNRTI-based	88 (26.3)	12 (18.8)		3.4 [0.9–12.7]	.07
Treatment group			<.0001		
Switched treatment	221 (66.0)	26 (40.6)		Ref.	
Treatment-naïve	70 (20.9)	9 (14.1)		0.6 [0.1–4.2]	.63
Failed treatment	44 (13.1)	29 (41.3)		4.4 [1.4–14.0]	.012
Adherence class			<.0001		
>95%	211 (63.0)	20 (31.2)		Ref.	
90%–95%	39 (11.6)	3 (4.7)		0.5 [0.1–2.1]	.35
80%–90%	47 (14.0)	5 (7.8)		0.8 [0.2–2.6]	.69
60%–80%	29 (8.7)	13 (20.3)		3.2 [1.0–10.0]	.043
<60%	9 (2.7)	23 (35.9)		5.9 [1.5–23.7]	.012
Longest treatment interruption, log mean (SD), h	1.63 (0.28)	2.06 (0.48)	<.0001	4.6 [1.3–16.9]	.02

Abbreviations: aOR, adjusted odds ratio; bPI, boosted protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; VR, virological replication with HIV-RNA >50 cp/mL.

DTG-based

ravir-based (n = 102)	β (SE)	*P* value	$R^{2\%}$
Adherence (+10%)	0.017 (.010)	.12	12% (+2%)
*Model 2**			
Longer TI	0.076 (.049)	.13	12% (+2%)
*Model 3**			
Adherence (+10%)	−0.002 (.070)	.97	
Longer TI	−0.106 (.362)	.77	12% (+2%)
Adherence × Longer TI	0.007 (.040)	.85	

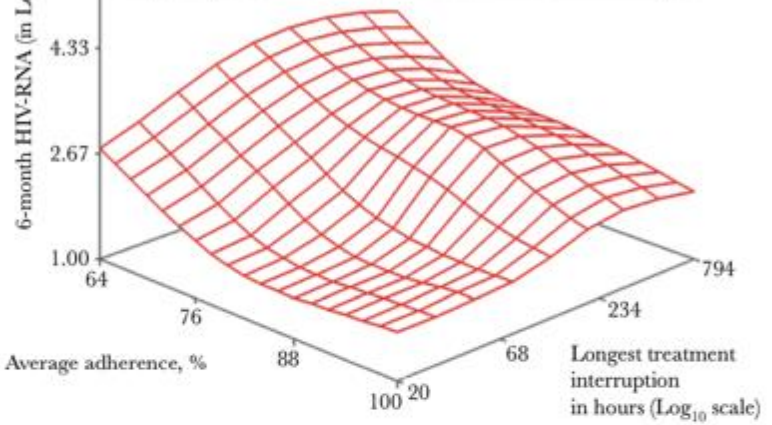
[¥]R^2 model without adherence measurement was 10%; *All models included age, sex switch vs failing vs naive group, baseline HIV-RNA, baseline CD4-cell count; TI: Treatment interruption



RAL-based

altegravir-based (n = 90)	β (SE)	*P* value	$R^{2\%}$
*odel 1**			
Adherence (+10%)	−0.420 (.039)	<.001	65% (+49%)
*Model 2**			
Longer TI	0.954 (.182)	<.001	37% (+21%)
*Model 3**			
Adherence (+10%)	0.226 (.194)	.25	
Longer TI	3.079 (.904)	.001	70% (+54%)
Adherence × Longer TI	−0.332 (.100)	.0015	

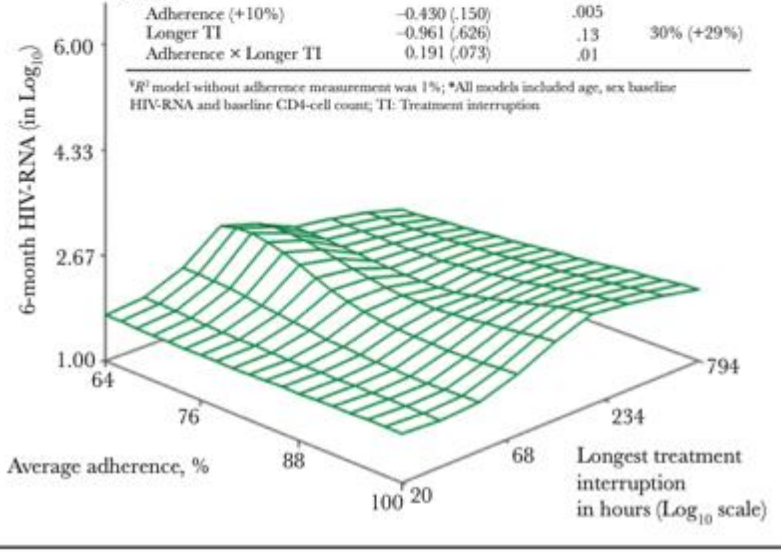
[¥]R^2 model without adherence measurement was 16%; *All models included age, sex switch vs failing vs naive group, baseline HIV-RNA, baseline CD4-cell count; TI: Treatment interruption



NNRTI-based

n = 100)	β (SE)	*P* value	$R^{2\%}$
+10%)	−0.118 (.024)	<.001	21% (+20%)
*Model 2**			
Longer TI	0.953 (.179)	<.001	36% (+35%)
*Model 3**			
Adherence (+10%)	−0.430 (.150)	.005	
Longer TI	−0.961 (.626)	.13	30% (+29%)
Adherence × Longer TI	0.191 (.073)	.01	

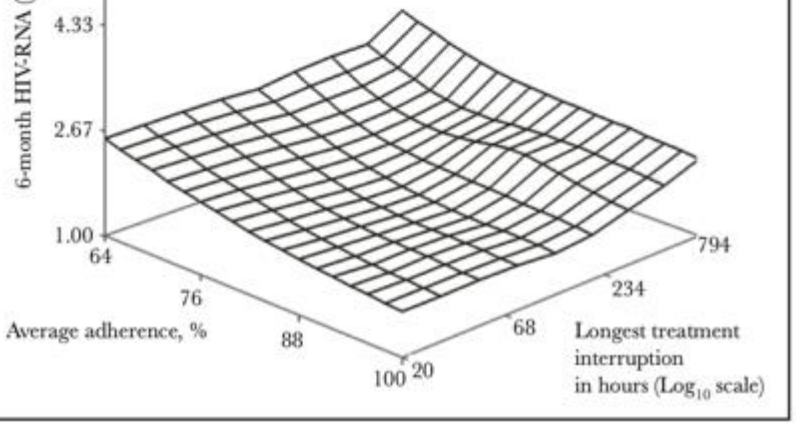
[¥]R^2 model without adherence measurement was 1%; *All models included age, sex baseline HIV-RNA and baseline CD4-cell count; TI: Treatment interruption



bPIs-based

i-based (n = 107)	β (SE)	*P* value	$R^{2\%}$
*odel 1**			
Adherence (+10%)	−0.384 (.030)	<.001	78% (+37%)
*Model 2**			
Longer TI	1.021 (.186)	<.001	55% (+14%)
*Model 3**			
Adherence (+10%)	0.307 (.150)	.09	
Longer TI	2.537 (.681)	.0003	81% (+40%)
Adherence × Longer TI	−0.285 (.072)	.0002	

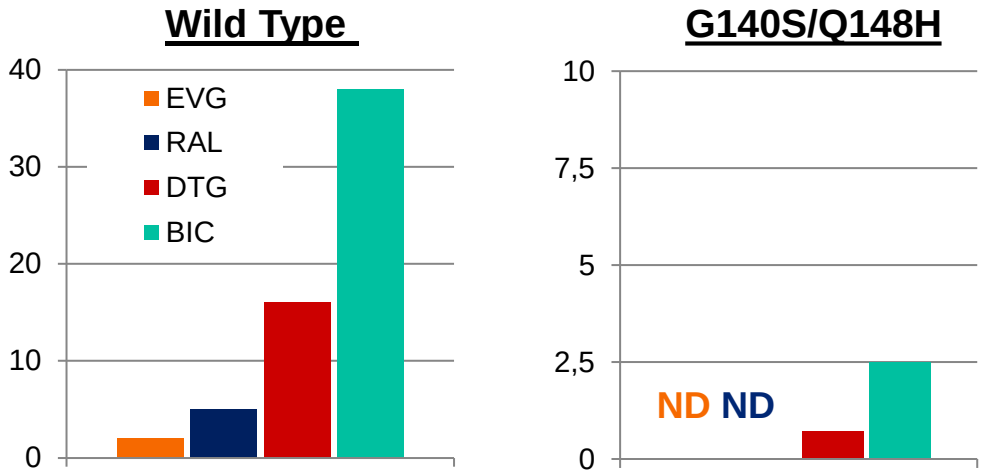
[¥]R^2 model without adherence measurement was 0.41; *All models included age, sex switch vs failing vs naive group, baseline HIV-RNA, baseline CD4-cell count; TI: Treatment interruption



Dissociation Kinetics & In Vitro Resistance Profile and G140S+Q148H Mutant Integrase-DNA Complexes[1]

- Longer dissociation half-life is predicted to correlate with more potent antiviral activity and a potentially higher genetic barrier to resistance

Mean Dissociation Half-life (hours)



Phenotypic Analysis of Clinical Isolates* G140S/Q148H ± Other INSTI-R (n=16)

INSTI	Fold-Change vs WT†	% of Isolates with EC_{50} FC ≤4.0‡	*P*-value vs BIC
RAL	>143	0%	<0.001
EVG	>150	0%	<0.001
DTG	7.6 ± 4.3	25%	<0.001
BIC	3.4 ± 1.7	75%	--

* Patient-derived clinical isolates with INSTI-R (Monogram Biosciences).
† Mean ± standard deviation.
‡ The lower clinical cut-off for reduced susceptibility to DTG on the PhenoSense IN assay is 4-fold.

BIC was associated with longest dissociation half-life from wild-type and G140S/Q148H integrase mutants and greater in vitro phenotypic activity against G140S/Q148H integrase mutants

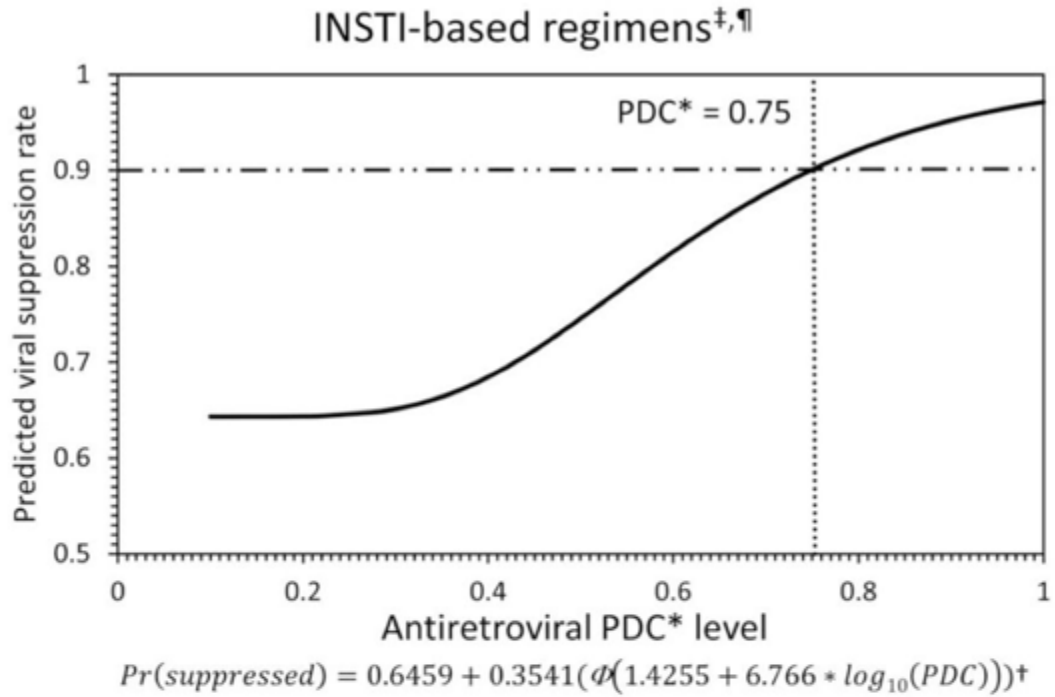
EC, effective concentration; FC, fold change; ND, not detected; $T_{1/2}$, half-life

1. White K, et al. CROI 2017. Seattle, WA. Poster #497. 2. Hightower K, et al. Antimicrob Agents Chemo 2011;55(10):4552-4559.

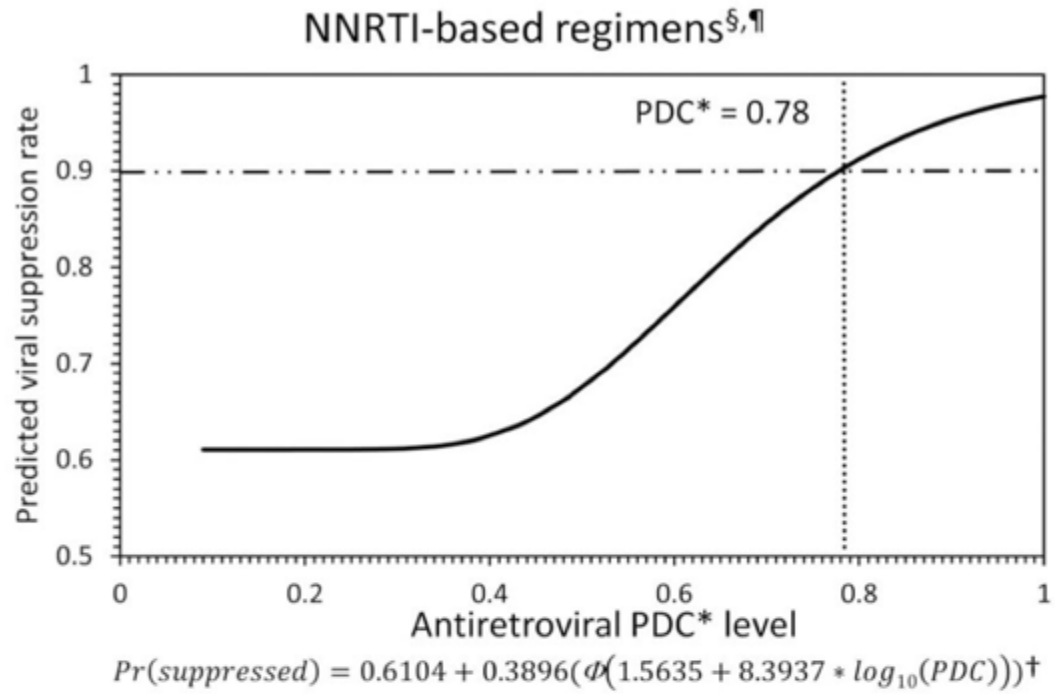
Antiretroviral Adherence Level Necessary for HIV Viral Suppression Using Real-World Data

Byrd et al., J Acquir Immune Defic Syndr. 2019

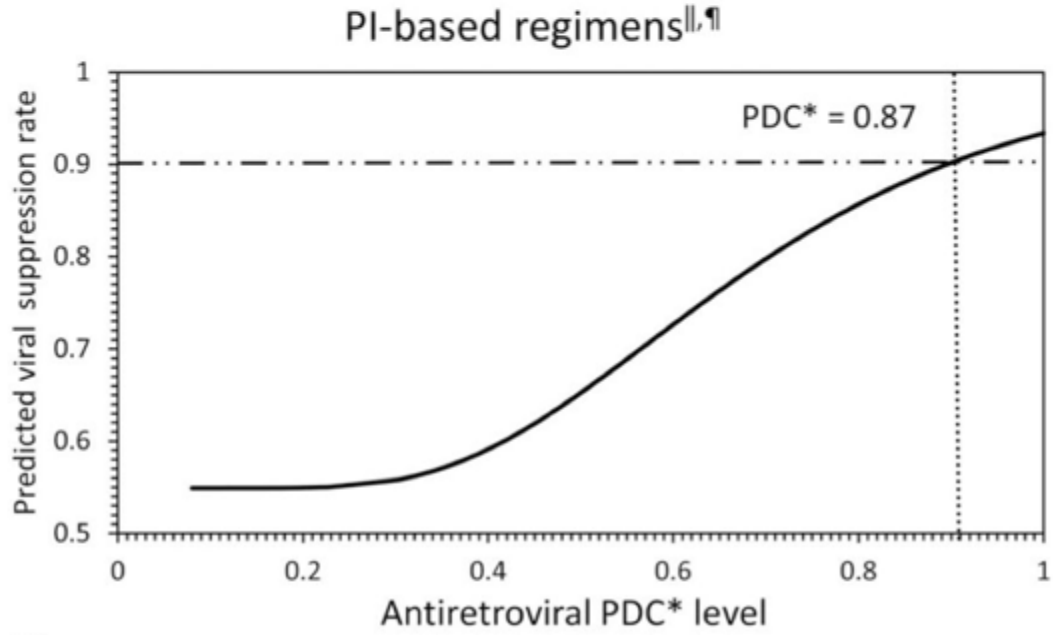
- Lower adherence level of ≥90% has been set by the Pharmacy Quality Alliance.
- Given the enhanced pharmacokinetic profiles of newer ARV medications, even the lower adherence level of ≥90% may not be necessary to achieve HIV viral suppression
- Patient-centered HIV Care Model (PCHCM) PCHCM project partnered community-based HIV-specialty pharmacists with HIV medical providers and required the partnered pharmacists and medical providers to share patient clinical information, identify therapy-related problems, and develop therapy-related action plans.
- 765 adult pts in United States from 2014 to 2016.
- The PDC: proportion of days covered



$$Pr(suppressed) = 0.6459 + 0.3541(\Phi(1.4255 + 6.766 * log_{10}(PDC)))\dagger$$

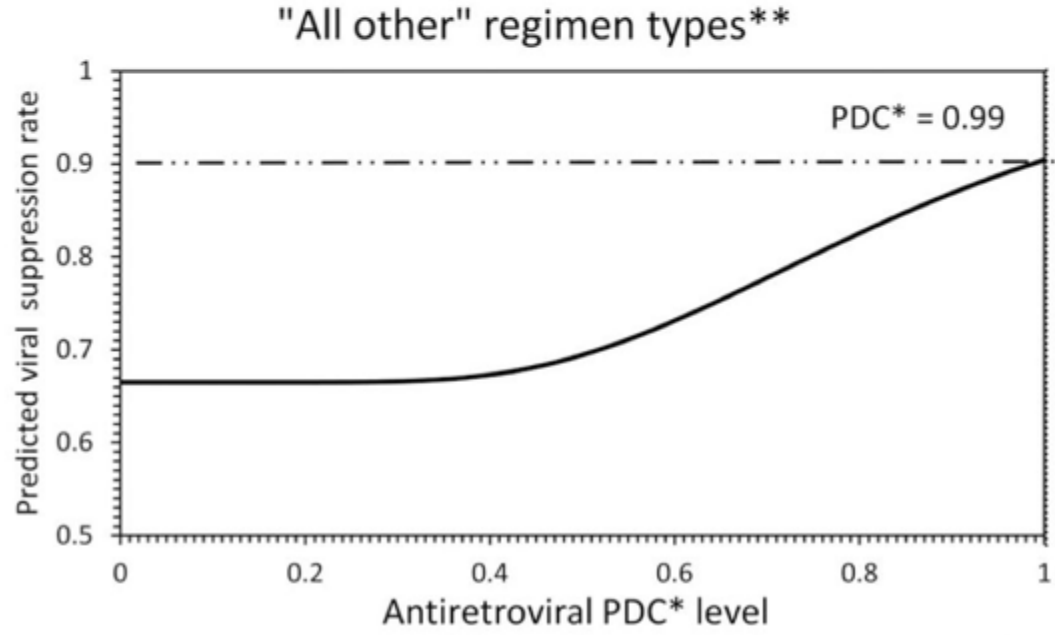


$$Pr(suppressed) = 0.6104 + 0.3896(\Phi(1.5635 + 8.3937 * log_{10}(PDC)))\dagger$$



B

$$Pr(suppressed) = 0.5665 + 0.4335(\Phi(1.0791 + 5.8251 * log_{10}(PDC)))\dagger$$



$$Pr(suppressed) = 0.6745 + 0.3255(\Phi(0.5422 + 6.608 * log_{10}(PDC)))\dagger$$

AIDS. 2018 March 27; 32(6): 761–765. doi:10.1097/QAD.0000000000001744.

Plasma and Intracellular Pharmacokinetics of Tenofovir in Patients Switched from Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide

Anthony T. PODANY[1], **Sara H BARES**[2], **Joshua HAVENS**[2], **Ravi Dyavar SHETTY**[1], **Jennifer O'NEILL**[2], **Sarah LEE**[3], **Courtney V. FLETCHER**[1,2], **Susan SWINDELLS**[2], and **Kimberly K. SCARSI**[1]

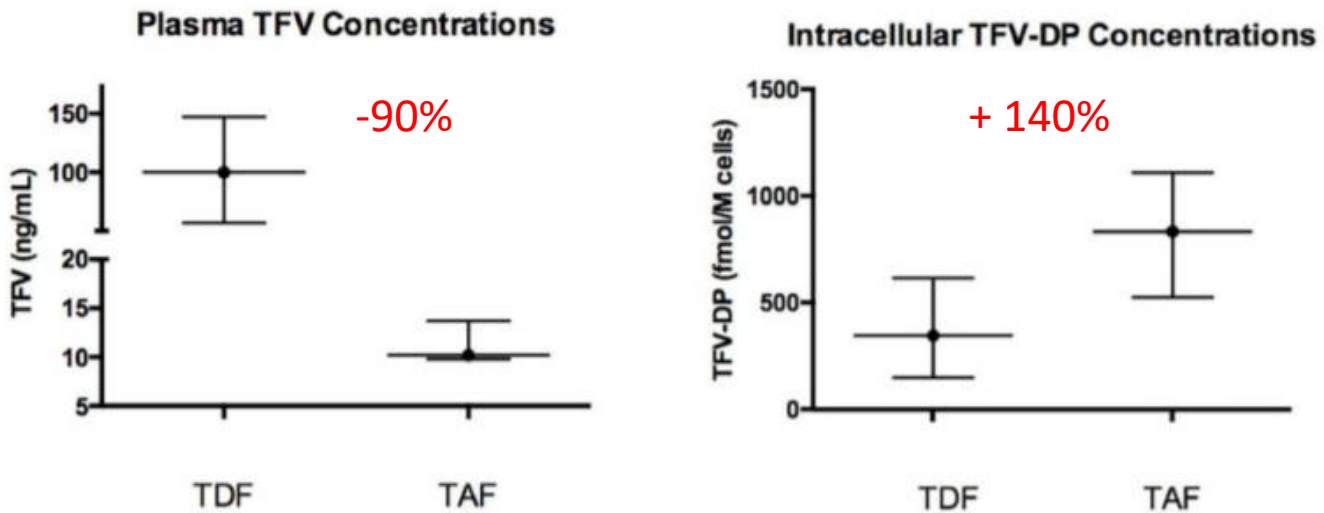


Figure 1.

Whisker plot of plasma tenofovir and PBMC tenofovir diphosphate concentrations during TDF and TAF based dosing. Data presented as 25th, 50th and 75th percentiles.

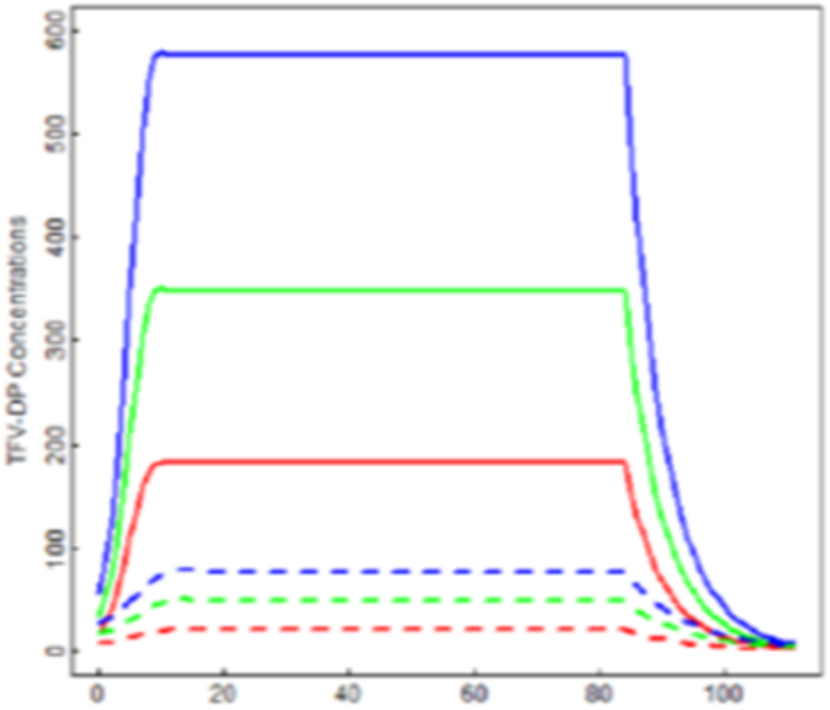
Tenofovir-diphosphate in peripheral blood mononuclear cells during low, medium, and high adherence to F/TAF vs. F/TDF (Yager, AIDS sept 2021)

--TDF - TAF

100%
67%
33%

Figure Legends:

Figure 1. Predicted TFV-DP concentrations in PBMC following F/TDF and F/TAF. Model-fitted TFV-DP in PBMC (fmol/10^6 cells) by study day for 33% dosing (red), 67% dosing (green) and 100% dosing (blue). Solid lines are concentrations following F/TAF dosing; dashed lines are concentrations following F/TDF dosing. Prior to steady state, a nonlinear mixed effect model with tensor product of natural b-spline transformation of study day and study arm was used to model concentrations. The estimate was constant over time at steady state, and then an exponential decay was modeled during washout.



Does increased intracellular TFV-DP matter?
1- Potency

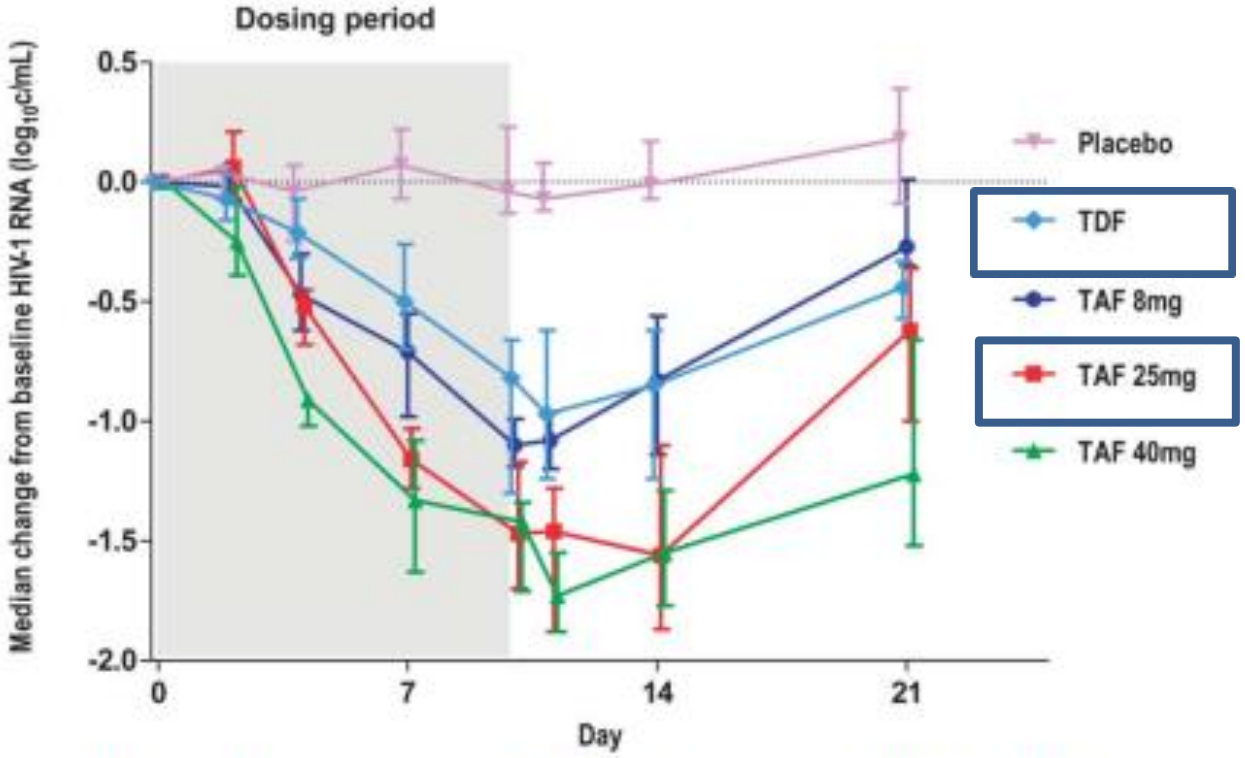


FIGURE 1. Median change from baseline in HIV-1 RNA.

BUT no difference of *efficacy* between TAF-based and TDF-based regimens has been observed in any clinical trial

Does increased intracellular TFV-DP matter?
2- Genetic Barrier

Antiviral Activity of Tenofovir Alafenamide against HIV-1 with Thymidine Analog-Associated Mutations and M184V

Nicolas Margot,[a] Renee Ram,[a] Michael Abram,[a] Richard Haubrich,[a] Christian Callebaut[a]

TABLE 3 Multicycle phenotypic sensitivities of patient-derived TAM-containing mutants with or without M184V

		Mean EC_{50} fold change (SD) compared to the wild type[b]						
No. of TAMs[a]	*n*	TAF	TDF[c]	AZT	ABC	FTC	DTG	DRV
3 TAMs	3	2.9 (1.3)	3.0 (1.4)	>72 (27)	2.4 (0.4)	2.0 (0.5)	0.6 (0.3)	2.2 (2.7)
3 TAMs + M184V	2	2.1 (0.4)	2.1 (0.9)	14.3 (13.0)	5.1 (0.1)	>126 (0)	0.8 (0.2)	0.8 (0.0)
4 TAMs	2	5.4 (3.8)	6.4 (4.4)	>91 (0)	4.3 (3.2)	13.9 (17)	0.6 (0.1)	0.9 (0.3)
4 TAMs + M184V	2	1.6 (1.0)	1.8 (1.1)	>36 (41)	11.7 (10.2)	>126 (0)	0.6 (0.1)	1.0 (0.5)
5 TAMs	3	10.0 (3.1)	9.3 (4.6)	>91 (0)	10.0 (3.9)	7.1 (4.5)	1.1 (0.5)	0.7 (0.2)
5 TAMs + M184V	2	3.8 (0.6)	4.3 (0.8)	>82 (12.6)	8.3 (1.5)	>126 (0)	0.9 (0.4)	1.0 (0.2)

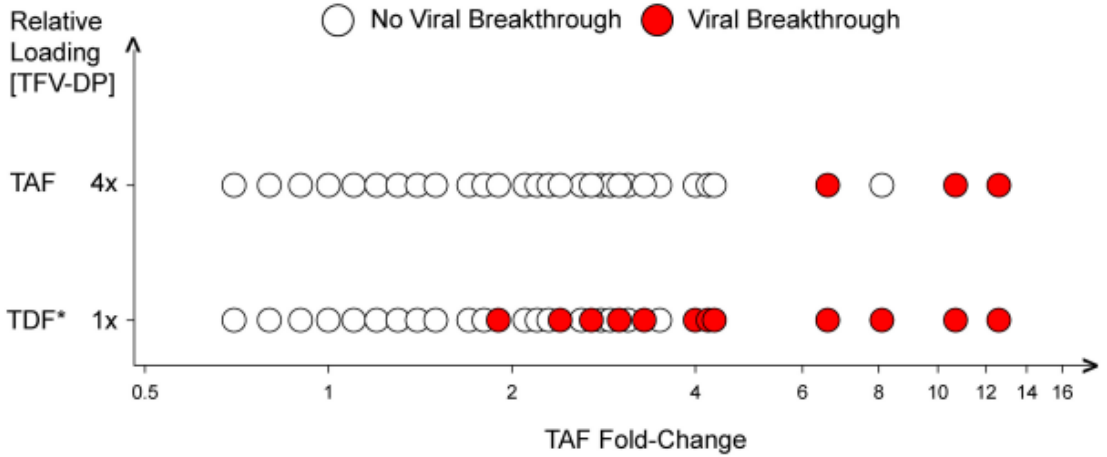


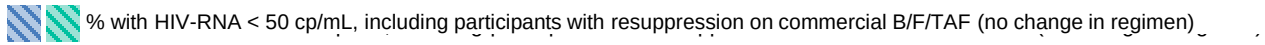
FIG 5 Viral breakthrough of selected viruses ($n = 68$, see the supplemental material) in the presence of physiological concentrations of TAF and TDF. MT-2 cells were incubated overnight with either TDF or TAF at concentrations reflective of *in vivo* loading achieved with the two prodrugs of TFV (TDF, 50 μM [$1\times EC_{95}$ corresponding to an $IQ_{95} = 1$]; TAF, 0.8 μM [$4\times EC_{95}$ corresponding to an $IQ_{95} = 4$]) and infected with HIV-1 mutants. Mutant viruses tested (each represented by a circle) are plotted against the TAF EC_{50}-fold changes measured for the mutants. *, TFV, the *in vitro* equivalent of TDF, was used in these experiments.

The 4-fold increase in intracellular TFV-DP concentration upon dosing with TAF compared to TDF is associated with an **increase in the resistance threshold** for TAF compared to TDF

Pooled analysis: Studies 4030, 4580, 1844, 1878 and 4449

Virologic Outcomes by Pre-existing TAMs: Last On-treatment Study Visit

	%	n/N	Participants with HIV-RNA < 50 cp/mL at last visit, %		Median B/F/TAF duration, weeks
Pooled B/F/TAF	n=1808	1787/1808	99	99	72
≥1 TAM	9	163/166	98	99	71
1–2 TAMs	6	106/108	98	98	72
≥3 TAMs	3	57/58	98	100	63
≥3 TAMs (M41L and/or L210W)	2	36/37	97	100	62
≥3 TAMs (M41L or L210W) + M184V/I	1	26/26	100	100	60
≥1 TAM only NRTI-R	5	88/90	98	99	72
≥1 TAM + other NRTI-R	4	75/76	99	99	63
≥1 TAM + M184V/I	4	69/70	99	99	63
≥1 TAM + K65R	<1	4/4	100	100	73
≥1 TAM + NNRTI-R	4	71/72	99	100	64
≥1 TAM + PI-R	3	47/48	98	100	64
≥1 TAM + secondary INSTI-R*	4	68/68	100	100	69



High rates of virologic suppression were maintained through 72 weeks after switching to B/F/TAF, regardless of pre-existing TAMs

*No participants with ≥ 1 TAM and primary INSTI-R received B/F/TAF
R, resistance; TAM, thymidine analog mutation
Andreatta K, et al. EACS 2021, Poster PE1/6

Does increased intracellular TFV-DP matter?
3- Forgiveness?

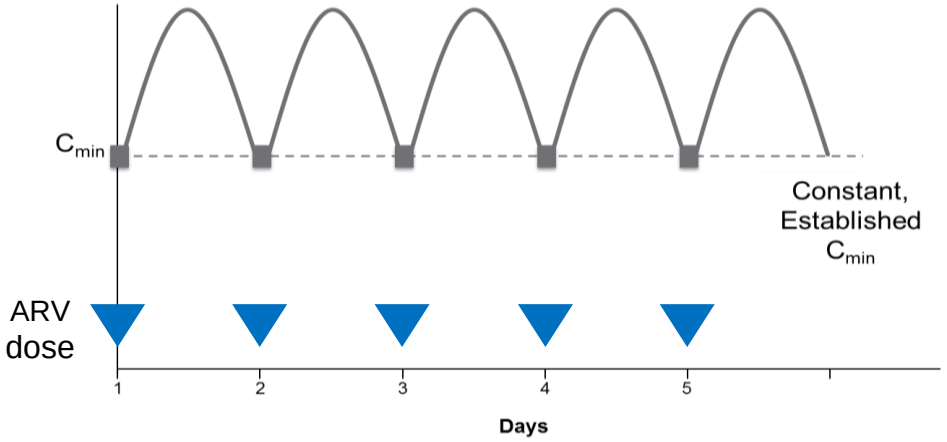
Forgiveness Simulation Model[1]

In vitro

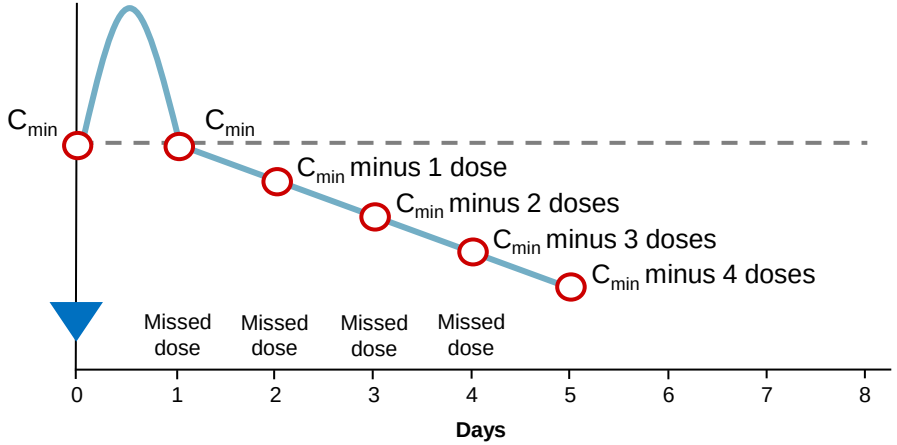
Outcome

In vitro simulation of drug C_{min} pharmacokinetics, and the effect of two and four consecutive missed daily oral doses

Optimal Adherence



With 1–4 Consecutive Missed Doses



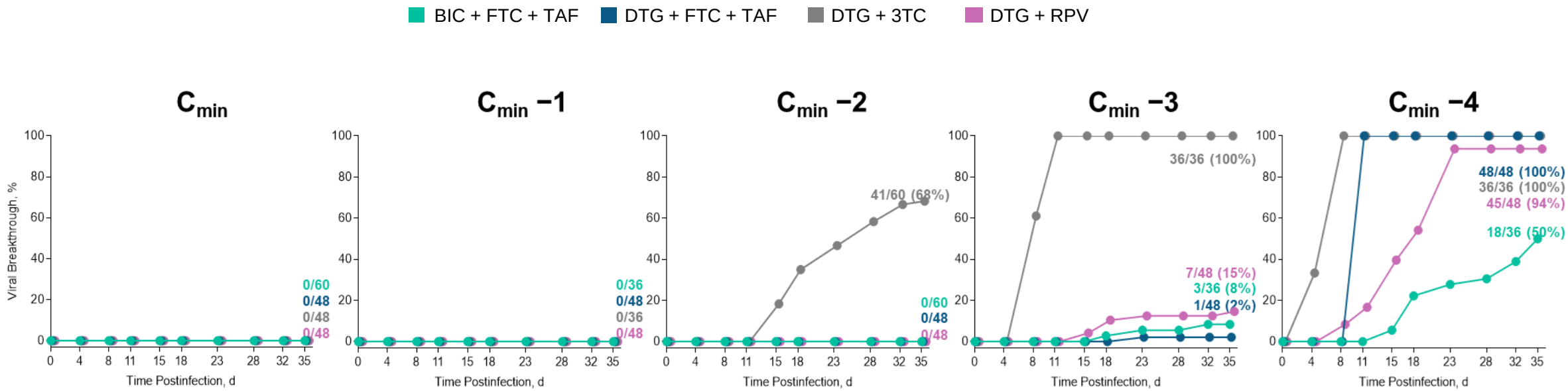
- **Drug resistance occurs when HIV is replicating in the presence of suboptimal concentrations of drugs[2]**
- **Although short lapses in adherence to ARV drugs can lead to virologic failure and emergence of drug resistance, certain drug regimens have high levels of forgiveness[2]**
- **There is potential for resistance development associated with low drug exposure, inconsistent dosing, pre-existing drug resistance or HIV-1 subtype[3]**

C_{min}, minimum concentration; STR, single-tablet regimen

1. Acosta R, et al. EACS 2021, Poster PE1/10; 2. Acosta R, et al. IDWeek 2021, Poster 888; 3. Cutrell A, et al. AIDS 2021;35:133-142

Viral Breakthrough *In Vitro*

MT-2 cells were infected with HIV-1 IIIb; cultured in the presence of fixed concentrations of BIC+FTC+TAF, DTG+FTC+TAF, DTG+3TC, or DTG+RPV, and monitored for viral breakthrough

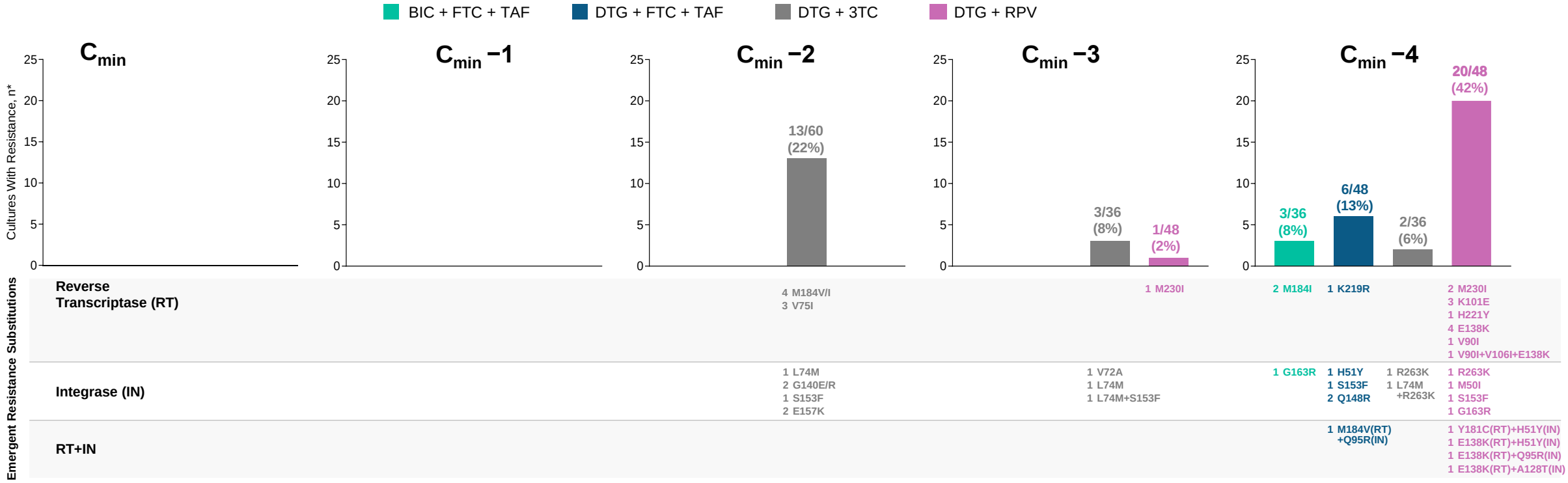


Viral breakthroughs were seen for all regimens but at different frequencies and time of onset; BIC+FTC+TAF had no breakthrough until C_{min} −3

In vitro viral breakthrough experiments should be analyzed comparatively; controlled clinical trials assessing the impact of missed doses of these ARV combinations have not been conducted
C_{min}, minimum concentration
Acosta R, et al. EACS 2021, Poster PE1/10; Acosta R, et al. IDWeek 2021, Poster 888

Resistance Development *In Vitro*

Deep sequence was performed in virus recovered at the time of breakthrough to identify emergent drug resistance

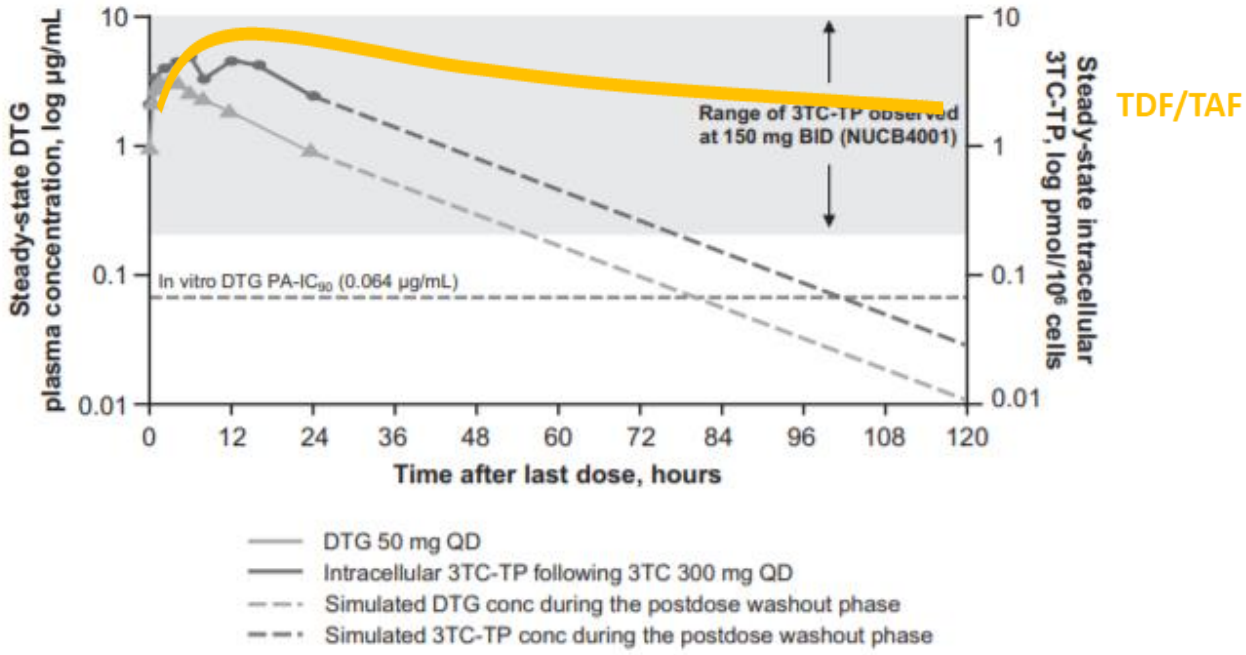


Emergent drug resistance was seen for all regimens occurring at differing frequencies and time of onset; there was no resistance for BIC+FTC+TAF at C_{min} −3, emergence occurred at C_{min} −4

*Cultures with resistance contained 1 or more known resistance-associated substitutions
C_{min}, minimum concentration
Acosta R, et al. EACS 2021, Poster PE1/10; Acosta R, et al. IDWeek 2021, Poster 888

..due to availabliity of effective 2DRs, do we still need of TAF/TDF-related forgiveness?

DTG and 3TC Have Complementary PK Profiles



TDF/TAF

FIG. 1. Steady-state DTG and intracellular 3TC-TP concentration-time profiles after administration of DTG 50 mg or 3TC-TP 300 mg daily.[34,41,42] BID, twice daily; conc, concentration; DTG, dolutegravir; PA-IC_{90}, protein-adjusted 90% inhibitory concentration; QD, once daily; 3TC-TP, lamivudine triphosphate.

The PK profiles of DTG and 3TC are well matched. Adequate plasma concentrations of DTG and intracellular concentrations of 3TC-TP are maintained for 3 days after the last dose

Boffito et al, AIDS RESEARCH AND HUMAN RETROVIRUSES 2020

IMPACT OF TREATMENT ADHERENCE ON EFFICACY OF DTG + 3TC AND DTG + TDF/FTC: POOLED ANALYSIS OF THE GEMINI-1 AND -2 CLINICAL STUDIES

Mounir Ait-Khaled,[1] Juan Sierra Madero,[2] Vicente Estrada Perez,[3] Roberto Gulminetti,[4] Debbie Hagins,[5] Hung-Chin Tsai,[6] Choy Man,[7] Jörg Sievers,[1] Rimgaile Urbaityte,[8] Richard Grove,[8] Andrew Zolopa,[7] Brian Wynne,[7] Jean van Wyk[1]

Methods

- **Association between adherence and proportion of participants with HIV-1 RNA <50 c/mL was evaluated at Week 48** using the **FDA Snapshot algorithm** and an analysis based on the **last available on-treatment viral load by Week 48** (assessment of virologic response not accounting for discontinuations for non-virologic reasons)
- **Percent adherence** calculated as:
  - **number of pills taken** (difference between the number of pills available and the number of pills returned) **per number of pills prescribed estimated using pill count data**
- Participants were **stratified by ≥90% vs <90% adherence**
- Unadjusted treatment differences with exact 95% CIs were derived for proportion of participants with HIV-1 RNA <50 c/mL using both FDA Snapshot endpoint and last available on-treatment viral load through Week 48

1. Cahn et al. *Lancet*. 2019;393:143-155. **2.** Cahn et al. HIV Glasgow 2020; Virtual. Poster P018. **3.** Altice et al. *Patient Prefer Adherence*. 2019;13:475-490. **4.** Sax et al. *Lancet*. 2017;390:2073-2082.

Ait-Khaled et al. IDWeek 2020™; Virtual. Poster 1024.

Adherence Results in GEMINI-1 and -2 (ITT-E Population)

- Baseline HIV-1 RNA and CD4+ cell counts were comparable across adherence categories

Adherence results	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Adherence category, n (%)[a]		
<90%	**35 (5)**	**34 (5)**
≥90%	**679 (95)**	**677 (94)**
HIV-1 RNA by adherence category, median (range), log_{10} c/mL		
<90%	4.39 (2.82-5.75)	4.35 (3.07-5.88)
≥90%	4.43 (1.59-6.27)	4.48 (2.11-6.37)
CD4+ cell count by adherence category, median (range), cells/mm^3		
<90%	407.0 (41-1399)	415.0 (19-929)
≥90%	427.0 (19-1364)	440.0 (19-1497)

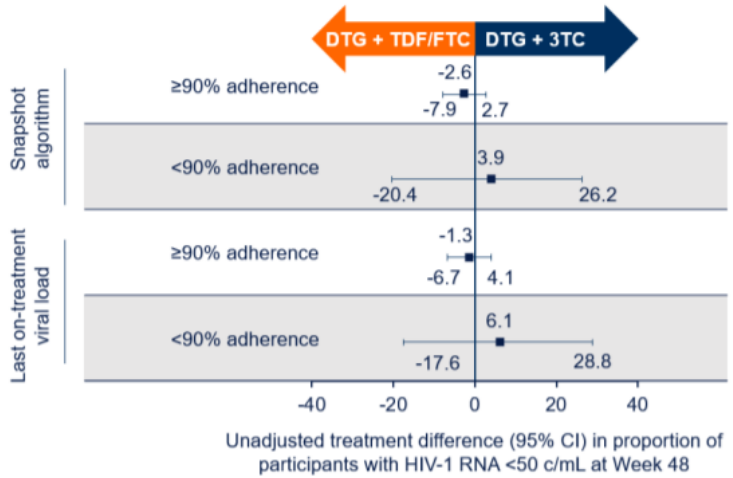
- A high proportion of participants had complete data records for the assessment of treatment adherence
- **In each treatment group, 5% of participants had <90% adherence**
- Demographics and baseline characteristics of participants in GEMINI-1 and -2 were well balanced between treatment groups[1,2]

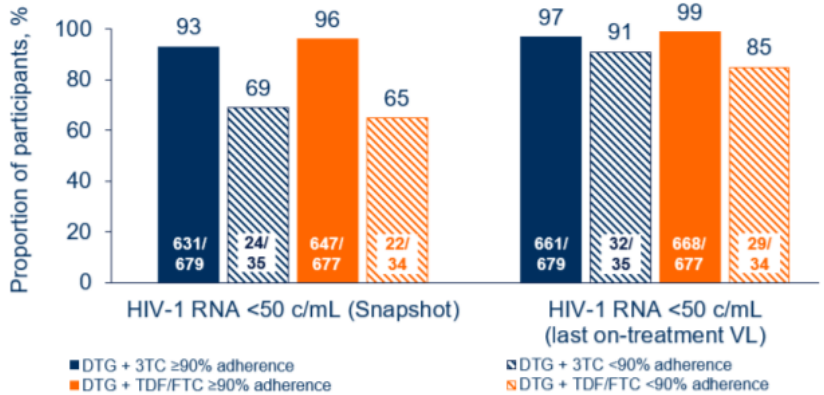
[a]Adherence categories only include participants with derived study drug adherence data.

Ait-Khaled et al. IDWeek 2020™; Virtual. Poster 1024.

Response Rates Were High in Participants With ≥90% Adherence, and Impact of Adherence Was Similar Between Treatment Groups

- The proportion of participants with HIV-1 RNA <50 c/mL at Week 48 was lower in those with <90% adherence compared with those with ≥90% adherence, regardless of treatment regimen





Snapshot Outcomes by Adherence Category

Outcomes, n (%)	DTG + 3TC ≥90% (N=679)	DTG + 3TC <90% (N=35)	DTG + TDF/FTC ≥90% (N=677)	DTG + TDF/FTC <90% (N=34)
HIV-1 RNA <50 c/mL	**631 (93)**	**24 (69)**	**647 (96)**	**22 (65)**
HIV-1 RNA ≥50 c/mL	**16 (2)**	**4 (11)**	**9 (1)**	**4 (12)**
Data in window and HIV-1 RNA ≥50 c/mL	8 (1)	0	4 (1)	1 (3)
Discontinued for lack of efficacy	3 (<1)	2 (6)	2 (<1)	0
Discontinued for other reason and HIV-1 RNA ≥50 c/mL	4 (1)	1 (3)	2 (<1)	3 (9)
Change in ART	1 (<1)	1 (3)	1 (<1)	0
No virologic data at Week 48	**32 (5)**	**7 (20)**	**21 (3)**	**8 (24)**
Discontinued study for AE or death	9 (1)	1 (3)	8 (1)	4 (12)
Discontinued study for other reason	21 (3)	6 (17)	13 (2)	4 (12)
On study but missing data in window	2 (<1)	0	0	0

1. Cahn et al. *Lancet.* 2019;393:143-155. **2.** Cahn et al. *J Acquir Immune Defic Syndr.* 2020;83:310-318.

Ait-Khaled et al. IDWeek 2020™; Virtual. Poster 1024.

Discussion

- In this study, ***adherence level appeared to have a similar impact on the 2DR and 3DR***; overall, response rates were high in those with ≥90% adherence
  - Response rates were high in participants with <90% adherence when last on-treatment VL was assessed
  - The high rates of response across adherence categories is supported by a real-world database analysis that suggests ≥80% adherence as a threshold for achieving virologic suppression[1]
- ***Limitations of this analysis include the small number of participants in the lower adherence*** subgroup and the difficulty in accurately measuring adherence[2]

Conclusions

- In the GEMINI studies, a lower proportion of participants with <90% adherence achieved HIV-1 RNA <50 c/mL at Wk 48 regardless of regimen
- The impact of lower adherence on virologic response was similar between treatment groups
- These results provide additional information about the robustness of DTG + 3TC compared with 3-drug DTG-containing regimens and suggest similar regimen forgiveness

1. Byrd et al. *J Acquir Immune Defic Syndr*. 2019;82:245-251. **2.** Altice et al. *Patient Prefer Adherence*. 2019;13:475-490.

Real life scenarios where comparative forgiveness of 2DRs and 3DRs still needs to be investigated

- ✓ Naive pts with very high VLs and low CD4+
- ✓ Unavailability of GRT (e.g. rapid HAART)
- ✓ Pregnancy and other PK changes
- ✓ Confirmed or suspected (lack of GRTs) previous selection of resistance mutations (e.g. M184V , INI-R)
- ✓ Subjects at risk of low adherence

Conclusions

- ✓ TAF/TDF (along with FTC) has been considered as a milestone in the evolution of HAART, allowing highly forgiving regimens
- ✓ In the era of increasing use of 2DRs without TAF/TDF , TAF-based 3DRs, however, remain a gold standard in different clinical scenarios
- ✓ In vitro, 3DRs confirmed to be more forgiving as compared to 2DRs, therefore forgiveness of these regimens need to be comparatively evaluated in the clinical setting