Clinical pharmacology of TAF-based regimen

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Disclosures

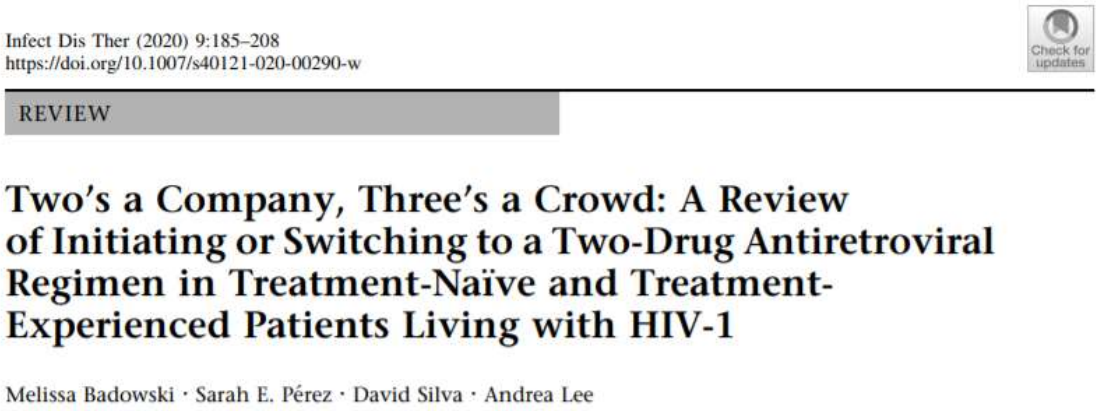
Advisory Boards and/or speaker's fees in last 2 years:

BMS, Gilead, Viiv, Jannssen-Cilag, Abbvie, Angelini, Pfizer

Eagerness on trials data and clinical experience on 2DRs

HIV treatment has evolved from a time where 2DRs were once considered a novel concept to current times where they are a reality.

As 2DRs are reducing the number of medications required to manage HIV, while maintaining durable efficacy, 3DR may no longer remain the standard of care but become ***the antiquated way of the past (!!)***



Infect Dis Ther (2020) 9:185–208
https://doi.org/10.1007/s40121-020-00290-w

Check for updates

REVIEW

Two's a Company, Three's a Crowd: A Review of Initiating or Switching to a Two-Drug Antiretroviral Regimen in Treatment-Naïve and Treatment-Experienced Patients Living with HIV-1

Melissa Badowski · Sarah E. Pérez · David Silva · Andrea Lee

Question 1

Which is the main difference between 2DRs and 3DRs?

The lack of TAF(TDF) in 2DRs!

Question 2

Which was the impact of TAF/TDF on HAART?

TDF availability (along with FTC) has been a milestone of HAART history, making possible a new concept of backbone

A5202: Study Design

HIV-1 RNA ≥1000 c/mL
Any CD4+ count
≥ 16 years of age

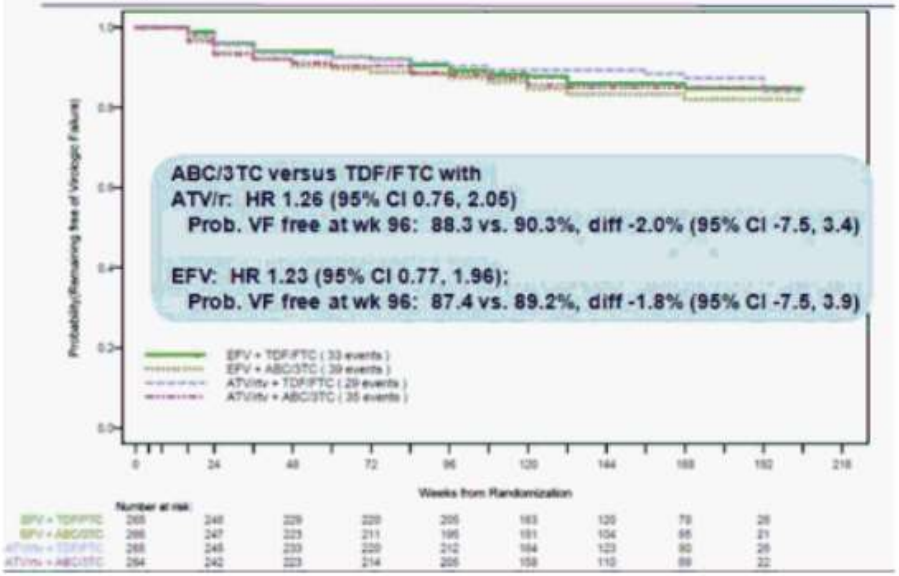
ART-naïve
1857 enrolled
Randomized 1:1:1:1

tratified by screening HIV-1 RNA
(< or ≥ 100,000 c/mL)

Enrolled 2005-2007
Followed through Sept 2009,
96 wks after last pt enrolled

Arm		
A	TDF/FTC QD + ABC/3TC Placebo QD	EFV QD
B	ABC/3TC QD + TDF/FTC Placebo QD	EFV QD
C	TDF/FTC QD + ABC/3TC Placebo QD	ATV/r QD
D	ABC/3TC QD + TDF/FTC Placebo QD	ATV/r QD

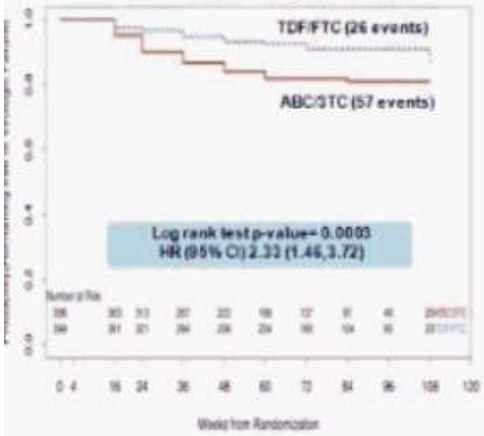
ABC/3TC vs. TDF/FTC
Time to Virologic Failure
(End of Study: Low Viral Load Stratum)



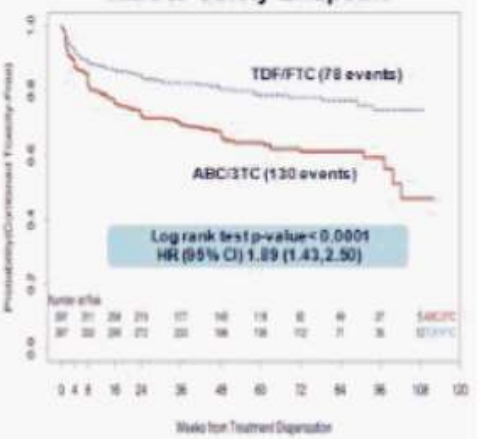
ABC/3TC vs. TDF/FTC
Primary Virologic and Safety Endpoints
(High Viral Load Stratum at DSMB Action)

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

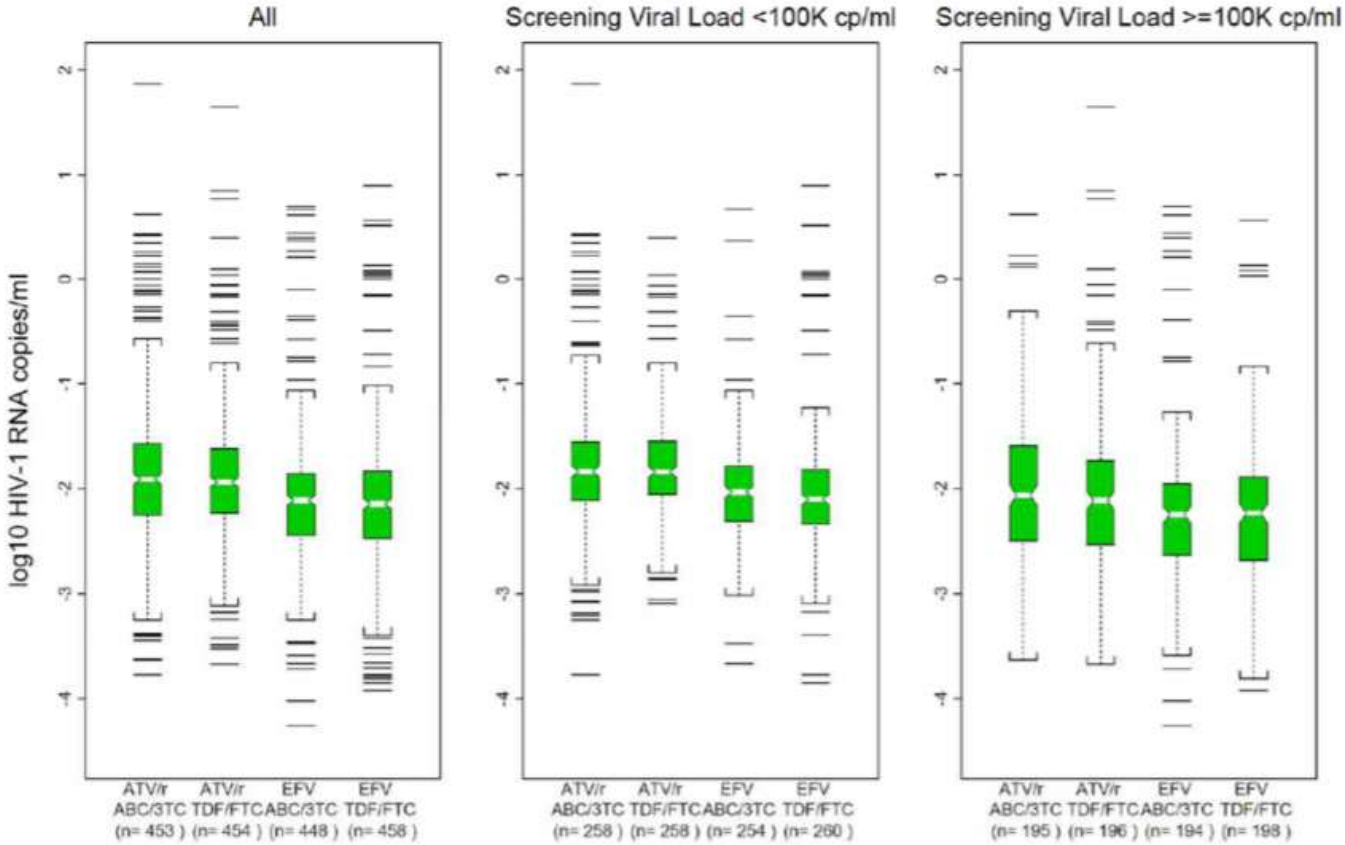
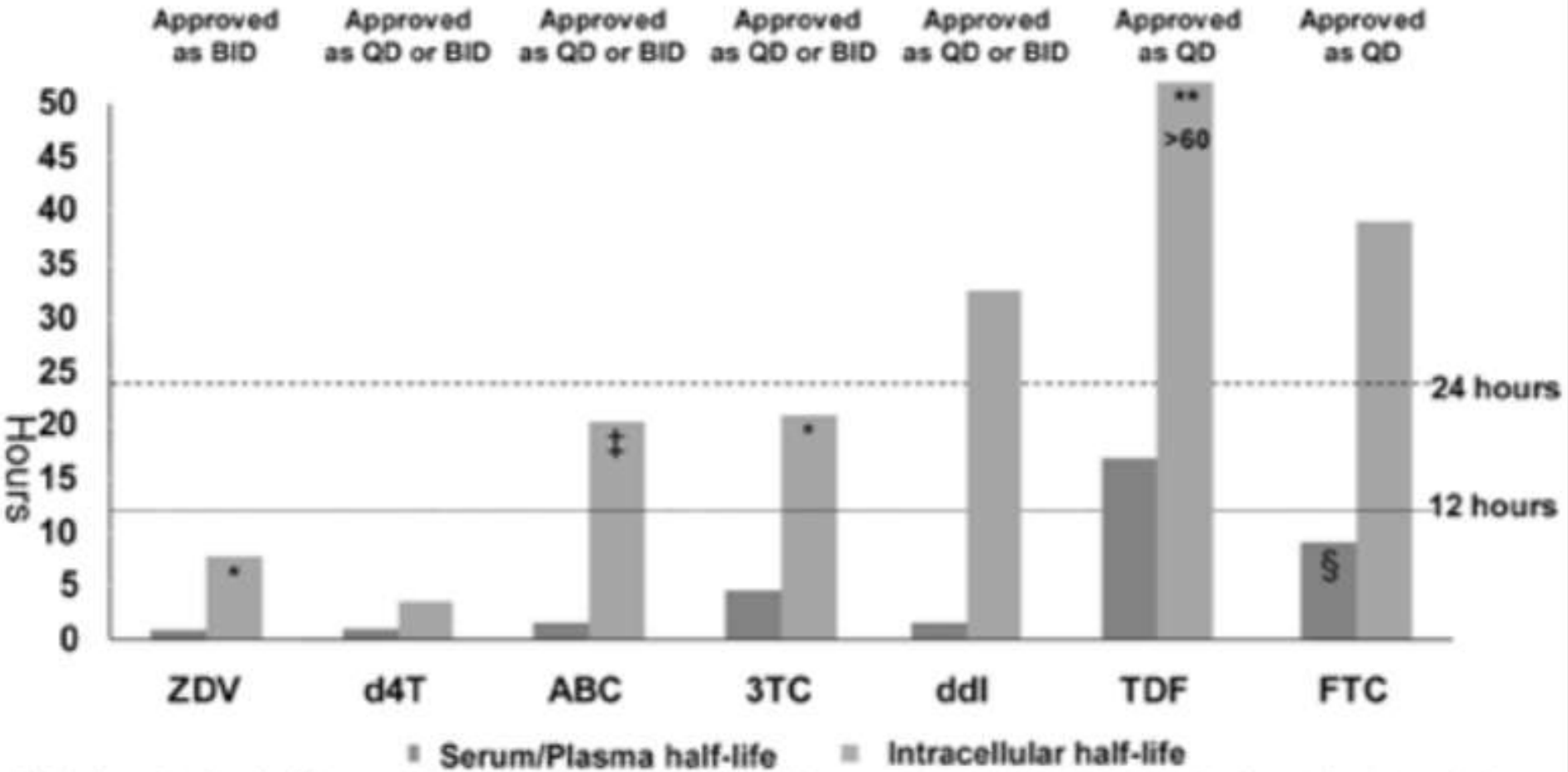


Figure 1.
Box Plot of 4 Week Viral Load Change from Entry by Regimen and Screening Viral Load Strata

The early decline in plasma HIV-1 RNA from baseline **does not appear to explain the difference** in primary efficacy outcomes observed in ACTG A5202 between the NRTIs.

HIV Clin Trials 2013

Cross Study Comparison
Pharmacokinetics of NRTIs

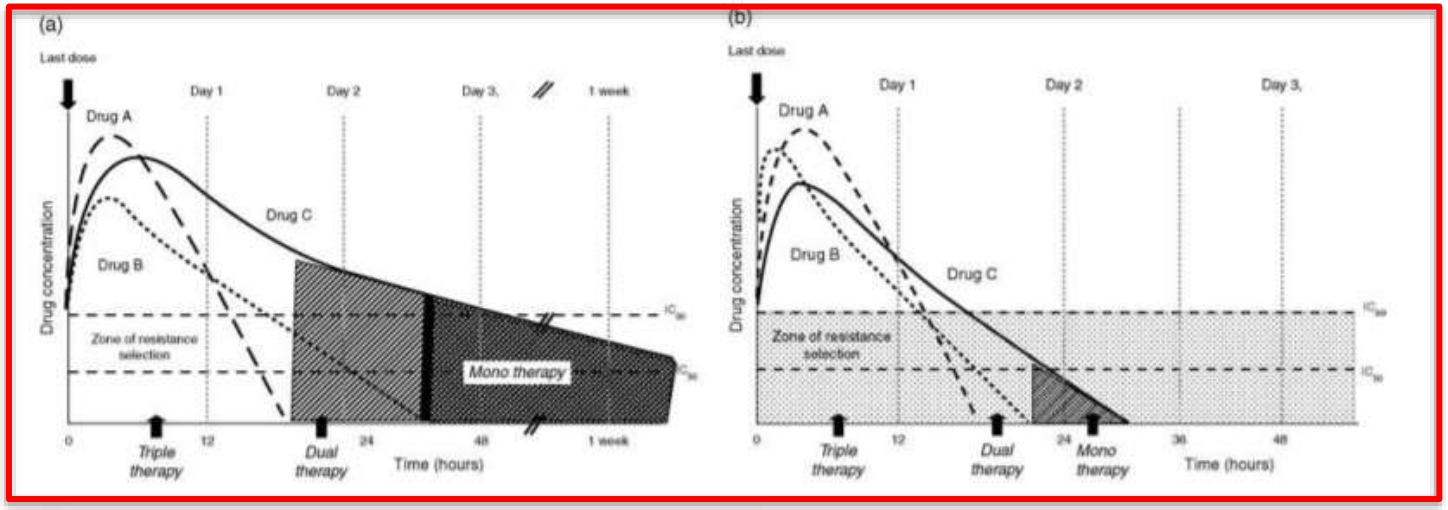


†Data from Centers for Disease Control and Prevention. *MMWR Recomm Rep.* 2002;51(RR-7):1-64 unless otherwise noted
*Anderson et al. AIDS 2003; 17(15):2159-2168. ‡Piliero et al. ICAAC 2003.
**Hawkins et al. 5th IWCPHT 2004 §Wang et al. IAC 2002; #4546.

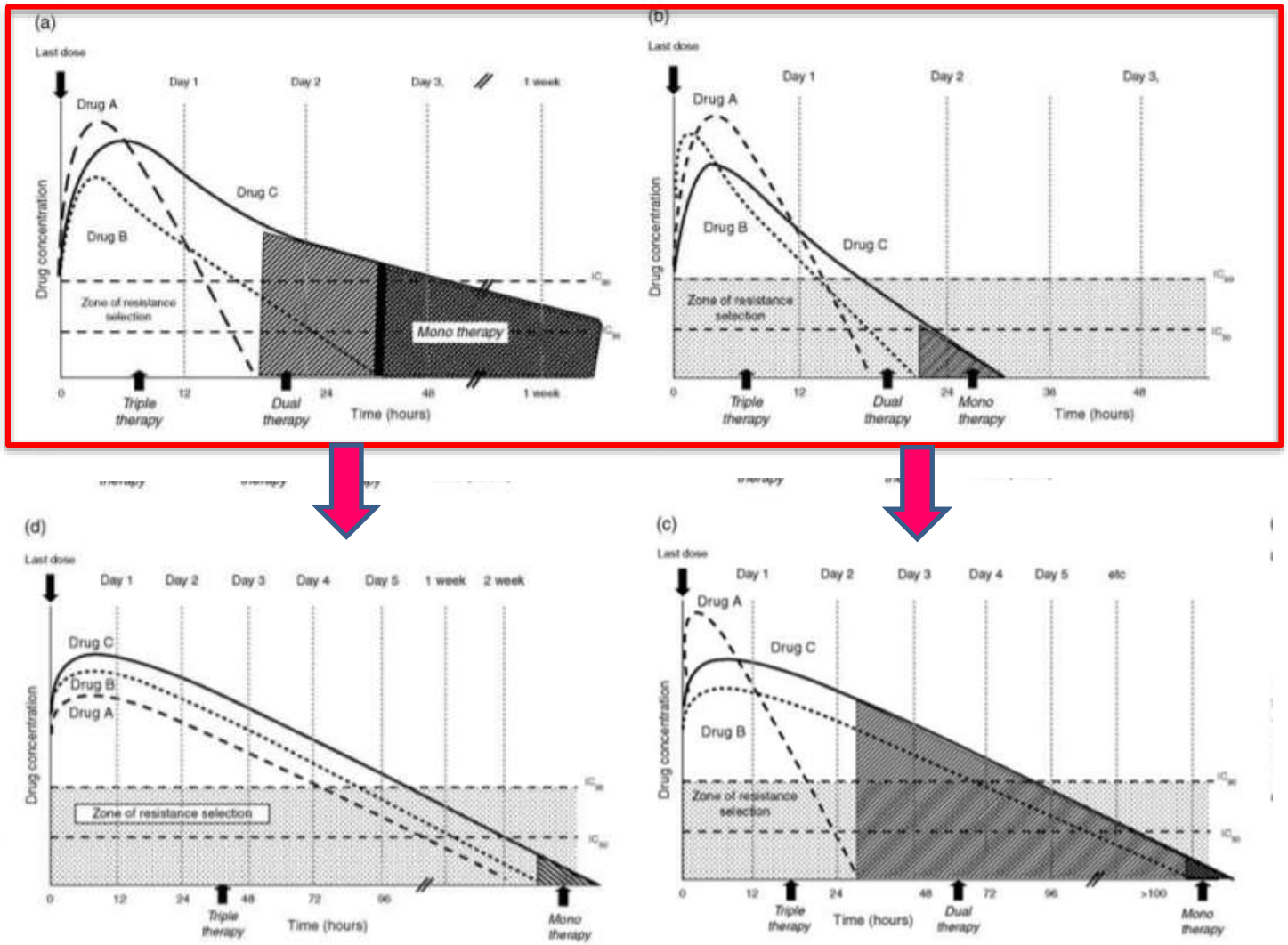
Forgiveness

- 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



Taylor S, AIDS 2007



Taylor S, AIDS 2007

- The long plasma half-lives of FTC, TDF, and EFV (mean t1/2 of 11, 18.5, and 164 hours, respectively), and in particular their consequent dosing **symmetry**, may protect against the emergence of the M184V/I mutation.
- In contrast, 3TC and ZDV have shorter plasma half-lives (0.5–3.0 and 5–7 hours, respectively)

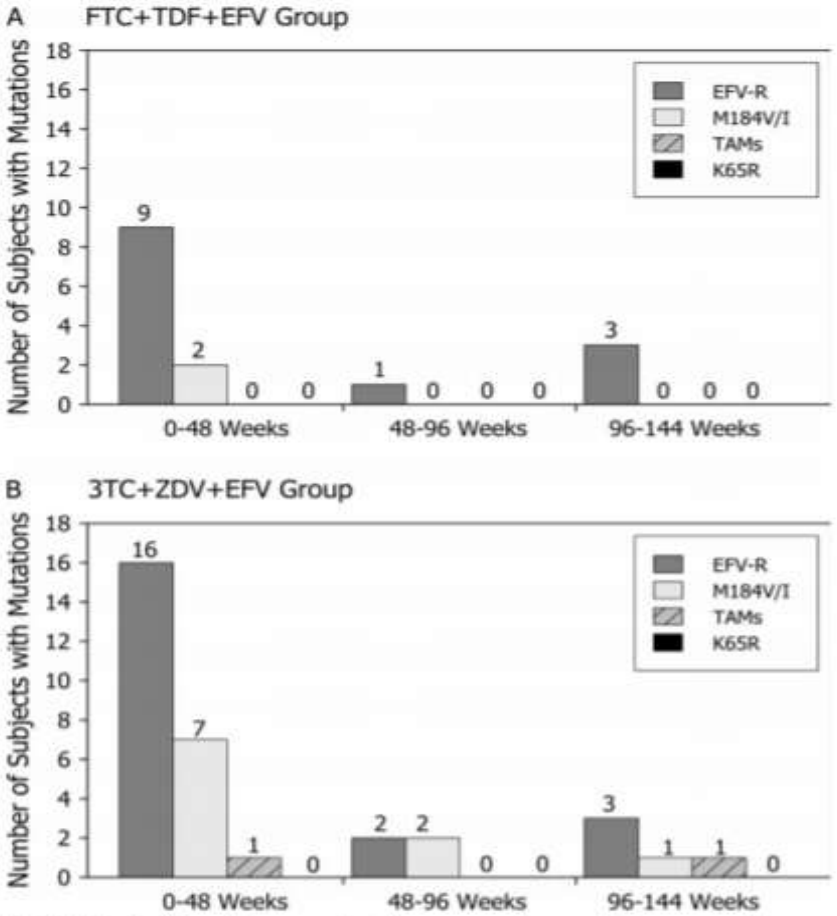
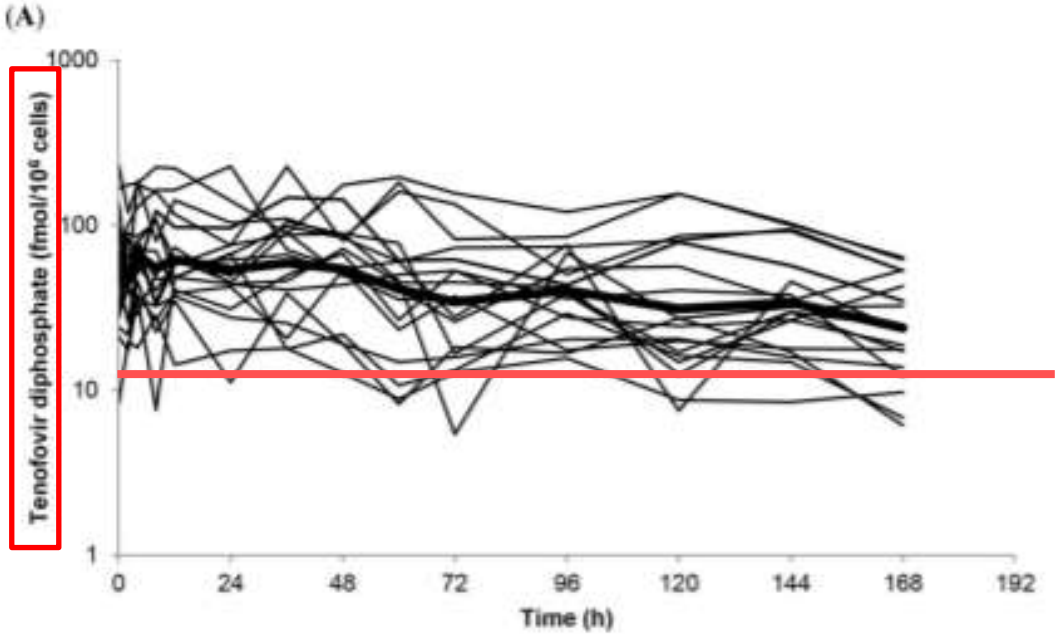


FIGURE 1. Development of reverse transcriptase resistance among subjects receiving either FTC + TDF + EFV (A) or 3TC + ZDV + EFV (B) in Study 934 at Weeks 48, 96, and 144. For each type of RT resistance, the number of cases developing in each time frame is indicated.

Margot et al JAIDS 2009

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

Comparison of HIV Virologic Failure Rates Between Patients with Variable Adherence to Three Antiretroviral Regimen Types

Gordon, AIDS Pat Care and STDs 2015

- Medication possession ratios (MPRs) were calculated to determine adherence, and HIV RNA PCR levels drawn 12-18 months after the initial pharmacy claim for the measured drug were used to determine virologic failure

- Although the gold-standard adherence threshold for older ARV regimens has been 95%, an 80-90% adherence appears sufficient to maintain virologic suppression in patients treated with TDF/FTC containing regimen (EFV, DRV/r, RAL)

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]

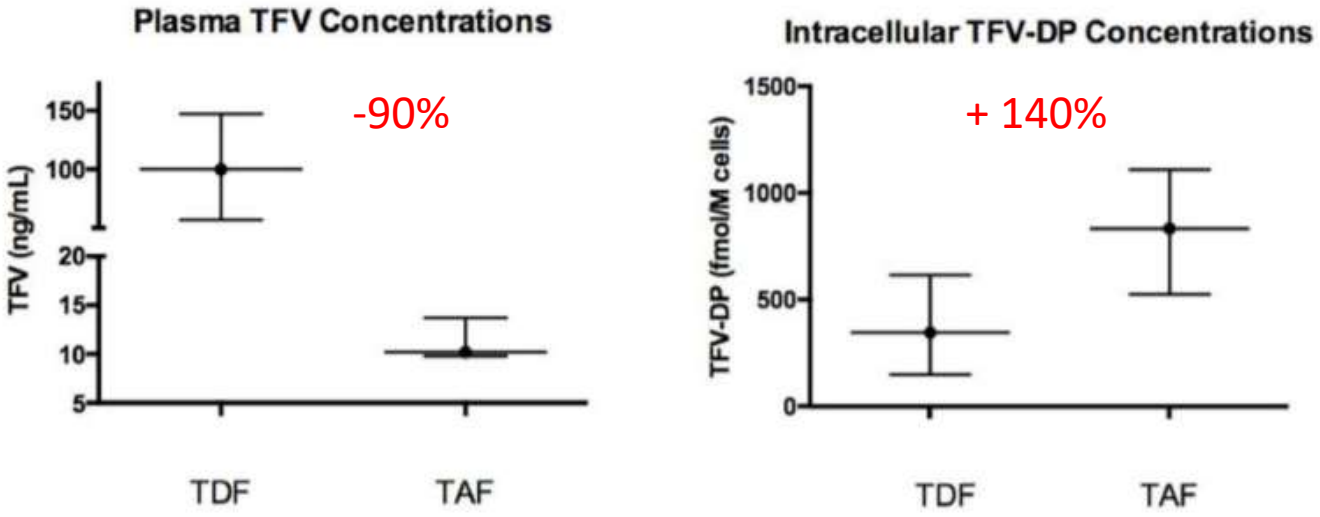


Figure 1.

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

Question 3

Nowadays, do we still need of TAF/TDF-related forgiveness?

DTG and 3TC Have Complementary PK Profiles

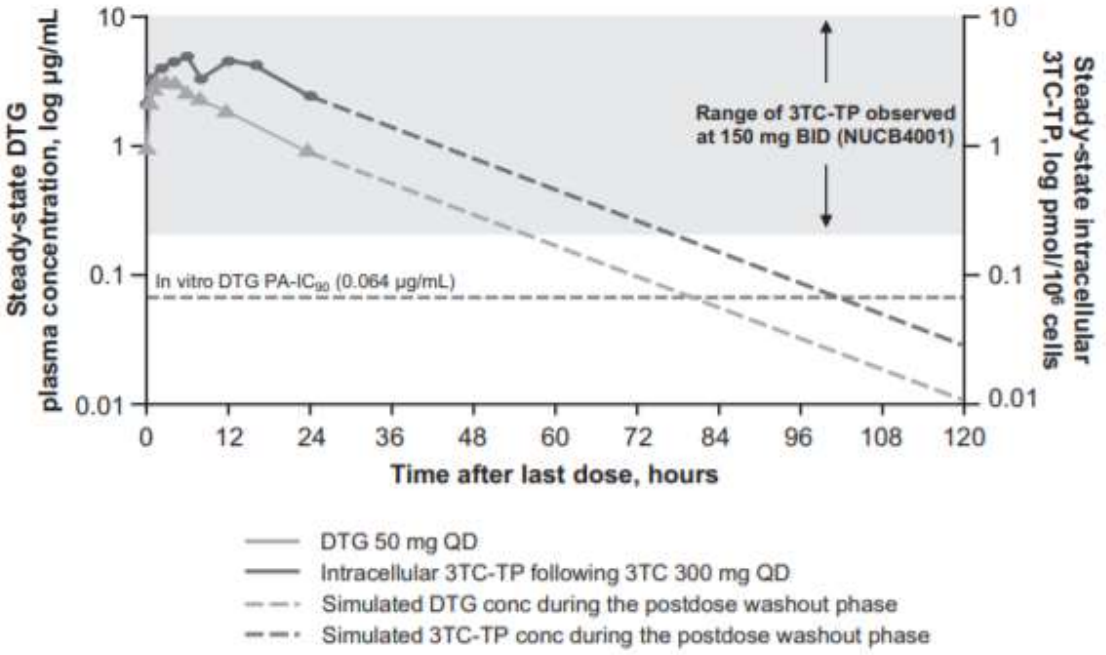


FIG. 1. Steady-state DTG and intracellular 3TC-TP concentration-time profiles after administration of DTG 50 mg or 3TC-TP 300 mg daily.[34,41,42] BID, twice daily; conc, concentration; DTG, dolutegravir; PA-IC_{90}, protein-adjusted 90% inhibitory concentration; QD, once daily; 3TC-TP, lamivudine triphosphate.

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)

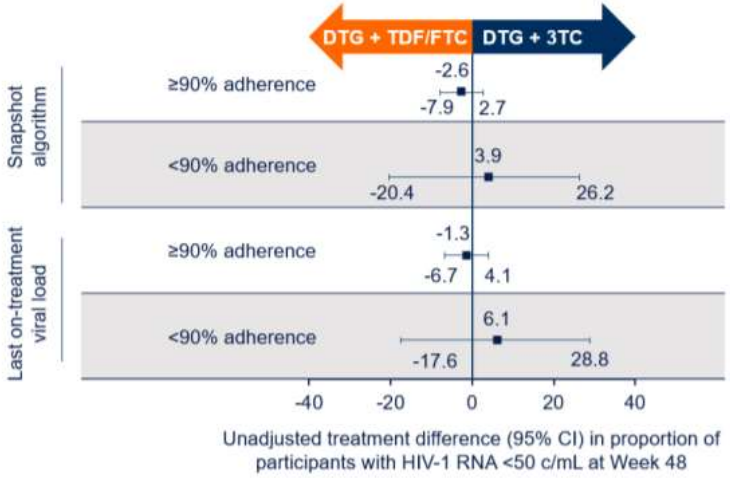
- A high proportion of participants had complete data records for the assessment of treatment adherence
- **In each treatment group, 5% of participants had <90% adherence**
- Demographics and baseline characteristics of participants in GEMINI-1 and -2 were well balanced between treatment groups[1,2]

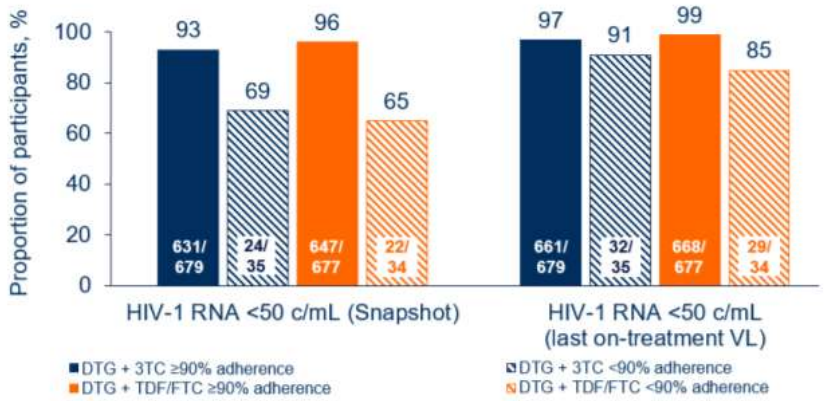
[a]Adherence categories only include participants with derived study drug adherence data.

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	DTG + 3TC		DTG + TDF/FTC	
Outcomes, n (%)	**≥90% (N=679)**	**<90% (N=35)**	**≥90% (N=677)**	**<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

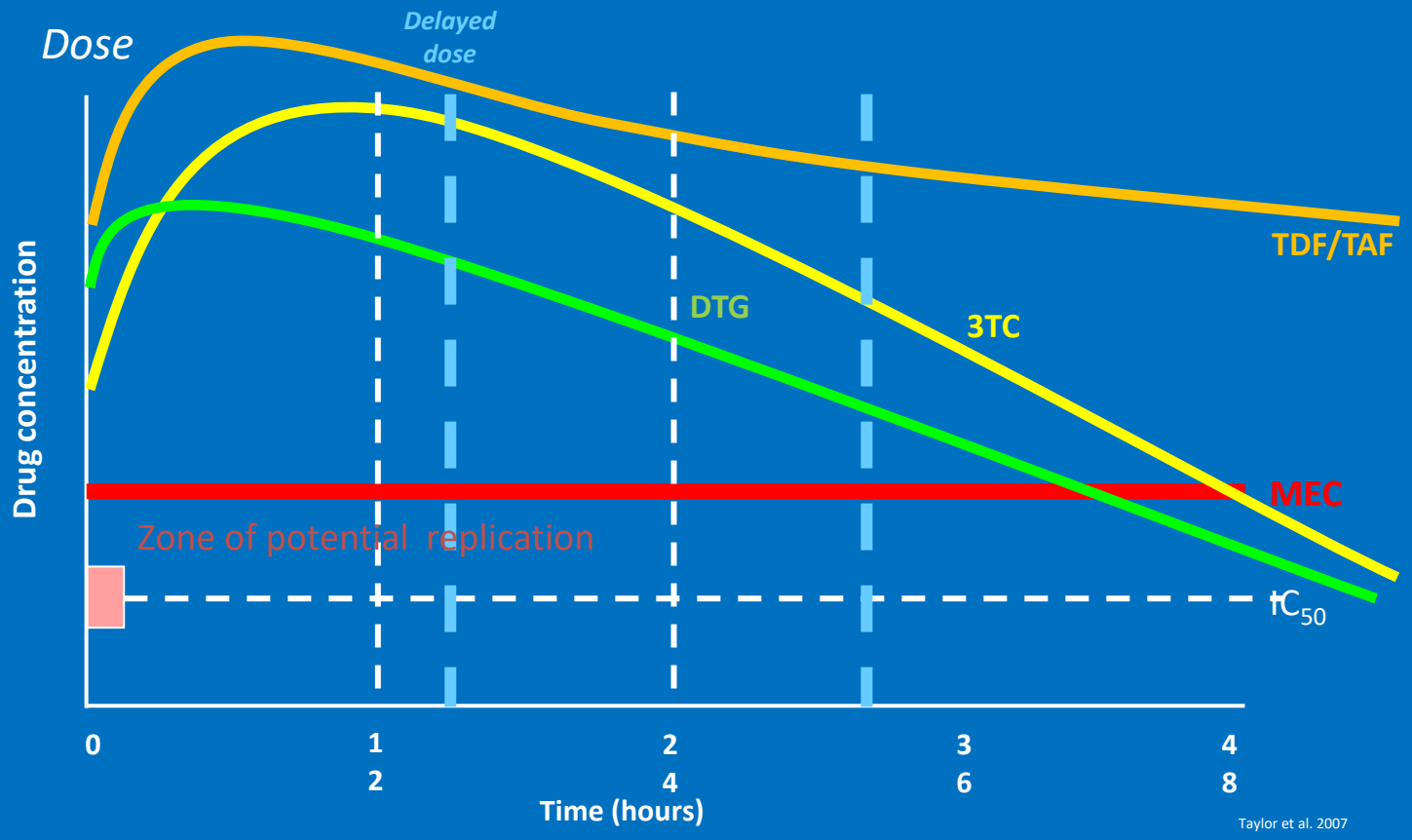
1. Byrd et al. *J Acquir Immune Defic Syndr*. 2019;82:245-251. **2.** Altice et al. *Patient Prefer Adherence*. 2019;13:475-490.

Question 3

Nowadays, do we still need of TAF/TDF-related forgiveness?

Yes!

T/2 & “forgiveness”



Taylor et al. 2007

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

BHIVA
British HIV Association

Initiation of antiretroviral treatment (ART) during the coronavirus pandemic

Suggested first-line ART algorithm if investigations/follow-up restricted

- ART options should still be discussed and, where necessary, tailored according to patient needs and requirements.
  - **Recommended:** bictegravir/tenofovir–alafenamide/emtricitabine (Biktarvy) unless contra-indicated due to:
    - drug-drug interactions.
    - new diagnosis in a pregnant woman (follow BHIVA guidelines).
  - **Alternative:** whichever alternative regimen is clinically appropriate and acceptable to the patient can be used if bictegravir/tenofovir–alafenamide/emtricitabine are unsuitable or not tolerated, based on individual patient characteristics and the capacity of a service to provide advice and monitoring.

In Vitro “Forgiveness” Studies: BIC+FTC+TAF vs DTG+3TC

In Vitro Model Design and Objectives

Objectives

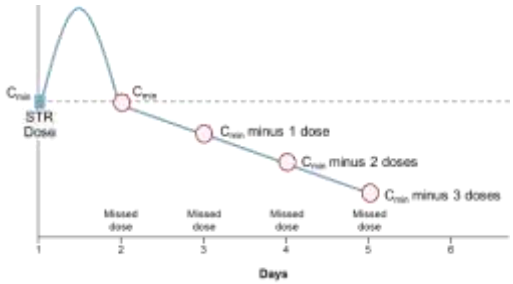
Investigate the BIC + FTC + TAF and DTG + 3TC forgiveness in conditions mimicking optimal or suboptimal adherence

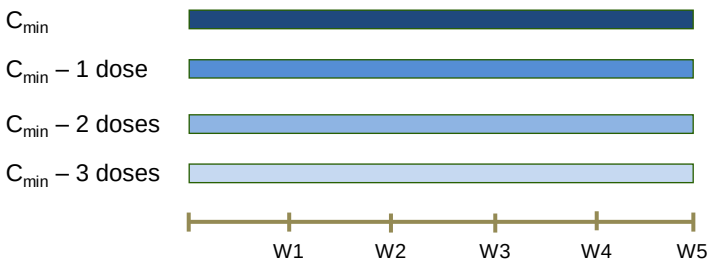
In Vitro Model Design

- Cells infected with either WT or low level M184V virus
- Culture for 5 weeks
- At constant drug concentrations

Assessments

- Viral breakthrough
- Deep sequence supernatant virus (at breakthrough)





Comparative *in vitro* study to answer **3 key questions** :

1. Frequency of breakthrough
2. Speed of breakthrough
3. Consequences of breakthrough*

* Defined as % and type of emergent resistance

WT, Wild Type

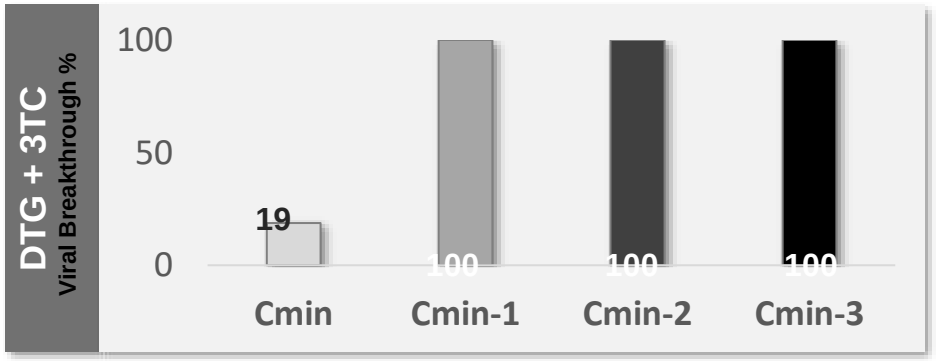
Mulato A, et al. IAS 2019. Mexico City, Mexico. TUPEA103

Frequency of Viral Breakthrough*

In Vitro “Forgiveness” Studies: BIC+FTC+TAF vs DTG+3TC – WT Virus**

Frequency of viral breakthrough with BIC + FTC + TAF

Only in the **lowest** drug concentration tested (Cmin -3)



Frequency of viral breakthrough with DTG + 3TC

At **all** concentrations studied
(Cmin, Cmin -1, Cmin -2, and Cmin -3)

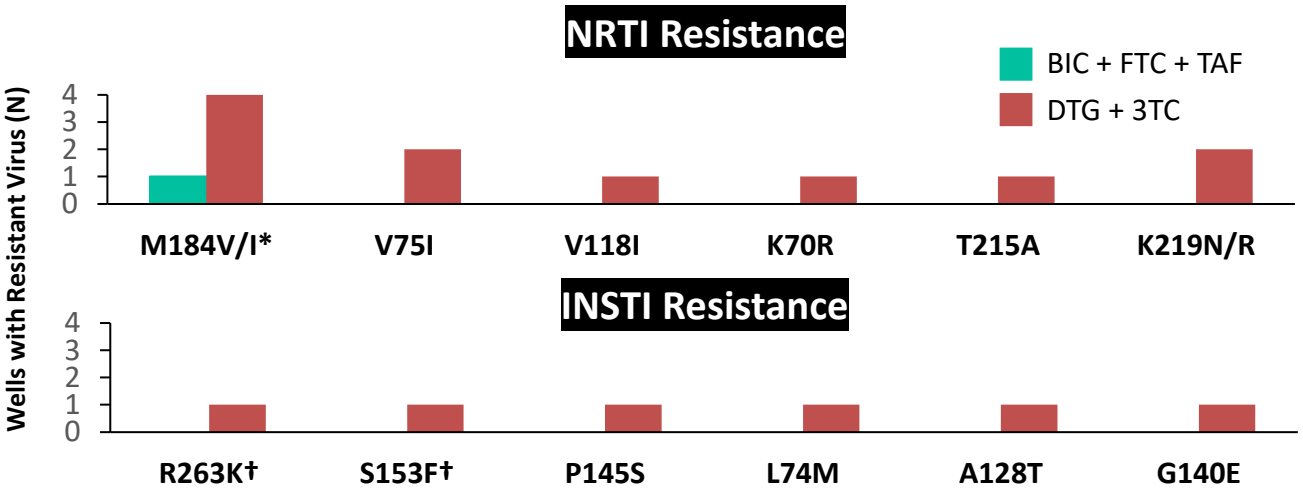
* At the end of the W5 culture; ** HIV IIIb strain

Mulato A, et al. IAS 2019. Mexico City, Mexico. TUPEA103

Analysis with Wild-type HIV-1 (HIV IIIb strain): Emergent Resistance

In Vitro "Forgiveness" Studies: BIC+FTC+TAF vs DTG+3TC

In vitro simulation of B/F/TAF vs DTG+3TC's "forgiveness" (extent of viral breakthrough/rebound and resistance emergence) under sub-optimal drug adherence conditions of up to 3 consecutive missed doses



- More resistance with DTG+3TC (15/144) vs BIC+FTC+TAF (1/144)
- BIC+FTC+TAF: M184V/I occurred once and was in the 3 missed doses experiments

***In vitro* emergent drug resistance was less common with BIC+FTC+TAF compared to DTG+3TC in wild-type HIV**

* M184V and M184I cause high-level resistance to FTC and 3TC and increased sensitivity to TAF
† R263K and S153F have been previously selected by DTG and cause reduced susceptibility to DTG. The well with R263K in IN also had T215A and K219R present.
Mulato A, et al. IAS 2019. Mexico City, Mexico. TUPEA103

‡

Assessing Barrier to Resistance: Viral Breakthrough & Resistance Development

***In vitro* model evaluating viral breakthrough frequency and emergent resistance with drug exposures mimicking full and suboptimal adherence with BIC+FTC+TAF and DTG+3TC**

Constant Levels[1,2]

In Vitro Dosing for Weeks 1-5	N	Breakthrough (%) & Resistance (n)*			
		BIC+FTC+TAF		DTG+3TC	
C_{min}	60	0	0	15%	RT: V118I (T215A+K219R +R263K) IN: P145S
C_{min}-1	36	0	0	67%	RT: K70R
C_{min}-2	60	0	0	90%	RT: M184V/I (4), K219N, V75I (2) IN: L74M, A128T, G140E, S153F
C_{min}-3	36	72%	RT: M184I	100%	IN: L74M, L74M+S153F
C_{min}-4[2]	36	86%	IN: G163R	100%	RT: M184I, T215I IN: M50I

Weekly Alternating Levels[2]

In Vitro Dosing for Weeks 1-5	N	Breakthrough (%) & Resistance (n)*			
		BIC+FTC+TAF		DTG+3TC	
C_{min} constant	12	0	0	0	0
Alternate C_{min} & C_{min}-1	12	0	0	0	0
Alternate C_{min} & C_{min}-2	12	0	0	0	0
Alternate C_{min} & C_{min}-3	12	0	0	58%	RT: M184I (2), V75I
Alternate C_{min} & C_{min}-4	12	0	0	100%	RT: M184I (4)

- **BIC+FTC+TAF demonstrated a high barrier to resistance *in vitro***
- **In contrast viral breakthrough and resistance was observed with DTG+3TC with suboptimal adherence levels**
  - **Levels simulating constant suboptimal adherence and intermittent lapses in adherence**

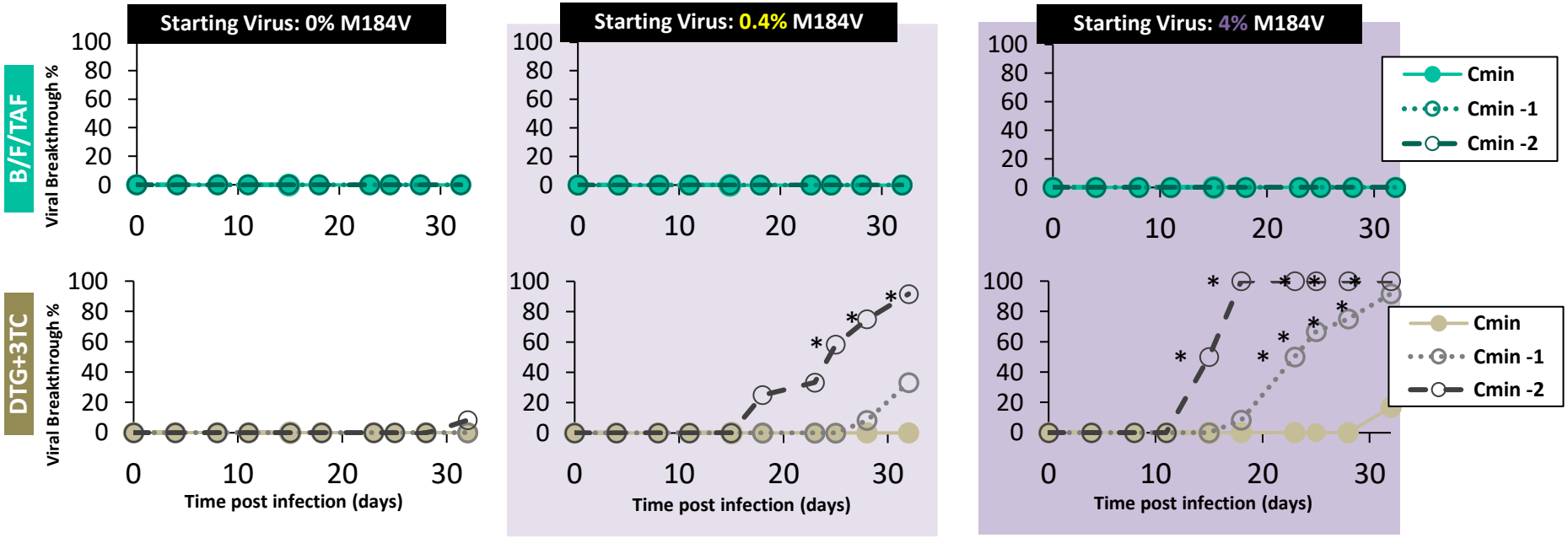
B, bictegravir; D, dolutegravir; F, emtricitabine
*Mutation observed in 1 well unless otherwise noted in brackets

1. Mulato A, et al. IAS 2019. Mexico City, Mexico. Poster TUPEA244. 2. Mulato A, et al. IDWeek 2020, Poster 1448

Analysis with Pre-existing M184V in Inoculum (HIV-1 xxLAI strain): Viral Breakthrough

In Vitro "Forgiveness" Studies: BIC+FTC+TAF vs DTG+3TC

In vitro simulation of B/F/TAF vs DTG+3TC's "forgiveness" (extent of viral breakthrough/rebound and resistance emergence) under sub-optimal drug adherence conditions of up to 3 consecutive missed doses

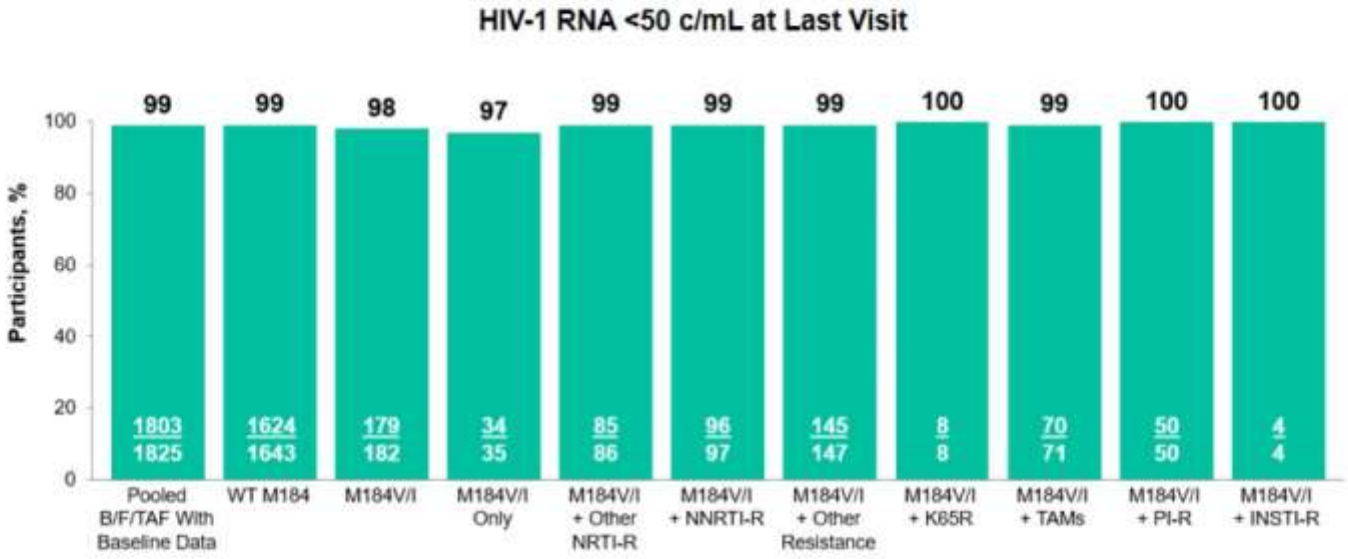


BIC+FTC+TAF had less *in vitro* viral breakthrough compared to DTG+3TC with or without pre-existing M184V in the inoculum

* P-value < 0.05 (Fisher's Exact test, comparing B+F+TAF and DTG+3TC)

Mulato A, et al. IAS 2019. Mexico City, Mexico. TUPEA103

Virologic Suppression by Preexisting M184V/I in Pooled B/F/TAF Group



B/F/TAF was highly effective and durable in virologically suppressed PLWH, including those with known or undocumented M184V/I at baseline

Andreatta K, et al. HIV Drug Therapy 2020. Glasgow. P123

Conclusions

- ✓ TAF/TDF (along with FTC) has been considered as a milestone in the evolution of HAART, allowing once daily dosing and 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

Thank you

Edward Jenner, the pioneer of smallpox vaccine, sees off the anti-vaccinators (1868)