AGIDEI
ASOCIACION GALLEGA PARA LA INVESTIGACION Y DOCENCIA EN ENFERMEDADES INFECCIOSAS

28 de Enero de 2022, Vigo.

El impacto de la robustez de la terapia antirretroviral en la práctica clínica.

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FIGHT AIDS AND INFECTIOUS DISEASES FOUNDATION

Salut/ Germans Trias i Pujol Hospital

Conflictos de interés

He participado en reuniones de consultoría, realizado presentaciones educacionales o recibido becas de investigación de Gilead Sciences, ViiV Healthcare, TheraTechnologies y Janssen Cilag.

Barrera frente a la resistencia: una característica favorable de un régimen en cualquier situación.

"El desarrollo de resistencia a antiretrovirales del VIH es un **efecto adverso en gran parte irreversible**, que condiciona las opciones futuras de tratamiento."

- Con una correcta **elección de la pauta de TAR** podemos minimizar o incluso evitar su aparición.
- **Su importancia a menudo está infravalorada** en guías de TAR y en los propios ensayos clínicos por escasa regulación de las agencias del medicamento en la definición de PDVF, qué muestras y de qué participantes se van a genotipar.

Opinión personal Josep M Llibre

1. ¿Qué es la barrera frente al desarrollo de resistencias de un fármaco/régimen y en que características se basa?.

Barrier to resistance and resistance selection in RCTs

Easily seen, difficult to understand

= Barrier that a treatment exerts against HIV-1 to prevent the development of resistance to the drug/regimen… when virological suppression fails

- **PK/PD Barrier: IQ** (n times C_{min} > EC_{90}), intracellular levels, stable PK, homogeneous PK of components
- **Intrinsic barrier to resistance**: how resistance appears through *in vitro* passage, and impact of every isolated mutation into phenotypic resistance
- **Drug design: Stability of the attachment to the receptor pocket, dissociation rate** (among others)
- **Cross-resistance degree**: Differentiation against common pathways of resistance to others drugs in the class

Clinical data: Triple ART, mono/dual therapy, ART-naïve/switch

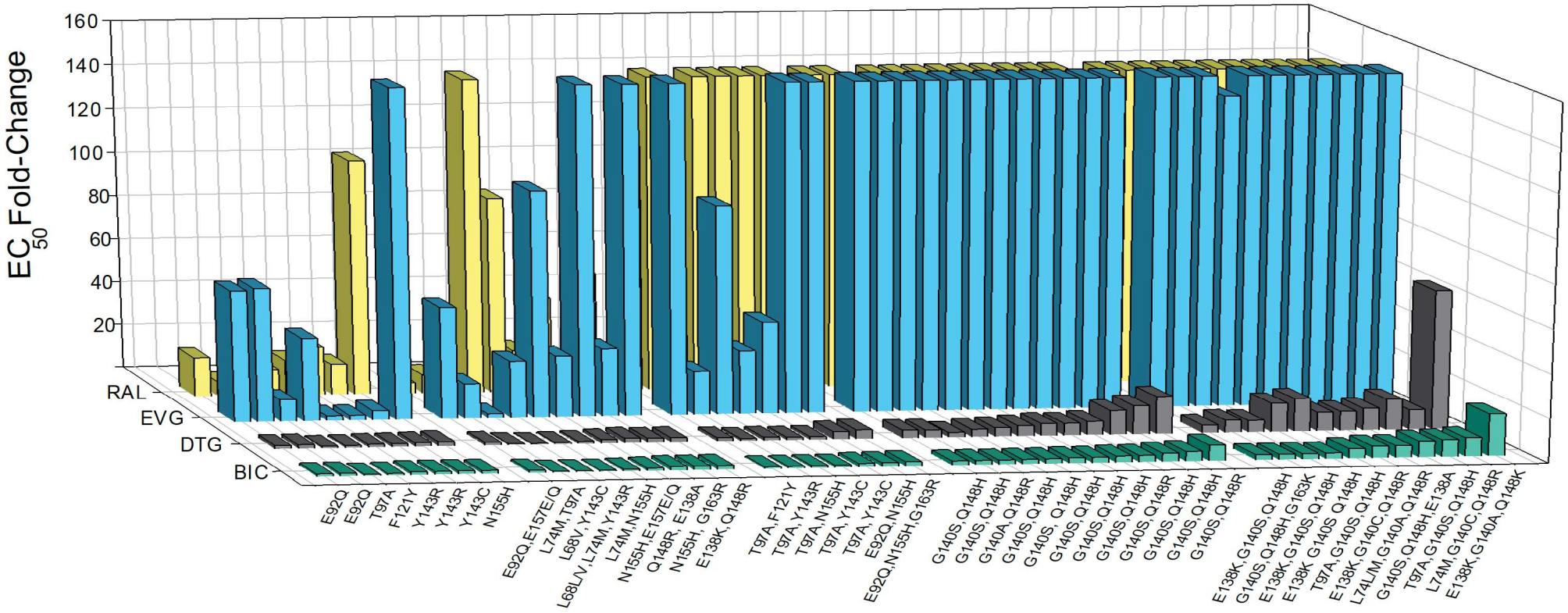
Anyway, resistance with ANY ART is very low in RCTs (<1% at 48 weeks)!

A drug with a very low barrier to resistance can have a high efficacy (i.e. EFV)

C_{min}, minimum concentration; **EC_{90},** 90% maximal effective concentration; **IQ,** inhibitory quotient
PD, pharmacodynamics; **PK,** pharmacokinetics; **RCT,** randomised clinical trial

Llibre JM – Personal Communication

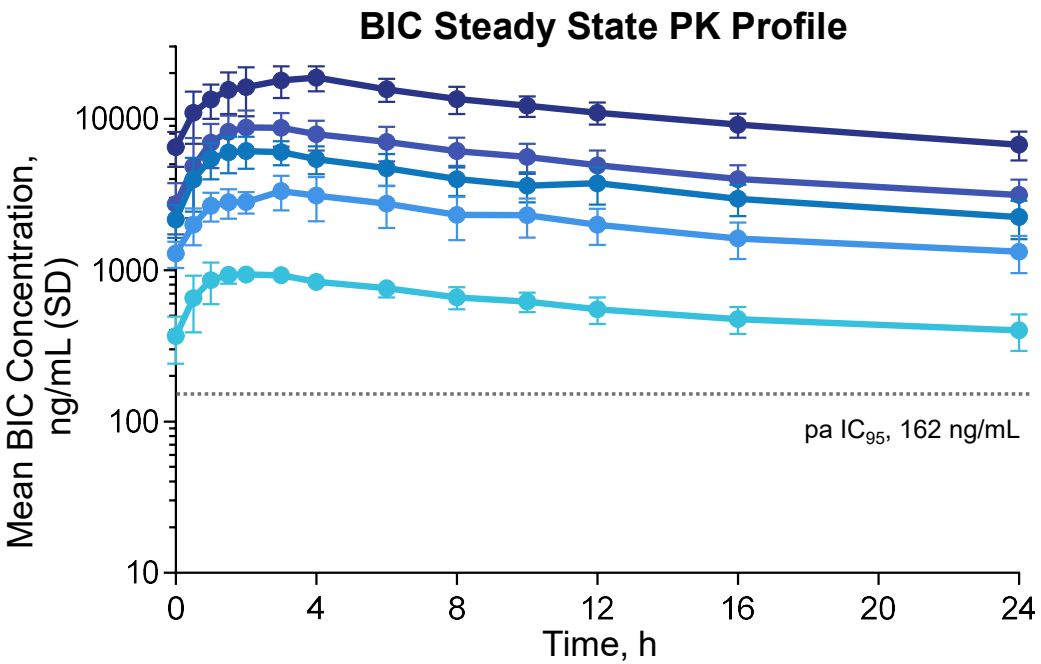
Activity of BIC against Against Patient Isolates with INSTI-Resistance



No single primary INSTI-R or Primary + Secondary INSTI-R display resistance against BIC.
BIC shows improved resistance profile than DTG, RAL, and EVG against a number of patient-derived isolates with high-level INSTI resistance – particularly for E92Q+N155H or Q148R/H/K+G140A/C/S in IN.

K White. 14th European Workshop on HIV & Hepatitis, May 25-27, 2016, Rome, Italy. #P-01. M Tsiang. Antimicrob Ag Chemother 2016; 60:7086 –7097

BIC Pharmacokinetic Profile. Healthy Subjects



	BIC PK Parameters*		
	AUC_T, h·ng/mL	C_T, ng/mL	$t_{½}$, h
300 mg	277,000 (17)	6,760 (22)	18.1 (17.9, 20.5)
100 mg	127,000 (24)	3,150 (26)	18.9 (18.0, 20.0)
50 mg	89,700 (23)	2,240 (28)	16.7 (15.8, 17.1)
25 mg	50,000 (27)	1,320 (28)	18.1 (16.6, 19.6)
5 mg	14,400 (17)	401 (27)	18.5 (16.8, 20.0)

*Data presented as mean (%CV), $t_{1/2}$ median (Q1, Q3).

- **$t_{½}$: ~18 hours**
- **Inhibitory quotient (C_{min}/pa-IC_{95})** for 50 mg: **13.4** (pa-IC_{95}, 162 ng/mL).

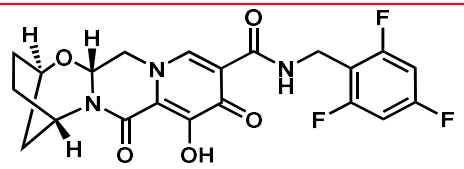
DTG 50 mg: IQ (pa-IC_{90}) **18.7.** [2] **EFV 600 mg**: IQ (pa-IC_{95}) **14**. [3]

1. Gallant J, et al. ASM Microbe 2016, poster PW-030. CROI 2017. J Gallant. J Acquir Immune Defic Syndr 2017;75:61–66). 2. J van Lunzen. Lancet Infect Dis 2012;12: 111–18. 3. EP Acosta. AAC 2012; 56(11): 5938–5945

Bictegravir

Chemical Structure and Profile

Bictegravir



- **Metal-chelating core**
- **2,4,6-trifluorophenyl ring**
- **[3.2.1] oxaza bridging bicyclic side chain**

	RAL	EVG	DTG	BIC
Human Plasma Half-Life	9 hours	8.7 hours	14 hours	18 hours
WT IN-DNA Dissociation Half-life, hours	5.2	1.5	16	38
G140S/Q148H IN-DNA Dissociation Half-life, h	--	--	0.65	2.5
G140S/Q148H Mean Fold Change vs WT	>143	>150	7.6	3.4

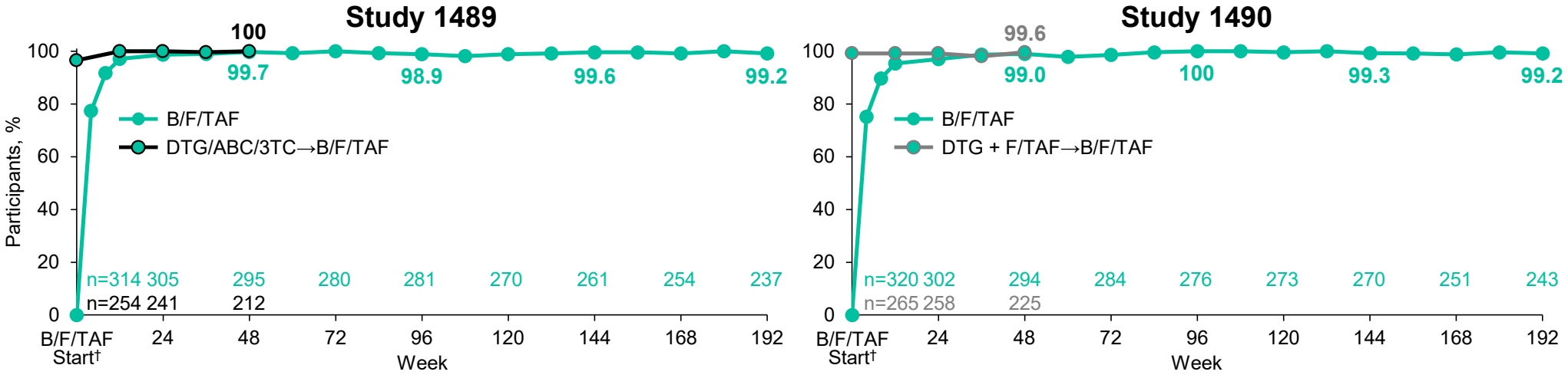
P<0.001

1. Gallant J, et al. ASM 2016. Boston, MA. Poster #415. 2. Isntress US Prescribing Information. Merck & Co. February 2015. 3. Lazerwith SE, et al. ASM 2016. Boston, MA. Poster #414. 4. Tivicay Prescribing Information, ViiV Healthcare. June 2018. 5. Tsiang M, et al., AAC 7. White K, et al. CROI 2017. Seattle, WA. Poster 0893. 8. Zhang H, et al. CROI 2017. Seattle, WA. Oral #40.

Virologic Outcomes Through Week 192 on B/F/TAF

HIV-1 RNA <50 Copies/mL, Missing = Excluded*

K Workowski. CROI 2021 virtual. #2268
RK Acosta. J Antimicrob Chemother 2021; doi:10.1093/jac/dkab115
A Pozniak. 18th European AIDS Conference, October 27–30, 2021, London, UK: Poster PE2/68



*Calculated using US FDA Snapshot algorithm; †B/F/TAF group were treatment-naïve at B/F/TAF start; DTG groups switched from DTG-containing regimens to B/F/TAF.

- Efficacy was >98% after Week 48 at each study visit through Week 192 in both studies for all participants
- HIV-1 RNA <50 copies/mL was maintained in participants who switched from DTG-containing regimens to B/F/TAF at Weeks 144–192

ONCEMRK: Resistance Testing in PDVF

- 6.8% of subjects in each treatment group had PDVF (VL >40 c/mL X 2)
- **Resistance testing required VL at least 500 c/mL.**
  - RAL QD group: 14 subjects tested, 9 had no resistance or failed testing (…n=
    - 5 (0.9%) had documented resistance (including RAL resistance in 4)
    - All with CD4 <200 cells, most with VL >100.000 c/mL.

	Failure Type/Time	RAL	FTC	TDF	Comments
1	NR / wk 24	V151I, N155H	M184V	-	
2	NR / wk 24	N155H	M184M/I/V	-	BL RNA >10^6, CD4 <20 Resistance test wk 48
3	NR / wk 24	L74M, E92Q	M184V	-	BL RNA >10^6, CD4 <20
4	RB / wk 16	N155H, I203M	M184V	-	Resistance test wk 36
5	RB / wk 24	-	V118I, M184M/I/V	-	Resuppressed

NR = non-response, RB = rebound.

  - RAL BID group: 3 subjects tested – 2 had no resistance; 1 failed all testing

Resistance rates in other large RAL BID studies (STARTMRK, ACTG 5257): 2-3% for any resistance and 1.4-1.8% for Integrase resistance.

P Cahn. Lancet HIV 2017; http://dx.doi.org/10.1016/S2352-3018(17)30128-5

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

Update 3 June 2021

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

1

Changes Since the Last Revision of the Guidelines

Since the last revision of these guidelines, the Panel has made several important changes to the recommendations for initial therapy in people with HIV. Among these changes, the following deserve emphasis:

- Raltegravir (RAL), in combination with FTC or 3TC and TDF or TAF, is now recommended as an *Initial Regimen in Certain Clinical Circumstances*. This change is made primarily because RAL has a lower barrier to resistance than DTG or bictegravir (BIC), it is not part of any single-tablet regimen (STR), and RAL-containing regimens have a higher pill burden than those containing DTG or BIC.

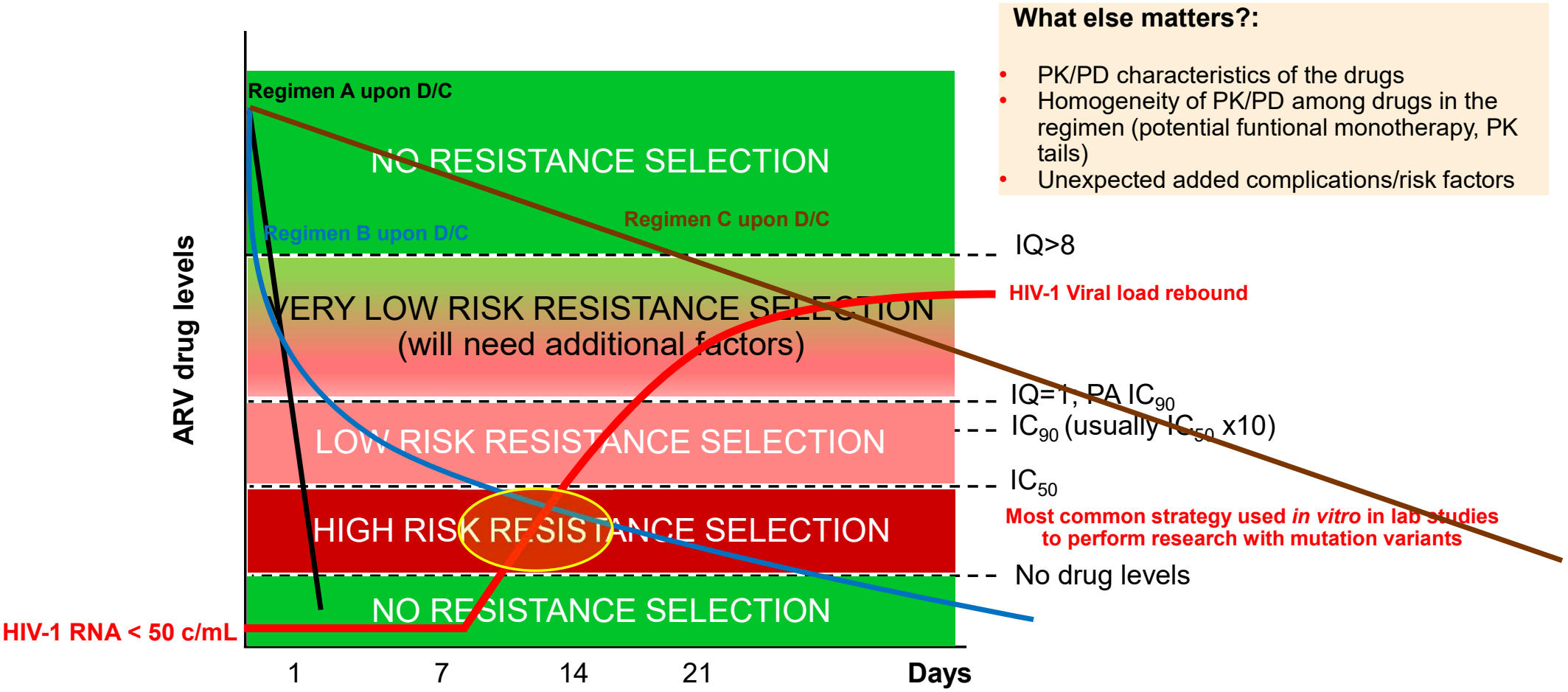
2

IAS-USA October 2020: Raltegravir-containing regimens have a higher pill burden (3 pills per day) and a lower barrier to resistance. JAMA 2020; doi:10.1001/jama.2020.17025.

Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf

2. ¿Qué aportan los datos *in vitro*?

Resistance selection: Everything relies on the **IQ (Drug levels/MIC),** the mutational potential of a given microorganism and the impact of every mutation



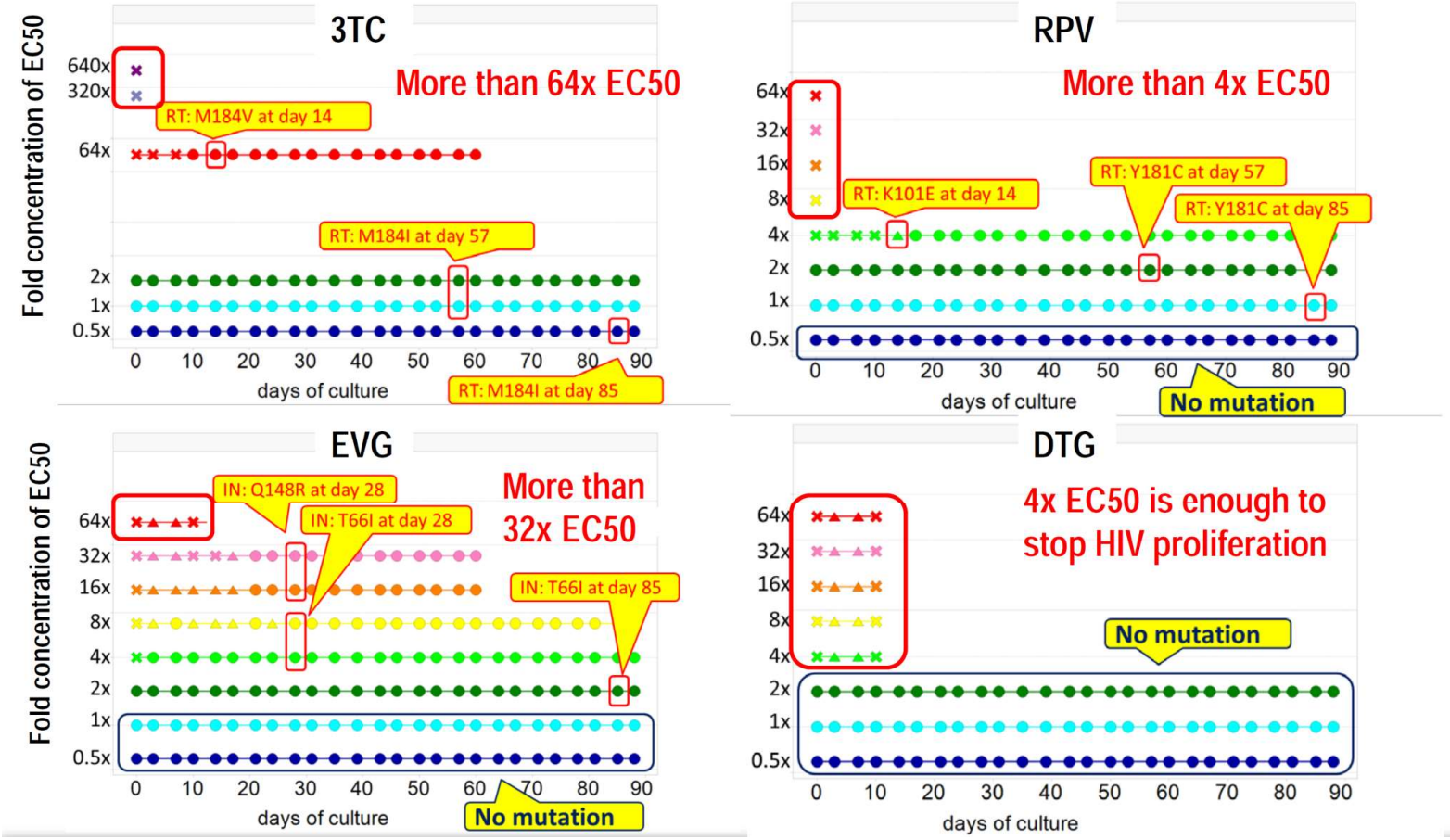
What else matters?:

- PK/PD characteristics of the drugs
- Homogeneity of PK/PD among drugs in the regimen (potential funtional monotherapy, PK tails)
- Unexpected added complications/risk factors

Josep M Llibre. Personal communication

• Passage under constant drug concentrations through 85 days on MT-2 cells and NL432 Virus.

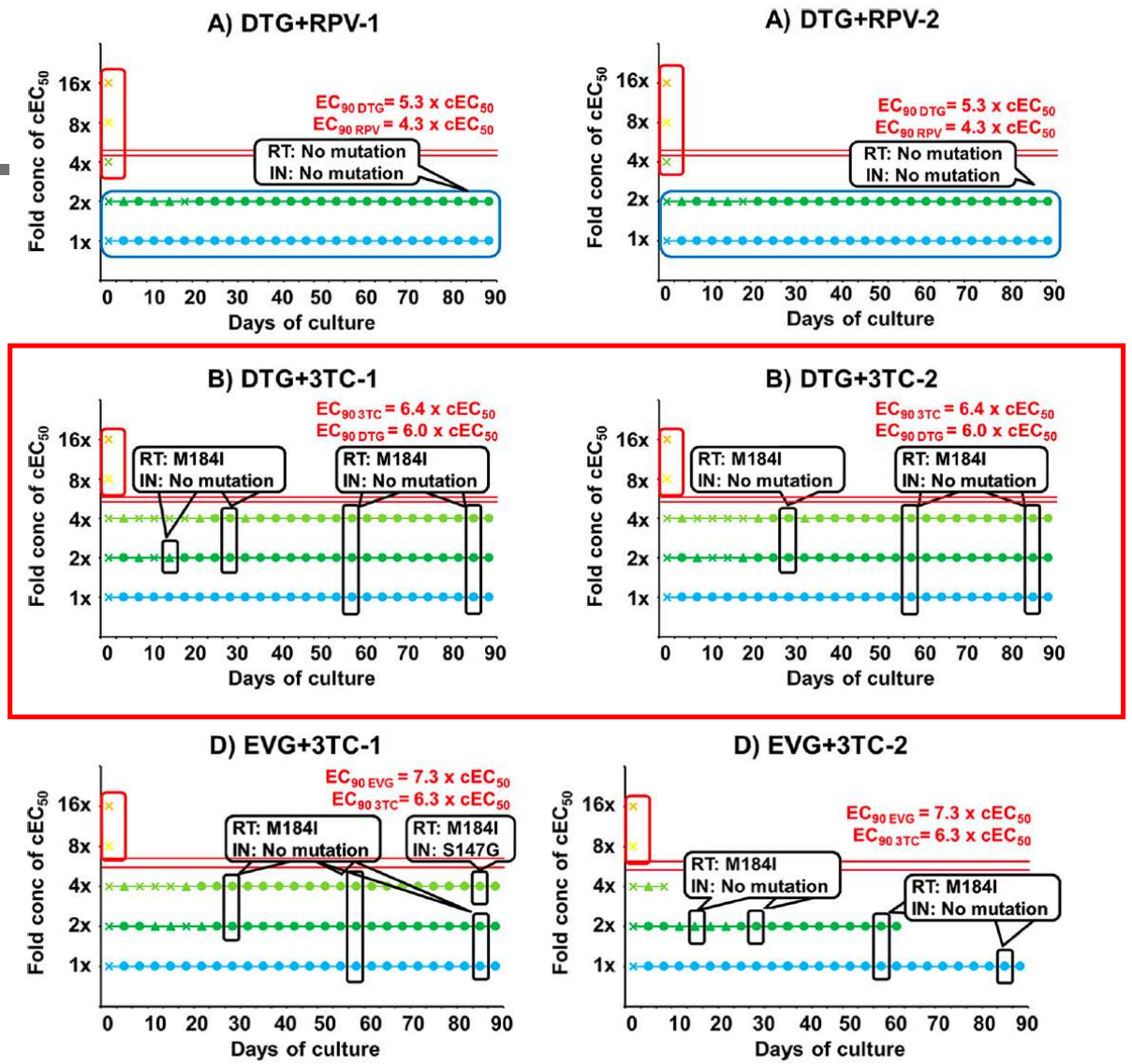
Passage results of single compounds



Yoshinaga T. 13th Eur Meeting on HIV & Hepatitis - Treatment Strategies & Antiviral Drug Resistance. June 2015. Barcelona, Spain. T Yoshinaga. AAC 2019; 63(3): e02104-18

Passage of dual compounds

Duplicate Wells reported separatelly (-1 and -2)

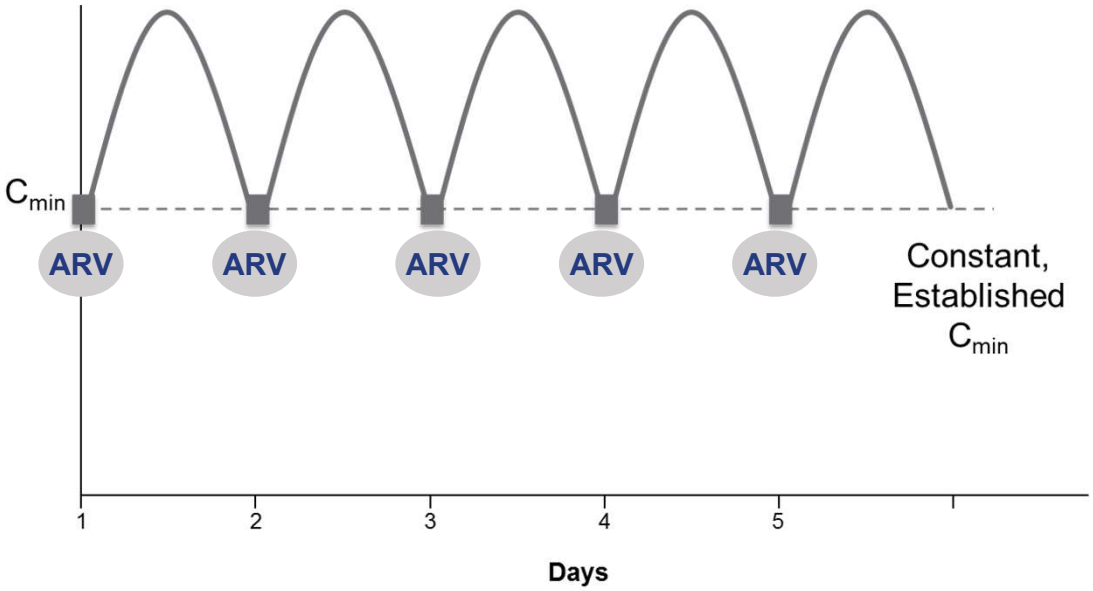


T Yoshinaga. Antimicrob Agents Chemother 2019; 63(3): e02104-18

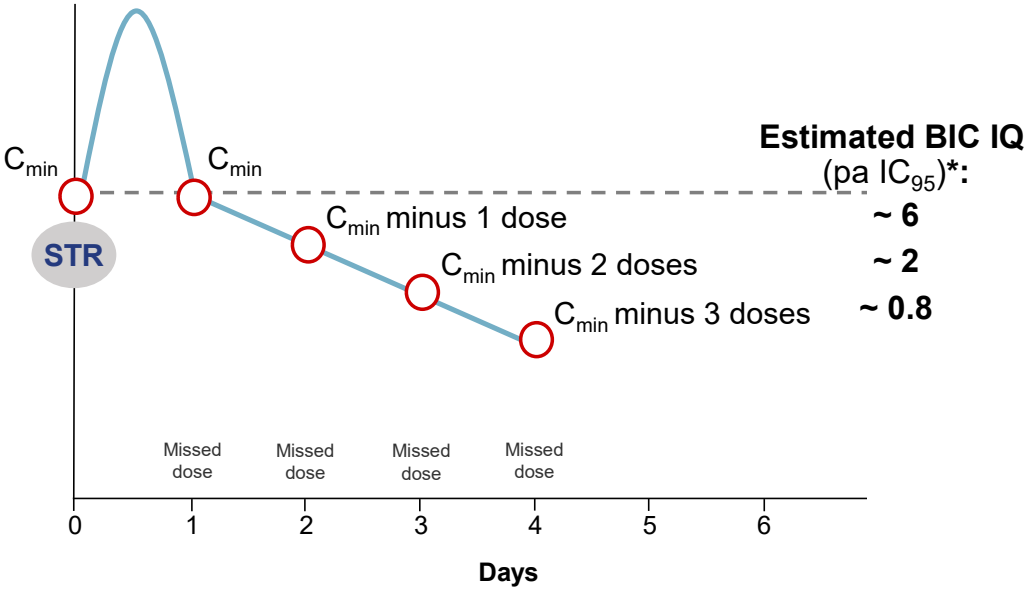
Exploring the antiviral activity at low drug *in vitro* concentrations

- Missing ARV doses results in a predictable decrease of systemic exposures to each drug in the regimen based on its established clinical half-life ($t_{1/2}$)

Optimal Adherence

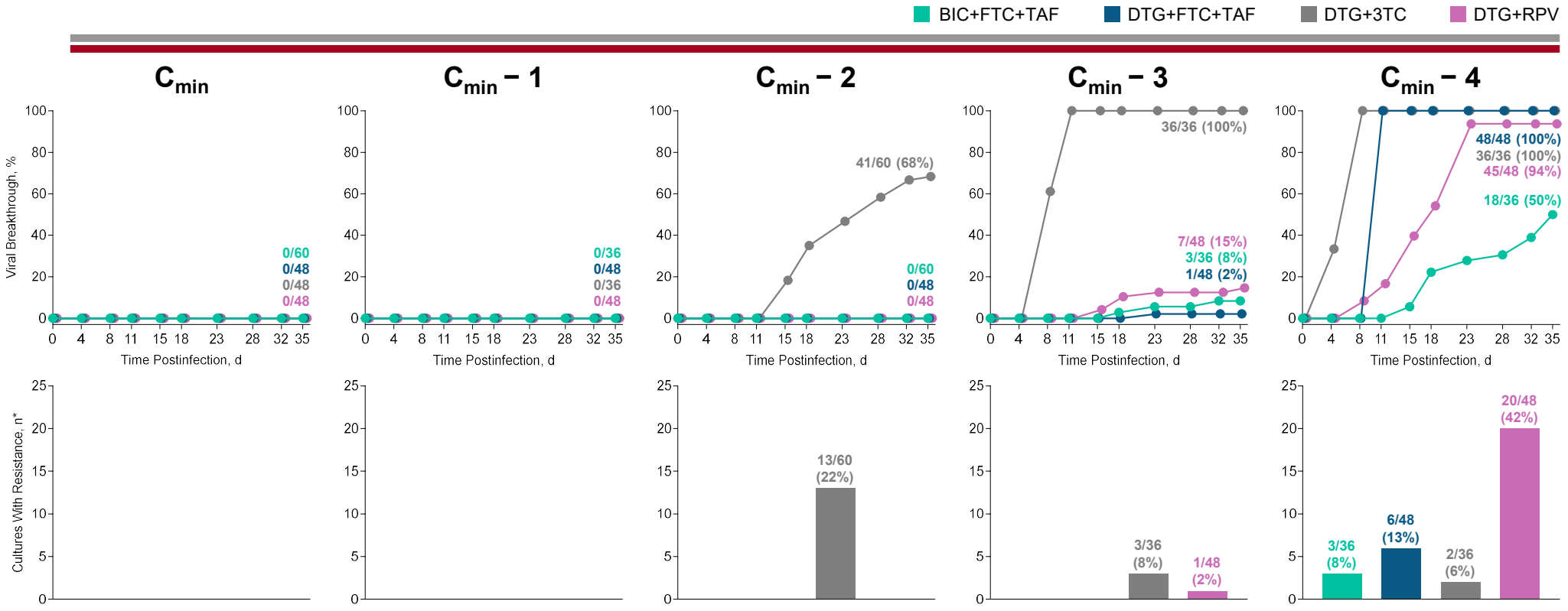


With 1 – 3 Consecutive Missed Doses



Mulato A. et. al. IDweek 2020 Poster 1448. *JM Llibre personal communication, based on BIC Cell Culture Drug Concentrations used reported at: A Mulato. J Acquir Immune Defic Syndr 2021;86:369–377.

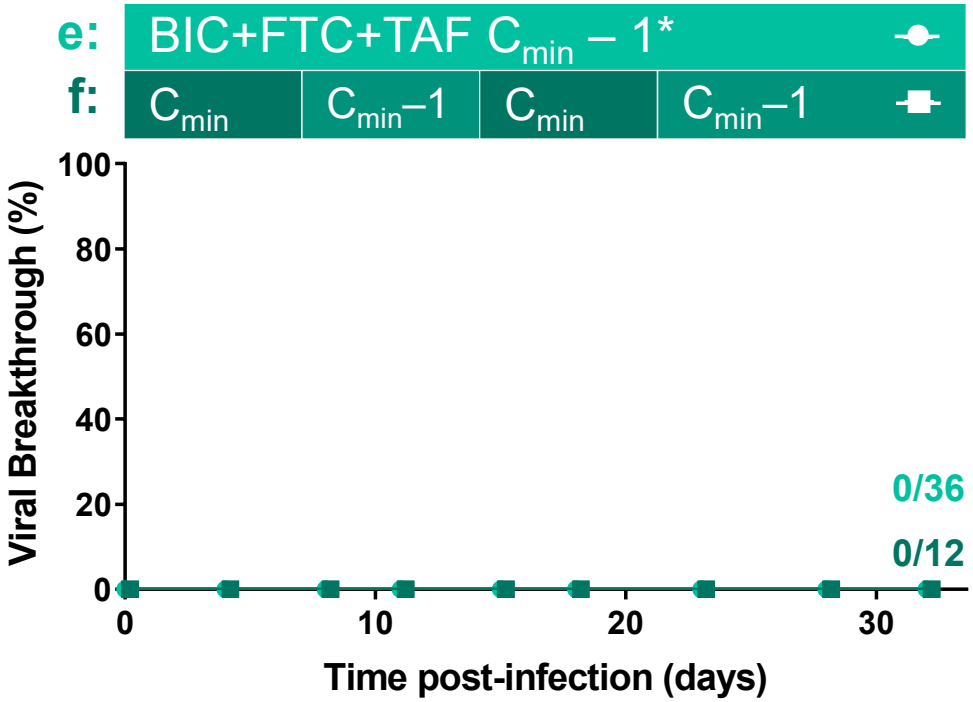
Results: Time to Viral Breakthrough with low drug concentrations.

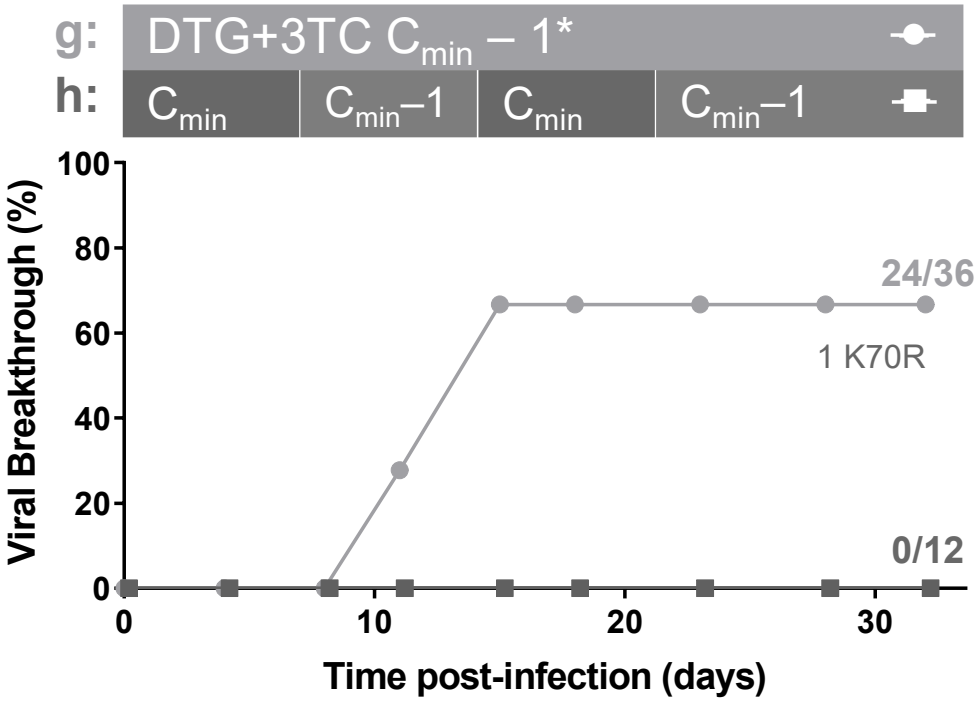


Emergent Resistance Substitutions	C_{min}	$C_{min}-1$	$C_{min}-2$	$C_{min}-3$	$C_{min}-4$
RT			4 M184V/I 3 V75I	1 M230I	2 M184I 1 K219R 2 M230I 3 K101E 1 H221Y 4 E138K 1 V90I 1 V90I+V106I+E138K
IN			1 L74M 2 G140E/R 1 S153F 2 E157K	1 V72A 1 L74M 1 L74M+S153F	1 G163R 1 H51Y 1 S153F 2 Q148R 1 R263K 1 L74M +R263K 1 R263K 1 M50I 1 S153F 1 G163R
RT+IN					1 M184V(RT) +Q95R(IN) 1 Y181C(RT)+H51Y(IN) 1 E138K(RT)+H51Y(IN) 1 E138K(RT)+Q95R(IN) 1 E138K(RT)+A128T(IN)

RK Acosta. IDWeek 2021 Virtual Conference, Sep 29 – Oct 3, 2021: Poster 888

PK mimicking every other day non-adherence
Time to Viral Breakthrough: C_{min} – 1, Constant and Alternating

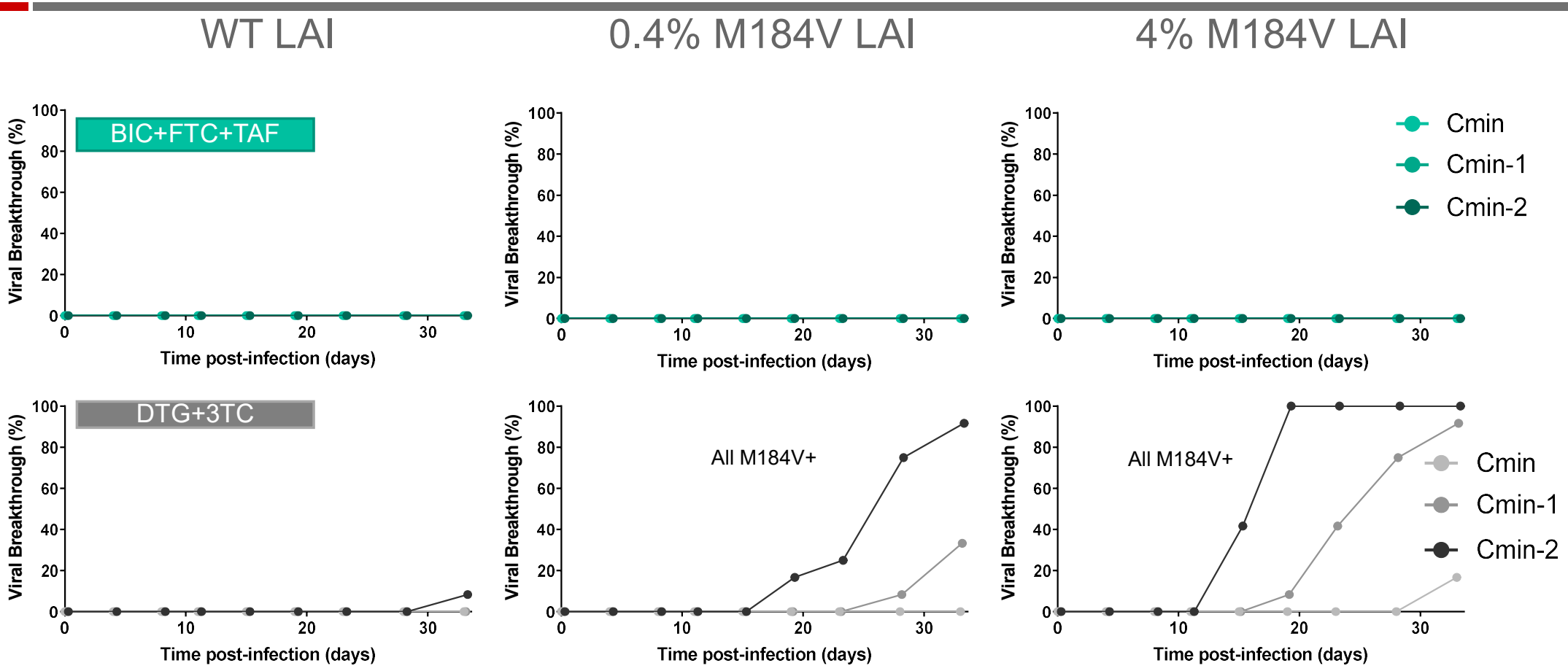




1 K70R in RT

A Mulato. ID Week 2020, virtual, October 21-25, 2020. #1448.

Time to Viral Breakthrough: impact of Low Level M184V



Mulato A. et. al. J Acquir Immune Defic Syndr. 2021 Mar 1;86(3):369-377

3. ¿Qué importancia tiene la barrera frente al desarrollo de resistencias de un régimen en un *switch*?. Datos clínicos.

Prevalence and Risk Factors for Pre-existing M184V/I

Pooled analysis on prevalence and risk factors for pre-existing M184V/I among virologically suppressed clinical trial participants and the impact of pre-existing M184V/I on virologic outcomes after switching to B/F/TAF (n=1545)

- Of the 132 participants with M184V/I detected, 77% had other resistance mutations

M184V/I with Other Mutations (N=101)	
+ NNRTI-R	52%
+ Other NRTI-R	47%
+ TAMs	40%
+ PI-R	20%
+ Primary INSTI-R*	4%

Risk Factors for Pre-Existing M184V/I†	OR (95% CI)	p-value
History of Non-M184V/I NRTI resistance	4.6 (2.9, 7.3)	< 0.001
History of NNRTI resistance	2.8 (1.9, 4.2)	< 0.001
Black race (vs non-Black)	2.6 (1.7, 4.0)	< 0.001
History of PI resistance	1.9 (1.1, 3.3)	0.029
CD4 <500 cells/μL (vs ≥500)	1.6 (1.0, 2.4)	0.035
Hispanic ethnicity	1.8 (1.1, 3.0)	0.014
HIV status: symptomatic or AIDS (vs asymptomatic)	1.7 (1.1, 2.8)	0.024
Time since ART start (per year)	1.1 (1.1, 1.1)	< 0.001

M184V/I at baseline was associated with resistance (non-M184V/I NRTI, NNRTI, or PI), Black race, CD4 count <500 and a longer ART duration

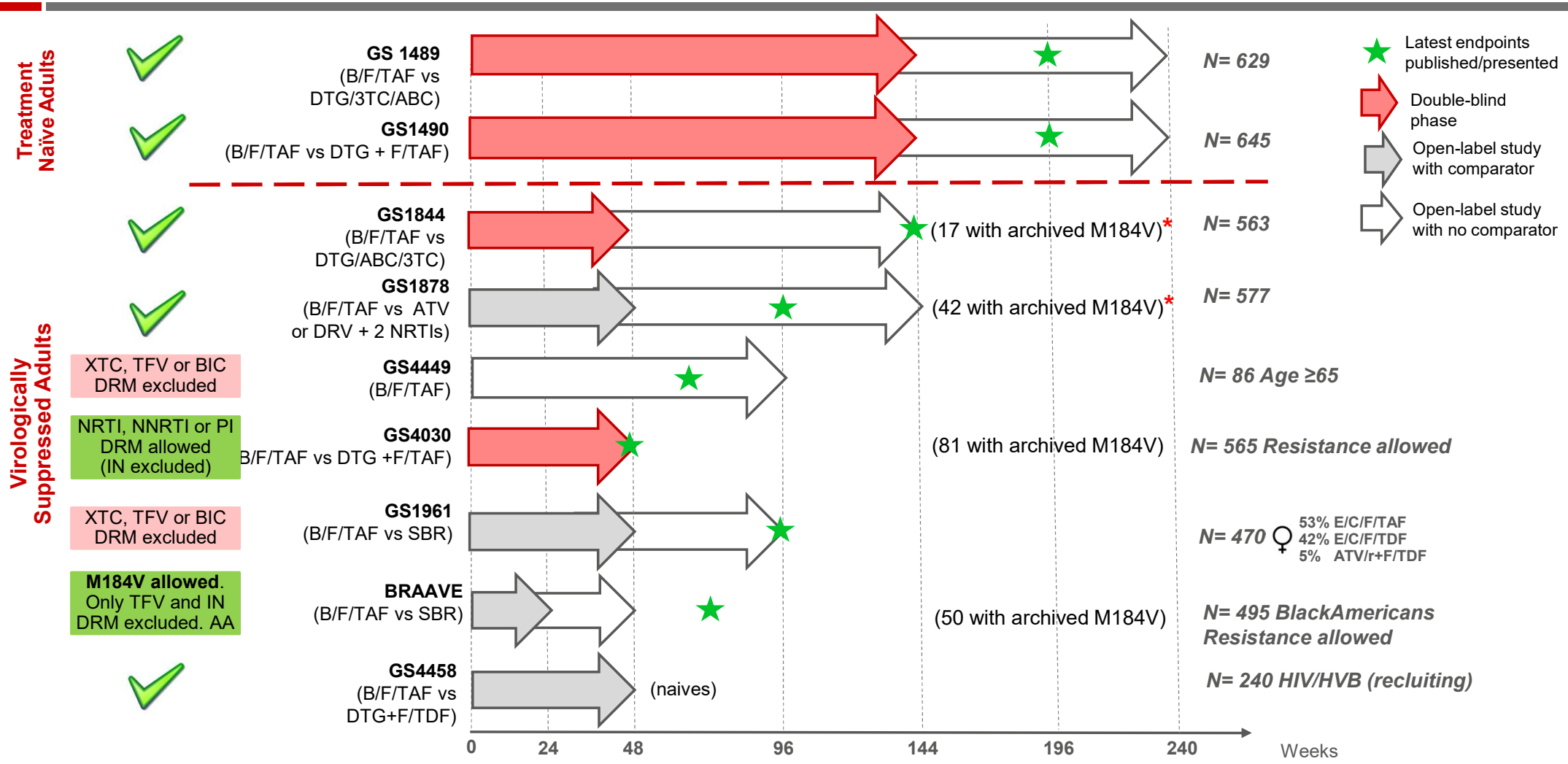
* Primary INSTI-R substitutions observed with M184V/I: T97A (n=2) and Y143H, Q148R, and N155H (n=1 each)
† Studies 4449 and 1474 excluded from analysis

Andreatta K, et al. EACS 2019. Basel, Switzerland. PE13/21. Andreatta K. et al. HIV Drug Therapy, Glasgow 2020. #P123

Orkin C, et al.Lancet HIV. 2020;7(6):e389-400 ; Arribas J, et al. vIAS 2021, PEB151; Workowski K, et al. vCROI 2021, 415; Gallant J, et al. Lancet 2017;390:2063-2072; Sax PE, et al. Lancet 2017;390:2073-2082; Pozniak A, et al. EACS 2021, PE2/68 2; Daar E, et al. Lancet HIV 2018;5:e347–56; Andreatta K, et al. EACS 2021. PE 1/19; Andreatta K, et al. EACS 2021. PE 1/19; Andreatta K, et al. vIAS 2021, PEB172; Kityo C, et al. JAIDS 2019 Nov 1;82(3):321-328; Maggiolo, et al, Infect Dis 2021; Maggiolo F, et al. vIAS 2021, PEB160; Acosta R, et al. JAIDS 2020;85:363–371; Hagins D, et al. Open for

BIC/FTC/TAF:

No HIV resistance emergence (any) across all the switch program



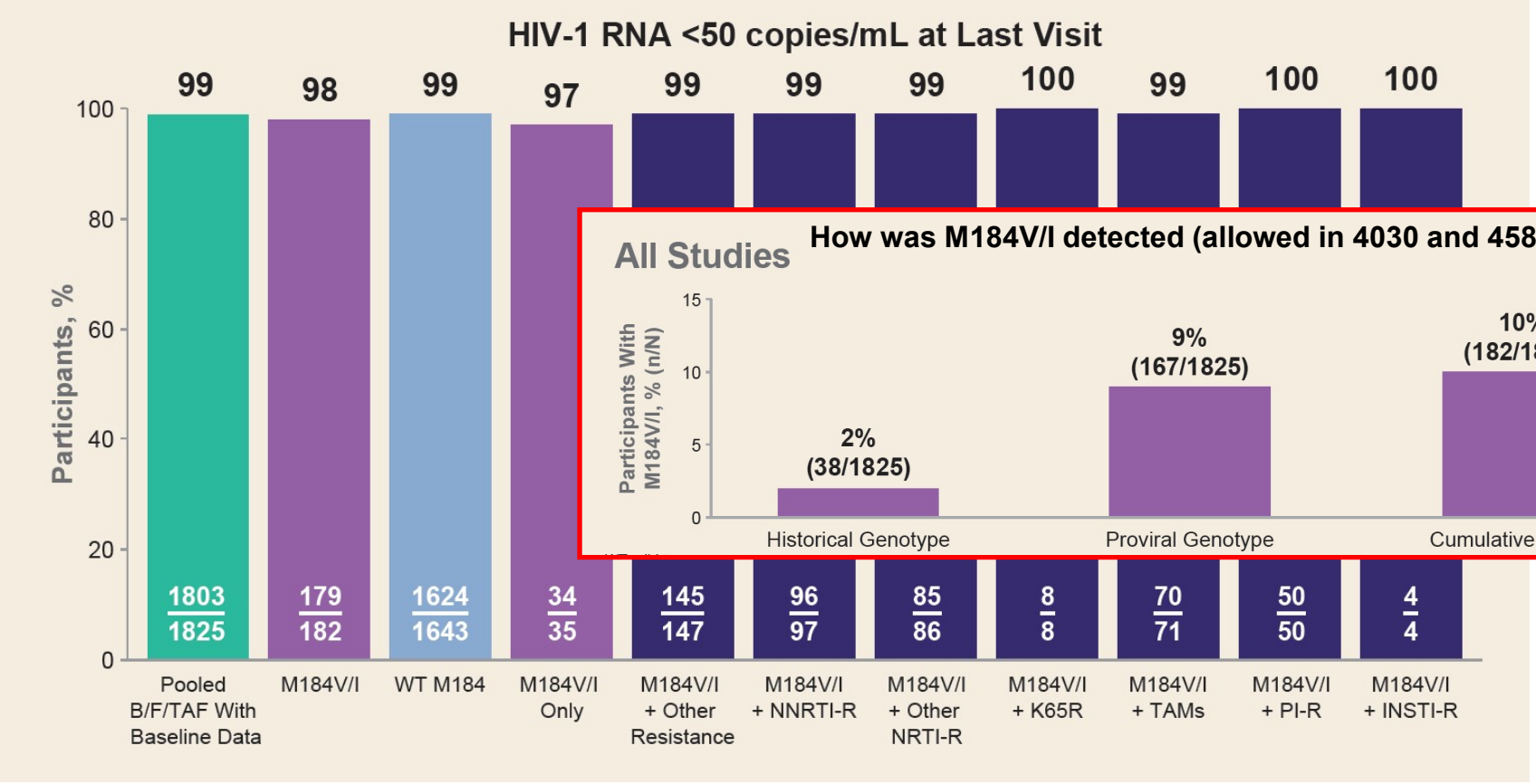
Overview of B/F/TAF Switch Studies in Adults With Suppressed HIV

Study	Resistance Criteria	BL ARV Regimen	Participants, n	Study Regimen	
				BL Through Week 48	Week 48 Through End of Study
4030	NRTI-R, NNRTI-R, PI-R allowed; INSTI-R excluded	DTG + either F/TAF or F/TDF	284	B/F/TAF	—
			281	DTG + F/TAF	—
4580	NNRTI-R or PI-R allowed; INSTI-R excluded; NRTI-R: M184V/I, ≤2 TAMs allowed, K65R/E/N, T69 insertions, ≥3 TAMs excluded	Any 3rd agent + 2 NRTIs	330	B/F/TAF	B/F/TAF
			165	SBR (BL–Week 24) / B/F/TAF (Week 24–48)	B/F/TAF
1844	FTC-R or TFV-R excluded	DTG + ABC/3TC (either STR or MTR)	282	B/F/TAF	B/F/TAF
			281	DTG/ABC/3TC	B/F/TAF
1878	FTC-R or TFV-R excluded	Boosted DRV or ATV + either F/TDF or ABC/3TC	290	B/F/TAF	B/F/TAF
			287	SBR	B/F/TAF
4449	FTC-R, TFV-R, and BIC-R excluded	E/C/F/TAF or any 3rd agent + F/TDF	86	B/F/TAF	B/F/TAF

K Andreatta. 18th European AIDS Conference, October 27–30, 2021, London, UK: Poster PE1/6

Meta-analysis:virologic suppression rates to BIC/F/TAF in switch with prior DRMs

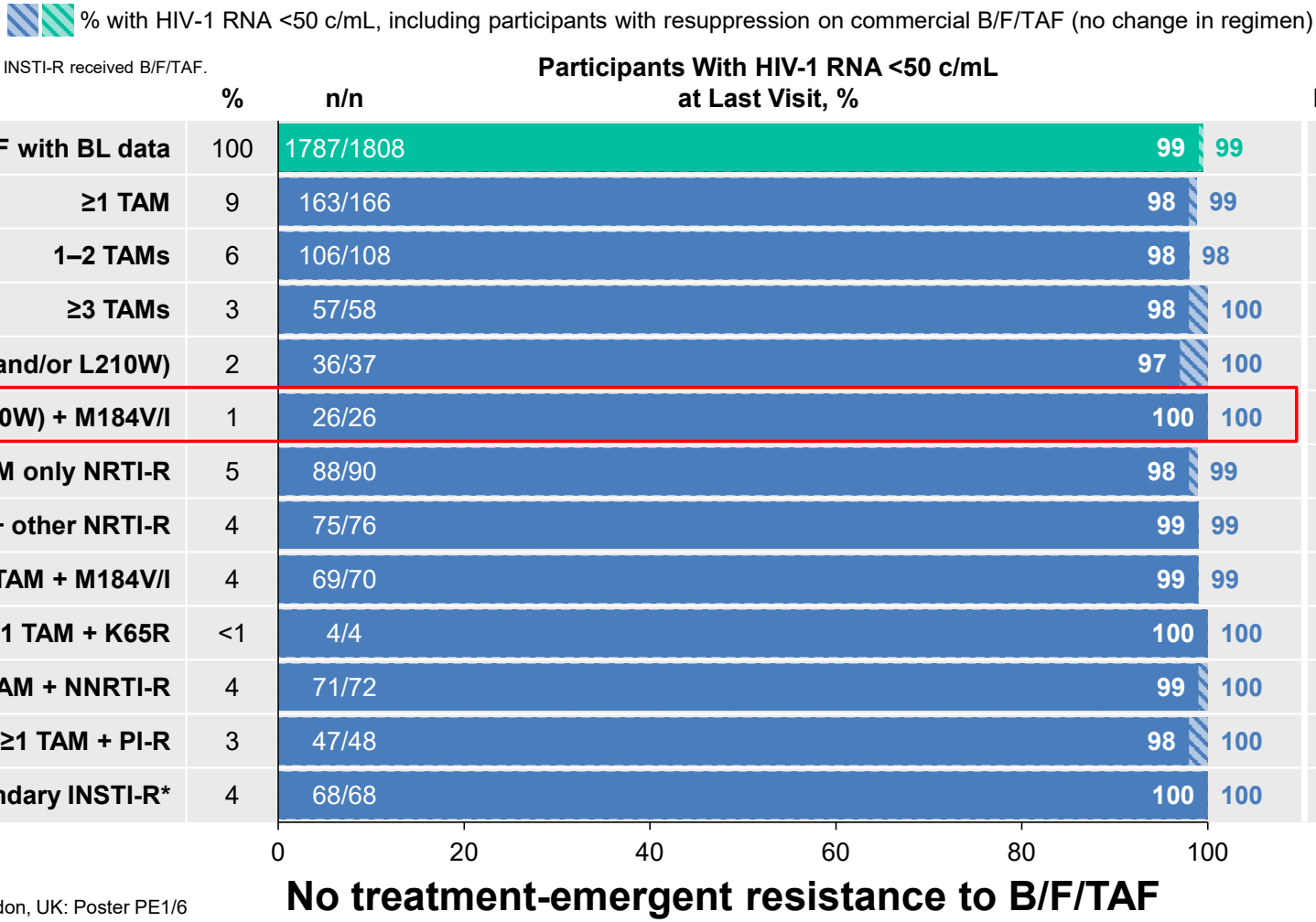
Virologic Suppression by Study and Preexisting M184V/I



M184V/I detected in 182/1825 virol. suppressed pts (10%), most previously undocumented by historical genotype

K Andreatta. HIV Glasgow 2020, 5–8 October, 2020. P123.

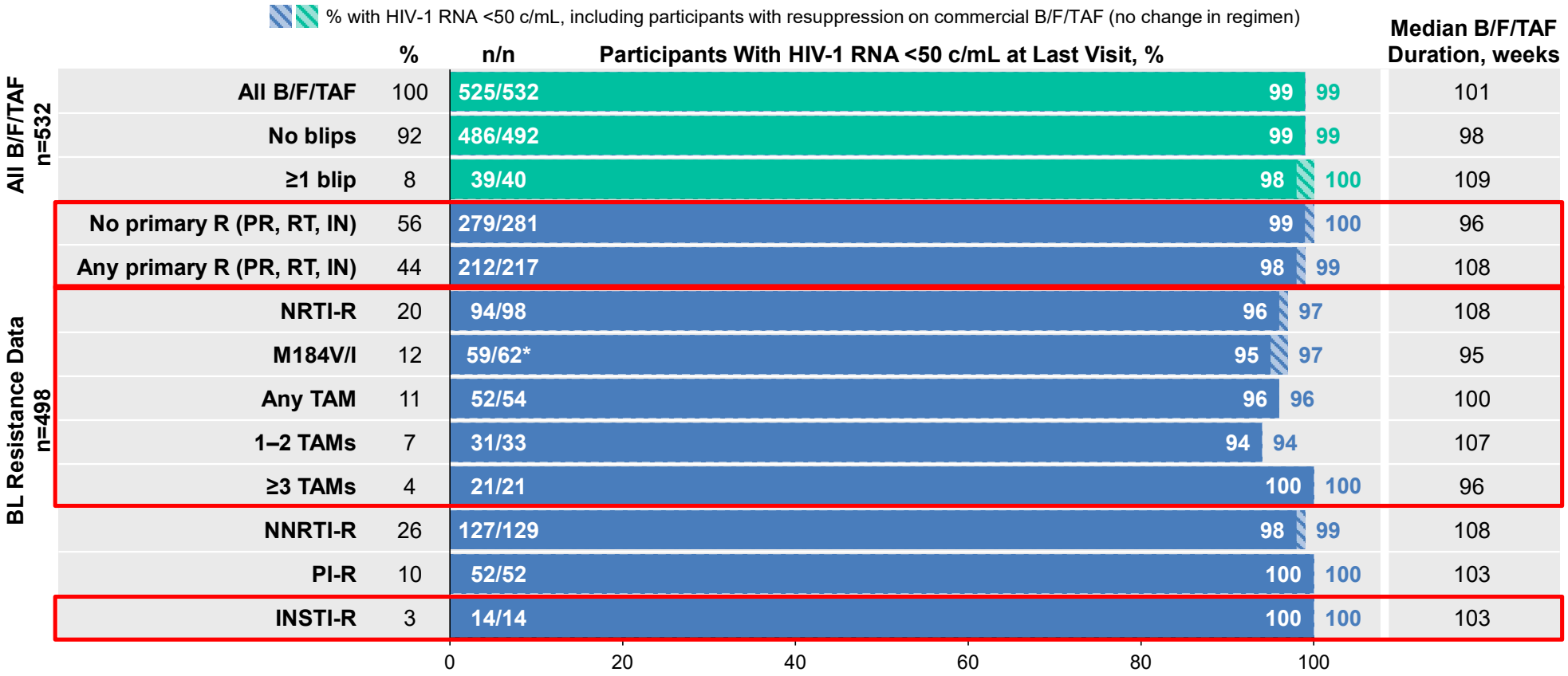
Virologic Suppression at Last On-Treatment Study (median 72 weeks) Visit by Preexisting TAMs: Pooled B/F/TAF-Treated Analysis



No treatment-emergent resistance to B/F/TAF

K Andreatta.
18th EACS, October 27–30, 2021, London, UK: Poster PE1/6

GS 1878. BIC/F/TAF switch from bPI (Entry: No FTC of TAF resistance, no prior VF). Virologic Outcomes by Archived Resistance or Blips in All B/F/TAF Group.



- High efficacy was maintained in participants with archived resistance or viral blips

*Of 3 participants with M184V/I and HIV-1 RNA ≥50 c/mL at their last visit, 2 had HIV-1 RNA <100 c/mL (1 resuppressed on commercial B/F/TAF and 1 on ATV/ritonavir + F/tenofovir disoproxil fumarate), and 1 experienced confirmed virologic failure with HIV-1 RNA of 2860 c/mL, documented poor adherence, undetectable BIC plasma concentrations, and no treatment-emergent resistance, and discontinued at the following visit with HIV-1 RNA of 1510 c/mL.

NADIA: Second line Salvage. Baseline characteristics.

DTG vs DRV & TDF vs AZT

Characteristic	DTG group (N= 235)	DRV group (N=229)	TDF group (N=233)	ZDV group (N=231)	Overall (N=464)
Female sex – no (%)	140 (59.6)	142 (62.0)	140 (60.1)	142 (61.5)	282 (60.8)
Median age (IQR) – yr	33 (28-40)	35 (28-42)	34 (28-43)	35 (28-40)	34 (28-41)
CD4+ lymphocyte count, Median (IQR) – per mm^3	189 (58-388)	202 (84-357)	200 (77-388)	191 (58-340)	194 (68-367)
< 50 per mm^3 – no (%)	54 (23.0)	39 (17.0)	45 (19.3)	48 (20.8)	93 (20.0)
50-199 per mm^3 – no (%)	71 (30.2)	74 (32.3)	70 (30.0)	75 (32.5)	145 (31.3)
200-349 per mm^3 – no (%)	43 (18.3)	56 (24.5)	47 (20.2)	52 (22.5)	99 (21.3)
> 350 per mm^3 – no (%)	67 (28.5)	60 (26.2)	71 (30.5)	56 (24.2)	127 (27.4)
HIV-1 VL, Median (IQR) – log_{10} copies/ml	4.5 (3.9-5.1)	4.4 (3.8-5.1)	4.4 (3.9-5.1)	4.4 (3.9-5.1)	4.4 (3.9-5.1)
<100,000	169 (71.9)	167 (72.9)	171 (73.4)	165 (71.4)	336 (72.4)
≥100,000	66 (28.1)	62 (27.1)	62 (26.6)	66 (28.6)	128 (27.6)
K65R/N present at baseline – no (%)	120 (52.9)	107 (47.6)	116 (50.7)	111 (49.8)	227 (50.2)
M184V/I present at baseline – no (%)	196 (86.3)	195 (86.7)	201 (87.8)	190 (85.2)	391 (86.5)
Int/high TDF resistance –no (%)	139 (61.2)	125 (55.8)	132 (57.9)	132 (59.2)	264 (58.5)
Int/high ZDV resistance – no (%)	45 (19.8)	38 (17.0)	41 (18.0)	42 (18.8)	83 (18.4)
Int/high 3TC resistance – no (%)	213 (93.8)	202 (90.2)	212 (93.0)	203 (91.0)	415 (92.0)

N Paton. CROI 2021; #94. NEJM 2021; ;385:330-41.

NADIA: Second line Salvage. Efficacy outcomes: DTG vs DRV/r

Outcome	DTG Group (N=235)	DRV Group (N=229)	Difference (95% CI) %	P
HIV-1 RNA level (primary outcome) – no (%)				
< 400 copies/ml (ITT)	212(90.2)	210 (91.7)	-1.49 (-6.7 to 3.7)	0.576
≥ 400 copies/ml	20 (8.5)	16 (7.0)	-	
No virological data - Withdrew because of AE/death - Withdrew for other reasons	3 (1.3) 2 (0.9) 1 (0.4)	3 (1.3) 3 (1.3) 0	-	
HIV-1 RNA level (sensitivity analyses, secondary, other outcomes) – no (%)				
< 400 copies/ml (adjusted)	88.2	89.8	- 1.6 (-6.9 to 3.6)	0.541
VL < 400 copies (per protocol)	205 (92.3)	204 (93.2)	-0.8 (-5.6 to 4.0)	0.744
VL < 1000 c/ml (ITT)	217 (92.3)	213 (93.0)	-0.7 (-5.4 to 4.1)	0.781
VL< 50 c/ml (ITT)	190 (80.9)	182 (79.5)	1.4 (-5.9 to 8.6)	0.710
Rebound (secondary outcome) – no (%)				
VL rebound ≥ 1000 c/ml, confirmed (ITT)	14 (6.0)	13 (5.7)	0.3 (-4.0 to 4.5)	0.897
VL rebound ≥ 1000 c/ml, confirmed with ≥1 major RM to DTG or DRV*	4*	0	-	-

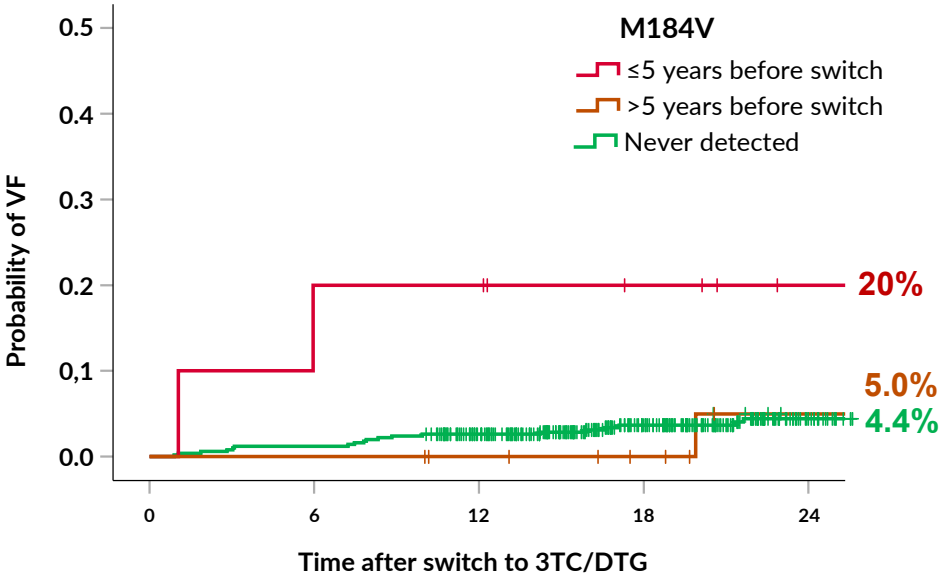
* ≥1 major DTG mutation: 4 (1) T66TA, G118R, E138K, G149GA, G163GR (high-level); (2) E138K, G140A, Q148R (high-level); (3) T66I, G118R, E138K, G149GA (high-level); (4) R263K, M50I (intermediate level).

≥1 major DRV mutation: 0

N Paton. CROI 2021; #94. NEJM 2021; ;385:330-41.

Impact of previous M184V on VF risk in switch to DTG/3TC in real life

- EU retrospective study.
- **N=533** subjects switched to DTG/3TC with HIV-RNA <50 c/mL.
- At least **1 previous VF registered: 39%.**
- **Previous M184V detected: 6.9%** (5.4% only RNA, 1% only DNA)
- Overall probability VF:
  - 2.8% 1ST year, 4.8% 2ND year.
  - No significant difference in the probability of VF or blips according to the presence/absence of M184V (1 yr: 5.4% vs 2.6%; 2 yrs: 9.2% vs 4.4%; p=0.345).
  - **Significantly higher probability of VF** in **individuals with M184V detected ≤5 yrs before switch** compared to those with M184V detected >5 yrs and those without M184V (p=0.04).
- Biasses not excluded.



MM Santoro. *European Meeting on HIV & Hepatitis 2021, Abstract #13*

Take homes.

- **The emergence of HIV-1 resistance must be seen as a preventable drug-related side effect**.

- **The clinical relevance** of a high resistance barrier is **pivotal to preserve ART efficacy**.
- ***In vitro*** drug challenges uncover **differences in HIV breakthrough rates and resistance selection between BIC/F/TAF vs DTG/3TC or DTG/RPV, both in RT and the IN, with wild-type HIV or low-level M184V**. Differences not seen simulating regular adherence or in real life so far.
- **TFV synergy and hypersusceptibility with M184V might play a major role**.

- **Archived resistance is common** (8-10%), **often not suspected by clinicians**, even with no prior known VF.
- **Prior archived NRTI resistance at switch has no impact on BIC/F/TAF or DRVc/F/TAF efficacy**. Robust data.
- **No resistance selection** with BIC/F/TAF or DRV/c/F/TAF in this scenario.
- Extra caution advised **in high risk situations (low CD4, high VL, irregular adherence)**.