AGIDEI
ASOCIACION GALLEGA PARA LA INVESTIGACION Y DOCENCIA EN ENFERMEDADES INFECCIOSAS

XVII CURSO EN AVANCES EN INFECCIÓN VIH Y HEPATITIS VIRALES

Vigo, 12 y 13 de Mayo de 2023

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

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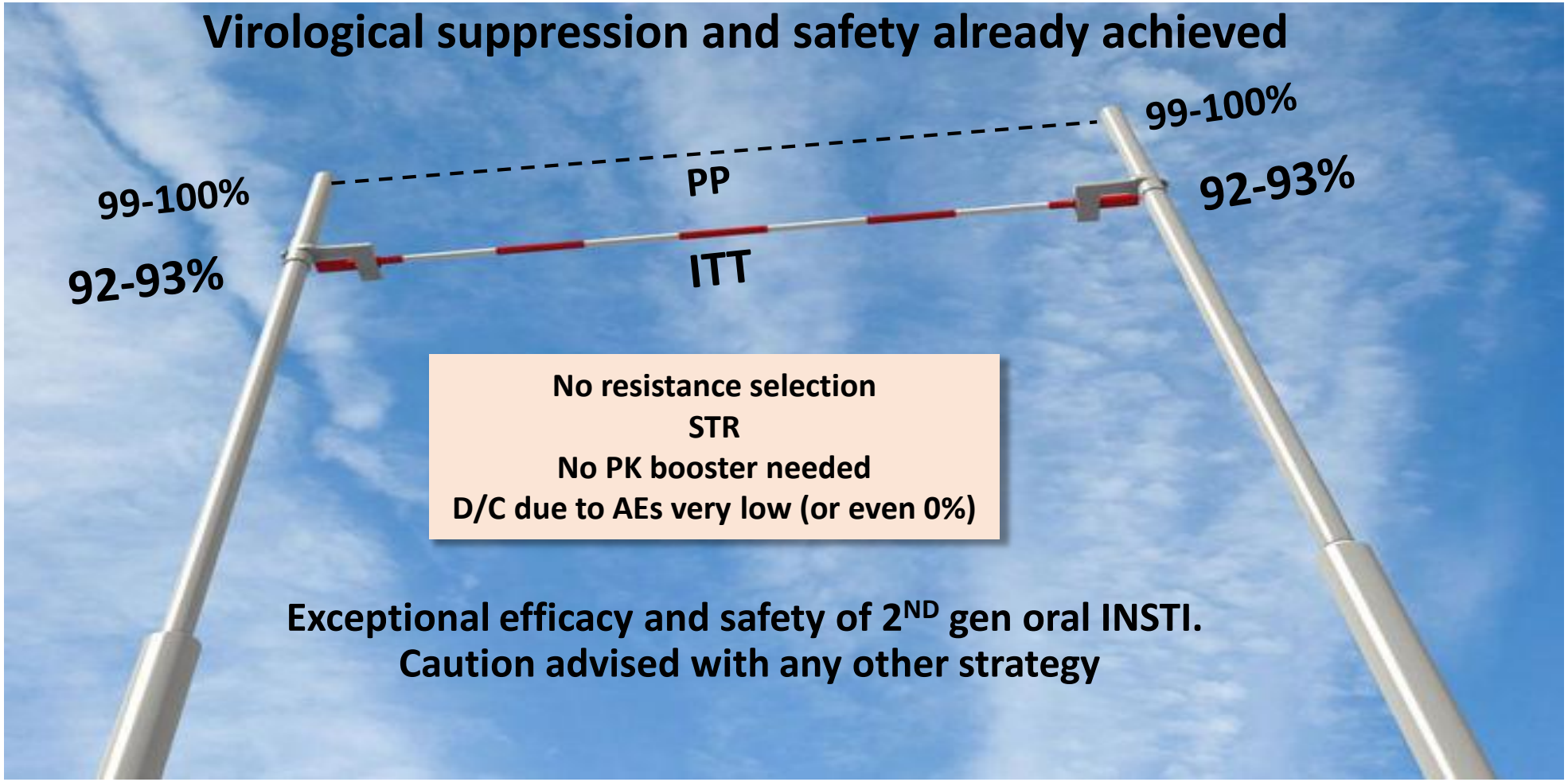
Conflictos de interés

- He participado en reuniones de consultoría, realizado presentaciones educacionales o recibido becas de investigación de Gilead Sciences, ViiV Healthcare, TheraTechnologies y Janssen Cilag.
- Soy miembro del panel de Guías de TAR en GeSIDA.

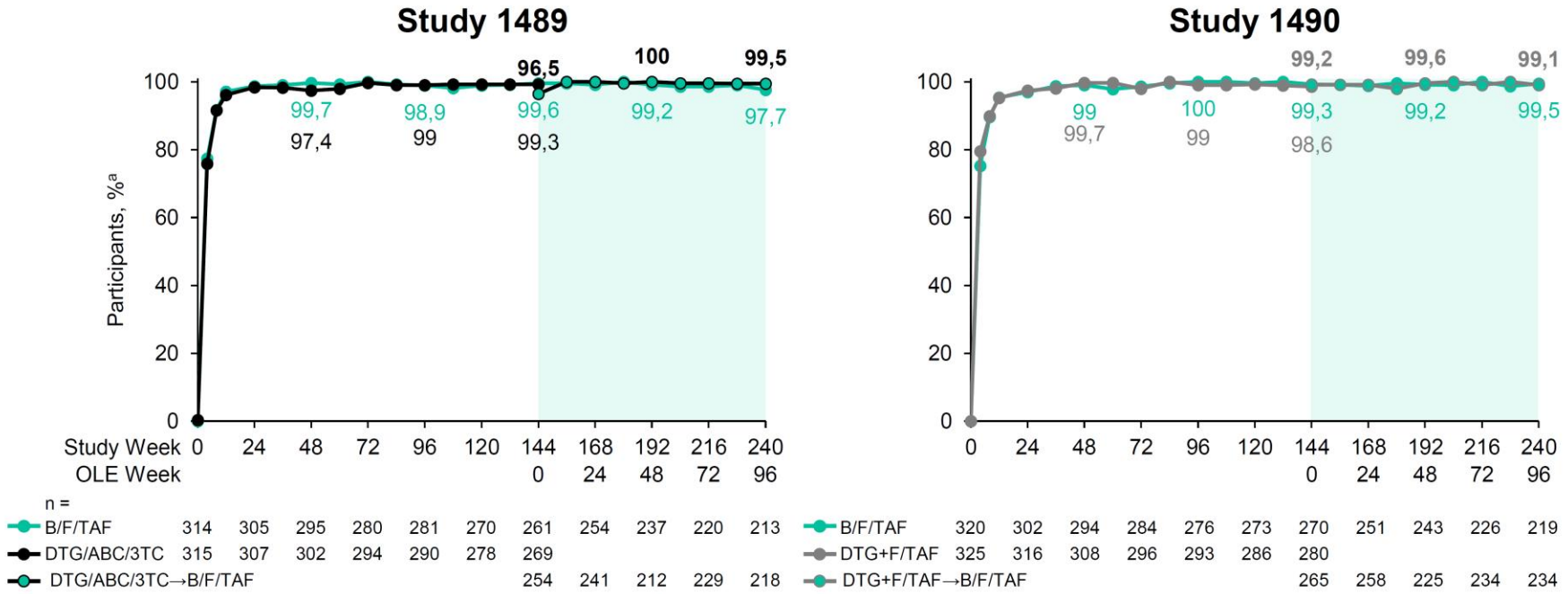
In the 2ND gen INSTI era the bar of ART efficacy is really high:
Advantages & limitations.



Snapshot ITT (-PP) efficacy in **initial ART** in phase 3 RCTs, **48 weeks**, VL <50 copies/mL. **BIC/F/TAF vs DTG/ABC/3TC (n=629)**

J Gallant. GS-US-380-1489 Study (BIC/F/TAF vs DTG/ABC/3TC). Lancet 2017; 390: 2063–72

Virologic Outcomes Through Week 240/OLE : HIV-1 RNA < 50 Copies/mL (M = E)



C Orkin. HIV Glasgow 2022, 23-26 Oct, Glasgow, UK: P088

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?.**
2. **Qué importancia tiene en la prescripción clínica?**

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

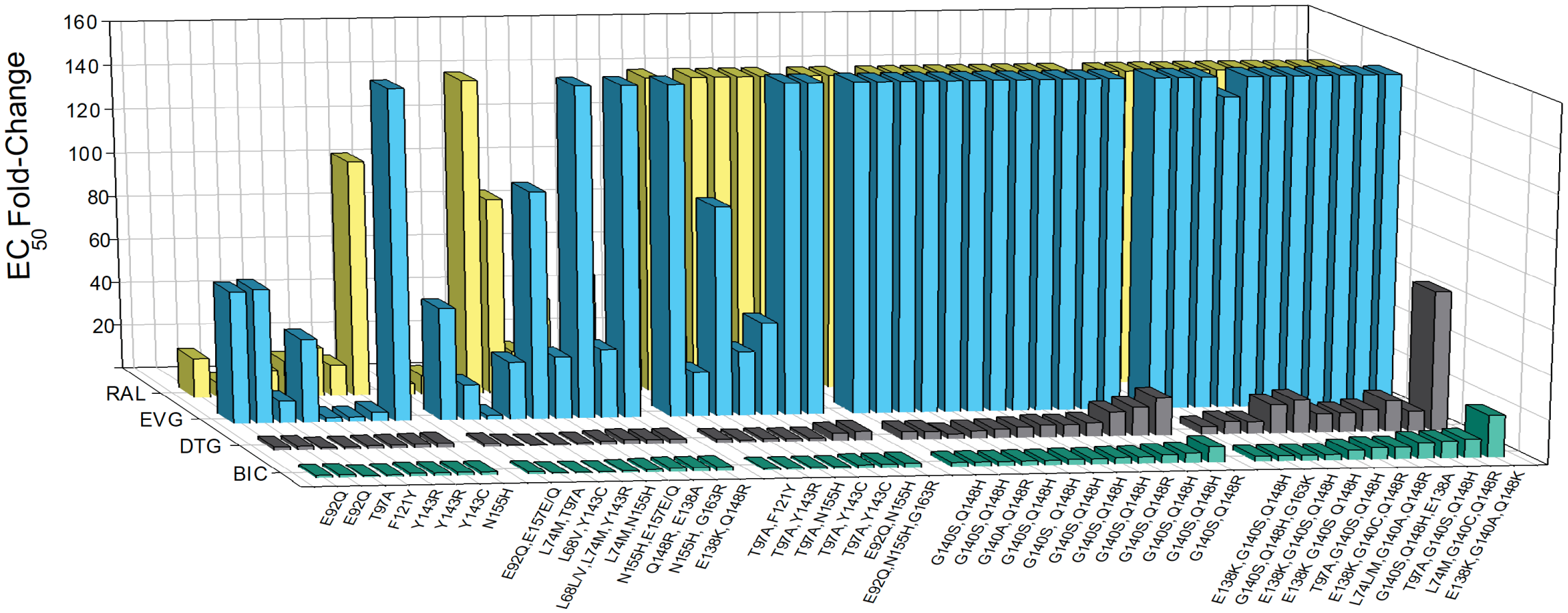
Clinical data: Triple ART, mono/dual therapy, ART-naïve/switch

- Anyway, reported 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

Dissociation time of INSTI

	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.

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

BIC/F/TAF, DTG + F/TAF or DRV/c/F/TAF positioning in ALL treatment guidelines

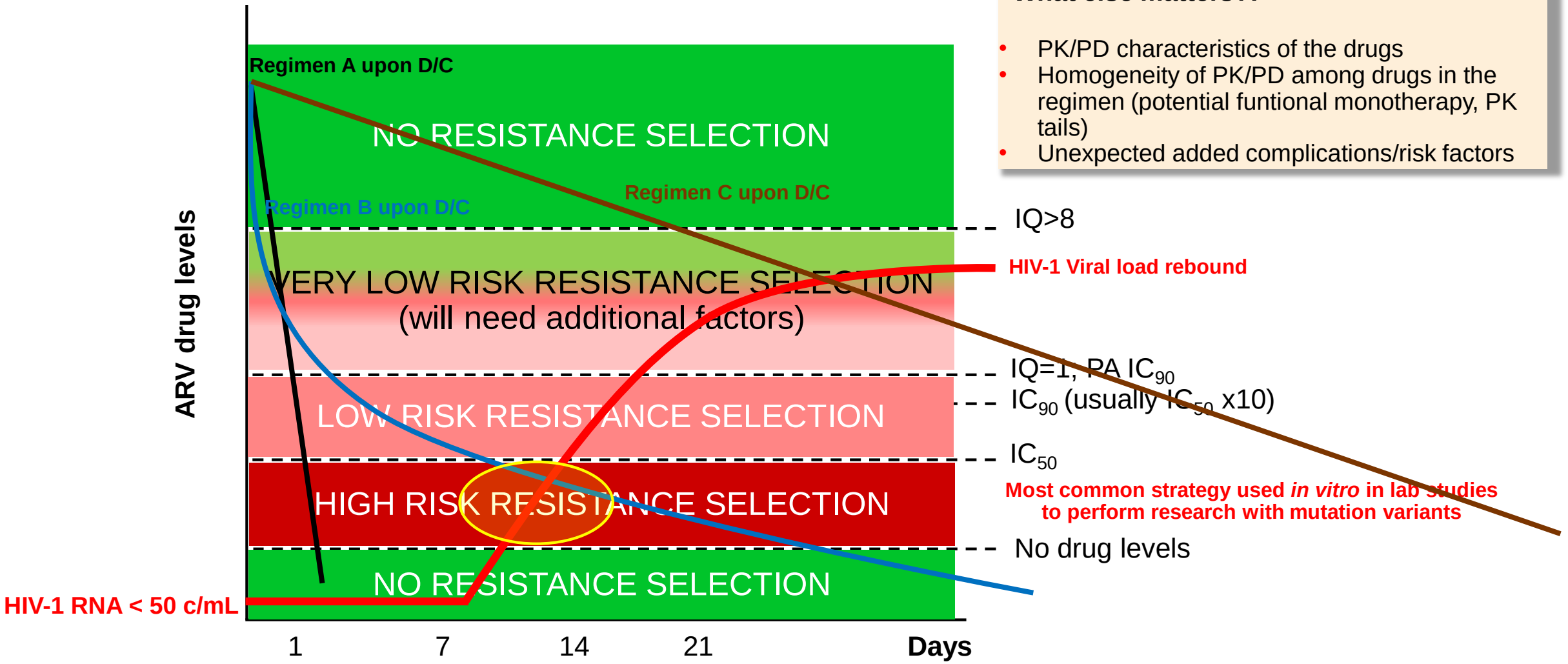
- **Preferred regimen** in ALL guidelines **with no restrictions or caveats (BIC/F/TAF)**.

1. Specifically recommended in **immediate ART initiation.**
2. Specifically recommended **in low-level viremia**.
3. Specifically recommended **in subjects infected on PrEP** with TDF/FTC.
4. Specifically recommended in **switch in subjects with archived NRTI resistance**.

EACS Guidelines 11.1. October 2022. Available at: https://www.eacsociety.org/files/guidelines-10.1_finaljan2021_1.pdf. IAS-USA Guidelines. RT Gandhi. JAMA. doi:10.1001/jama.2022.22246, Published online December 1, 2022. DHHS. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Updated September 21, 2022. GeSIDA/PNS TAR en adultos infectados por el VIH (Actualización enero 2023). Disponible en: https://gesida-seimc.org

2. ¿Qué importancia tienen 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

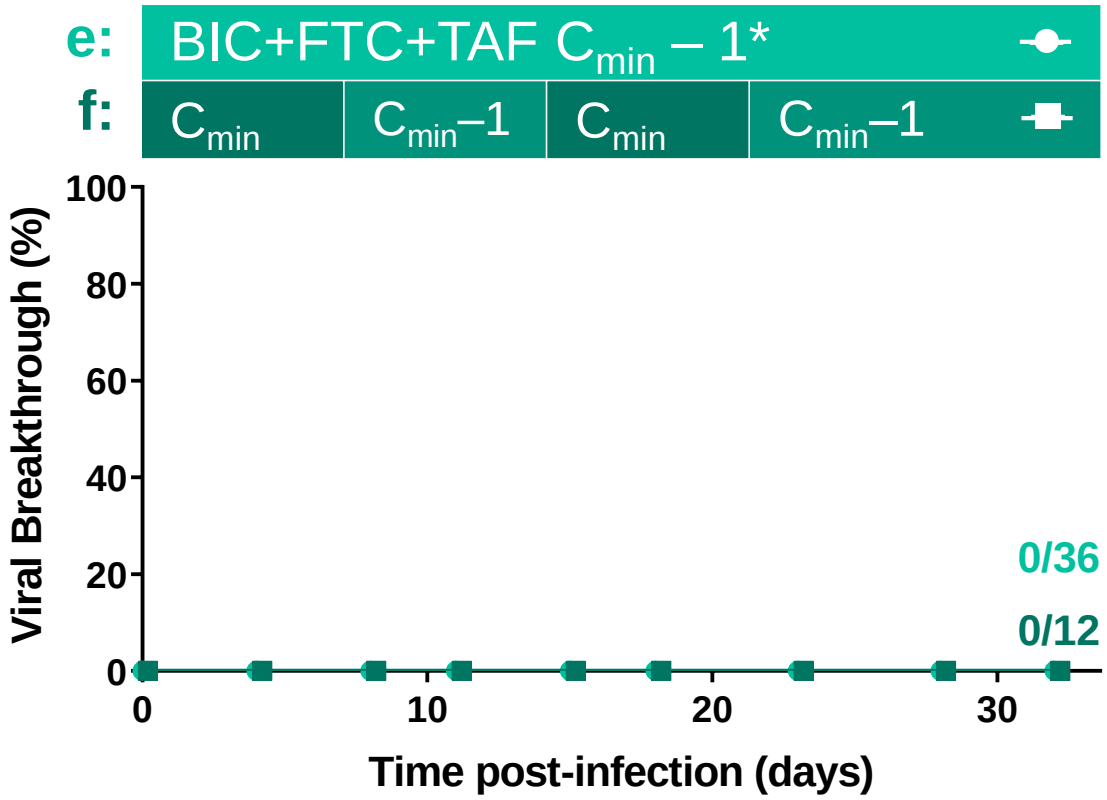


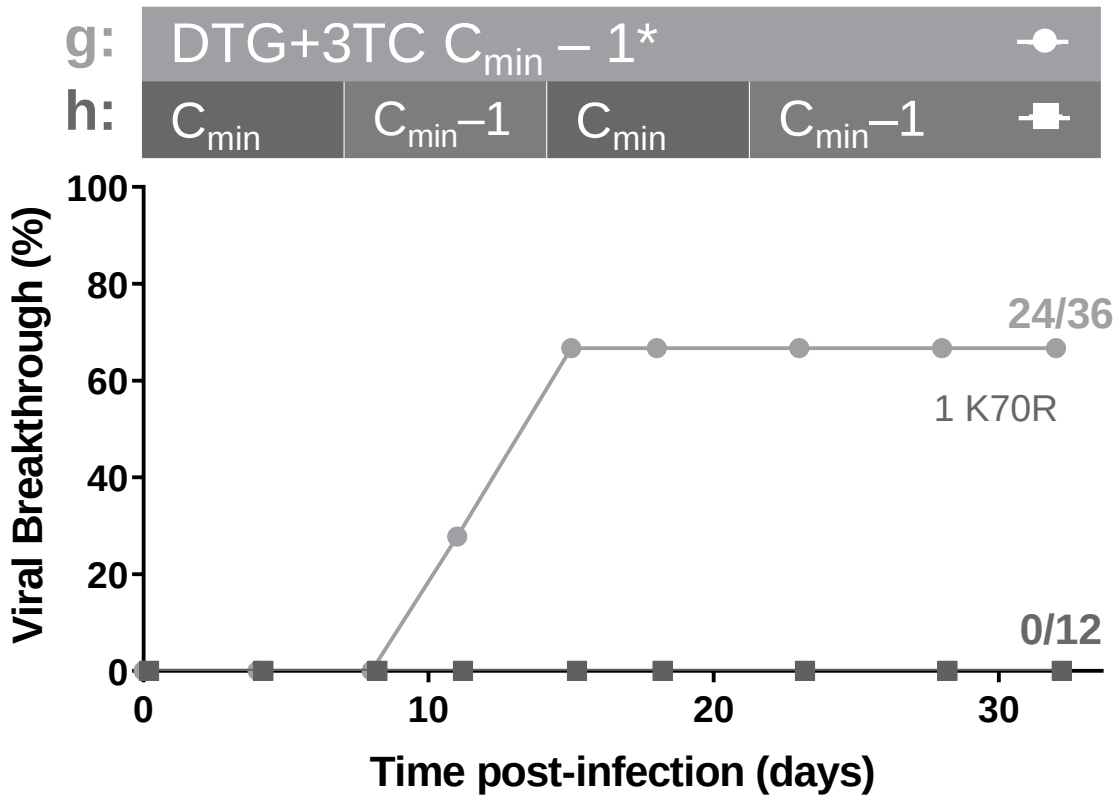
What else matters?:

- 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

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

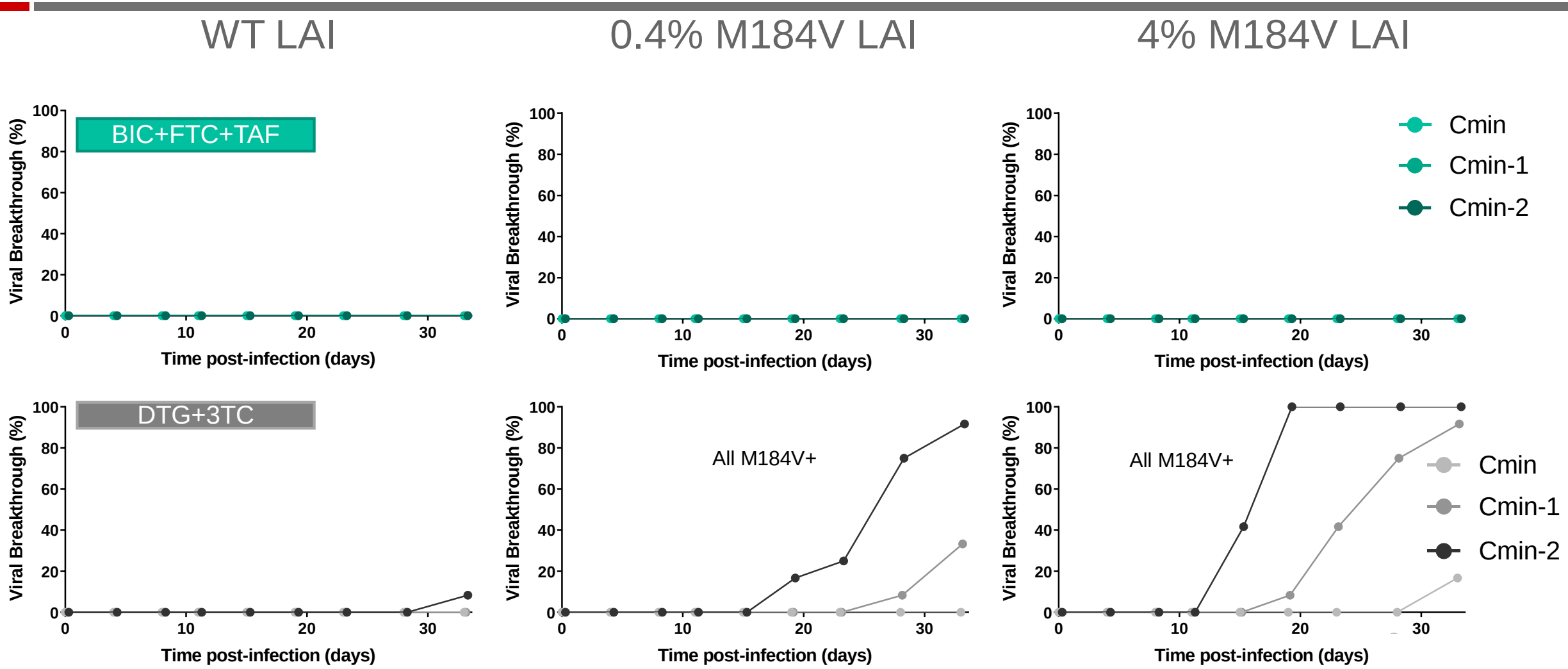




1 K70R in RT

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

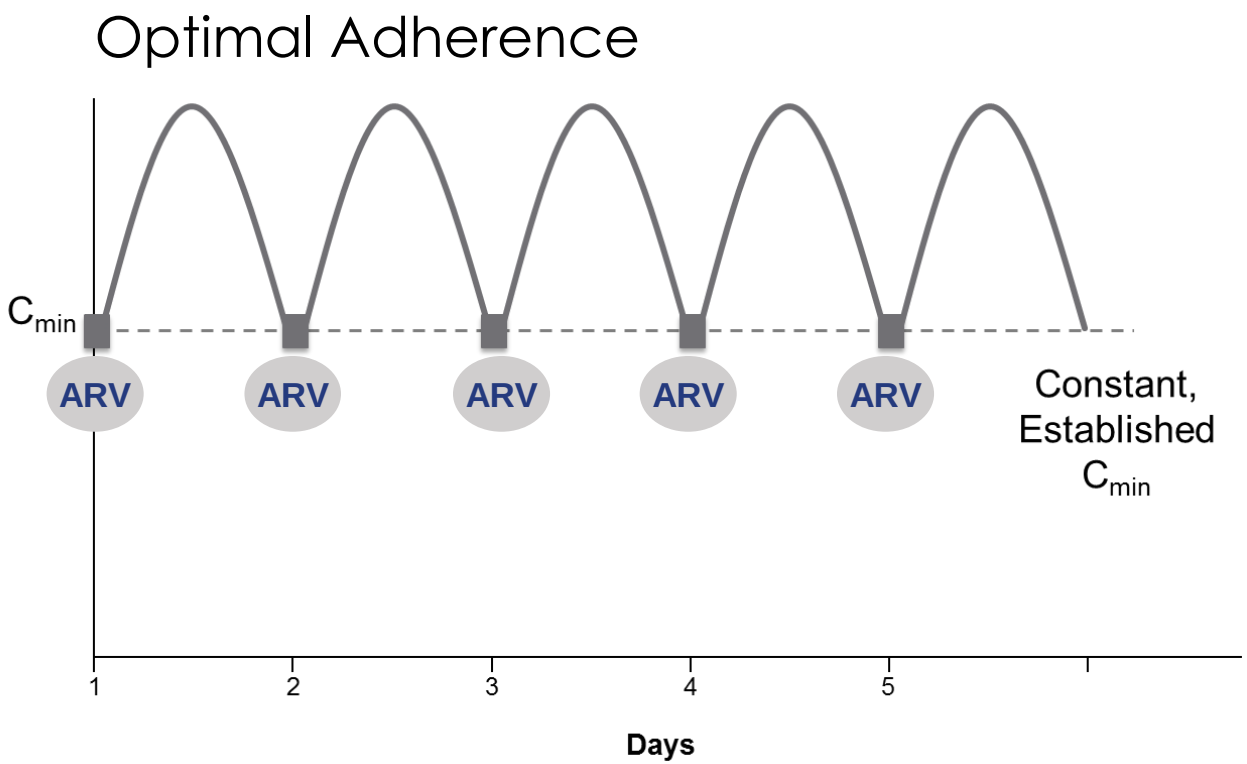
Time to Viral Breakthrough: impact of Low Level M184V

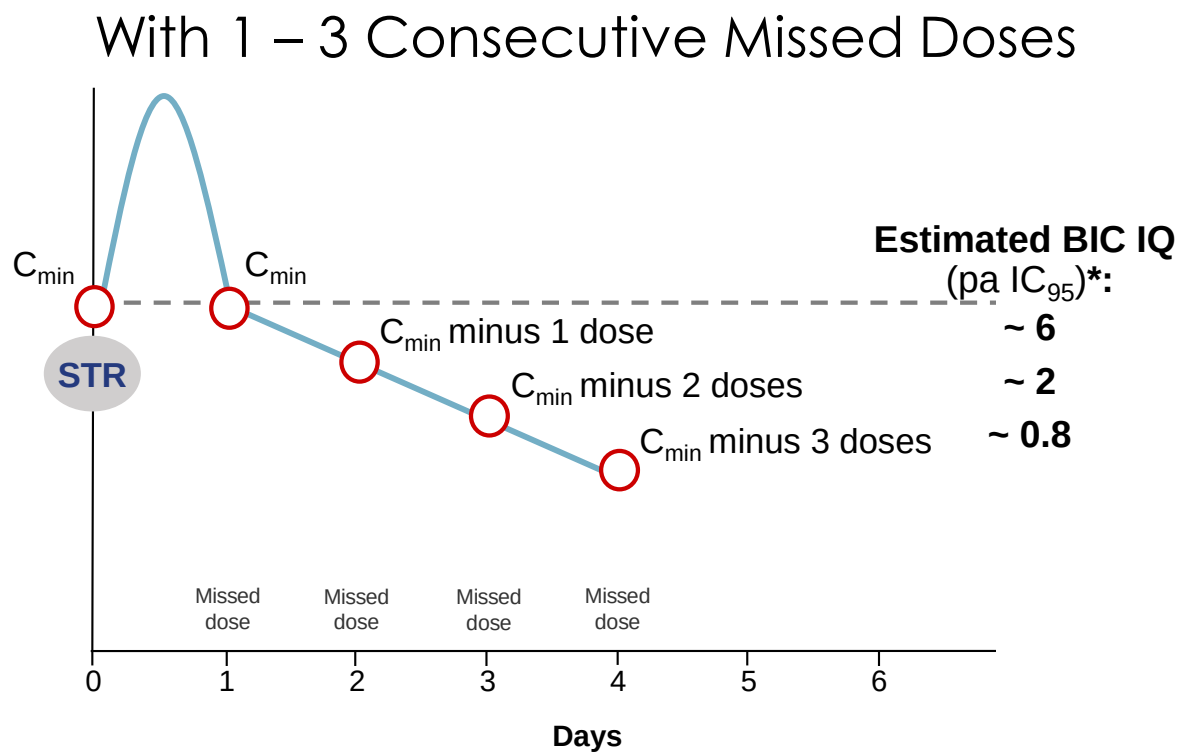


Mulato A. et. al. J Acquir Immune Defic Syndr. 2021 Mar 1;86(3):369-377

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

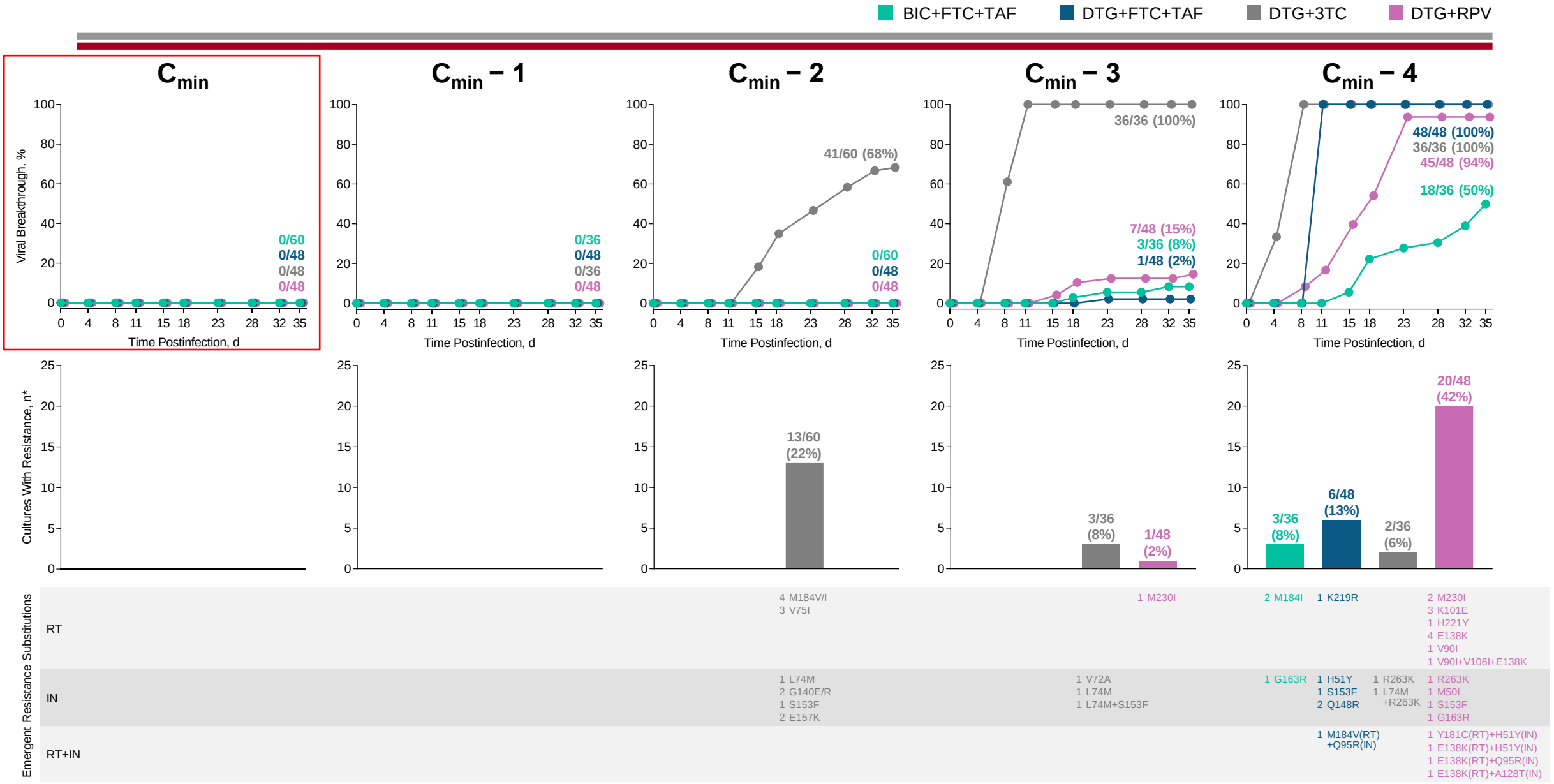
- Missing ARV doses results in a predictable decrease of systemic exposures to each drug in the regimen based on its established clinical half-life ($t_{1/2}$)





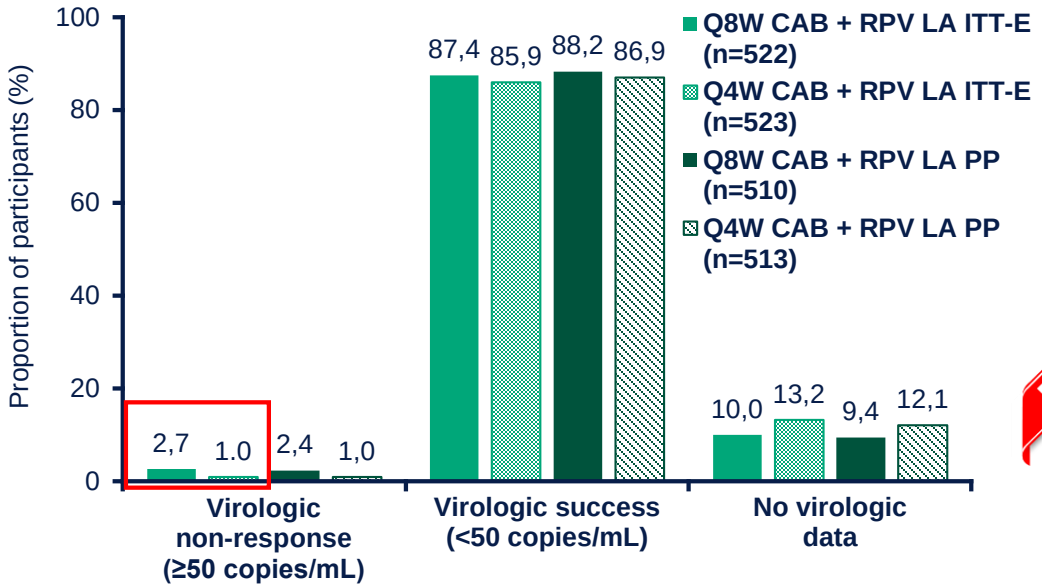
Mulato A. et. al. IDweek 2020 Poster 1448. *JM Llibre personal communication, based on BIC Cell Culture Drug Concentrations used reported at: A Mulato. J Acquir Immune Defic Syndr 2021;86:369–377.

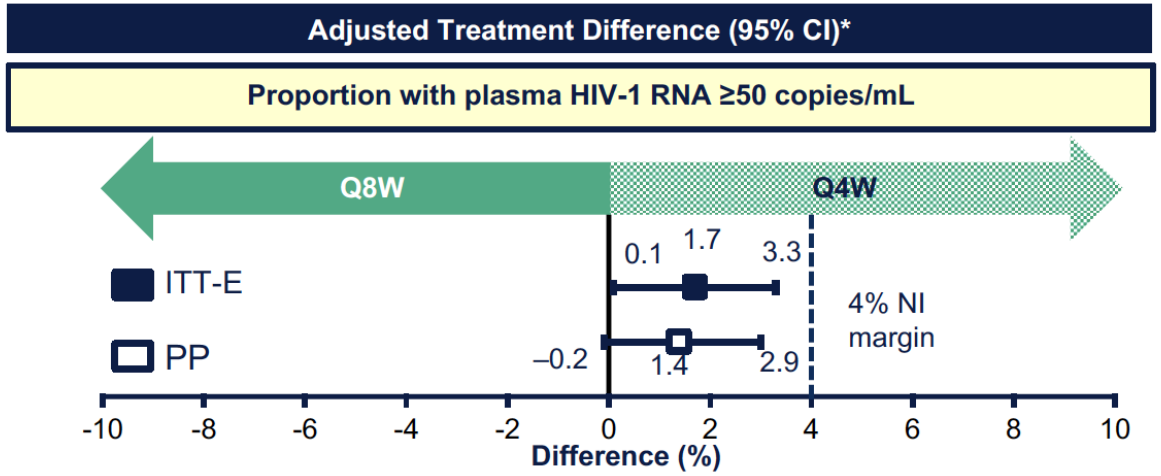
Results: Time to Viral Breakthrough with low drug concentrations.



ATLAS-2M: LA CAB+RPV Q4 or (

Virologic Outcomes at Week 152





Through Wk 152, 13 participants had CVF:

- Q8W, n = 11 (+1)◆ (2,7%)*; p=0.0075, **OR 5.4.**
- Q4W, n = 2 (0,5%)*

* Participants reaching week 152 (excluding D/C for "other reasons" or AE/death): n=452
◆ An additional participant had a non-protocol-defined virologic failure at Week 48 (Q8W)

NEW

Most CVF:

- In first 48 weeks.
- **Have high-level NNRTI and INSTI resistance**.
- **CAB & RPV administered within window period**.
- Only 50% have ≥2 baseline factors (proviral RPV RAMs, HIV-1 subtype A6/A1, BMI ≥30 kg/m^2), associated with increased risk of failure.
- L74I has greater *in vitro* fitness but does not explain the resistance pathway by itself **
- Nearly all achieved viral resuppression on a bDRV regimen.

Overton et al. CROI 2022; Virtual. Poster 479.
**ZX Hu. vCROI 2022; #506

SOLAR Study. Participants With Confirmed Virologic Failure (CVF)

Sex at birth, country	Baseline BMI (kg/m²)	HIV-1 subtype at baseline	Viral load at SVF/CVF (copies/mL)	RPV RAMs observed at baseline (proviral DNA)	INI RAMs observed at baseline (proviral DNA)	RPV RAMs observed at failure (viral RNA)	INI RAMs observed at failure (viral RNA)	Phenotypic resistance (fold-change) to RPV/CAB	SVF timepoint (month)
Participants With CVF in the mITT-E Population									
Male, Italy*	21.5	B	1327/1409	None	None	M230L	Q148R	3.2/3.1	6
Male, Spa			6348/419	None	G140G/R	K101E	G118R	1.9/8.4	11
Participant With CVF in the ITT-E Population‡									
Male, United Stat			3797/928	Assay failed	Assay failed	E138E/K + Y181Y/C	None	4.2/assay failed	3

0.7% vs 1.5% in ATLAS-2M*

- Two (0.4%) participants receiving CAB + RPV LA in the mITT-E population, and one additional participant receiving CAB + RPV LA in the ITT-E population, met the CVF criterion through Month 12
  - Two of the participants had on-treatment RPV and/or INI RAMs (genotyping for third participant failed at baseline)
- No participants in the BIC/FTC/TAF arm met the CVF criterion through Month 12

*Prior to enrolling in the study, the participant received BIC/FTC/TAF, and after discontinuation re-suppressed on DRV/c/FTC/TAF during long-term follow-up. †Prior to enrolling in the study, the participant had received dolutegravir/lamivudine/abacavir and BIC/FTC/TAF; they re-suppressed on BIC/FTC/TAF and darunavir/cobicistat/emtricitabine/tenofovir alafenamide during long-term follow-up. The participant did not continue in the long-term follow-up phase. ‡Prior to enrolling in the study, the participant had received prohibited prior ART with at least three prior INI regimens; they re-suppressed on BIC/FTC/TAF during long-term follow-up. This participant was excluded from the mITT-E population due to significant and persistent non-compliance to protocol entry requirements at the study site. §Participant had HIV-1 subtype C at Month 3. Baseline analysis failed.
DRV, darunavir; ITT-E, intention-to-treat exposed; LA, long-acting; mITT-E, modified intention-to-treat exposed; NA, not available; RAM, resistance-associated mutation; SVF, suspected virologic failure.

CAB RPV LA Q8w Paris Cohort. Trough concentrations

	Drug trough concentrations	At 1 month (n=58)	At 3 months (n=56)
CAB	**Trough < 1120 ng/mL**, n (%)	**35 (60)**	**43 (77)**
	Median trough, ng/mL (IQR)	**976 (706 – 1434)**	**701 (440 – 1087)**
	No lead-in (n=42)	*951 (681 – 1196)*	*625 (397 – 880)*
	Lead-in (n=16)	*1213 (908 – 1479)*	*1103 (689 – 1246)*
RPV	**Trough < 32 ng/mL**, n (%)	**16 (28)**	**15 (27)**
	Median trough, ng/mL (IQR)	**48 (29 – 66)**	**43 (32 – 55)**
	No oral rilpivirine before switch (n=25)	*47 (35 – 68)*	*44 (30 – 58)*
	Oral rilpivirine before switch (n=33)	*49 (29 – 62)*	*43 (32 – 53)*

- Thresholds: 1st quartiles in FLAIR/ATLAS/ATLAS-2M pooled population[1]: CAB 1120 ng/mL, RPV 32 ng/mL
- Protein-adjusted 90% inhibitory concentrations ($PAIC_{90}$)[2]:
  - $PAIC_{90}$: CAB 166 ng/mL, RPV 12 ng/mL
  - $4xPAIC_{90}$: CAB 664 ng/mL, RPV 48 ng/mL

1.7% at month 8 in switch

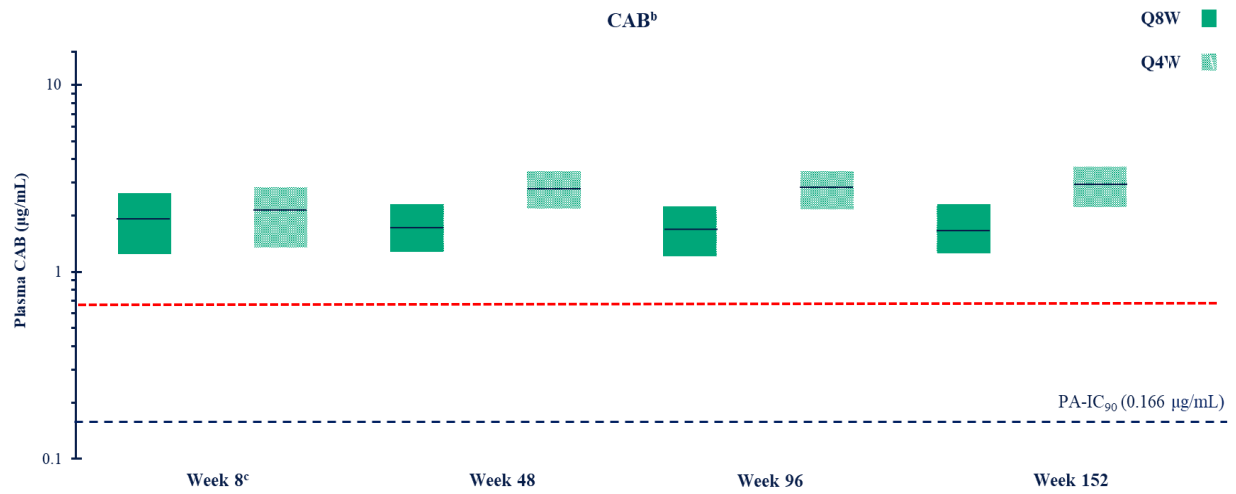
- **High intra- and inter-individual variability**
- **1 VF at M1** and C_t CAB = 701 ng/mL, C_t RPV = 28 ng/mL (subtype AG, BMI 29.4, VL<50 c/mL x 1.8 y on DTG/ABC/3TC)
- No oral lead-in and high BMI associated with low trough concentrations

[1]*Cutrell et al, AIDS, 2021,* [2]*Margolis et al, LATTE, Lancet Infect. Dis., 2015*

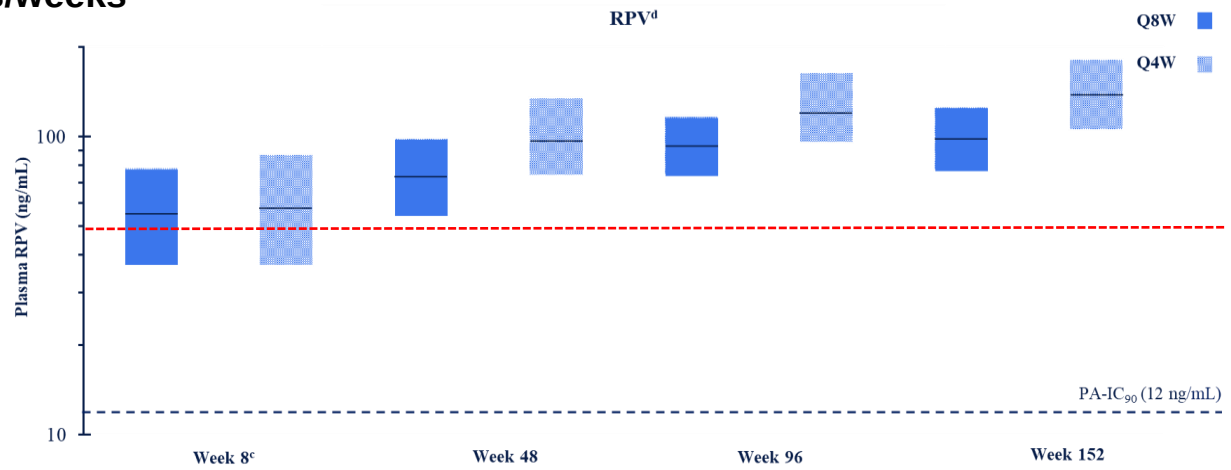
ATLAS 2M. CAB and RPV concentrations irrespective of prior exposure through Week 152

Median (IQR) trough concentrations.

1. Important **interpatient variability with LA**
2. **Considerable n of subjects below IQR_{25}**
3. **Concentrations maintained during days/weeks**



0.664 µg/mL
4 x $PA\text{-}IC_{90}$



4 x $PA\text{-}IC_{90}$ (48 ng/mL)
Minimal conc. for therapeutic response (50 ng/mL)

Strategies aimed at reducing the risk/consequences of VF with CAB + RPV Q8W despite proper prescription

- **Longer needle (5 cm) in people with obesity (BMI >30)**
- **Frequent VL monitoring**: every 8 weeks (ATLAS 2M and SOLAR, BHIVA guidelines[1])
- VL monitoring **in all unplanned missed visits and delayed dosing** of LA CAB and RPV (DHHS[2])
- **Reducing the risk of archived NNRTI or IN mutations**:

  Baseline proviral DNA in PBMCs: IAS/USA Guidelines, MSC Español (AEMPS, IPT)

  Excluding subjects exposed to NNRTIs: SOLAR

- Identifying subjects with low RPV/CAB through levels and switching them off Q8M

1. BHIVA Guidelines 2022. Available at: Available at: https://www.bhiva.org/HIV-1-treatment-guidelines
2. DHHS Guidelines, Updated September 21, 2022. Available at: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new-guidelines

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

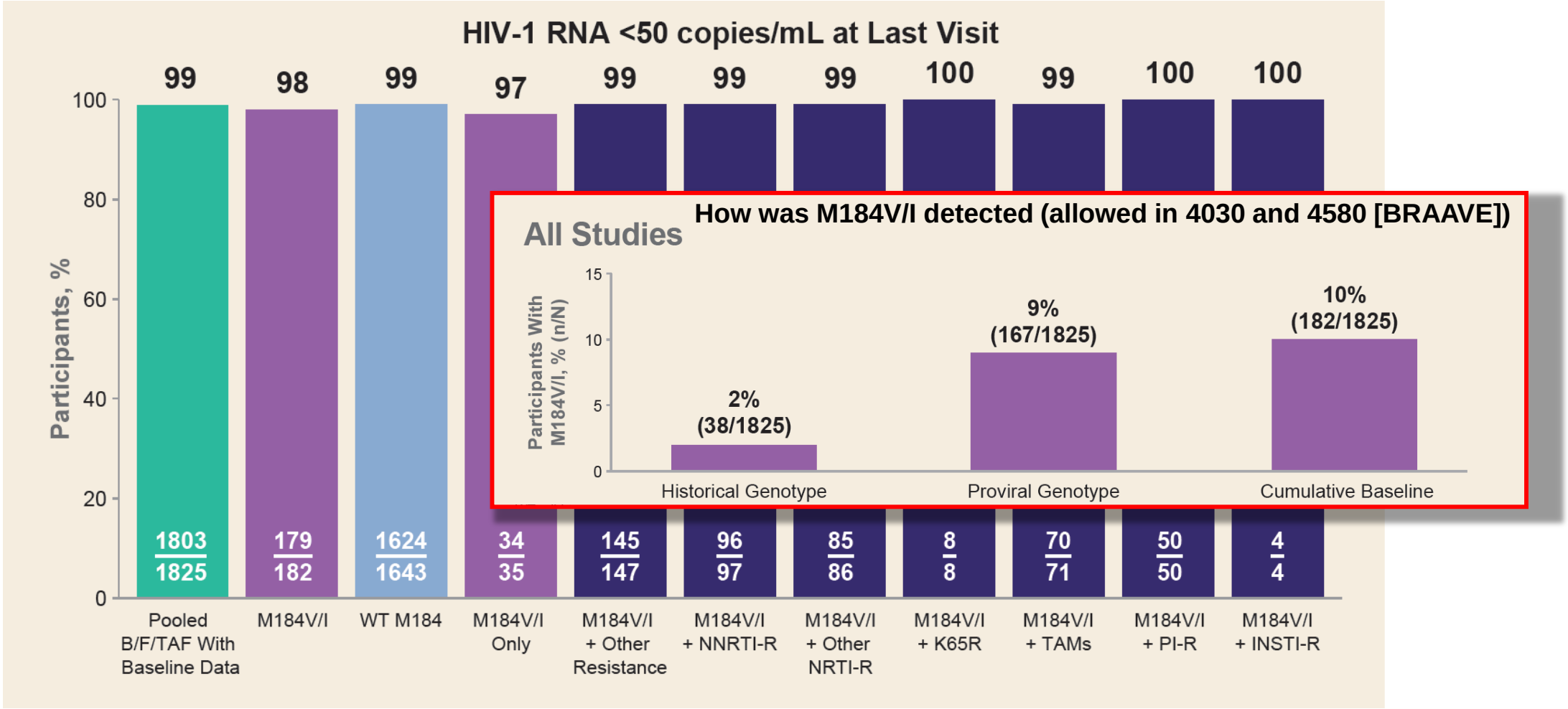
M184V/I at baseline was associated with resistance (non-M184V/I NRTI, NNRTI, or PI), Black race, CD4 count <500 and a longer ART duration

* 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

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

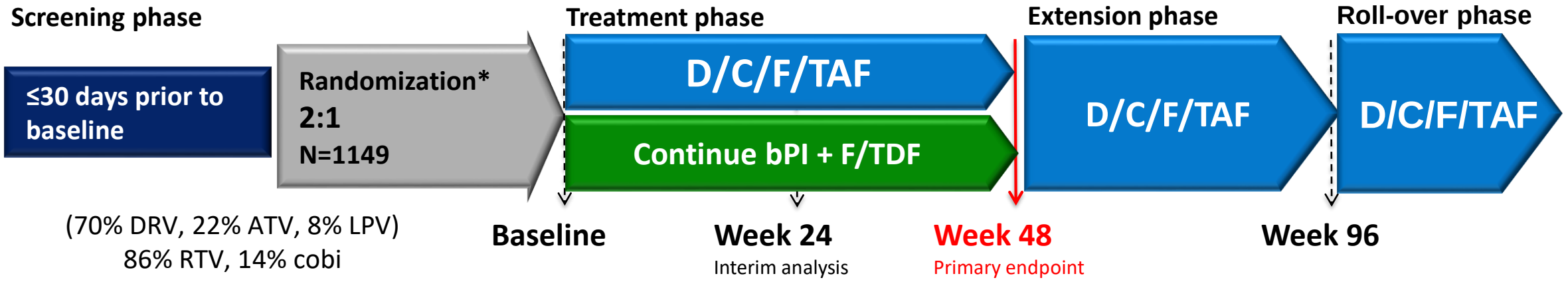
Virologic Suppression by Study and Preexisting M184V/I



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.

EMERALD: Open-label, Randomized, Phase III Trial



Key inclusion criteria:

- Previous ART VF allowed **(15% overall; 7% VF on a PI). 70% receiving DRV.**
- Absence of history of VF on DRV, and if historical genotype available, absence of DRV RAMs[†]
- **Viral load (VL) <50 c/mL for ≥2 months** before screening; **one 50≤VL<200 c/mL within 12 months prior to screening allowed**

116/763 had prior VF. 31/116 (32%, 4% overall) had an archived M184V/I

Erkki Lathouwers. HIV Glasgow 28–31 October 2018; #294.

Orkin C, et al. IDWeek 2017. Abstract 1689b. C Orkin. Lancet HIV 2018; 5: e23–34

Switch ART recommendation with archived NRTI resistance

IAS–USA
International Antiviral Society–USA

Similar results have been seen with switches to BIC/FTC/TAF in people with resistant virus.[43,44] Preexisting M184V/I mutations had no effect on efficacy in this setting.[45] In addition, prospective studies of people with treatment failure show high rates of viral suppression with dolutegravir plus 2 nRTIs,[46,47] implying that this regimen would maintain suppression regardless of nRTI resistance. By contrast, switches to first-generation InSTIs (raltegravir

GeSIDA
GRUPO DE ESTUDIO DEL SIDA-SEIMC

seimc

En los pacientes con MR a ITIAN previas se ha comprobado que los cambios a BIC/FTC/TAF, DTG+FTC/TAF o DTG/3TC/ABC pueden mantener la eficacia virológica, especialmente en PVV con CVP suprimida previa al cambio durante más de seis meses[12,13]. Las combinaciones de TAF/FTC/DRV/c + DTG o TAF/FTC/BIC + DRV/c [14], con

RT Gandhi. JAMA 2022; doi:10.1001/jama.2022.22246. Disponible en: https://gesida-seimc.org/category/guias-clinicas/.

Take homes.

- **The <u>emergence of HIV-1 resistance</u>** must be seen as **<u>a preventable drug-related AE</u>**.
- **The clinical relevance** of a high resistance barrier is **pivotal to preserve ART efficacy**.
- **Archived NRTI resistance is common** (8-10%), **often not suspected by clinicians**, even with no prior known VF.
- **It has no impact at switch on BIC/F/TAF or DRVc/F/TAF efficacy**. Robust data → Guidelines.
- **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)**.