SCUOLA DI SPECIALIZZAZIONE IN MALATTIE INFETTIVE E TROPICALI
PANDORA ID - 24
TIME TO WEBINAR IN INFECTIOUS DISEASES
HIV INFECTION:
FROM PATHOGENESIS
TO NEW TREATMENT OPTIONS
Milano, 2 Maggio 2024
Centro Congressi StaHotels Ritz

Terapia antiretrovirale duplice e triplice nel paziente naive

Diego Ripamonti
Malattie Infettive
Bergamo

dichiarazione sul conflitto d’interessi

Il sottoscritto **RIPAMONTI DIEGO**
in qualità di relatore

ai sensi dell’art. 76 sul Conflitto di Interessi, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara

che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Janssen, Merck, Gilead, ViiV Healthcare

GUIDELINES for the treatment of HIV-1 infection in naive PWH

IAS-USA, DHHS, EACS

Global Recommended Initial ART Regimens

3DR (II-based)

IAS-USA 2022[1]
FOR MOST PEOPLE WITH HIV
BIC[±]/FTC/TAF[¥]
DTG[±] + TAF[¥]/FTC or TDF[¥]/(FTC or 3TC)
DTG[±]/3TC[¤]

DHHS 2023[2]
FOR MOST PEOPLE WITH HIV WITH NO HISTORY OF CAB-LA PrEP
BIC/FTC/TAF[‡]
DTG/3TC[‡]/ABC[**]
DTG + (TAF or TDF)[*] + (FTC or 3TC[‡])
DTG/3TC[§]
FOR MOST PEOPLE WITH HIV WITH A HISTORY OF CAB-LA PrEP[§§]
bDRV + (TAF or TDF)[*] + (FTC or 3TC[‡])

EACS 2023[3]
RECOMMENDED REGIMENS[Ω]
BIC/FTC/TAF[II]
DTG + ABC/3TC[I,II] or DTG/ABC/3TC[I,II]
DTG + (TAF/FTC or TDF/XTC)[II,III]
RAL[‡] + TAF/FTC or TDF/XTC[II,III,IV]
XTC + DTG or 3TC/DTG[II,V]
DOR + (TAF/FTC or TDF/XTC) or TDF/3TC/DOR[II,III,VI]

2DR

bPI

Dora

Click on the blue annotation symbols to access footnotes

Recommended for rapid start

1. Gandhi RT, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2022 Recommendations of the International Antiviral Society–USA Panel. JAMA. 2023;329(1):63–84. Available at:https://jamanetwork.com/journals/jama/fullarticle/2799240. Accessed January 2023
2. DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV, March 2023. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed May 2023
3. EACS. Guidelines Version 12.0, October 2023. Available at https://eacs.sanfordguide.com/. Accessed November 2023

BIC/FTC/TAF vs DTG-based 3D regimen as first-line therapy: 48-week data

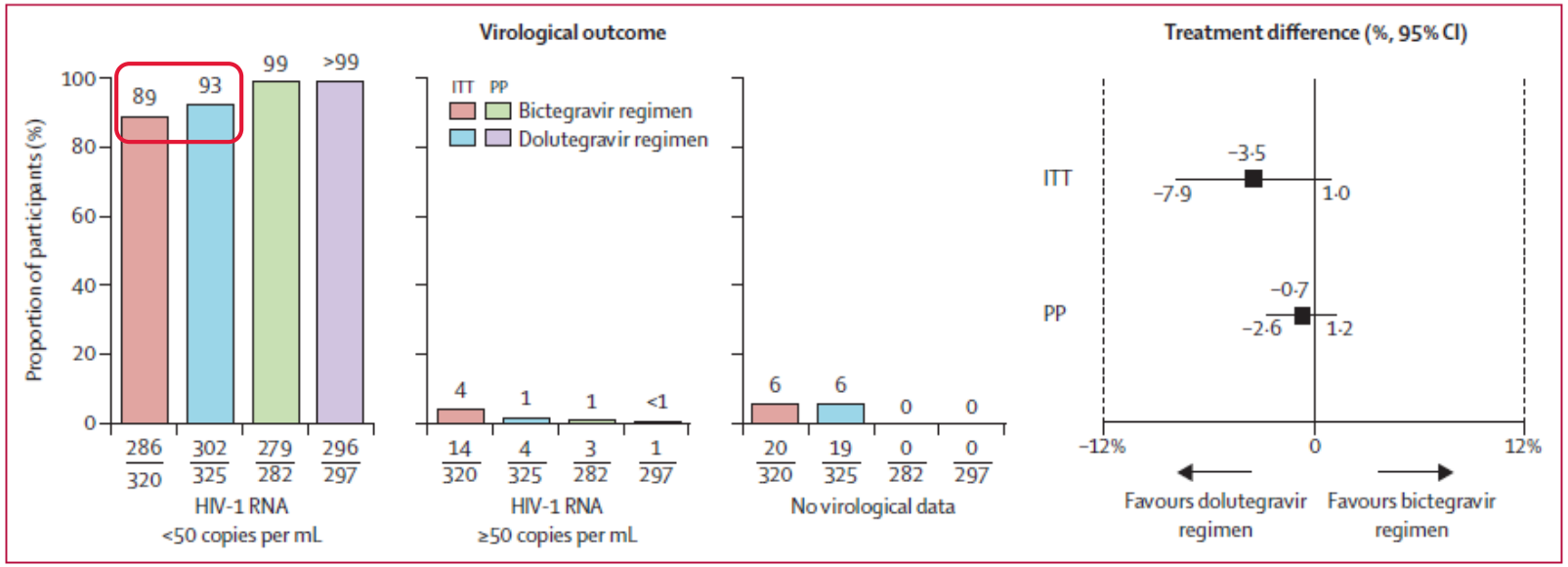


Figure 2: **Virological outcome at week 48**

GS-US-380–1490 study
BIC/FTC/TAF (320 pts) *versus*
DTG + FTC/TAF (325 pts)

DRMs (virological failure N):
BIC/FTC/TAF: 0 (14)
DTG + FTC/TAF: 0 (4)

Sax EP et al. Lancet 2017;390: 2073–82

	B/F/TAF group (n=314)	DTG/ABC/3TC group (n=315)	B/F/TAF *vs* DTG/ABC/3TC	
			Difference (95% CI)*	p value†
HIV-1 RNA <50 copies per mL	290 (92·4%)	293 (93·0%)	−0·6% (−4·8 to 3·6)	0·78
HIV-1 RNA ≥50 copies per mL	3 (1·0%)	8 (2·5%)	..	..
HIV-1 RNA ≥50 copies per mL	2 (0·6%)	6 (1·9%)	..	..
Discontinued because of poor efficacy	0	0	..	..
Discontinued for other reasons (last available HIV-1 RNA ≥50 copies per mL)‡	1 (0·3%)	2 (0·6%)	..	..

GS-US-380–1489 study
BIC/FTC/TAF (314 pts) *versus*
DTG/ABC/3TC (315 pts)

DRMs (virological failure N):
BIC/FTC/TAF: 0 (3)
DTG/ABC/3TC: 0 (8)

Gallant J et al. Lancet 2017;390: 2063–72

BIC/FTC/TAF vs DTG-based 3D regimen as first-line therapy: 144-week data

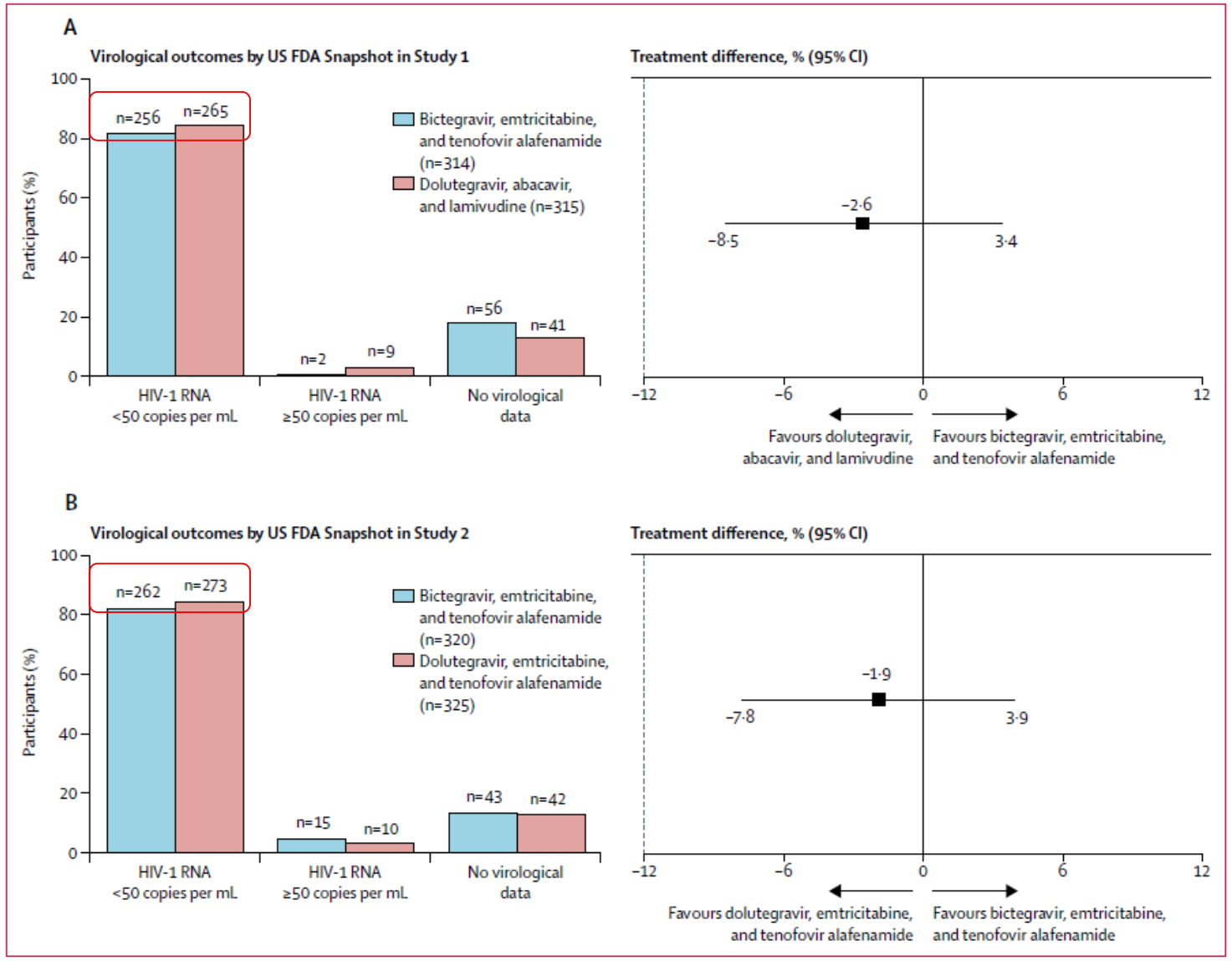


Figure 3: **Virological outcomes at week 144**
Percentage treatment difference was adjusted for both studies. FDA=Food and Drug Administration.

GS-US-380–1489 study

BIC/FTC/TAF (314 pts) *versus*
DTG/ABC/3TC (315 pts)

DRMs (virological failure N):
BIC/FTC/TAF: 0 (2)
DTG/ABC/3TC: 0 (9)

GS-US-380–1490 study

BIC/FTC/TAF (320 pts) *versus*
DTG + FTC/TAF (325 pts)

DRMs (virological failure N):
BIC/FTC/TAF: 0 (15)
DTG + FTC/TAF: 0 (10)

Orkin et al. Lancet HIV 2017;390: 2063–72

REAL LIFE: Long-term outcomes of BIC/FTC/TAF as first-line therapy (ICONA cohort)

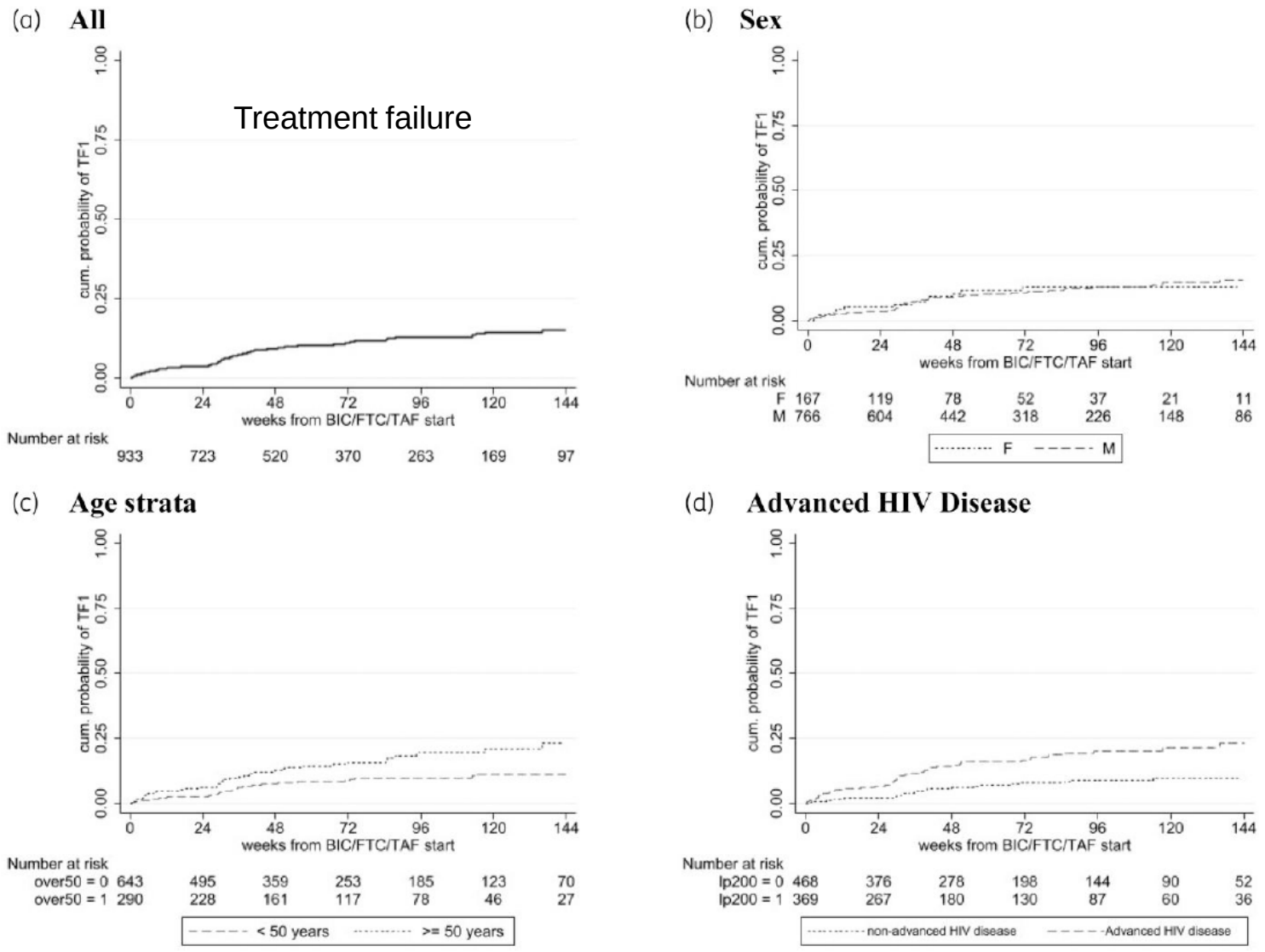


Figure 1. Kaplan–Meier curves and probabilities of TF at different timepoints among naive PWH initiating BIC/FTC/TAF: (a) all and according to (b) sex, (c) age strata and (d) advanced HIV disease.

933 ART-naive:
- CD4 < 200 cells = **38.8**%
- HIV-RNA >10^5 c/ml = **52.2**%
- late presenter: **57**%
- HCV Ab + = 4.6%
- HBsAg + = 2.7%

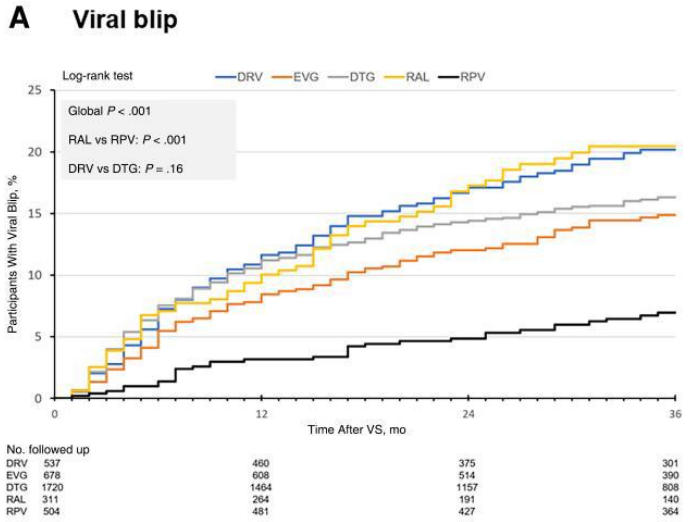
Median follow-up of 69.8 weeks

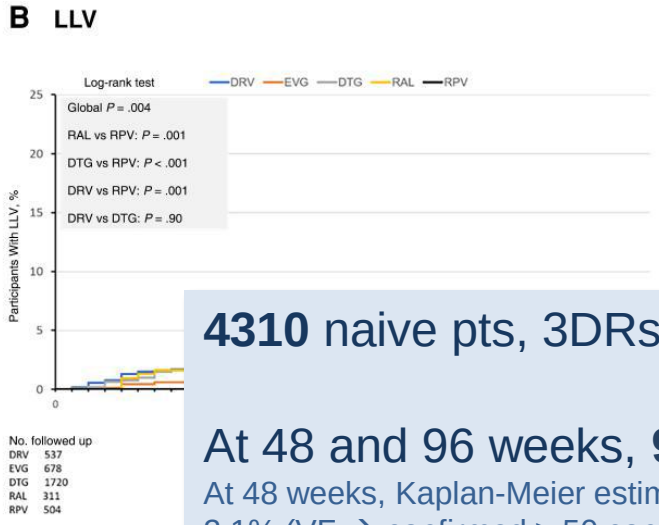
Probability:
- Treatment failure = 89 (**9.6**%)
- Virological failure = 38 pts
- Discontinuation = 38 pts

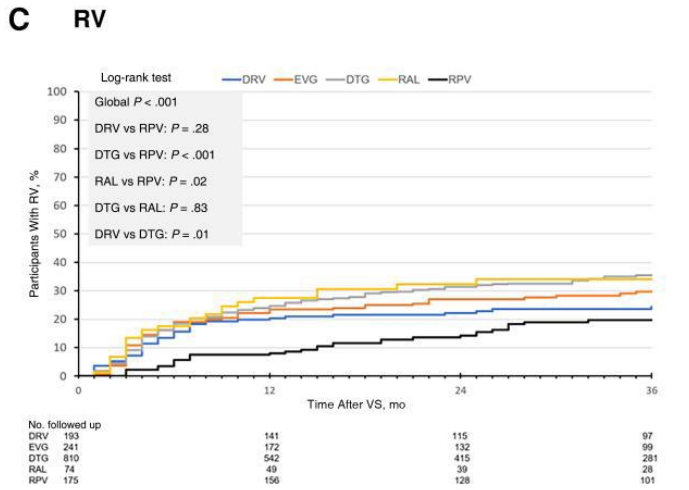
d'Arminio Monforte A et al JAC; March 2024

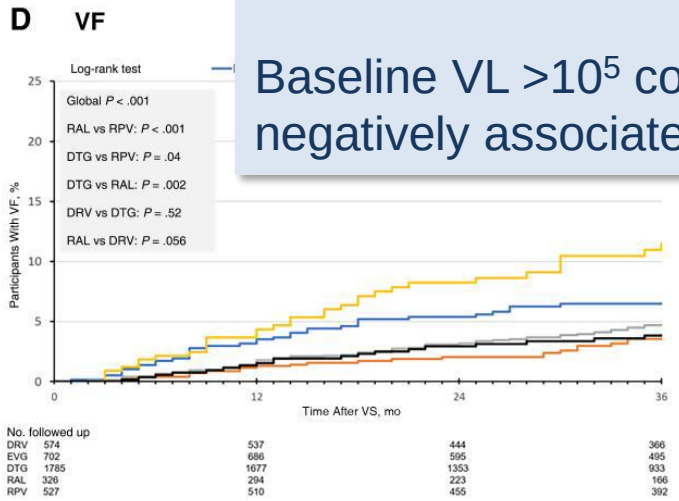
Plasma HIV RNA and CD4+ T-Cell Counts Are Determinants of Virological Nonsuppression Outcomes with Initial Integrase Inhibitor-Based Regimens:

Prospective RESPOND Cohort Study (International Cohort Consortium of Infectious Diseases) Study Group









4310 naive pts, 3DRs (72% on INSTI-based), in 2014 - 2020.

At 48 and 96 weeks, **91.0% and 93.3%** achieved VS.

At 48 weeks, Kaplan-Meier estimates of rates were 9.6% (**blips)**, 2.1% (**LLV)**, 22.2% **(RV)**, 2.1% (VF → confirmed > 50 copies**).**

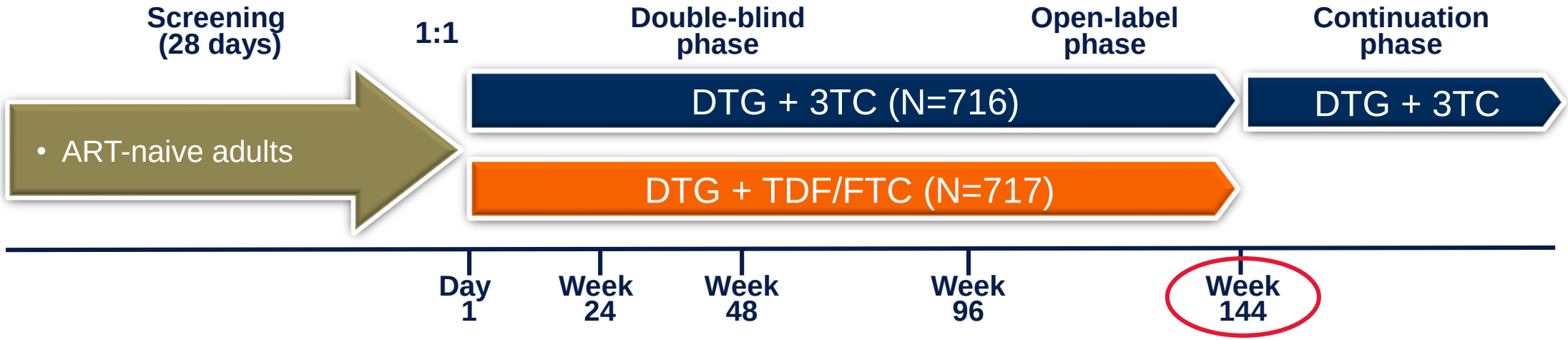
Baseline VL >10^5 copies/mL and CD4+ ≤200/µL were negatively associated with VS at weeks 48

Alvarez H et al. CID 2023:77 ; 593

GEMINI 1&2 trials

DTG + 3TC *versus* DTG + FTC/TDF

Identically designed, randomized, double-blind, parallel-group, multicenter, non-inferiority studies



Eligibility criteria
- VL 1000-500,000 c/mL at screening
- ≤10 days of prior ART
- No major RT or PI resistance mutation
- No HBV infection or need for HCV therapy

Primary endpoint at Week 48: participants with HIV-1 RNA <50 c/mL (ITT-E Snapshot)[a]

Countries

Argentina	Australia	Belgium
Canada	France	Germany
Italy	Republic of Korea	Mexico
Netherlands	Peru	Poland
Portugal	Romania	Russian Federation
South Africa	Spain	Switzerland
Taiwan	United Kingdom	United States

Baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm^3).

[a]–10% non-inferiority margin for individual studies.

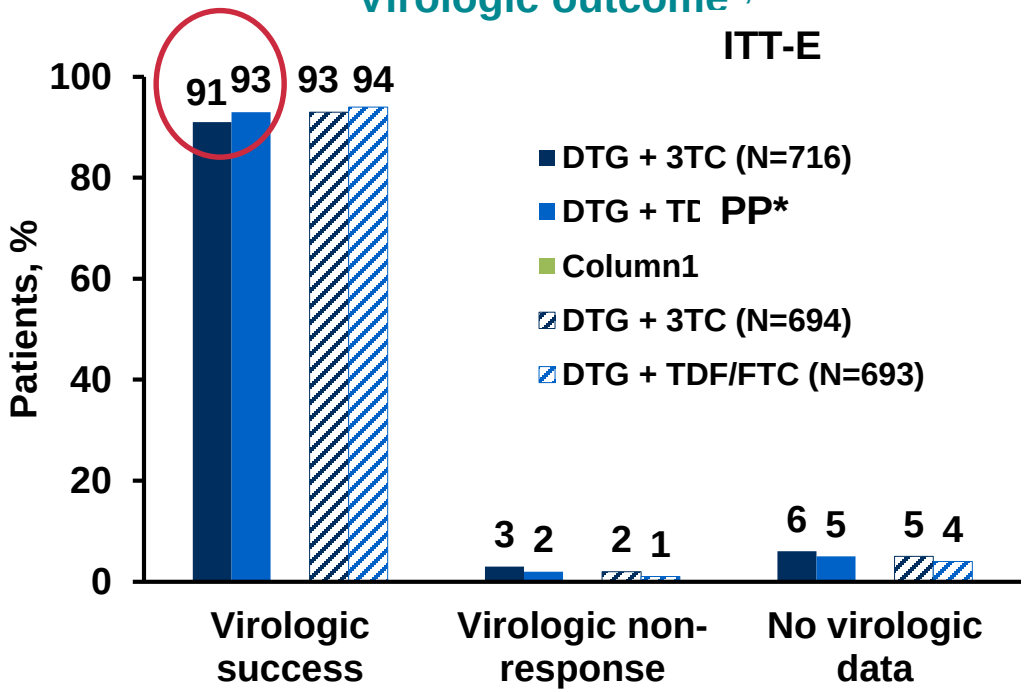
Cahn et al. IAS 2019; Mexico City, Mexico. Slides WEAB0404LB.

GEMINI 1&2 trials

DTG + 3TC *versus* DTG + FTC/TDF

week 48

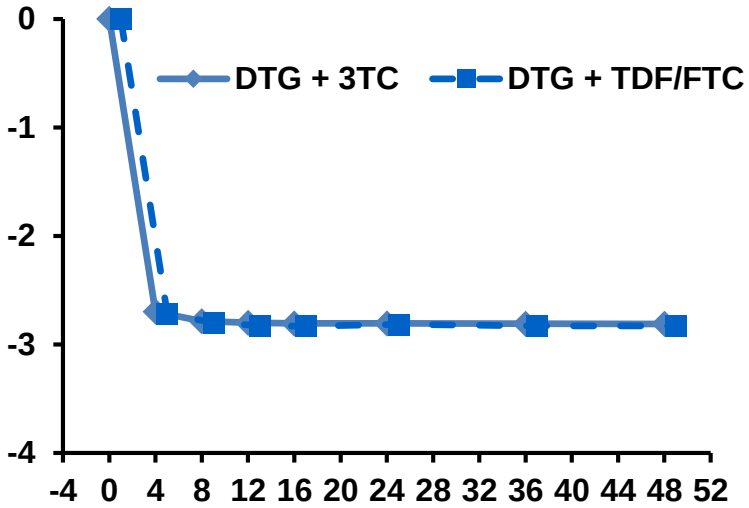
Virologic outcome[1,2]



- Data pooled from both GEMINI-1 and -2 studies
*PP population consisted of subjects in the ITT-E population except those with protocol violations that could affect assessment of antiviral activity; †Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm^3).[1] PP, per protocol

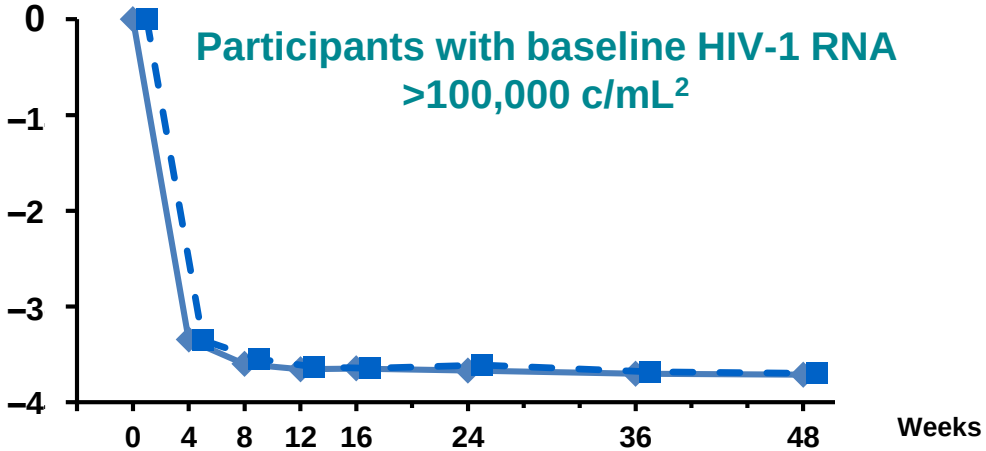
Adapted from: 1. Cahn P, et al. Lancet 2019;393:143–55
2. Cahn P, et al. IAS 2018. TUAB0106LB

Viral Load Decline by study arm



DTG + 3TC, n	716	704	681	688	674	664
DTG + TDF/FTC, n	717	699	688	688	681	675

Participants with baseline HIV-1 RNA >100,000 c/mL[2]



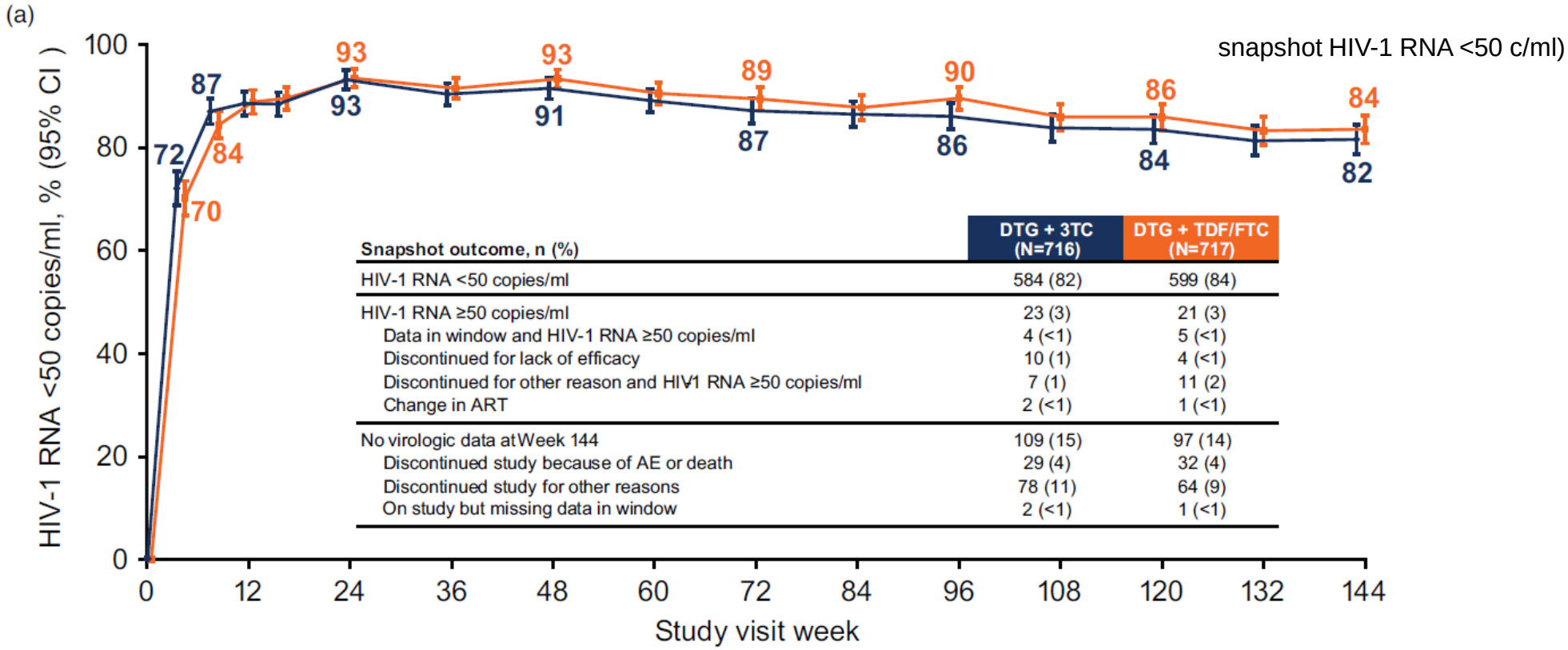
	140	138	139	135	135	138	132	132
	153	152	153	151	149	145	141	139

Adapted from: 1. Cahn P, et al. Lancet 2019;393:143–55 plus supplementary appendix
2. Eron J, et al. HIV DART and Emerging Viruses 2018. Oral Presentation 7

GEMINI 1&2 trials

DTG + 3TC *versus* DTG + FTC/TDF

No emergence of resistance



Snapshot outcome, n (%)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
HIV-1 RNA <50 copies/ml	584 (82)	599 (84)
HIV-1 RNA ≥50 copies/ml	23 (3)	21 (3)
Data in window and HIV-1 RNA ≥50 copies/ml	4 (<1)	5 (<1)
Discontinued for lack of efficacy	10 (1)	4 (<1)
Discontinued for other reason and HIV1 RNA ≥50 copies/ml	7 (1)	11 (2)
Change in ART	2 (<1)	1 (<1)
No virologic data at Week 144	109 (15)	97 (14)
Discontinued study because of AE or death	29 (4)	32 (4)
Discontinued study for other reasons	78 (11)	64 (9)
On study but missing data in window	2 (<1)	1 (<1)

One DTG + 3TC participant (with no adherence), not meeting CVW criteria, developed M184V (week 132) and R263R/K (week 144) conferring a 1.8-fold change in susceptibility to DTG.

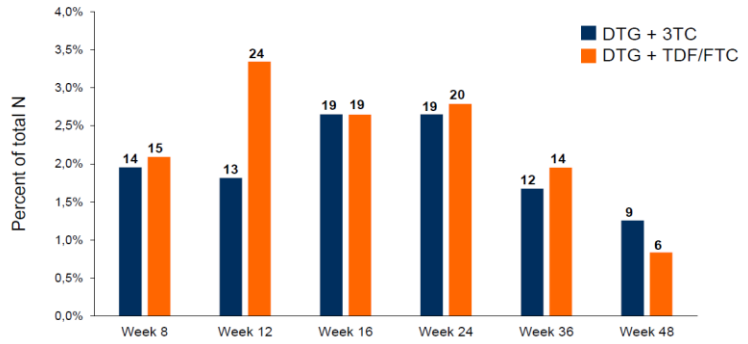
Cahn P et al. AIDS. 2022 ;36:39-48.

GEMINI 1&2 trials

DTG + 3TC *versus* DTG + FTC/TDF

Blip Frequencies and Number by Visit

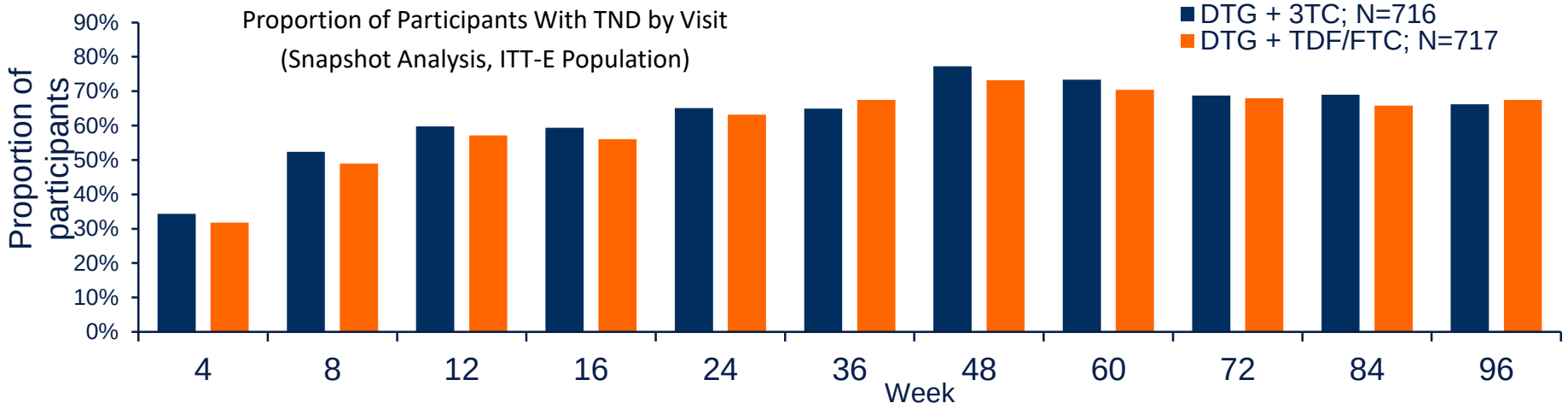
- Similar 'blip' frequencies were seen across arms



Bold numbers on chart are # of blips at given week visits. Note that individual subjects in Category 1a can have had more than one blip.

Underwood et al. IAS 2019; Mexico City, Mexico. Poster MOPEB231.

10th IAS Conference on HIV Science; July 21-24, 2019; Mexico City, Mexico

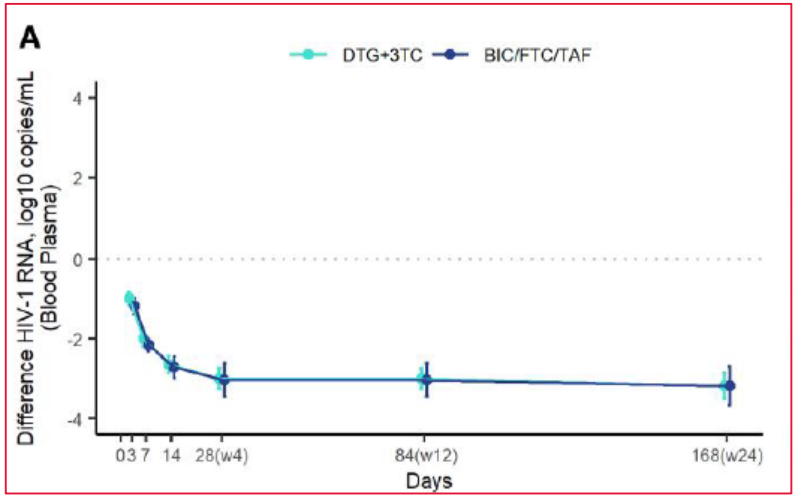


Underwood M et al. EACS 2019; Basel, Switzerland. Slides PS8/2.

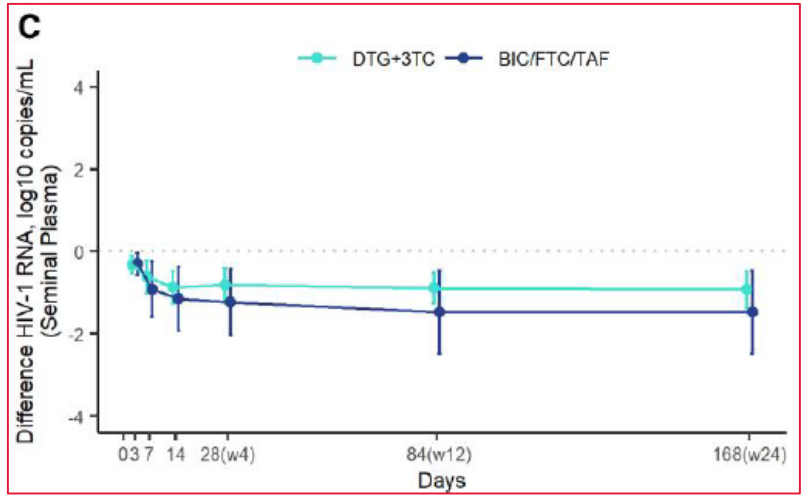
Decay kinetics of HIV-1-RNA in seminal plasma with **DTG/3TC** *versus* **3DR** in treatment-naive PLWH

25 individuals

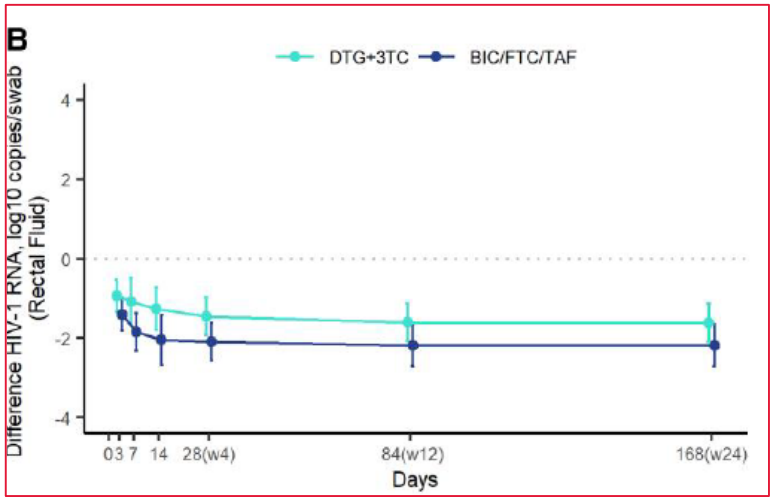
blood fluid



seminal fluid



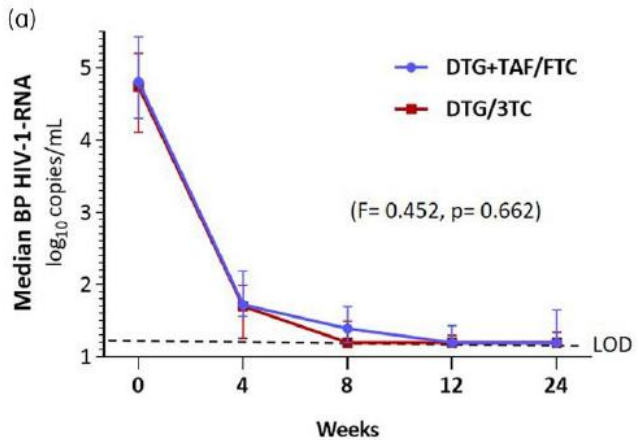
rectal fluid



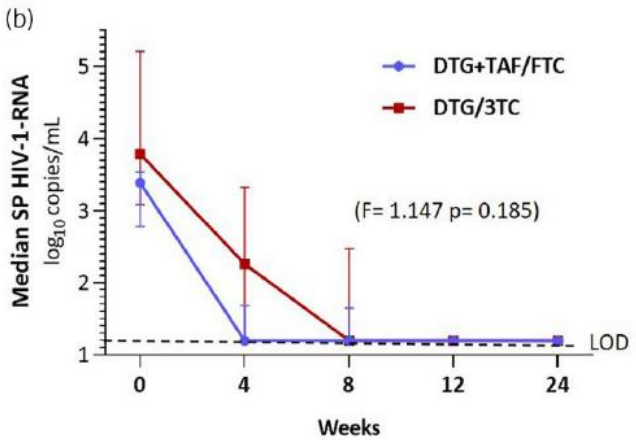
Scevola S et al. JID 2023;228:919–25

31 individuals

blood fluid

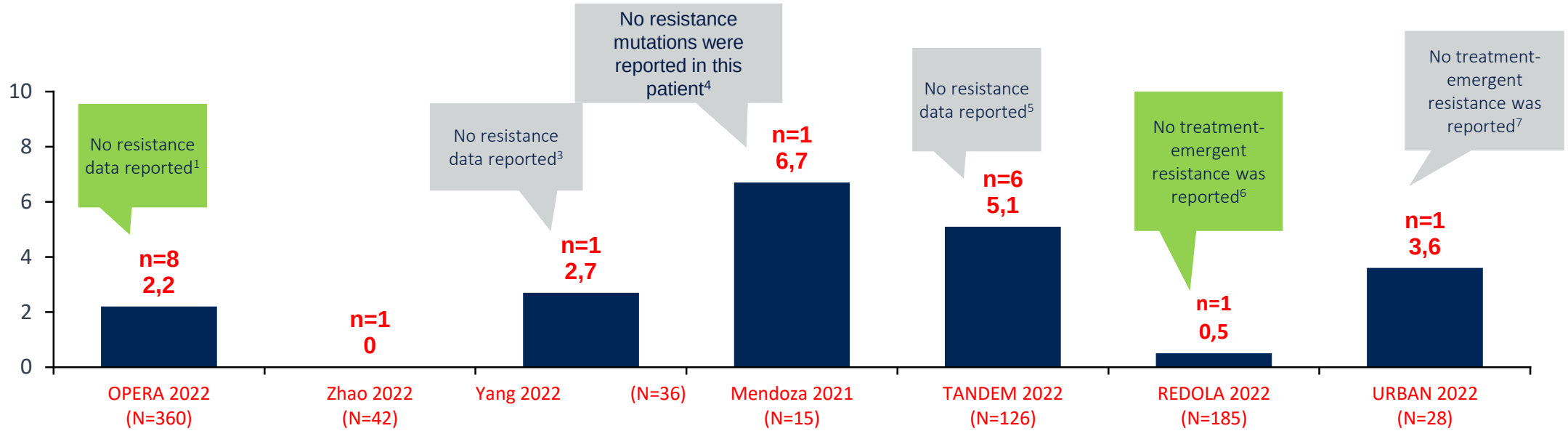


seminal fluid



Saborido-Alconchel A et al. JAC 2023;78:2354–2360

Virologic failure and resistance in treatment-naïve pts treated with DTG + 3TC **in real-world studies**



Timepoint	24 weeks[1]	48 weeks[2]	48 weeks[3]	48 weeks[4]	Mean 1.3 years[5]	96 weeks[6]	2 years[7]
Comments	Eight patients developed VF at Week 24. Incidence rate over follow-up: 1.74/100 PY (95% CI: 0.87, 3.49)	One patient had detectable VL after COVID-19 vaccination not considered VF caused by treatment	One patient had VF due to non-adherence (skipping pills for 75 days)	One patient had VF; time to VF was 31.3 weeks	Six patients rebounded following virologic suppression	One patient developed VF at Week 96 but continued DTG/3TC and achieved VL<50 c/mL	One patient discontinued for virologic reasons

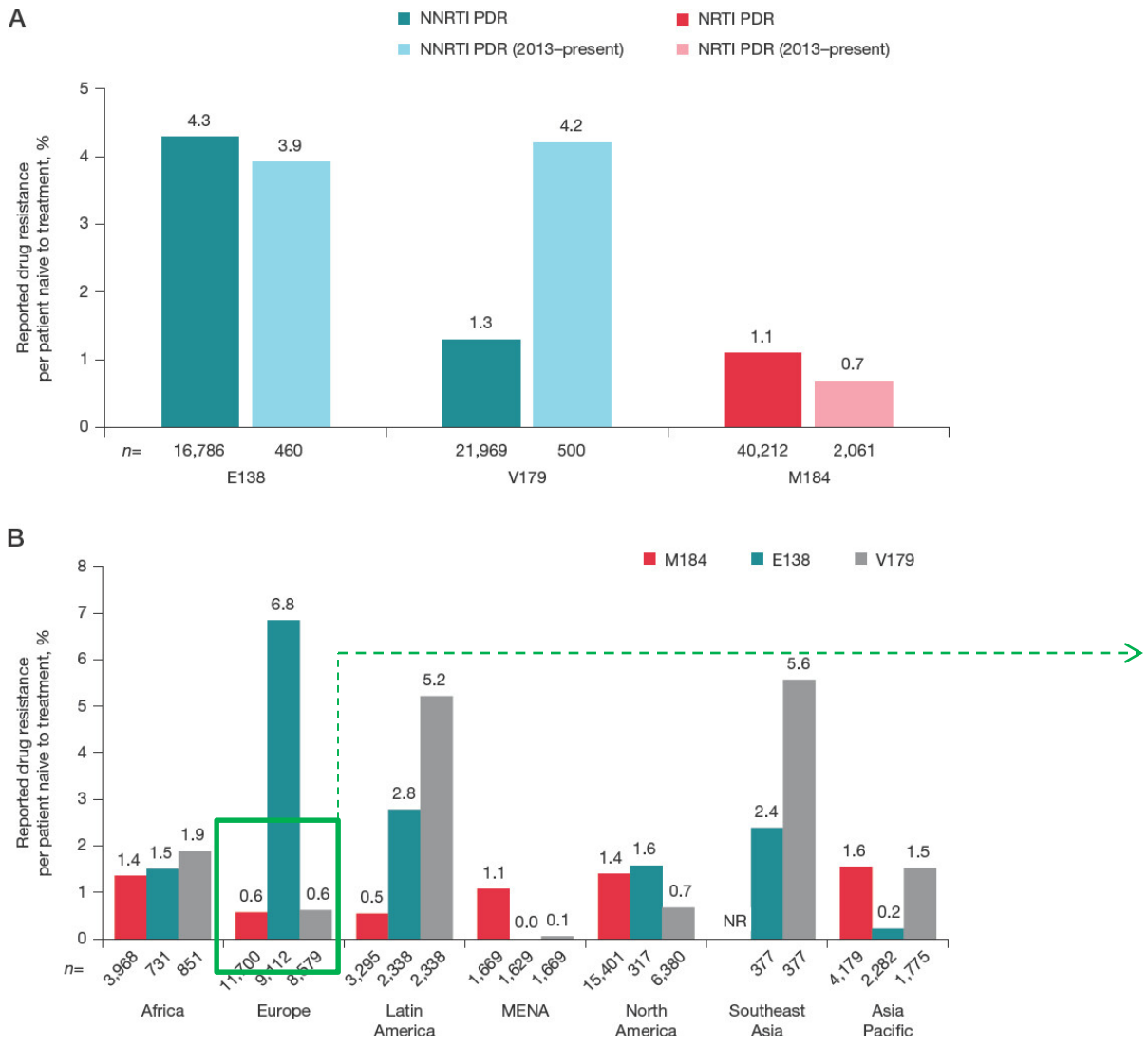
No treatment-emergent resistance has been reported in ART-naïve patients treated with DTG + 3TC in real life.
These data reinforce the high barrier to resistance of DTG+3TC observed in GEMINI-1 and -2 and DTG/3TC in STAT[8-10]

1. Pierone G, et al. HIV Glasgow 2022; Poster 057 **[119]** 2. Zhao F, et al. J Acquir Immune Defic Syndr, 2022; 91(S1): S16-S19 **[115]** 3. Yang X, et al. Expert Rev Anti Infect Ther 2022, doi:10.1080/14787210.2022.2128766 **[114]** 4. Mendoza I, et al. Ann Pharmacother 2021;10600280211034176 **[66]** 5. Schneider S, et al. AIDS 2022. Poster EPB147 **[108a]** 6. Pulido F, et al. HIV Glasgow 2022. Poster P059 **[20c]** 7. Beer D et al. HIV Glasgow 2022. Poster 177 **[87c]** 8. Cahn P, et al. Lancet 2019;393:143–55 9. Cahn P, et al. J Acquir Immune Defic Syndr 2020;83:310–8 10. Rolle CP, et al. AIDS 2021;35:1957–65

Includes unique cohorts reporting VF outcomes for ≥10 treatment-naïve patients receiving DTG + 3TC; reported outcomes vary between studies. Potential overlap between patient cohorts cannot be ruled out; *Definitions of VF: REDOLA, two consecutive plasma HIV-1 RNA ≥50 c/mL; Mendoza, confirmed HIV-1 RNA >50 c/mL without documented suboptimal compliance; URBAN, investigator's discretion, TANDEM, Yang and Zhao, not specified; ‡Three patients excluded from URBAN due to missing data
CI, confidence interval; **PY,** person-years; **PYFU,** person-years of follow-up

Transmitted Drug Resistance in treatment-naïve PLWH

Review with > 60.000 ART-naive PLH



Vannappagari V et al. Antivir Ther. 2019;24(6):393-404.

MeditRes is a consortium that includes ART-naive PWH newly diagnosed in France, Greece, Italy, Portugal, and Spain during 2018–2021: **2705** patients

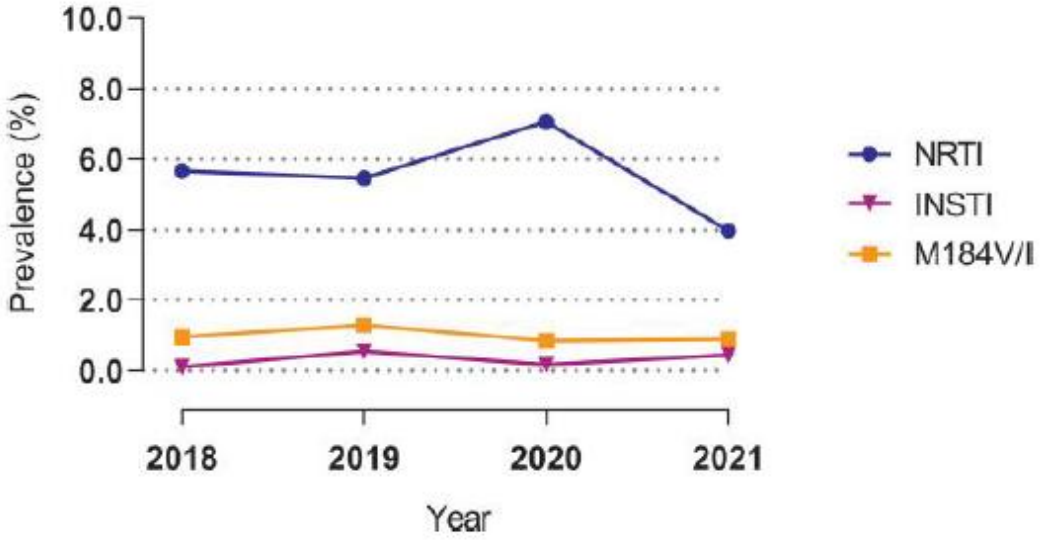


Figure 1. Prevalence of INSTI and NRTI surveillance drug resistance mutations across the 4-year study period. Abbreviations: INSTI, integrase strand transfer inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor.

de Salazar A et al. CID 2023; 76:1629

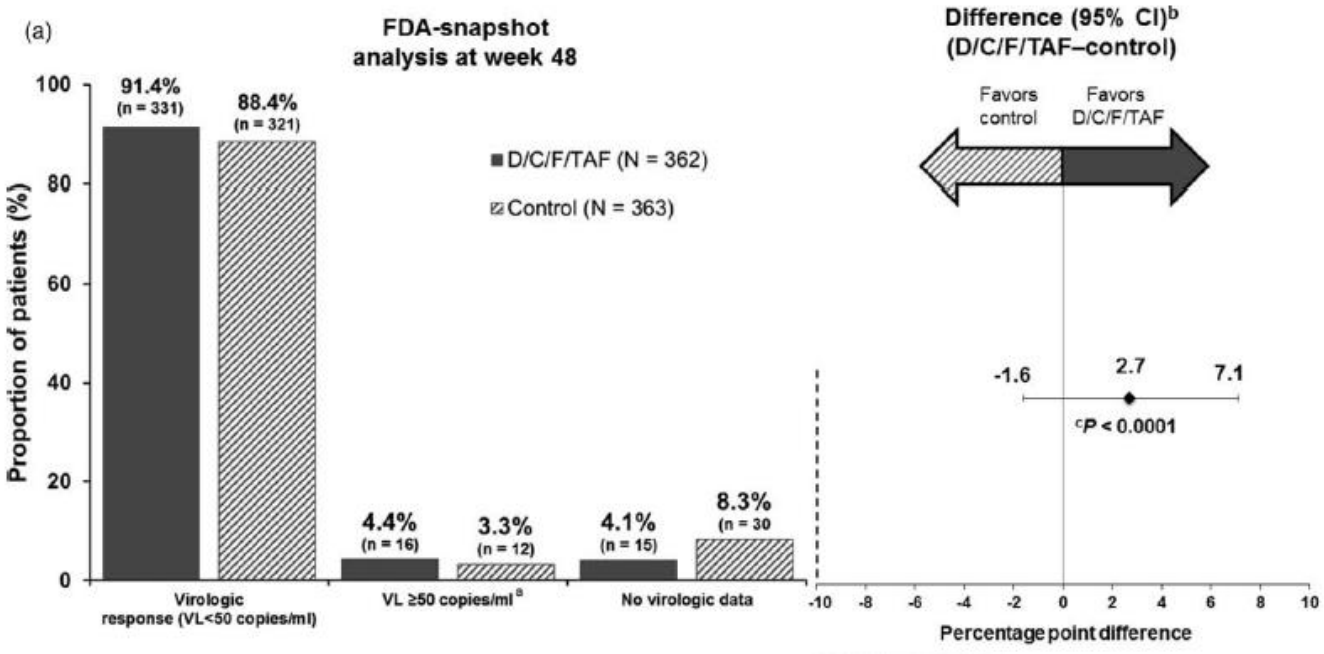
boosted DRV?

doravirine?

rapid ARV?

Boosted PI-based STR

AMBER: naive
DRV/c/FTC/TAF *versus* DRV/c + FTC/TDF



Eron JJ et al. AIDS 2018

1125 pazienti in STR, a 48 weeks:
PI-emergent mutations: 0

Lathouwers et al. AIDS Res Hum Retroviruses. 2020

EMERALD: experienced
switch to DRV/c /FTC/TAF (STR)

Orkin C et al. Lancet HIV 2018

Risk of virological failure with DRMs for NNRTI-based regimens in naive patients

Study Follow-up	Study arms	HIV RNA < 50 c/ml (%)	Virological failures	NNRTI emergent resistance (NRTI resist)
Study 934 [1] 144 weeks	TDF+3TC+ **EFV** d4T+3TC+ **EFV**	82 81	47 (16%) 49 (16%)	**26**/47 (18 with 184V; 8 65R) **24**/49 (17 with 184V; 2 65R)
ECHO [2] 48 weeks	2NRTIs + **RPV** 2NRTIs + **EFV**	83 83	45 (13%) 19 (6%)	**26**/40 (+28 184V; 3 65R) **8**/13 (+ 4 184V)
DRIVE-AHEAD [3] 48 weeks	2NRTIs + **EFV** 2NRTIs + **DORA**	81 84	22 (6%) 14 (3.8%)	**7**/13 (5 with 184V) ** **12**/14 (5 with 184V)
DRIVE-FORWARD [4] 48 weeks	2NRTIs + **DRV-r** 2NRTIs + **DORA**	80 84	24 (%) 19 (11%)	0/8 (0) ** 0/7 (0)

** Testing for genotype required samples with HIV-1 RNA > 400 copies/ml

Week-96 data
AHEAD: 78% vs 74%
FORWARD: 73% (dora) vs 66%

1 Gallant JE et al. JAMA 2004
2 Molina JM et al. Lancet 2011
3 Orkin C et al. CID 2019
4 Molina JM Lancet HIV 2018

RAPID ART

STUDY	Regimen	Timing	N. of patients	ITT analysis (at week 48)	Baseline resistance	New resistence mutations (VF)
BIC NOW[1]	BIC/FTC/TAF	first visit (0-7 days)	208	84,1% *	0	0 (3)
STAT[2]	DTG/3TC	< 14 days	131	82% **	1 (M184V)	0 (2)
DIAMOND[3]	DRV-c/FTC/TAF	< 14 days	109	84%	2 (M184V)	0 (0)
FAST[4]	BIC/FTC/TAF	first visit (5-17 days)	112	84.8%	1 (M184V)	0 (14)
RAINBOW[5] *with advanced disease*	BIC/FTC/TAF	< 7 days	30	90%	0	0 (2)

1. Hidalgo-Tenorio C et al. Int J Antimicrob Agents. 2024 Apr 2:107164.
2. Rolle CP et al. Open Forum Infect Dis. 2023 Mar 1;10(3):ofad101.
3 Huhn GD et al. CID 2020:71(15 December);3111-17
4 Bachelard A et al. JAC 2023;78:769–778
5 Camici M et al. International Journal of Antimicrobial Agents 63 (2024) 107049

* **HBV coinfection**:
BIC NOW: 9
FAST: 2

** **ARV change in 10 pts**
HBV coinfection: 5
M184V mutation; 1
others 4

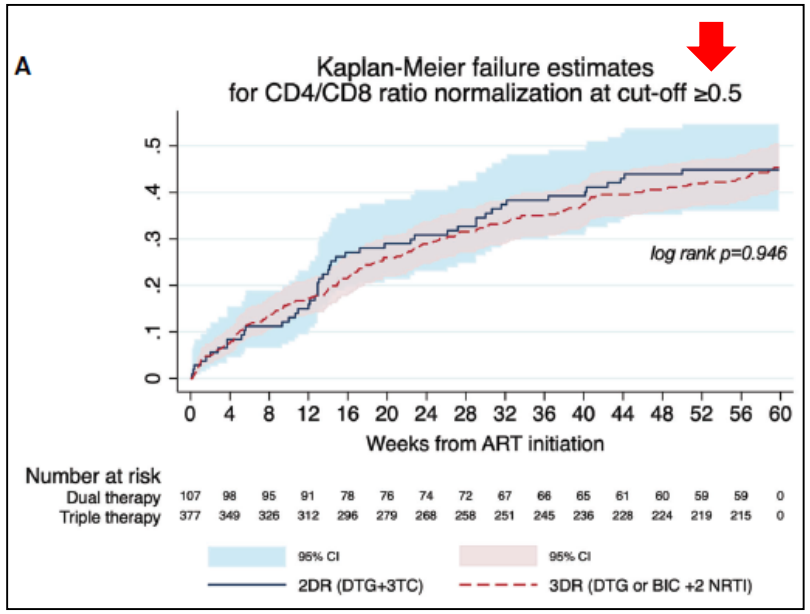
Grazie per l'attenzione

Back up slides

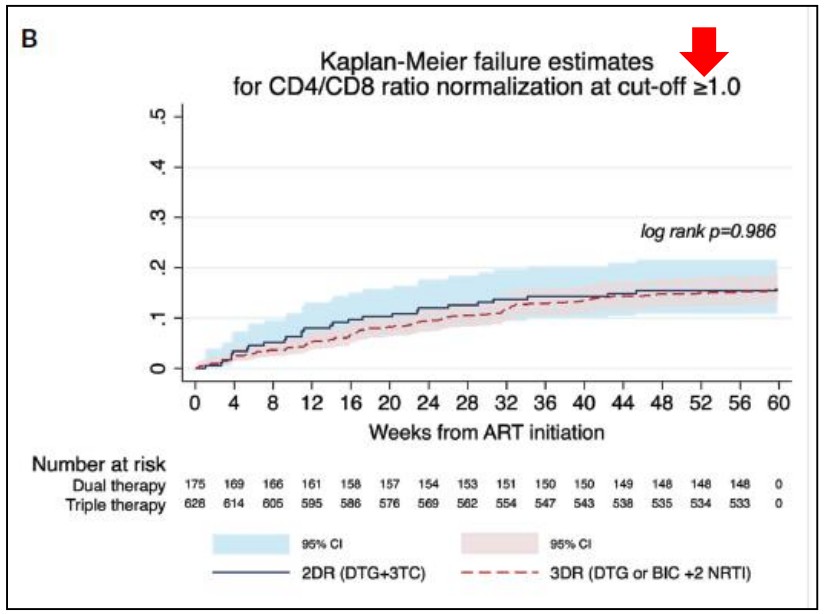
3DR versus 2DR (integrase-based) in ART-naïve pts: the effect on CD4/CD8 ratio recovery at week 48

At baseline: (median age: 37 ys), male: 88%, median CD4/CD8 ratio: 0.30

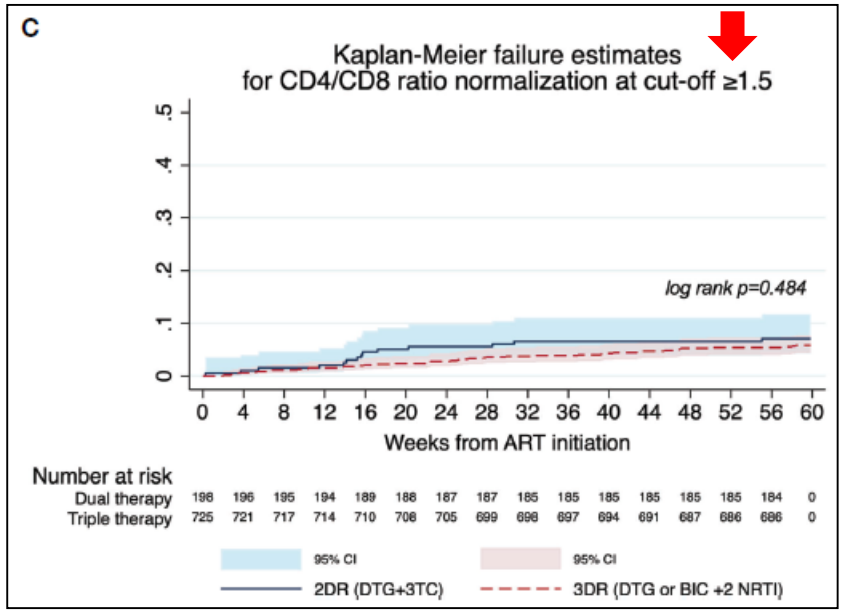
DTG/3TC: 108; Triple: 377



DTG/3TC: 176; Triple: 629



DTG/3TC: 198; Triple: 726



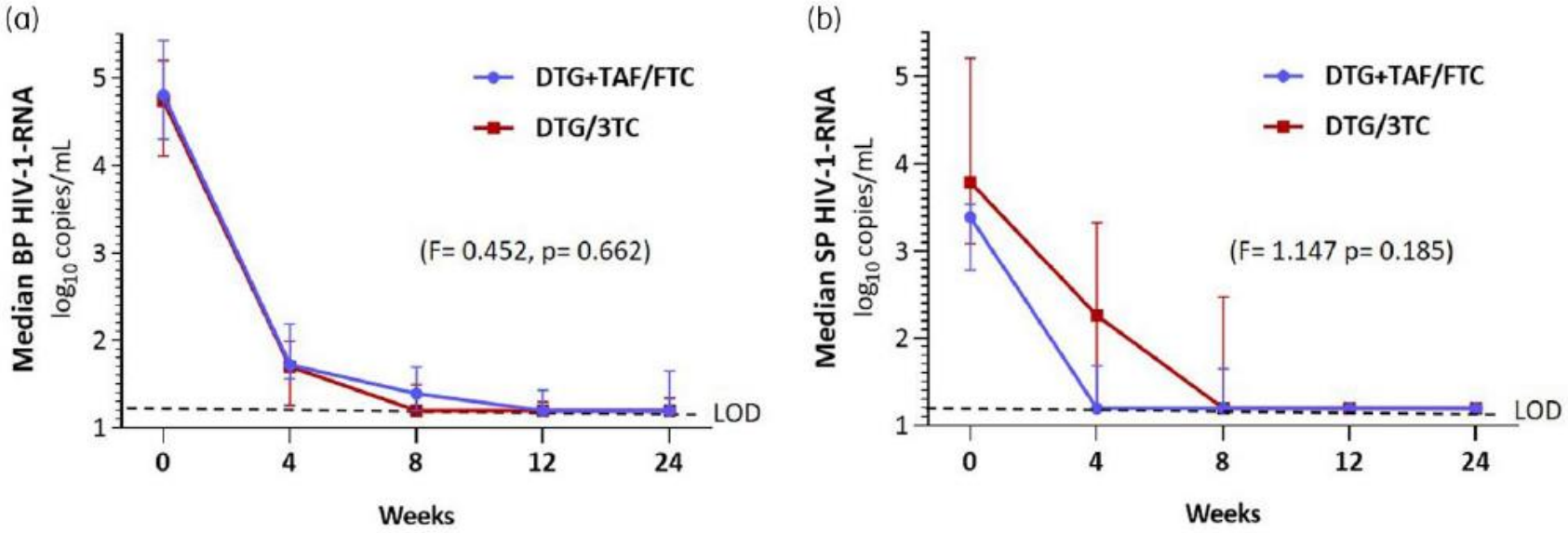
CD4/CD8 ratio recovery **rates are similar** during the first 48 weeks after ART initiation with DTG+3TC or three-drug INSTI-based regimens.

Martinez-Sanz J t al. Front Immunol (2022)13(March):1–6.

Decay kinetics of HIV-1-RNA in seminal plasma with **DTG/3TC** *versus* **DTG** +FTC/TAF in treatment-naive PLWH

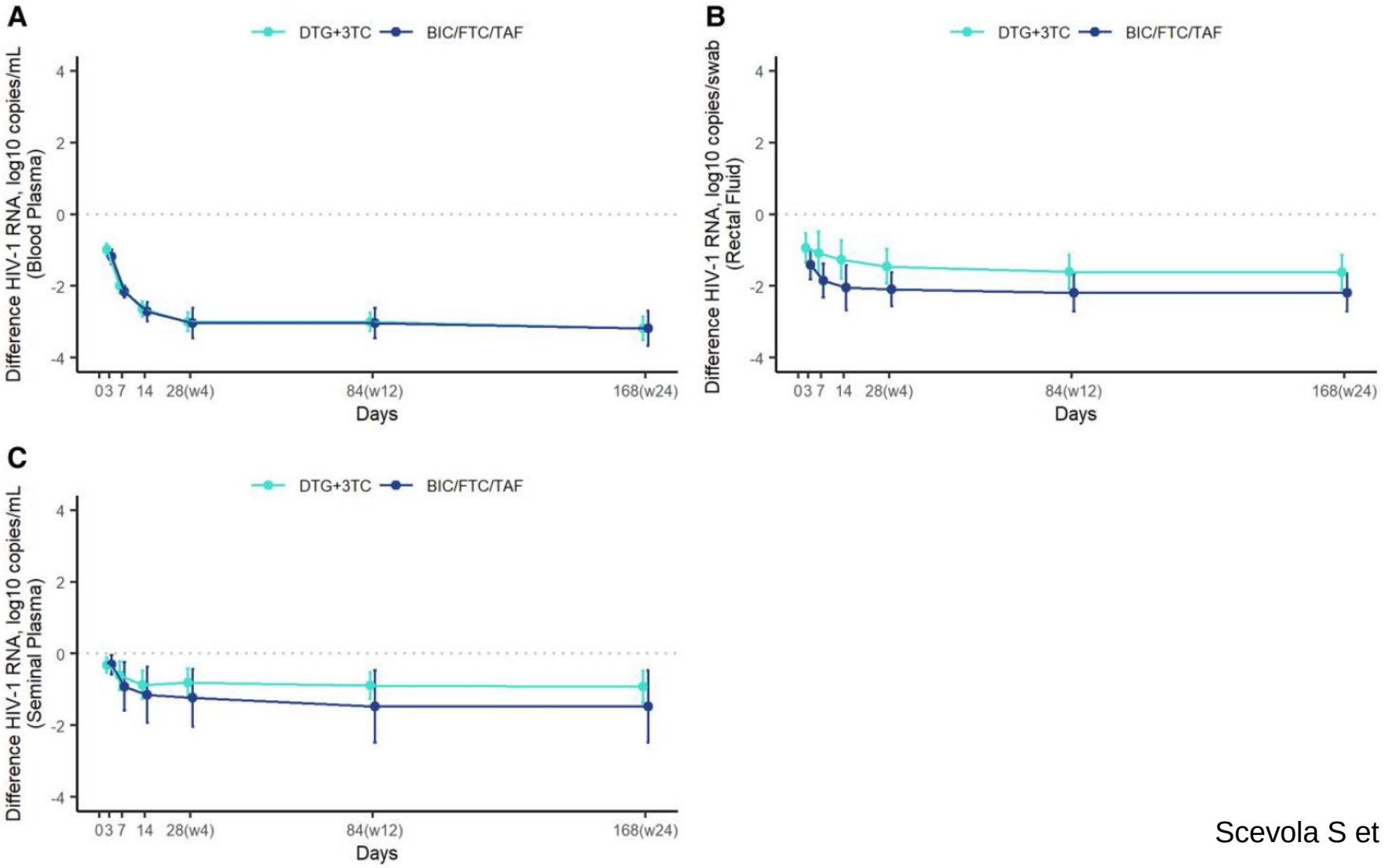
Table 1. Baseline demographic and clinical characteristics

Characteristic	DTG+TAF/FTC ($n=15$)	DTG/3TC ($n=16$)	*P* value
Age, years	28 (24–43)	27 (24–35)	0.861
Risk for HIV-1 infection, MSM	15	14	
Smoker, yes	3 (20.0)	4 (25.0)	0.739
Recreational drugs, yes	1 (6.7)	4 (25.0)	0.333
BMI, kg/m^2	23.5 (22.5–25.2)	22.6 (19.9–25.9)	0.512
CD4+ T cell counts/mm^3	394 (239–558)	454 (347–638)	0.295
CD4+/CD8+ ratio	0.57 (0.28–1.08)	0.50 (0.42–0.73)	0.843
BP HIV-1-RNA, $\log_{10}$ copies/mL	4.81 (4.30–5.43)	4.76 (4.09–5.23)	0.469
SP HIV-1-RNA, $\log_{10}$ copies/mL	3.39 (2.78–3.54)	3.80 (2.51–5.21)	0.276



Saborido-Alconchel A et al. JAC 2023;78:2354–2360

Decay of HIV RNA in Seminal Plasma and Rectal Fluid with **DTG/3TC** vs **BIC**/F/TAF



Scevola S et al. JID 2023;228:919–25

48-Week effectiveness and tolerability of (DTG) + (3TC) in-naïve antiretroviral adults living with HIV: A multicenter real-life cohort

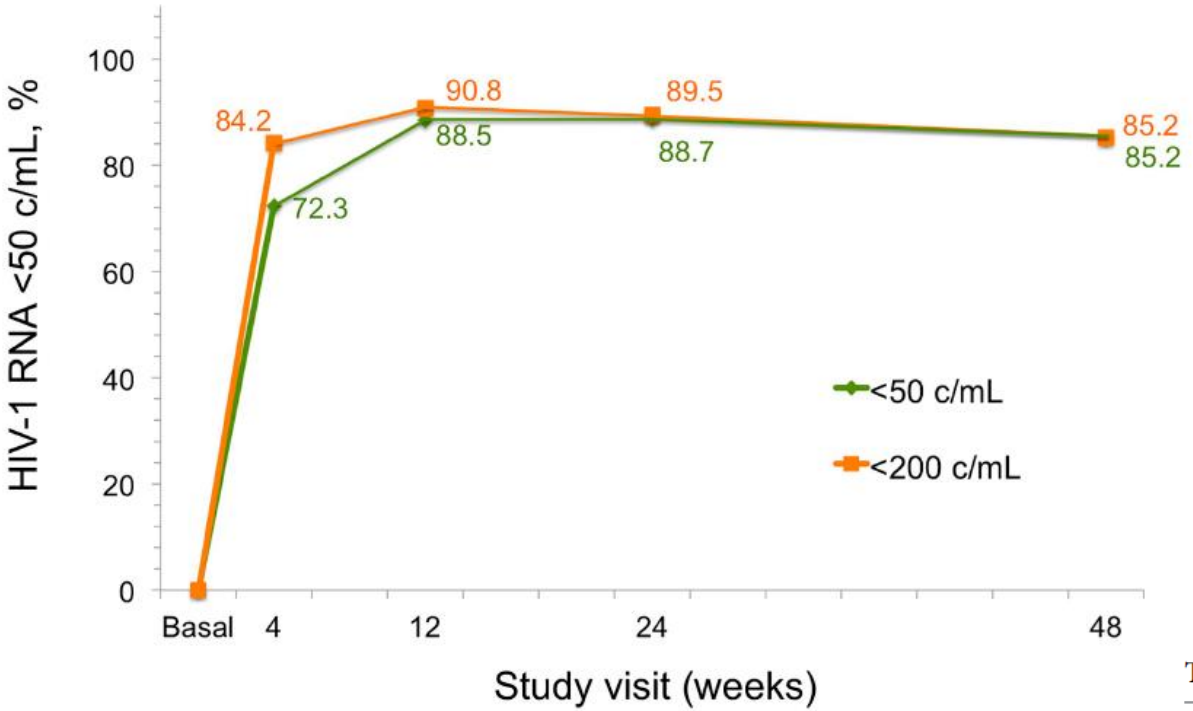


Fig 1. Proportion of participants with plasma HIV-1 RNA < 50 c/mL through week 48 by intention to treat (missing = failure) analysis.

As Spanish national guidelines allows starting ART without having the results of baseline HIV genotype testing.

Table 4. Disposition of the participants at week 48.

All participants	135
HIV-1 VL < 50 c/mL, n (%)	115 (85.2)
DISCONTINUATION, n (%)	6 (4.4)
• HIV-1 VL > 200 copies/mL	1 (0.7)
• CNS AE	3 (2.2)
• M184V mutation in bDRT	2 (1.5)
LOST TO FOLLOW- UP, n (%)	14 (10.4)

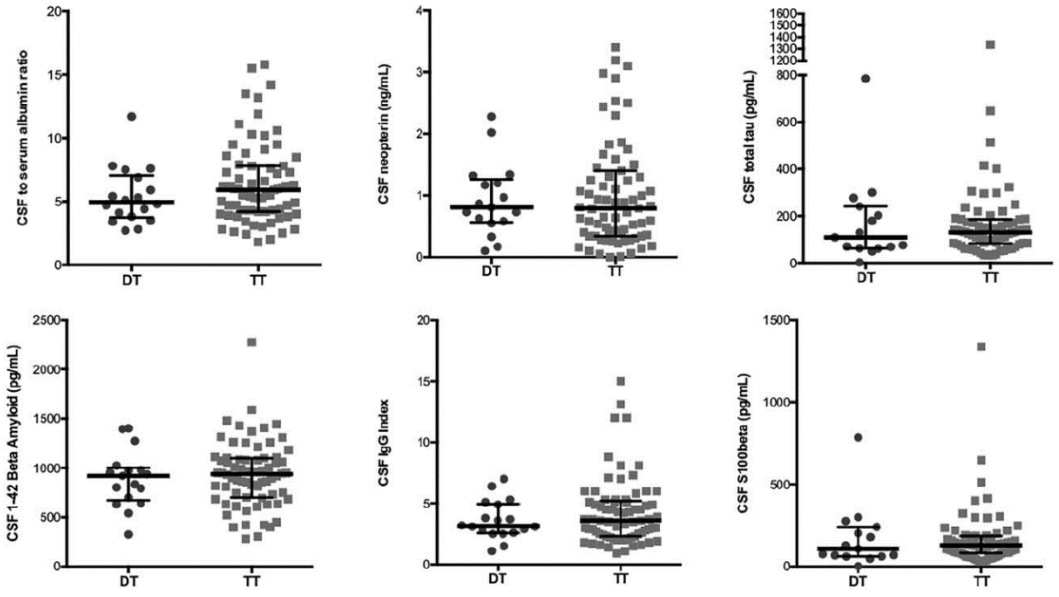
Cabello-Ubeda A, et al. PLoS ONE 17(11): e0277606

Dual antiretroviral therapies and Neuro-Cognitive Impairment

Objective: Aim of this study was to compare cerebrospinal fluid (CSF) virological control, biomarkers and neurocognition of neurologically symptomatic patients on dual antiretroviral therapies (dual therapy) vs. 2 nucleoside reverse transcriptase inhibitors-based three-drug regimens (triple therapy).

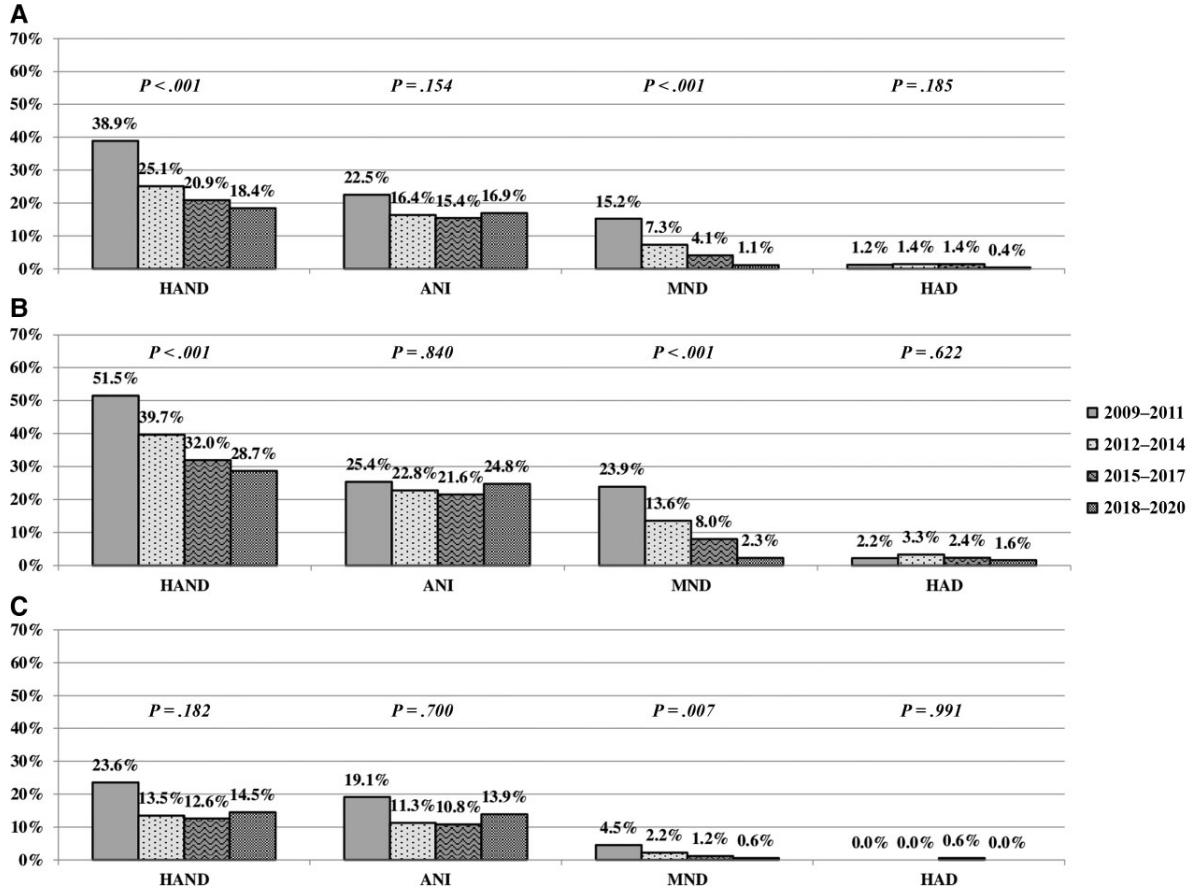
Design: Retrospective monocentric cross-sectional study.

A total of 78 patients on triple therapy and 19 on dual therapy



Trunfio M et al. AIDS 2020 34;13:1899-1906

1424 PLWH were enrolled during four 3-years periods. HAND prevalence was 24%, declined from 39% to18% in more recent years.



Mastrorosa I et al Clin Infect Dis. 2022 Aug 19

Bictegravir/emtricitabine/tenofovir alafenamide as initial treatment for HIV-1: five-year follow-up from two randomized trials

Paul E. Sax,[a,*] José R. Arribas,[b] Chloe Orkin,[c] Adriano Lazzarin,[d] Anton Pozniak,[e] Edwin DeJesus,[f] Franco Maggiolo,[g] Hans-Jürgen Stellbrink,[h] Yazdan Yazdanpanah,[i] Rima Acosta,[j] Hailin Huang,[j] Jason T. Hindman,[j] Hal Martin,[j] Jared M. Baeten,[j] and David Wohl,[k] on behalf of the GS-US-380-1489 and GS-US-380-1490 study investigators

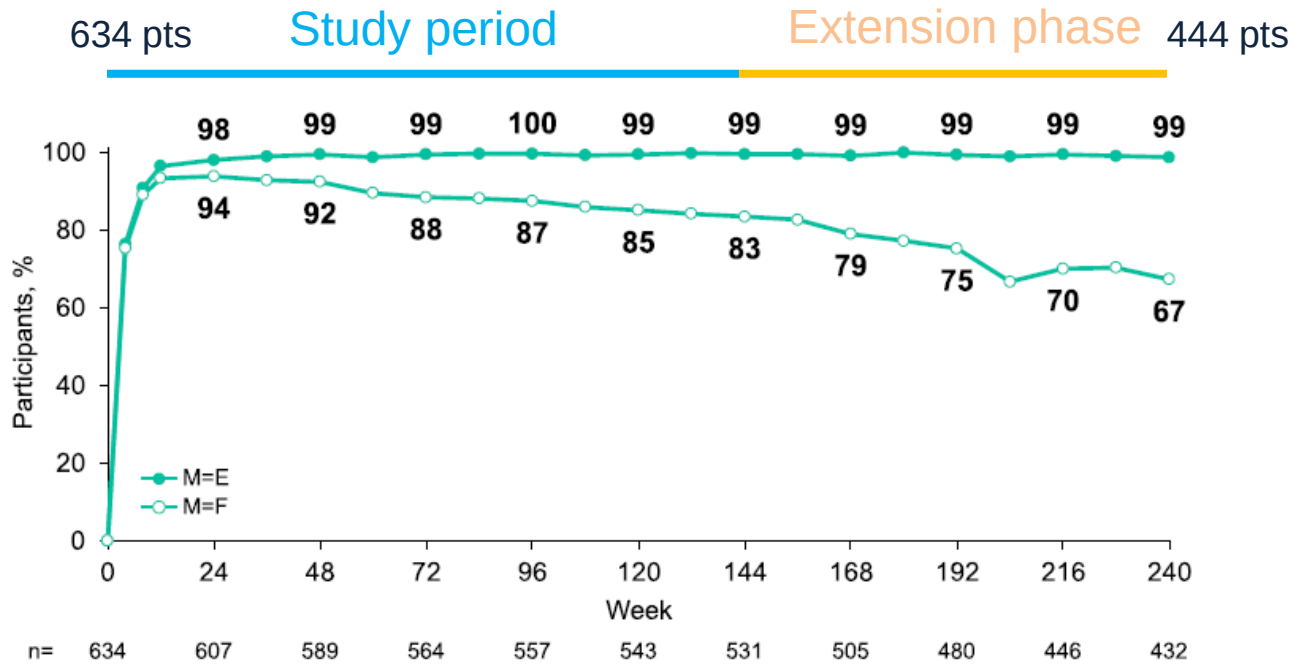


Fig. 2: **Virologic outcomes through 240 weeks (missing = excluded and missing = failure).** Percent of participants with plasma HIV-1 RNA <50 copies/mL; n = participants with non-missing HIV-RNA value.

9 pts with CFV over 5 years.
Emergent mutations: 0

Sax PE et al. eClinicalMedicine 2023