AGIDEI
ASOCIACION GALLEGA PARA LA INVESTIGACION Y DOCENCIA EN ENFERMEDADES INFECCIOSAS

30 de Mayo 2025, Vigo

TAR de inicio ¿siguen siendo necesarios 3 fármacos?.

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FLS SCIENCE FOSTERING LEARNING & SHARING

Fundación Lucha contra las Infecciones

Salut/ Germans Trias i Pujol Hospital

Disclosures

- I’ve received honoraria for advisory boards and educational presentations from ViiV Healthcare, Gilead Sciences and Merck Sharp & Dohme.
- I’ve been an expert testimony for Gilead Sciences.
- I’m a member of the expert panel for the GeSIDA ART Guidelines 2025.

Take homes

- **High rates of virological response**, **low rates of D/C due to AEs, long term efficacy and safety** with preferred 2ND gen INSTI regimens.
- **Guidelines are being more and more restrictive** with preferred options in initial ART.
- **Zero or extremelly low resistance selection, respectively,** with 3DR based on BIC or DTG, and DTG/3TC.
- In some **special situations** the **high barrier against resistance** of **DTG- and BIC-3DR is preferred**.

- **DTG/3TC and BIC/FTC/TAF are sometimes interchangeable,** but **some restrictions apply to DTG/3TC that must be observed.**

Unmet needs and caution with new and LA ART

- **Need to select proper candidates** (HIV Subtype, archived resistance, baseline sensitivity [bNAbs])
- **HIV resistance emergence prevention** (low resistance barrier)
- Inter-individual and intra-individual **drug level** (C_{trough}) **variability (LA)**
- **Hepatitis B** (no NRTIs, no TDF)
- **Pregnancy**
- **Children**, Adolescents
- **DDI** with tuberculosis treatment
- **Implementation in LMIC** (framework, cold chain; LA)
- **Parenteral need (LA)**

Characteristics required for preferred regimens

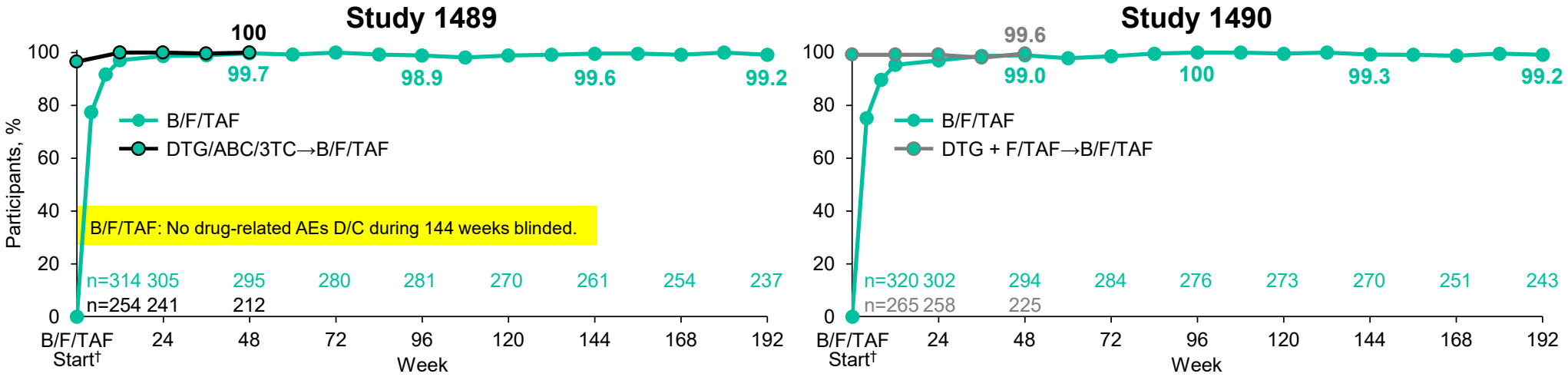
- Have **proven non-inf** to other **preferred regimens**
- Applicable to **most patients**
- **High viral suppression** rates
- **Low pill burden (STR)** and daily intakes
- High **barrier to resistance**
- **Excellent tolerability**
- **Low risk for DDI**
- **Generic forms** of drugs are **encouraged** (EACS). DTG compound patent expiration 2026-2029 (MPP). EMA-approval 21 January 2014 .

GESIDA TAR Enero 2025. Available at: https://guiasclinicas.gesida-seimc.org/. **IAS-USA.** RT Gandhi. *JAMA*. 2025;333(7):609-628. **EACS Guidelines** 12.1. October 2024. Available at: https://www.eacsociety.org/guidelines/eacs-guidelines/. **Medicines Patent Pool**. Available at: efaidnbmnnnibpcajpcglclefindmkaj/https://medicinespatentpool.org/uploads/2017/07/ARV-Snapshot_April2014Rev.pdf

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

Who is non-inf to BIC/F/TAF in initial ART?... And what's the added benefit?

	Comparator	Main endpoint (48 w)	Caveats
GS-1489 [1] Phase 3	**DTG/ABC/3TC**	Dif –0·6%, 95%CI –4.8 to 3.6 ✓	Removed due to ABC limitations
GS-1490 [2] Phase 3	**DTG + FTC/TAF**	Dif –3.5%, 95%CI –7.9, +1.0 ✓	Not co-formulated. More expensive
DOMINO [3] Phase 2	**GSK254 + 2 NRTIs**	Lower efficacy, more DR AEs	Maturation inh development stopped.
CALIBRATE [4] Phase 2	**LEN + F/TAF or BIC or TAF**	Pooled LEN groups lower efficacy, higher rates HIV-RNA >50 c/mL	Emergent LEN DRMs 1.5%
MK-020 [5] Phase 3	**DOR/ISL 0.75 mg**	Dif 0.6%, 95%CI -4.5, +5.8 ✓	ISL 0.75 mg D/C due to lymph/CD4 toxicity
LAPTOP [6] Phase 4	**DRV/c/FTC/TAF**	Dif 0.7%, 95%CI 0.48, 1.0 (composite) ✓	More VF and drug-related AEs with DRV/c

1. J Gallant. Lancet 2017; 390: 2063–72. **2**. PE Sax. Lancet 2017; 390: 2073–82. **3**. SR Joshi. 19TH EACS 2023; Warsaw, Poland. **4**. SK Gupta. Lancet HIV 2023; 10: e15–23. **5**. JK Rockstroh. Clin Infec Dis 2025; https://doi.org/10.1093/cid/ciaf077 . **6**. GM Behrens. CROI 2025, SF, CA, US. #658.

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Qué evalúa un RCT comparativo

Endpoint pral (No-inf / superioridad)	**Eficacia virológica pura y D/C por EAs**

Current strategies aiming at designing new ART regimens:
"Reduce"

No new 3DR STRs in development.

4 ways to try to improve current supreme triple ARV regimens:

1. Reduce the **number of drugs (3→2)**: DTG/RPV, DTG/3TC, CAB/RPV, DOR/ISL, LEN/ISL.
2. Reduce the **dose of drugs** (EFV 400, DRV/r 600/100 QD, ISL 0.25)
3. Reduce the **number of weekly doses** (QUATOR, 4 days a week)
4. Reduce **interval between dosing** with **LA ART**: IM CAB/RPV Q2M, SC LEN Q6M (Q12M?), SC bNAbs Q6M, oral weekly ISL/LEN (monthly?), yearly implants…


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Guideline recommendations for Initial ART in adults. It's not only yes or no.

Main new trends since 2022-2023:

- DTG/3TC preferred in all guidelines.
- ABC removed.
- RAL removed.

Preferred/recommended Recommended in certain clinical situations

	DHHS "Recommended for most people"	EACS "Recommended"	IAS-USA "Recommendation for most people"	GeSIDA "Preferred"
DTG/3TC	HBsAg negative HIV-VL < 500,000 copies/mL Must have baseline genotype Not for rapid start (TDR, HBV)	HBsAg negative HIV-VL < 500,000 copies/mL DTG: Weight increase Not after PrEP failure	HBsAg negative; No 3TC resistance HIV-VL < 500,000 copies/mL Limited data CD4 <200 cells, not OIs Not for rapid start (TDR, VL, HBV).	HBsAg negative Not after PrEP failure ~~CD4 count >200 cells~~
DTG/TFV/XTC	TDF renal and bone toxicity but better lipid profile.	TDF renal and bone toxicity (boosted regimens) DTG, TAF weight increase	TDF renal and bone toxicity TAF greater weight gain	
BIC/FTC/TAF		Weight increase (BIC, TAF)	TAF greater weight gain	
DOR + TFV/XTC		Weight increase (TAF) TDF renal and bone toxicity		
DTG/ABC/3TC	HLA-B*5701 negative Potential impact on CVR HBsAg negative	HLA-B*5701 negative HBsAg negative Weight increase (DTG) Cardiovascular risk (ABC)	**NOT RECOMMENDED** Concerns with ABC and CVD. HLA-B*5701 negative; ABC HS HBsAg negative	Increased CVR (ABC) HLA-B*5701 negative HBsAg negative
RAL/TFV/XTC	**OTHER**: No STR, lower resistance barrier, higher pill number	QD or BID Weight increase (RAL)	**OTHER**: Only in pregnancy, TBC	400 mg BID

EACS Guidelines 12.1. October 2024. Available at: https://www.eacsociety.org/guidelines/eacs-guidelines/. **IAS-USA Guidelines**. RJ Gandhi. JAMA 2024; doi:10.1001/jama.2024.24543
DHHS Guidelines. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Update September 12, 2024. **GESIDA** TAR Enero 2025. Available at: https://guiasclinicas.gesida-seimc.org/.

ART options recommended in special situations: the importance of a high barrier to resistance

1. **Immediate ART initiation with no baseline results:** BIC/F/TAF, DTG + F/TAF or ~~DRV/c/F/TAF~~.
2. **Subjects infected on PrEP** with TDF/FTC: BIC or DTG + F/TAF (or ~~DRV/c/F/TAF~~).
   - **Subjects infected on PrEP with CAB LA**: DRV/c/F/TAF.
3. **Low-level viremia:** BIC, DTG or DRV/c 3DR.
4. **Switch in subjects with archived NRTI resistance:** BIC, DTG or DRV/c 3DR.
5. When antiretroviral **drug history and previous failures are uncertain/unknown.**
6. **Intensify adherence counselling before switching/genotyping HIV & in VF** with regimens with a high resistance barrier and no risk factors for resistance (BIC, DTG 3DR).

EACS Guidelines 12.1. October 2024. Available at: https://www.eacsociety.org/guidelines/eacs-guidelines/. **IAS-USA Guidelines**. RJ Gandhi. JAMA 2024; doi:10.1001/jama.2024.24543
DHHS Guidelines. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Update September 12, 2024. **GESIDA** TAR Enero 2025. Available at: https://guiasclinicas.gesida-seimc.org/.

Extra data asked to DTG/3TC vs 3DR beyond standard virological suppression: any potential impact below 50 c/mL?

- **Specific Virological issues**, sensitivity analyses:
  - **Initial VL decay**
  - **Proportion with TND or TD (below 40 c/mL)**
  - **Blips**
  - **Low adherence**
  - **Virologic failure rates**
- **HIV sanctuaries** (CNS, genital tract), **HIV reservoir**
- **Inflammation and Immune activation markers**
- **Blood telomere length**

DOLCE: Study Design

✓ **Phase IV, exploratory, open-label , multicenter study including naïve PLWHIV in 11 sites in Argentina and Brazil**

Median CD4 116 cells (43% <100)
HIV-RNA: 61% >10^6 c/mL (23% >500.000)
CDC C: 33%

ARV- naïve subjects,
≥18 years old
CD4 ≤ 200 cells/mm3.
HIV-1 RNA >1,000 copies/mL, no upper limit
HBsAg negative
(N=229)
Exclusion: Active OI or DRMs

(N=12 excluded)

Participants were randomly assigned in a 2:1 ratio
N=229 out of 265

Dual Therapy
DTG + 3TC (STR) QD,
(n=152)

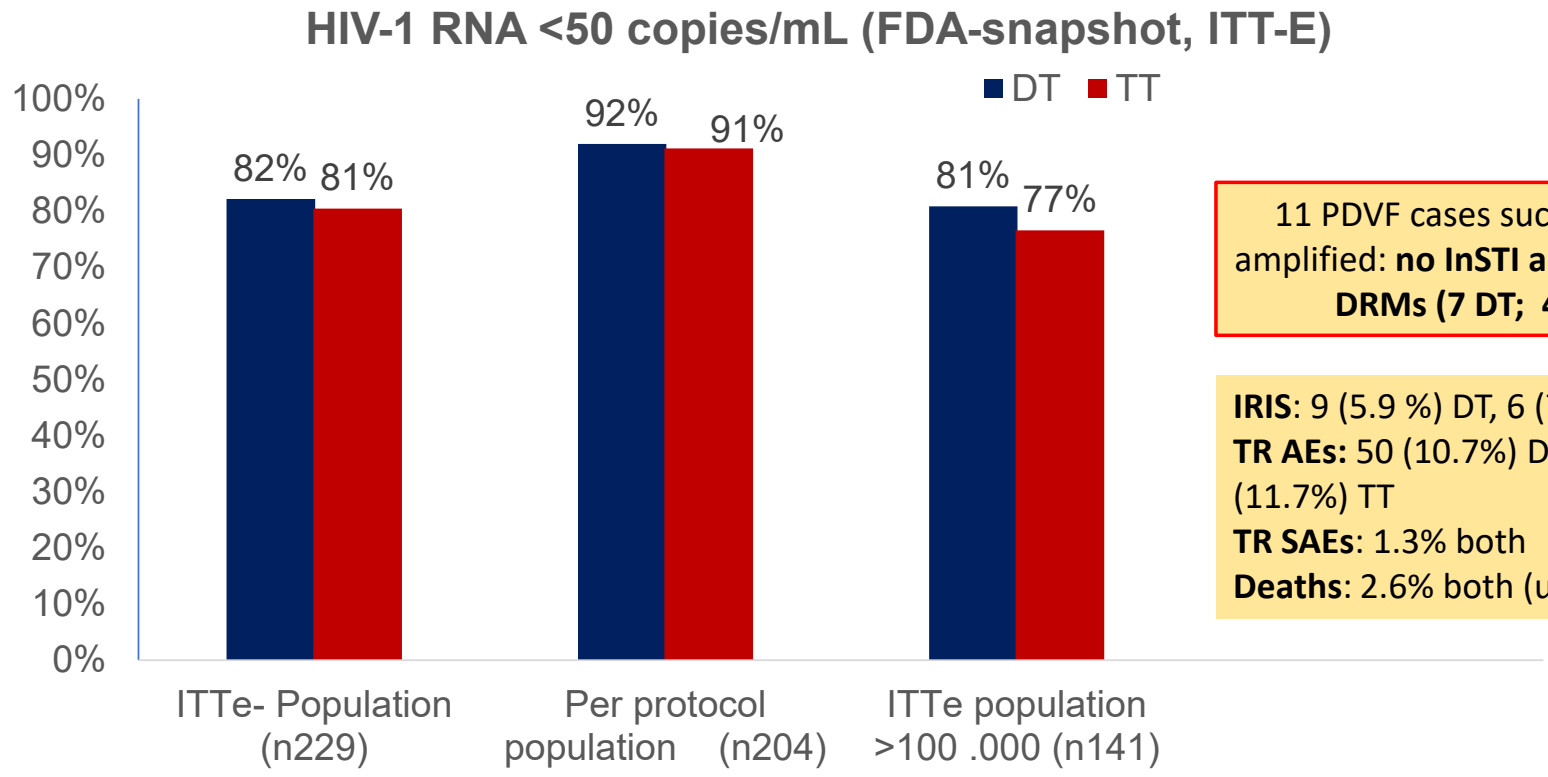
Triple Therapy:
DTG QD + TDF/XTC, QD, FDC
(n=77)

Wk 48
primary endpoint

- **Randomization was stratified by country and by plasma HIV-1 RNA at screening (> or ≤ 100.000 copies/mL).**
- **Treatment period: 48 weeks, followed by a 4 week period to document late adverse events.**

Figueroa MI, et al. O24. HIV Glasgow 2024. #O24

DOLCE study : Virologic Outcomes at Week 48



11 PDVF cases successfully amplified: **no InSTI and no NRTI DRMs (7 DT; 4 TT)**

IRIS: 9 (5.9 %) DT, 6 (7.7%) TT
TR AEs: 50 (10.7%) DT, 33 (11.7%) TT
TR SAEs: 1.3% both
Deaths: 2.6% both (unlikely TR)

Adjusted risk Difference (95% CI) : 2.0%(-8.7;12.8%)]

Adjusted risk Difference (95% CI) : 1.8% (-6.3% ; 9.9%)

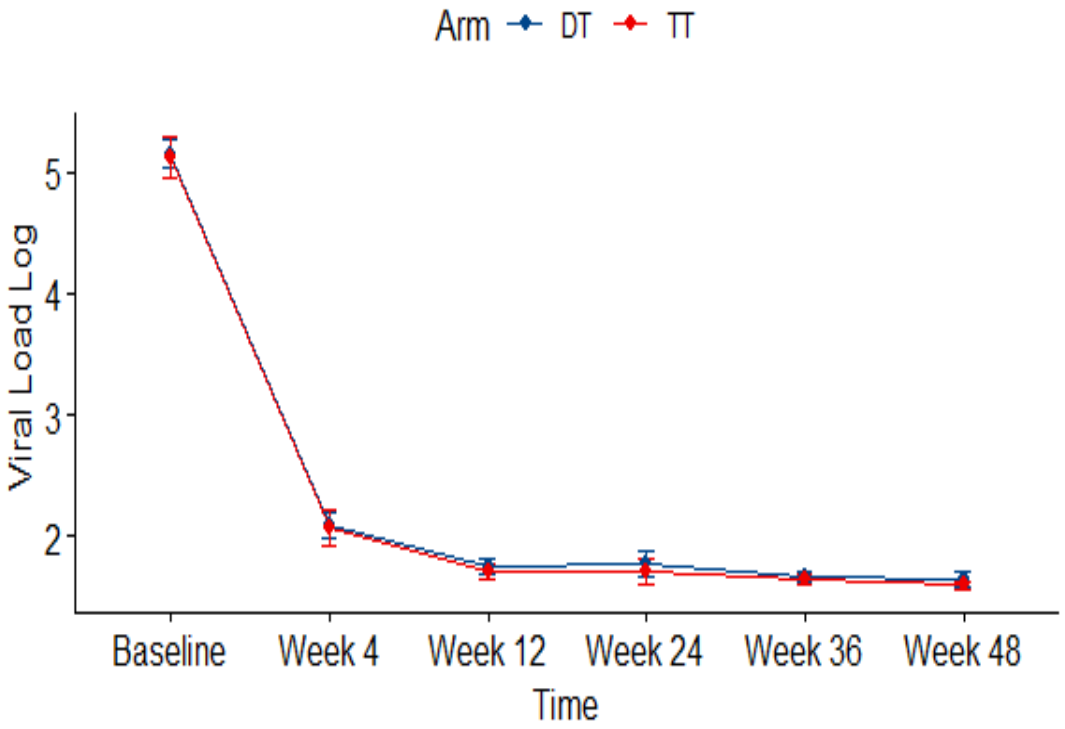
Adjusted risk Difference (95% CI) : 5.1% (-10.1% ; 20.3%)

***Cases excluded from the per protocol analysis: 10 VL failures at week 24 or 36 (5 at week 24, and 5 at week 36); and 15 non-virological failures withdrawals from the study.**

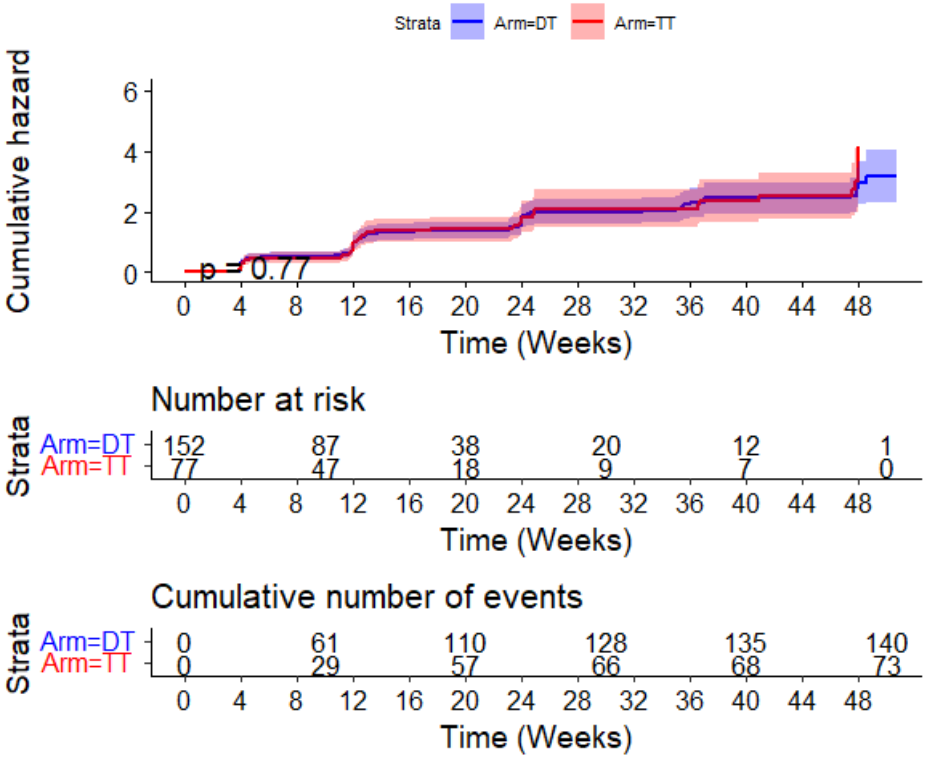
Figueroa MI, et al. O24. HIV Glasgow 2024. #O24

DOLCE. RESULTS – Efficacy: VL change over time

Mean Viral Load log over time



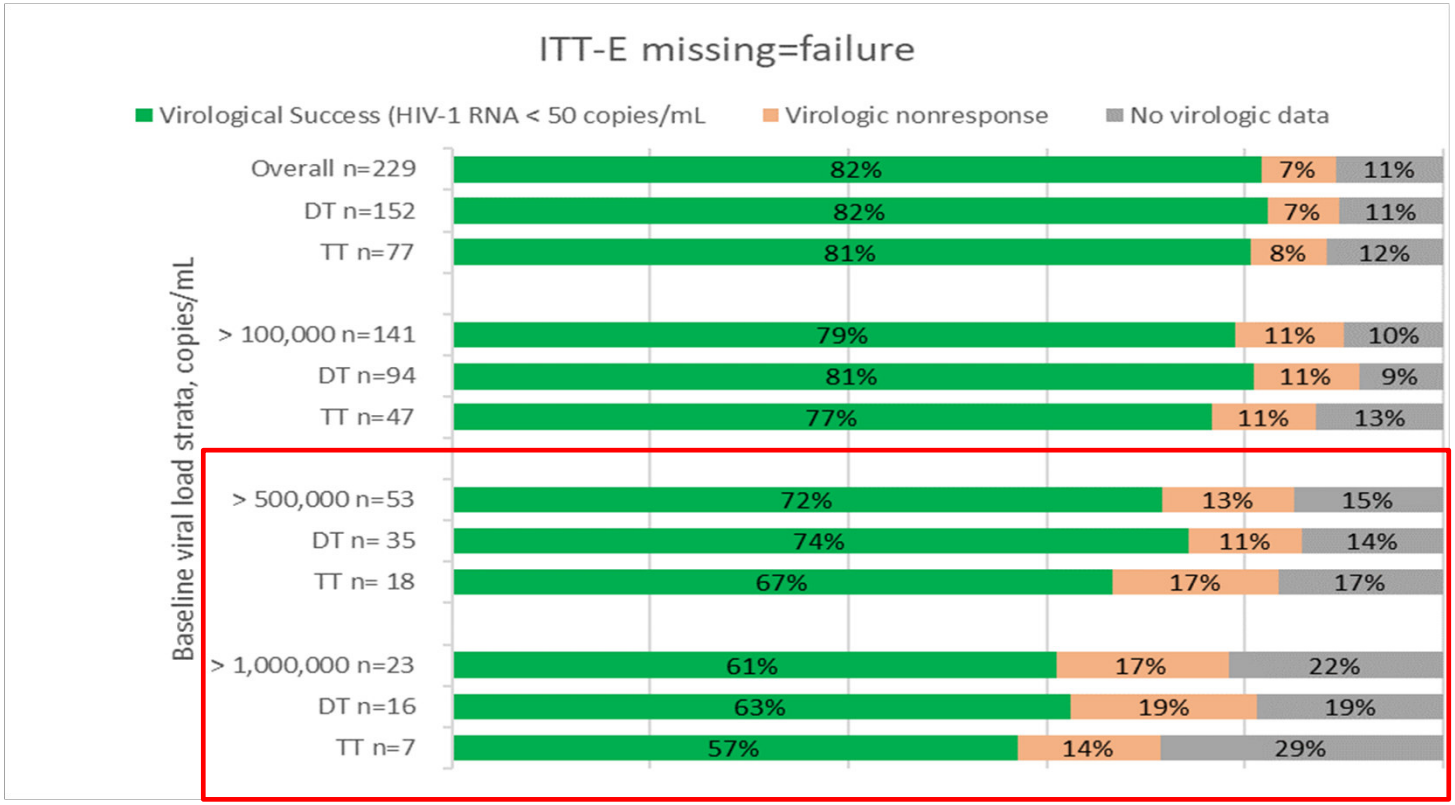
Cumulative hazard curve.
Time to Viral Load Suppression



Figueroa MI, et al. O24. HIV Glasgow 2024. #O24

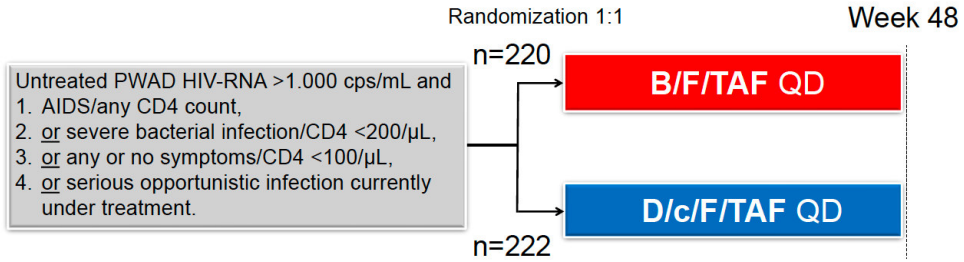
Virologic Outcomes at Week 48 in PLWH with high VL

Median CD4 count: 116 cells; 61% **HIV-RNA >100.000 c/mL**, 23% **>500.000 c/mL**. **CDC C** 33%.



Figueroa MI, et al. O24. HIV Glasgow 2024. #O24

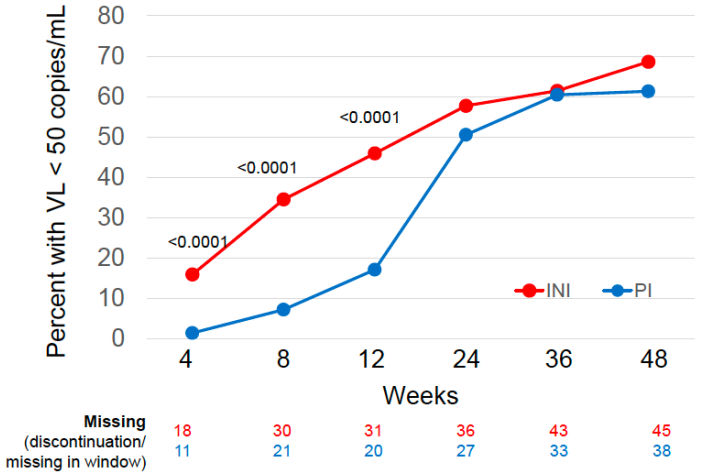
LAPTOP: BIC/F/TAF vs DRV/c/F/TAF in naives with advanced HIV disease

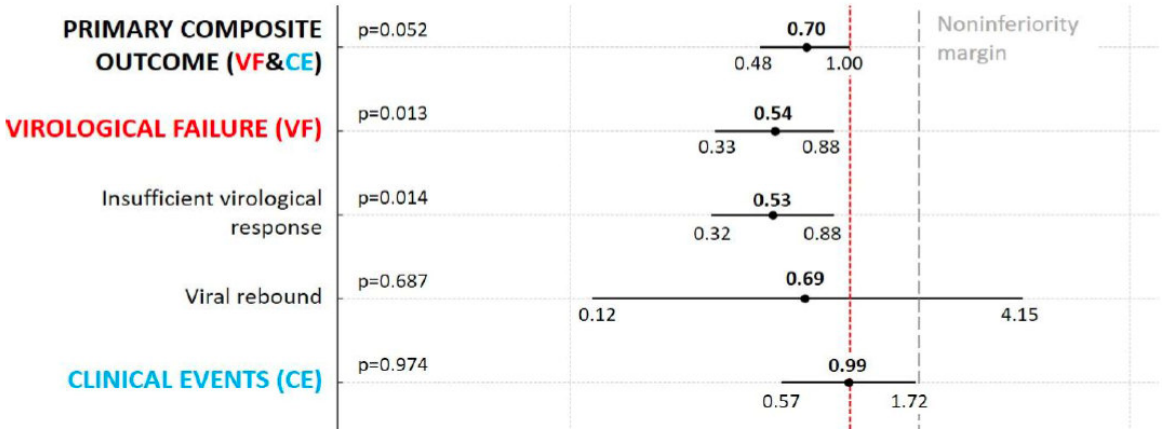


- **Median CD4 count 41 cells**.
- 86% CD4 < 100 cells, 45% VL > 500.000 c/mL.

- **CVF**: 12 DRV/c vs 2 BIC (GRT pending).
- **More AEs and drug-related AEs with DRV/c (p<0.05)**
- No diff weight gain (not shown)

Percent of individuals with VL <50 copies/mL





G Behrens. CROI 2025 San Francisco, CA. #658.

DTG/3TC is non-inferior to DTG + TDF/FTC in initial ART

THE CHALLENGE

Triple DTG- or BIC-based ART is extremelly effective and safe, no restrictions, and we have overwhelming data.

WHY RISK with DTG/3TC in special situations?

Potential increase in virol failure and resistance?

If a third drug (TXF) is not really needed, why include it in a lifelong ART?

WHY RISK with DTG- or BIC-based 3DR including TXF in people with no special situations?

Potential increase in unnecessary long-term toxicity?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