JORNADAS 2020 FORMATOWEBINAR

DE ACTUALIZACIÓN EN ATENCIÓN FARMACÉUTICA
AL PACIENTE CON PATOLOGÍAS VÍRICAS

Actualización y Futuro en el Tratamiento de la Infección por VIH

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ORGANIZA:

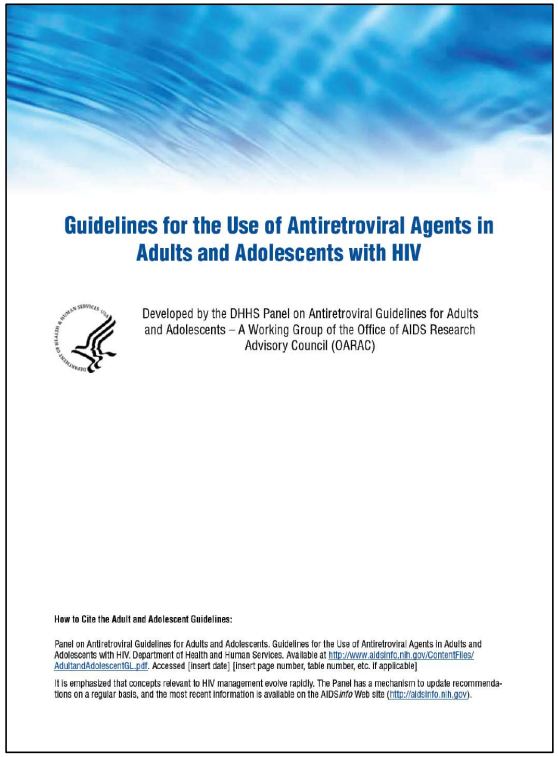
sefh Sociedad Española de Farmacia Hospitalaria · ghevi Grupo de trabajo de Hepatologías Víricas de la sefh · vih Grupo de trabajo de Atención Farmacéutica al Paciente de VIH de la sefh · fefh Fundación Española de Farmacia Hospitalaria

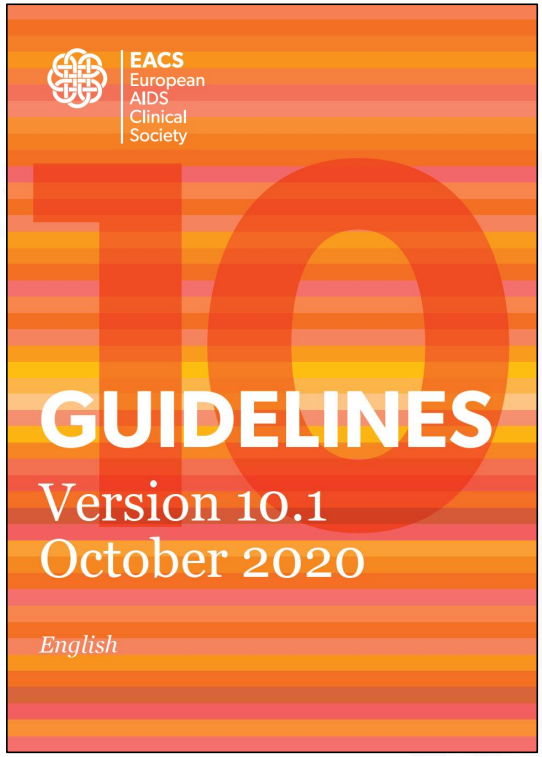
1 Tratamiento Antirretroviral Actual

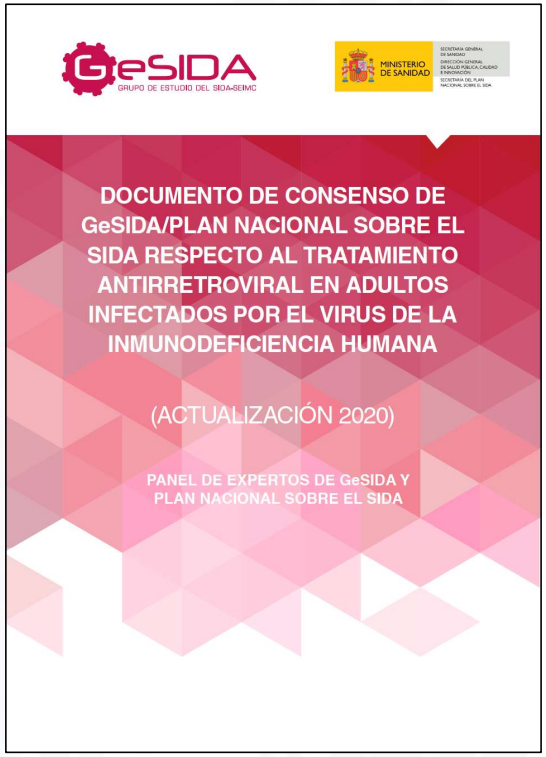
Guidelines 2019/2020

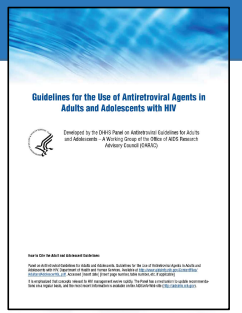
HIV Guidelines.

What to Start.







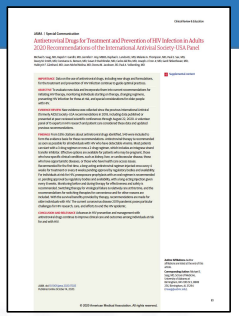


DHHS Guidelines December, 2019

What to Start: Recommended regimens

Recommended Initial Regimens for Most People with HIV
Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.
INSTI plus 2 NRTIs:
Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.
• BIC/TAF/FTC **(AI)**
• DTG/ABC/3TC **(AI)—if HLA-B*5701 negative**
• DTG plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
• RAL plus (TAF or TDF)[a] plus (FTC or 3TC) (**BI** for TDF/[FTC or 3TC], **BII** for TAF/FTC)
INSTI plus 1 NRTI:
• DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

DHHS Guidelines. December 2019.



IAS-USA Panel Guidelines 2020

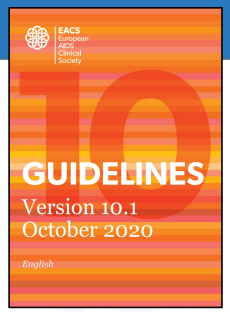
What to Start: Recommended regimens

Recommended for Most People With HIV[a]

- Bictegravir/tenofovir alafenamide/emtricitabine (evidence rating: AIa)
- Dolutegravir plus (all evidence ratings: AIa)
  - Tenofovir alafenamide/emtricitabine
  - Tenofovir disoproxil fumarate/emtricitabine
  - Tenofovir disoproxil fumarate/lamivudine
- Dolutegravir/lamivudine with caveats[b] (evidence rating: AIa)

[b] Not recommended for rapid start because baseline laboratory evaluation results must be reviewed before initiation. Also not recommended for patients with chronic hepatitis B or HIV RNA level above 500 000 copies/mL, and perhaps a CD4 cell count below 200/μL, although the latter is unclear. Close monitoring for adherence and virological response is needed. Not recommended for patients being treated for an active opportunistic infection.

IAS/USA Panel Guidelines; October 2020.

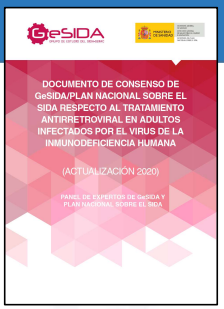


EACS Guidelines 2018

What to Start: Recommended regimens

Regimen	Main requirements	Additional guidance (footnotes)
Recommended regimens		
2 NRTIs + INSTI		
ABC/3TC + DTG ABC/3TC/DTG	HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, cardiovascular risk) II (Weight increase (DTG))
TAF/FTC or TDF/FTC or TDF/3TC + DTG		III (Weight increase (DTG, TAF)) IV (TDF: prodrug types. Renal and bone toxicity. TAF dosing)
TAF/FTC/BIC		II (Weight increase (BIC))
TAF/FTC or TDF/FTC or TDF/3TC + RAL qd or bid		IV (TDF: prodrug types. Renal and bone toxicity. TAF dosing) V (RAL: dosing)
1 NRTI + INSTI		
3TC + DTG or 3TC/DTG	HBsAg negative HIV-VL < 500,000 copies/mL	

EACS Guidelines. V 10.1. October 2020.



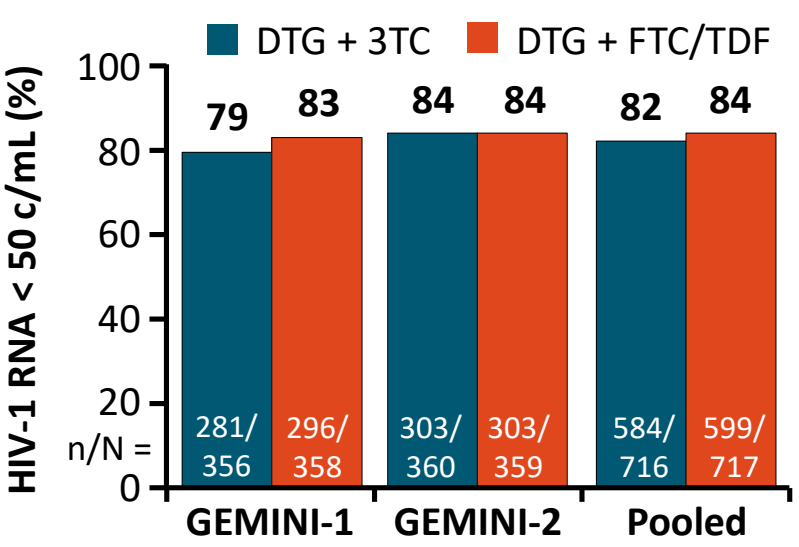
GeSIDA Guidelines 2020

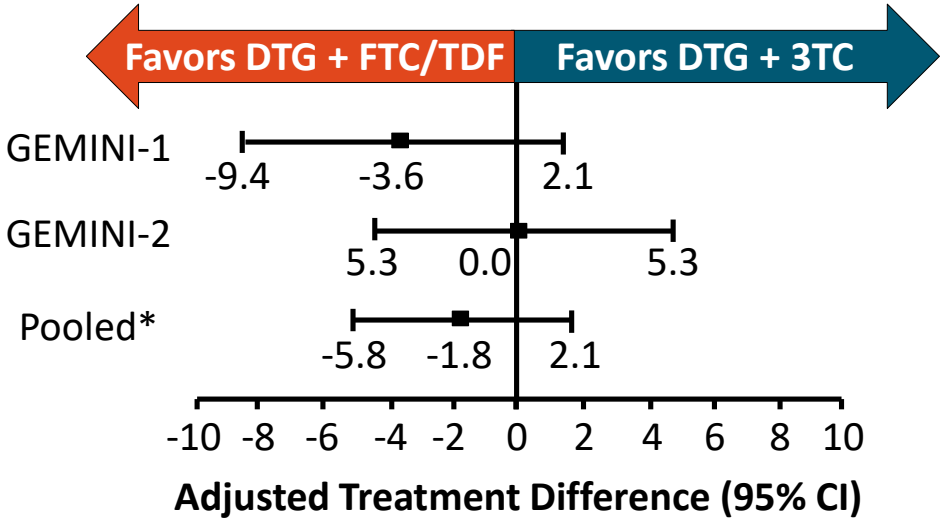
What to Start: Preferred regimens

3er Fármaco	Pauta†	Comentarios‡
Preferentes. *Pautas aplicables a la mayoría de los pacientes y que en ensayos clínicos aleatorizados han mostrado una eficacia no inferior a otras pautas también consideradas actualmente como preferentes o superior frente a otras pautas y presentan ventajas adicionales en tolerancia, toxicidad o un bajo riesgo de interacciones farmacológicas*		
INI	BIC/FTC/TAF	
	DTG/ABC/3TC	-ABC está contraindicado en pacientes con HLA-B*5701 positivo -DTG no debe utilizarse en mujeres que deseen quedarse embarazadas o mujeres en edad fértil que no utilicen medidas anticonceptivas eficaces. -No utilizar en pacientes con hepatitis B crónica
	DTG+FTC/TAF**	- DTG no debe utilizarse en mujeres que deseen quedarse embarazadas o mujeres en edad fértil que no utilicen medidas anticonceptivas eficaces
	RAL+FTC/TAF*	-RAL puede administrarse indistintamente como 1 comprimido de 400 mg cada 12 horas, o 2 comprimidos de 600 mg (nueva formulación) cada 24 horas
	DTG/3TC	- No recomendado en pacientes con cifra basal de CD4+ menor de 200/µL - DTG no debe utilizarse en mujeres que deseen quedarse embarazadas o mujeres en edad fértil que no utilicen medidas anticonceptivas eficaces - No utilizar en pacientes con hepatitis crónica por VHB

GEMINI 1-2: Viral Suppression Through Wk 144 With DTG + 3TC vs DTG + FTC/TDF as Initial ART

- Parallel, international, randomized, double-blind phase III noninferiority studies comparing initial ART with DTG + 3TC (n = 717) vs DTG + FTC/TDF (n = 716)
  - DTG + 3TC noninferior at Wk 48 primary analysis (HIV-1 RNA < 50 copies/mL by ITT-E Snapshot)[1] and at Wk 96[2]; current analysis through Wk 144[3]





*Adjusted for BL HIV-1 RNA (≤ 100,000 vs > 100,000 copies/mL), BL CD4+ cell count (≤ 200 vs > 200 cells/mm^3) and study (GEMINI-1 vs GEMINI-2).

1. Cahn. Lancet. 2019;393:143. 2. Cahn. IAS 2019. Abstr WEAB0404LB. 3. Cahn. HIV Glasgow 2020. Abstr P018.

GEMINI 1-2: Virologic Outcomes at Wk 144 Snapshot Analysis

Snapshot Outcome, n (%)	DTG + 3TC (n = 716)	DTG + FTC/TDF (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 HIV-1 RNA ≥ 50 copies/mL	7 (1)	11 (2)
▪ Change in ART	2 (< 1)	1 (< 1)
No virologic data	109 (15)	97 (14)
▪ Discontinued study due to 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)

*Included protocol deviation, loss to follow-up, physician decision, withdrawal by patient, and lack of efficacy.

- **Met CVW criteria**: n = 12 (2%) with DTG + 3TC (1 since Wk 96), n = 9 (1%) with DTG + FTC/TDF (2 since Wk 96)
  - No participant with CVW had treatment-emergent INSTI or NRTI resistance mutations
- 1 patient in DTG + 3TC arm without CVW reported nonadherence and developed M184V at Wk 132 (HIV-1 RNA 61,927 c/mL) and R263R/K at Wk 144 (HIV-1 RNA 135 c/mL), resulting in 1.8-fold change in DTG susceptibility; patient regained virologic suppression after switch to DTG QD + DRV/COBI after Wk 144

Cahn. HIV Glasgow 2020. Abstr P018.

GEMINI 1-2: Virologic Response by Baseline Parameters

HIV-1 RNA < 50 c/mL at Wk 144 by Subgroup, % (n/N)	DTG + 3TC	DTG + FTC/TDF
Baseline HIV-1 RNA level, copies/mL		
▪ ≤ 100,000	81 (469/576)	84 (471/564)
▪ > 100,000	82 (115/140)	84 (128/153)
Baseline CD4+ cell count, cells/mm^3		
▪ > 200	83 (542/653)	84 (557/662)
▪ ≤ 200	67 (42/63)	76 (42/55)

Cahn. HIV Glasgow 2020. Abstr P018.

THE STAT STUDY: Test and Treat (3TC/DTG)

Patients

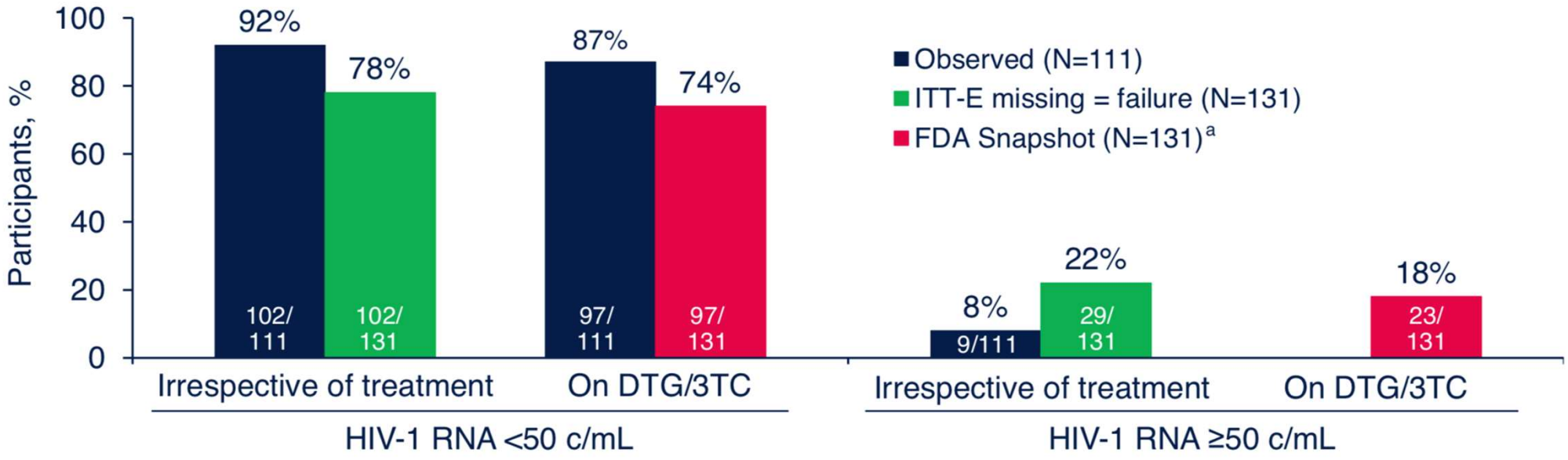
Table 1. Selected Baseline Demographics and Participant Characteristics (ITT-E Population)

Characteristic	DTG/3TC (N=131)
Time to enrollment since diagnosis, median (range), days	5 (0-15)
HIV-1 RNA, median (range), c/mL, n (%)[a,b]	63,056 (<40 to 68,706,840)[c]
<100,000	79 (60)
100,000 to <500,000	32 (24)
500,000 to <1,000,000	9 (7)
≥1,000,000	10 (8)
CD4+ cell count, median (range), cells/mm^3[b]	389.0 (<20 to 1466)[d]
<200, n (%)	37 (28)
HBV co-infection, n (%)[b,e]	7 (5)
M184V resistance mutation, n (%)[b]	1 (<1)

[a]1 (<1%) participant had missing plasma HIV-1 RNA results at BL. [b]BL resistance was identified at Week 4, and HIV-1 viral load, CD4+ cell count, and HBV co-infection were identified at Week 1 from samples taken at BL. [c]Lower limit of quantification is <40. [d]Lower limit of quantification is <20. [e]2 participants with HBV co-infection remained on DTG/3TC.

THE STAT STUDY:
Results

Figure 1. Results of Efficacy Analyses: Virologic Outcomes at Week 24



[a]11 (8%) of 131 participants had no virologic data at Week 24.

THE STAT STUDY:
Results

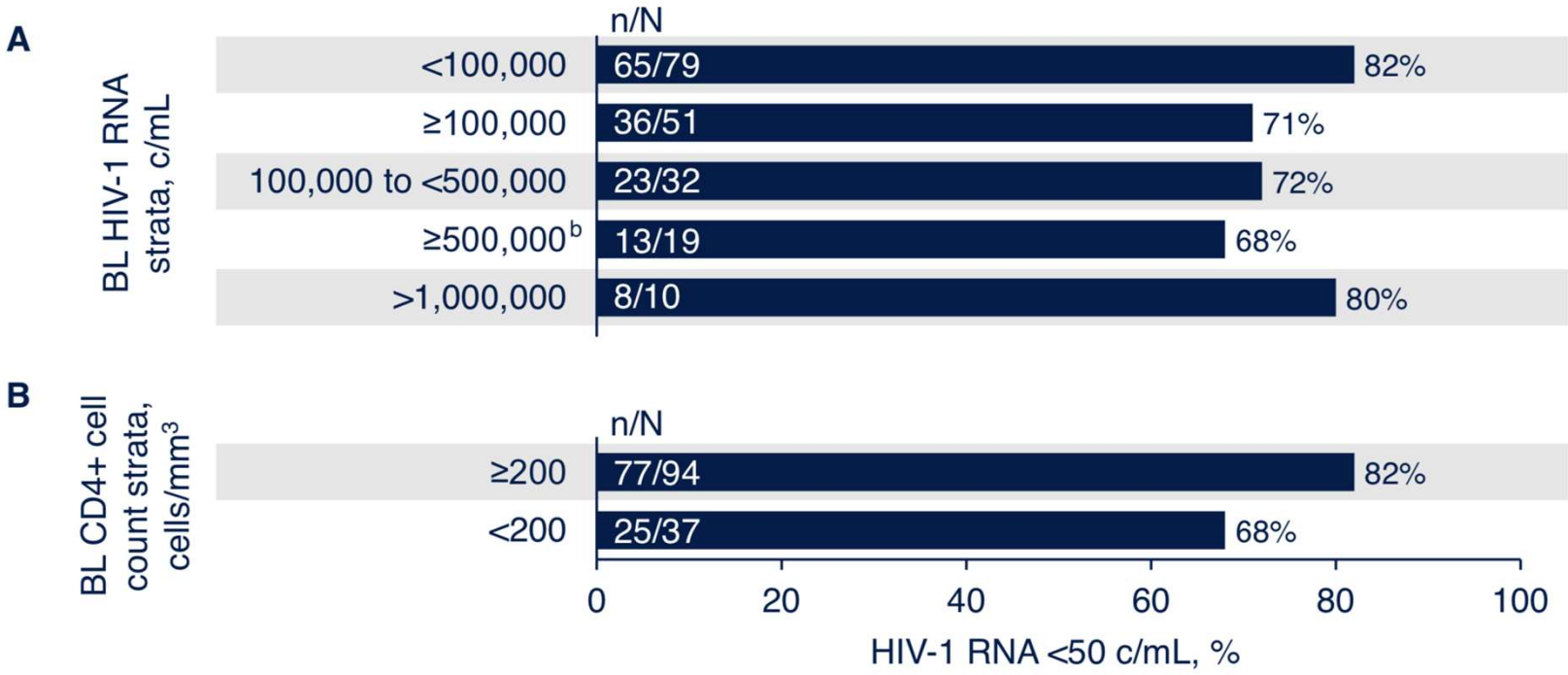
Table 3. Participants Who Switched From DTG/3TC at Any Time Point by Week 24

Reason for switch	Visit window	Modified ART	Plasma HIV-1 RNA at Week 24
BL HBV	Week 1	DTG/3TC + TAF	<40 c/mL
BL HBV	Week 1	BIC/FTC/TAF	NA[a]
BL HBV	Week 4	DTG + TDF/FTC	<40 c/mL
BL HBV	Week 4	BIC/FTC/TAF or DTG + TDF/FTC[b]	49 c/mL
Decision by participant or proxy	Week 4	BIC/FTC/TAF	NA[c]
BL HBV	Week 8	DTG/3TC + TAF	<40 c/mL
BL M184V	Week 8	DTG/RPV	NA[d]
AE (rash)	Week 12; Week 12	COBI/DRV/FTC/TAF; BIC/FTC/TAF[e]	<40 c/mL

[a]Participant on study but missing data in window. Participant had HIV-1 RNA <40 c/mL at Week 36. [b]Participant participates in another double-blind clinical trial with a tenofovir-based regimen; switched to either Biktarvy or Truvada + Tivicay. [c]Participant withdrew consent after switch from DTG/3TC. [d]Participant had HIV-1 RNA 18,752 c/mL at baseline, <40 c/mL on Day 47, switched to DTG/RPV on Day 49, and had last HIV-1 RNA 54 c/mL on Day 57; participant withdrew consent (due to relocation) on Day 106 (Week 12). [e]Participant switched ART twice.

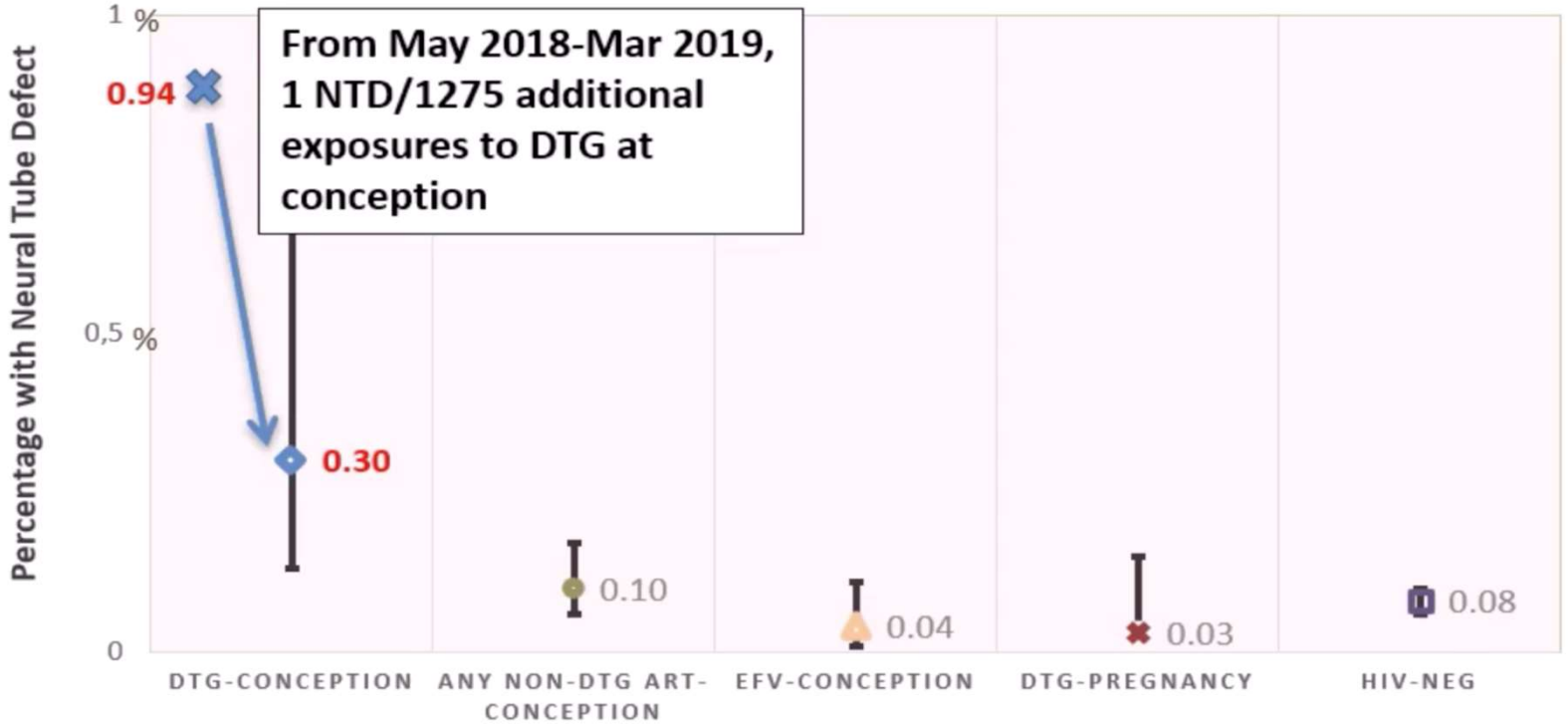
THE STAT STUDY:
Results

Figure 2. Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 24 by BL (A) HIV-1 RNA[a] and (B) CD4+ Cell Count (ITT-E Missing = Failure Analysis)



[a]1 (<1%) participant had missing plasma HIV-1 RNA results at BL. [b]Of the 19 participants with BL viral load ≥500,000 c/mL, 13 (68%) were suppressed to <50 c/mL, 4 remain on study with viral load >50 c/mL (3 <200 c/mL), and 2 discontinued.

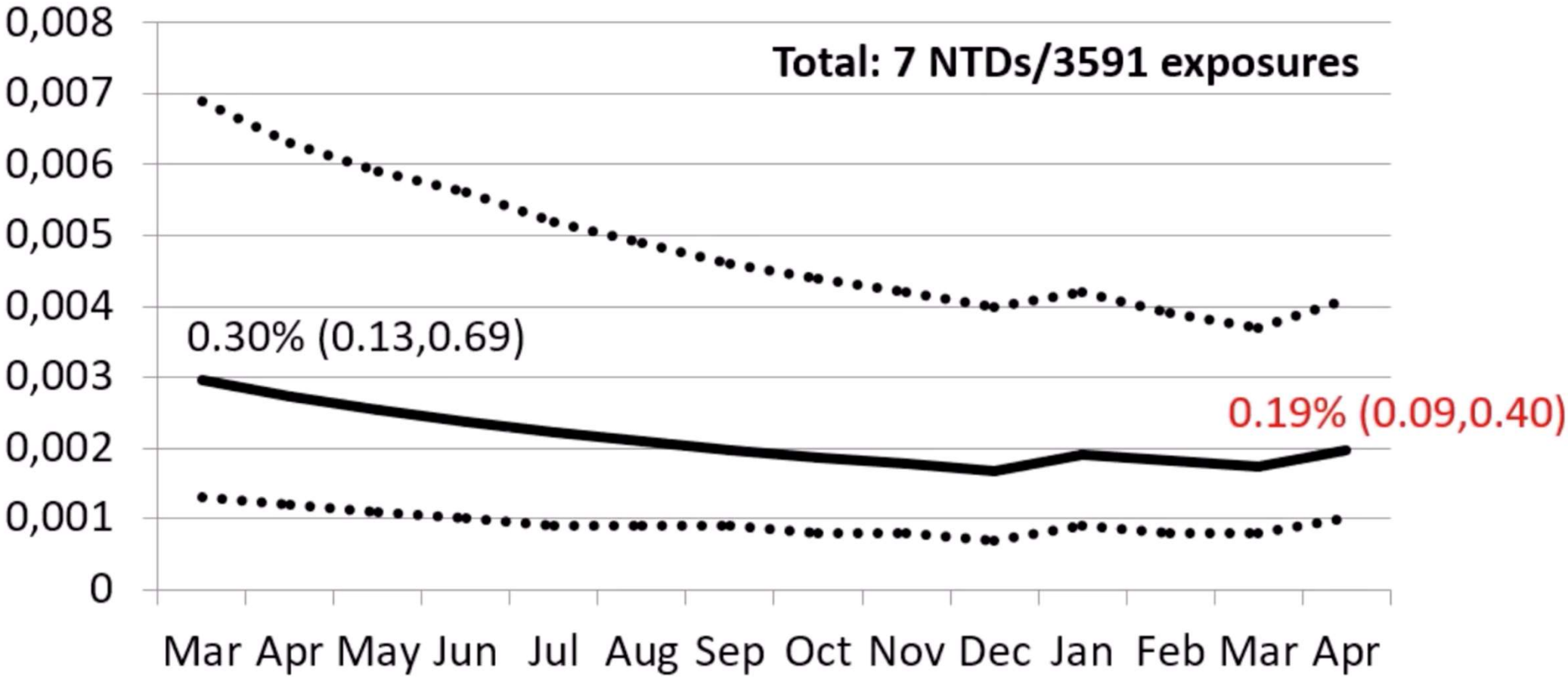
Tsepamo Results as of March 2019



NTDs/Exposures	5/1683	15/14792	3/7959	1/3840	70/89372
% with NTD (95% CI)	0.30% (0.13, 0.69)	0.10% (0.06, 0.17)	0.04% (0.01, 0.11)	0.03% (0.0, 0.15)	0.08% (0.06, 0.10)
Prevalence Difference (95% CI)	ref	**0.20% (0.01, 0.59)**	**0.26% (0.07, 0.66)**	**0.27% (0.06, 0.67)**	**0.22% (0.05, 0.62)**

Zash et al. NEJM 2019

NTD Prevalence (95% CI) with DTG at conception, Apr 1, 2019-April 30, 2020



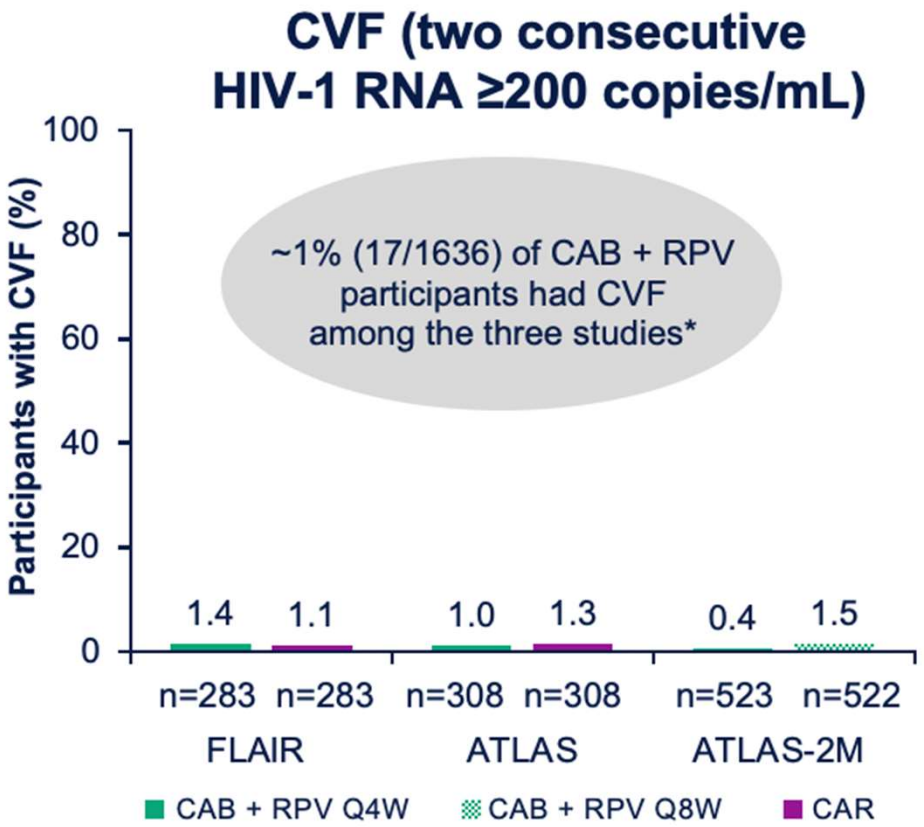
2 Futuro: Nuevos Fármacos

A COMBINATION OF VIRAL AND PARTICIPANT FACTORS INFLUENCES VIROLOGIC OUTCOME TO LONG-ACTING CABOTEGRAVIR + RILPIVIRINE: MULTIVARIABLE AND BASELINE FACTOR ANALYSES ACROSS ATLAS, FLAIR AND ATLAS-2M PHASE 3 STUDIES.

Margolis D, et al.

Glasgow 2020

Multivariable Analysis: Participant, Baseline Virus and PK Factors Explored in Relation to CVF Outcome Through Week 48



Factors explored in the MVA:

- CAB and RPV PK (i.e. initial trough concentrations at Week 8) and pre-existing resistance mutations,† adjusting for the following covariates:
  - Sex at birth
  - BMI
  - HIV-1 subtype
  - Q4W and Q8W regimen

*13 of 17 participants who met the CVF criterion were CAB + RPV naive at study entry and received at least one LA injection were included in the multivariable analysis; three participants with CVF were excluded as they rolled over from ATLAS. An additional participant in FLAIR was excluded because CVF occurred prior to receiving LA injection (withdrawn due to false-positive pregnancy test).
†Pre-existing INSTI, as well as L74I polymorphism, RPV and NNRTI RAMs (observed in plasma or peripheral blood mononuclear cells).
BMI, body mass index (kg/m^2); CAB, cabotegravir; CAR, current antiretroviral regimen; CVF, confirmed virologic failure; LA, long-acting; MVA, multivariable analysis; NNRTI, non-nucleoside reverse transcriptase inhibitor; PK, pharmacokinetic; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

Multivariable Analysis: Four Factors Were Associated With an Increased Odds Ratio of CVF, Three Are Baseline Factors

Parameter	Final Model OR (95% CI), p-value*
RPV RAM(s) at baseline†	37.24 (8.44–>99), p<0.001
Log_2 of *post hoc* Week 8 RPV trough concentration	4.17 (1.59–11.11), p=0.004
Baseline HIV-1 subtype A6/A1	6.59 (1.82–25.26), p=0.005
BMI (kg/m^2) at baseline	1.13 (1.03–1.25), p=0.014
Pre-specified INSTI mutation (excluding L74I non-M mixture) at baseline‡	0.11 (0.01–0.83), p=0.029
Log_2 of *post hoc* Week 8 CAB trough concentration	Not significant
Female at birth	Not significant
Q8W regimen	Not significant
L74I (non-M mixture) INSTI polymorphism at baseline	Not significant
NNRTI RAM(s) (excluding RPV RAMs) at baseline‡	Not significant

*Odds ratios (ORs), 95% penalised profile CIs and penalised likelihood ratio p-values are provided. Covariates with p<0.05 in the final backwards elimination model are presented. CAB and RPV PK parameters were log_2-transformed; therefore, the corresponding ORs are per halving of each variable.
†Identified per the IAS–USA 2019 list of mutations.[1]
‡Identified per the IAS–USA list of mutations associated with resistance to bictegravir, CAB, dolutegravir, elvitegravir or raltegravir[1] and observed mutations during *in vitro* passage of dolutegravir or seen in a previous dolutegravir study (NCT01328041) in INSTI-experienced subjects.
BMI, body mass index (kg/m^2); CAB, cabotegravir; CI, confidence interval; CVF, confirmed virologic failure; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; OR, odds ratio; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

1. Wensing AM, et al. *Top Antivir Med.* 2019;27(3):111–121.

Multivariable Analysis: A Combination of Baseline RPV RAMs*, Subtype A6/A1 or BMI ≥30 Modestly Increased the Risk of Virologic Failure

Factor	CVF, n (%)	HIV-1 RNA <50 copies/mL, n (%)
No baseline factors	3/732 (0.41)	694/732 (95)
Any one baseline factor	1/272 (0.37)	261/272 (96)
Two or more baseline factors	**9/35 (26)**	**25/35 (71)**
TOTAL [95% CI]	13/1039 (1.3) [0.67–2.13]	980/1039 (94) [92.74–95.65]

- Sensitivity and specificity of at least two baseline factors is optimal

	PPV	NPV	Sensitivity	Specificity
Two or more factors	26%	99.6%	69%	97.5%
Any one factor	<1%	98%	8%	74%

*Identified per the IAS–USA 2019 list of mutations.[1]
BMI, body mass index (kg/m2); CAB, cabotegravir; CI, confidence interval; CVF, confirmed virologic failure; LA, long-acting; NPV, negative predictive values; PPV, positive predictive values; RAM, resistance-associated mutation; RPV, rilpivirine.
1. Wensing AM, et al. *Top Antivir Med*. 2019;27(3):111–121.

JRA

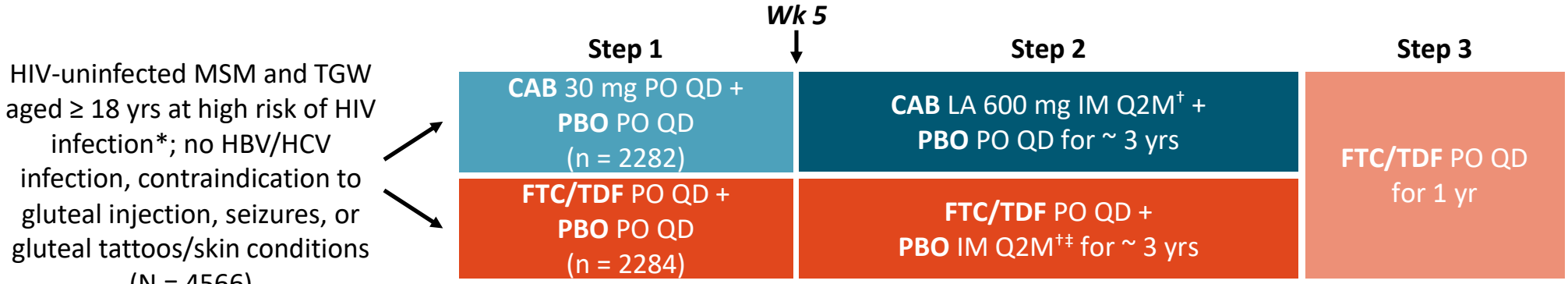
HPTN 083: LONG-ACTING INJECTABLE CABOTEGRAVIR VERSUS DAILY, ORAL F/TDF FOR PREP.

Landovitz R, et al.

AIDS 2020

HPTN 083: Study Design

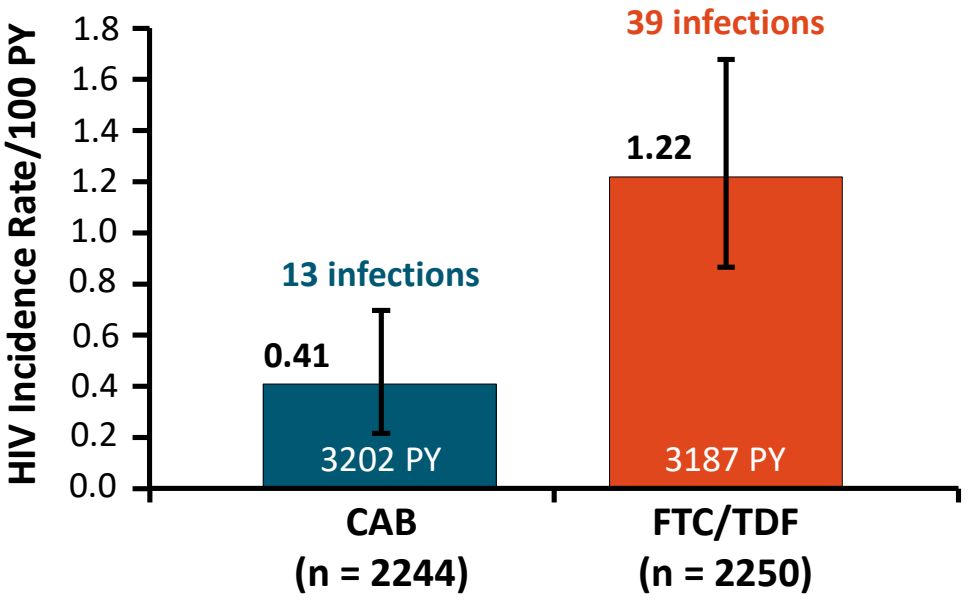
- International, randomized, double-blind phase IIb/III study
  - At interim analysis on May 14, 2020, with 25% of endpoints accrued, DSMB recommended termination of blinded study due to crossing of prespecified O'Brien-Fleming stopping bound
  - Planned N = 5000, with ≥ 50% aged < 30 yrs; ≥ 10% TGW; ≥ 50% black participants in US



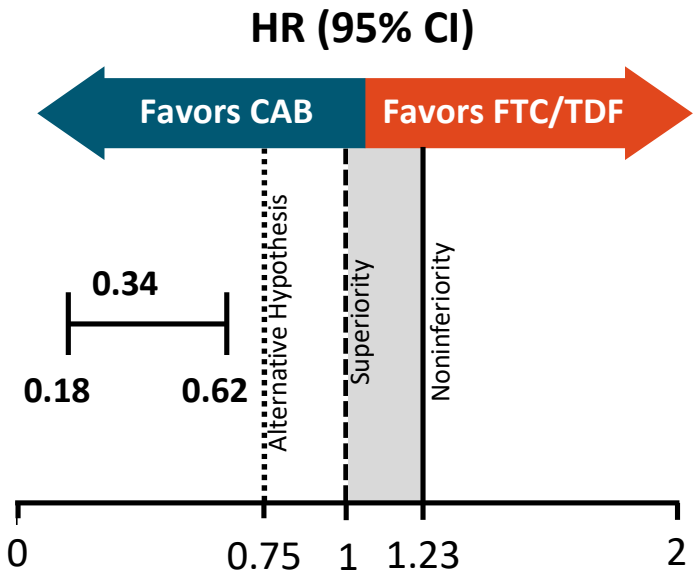
*Any noncondom receptive anal intercourse, > 5 partners, stimulant drug use, incident rectal or urethral STI or incident syphilis in past 6 mos; or SexPro Score ≤ 16 (US only).
†First 2 doses given in Wks 5 and 9 then every 2 mos thereafter.
‡PBO for CAB injection was a 20% intralipid solution.

HPTN 083: HIV Incidence

- Pooled incidence: 0.81 per 100 PY (95% CI: 0.61-1.07)
  - 52 HIV infections in 6389 PYFU



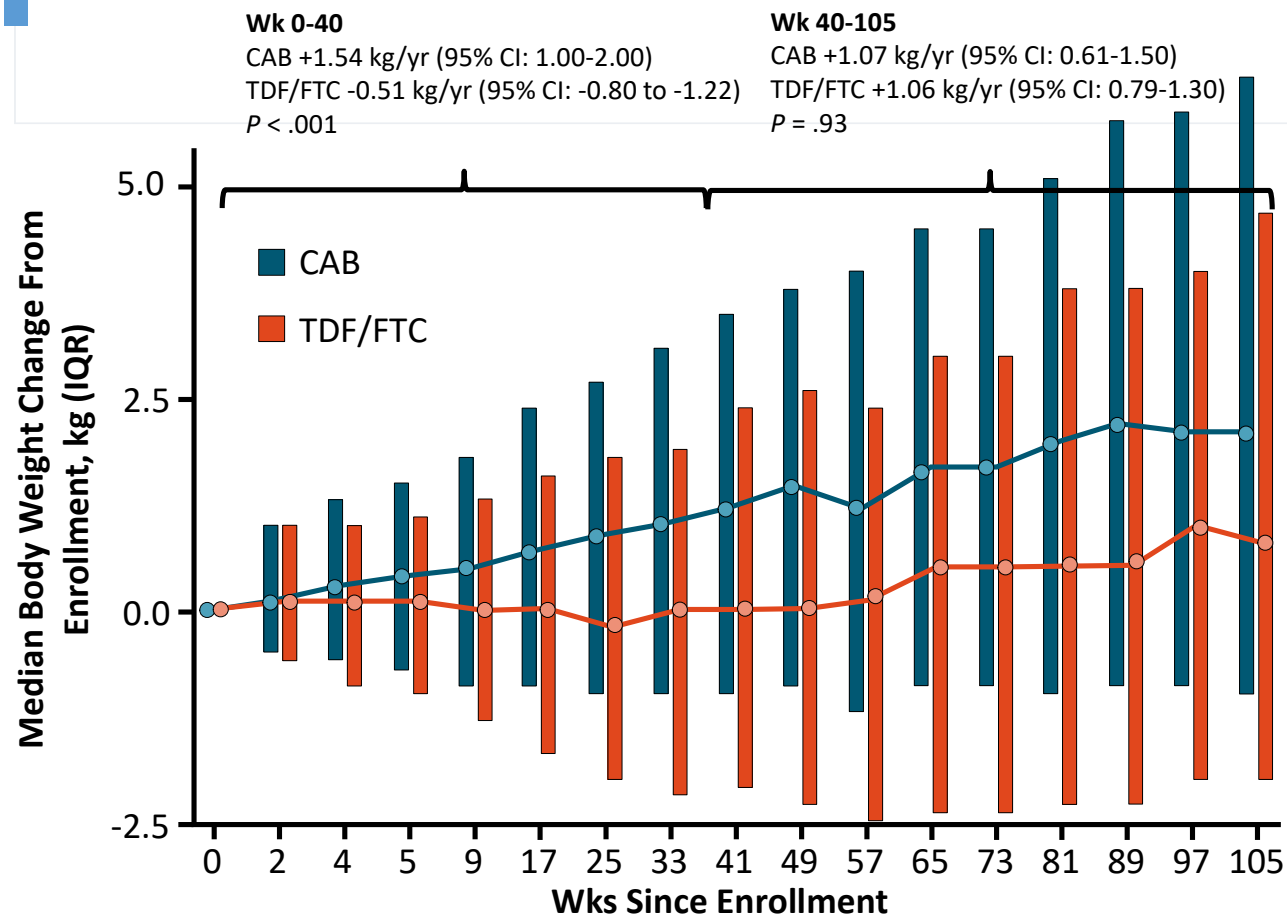
- LA CAB met alternative hypothesis (HR: 0.75) and demonstrated statistically significant superiority vs FTC/TDF



HPTN 083: Timing of Incident HIV Infections

- **CAB arm: n = 13***
  - Before receiving any study treatment: n = 2
  - During Step 1 (oral CAB lead-in): n = 3
  - During Step 2 (IM CAB): n = 5
  - Following extended on-study hiatus from CAB: n = 5
- **FTC/TDF arm: n = 39†**
  - Before receiving any study treatment: n = 3
  - During Step 2 (blinded oral FTC/TDF): n = 39‡

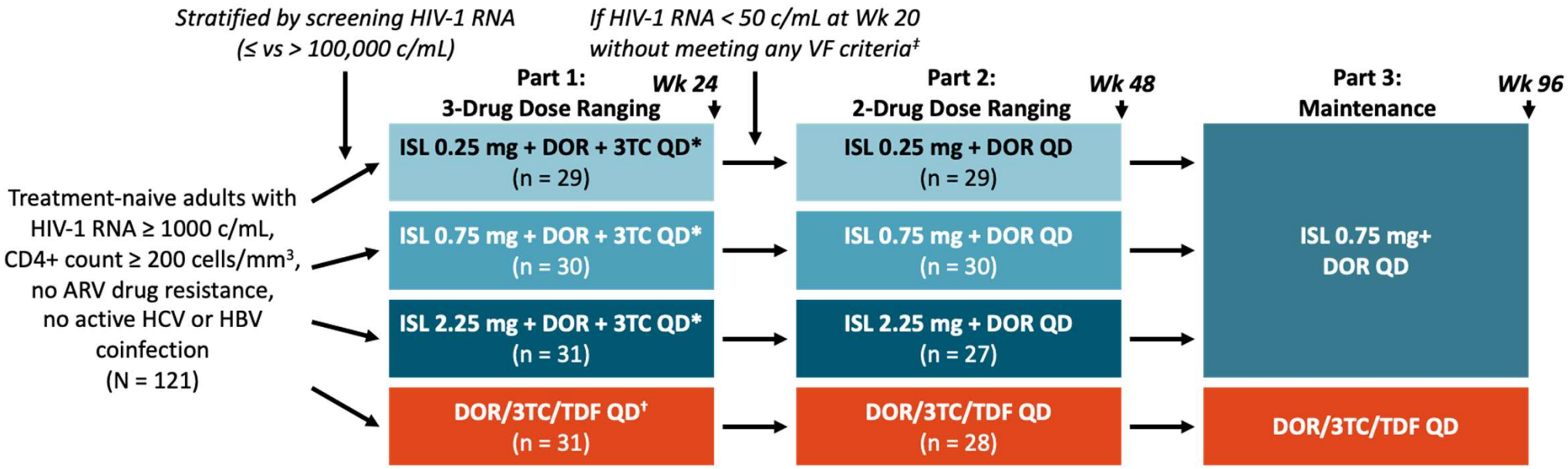
HPTN 083: Change From Baseline in Weight



- Overall, significantly greater median weight increase from BL with CAB vs FTC/TDF ($P < .001$)
  - CAB: +1.30 kg/yr (95% CI: 0.99-1.60)
  - FTC/TDF: +0.31 kg/yr (95% CI: -0.12 to -0.49)

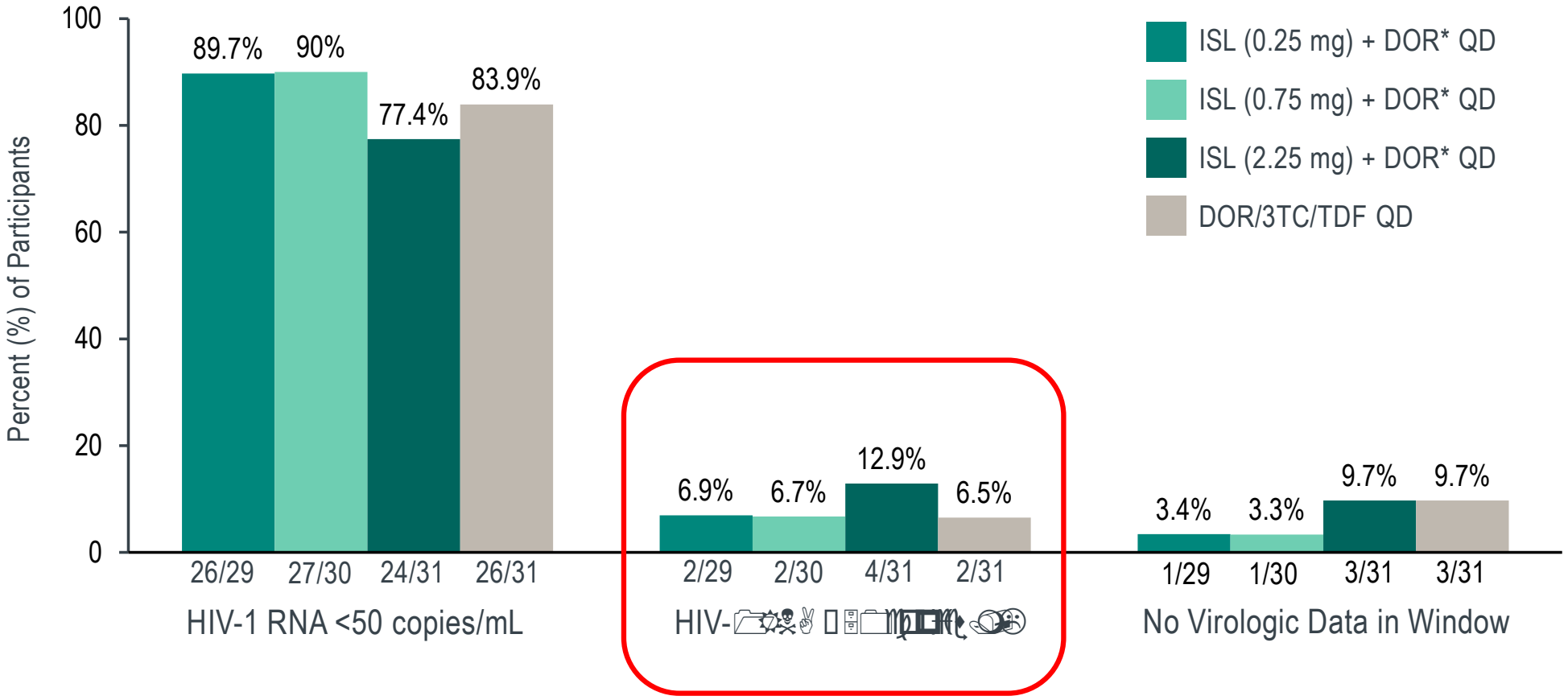
Background

- **Islatravir** (ISL) is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- **P011**: International, randomized, double-blind phase IIb trial



Current Analysis Objective: To characterize participants who discontinued with protocol defined virologic failure.

Virologic Outcomes Through Week 48 (FDA Snapshot Approach)

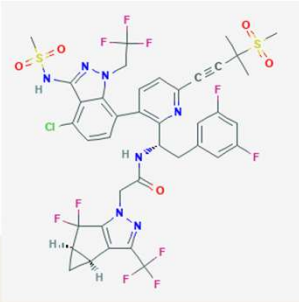


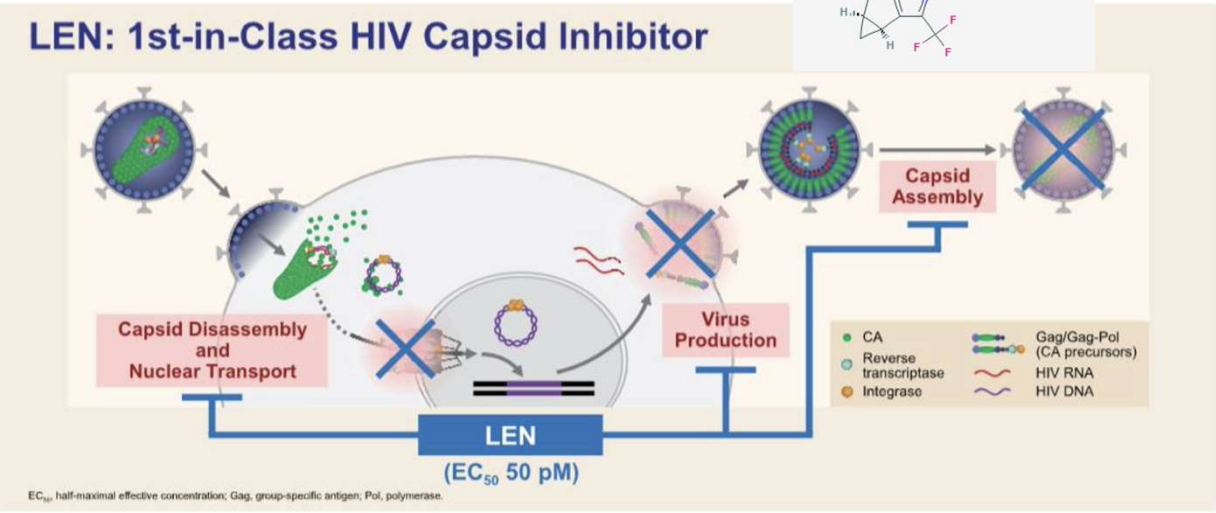
*Participants initially received ISL+DOR+3TC and switched to ISL+ DOR during the week 24-48 period of the study.

Lenacapavir (GS-6207) PK Study

Lenacapavir

- Novel, 1st in-class selective HIV-1 capsid inhibitor
- EC_{50}: 50 pM
- In clinical development as component of long-acting ART[1]
- Potent anti-HIV activity observed following single-dose SC administration[2]
- Oral and SC formulations in development[3]





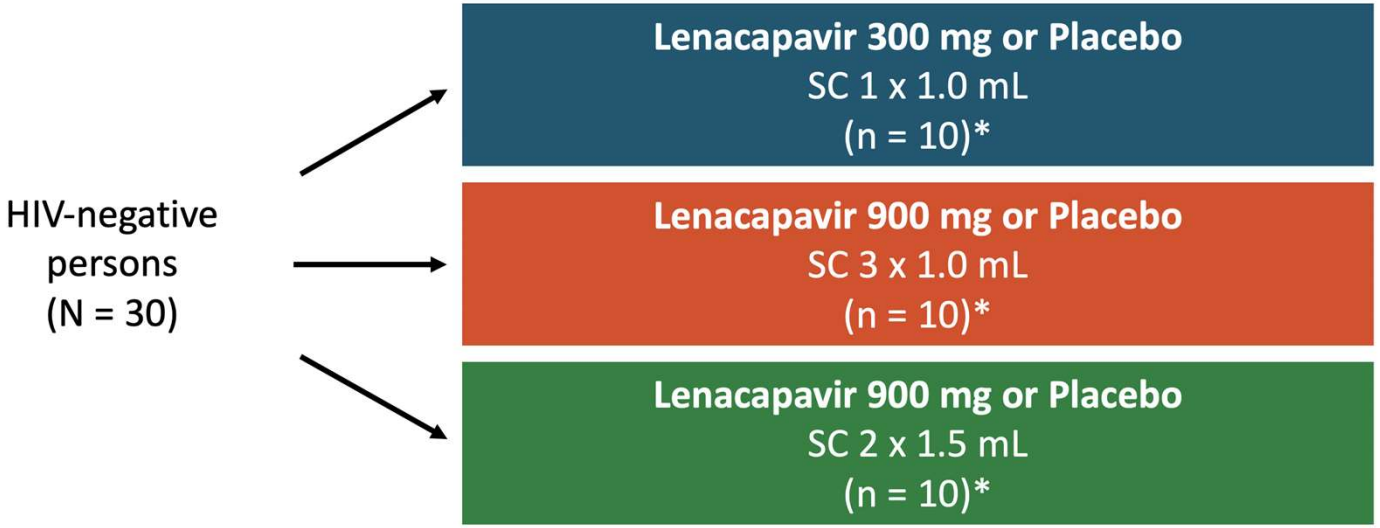
♦ Inhibition of multiple CA-dependent functions essential for viral replication

Current study evaluated tolerability, safety, PK of lenacapavir SC following single-dose administration at escalating doses in HIV-negative volunteers[4]

1. Yant. Nat Med. 2019;25:1377. 2. Daar. CROI 2020. Abstr 469. 3. Begley. CROI 2020. Abstr 470. 4. Begley. AIDS 2020. Abstr PEB0265.

Lenacapavir PK Study: Study Design

- Randomized, blinded, placebo-controlled, dose escalation phase I study



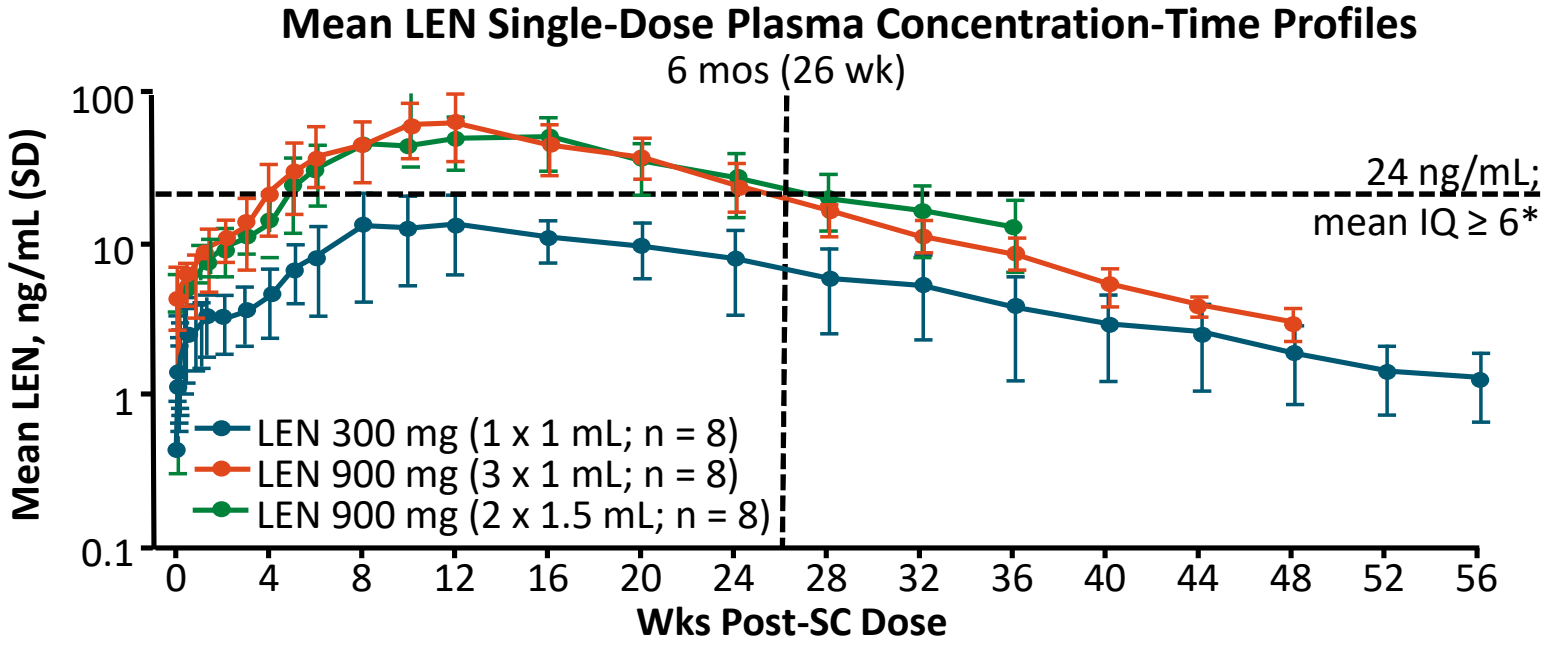
- Endpoints: safety, tolerability, PK
  - PK measured through Day 449

*Participants randomized 4:1 lenacapavir vs placebo. Treatment administered as a single dose.

Begley. AIDS 2020. Abstr PEB0265.

Lenacapavir PK Study: PK Profile

- Per antiviral activity, mean lenacapavir target plasma concentration is 24 ng/mL, corresponding to mean inhibitory quotient ≥ 6 (range: 6.2-20.3)



*Protein-adjusted EC_{95}: macrophages, 1.16 ng/mL; CD4+ cells, 2.32 ng/mL, MT-4 cells, 3.87 ng/mL.

Begley. AIDS 2020. Abstr PEB0265.

Conclusiones

- Se incorporan las pautas de dos fármacos como régimen preferente de inicio en todas las guías de tratamiento antirretroviral
- Quedan algunos aspectos aún controvertidos en cuanto a la unanimidad e interpretación por los expertos de las limitaciones de las pautas de dos fármacos
- La incorporación de cabotegravir LA puede ser un avance importante en la PrEP
- El futuro del TAR parece escribirse en clave de fármacos de administración prolongada, con reducción en el número de dosis