



Futuro del Tratamiento Antirretroviral: Nuevos Fármacos, Nuevas Formulaciones

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1

Tratamiento Antirretroviral Actual

HIV Guidelines

When to Start. What to start.



Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Special Communications

Special Communication

**Antiretroviral Treatment of Adult HIV Infection
2014 Recommendations
of the International Antiviral Society-USA Panel**

Haldy J.F. Gindoff, MD; Judith A. Aberg, MD; Joseph J. Eron, MD; Jennifer F. Hoy, MBS, FRACP; Anzko Tolent, MD, PhD; Constance A. Benson, MD; David M. Burger, PharmD, PhD; Pedro Cahn, MD, PhD; Joel E. Gallant, MD, MPH; Marshall J. Glesby, MD, PhD; Peter Hain, MD, PhD; Michael S. Saag, MD; David L. Thomas, MD, MPH; Donna M. Jacobsen, BS; Paul A. Volberding, MD

IMPORTANCE New data and antiretroviral regimens expand treatment choices in resource-rich settings and warrant an update of recommendations to treat adults infected with human immunodeficiency virus (HIV).

OBJECTIVE To provide updated treatment recommendations for adults with HIV, emphasizing when to start treatment, what treatment to start, the use of laboratory monitoring tools, and managing treatment failure, switches, and simplification.

DATA SOURCES, STUDY SELECTION, AND DATA SYNTHESIS: An International Antiviral Society-USA panel of experts in HIV research and patient care considered previous data and reviewed new data since the 2012 update with literature searches in PubMed and EMBASE through June 2014. Recommendations and ratings were based on the quality of evidence and consensus.

RESULTS: Antiretroviral therapy is recommended for all adults with HIV infection. Evidence for efficacy and quality of life of treatment with first-line combination therapy is strong. Recommended initial regimens include 2 nucleoside reverse transcriptase inhibitors (NRTI) zidovudine or zalcitabine plus didanosine (ddi) or zalcitabine plus zidovudine (ddi/zidv) and a third-agent or boosted drug, which should be an integrase strand transfer inhibitor (dolutegravir, elvitegravir, or raltegravir), a nonnucleoside reverse transcriptase inhibitor (efavirenz or efavirenz), or a boosted protease inhibitor (darunavir or atazanavir). Alternative regimens are available. The evidence for treatment with second-line and third-line regimens is less strong. NRTI-sparing options may be considered. New guidance for optimal timing of monitoring of laboratory parameters is provided. Specific treatment failure warrants rapid confirmation, performance of resistance testing while the patient is receiving the failing regimen, and evaluation of reasons for failure before consideration of switching therapy. Regimens for adverse effects, co-infection, or to reduce costs should not replace first-line antiretroviral therapy.

CONCLUSIONS AND RELEVANCE After confirmed diagnosis of HIV infection, antiretroviral therapy should be initiated in all individuals who are willing and ready to start treatment. Regimens should be selected or changed based on resistance test results with consideration of dosing frequency, pill burden, adverse toxic effect profiles, comorbidities, and drug interactions.

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October 2017

English

Documento de consenso de GeSIDA/Plan Nacional sobre el Sida
respecto al tratamiento antirretroviral en adultos con infección
por el virus de la inmunodeficiencia humana
(Actualización enero 2015)

Panel de expertos de GeSIDA y Plan Nacional sobre el Sida*



HIV Guidelines When to Start

All HIV-infected patients, irrespective of CD4 count



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Chief of Review & Education

Special Commentaries

Antiretroviral Treatment of Adult HIV Infection 2014 Recommendations of the International Antiviral Society-USA Panel

Hughes MD, Garofalo MD, Agha A, Jiang MD, Joseph J, Evans MD, Jennifer F, May MBBS, FRACD,
Joshi-Harris MD, PhD, Corcos A, Dennis MD, Gendle J, Hargrett-Neale MD, PhD, Hirsch VM, PhD,
Jain E, Galloway MD, MPH, Marshall J, Coady MD, PhD, Pines Tom, MD, PhD, Michael's Tang MD,
Dent L, Thomas MD, MPH, Dore M, Jackson B, Paack, Volberding MD

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RESULTS: Antiretroviral therapy is recommended for all adults with HIV infection. Evidence for benefits of treatment and quality of available data increase at lower CD4 cell counts. Recommended initial regimens include 2 nucleoside reverse transcriptase inhibitors (zidovudine, didanosine, lamivudine, or tenofovir disoproxil fumarate/emtricitabine) and a third agent (efavirenz or boosted protease inhibitor or integrase strand transfer inhibitor [dolutegravir, raltegravir, or elvitegravir]). A third nucleoside reverse transcriptase inhibitor (abacavir or bictegravir) or a boosted protease inhibitor (darunavir or atazanavir). Alternative regimens are available. Boosted protease inhibitor monotherapy is generally not recommended, but HIV-sparing approaches may be considered. New guidance for optimal timing of monitoring of laboratory parameters is provided. Suspected treatment failure warrants rapid confirmation, performance of resistance testing with the patient in receiving the failing regimen, and evaluation of reasons for failure before consideration of switching therapy. Regimen switches for adverse effects, convenience, or to reduce costs should not preclude antiretroviral potency.

CONCLUSIONS AND RELEVANCE: After confirmed diagnosis of HIV infection, antiretroviral therapy should be initiated in all individuals who are willing and ready to start treatment. Regimens should be selected or changed based on resistance test results with consideration of drug frequency, pill burden, adverse toxic effect profiles, comorbidities, and drug interactions.

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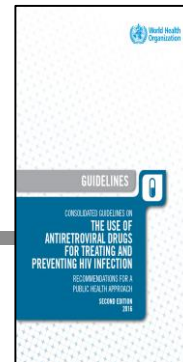
English

Documento de consenso de GeSIDA/Plan Nacional sobre el Sida
respecto al tratamiento antirretroviral en adultos con infección
por el virus de la inmunodeficiencia humana
(Actualización enero 2015)

Panel de expertos de GeSIDA y Plan Nacional sobre el Sida*



WHO Clinical Guidelines 2016: Antiretroviral Therapy



When to Start ART

 4.3.1 When to start ART in adults (>19 years old)	ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count (strong recommendation, moderate-quality evidence). As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with a CD4 count ≤ 350 cells/mm³ (strong recommendation, moderate-quality evidence).
 4.3.2 When to start ART in pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV, regardless of WHO clinical stage and at any CD4 cell count and continued lifelong (strong recommendation, moderate-quality evidence).

Antiretrovirals available in 2018 in Europe

NRTIs

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

NNRTIs

- Delavirdine
- Efavirenz
- Etravirine
- Nevirapine
- Nevirapine XR
- Rilpivirine

PIs

- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

INIs

- Raltegravir
- Dolutegravir
- Elvitegravir

Fusion inhibitors

- Enfuvirtide

CCR5 Inhibitors

- Maraviroc

PK Boosters

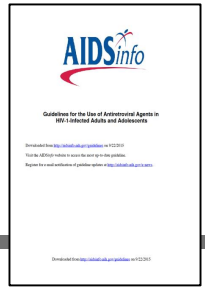
- Ritonavir
- Cobicistat

STR

- Atripla
- Eviplera
- Odefsey
- Stribild
- Genvoya
- Triumeq
- Symtuza

¿Con qué empezar?

Recomendaciones DHHS, 2017



- The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) classifies the following regimens as **Recommended Initial Regimens for Most People with HIV (in alphabetical order)**:
 - Dolutegravir/abacavir/lamivudine^a—only for patients who are HLA-B*5701-negative (**AI**)
 - Dolutegravir plus tenofovir/emtricitabine^{a,b} (**AI**)
 - Elvitegravir/cobicistat/tenofovir/emtricitabine^b (**AI**)
 - Raltegravir plus tenofovir/emtricitabine^{a,b} (**AI** for tenofovir disoproxil fumarate, **All** for tenofovir alafenamide)^{a,b}

¿Con qué empezar?

IAS-USA Guidelines, 2018



Generally Recommended:

- BIC/TAF/FTC
- DTG/ABC/3TC
- DTG-TAF/FTC

Other recommended

- DRV/c/TAF (or TDF)/FTC
- DRV/r/TAF (or TDF)/FTC
- EFV/TDF/FTC
- EVG/c/TAF (or TDF)/FTC
- RAL-TAF (or TDF)/FTC
- RPV/TAF (or TDF)/FTC

- Rapid start (including same day as diagnosis) ART
- NNRTIs and abacavir should not be used for rapid ART start
- Recommendations against routine use of MAC prophylaxis
- CD4 cell counts every 6 months until counts $>250/\mu\text{L}$ for at least 1 year with concomitant viral suppression
- 2-1-1 PrEP

¿Con qué empezar?

Recomendaciones GESIDA, 2017



3er Fármaco	Pauta [†]	Comentarios [‡]
Preferentes. Pautas aplicables a la mayoría de los pacientes y que en ensayos clínicos aleatorizados han mostrado una eficacia superior frente a otras o mostrando no-inferioridad presentan ventajas adicionales en tolerancia, toxicidad o un bajo riesgo de interacciones farmacológicas.		
INI	DTG/ABC/3TC	- ABC está contraindicado en pacientes con HLA-B*5701 positivo
	DTG+FTC/TAF	
	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*.

2 Futuro: Nuevos Fármacos, Viejas Familias

Antiretrovirals available in 2018 in Europe

NRTIs

- Abacavir
- Didanosine
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- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

NNRTIs

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- Efavirenz
- Etravirine
- Nevirapine
- Nevirapine XR
- Rilpivirine

PIs

- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

INIs

- Raltegravir
- Dolutegravir
- Elvitegravir

Fusion inhibitors

- Enfuvirtide

CCR5 Inhibitors

- Maraviroc

PK Boosters

- Ritonavir
- Cobicistat

STR

- Atripla
- Eviplera
- Odefsey
- Stribild
- Genvoya
- Triumeq
- Symtuza

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- Etravirine
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- Nevirapine XR
- Rilpivirine
- **Doravirine**

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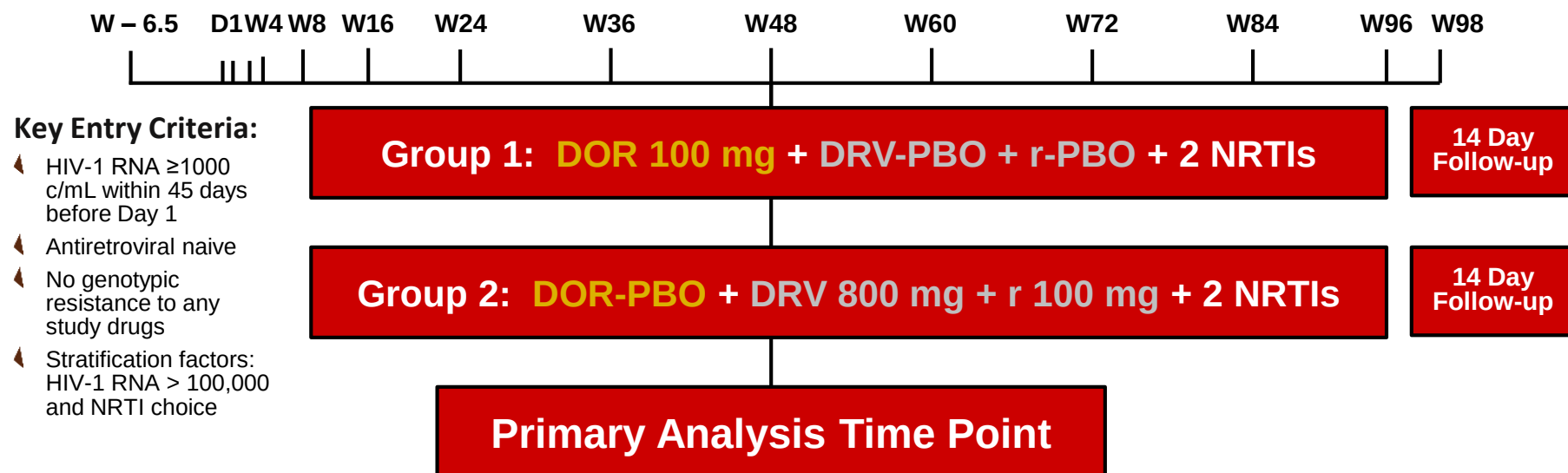
STR

- Atripla
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Doravirine

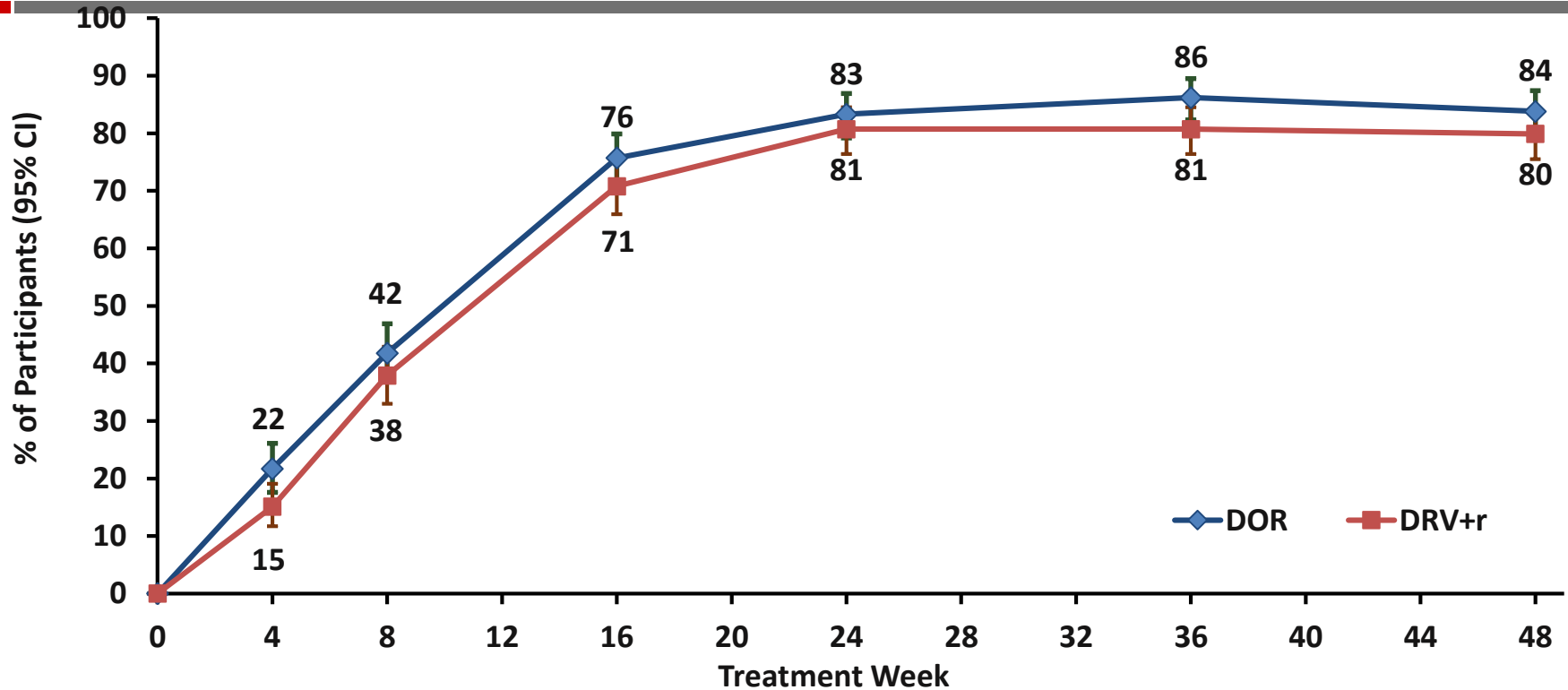
- Doravirine is a novel NNRTI
- **High *in vitro* potency** vs broad panel of isolates including common NNRTI-resistant variants⁴
- **Primary metabolism by CYP3A4**; not an inducer or inhibitor⁵
- **Once daily dosing** (without regard to food)
- **No interactions expected with proton pump inhibitors**

Doravirine vs Darunavir in Naïves: Design



Source: Molina JM, et al. 24th CROI; Seattle, WA; February 13-16, 2017. Abst. 45LB.

Doravirine vs Darunavir in Naïves: Efficacy

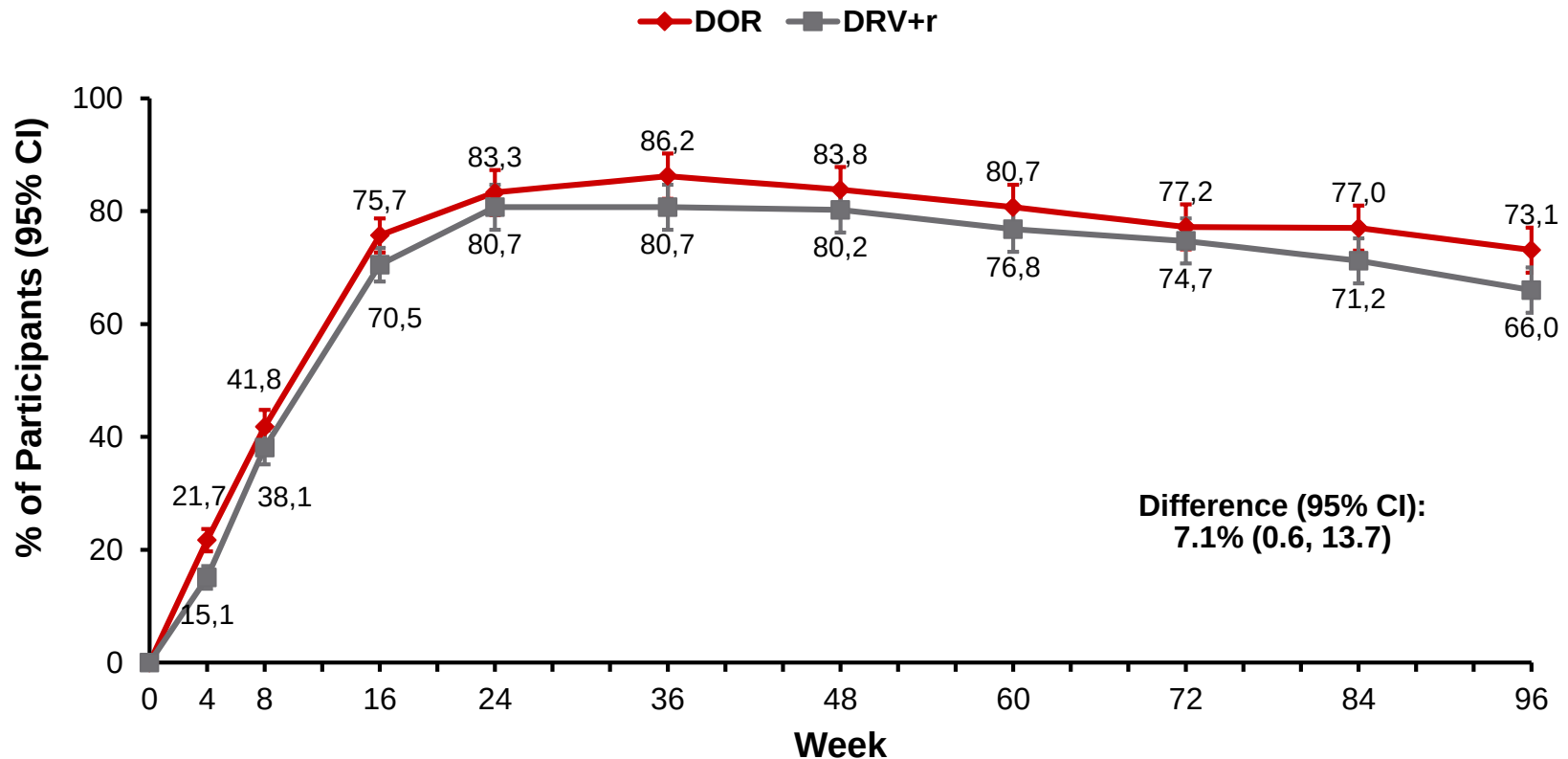


Difference (95% CI): 3.9% (-1.6%, 9.4%)

† FDA Snapshot Approach

Source: Molina JM, et al. 24th CROI; Seattle, WA; February 13-16, 2017. Abst. 45LB.

DRIVE-FORWARD Study: Doravirine vs Darunavir in naïve at 96 weeks



- 2/383 (0.5%) participants on doravirine developing resistance to any study drug

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NRTIs

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Fusion inhibitors

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- **Bictegravir**

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CCR5 Inhibitors

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BICTEGRAVIR

- Bictegravir is a novel specific inhibitor of HIV-1 integrase strand transfer activity¹
- Structurally related to Dolutegravir. Unboosted
- Active against diverse subtypes of wild-type HIV-1 clinical isolates and HIV-2²
- Low cytotoxicity in multiple non-target human cell lines and in primary human hepatocyte²
- Average human T_{1/2} of ~19 hours, allowing for once daily dosing³
- Close to clinic.

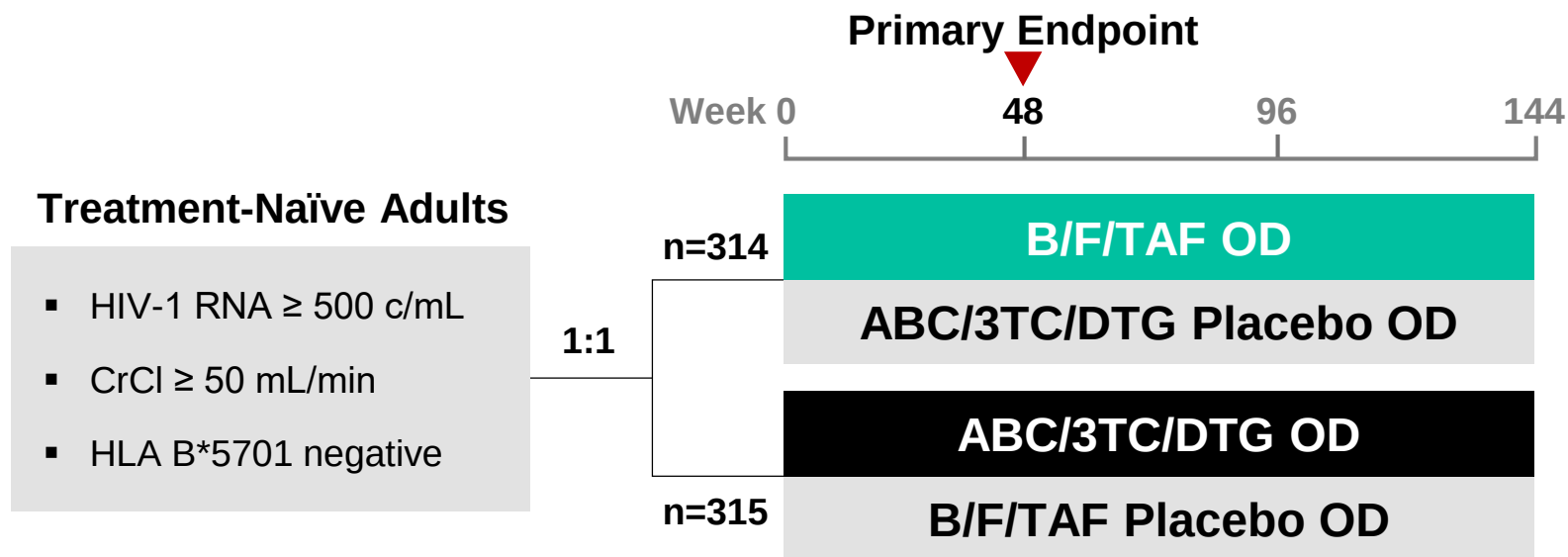
Source: 1. Lazerwith S, et al. ASM 2016; Boston, MA. Poster #414

2. Tsiang M, et al. ASM 2016; Boston, MA. Poster #416

3. Gallant J, et al. ASM 2016. Boston, MA. Poster #415

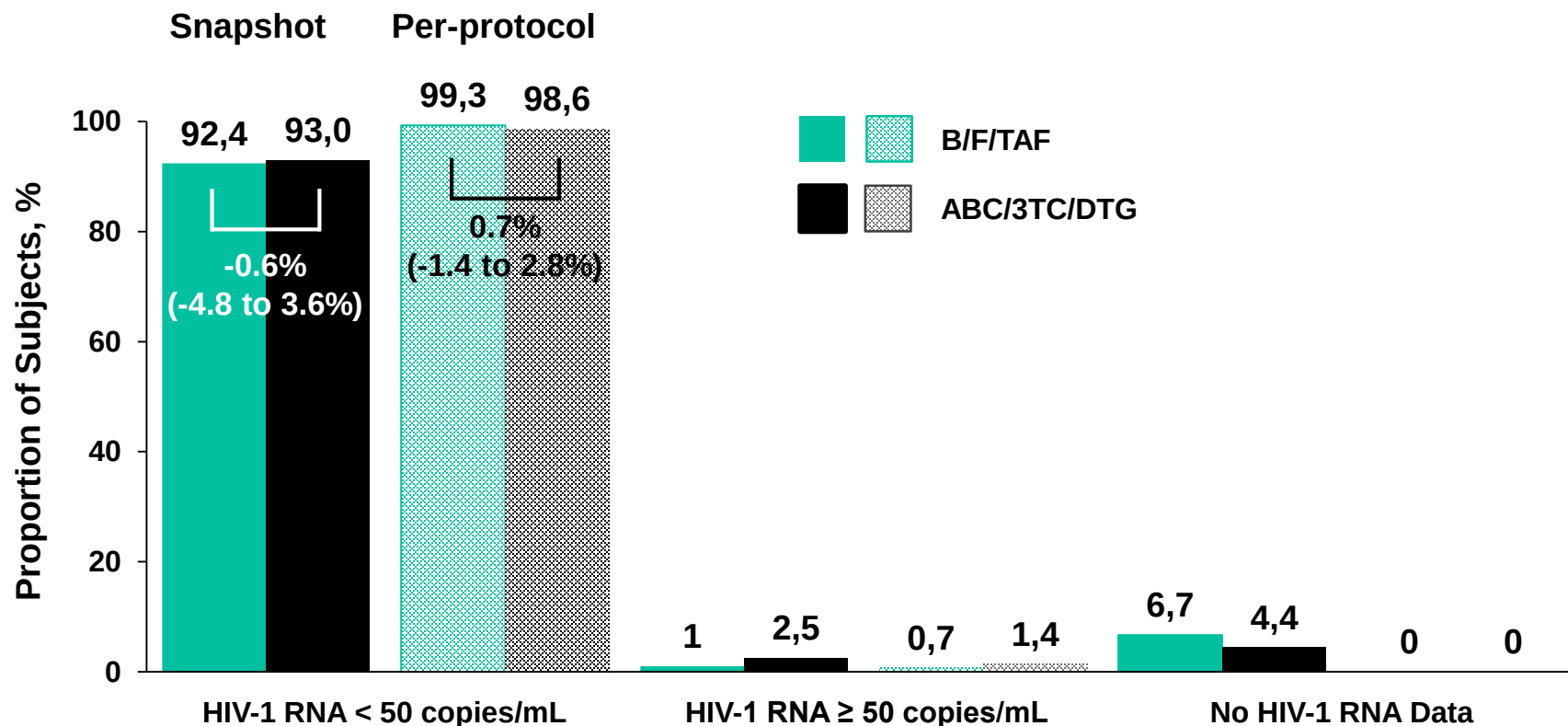
Phase 3 Randomized Controlled Clinical
Trial of Bictegravir in a Fixed Dose
Combination, B/F/TAF, vs DTG/ABC/3TC in
Treatment-Naïve Adults at Week 48

Study Design



- Phase 3, randomized, double-blind, active-controlled study (ClinicalTrial.gov NCT02607930)
 - Stratified by HIV-1 RNA, CD4 cell count, geographic region
 - North America and Europe
 - Chronic hepatitis C virus infection allowed
- Treatment-naïve, HIV-1-infected adults were randomized 1:1 to receive B/F/TAF 50/200/25 mg or ABC/3TC/DTG 600/300/50 mg with matching placebo once daily
- **Primary endpoint:** HIV-1 RNA < 50 copies/mL at Week 48 by FDA Snapshot algorithm (12% NI margin)

Virologic Outcome at Week 48 by FDA Snapshot Analysis

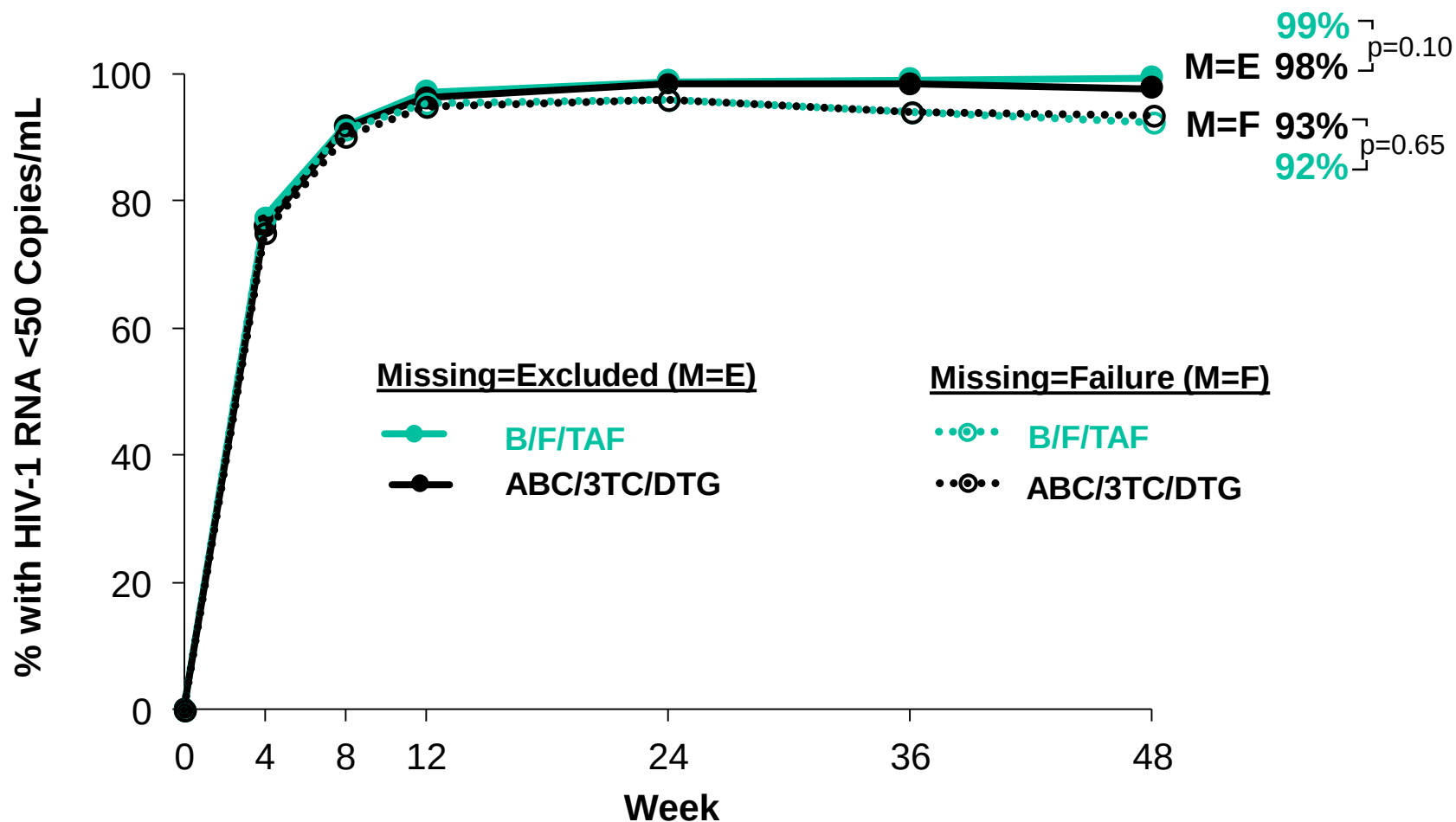


Mean changes in CD4 cell count (cells/ μ L) at Week 48: +233 B/F/TAF vs +229 ABC/3TC/DTG ($p=0.81$)

B/F/TAF vs ABC/3TC/DTG: Non-inferior efficacy at Week 48

Confirmed by pre-specified sensitivity analyses (PP, M=E, and M=F)

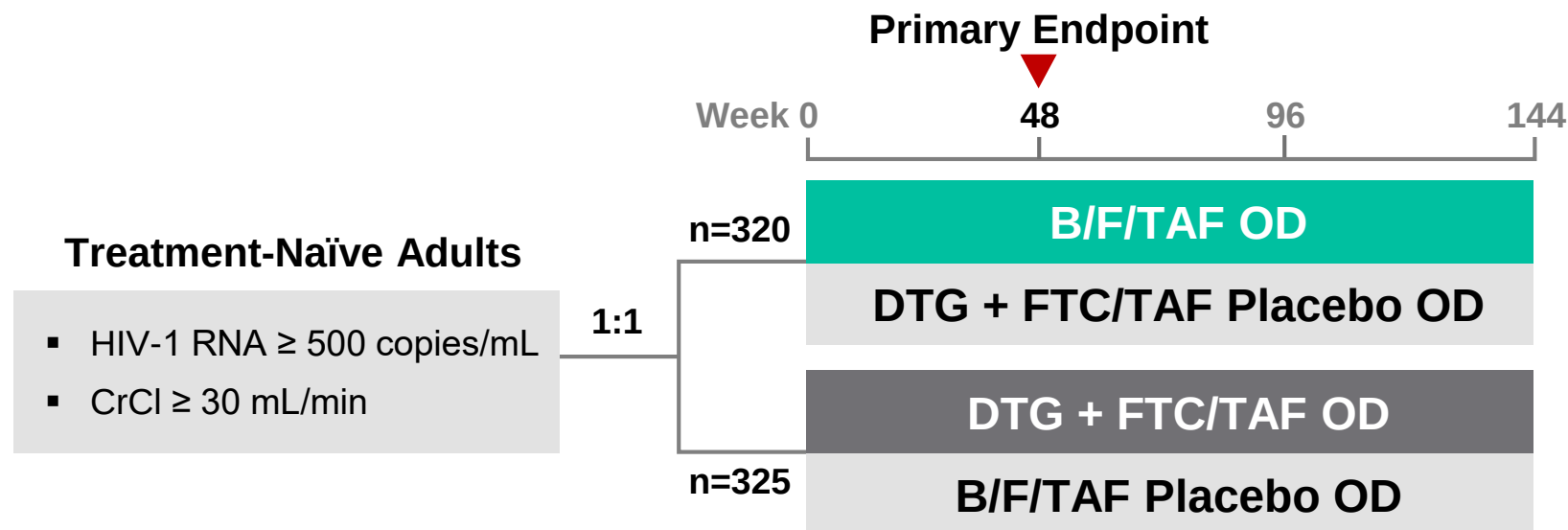
Efficacy Through Week 48 (M=E and M=F)



B/F/TAF vs. ABC/3TC/DTG: non-inferior efficacy at Week 48

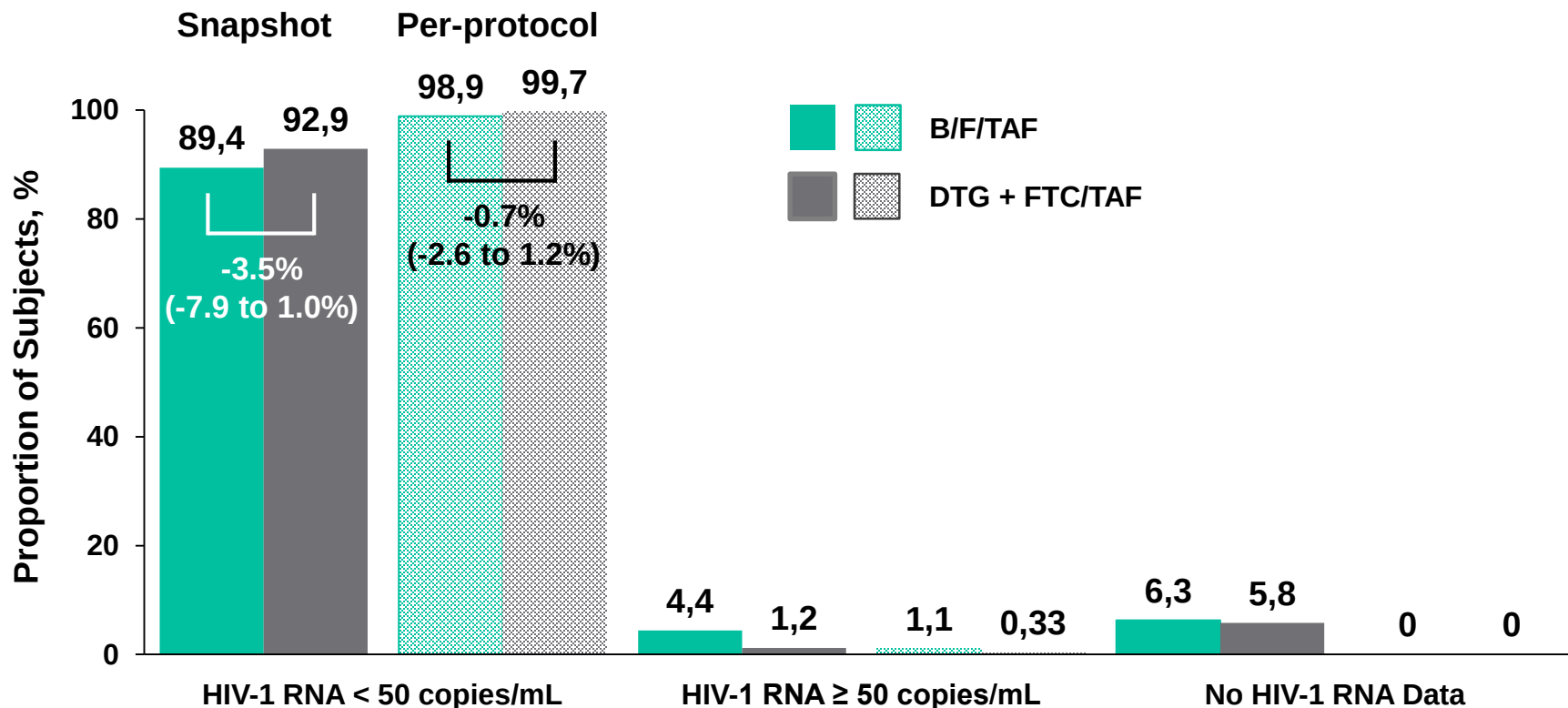
Phase 3 Randomized, Controlled, Clinical Trial
of Bictegravir Coformulated With FTC/TAF in a
Fixed-Dose Combination vs Dolutegravir +
FTC/TAF in Treatment-Naïve HIV-1–Positive
Adults: Week 48 Results

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Virologic Outcome at Week 48 by FDA Snapshot Analysis

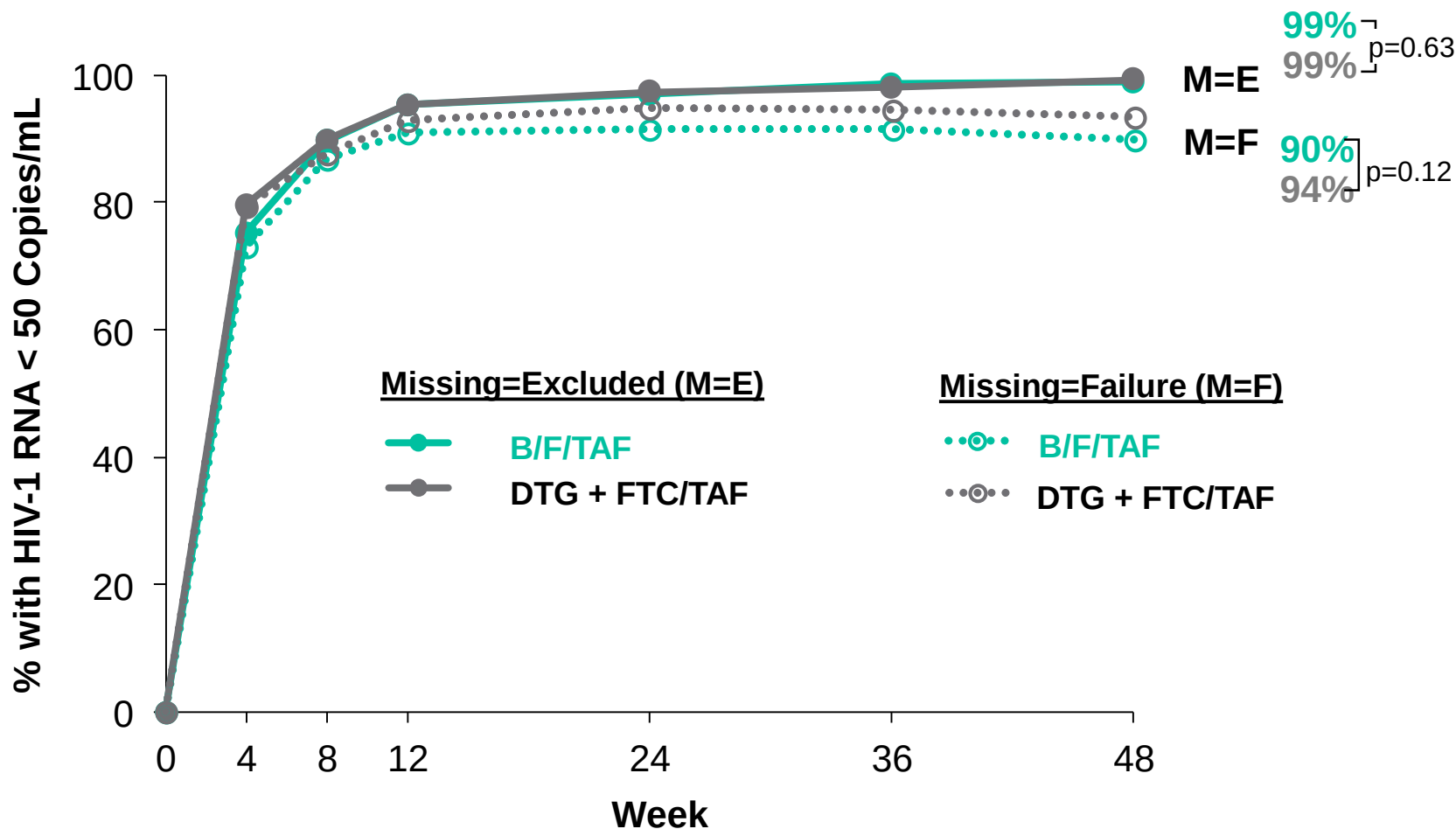


Mean changes in CD4 cell count (cells/ μ L) at Week 48: +180 BIC vs +201 DTG (p=0.10)

BIC vs DTG with FTC/TAF: Non-inferior efficacy at Week 48

Confirmed by pre-specified sensitivity analyses (PP, M=E, and M=F)

Efficacy Through Week 48 (M=E and M=F)



BIC vs. DTG: non-inferior efficacy at Week 48

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PK Boosters

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- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

INIs

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- Dolutegravir
- Elvitegravir
- **Bictegravir**

Fusion inhibitors

- Enfuvirtide

Entry Inhibitors

- Maraviroc
- **Fostemsavir**
- Ibalizumab
- **Pro140**
- **UB-421**

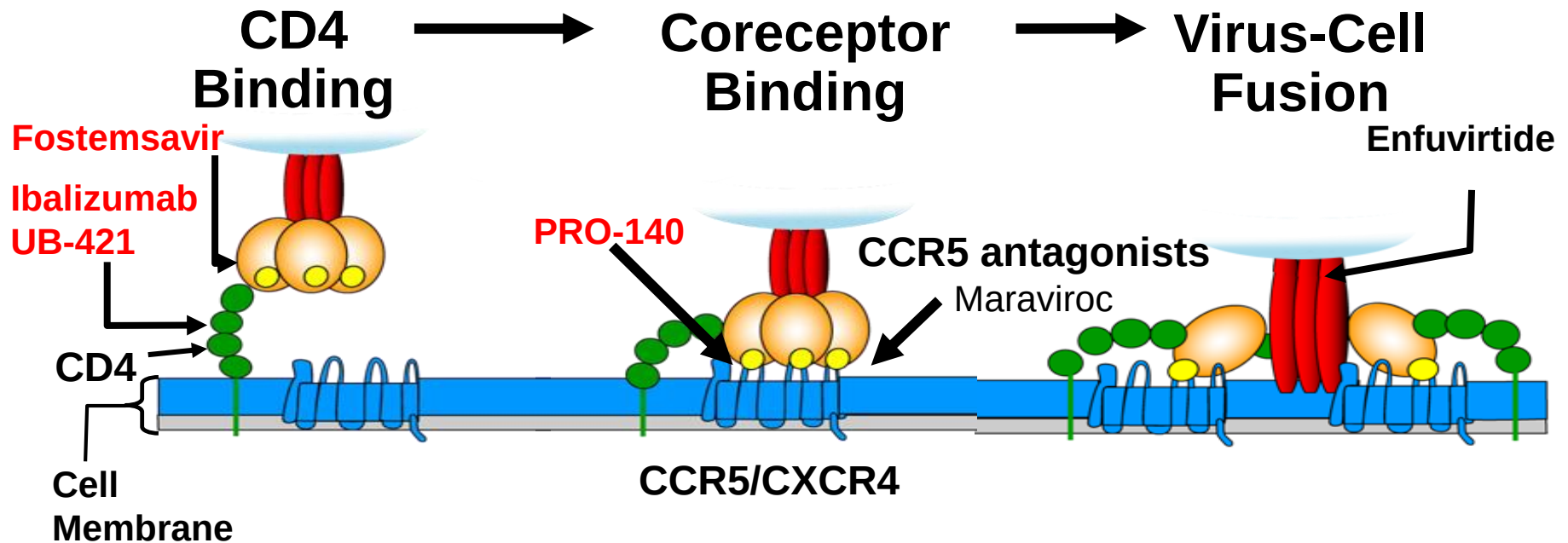
PK Boosters

- Ritonavir
- Cobicistat

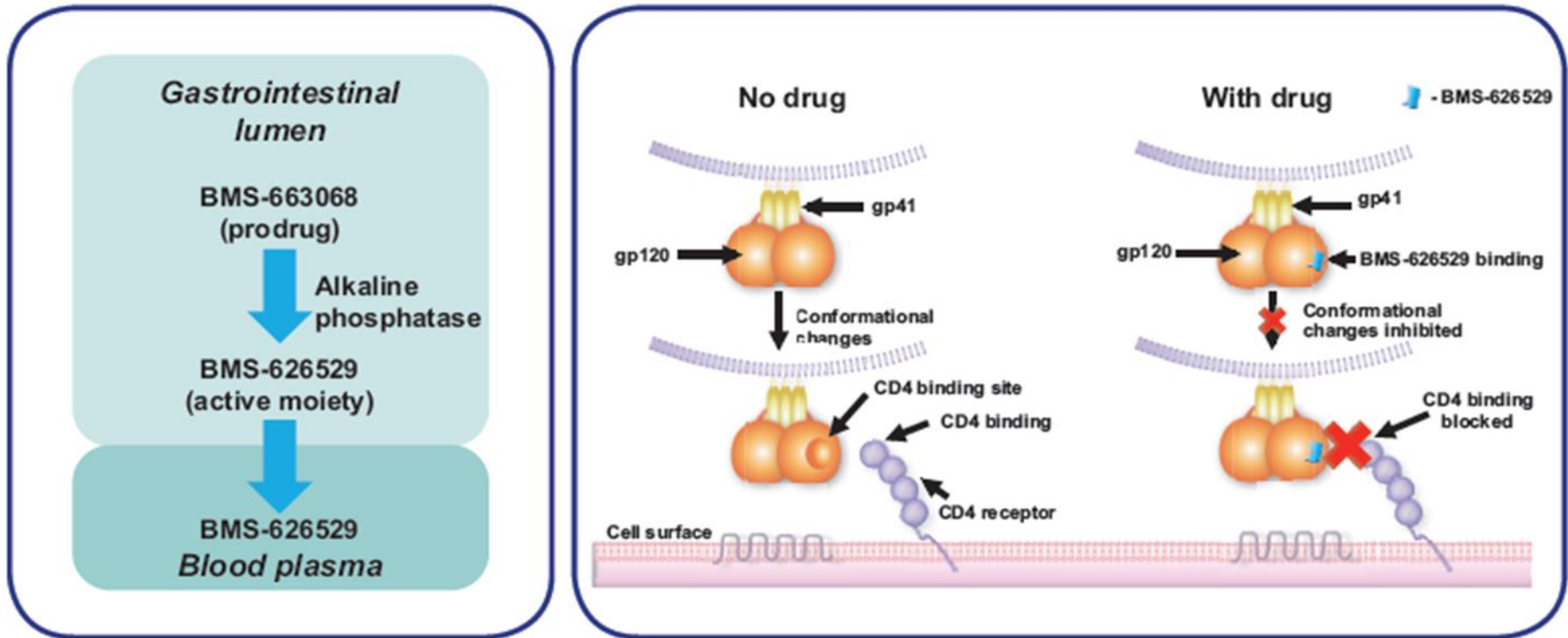
STR

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Entry Inhibitors



Fostemsavir: Inhibidor del acoplamiento

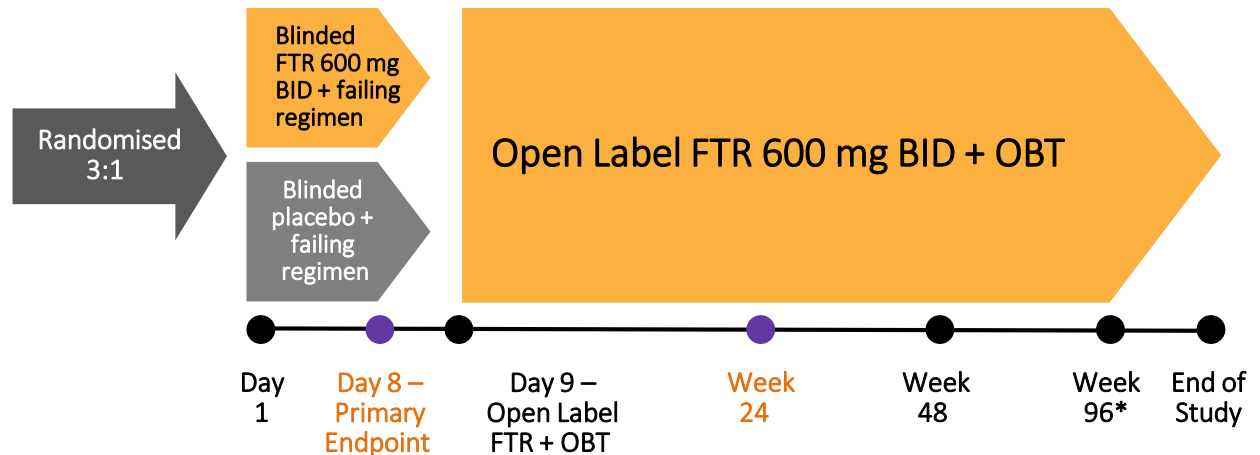


BRIGHTE study: FOSTEMSAVIR in HIGHLY TREATMENT EXPERIENCED PATIENTS

Randomised Cohort :

HTE participants failing current regimen with confirmed HIV-1 RNA $\geq$ 400 c/mL and:

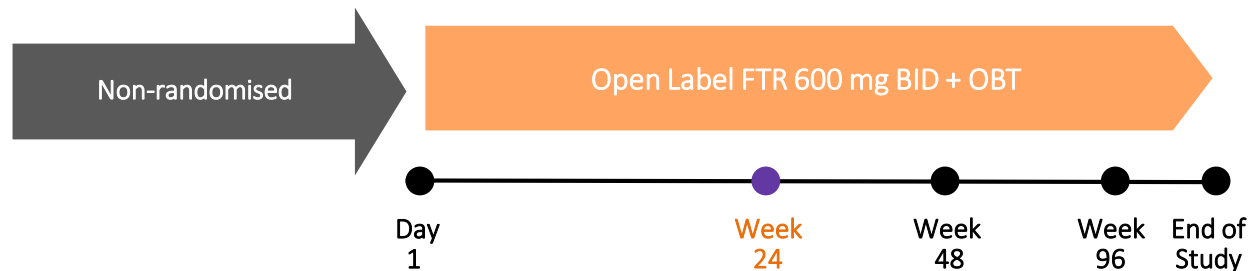
- 1 or 2 ARV classes remaining & $\geq$ 1 fully active & available agent per class
- Unable to construct viable regimen from remaining agents



Non-randomised Cohort :

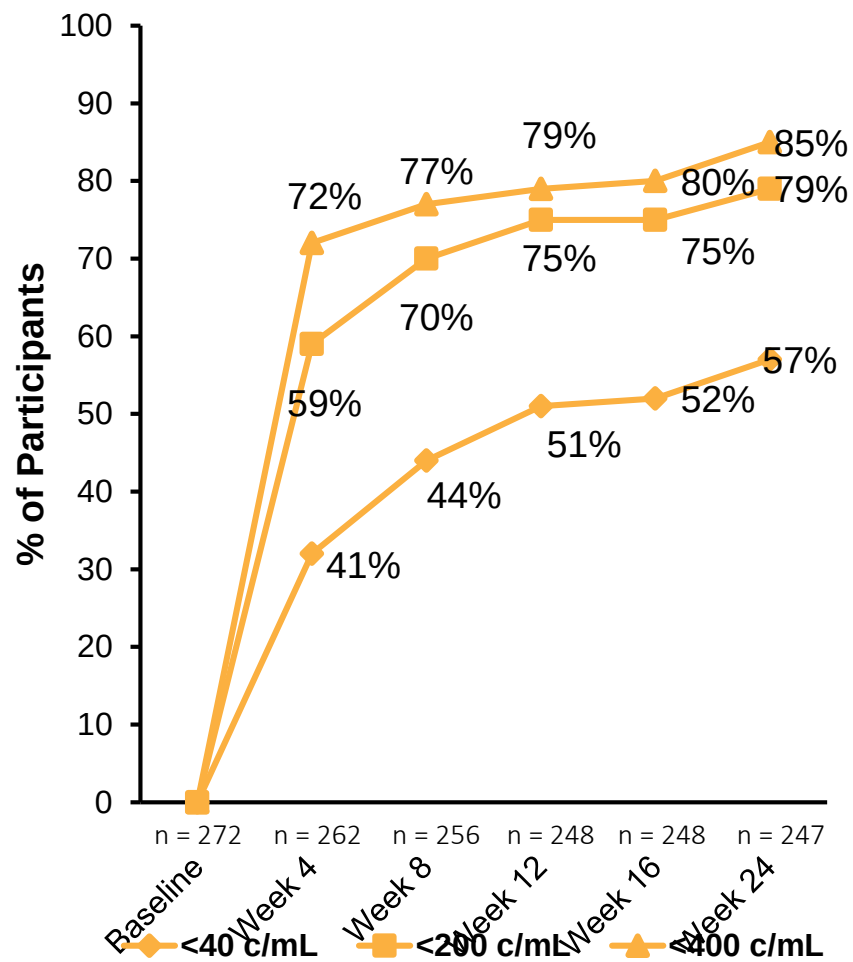
HTE participants, failing current regimen with confirmed HIV-1 RNA $\geq$ 400 c/mL and:

- 0 ARV classes remaining and no remaining fully active approved agents

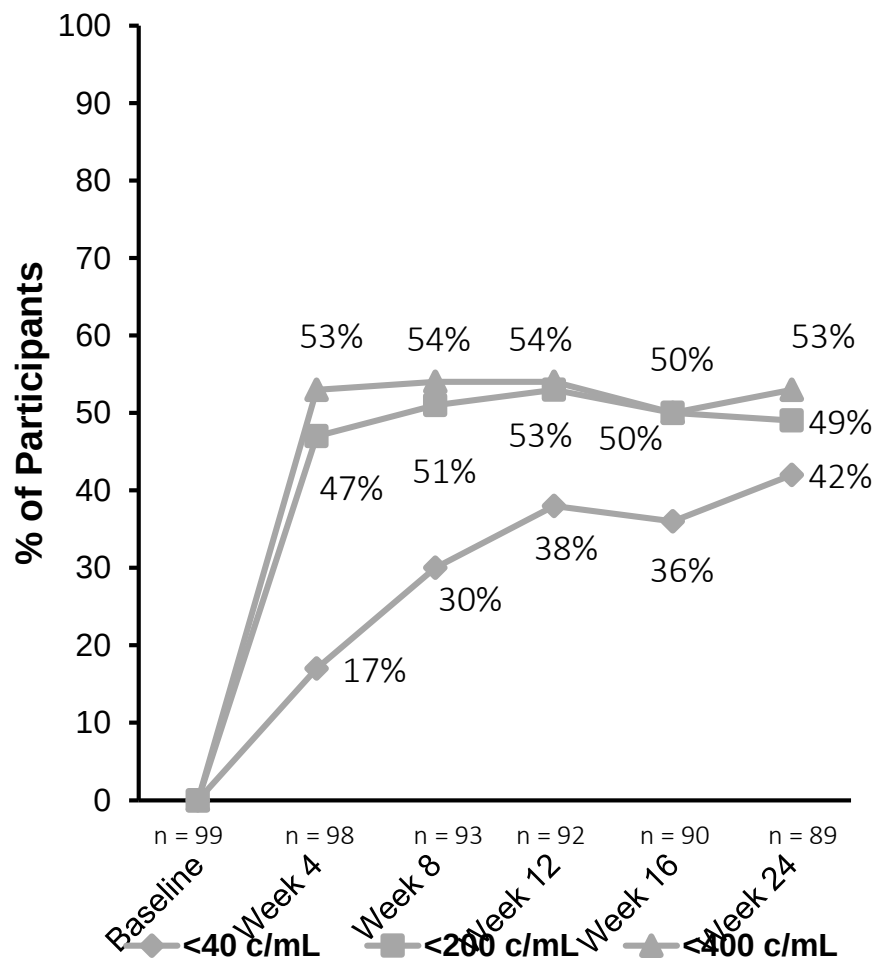


BRIGHTE study: Results

Randomised Cohort

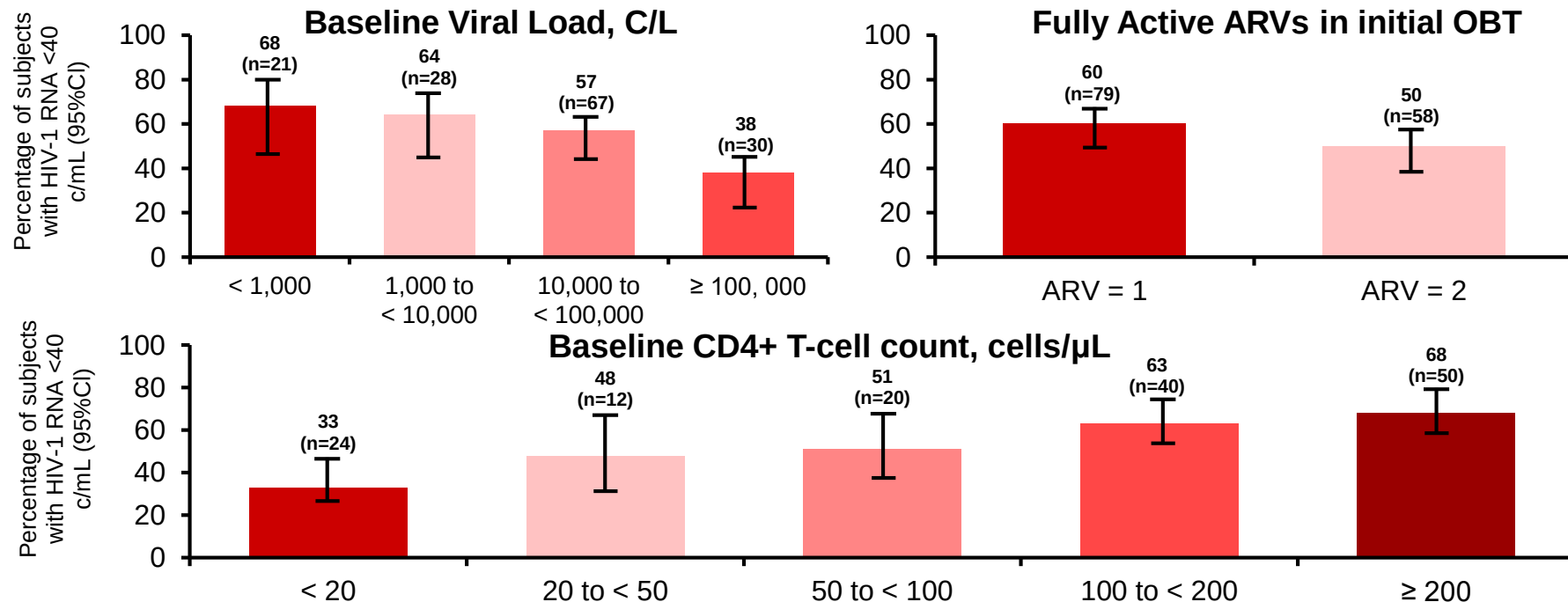


Non-randomised Cohort



BRIGHTE study: Results by Baseline Characteristics

Disease Characteristics



- Higher response rates:

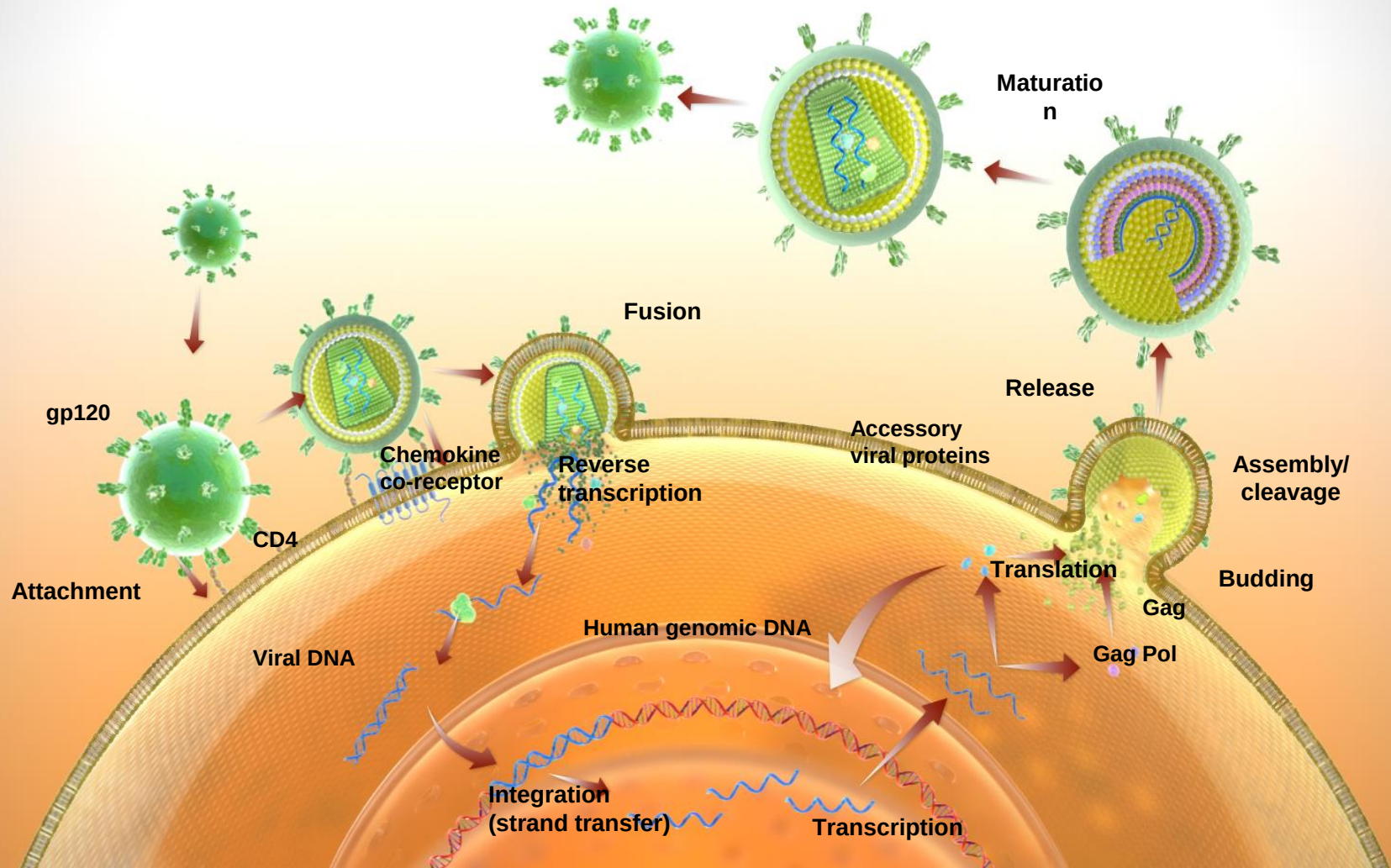
- Participants with a baseline VL <100,000 c/mL (60%) vs baseline VL ≥100,000 c/mL (38%)
- Participants with a baseline CD4+ T-cell counts of ≥50 cells/μL (63%) vs baseline CD4+ T-cell counts of <50 cells/μL (37%)

- No difference in response by age, gender, race, and region subgroups

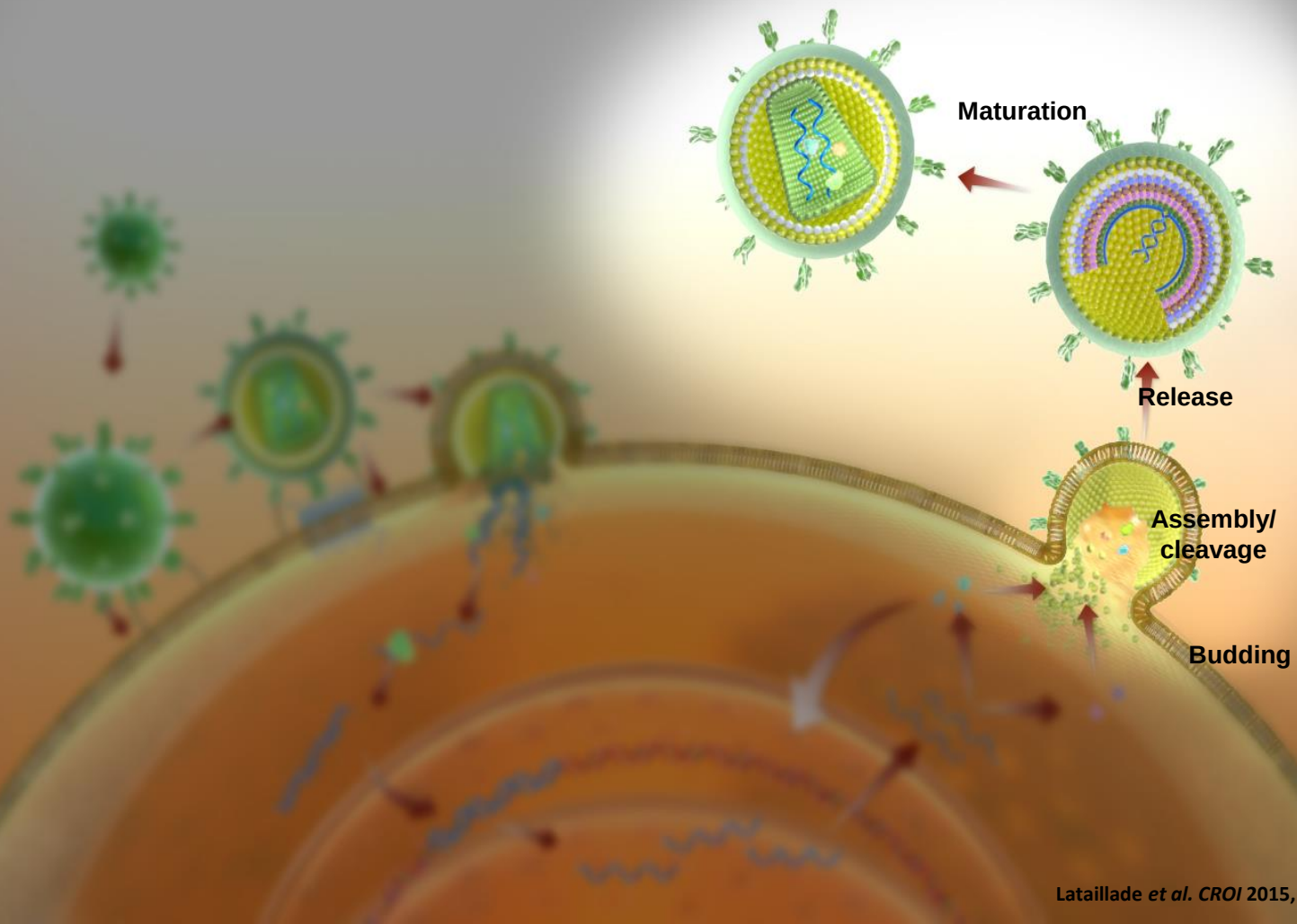
a Analysis performed using FDA Snapshot algorithm

3 Futuro: Nuevas Familias

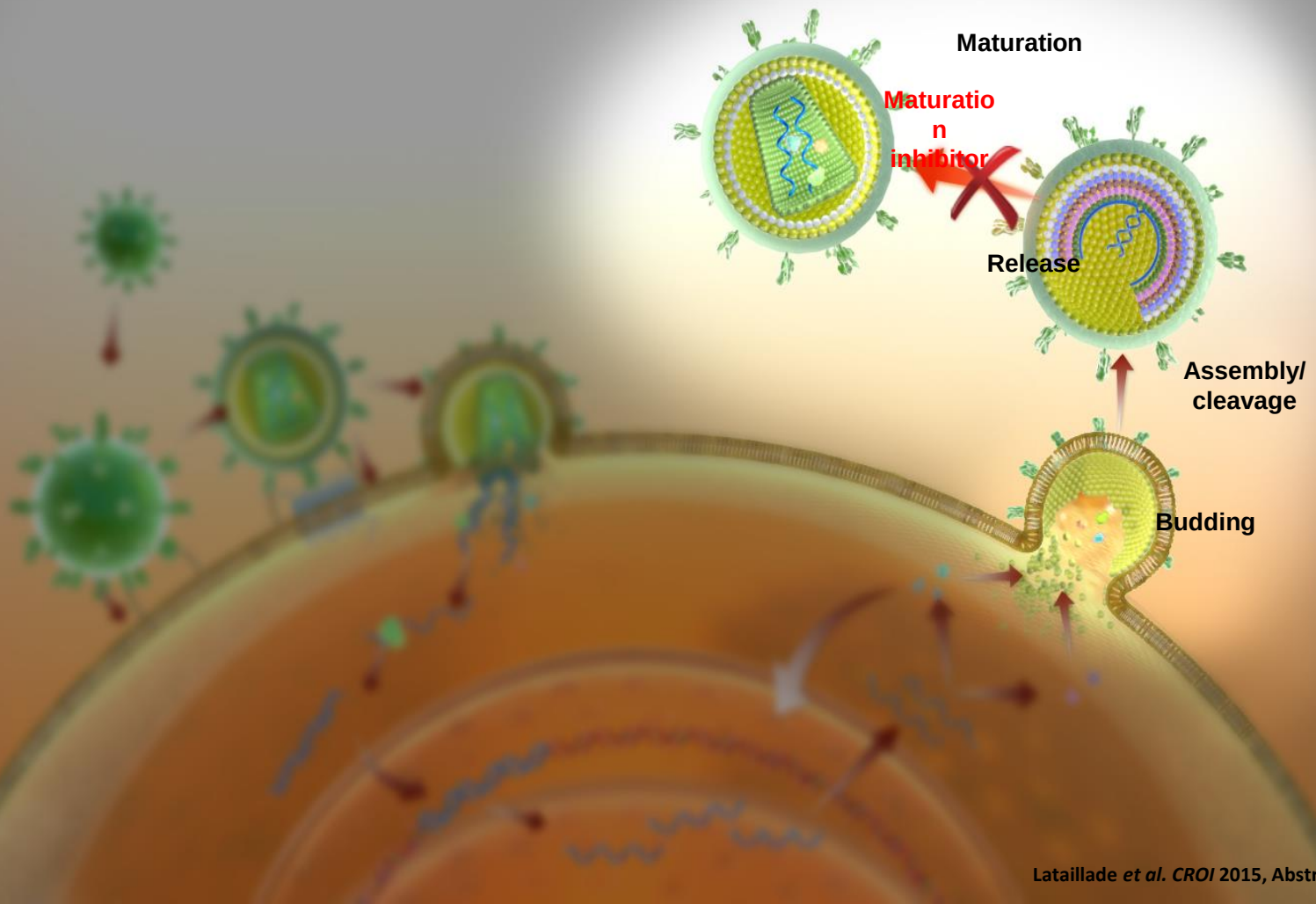
Maturation Inhibitors (MIs): BMS-955176 HIV-1 Lifecycle



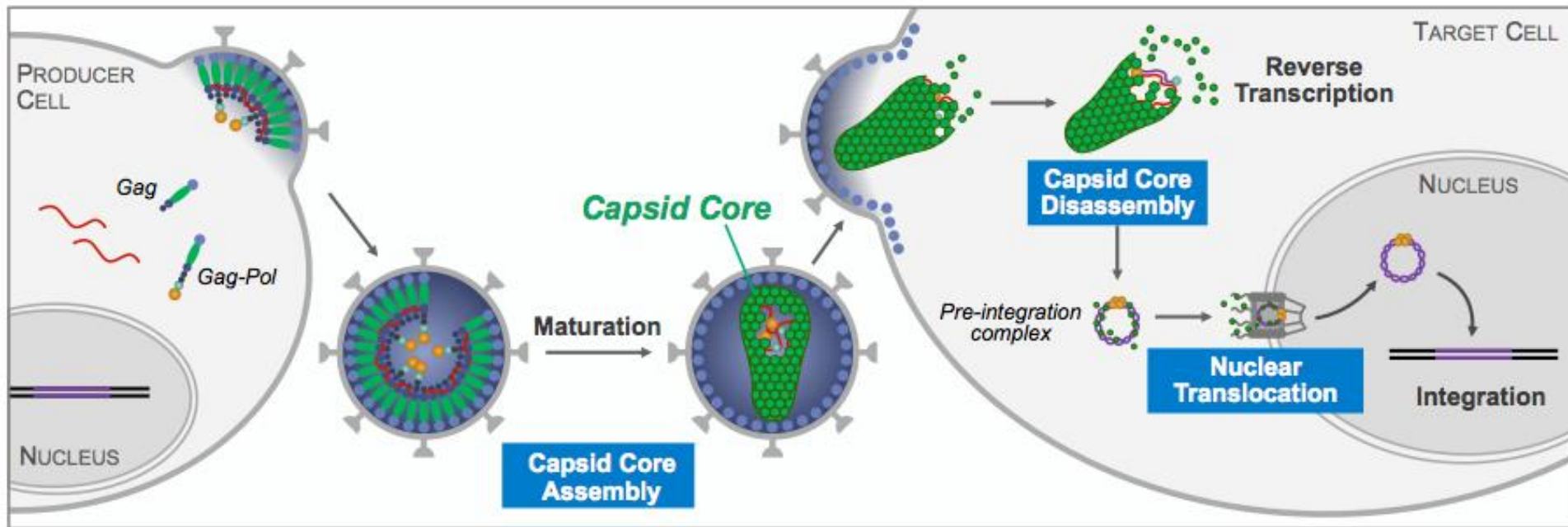
Maturation Inhibitors (MIs): BMS-955176 HIV-1 Lifecycle



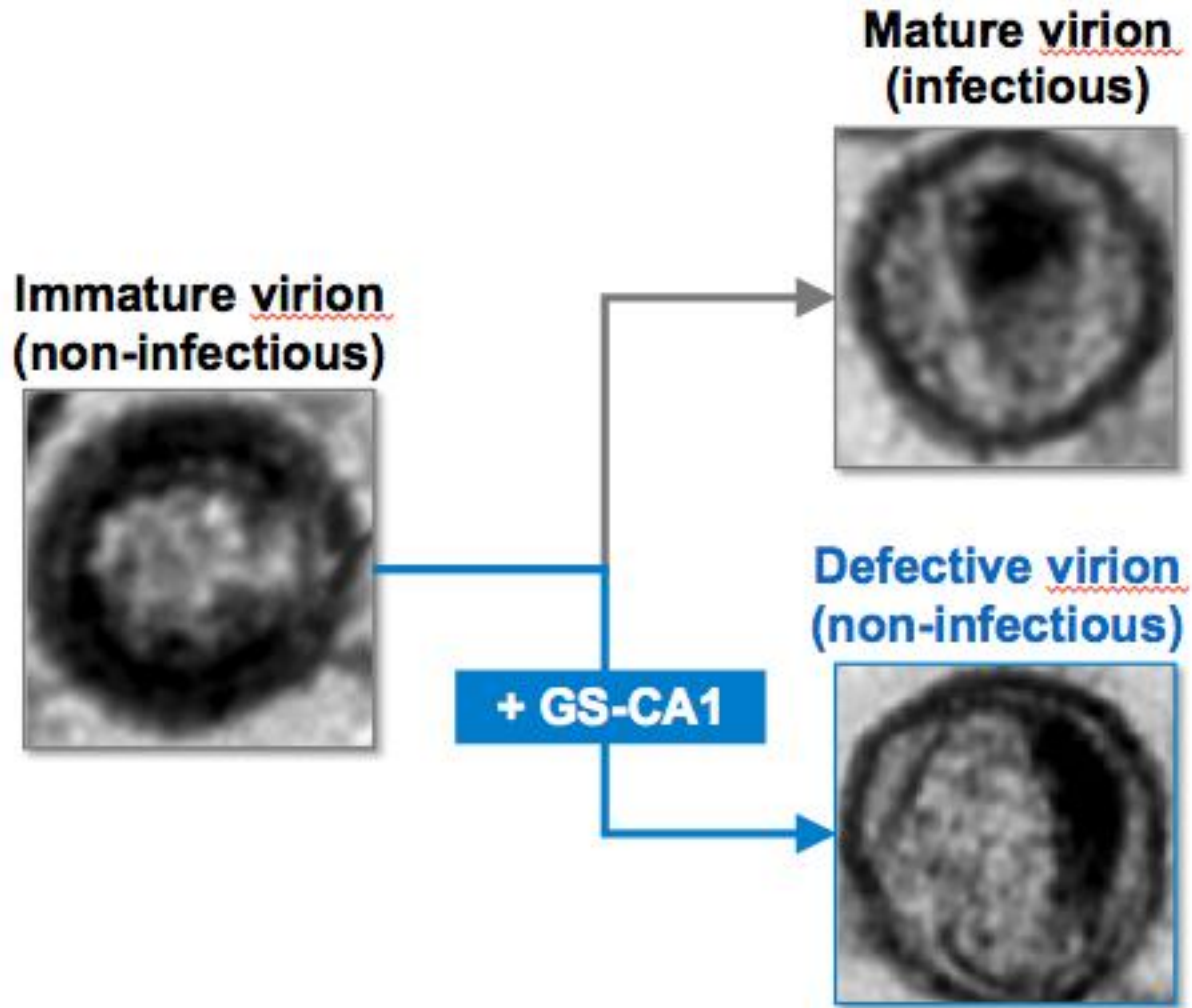
Maturation Inhibitors (MIs): BMS-955176 HIV-1 Lifecycle



GS-CA1: el primer inhibidor de la cápside



GS-CA1: un nuevo inhibidor de la cápside



GS-CA1: principales características

- Actúa a nivel picomolar
 - EC50 de DTG: 1.200 pM
 - EC50 de GS-CA1: 140 pM
- Unión a región muy conservada
 - Mutantes con escasa capacidad replicativa
- Posibilidad de formulación “long-acting”
 - 1 inyección sc mensual

Nuevos Fármacos: Usos Potenciales

- **Doravirina:**
 - Perfil de resistencias distinto, mejor tolerabilidad
 - Tratamiento de inicio, ¿simplificación?, ¿rescate?
- **Bictegravir:**
 - Tratamiento de inicio, simplificación, rescate
 - Nuevo STR
- **Inh. de la entrada:**
 - Tratamiento de rescate.
 - Posibilidad administración prolongada
- **Inh. Maduración:**
 - Interrumpido desarrollo?
- **Inh. Cápside:**
 - Administración prolongada

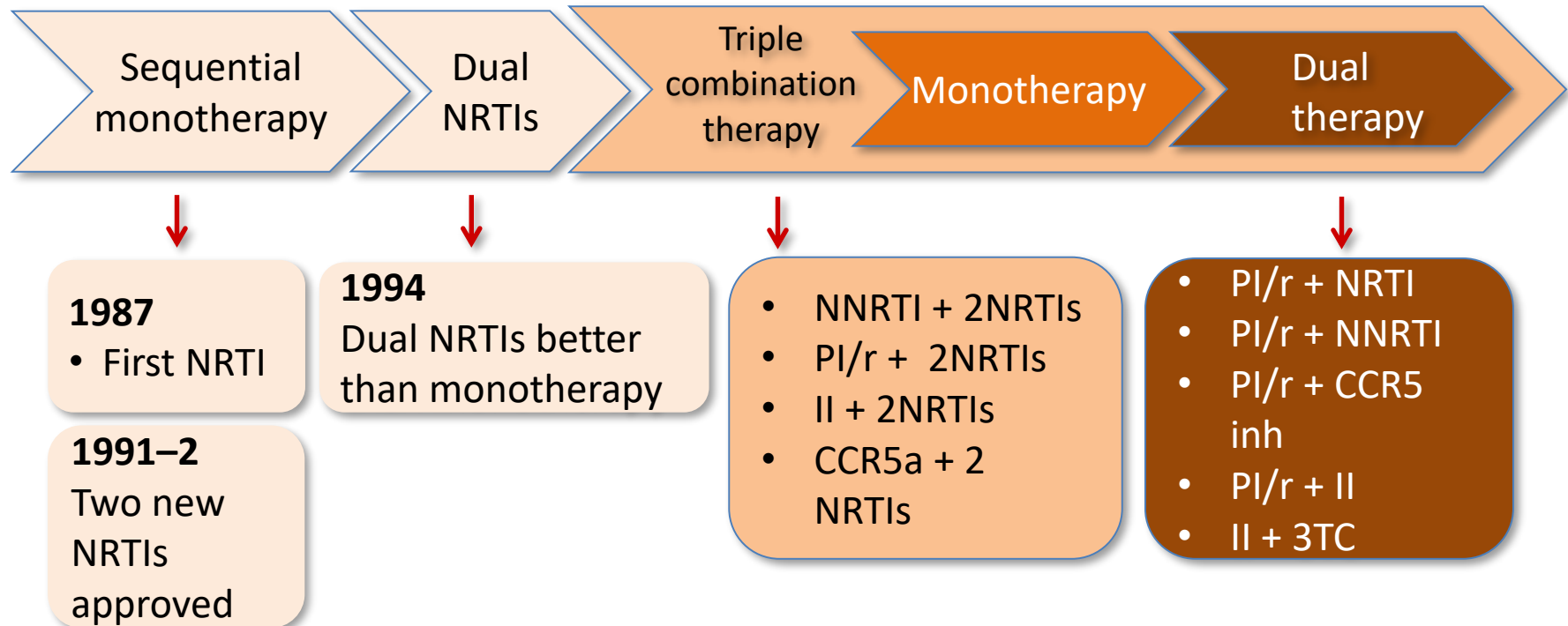
4

Futuro:

Nuevas Estrategias

Biterapias

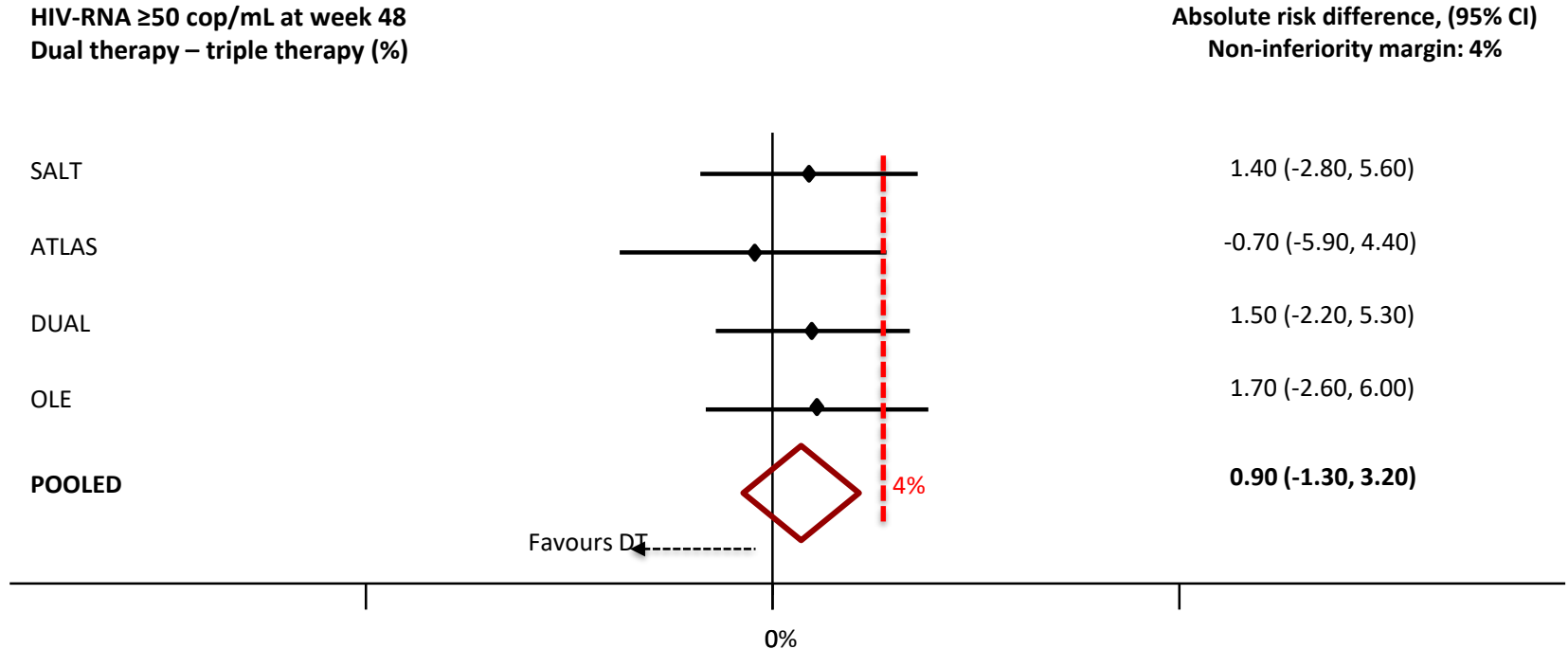
Número de Fármacos: Evolución del TAR



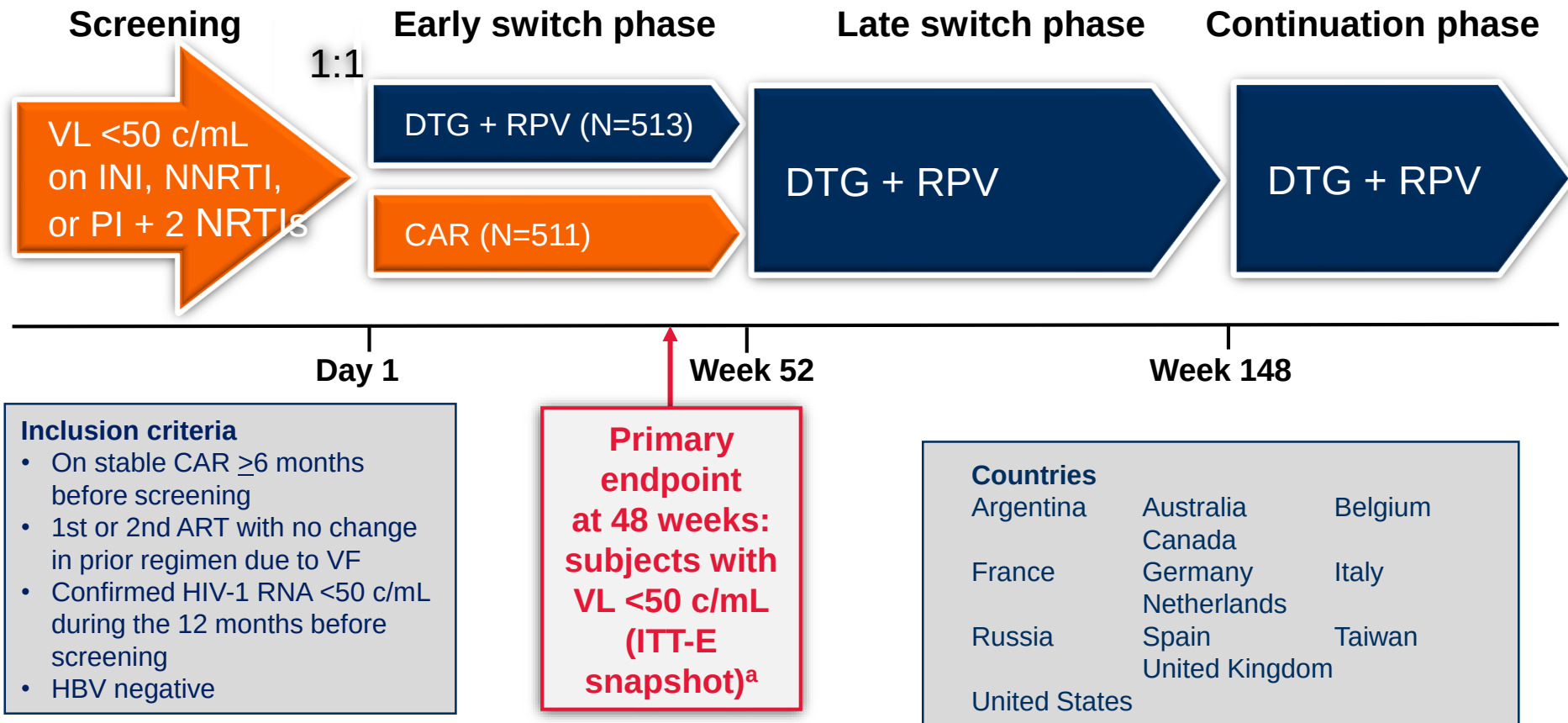
Combinations of bPI + 3TC: Switch in suppressed patients

At 48w, 4% of patients on DT vs. 3.04% on TT had HIV-RNA ≥ 50 cop/mL

Difference 0.9% (95%CI, -1.3% to 3.2%)



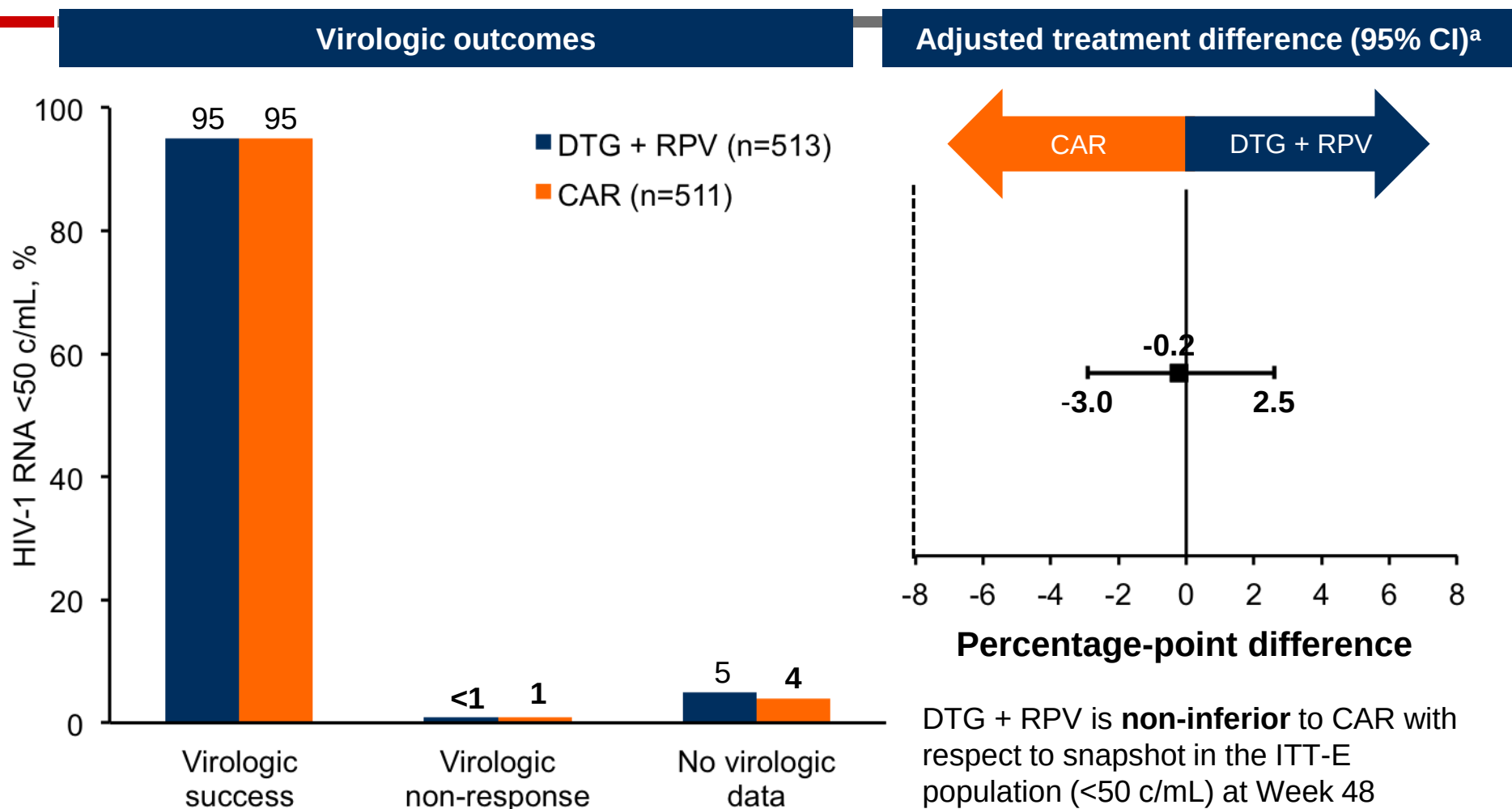
SWORD-1 and SWORD-2 Phase III Study Design



^a-8% non-inferiority margin for pooled data

-10% non-inferiority margin for individual studies

Snapshot Outcomes at Week 48 (Pooled)



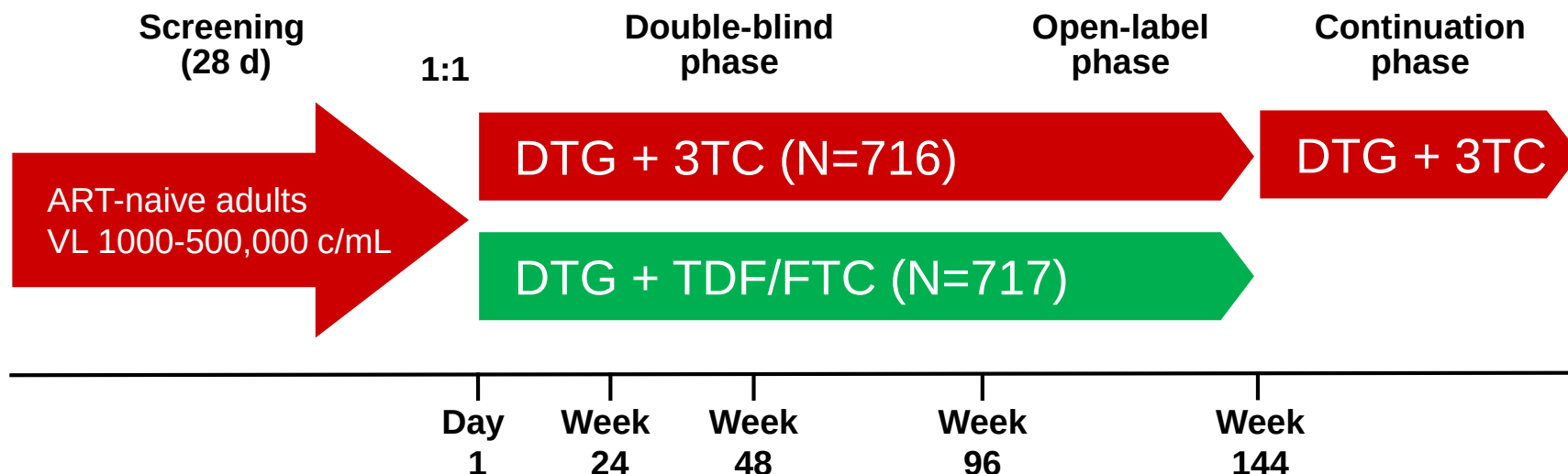
ACTG A5353: 3TC + Dolutegravir

Primary Objective (snapshot at 24 weeks)

	Baseline viral load		Total N=120
	> 100,000 cpm N=37	≤ 100,000 cpm N=83	
Virological suppression HIV-1 RNA < 50 c/m [95% CI]	33 (89%) [75%,97%]	75 (90%) [82%,96%]	108 (90%) [83%,95%]
No suppression HIV-1 RNA ≥ 50 c/m	3 (8%) 3	2 (2%) 0	5 (4%) 3
Discontinuation with CV > 50 c/m*	0	2	2
No virological data	1 (3%)	6 (7%)	7 (6%)
Discontinuation for other reasons#	1	5	6
In study but without data	0	1	1

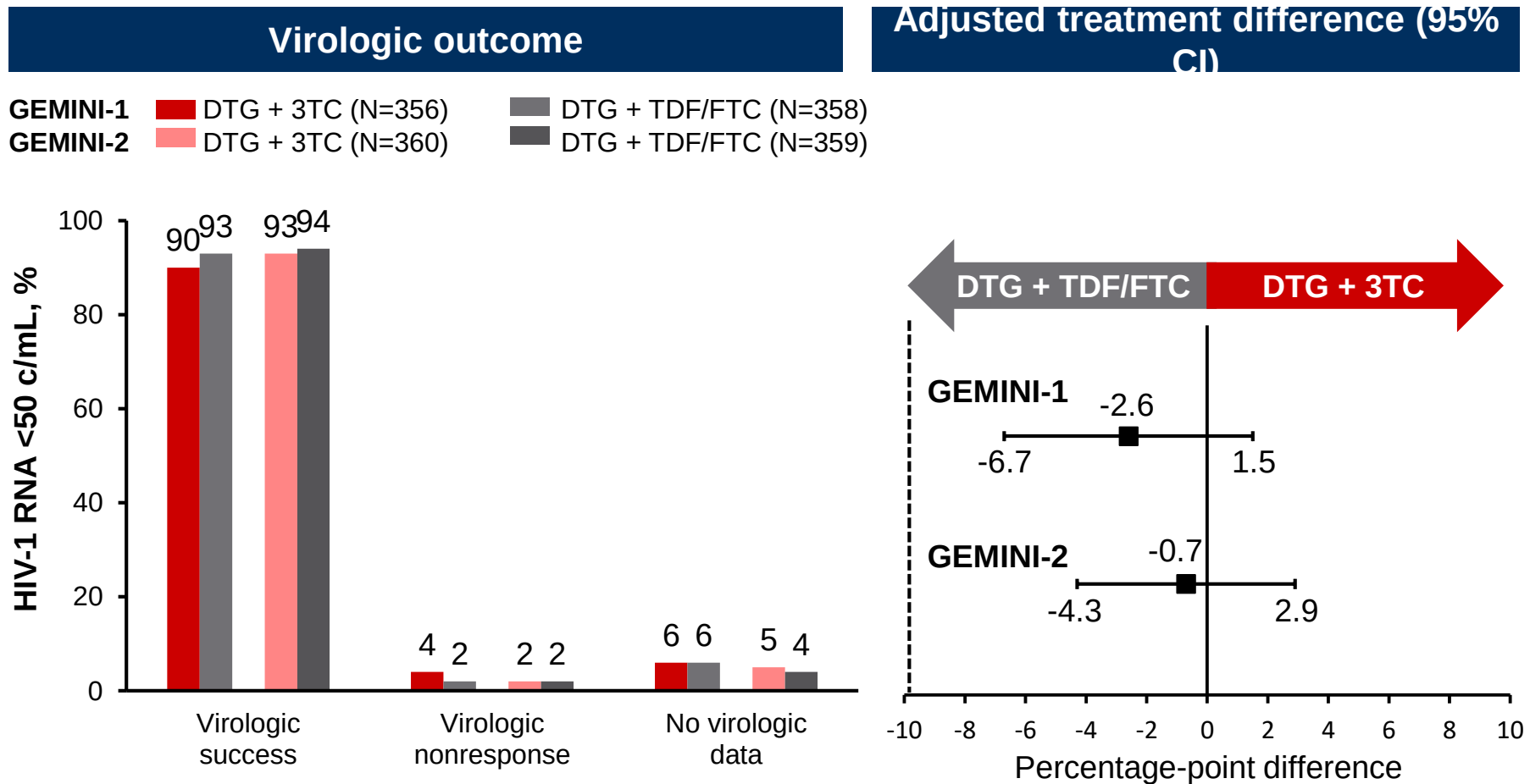
* Poor adherence; # Lost of follow-up, pregnancy.

GEMINI 1 and 2: Study design



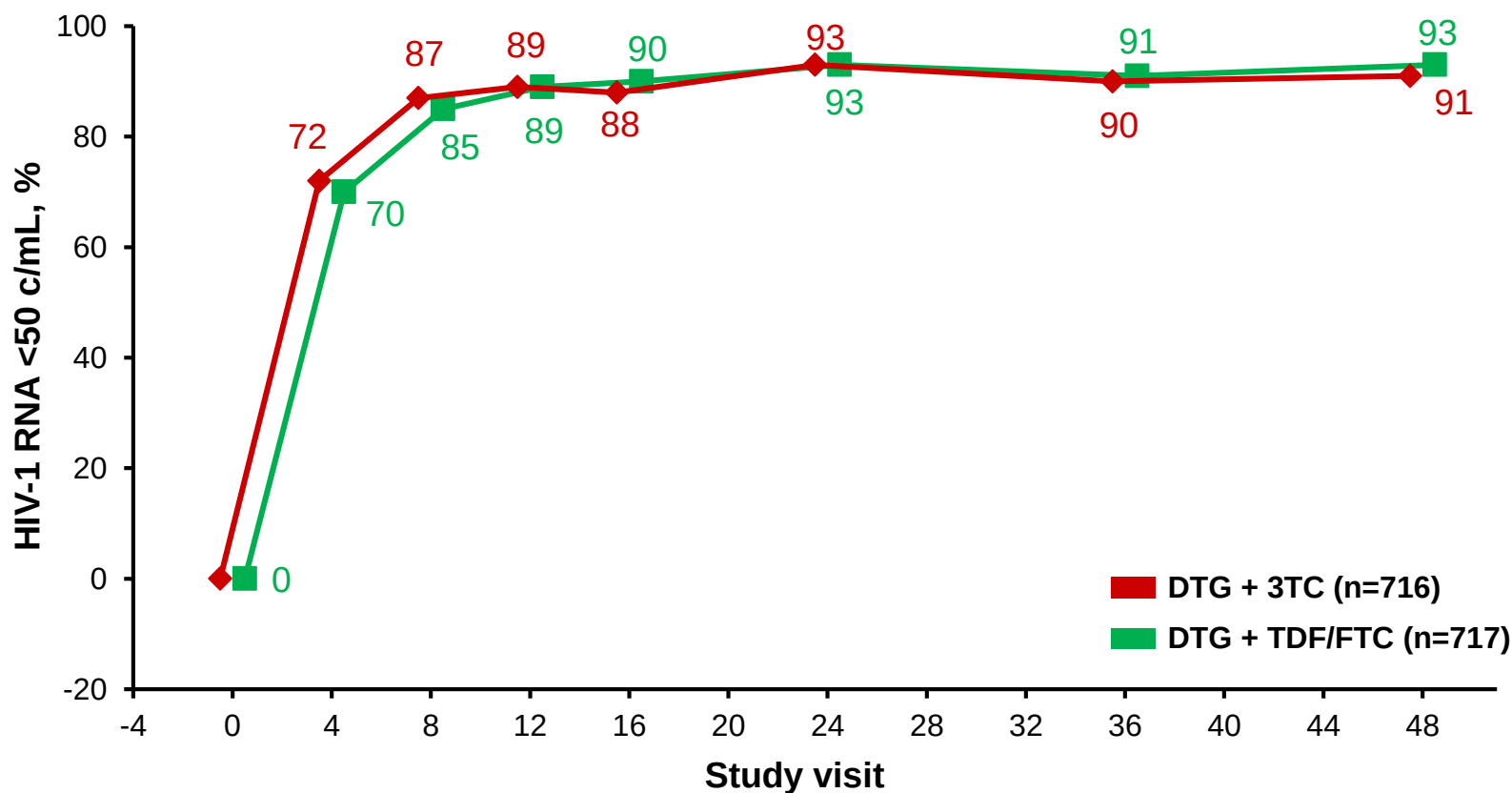
- Eligibility criteria
 - ≤10 days of prior ART
 - No evidence of pre-existing viral resistance based on presence of any major resistance-associated mutation
 - No HBV infection or need for HCV therapy

GEMINI 1 and 2: Snapshot Outcomes at Week 48



GEMINI 1 and 2: Results

Snapshot Analysis by Visit: Pooled ITT-E Population



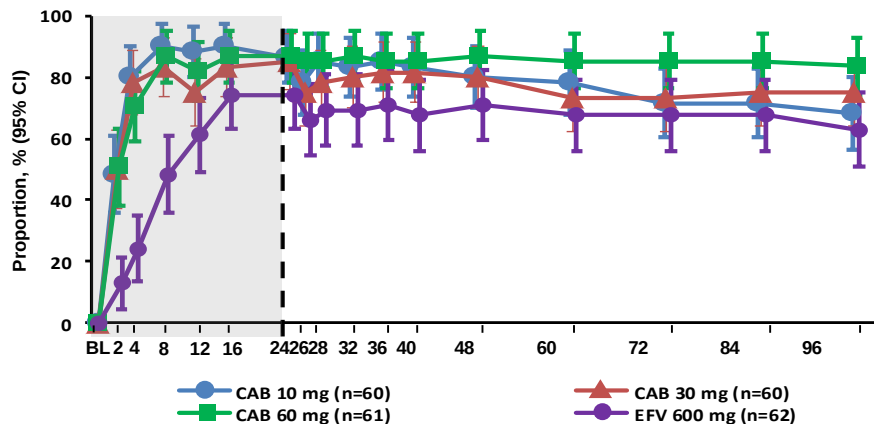
5 Futuro: Nuevas Estrategias Administración Prolongada

Nuevas Estrategias: Fármacos de Acción Prolongada

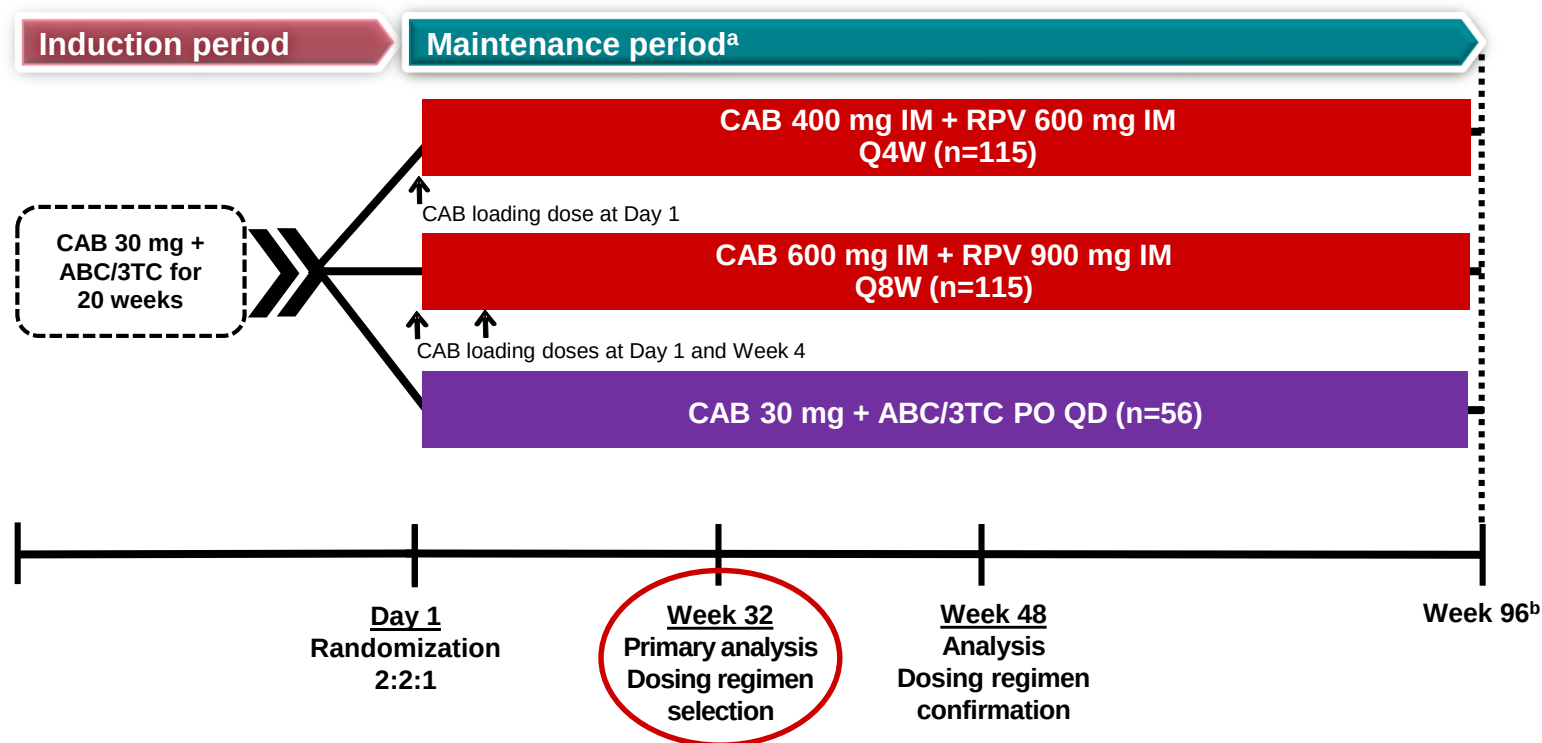
Cabotegravir + Rilpivirine as
Long-Acting Maintenance Therapy:
LATTE-2 Week 32 Results

Background

- **CAB** is an HIV-1 integrase inhibitor
 - Oral 30 mg tablet ($t_{1/2}$, ~40 hours)
 - **LA nanosuspension 200 mg/mL** ($t_{1/2}$, ~20-40 days)
- **RPV** is an HIV-1 NNRTI
 - Oral 25 mg tablet ($t_{1/2}$, ~50 hours)
 - **LA nanosuspension 300 mg/mL** ($t_{1/2}$, ~30-90 days)
- **Oral 2-drug CAB + RPV proof of efficacy through Week 96 in LATTE-1**



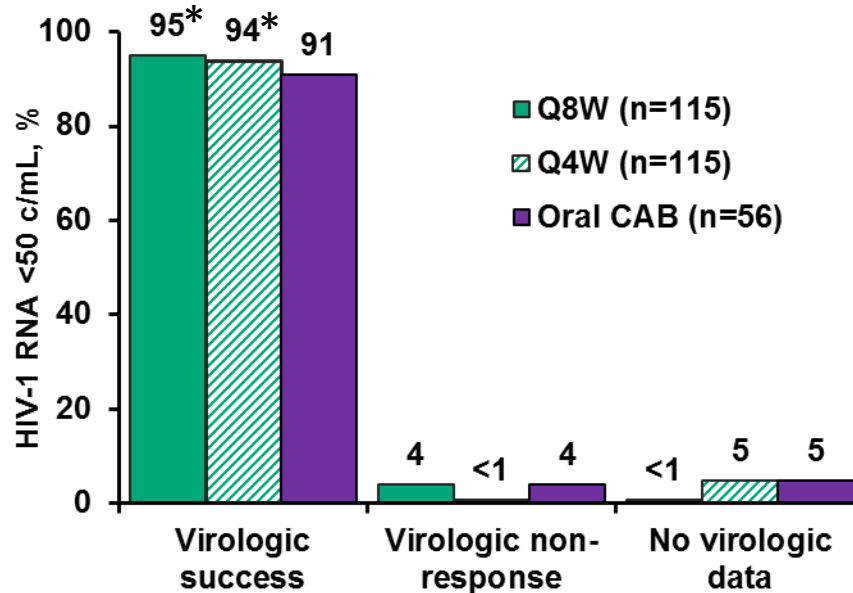
LATTE-2 Study Design



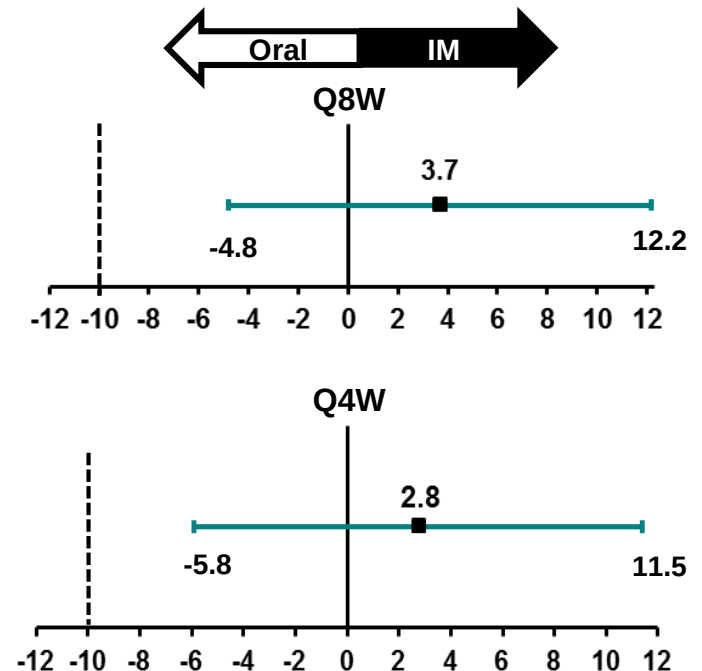
ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; ULN, upper limit of normal. ^aSubjects who withdrew after at least 1 IM dose entered the long-term follow-up period. ^bSubjects can elect to enter LA Extension Phase beyond Week 96.

LATTE-2 Week 32 Primary Endpoint: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

Virologic outcomes



Treatment differences (95% CI)

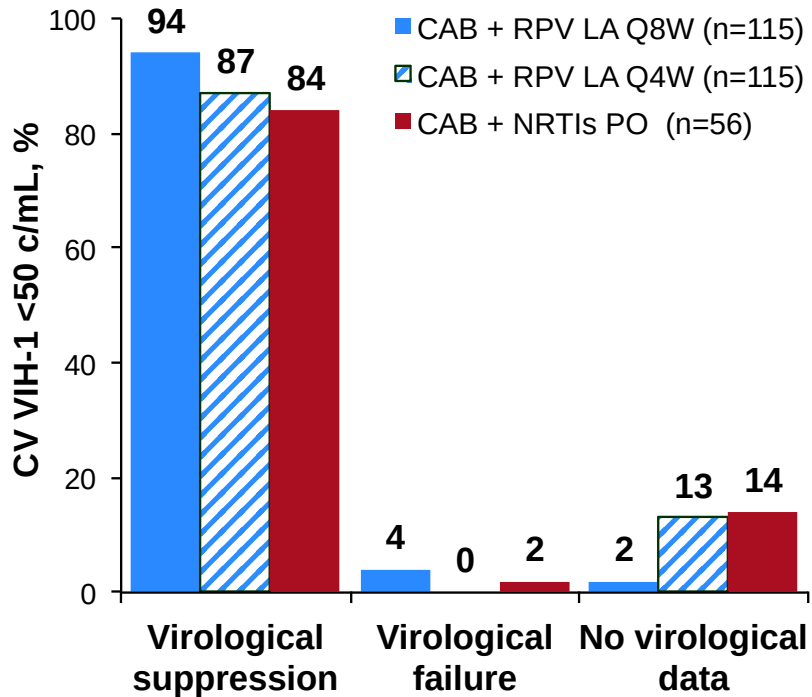


Both Q8W and Q4W comparable to oral CAB at Week 32

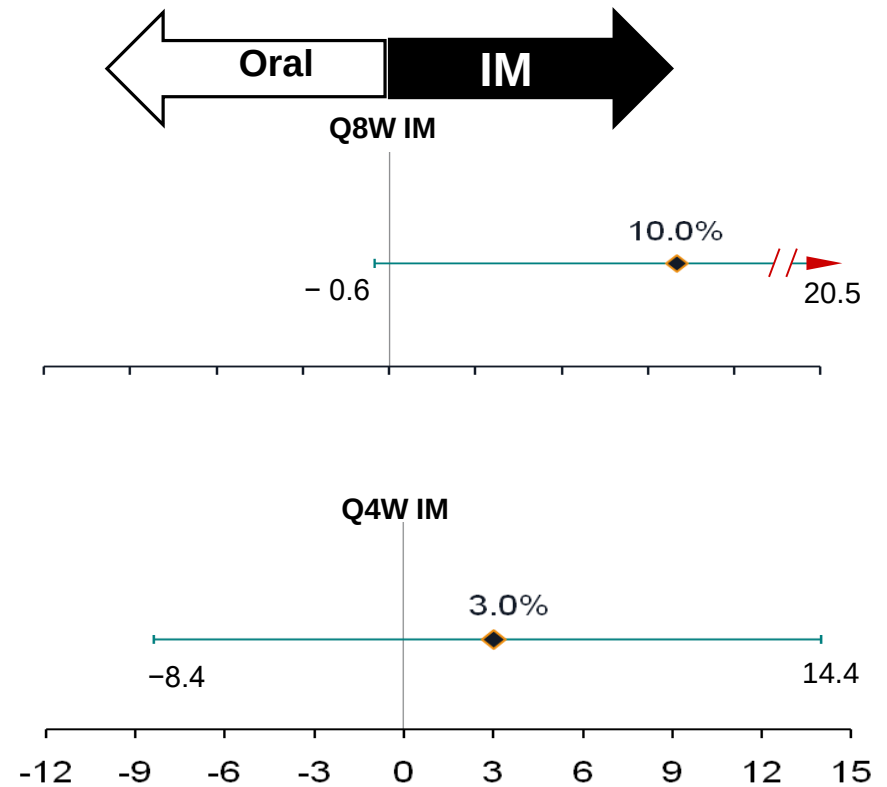
*Met pre-specified threshold for concluding IM regimen is comparable to oral regimen (Bayesian posterior probability >90% that true IM response rate is no worse than -10% compared with the oral regimen).

LATTE-2 : Efficacy at week 96 (ITT-ME Snapshot)

Virological Response



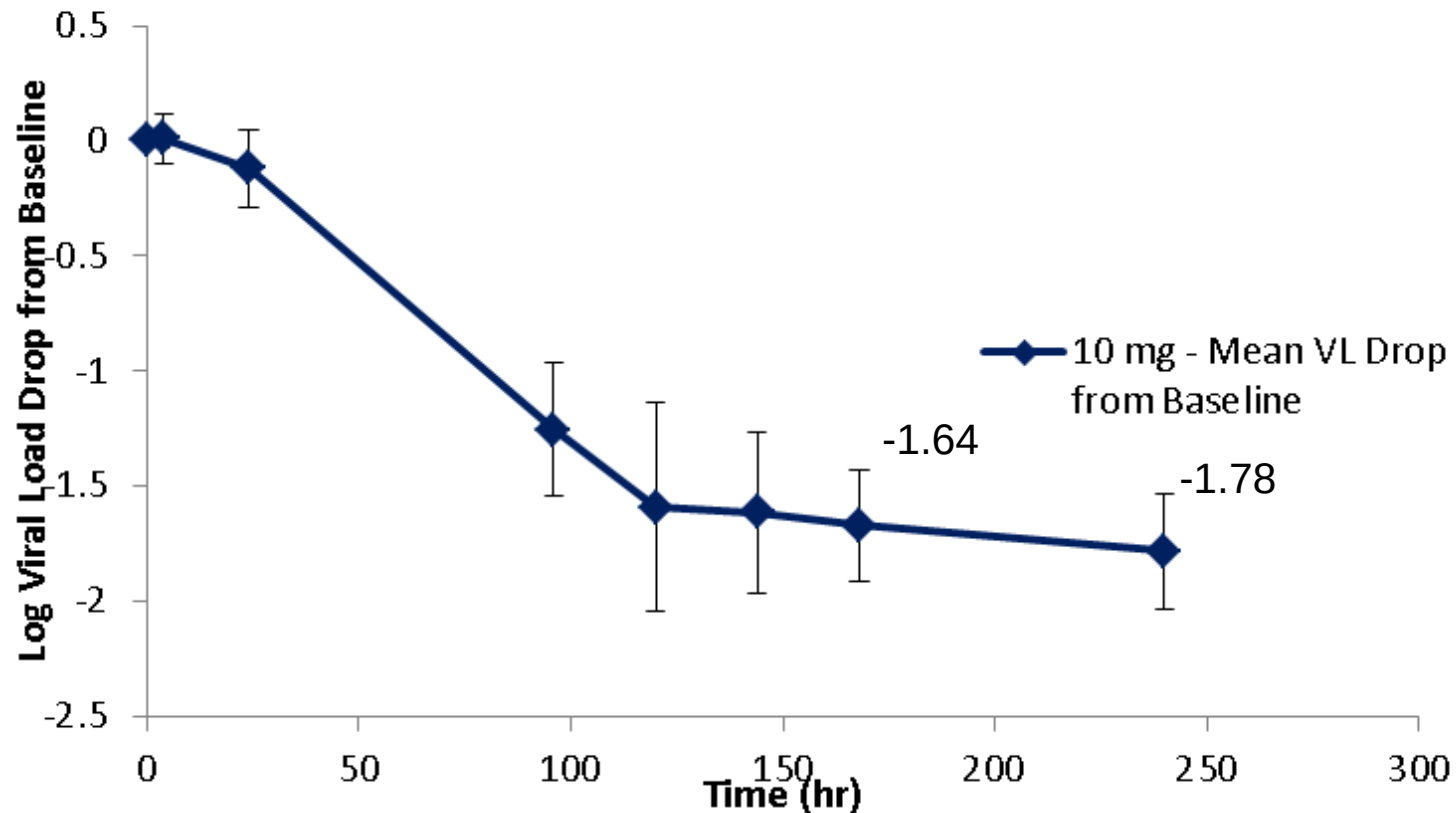
Differences in treatment (IC 95%)



Nuevas Estrategias: Fármacos de Acción Prolongada

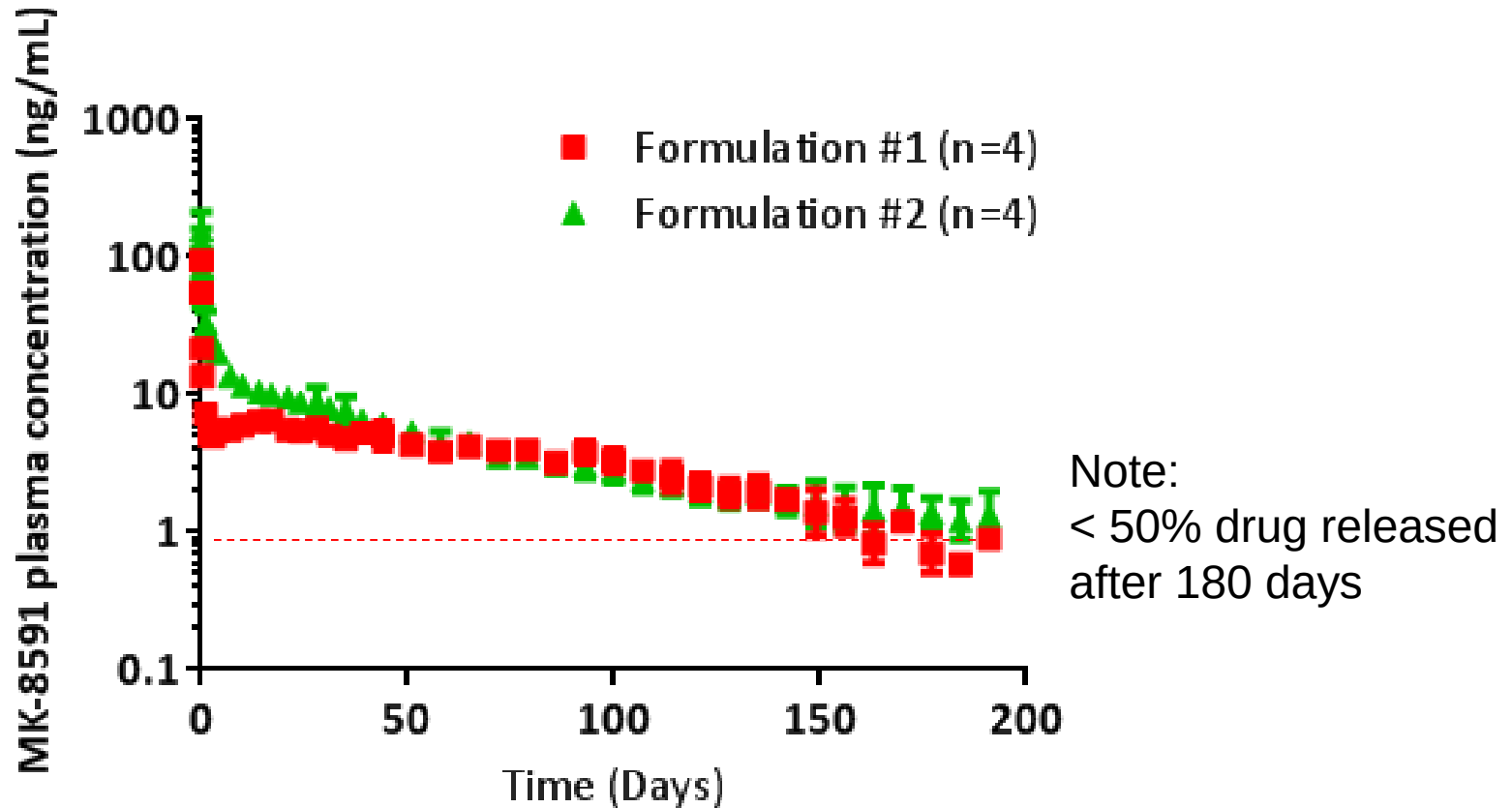
**Long-acting Oral and Parenteral
Dosing of MK-8591 for HIV
Treatment or Prophylaxis**

Reducción de C.V. Tras 10 mg (oral)



- Persistent reduction of VL through 10 days with a single 10 mg dose of MK-8591 p.o.
- Low projected daily dose amenable to extended duration parenteral formulation

MK-8591 parenteral formulations release for >180 days



>180 day extended release after a single injection in rat

Conclusiones

- **Tratamiento Antirretroviral Actual**

- Excelencia en todas las características

- **Futuro**

- Nuevos fármacos de viejas familias y nuevas familias de fármacos para satisfacer las necesidades no cubiertas
- Fármacos de administración parenteral y de acción prolongada (administración cada 2, 3, 6 o 12 meses)
- Reducción del número de fármacos