PASADO, PRESENTE Y FUTURO DEL TRATAMIENTO ANTIRETROVIRAL

María José Rolón

Noviembre , 2022

EPIDEMIOLOGÍA:

Summary of the global HIV epidemic, 2021

	People living with HIV in 2021	People acquiring HIV in 2021	People dying from HIV-related causes in 2021
Total	38.4 million [33.9–43.8 million]	1.5 million [1.1–2.0 million]	650 000 [510 000–860 000]
Adults (15+ years)	36.7 million [32.3–41.9 million]	1.3 million [990 000–1.8 million]	560 000 [430 000–740 000]
Women (15+ years)	19.7 million [17.6–22.4 million]	640 000 [480 000–870 000]	240 000 [180 000–320 000]
Men (15+ years)	16.9 million [14.6–19.7 million]	680 000 [500 000–920 000]	320 000 [250 000–430 000]
Children (<15 years)	1.7 million [1.3–2.1 million]	160 000 [110 000–230 000]	98 000 [67 000–140 000]

Source: UNAIDS/WHO estimates

Updated: July 2022

World Health Organization

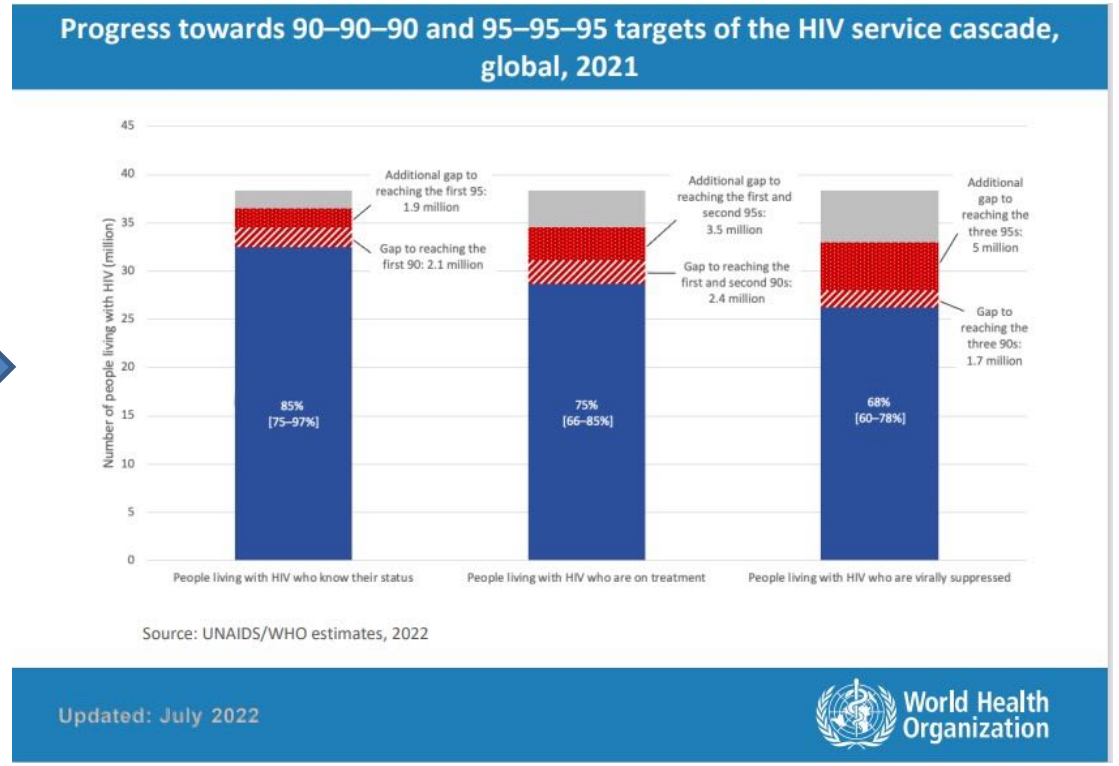
OBJETIVOS 3030

Un objetivo ambicioso para erradicar el VIH
Targets

The treatment target

95%	95%	95%
Diagnosticados	En tratamiento	Suprimidos virológicamente

Michel Sidibé. Executive Director's report – unaids. Disponible en:
http://www.unaids.org/sites/default/files/media_asset/20140701_SP_EXD_PCB34_en.pdf



VIH y sífilis en números

Se estiman 140.000 personas con VIH

Año 2020

65% de las personas con VIH se atiende en el sistema público

65.000 personas en tratamiento en el sistema público

En promedio se notifican

4.500 casos de VIH por año

Mediana de edad de diagnóstico de VIH*

Años 2019-2020

- 35 años mujeres cis
- 32 años varones cis
- 30 años mujeres trans

Prevalencia de VIH

- 34% Mujeres trans
- 12 a 15% Hombres que tienen sexo con hombres
- 2 a 5% Trabajadoras/es sexuales

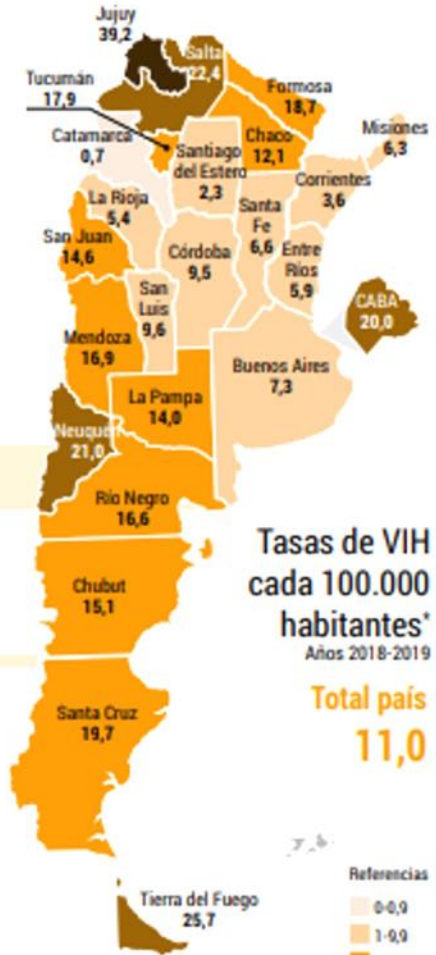
Mortalidad por sida

Tasa por 100 mil habitantes

Año 2019

Fuente: Dirección de Estadísticas e Información de la Salud.

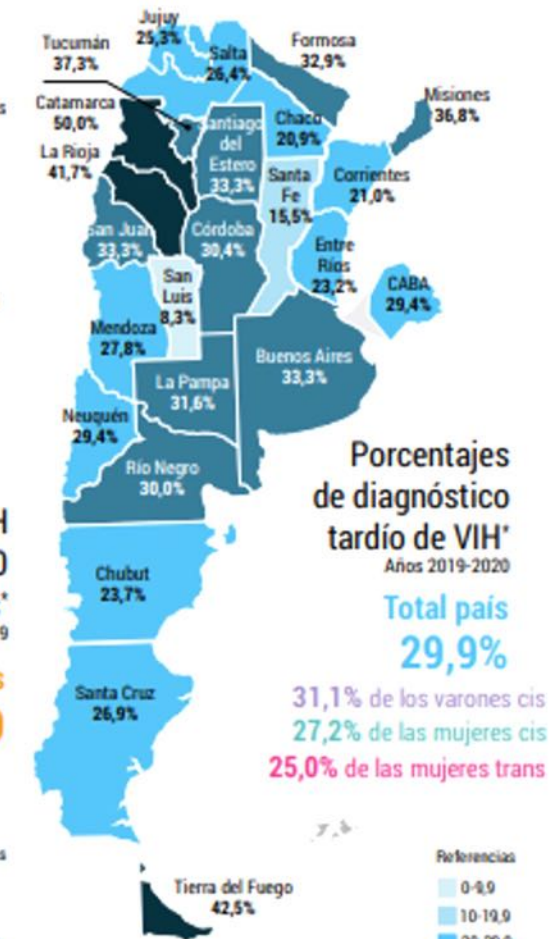
* Fuente: Sistema Nacional de Vigilancia de la Salud (SNVS 2.0) / 2019 y 2020 son años no cerrados, con posibilidad de ajustes en futuros boletines.
Nota: para cada indicador se seleccionaron los años con información más completa y comparable.



Tasas de VIH cada 100.000 habitantes*

Años 2018-2019

Total país **11,0**



Porcentajes de diagnóstico tardío de VIH*

Años 2019-2020

Total país **29,9%**

31,1% de los varones cis
27,2% de las mujeres cis
25,0% de las mujeres trans

Sífilis congénita

Tasa nacional cada 1.000 nacidos vivos

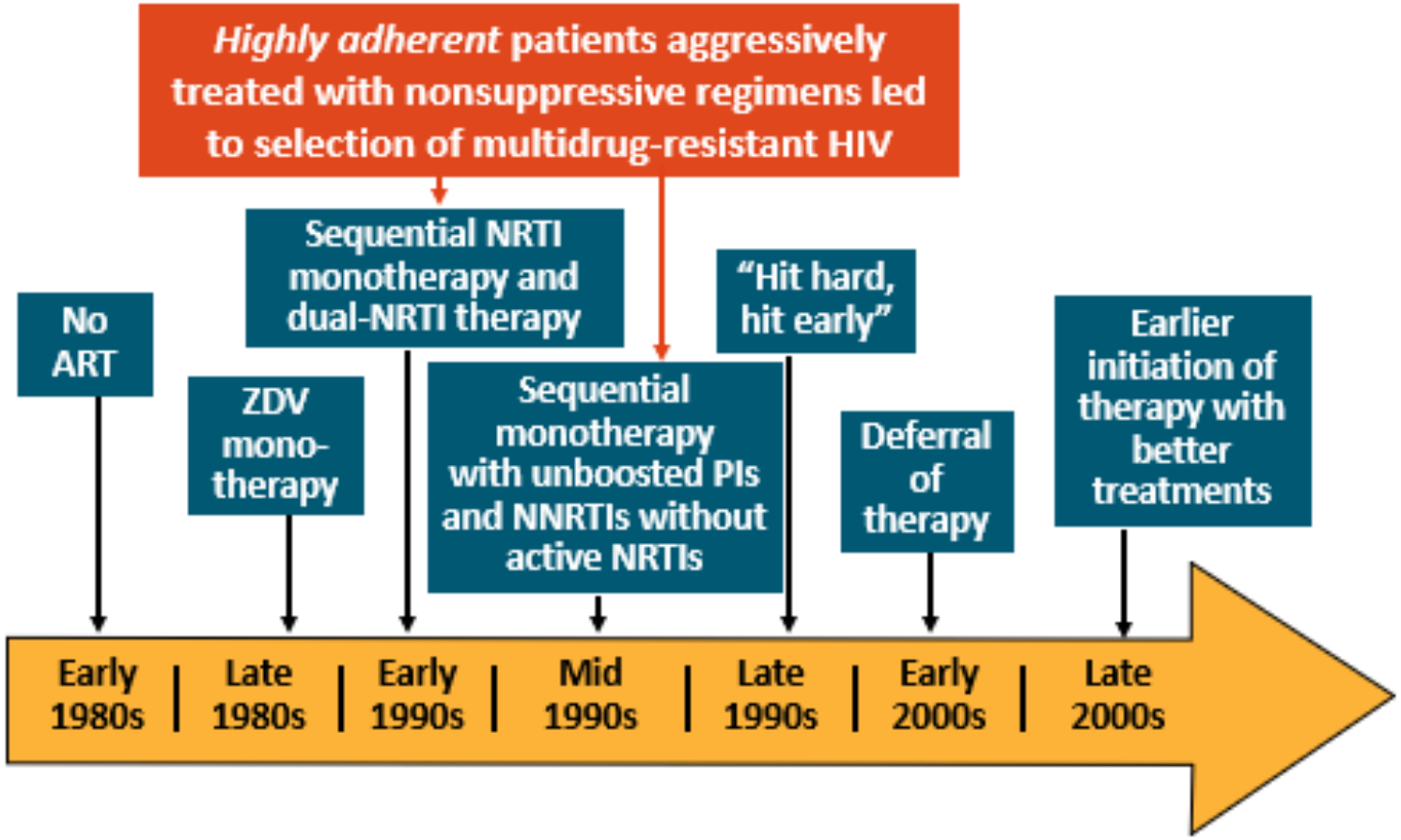
1,14

Fuente: Dirección Nacional de Epidemiología e Información Estratégica. Año 2020

CUÁLES SON LOS OBJETIVOS DEL TARV ?

- Supresion virológica máxima y continua
  - Alta barrera a la resistencia
  - Mejorar / preservar la rta inmune
  - Mínima toxicidad y eventos adversos
  - Mínimas interacciones de drogas
  - Reducción de la actividad inflamatoria
  - Preservar la vida y la salud con la menor alteración en la calidad de vida

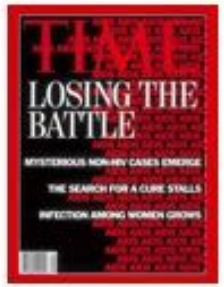
EVOLUCIÓN DEL TARV

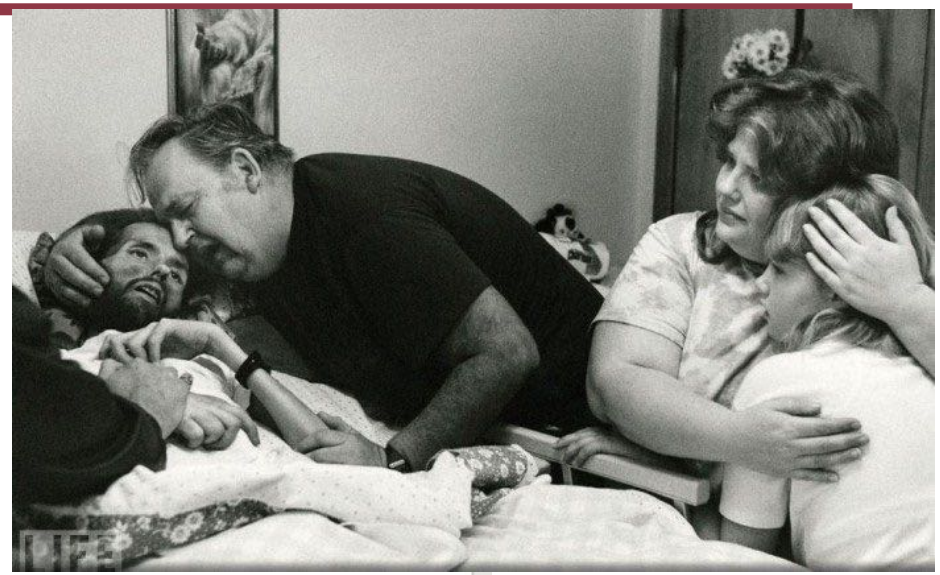


Slide credit: clinicaloptions.com

OPTIMIZACIÓN DEL TARV

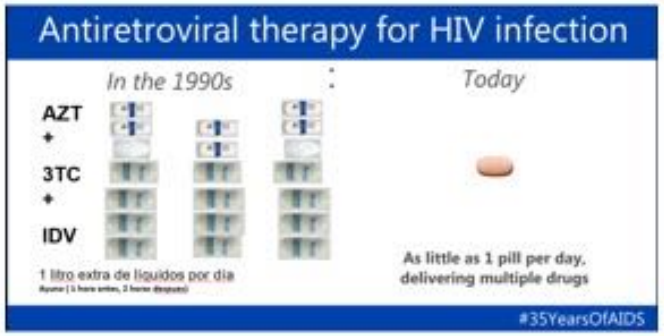
- Ppios de la epidemia :EFECTIVIDAD
  - ↑ **Eficacia**
  - Toxicidad
  - Tolerancia ↓





- REGÍMENES SIMPLIFICADOS
  - ↑ **Eficacia**
  - Toxicidad
  - Tolerancia

  TID → BID → QD

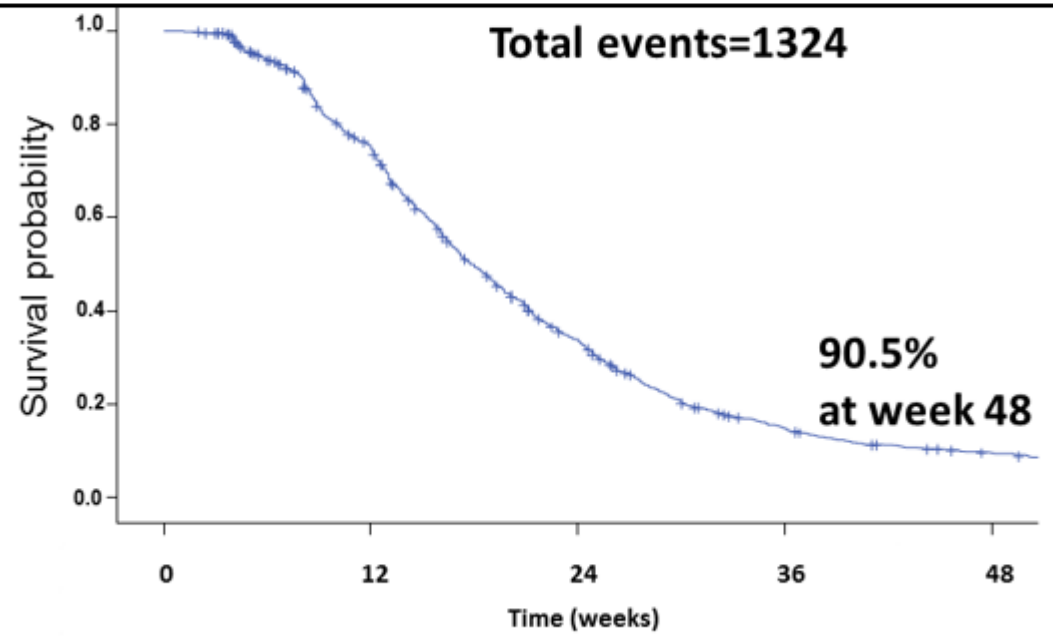


- TRATAMIENTO INDIVIDUALIZADO

SUPRESIÓN VIROLÓGICA

Mas del 90% de los pacientes alcanzan y mantienen supresion virologica a las 48 semanas del inicio del TARV

Full SET analysis: The median time (95% CI) to achieve VL<50 cps/mL in 1430 ART-naive patients starting HAART treatment is 18 (17-19) weeks



Santoro et al. Antivir Ther 2013

30 Years of HIV/AIDS

The Arrival of Treatment as Prevention

PLOS one
Publishing science, accelerating research
June 10, 2010

Decreases in Community Viral Load Are Accompanied by Reductions in New HIV Infections in San Francisco

M Das, GN Colfax et al.

THE LANCET
June 12, 2010

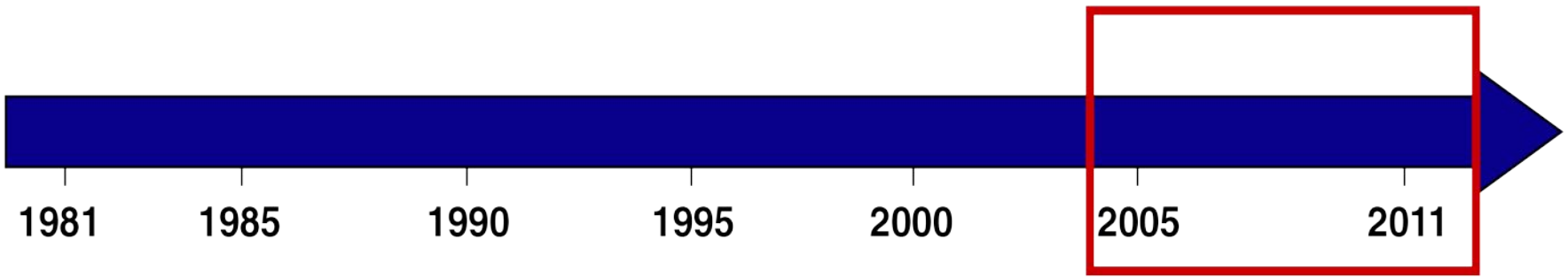
Heterosexual HIV-1 Transmission after Initiation of Antiretroviral Therapy: a Prospective Cohort Analysis

D Donnell et al.

THE LANCET
August 14, 2010

Association of Highly Active Antiretroviral Therapy Coverage, Population Viral Load, and Yearly New HIV Diagnoses in British Columbia, Canada: a Population-Based Study

JS Montaner, P Kendall, et al.



Number at risk

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Active on HAART	837	1960	2597	2994	3079	3120	3211	3356	3585	3913	4255	4654	5123	5413
New HIV diagnoses (all)	702	519	471	416	400	420	418	408	441	400	361	391	346	338
New HIV diagnoses (ever IDU)	NA	NA	NA	159	152	149	168	149	156	137	128	128	65	80
HIV tests done in BC (per 1000)	138	140	137	135	135	135	145	142	154	161	172	176	182	NA

Figure 1: **Number of active HAART participants and number of new HIV diagnoses per year in British Columbia, Canada, 1996–2009**
p values are for trend and were obtained from the generalised additive model. Injecting drug user (IDU) refers to individuals who have ever injected illicit drugs. HAART=highly active antiretroviral therapy. BC=British Columbia. NA=not available.

Undetectable = Untransmittable

- **HPTN 052:** 1763 HIV-serodiscordant couples
  - NO linked infections after 5 yrs of follow-up among HIV-uninfected partners of HIV-positive persons with stably suppressed HIV-1 RNA on ART[1]
- **PARTNER and Opposites Attract Studies:** 35,000 acts of condomless anal sex in serodiscordant couple
  - NO linked infections among HIV-uninfected partners of HIV-positive persons with stably suppressed HIV viral load on ART[2]
- **Partner 2 Study:** 76,088 acts of condomless sex among 782 HIV-serodiscordant MSM couples
  - NO linked infections after 1593 couple-yrs of follow-up among HIV-uninfected partners of HIV-positive persons with undetectable HIV viral load on ART[3]

1. Cohen. N Engl J Med 2016;375:830. 2. Bavinton. Lancet HIV. 2018;5:PE438. 3. Rodger. Lancet. 2019 [Epub]

Slide credit: clinicaloptions.com

Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study

Alison J Rodger, Valentina Cambiano, Tina Bruun, Pietro Vernazza, Simon Collins, Olaf Degen, Giulio Maria Corbelli, Vicente Estrada, Anna Maria Geretti, Apostolos Beloukas, Dorthe Raben, Pep Coll, Andrea Antinori, Nneka Nwokolo, Armin Rieger, Jan M Prins, Anders Blaxhult, Rainer Weber, Ame Van Eeden, Norbert H Brockmeyer, Amanda Clarke, Jorge del Romero Guerrero, Francois Raffi, Johannes R Bogner, Gilles Wandeler, Jan Gerstoft, Felix Gutiérrez, Kees Brinkman, Maria Kitchen, Lars Ostergaard, Agathe Leon, Matti Ristola, Heiko Jessen, Hans-Jürgen Stellbrink, Andrew N Phillips, Jens Lundgren, for the PARTNER Study Group*

Summary

Background The level of evidence for HIV transmission risk through condomless sex in serodifferent gay couples with the HIV-positive partner taking virally suppressive antiretroviral therapy (ART) is limited compared with the evidence available for transmission risk in heterosexual couples. The aim of the second phase of the PARTNER study (PARTNER2) was to provide precise estimates of transmission risk in gay serodifferent partnerships.

Methods The PARTNER study was a prospective observational study done at 75 sites in 14 European countries. The first phase of the study (PARTNER1; Sept 15, 2010, to May 31, 2014) recruited and followed up both heterosexual and gay serodifferent couples (HIV-positive partner taking suppressive ART) who reported condomless sex, whereas the PARTNER2 extension (to April 30, 2018) recruited and followed up gay couples only. At study visits, data collection included sexual behaviour questionnaires, HIV testing (HIV-negative partner), and HIV-1 viral load testing (HIV-positive partner). If a seroconversion occurred in the HIV-negative partner, anonymised phylogenetic analysis was done to compare HIV-1 *pol* and *env* sequences in both partners to identify linked transmissions. Couple-years of follow-up were eligible for inclusion if condomless sex was reported, use of pre-exposure prophylaxis or post-exposure prophylaxis was not reported by the HIV-negative partner, and the HIV-positive partner was virally suppressed (plasma HIV-1 RNA <200 copies per mL) at the most recent visit (within the past year). Incidence rate of HIV transmission was calculated as the number of phylogenetically linked HIV infections that occurred during eligible couple-years of follow-up divided by eligible couple-years of follow-up. Two-sided 95% CIs for the incidence rate of transmission were calculated using exact Poisson methods.

Findings Between Sept 15, 2010, and July 31, 2017, 972 gay couples were enrolled, of which 782 provided 1593 eligible couple-years of follow-up with a median follow-up of 2·0 years (IQR 1·1–3·5). At baseline, median age for HIV-positive partners was 40 years (IQR 33–46) and couples reported condomless sex for a median of 1·0 years (IQR 0·4–2·9). During eligible couple-years of follow-up, couples reported condomless anal sex a total of 76 088 times. 288 (37%) of 777 HIV-negative men reported condomless sex with other partners. 15 new HIV infections occurred during eligible couple-years of follow-up, but none were phylogenetically linked within-couple transmissions, resulting in an HIV transmission rate of zero (upper 95% CI 0·23 per 100 couple-years of follow-up).

Interpretation Our results provide a similar level of evidence on viral suppression and HIV transmission risk for gay men to that previously generated for heterosexual couples and suggest that the risk of HIV transmission in gay couples through condomless sex when HIV viral load is suppressed is effectively zero. Our findings support the message of the U=U (undetectable equals untransmittable) campaign, and the benefits of early testing and treatment for HIV.

Funding National Institute for Health Research.

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See Online/Comment http://dx.doi.org/10.1016/S0140-6736(19)30701-9

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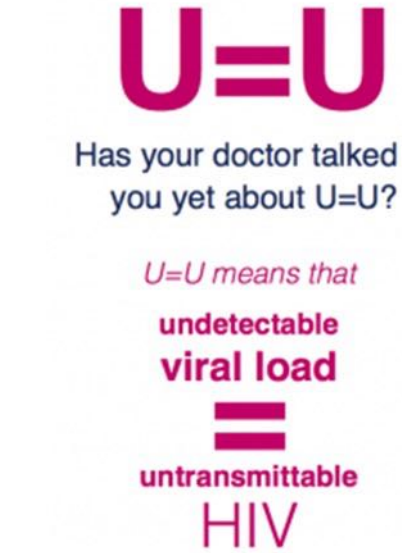


	Number of linked transmissions	Upper 95% CI limit*	Couple-years of follow-up	Number of condomless sex acts	HIV-negative men reporting sex act, n/N (%)†
Condomless anal sex	0	0·23	1593	76088	778/779 (99·9%)
Insertive condomless anal sex	0	0·27	1343	52087	709/777 (91·2%)
Receptive condomless anal sex with ejaculation	0	0·57	650	20487	436/776 (56·2%)
Receptive condomless anal sex without ejaculation	0	0·43	865	22995	577/773 (74·6%)
Any condomless sex with an STI‡	0	3·17	116	6090	NA

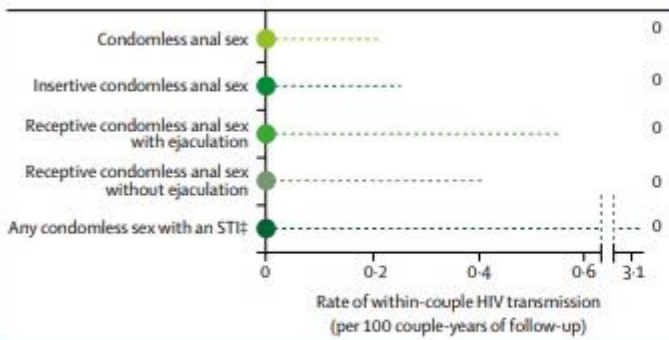
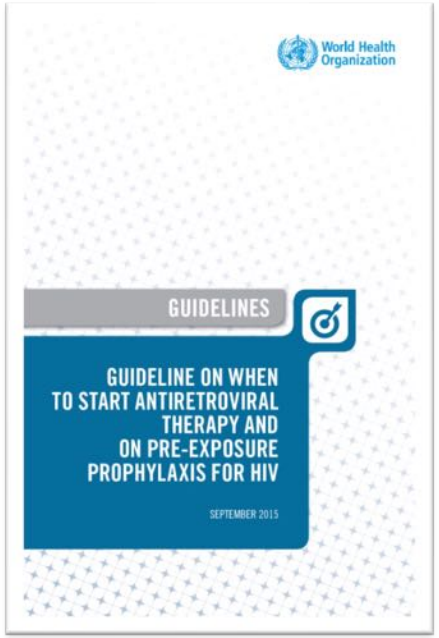


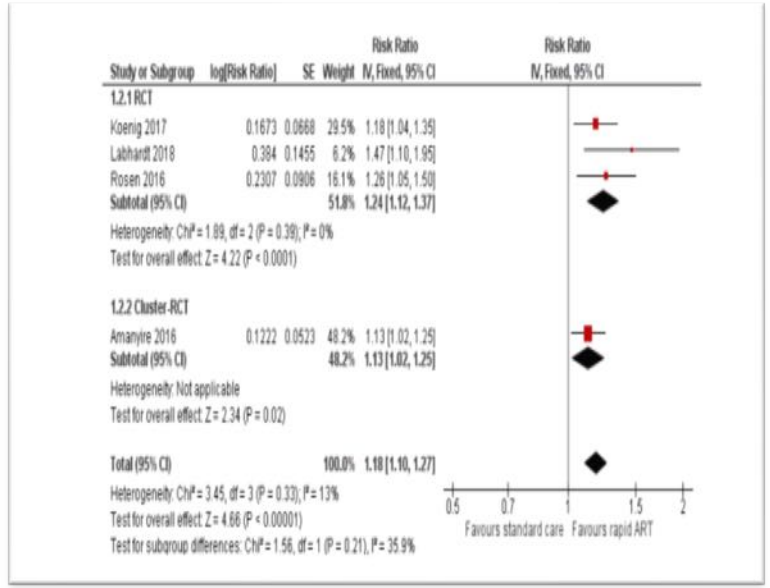
Figure 1: **Rate of within-couple HIV transmission through condomless sex according to sexual behaviour reported by the HIV-negative partner**
STI=sexually transmitted infection. NA=not applicable. *Estimated using the exact Poisson method. †Numerator is the number of HIV-negative men within the eligible couples ever reporting that specific sexual act and denominator is the group-specific number of HIV-negative participants who contributed eligible couple-years of follow-up. ‡Refers to STIs (excluding HIV) self-reported by the HIV-negative partner.

CUÁNDO EMPEZAR ?ESTRATEGIAS DE INICIO

- ✓TESTEAR y TRATAR
- ✓INICIO TEMPRANO
- ✓COMBINACIONES FIJAS



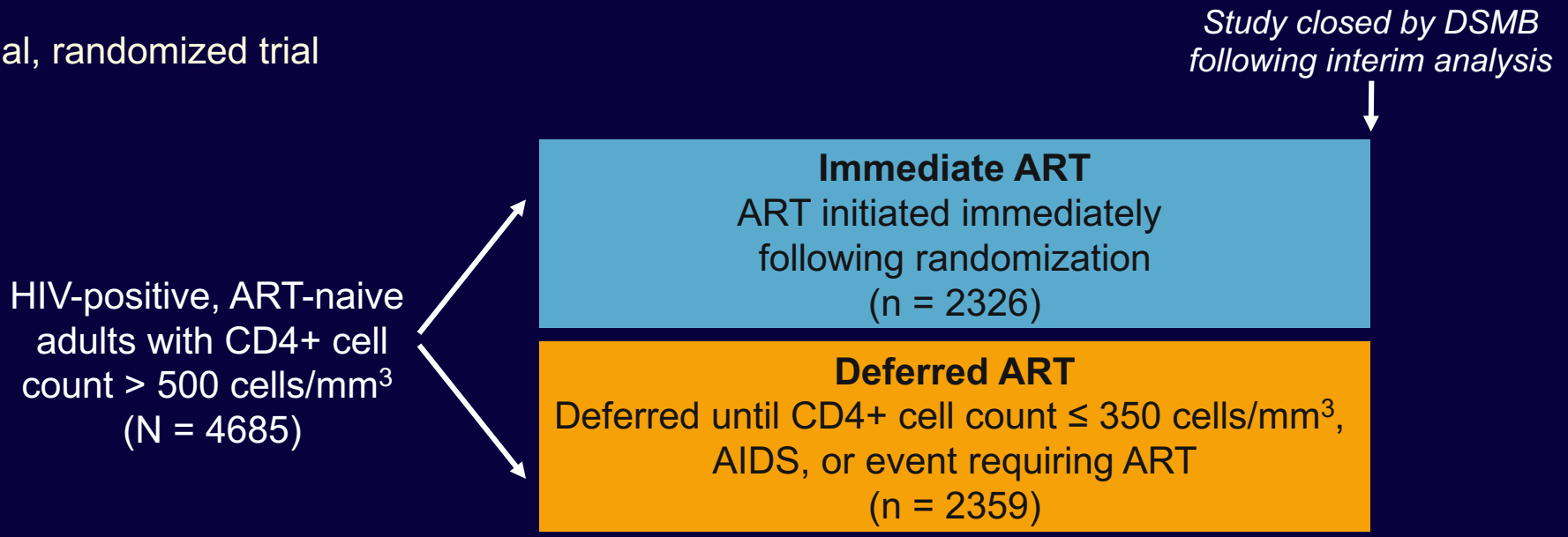
Same day initiation improves range of ART outcomes



WHO, 2015; Mateo-Urdiales , 2019

START: Immediate vs Deferred Therapy for Asymptomatic, ART-Naive Pts

- International, randomized trial

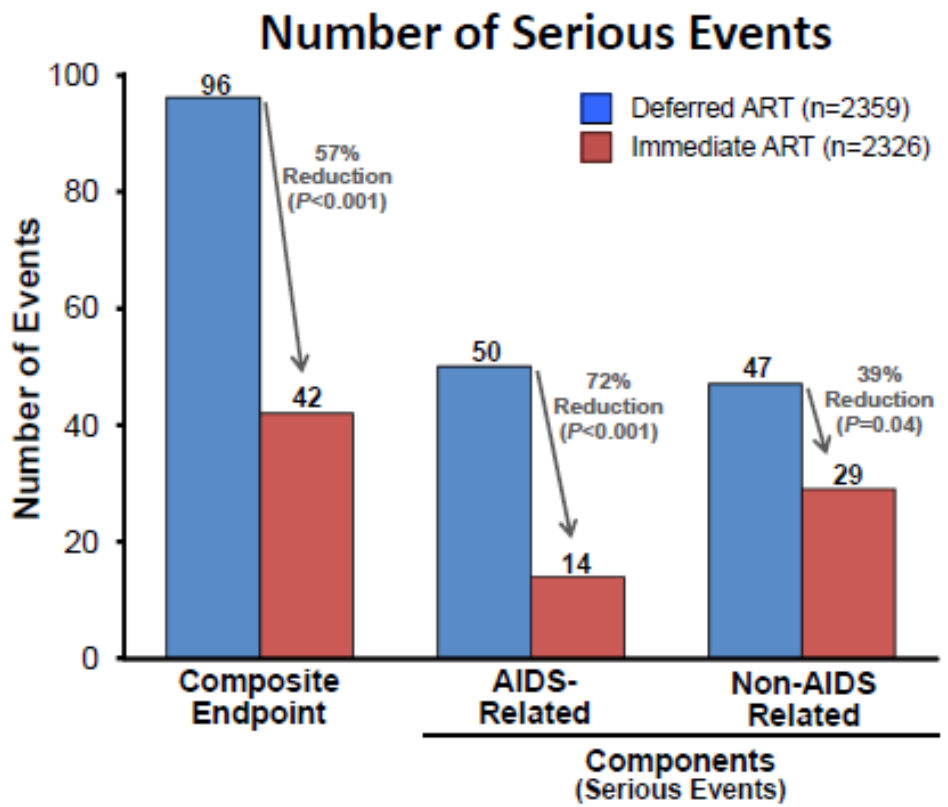


- Composite primary endpoint: any serious AIDS-related (AIDS-related death or AIDS-defining event) or non-AIDS–related event (non-AIDS–related death, CVD, end-stage renal disease, decompensated liver disease, non-AIDS–defining cancer)
- Mean follow-up: 3 yrs; median baseline CD4+ cell count: 651 cells/mm^3; median baseline HIV-1 RNA: 12,759 copies/mL
- Median CD4+ cell count at initiation of ART for deferred group: 408 cells/mm^3

INSIGHT START Study Group. N Engl J Med. 2015;373:795-807. Lundgren J, et al. IAS 2015. Abstract MOSY0302.

HIV Therapy Recommended Regardless of CD4: START

- HIV-infected adults with CD4 >500
- Randomized to immediate or deferred ART
- TB, KS, lymphoma — most common AIDS-related events — all less frequent in immediate-ART group
- Cancer rates (combining AIDS/non-AIDS) lower in immediate-ART group



Lundgren J, et al. 8th IAS Conference. Vancouver, 2015. Abstract MOSY0301.
The INSIGHT START Study Group. *N Engl J Med*. 2015;July 20. Lifson A et al, CROI 2016, #475; Borges et al, CROI 2016, #160

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

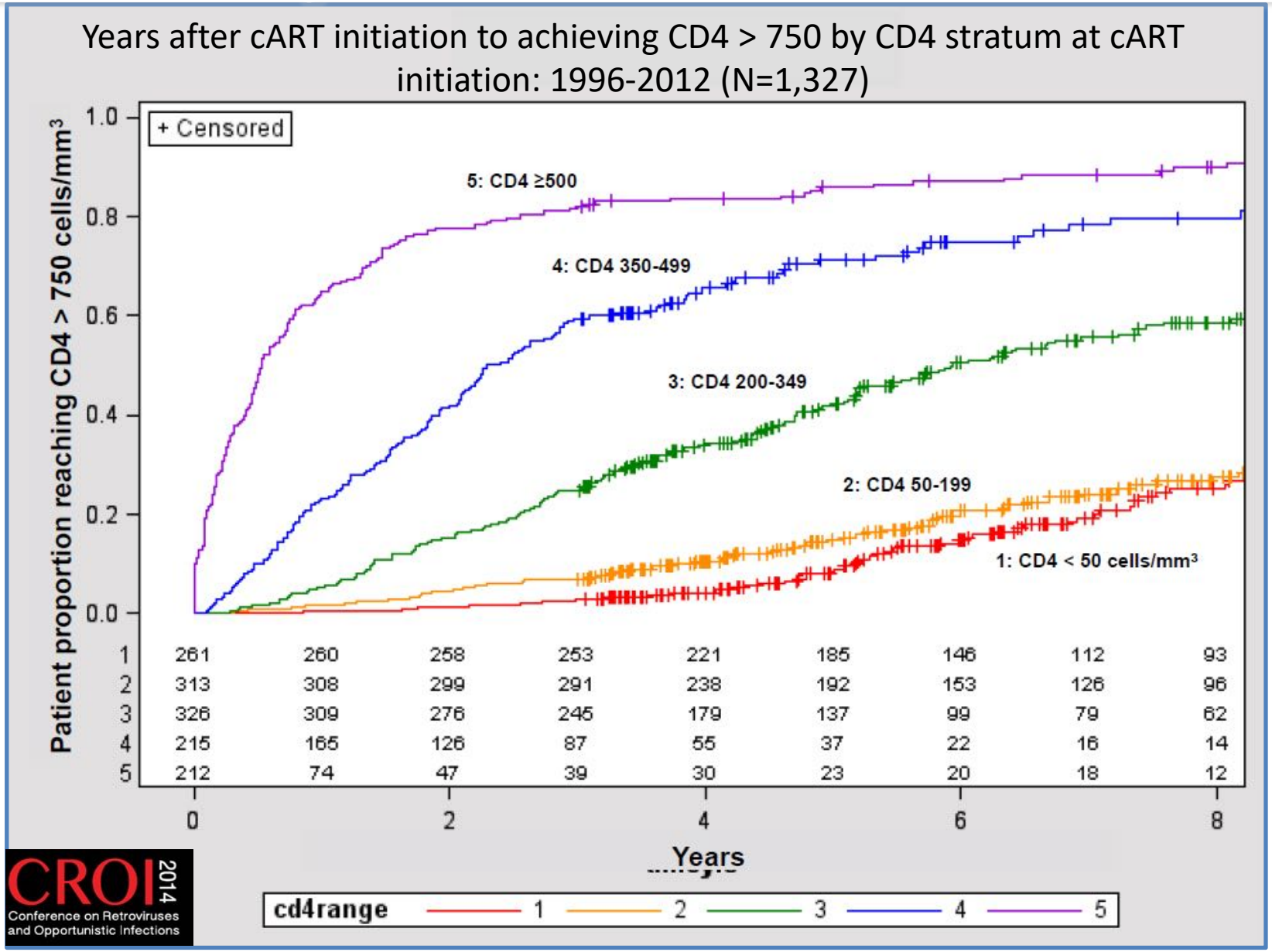
53% Reduction in Risk of AIDS, Serious Non-AIDS Event or Death with Early ART

	Early	Deferred	HR	P value
PRIMARY composite: AIDS, serious non-AIDS, or death	41	86	0.47	<0.001

- Reduced AIDS-related events - Most common events:
  - Pulmonary TB
  - Kaposi's sarcoma
  - Non-Hodgkins lymphoma
- Reduced serious non-AIDS events - Most common events:
  - Cancer
  - Heart attack
  - Deaths other than AIDS or non-serious AIDS
- No difference AE between arms

NEJM 2015; epub July 20, 2015

Higher CD4 at ART Initiation Predicts Greater Long Term Likelihood of CD4 Normalization



F. Palella et al., CROI 2014, Abstract 560

EACS, IAS-USA Recommendations on Timing of ART Initiation

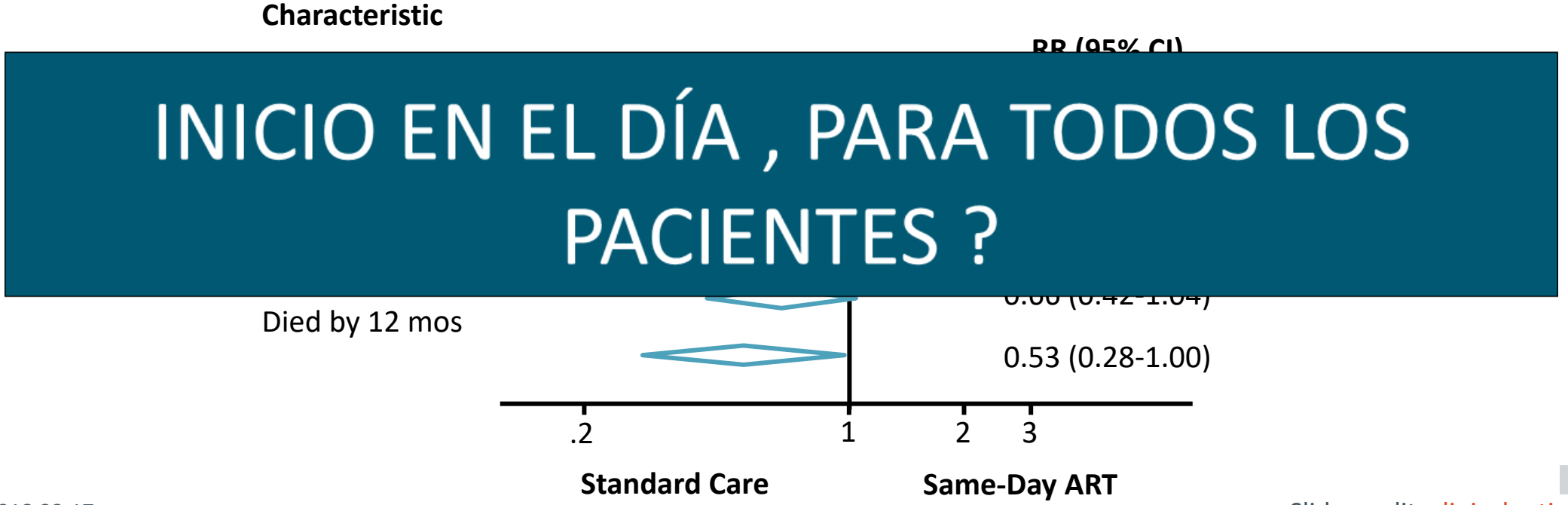
- **IAS-USA guidelines[1]**
  - *"ART should be initiated **as soon as possible after diagnosis, including immediately after diagnosis**, unless patient is not ready to commit to starting therapy (evidence rating AIa)"*
- **EACS guidelines[2]**
  - Evidence accumulating for same-day ART initiation
  - Requires identification of person's readiness to start and adhere to regimen
  - **Consider same-day ART:**
    - In primary HIV infection, especially with meningoencephalitis
    - In persons wishing to start immediately
    - To prevent loss to follow-up
- **WHO[3]**
  - *"ART initiation should be offered **on the same day** to people who are ready to start (Strong recommendation)"*

Take-home Message: Do not delay treatment!

Slide credit: clinicaloptions.com

Improved Clinical Outcomes With Rapid ART Initiation

- Systematic review of rapid ART initiation (including 4 RCTs)
  - In the 4 RCTs, compared with standard care, **same-day ART increased** likelihood of ART initiation in first 90 days, patient retention, and viral suppression at 12 mos



Ford. AIDS. 2018;32:17.

Slide credit: clinicaloptions.com

Inicio del Tratamiento Antiretroviral

SE RECOMIENDA OFRECER TARV SIN DEMORA A TODAS LAS PERSONAS CON VIH INDEPENDIENTEMENTE DE SU RECUENTO DE LINFOCITOS CD4+ (AI).

Situaciones especiales :

- ✓Tuberculosis
- ✓Criptococosis

Sociedad Argentina de Infectología - VII Consenso Argentino de Terapia Antirretroviral Act 2021

Situaciones en la que se debe posponer el inicio del TARV : TB

- Los pacientes con TB sin compromiso del SNC y con CD4 <50 cél/mm^3 deben iniciar TARV dentro de las 2 primeras semanas de iniciado el tratamiento anti TBC
- Los pacientes con TB y CD4 >50 cél/mm^3 o TB meníngea deberían iniciar el TARV dentro de las 8 a 12 semanas de iniciado el tratamiento anti TB.

EVALUACION INICIAL Y SEGUIMIENTO DE PACIENTES CON INFECCIÓN POR VIH, SADI 2019
Banc F, Sok T, Rekacewicz C, et al. Earlier versus Later Start of Antiretroviral Therapy in HIV-Infected Adults with Tuberculosis. *N Engl J Med*. 2011;365(16):1471-1481.
Havlir D, Kendall M, Ive P, et al. Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis. *N Engl J Med*. 2011;365(16):1482-1491.
Abdool S, Grobler A, Sc M, et al. Integration of Antiretroviral Therapy with Tuberculosis Treatment. *N Engl J Med*. 2011;365(16):1492-1501.

Situaciones en la que se debe posponer el inicio del TARV : Criptococosis

- No se recomienda el inicio del TARV durante las primeras 2 semanas del tratamiento antifúngico (fase de inducción) **(BII).**
- Si el paciente presenta en la evaluación inicial deterioro neurológico, antigenorraquia elevada, hipertensión endocraneana o baja respuesta inflamatoria en el LCR (<5 cél./$mm^{3)}$ se recomienda diferir el inicio del TARV entre 4-6 semanas **(AI).**
- El inicio más temprano (dentro de las 2-4 semanas) puede considerarse si hay acceso a terapia combinada con anfotericina B más flucitosina o fluconazol y si se logra la negativización del cultivo de LCR luego de la inducción **(BII).**
- Si la infección oportunista se presenta durante el transcurso de un TARV iniciado con anterioridad, este evento no debe ser motivo de suspensión del mismo **(AI).**

EVALUACION INICIAL Y SEGUIMIENTO DE PACIENTES CON INFECCIÓN POR VIH, SADI 2019

Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(3):291-322.
Bisson GP, Molefi M, Bellamy S, et al. Early Versus Delayed Antiretroviral Therapy and Cerebrospinal Fluid Fungal Clearance in Adults With HIV and Cryptococcal Meningitis. Clin Infect Dis. 2013;56(8):1165-73.
Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. N Engl J Med. 2014;370(26):2487-98.
Jarvis JN, Bicanic T, Loyse A, et al. Determinants of Mortality in a Combined Cohort of 501 Patients With HIV-Associated Cryptococcal Meningitis: Implications for Improving Outcomes. Clin Infect Dis; 2014;58(5):73645.

Terapia Antirretroviral

Tratamiento precoz a TODOS los pacientes es una estrategia clave para reducir la morbimortalidad en personas HIV positivas y eliminar la transmisión.

Considerar inicio de TARV el día del diagnóstico.

Tratamiento antirretroviral

CUÁNDO INICIAR EL TARV

Se recomienda iniciar lo antes posible el TARV en todas las PcVIH independientemente de su estadio clínico y su recuento de CD4[1].

Si la persona está preparada y no existen condiciones clínicas que lo impidan, se recomienda fuertemente el inicio de TARV el mismo día de la visita inicial[7]

Organización Panamericana de la Salud

Organización Mundial de la Salud
OFICINA REGIONAL PARA LAS Américas

Dirección de Sida, ETS, Hepatitis y TBC

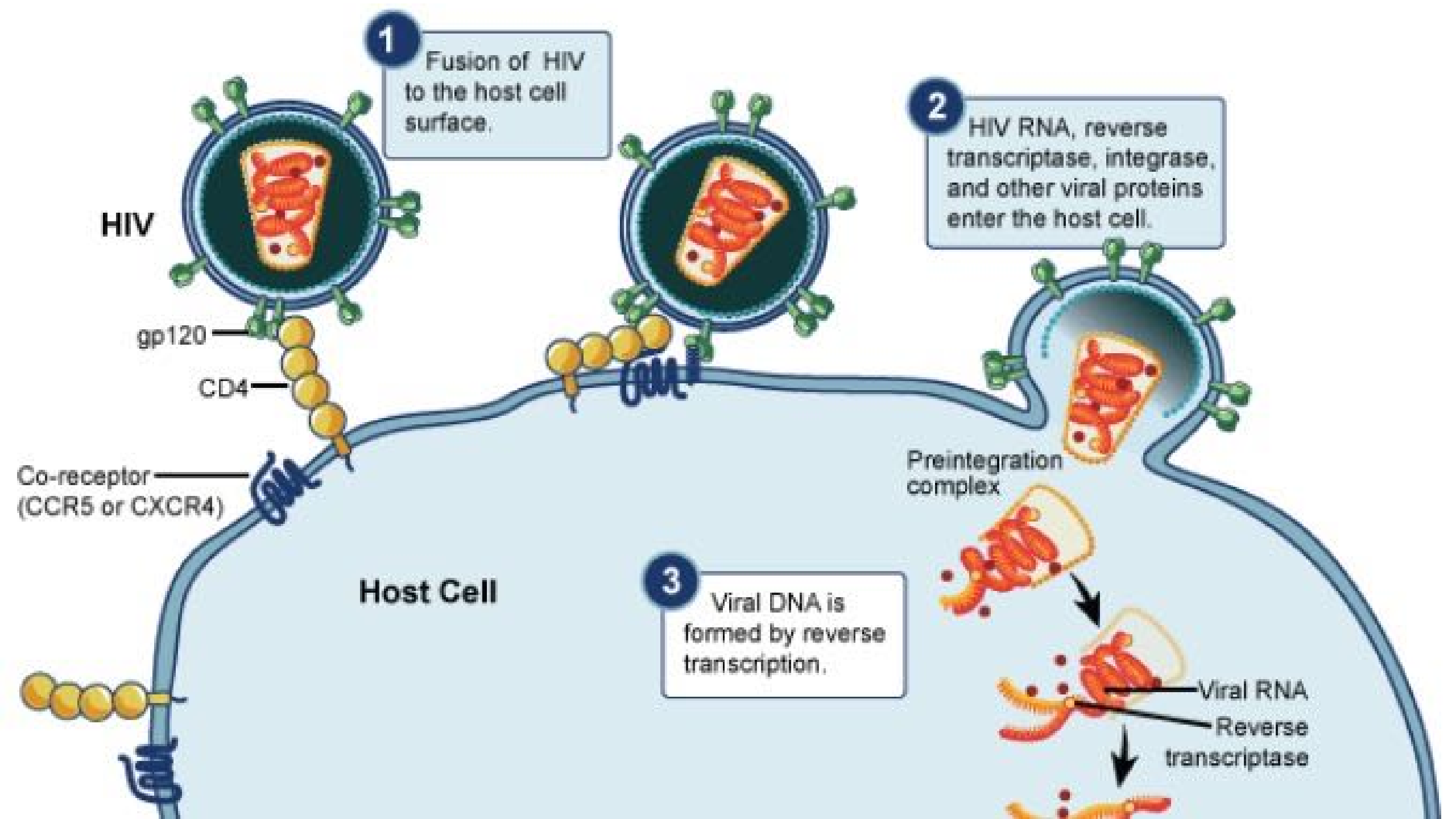
Secretaría de Gobierno de Salud

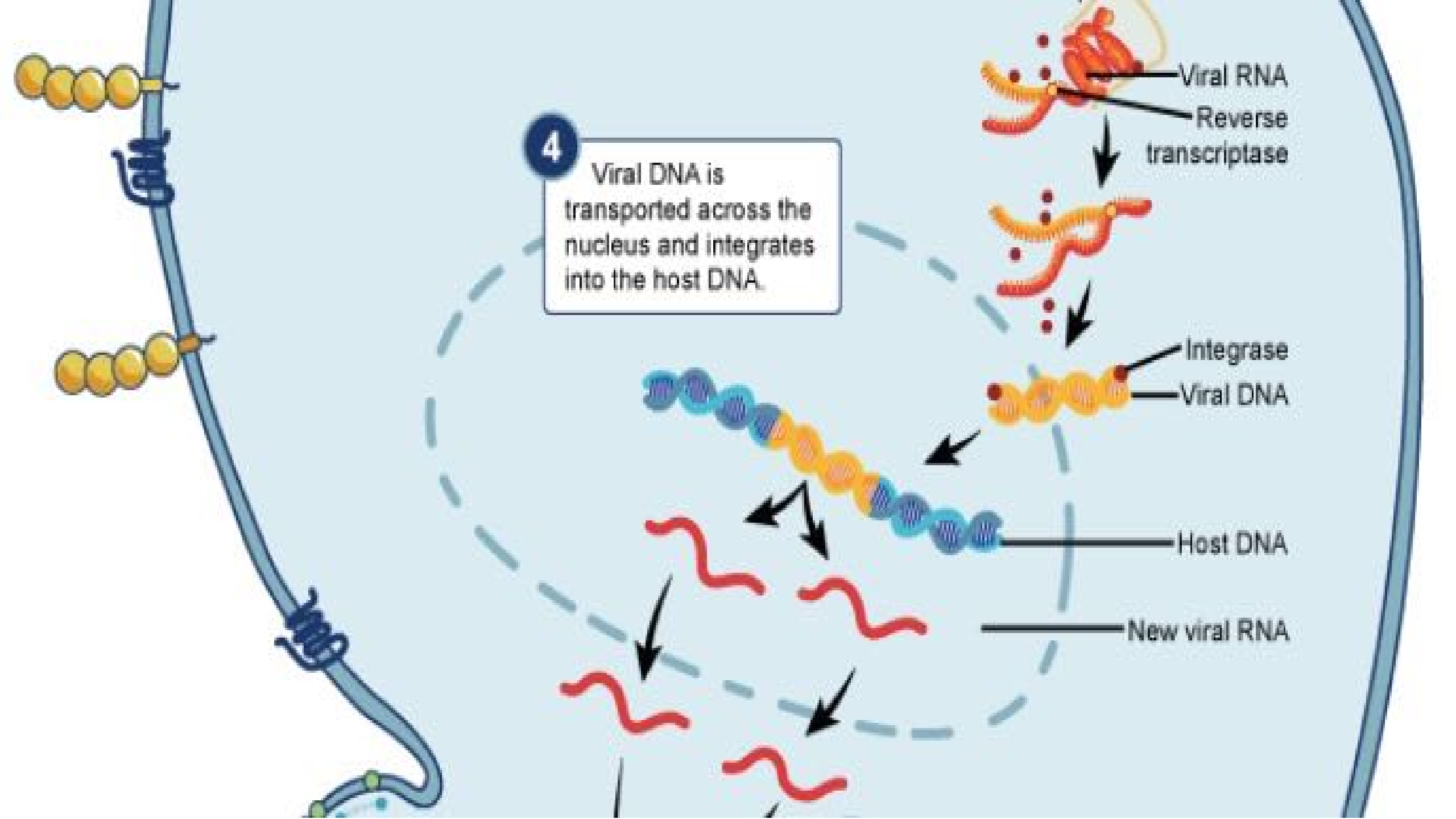
Ministerio de Salud y Desarrollo Social
Presidencia de la Nación

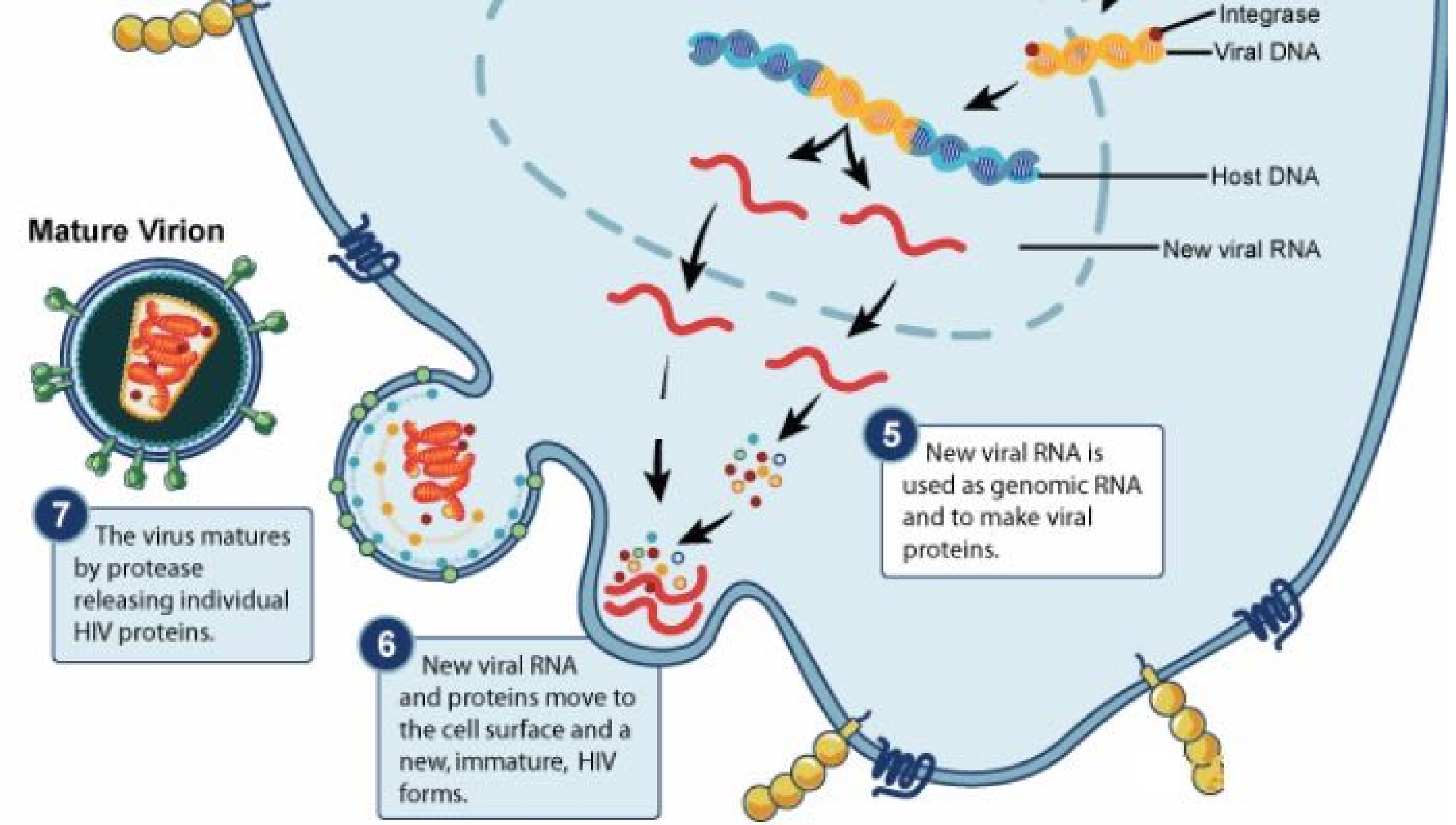
Tratamiento antirretroviral

Debe seleccionarse el esquema de mejor posología (menor número de comprimidos y tomas diarias), menor toxicidad y mayor barrera genética

DSyETS, 2019

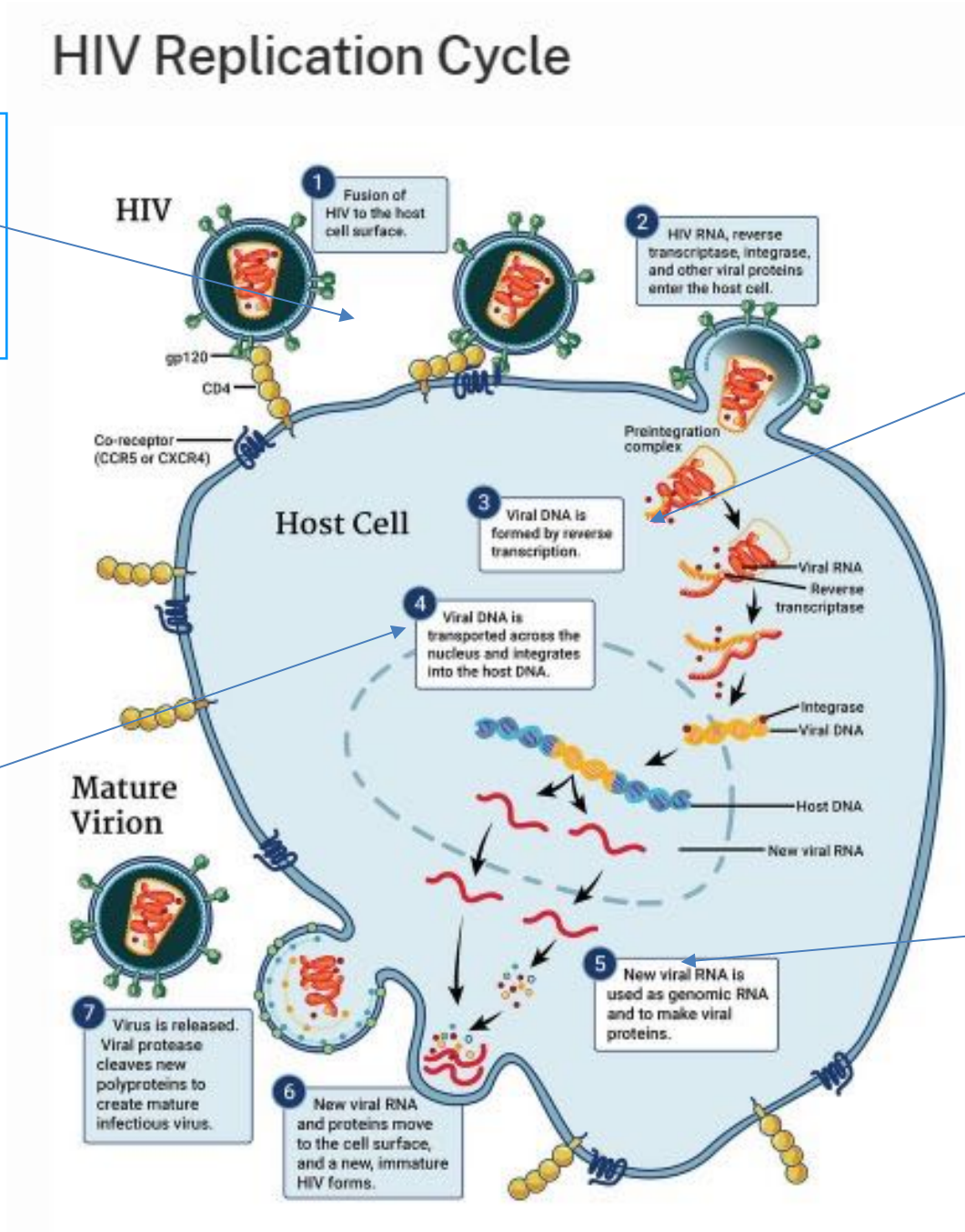

1
Fusion of HIV to the host cell surface.
HIV
gp120
CD4
Co-receptor (CCR5 or CXCR4)
2
HIV RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell.
Preintegration complex
Host Cell
3
Viral DNA is formed by reverse transcription.
Viral RNA
Reverse transcriptase


4
Viral DNA is transported across the nucleus and integrates into the host DNA.
Viral RNA
Reverse transcriptase
Integrase
Viral DNA
Host DNA
New viral RNA


Integrase
Viral DNA
Host DNA
New viral RNA
Mature Virion
5
New viral RNA is used as genomic RNA and to make viral proteins.
6
New viral RNA and proteins move to the cell surface and a new, immature, HIV forms.
7
The virus matures by protease releasing individual HIV proteins.

INHIBIDORES DE LA ENTRADA
Antag CCR5 : MARAVIROC
Inhib de fusion : ENFUVIRTIDE Inhib post fusion :IBALIZUMAB
Inhib de la fijación :FOSTEMSAVIR

INHIBIDORES DE LA INTEGRASA
Raltegravir
Elvitegravir
Dolutegravir
Bictegravir
Cabotegravir



INHIBIDORES DE LA TRANSCRIPTASA REVERSA
ZDV
3TC
FTC
ABC
TDF
Nevirapina
Efavirenz
Etravirina
Rilpivirina
Doravirina

INHIBIDORES DE LA PROTEASA
RTV
FPV LPV
ATV
DRV

Factores para Seleccionar el Regimen ARV

- **Carga viral basal**
- **Comorbidilidades** (ECV , drogas, alcohol, hepatopatías, status psiquiátrico, nefropatías, TB)
- **Coinfección HBV**
- **Genero, embarazo**
- **Genotipo basal**
- **Nivel de CD4+**
- **HLA-B*5701 (abacavir): Solo con test (-)**
- **Emergencia** (embarazo de término, PEP)

Regímenes preferidos: recomendados como regímenes iniciales para la mayoría de las personas con VIH, en base a eficacia virológica demostrada, perfil de toxicidad-tolerancia y posología favorables [67-75].

DTG/TDF/3TC *		**A1**	**Alta barrera genética.** **DISPONIBLES COFORMULADOS en 1 comprimido para administrar CADA 24 HS.**
BIC/TAF/FTC #		**A1**	
DTG/ABC/3TC °		**A1**	
DTG	TDF/FTC o TDF/3TC o TAF/FTC#	A1	○ Alta barrera genética ○ 2 comprimidos cada 24 hs. ○ TDF no iniciar con clearance de creatinina < de 50
DTG	ABC/3TC	A1	Uso de ABC: ○ Con HLA-B*5701 negativo. ○ Valorar riesgo cardiovascular. ○ HBs Ag negativo.
DTG/3TC		A1	○ Con CV < 500000 copias y ○ CD4 >200 ○ Prueba de resistencia basal que asegure sensibilidad a 3TC ○ HBsAg no reactivo
DTG	3TC	A1	

Terapia Antirretroviral

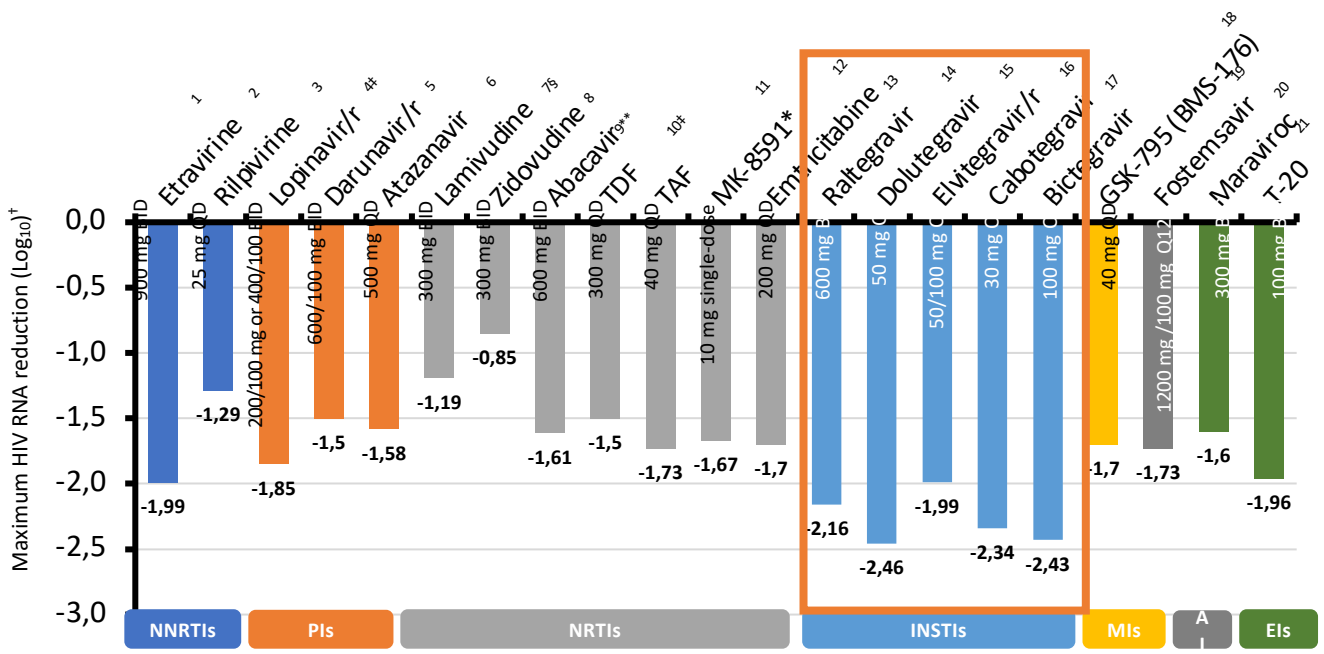
Esquema general de inicio: 3 drogas

2 INTI +

- 1 INNTI
- 1 IP
- 1 IIn

INSTIs Exhibit Higher Antiviral Activity vs Other Drug Classes

PoC ART monotherapy: maximum change in HIV RNA (log_{10}) over 7–14 days

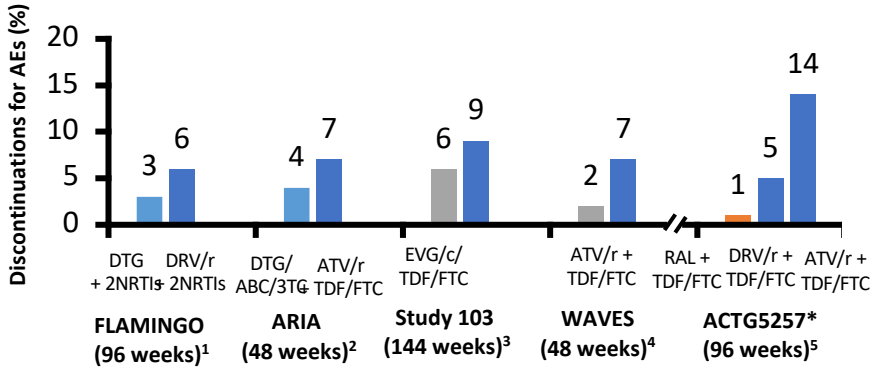


INSTIs:
Also active against HIV-2

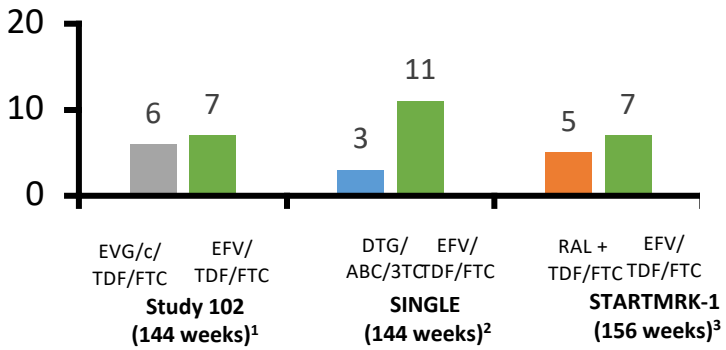
*Single dose. †Mean / median value as available. ‡Day 21. §Week 24. **Day 28.
AI = attachment inhibitor; ART = antiretroviral therapy; BID = twice daily; EI = entry inhibitor;
INSTI = integrase strand transfer inhibitor; MI = maturation inhibitor;
NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor;
PI = protease inhibitor; PoC = proof of concept; QD = once daily; TAF = tenofovir alafenamide fumarate;
TDF = tenofovir disoproxil fumarate.

TOXICITY/TOLERABILITY:
INSTI-Containing Regimens Were Associated With Fewer Discontinuations Due to AEs Than EFV/TDF/FTC and PIs in Treatment-Naïve Patients

Discontinuations from Phase 3 studies in treatment-naïve patients: INSTIs vs PIs



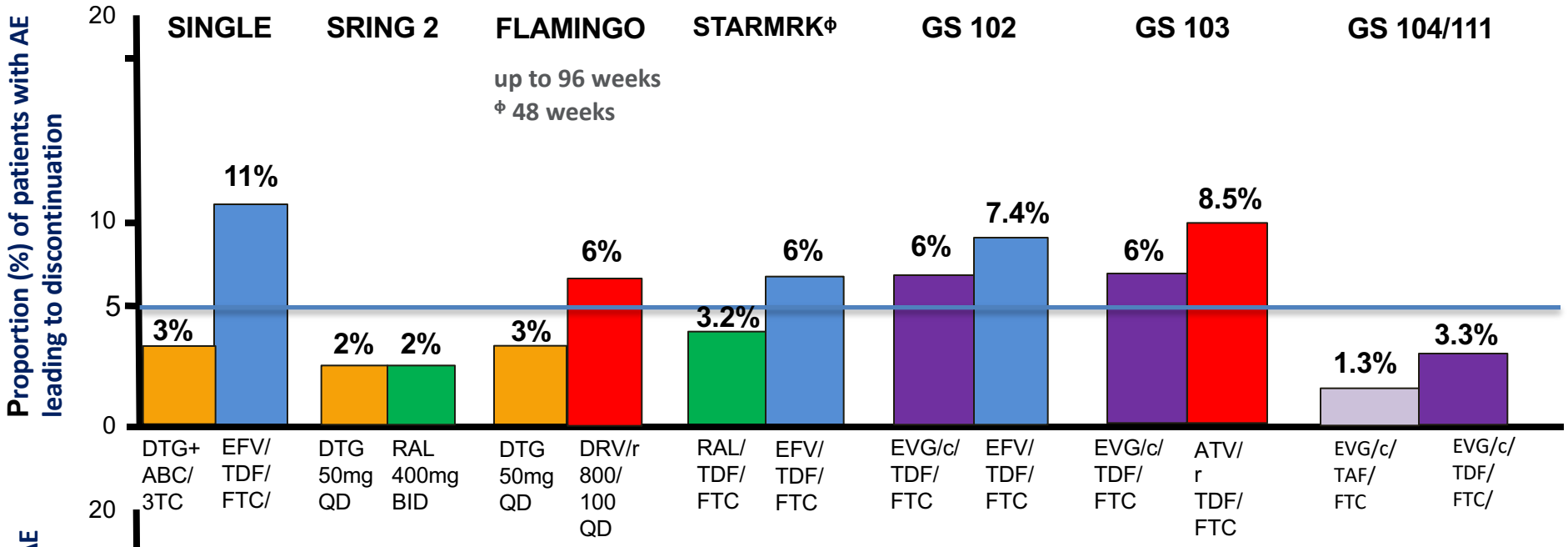
Discontinuations from Phase 3 studies of treatment-naïve patients: INSTIs vs NNRTIs

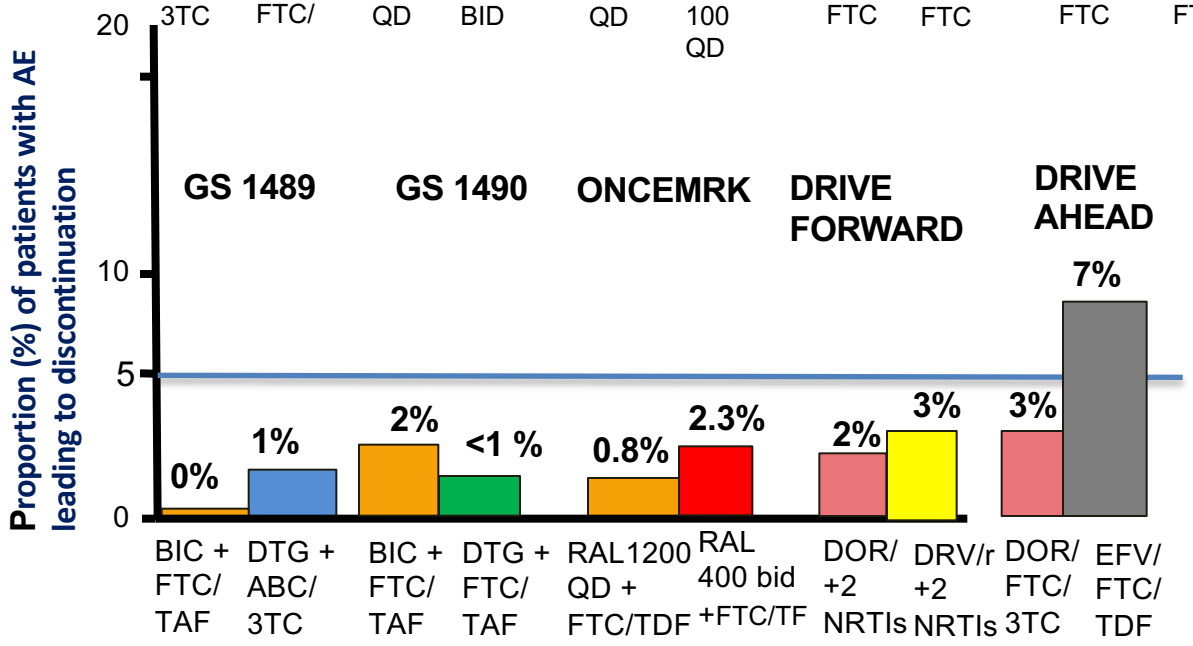


1. Molina et al. *Lancet HIV* 2015; 2:e127–36;
2. Orrell et al. Lancet 2017 [Epub ahead of print];
3. Clumeck et al. *J Acquir Immune Defic Syndr* 2014;65:e121–4;
4. Squires et al. *Lancet HIV* 2016;3:e410–20;
5. Lennox et al. *Ann Intern Med* 2014;161:461–71.

1. Wohl et al. *J Acquir Immune Defic Syndr* 2014;65:e118–20;
2. Walmsley et al. *J Acquir Immune Defic Syndr* 2015;70:515–9;
3. Rockstroh et al. *Clin Infect Dis* 2011;53:807–16.

Safety





1. Eron J Jr, et al. Lancet 2006;368:476-482. 2. Walmsley SL, et al. J. Infect Dis 2009;50:367-374. 3. Ortiz R, et al. AIDS 2008; 22: 1389-1397. 4. Molina JM, et al. Lancet 2008; 372:646-655. 5. Gathe J, et al. CROI 2008. Abstract 775. 6. Arribas J. et al. JAIDS 2017, 75:211-218. 7. De Miguel R. et al. Exp Opinion on Drug Safety 2018 Feb;17(2):217-223. 8. Gallant J, et al. IAS 2017. Abstract MOAB0105LB. 9. Sax PE, et al. IAS 2017. Abstract TUPDB0201LB. 10. Cahn P, et al. IAS 2017. Abstract TULBPEB20.
11. Di Perri G, et al. EACS 2017. Abstract BPD1/3

Gentileza I. Cassetti Managment naive LATAM2019

TRATAMIENTOS ALTERNATIVOS

Regímenes alternativos: Son regímenes eficaces y tolerables, pero con algunas desventajas como interacciones medicamentosas, baja barrera genética, mayor número de comprimidos diarios o requerimiento de alimentación.

DRV/cobi/TAF/FTC		**A1**	Precaución con Interacciones medicamentosas
DRV/r 800/100	TDF/3TC o TDF/FTC	A1	
	ABC/3TC	B2	Carga viral menor a 100.000 copias con abacavir
EVG/cobi/TAF/FTC EVG/cobi/TDF/FTC		B1	o Barrera genética menor que otros INSTI. o Precaución con interacciones medicamentosas.
RAL 400 o RAL 600	TDF/FTC o TDF/3TC	B1	Barrera genética menor que otros INSTI
	TAF/FTC	B2	
DOR/TDF/3TC		B1	
DOR	TAF/FTC	B3	
RPV/TDF/FTC		B1	o Con CV <100.000 copias/ml y CD4 >200 cél./mm3. o Precaución con interacciones medicamentosas. o Requiere toma con alimentos.
EFV/TDF/FTC o EFV/TDF/3TC		B1	o Efectos adversos sobre SNC. o Precaución con interacciones medicamentosas.
EFV 600	TAF/FTC	B2	
DRV/r 800/100	RAL	C1	o Con CV <100.000 copias/ml y CD4 >200 cél./mm3 o Uso de RAL 400 mg cada 12 hs.
DRV/r 800/100	3TC	C1	o Con CV <100.000 copias/ml y CD4 >200 cél./mm3. o Con resultado de prueba de resistencia basal.
Coinfección TBC	RAL 400 u 800 c/12 hs	TDF/3TC o TDF/FTC	

Actualización 2021
del VII Consenso Argentino de

Regímenes preferidos: recomendados como regímenes iniciales para la mayoría de las personas con VIH, en base a eficacia virológica demostrada, perfil de toxicidad-tolerancia y posología favorables [67-75].

DTG/TDF/3TC *	A1	Alta barrera genética.

Teniendo en cuenta estas consideraciones se recomienda que el tratamiento esté basado en un INSTI de alta barrera genética + dos INTI: DTG + TDF/FTC o TDF/3TC o TAF/FTC o ABC/3TC o BIC/TAF/FTC o biterapia con DTG + 3TC

Se recomienda elegir esquemas coformulados que permitan indicar el TARV en un solo comprimido al día.

DTG	3TC	A1	○ Prueba de resistencia basal que asegure sensibilidad a 3TC ○ HBsAg no reactivo

✓ INSTI de alta barrera genética + 2 INTI

✓ DTG / 3TC

TRATAMIENTO ANTIRETROVIRAL EN EL EMBARAZO

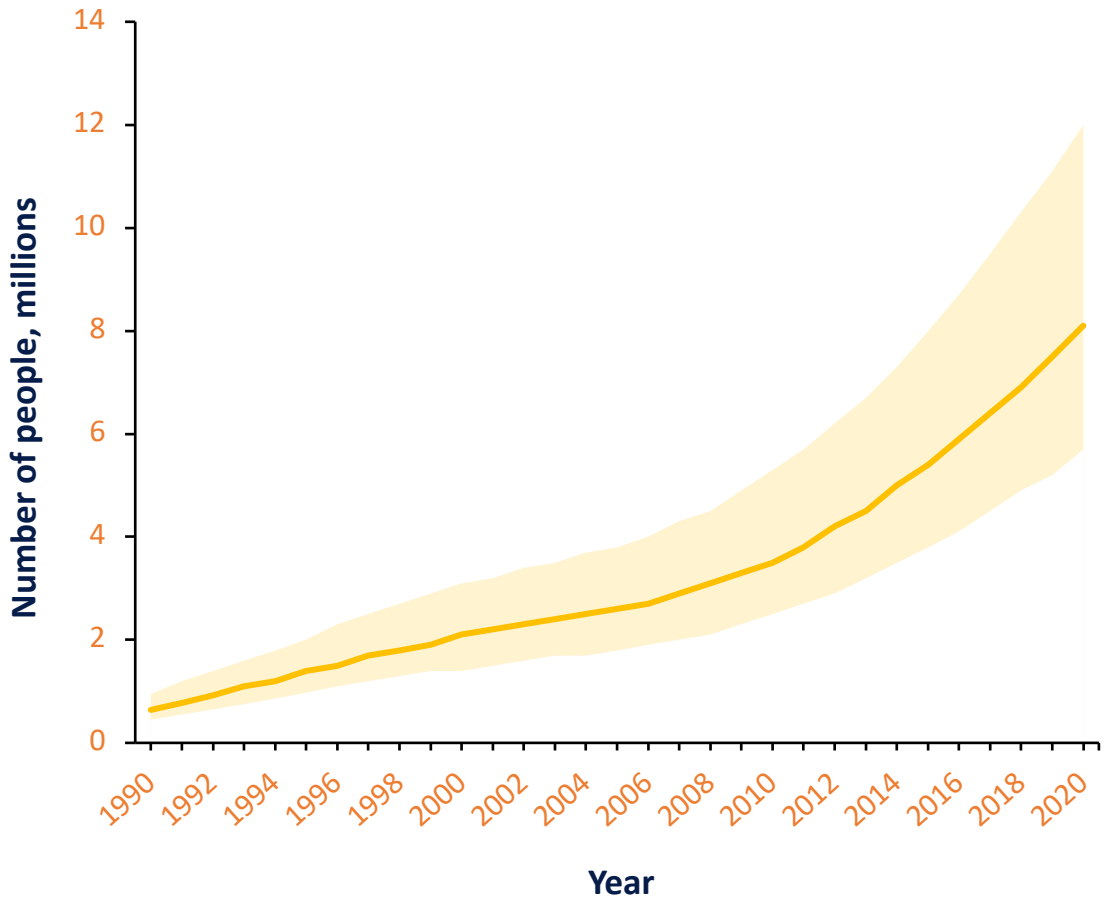
	INTI	TERCERA DROGA	COMENTARIOS
REGÍMENES PREFERIDOS	TDF/FTC TDF/3TC **TAF /FTC**	DTG*	TDF/FTC o TDF/3TC es la asociación de elección para el tratamiento de las embarazadas con HBs Ag positivo
REGIMENES ALTERNATIVOS	ABC/3TC	RAL DRV/r	ABC/3TC requiere testeo previo de HLA-B*5701. DRV se debe indicar en dosis de DRV 600 mg/RTV 100 mg c/12 hs. En pacientes que se embarazan intratratamiento con DRV 800 mg/RTV 100 mg y mantienen la supresión virológica, no hay evidencia suficiente que justifique la modificación de la dosis. TAF mostró similar perfil de seguridad que TDF/FTC, pero podría asociarse a mayores incrementos de peso

FUTURO DEL TARV

- *NUEVAS ESTRATEGIAS*
- *NUEVAS POSOLOGÍAS*
- *NUEVOS MECANISMOS DE ACCIÓN*

Globally, the Number of PLHIV Aged ≥50 Years Is Increasing

People aged ≥50 years living with HIV[1]



Based on latest UNAIDS global estimates, the **proportion of PLHIV aged ≥50 years** has increased from:[1]

in **2000** in **2020**

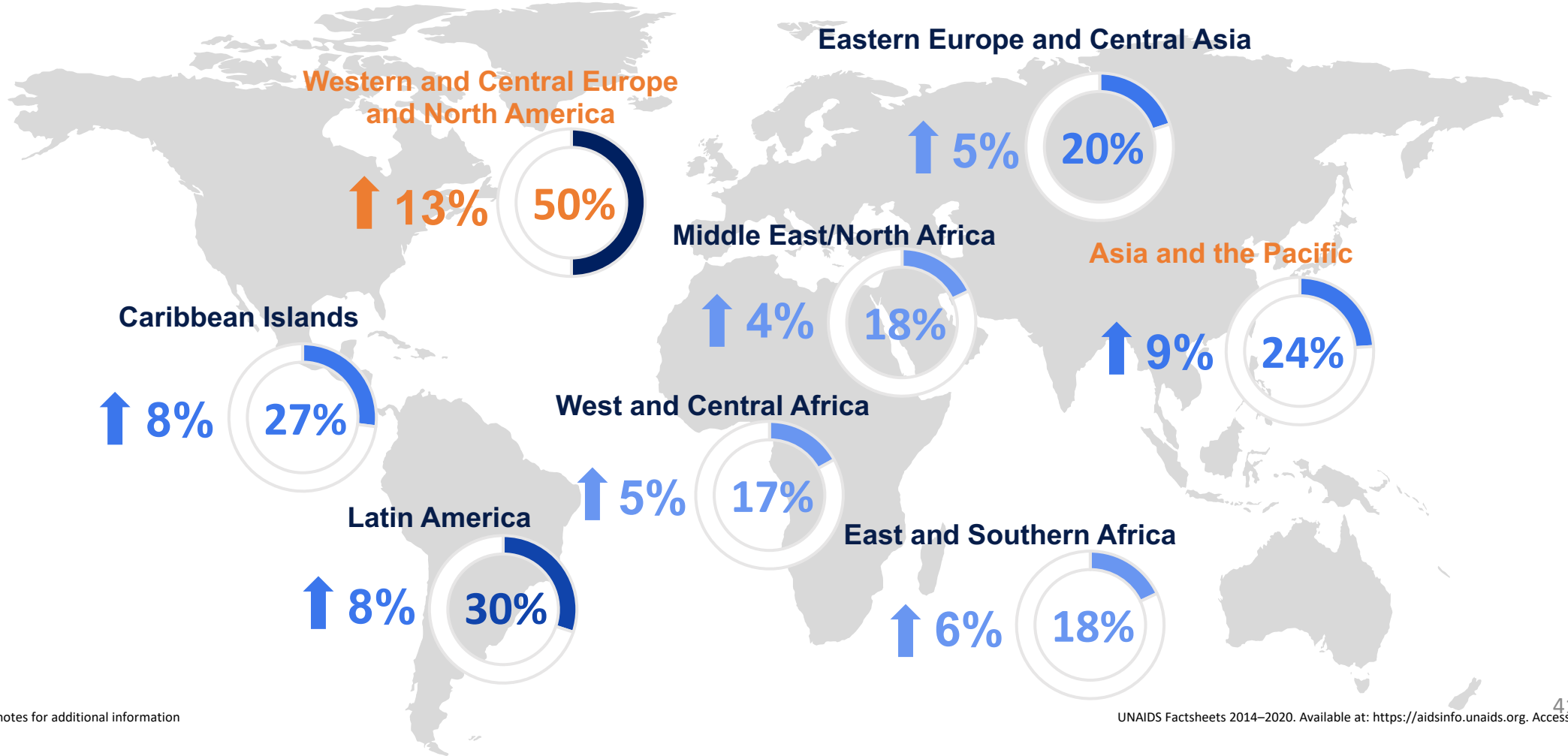
Individual-based model analysis of the ageing HIV population indicate this will **rise to 73% by 2030**[2]

UNAIDS, The Joint United Nations Programme on HIV/AIDS

1. UNAIDS. People living with HIV – epidemiological estimates, 2021. Available at: https://aidsinfo.unaids.org. Accessed Jan 2022
2. Smit M, et al. Lancet Infect Dis 2015;15:810–8

In Many Regions, the Fastest Growing Cohort of PLHIV Are Those Aged ≥50 Years

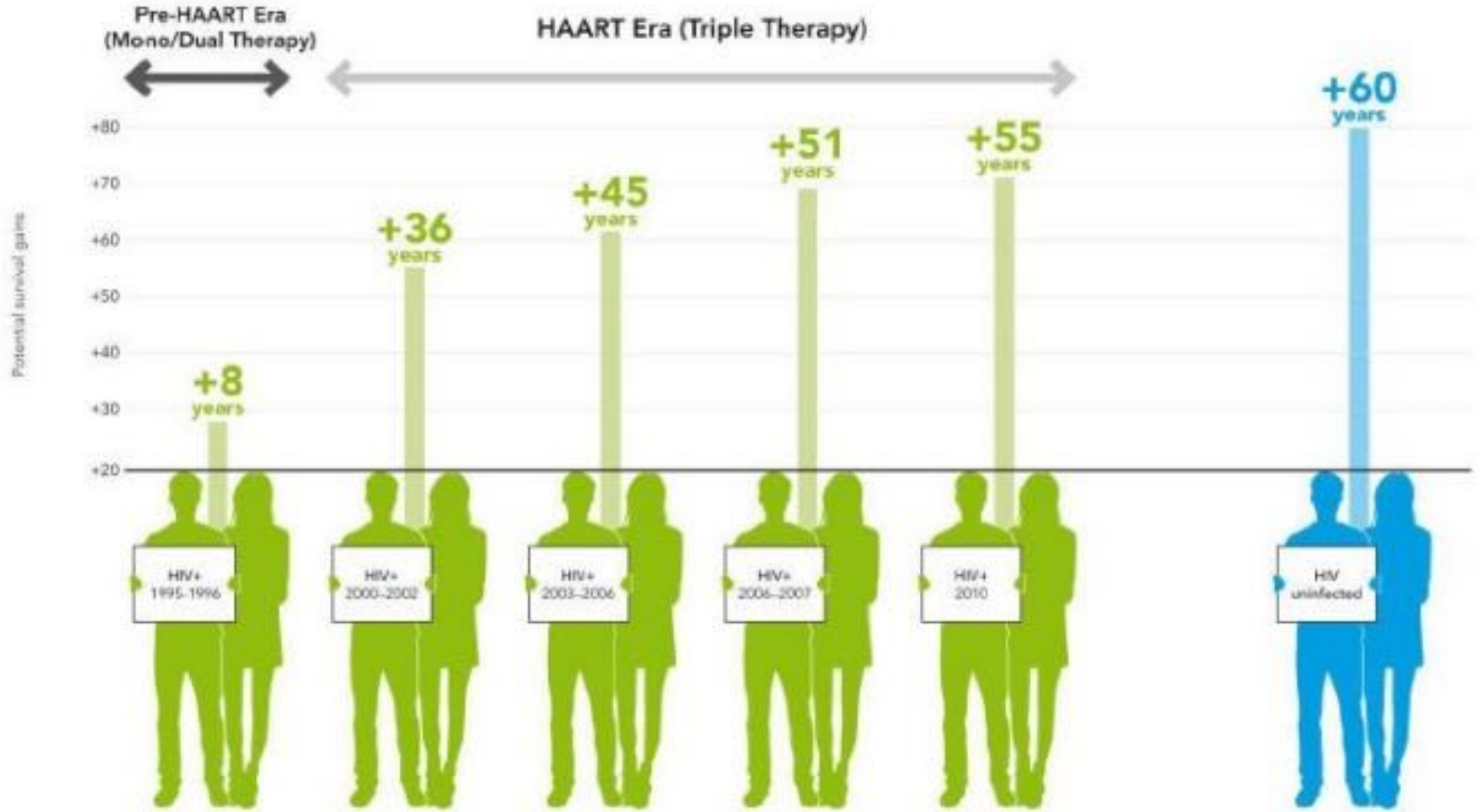
Proportion of PLHIV aged >50 years in each region (2020 UNAIDS estimates), and increase in proportion since 2014



See slide notes for additional information

UNAIDS Factsheets 2014–2020. Available at: https://aidsinfo.unaids.org. Accessed Jan 2022

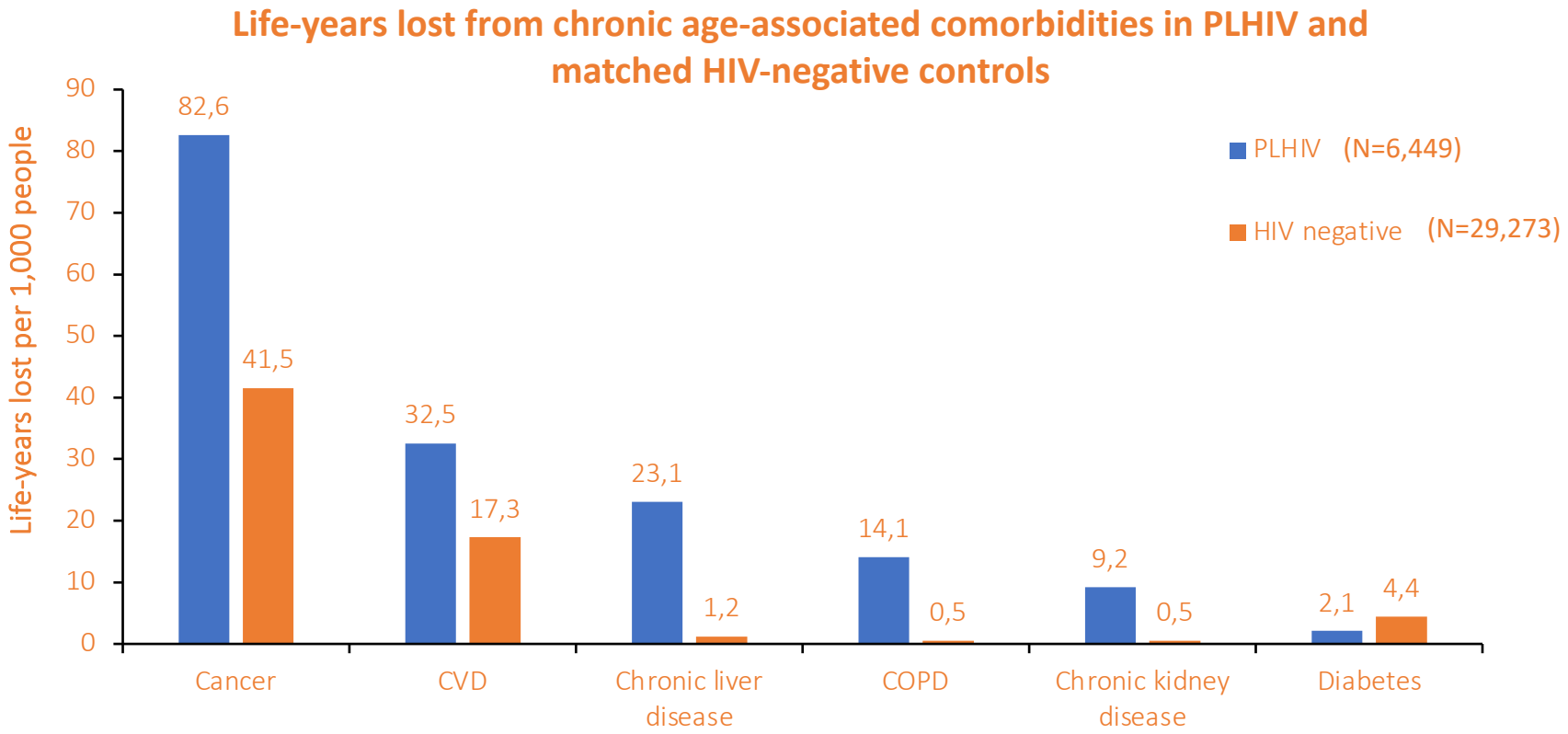
HIV treatment can normalize survival



Expected impact of HIV treatment in survival of a 20 years old person living with HIV in a high income setting (different periods)

UNAIDS

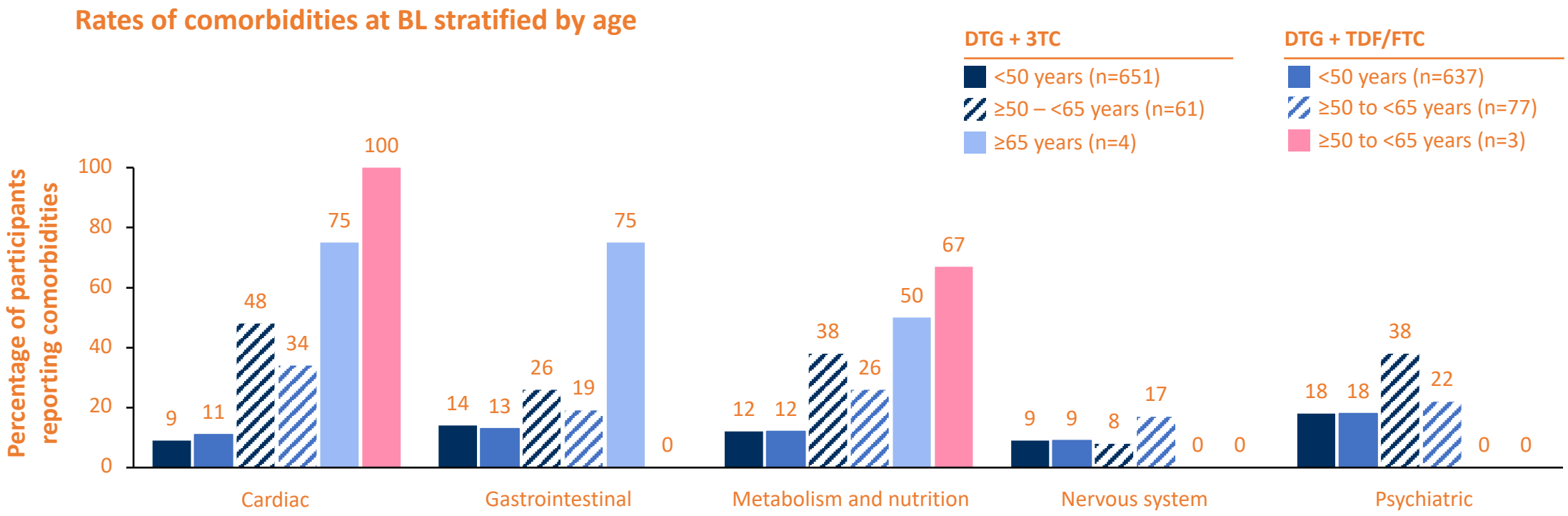
PLHIV Experience Greater Life-years Lost From Age-associated Chronic Comorbidities Compared With HIV-negative Individuals



Excess life-years lost in PLHIV likely reflect persistent inflammation and ARV toxicities, as well as socioeconomic and lifestyle differences between people with and without HIV

Nanditha N, et al. International Workshop on HIV and Aging 2021. Abstract 13

In GEMINI-1 and -2, Older Adults Living With HIV Were More Likely to Report Comorbidities and Polypharmacy

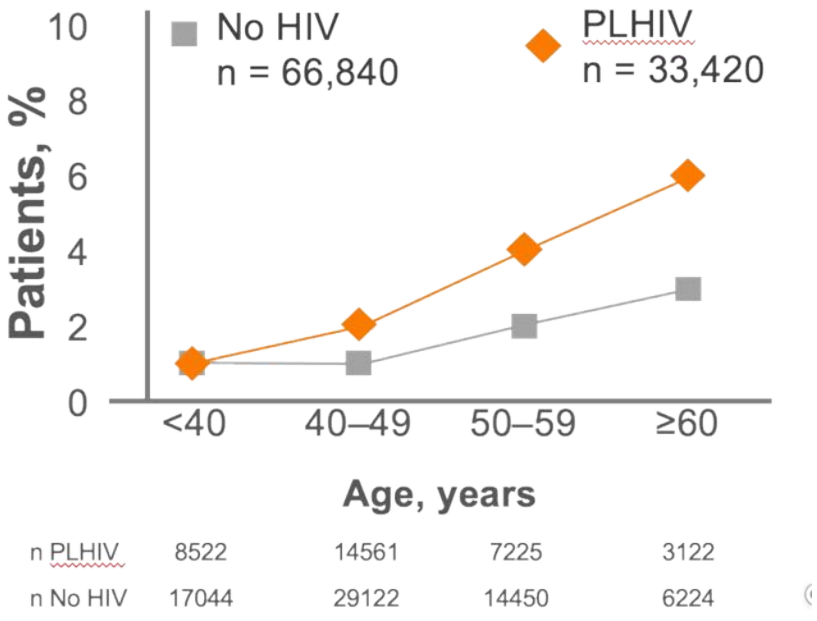


- Use of co-medications ranged from 37% for patients aged <50 years, to 68% in patients aged ≥50 – <65 years, rising to 100% in the seven patients who were aged ≥65 years

Spinelli F, et al. EACS 2021. Poster PE2/60

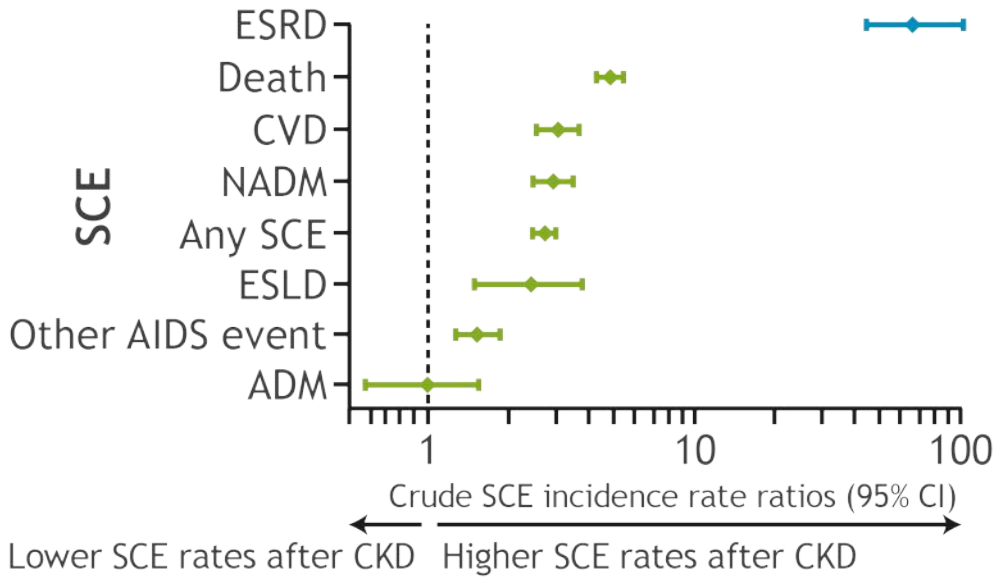
Prevalence of renal disease is higher in PLHIV and increases with age

Rate of renal disease* according to HIV status and age[1]



Serious clinical events in PLHIV and CKD† (D:A:D Study)[2]

(n = 2467)



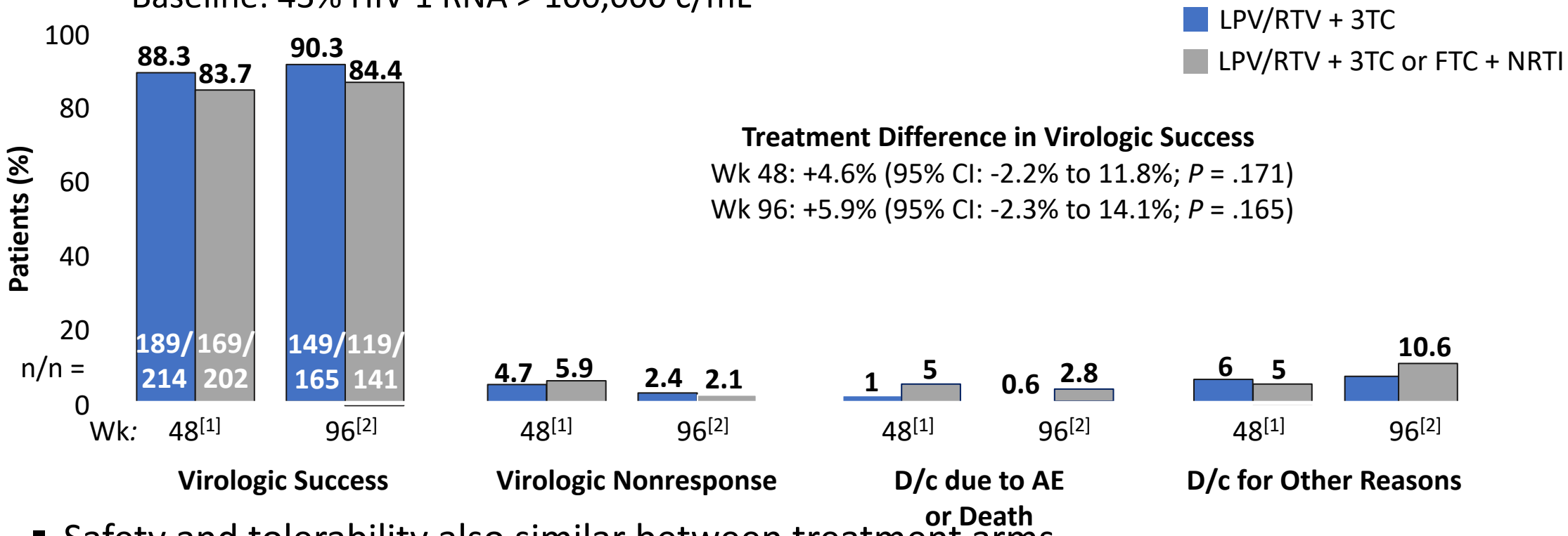
*Including renal insufficiency, renal failure and glomerulonephritis.
†Confirmed ≥3 months apart, eGFR <60 mL/min/1.73 m² or 25% eGFR decrease when eGFR ≤60 mL/min/1.73 m².
ADM, AIDS-defining malignancy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESLD, end-stage liver disease; ESRD, end-stage renal disease; NADM, non-AIDS-defining malignancy; PLHIV, people living with HIV; SCE, serious clinical event.
1. Adapted from: Goulet J, et al. Clin Infect Dis 2007;45:1593–1601. 2. Ryom L, et al CROI 2018, abstract 75.

NUEVAS ESTRATEGIAS

TERAPIA DUAL : PREVENCIÓN DE TOXICIDADES

GARDEL: LPV/RTV + 3TC Noninferior to Triple ART in Treatment-Naive Patients at Wks 48 and 96

- International, open-label, randomized phase III study (N = 426)
  - Baseline: 43% HIV-1 RNA > 100,000 c/mL



Treatment Difference in Virologic Success

Wk 48: +4.6% (95% CI: -2.2% to 11.8%; *P* = .171)

Wk 96: +5.9% (95% CI: -2.3% to 14.1%; *P* = .165)

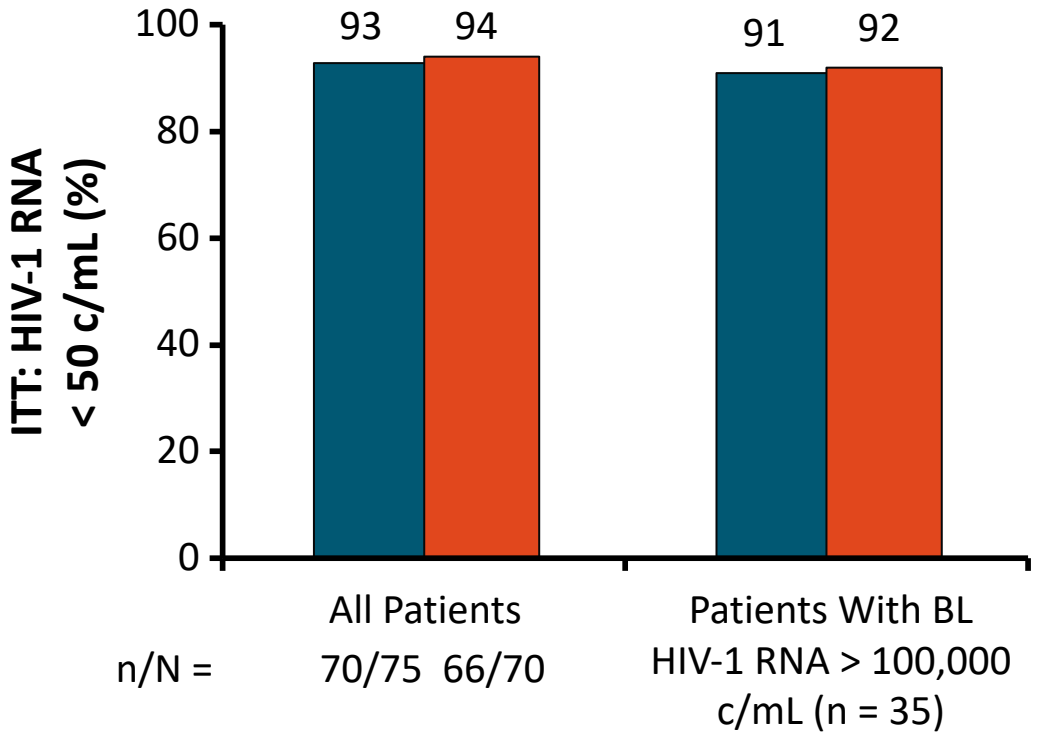
- Safety and tolerability also similar between treatment arms

1. Cahn. Lancet Infect Dis. 2014;14:572. 2. Cahn. EACS 2015. Abstr 961.

Slide credit: clinicaloptions.com

ANDES: DRV/RTV + 3TC Noninferior to Triple ART in Treatment-Naive Patients at Wk 48

- Multicenter, open-label, randomized phase IV study (N = 145)
  - Baseline: 24% HIV-1 RNA > 100,000 c/mL



Treatment Difference
All patients: -1.0% (95% CI: -7.5% to 5.6%)
Patients with high BL HIV-1 RNA: -1.4%
(95% CI: -17.2% to 14.4%)

- 1 virologic failure with DRV/RTV + TDF/3TC
- No significant difference in AEs leading to d/c, serious AEs, or deaths between arms

Figueroa. CROI 2018. Abstr 489.

Slide credit: clinicaloptions.com

Research article

Dolutegravir–lamivudine as initial therapy in HIV-1 infected, ARV-naive patients, 48-week results of the PADDLE (Pilot Antiretroviral Design with Dolutegravir LamivudinE) study

Pedro Cahn[*1], María José Rolón[1], María Inés Figueroa[1], Ana Gun[2], Patricia Patterson[1] and Omar Sued[1]

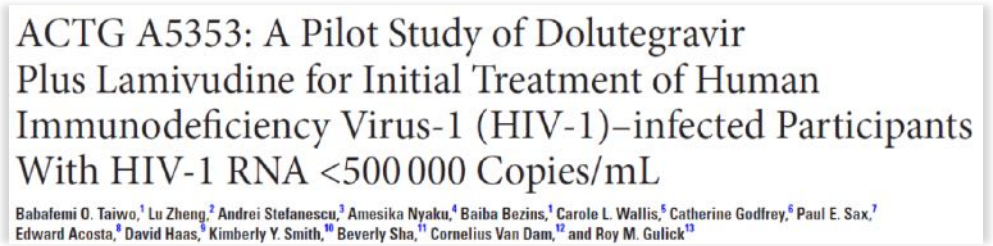
[*]Corresponding author: Pedro Cahn, Fundación Huésped, Buenos Aires C1202ABB Argentina. (pedro.cahn@huesped.org.ar)

#W96	SCR	BSL	DAY 4	DAY 7	W.2	W.3	W.4	W.6	W.8	W.12	W.24	W.36	W.48	W 96
1	5.584	10.909	383	101	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
2	8.887	10.233	318	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
3	67.335	151.569	1.565	1.178	97	53	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
4	99.291	148.370	3.303	432	178	55	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
5	34.362	20.544	1.292	570	107	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
6	16.024	14.499	1.634	162	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
7	37.604	18.597	819	61	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
8	25.071	24.368	1.377	Not done	105	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
9	14.707	10.832	516	202	< 50	< 50	< 50	< 50	< 50	< 50	< 50	SAE		
10	10.679	7.978	318	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	<50
11	50.089	273.676	68.129	3.880	784	290	288	147	< 50	< 50	< 50	< 50	< 50	70/<50 *
12	13.508	64.103	3.296	135	351	84	67	< 50	< 50	< 50	< 50	< 50	< 50	< 50
13	28.093	33.829	26.343	539	61	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
14	15.348	15.151	791	198	< 50	61	64	< 50	< 50	< 50	< 50	< 50	< 50	< 50
15	23.185	23.500	4.217	192	< 50	< 50	< 50	Not done	< 50	< 50	< 50	< 50	< 50	< 50
16	11.377	3.910	97	143	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
17	39.100	25.828	1.970	460	52	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
18	60.771	73.069	2.174	692	156	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
19	82.803	106.320	2.902	897	168	76	< 50	< 50	< 50	< 50	< 50	PDVF		
20	5.190	7.368	147	56	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	<50

ITT-e: 90% < 50 copies/mL at W 48 & 96
Observed data: 95% <50 copies/mL
n=1 with PDVF; No mutations detected

FUNDACIÓN HUÉSPED
PREVENCIÓN . CIENCIA . DERECHOS

Cahn: JIAS 2017



ACTG A5353: A Pilot Study of Dolutegravir Plus Lamivudine for Initial Treatment of Human Immunodeficiency Virus-1 (HIV-1)–infected Participants With HIV-1 RNA <500 000 Copies/mL

Babafemi O. Taiwo,[1] Lu Zheng,[2] Andrei Stefanescu,[3] Amesika Nyaku,[4] Baiba Bezins,[1] Carole L. Wallis,[5] Catherine Godfrey,[6] Paul E. Sax,[7] Edward Acosta,[8] David Haas,[9] Kimberly Y. Smith,[10] Beverly Sha,[11] Cornelius Van Dam,[12] and Roy M. Gulick[13]

Virologic Outcome at Wk 24, n (%) [Primary endpoint]	Baseline HIV-1 RNA, copies/mL		Total (N = 120)
	> 100,000 (n = 37)	≤ 100,000 (n = 83)	
Success (pVL<50 copies/mL)	33 (89)	75 (90)	108 (90)
Nonsuccess	3 (8)	2 (2)	5 (4)
No data	1 (3)	6 (7)	7 (6)

n = 3 with PDVF; n = 1 with emergent M184V and R263RK

ITT-e: 90% < 50 copies/mL at W 24

Taiwo: CID 2018,

Gentileza Dr P.Cahn

GEMINI-1 and -2: DTG + 3TC vs DTG + FTC/TDF in Treatment-Naive Patients

- Parallel, international, randomized, double-blind phase III noninferiority studies[1]

Stratified by HIV-1 RNA (≤ vs > 100,000 copies/mL), CD4+ cell count (≤ vs > 200 cells/mm³)

Primary Analysis Wk 48

Wk 144

ART-naive adults with HIV-1 RNA 1000-500,000 copies/mL, ≤ 10 days on previous ART, no major resistance associated mutation, no HBV infection or HCV requiring therapy (N = 1433)

DTG + 3TC PO QD (n = 716)

DTG + FTC/TDF PO QD (n = 717)

Continuation of DTG + 3TC permitted

- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (FDA Sna
- pshot) (noninferiority margin: -10%)[2]
  - **DTG + 3TC** vs **DTG + FTC/TDF**: **91%** vs **93%** (difference: -1.7%; 95% CI: -4.4% to 1.1%)
  - No treatment-emergent INSTI or NRTI mutations in patients with VF in either arm

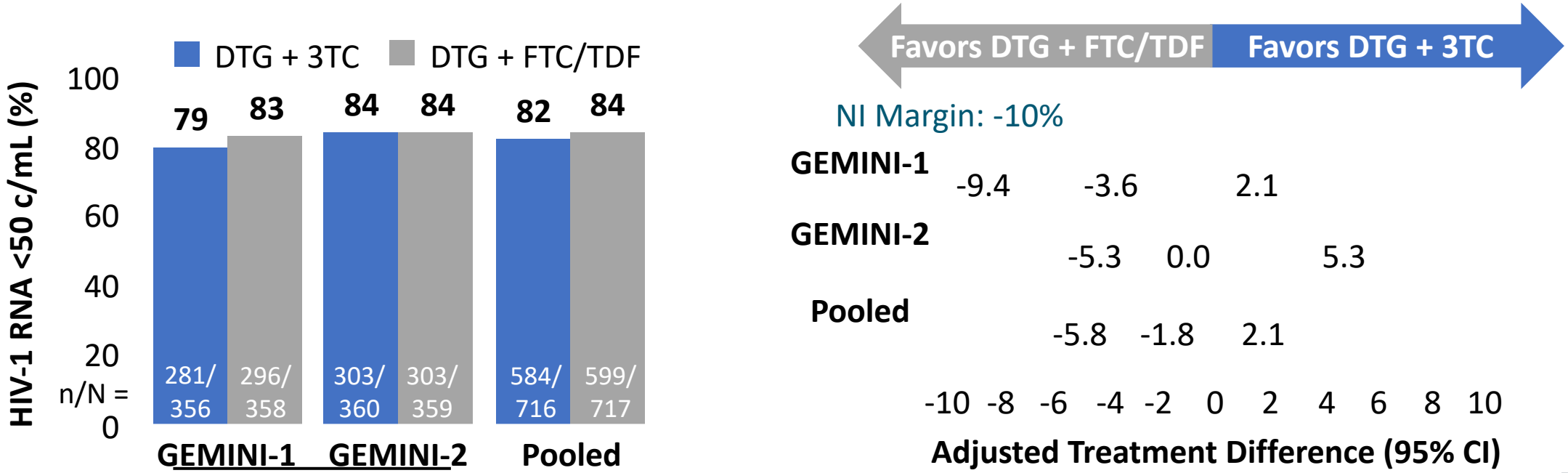
Screening within 28 days of study start; studies double blinded until Wk 96, open label until Wk 144.

Cahn: Lancet. 2019 Jan 12;393(10167):143-155

GEMINI-1 and -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 = 716) vs DTG + FTC/TDF (n = 717)
  - DTG + 3TC noninferior at Wk 48 (primary analysis HIV-1 RNA <50 c/mL, ITT-E Snapshot)[1] and Wk 96[2]

Wk 144 Virologic Efficacy[3]

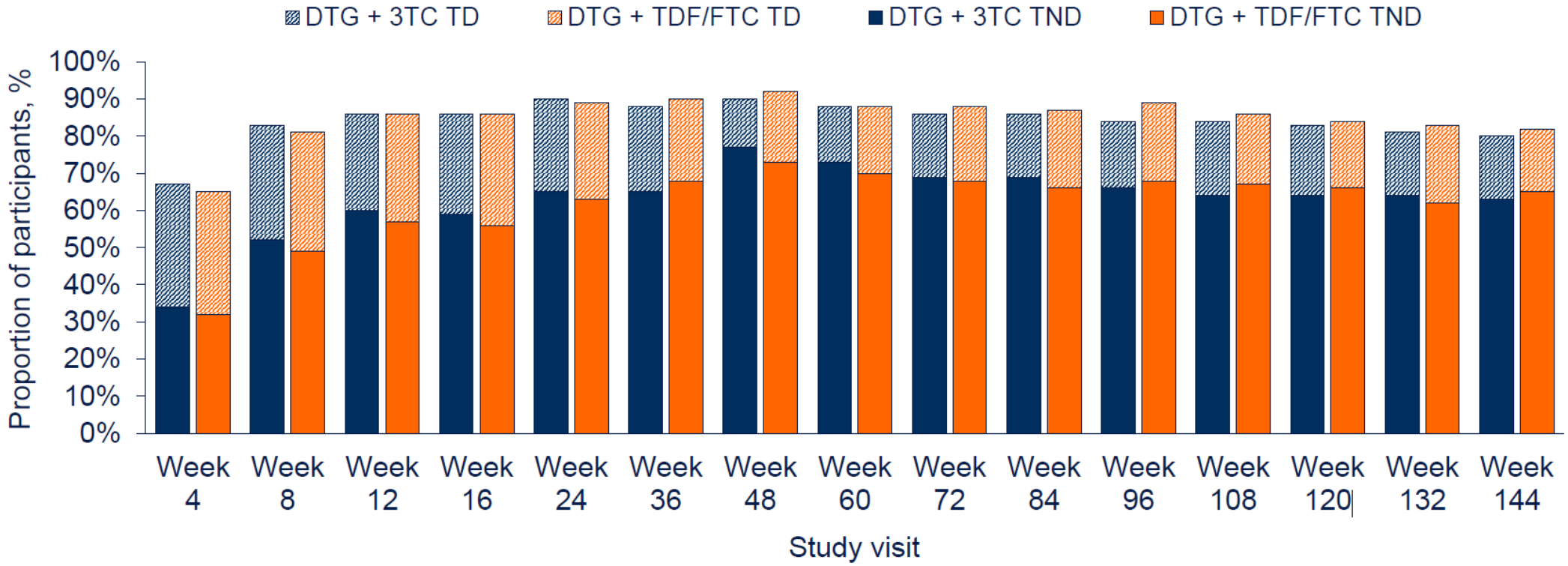


1. Cahn. Lancet. 2019;393:143. 2. Cahn. JAIDS. 2020;83:310. 3. Cahn. HIV Glasgow 2020. Abstr P018.

Slide credit: clinicaloptions.com

Participant Proportions With TND or TD Were Similar Across Arms From Week 4 Through Week 144, ITT-E Population

- Proportions with TND trended upward through ~Week 48 and were similar between arms at all visits
- The proportions that had highest TD occurred in earlier visits and decreased to stabilize around Week 48

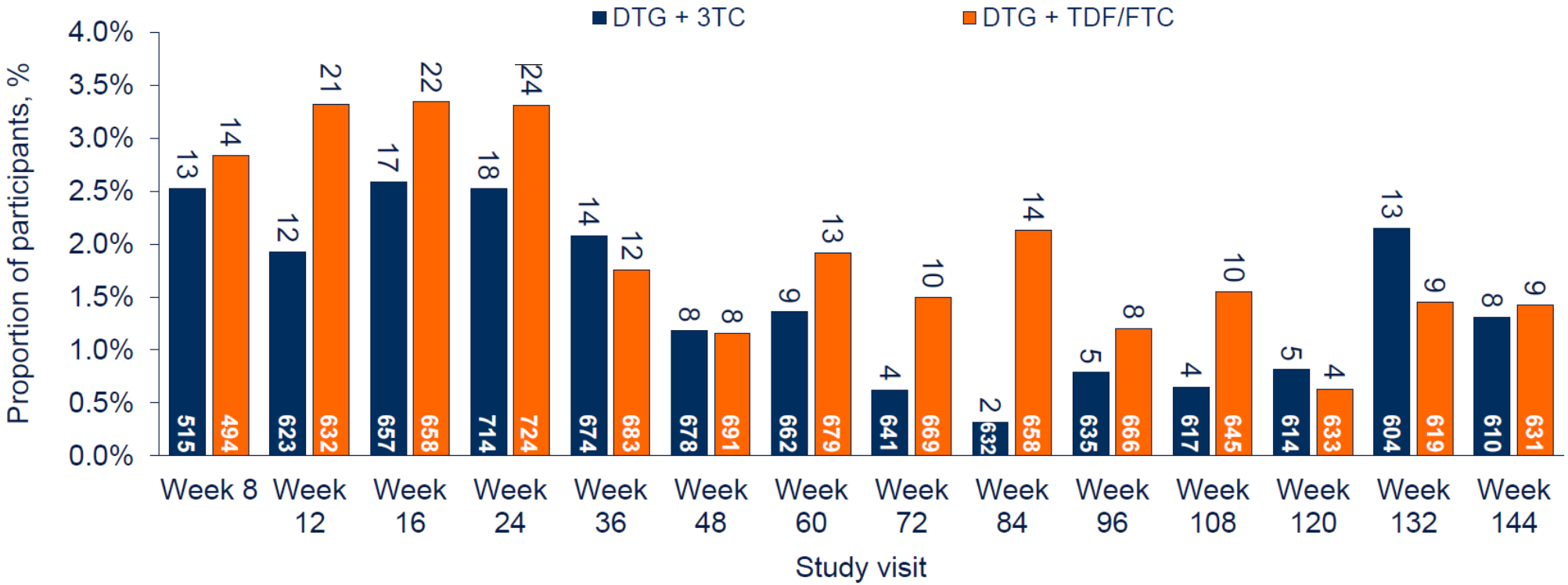


[a]Percentages calculated for DTG + 3TC and DTG + TDF/FTC in the figure used, respectively, N=716 and N=717 ITT-E population as denominators.

Underwood et al. IAS 2021; Virtual. Poster PEB163.

Participant Proportions[a] With 'Blips' Were Similar Across Arms by Visit Through Week 144, ITT-E Population

- 'Blip' proportions were higher early and decreased around Weeks 36 to 48
- The proportion of 'blips' was generally numerically lower for DTG + 3TC but similar across arms through Week 144



[a]The denominator is in white overlaid on the vertical bars and is the total number of observations from all participants with data for the specified visit window. Numbers on tops of bars are # of 'blips' at given week visits. Note that individual can have had more than one 'blip.'

Underwood et al. IAS 2021; Virtual. Poster PEB163.

DESAFÍOS DEL TARV : BITERAPIA

NAIVE

- EFICACIA
  - Durabilidad
  - TND /TD
  - Blips
- SEGURIDAD
- TOLERANCIA
- Experiencia en la vida real

SWITCH A BITERAPIA

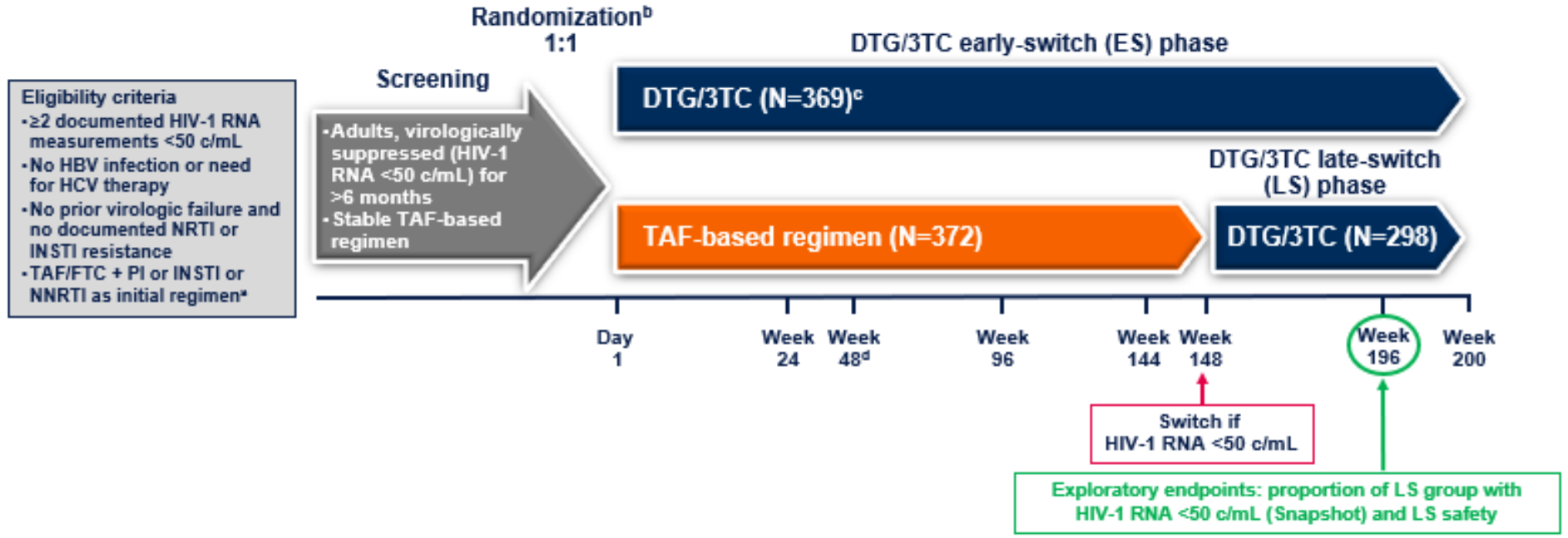
- **<u>MEJORAR LA ESTRATEGIA DE TARV : ESTRATEGIA A LARGO PLAZO</u>**
  - Disminuir número de comprimidos
  - Mejorar tolerancia
  - ADHERENCIA
  - Prevenir toxicidades
  - Minimizar interacciones

- **<u>CRITERIOS PARA EL SWITCH :</u>**
  - Indetectable x mas de 6 meses
  - Sin antecedents de fallo
  - Sin mutaciones conocidas
  - No HVB

ESTRATEGIAS DE SWITCH PREVENTIVO

TANGO Study Design

Phase 3 randomized, open-label, multicenter, parallel-group, non-inferiority study

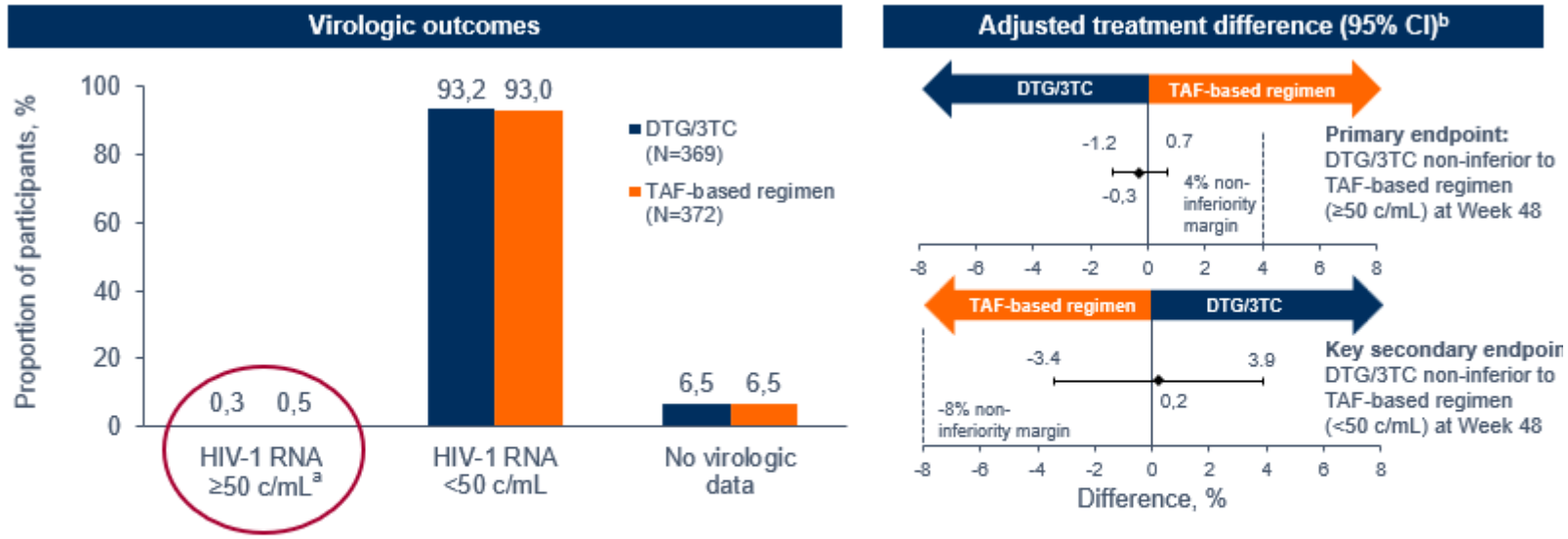


[a]Participants with initial TDF treatment who switched to TAF ≥3 months before screening, with no changes to other drugs in their regimen, were also eligible. [b]Stratified by baseline third agent class (PI, INSTI, or NNRTI). [c]2 participants excluded who were randomized but not exposed to study drug. [d]Primary endpoint was proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot, ITT-E), with a 4% non-inferiority margin.

De Wit et al. HIV Drug Therapy Glasgow 2022: Virtual and Glasgow, Scotland. Slides MO41.

ESTRATEGIAS DE SWITCH PREVENTIVO

DTG/3TC IS NON-INFERIOR TO TAF-BASED REGIMEN AT WEEK 48



- In the per-protocol population, 0/352 participants in the DTG/3TC group and 2/358 participants in the TAF-based regimen group had HIV-1 RNA ≥50 c/mL at Week 48 (adjusted difference, −0.6; 95% CI, −1.3 to 0.2)[b]

[a]Primary endpoint (Snapshot virologic non-response, ITT-E). [b]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline third agent class.

van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

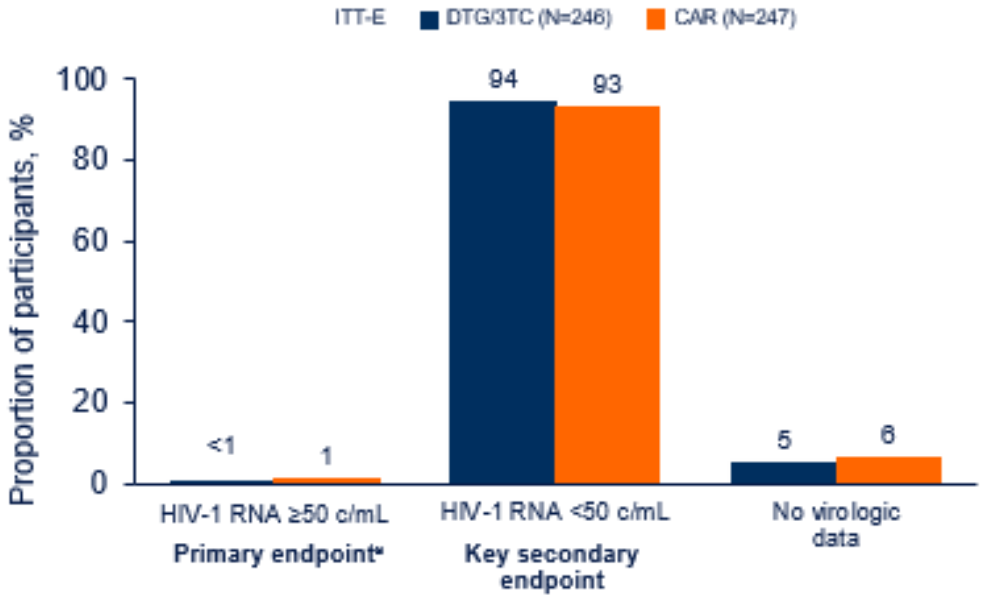
10th IAS Conference on HIV Science; July 21–24, 2019; Mexico City, Mexico

ESTRATEGIAS DE SWITCH PREVENTIVO

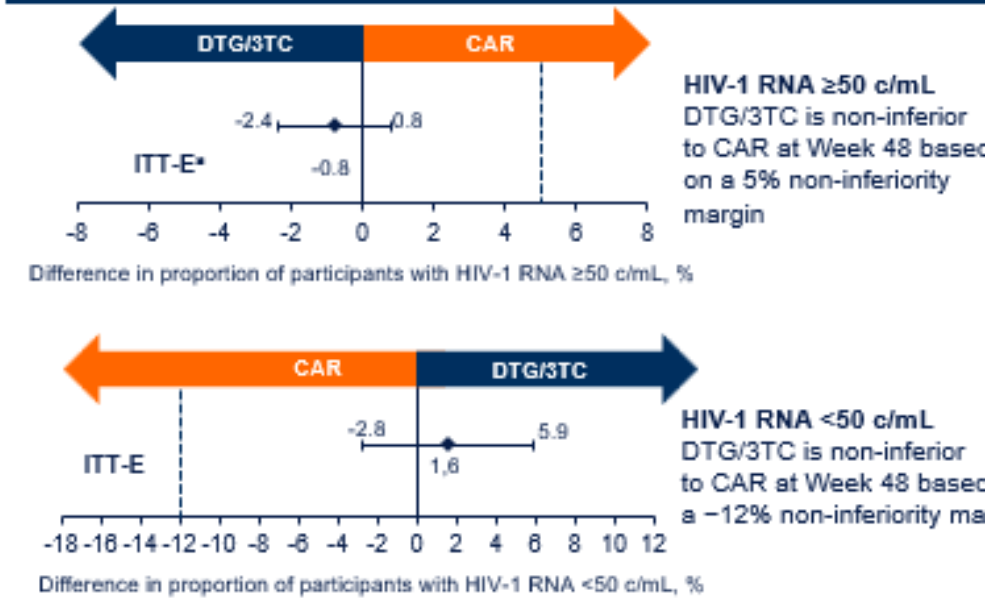
SALSA Phase III Study Design

Randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study

Virologic outcomes (Snapshot analysis)



Adjusted treatment difference (95% CI)[b]



- In the per-protocol population, 1/222 (0.5%) in the DTG/3TC group and 3/234 (1.3%) in the CAR group had HIV-1 RNA ≥50 c/mL at Week 48 (adjusted difference, −0.8%; 95% CI, −2.5% to 0.9%)

[a]Primary endpoint (Snapshot virologic non-response, ITT-E). [b]Based on Cochran-Mantel-Haenszel stratified analysis (DTG/3TC − CAR) adjusting for baseline third agent class.

Llibre et al. IAS 2021; Virtual. Slides OALB0303.

ESTRATEGIAS DE SWITCH A TERAPIA DUAL

Two-year outcomes of DTG+3TC in ART-naïve and pre-treated people living with HIV in Germany: real-world data from the German URBAN cohort

D Beer[1], J Scherzer[2], S Noe[3], S Scholten[4], C Wyen[5], N Postel[6], O Degen[7], M Sabranski[8], B Westermayer[9], K Dymek[2]

[1]Clinical Care, PZB Aachen - Praxis Dr. H. Knechten, Aachen, Ger
Munchen am Goetheplatz, Munich, Germany; [4]Clinical Care, Praxi
Germany; [6]Clinical Care, Prinzmed, Munich, Germany; [7]Clinical Ca
Study Center, Hamburg, Germany; [9]Medical Affairs, GlaxoSmithKl

REDOLA: Real-World Cohc
Baseline Drug Resistance T

TANDEM

Real-world Treatment Experience of Single-Tablet DTG/3TC in Those Naive to Treatment With Baseline Viral Loads ≥100,000 copies/mL in the United States

P Benson,[1] C Donovan,[2] G Harper,[3] D Merrill,[2] K Mycock,[3] A Oglesby,[2] J Patarroyo,[2] A Metzner[2]

[1]Be Well Medical Center, Berkley, MI, USA; [2]ViiV Healthcare, Durham, NC, USA; [3]Adelphi Real World, Bollington, Cheshire, UK

Real-world Treatment Experience of Treatment-

DUALING: Real-World Evidence comparing switching to DTG/3TC vs DTG 3-Drug Regimen

Treatment With Single-Tablet DTG/3TC in a Test and Treat Setting in the United States

J Kuretski,[1] C Donovan,[2] G Harper,[3] D Merrill,[2] K Mycock,[3] A Oglesby,[2] A Metzner,[2] J Patarroyo[2]

[1]Midway Specialty Care Center, West Palm Beach, FL, USA; [2]ViiV Healthcare, Durham, NC, USA; [3]Adelphi Real World, Bollington, Cheshire, UK

CAMBIANDO EL PARADIGMA

- ✓ POTENCIA
- ✓ DURABILIDAD
- ✓ = AEs Y eventos clínicos
- ✓ Costo ?
- ✓ POTENCIAL EXPOSICIÓN A TOXICIDAD DE UNA TERCERA DROGA

- ✓ POTENCIA
- ✓ DURABILIDAD
- ✓ = AEs Y eventos clínicos
- ✓ Costo ?

GAPS :
TB
EMBARAZO
R ARCHIVADAS
Rol deM184 V
Test and treat ?
CV > 500.000 copias

En vías a la optimización del TARV …..

CUÁL ES EL VALOR DE LA TERCERA DROGA ?

Terapia Antirretroviral

Esquema general de inicio: 3 drogas

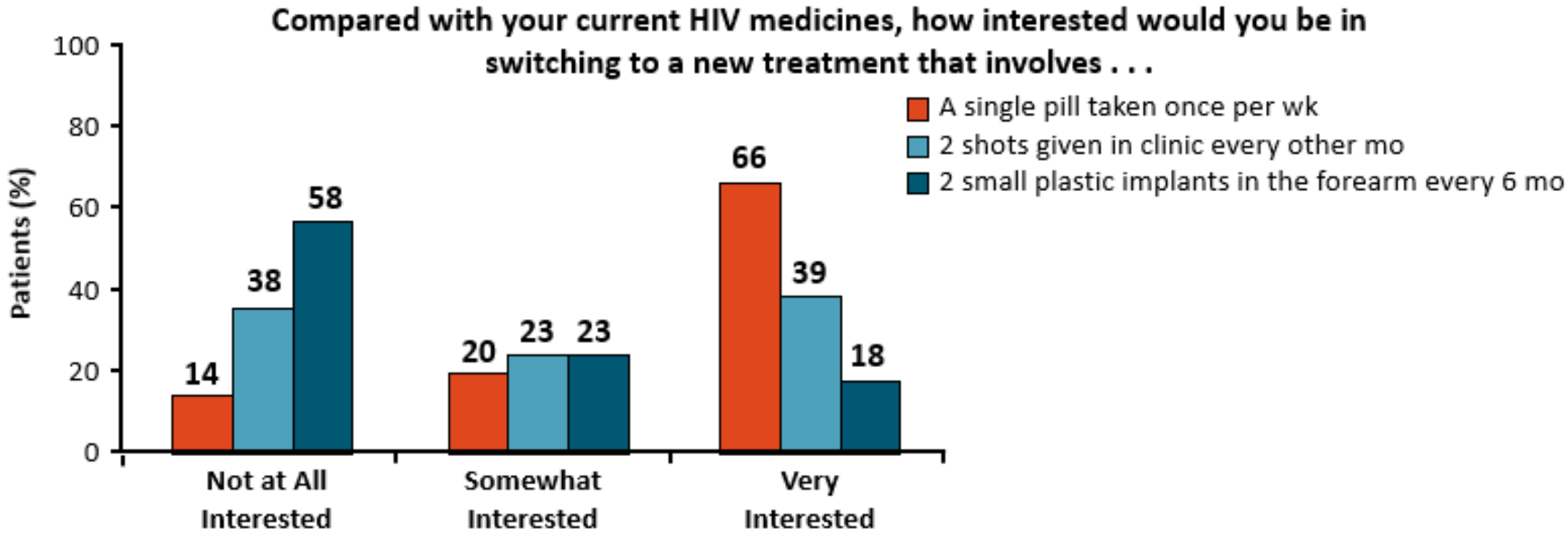
2 INTI + 1 INNTI / 1 IP / 1 IIn

Nueva opción de inicio: 2 drogas

BITERAPIA : 1 INNT + 1 IIN

Survey: Preferences on Mode of ART Administration in Treatment-Experienced Patients

- Survey of patients with HIV in North and South Carolina (N = 263, mean 12 yr on ART, 59% on single-pill daily ART)
  - Greater interest in injection in those with higher education or younger age

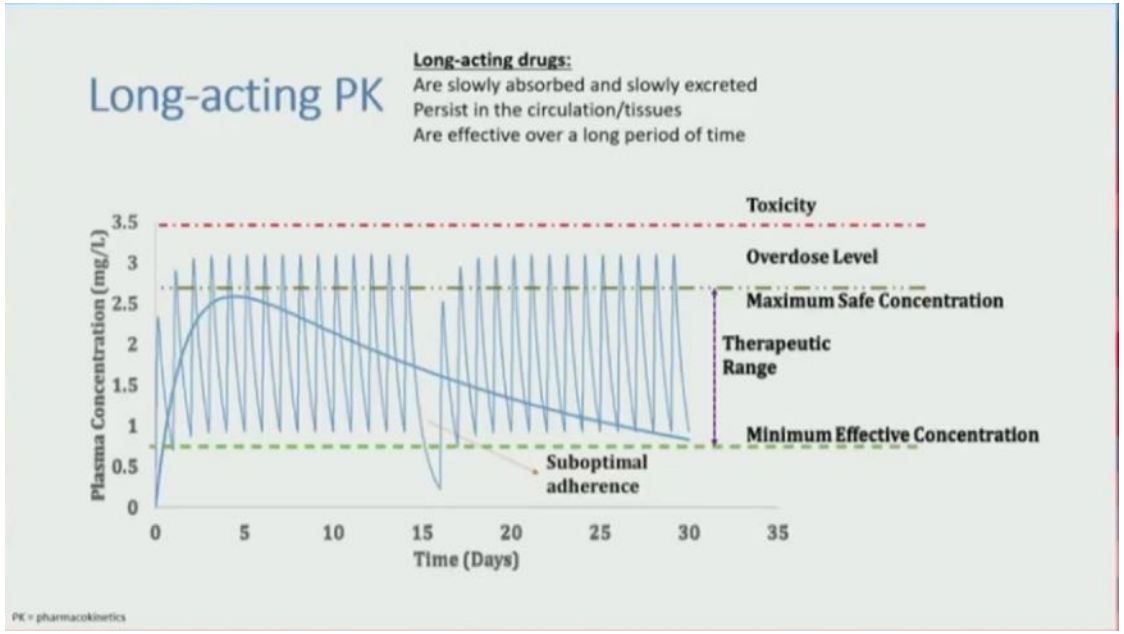


Derrick. Open Forum Infectious Diseases. 2018;5:10.

Slide credit: clinicaloptions.com

NUEVAS POSOLOGÍAS :TRATAMIENTOS DE ACCIÓN PROLONGADA

Route of delivery	Oral	Parenteral	Implant / Device
Dosing frequency	≥ 1 week	≥ 1month	≥ 6months



TRATAMIENTOS DE ACCIÓN PROLONGADA

Long-Acting Antiretroviral Therapy: Potential Opportunities and Challenges

OPPORTUNITIES

- Less frequent dosing
- Avoidance of "pill fatigue"
- Oral dosing by-passed; bioavailability ~100%
- Less adverse events
- Less drug-drug interactions
- Protection of health privacy
- Avoidance of HIV-related stigma
- Improved adherence?

CHALLENGES

- Large injection volumes
- Need for oral lead in
- Management of missed doses
- Coverage of the "tail"
- Development of drug resistance
- Management of drug-drug interactions
- Management of serious adverse events
- Unknown dosing for children & pregnant women

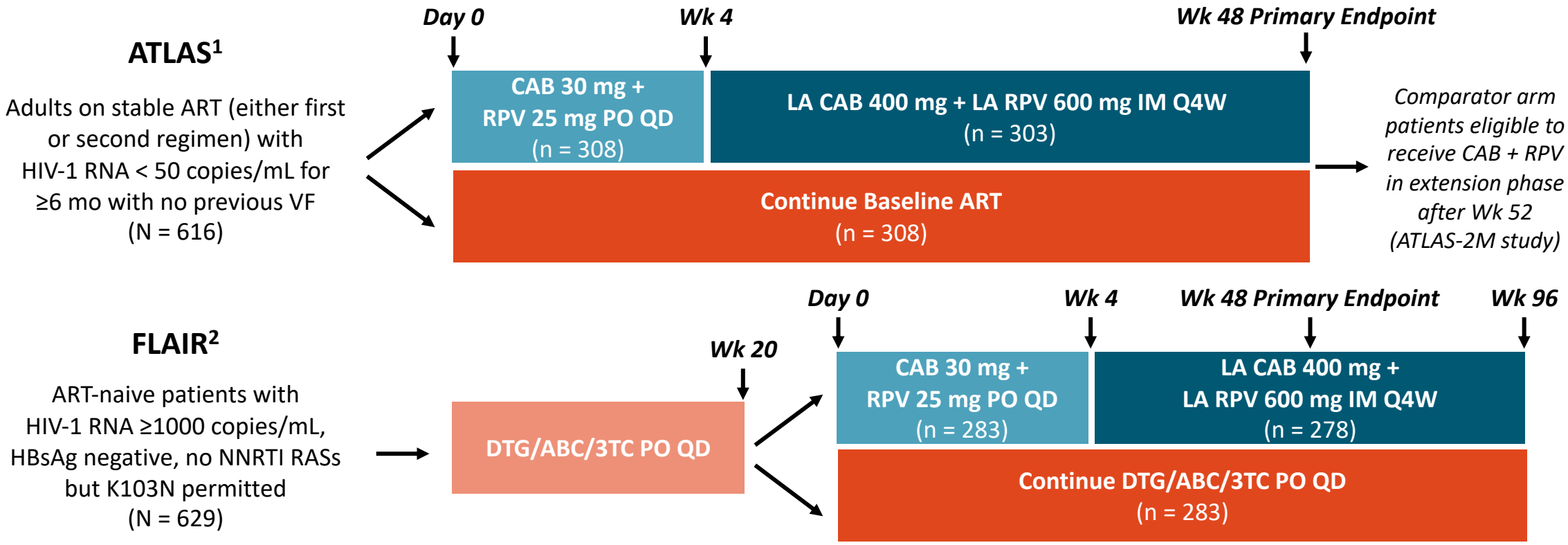
TRATAMIENTOS DE ACCIÓN PROLONGADA

LA ARVs in Development or Clinical Use

ARV Class	Agent	Formulation	Development Stage
NRTI	MK-8591	Implant	Preclinical
	TAF	Implant	Preclinical (Px)
	GS-9131	Implant	Preclinical
NNRTI	Rilpivirine	Injectable	Phase III/NDA
	Elsulfavirine	Injectable	Preclinical
PI	Atazanavir	Injectable	Preclinical
	Ritonavir	Injectable	Preclinical
INSTI	Cabotegravir	Injectable	Phase III/NDA, Phase II/III (Px)
	Raltegravir	Injectable	Preclinical
Entry Inhibitors	Ibalizumab	Intravenous	FDA Approved (Tx)
	PRO 140	Intravenous and Injectable	Phase III
	Albuvirtide	Intravenous and injectable	Approved in China
	bNAbs (e.g., VRC01)	Intravenous	Phase II/III
	Combinectin	Intravenous	Preclinical
Capsid Inhibitors	GS-CA1	Injectable	Preclinical

ATLAS and FLAIR: Long-Acting Intramuscular CAB + RPV After Initial Virologic Suppression With Oral Therapy

- Multicenter, randomized, open-label phase III noninferiority trials

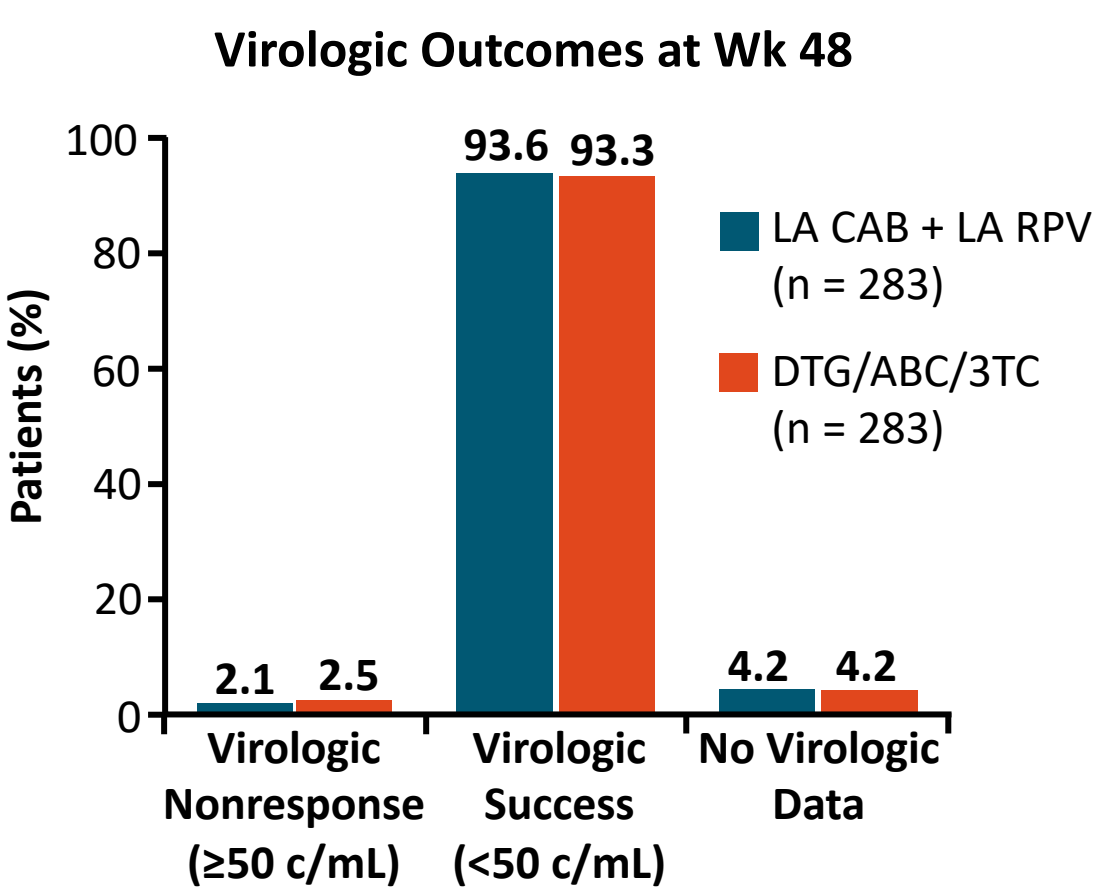


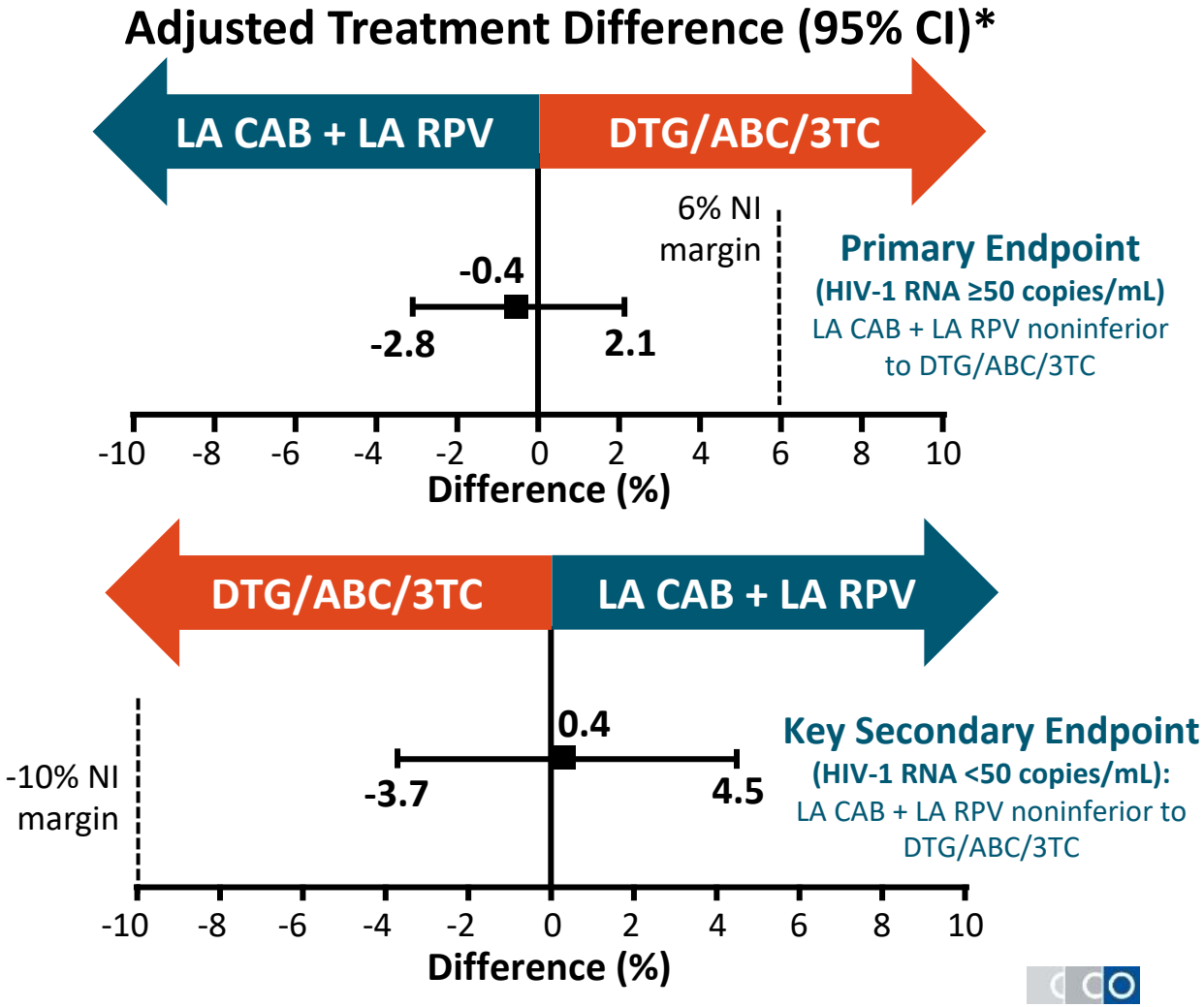
- Primary endpoint for both trials: HIV-1 RNA ≥50 copies/mL at Wk 48 by FDA Snapshot in ITT-E

1. Swindells. NEJM. 2020;382:1112. 2. Orkin. NEJM. 2020;382:1124.

Slide credit: clinicaloptions.com

FLAIR: LA CAB + RPV Maintenance After Oral DTG/ABC/3TC Induction





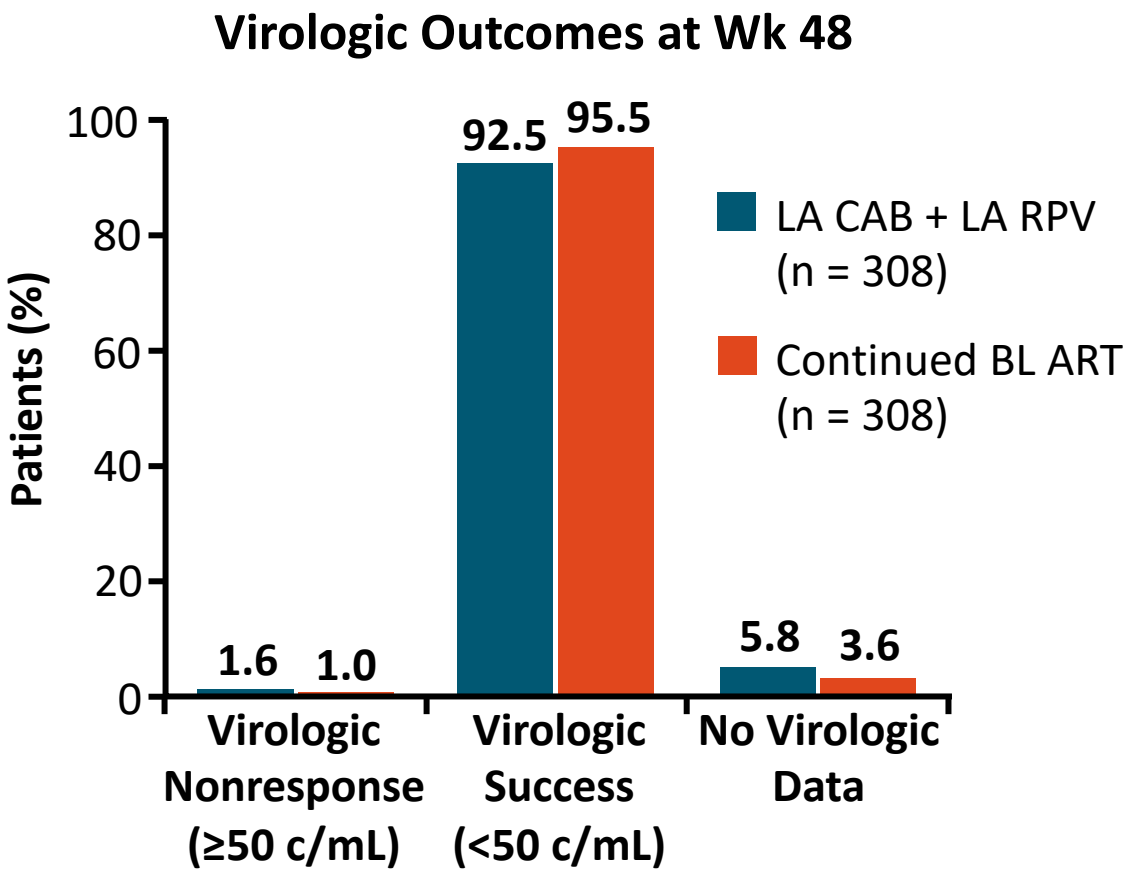
- Noninferiority also observed at Wk 96
- No additional CVF during Wk 48 to 96 in CAB + RPV arm

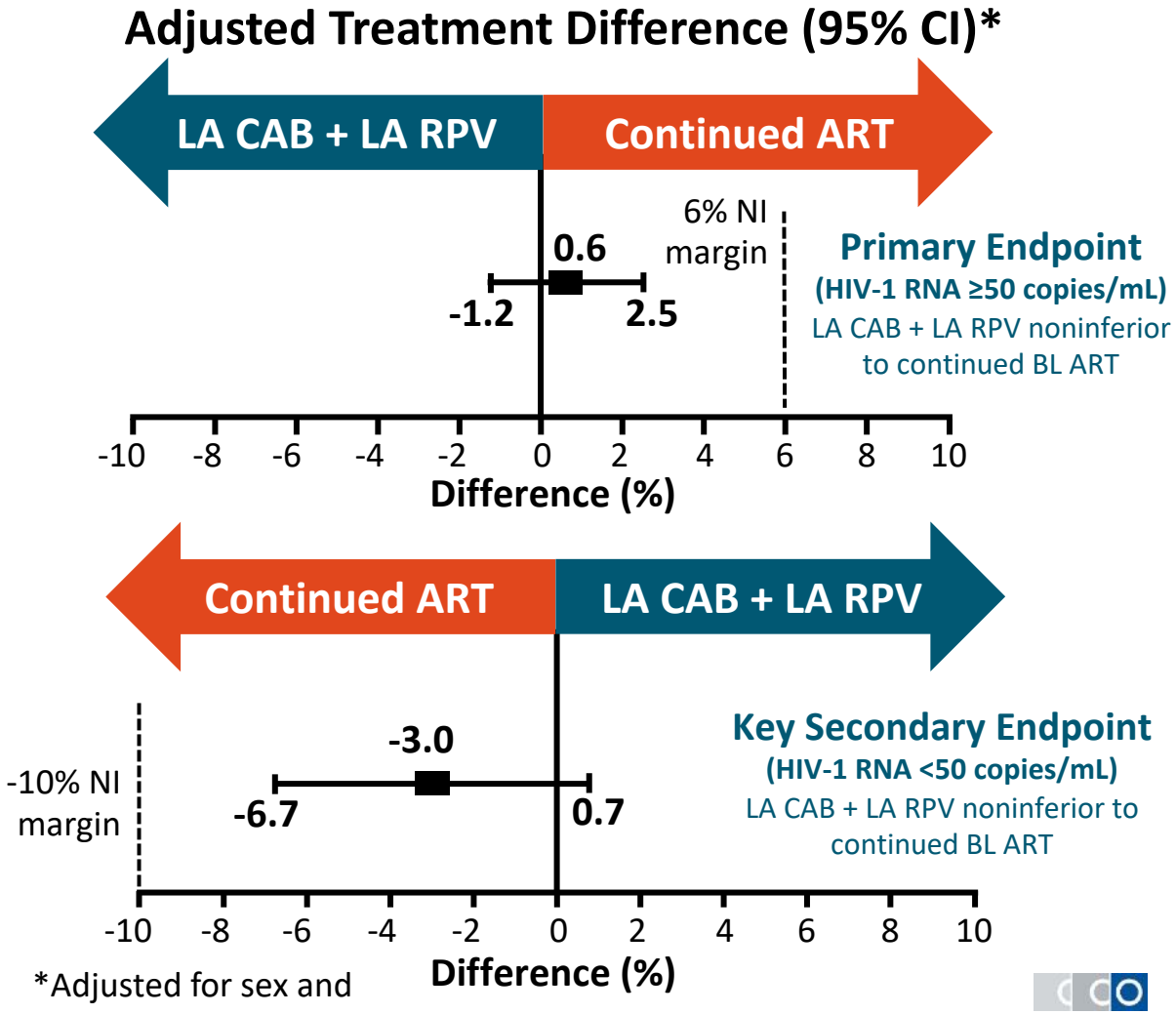
Orkin. NEJM. 2020;382:1124. Orkin. CROI 2020. Abstr 482LB.

*Adjusted for sex, BL HIV-1 RNA (<vs ≥100,000 c/mL).

Slide credit: clinicaloptions.com

ATLAS: Switch to LA CAB + RPV vs Continued 3-Drug ART in Virologically Suppressed Adults



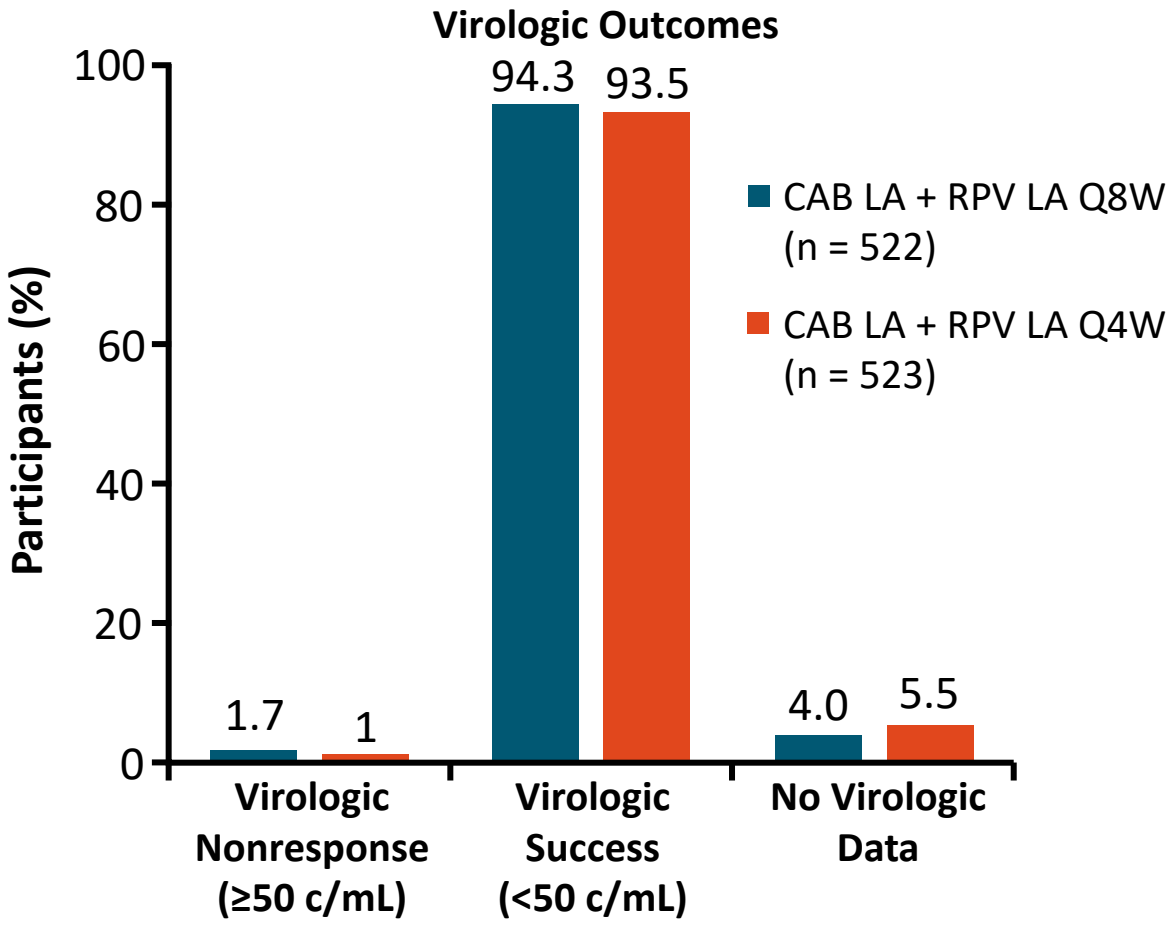


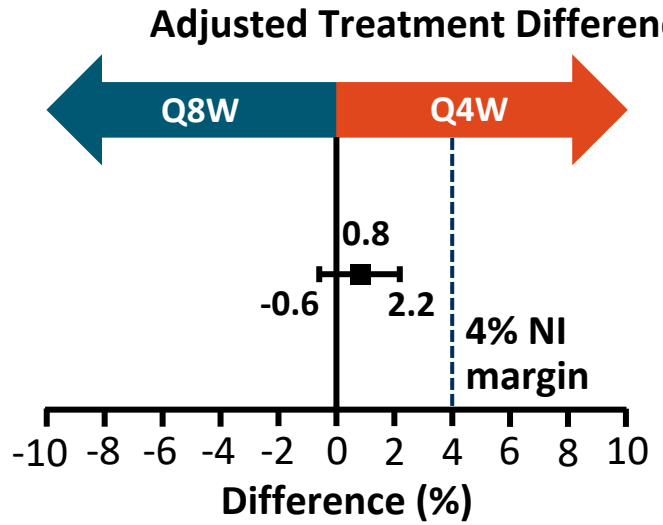
*Adjusted for sex and BL third agent class.

Swindells. NEJM. 2020;382:1112.

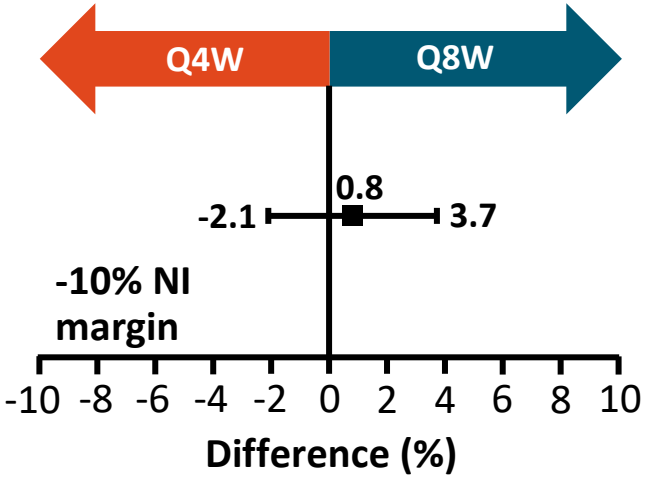
Slide credit: clinicaloptions.com

ATLAS-2M: Virologic Outcomes at Wk 48 in ITT-E by FDA Snapshot





Primary endpoint (HIV-1 RNA ≥50 c/mL): CAB LA + RPV LA Q8W noninferior to Q4W



Key secondary endpoint (HIV-1 RNA <50 c/mL): CAB LA + RPV LA Q8W noninferior to Q4W

*Based on Cochran-Mantel-Haenszel analysis adjusting for prior CAB + RPV exposure.

Overton. Lancet. 2021;396:1994.

Slide credit: clinicaloptions.com

Factors That May Contribute to Risk of Treatment Failure With Long-Acting CAB/RPV

- Post hoc analysis of phase III data (Wk 48)
  - ATLAS and FLAIR (Q4W dosing)
  - ATLAS-2M (Q4W and Q8W dosing)
- Backwards elimination model (10 covariates)
- Factors associated with increased odds of confirmed virologic failure:
  - RPV RAMs at baseline (OR: 40.36; *P* <.001)
  - Log_2 of post hoc Wk 8 RPV trough concentration (OR: 5.00; *P* = .002)
  - Baseline HIV-1 subtype A6/A1 (OR: 5.92; *P* = .008)
  - BMI ≥30 kg/m^2 at baseline (OR: 1.13; *P* = .020)
- Q8W dosing was not a significant factor

Baseline Factors	Patients, % (n)*	CVF, % (n)	HIV-1 RNA <50 c/mL, % (n)
None	70.5 (732)	0.41 (3)	94.8 (694)
1	26.2 (272)	0.37 (1)	96.0 (261)
≥2	3.37 (35)	25.71 (9)	71.4 (25)

*For CVF analysis, N = 1039

Cutrell. AIDS. 2021;[Epub].

Slide credit: clinicaloptions.com

NUEVOS MECANISMOS DE ACCIÓN

CD4 Cell Receptor Attachment
gp120 (V1,V2 loop) initially binds to CD4 (weak) inducing conformational change and V3 loop exposure

Co-receptor Binding
Rapid binding to chemokine co-receptor stabilises attachment and exposes gp41 fusion peptide

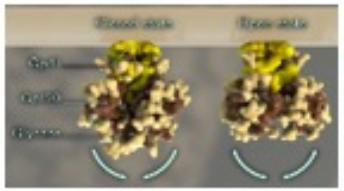
Membrane Fusion
gp41 hairpin folding enables viral-cell membrane fusion

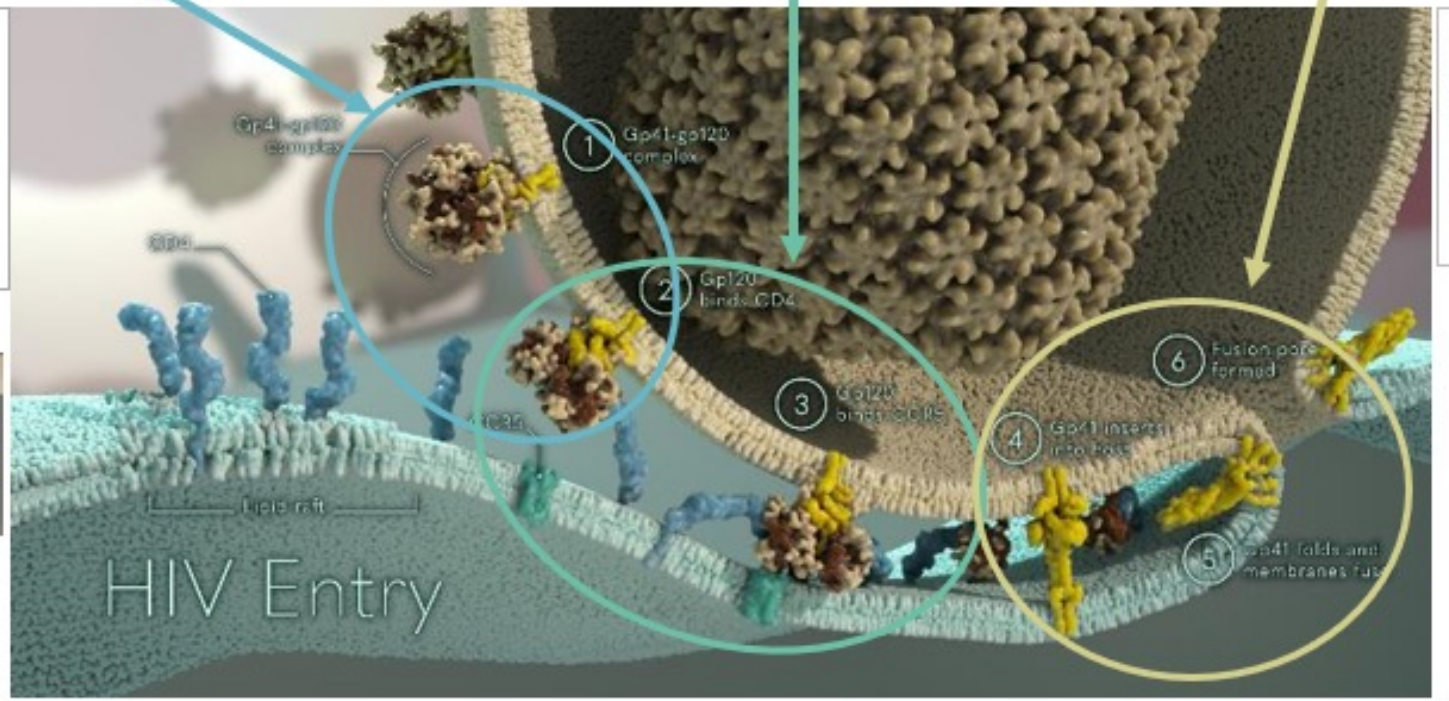
Gp120 Fostemsavir

CD4 (Ibalizumab) CCR5 (Maraviroc)

gp41 (Enfuvirtide)

gp120 oscillates between different conformations. TMR binds gp120 and "locks" it into the closed conformation (state 1), and is unable to attach to CD4.





Key
1. Nascent gp120-g41complex
2. gp120 binds to CD4
3. gp120 binds CCR5
4. gp41 inserts into host
5. gp41 folds/membranes fuse
6. Fusion pore formed

Click to add footnotes

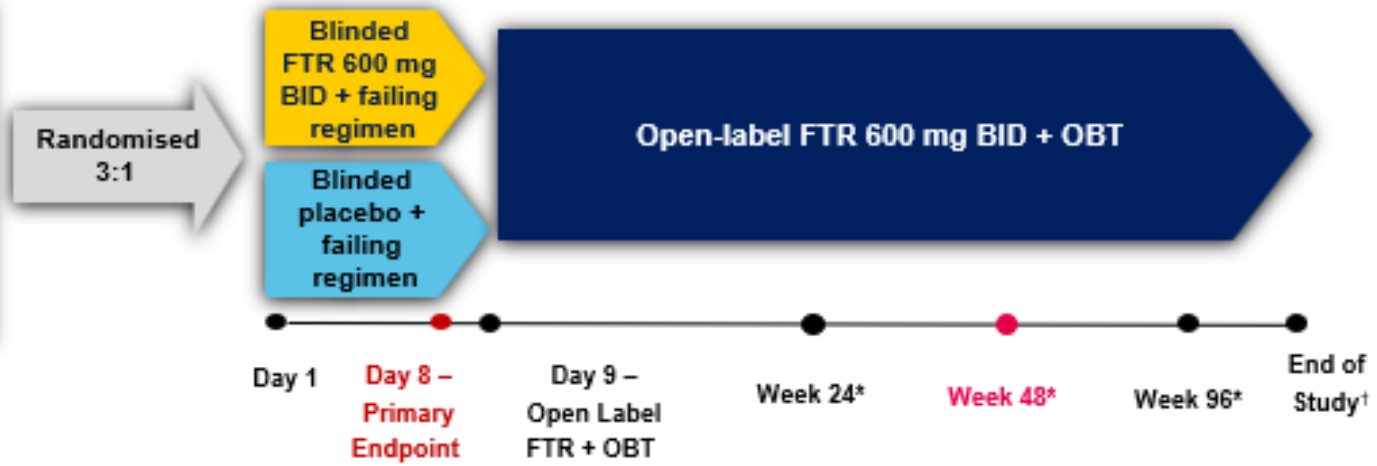
Wilen B, et al. Cold Spring Harb Perspect Med 2012;2:a006866

Phase III Study: Study Design and Endpoints

BRIGHTE

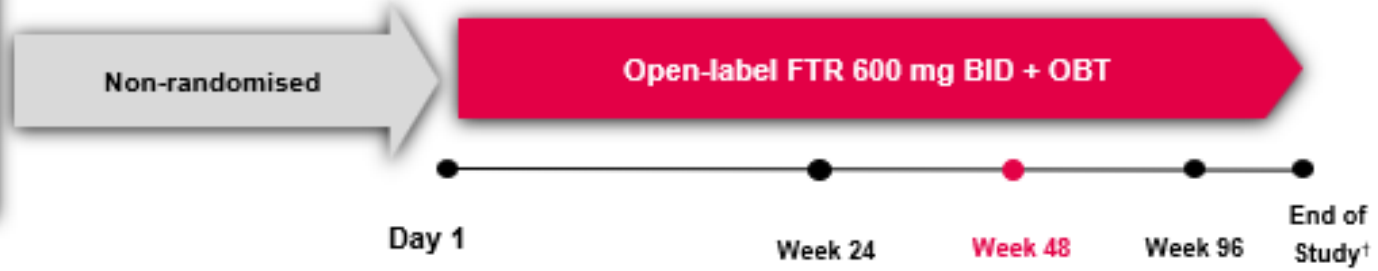
Randomised Cohort §:
HTE participants failing current regimen with confirmed HIV-1 RNA ≥ 400 c/mL and:

- 1 or 2 ARV classes remaining & ≥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 ≥ 400 c/mL and:

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

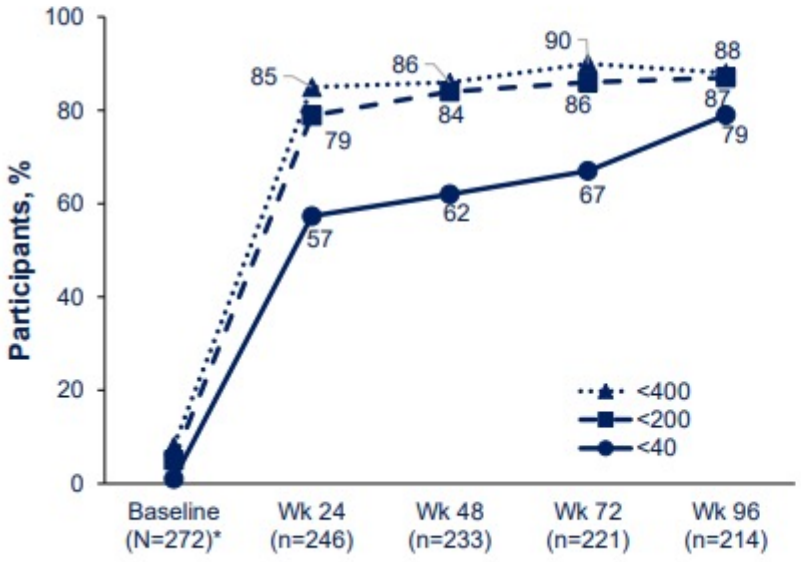


FOSTEMSAVIR

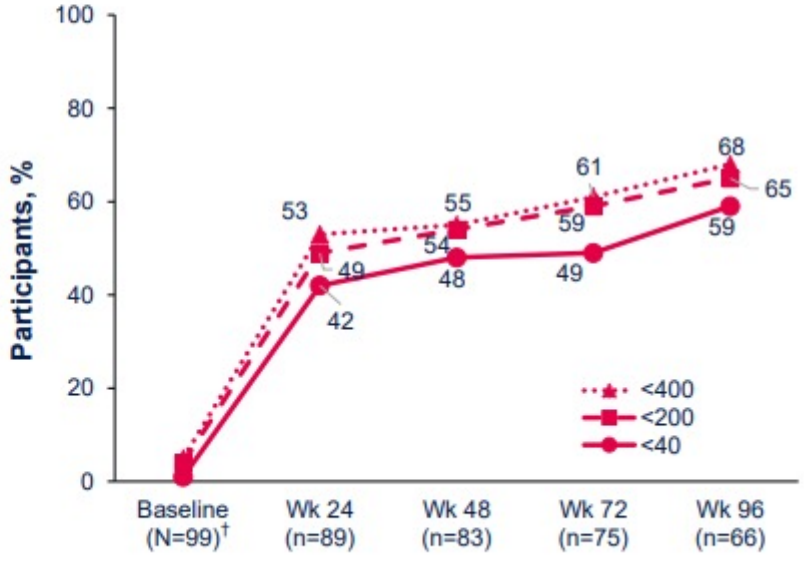
BRIGHTE: Virologic Response Over Time (Observed Analysis)

BRIGHTE

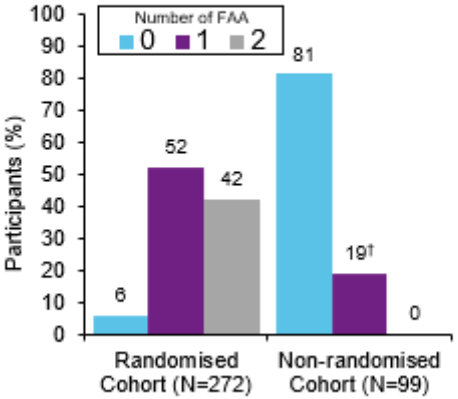
Randomized cohort (N=272)[1]



Non-randomized cohort (N=99)[1]

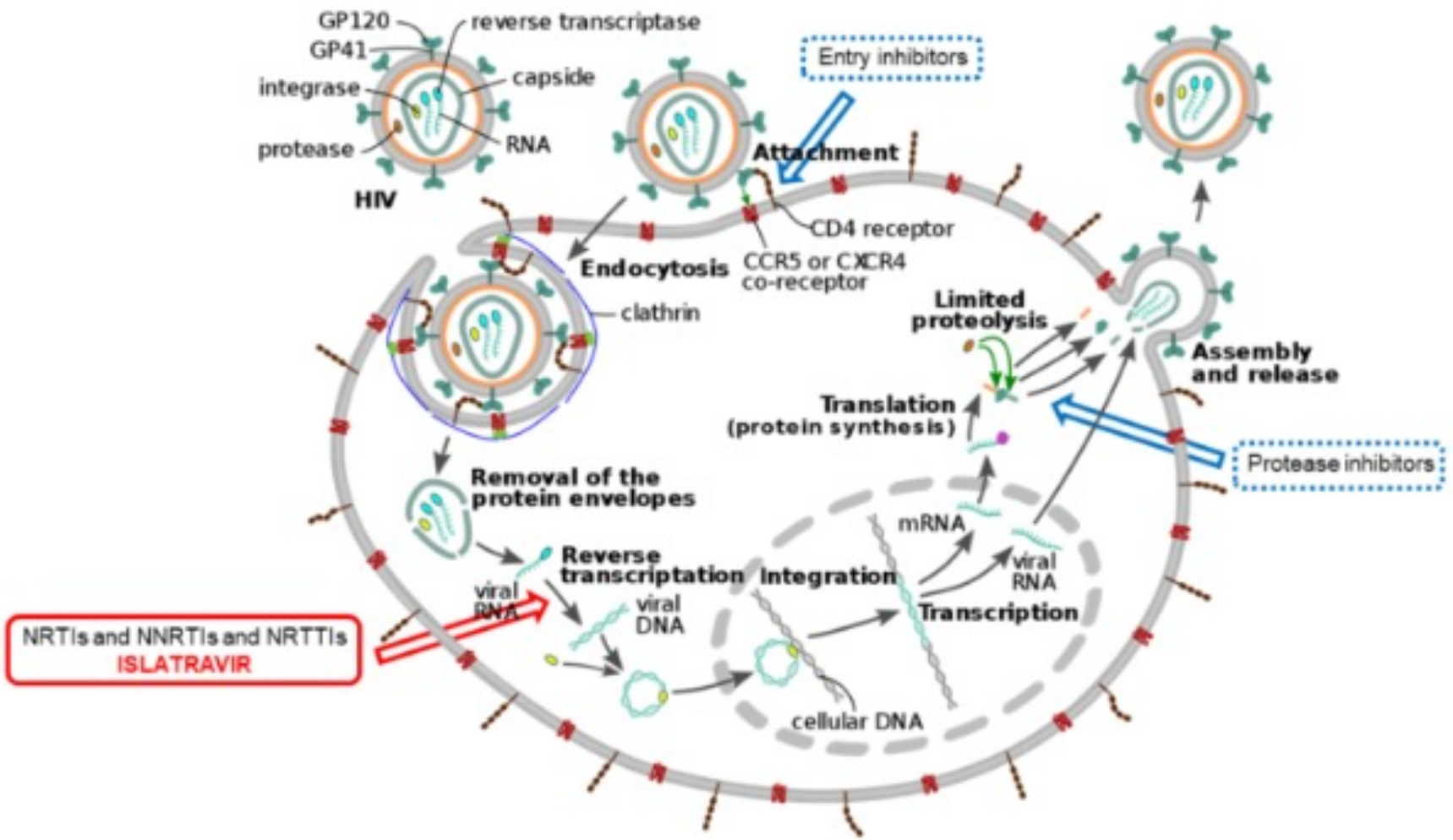


Fully Active and Available ARV (FAA) in initial OBT



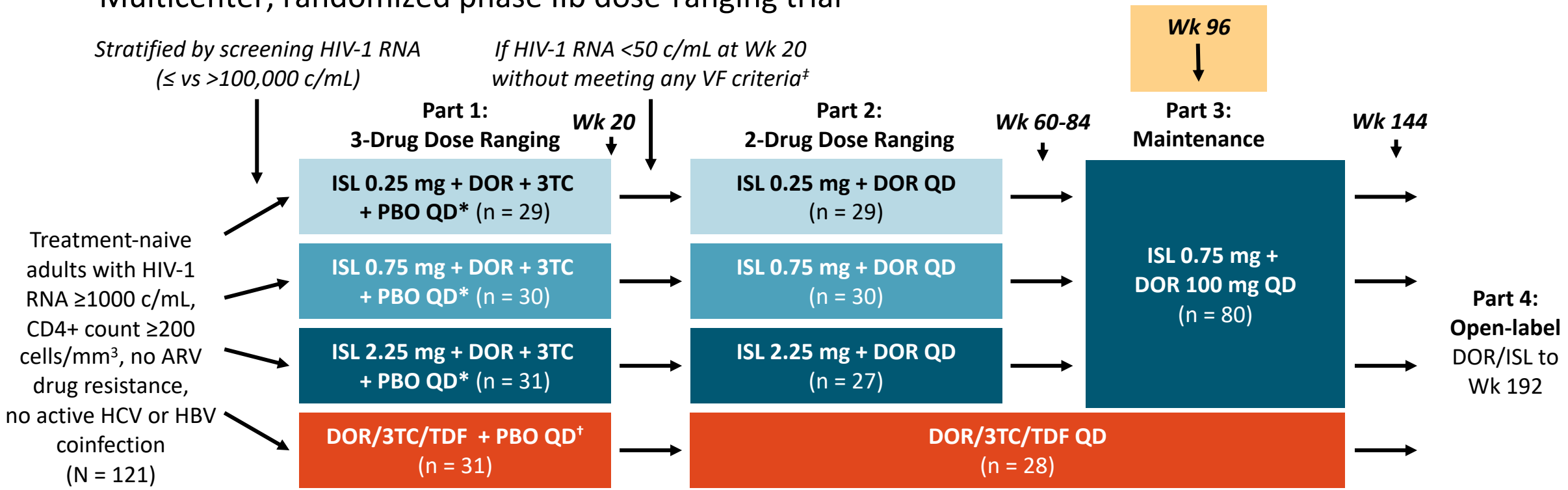
*At baseline 8 participants had HIV-1 RNA <400 c/mL, 5 had HIV-1 RNA <200 c/mL, and 1 had HIV-1 RNA <40 c/mL[2]
†At baseline 5 participants had HIV-1 RNA <400 c/mL, 4 had HIV-1 RNA <200 c/mL, and 1 had HIV-1 RNA <40 c/mL[2]

1. Lataillade M, et al. Lancet HIV 2020;7:e740–51
2. Lataillade M, et al. IAS 2019. Oral MOAB0102


GP120
GP41
integrase
protease
reverse transcriptase
capside
RNA
HIV
Entry inhibitors
Attachment
CD4 receptor
CCR5 or CXCR4
co-receptor
Endocytosis
clathrin
Limited
proteolysis
Assembly
and release
Translation
(protein synthesis)
Protease inhibitors
Removal of the
protein envelopes
mRNA
Reverse
transcriptation
viral
RNA
viral
DNA
Integration
viral
RNA
Transcription
NRTIs and NNRTIs and NRTTIs
ISLATRAVIR
cellular DNA

Protocol 011 Islatravir + Doravirine in Treatment Naive Adults: Wk 96 Safety Analysis

- Multicenter, randomized phase IIb dose-ranging trial



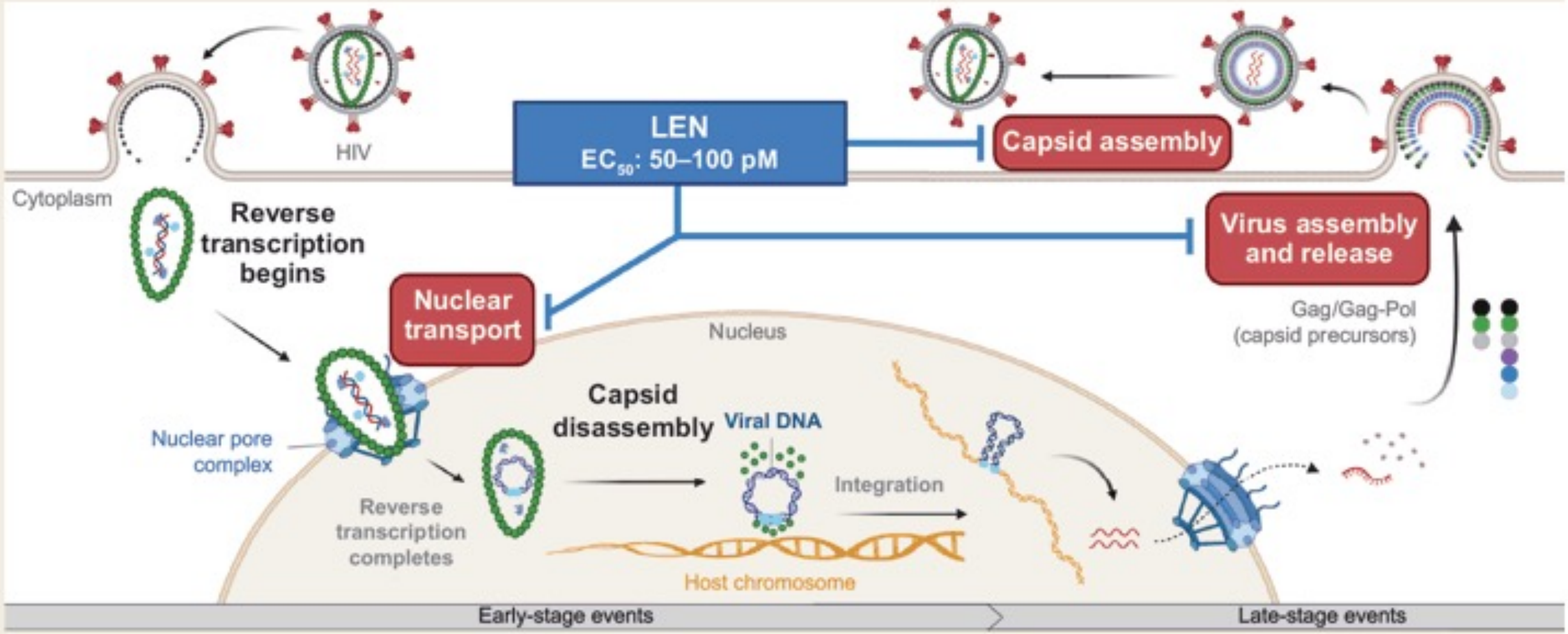
*Received placebo for DOR/3TC/TDF. †Received placebo for ISL + DOR + 3TC. ‡If HIV-1 RNA ≥50 c/mL at Wk 20, continued Part 1 until HIV-1 RNA <50 c/mL and, if not meeting any VF criteria, transitioned to Part 2.

- Baseline participant characteristics (ISL combined groups vs DOR/3TC/TDF)[2]: male (93.3% vs 90.3%), White race (75.6% vs 77.4%), Black race (21.1% vs 16.1%), median age (28.5 vs 27.0 yr)

1. Cunningham. IAS 2021. Abstr OAB0304. 2. Molina. Glasgow 2020. Abstr P0415.

Slide credit: clinicaloptions.com

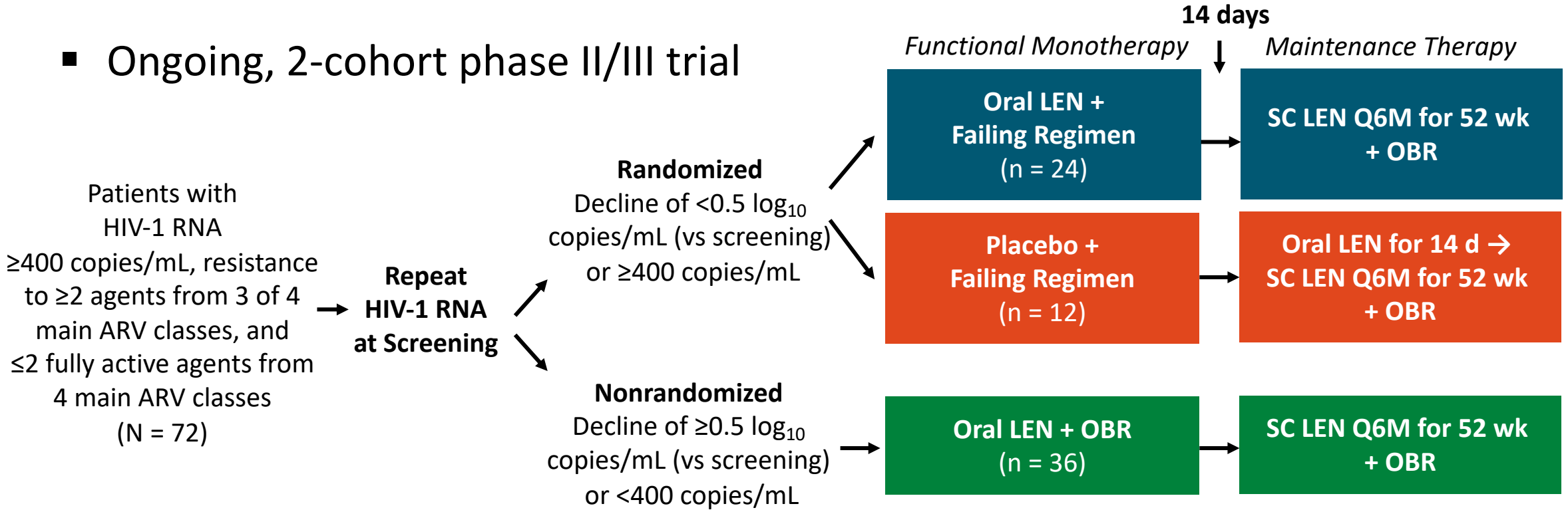
Lenacapavir Targets Multiple Stages of HIV Replication Cycle[1,2]



EC_{50}, half-maximal effective concentration; Gag, group antigens; LEN, lenacapavir; Pol, polymerase.

CAPELLA: Study Design

- Ongoing, 2-cohort phase II/III trial



Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15 and Q6M thereafter.

- Current analysis: safety and efficacy (FDA Snapshot) of LEN + OBR at Wk 26 and 52

Ogbuagu. CROI 2022. Abstr 491.

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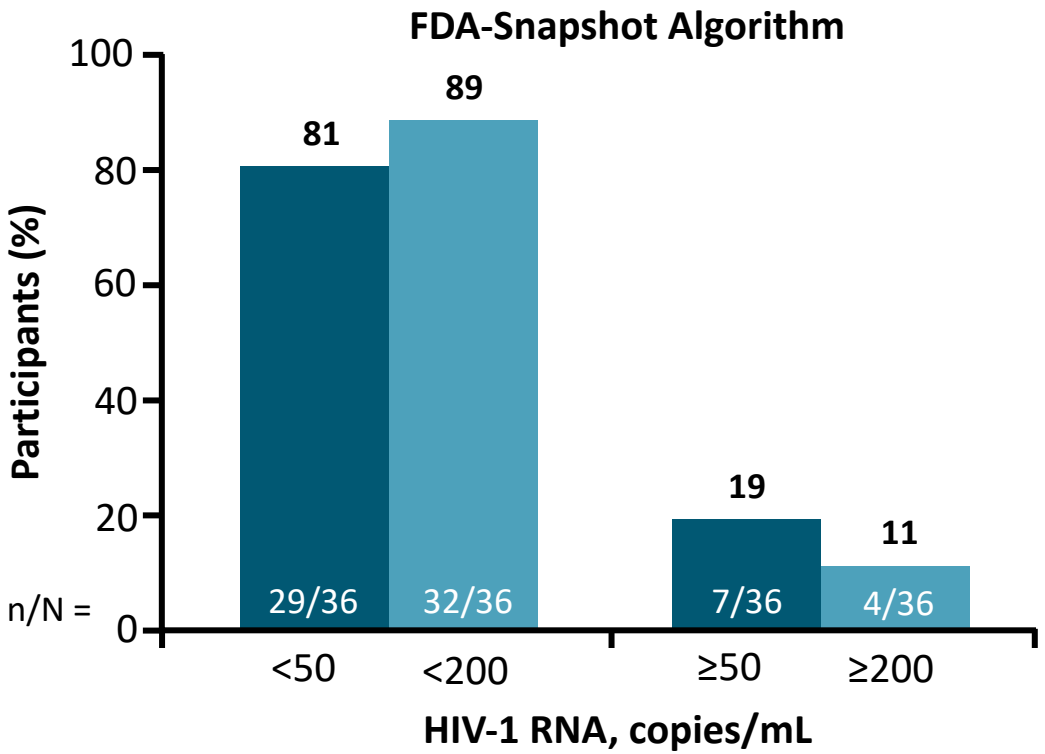
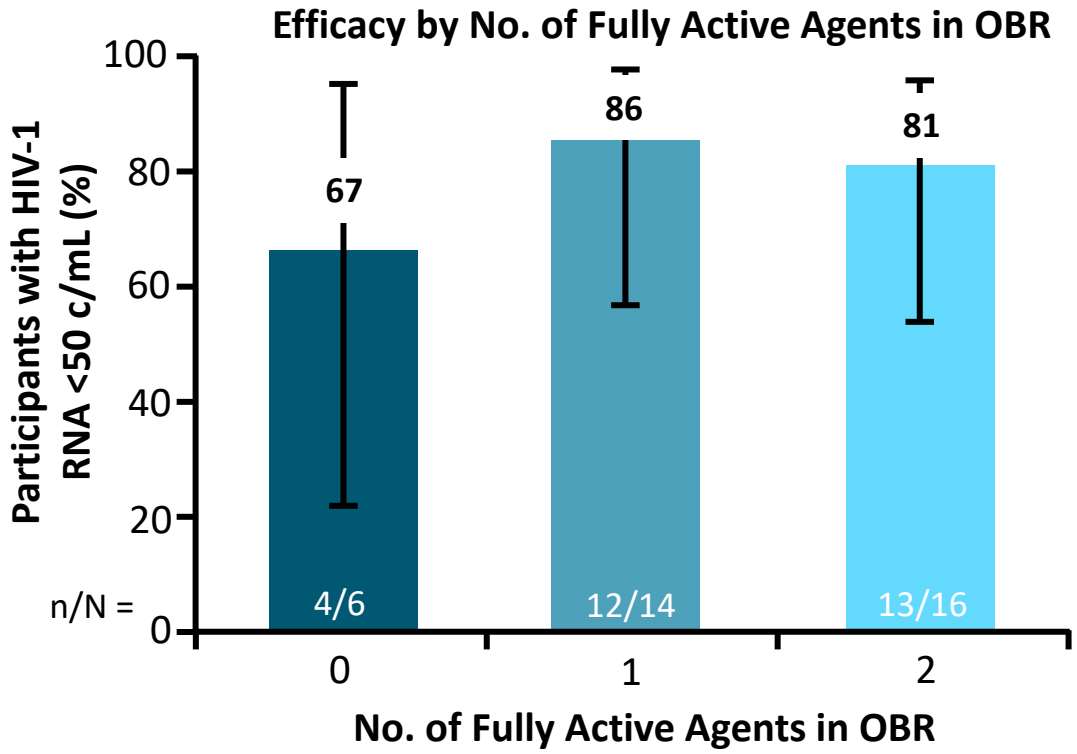
CAPELLA Secondary Endpoints: Wk 26 Efficacy in Randomized Cohort



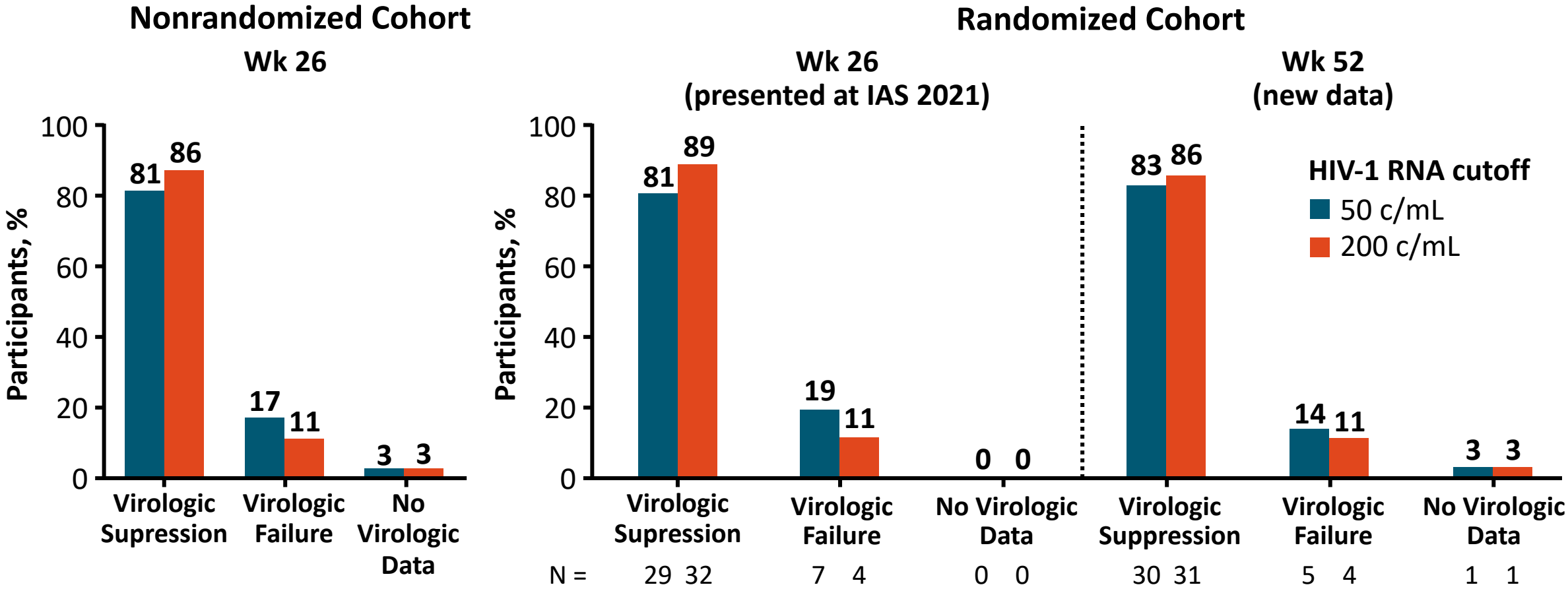


- **Mean change in CD4+ cell count: +81 cells/mm^3**
- Proportion of participants with very low CD4+ cell count (<50 cells/mm^3) **decreased from 22% (8 of 36) at baseline** to **0% (0 of 34) at Wk 26**

Molina. IAS 2021. Abstr OALX01LB02.

Slide credit: clinicaloptions.com

CAPELLA: LEN Efficacy at Wk 26 and 52



- CD4+ count increased by 83 cells/mm³ at Wk 52 in randomized cohort

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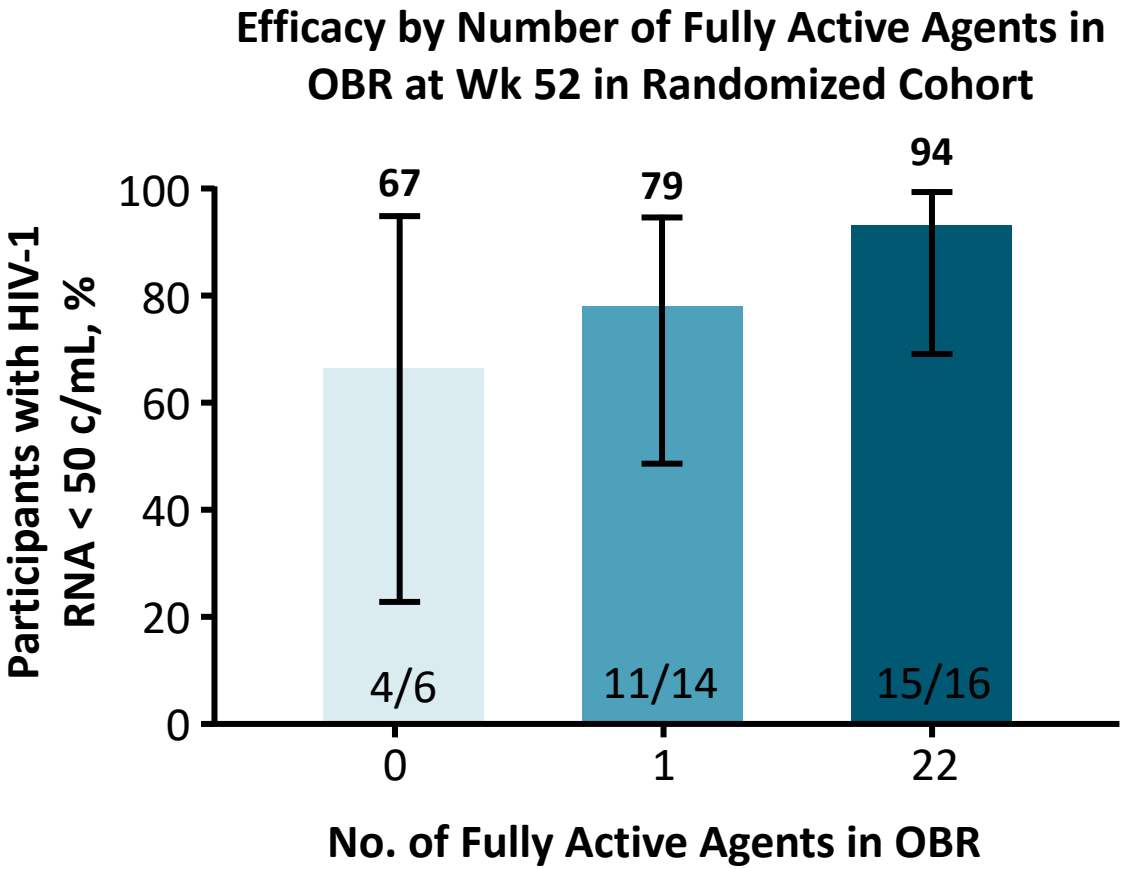
CAPELLA: LEN Efficacy by Fully Active Agents and Emergent Resistance



Emergent LEN Resistance, n (%)	Randomized Cohort (n=36)	Nonrandomized Cohort (n =36)
Participants meeting criteria for resistance testing	11 (31)	10 (28)
Emergent LEN resistance	4 (11)	4 (11)
▪ M661	4	2
▪ Q67H/K/N	1	2
▪ K70H/N/R/S	1	3
▪ N74D/H/S	3	0
▪ A105S/T	3	1
▪ T107A/C/N	1	3

- All 8 persons with emergent LEN resistance were high risk for resistance (0 active drugs in OBR, n = 4; inadequate adherence to OBR, n = 4)

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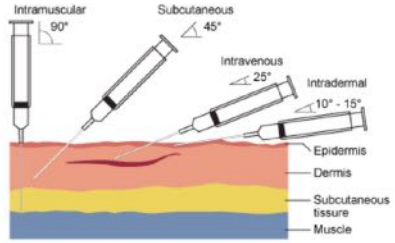
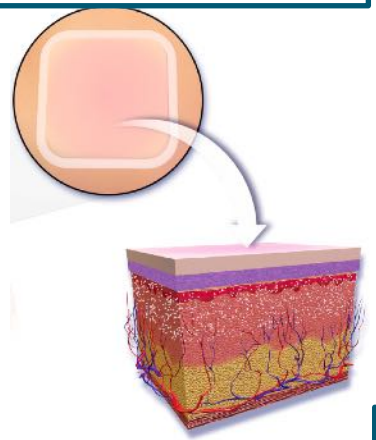
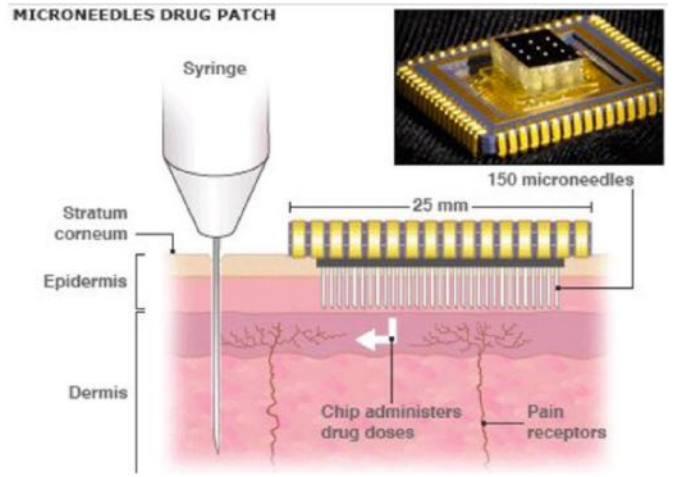
Technology for Drug Delivery

Long-acting depot injections

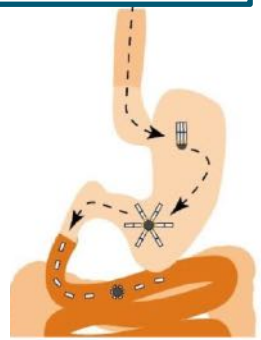


Microneedle drug patch

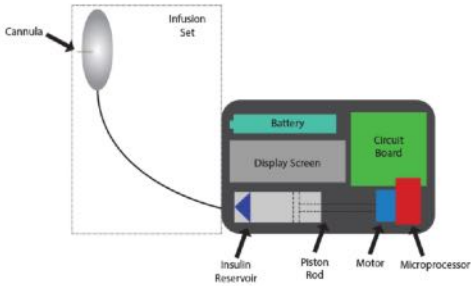




Novel oral formulations



Wearable infusion pump



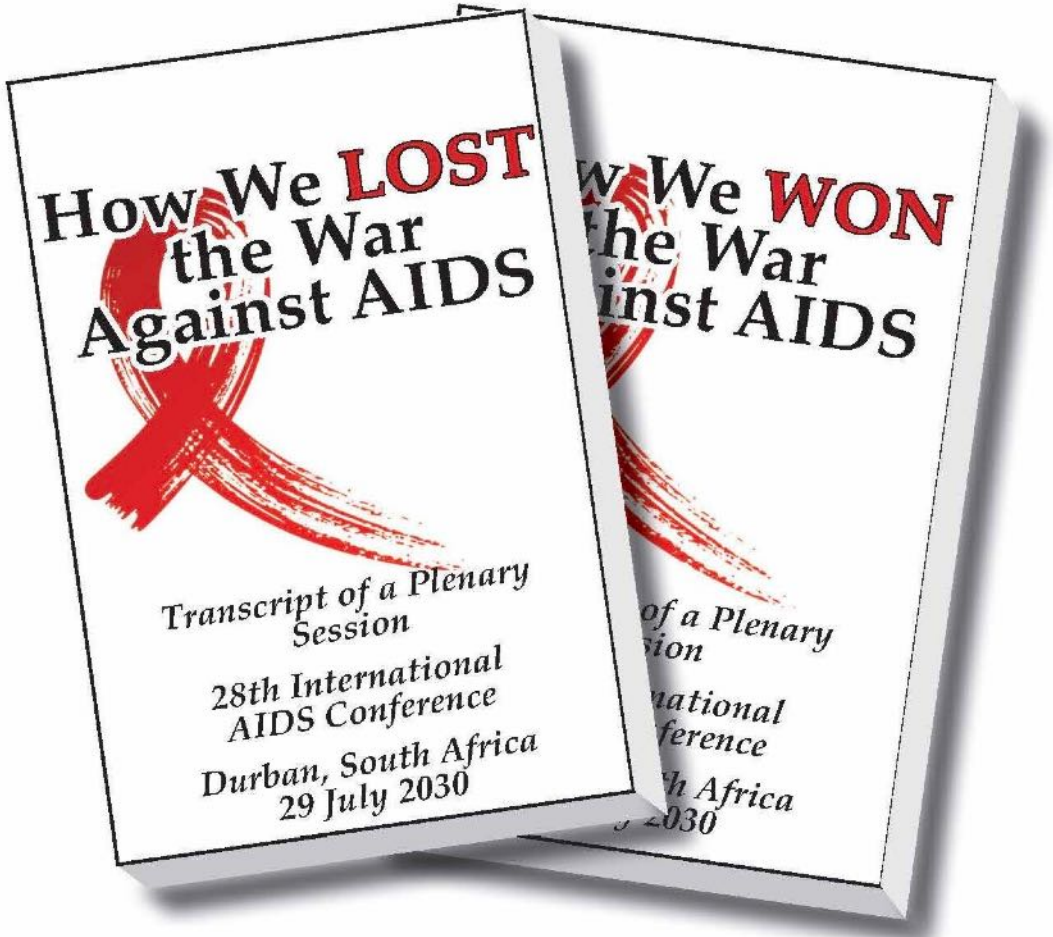
Vaginal rings

Subdermal implant

Thanks to Kim Scarsi

HIV and AIDS in 2030

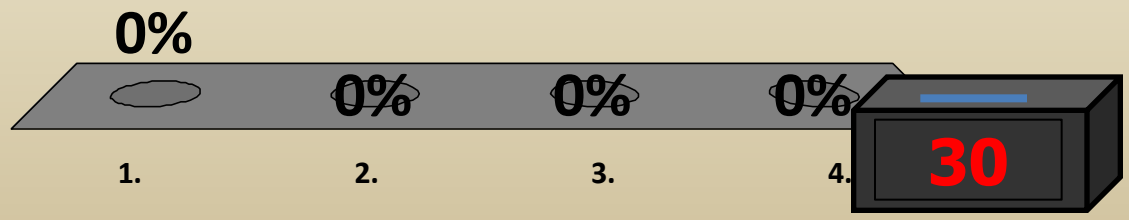
A Choice Between Two Futures



Concurre un paciente a la consulta , refiriendo resultado de testeo rápido para HIV positivo, con una carga viral confirmatoria de 123.000 copias/ml , con CD4 : 50 cels/ ml , refiere intensa cefalea y malestar general desde que recibió su diagnóstico . ¿Cuál es su conducta?

1. Indica inicio inmediato de tratamiento antiretroviral
2. Inicia plan de estudio para descartar infecciones oportunistas
3. Explica al paciente las alternativas actuales, para que el mismo decida el momento de inicio de tratamiento
4. Solicita carga viral confirmatoria y nuevo CD4 para decidir la conducta terapéutica

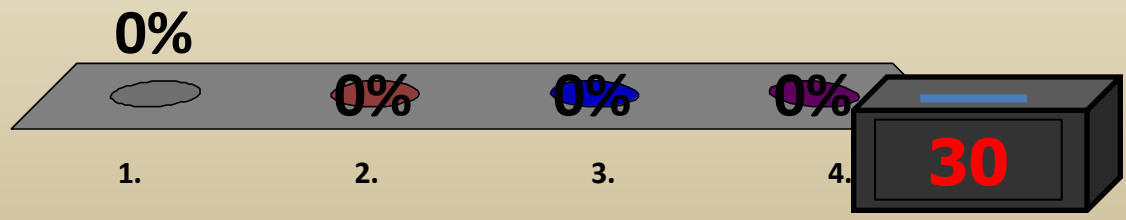
Contador de contestaciones



Cual de los siguientes enunciados es incorrecto en cuanto a la indicación de terapia dual con dolutegravir y lamivudina?

1. No debe indicarse a pacientes con mutaciones a lamivudina en el test de resistencia basal
2. No debe indicarse en pacientes con hepatitis B
3. No debe indicarse en mujeres embarazadas
4. No debe indicarse a mayores de 50 años

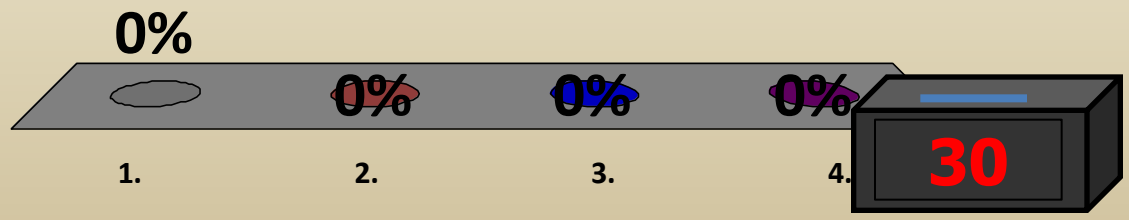
Contador de contestaciones



Cuáles son los objetivos del tratamiento antiretroviral ?

1. Lograr una Supresión virológica máxima y continua
2. Reducir la actividad inflamatoria
3. Preservar la vida y la salud con la menor alteración en la calidad de vida
4. Todas son correctas

Contador de contestaciones



GRACIAS !