19ª edición

POSTCROI

Nuevos fármacos, estrategias terapéuticas y PrEP

Judit Villar García
Hospital del Mar, Barcelona

19ª edición

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CROI 2022

CONTENIDO:

- Nuevos fármacos
- Nuevas estrategias terapéuticas
- PrEP

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CONTENIDO:

- **Nuevos fármacos**
- **Nuevas estrategias terapéuticas**
- **PrEP**

Opening Session

Plenary Sessions

Oral Abstract Sessions

Interactive Sessions

Poster Sessions

Symposia

Workshops

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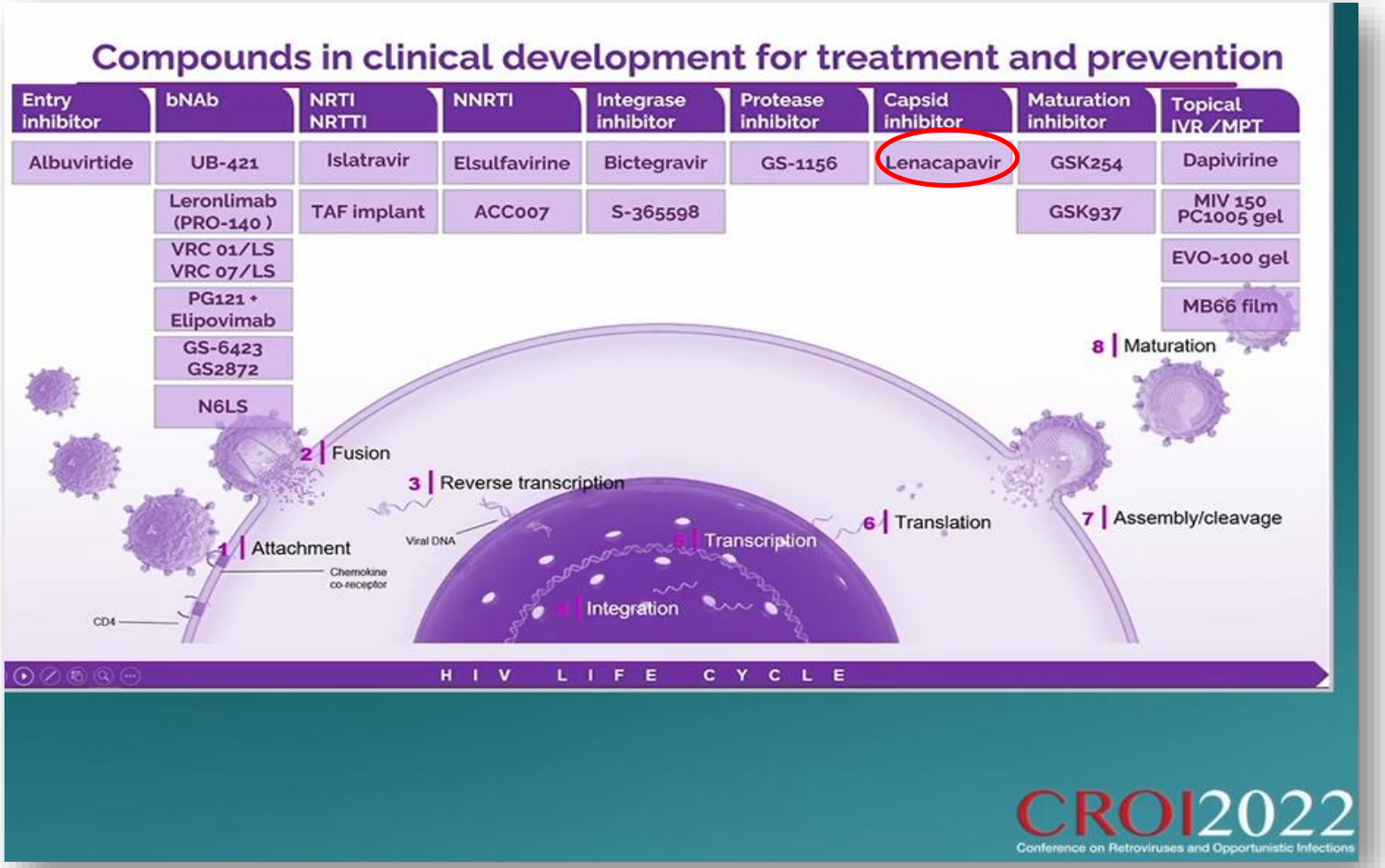
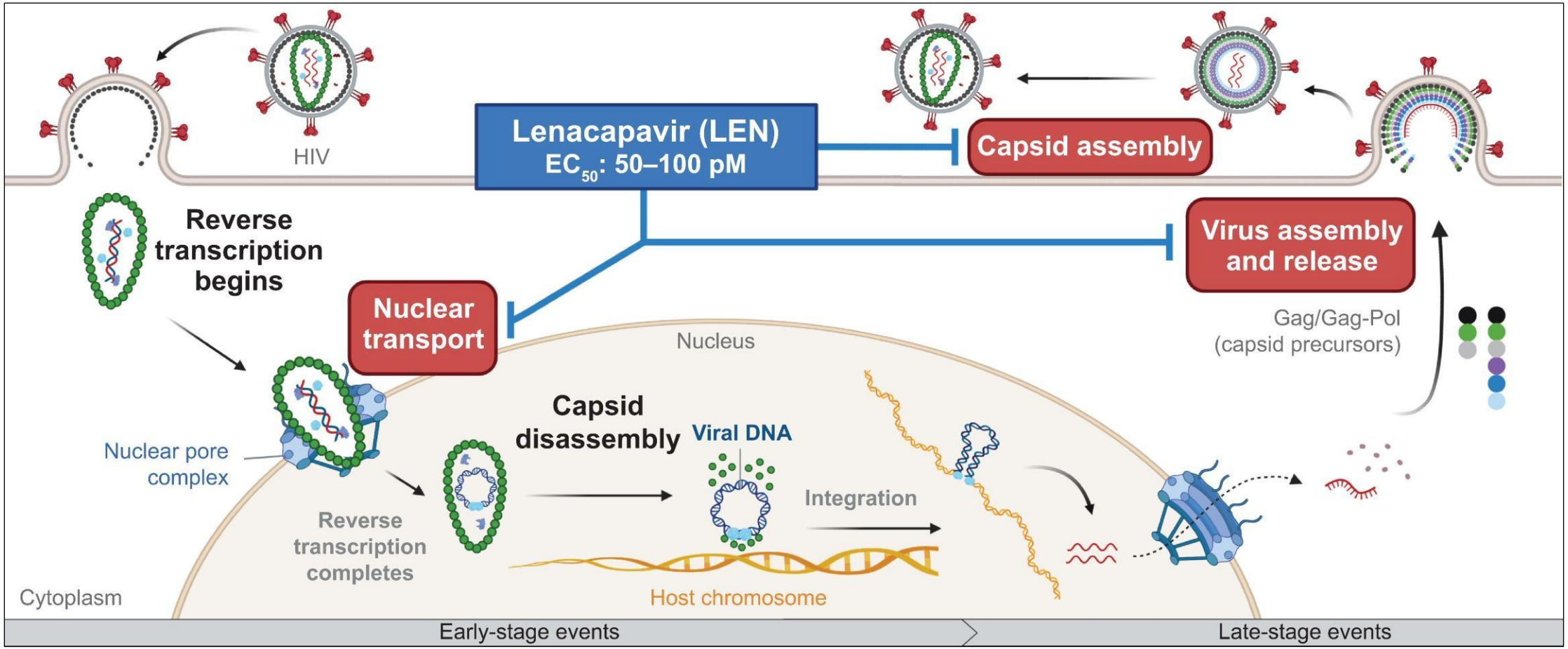
Nuevos **fármacos**



LEN Targets Multiple Stages of HIV Replication Cycle



EC_{50}, half-maximal effective concentration.

Link JO, et al. Nature 2020;584:614-8; Bester SM, et al. Science 2020;370:360-4.

S Gupta Oral Session #68

Introduction

- Lenacapavir (LEN, GS-6207) is a long-acting first-in-class inhibitor of HIV-1 capsid protein
  - In clinical development for treatment and prevention of HIV-1 infection
- Highly potent activity (EC_{50}: 50–100 pM), with a low clearance and slow release kinetics[1]
  - Can be administered orally (daily or weekly) or subcutaneously (every 6 months)[2-4]
- CALIBRATE was designed to generate exploratory clinical data to support the future development of LEN-containing regimens

Capella	Phase 2/3 in heavily Tx-experienced PWH[5,6]	LEN + OBR	Week 52	83% virologic suppression (CROI 2022)[7]
Calibrate	Phase 2 in Tx-naïve PWH[8]	LEN + F/TAF	Week 28	94% virologic suppression

F/TAF, emtricitabine/tenofovir alafenamide; OBR, optimized background regimen; PWH, people with HIV; Tx, treatment.

1. Link JO, et al. Nature 2020;584:614-8; 2. Begley R, et al. AIDS 2020, abstr PEB0265; 3. Begley R, et al. CROI 2020, abstr 470; 4. Daar E, et al. CROI 2020, abstr 469; 5. Segal-Maurer S, et al. CROI 2021, abstr 127; 6. Molina J-M, et al. IAS 2021, abstr OALX01LB02; 7. Ogbuagu O, et al. CROI 2022, abstr 1047; 8. Gupta SK, et al. IAS 2021, abstr OALB0302.

Study Design

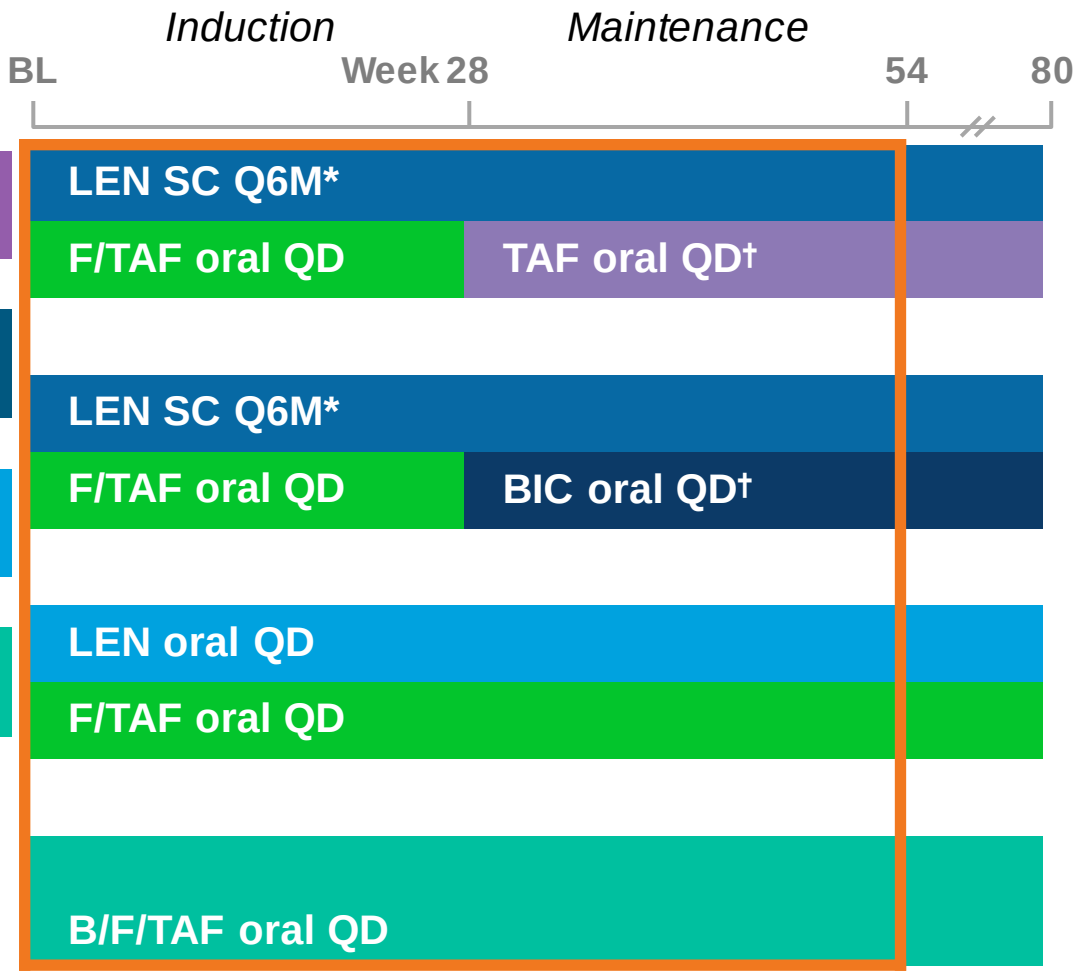
Treatment naïve
N=182

Key eligibility criteria:

- ARV naïve
- HIV-1 RNA ≥200 copies/mL
- CD4+ cell count ≥200 cells/µL

Open label

Randomized



15% >100.000 copias
Mediana Cd4: 430 cél/ml

*LEN oral lead-in (600 mg on Days 1 and 2, 300 mg on Day 8) followed by LEN SC 927 mg on Day 15; F/ TAF 200/25 mg; †Participants in TG 1 and 2 will need HIV-1 RNA results <50 copies/mL at Weeks 16 and 22 to initiate either TAF 25 mg or BIC 75 mg at Week 28; those with HIV-1 RNA ≥50 copies/mL will discontinue study at Week 28; ‡LEN 600 mg on Days 1 and 2, followed by LEN 50 mg from Day 3; F/TAF 200/25 mg; §B/F/TAF 50/200/25 mg.

ARV, antiretroviral; BIC, B, bictegravir; BL, baseline; QD, once daily; Q6M, every 6 months; SC, subcutaneous; TG, treatment group.

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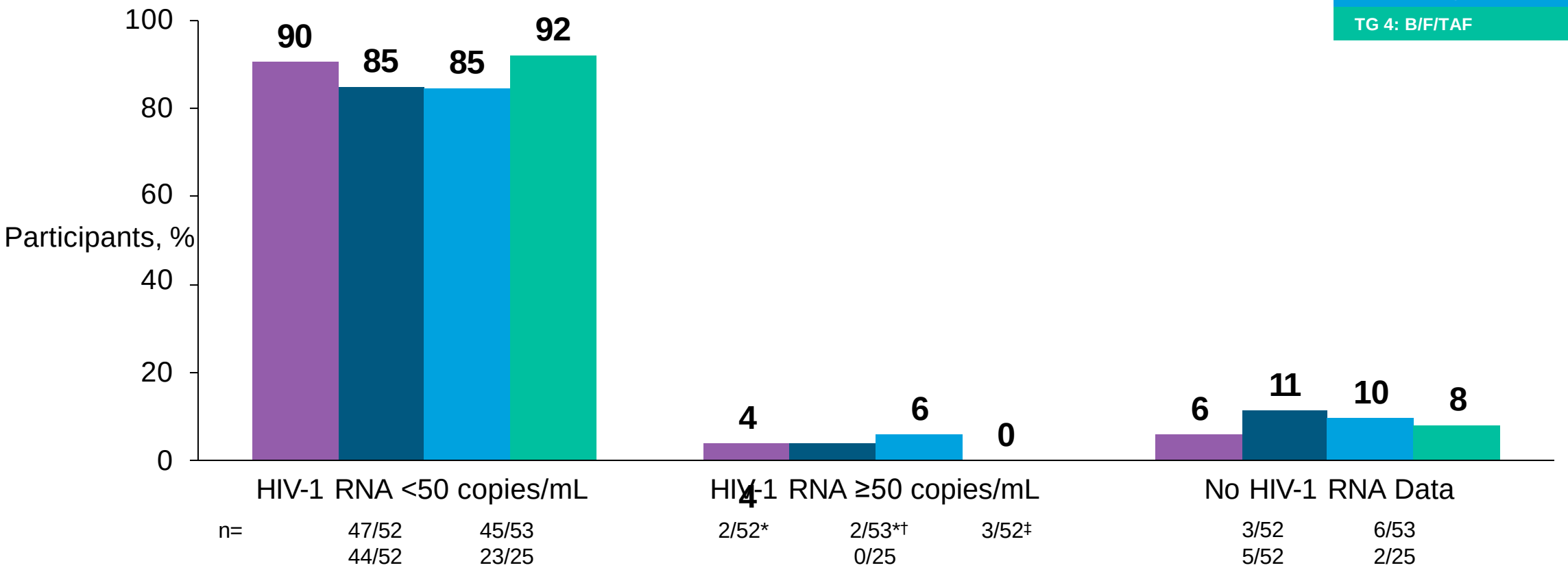
Efficacy at Week 54 (FDA Snapshot)



- In the pooled SC LEN group (TG 1+2: initially in combination with F/TAF, then with TAF or BIC), 88% (92/105) achieved and maintained virologic suppression at Week 54

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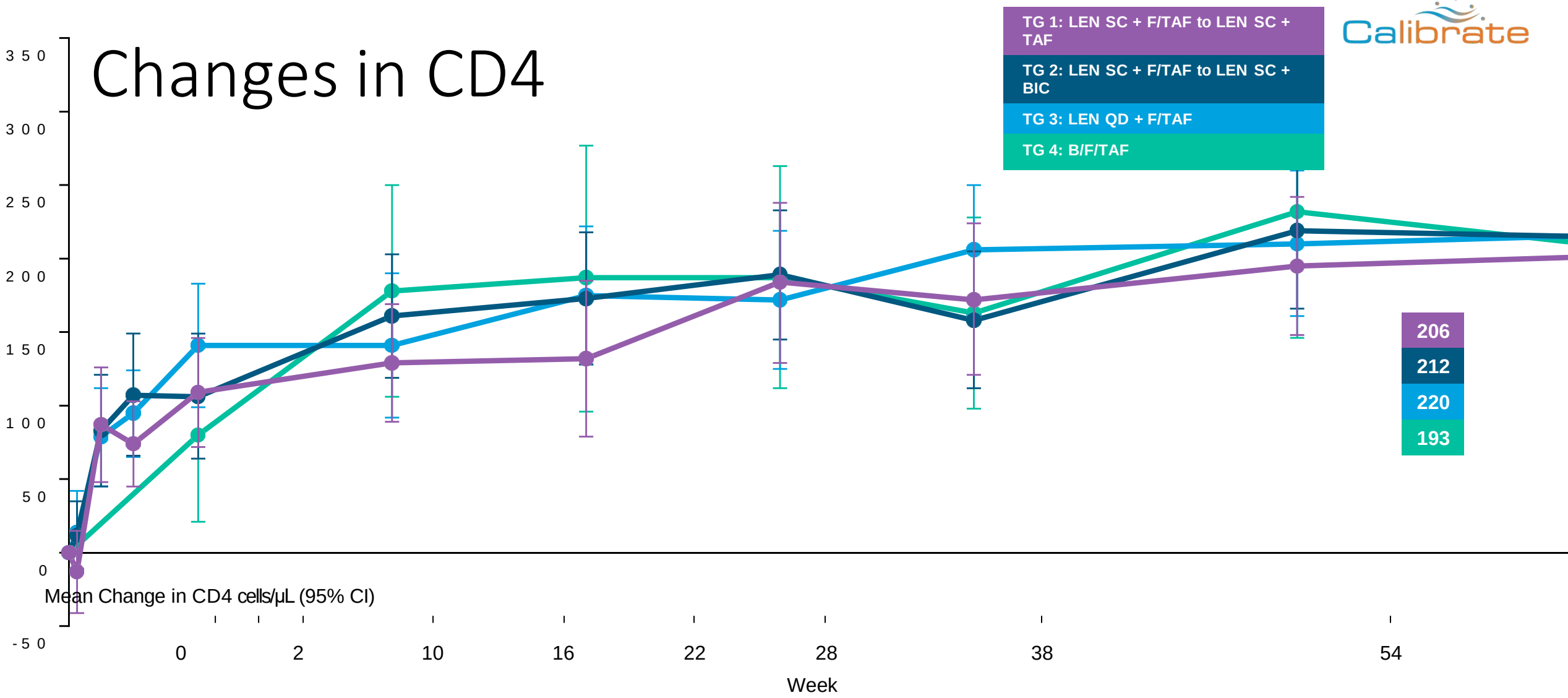
*3 participants (2 in TG 1 and 1 in TG 2) discontinued due to not meeting the protocol criteria of having HIV-1 RNA <50 copies/mL prior to Week 28;
†1 participant discontinued on Day 2; ‡2 of the 3 participants with HIV-1 RNA ≥50 copies/mL at Week 54 were suppressed in subsequent visit.

Changes in CD4



- Baseline CD4 of the overall study population: median 437 cells/µL

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Resistance Analysis*

Calibrate

TG 1: LEN SC + F/TAF to LEN SC + TAF
TG 2: LEN SC + F/TAF to LEN SC + BIC
TG 3: LEN QD + F/TAF
TG 4: B/F/TAF

Participants, n	TG 1 n=52	TG 2 n=53	TG 3 n=52	TG 4 n=25
Participants meeting the resistance testing criteria	1	1	3	1
Emergent LEN resistance	0	1	1	0

- Emergent LEN resistance in 2/157 (1.5%) participants
  - One participant in TG 2 developed Q67H+K70R (LEN fold change=20) in CA at Week 10, preceded by M184M/I in RT (IDWeek 2021)†
    - Pattern of mutation emergence suggests incomplete adherence to F/TAF
  - One participant in TG 3 developed Q67H (LEN fold change=7) in CA at Week 54
    - Nonadherence to F/TAF as assessed by pill count and drug levels
  - Both participants later re-suppressed on a regimen of INSTI + 2 NRTI

*Genotypic and phenotypic resistance testing performed on any participants with confirmed HIV-1 RNA ≥50 copies/mL and <1 $\log_{10}$ HIV-1 RNA reduction from Day 1 at the Week 10 visit, at any visit after achieving HIV-1 RNA <50 copies/mL and a rebound to ≥50 copies/mL, and at any visit, with >1 $\log_{10}$ increase from the nadir; †Previously presented (Gupta SK, et al. IAS 2021, abstr OALB0302, VanderVeen L, et al. IDWeek 2021, oral 73).
CA, HIV capsid; INSTI, integrase strand transfer inhibitor; NRTI, nucleotide reverse transcriptase; RT, reverse transcriptase.

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Adverse Events (excluding ISRs)

≥10% Participants in LEN total, %	LEN Total TG 1+2+3 n=157	B/F/TAF TG 4 n=25
Headache	13%	12%
Nausea	13%	4%
COVID-19	10%	12%

- No SAEs related to study drug
- No Grade 4 AEs related to study drug
- No discontinuations due to non-ISR AEs
- Gastrointestinal AEs: SC LEN (TG 1+2) vs oral LEN (TG 3)
  - Nausea: 14% vs 12%
  - Diarrhea: 7% vs 10%
  - Vomiting: 4% vs 8%

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ISR, injection site reaction; SAE, serious adverse event.

Injection Site Reactions

ISR Types*	After 1st SC Dose at Week 1 n=103†	After 2nd SC dose at Week 26 n=95†	Median duration (days)
Swelling	14%	12%	11
Erythema	14%	18%	5
Pain	15%	9%	4
Nodule	11%	8%	195
Induration	9%	6%	202

- Mostly Grade 1 or 2 ISRs
  - One Grade 3 ISR (nodule) after the second SC dose
- Three participants discontinued due to ISRs:
  - Two due to induration (both Grade 1, after the first SC dose)
  - One due to erythema and swelling (Grade 1, after the second SC dose)

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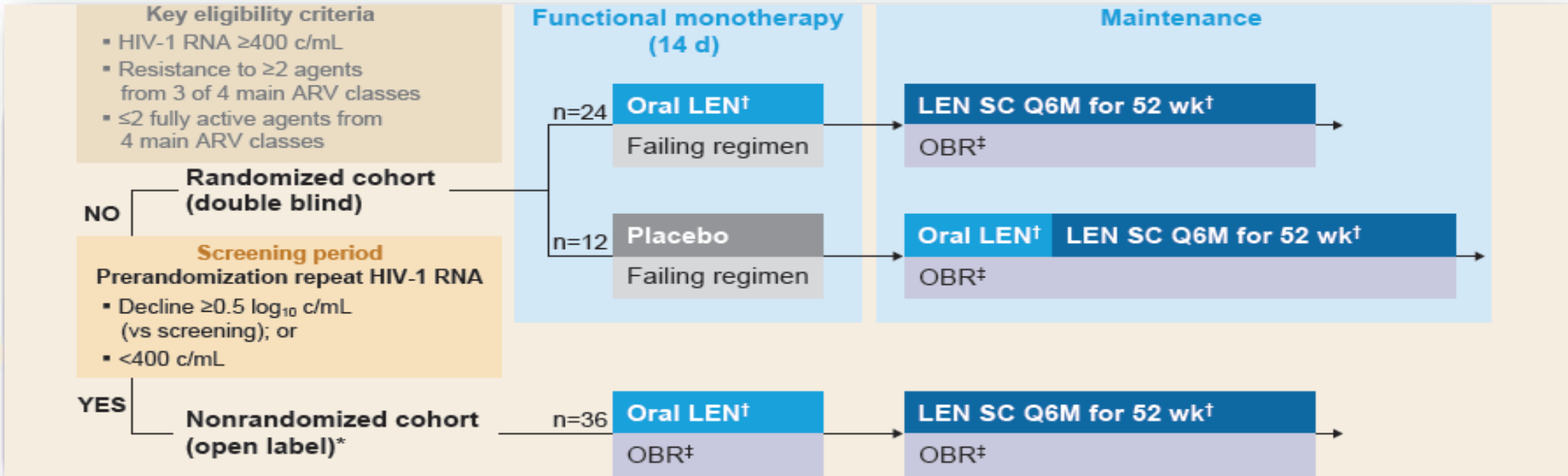
*Includes those >5% at both Weeks 1 and 26; †TG 1+2 (ie, those who received ≥1 dose of SC LEN and still on study or last study date in 2-week interval).

Lenacapavir in Heavily Treatment-Experienced people (Ph II/III)



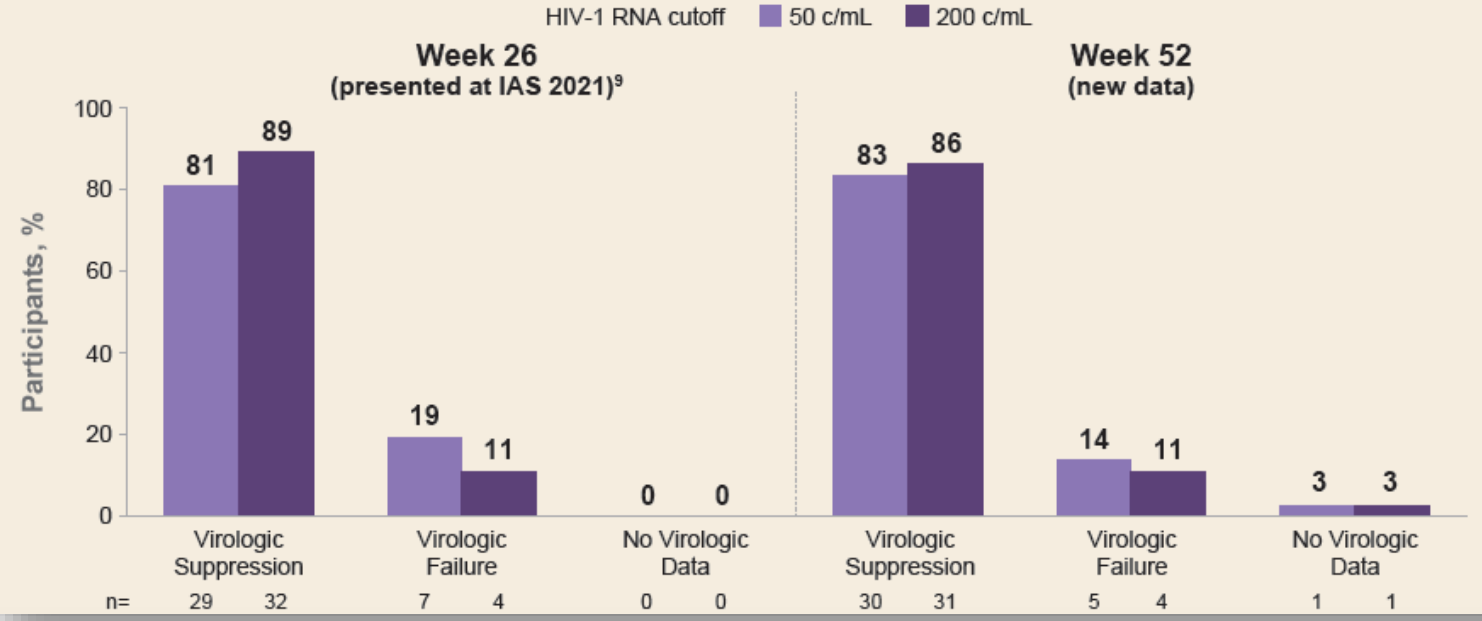
Primary endpoint achieved in prior analysis: ≥0.5-log decline in HIV-1 RNA with oral LEN 88% vs placebo 17% at Day 14 in randomized cohort (*P* <.0001)[1]

Secondary endpoints: HIV-1 RNA <50 c/mL, <200 c/mL at Week 26 in randomized cohort[2]

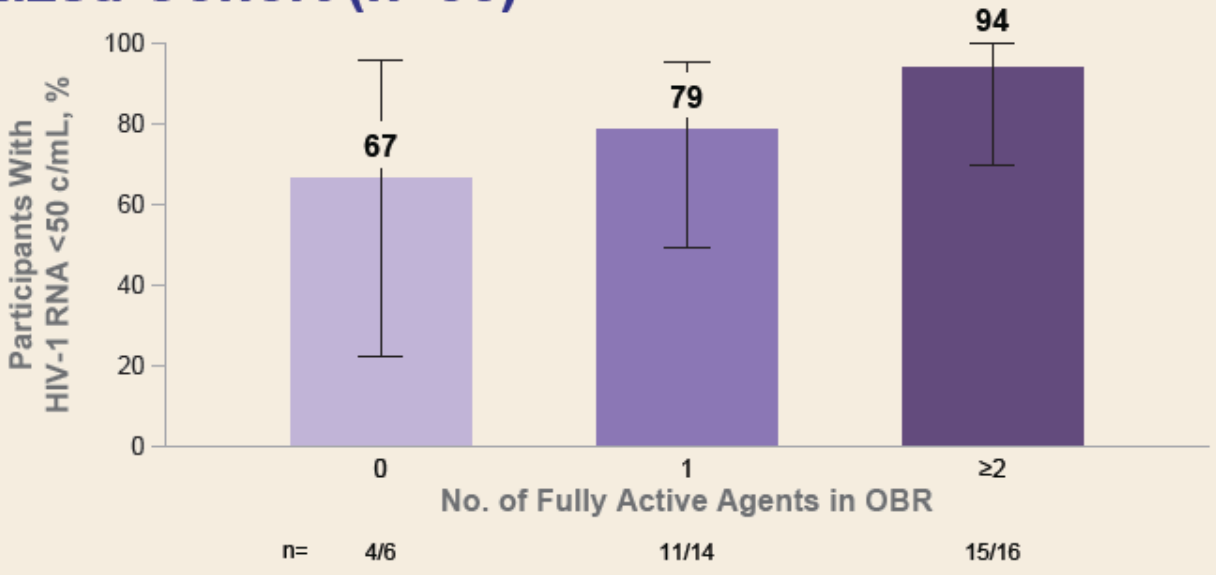
*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8.
†SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15.

1. Segal-Maurer. CROI 2021. 2. Molina. IAS 2021. Abstr OALX01LB02.

Efficacy in Randomized Cohort (n=36)



Efficacy by No. of Fully Active Agents in OBR at Week 52 in Randomized Cohort (n=36)



O Ogbuagu Poster #1047

Emergent LEN Resistance*

n (%)	Randomized Cohort: n=36 (presented at IAS 2021, EACS 2021)[9,10]	Nonrandomized Cohort: n=36
Participants meeting criteria for resistance testing	11 (31)	10 (28)
Emergent LEN resistance†	4 (11)	4 (11)
M66I	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

*Capsid genotypic and phenotypic resistance testing performed on any participants with confirmed HIV-1 RNA ≥50 c/mL and <1 $\log_{10}$ HIV-1 RNA reduction from Day 1 at Week 4 visit, at any visit after achieving HIV-1 RNA <50 c/mL and rebound to ≥50 c/mL, and at any visit with >1 $\log_{10}$ increase from nadir; HIV-1, protease, reverse-transcriptase, and integrase genotypic and phenotypic testing were performed if rebound or suboptimal virologic response were confirmed; †Developed during maintenance period (Week 4 [n=5], Week 10 [n=2], and Week 26 [n=1]).

- No additional participants with LEN resistance were observed in the randomized cohort after Week 26
- All 8 participants with emergent LEN resistance remained on LEN
  - All 8 participants were at high risk of emergent LEN resistance: no fully active drugs in OBR (n=4) or inadequate adherence to OBR (n=4)
  - 3 participants resuppressed at a later visit: 1 without and 2 with OBR change

O Ogbuagu Poster #1047

Adverse Events (excluding ISRs)*

≥10% Total in Any Grade, % (n)	Total LEN: N=72
Diarrhea	13 (9)
Nausea	13 (9)
COVID-19	11 (8)

*Serious adverse events (AEs) not related to study drug: malignant neoplasm and dizziness (n=1); abdominal pain, pancreatic mass, *Clostridium difficile* colitis, and angina pectoris (n=1); anal squamous cell carcinoma, proctalgia, impaired healing, and anal cancer (n=1); femoral neck fracture (n=1); COVID-19 (n=2); pneumonia (n=1); and septic shock, renal impairment, and shock (n=1). ISRs, injection-site reactions.

Incidence of ISRs Related to SC LEN*

ISR Types, %	After 1st SC Dose at Week 1 N=72	After 2nd SC Dose at Week 26 n=70	Median Duration, d
Swelling	26	13	12
Erythema	24	11	6
Pain	22	21	3
Nodule	22	11	180
Induration	11	10	118

*Only includes AEs related to LEN and excludes those not related to it.

- Mostly Grade 1 or 2 ISRs
- No Grade 4 ISRs, but 2 participants had Grade 3: 1 participant with swelling and erythema, which resolved in 4 and 8 d, respectively, and 1 participant with pain, which resolved in 1 d
- All nodules were Grade 1, except in 1 participant who had 2 AEs of Grade 2 nodules, each after the 2nd and 3rd injections (both resolved after 3 d)
- 1 participant discontinued study drug at Week 52 due to an ISR (nodule; Grade 1)

O Ogbuagu Poster #1047

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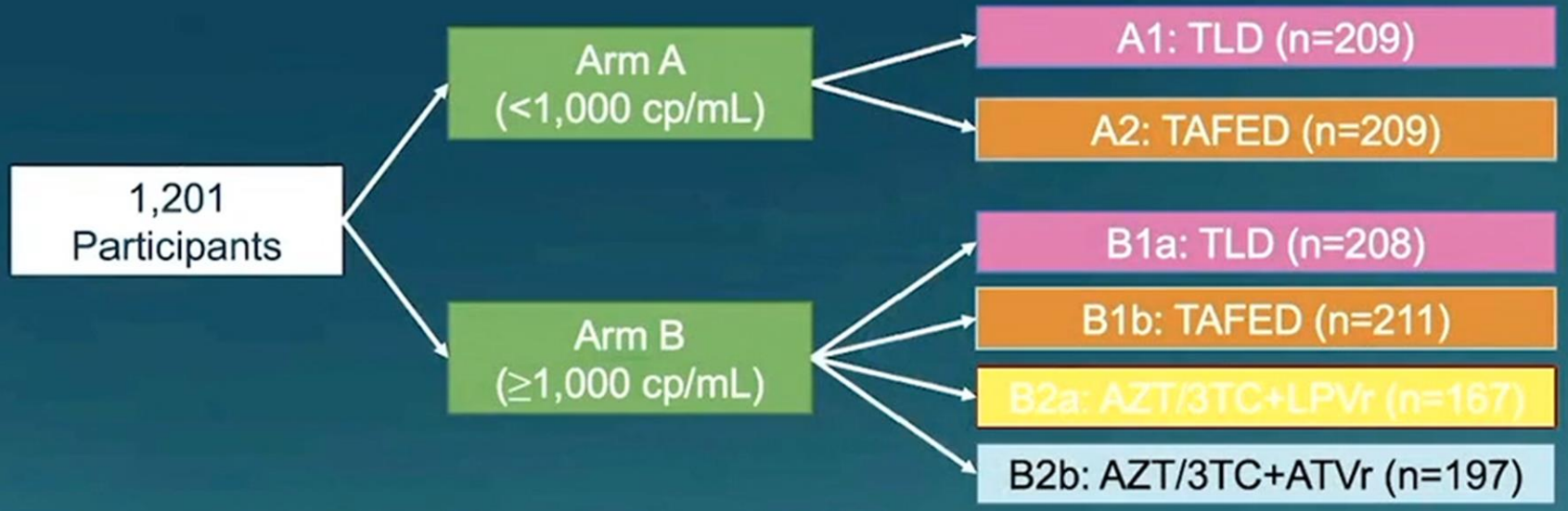
Nuevas estrategias

VISEND STUDY: Trial Design

- 144-week randomised, open-label, noninferiority study in Zambia:



- Post-baseline visits at week 12, 24, 48, 72, 96, and 144
- Enhanced counselling for two consecutive VL ≥50 cp/mL and genotypic resistance testing for individuals with two consecutive VL ≥1,000 cp/mL
- Primary endpoint: Proportion VL<1,000 cp/mL at Week 144 (FDA snapshot)

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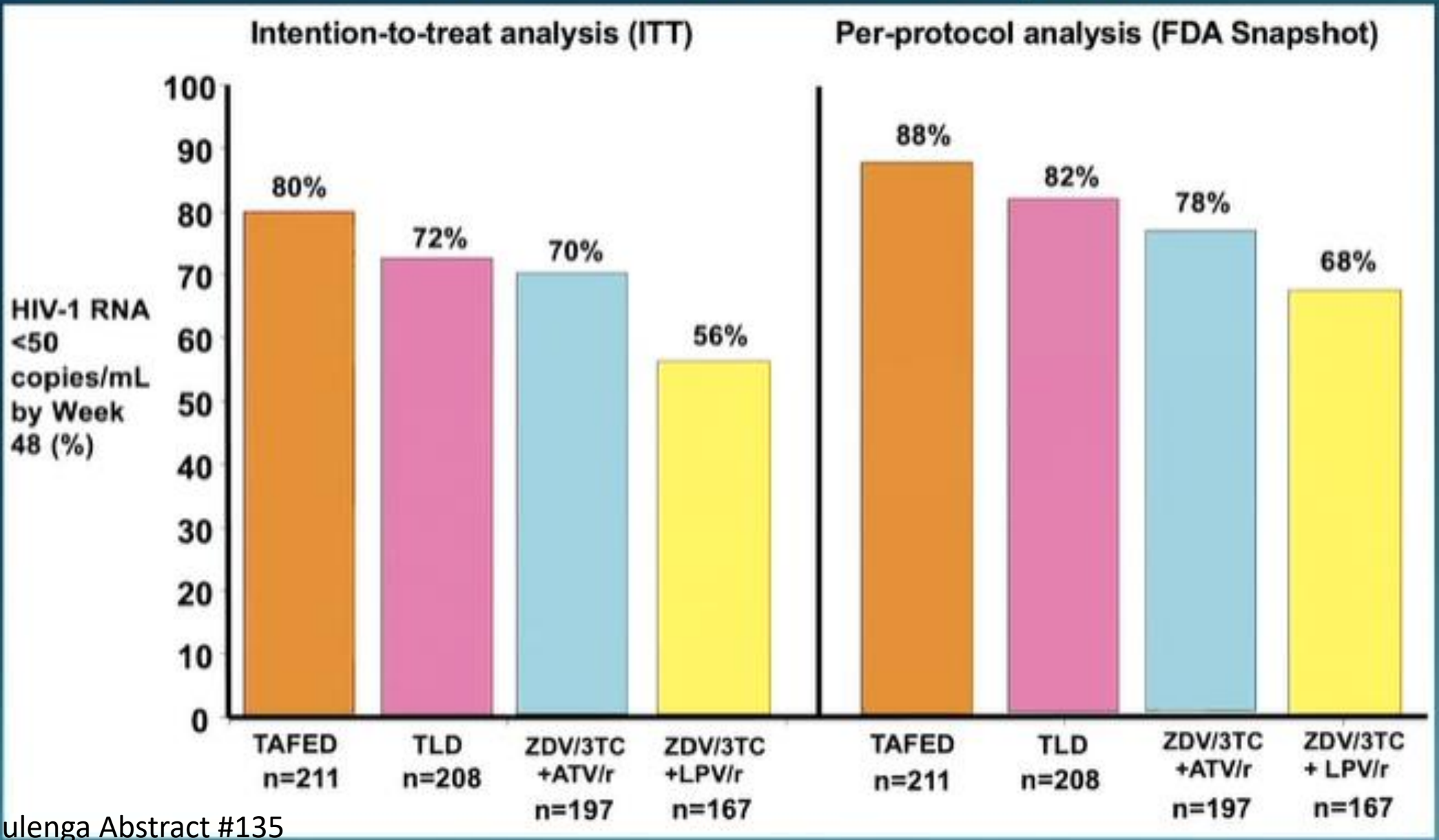
L Mulenga Abstract #135

VISEND ARM B: HIV-1 RNA <50 cp/mL



L Mulenga Abstract #135

NADIA 96 WEEKS

Background

NADIA

WHO Public Health Approach

- Second-line therapy (after EFV +2NRTI failure):
  - DTG + 2NRTIs
  - Switch TDF/3TC [first-line] to ZDV/3TC [second-line] – no resistance testing for NRTI selection
- Simplified monitoring: sparse VL, safety tests

NADIA Aims

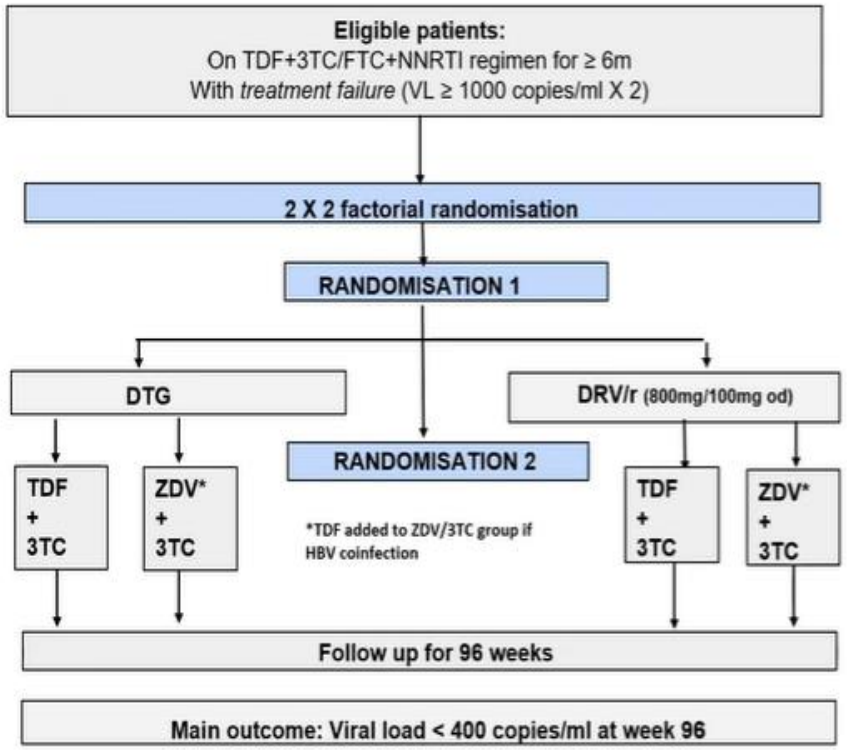
- Is DTG non-inferior to PI (DRV/r) in second-line therapy (when NRTI resistance high)
- Is TDF/3TC non-inferior ZDV/3TC in second-line therapy?
- Tested in settings with treatment delivery, monitoring relevant to public health approach

NADIA Week 48 results

- DTG non-inferior to DRV/r (but 4 cases of DTG resistance)
- TDF/3TC non-inferior to ZDV/3TC

Paton, Musaazi, Kityo et al. NEJM 2021; 385: 330-4

NADIA Trial Design



Uganda, Kenya, Zimbawe N: 464 Mediana Cd4 194 cél/m, y CV >100.000 (28%). M184V/I (86%); K65R/N (50%)

N Paton Abstract #137

Efficacy outcomes (W96): DTG vs DRV/r

Outcome	Dolutegravir Group (N=235)	Darunavir Group (N=229)	Difference (95% CI) %	P
HIV-1 RNA level, intention-to-treat population – no (%)				
< 400 copies/ml (ITT)	211(89.8)	199 (86.9)	2.9 (-3.0 to 8.7)	0.332
≥ 400 copies/ml	20 (8.5)	25 (10.9)	-	
No virological data - Withdrew because of AE/death - Withdrew for other reasons	4 (1.7) 3 (1.3) 1 (0.4)	5 (2.2) 5 (2.2) 0	-	
HIV-1 RNA level < 400 c/ml (sensitivity analyses) – no (%)				
< 400 copies/ml (adjusted)	90.2	86.7	3.5 (-2.9 to 9.8)	0.278
VL < 400 copies (per protocol)	201 (92.2)	192 (91.0)	1.2 (-4.0 to 6.5)	0.652
Secondary and other efficacy outcomes – no (%)				
VL < 1000 c/ml (ITT)	213 (90.6)	203 (88.6)	2.0 (-3.6 to 7.5)	0.481
VL< 50 c/ml (ITT)	189 (80.4)	172 (75.1)	5.3 (-2.2 to 12.9)	0.168
VL rebound ≥ 1000 c/ml, confirmed	20 (8.5)	26 (11.3)	-2.8 (-8.3 to 2.6)	0.306
VL rebound ≥ 1000 c/ml, confirmed with ≥1 major RM to DTG or DRV*	7	0	-	-

Efficacy Outcomes (W96): TDF vs ZDV

Outcome	Tenofovir Group (N= 233)	Zidovudine Group (N= 231)	Difference (95% CI) %	P
HIV-1 RNA level, intention-to-treat population – no (%)				
< 400 copies/ml (ITT)	214 (91.8)	196 (84.8)	7.0 (1.2 to 12.8)	0.019
≥ 400 copies/ml	13 (5.6)	32 (13.9)	-	-
No virological data - Withdrew because of AE/death - Withdrew for other reasons	6 (2.6) 6 (2.6) 0	3 (1.3) 2 (0.9) 1 (0.4)	-	-
HIV-1 RNA level < 400 c/ml (sensitivity analyses) – no (%)				
< 400 copies/ml (adjusted)	92.4	84.5	7.9 (1.9 to 14.0)	0.01
< 400 copies (per protocol)	206 (95.4)	187 (87.8)	7.6 (2.4 to 12.8)	0.005
Secondary and other efficacy outcomes – no (%)				
< 1000 c/ml	216 (92.7)	200 (86.6)	6.1 (0.6 to 11.6)	0.03
< 50 c/ml	188 (80.7)	173 (74.9)	5.8 (-1.8 to 13.3)	0.133
VL rebound ≥ 1000 c/ml, confirmed (ITT)	13 (5.6)	33 (14.3)	-8.7 (-14.4 to -3.3)	0.002
VL rebound ≥ 1000 c/ml, confirmed with ≥1 major RM to DTG or DRV*	2	5	-	-

* ≥1 major DTG mutation: 7
≥1 major DRV mutation: 0

N Paton Abstract #137

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IMPROVING INTESTINAL BARRIER USING GLUCAGON-LIKE PEPTIDE-2 ANALOG REDUCES ARTERIAL INFLAMMATION IN PEOPLE WITH HIV

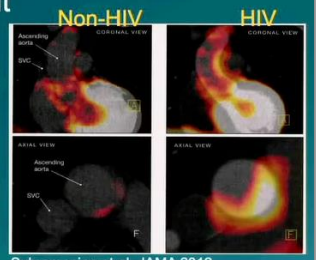
Coauthors: Caroline Diggins, Shibani Mukerji, Douglas Kwon, Charles Saylor, Lediya Cheru, Jae Sim, Meaghan Flagg, Björn Corleis, Emily Rudmann, Shady Abohashem, Ahmed Tawakol

Janet Lo, M.D., M.MSc.

Massachusetts General Hospital and Harvard Medical School
Boston, MA / USA

Cardiovascular Comorbidity in PWH

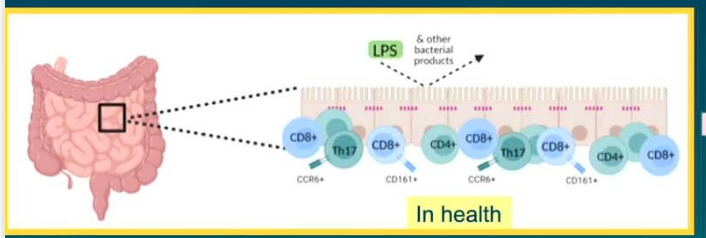
- Stroke and coronary artery disease are higher in people in PWH
- Immune activation contributes to atherosclerosis development
- ^{18}F-fluorodeoxyglucose (FDG) uptake, a measure of macrophage metabolic activity in atherosclerotic plaque, that predicts cardiovascular events, is increased in PWH
- Several studies have established intestinal permeability and microbial translocation as important causes of systemic inflammation in HIV/SIV

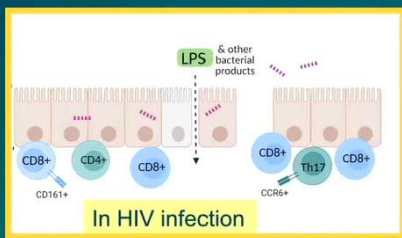


Subramanian et al. JAMA 2012

Currier et al. JAIDS 2003; Triant et al. JCEM 2007; Lo et al. AIDS 2010; Chow et al. JAIDS 2012; Freiberg et al. JAMA Int Med 2013
Figueroa et al. JACC Cardiovasc Imaging; Marnane et al. Ann Neurology 2012; Kelly et al. Stroke 2019
Brenchley et al. Nat Med 2006; Ancuta et al. PLoS One 2008 ; Lederman et al. Adv Immunol 2013; Somsouk et al. AIDS 2015

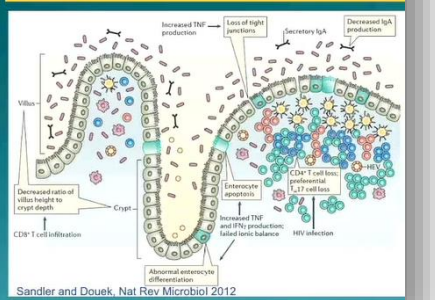
Intestinal Barrier in Health and with HIV





Intestinal damage with HIV infection
Immune changes including:
- CD4+ T cells in the GI tract are depleted during HIV infection, especially Th17 cells
- Loss of IL-17 producing CD161+CD8+ mucosal associated invariant T cells

Structural damage:
- Enterocyte apoptosis
- Decreased tight junction and adherens junction protein expression
- Increased intestinal permeability



Sandler and Douek, Nat Rev Microbiol 2012

Brenchley et al. Nature Medicine 2006; Guadalupe et al. J of Virology 2006'; Estes et al. PLoS Pathog 2010; Nazli et al. PLoS Pathog 2010; Klatt et al. Mucosal Immunol 2012; Cosgrove et al. Blood 2013

J. Lo HIV Antivirals and Outcomes Abstract #134

Intervention: Glucagon-like peptide-2

- GLP-2 is a gastrointestinal hormone released by intestinal L-cells that regulates intestinal epithelial cell growth and functions related to absorption of nutrients
- GLP-2 restores intestinal epithelium and promotes mucosal healing
- In animal models of intestinal injury, GLP-2 reduces intestinal permeability, microbial translocation and intestinal inflammation
- A GLP-2 analog, teduglutide, is FDA approved for short bowel syndrome

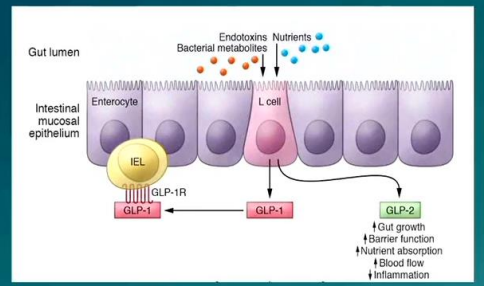
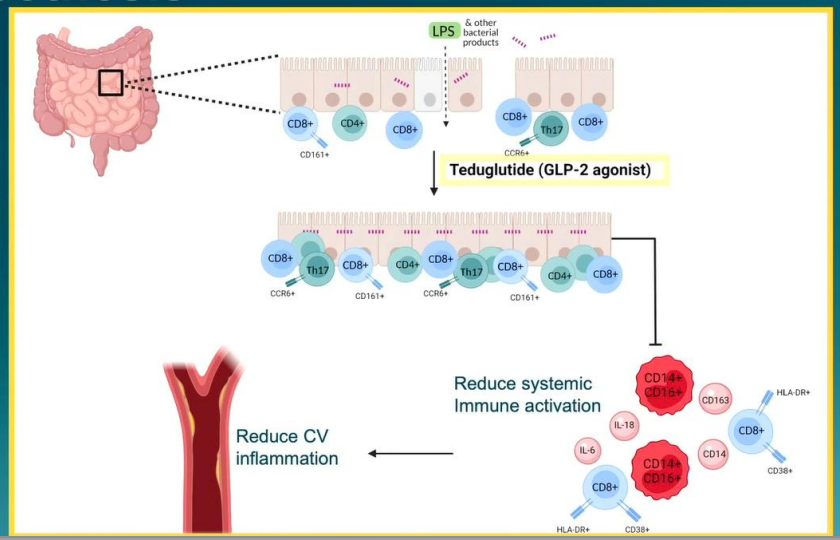


Figure modified from Drucker et al. JCI 2017

Drucker et al. AJP 1999
Cani et al. Gut 2009
Drucker et al. JCI 2017

Hypothesis



Study Design

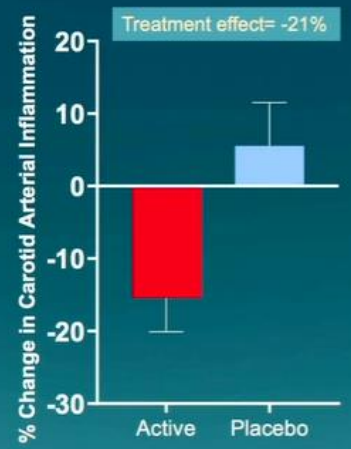
Double-blind, placebo-controlled, randomized (1:1) proof of concept trial of GLP-2 analog teduglutide 0.05mg/kg/day SC vs placebo in PWH on ART

Intestinal biopsies
FDG-PET for Arterial inflammation
Plasma and sera collection
PBMC Collection
Targeted metabolites assessed in plasma by LC-MS/MS

Intestinal biopsies
FDG-PET for Arterial inflammation
Plasma and sera collection
PBMC Collection
Targeted metabolites assessed in plasma by LC-MS/MS

J. Lo HIV Antivirals and Outcomes Abstract #134 CROI 2022

Results: Primary Endpoint
Change in Arterial Inflammation

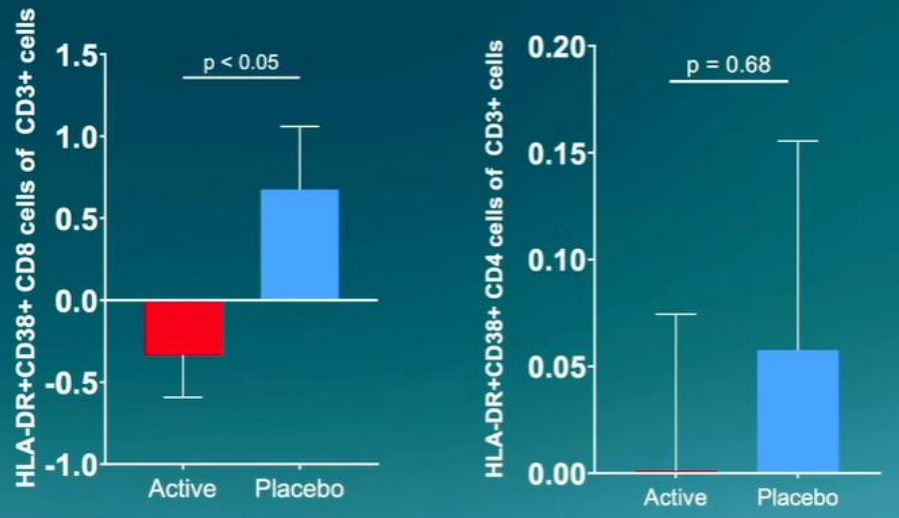


Primary analysis
Carotid arterial inflammation:
Target-to-background ratio of most diseased segment of index carotid vessel,
ANCOVA p=0.01

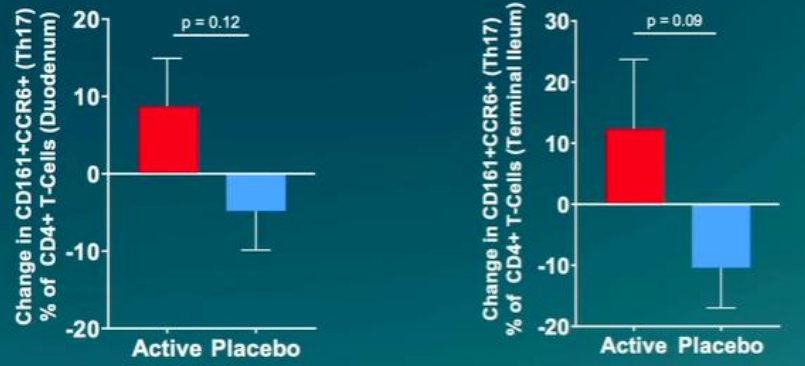
ITT (including participant in placebo group who stopped ART)
ANCOVA p=0.03

Sensitivity analysis:
- Adjusting for statin use, carotid arterial inflammation decreased with teduglutide compared to placebo (p=0.02)
- Adjusting for smoking status, carotid arterial inflammation decreased with teduglutide compared to placebo (p=0.03)

Teduglutide reduced peripheral activated CD8+ cells

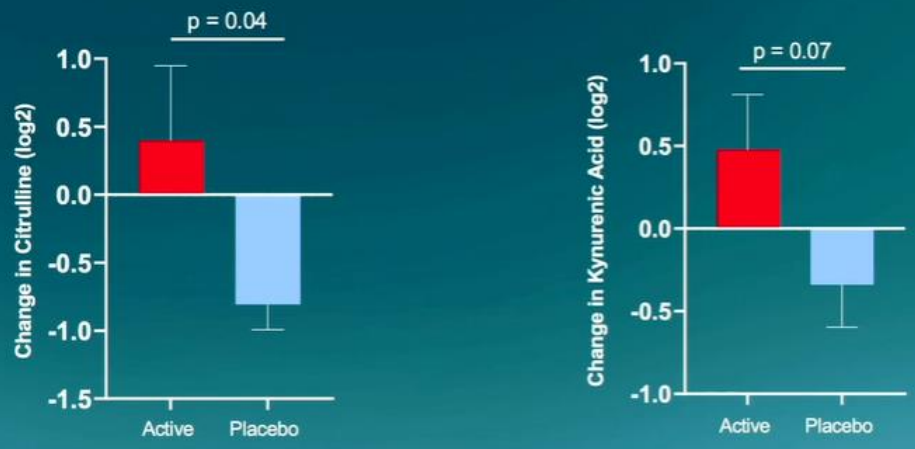


Change in intestinal Th17 cells



In teduglutide treated group, change in duodenal Th17 cells related to change in citrulline, a marker of small bowel health: **r = 0.98, p = 0.002**

Teduglutide prevented the decline of citrulline, a measure of small intestinal functional mass



J. Lo HIV Antivirals and Outcomes Abstract #134

CROI 2022

THE COOPERATIVE RE-ENGAGEMENT CONTROLLED TRIAL (CoRECT): DURABLE VIRAL SUPPRESSION ASSESSMENT

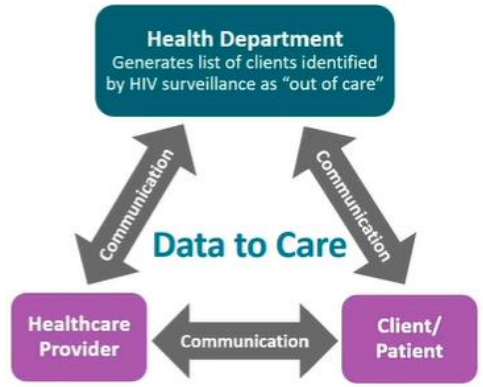
Jesse O'Shea[1], Robyn Neblett Fanfair[1], George Khalil[1], Tiffany Williams[2], Kathleen Brady[3], Alfred DeMaria[4], Liisa Randall[4], Heidi Jenkins[5], Nasima Camp[2], Crystal Lucas[3], Marianne Buchelli[5], Taraz Samandari[1], Paul J. Weidle[1]

[1]Division of HIV Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA
[2]Social and Scientific Systems Inc.
[3]Philadelphia Department of Public Health, Philadelphia, PA, USA
[4]Bureau of Infectious Disease and Laboratory Sciences, Massachusetts Department of Public Health, Boston, MA, USA
[5]Connecticut Department of Public Health, Hartford, CT, USA

Disclosure: None

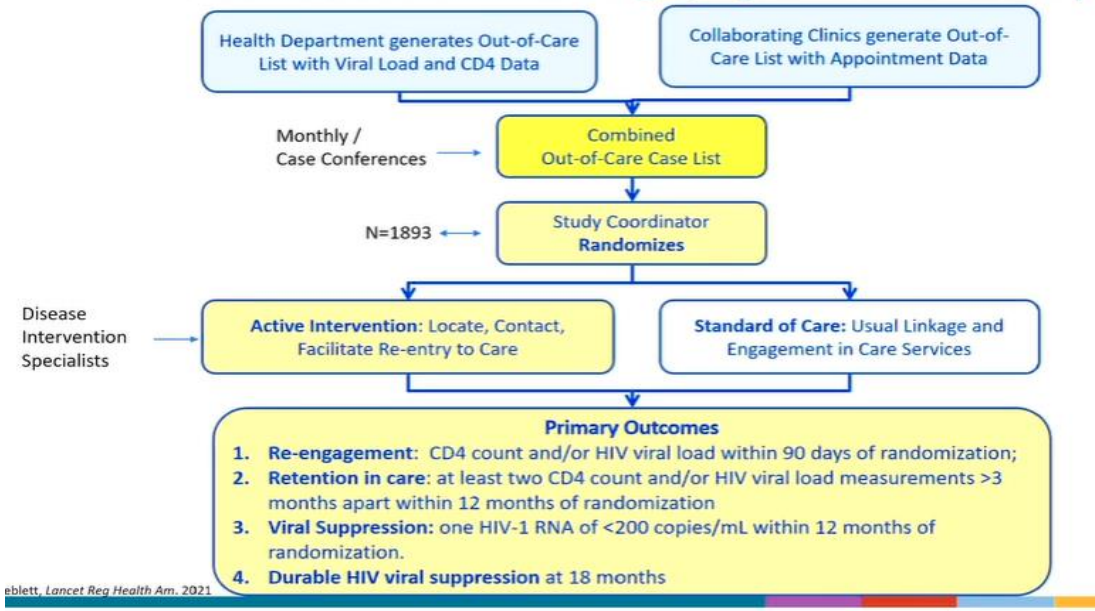
Introduction

- Retention in care and viral suppression improve HIV outcomes among people with HIV (PWH).
  - However, these rates remain suboptimal nationally (50-60%).
- Data to Care (D2C) is a strategy with goals of improving the HIV continuum by using HIV surveillance data to identify and re-engage PWH who may be newly out-of-care (OOC).



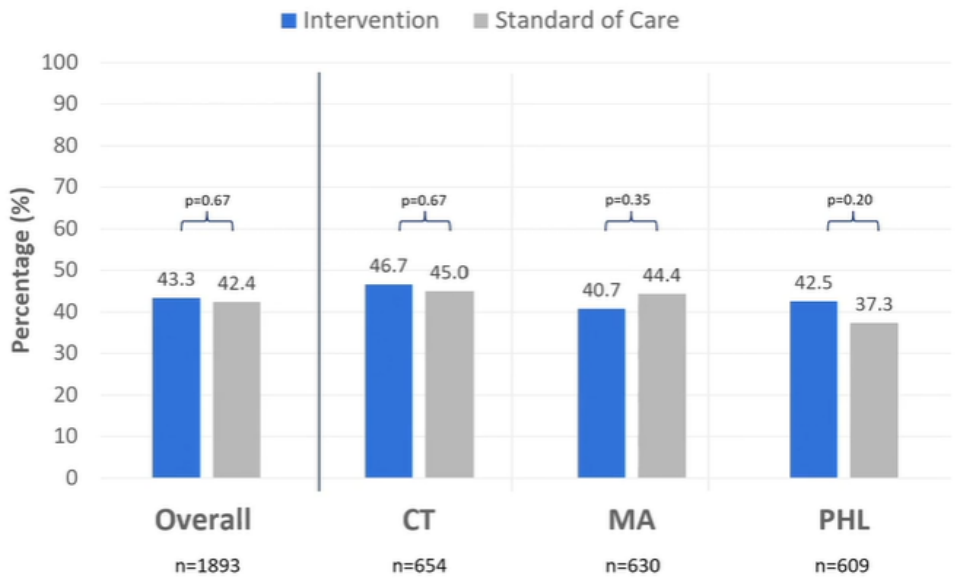
Monitoring Selected National HIV Prevention and Care Objectives By Using HIV Surveillance Data United States and 6 Dependent Areas, 2019
https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-26-no-2/content/national-profile.html
https://www.cdc.gov/hiv/effective-interventions/treat/data-to-care/

Randomized Control Trial Design (August 2016 – June 2018)



eblett, *Lancet Reg Health Am.* 2021

Results: % Achieving Durable Viral Suppression



DO INCENTIVE VOUCHERS IMPROVE HIV TREATMENT OUTCOMES AMONG KEY POPULATIONS IN INDIA?

Sunil Solomon

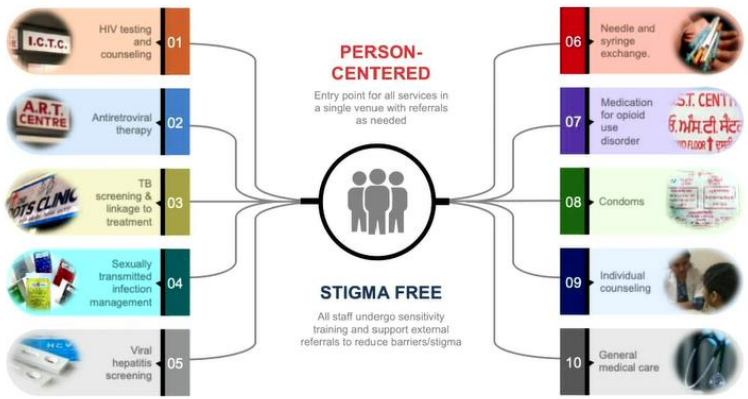
Johns Hopkins University School of Medicine
Baltimore, MD

Design of the Intervention

Behavior	Incentive Value	Frequency
Pre-ART follow-up	INR 250 (USD ~3.5)	Once every 6 months
ART initiation	INR 500 (USD ~7)	One time
Motivational interviewing	INR 100 (USD ~1.3)	Once every 3 months
Timely ART refill	INR 150 (USD ~2)	Once per documented refill (ART usually dispensed monthly)

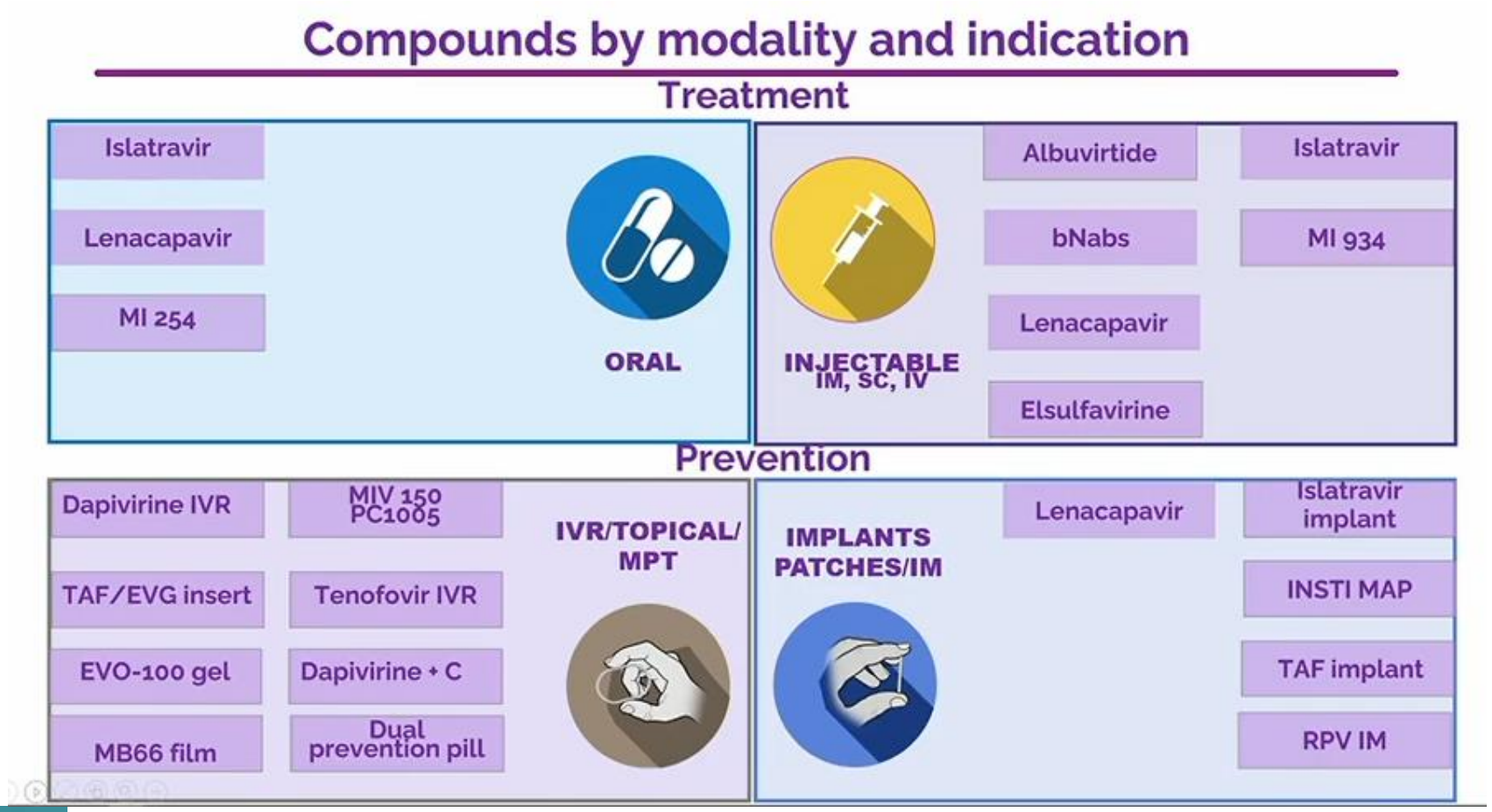
Study Overview

- Pair-matched (n=8 pairs) cluster randomized trial among MSM and PWID clients registered at an Integrated Care Center (ICC)



Viral suppression over time

PrEP



CROI 2022

CROI 2022: more HIV prevention choices are finally becoming a reality…with even more on the horizon

5 PrEP AGENTS HAVE (OR ARE PENDING) APPROVAL

- **Tenofovir/emtricitabine (TDF/FTC)** – US FDA approved (2012) and licensed for use as PrEP in many countries; recommended by WHO
- **TDF** – Recommended by WHO
- **Tenofovir alafenamide/emtricitabine (TAF/FTC)** – FDA approved for MSM, transgender women who have sex with men – but not for receptive vaginal sex (2019)
- **Dapivirine ring –** EMA: "positive scientific opinion" (2020). WHO recommended as "complementary prevention approach in addition to othe safer sex practices" (2021). FDA review pending
- **Cabotegravir long-acting injectable** – FDA approved for PrEP for men and women (2021)

L. Oluoch Workshop 12 Feb CROI 2022

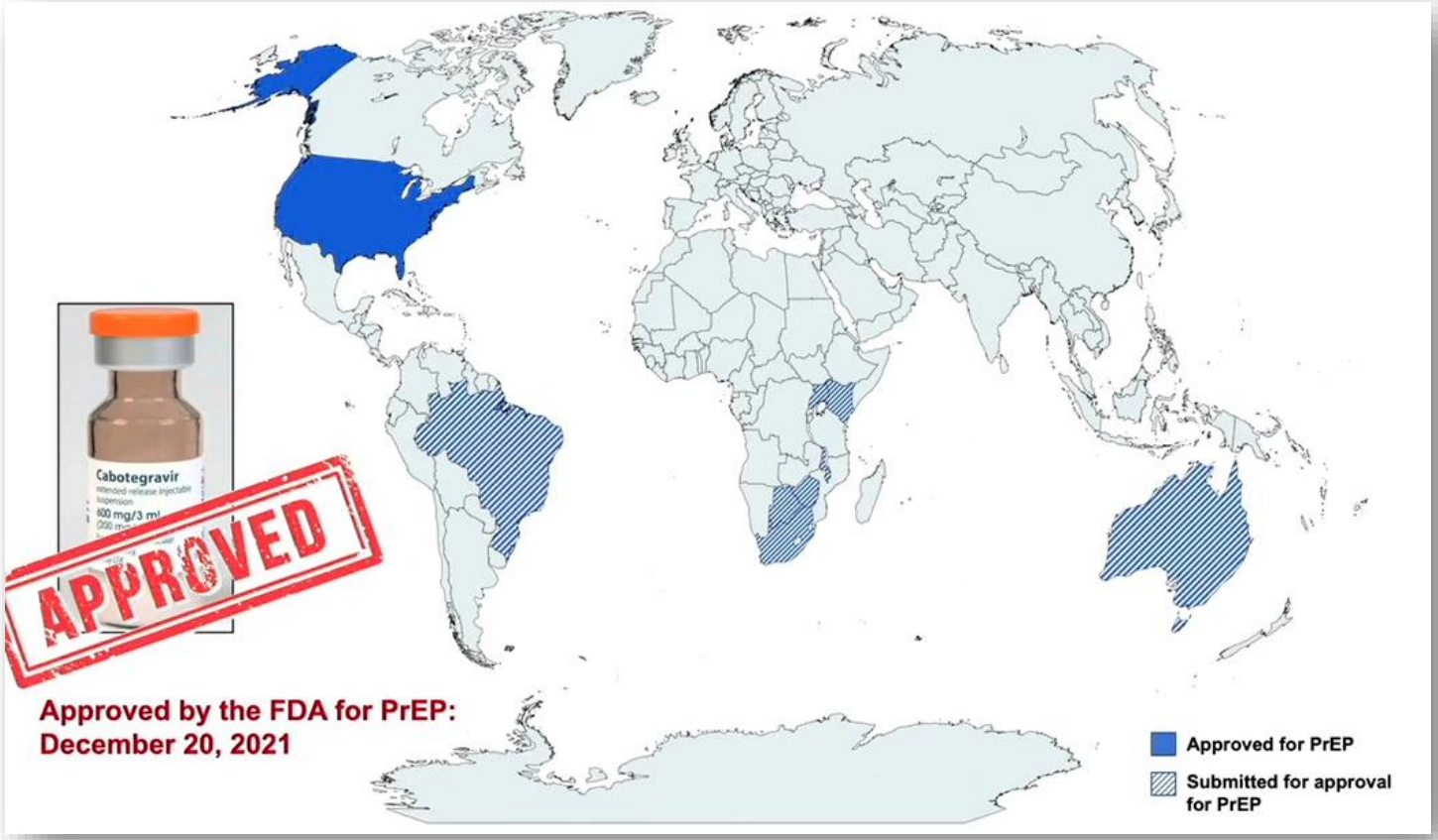
Background

HPTN 083: Phase 2b/3 randomized controlled trial of increased-risk, HIV-uninfected MSM + TGW at 43 sites in 7 countries

HPTN 083 and 084 demonstrated that long-acting injectable cabotegravir (CAB-LA) is superior to daily oral TDF/FTC for HIV PrEP across populations and regions

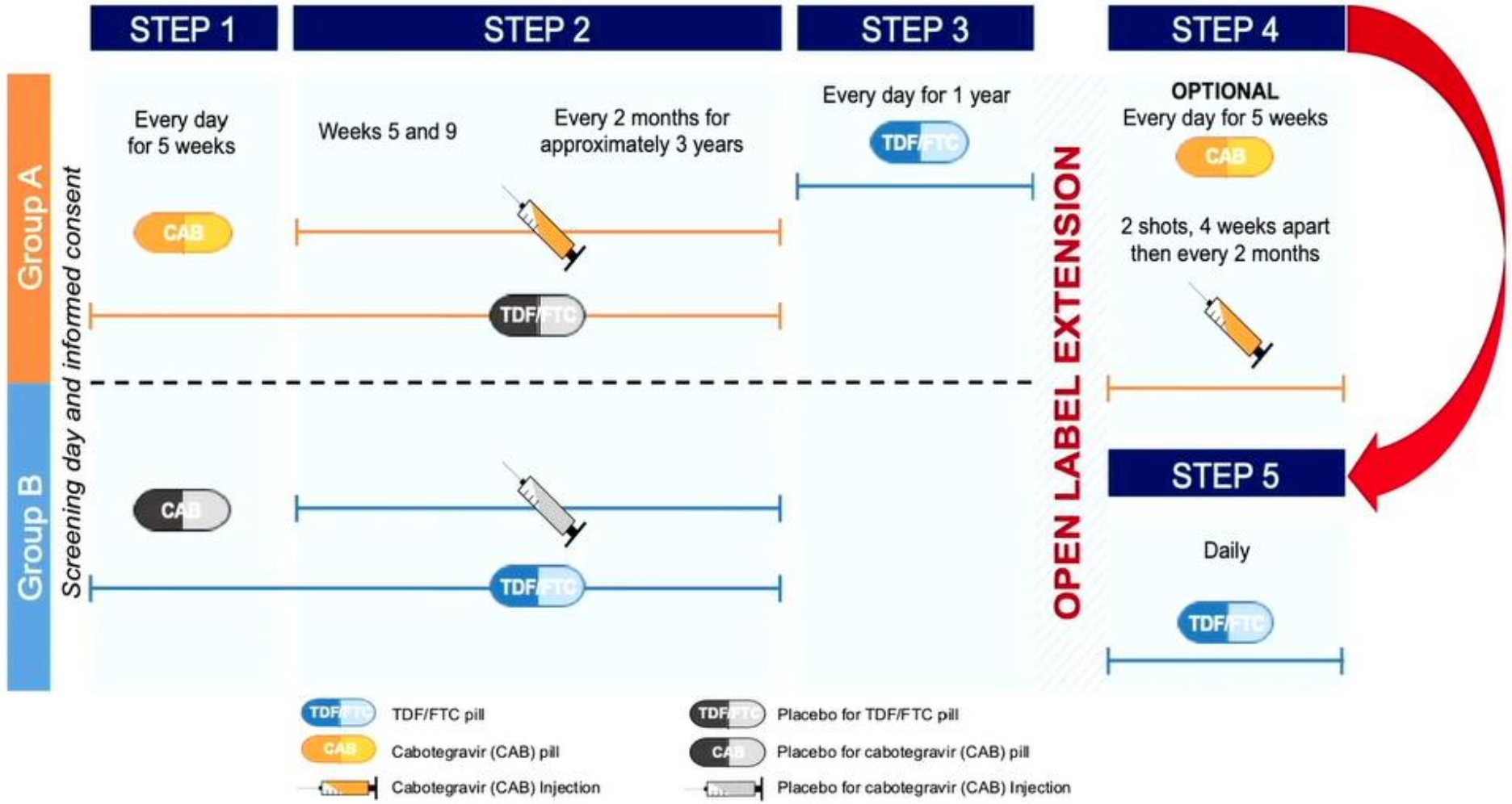
4566 participants were enrolled, 37.2% from the US, 43% from Latin America, 16.5% from Asia, and 3.3% from Africa

- 12.5% transgender women
- 49.8% of US enrollment is Black
- 67.4% < 30 yo



RJ Landovitz Abstract #96

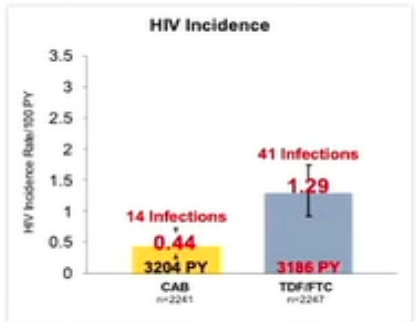
HPTN 083 Study Design

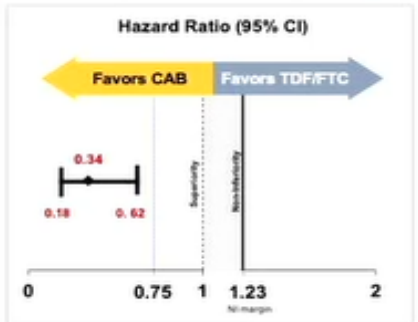


RJ Landovitz Abstract #96

HIV Incidence: CAB vs. TDF/FTC

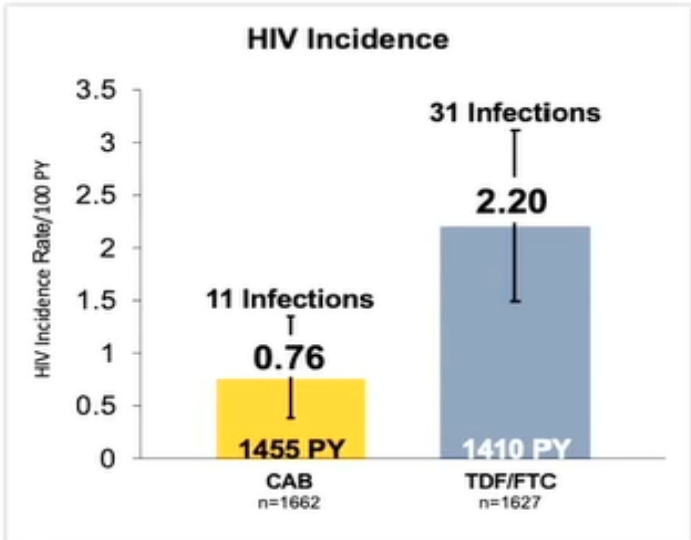
Updated Primary Blinded Period

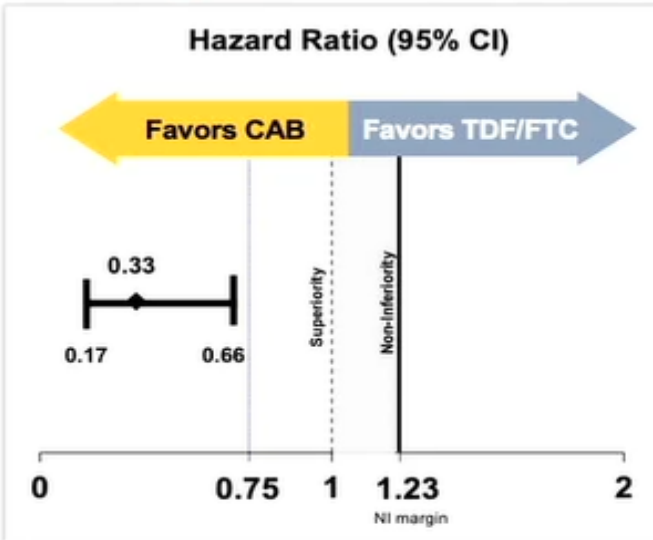




CI, confidence interval

Year 1 Unblinded Analysis Period



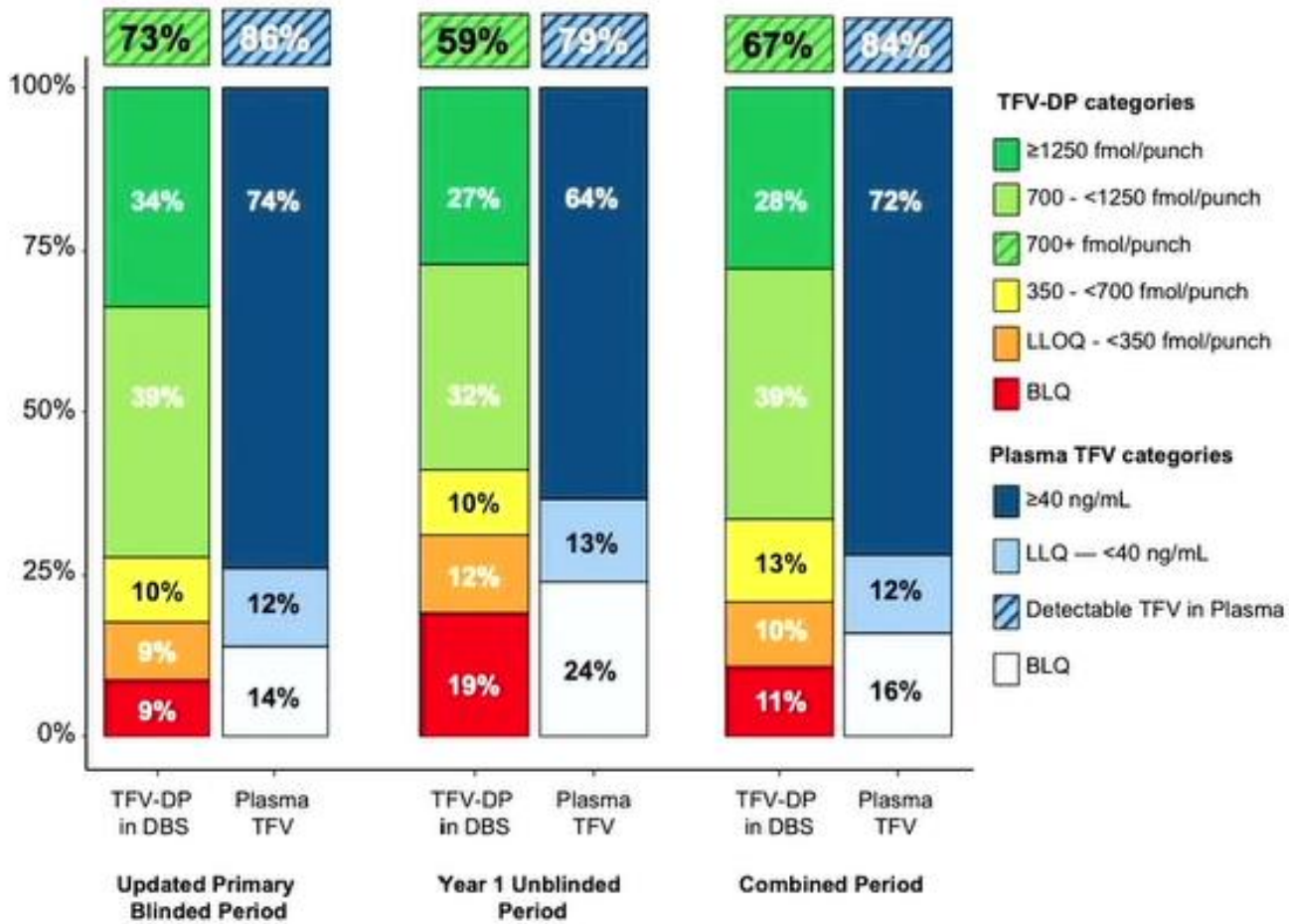


CI, confidence interval

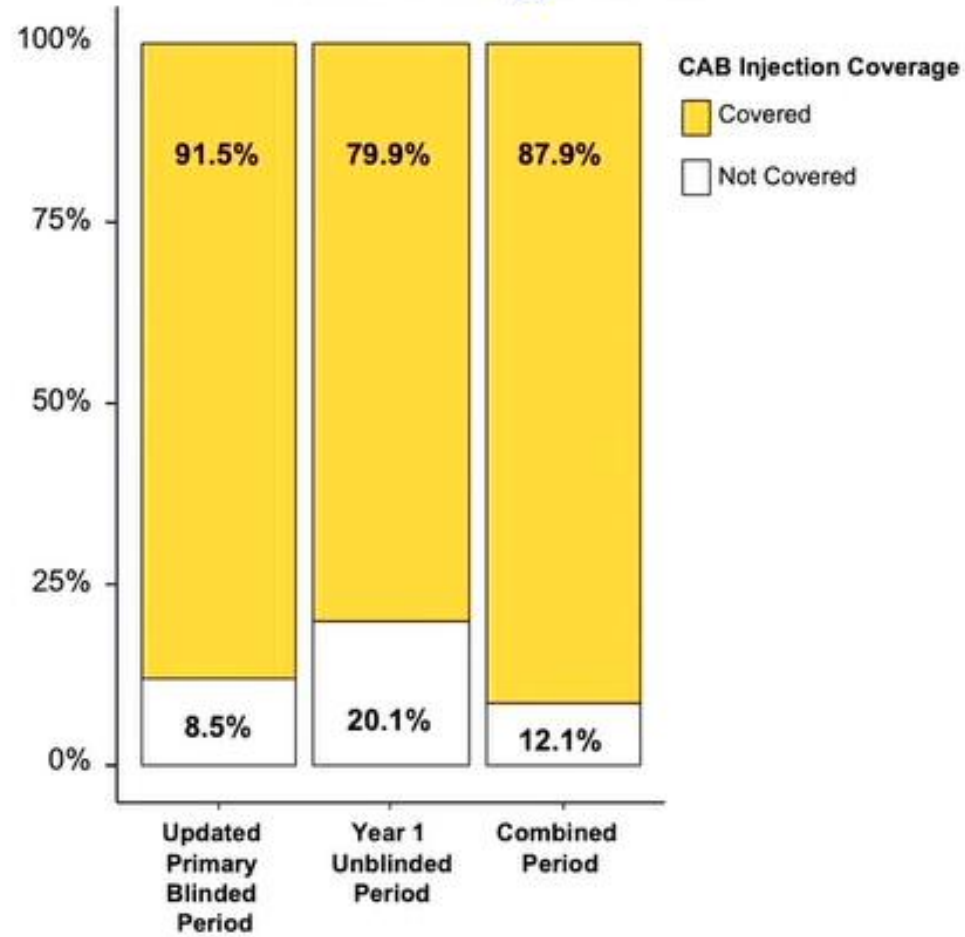
RJ Landovitz Abstract #96

Study Product Adherence

TDF/FTC



Cabotegravir



Initial injection = 6 weeks of coverage
Subsequent injections = 10 weeks of coverage
Injection given >16 weeks after the prior = 6 weeks of coverage

RJ Landovitz Abstract #96

CAB-LA PrEP: Early detection of HIV infection may reduce INSTI resistance risk

Susan Eshleman, MD/PhD

Johns Hopkins University School of Medicine
Baltimore, MD USA

INSTI Genotyping

Prior testing – HPTN 083 CAB arm

- CAB arm: 16 HIV infections among 2,282 enrolled (4 baseline, 12 incident)
- VL >500 c/mL - GenoSure PRIme assay (Monogram Biosciences)
- 5/16 cases had INSTI resistance (includes 1 baseline case)
- 2 cases had no results (VL <500 at all visits)

Marzinke, JID 2021; 224:1581

Low VL INSTI resistance testing

- Qualitative RNA test positive (LLOD 30 copies/mL), VL <500 c/mL
- Single genome sequencing assay (Univ of Pittsburgh)
  Halvas, J Clin Invest 2020; 130:5847
- INSTI RAMs - Stanford HIV Resistance Database

Risk of Resistance

- In HPTN 084- No sero-converters in the CAB arm had integrase resistance.
- HPTN 083- 5/13 with integrase resistance
- Use of Qual RNA assay would detect HIV infection potentially in time

Case	Initial Viremia	Viremia Visit 2	Viremia Visit 3
A2 (0, 60,69)	None	E138K, Q148K	E138K, Q148K
C1 (0, 10,14)	Q148R	E138 E/K, G140 G/S, Q148R	E138 E/K, G140 G/S, Q148R
C3 (0, 1)	E138A, Q148R	E138 E/K, G140 G/S, Q148R	Not applicable
D3 (0,112,117)	None	263K	236K
D4 (0)	G140A, Q148R	Not applicable	Not applicable

Marzinke, JID 2021

Key Findings

In 5/7 cases, major INSTI RAMs were first detected in samples with low VLs - not just in high VL "breakthrough" samples

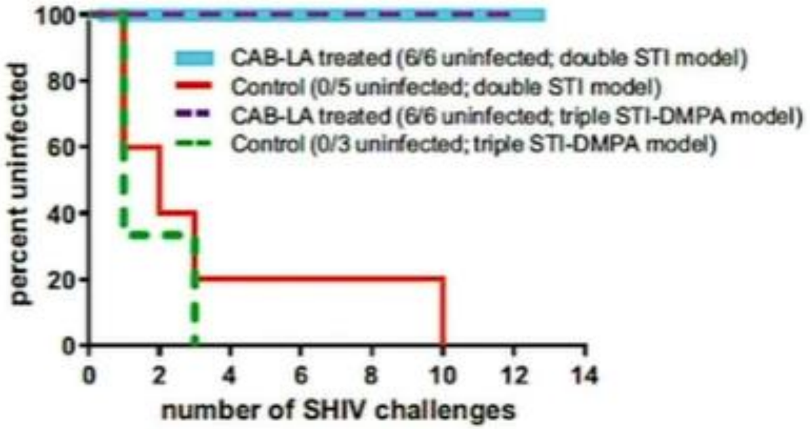
Use of a RNA assay for HIV screening would have detected infection before a **major** INSTI RAM was detected (4 cases) or before **additional major** INSTI RAMs accumulated (2 cases)

S Eshelman Abstract #95

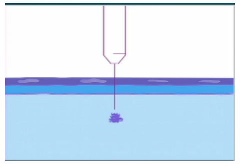
MACAQUE MODEL: CAB-LA PROTECTS AGAINST HIV – EVEN IN PRESENCE OF STI

- STIs increase HIV risk
- Do treatable STIs impact PrEP efficacy?
- Previous macaque model suggested slightly decreased TDF/FTC efficacy in presence of chlamydia and *T. vaginalis*
- Macaque model of vaginal infection with C trachomatis, T vaginalis, syphilis, DMPA; CAB-treated vs controls
  - Multiple vaginal SHIV challenges
  - CAB-LA present in vaginal secretions; high concentrations in plasma

All CAB-treated animals protected; controls infected after median of 2 challenges



Vishwanathan SA. AIDS;2022:36:169



IN SITU FORMING IMPLANTS WITH CABOTEGRAVIR FOR ULTRA LONG-ACTING PREP

ID 00855

I Massud[1], M Kovarova[2], A Wong-Sam[1], C Dinh[1], E Edwards[1], V Mrotz[1], J Mitchell[1], W Heneine[1], I C Young[4], R Shrivastava[2], J V Garcia[2], C Dobard[1], G García-Lerma[1], S R Benhabbour[3,4]
[1]Centers for Disease Control and Prevention, Atlanta, GA, United States.
[2]International Center for the Advancement of Translational Science, Division of Infectious Diseases, Center for AIDS Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.
[3]Joint Department of Biomedical Engineering, North Carolina State University and The University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.
[4]Division of Pharmacoengineering and Molecular Pharmaceutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.

BACKGROUND

- Bi-monthly Cabotegravir long-acting (CAB LA) is available as a new option for HIV prevention. Biodegradable in situ forming implants (ISFI) releasing CAB represent an attractive ultra long-acting delivery platform that can provide sustained drug release for several months to years but can be removed to terminate treatment if needed. We evaluated drug release, drug tail after removal, and PrEP efficacy of CAB ISFIs in macaques.

ISFIs releasing CAB were safe and fully protected macaques from rectal SHIV infection for up to 6 months

Figure 1.

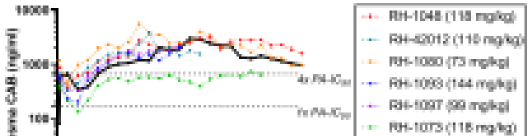


Table 1. Median (range) CAB concentrations in plasma (n= up to 6) and tissues (n=3)

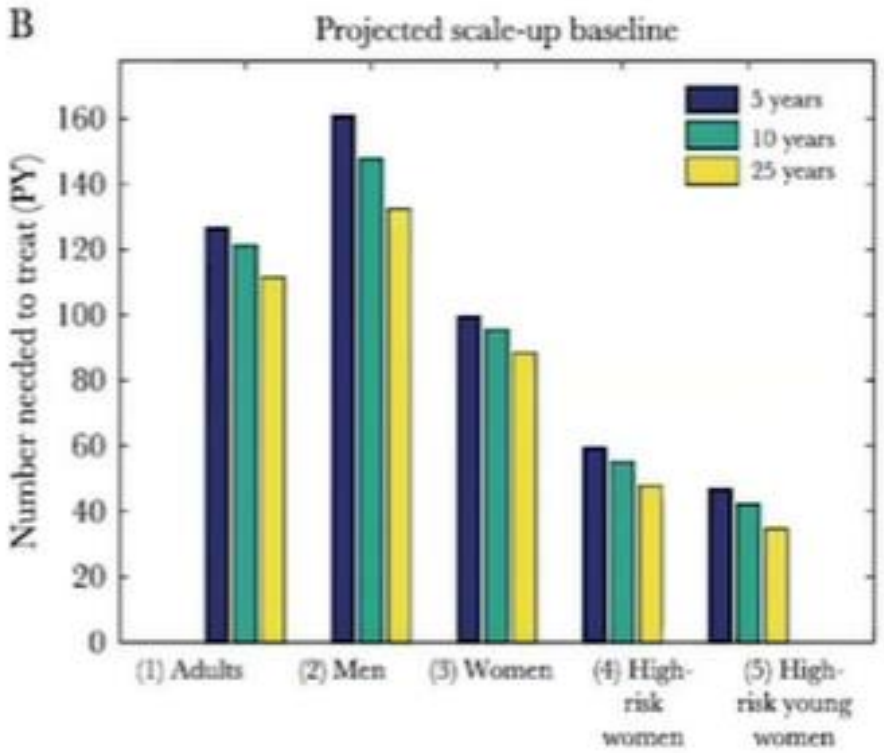
	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Plasma ng/mL	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Vaginal tissue ng/g (n=3)		[illegible]	[illegible]	[illegible]			
Rectal tissue ng/g (n=3)		[illegible]	[illegible]	[illegible]			

RESULTS (CONTINUED)

- **CAB ISFI-treated animals** exposed twice-weekly to SHIV starting at week 4 (n=2) or week 12 (n=2) post administration (**Fig 2A and 2B**, respectively) **were fully protected** after 8 SHIV exposures (total of 32 exposures). Plasma CAB levels in animal RA-1048 remained above 4x PA-IC_{90} at week 24 and **maintained full protection** following an additional 6 SHIV exposures (**Fig 2B**).

MODELING: CAB COULD SUBSTANTIALLY IMPACT SOUTH AFRICA'S HIV EPIDEMIC

- Assuming
  - 90% efficacy for preventing HIV
  - Mean duration of continuous use of 5 years
- Delivering CAB LA to 10% of adults could avert >15% of new HIV infections from 2023 to 2050
- Delivering CAB to 10% of "high-risk young women" could decrease HIV incidence by 5%



Smith JA. JiD 2021;224:1179

L. Oluoch CROI 2022

PrEP LENACAPAVIR 6 monthly subcutaneous injection

	Trial name (protocol number)	Population	Active comparator	Study design	Primary Endpoint
Phase 3	PURPOSE 1	Adolescent girls and young women at high risk	FTC/TDF or FTC/TAF	Randomized, double blind, placebo-controlled	LEN vs bHIV F/TAF vs bHIV
	PURPOSE 2	Men, TGM and non-binary people who have sex with men; transgender women at high risk	FTC/TDF	Randomized, double blind, placebo-controlled	LEN vs bHIV

Study design: counterfactual analysis

Use of recency assays to identify incident infections in screening population as a comparator

PURPOSE 1:
- **External control**: bHIV in those not on PrEP based on recency assay in screened population, historical data from ECHO, HVTN, PrEPVACC
- Dosing: Day 1 - LEN 927mg SC + 600mg oral, Day 2 - 600mg oral, followed by 927mg SC q26weeks; F/TAF 200/25mg oral daily, F/TDF 200/300mg oral daily
- **Internal Active Control**: F/TDF
- Locations: South Africa and Uganda

PURPOSE 2
- **External controls**: bHIV in those not on PrEP based on recency assay in screened population, rectal gonorrhea surrogate (Mullick & Murray 2018); CDC data background HIV incidence estimation (only for the US)
- Dosing: Day 1 - LEN 927mg SC + 600mg oral, Day 2 - 600mg oral, followed by 927mg SC q26weeks; F/TDF 200/300mg oral daily
- **Internal Active Control:** F/TDF and bHIV placebo-estimation (Glidden, et al IDWeek 2020)
- Locations: US, Peru, Brazil, South Africa

PURPOSE 1 NCT04994509; PURPOSE 2 NCT04925752

LONG ACTING LENACAPAVIR PROTECTS AGAINST INTRAVENOUS CHALLENGE WITH SIMIAN-TROPIC HIV

00866

Adrienne E. Swanstrom[1], Bing Lu[2], Kelly Wang[2], Jim Zheng[2], Matthew W. Breed[3], Kristin E. Killoran[3], Joshua Kramer[3], Jorden L. Welker[1], Paul D. Bieniasz[4], Theodora Hatziioannou[4], Robert J. Gorelick[1], Wade Blair[2], Stephen R. Yant[2], Jeffrey D. Lifson[1], **Gregory Q. Del Prete[1]**

[1]AIDS and Cancer Virus Program, and [3]Laboratory Animal Sciences Program, Frederick National Laboratory for Cancer Research, Frederick, MD, USA; [2]Gilead Sciences, Foster City, CA, USA; [4]Laboratory of Retrovirology, Rockefeller University, New York, NY, USA

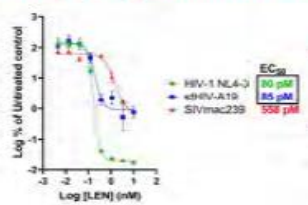
Conclusions

- A single subcutaneous LEN injection effectively prevented simian-tropic HIV infection in a stringent, high dose intravenous challenge model
- These findings highlight the utility of this stHIV/PTM model and support the ongoing clinical development of long-acting LEN for PrEP

Results

1. LEN Potency against stHIV In Vitro

SupT1-CCR5+ cells



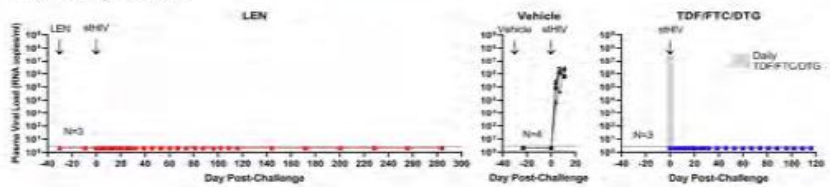
- stHIV-A19 and HIV-1 equally sensitive to LEN
- LEN more potent against stHIV than SIVmac239

stHIV-A19 vs Lenacapavir

stHIV-A19 CA Sequence

3. LEN PrEP vs IV stHIV Challenge

Plasma Viral Loads



*LOD = 2.8 vRNA copies/ml (dashed line)

ISLATRAVIR: POTENT, LONG-ACTING ARV

First in class nucleoside reverse transcriptase translocation inhibitor (NRTTI) – inhibits translocation, delays chain termination

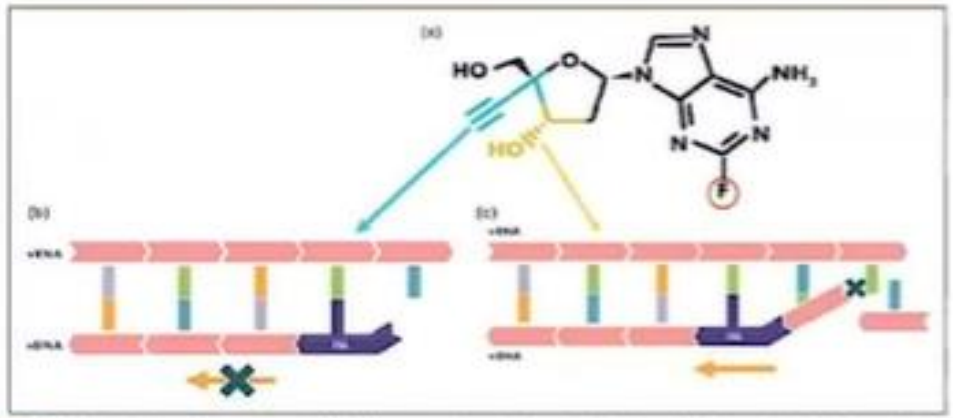
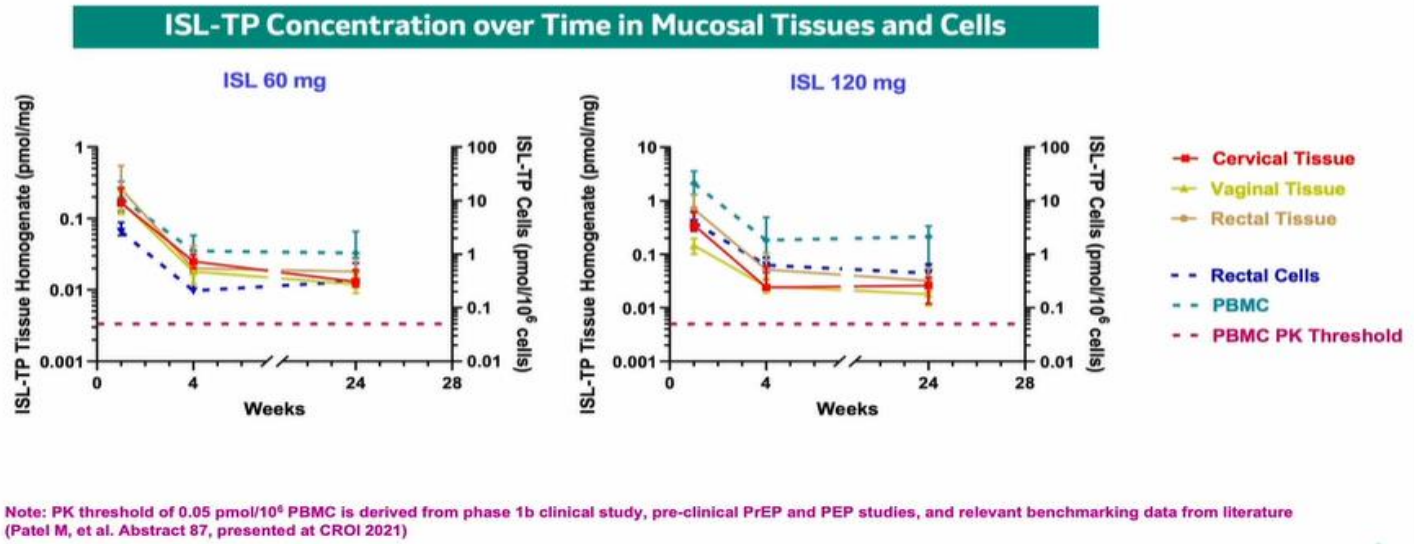


FIGURE 1. Islatravir is a first-in-class nucleoside reverse transcriptase translocation inhibitor with multiple mechanisms of action. (a) Structure of islatravir with the 4′-ethynyl group in aqua, the 3′-hydroxyl group in mustard and the 2-fluoro group circled in red. (b) Translocation inhibition and immediate chain termination because of ISL binding and incorporation into the DNA chain. (c) Delayed chain termination because of the 4-ethynyl and 3′-hydroxy groups preventing further nucleotide incorporation.

- Long intracellular $t_{1/2}$ (~190 h after oral administration)
- Potent: Intracellular concentration of ISL-TP in PBMCs at IC_{50}=9.7 fmol/10^6 cells
- Antiviral efficacy in HIV treatment studies
- Oral once-weekly ISL prevented SHIV transmission in rectal challenge studies of male rhesus macaques
- Under study as monthly oral; yearly implants well tolerated in Phase 1

Markowitz M. Curr Op HIV/AIDS 2020;15:27
Ankrom W. CROI 2021; #2101
Matthews RP. Nature Med 2021;27:1712

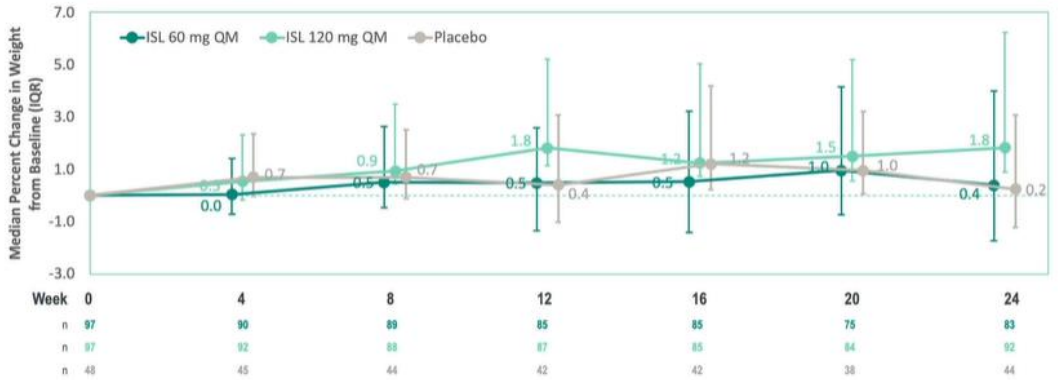
Comparable ISL-TP levels across tissue types and cells



Note: PK threshold of 0.05 pmol/10^6 PBMC is derived from phase 1b clinical study, pre-clinical PrEP and PEP studies, and relevant benchmarking data from literature (Patel M, et al. Abstract 87, presented at CROI 2021)

Mc Donald
Abstract #1238

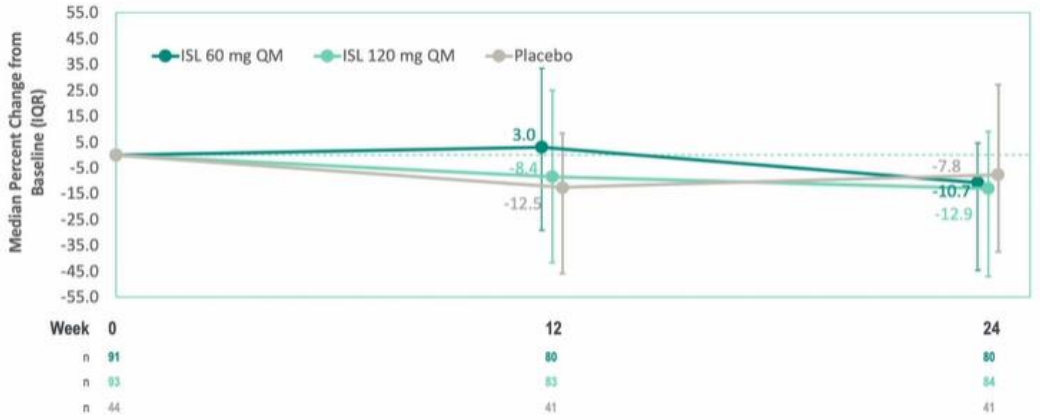
Weight: Median percent change from baseline through week 24



- Median percent changes from baseline in weight were small and comparable for ISL 60 mg QM and placebo groups
- Slight increases in weight were observed for participants in the ISL 120-mg QM group

IQR, interquartile range.

RBP/Creatinine Ratio: Median percent change from baseline through week 24



- Small and similar decreases in urinary retinol-binding protein/creatinine ratios were seen across all treatment groups during the active treatment phase

Hendrix Abstract #83

TWO PHASE 3 RCTs OF ISLATRAVIR BEGAN IN 2021…

- **IMPOWER 22**
  - Monthly oral ISL and placebo vs TDF/FTC and placebo
  - Cis-gender women in Africa and USA
- **IMPOWER 24**
  - Monthly oral ISL and placebo vs either TDF/FTC and placebo or TAF/FTC and placebo
  - Cisgender men and transgender women who have sex with men

MERCK

Media > News releases > News release

Merck Announces Clinical Holds on Studies Evaluating Islatravir for the Treatment and Prevention of HIV-1 Infection

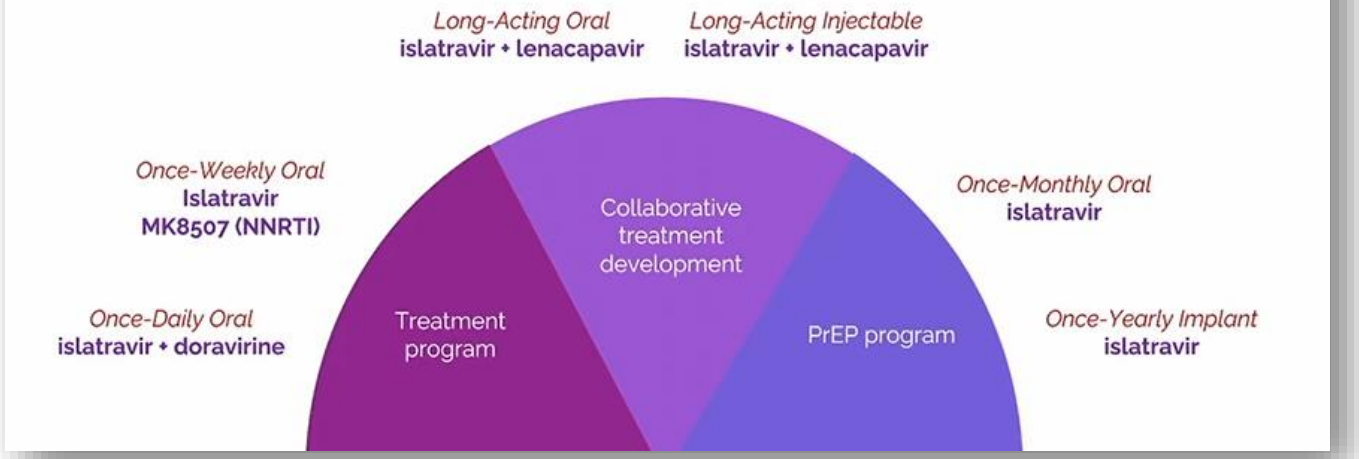
Due to decrease in lymphocytes and CD4+ cells in some participants

https://www.merck.com/news/merck-announces-clinical-holds-on-studies-evaluating-islatravir-for-the-treatment-and-prevention-of-hiv-1-infection/

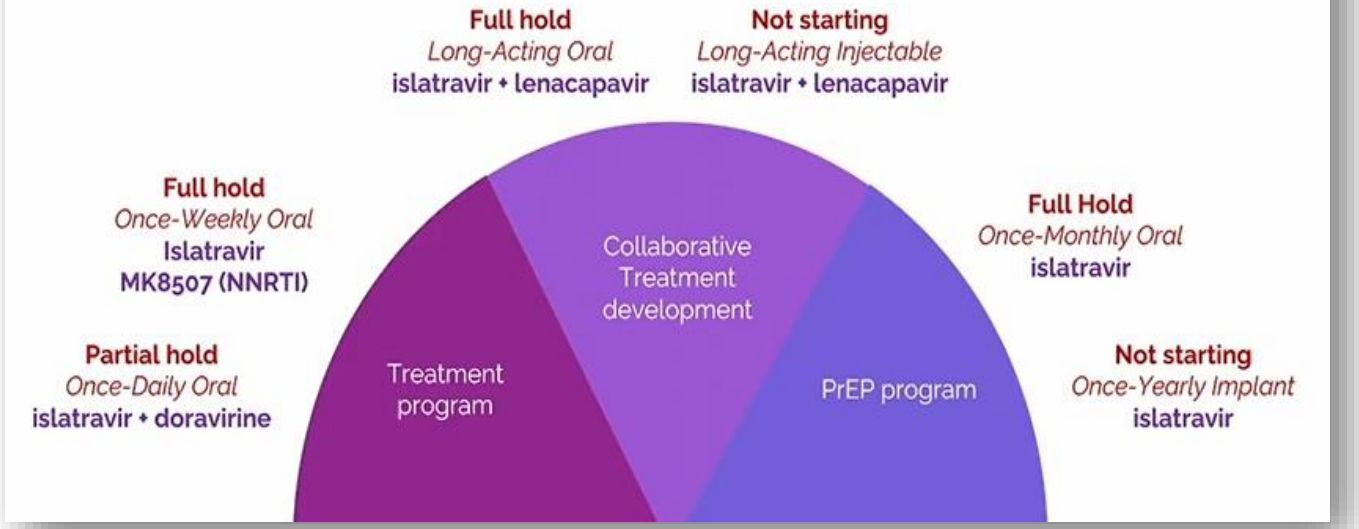
Hipótesis: análogos de la adenosina → Hallazgos similares en TDF/DDI

L. Oluoch Workshop 12 Feb CROI 2022

Islatravir : Nucleoside Reverse Transcriptase Translocation Inhibitor



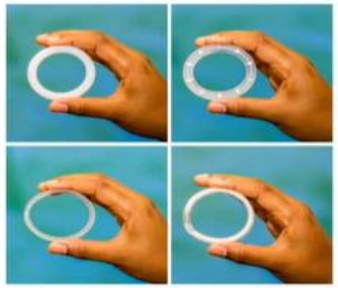
Islatravir development : Current Status



TENOFOVIR RING

Background

- Vaginal rings offer a user-centered, reversible, long-acting prevention approach
- Several studies have evaluated tenofovir (TFV) in topical formulations for HIV prevention*
  - TFV 1% vaginal gel demonstrated protection in CAP004
  - BUT not consistently effective likely due to low adherence
  - Topically delivered TFV may also prevent HSV-2 acquisition
- Extended duration vaginal rings (q 3 months) could:
  - Help increase adherence and thus, effectiveness
  - Reduce cost as well as clinic and user burden



*Abdool Karim Q et al. Science 2010 and 2020; Marrazzo JM et al. NEJM 2015; Delany-Moretlwe S et al. Lancet ID 2018; Marrazzo JM et al. JID 2019

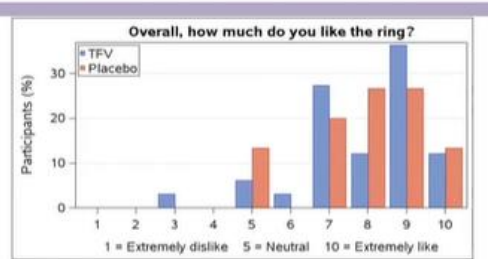
MTN-038 Overview

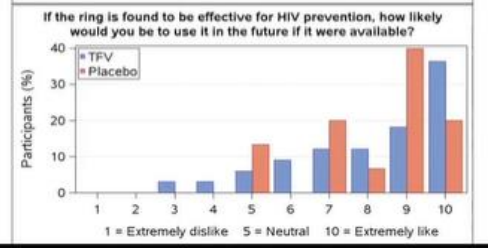
- Phase I (safety, PK, acceptability), 2-arm, randomized (2:1) trial:
  - 1.4 g TFV polyurethane ring
  - Placebo ring
- 49 HIV-uninfected participants assigned female sex at birth
  - Healthy
  - Age 18-45
- 3 study sites
  - University of Pittsburgh
  - University of Alabama at Birmingham
  - San Francisco Department of Public Health

Acceptability

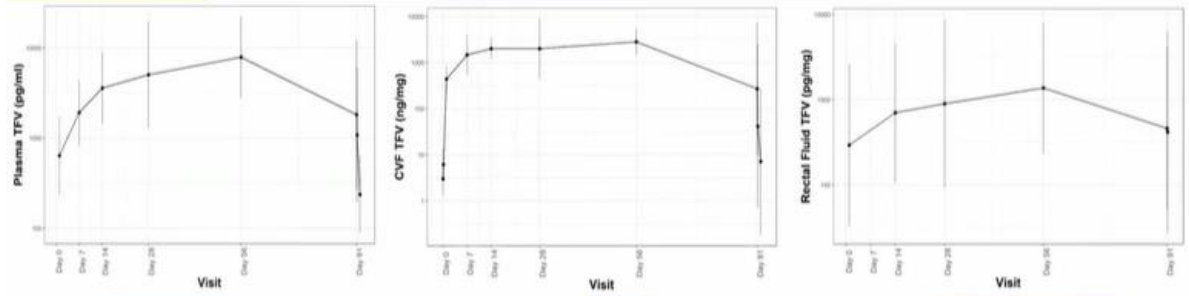
On 10-point Likert Scale:

- Most participants liked the rings
  - Median (IQR): 8 (7-9)
- Most were likely to use the ring if found effective
  - Median (IQR): 9 (7-10)





Geometric mean TFV concentrations in plasma, CVF, and rectal fluid



- T_{max} was 34 days for CVF and rectal fluid, 59 days in plasma
- Mean TFV concentrations declined at day 91 across compartments

A Liu Oral Abstract Sessions #82

AC MONOCLONALES

PHASE 1 TRIAL OF SUBCUTANEOUSLY ADMINISTERED VRC07-523LS AND PGT121

00856

Sharana Mahomed[1], Nigel Garrett[1], Edmund Capparelli[2], Farzana Osman[1], Tanuja Gengiah[1], Derseree Archary[1], Cheryl Baxter[1], Penny Moore[3], Quarraisha Abdool Karim[1], Dan Barouch[4], Patricia E. Fast[5], John R. Mascola[6], Julie E. Ledgerwood[6], Lynn Morris[3], Salim S. Abdool Karim[1] for the CAPRISA 012A study team

[1]Centre for the AIDS Programme of Research in South Africa, Durban, South Africa, [2]University of California San Diego, San Diego, CA, United States, [3]National Institute for Communicable Diseases, Johannesburg, South Africa, [4]Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Boston, MA, USA, [5]International AIDS Vaccine Initiative, New York, NY, United States, [6]Vaccine research Centre (VRC), National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland, USA.

LONG ACTING **DORAVIRINE** FOR TREATMENT AND PREVENTION OF VAGINAL VIH TRANSMISSION (M Kovarova)

Ratones, 5 meses

Injectable long-acting ISFI formulation of doravirine protects from multiple high-dose vaginal HIV exposures.

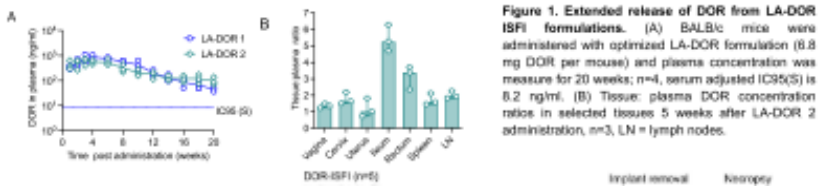
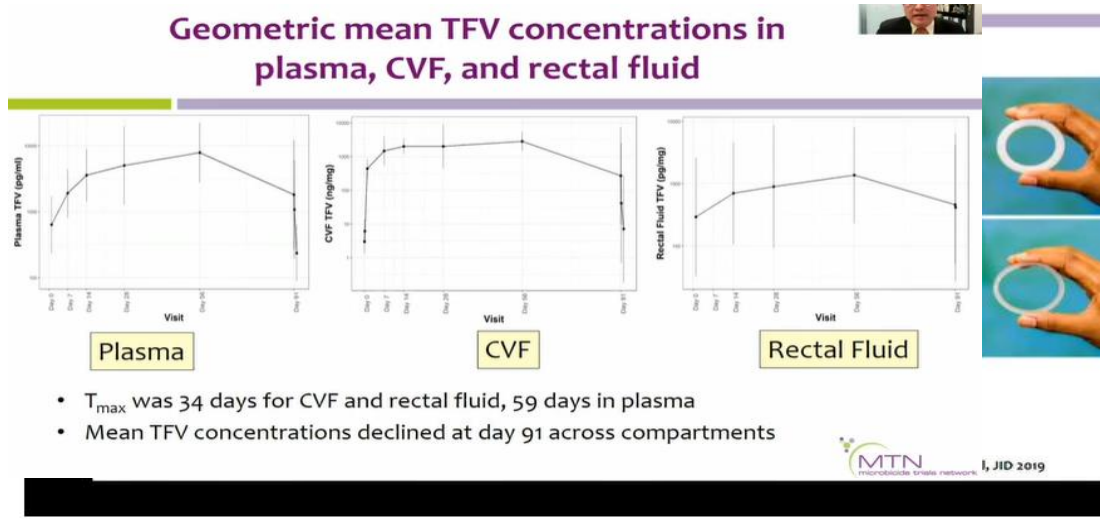


Figure 1. Extended release of DOR from LA-DOR ISFI formulations. (A) BALB/c mice were administered with optimized LA-DOR formulation (8.8 mg DOR per mouse) and plasma concentration was measure for 20 weeks; n=4, serum adjusted IC95(5) is 8.2 ng/ml. (B) Tissue: plasma DOR concentration ratios in selected tissues 5 weeks after LA-DOR 2 administration, n=3, LN = lymph nodes.

TENOFOVIR RING



A Liu Oral Abstract Sessions #82

Evaluating Adherence

Ring adherence

Based on estimated dapivirine release calculated using residual drug (RD) levels in returned rings

Non-use
- RD levels showing release of <0.9mg

Some use
- RD levels showing release of 0.9 to <4.0mg

Consistent with 28 days of use
- RD levels showing release of ≥4.0mg

Oral PrEP adherence

Measured via tenofovir diphosphate (TFV-DP) levels in dried blood spots (DBS)

Non-use
- TFV-DP levels of <16fmol/DBS punch

Some use
- TFV-DP levels of 16-700fmol/DBS punch

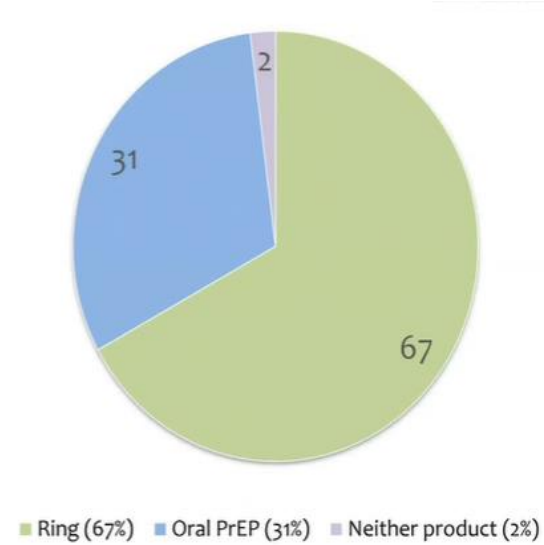
High adherence
- TFV-DP levels of ≥ 700fmol/DBS punch

We compared the proportion of visits with high adherence between the crossover and choice periods for each product

Product Choice in Period 3

Of 227 (92%) participants who reached the choice period, more than 2/3 (152) chose the ring

Randomization sequence in the crossover period was not associated with product choice



Higher adherence when given a choice (MTN-034)

HPTN HIV Prevention Trials Network

Estimating benefits from using on-demand oral PrEP by MSM in US and Thailand: A Modeling study

00836

Sarah Stansfield,[1] Mia Moore,[1] Marie-Claude Boily,[2] James P Hughes,[1,3] Deborah Donnell,[1,3] Dobromir Dimitrov[1,3]
[1]Fred Hutchinson Cancer Research Center, Seattle, Washington, USA, [2]Imperial College London, UK, [3]University of Washington, Seattle, USA

ACKGROUND

Daily and on-demand pre-exposure prophylaxis (PrEP) with oral TDF-FTC are both effective at preventing HIV acquisition among men who have sex with men (MSM)

Only daily PrEP is recommended in the US

GOAL: identify sub-groups of MSM who would have higher effectiveness or significantly lower pills taken with similar effectiveness when using on-demand PrEP

ETHODS

Simulated the reduction in HIV risk in two synthetic cohorts of 10,000 MSM prescribed oral PrEP in Harlem and Bangkok

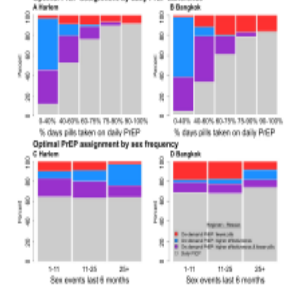
PrEP adherence and sexual behavior patterns were calibrated to data from the HIV Prevention Trials Network (HPTN) 067. PrEP efficacy was based on number of pills per week (Anderson, 2012, Sci Transl Med)

PrEP effectiveness was based on the number of pills taken around individual's sex acts

Individuals were assigned daily PrEP for 6 months and on-demand PrEP for 6 months (2-1-1 regime, with 2 pills the day

MSM with low adherence to daily PrEP (not low sex frequency) **benefit most from switching to on-demand PrEP**

FIGURE 3. Those for whom on-demand 2-1-1 PrEP was optimal by adherence to daily PrEP (A & B) and sex frequency (C & D) in the trial-based analysis



CONCLUSIONS

Oral PrEP adherence	Chose oral PrEP	Chose ring/neither	p-value
Red/yellow at least once	32 (20%)	129 (80%)	<0.001
Always green	39 (58%)	28 (42%)	

Non-use (red): TFV-DP levels of <16fmol/DBS punch
Some use (yellow): TFV-DP levels of 16-700fmol/DBS punch
High adherence (green): TFV-DP levels of ≥ 700fmol/DBS punch

Ring adherence	Chose ring	Chose oral PrEP/neither	p-value
Red/yellow at least once	134 (67%)	65 (33%)	0.85
Always green	19 (66%)	10 (35%)	

Non-use (red): RD levels showing release of <0.9mg
Some use (yellow): RD levels showing release of 0.9 to <4.0mg
Consistent with 28 days of use (green): RD levels showing release of ≥4.0mg

High adherence to oral PrEP in the crossover period was strongly associated with choice of oral PrEP (p<0.001)

No such association was observed for ring choice (p=0.85)

Ngure et al CROI 2022 Abstract #88 LB

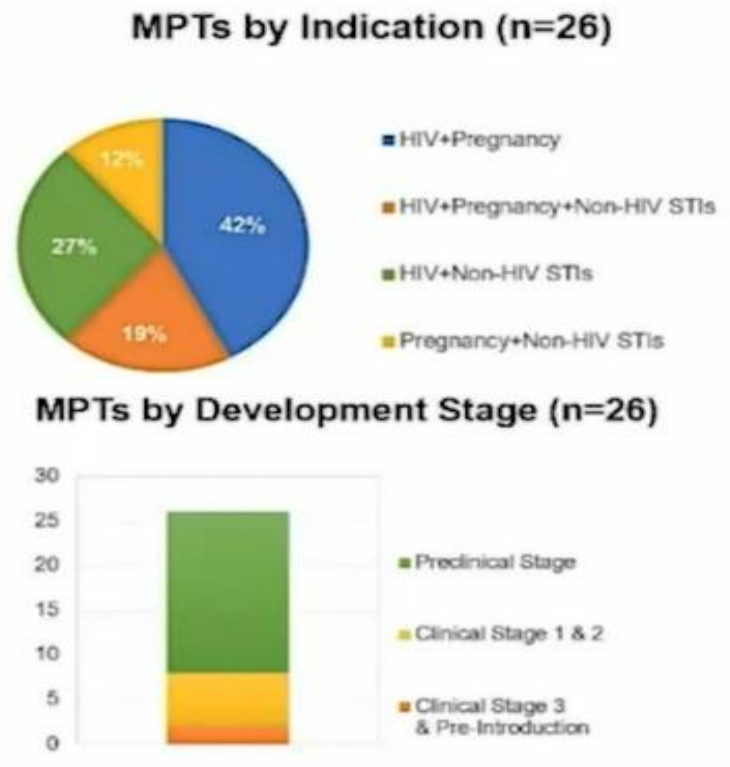
MULTIPURPOSE TECHNOLOGY: POTENTIAL FOR DECREASING MULTIPLE HEALTH RISKS

- Globally, major health risks for young women are unintended pregnancy and HIV and other STIs
- Important considerations for MPT development:
  - Minimal to no drug-drug interactions
  - Minimal to no systemic or local side effects
  - Easy to manufacture and administer with minimal discomfort
  - Easy removal or reversal of formulation in case of emergency or adverse effects
  - Preferences of target populations

- Intravaginal Rings (IVR)
- Gels (Vaginal & Rectal)
- Films (Vaginal & Rectal)
- Fast Dissolving Inserts (Vaginal & Rectal)
- Oral Pills
- Implants (Subcutaneous)
- Microarray Patches
- Injectables (Subcutaneous)
- Enemas (Rectal)

The Initiative for Multipurpose Technologies. https://mpts101.org

Young IC, Benhabbour SR. Polymers 2021;13:2450



L. Oluoch Workshop 12 Feb CROI 2022

LONG-ACTING INJECTABLE FOR PREVENTION OF HIV AND UNPLANNED PREGNANCY

Isabella Young

New Investigator Scholarship Recipient

University of North Carolina at Chapel Hill
Chapel Hill, NC, USA

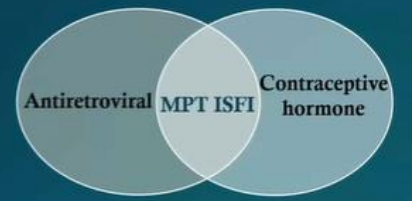
Unmet need for long-acting multipurpose prevention technologies (MPTs)

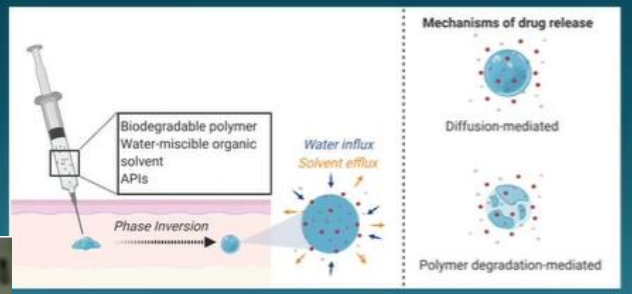
PROBLEM

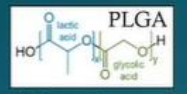
- 38 million people worldwide are living with HIV
- Approximately 50% of all pregnancies are unplanned
- Condoms are the only multipurpose prevention technology (MPT)

SOLUTION – Injectable MPT in situ forming implant (ISFI)

- Long-acting (> 3 months)
- Subcutaneous administration
- Biodegradable and removable





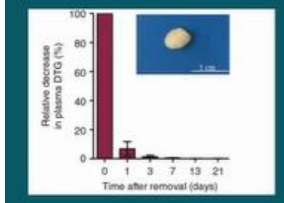


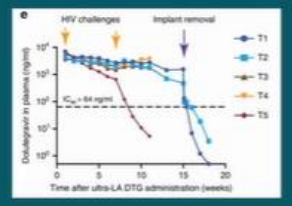
MPT ISFI Phases of Development

PHASE 1

Assess feasibility of an MPT ISFI with Dolutegravir (DTG) + contraceptive (medroxyprogesterone acetate (MPA, Depo Provera®) or etonogestrel (ENG, Nexplanon®))

- **DTG ISFI** demonstrated feasibility and ultra-long-acting release from ISFI[1]
- Ability to remove **(only if needed)**[1]
- PK and efficacy studies in humanized mouse models showed protection against HIV[1]





PHASE 2

Engineer a more clinically translational MPT ISFI with Cabotegravir (CAB) and MPA or ENG

- Apretude (CAB LA) for HIV prevention approved December 2021
- Cabenuva (CAB + RPV) for HIV treatment approved January 2021

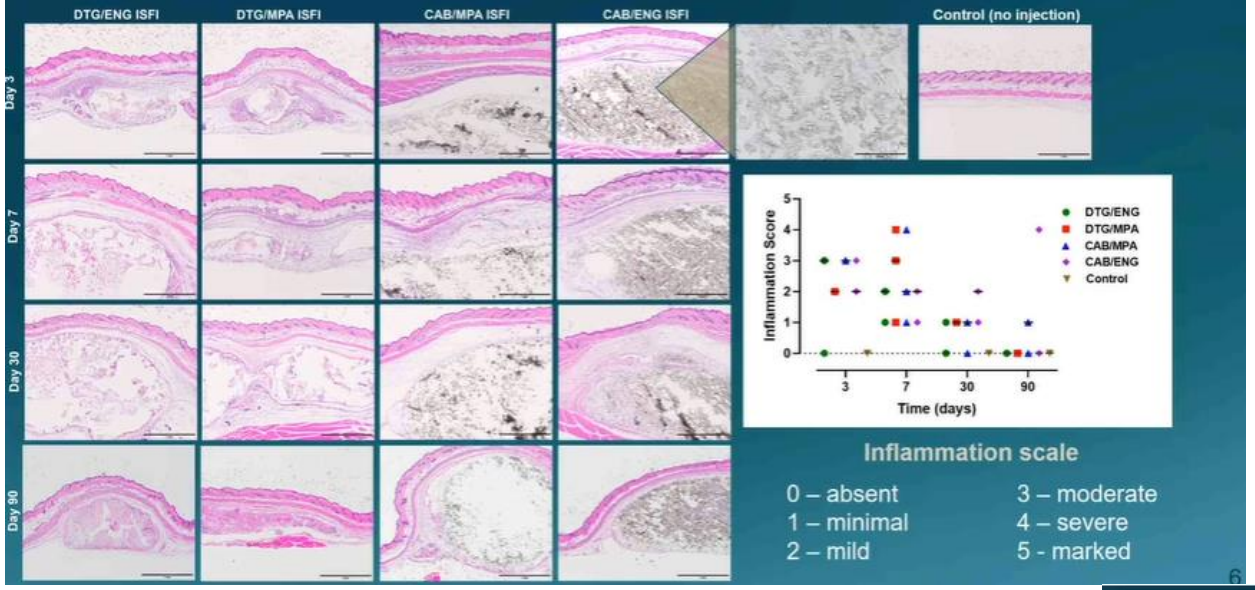
[1]Benhabbour, S.R., Kovarova, M., Jones, C. *et al.* Ultra-long-acting tunable biodegradable and removable controlled release implants for drug delivery. *Nat Commun* **10**, 4324 (2019). https://doi.org/10.1038/s41467-019-12141-5

90 días, ratones DTV o CAB

I Young . Oral Abstract Sessions #80

Assessment of local inflammation

Hematoxylin and eosin (H&E) stain of excised depot and surrounding subcutaneous tissue (N=3 per group per timepoint)



Inflammation scale

0 – absent
1 – minimal
2 – mild
3 – moderate
4 – severe
5 - marked

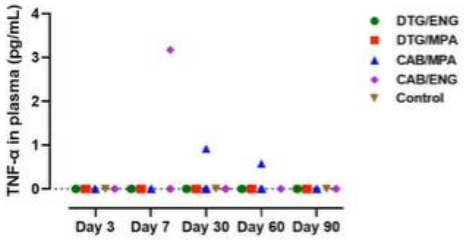
6

Assessment of systemic inflammation

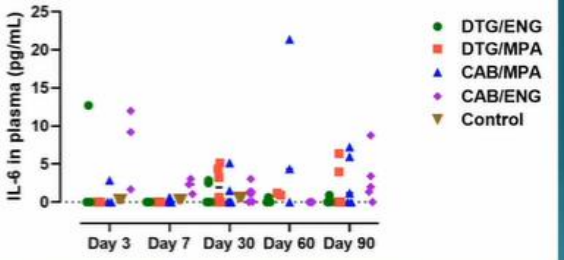
Utilize enzyme-linked immunosorbent assay (ELISA) to detect **TNF-α and IL-6** (major pro-inflammatory cytokines responsible for immune response activation) at 3, 7-, 30-, 60-, and 90-days post-injection (n=3-6 per group per timepoint)

Tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) are inflammatory cytokines produced by macrophages and/or monocytes at the site of inflammation

TNF-α



IL-6



I Young . Oral Abstract Sessions #80

Pharmacokinetic study of islatravir and etonogestrel implants in macaques

00444

Michele B Daly[1], Andres Wong-Sam[1], Linying Li[2], Archana Krovi[2], Gregory Gatto[2], Victoria Mrotz[1], Catalina Forero[1], Joy Gary[1], James Mitchell[1], Ariane Van der Straten[3], Walid Heneine[1], Gerardo García-Lerma[1], Charles Dobard[1], Leah M. Johnson[2]
[1]Centers for Disease Control and Prevention, Atlanta, GA, US, [2]RTI International, Research Triangle Park, NC, US, [3]University of California San Francisco, Center for AIDS Prevention Studies, San Francisco, CA, US

BACKGROUND

Prevention of HIV and unintended pregnancies are public health priorities. Methods that provide sustained release of drugs can improve patient adherence and increase efficacy of medications that require consistent dosing. **Long-acting (LA)** implants have been successfully used for contraception including the FDA-approved Nexplanon implant which releases the hormone **etonogestrel (ENG)** to prevent unintended pregnancy for up to 3 years.

LA products for HIV **pre-exposure prophylaxis (PrEP)** are building upon these models. **Islatravir (ISL)** is a novel nucleoside reverse transcriptase translocation inhibitor that is phosphorylated within cells to the active metabolite **ISL-triphosphate (ISL-TP)**. The long half-life and potency of ISL make it an attractive candidate for delivery by an implant for LA PREP.

Here, we evaluated safety and pharmacokinetics of ISL and ENG implants in female pig-tailed macaques.

METHODS

Biodegradable implants with sustained delivery of **ISL** and **ENG** for >3 months in nonhuman primates show promise for multi-purpose prevention of HIV and pregnancy.

RESULTS

Figure 2. Concentrations of ISL-TP in PBMCs

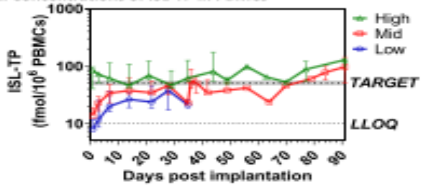


Figure 2. (Left) PBMC ISL-TP levels for the low (blue), mid (red) and high (green) ISL groups. The pharmacokinetic target of 50 fmol ISL-TP/10^6 PBMCs (Target) and lower limit of quantification (LLOQ) are shown with dashed lines.

Figure 4. Heat map of implant-site reactions

Figure 4. Implants for each animal (column) and the weekly Draize score (ranging from 0 - 4) are shown.

SUMMARY OF RESULTS

- Plasma ISL and ISL-TP in PBMCs were sustained for >3 months. Dose linearity was observed (**Fig 2, Table 1**).
- ISL-TP was detected in vaginal and rectal tissue (**Table 1**).
- ISL did not alter natural cycling of p4 (**Fig 3A**, day 0-35).
- ENG levels were stable and sufficient to suppress p4 production by day 14 post implantation (**Fig 3A and 3B**).

MB Daily Abstract# 444

I Young
Next-generation
Islatravir/Etonogestrel/Ethinyl Estradiol MPT
Intravaginal Ring
Abstract # 445

First-in-line 3D-printed MPT IVR demonstrates sustained drug release and was well-tolerated in sheep and macaques

- 3D CLIP IVRs were loaded with EFdA, ENG, and EE (3.7 wt%, 0.19 wt%, and 0.04 wt% respectively) for in vitro release study in SVF (sheep pH 7). Release samples were collected and drugs quantified by HPLC. All drugs exhibited low burst in the first 24 h (<10%) and sustained zero order release over 180 day **(Fig.2).**

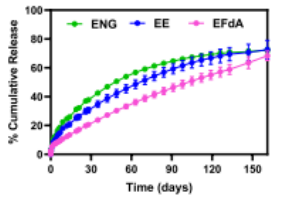


Fig. 2 In vitro release of EFdA/EE/ENG in simulated vaginal fluid (SVF, sheep pH 7) at 37℃.

- MPT IVRs were administrated to 4 female sheep (4.03-6.48 mg/kg EFdA, 0.2-0.3 mg/kg ENG, and 0.05-0.07 mg/kg EE) for a 21-day pharmacokinetic study. Plasma, vaginal biopsies, and fluids were collected **(Fig. 3).**
- Macaque-sized IVRs (25 mm OD & 6.0 mm CSD) with Islatravir were administered to 3 female non-human primates for a 30-day pharmacokinetic study. Plasma, PBMCs, vaginal biopsies, and fluids were collected. **(Fig. 4).**

Fig. 3

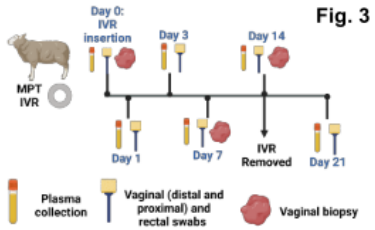
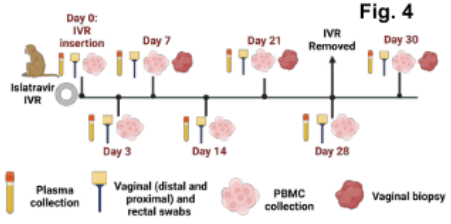


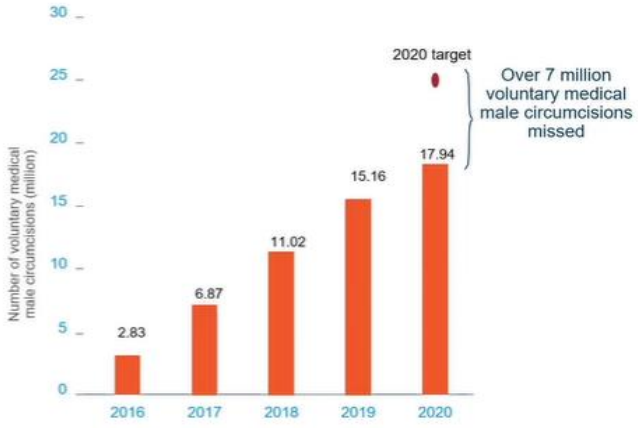
Fig. 4



Circuncisión

Introduction

- Voluntary Medical male circumcision (VMMC) is protective against HIV infection, with >60% protection
- Zambia and South Africa are among the 15 priority countries with a target to expand medical male circumcision coverage to 80%
- Traditional male circumcision (TMC) practiced as a rite of passage to adulthood in many Southern African communities

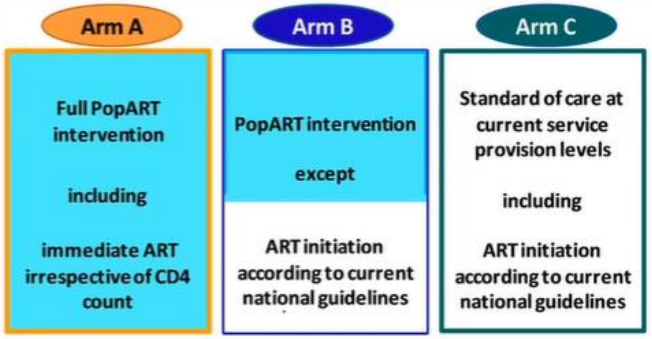


Cumulative number of voluntary medical male circumcisions 15 priority countries from 2016–2020, and targets for 2020

Source: UNAIDS Global AIDS Monitoring, 2021 (https://aidsinfo.unaids.org/).

Study population

- HPTN 071 (PopART) is a cluster-randomized trial
  - Impact of a combination prevention package on population-level HIV incidence in Zambia and South Africa
- Included 21 study communities (12 in Zambia and 9 in South Africa) and 7 matched triplets
- Communities in each matched triplet are assigned to:
  - Arm A
  - Arm B
  - Arm C
- Arms A and B included referral for medical male circumcision (MMC) for HIV-uninfected men



11,000 varones
3 años

KB Zewide Abstract #87

Male circumcision status and HIV incidence during HPTN 071 follow-up

Circumcision status	Incidence HIV infections (rate per 100 person-yr)	Adjusted hazard ratios[1] (95% CI)	P value
Medical	11/3458 (0·31)	0·30 (0·16, 0·55)	<0·0001
Traditional	39/4166 (0·94)	0·84 (0·54, 1·31)	0·45
Uncircumcised	92/9402 (0·97)	Ref.	Ref.

[1]Adjusted for community and age.

PrEP EN GESTACIÓN

HPTN HIV Prevention Trials Network

Evaluation of CAB-LA Safety and PK in Pregnant Women in the Blinded Phase of HPTN 084

00700

Author **Sinead Delany-Moretlwe**[1], James P. Hughes[2], Xu Guo[2], Brett Hanscom[3], Craig W. Hendrix[4], Jennifer Farrior[5], Ribka Berhanu[1], Alex Rinehart[6], Susan Ford[6], James Rooney[7], Adeola Adeyeye[8], Raphael Landovitz[9], Myron Cohen[10], Mina C. Hosseinipour[11], Mark A. Marzinke[4] on behalf of HPTN 084 study group Institutions: 1 Wits RHI, University of the Witwatersrand Johannesburg, South Africa, 2 University of Washington, Seattle, WA, United States, 3 Fred Hutchinson Cancer Research Center, Seattle, WA, United States, 4 The Johns Hopkins University School of Medicine, Baltimore, MD, United States, 5 FHI 360, Durham, NC, United States, 6 ViiV Healthcare, Research Triangle Park, NC, United States, 7 Gilead Sciences, Inc, Foster City, CA, United States, 8 National Institute of Allergy and Infectious Diseases, Bethesda, MD, United States, 9 University of California Los Angeles, Los Angeles, CA, United States, 10 University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

BACKGROUND

HPTN 084 is a phase 3 randomized, double-blind, double-dummy trial that showed that long-acting injectable cabotegravir (CAB-LA 600 mg Q8 weekly) was superior to tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in preventing HIV in women in sub-Saharan Africa. Participants were required to use long-acting contraception; pregnancies however occurred during the trial. We report on the safety and pharmacokinetics of CAB-LA in women who became pregnant during the blinded phase of HPTN 084.

METHODS

If a participant had a positive pregnancy test, blinded study product was withheld and she was offered open-label TDF/FTC. Positive pregnancy tests were confirmed at a 2nd visit four weeks later, and, if CONFIRMED, TDF/FTC was continued through pregnancy outcome and until cessation of breastfeeding. Participants with CONFIRMED pregnancy were unblinded to study arm, and continued follow-up visits; Live infants were assessed at birth and 12 months. Adverse events (AEs) post-confirmation of pregnancy were compared between study arms from time of first positive pregnancy test to last pregnancy follow up visit. Only participants who received at least one injection were included in the safety analysis. The apparent terminal phase half-life (t1/2app) of CAB-LA in pregnant women in HPTN 084 (n=18/29; with at least ≥3 CAB samples available after injection cessation) was compared to non-pregnant women from HPTN 077 (n=39), a phase 2 safety and pharmacokinetics study. Multivariate linear regression assessed factors associated with t1/2app

TABLE 1. Pregnancy incidence, by study group

	CAB LA N=1614	TDF/FTC N=1610
No. of pregnancies*	39	37
Person-years	1915.5	1980.9
Incidence rate (95% CI)	2 (1.4, 2.8)	1.9 (1.3, 2.6)
No. CONFIRMED pregnancies	29	20
Person years	1915.5	1980.9
Incidence rate (95% CI)	1.5 (1.0, 2.2)	1.0 (0.6, 1.6)

Residual CAB-LA was generally well tolerated in pregnant women. The $t_{1/2app}$ was comparable between pregnant and non-pregnant women. Ongoing studies will examine the safety and pharmacology of CAB-LA in women who choose to continue CAB-LA through pregnancy.

RESULTS - SAFETY

There were 49 confirmed pregnancies (29 CAB, 20 TDF/FTC) in 48 participants during the blinded phase of the study. Pregnancy incidence was 1.3 per 100 person-years (py). CAB-LA participants (n=6) experienced more pregnancy-associated AE than TDF/FTC participants (n=1). All pregnancy-associated AE (n=10) were judged as unrelated to study product and grade 1-3. No congenital anomalies were observed. Of the 43 participants (26 CAB-LA, 17 TDF/FTC) with confirmed pregnancy who received at least one injection, the incidence of ≥ grade 2 AEs in the CAB arm was 113/100 py (95% CI: 69.3-185.4/100 py) vs. 166/100 py (95% CI: 102.2-271.0/100 py) in the TDF/FTC arm (p=0.064).

TABLE 2. Adverse events – pregnancy, postpartum and perinatal conditions

	CAB LA N = 9 events	TDF/FTC N = 1 event
Hyperemesis gravidarum	2	1
Pregnancy-induced hypertension	1	0
Pre-eclampsia	1	0
Oligohydramnios	1	0
Premature rupture of membranes	2	0
Incomplete abortion	2	0

TABLE 3. Pregnancy outcomes, by study group

	CAB LA N=29	TDF/FTC N=20
Known pregnancy outcomes*	27	18
Live births	22 (82%)	14 (78%)
Pregnancy Loss - total	5 (18%)	4 (22%)
>=37 weeks	0	0
20-36 weeks	1	3
<20 weeks	4	1
Ectopic pregnancies	0	0
Congenital anomalies**	0	0

RESULTS - PHARMACOKINETICS

FIGURE 1. Linear regression of $\log_{10}$ [CAB] vs. time, for HPTN 084 and HPTN 077

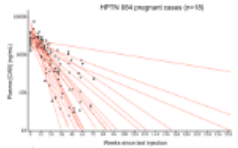


FIGURE 2. C

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PREGNANCY AND BIRTH OUTCOMES IN PREP EXPOSED & UNEXPOSED PREGNANT SOUTH AFRICAN WOMEN

00705

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BACKGROUND

- There are few safety data on the use of oral PrEP in pregnancy presenting a barrier to implementation in some settings

METHODS

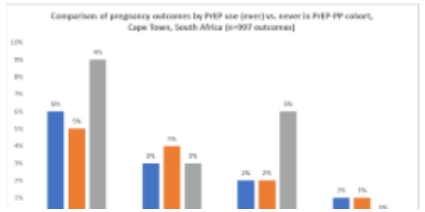
- Based at a primary care facility in Cape Town, the **PrEP in pregnancy and postpartum (PrEP-PP) study** offered HIV prevention counseling and PrEP to consenting pregnant women (≥16 years) without HIV from their first antenatal care (ANC) visit through 12 months' postpartum
- We compared **pregnancy and birth outcomes including pregnancy loss** (miscarriage, stillbirth, termination) and **birth outcomes** (birthweight [median], low-birth weight [<2500 grams], pre-term [<37 weeks' gestation] and neonatal death) between PrEP exposed (any PrEP use while pregnant) vs. unexposed (no PrEP use in pregnancy), abstracted from routine health records, and compared these with clinic-wide statistics from the same period
- Analysis of miscarriage and stillbirth were restricted to women who entered before 20 and 28 weeks, respectively
- Analysis of birth outcomes included all women with available data

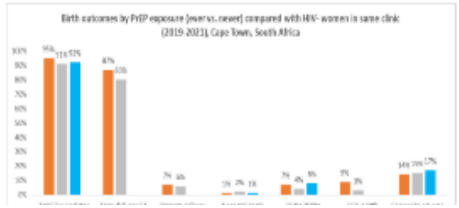
Rate of adverse pregnancy and birth outcomes high in the population
PrEP exposure in pregnancy is not associated with any increased adverse pregnancy or birth outcomes
Oral PrEP should be integrated into PMTCT and ANC care in high HIV incidence communities

PrEP-PP Pre-exposure Prophylaxis in Pregnancy & Postpartum

RESULTS

- Between August 2019 and January 2022, we ascertained n=997 pregnancy outcomes
  - Median gestation at first ANC= 23 weeks [IQR, 14-31]
  - Median maternal age=26 years [IQR, 22-31]
- 93% (n=931) were PrEP exposed
- Overall, 94% had singleton live births
- We recorded 5% miscarriages or stillbirths in the PrEP exposed group vs. 9% in the unexposed group (p=0.06)
- **There were no differences in birth outcomes between the PrEP-exposed vs. unexposed (composite adverse birth outcome=14% in both groups; p=0.99).**
- **Among the PrEP exposed, there was no association with duration of antenatal exposure and birth outcomes (p=0.84).**
- Comparing statistics on birth outcomes in HIV-uninfected women, the frequency of adverse birth outcomes was similar to levels in the PrEP exposed cohort (p>0.05).





CONCLUSIONS

While the overall frequency of adverse pregnancy and birth outcomes is high in this setting, **these reassuring data suggest no differences in pregnancy outcomes comparing women exposed to PrEP to women with no exposure to PrEP.**

ADDITIONAL KEY INFORMATION

Clinical trials reference: NCT03902418

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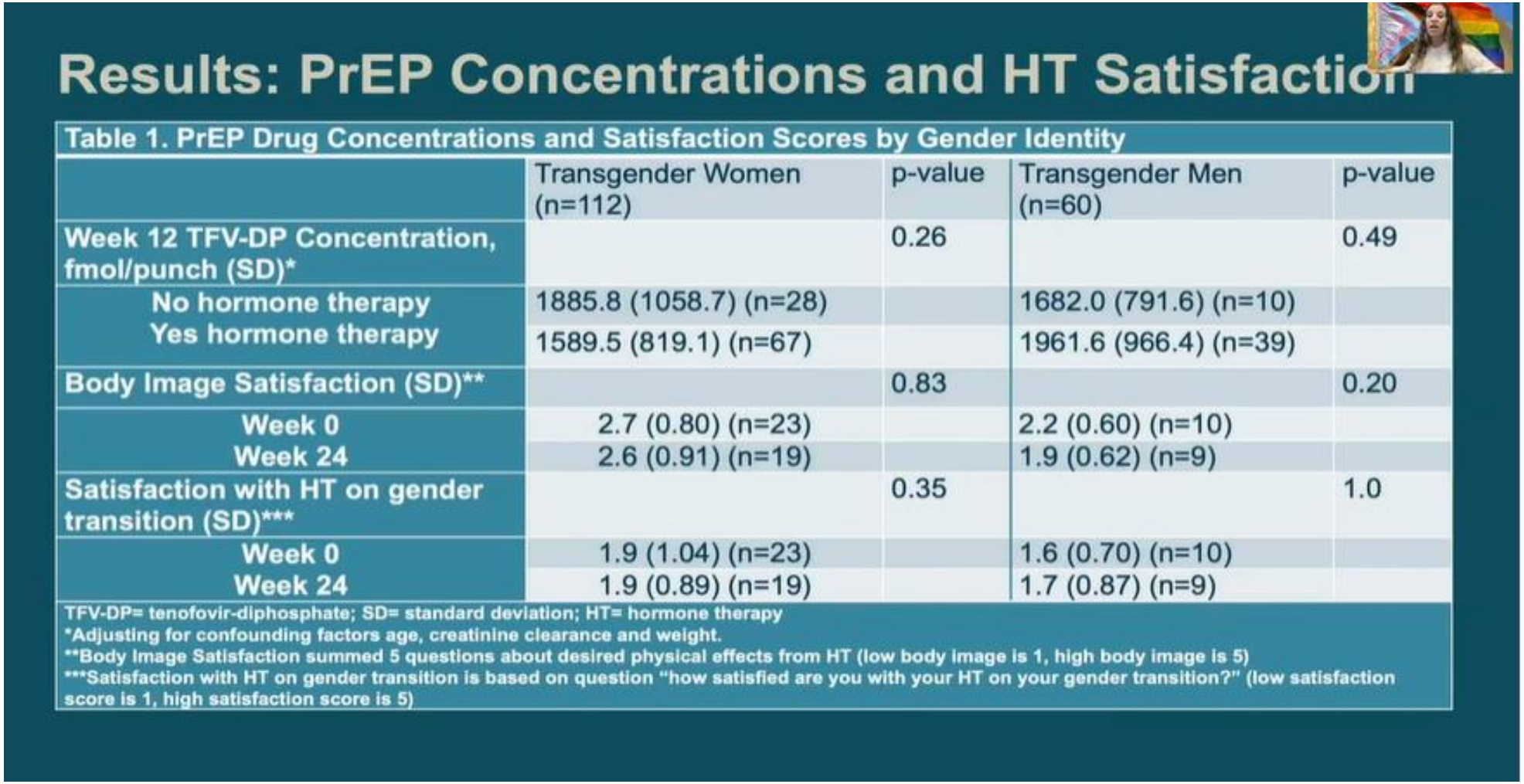
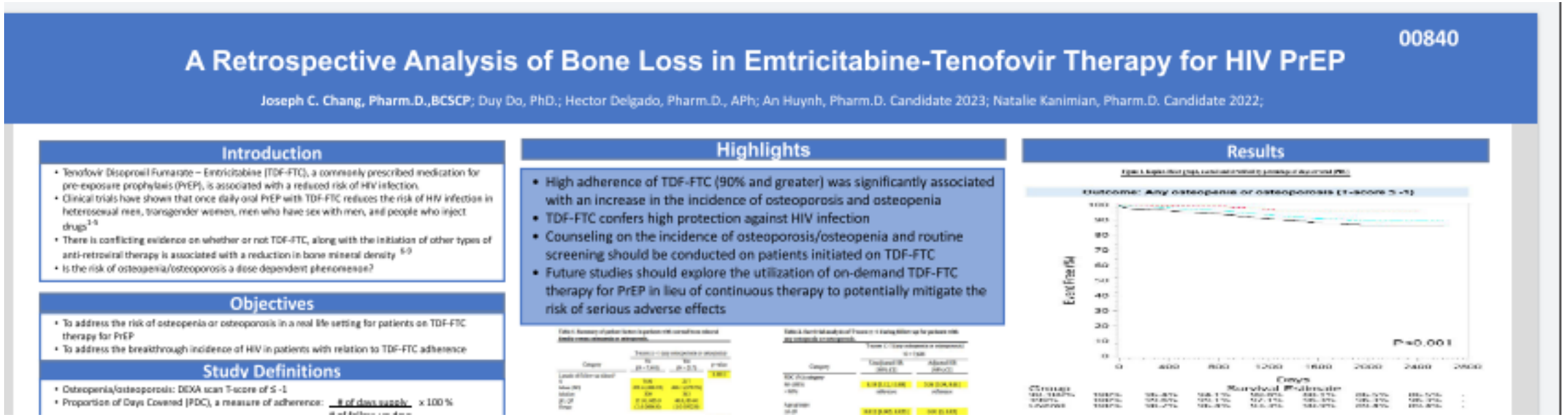
Interacciones PrEP y hormonas



J Blumenthal Abstract #84



- Of **7,698** patients, **217** developed osteopenia or osteoporosis by dexa SCAN (T-score ≤ -1)
- Average follow-up time for the cohort is **502**.6 days
- Patients in a continuous tto (90.8%) were more likely to develop osteopenia/osteoporosis compared to a demand (9.2%) (p<0.001)
- Hepatitis B, CVD, CKD, age, baseline eGFR<90 mL/min/1.73 m2 and BMI were not associated with an increase in the risk of osteopenia/osteoporosis after adjusting for other confounders
- Obesity conveyed a protective effect on the incidence of osteoporosis/osteopenia
- This study was able to confirm that TDF-FTC is highly effective against HIV infection even with low adherence rate patients

HIV DRUG RESISTANCE AND CLUSTERING PATTERNS AMONG PREVIOUS PREP USERS WHO SEROCONVERTED

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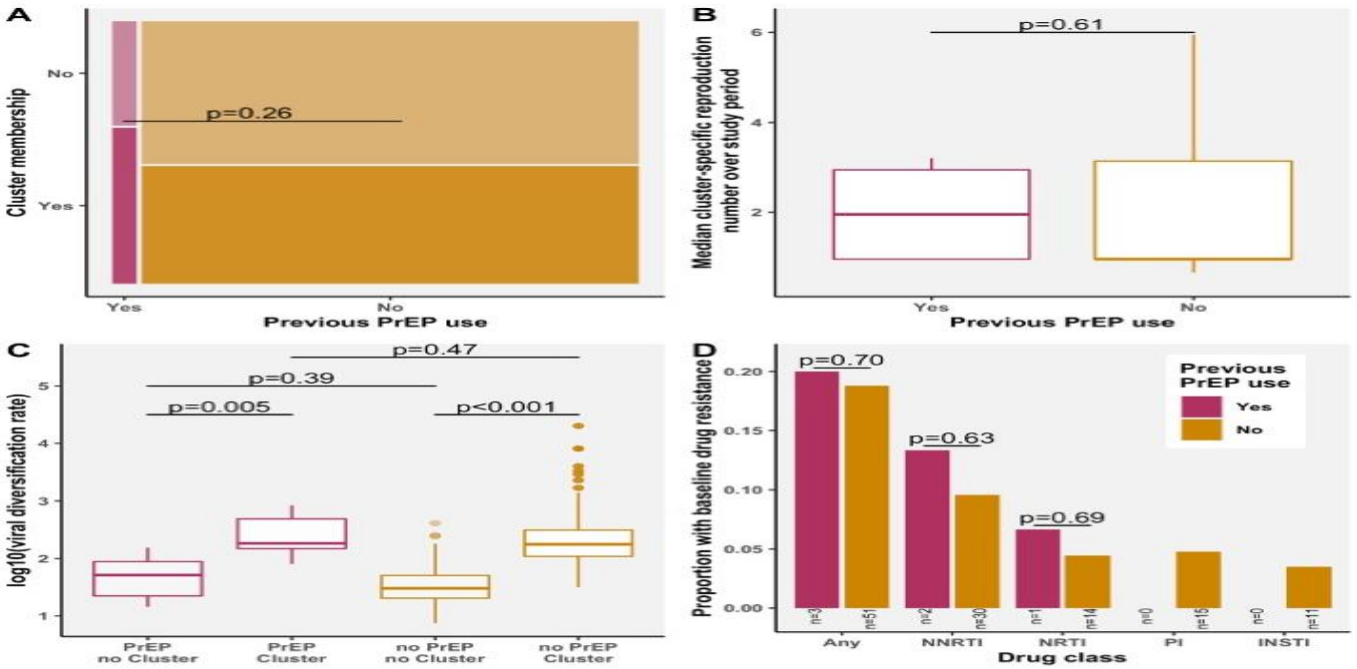

A comparison of the proportion of PUWS and NPUWS who joined phylogenetic clusters, using a two-sided chi-squared statistical test. B) The median cluster-specific reproduction number (of clusters with 20 or more members) in the study period of clusters joined by either PUWS or NPUWS was compared using a Kruskal-Wallis test. C) The phylogenetic viral diversification rate was compared by PrEP use and by clustering using a Kruskal-Wallis test, followed by pairwise Mann-Whitney tests. D) The proportion of PUWS and NPUWS with baseline drug resistance mutations to any or specific drug classes were compared using two-sided chi-squared tests.

Desde 2018 hasta 2021, 7465 personas recibieron PrEP con 15 (0,20 %) infecc. comparado con 314 nuevas infecc,.en no usuarios de PrEP.

El uso previo de PrEP no se asoció con la agrupación filogenética, las tasas de diversificación viral, o la resistencia a los fármacos.

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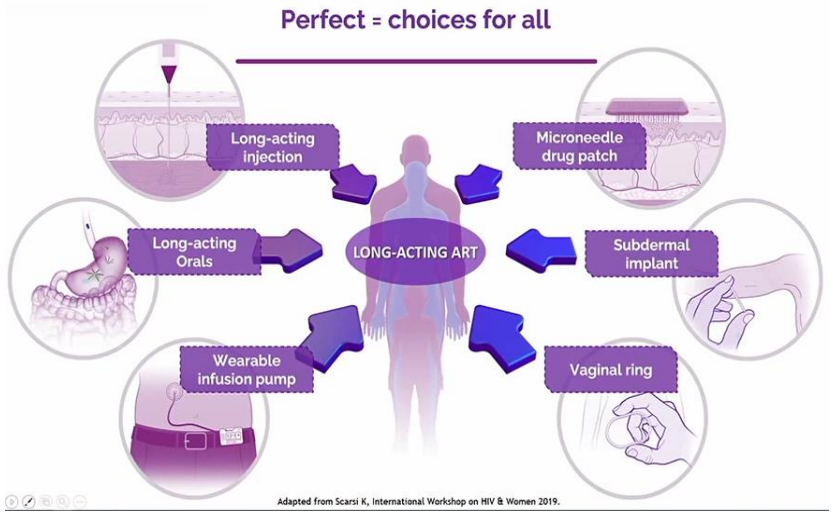
CONCLUSIONES



La PrEP se postula como la estrategia más eficaz en la actualidad para controlar la pandemia VIH, pero la implementación es lenta y desigual.
Diversificar las modalidades de PrEP permite que la selección individual aumente la adherencia.
La PrEP oral a demanda disminuiría los efectos adversos.
Los LA han supuesto un cambio en el paradigma para PrEP (y tratamiento), siendo el acceso (económico, logístico) sus principales limitaciones.
Es fundamental poder diagnosticar precozmente en pacientes bajo LA el fracaso virológico o las infecciones incidentes mediante métodos más sensibles que la serología.

Muchas gracias

jvillar@hospitaldelmar.cat

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