HIV Cases That Arrive in the ED and UC

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Disclosure

I have no financial interests or relationships to disclose.

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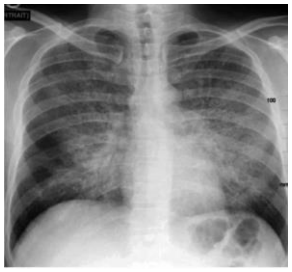
Learning Objectives

1. To discuss HIV treatment paradigms in 2024
2. To review HIV prevention options
3. To summarize HIV-related comorbidities relevant for ED/UC management

Case #1

48-year-old man with HIV CD4 92, HIV viral load 258,000 arrives in the ER with shortness of breath, cough, fevers and malaise for ~ 3 weeks. Given AIDS diagnosis, work-up fundamentally led to diagnosis of PjP pneumonia.

Patient has been living with HIV for over 10 years but unable to take oral ART mainly due to stigma- doesn't want his brother (with whom he lives) to know he has HIV infection.



Which HIV Regimen Has Been Shown to Increase Adherence in Those with Challenges to Taking ART?

A. Bictegravir/tenofovir alafenamide (TAF)/emtricitabine
B. Darunavir/cobicistat/TAF/emtricitabine (FTC)
C. Dolutegravir/abacavir/lamivudine
D. Long acting cabotegravir/rilpivirine

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INSTIs 1ST LINE AT THIS POINT FOR HIV TREATMENT WORLDWIDE

Study	Population	Comparator	Outcome	Resistance
BICTEGRAVIR				
1489	Naïve	DTG/ABC/3TC	Non-inferior	0
1490	Naïve	DTG+FTC/TAF	Non-inferior	0
1844	Suppressed	DTG/ABC/3TC	Non-inferior	0
1878	Suppressed	Boosted PI + 2 NRTIs	Non-inferior	0 to INSTI but 1 L74V in PI arm
1961 (women)	Suppressed	E/C/F/(TAF or TDF) ATV+RTV + FTC/TDF	Non-inferior	0 to INSTI but 1 M184V in ELV/cobi
DOLUTEGRAVIR				
SINGLE	Naïve	EFV/TDF/FTC	Superior	0 in DTG arm; 7 in EFV
FLAMINGO	Naïve	DRV/r with 2 NRTI backbone	Superior	0 in either
SPRING-2	Naïve	RAL with 2 NRTI backbone	Non-inferior	0 in DTG; 1 INSTI/NRTI in RAL

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Patient States He Will Not Take Oral ART at This Time; Which Long-acting Regimen Has Been Approved for Those with Viremia?

A. Cabotegravir/rilpivirine
B. Lenacapavir/cabotegravir
C. Lenacapavir + cabotegravir/rilpivirine
D. No long-acting ART FDA-approved for this indication

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Only Combination Treatment for LA ART -Cabotegravir (CAB)/ Rilpivirine (RPV)- 3 Registrational Trials + SOLAR- Approved 2021

	Confirmed Virologic failure rate & resistance
FLAIR: CAB/RPV LA in treatment naïve participants (K103N mutation allowed); First put on DTG/ABC/3TC for 20 weeks then LA ART with virologic suppression (n=283)	**1.8% at 124 weeks;** 4 out of 5 with emergent INSTI/NNRTI resistance
ATLAS: CAB/RPV LA in treatment experienced participants every 4 weeks (K103N okay); on suppressive regimen for 6 months prior to switch (n=308)	**0.9% at 96 weeks;** 3 out of 3 with emergent INSTI/NNRTI resistance
ATLAS 2M: CAB/RPV LA in treatment experienced participants every 8 weeks (higher dose 600mg/900mg) after VS x ≥ 6 months (n=522 every 8 weeks)	**2.3% at 152 weeks;** 11 out of 12 with emergent INSTI/NNRTI resistance
SOLAR: CAB/RPV LA every 8 weeks in treatment experienced participants (47% expressed internal or external stigma) switched BIC/TAF/FTC when VS (n=447)	**0.7% at 48 weeks;** 3 out of 3 with emergent INSTI/NNRTI resistance

Orkin C. Lancet HIV 2021; Swindells S. AIDS 2022; Overton E. CID 2023; Ramgopal M. Lancet HIV 2023

Credit to Drs. Urvi Parikh and Catherine Koss for summary of virologic failure and resistance data from each trial

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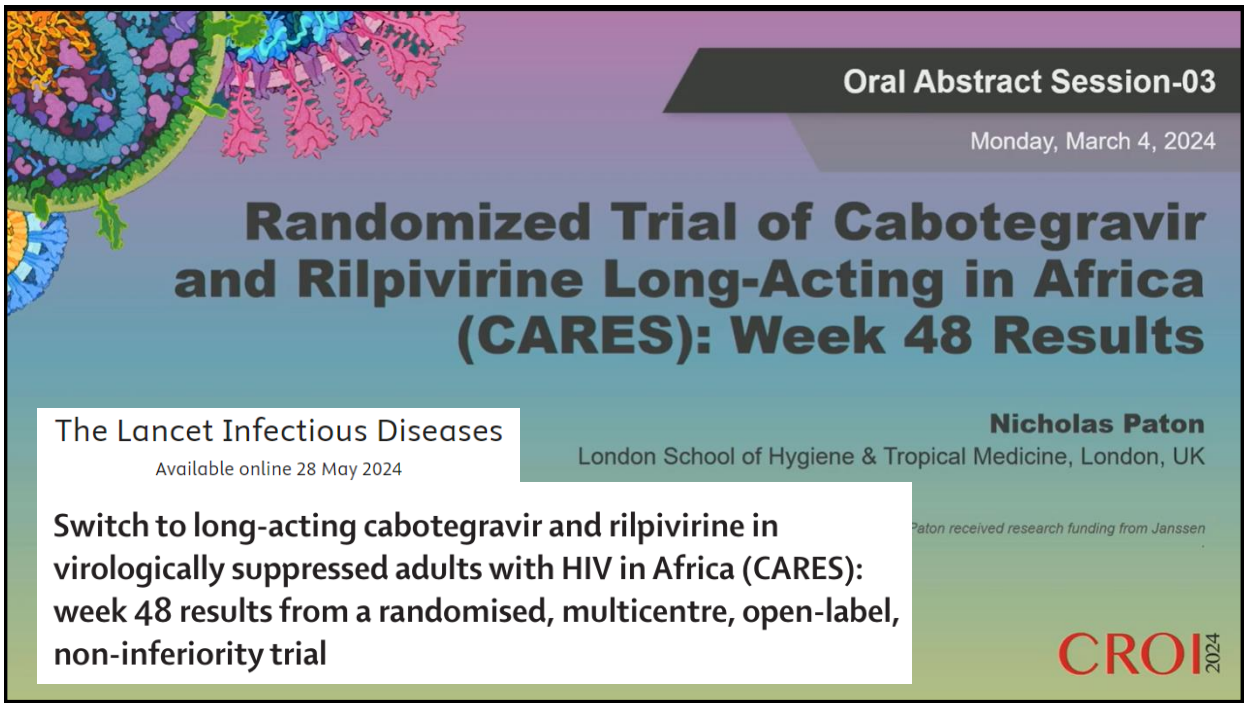

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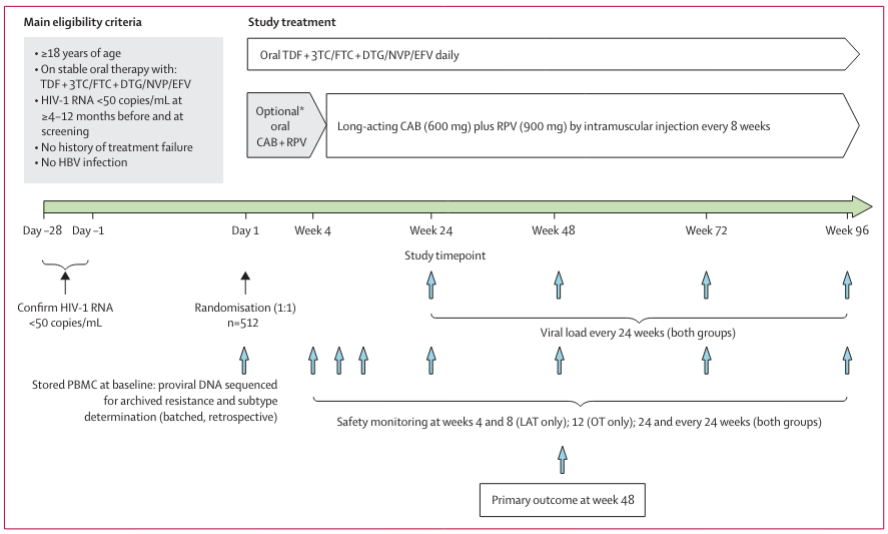
CARES Trial- CAB/RPV in LMICs

The Lancet Infectious Diseases
Available online 28 May 2024



CARES Study Sites

Uganda (N=244, 47.7%)

Kenya (N=162, 31.6%)

South Africa (N=106,20.7%)

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Archived DNA Run Later

Baseline Characteristics

Characteristic	CAB + RPV LA (n=255)	Oral ART (SOC) (n=257)	Overall (N=512)
Female sex, n (%)	146 (57.2)	149 (58.0)	295 (57.6)
Age, median (IQR), years	43 (36-51)	42 (35-49)	42 (35-51)
BMI≥30 kg/m², n (%)	57 (22.4)	51 (19.8)	108 (21.1)
Black race, n (%)	254 (99.6)	256 (99.6)	510 (99.6)
Time on first-line ART, median (IQR), years	8 (4-13)	7 (4-13)	8 (4-13)
Prior exposure to NNRTI, n (%)	189 (73.7)	191 (74.3)	380 (74.2)
INSTI regimen at screening	231 (90.6)	240 (93.4)	471 (92.0)
NNRTI regimen at screening	24 (9.4)	17 (6.6)	41 (8.0)
*Archived DNA analysis * †*			
Viral subtype A1, n/n (%)	119/213 (55.9)	115/201 (57.2)	234/414 (56.5)
RPV resistance mutations, n/n (%)	25/200 (12.5)	26/177 (14.7)	51/377 (13.5)
RPV intermediate/high-level resistance, n/n (%)	17/200 (8.5)	21/177 (11.9)	38/377 (10.1)
CAB resistance mutations, n/n (%)	15/95 (15.8)	14/85 (16.5)	29/180 (16.1)
CAB intermediate/high-level resistance, n/n (%)	10/95 (10.5)	5/85 (5.9)	15/180 (8.3)

- * Retrospective, batched sequencing performed on archived viral DNA extracted from PBMCs stored at baseline
- † Viral subtype, resistance mutations and drug susceptibility were determined using the Los Alamos National Laboratory Panel, and Stanford algorithm respectively

Kityo et al. CROI 2024; Virtual and Denver, CO.

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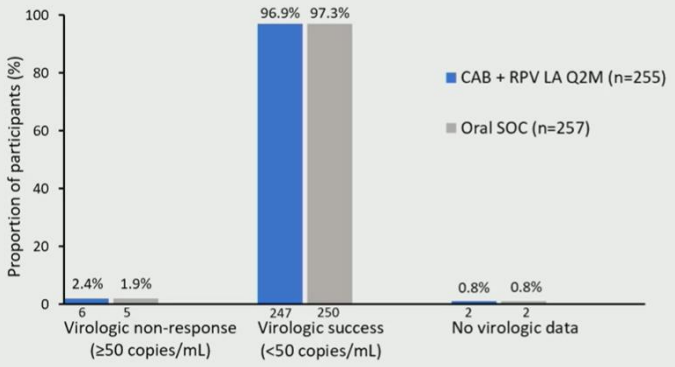
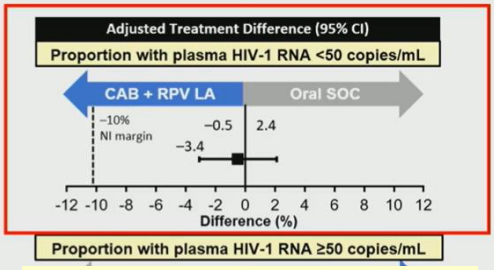
Virologic Outcomes at Week 48 (ITT)





96% injections given within 7-day window; importantly, treatment satisfaction improved; public health approach (VL only every 24 weeks); 2 treatment failures with NNRTI & INSTI resistance

Primary outcome - proportion with plasma HIV-1 RNA <50 copies/ml:

- Main analysis (ITT): adjusted difference -0.5% (95% CI, −3.4 to 2.4), **meeting the non-inferiority criterion**
- Sensitivity analysis (per-protocol): adjusted difference -0.3% (95% CI, -3.0 to 2.3) **confirming non-inferiority**

Note: minor changes in numbers from abstract

Kityo C. Lancet ID 2024

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But Wasn't the Point to Use Them in Adherence-challenged?

Treatment of psychiatric disorders

Adherence Challenges and Long-Acting Injectable Antipsychotic Treatment in Patients with Schizophrenia

Contraception

Long-Acting Reversible Contraception for Adolescents: A Review of Practices to Support Better Communication, Counseling, and Adherence

Substance use disorder treatment

What is long-acting (XR) buprenorphine injection?

Long-acting buprenorphine injection (XR-buprenorphine, currently available brand name: Sublocade) is an injectable formulation of buprenorphine that is given once a month to assist people in obtaining and sustaining long-term recovery from opioid use disorder (OUD). There may be additional XR-

Long-acting injectable naltrexone for the treatment of alcohol dependence

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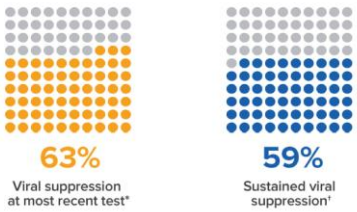
Adherence Challenges with ART

Figure 4. Percentage of adults with diagnosed HIV who were virally suppressed during the 12 months befo interview—Medical Monitoring Project, United States, 2020



Overall rates of VS in US 59% sustained (CDC HIV Special Surveillance Report 8/23)

Rates of virologic suppression worldwide:

- **In adults on ART, 79% suppression at 1 year, 65% by 3 years**
- In children/adolescents on ART, 36% suppression at 1 year, 24% at 3 years (Han. Lancet HIV 2021)

Barriers to ART adherence:

- Systematic review of 125 studies identified main barriers to ART adherence
  - Forgetting
  - Being away from home
  - Change to daily routine
  - Depression
  - Alcohol/substance misuse
  - Secrecy/stigma
  - Feeling sick
  - Far distance to clinic
  - Stock outs

McComsey, G. A., et al. Real-World Adherence to Antiretroviral Therapy Among HIV-1 Patients Across the United States. *Advances in therapy, 2021*
Min Han W et al. Global estimates of viral suppression in children and adolescents and adults on antiretroviral therapy adjusted for missing viral load measurements: a multiregional, retrospecti cohort study in 31 countries. Lancet HIV 2021.
Shubber, Z., et al. Patient-Reported Barriers to Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis. *PLoS medicine, 2016.* 13(11), e1002183.
Altice, F., et al. . Adherence to HIV treatment regimens: systematic literature review and meta-analysis. *Patient preference and adherence*, 2019

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HIV TRANSMISSIONS IN 2016

% OF PEOPLE WITH HIV	STATUS OF CARE	ACCOUNTED FOR X% OF NEW TRANSMISSIONS*
15%	didn't know they had HIV	38%
23%	knew they had HIV but weren't in care	43%
11%	in care but not virally suppressed	20%
51%	taking HIV medicine and virally suppressed	0%

*Values do not equal 100% because of rounding

ACTG

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Is HIV epidemic control by 2030 realistic?

Chris Beyrer, Georgia D Tomaras, Huub C Gelderblom, Glenda E Gray, Holly E Janes, Linda-Gail Bekker, Gregorio Millett, Giuseppe Pan, Susan Buchbinder, Lawrence Corey

THE LANCET HIV

UNAIDS Update 2024 (AIDS at a Crossroads):

- 39.9 million people with HIV (highest) not counting Russia so probably >40 million
- 1.3 million new infections last year unchanged from 2022 update
- 630K deaths last year unchanged from 2022 update
- 43.3 million deaths total from beginning of epidemic and 88.4 infections
- Only 77% on ART (72% suppressed)
- Stigma, rise of anti-LGBTQ sentiment, 8% loss of funding from 2020-23 playing roles

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AIDS Funding Down 8% 2020-2023; PEPFAR Just Cut 6%

Slow progress in reducing stigma, discrimination, social inequalities and violence

The 10–10–10 and the 30–80–60 targets set for 2025 are not within reach. Stigma, discrimination, social inequalities and gender-based violence make it hard for people to stay free of HIV and protect their health *(18)*. People from key populations are especially vulnerable *(19)*. Recognition of these hindrances has increased, but it is not yet sufficiently reflected in laws, policies and practices. Rising authoritarianism and attacks on human and civil rights are making it even more difficult to remove these barriers *(20)*.

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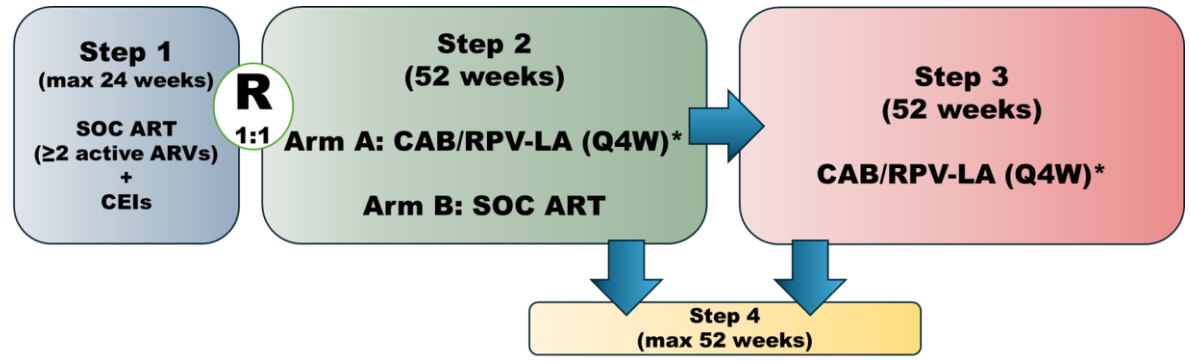
A5359 Study Design



CEIs= conditional economic incentives
*Optional Oral lead-in

Primary Outcome: Regimen failure defined as the earliest occurrence of confirmed virologic failure or treatment discontinuation in Step 2

LATITUDE

ACTG

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ACTG A5359 LATITUDE: Baseline Characteristics

Characteristic	Step 1 Total (N = 434)
Median age, yr (Q1, Q3) ▪ ≤30, n (%) ▪ 31-50, n (%) ▪ ≥51, n (%)	40 (32, 51) 88 (20) 232 (53) 114 (26)
Female at birth, n (%)	129 (30)
Transgender spectrum, n (%)	21 (5)
Race, n (%) ▪ Black ▪ White ▪ Other/multiple/unknown	 277 (64) 117 (27) 40 (9)
Hispanic or Latino/a, n (%)	75 (17)
Current or previous injection drug use, n (%)	61 (14)
Nonadherence criteria, n (%) ▪ Lost to f/u ▪ Poor response ▪ Both	 87 (20) 283 (65) 64 (15)
Median time since HIV diagnosis, yr (Q1, Q3)	13 (7, 21)

Step 2

Characteristic	LA CAB + RPV (n = 146)	SoC (n = 148)
BL HIV-1 RNA >200 c/mL, n (%)	24* (17)	10 (7)
Median BL CD4 count, cells/mm^3 (Q1, Q3)	417 (198, 688)	374 (198, 605)

*Includes 8 participants with HIV-1 RNA >10,000 c/mL.

- **80% Government funded program**
- 3% Self-pay
- 7% Private
- 10% Other

- 61% In own house/apt
- 14% Parents' house
- 13% Someone Else's House
- **10% Unstable/Homeless***

*Shelter/Welfare hotel, Halfway/Boarding House On the Street, Residential Treatment Facility

Rana. CROI 2024. Abstr 212.

Courtesy of CCO

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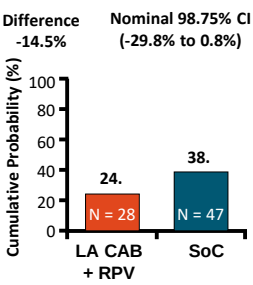
ACTG A5359 LATITUDE: Efficacy Outcomes

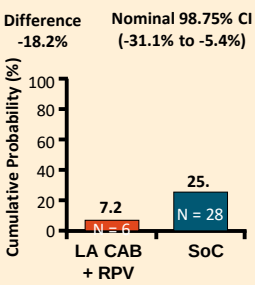
Primary Outcome

Regimen Failure

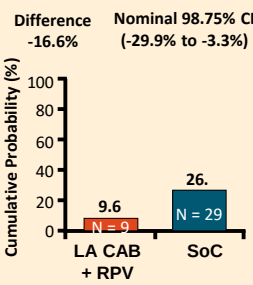


Secondary Outcomes

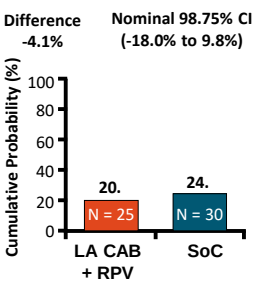
Virologic Failure



Treatment-Related Failure



Permanent Treatment Discontinuation



1 additional virologic failure after Wk 24 included in secondary endpoints, but not primary

Rana. CROI 2024. Abstr 212.

Courtesy of CCO

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Demonstration Project at Ward 86 HIV Clinic

Inclusion criteria of trials:

- Virologically suppressed x at least 16 weeks on oral regimen first
- No history of virologic failure
- Only K103N in NNRTI; no INSTI mutations
- Oral CAB/RPV x 28 days but direct-to-inject approved FDA March '22

Inclusion criteria of Ward 86

- Need not be virologically suppressed or take oral ART before injectables
- No RPV or INSTI mutations (strengthened criteria later)
- **Express willingness to come to clinic q4 weeks, contact information, outreach from staff**
- Rigorous protocol, Biweekly review of patients

Descriptive statistics summarized patient characteristics, median/range number of injections received, viral suppression outcomes, stratified by viral load ≥30 copies/mL at LA-ART initiation; Kaplan Meier plot for viremic

Gandhi Annals of Internal Medicine 2023 518

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48 Week Follow-up Results of Our Demonstration Project

- 286 PWH received ≥1 dose of LA-ART at Ward 86 as of Jan 2024 (101 with baseline VL ≥50 copies/mL)
- **59 started LA-CAB/RPV with VL ≥50 copies/mL by Dec 2022 who had 48 weeks of data**
  - 86% with baseline VL ≥1000; 69% ≥10,000
  - Half with CD4 <200
  - 52% experiencing homelessness/unstable housing
  - 61% using stimulants; 10% using opioids

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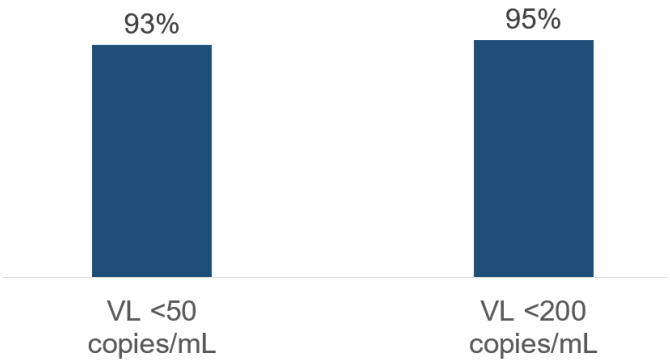
HIV Viral Suppression at 48 Weeks Following Initiation of LA-CAB/RPV with Baseline HIV RNA ≥50 Copies/mL (n=59)



Hickey M et al. CROI 2024

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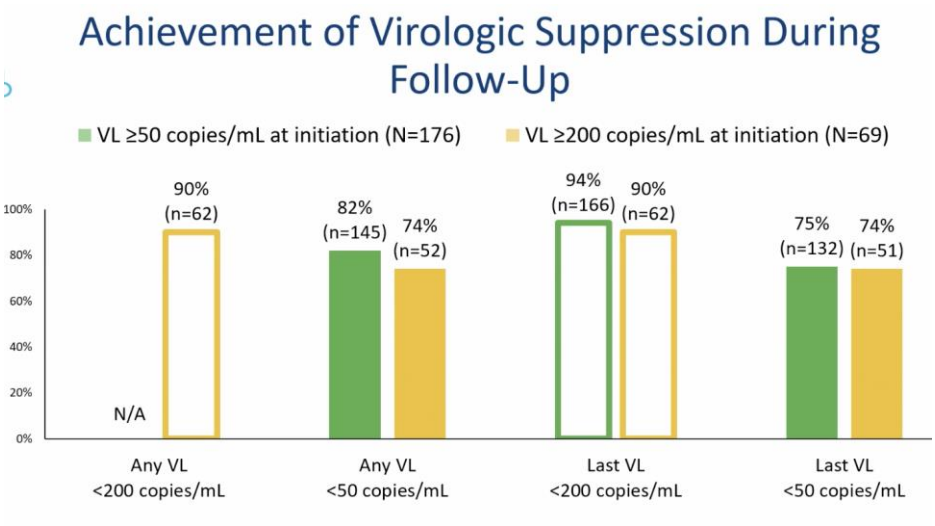
OPERA COHORT (Represents 14% of PWH in US, EMR) - 176 Started LA ART with Viremia >50, 82% VS Rate <50 (94% <200)



Hsu BK. ID Week 2023 (October 11-15), Boston, MA

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LA CAB + RPV in Patients with Viremia – Small Study (n=12)

University of Mississippi Network[1]

- Adult Special Care Clinic, a Ryan White–funded HIV clinic at the University of Mississippi
- CAB/RPV LA offered as a salvage option for patients with viremia despite ART optimization and intensive case management strategies
- **12 patients;** Follow-up : 1 to 17 months
- Despite historical poor adherence to oral therapy, adherence to injection visits was very good with 94% on-time injections
- HIV RNA < 50 c/mL : all patients, within 3 months, no discontinuations

Brock JB. Clin Infect Dis 2023

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March 1, 2024

Updated Treatment Recommendation on Use of Cabotegravir and Rilpivirine for People With HIV From the IAS-USA Guidelines Panel

Paul E. Sax, MD[1]; Melanie A. Thompson, MD[2]; Michael S. Saag, MD[3]; et al

JAMA

- *When supported by **intensive follow-up** and **case management services**, injectable LA CAB + RPV may be **considered for people with viremia** who meet the criteria below when **no other treatment options are effective** due to a patient's persistent inability to take oral ART:*
  - ***Unable to take oral ART** consistently despite extensive efforts and clinical support*
  - ***High risk of HIV disease progression** (CD4 cell count <200/μL or history of AIDS-defining complications)*
  - ***Virus susceptible to both CAB and RPV***
- *If applicable, patients should also be referred for treatment of substance use disorder and/or mental illness.*

Sax. JAMA. 2024; Chen OFID 2023

IAS-USA guidelines cites our data at Ward 86, the 12-person U Miss study, the OPERA cohort, links to A5359, and a modeling study showing benefits greatest for those with worse immunosuppression

DHHS silent so far

FDA wants a randomized study for those with viremia

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Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis

AIDS: July 15, 2021 - Volume 35 - Issue 9 - p 1333-1342

Conclusion: CVF is an infrequent multifactorial event, with a rate of approximately 1% in the long-acting CAB+RPV arms across Phase 3 studies (FLAIR, ATLAS and ATLAS-2M) through Week 48. Presence of at least two of proviral RPV RAMs, HIV-1 subtype A6/A1 and/or BMI at least 30 kg/m^2 was associated with increased CVF risk. These findings support the use of long-acting CAB+RPV in routine clinical practice.

BMI, low rilpivirine troughs, **presence of two proviral RPV RAMS**, HIV-1 subtype A1/A6 associated with increased risk of failure (updated CID 2023)

Clinical Infectious Diseases
MAJOR ARTICLE

Expanded Multivariable Models to Assist Patient Selection for Long-Acting Cabotegravir + Rilpivirine Treatment: Clinical Utility of a Combination of Patient, Drug Concentration, and Viral Factors Associated With Virologic Failure

Chloe Orkin,[1,2] Jonathan M. Schapiro,[3] Carlo F. Perno,[4] Daniel R. Kuritzkes,[5] Parul Patel,[6] Rebecca DeMoor,[6] David Dorey,[7] Yongwei Wang,[8] Kelong Han[8]

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Case #2

34-year-old man-who-has-sex-with-men (MSM) with a history of congenital osteoporosis (celiac sprue, former Vitamin D deficiency) presents after a recent relationship ended to Urgent Care. He has heard about a new form of protection for HIV that "doesn't hurt bones" and also wants something that is easy to take. How do you advise him?

What Currently Approved Prep Medication Is the Best Option for this Patient?

A. Daily oral TDF/FTC
B. Daily oral TAF/FTC
C. Intermittent TDF/FTC
D. Intramuscular cabotegravir every 8 weeks
E. Subcutaneous lenacapavir every 6 months

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Pre-exposure Prophylaxis (PrEP) as an HIV Prevention Strategy

- PrEP - daily or intermittent anti-HIV medication taken by HIV-negatives
  - Started prior to exposure
  - Continued throughout risk periods
- Concept proven effective in other situations:
  - Malaria
  - Prevention of mother-to-child transmission
- Useful for people at intermittent/persistent high risk
- Tenofovir or tenofovir/emtricitabine (TDF/FTC)- was originally chosen as agent as once daily, long half-life, no food restrictions, relatively safe, high concentrations into genital tract

Paxton A et al. Pre-exposure prophylaxis for HIV infection: what if it works? *Lancet* 2007

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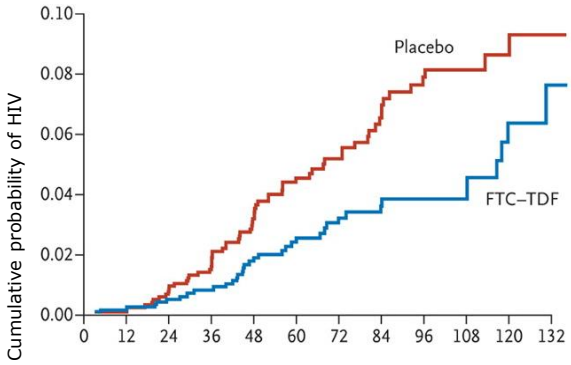
iPrEx: First Positive Trial Result MSM

- Randomly assigned 2499 HIV- MSM to TFV/FTC vs placebo
- Median 1.2 yrs f/u- 100 infected (36 TFV/FTC; 64 placebo; 44% reduction (p 0.005)
- ?Pill fatigue – only 50% of those on TFV/FTC had detectable drug levels



Grant RM. NEJM Nov 24, 2010

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Daily PrEP Trials with TDF/FTC–Adherence Everything

Trial	Population/Setting	Intervention	Reduction in HIV Infection Rate, %
iPrEX[1] (N = 2499)	MSM, 11 sites in US, S. America, Africa, Thailand	▪ Daily oral TDF/FTC	44% (95% CI 15-63, p 0.005)
Partners PrEP[2] (N = 4747)	Serodiscordant couples in Africa	▪ Daily oral TDF ▪ Daily oral TDF/FTC	▪ Women: 71%; men: 63% ▪ Women: 66%; men: 84%
TDF2[3] (N = 1219)	Heterosexual males and females in Botswana	▪ Daily oral TDF/FTC	62%* (underpowered for sex differences)
Bangkok TFV Study[6] (N= 2413)	IDU (use in last year) in Bangkok	▪ Daily oral TDF	49% (95% CI 9.6-72.2, p 0.01)
FEM-PrEP[4] (N = 2120)	High-risk women, Africa	▪ Daily oral TDF/FTC	▪ Study stopped early due to futility (adherence)
VOICE[5] (N = 5029)	High-risk women, Africa	▪ Daily oral TDF ▪ Daily oral TDF/FTC ▪ 1% TFV gel	▪ 1% TDF gel & daily oral TDF arm both stopped early, futile ▪ Daily TDF/FTC arm – no efficacy (adherence)
PROUD (N=523)[7]	High-risk men, U.K.	▪ Daily oral TDF/FTC, immediate vs deferred	86% (90% CI 58-96%, p=0.0002)

1. Grant RM. N Engl J Med. 2010. 2. Baeten JM. N Engl J Med. 2012 3. Thigpen MC. N Engl J Med. 2012; 4. Van Damme. N Engl J Med. 2012 5. Marrazzo J, N. Engl J. Med. 2015; 6. Choopanya Lancet June 2013; 7. McCormack. CROI 2015

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FEM-PrEP and VOICE: Adherence Issues (and Objective Measures Critical)

Adherence Measure	VOICE	FEM-PrEP
Self-report	91%	95%
Returned pill counts	92%	88%
Plasma TFV detection	29%	24%

Marrazzo et al. NEJM 2015; Van Damme et al. NEJM 2012

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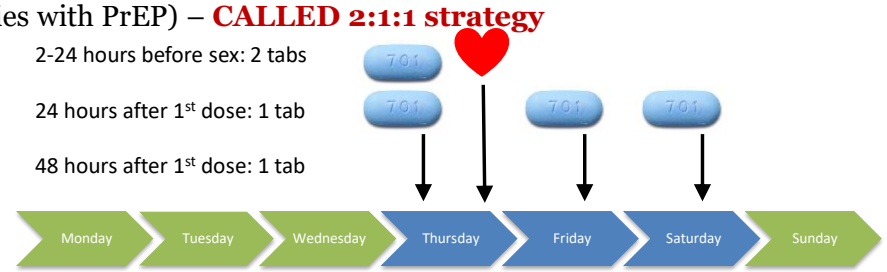
Event-based or Intermittent PrEP with TDF/FTC

IPERGAY Extension Study

TDF/FTC with dosing around the time of sex in MSM

361 MSM; 18 pills/month; 97% reduction in new HIV infections with intermittent PrEP (compared to control arm of IPERGAY RCT with daily PrEP)

Condomless sex increased from 77% to 86% (STIs didn't increase, but have in other studies with PrEP) – **CALLED 2:1:1 strategy**



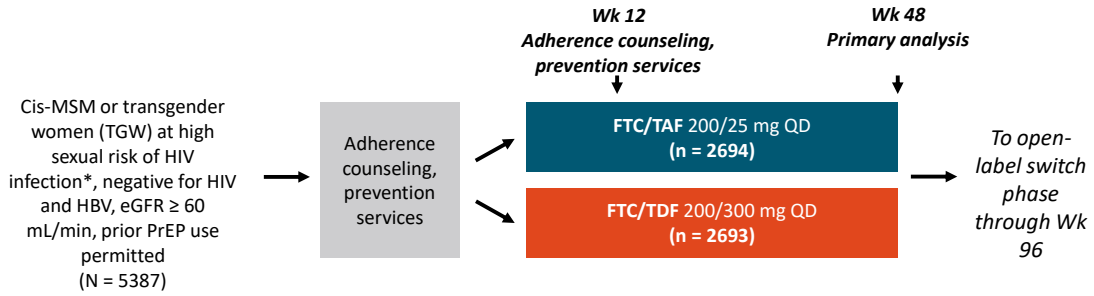
Ongoing risk: continue 1 tab daily until 48 hours after last exposure

Molina JM. Lancet HIV 2017 and IAS 2017.

34

DISCOVER: Daily FTC/TAF vs FTC/TDF for PrEP

- International, randomized, double-blind phase III noninferiority trial



*Defined as ≥ 2 episodes of condomless anal sex within past 12 wks or rectal gonorrhea, chlamydia, syphilis within past 24 wks.

- Primary endpoint: HIV incidence
- TGW, 1% to 2% (75 individuals total); Black 9%; White 84%; Hispanic 15%;

Mayer K et al. Lancet 2020

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DISCOVER- Efficacy Outcomes 96 weeks (TAF/FTC Noninferior & Slightly Better For Bone Health)

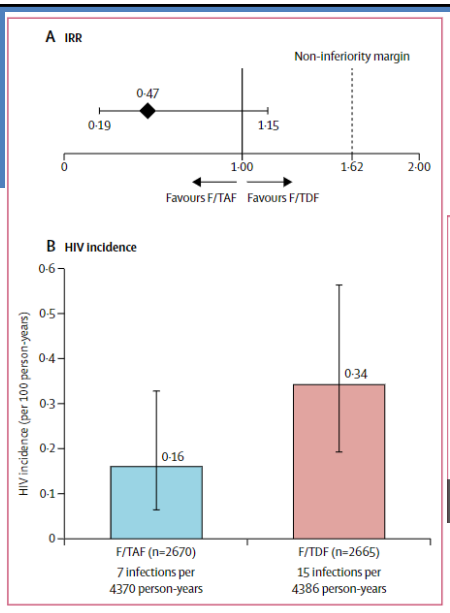
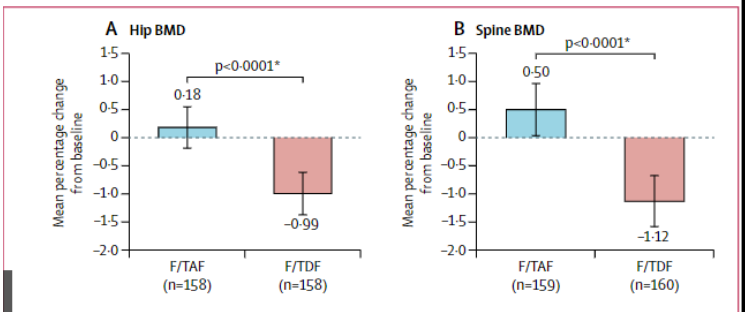


Figure 2: HIV IRR and incidence on F/TAF versus F/TDF at the primary efficacy analysis



Participants in TDF/FTC group lost weight in the first 24 weeks and returned to baseline at week 48 (mean change–0·1 kg); those in TAF/FTC group have a mean increase in bodyweight of 1·1 kg at week 48

Mayer K et al. Lancet 2020

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Case #2 Continued

Patient doesn't want to take TDF/FTC or TAF/FTC daily as he knows that both can be associated with renal insufficiency or loss of bone density- likes the idea of intermittent PrEP but says he may increase going out and not sure he wants to rely on the 2:1:1 strategy. He wants to see if there are any other options for him for PrEP.

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Undetectable = Untransmittable (U=U)

>150,000 condomless sex acts

Study	Population	Condomless Sex Acts	Transmissions within Partnership
PARTNER (JAMA 2016)	888 couples, 38% MSM; 62% heterosexual	58,000	**0**
Opposites Attract (Lancet 2018)	343 couples, 100% MSM	17,000	**0**
PARTNER2 (Lancet 2019)	783 couples 100% MSM	77,000	**0**

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Discontinuation, suboptimal adherence, and reinitiation of oral HIV pre-exposure prophylaxis: a global systematic review and meta-analysis

THE LANCET HIV

ARTICLES | VOLUME 9, ISSUE 4, E254-E268, APRIL 01, 2022

Jing Zhang*, Chunyan Li*, Junjie Xu*, Zhili Hu, Sarah E Rutstein, Joseph D Tucker, Jason J Ong, Yongjun Ji

- Systematic review, 41·0% of those on PrEP discontinued within 6 months; suboptimal adherence for those who stayed 37·7%
- Discontinuation rate higher in sub-Saharan Africa 47·5% than other regions
- Discontinuation rates lower in studies with adherence interventions than in those without (24·7% *vs* 36·7%, p=0·015). \
- Men who have sex with men and transgender women offered daily or non-daily dosing options had lower discontinuation rates than those offered daily dosing alone (21·6% *vs* 31·5%; p<0·001).
- **Though oral PrEP important, we need other options**

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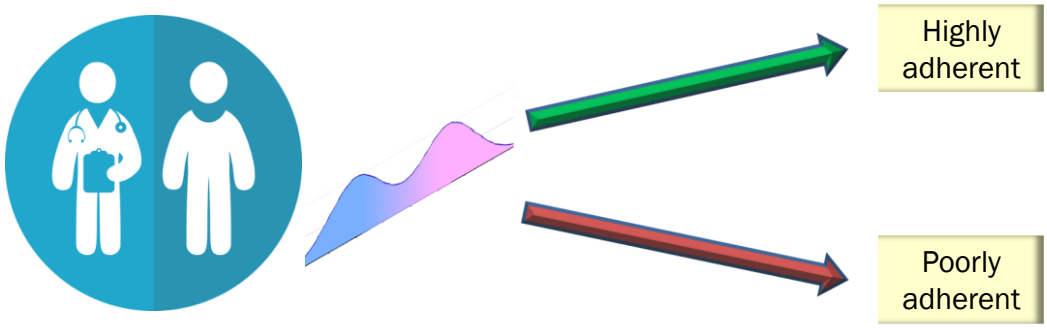
Bimodal Population: Patient with Challenges to PrEP/ART Adherence Would Benefit from Long-acting PrEP/ART



Would then KNOW date of “medication consumption” (not adherence, but coming in), pharmacies or mobile vans administering the shots, home health

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Equity in access to long-acting injectables in the USA

THE LANCET HIV

Cabotegravir, an integrase strand transfer inhibitor, and rilpivirine, a non-nucleoside reverse transcriptase inhibitor, recently received regulatory approval in the Canada, the EU, and the USA as a monthly intramuscular long-acting injectable (LAI) antiretroviral therapy regimen in adults with HIV-1 who are virologically

Published Online February 4, 2022 https://doi.org/10.1016/S2352-3018(22)00031-5

*J Carlo Hojilla, Monica Gandhi, Derek D Satre, Mallory O Johnson, Parya Saberi

- Critically important population for Ending the HIV epidemic
- Equitable access across the US and across the world important
- WHO strongly endorsed Cabotegravir LA PrEP at International AIDS Conference, Montreal, July 28, 2022

ViiV HEALTHCARE AND THE MEDICINES PATENT POOL SIGN NEW VOLUNTARY LICENSING AGREEMENT TO EXPAND ACCESS TO INNOVATIVE LONG-ACTING HIV PREVENTION MEDICINE

London, 28 July 2022 - ViiV Healthcare, the global specialist HIV company majority owned by GSK, with Pfizer and Shionogi as shareholders, and the Medicines Patent Pool (MPP) today announced the signing of a new voluntary licensing agreement for patents relating to cabotegravir long-acting (LA) for HIV pre-exposure prophylaxis (PrEP) to help enable access in least developed, low-income, lower middle-income and Sub-Saharan African countries[1,2].

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HPTN 083: Efficacy and Safety of LA Injectable CAB vs Daily Oral TDF/FTC for PrEP in MSM and TGW

- International, randomized, double-blind phase IIb/III study

HIV-uninfected MSM and TGW ≥ 18 yrs of age at high risk of HIV infection*; no HBV/HCV infection, (N = 4566)

Step 1 (Wk 5)	Step 2 (Wk 13)	Step 3 (Wk 21)
CAB 30 mg PO QD (n = 2282)	CAB LA 600 mg IM Q8W†	TDF/FTC PO QD
TDF/FTC PO QD (n = 2284)	TDF/FTC PO QD	TDF/FTC PO QD

*Any noncondom receptive anal intercourse, > 5 partners, stimulant drug use, incident rectal or urethral STI (or incident syphilis) in past 6 mos; or SexPro Score ≤ 16 (US only).
†First 2 doses given 4 wks apart then every 8 wks thereafter.

- Primary endpoints: incident HIV infections, grade ≥ 2 AEs

Landovitz. NEJM 2021.

HPTN 083

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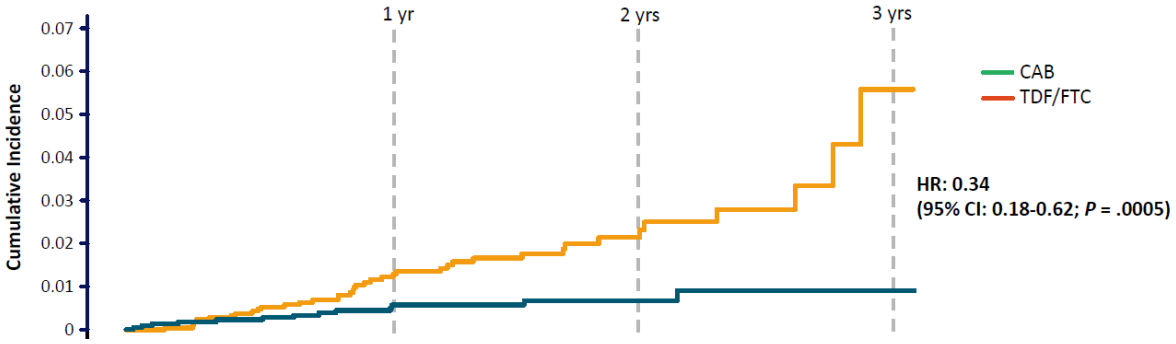
HPTN 083: HIV Incidence (ITT) With LA Injectable CAB vs Daily Oral TDF/FTC PrEP

66% reduction over daily TDF/FTC



66% superiority maintained into the year of unblinding

Landovitz. NEJM 2021; Landovitz Lancet HIV 2023

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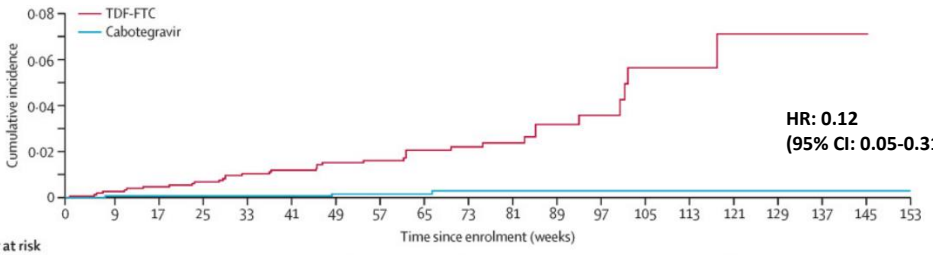
Other Major Update in Prevention from AIDS 2024: CAB Safety in Pregnancy- Cisgender Women Study

HPTN 084 Long-acting Injectable For the Epidemic

88% reduction over daily TDF/FTC- **few (6) failures and none with INSTI resistance**



Number at risk																			
TDF-FTC	1610	1490	1429	1410	1353	1260	1160	984	800	656	485	306	201	115	70	63	52	22	3	0
Cabotegravir	1614	1488	1441	1429	1371	1279	1181	988	801	647	482	304	204	116	67	58	50	23	3	2
Cumulative number of events																			
TDF-FTC	0	4	7	10	15	17	21	22	26	27	28	31	32	35	35	36	36	36	36	36
Cabotegravir	0	1	1	1	2	2	3	3	3	4	4	4	4	4	4	4	4	4	4	4

S Delany-Moretlwe. Lancet 2022

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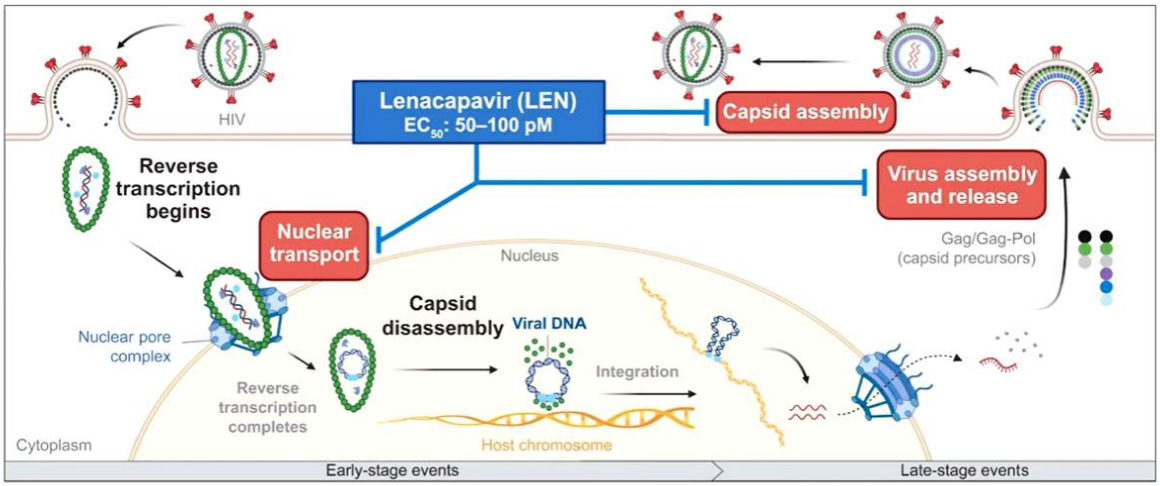
LEN Targets Multiple Stages of HIV Replication Cycle



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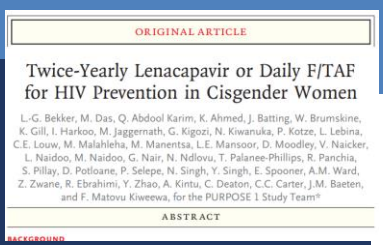
ORIGINAL ARTICLE

Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women

L.-G. Bekker, M. Das, Q. Abdool Karim, K. Ahmed, J. Batting, W. Brumskine, K. Gill, I. Harkoo, M. Jaggernath, G. Kigozi, N. Kiwanuka, P. Kotze, L. Lebina, C.E. Louw, M. Malahleha, M. Manentsa, L.E. Mansoor, D. Moodley, V. Naicker, L. Naidoo, M. Naidoo, G. Nair, N. Ndlovu, T. Palanee-Phillips, R. Panchia, S. Pillay, D. Potloane, P. Selepe, N. Singh, Y. Singh, E. Spooner, A.M. Ward, Z. Zwane, R. Ebrahimi, Y. Zhao, A. Kintu, C. Deaton, C.C. Carter, J.M. Baeten, and F. Matovu Kiweewa, for the PURPOSE 1 Study Team*

ABSTRACT

BACKGROUND

PURPOSE
Prevention with PURPOSE

Twice-Yearly Lenacapavir or Daily Oral Emtricitabine/Tenofovir Alafenamide for HIV Prevention in Cisgender Women: Interim Analysis Results from the PURPOSE 1 Study

Linda-Gail Bekker, MBChB, PhD, on behalf of the PURPOSE 1 Study Team
The Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa

Bekker LG. SS0407

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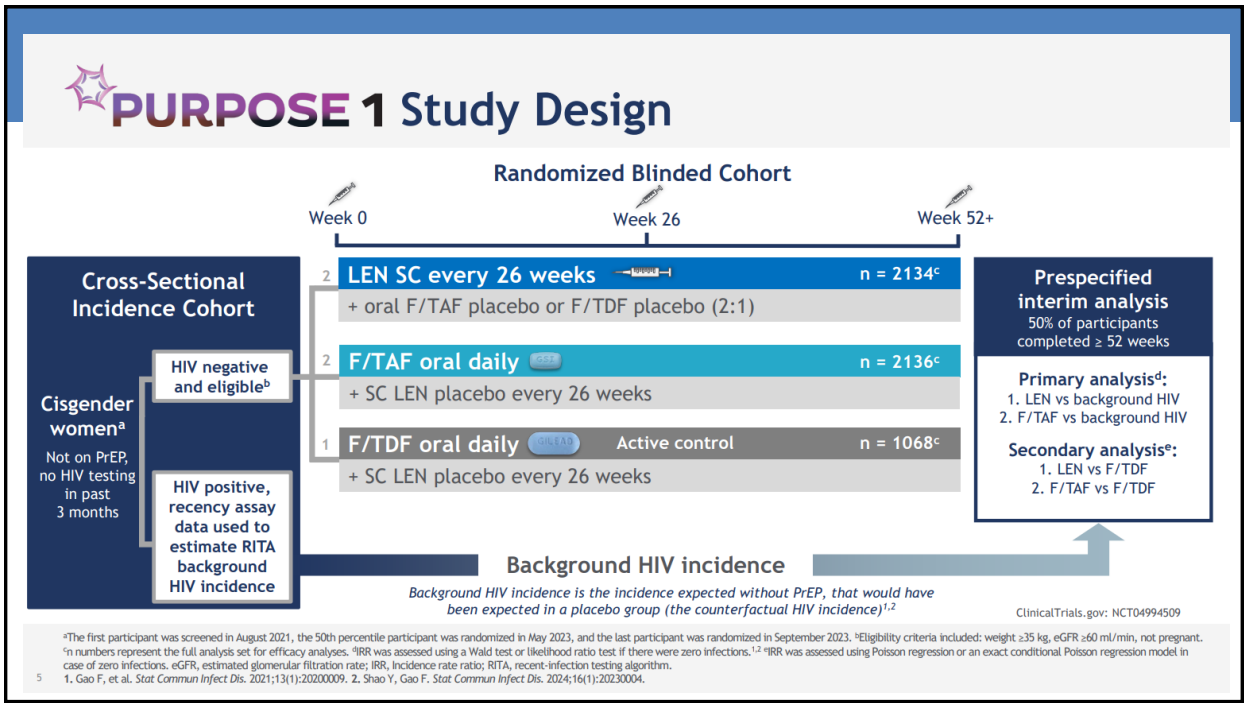

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Baseline Characteristics

Characteristic	LEN, n = 2138	F/TAF, n = 2137	F/TDF, n = 1070
Age, years, median (range)	21 (16-25)	21 (16-26)[a]	21 (16-25)
Age 16 to <18, years, n (%)	56 (2.6)	45 (2.1)	23 (2.1)
Black race,[b] n (%)	2135 (99.9)	2136 (100)	1068 (99.8)
Highest education level college/university,[c] n (%)	183 (8.6)	198 (9.3)	109 (10.2)
Marital status, n (%)			
Married	26 (1.2)	30 (1.4)	17 (1.6)
Living with primary partner	148 (6.9)	132 (6.2)	73 (6.8)
STIs, n (%)			
Chlamydia trachomatis	520 (24.3)	562 (26.3)	263 (24.6)
Neisseria gonorrhoeae	197 (9.2)	178 (8.3)	90 (8.4)
Trichomonas vaginalis	154 (7.2)	165 (7.7)	82 (7.7)
Syphilis	57 (2.7)	63 (2.9)	29 (2.7)
Any prior use of PrEP, n (%)	143 (6.7)	121 (5.7)	71 (6.6)
Any prior HIV testing, n (%)	1713 (80.1)	1731 (81.0)	860 (80.4)
Median time since last HIV test, months (Q1, Q3)	6.8 (4.7, 11.5)	6.6 (4.8, 11.0)	6.5 (4.6, 11.0)

Participants

84.3% South Africa

15.7% Uganda

Baseline demographics and clinical characteristics were balanced across randomized groups

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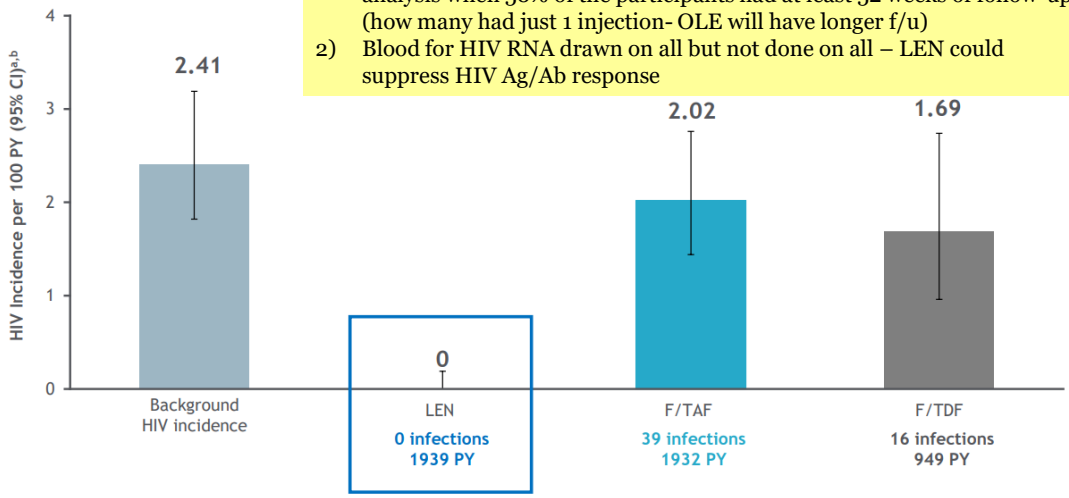
Zero HIV Infections in Cisgender Women receiving LEN

Two caveats:
1) Range of follow-up time not provided – this was a planned interim analysis when 50% of the participants had at least 52 weeks of follow-up (how many had just 1 injection- OLE will have longer f/u)
2) Blood for HIV RNA drawn on all but not done on all – LEN could suppress HIV Ag/Ab response



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Women need 4 doses a week like men do (Marrazzo JAMA 2024 analysis important) = FDA may not approve TAF/FTC in woman based on adherence-effectiveness data

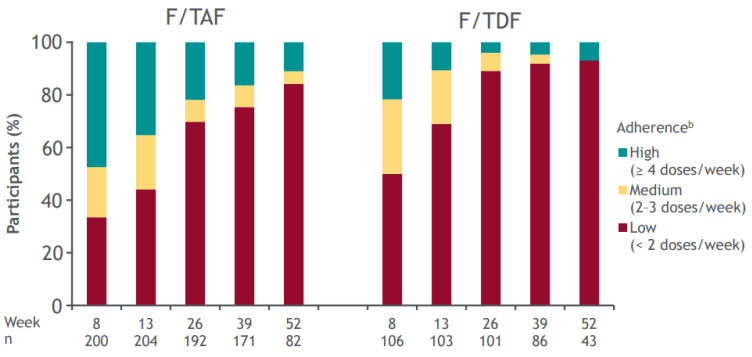
Adherence to Injections Was High While Adherence to Oral F/TAF and F/TDF Was Poor

Injection Adherence in All Participants

Injections were on time[a] for:
- 91.5% (4545/4967) at Week 26
- 92.8% (2025/2181) at Week 52

On-time injection similar on LEN and placebo (F/TAF and F/TDF)

Adherence by TFV-DP Concentration in 10% Cohort



On-time adherence to injections was high
Most participants in both the F/TAF and F/TDF groups had low adherence to oral tablets, and adherence declined over time

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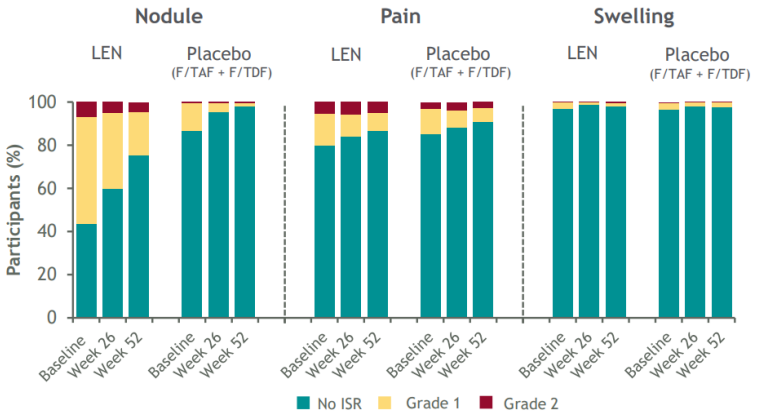
Nodules 30-60% in this analysis; Our experience & the biology of the depot under skin makes nodules seem more universal than that; in terms of pain & discontinuation, in all clinical trials, ppts paid for participation

Injection Site Reaction Frequency Diminishes With Subsequent Injections

- LEN is injected into the SC space and forms a drug depot that may be palpable under the skin but is usually not visible
- As the drug elutes over time, the depot gets smaller, and the nodules resolve or reduce in size substantially prior to the next injection
- **ISRs, including nodules, decreased with subsequent doses (also observed with HIV treatment[1])**



Among 25,229 injections, only four ISRs led to discontinuation

51

Pregnancies Were Common and Outcomes Similar to Expected Rates in the Population

Participants and Pregnancies, n (%)	LEN n = 2138	F/TAF n = 2137	F/TDF n = 1070
Participants with confirmed pregnancies	184	208	95
Confirmed pregnancies	193	219	98
Completed pregnancies	105 (54.4)	119 (54.3)	53 (54.1)
Ongoing pregnancies	88 (45.6)	100 (45.7)	45 (45.9)
Births[a]	55 (28.5)	45 (20.5)	21 (21.4)
Interrupted pregnancies	50 (25.9)	74 (33.8)	32 (32.7)
Induced abortion	30 (15.5)	40 (18.3)	20 (20.4)
Spontaneous miscarriage[b]	20 (10.4)	34 (15.5)	12 (12.2)

Never indication in pre-testing to think LEN had adverse effects on pregnancy so should be approved readily for this

Expected spontaneous miscarriage rate[1,2]:

- ~10-20% of clinically recognized pregnancies
- ~30% of biochemically detected pregnancies

Available pregnancy outcomes were similar to those expected for the population[3]

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PURPOSE 2

September 12, 2024

Gilead's Twice-Yearly Lenacapavir for HIV Prevention Reduced HIV Infections by 96% and Demonstrated Superiority to Daily Truvada® in Second Pivotal Phase 3 Trial

– 99.9% of Participants Did Not Acquire HIV Infection in the Lenacapavir Group, with 2 Incident Cases Among 2,180 Participants –

– PURPOSE 2 Trial Results for Cisgender Men and Gender-Diverse People Add to the Body of Evidence for the Investigational Use of Lenacapavir for HIV Prevention –

– Gilead Stopped the Blinded Phase of the Trial at Interim Analysis and Will Offer Open-Label Lenacapavir to All Participants –

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Price point Gilead = rumors of $12,000 to $43,000 a year

The Guardian

HIV drug could be made for just $40 a year for every patient

Generic version of a drug already on the market, which can suppress and prevent HIV, would still yield 30% profit if the current price was slashed, researchers say

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Case #3

53-year-old man with HIV on long-standing ART with suppressed viral load and high CD4 count (662), HTN well controlled, mild DM on diet control (Ha1C 6.1), past history of smoking not currently, family history of MI (father 55) who presents to the ER with chest pain, left sided, no SOB, no back pain, no radiation, not exertional. Aching chest pain and worsened with palpation. Troponin not elevated; EKG normal. Stress test scheduled and to be discharged

Patient has normal cholesterol last time checked but ASCVD calculation is 7.5% - asks if he should be on anything to prevent heart attacks

What Medication Should You Start in the ER for this Patient Based on Cardiovascular Risk Factors?

A. Aspirin
B. Another daily oral hypertensive
C. Statin
D. Insulin
E. Varenicline (Chantix)

REPRIEVE

Randomized Trial to Prevent Vascular Events in HIV

Beyond diet, exercise, control other risk factors for cardiovascular disease; showed a 35% reduction in major adverse CV event among PWH with statin (clearly most important for moderate-high risk groups)

Clinical Infectious Diseases

MAJOR ARTICLE Clin Infect Dis. 2023 Sep 12;

Weight gain after antiretroviral therapy initiation and subsequent risk of metabolic and cardiovascular disease

Participants who experienced >10% weight gain in 1st year of ART had an increased risk of DM (HR 2.01), metabolic syndrome (HR 2.24), and cardiometabolic outcomes (HR 1.54)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Triin Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., Carlos D. Malvestutto, M.D., M.P.H., Gerald S. Bloomfield, M.D., M.P.H., Judith S. Currier, M.D., Esteban Martinez, M.D., Ph.D., Jhoanna C. Roa, M.D., Marissa R. Diggs, B.A., Evelynne S. Fulda, B.A., Kayla Paradis, M.B.A., Stephen D. Wiviott, M.D., Borek Foldyna, M.D., Sara E. Looby, Ph.D., Patrice Desvigne-Nickens, M.D., Beverly Alston-Smith, M.D., Jorge Leon-Cruz, M.S., Sara McCallum, M.P.H., Udo Hoffmann, M.D., M.P.H., Michael T. Lu, M.D., M.P.H., Heather J. Ribaudo, Ph.D., and Pamela S. Douglas, M.D., for the REPRIEVE Investigators*

ABSTRACT

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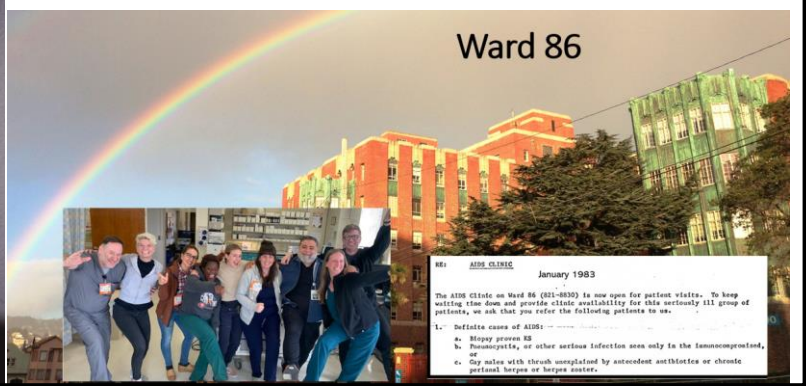
stop aids. make the promise

Thank you to 9th Annual Primary Care Update on Urgent Care & Emergency, Division of HIV, ID and Global Medicine at UCSF, the HIV movement, and Ward 86!



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