AETC AIDS Education & Training Center Program Mountain West

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2026 CROI Update

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CROI Updates: HIV and STI Prevention

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Disclosures

No conflicts of interest to disclose

Disclaimer

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Objectives

- Review updates in on demand versus daily oral PrEP
- Review updates in lenacapavir as PrEP
- Discuss investigational long-acting PrEP agents

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Updates in HIV PrEP: Daily v On-Demand

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ANRS PREVENIR: Final Results

- Cohort in France of ~3000 MSM and [redacted] at risk for HIV acquisition from 2017 to 2025
- Comparison of **daily** versus **on-demand** TDF/FTC for PrEP
  - Regimen chosen by patient, switch allowed
- Participants majority MSM (98.7%), born in France (82.5%); 47% chose on-demand dosing regimen
  - Percent using each regimen stayed roughly the same throughout the study
  - 59% who started on daily switched at least once to on-demand; 52% the other way

ANRS PREVENIR: Final Results

PrEP Dosing Regimen	Follow-Up Pts-years	Nb Cases	HIV Incidence /1000 PY (95% CI)	P-value
Daily PrEP Users	4974	3	0.6 (0.1 – 1.8)	0.4
On Demand PrEP users	4786	7	1.5 (0.6 - 3.0)	
Switch PrEP users	3370	3	0.9 (0.2 – 2.6)	

- Overall HIV incidence in cohort **low** (13 cases, or 0.99/1000 PY)
- Most new infection occurred in those who **discontinued PrEP**
- **No significant difference** in incidence of HIV between oral PrEP modality

Oral Abstract 127, CROI 2026

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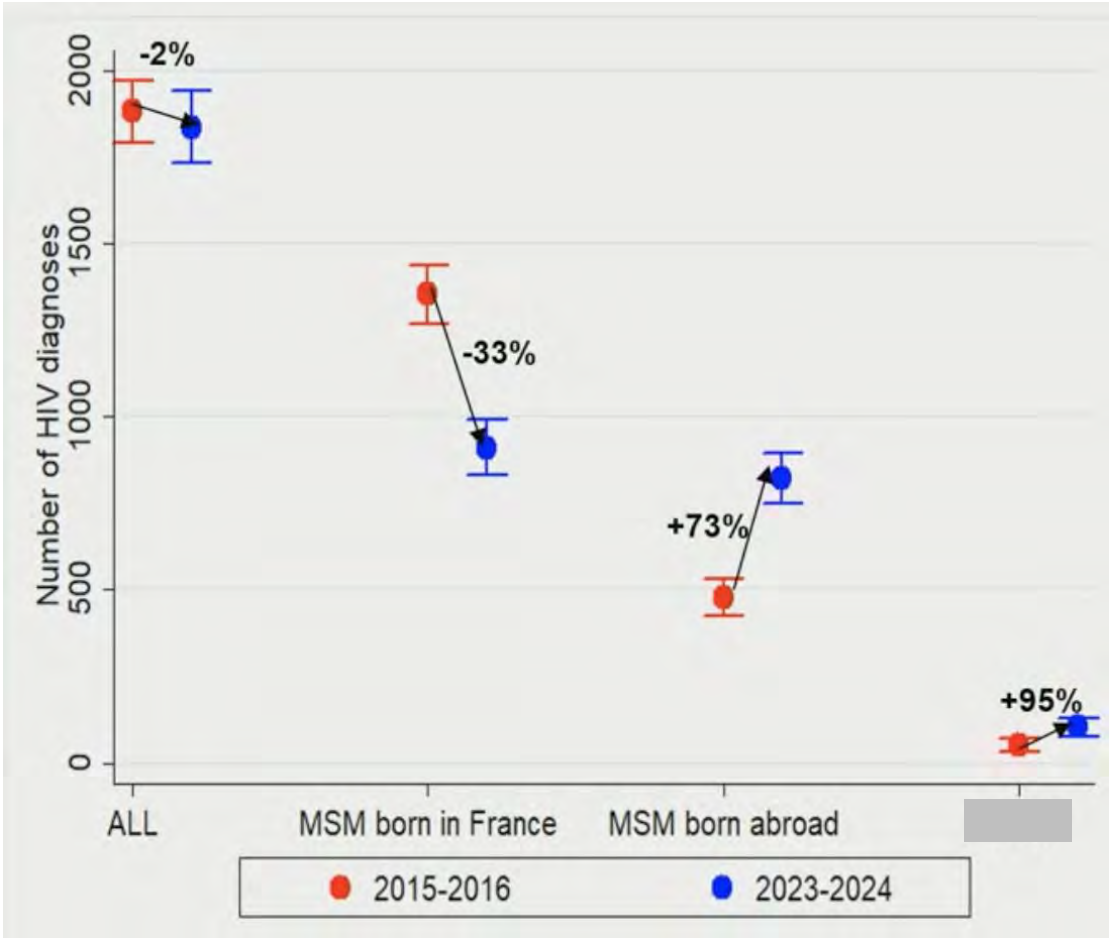
ANRS PREVENIR: Final Results

- Overall minimal decrease in new diagnosis of HIV, but:
  - significant **decrease** in MSM born in France
  - significant **increase** in those born abroad
- High rates of bacterial STI (53.7/100 PY)
- Well tolerated, higher discontinuation rate in on-demand (GI side effects)



Oral Abstract 127, CROI 2026

Oral PrEP Takeaways

- Both oral daily and on-demand PrEP remain highly effective options for HIV prevention
- High degree of dynamism of choice of methodology, though overall percentages in each group remained fairly static
- Need to consider specific populations in PrEP reach - or there will be little impact on the overall epidemic

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Updates in HIV PrEP: LEN for PrEP

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PURPOSE Trials Overview: Lenacapavir for PrEP

	Population	Arms	Incident HIV Infections in oral PrEP arms*	Incident Infections in LEN Arm*
PURPOSE-1	Adolescent girls and young women (SA and Uganda)	LEN v F/TAF v F/TDF (2:2:1)	77	2
PURPOSE-2	MSM and [redacted] (Global)	LEN v F/TDF (2:1)	12	3
PURPOSE-3	*Adult women (US)*	*LEN v F/TDF (1:1)*	----	----
PURPOSE-4	*People who inject drugs (US)*	*LEN v F/TDF(2:1)*	----	----

*by end of randomized blinded phase

Purpose Studies, Gilead (purposestudies.com)

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PURPOSE Trials Overview: Lenacapavir for PrEP

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*by end of randomized blinded phase

Purpose Studies, Gilead (purposestudies.com)

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Lenacapavir for PrEP: Updates from PURPOSE -1

- PURPOSE-1: LEN for PrEP in adolescent girls and young women (AGYW) showed **100% efficacy**
- At end of primary analysis, **ZERO** new infections in LEN arm
- By end of randomized blinded phase, **TWO** new infections in LEN arm

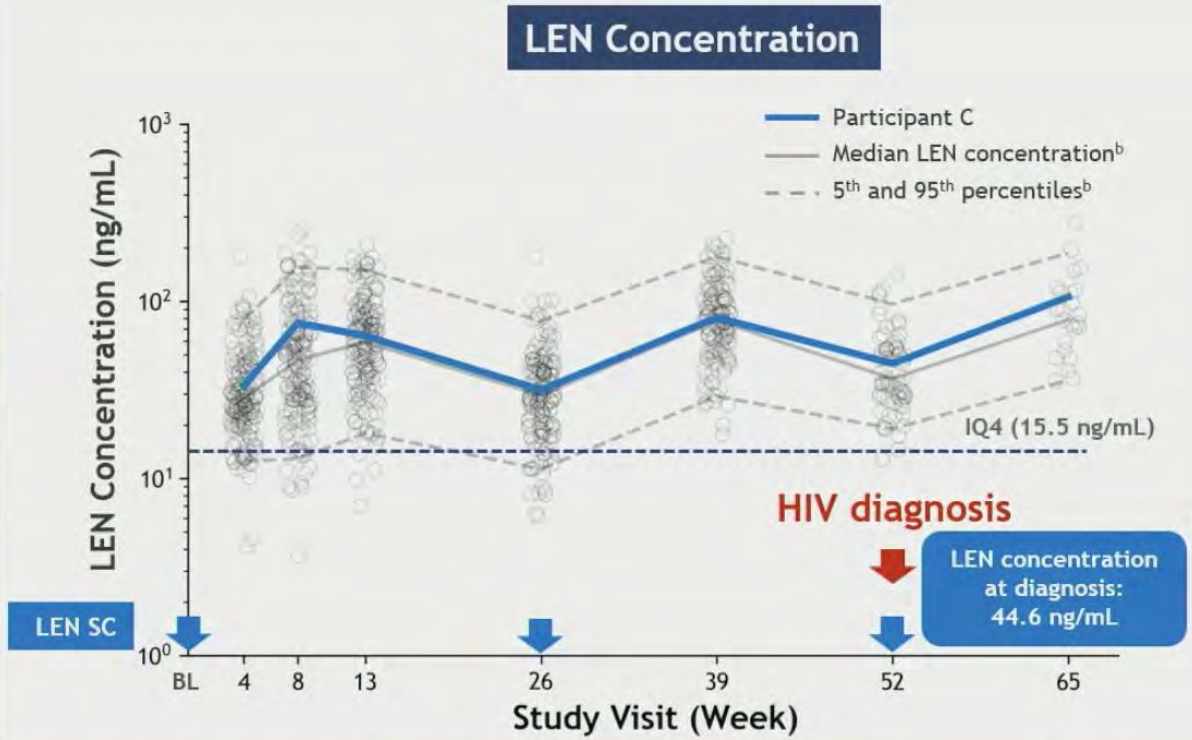
Oral Abstract 128, CROI 2026

Lenacapavir for PrEP: Updates from PURPOSE -1

LEN Plasma Concentrations in Participant C

- Young woman tested positive for chlamydia at Week 52
- HIV diagnosed clinically on-study at Week 65 by typical serologic testing; retrospective RNA test found to be positive at Week 52/OLE Day 1

HIV Diagnostics	LEN (Randomized Blinded Phase)							LEN (OLE)
Study visit week	BL	4	8	13	26	39	52/ OLE D1	65/ OLE W13
Study day	0	30	57	92	183	274	365	456
Rapid Ag/Ab	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Central Ag/Ab	(-)	(-)				(-)	(-)	(+)
HIV-1/2 Ab diff								Ind.
Qualitative RNA								(+)
Quantitative RNA, c/mL	(-)					(-)	47[a]	78



Participant C received all LEN injections on time and was diagnosed with standard HIV serologic testing; LEN concentrations were within the range of the prespecified subset of participants analyzed for PK[b]

Oral Abstract 128, CROI 2026

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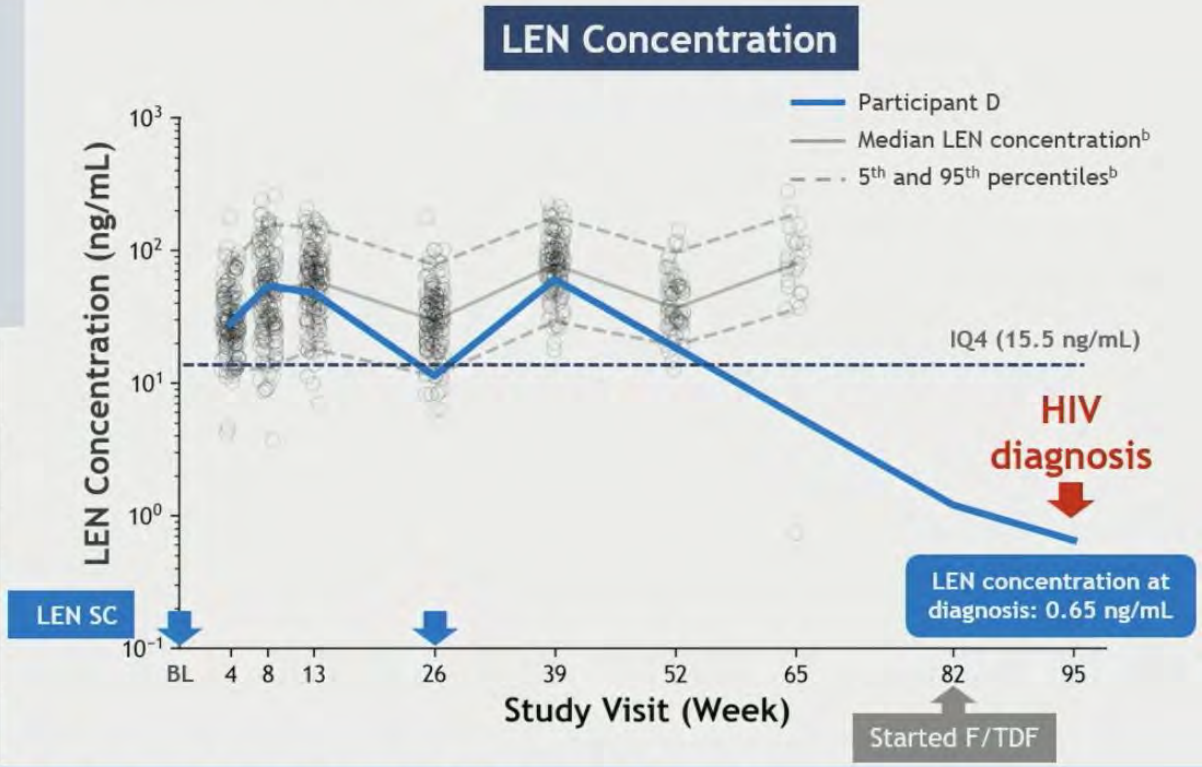
Lenacapavir for PrEP: Updates from PURPOSE -1

LEN Plasma Concentrations in Participant D

- Young woman had last LEN injection at Week 26, then missed Week 52 injection
- Transitioned to open-label F/TDF at Week 82; HIV-negative at that time
- HIV diagnosed at Week 95, 487 days after last LEN injection

HIV Diagnostics	LEN (Randomized Blinded Phase)							Open-label F/TDF	
Study visit week	BL	4	8	13	26	39	52	82	95
Study day	0	30	57	92	183	271		579[a]	670
Rapid Ag/Ab	(-)	(-)	(-)	(-)	(-)	(-)	Missed	(-)	(+)
Central Ag/Ab	(-)	(-)	(-)				Missed	(-)	(+)
HIV-1/2 Ab diff									(HIV-1+)
Qualitative RNA									
Quantitative RNA, c/mL	(-)							(-)	134,000



Participant D was diagnosed with HIV-1 after LEN discontinuation, while receiving open-label F/TDF, approximately 16 months after the last LEN injection

Oral Abstract 128, CROI 2026

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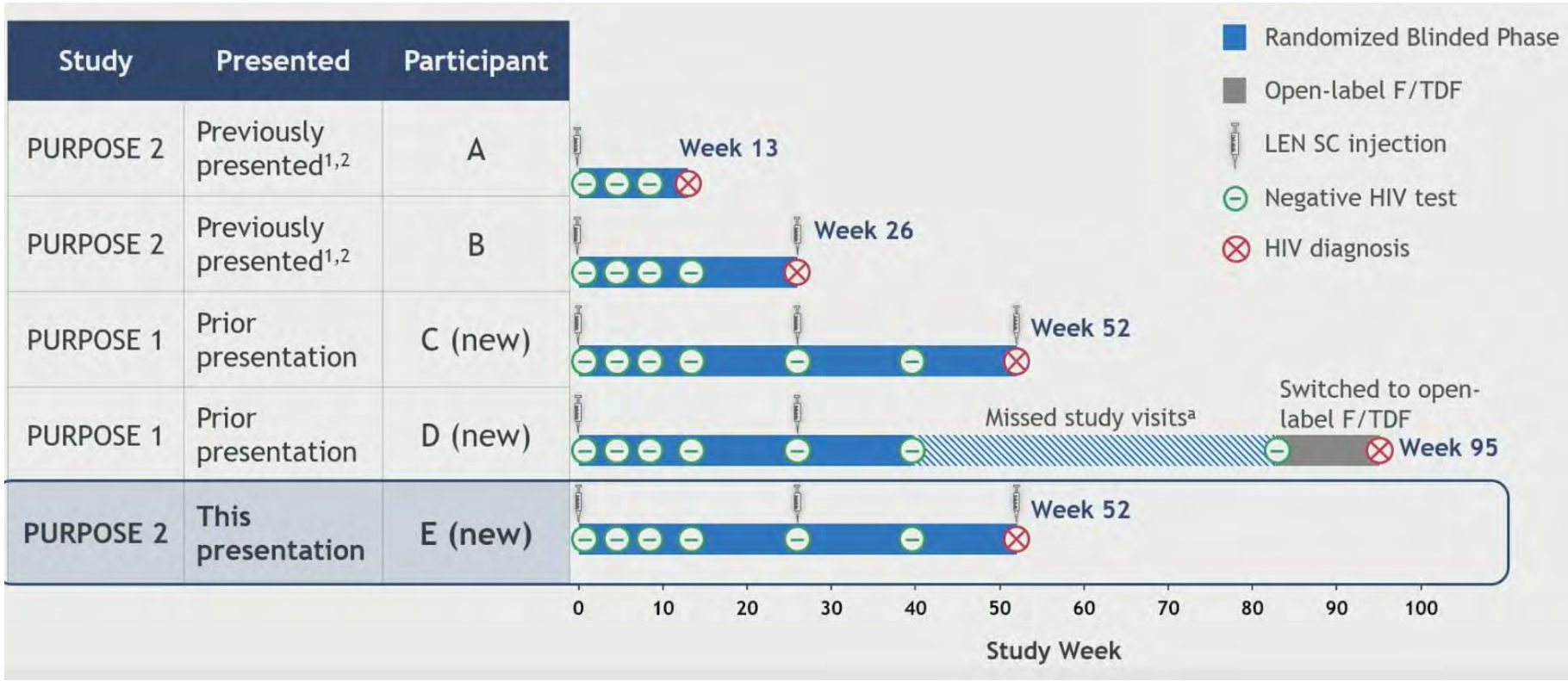
Lenacapavir for PrEP: Updates from PURPOSE-2

- PURPOSE-2: LEN for PrEP in MSM showed high efficacy
- At end of primary analysis, **TWO** new infections in LEN arm
- By end of randomized blinded phase, **ONE** additional new infection in LEN arm



Oral Abstract 129, CROI 2026

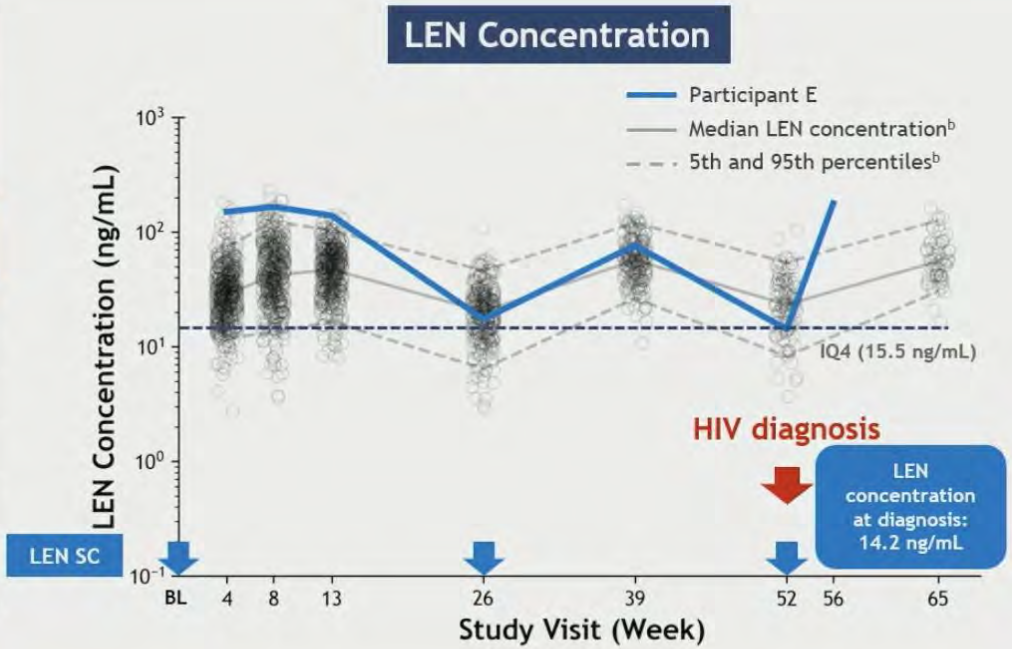
Lenacapavir for PrEP: Updates from PURPOSE-2

LEN Plasma Concentrations in Participant E with Seroconversion

- Young person with history of rectal chlamydia at screening and Week 26 (Day 176), and rectal gonorrhea at Week 26 (Day 176)
- Diagnosed with HIV at Week 52 (Day 352)

HIV Diagnostics	LEN (Randomized Blinded Phase)						
Study visit week	BL	W4	W8	W13	W26	W39	W52/ OLE D1
Rapid Ag/Ab	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Central Ag/Ab	(-)	(-)	(-)	(-)	(-)	(-)	(+)
HIV-1/2 Ab diff							Ab (-)
Quantitative RNA, c/mL	ND					ND[a]	2,020,000

HIV diagnosis

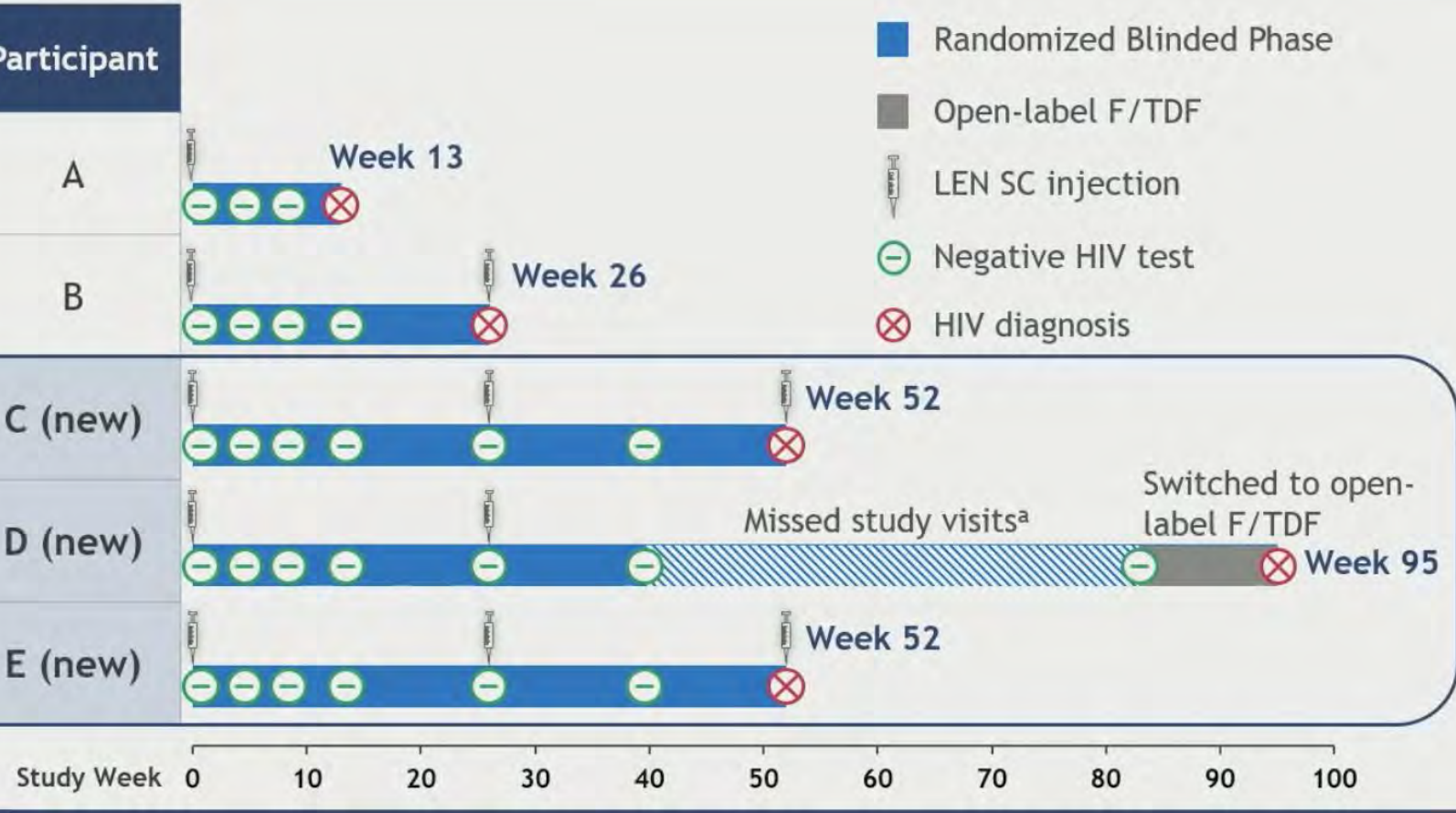


Participant E was diagnosed with standard HIV testing at Week 52. This participant received all injections on time and LEN concentrations were generally within the range of the prespecified subset of participants analyzed for PK[b]

Oral Abstract 129, CROI 2026

PURPOSE Studies: Resistance Analyses

Study	Presented	Resistance mutations	Participant
PURPOSE 2	Previously presented[1,2]	N74D	A
PURPOSE 2	Previously presented[1,2]	N74D	B
PURPOSE 1	These presentations	N74D	C (new)
PURPOSE 1	These presentations	-	D (new)
PURPOSE 2	These presentations	Q67H, K70R	E (new)



Of the 5 HIV infections acquired on LEN in the PURPOSE studies, 3 had the N74D resistance mutation

Oral Abstract 130, CROI 2026

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Takeaways: PURPOSE Studies

- Injection site reactions remained common and low grade; no further ISR related discontinuations in either trial
- In those who did acquire HIV on LEN, most common acquired RAM was capsid N74D, felt likely to be due to monotherapy rather than transmitted resistance
- LEN remains highly efficacious as a PrEP option
  - Breakthrough infections, even with therapeutic levels and on time injections, are a **rare** possibility
  - Unlike CAB-LA, diagnoses were made in a timely manner with HIV Ag/Ab testing

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Updates in HIV PrEP: Investigational LAI

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Investigational LAI PrEP: NRTTI (MK-8591) implants fail to protect macaques against SHIV with M184V

- Can exposure to drug resistant virus diminish PrEP efficacy?
  - Prior macaque models demonstrate efficacy of F/TDF in SHIV with M184V (diminished with K65R)
- SC polycaprolactone islatravir (ISL) implants for PrEP
  - Removable, biodegradable implant
  - Preclinical macaque data has shown ISL concentrations within safety parameters, high efficacy against repeated vaginal exposure to WT SHIV
  - M184V reduces HIV-1 susceptibilities to ISL
- Can PCL implants with ISL protect macaques from rectal exposure to WT SHIV AND does M184V impact efficacy?

Oral Abstract 125, CROI 2026
Cong et al. J Virol 2011; Cong et al. J Infect Dis 2013

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Investigational LAI PrEP: NRTTI (MK-8591) implants fail to protect macaques against SHIV with M184V

- Study Design:
  - Macaques with ISL implant exposed (twice weekly rectal exposure) with WT SHIV versus M184V SHIV
- **Reduced efficacy of ISL implant with M184V SHIV**
  - Plasma and PMBC levels were therapeutic
  - Complete protection by ISL with exposure WT SHIV
  - 4/5 infected after exposure to M184V SHIV
- Removal of implant resulted in rapid drop in ISL levels, avoiding the issue of a “tail”
- *What happens in HIV-1, and with transmitted, non-engineered virus?*

Oral Abstract 125, CROI 2026
Cong et al. J Virol 2011; Cong et al. J Infect Dis 2013

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STI Prevention

Meningococcal B (4CMenB) Vaccination for the Prevention of Gonorrhea in MSM

- Observational studies show 4CMenB may show cross-protection against gonorrhea (GC), though previous trials have not borne out (ANRS DOXYVAC)
  - Vaccination programs have been implemented in Spain and the UK for those at high risk

- **GoGoVax**: evaluated efficacy of 4CMenB against GC in MSM at high risk
  - 1º outcome: incidence of first and all episode GC four or more weeks after two dose vaccination
  - 2º outcomes:
    - incidence of symptomatic or asymptomatic first episode gonorrhea
    - incidence of first episode GC by infection site

Oral Abstract 197, CROI 2026
Ladhani et al. Lancet Infect Dis. 2014

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Meningococcal B (4CMenB) Vaccination for the Prevention of Gonorrhea in MSM

- Randomized, double blind trial at 7 Australian clinics
  - Adult MSM with GC or syphilis in last 18 months either on PrEP or HIV on ART
  - Received two doses of 4CMenB or placebo 2 months apart with follow up visits every 3 months for 2 years
  - Received STI testing including 3 site GC nucleic acid amplification testing (NAAT)

- Characteristics well balanced between groups:
  - ~90% with prior gonorrhea
  - ~19% with prior syphilis
  - ~60% with > 10 sexual partners
  - ~35% with no condom use with casual partners

Oral Abstract 197, CROI 2026

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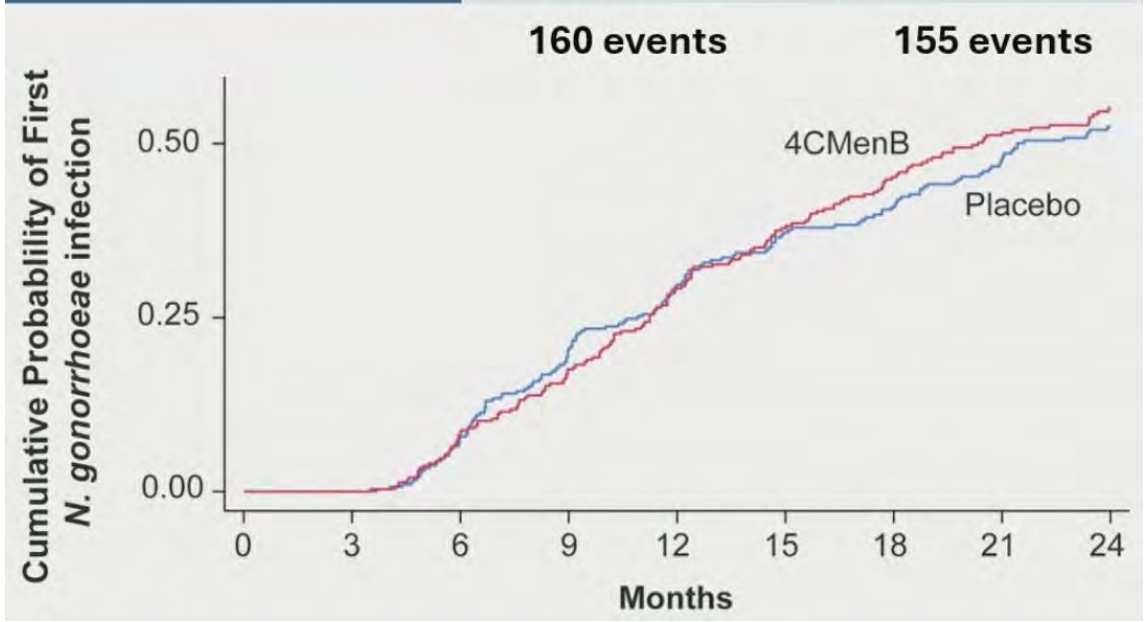
4CMenB was NOT effective in reducing gonorrhea incidence

Gonorrhea	4CMenB Incidence (per 100 PY)	Placebo Incidence (per 100 PY)
Per-protocol population (N=587)		
First-episode	48.1	47.8
	160 events	155 events



- No difference in groups for asymptomatic versus symptomatic infection
- No difference based on site of infection
- No difference based on number of sexual partners, condom use, group sex, or length of follow up

Oral Abstract 197, CROI 2026

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Takeaways: 4CMenB for GC Prevention

- No impact of meningococcal vaccination in MSM at high risk of GC acquisition, consistent with prior studies
- Unclear efficacy in other populations (i.e. women, lower GC incidence settings)
- Unclear impact of prior GC infection on protection from future infection
- To explore further: impact of third dose? Mucosal versus systemic immunity?

Oral Abstract 197, CROI 2026

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Conclusions

- On demand oral PrEP and daily oral PrEP remain highly effective options for HIV prevention, though inequity in access remains a barrier
- Lenacapavir as PrEP remains a robust option with few breakthrough infections
- Single agent NRTTIs as LAI PrEP may be vulnerable to common mutations such as M184V
- In MSM at high risk for GC acquisition, 4CMenB meningococcal vaccination was not effective in reducing gonorrhea incidence

Acknowledgment

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CROI 2026 Report Back: Treatment Updates

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Disclosures

No conflicts of interest or relationships to disclose.

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Outline

- Noncanonical Mutations
- CAB-RPV Updates
- New Medications

Noncanonical Mutations

Abstracts on Noncanonical Mutations

1. Mutations in *env* as a gateway for acquisition of INSTI resistance[1]
2. Nucleocapsid mutations in virologic failure (VF) of INSTI-based ART[2]
3. Noncanonical mutations in TLD-treated PWH with unexplained VF[3]
4. Characterization of mutations outside integrase in PWH with DTG VF[4]

1-Hikichi Y et al, CROI 2026 #551. 2-Le Hingrat Q et al, CROI 2026 #585. 3-Coetzee N et al, CROI 2026 #553. 4-Ngueko AMK et al, CROI 2026 #550.

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What are Noncanonical Mutations?

- HIV drug resistance mutations that occur outside the drug target site
  - Noncanonical resistance mechanisms have been identified for INSTIs, PIs, NNRTIs, and NRTIs
- What might they do?
  - Restore viral fitness caused by drug resistance mutations (DRMs) in drug target sites
  - Enhance resistance when occurring with DRMs at the drug target sites
  - Independently cause resistance even in the absence of DRMs at drug target site
  - Prime the emergence of resistance variants with DRMs at drug target sites
- *Clinical relevance is unknown*

Inzaule S et al, AIDS 2025.

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HIV-1 Genome Contains 9 Genes that Encode 15 Viral Proteins

Genes

Proteins

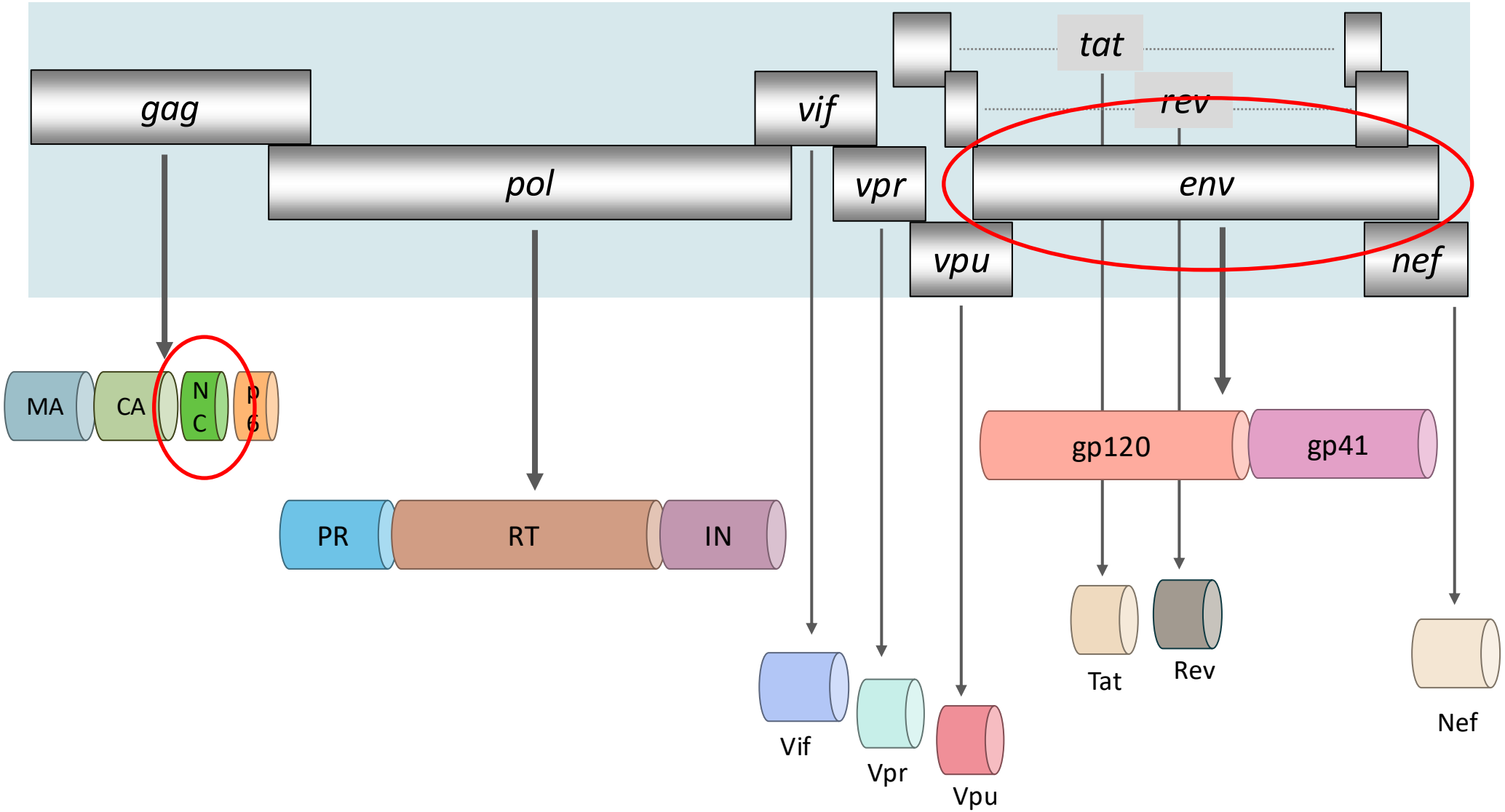

Illustration: David H. Spach, MD. Slide from David H. Spach, MD.

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Abstracts on Non-Canonical Mutations

1. Mutations *in env* as a gateway for acquisition of INSTI resistance[1]
   - Prior evidence that HIV-1 develops resistance to DTG by sequentially acquiring mutations in *env*, nucleocapsid, and in some cases, integrase
   - Here, serial passage (~2y) of multiple HIV-1 isolates in PBMCs in presence of DTG and RAL
     - HIV exposed to RAL developed canonical INSTI-RAMs
     - In contrast, *env* mutation was a gateway for stepwise acquisition of higher level INSTI-R

2. Nucleocapsid mutations in virologic failure (VF) of INSTI-based ART[2]
   - Of 145 PWH with VF on an INSTI-based regimen, 75% had nucleocapsid sequences
     - Nucleocapsid mutations were found in 12 PWH, but none had INSTI-R

1-Hikichi Y et al, CROI 2026 #551. 2-Le Hingrat Q et al, CROI 2026 #585.

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Abstracts on Non-Canonical Mutations

3. Noncanonical mutations in TLD-treated PWH with unexplained VF[1]

- Sequencing among 17 PWH with VF > 400 copies/mL on TLD in UTRA study
  - Nucleocapsid – emergence of N27S and M46L associated with low-level resistance
  - *Env* – emergence of T641I, associated with low-level INSTI-R in subtype C

4. Characterization of mutations outside integrase in PWH with DTG VF[2]

- Whole genome sequencing of 33 PWH in Cameroon with VF
  - 25.9% had at least 1 noncanonical mutation in gag and 100% in *env*
  - None of the 12 known noncanonical major mutations observed were significantly associated with INSTI-R
  - 17 novel mutations identified (3 in *gag*, 14 in *env*) in PWH with INSTI-R and 2 identified in PWH without INSTI-R

1-Coetzee N et al, CROI 2026 #553. 2-Ngueko AMK et al, CROI 2026 #550.

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CAB-RPV Updates

Updates in CAB-RPV

- CAB-RPV in Pregnancy
- CAB-RPV in Elevated BMI
- Virologic Failure with CAB-RPV

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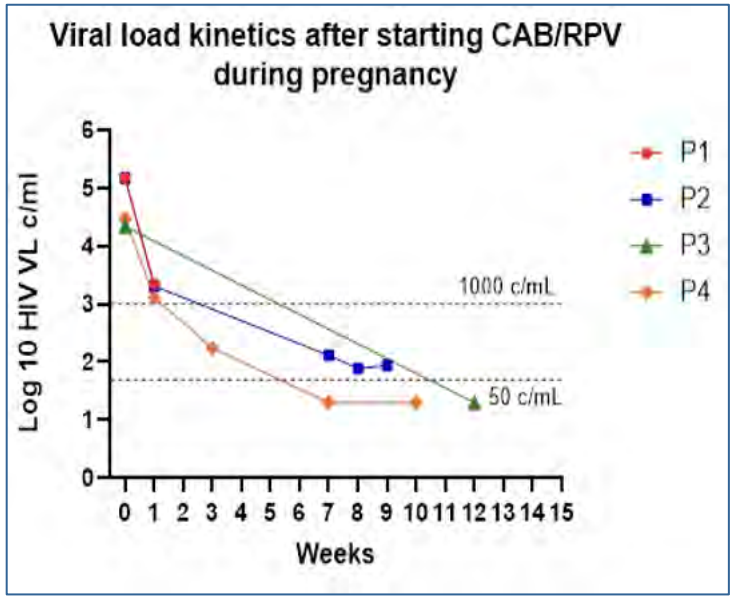
CAB-RPV in Pregnancy: Viral Kinetics

- Data regarding safety, efficacy, outcomes of CAB-RPV in pregnancy are emerging; outcomes were favorable in a multicenter retrospective review of 23 pregnant women prescribed LA CAB-RPV between 2021-2024[1]
- Case series of 4 individuals initiating LA CAB-RPV while pregnant and viremic; of 3 with paired VLs, median decay slope of **-1.6 log10 copies/mL per week** (range -1.36 to -1.83)[2]

Initial Regimen	Gestational age at first prenatal visit (weeks)	HIV VL at first prenatal visit (copies/mL)	Gestational age at switch to LA CAB/RPV (weeks)	HIV VL at switch to LA CAB/RPV (copies/mL)	Gestational age at delivery (weeks)	LA CAB/RPV Dosing frequency	HIV VL at delivery (copies/mL)
FTC/TAF/BIC	20	30,000	22	30,000	34	Monthly	< 20
FTC/TAF/BIC	8	42,440	17	22,000	38	Monthly	< 20
FTC/TAF/BIC	9	150,000	28	149,000	38	Monthly	89
FTC/TAF/BIC + DRV/c + DOR	16	111,000	36	150,000	37	Monthly	2,200



1- Short WR et al, CROI 2025 #1015. 2-Short WR et al, CROI 2026 #791.

CAB-RPV in Pregnancy: More Data on q8w Dosing is Needed

- RPV concentrations may drop in pregnancy[1,2]
- If CAB-RPV is used in pregnancy, most would use q4w dosing, as concerns exist that RPV concentrations may drop below the protein-adjusted EC95
- Multicenter retrospective chart review of pregnant PWH prescribed q8w CAB-RPV (1/2021-9/2025) to describe virologic, obstetric, and perinatal outcomes[3]
- 15 pregnant PWH met inclusion criteria[3]
  - All conceived while on q8w CAB-RPV
  - All had VS through pregnancy
  - Median number of VLs checked: 3 (IQR 3, 5)
- Although promising, more safety and drug level data in q8w dosing are needed

1-van der Wekken Pas L et al, CID, 2024. 2-Osiyemi O et al, Infect Dis Therapy, 2018. 3-Short WR et al, CROI 2026 #792.

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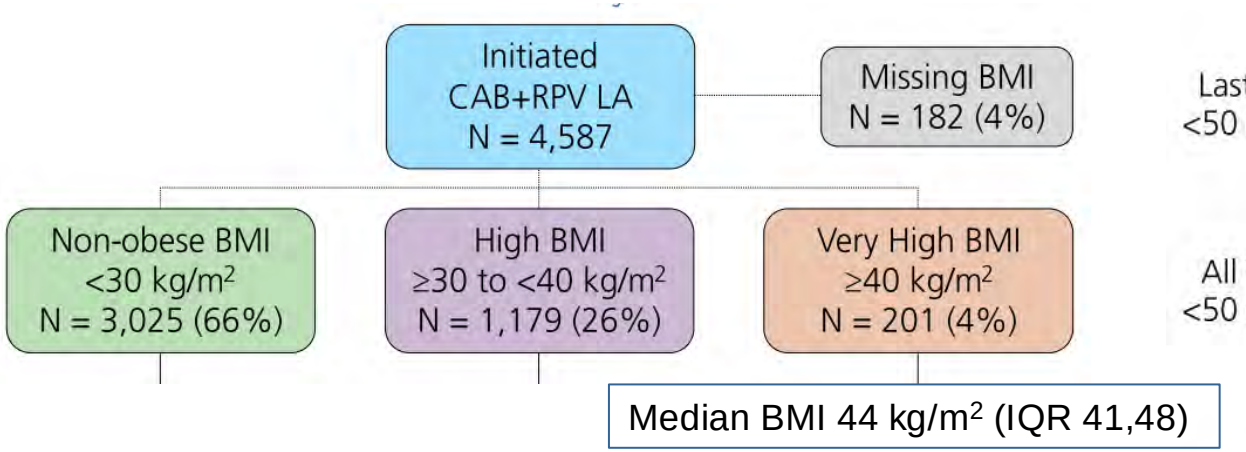
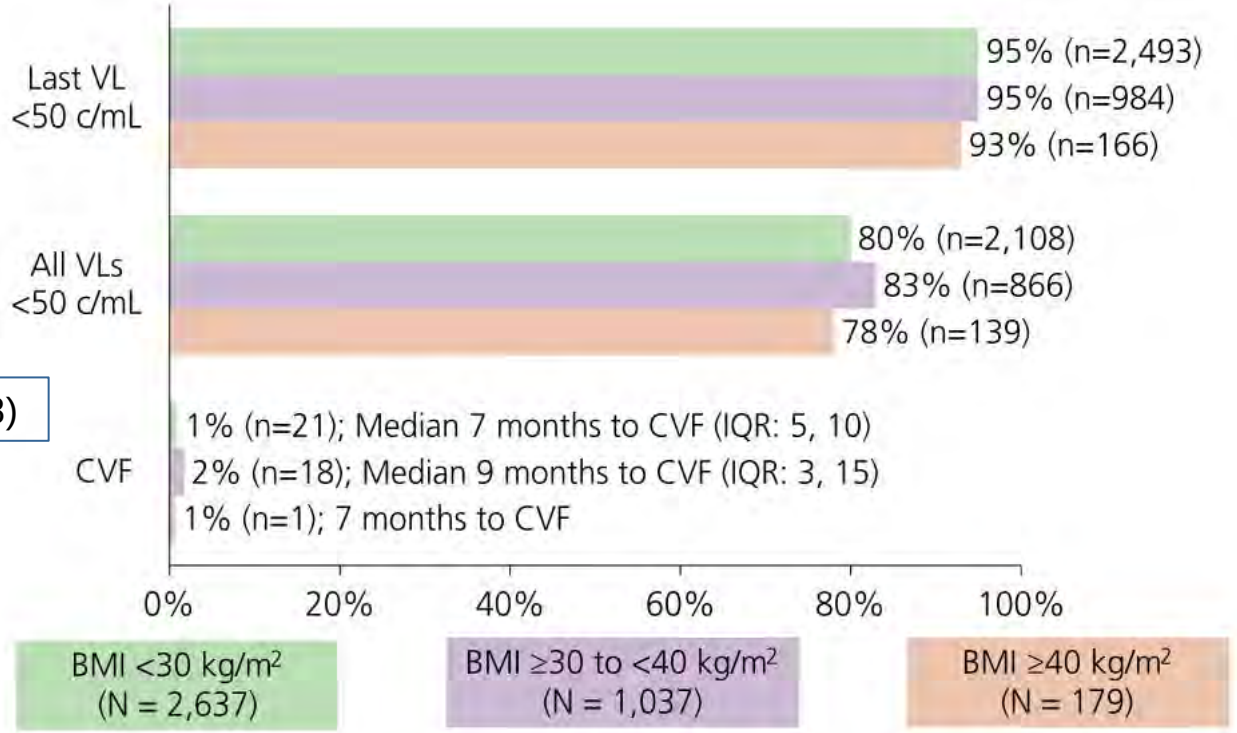
CAB-RPV in the OPERA Cohort with Elevated BMI

- PWH with viral suppression initiating LA CAB-RPV between 1/2021-12/2024





VS was maintained, regardless of BMI at initiation, including in individuals with BMI ≥ 40 kg/m^2

Levis B et al, CROI 2026 #534.

Virologic Failure with CAB-RPV in an Italian Cohort

- In a retrospective observational cohort of 2177 PWH who started CAB-RPV (3/2022-2/2025) in 22 Italian clinical centers, **45 (2.1%) had VF**
- Patient characteristics of persons with VF
  - Median ART duration prior to start: 11.9 years (IQR 7.5-17.4)
  - Median BMI prior to start: 25.2 kg/m^2 (IQR 23.4-28.9)
- Virologic outcomes of persons with VF
  - Median duration to VF 7 months (IQR 3.5-10.7)
  - Of the 45 VF, 87% were virally suppressed prior to switch
    - None had >1 of the following: subtype A6, BMI ≥ 30 kg/m2, pre-existing RPV-R
    - 43 had genotype at VF available; 75% had NNRTI-R or INSTI-R
    - 42/45 changed therapy after VF; of those, 93% re-suppressed

New Medications in the Pipeline

A Few New Medications in the Pipeline

Daily PO Regimens		
ISL-DOR	NRTTI + NNRTI	DRIVE 2 SIMPLIFY, ILLUMINATE A and B, MK-8591A-019
BIC-LEN	INSTI + Capsid Inhibitor	ARTISTRY 1 and 2
Weekly PO Regimens		
ISL-LEN	NRTTI + Capsid Inhibitor	GS-6041
ISL-ULO	NRTTI + NNRTI	MK-8591B-060
Long Acting bNAb-containing Regimens		
LEN-Tab-Zab	Capsid Inhibitor + bNAbs	NCT05729568
CAB-Lotivibart	INSTI + bNAb	EMBRACE

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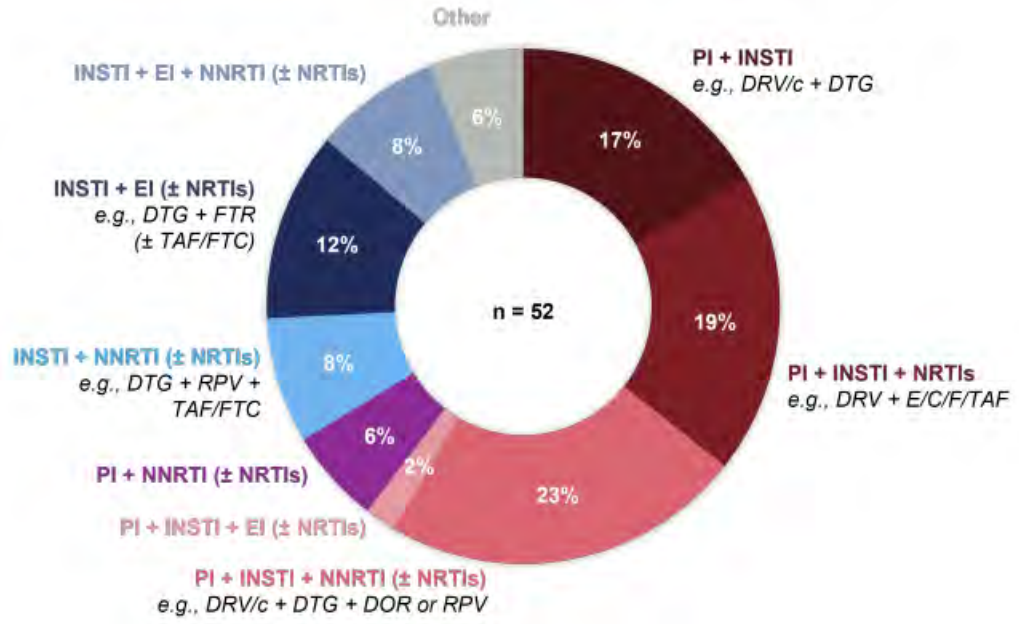
BIC-LEN in ARTISTRY-1

- Phase III, randomized, open-label trial of efficacy and safety of switch from complex regimen to BIC-LEN (75/50mg)
- 557 PWH randomized 2:1 to BIC-LEN versus continued complex regimen (CR)
  - Median ART treatment duration 28 years
  - 81% with another comorbidity
  - Median of 3 ARV tablets/day
  - Viral suppression was high and non-inferior to CR
    - No participant had emergent resistance
  - Drug-related AEs more frequent, but satisfaction higher, in BIC/LEN arm



Orkin C et al, CROI 2026 #OA10-181.

Conclusions

1. Noncanonical mutations (DRMs occurring outside the drug target site) *may* have an impact on INSTI susceptibility, but more clinical data are needed.
2. In observational cohorts of pregnant individuals on CAB-RPV, viral decay was rapid, and more data are needed on q8w dosing; for now, continue with q4w dosing while pregnant.
3. In an observational cohort of PWH on CAB-RPV, viral suppression was high, including in 200 PWH with BMI ≥ 40 kg/m^2.
4. There are many new medications in the pipeline.

Acknowledgment

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CROI 2026 Update: Co-Occurring Conditions

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Disclosures

No conflicts of interest or relationships to disclose.

Objectives

- Review updates in hepatitis B reactivation (HBVr) and new infection (HBVi)
- Review updates in management of disseminated tuberculosis (TB)
- Discuss weight loss and GLP1 receptor agonists (GLP1RAs)

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Updates on Hepatitis B

HBV Reactivation and Infection after Switch Off HBV-Active ART

- Guidelines recommend HBV treatment for all PWH with HBV given higher burden and faster progression of liver-related disease in PWH[1]
- Greater use of ART regimens without HBV activity with LAIs, 2DRs, and TFV-sparing regimens in aging PWH[1]
  - HBVr can occur if on ART regimens with only 3TC or FTC (no TFV or ETC)[1-5]
- Obs studies: HBVr (cAb+) risk low but varies after switch off HBV-active ART[1-5]
  - ~1-2% (US cohorts)[2,3] to 10% (Cameroon)[3,4], median ~9 mo[2,5] (3 wk-14 mo)[3]
  - Highest: prior HBsAg+ (up to 20%)[2], Lowest: no prior HBsAg+ (~1-2%)[2]
- CROI 2026:
  - What are predictors for HBVr/i and rates of hepatic flare after switching off HBV-active ART?
  - What is the prevalence of HBV co-infection in PWH on LAI CAB-RPV?

1-DHHS HIV Guidelines 2026; 2-Denyer et al IDWeek 2023; 3-Ring et al CROI 2025; 4-Abdullahi et al OFID 2018, 5-Dietrich et al AIDS 2026

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HBV Reactivation and Infection after Switch Off TFV-Based ART

- US cohort of adult PWH in routine care (CNICS, 5/2014-11/2024)
- Overall HBVr/i ***rare***: **21/5776 (0.4%)**
  - Over median 3.4 years follow up
  - TFV-sparing ART:
    - On XTC: **12/4652 (0.3%)**
    - No TFV and XTC: **9/1127 (0.8%)**
  - Hepatic flare (ALT≥100 U/L within 3 mo of HBVr/i) ***rare***: **3/21 (14%)**
  - Switched back to TFV: **5/21 (24%)**
- Strongest predictors for HBVr/i in multivariable LR: **CD4<200 at switch, Black and Asian race**
- **~30% without pre-switch sAg, cAb, sAb**

Outcome	Pre-switch HBV status	Pre-switch Serology	HBVi/r (N=21)	Total (N=5776)
HBVr	Prior HBV infection (HBcAb+)	HBsAb+	2 (0.27%)	740
		HBsAb-	0 (0%)	114
HBVi	No prior HBV infection (HBcAb-)	HBsAb+	4 (0.20%)	1954
		HBsAb-	9 (0.68%)	1315
HBVr/i	HBV status unknown (HBcAb missing)	HBsAb+	2 (0.20%)	1008
		HBsAb-	4 (0.62%)	648

Haser et al CROI 2026 #142

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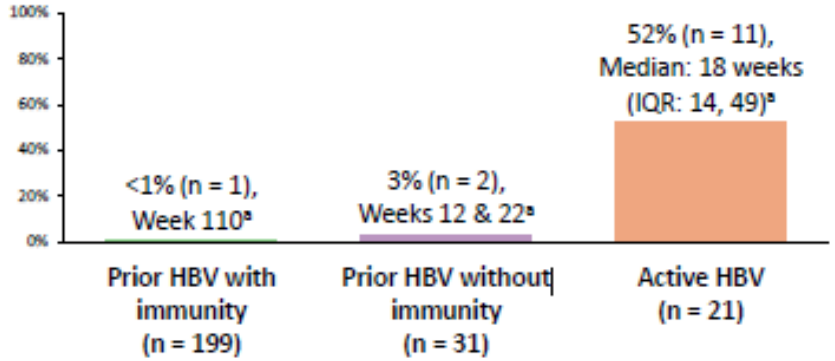
HBV Reactivation after Switch to LAI CAB-RPV

- In an obs cohort of adult PWH in routine care of 5275 starting LAI CAB-RPV (OPERA, 1/2021-12/2024), **747 (14%)** had lifetime HBV co-infection
- Of lifetime HBV: **85%** cAb+/sAb+, **10%** cAb+/sAb-, **5%** sAg or DNA+ (active HBV)
  - HBsAg or DNA infrequently checked at or after starting LAI CAB-RPV:
    - Baseline HBV DNA: 5-8% for cAb+, 37% for active HBV (46% detectable)
    - HBV labs within 12 mo of start: 31-42% for cAb+ (sAg or DNA), 60% for active HBV (DNA)
  - 95-100% HIV suppressed by end of follow up for all HBV serology groups

Figure 2. HBV reactivation among people with prevalent HBV and any follow-up HBV measurements



[a] Weeks from CAB+RPV LA start to HBV reactivation

Table 4. Use of anti-HBV agent(s) among people with HBV reactivation

	Prior HBV with immunity N = 1	Prior HBV without immunity N = 2	Active HBV N = 11
Concurrent anti-HBV agent(s) before reactivation, n (%)	0 (0)	0 (0)	1 (9)
Switched to oral ART with anti-HBV activity after reactivation, n (%)	0 (0)	2 (100)	5 (46)
Continued CAB+RPV after reactivation, n (%)	1 (100)	0 (0)	6 (54)
Added anti-HBV agent(s) to CAB+RPV, n (%)	0 (0)	---	5 (83)

Dieterich et al CROI 2026 #593

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Takeaways: HBV Reactivation and Infection when Switching Off HBV-Active ART

- In low HBV burden settings, HBVr is rare in PWH with evidence of prior HBV infection (with or without sAb+)[1-4]
  - HBVr/i in sAb+ may reflect waning HBV immunity[1,3,4] or new infection
  - Higher HBVr risk with known HBsAg+ in LAI CAB-RPV (similar to earlier studies)[1,2]
- Hepatic flare is rare but may be severe, typically resolves with HBV-active therapy[1-4]
- A full HBV battery (sAg, cAb, sAb) before ART switch is helpful to characterize risk of HBVr and HBVi and identify HBV immunization opportunities
- Routine monitoring of liver and/or HBV markers after switch, especially early-on based on risk, may help catch HBVr and HBVi[3,4]
  - High % of unknown values or lack of HBV labs in both studies
  - Current study numbers conservative = event-driven checks, not systematic checks
  - Further study needed to determine labs and tempo

1-Dietrich et al AIDS 2026; 2-Ring et al CROI 2025; 3-Swaine and Bhagani, Curr Opinion HIV and AIDS 2026 (one possible algorithm included); 4-DHHS guidelines

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Updates on Tuberculosis

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Management of Disseminated TB in HIV

- Disseminated TB occurs frequently with high morbidity and mortality (up to 25-30% globally) in PWH, especially in low CD4[1]
  - Hematogenous spread of TB = clinically defined as TB infection occurring in ≥2 non-continguous organs or isolation of TB from blood, marrow, or liver biopsy
  - Progression from primary infection or reactivation of latent focus and spread

- New management strategies needed to improve outcomes
  - Intensification of TB therapy
    - Reports of low plasma concentrations of standard TB drugs at standard doses[2,3]
  - Adjunctive steroids
    - Improves outcomes in TB meningitis and other respiratory infections[1,4]
    - High levels for markers of innate activation/chemotaxis[1]

1-Namale et al Trials 2024; 2-Gurumurthy et al Antimicrob Agents Chemother 2004; 3-McCallum et al CID 2021; 4-DHHS guidelines

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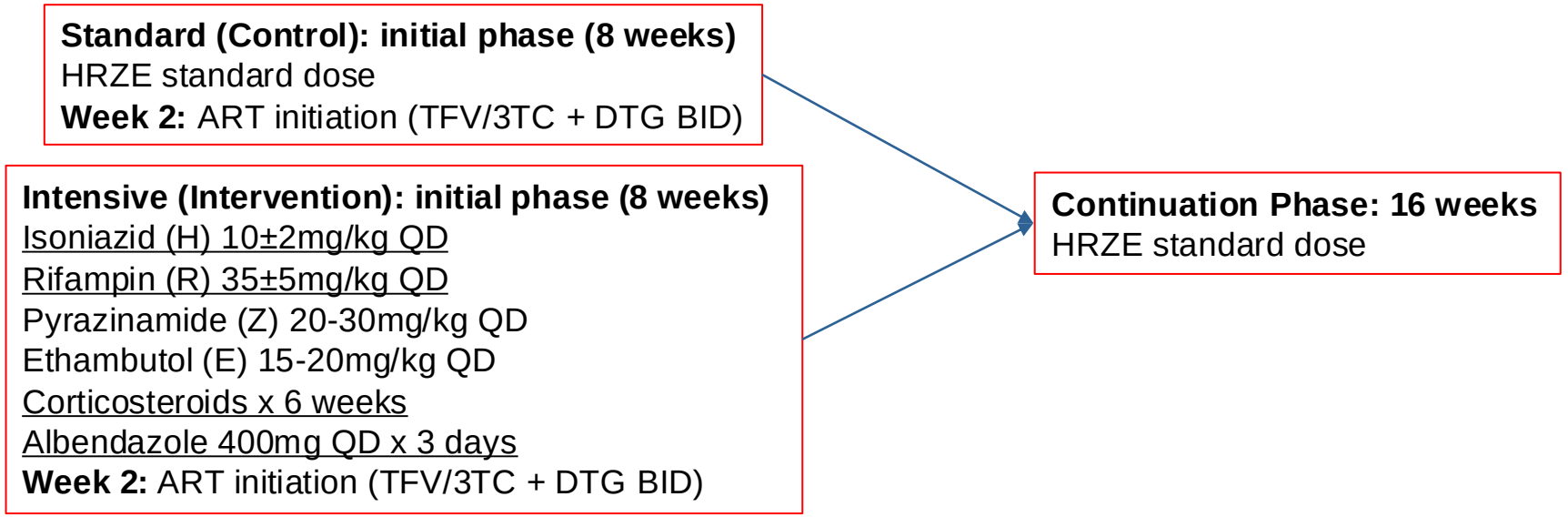
DATURA (ANRS 12424): Intensification of TB Therapy

- Phase 3 RCT in Cambodia, Cameroon, Mozambique, Uganda, and Zambia comparing **intensive TB treatment** vs **standard TB therapy (4/2022-12/2024, stopped early 12/2024 by interim analysis)**
- **Inclusion:** PWH ≥15y, CD4 ≤100, hospitalized with newly diagnosed TB: (Xpert [any fluid], urine LAM, CXR consistent with active TB)
- **Exclusion:** no TB therapy in last 6 mo, CNS sx, pericarditis, steroid contraindications, RIF-res TB, pregnant or breastfeeding, ALT>5ULN, CrCl<30



DATURA (ANRS 12424): Intensification of TB Therapy

- N=908 PWH (454 per arm), 802 disseminated ~50:50 in each arm
  - Median age 37, female 44%, median CD4 44, ART-naïve 70%
  - **Mortality similar** between arms **at 48 weeks overall** (**29% intensive vs 27% std**, aHR 1.13, P=0.41) and **within subgroups**: CD4 ≤50, CD>50, disseminated TB.
  - **Mortality similar at all key timepoints**: 2, 12, 24, 36, and 48 weeks
- Plasma PK (N=69): significantly higher Cmax and T>AUC for RIF and INH in intensive arm
- Grade 3-4 Adverse Events: 71% intensive vs 73% std (aRR 0.98, 95% CI 0.90-1.06)

	Intensified TB treatment, n (%)	Standard TB treatment, n (%)	Risk ratio [95% CI] [1]
Drug-induced liver injuries	76 (13.4)	29 (5.3)	2.7 [1.8;4.2]
Severe infectious diseases	54 (9.5)	58 (10.7)	0.8 [0.6;1.2]
TB worsening	37 (6.5)	27 (5.0)	1.4 [0.9;2.2]
AIDS-defining illnesses	17 (3.0)	22 (4.1)	0.8 [0.4;1.4]
Paradoxical TB-associated IRIS	16 (2.8)	35 (6.4)	0.5 [0.3;0.8]
Hyperglycaemia/diabetes	10 (1.8)	2 (0.4)	5.0 [1.3;32.4]

Adjusted for country, CD4 group, except in CD4 subgroup analyses. No significant interaction between any subgroup and intervention

NewStrat-TB: Adjunctive Steroids

- RCT at 3 hospitals in **Cape Town** with 2x2 factorial design:

  Std TB Rx + Pred 14 d — Std TB Rx + Placebo 14 d

  Intensified TB Rx + Pred 14 d — Intensified TB Rx + Placebo 14 d

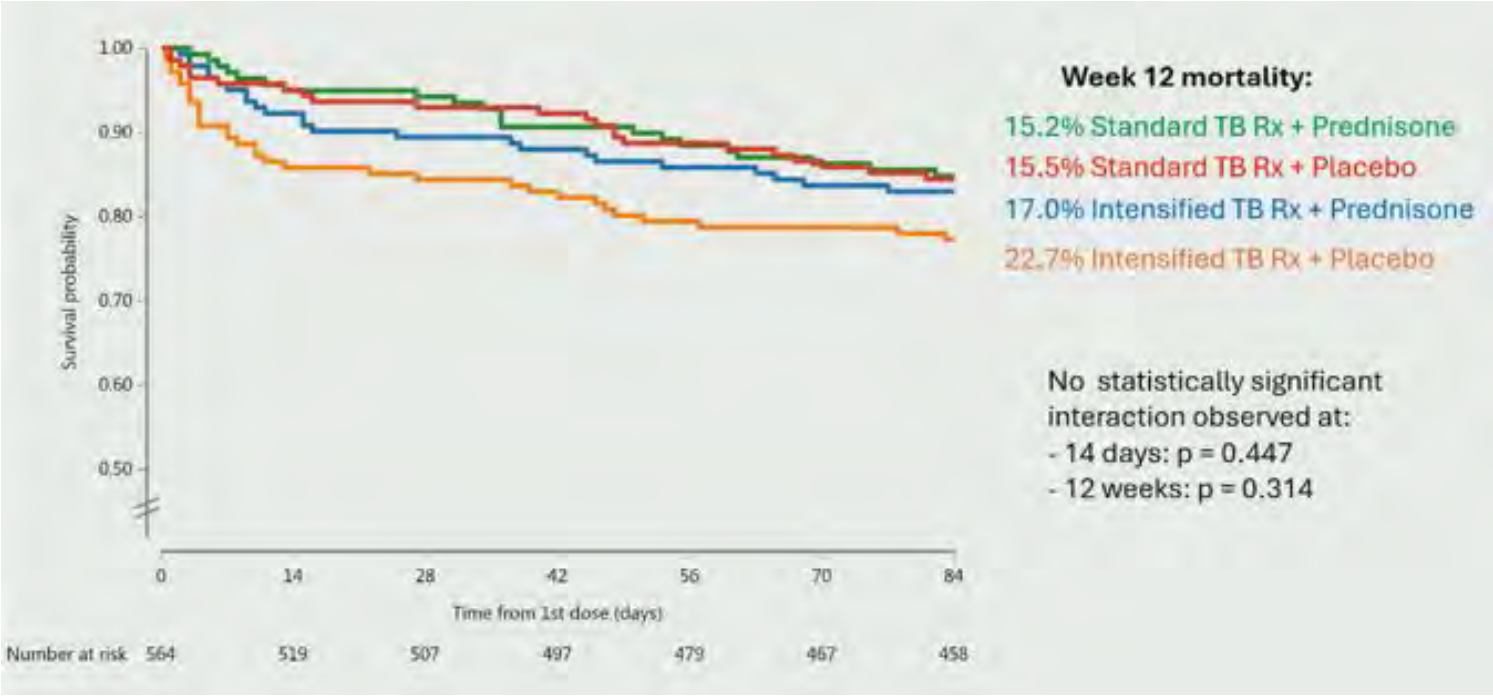
  After day 14: all participants receive std TB Rx to 6 mo

- **Intervention:**
  - Intensified TB Rx: HRZE with RIF 35mg/kg QD + levofloxacin
  - Prednisone: 1.5mg/kg QD
- **Inclusion:** PWH ≥18y and disseminated TB (+urine or blood Xpert Ultra or +urine LAM)
- **Exclusion:** TB Rx <30 d or >2 doses received, RIF-res TB, Neuro TB, ALT>120 IU/L or Tbili >34 umol/L, cryptococcal disease, pregnant or breastfeeding
- **Intensification evaluation ended early** (12/2024): **higher mortality (2 wks)** in intensification arm (11% vs 5%, 95% CI 1.5-10.3%, P=0.008) despite **similar mortality at 12 wks (primary)**
- **Prednisone evaluation continued after DSMB closed intensification evaluation**

NewStrat-TB: Adjunctive Steroids

- **No significant difference in mortality**
  - **14 days:** 7% vs 10%, P=0.185
  - **12 weeks** (primary): 18% vs 19%, P=0.588
  - No statistically significant interaction by intervention for 12 wk mortality
  - On visual inspection, prednisone may have reduced harmful effects of intensified treatment
- Prednisone x 14 days: well-tolerated, no significant difference in AEs

	Prednisone arm (n=355)	Placebo arm (n=357)
Age (years)	36 (30-43)	36 (30-43)
Female sex	189 (53%)	200 (56%)
CD4 count (cells/uL)	**43 (16-96)**	**44 (18-96)**
HIV viral load (log^{10} copies /mL)	**5.4 (3.9-6.0)**	**5.3 (3.0-5.9)**



Namale et al CROI 2026 #124

Takeaways: Management of Disseminated TB in PWH

- Disseminated TB occurs frequently in PWH, especially with low CD4, and has high morbidity and mortality
- Intensification of TB medications does not improve and possibly worsens mortality and toxicities
- Corticosteroids appears well-tolerated but did not improve mortality
- Further work greatly needed looking at other causes of death and alternate management strategies in disseminated TB among PWH

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Updates on Weight Loss and GLP1RAs

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Weight Loss, GLP1RA + Incretin Analogs, and Physical Activity

- PWH face higher levels of weight gain, cardiometabolic, and other co-occurring conditions than the general population, especially as PWH age[1]
- GLP1RA and other incretin analogs are highly efficacious for weight loss, diabetes, and evidence exists for management of multiple other co-occurring conditions (e.g., OSA, CHF, CVD, CKD, MASLD, SUD)[2,3]
- Lifestyle modifications are still important given risks of sarcopenia and weight rebound if GLP1RAs are stopped[4]
- More data needed for effectiveness and safety in PWH[1,5,6]
- Lightning round of abstracts for semaglutide, tirzepatide, and physical activity

1-DHHS guidelines; 2-Moiz et al EClinMed 2025; 3-Kong et al Nature Comm 2026; 4-Chen and Batsis, Diabetes 2025; 5-Gattu and Fourman, Curr Opin HIV AIDS 2025; 6-Lake et al Ann Int Med 2024

Semaglutide Abstracts

- In the CNICS cohort, semaglutide started for DM or weight loss was associated with **reductions in liver fibrosis score in PWH with probable metabolic liver disease[1], decreases in tobacco use in PWH using cigarettes[2]**, and **did not worsen depressive symptoms**
  - Greatest reductions in liver fibrosis score in PWH with most severe fibrosis (mean time on SG: 210 days). Good safety signal with respect to liver fibrosis score.
  - Semaglutide associated with ~25% reduction in # cigarettes/day (baseline mean 10.5 cigs/day) (mean time on SG: 375 days)

- In a phase 2 RCT, **PWH with lipohypertrophy** randomized to **32 weeks** of weekly semaglutide (up to 1mg/wk, N=54) or placebo (N=54) **did not** find significant changes in **subclinical vascular function or calcified plaque** but did find **improvements** in **lipids, abdominal fat, weight, BMI, and BP.**

1-Ma et al CROI 2026 #601; 2-Crane et al CROI 2026 #698; 3-Haidar et al CROI 2026 #447; 4-Eckard et al CROI 2026 #669

Tirzepatide Abstracts

1. At the UCSD Owen clinic (5/2022-12/2024), **tirzepatide** use was associated with **reduced wt** (14 kg, 14% body wt), **BMI** (mean 4.8), **BP**, **A1c** (mean 1.6%), and 10-year ASCVD over 12 mo follow up
   - Of the 61 PWH started on tirzepatide, 22 had DM and 39 did not have DM. Greater wt loss occurred in the non-DM group
   - 26% stopped tirzepatide in the first year due to insurance and supply-related challenges > side effects > lack of efficacy

2. In the CNICS cohort, PWH on **tirzepatide lost 3.1% more body wt** and **0.39% A1c than those on semaglutide**
   - Mean BMI 35-36, A1c 6.6-6.9%, ~53-54% with DM
   - Body wt: -3.1% SG vs -6.2% tirzepatide; A1c: -0.25% SG vs -0.64% tirzepatide
   - Greater loss on tirzepatide than SG by sex, BMI (>30 v <30), and DM status

1-Lee et al CROI 2026 #696; 2-Crane et al CROI 2026 #697

GYM Study: Home-Based Physical Activity Support in PWH with Sarcopenia

A 48-week, home-based intervention (Grow Your Muscle (GYM))[1] was feasible and effective in improving muscle strength and mass in PWH ≥50 with sarcopenia (N=69) and muscle mass in people without HIV >60 with sarcopenia (n=73)

- Sarcopenia = age-related condition with loss of muscle, strength, and function.
  - Strength: hand grip, chair-stand test; Mass: appendicular skeletal mass index, fat-free mass
- Intervention: Four 40-min sessions/wk of exercises focusing on major limb muscle groups and balance control, supported by a smartphone app (videos + remote monitoring) (N=36 PWH, N=37 PWOH)
- Control: no supported exercise regimen, recommended to get >150 min physical activity/wk (N=33 PWH, N=36 PWOH)

1-Bonato et al CROI 2026 #722

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Takeaways: Weight Loss, GLP1RA and Incretin Analogs, and Physical Activity

- PWH face higher levels of weight gain, cardiometabolic, and other co-occurring conditions than the general population, especially as PWH age
- Semaglutide and tirzepatide appear generally safe and beneficial for managing DM, weight, and a variety of related and co-occurring conditions in PWH
- Guided physical activity is helpful for improving muscle strength and mass in older PWH with sarcopenia, perhaps with applicability in other causes of sarcopenia

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Conclusions

- HBV reactivation and flare are rare in PWH in low burden settings but risk varies by prior HBV serologies and history
- Full HBV serologies should be obtained near switch off HBV-active ART to determine risk for reactivation and infection and immunization
- Routine monitoring of liver and/or HBV markers should be done after switch
- Treatment with intensified TB Rx or steroids for disseminated TB in PWH does not improve mortality
- Semaglutide and tirzepatide appear generally safe and beneficial for managing cardiometabolic and other co-occurring conditions in PWH

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