Pre Alexandra Calmy, Geneva University Hospitals

Scientific highlights
IAS 2025 (Kigali, Rwanda)

Cure, antiretroviral strategies, implementation science and more.

Geneva, September 3rd, 2025, IAS Webinar

IAS 2025

WE WILL NOT GO BACK!

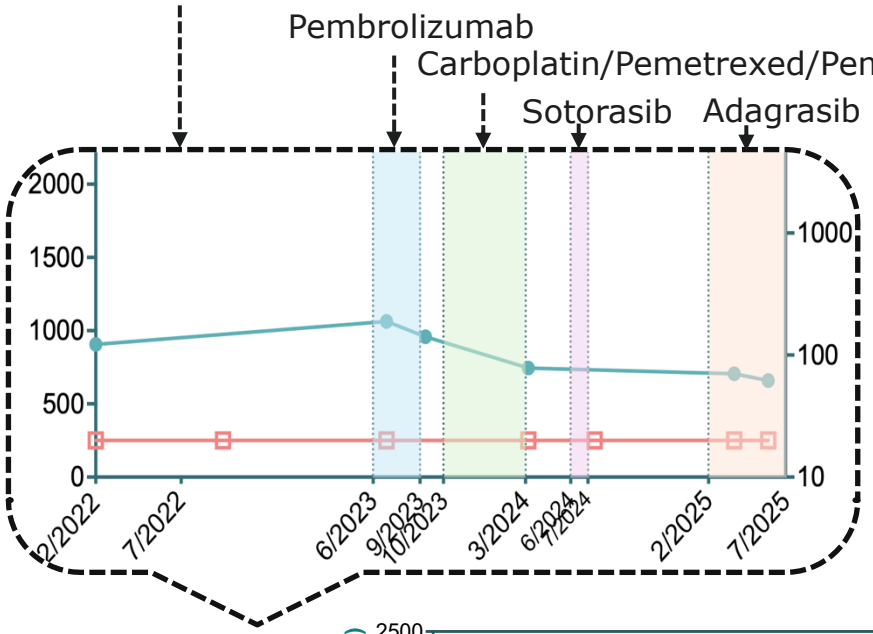
Content

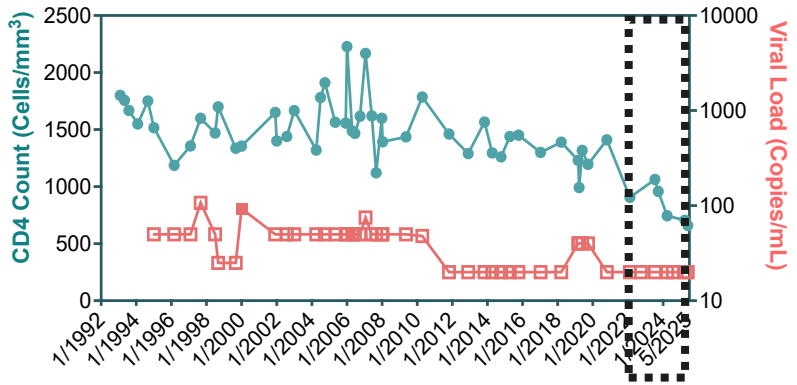
From track A to track D: a personalized pathway!

1. **Cure and Prevention – HIV in the corner**
2. ART strategies
3. Co-morbidities
4. Conclusions and Take-home messages

Loreen Willenberg *further evidence of natural HIV cure?*

Diagnosis of lung cancer





- HIV copies/ml
- Undetectable VL
- CD4+ T-cell count

SCIENCEINSIDER | HEALTH

‘Something remarkable has happened’: Cancer treatments bolster evidence of a natural HIV cure

In exclusive chat with *Science*, Loreen Willenberg describes remaining HIV-free even after immune-suppressing therapies for brain and lung tumors

15 JUL 2025 · 3:00 AM ET · BY JON COHEN

Loreen Willenberg, sitting outside of her California apartment last week, is the world’s most compelling case that the immune system alone can cure a person of an HIV infection. LOREEN WILLENBERG

CAR-T cell-secreted bNAbs mediate Fc-effector functions and reduce viral load in humanized mouse model of HIV infection

Fonctions effectrices des CAR-T sécrétant des bNAbs et réduction de la charge virale dans un modèle murin humanisé du VIH

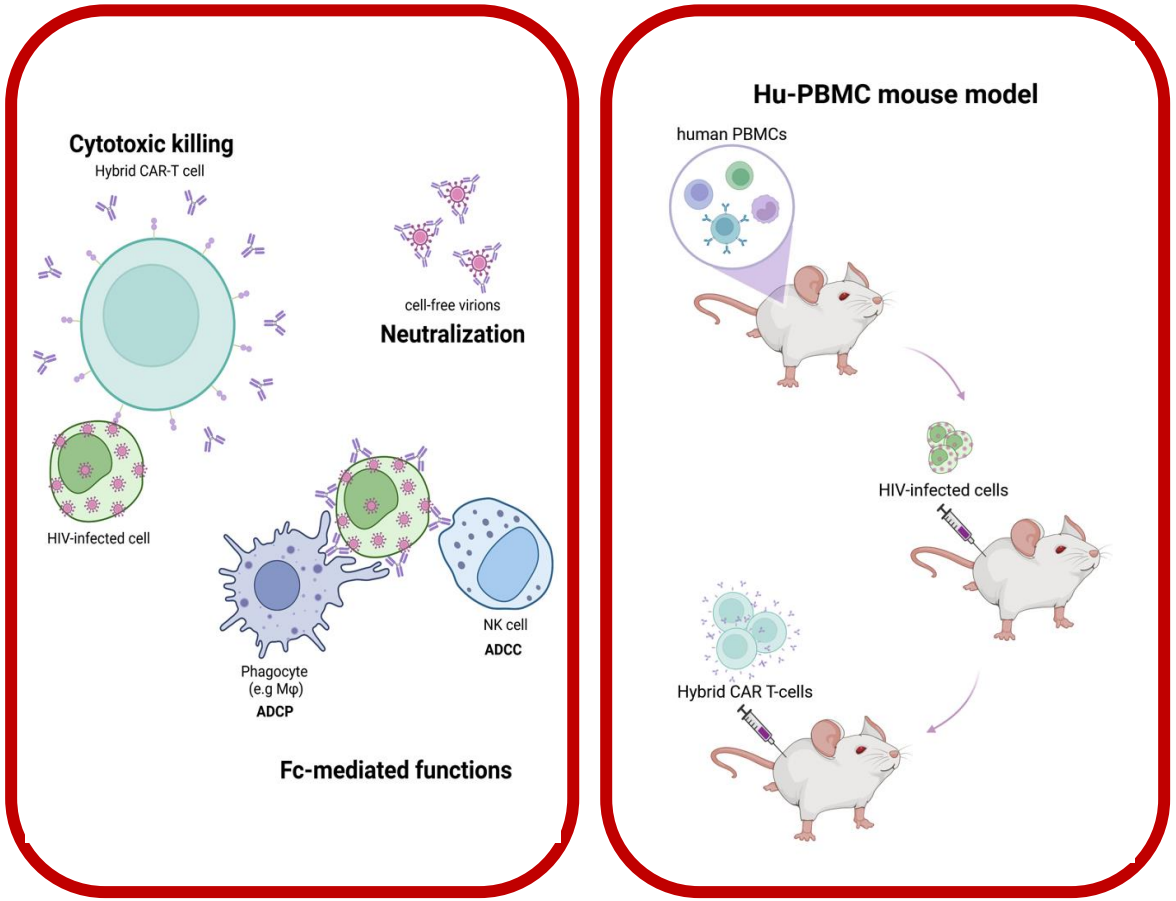
Z.Stylianidou[1] , S. Gerlo[1] , M. Wejda[1] , E. Burg[1] , E. De Smet[1] , Y. Noppe[1] , L. Vandekerckhove[1], W. Witkowski[1]
[1]HIV Cure Research Center, Ghent University, Faculty of Medicine and Health Sciences, Ghent, Belgium

***Can Hybrid CAR-T cells contribute to a functional cure*?**

Hybrid CAR-T cells represent a promising avenue toward a functional cure for HIV

Secretion of 3BNC117 (broadly neutralizing antibody) by hybrid CAR-T cells and HIV neutralization

- ✓ Secreted 3BNC117 induces Fc-dependent effector functions
- ✓ In vivo efficacy: elimination of infected cells and detection of 3BNC117 in the plasma of humanized mice



Vaccine science – Dr. Penny Moore (plenary)

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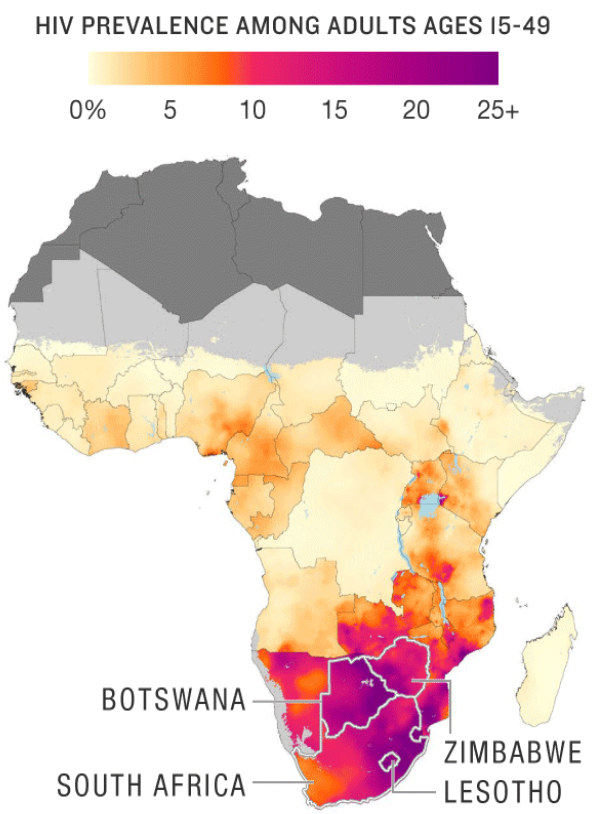
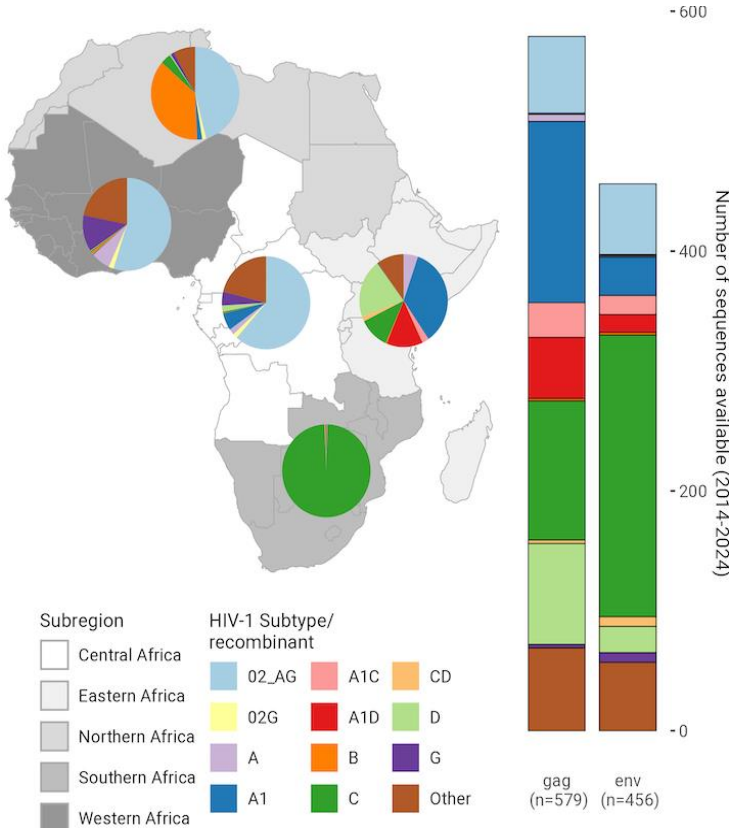
- **Gaps in key knowledge:**
  - **HIV sequence diversity**
  - **Host genetic diversity**
- AMP* (antibody mediated prevention) study – demonstrated proof of concep that an antibody vaccine could preven HIV acquisition
- Early life administration of 2 bNAbs as safe in infants, supporting further investigation into antibody-based strategies to prevent vertical transmission.



HIV Prevalence



HIV sequence coverage

Why is this important?

Broadly neutralizing antibodies (bNAbs) have a steadily growing role in HIV research, driven by insights from immunotherapy, cure science and vaccine development

Multifaceted prevention

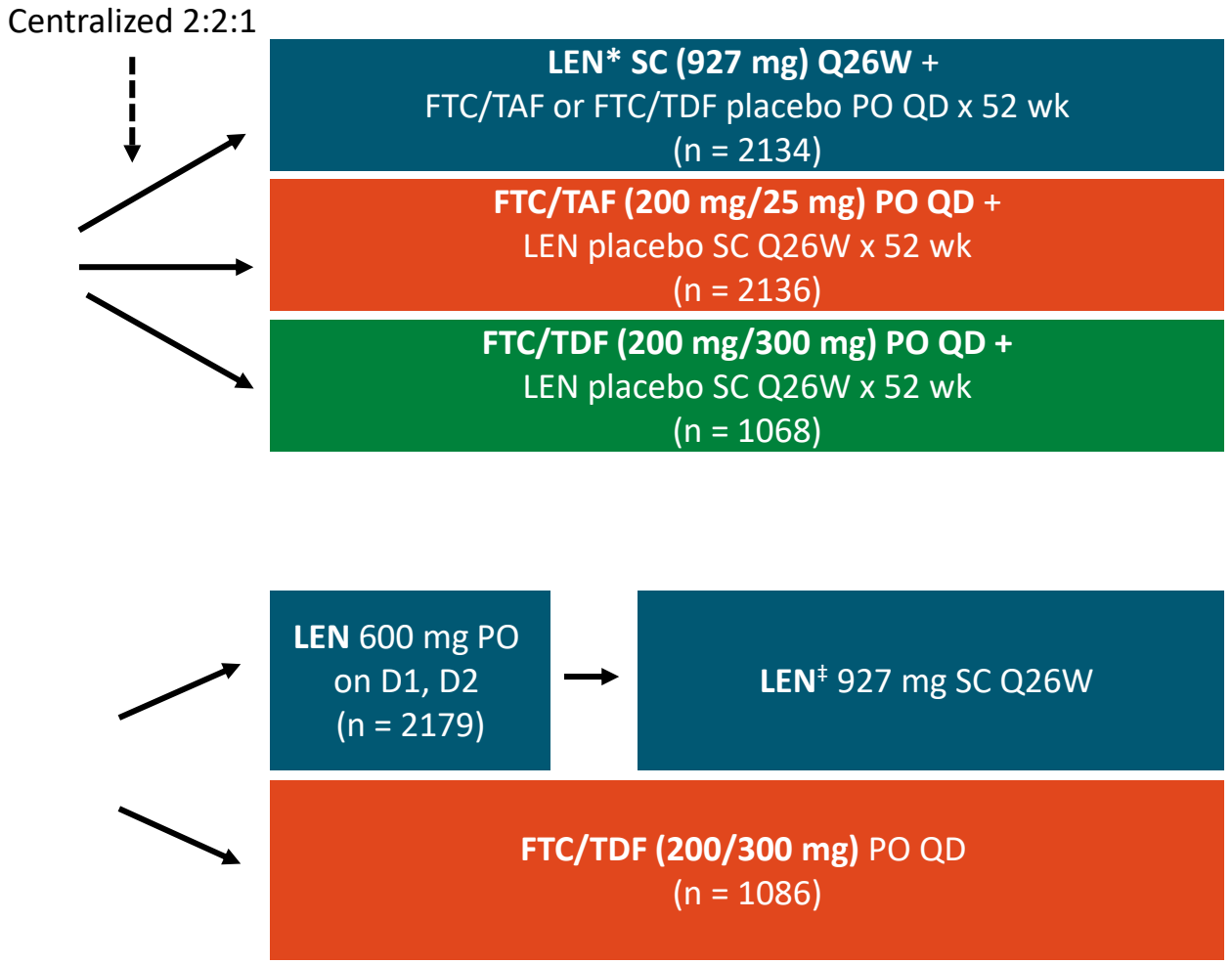
PURPOSE 1 and PURPOSE 2 Results in Adolescents and Young Adults: Study Designs

PURPOSE-1

Cisgender **women** aged 16-25 yr; sexually active with cisgender men and >1 vaginal intercourse within last 3 mo (not pregnant); unknown HIV status; no prior HIV testing or PrEP/PEP use in last 3 mo; ≥35 kg body weight; eGFR ≥60 mL/min
(N = 5338)

PURPOSE-2

Cisgender **men**, transgender women, transgender men, and gender nonbinary people with unknown HIV status; aged ≥16 yr; sexually active with ≥1 partner who is assigned male sex at birth within last 12 mo and 1 risk factor[†]; no prior HIV testing or oral PrEP/PEP use in last 3 mo; no prior LA PrEP use
(N = 3295)

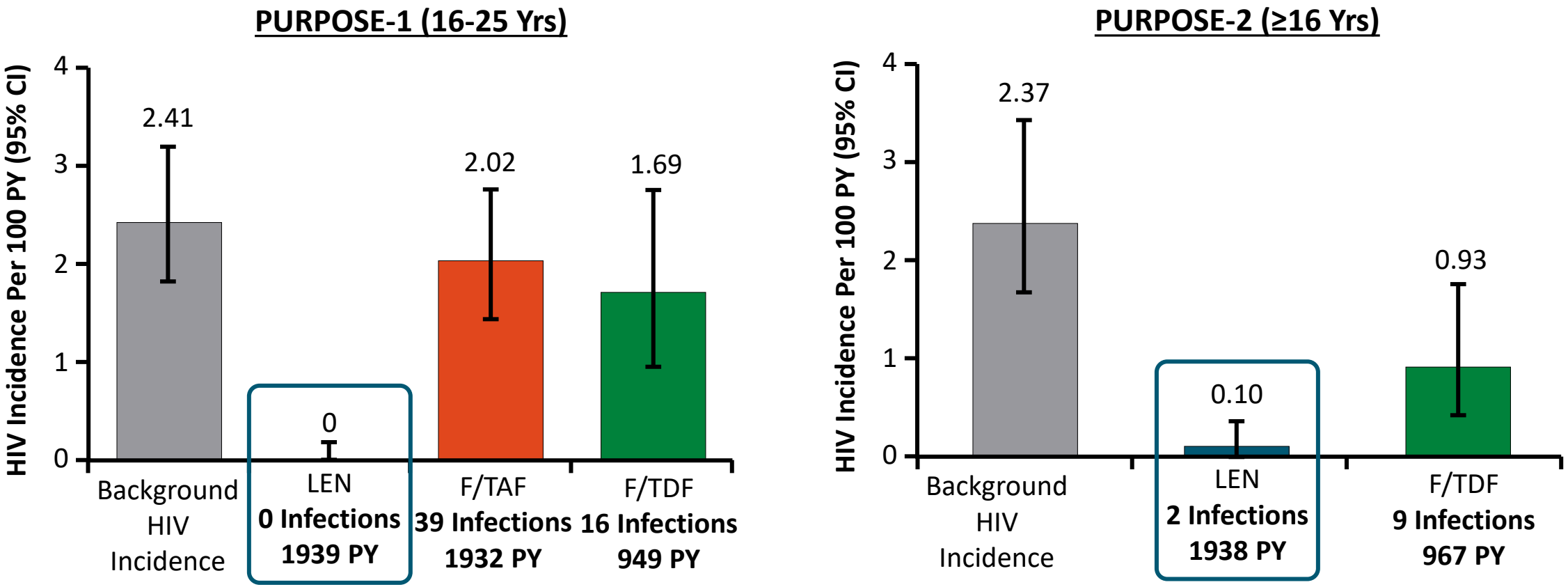


Gill. IAS 2025. Abstr OAC0503.

Slide credit: clinicaloptions.com

PURPOSE 1 and PURPOSE 2 Results in Adolescents and Young Adults: HIV Infections

Gill. IAS 2025. Abstr OAC0503. Reproduced with permission.



Injection-site reactions in youth were predominantly mild and aligned with those reported in the broader PURPOSE 1 and 2 study populations. **In the PURPOSE 1 and PURPOSE 2 studies, LEN efficacy and safety in adolescents and young adults were similar to those seen in adults**

Slide credit: clinicaloptions.com

Why is this important?

Phase 3 Purpose 1 and 2 trial data showed that LEN was efficacious and well tolerated among a broad range of populations, including pregnant and lactating women and adolescents and young people.

Lenacapavir was efficacious, safe, and well tolerated, with minimal exposure in breastfed infants (OAC0504).

WHO Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable PrEP

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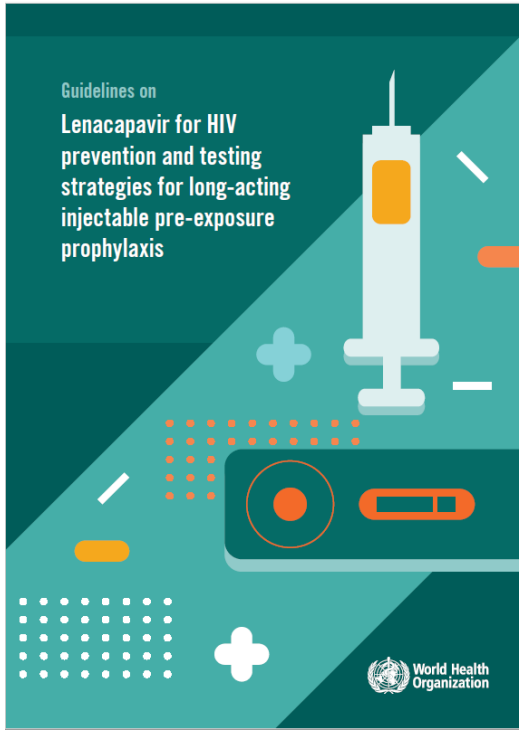
New recommendations

Recommendation [NEW]

Long-acting injectable lenacapavir should be offered as an additional prevention choice for people at risk of HIV, as part of combination prevention approaches. *(strong recommendation, moderate to high certainty of evidence)*

Recommendation [NEW]

Rapid diagnostic tests may be used for HIV testing for initiation, continuation and discontinuation of long-acting PrEP. *(strong recommendation, very low certainty of evidence)*.



World Health Organization

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Oral presentation OAS0106LB - **The growing toolbox of long-acting options**

Safety and Pharmacokinetics of MK-8527 Oral Once-monthly: a Phase 2 Study in Adults at Low Risk of HIV-1 Exposure

Kenneth Mayer[1,2], et al [1]Fenway Health and Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA – the once monthly oral pill study

Objectives: To evaluate the safety and pharmacokinetics of MK-8527 (3 mg, 6 mg, and 12 mg) oral once monthly, for 6 months, in adults with a low likelihood of HIV-1 exposure

MK-8527-007 phase 2 study

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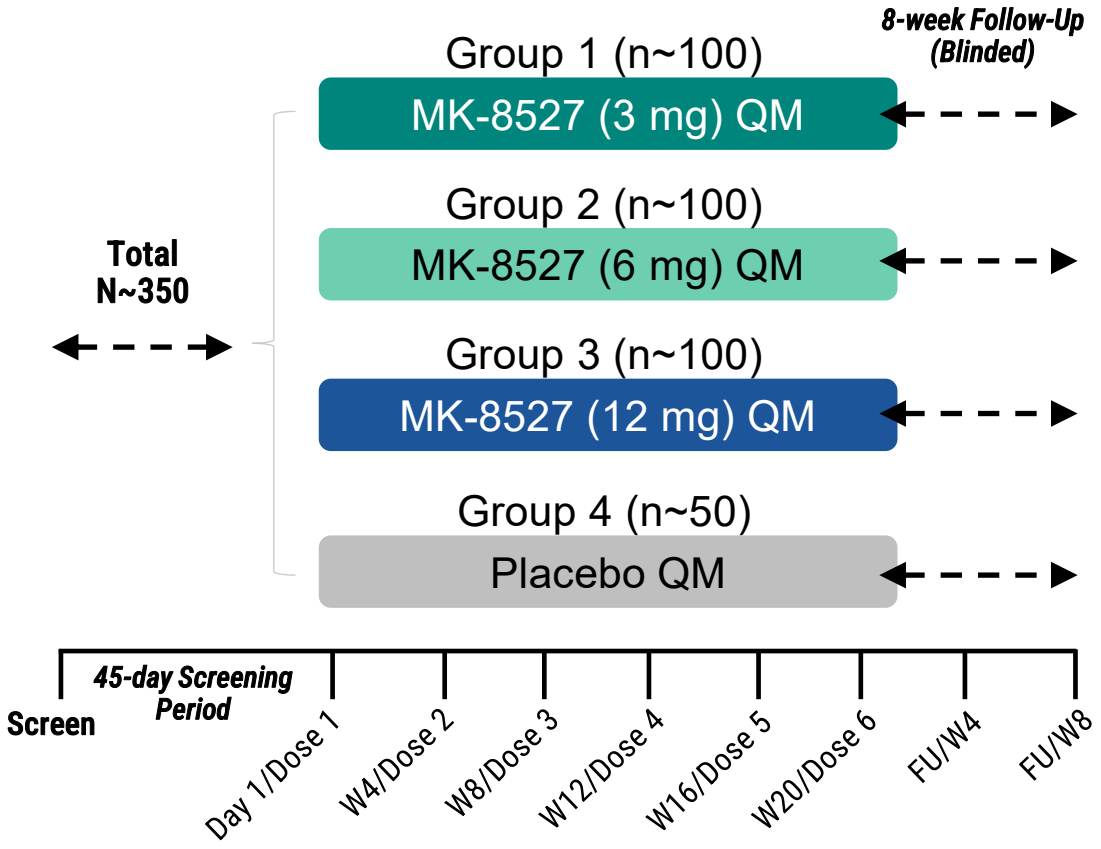
- **Key Inclusion Criteria ad**
  - Adults with low likelihood of HIV exposure
- **Participants randomized (2:2:2:1) to receive oral monthly doses of MK-8527 (3, 6, or 12 mg) or placebo for up to 6 consecutive months (1 dose every 4 weeks) from Day 1 to Week 20**
- The study was conducted in Israel (3 sites), South Africa (5), and the United States (10 sites)
- 328 participants – median age 28 - received all 6 doses, >30% women and > 30% enrolled in Africa

Phase 2 randomized double-blind, dose-ranging study



MK-8527-TP in PBMCs (PreP)

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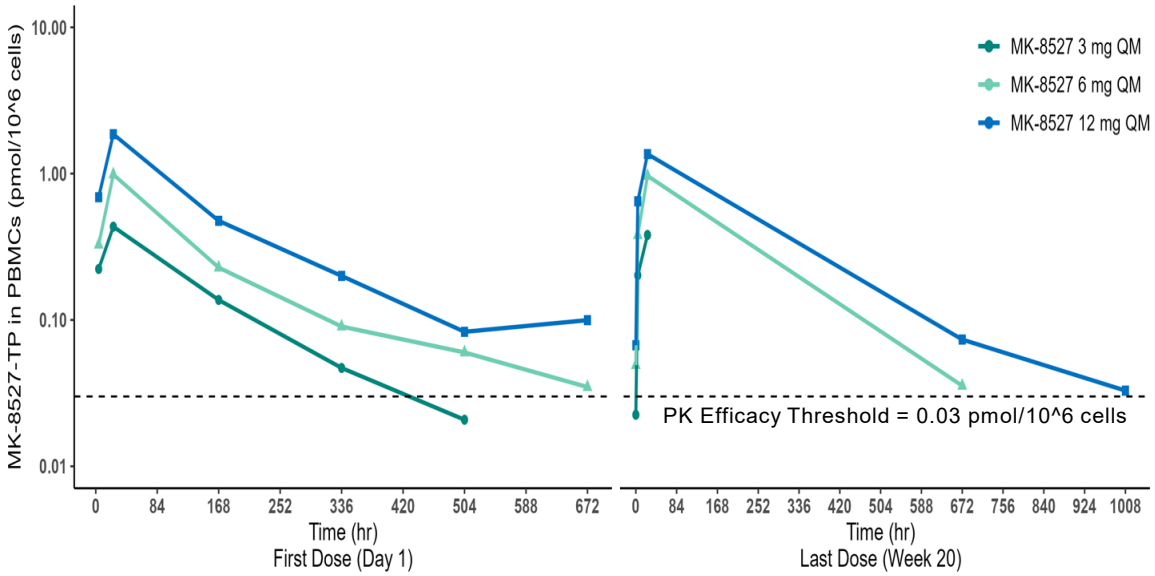
Concentration vs Time Profiles (semi-log scale)



- PK parameters for MK-8527-TP are dose-proportional
- Minimal accumulation of MK-8527-TP in PBMCs with monthly dosing

In this Phase 2 study conducted in adults with a low likelihood of HIV-1 exposure:

Six consecutive monthly doses of MK-8527 (3 mg, 6 mg, and 12 mg) were generally well tolerated.

The pharmacokinetics of MK-8527 and MK-8527-TP are dose-dependent.

These results support the clinical development of once-monthly oral MK-8527.
Phase 3 studies of once-monthly oral MK-8527, EXPrESSIVE-10 and EXPrESSIVE-11, are expected to begin in Q3 2025.

USAID initiated more than 3.7 million people on PrEP between FY17 – FY24

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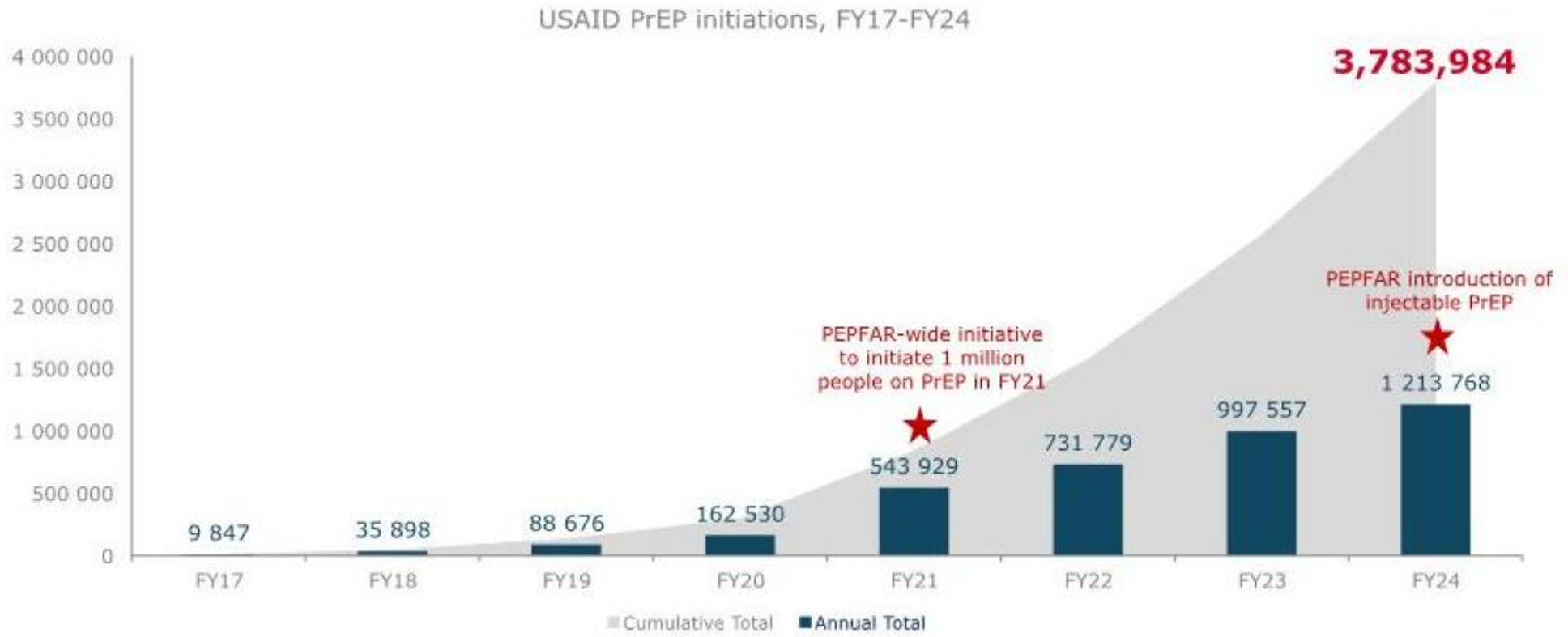

The challenge will be to sustain the global implementation of PrEP despite the withdrawal of U.S. funding

Take home messages: HIV Prevention and cure

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1. **Broadly neutralizing antibodies** – featured in both the cure and prevention sections.
2. In the **PURPOSE 1 and PURPOSE 2 studies**, twice-yearly subcutaneous **lenacapavir (LEN)** was demonstrated to be effective and safe in a broad range of populations.
3. **LEN PrEP** is now included in the new **WHO PrEP guidelines**.
4. **Once-monthly oral PrEP** is emerging—driving prevention forward by offering individualized options.
5. The impact of **budget cuts** on the HIV epidemic was shown, in one modeling study, to be extensive, with **community and prevention services** being most affected.
6. The Global Fund and Gilead Sciences announced an access agreement that will see Gilead supplying doses, at no profit, for up to two million people over 3 years.

HIV Vaccine in the Era of Twice-Yearly Lenacapavir PrEP: A Necessity or an Obsolete Option?

(Patt et al, New Eng J Med, April 24th, 2025)

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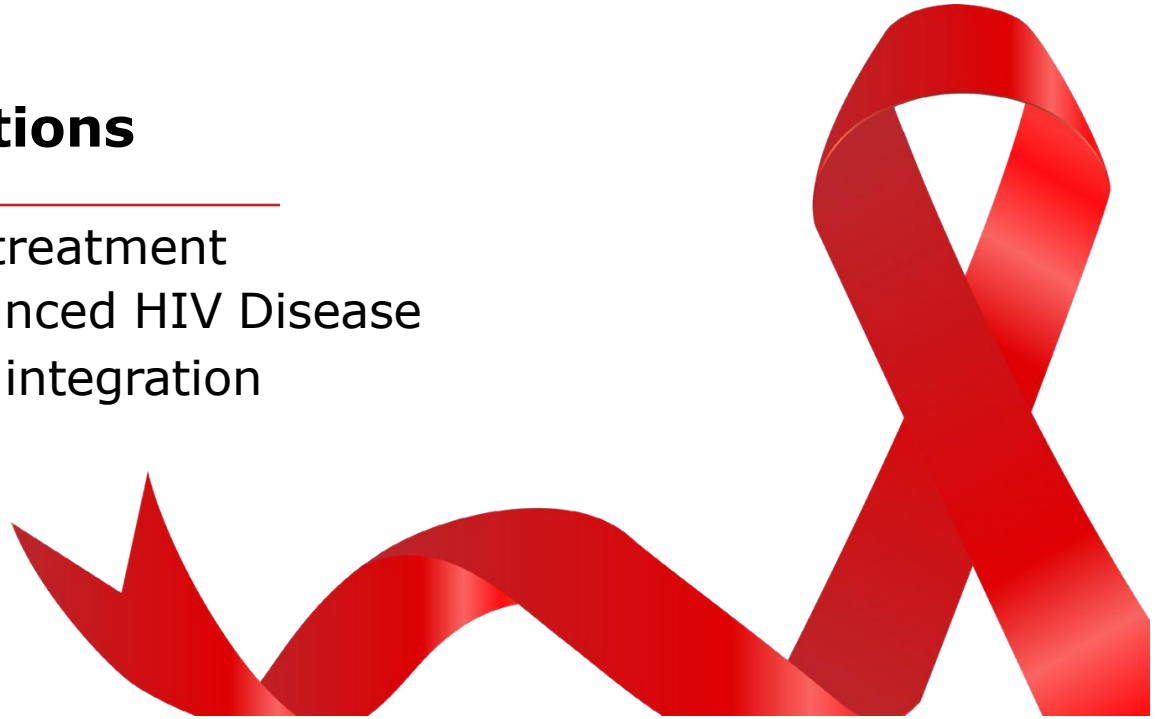
SAT11:

What's new in WHO guidelines: advancing prevention, testing and treatment for impact and sustainability

New recommendations

- HIV prevention and treatment
- Management of advanced HIV Disease
- Service delivery and integration



HIV guidelines New treatment recommendations

World Health Organization

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Treatment	Previous recommendations	New recommendations
Preferred and alternative PI options	ATV/r and LPV/r preferred PI options DRV/r as alternative PI option	DRV/r as **preferred** PI option
Preferred and alternative NRTI options	TDF as preferred option for ART initiation in adults and adolescents ABC as preferred NRTI option for ART initiation in children AZT or TAF as alternative options or used in special circumstances	**Adults, adolescents and children > 30 kg:** TDF or TAF as preferred option in initial and subsequent regimens (even if TDF or AZT previously used) **Children < 30 kg**: ABC as preferred option in initial regimens. ABC or TAF as preferred options in subsequent regimens (even if ABC or AZT previously used)
NRTI sequencing in subsequent regimens	AZT in subsequent regimen if TDF or ABC used in initial regimen (and vice versa)	
Dual ARV oral regimens	---	DTG+3TC as ART **simplification** strategy in adults and adolescents with undetectable HIV viral load*
Long-acting injectable regimens	---	CAB + RPV as alternative ART **switching** option in adults and adolescents with undetectable HIV viral load*

*no active HBV infection

The Medicines Patent Pool (MPP) and ViiV Healthcare announced a licensing agreement to allow generic production of CAB-LA for HIV treatment for use in combination with rilpivirine in 133 countries

Cassandra Fairhead et al , Royal Free Hospital, London

Systematic review and meta-analysis of the efficacy of intermittent antiretroviral therapy dosing

Can intermittent therapy be a crisis response to the sudden cuts in USAID and PEPFAR funding?

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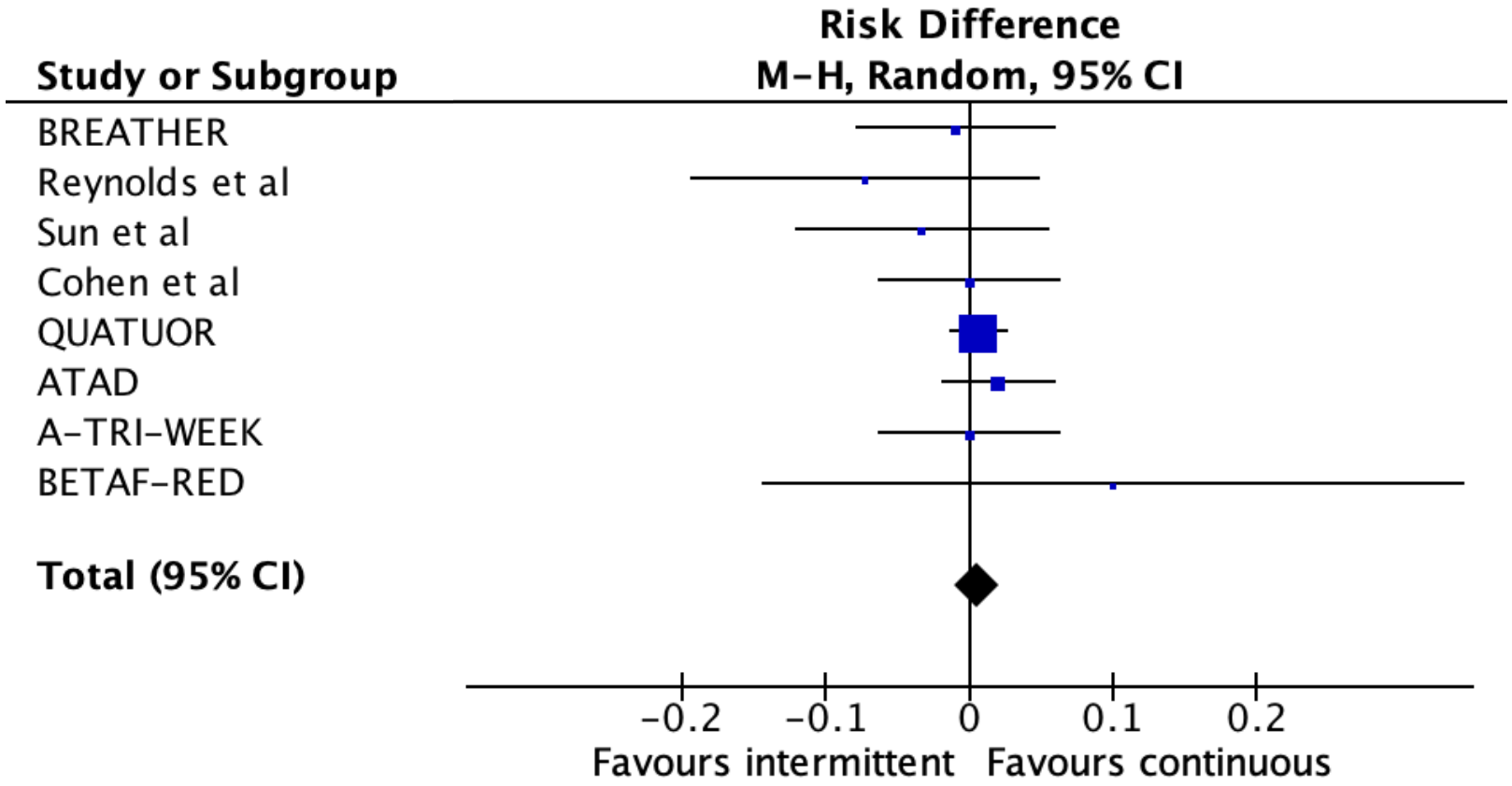
Efficacy (HIV RNA ≥50 copies/mL*), ITT analysis



Risk Difference 0.00
95%CI -0.01 to 0.02
***p*=0.54**

*A-TRI-WEEK: 37 copies/ml; Cohen and Reynolds et al: 400 copies/mL

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Short cycle ART with weekends off is inferior to continuous ART in adolescents living with HIV receiving TLD in sub-Saharan Africa:

BREATHER Plus 96-week results

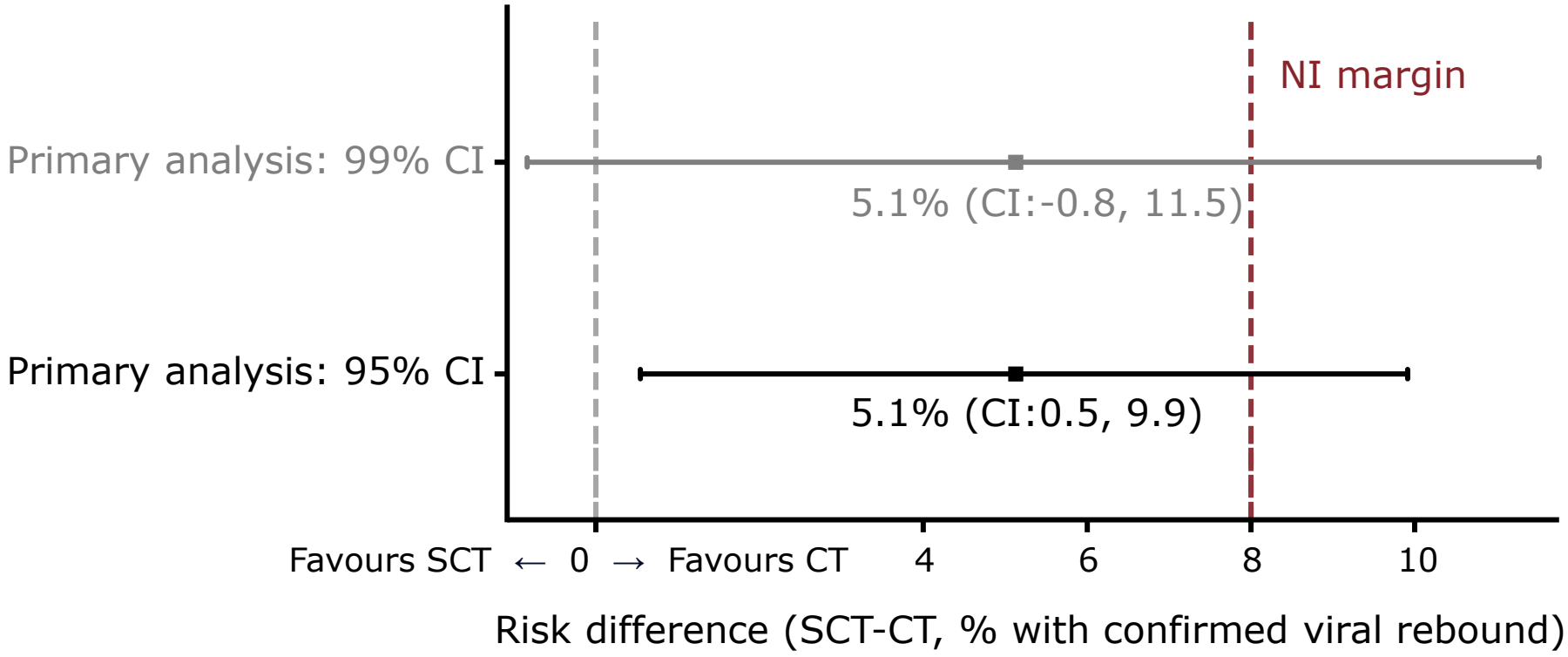
Adeodata R. Kekitiinwa *et al, on behalf of the BREATHER Plus trial team*

Session: Co-Chair's choice

Abstract code: OAS0104LB

Primary efficacy endpoint:

inferiority



Rate of confirmed virologic rebound by Wk 96 in SCT ART arm did not meet criteria for noninferiority to CT ART

SCT ART was inferior to CT ART (*P* = .034)

*2 consecutive plasma HIV-RNA ≥50 copies/mL

Why is this important?

In times of funding constraints, intermittent therapy may be a strategy worth exploring; however, results across different settings and populations may not be directly generalizable.

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Long-acting cabotegravir and rilpivirine in adults with suboptimal HIV control in sub-Saharan Africa

The IMPALA trial 48-week results

Fiona Cresswell

on behalf of Eugene Ruzagira, Loice Achieng Ombajo, Nigel Garret, Noela Owarwo, Eva Laker Odongpiny, Henry Mugerwa, Ibrahim Yawe, Sheetal Kassim, Sharana Mahomed, Awhonukeh Idahosa, Ingrid Eshun-Wisonova and the IMPALA trial team

Does LA injectable ART can be effective in people with suboptimal control in high- and low and medium-income countries?

Co-Chairs' choice, OAS01

Study rationale and design

- **Evidence gaps: sub-optimal HIV control in public health approach, prior HBV exposure (cAb+), women**
- Phase 3b, open-label, non-inferiority trial
- 7 sites: Uganda, Kenya, S. Africa (NCT05546242)

Population, n=540
≥18 y.o. with suboptimal HIV-1 control

1. **HIV-1 VL >1000 c/ml in prior 2 yrs despite being on ART**
2. **History of loss to follow- up (>4 wks)**
3. **Unlinked to HIV care ≥3 months since HIV diagnosis**

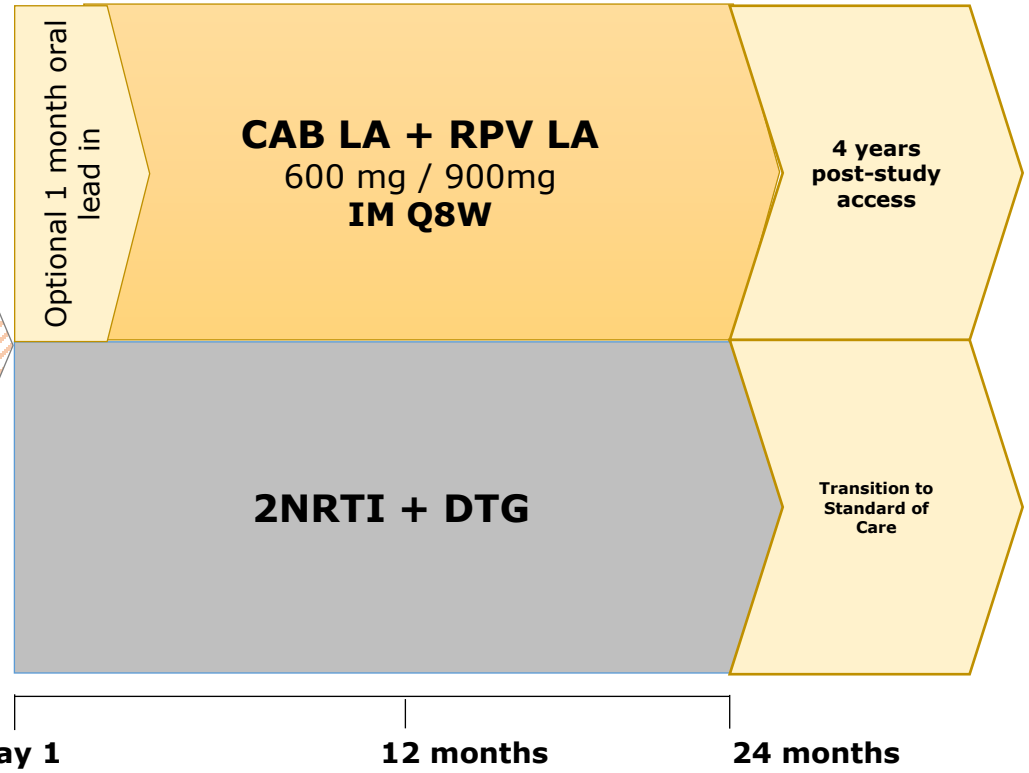
Key exclusions:
- Second-line ART
- Pregnant or breastfeeding
- Positive hepatitis B virus surface antigen

SCREENING PHASE

HIV-1 VL <200 c/ml for ≥3 months at the end of screening

2NRTI + DTG

1:1



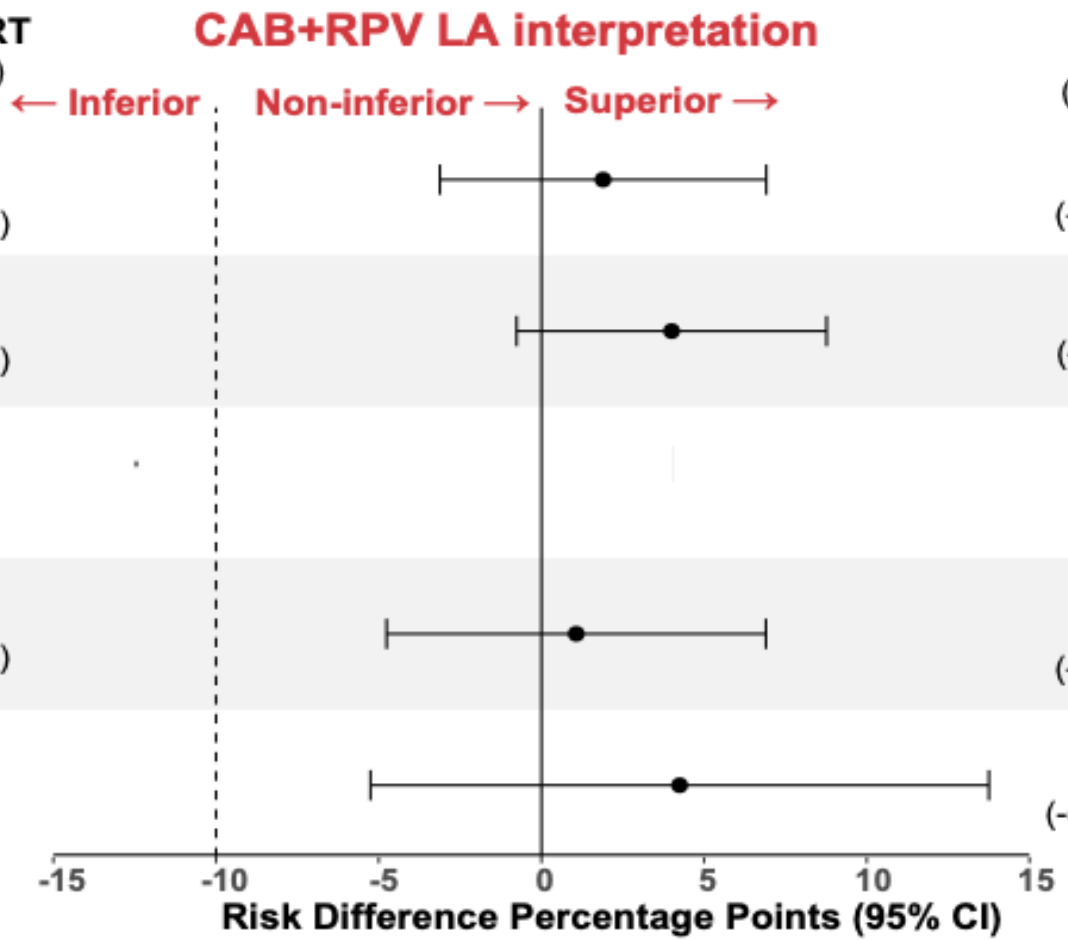
DTG = dolutegravir, CAB = cabotegravir, RPV = rilpivirine, IM = intramuscular, Q8W = 8-weekly dosing

Participants on the LA arm recevied their first injection at month 1
HIV1-VL is tested 4 times in year 1 and 2 times in year 2

Primary outcome at Week 48

- 99.0% retention. 98% of 2159 injections given within window

HIV-1 VL <50 c/mL	CAB+RPV % (n/N)	Oral ART % (n/N)	RD (95% CI)
Primary analysis (ITT-e)	91.0% (244/268)	89.2% (240/269)	+1.9 (-3.1, 6.9)
Per protocol analysis	93.9% (229/244)	89.9% (223/248)	+4.0 (-0.8, 8.8)
ITT-e subgroup analysis:			
Body mass index <30	90.0% (180/200)	89.0% (194/218)	+1.1 (-4.8, 6.9)
Body mass index ≥30	94.1% (64/68)	90.2% (46/51)	+4.2 (-5.3, 13.8)



demonstrating non-inferiority

demonstrating non-inferiority

Why is this important?

Long-acting injectable ART is effective in individuals with suboptimal viral control across high-, middle-, and low-income countries

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Tecovirimat for mpox - primary clinical outcome results from the randomized part of the

Unity trial

B. Grinsztejn, I. C. Olsen, S. Haviari, P. Cahn, N. Daabek, , S. W. Cardoso, M. S. T. da Silva, E. Telford, R. Trefiglio, O. Segeral, V. G. Veloso, Y. Yazdanphanah, and A. Calmy for the Unity Study

A phase III, multi-country, randomized, placebo-controlled, double-blinded superiority trial to assess the efficacy and safety of tecovirimat antiviral treatment for patients with mpox virus disease in Argentina (2), Brazil (6), and Switzerland (2)

with the primary objective of assessing the time from randomization to resolution of all lesions

The Unity trial

Screening

- Adults or adolescents 14+
- Mpox infection w one active lesion
- Confirmed by PCR or highly suspected
- No contraindication to study drug

N= 223

Randomization
1:1

Tecovirimat
14 days + SOC

Placebo
14 days + SOC

- Severe complications
- Severe immune suppression
- Pregnant and breastfeeding women

N= 223

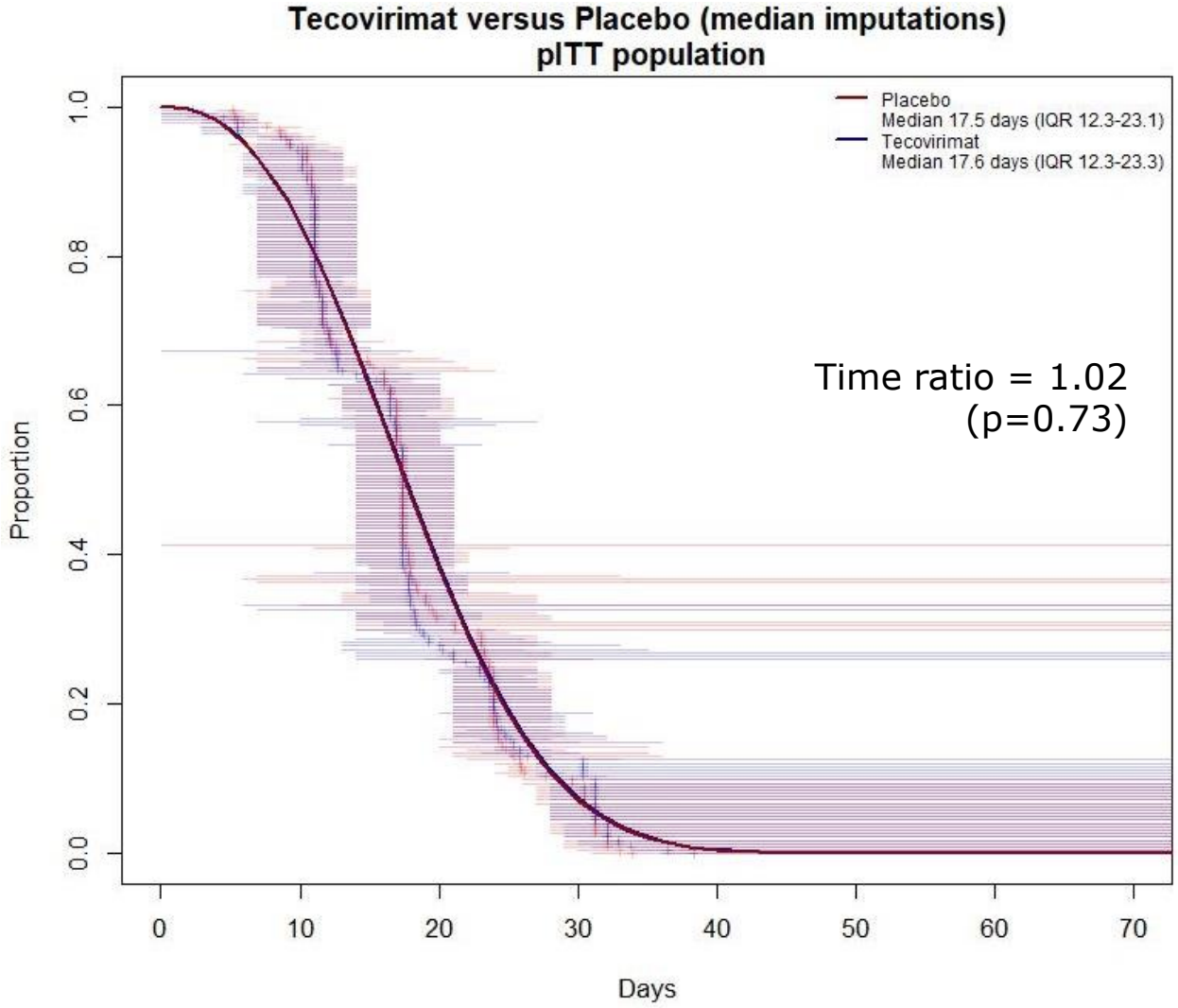
Open-label arm

Tecovirimat
14 days + SOC

Primary endpoint:

Time to complete lesion resolution

- ✓Median age was 34 years
- ✓(With) 95% identifying as MSM
- ✓(And) about two-thirds as non-white
- ✓94% were enrolled in Brazil.



Conclusions of the Unity trial

- The UNITY findings contribute to a growing body of evidence that **tecovirimat is safe** but **not efficacious** in leading to **faster resolution of mpox lesions**, even in a population with **higher prevalence of HIV coinfection**.
  - Results are **consistent** with STOMP (Clade II) and with PALM-007 (Clade I mpox).

Promising Investigational Drugs & Strategies – Pot Pourri

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HFR 10071 Phase IIa proof of concept study in treatment-naïve people with HIV of novel maturation inhibitor demonstrated a statistically significant reduction in HIV-1 RNA levels versus placebo over 14-day monotherapy period *(Kumarasami et al)*

Among 42 pregnancies with CAB exposure reported to the APR, most (39) were preconception exposures; 35 live births were reported with 1 birth defect *(Vannappagari, Abstr OAB0402)*

Phase II study of switching to once-weekly ISL + ULO vs continuing BIC/FTC/TAF supports further development with lower ISL dose *(Molina et al Abstr OAB0102)*

Promising Investigational Drugs & Strategies – Pot Pourri (2)

ACTG A5391/DO-IT Trial in people with obesity showed that switching to DOR ± TDF vs continuing INSTI + TAF/FTC did not result in significant weight change at 48 weeks (Koethe et al, Abstr OAB0206LB)

In the TECAIN study, use of trichloroacetic acid for treatment of AIN in people with HIV provided comparable efficacy to the standard-of-care treatment, electrocautery (Esser et al, Abstr OAB0203)

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Key Messages – track A

- **HIV reservoir is complex** – a roadmap for the development of cure interventions
  - Immunotherapy, gene therapy, virus specific-targets, host genetics enable
- **HIV vaccines are necessary** – both for prevention and cure
  - **The vaccine likely has a broader and more lasting impact, reaching diverse populations**
  - Innovative, combination, rapid pre-clinical and clinical studies for globe are essential.
- **HIV viral biology is being elucidated** – better understanding of HIV virology enables new approaches
  - MX2, TIP, excision strategies, CAR-T cells, enhanced bnAbs are in development
- **Challenges are substantial, but our knowledge and toolkits are expanding, and the future holds opportunities for the global scientific community to seize.**

Key Messages – track B

- Relevant studies have been presented, with a strong emphasis on long-acting ART—both injectable and oral—as well as on the use of two-drug combinations and intermittent ART in low- and middle-income countries.

- Some of these strategies have been incorporated into guidelines, such as the WHO's recommendation of long-acting CAB-RPV for suppressed individuals, or DTG-3TC for treatment simplification

- Although funding constraints have been a recurring theme throughout the conference, the key message we must take away is…we will not go back.

The Critical Role of Funding and Political Will for Prevention - Track C report

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Political commitments—through sustained funding, alignment with PrEP preferences, and the elimination of stigma and discrimination—are key to driving PrEP uptake and advancing HIV prevention.
We must, and will, move forward without turning back

General Context – Track D

Addressing social determinants of health is essential in HIV management because they directly impact individuals' risk of infection, access to services, and treatment outcomes.

Acknowledgements

Juan Ambrosioni

Justyna Gaczorek

Julia Vanian

Thanks to all of you for your attention!