

# IAS 2023

# Knowledge Toolkit

Highlights of the 12th IAS  
Conference on HIV Science

Produced by NAM aidsmap and IAS – the International AIDS Society

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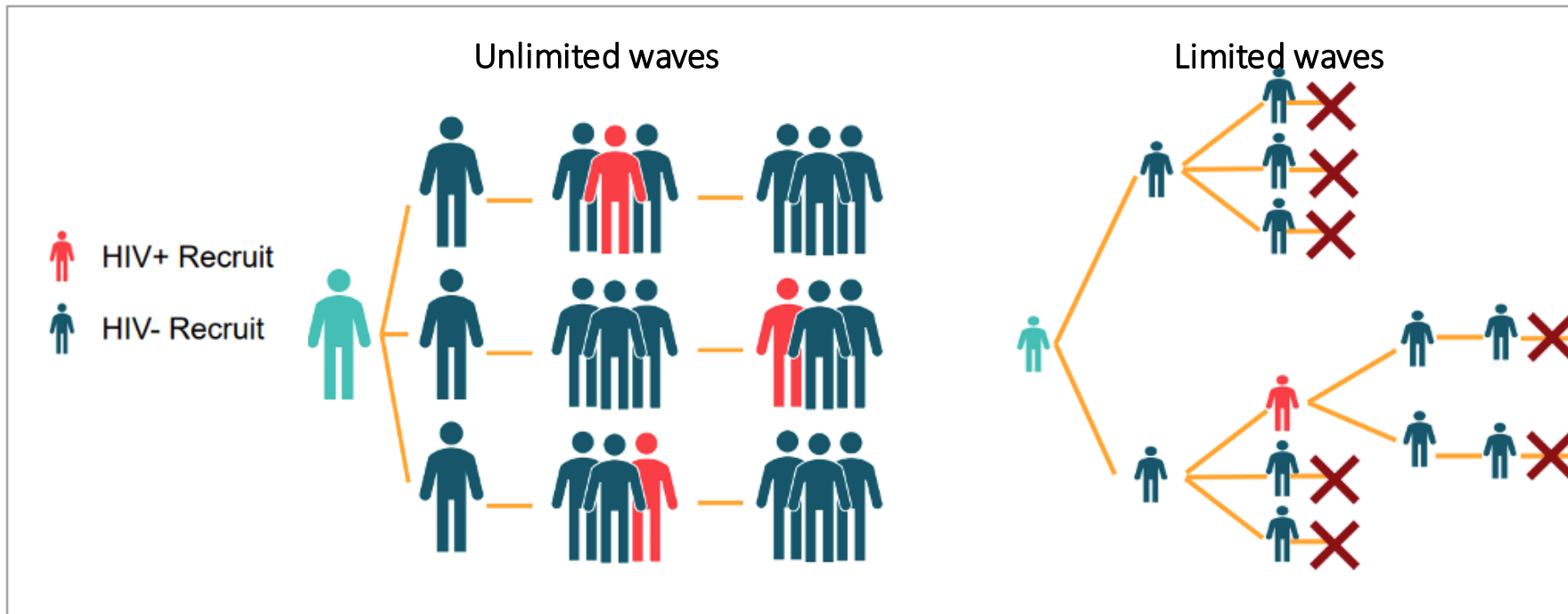
# Towards HIV elimination

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## Social network approaches to HIV testing

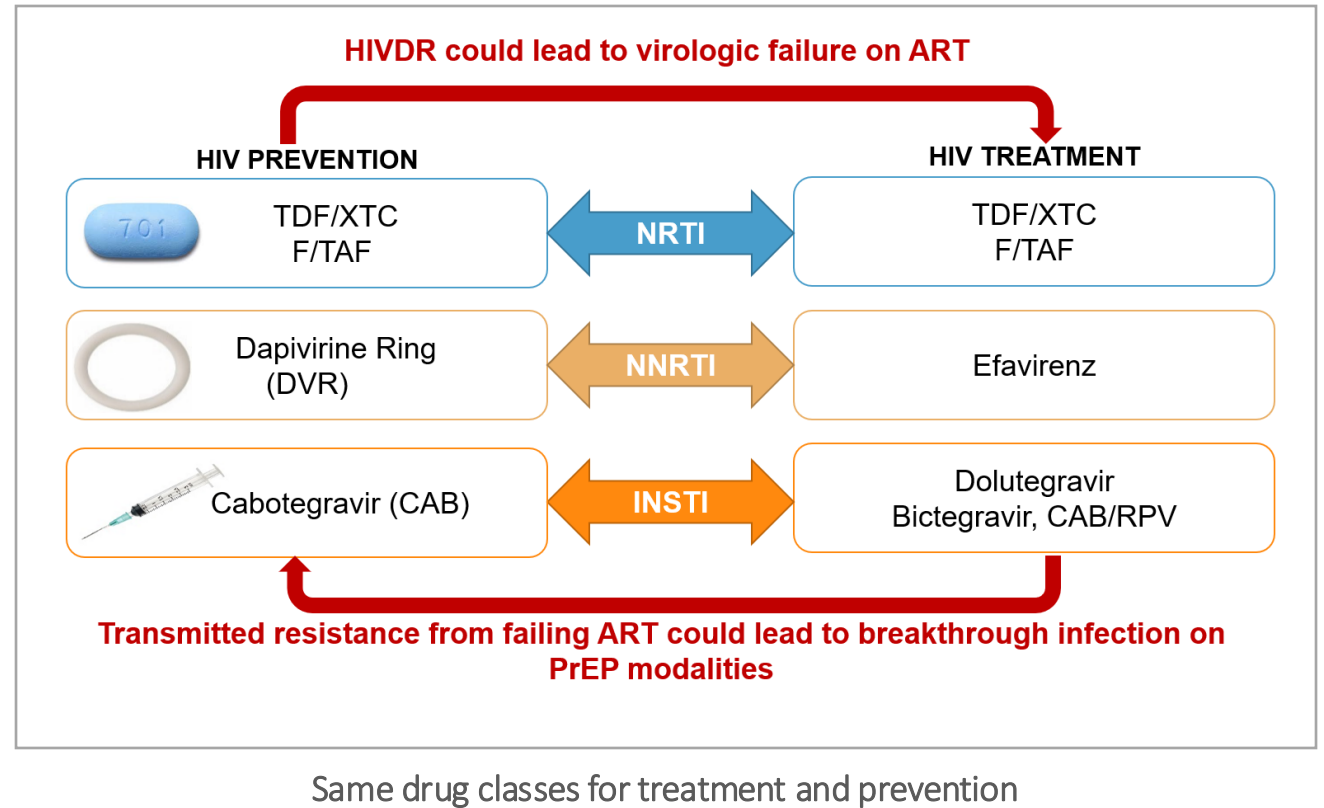
- ▶ Should social network-based approaches (SNA) be offered as an additional HIV testing approach?
- ▶ Systematic review looked at 47 studies published from 2010 to 2022.



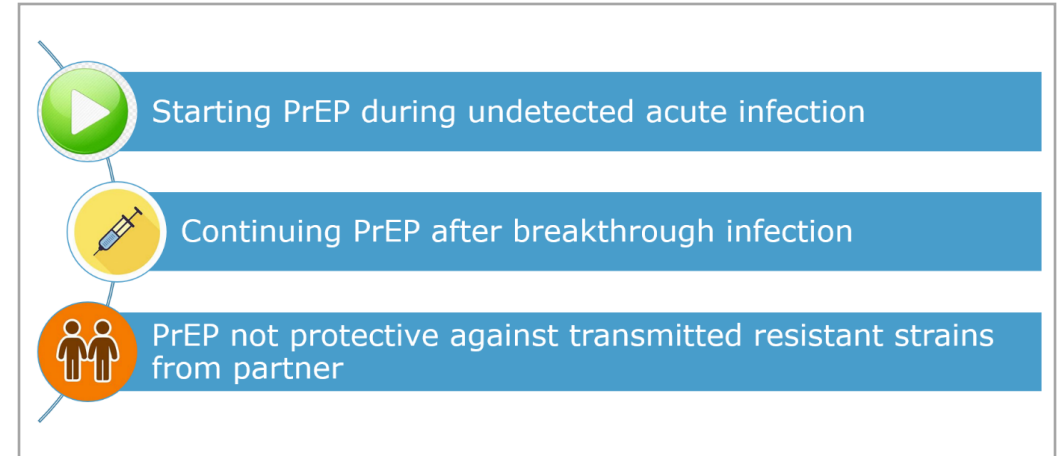
- ▶ Studies comparing SNA with other testing approaches showed:
  - Uptake of HIV testing may be higher among social contacts/partners of test promoters using SNA.
  - The proportion of first-time testers is probably higher.
  - The proportion of people newly testing positive for HIV may be higher.
- ▶ No studies reported serious adverse events or social harms linked to SNA.
- ▶ Key variables included the availability of HIV self-test kits and who promoted the test.
- ▶ Review concluded that SNA should be offered as an additional testing approach: SNA improves choice; benefits likely outweigh risks; and appears to be good value.
- ▶ The World Health Organization will update its recommendation on SNA later this year, expanding from recommending this approach for key populations to all populations.

## HIV testing and long-acting PrEP

- ▶ Oral PrEP research shows that drug resistance can occur when PrEP is started during undiagnosed acute HIV infection.
- ▶ Using the same drug classes during prevention and treatment means resistance from prevention could lead to treatment failure; and transmitted resistance from treatment could lead to prevention failure.



- ▶ Drug resistance is also a risk for people who acquire HIV while on long-acting PrEP.
- ▶ Long-acting PrEP suppresses viral replication, delaying seroconversion and making HIV diagnosis challenging.
- ▶ Delays in diagnosis can lead to drug resistance developing.
- ▶ In dapivirine ring studies, resistance identified appeared to be transmitted.
- ▶ With long-acting cabotegravir (CAB-LA), resistance developing through breakthrough infections is a concern.



Resistance risk on PrEP

- ▶ In HPTN 083, there were 34 breakthrough HIV infections in 2,282 participants in the CAB-LA arm.
- ▶ There were several cases of drug resistance and delayed seroconversion among those with breakthrough infections.

	<b>Recent CAB PrEP (&lt;6 months) N = 18</b>	<b>No recent CAB PrEP (&gt;6 months) N = 14</b>
Major INSTI mutations	10 (56%)	0 (0%)
Delayed Seroconversion	14 (78%)	1 (7%)

Updated HPTN 083 analysis of participants who acquired HIV

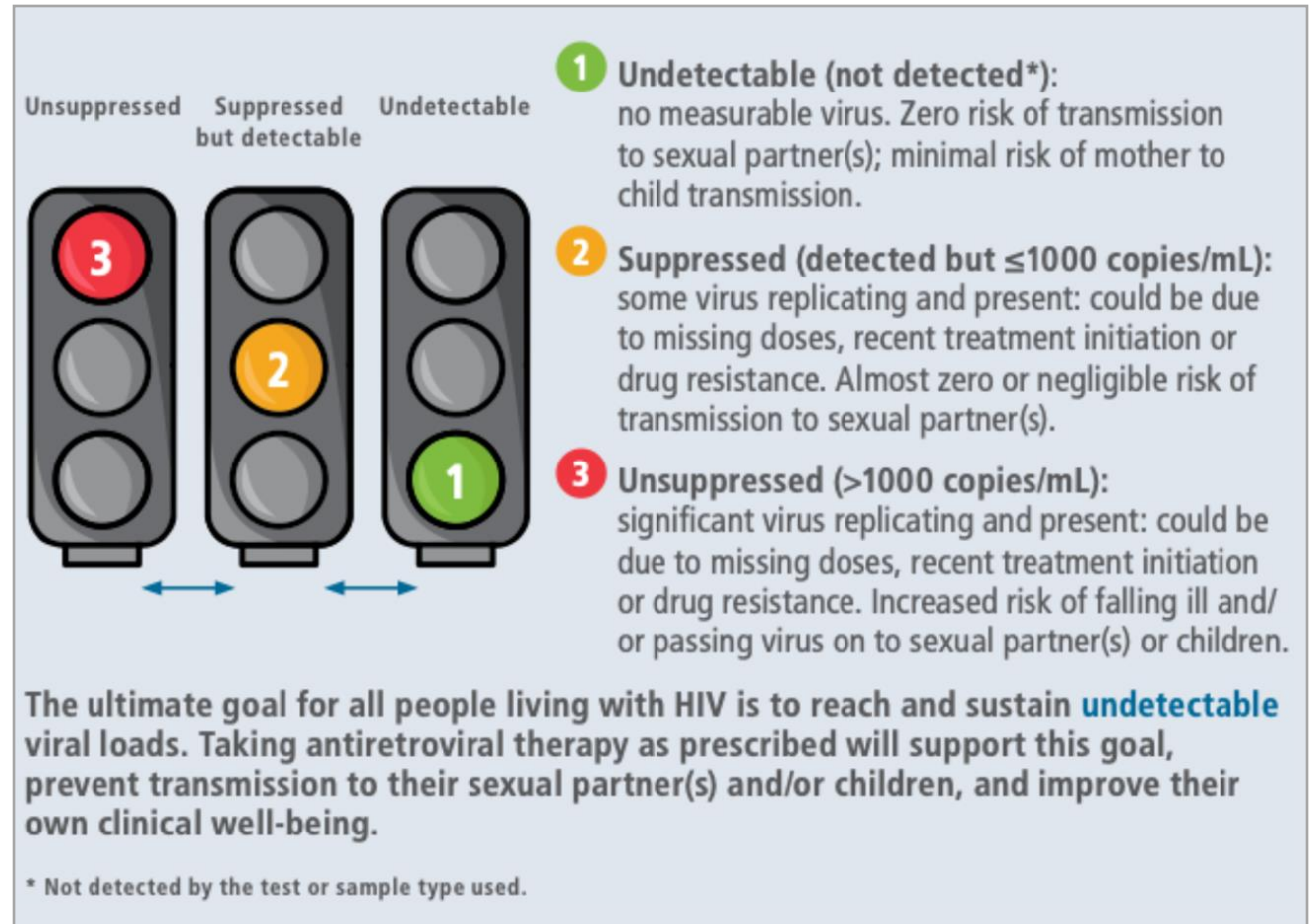
- ▶ With CAB-LA, need to consider delayed immune response due to low levels of nucleic acid. This may lengthen the window period.
- ▶ In HPTN 083, most incident cases could have been detected earlier with HIV RNA testing.
- ▶ In some cases, HIV RNA levels were too low to have been detected.

SPECIFICATIONS	3rd Gen	4th Gen	5th Gen
<b>Detects</b>	IgG, IgM HIV-1, HIV-2 and Group O	IgG, IgM HIV-1, HIV-2 and Group O, hiv-1 p24	IgG, IgM HIV-1, HIV-2 and Group O, hiv-1 p24
<b>Sensitivity</b>	>99.5	99.5	99.5
<b>Specificity</b>	>99.5	>99.8	100%
<b>Window period</b>	2-3 weeks	2 weeks	2 weeks
<b>Result produced</b>	single result	single result, no differentiation between antigen and antibody	differentiation between HIV 1, HIV-2, and p 24 antigen

Evolution of HIV testing assays

## The role of viral suppression

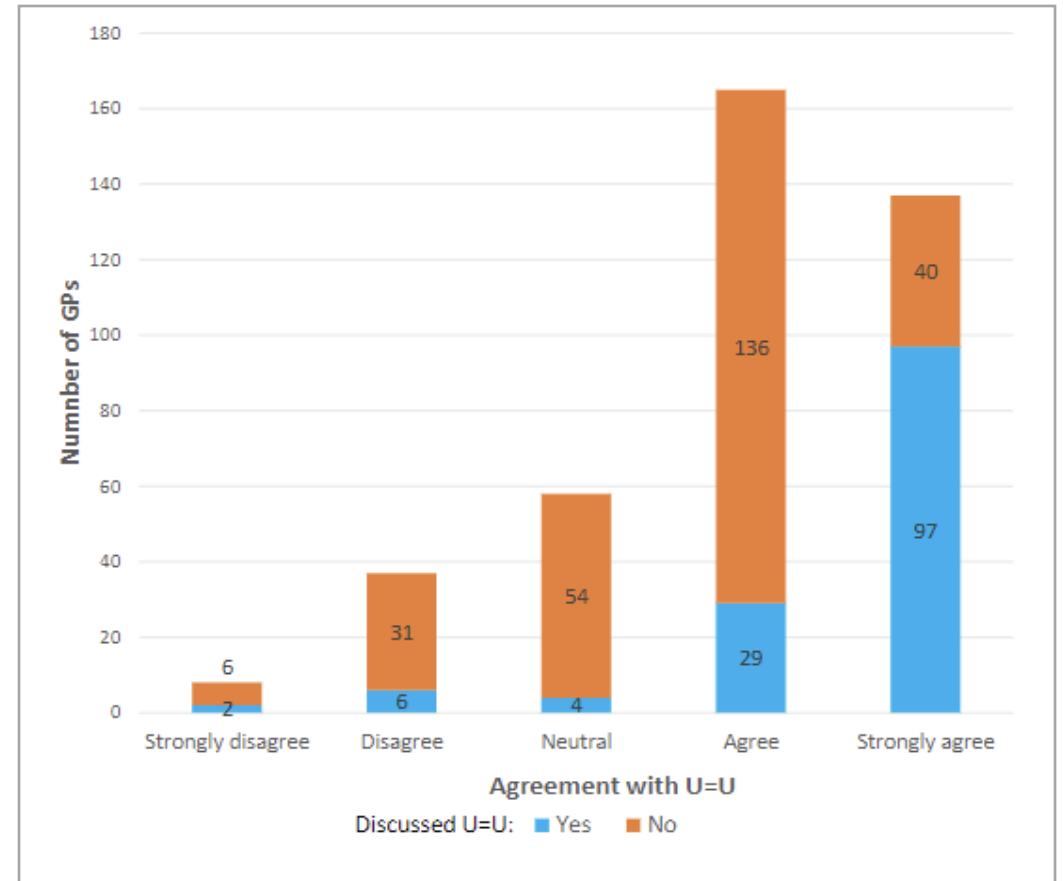
- ▶ WHO launched a policy brief on the role of HIV viral suppression in improving individual health and reducing transmission.
- ▶ The brief distinguishes between three categories of viral load:
  - Undetectable
  - Suppressed
  - Unsuppressed



- ▶ According to WHO, people living with HIV who have an undetectable viral load using any WHO-approved test and continue taking medication as prescribed have “zero risk” of transmitting HIV to their sexual partner(s).
- ▶ People living with HIV who have a suppressed but detectable viral load and are taking medication as prescribed have “almost zero or negligible risk” of transmitting HIV to their sexual partner(s).
- ▶ WHO recommends additional options and sample types of viral load testing technologies. It emphasizes that prequalified tests and sample types, such as dried blood spot, often enable much better access to viral load testing.
- ▶ Routine viral load testing is still inaccessible for millions of people living with HIV, particularly in low- and middle-income countries. It is also important to provide CD4 cell count testing at HIV diagnosis and ART initiation for identifying advanced HIV disease.

## Undetectable equals Untransmittable (U=U)

- ▶ A survey was sent to general practitioners (GPs) in Australia to explore agreement with U=U and discussion with clients.
- ▶ Most (74.2%) agreed with U=U, but only 33.9% had ever discussed U=U with clients.
- ▶ Key barriers were:
  - Lack of relevant client presentations (48.7%)
  - Lack of understanding about U=U (39.9%)
  - Difficulty identifying those who would benefit (6.6%)

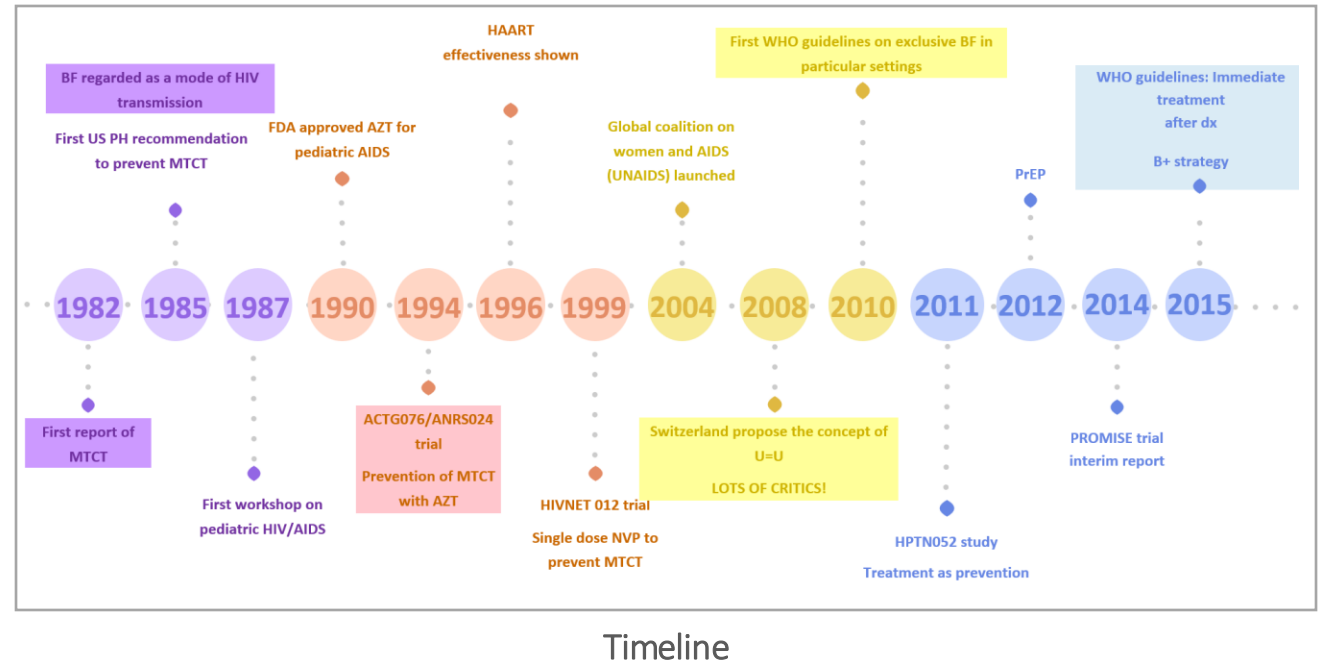


GPs who agreed with U=U and whether they had discussed it with people in their care

- ▶ In South Africa, the U=U message has been shown to be effective in increasing HIV testing uptake in men compared to standard testing invitations.
- ▶ A study team analysed the mean cost of a U=U messaging intervention and its cost-effectiveness.
- ▶ The cost of U=U messaging was lower than conventional HIV testing messaging.
- ▶ It was also at the lower end of the cost ranges of HIV self-test distribution models targeted at men in previous work.

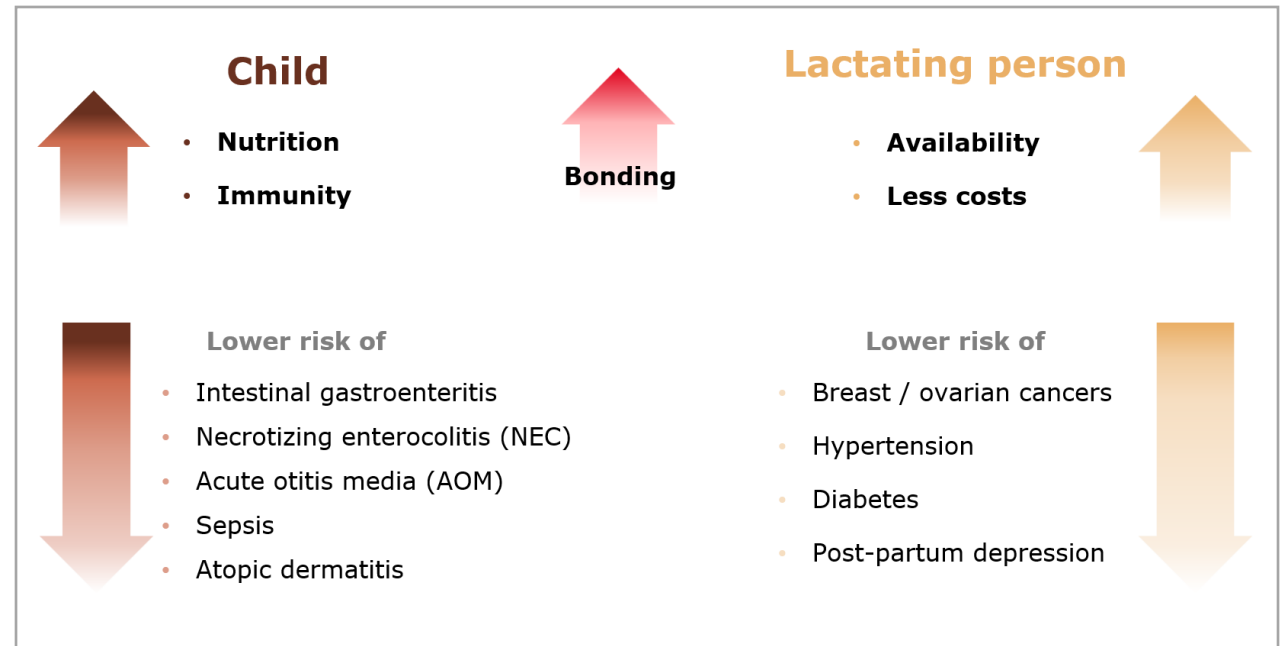
## Pregnancy and breastfeeding in the U=U era

- ▶ Early in the HIV pandemic, breastfeeding was identified as a mode of HIV transmission.
- ▶ In 2008, the concept of U=U was proposed for sexual transmission, but there are evidence gaps on breastfeeding.
- ▶ In 2023, US guidelines began to include breastfeeding options for people living with HIV on ART.



- ▶ If a mother starts ART before conception and maintains an undetectable viral load, the risk of transmission during pregnancy and delivery may be zero.
- ▶ However, all infants in this scenario would receive neonatal post-exposure prophylaxis (neoPEP).
- ▶ There is increasing evidence on regarding shorter or no neoPEP.
- ▶ In 2019, Swiss recommendations changed – they no longer recommend neoPEP for infants of people who maintain an undetectable viral load during the ante- and post-natal period.

- ▶ In the Swiss HIV cohort, there were no cases of vertical transmission when infants were not given neoPEP.
- ▶ There are benefits to breastfeeding for both the child and person breastfeeding, including decreased risk of other health conditions.
- ▶ While some high-income countries are revising guidance, evidence gaps remain.



Benefits of breast/chest feeding

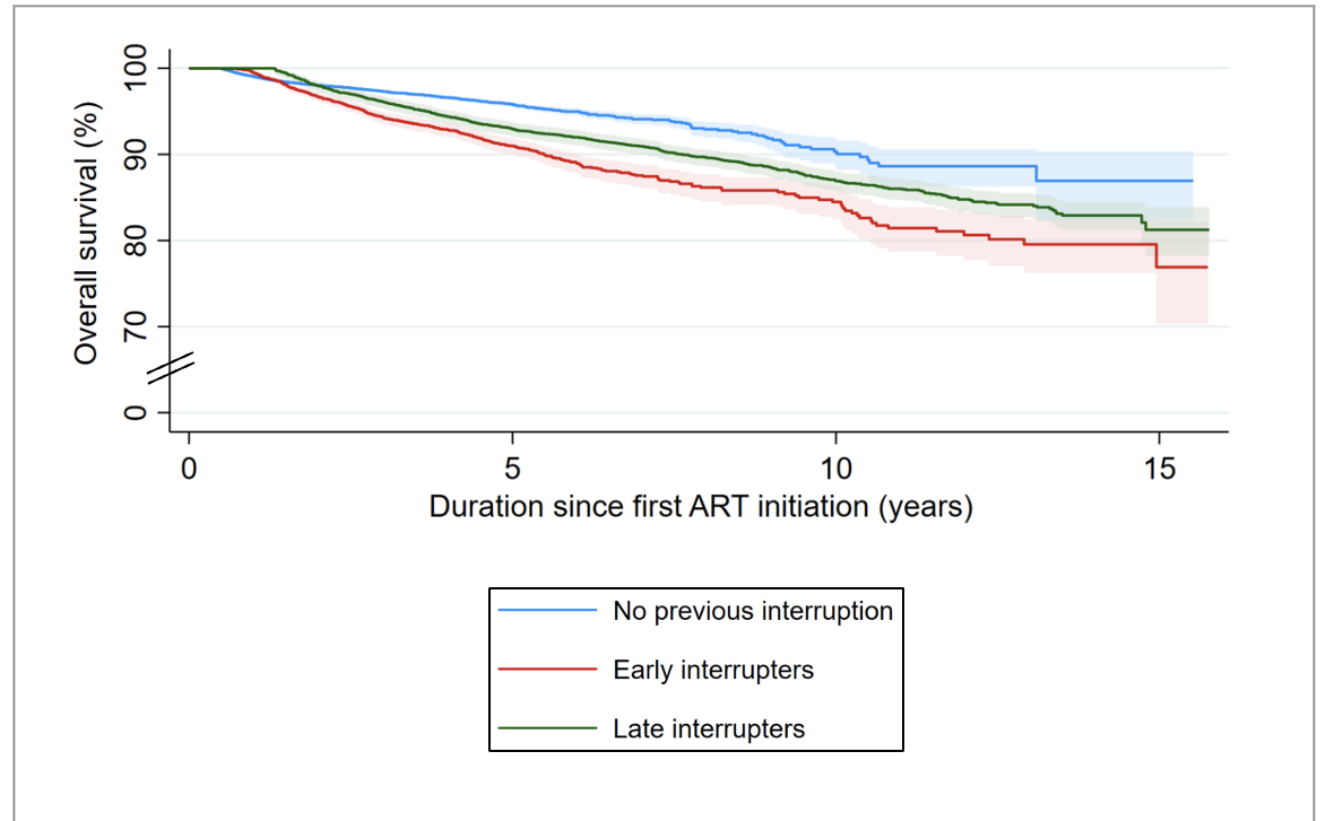
## Unplanned treatment interruptions

- ▶ Study examined mortality in 63,421 adults with HIV who started ART between 2014 and 2019 in South Africa.
- ▶ Care interruptions were defined as a gap in contact longer than 180 days.
- ▶ 22,593 people interrupted care, of whom 8,845 interrupted within the first 6 months of ART.

	Participants	Person-years	Deaths
No interruption	40 828	132 594	2 587
Early interrupters	8 845	18 429	427
Late interrupters	13 748	37 334	571
<b>Total</b>	<b>63 421</b>	<b>188 358</b>	<b>3 585</b>

Interruptions and deaths

- ▶ Those interrupting ART had an increased risk of death compared to those without an interruption:
  - Within 6 months of starting ART – adjusted hazard ratio (aHR) of 2.32
  - After 6 months – aHR 1.90
- ▶ This highlights the need to reduce interruptions and support re-engagement in care.



Survival curves by interruption group

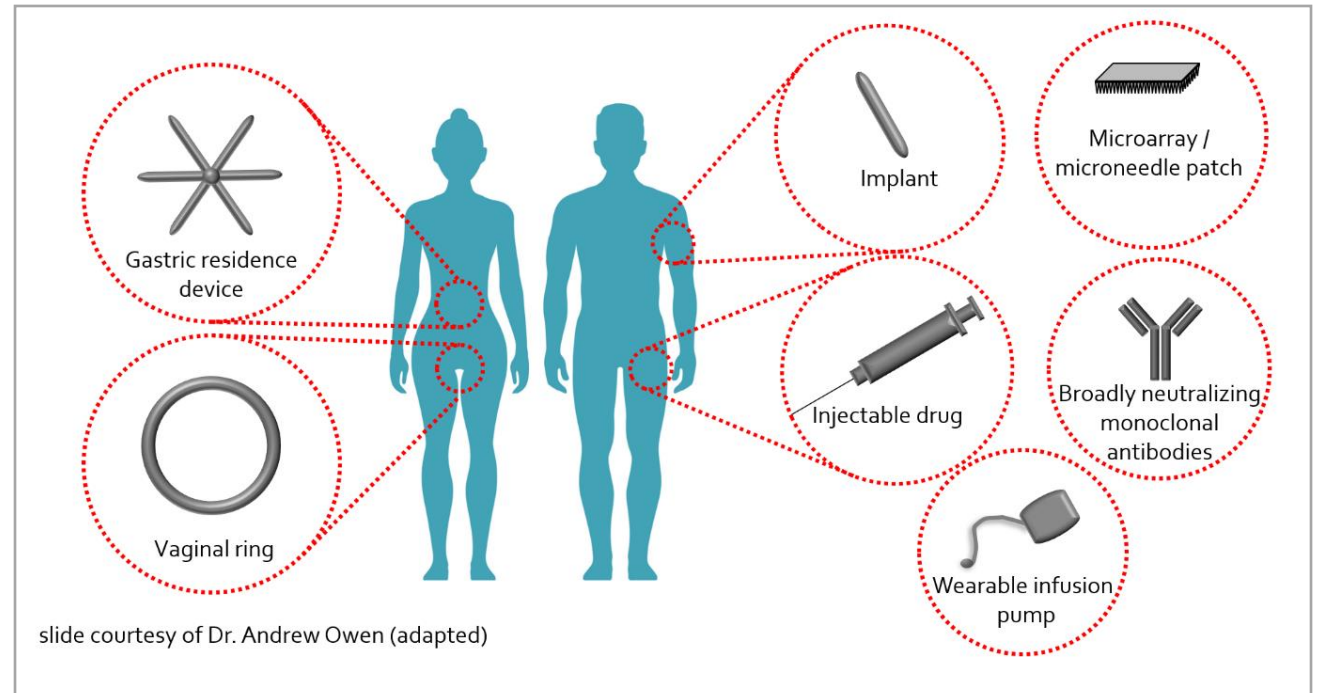
# Antiretroviral therapy (ART)

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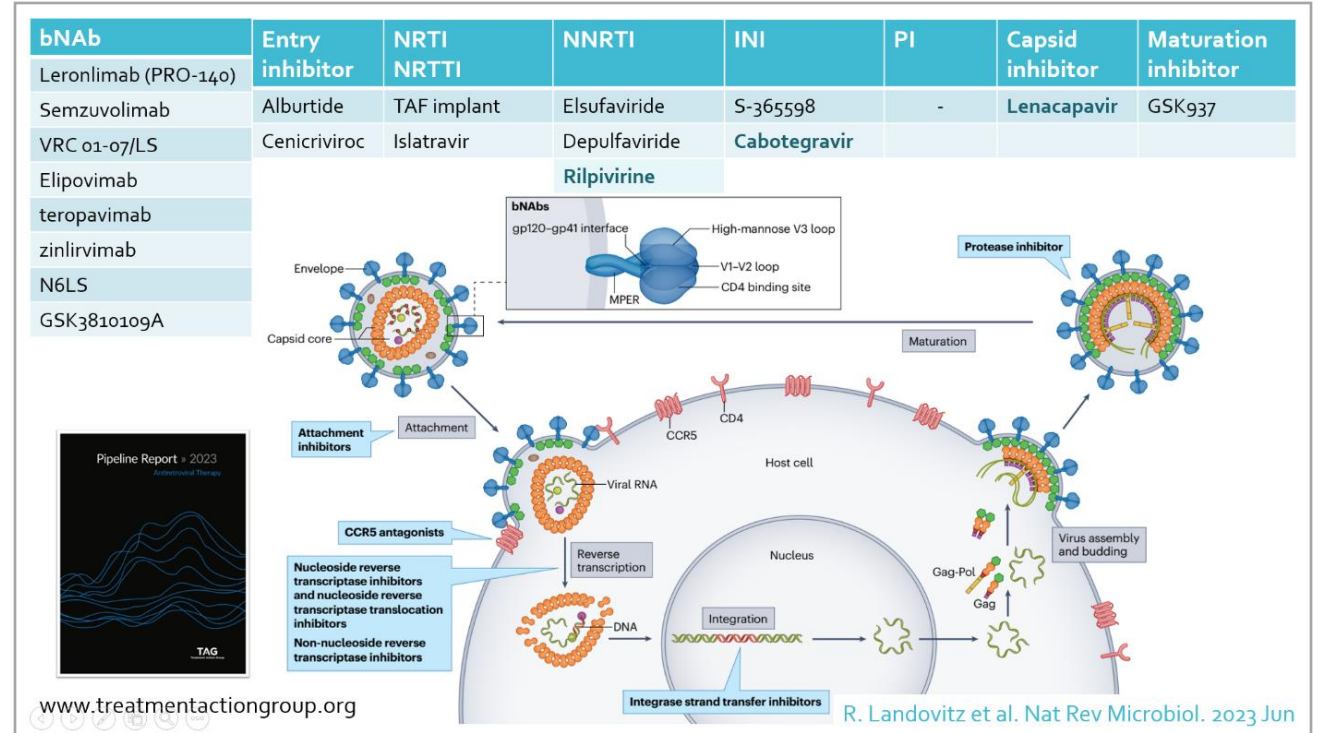
## Overview of long-acting ART

- ▶ Long-acting extended delivery systems include oral medications that are dosed once a week or less; injectable treatments dosed once a month or less; or implants, dosed twice a year or less.
- ▶ Other possibilities include microneedle patches, broadly neutralizing monoclonal antibodies, wearable infusion pumps, vaginal rings and gastric residence devices.



Drug delivery systems and long-acting technologies

- ▶ Many different long-acting antiretroviral drugs are in development that target different parts of the HIV lifecycle.



Long-acting ART pipeline

- ▶ Two long-acting antiretrovirals for HIV treatment are available in some high-income countries:
  - Long-acting cabotegravir and rilpivirine, an intramuscular injection given every four or eight weeks, approved for people with undetectable viral load
  - Lenacapavir, a sub-cutaneous injection given every six months, but which must be combined with oral antiretrovirals. Approved for people with multidrug-resistant HIV

LA- Cabotegravir + Rilpivirine	Lenacapavir
IM, every 4 or 8 weeks with/with out OLI	SC every 6 months Combined with oral ARV
<b>FDA/EMA Approved</b> Jan 2021; ART /4 weeks Feb 1, 2022: ART /8 weeks <u>Switch with undetectable VL</u>	<b>FDA/EMA Approved</b> Dec 2022: Twice-yearly treatment for PLH <u>multi-drug resistant HIV</u>

Approved long-acting and extended-release ARVs

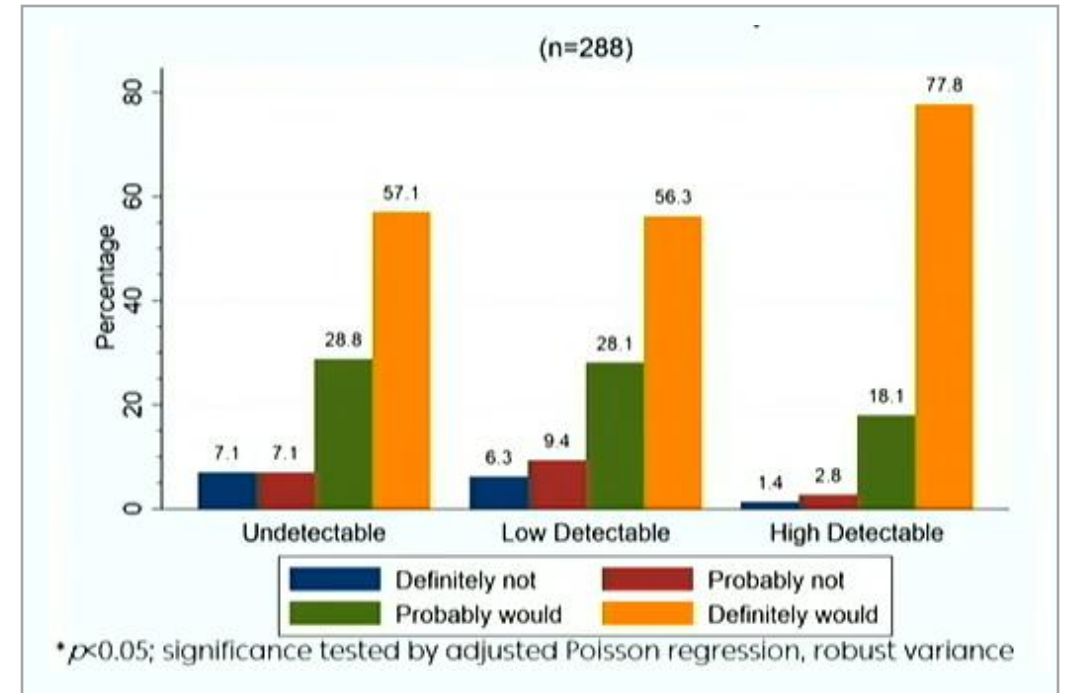
- ▶ Long-acting ART for HIV treatment may be a “game-changer” for HIV care and treatment.
- ▶ However, these drugs are currently available in only a few countries.



Long-acting cabotegravir and rilpivirine approvals

## Long-acting ART for adolescents

- ▶ The proportion of adolescents with viral suppression at 12 months ranges from 27% to 89%, globally.
- ▶ In a study of 13–24-year-olds living with HIV in the United States, a high level of interest in long-acting ART was noted. Those with an unsuppressed viral load showed particular interest.
- ▶ However, a study among South African young people found much lower interest (12%) in long-acting ART over daily oral regimens.



Interest in long-acting ART among young people in the US

## Long-acting ART in people with adherence challenges

- ▶ Long-acting cabotegravir (CAB) and rilpivirine (RPV) were approved based on trials with people who already had an undetectable viral load.
- ▶ A demonstration project at Ward 86 in San Francisco General Hospital offered long-acting CAB/RPV to people in its care who had adherence challenges with oral ART.

### Inclusion criteria of trials:

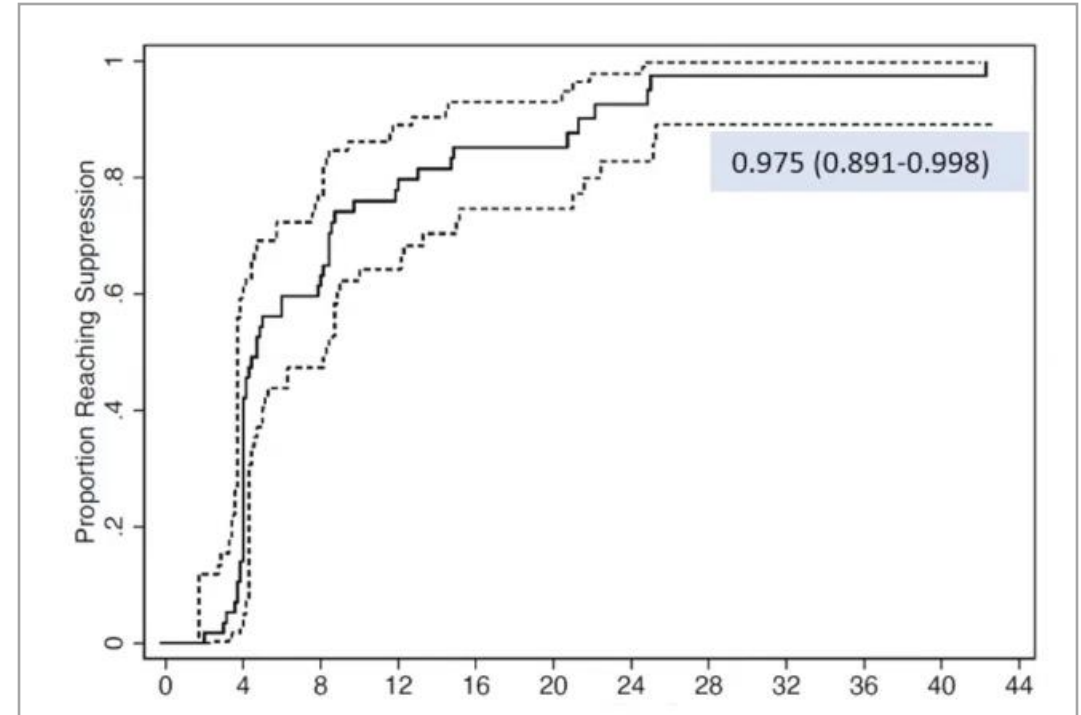
- Virologically suppressed x at least 16 weeks on oral regimen first
- No history of virologic failure
- Only K103N in NNRTI; no INSTI mutations
- Oral CAB/RPV x 28 days but direct-to-inject approved FDA March '22

### 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

Ward 86 demonstration project criteria

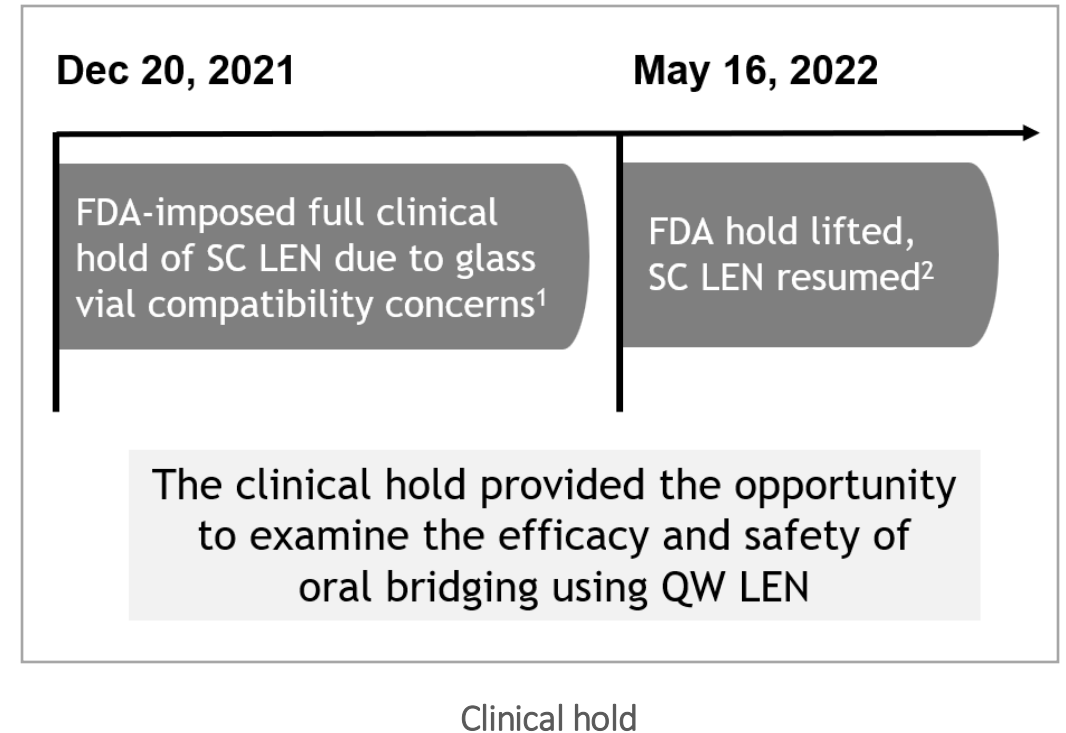
- ▶ Of 133 participants, 66% were unstably housed, and 33% reported substance use.
- ▶ In those with undetectable viral load at baseline, all maintained viral suppression.
- ▶ Among 57 people with an unsuppressed viral load at baseline, 55 had achieved viral suppression after 33 days.
- ▶ There were two early treatment failures. Both related to minor drug resistance mutations, and the study protocol was tightened.



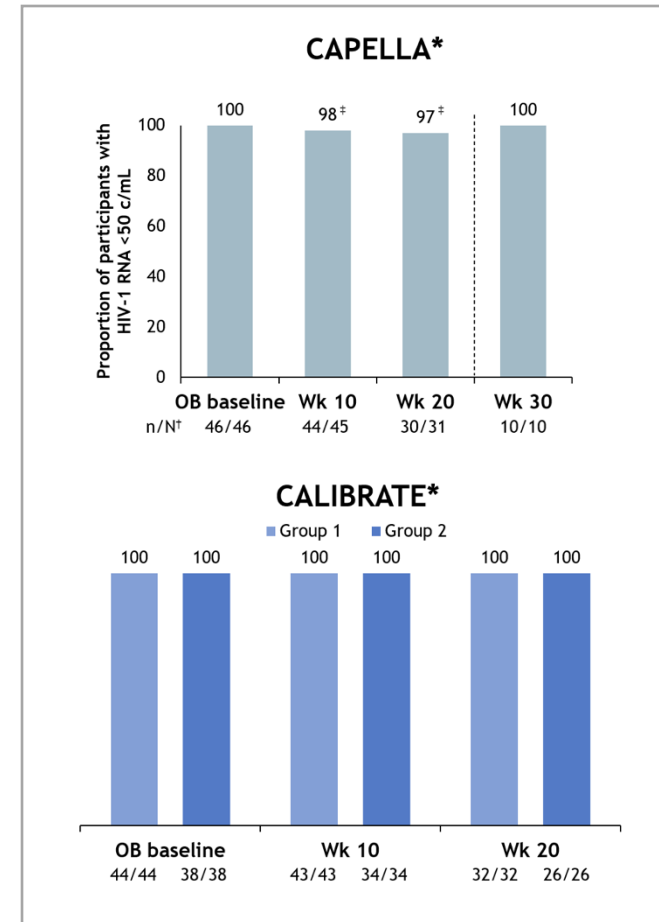
KM curve of probability of reaching virologic suppression (VL<30) on LA ART (n=57); dotted lines 95% CI

## Lenacapavir oral bridging

- ▶ Lenacapavir can be given by injection every six months or in an oral formulation.
- ▶ During a clinical hold on injections, 57 participants in the CAPELLA study and 82 participants in the CALIBRATE trial used “oral bridging” – switching to weekly oral dosing.
- ▶ All the CALIBRATE participants maintained viral suppression during the oral bridging period.



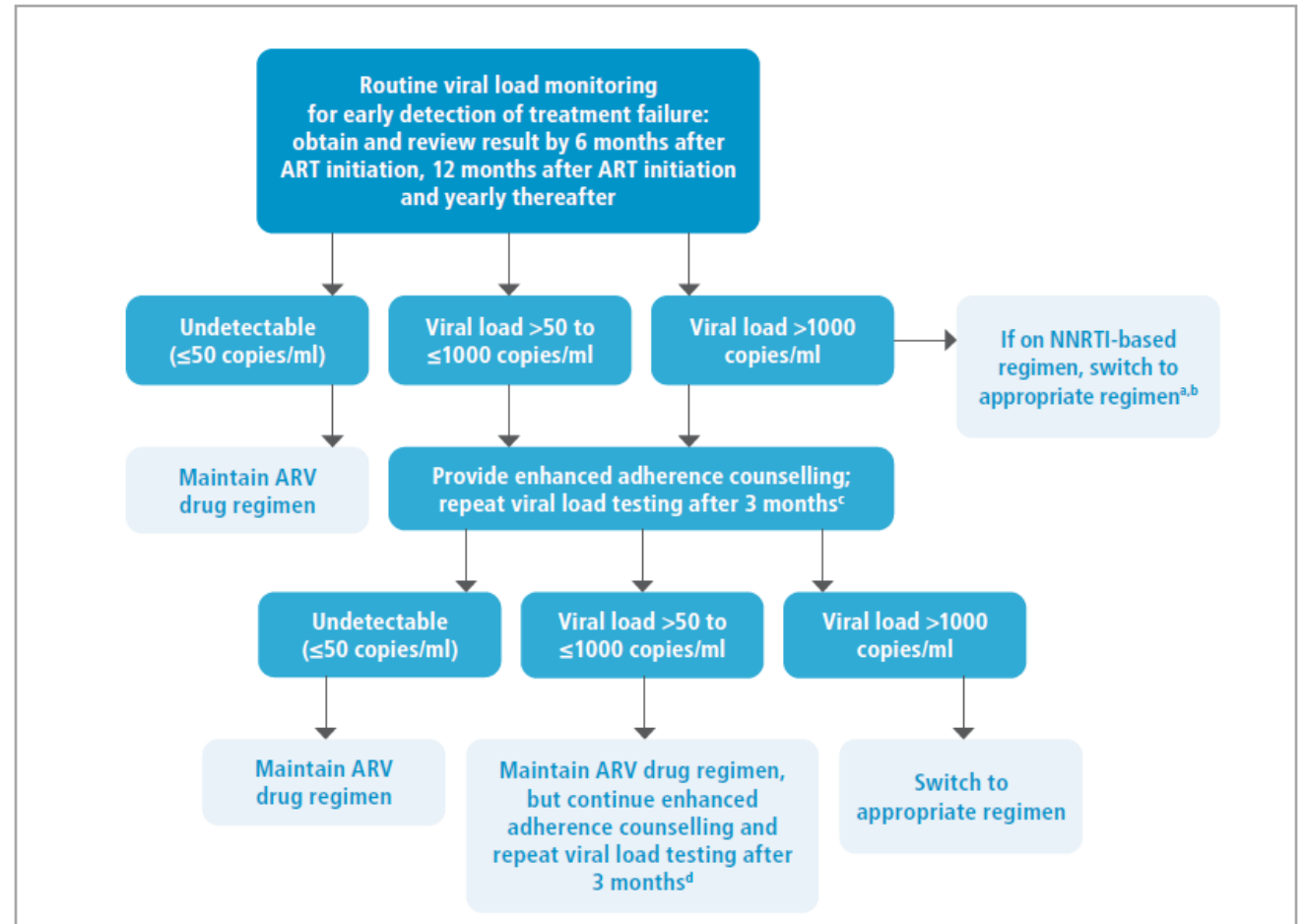
- ▶ With one exception, all CAPELLA participants with an undetectable viral load at the time of the switch maintained suppression.
- ▶ One participant experienced viral rebound after missing two oral doses, but re-suppressed after resuming injections.
- ▶ Of the 11 people in CAPELLA who had a detectable viral load at switch, three achieved viral suppression while taking the pills, and none saw a notable rise in viral load.



Efficacy during oral bridging

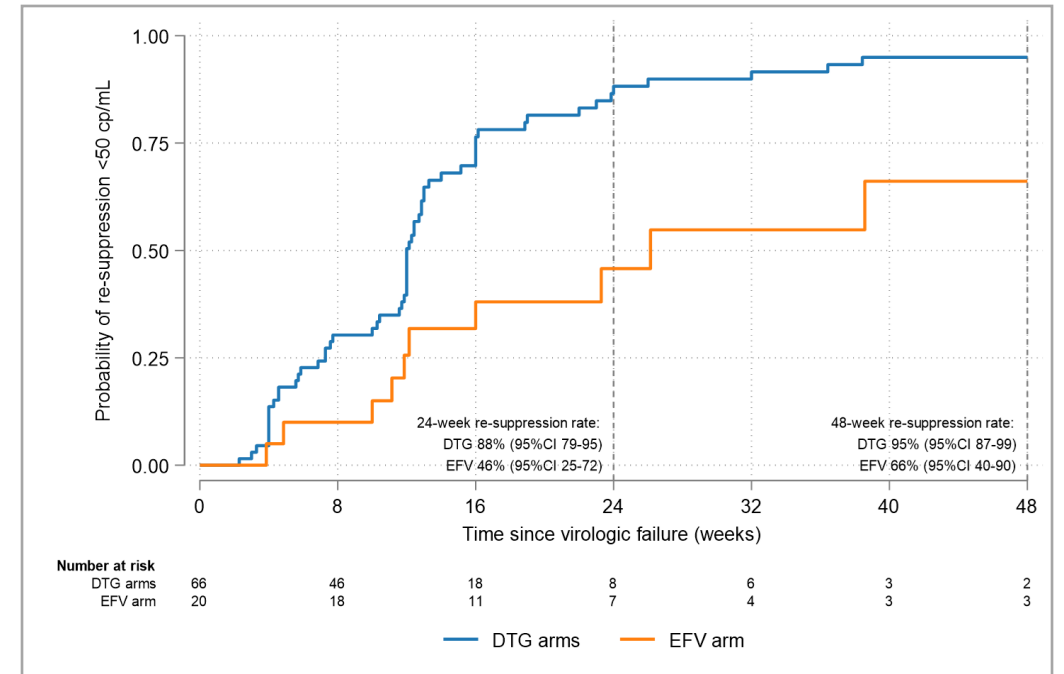
## Viral re-suppression without switching from dolutegravir

- ▶ Data from the ADVANCE trial, to examine outcomes of people who experienced viral rebound above 1,000 copies/mL.
- ▶ All received enhanced adherence counselling within 4 weeks.



WHO guidelines for virological failure

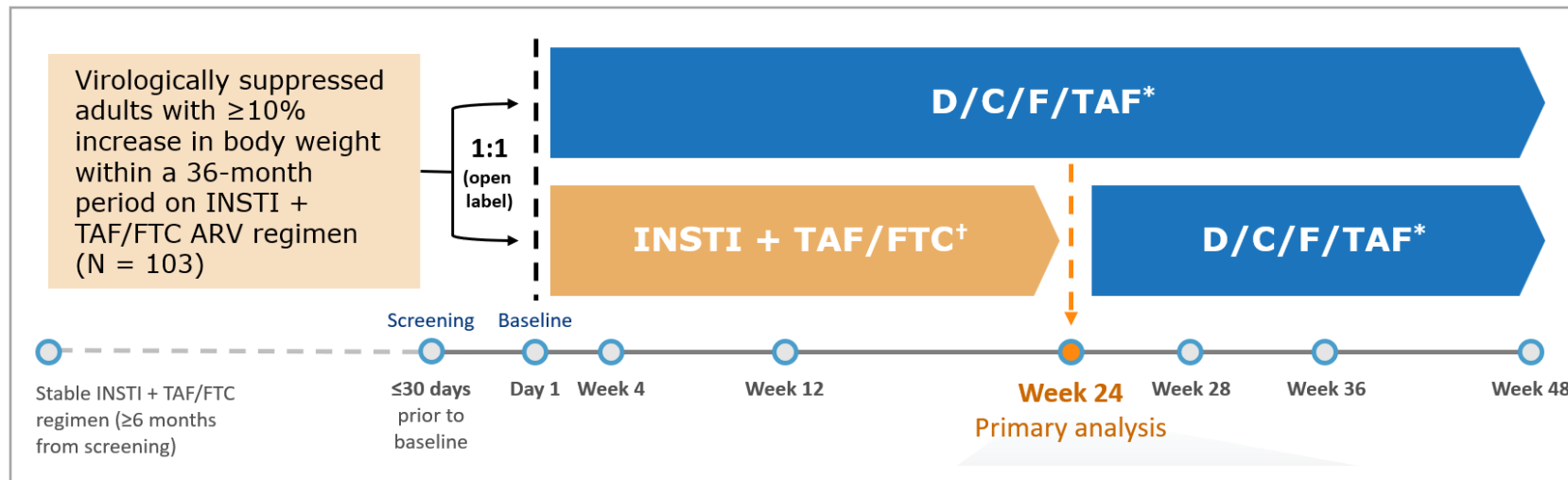
- ▶ The rate of viral re-suppression was significantly higher in people taking dolutegravir compared to people taking efavirenz.
- ▶ At week 24, 88% of people taking dolutegravir and 46% of people taking efavirenz had re-suppressed viral load. By week 48, it was 95% and 66%.
- ▶ The results support keeping people on dolutegravir-based treatment with adherence counselling.



HIV RNA re-suppression

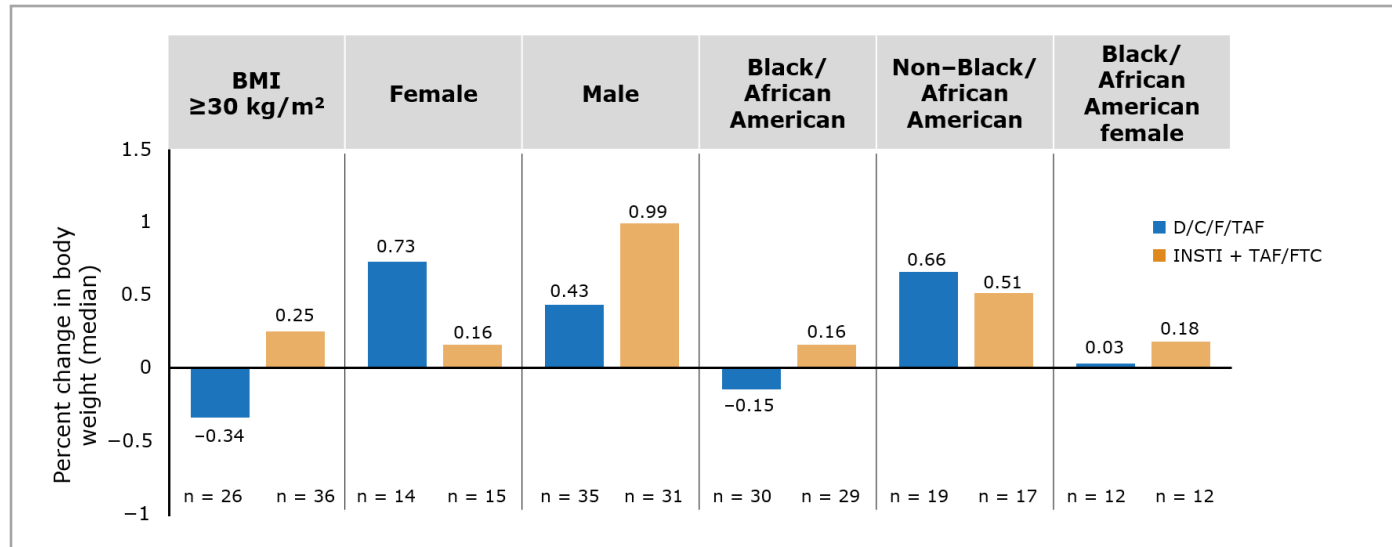
## Integrase inhibitors and weight gain

- ▶ In the DEFINE study in the US, people who had gained at least 10% of body weight on an integrase inhibitor-based regimen were randomized to stay on the regimen (n=50) or switch to a darunavir-based regimen (n=53).
- ▶ Participants were 30% female, 61% Black, median weight was 100kg, and median weight gain 14%.



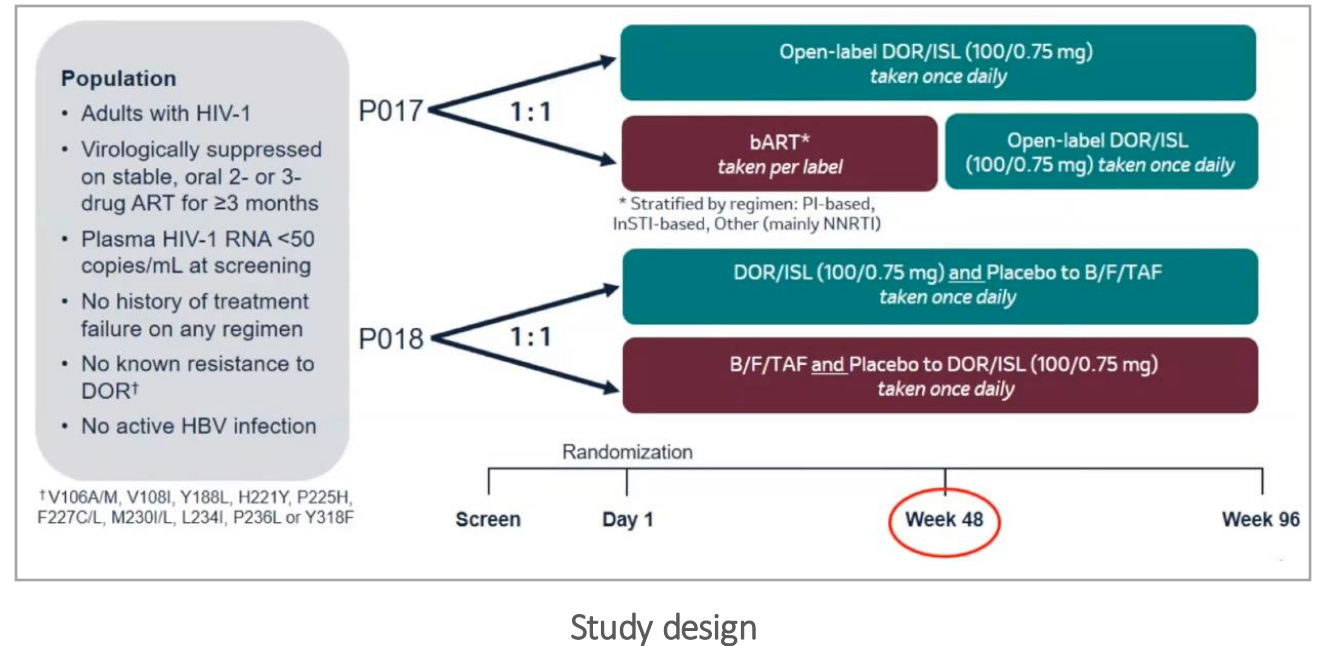
DEFINE study design

- ▶ There was no significant difference in percentage change in body weight between the study arms at week 24.
- ▶ The study is ongoing, but these early results suggest INSTI-related weight gain may not be reversible by switching treatment regimens.

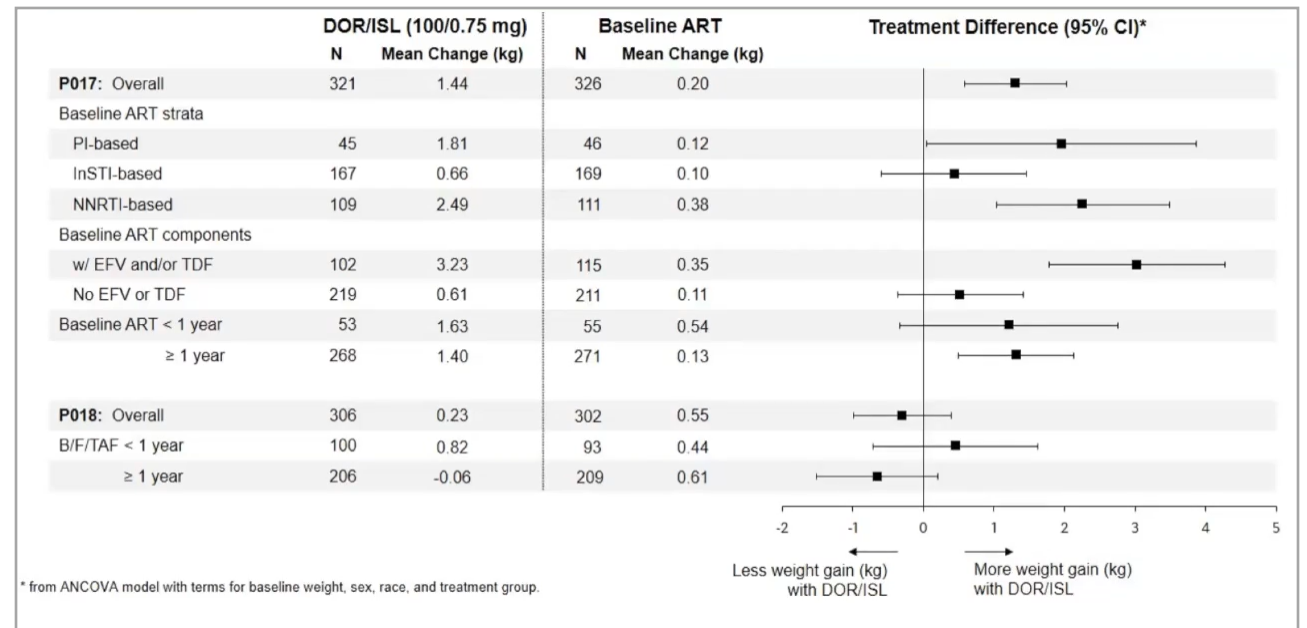


Changes in body weight across subgroups at week 24

- ▶ Another analysis looked at data from two studies of people switching to doravirine and islatravir.
- ▶ In study P017, participants either stayed on any existing regimen or switched to doravirine and islatravir.
- ▶ In study P018, participants either stayed on *Biktarvy* or switched to doravirine and islatravir.



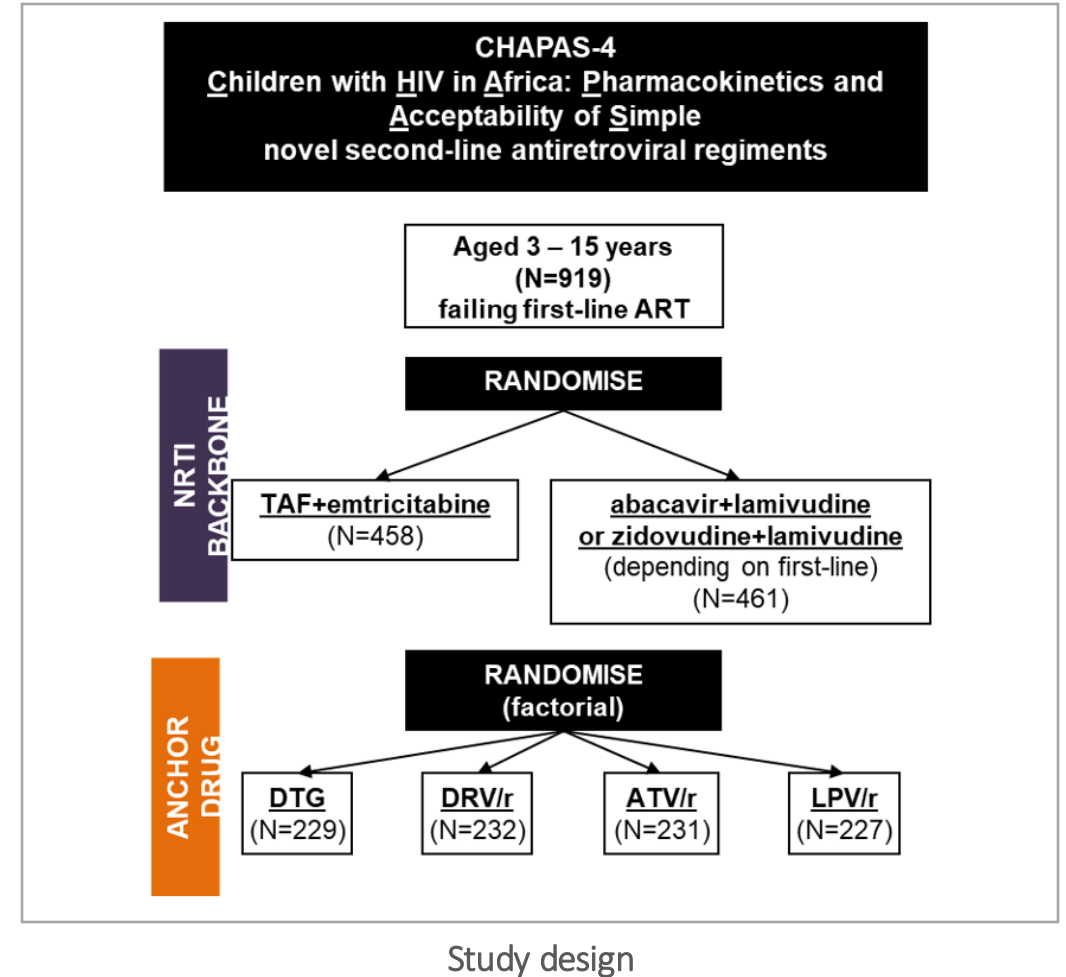
- ▶ In PO17, weight gain at week 48 was slightly higher in the doravirine arm when the comparator regimen contained efavirenz and/or tenofovir disoproxil.
- ▶ In PO18, there was no difference in weight gain between the two regimens.
- ▶ In summary, switching from an integrase inhibitor-based regimen to doravirine and islatravir did not reduce weight over 48 weeks.



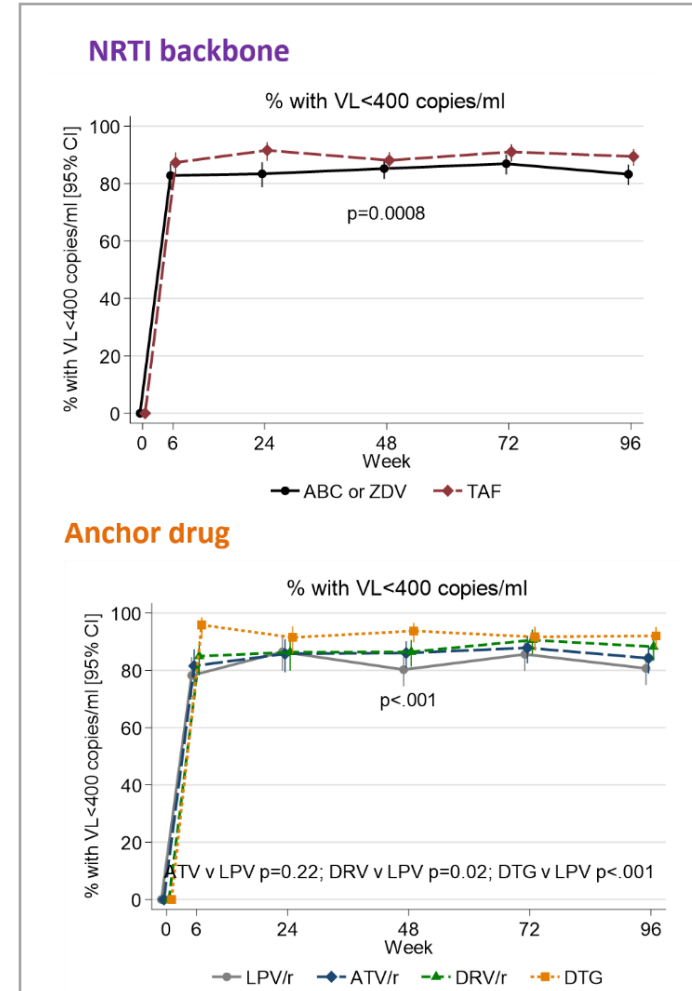
Weight change by baseline ART

## ART for children

- ▶ Children in the CHAPAS-4 study were randomized to one of two backbone regimens: TAF and emtricitabine; or standard of care (lamivudine with abacavir or zidovudine).
- ▶ They were also randomized to one of four anchor medicines: dolutegravir; darunavir/ritonavir; atazanavir/ritonavir; or lopinavir/ritonavir (standard of care).



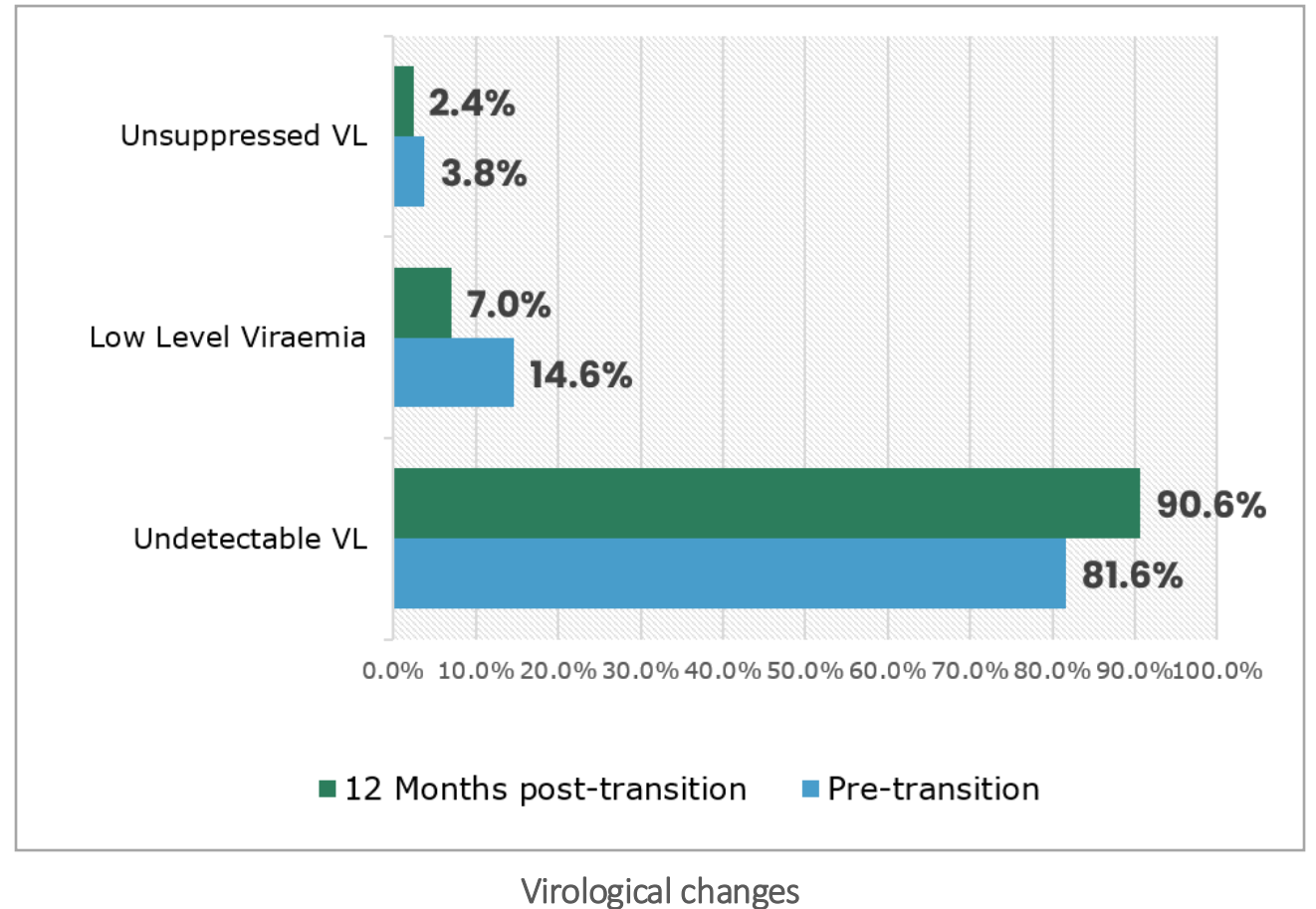
- ▶ Viral suppression was high in all study arms.
- ▶ Children had better viral suppression on TAF and emtricitabine compared to standard of care (abacavir/lamivudine or zidovudine/lamivudine) (89% vs 83%).
- ▶ Dolutegravir was more effective as an anchor medicine, in comparison to lopinavir/ritonavir and atazanavir/ritonavir (92% vs 83%).
- ▶ The authors highlight the need for child-friendly fixed-dose combinations of these medications.



Viral suppression

- ▶ Some programmes are transitioning children from protease inhibitor-based regimens to dolutegravir regimens.
- ▶ A retrospective cohort study included children (up to 9 years of age) who transitioned between July and December 2021 in Nigeria.
- ▶ 2,358 children (median age: 6 years) were transitioned from a protease inhibitor-based regimen to a dolutegravir-based regimen during the study.
- ▶ At baseline, 81.6% (n=1,924) had an undetectable viral load, 14.6% (n=345) had low-level viraemia, and 3.8% (n=89) had an unsuppressed viral load.

- ▶ There were improvements in viral suppression among those who transitioned.
- ▶ Programmes should prioritize dolutegravir-based regimens for children in order to improve treatment outcomes.



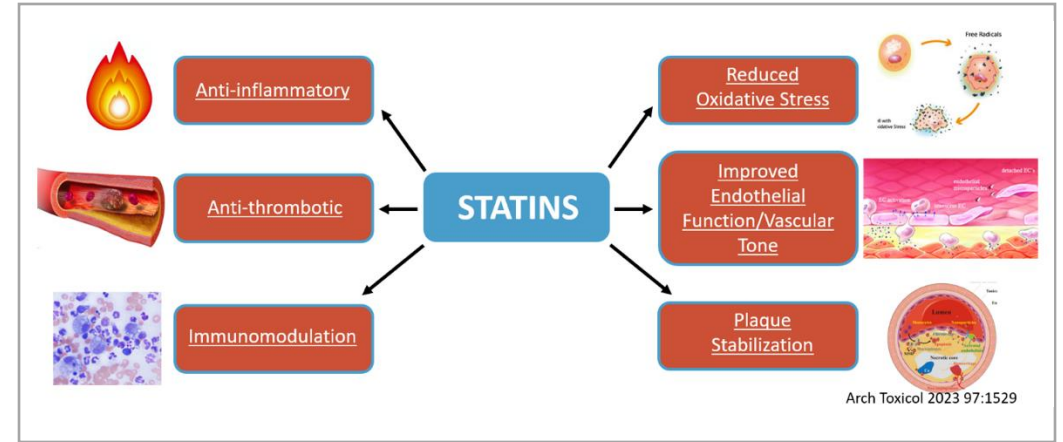
# Co-morbidities and co-infections

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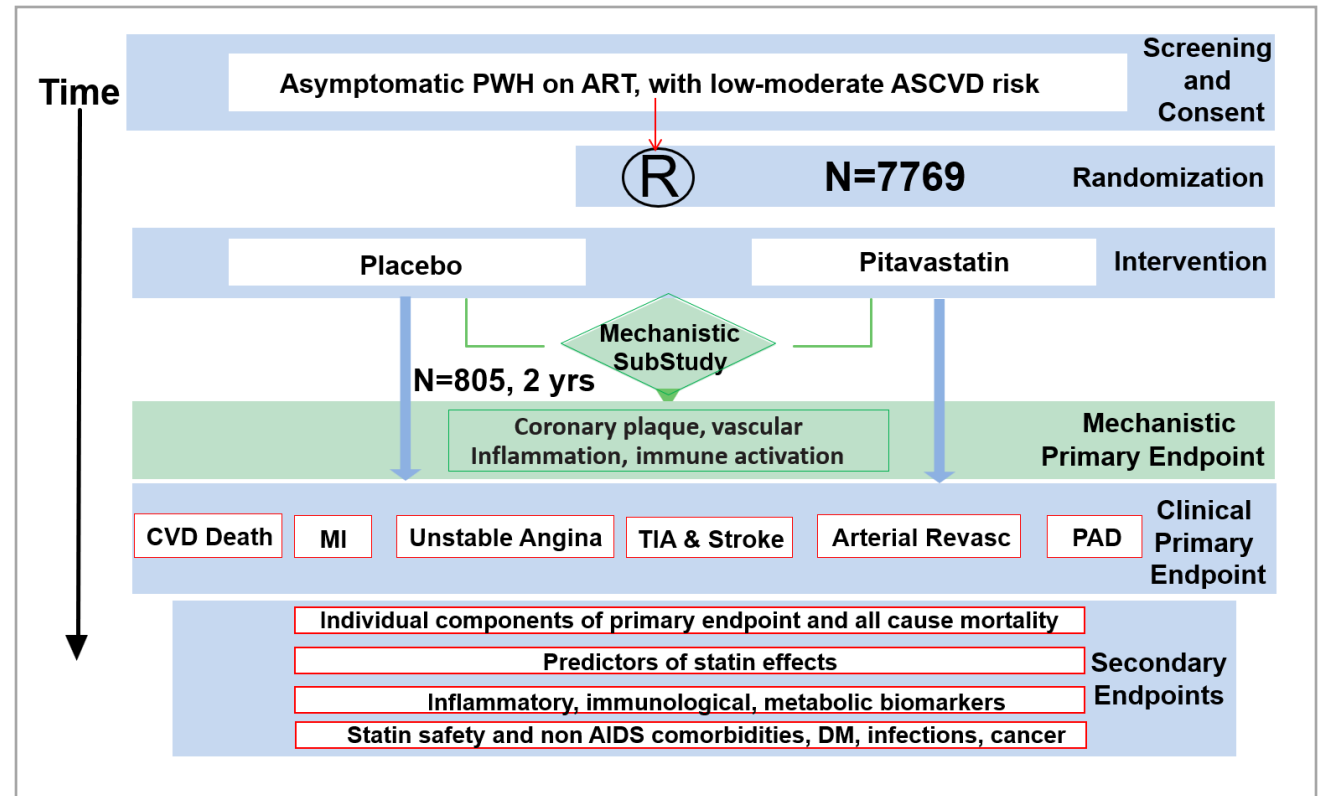
## Statins and HIV

- ▶ People living with HIV are twice as likely to develop cardiovascular disease (CVD), even when controlling for traditional risk factors, and at a young age.
- ▶ Pitavastatin has good LDL and anti-inflammatory properties, and few interactions with antiretrovirals.
- ▶ The REPRIEVE team hypothesized that pitavastatin would prevent major adverse cardiovascular events in people living with HIV at low to moderate risk of CVD, who would not typically be prescribed statins.



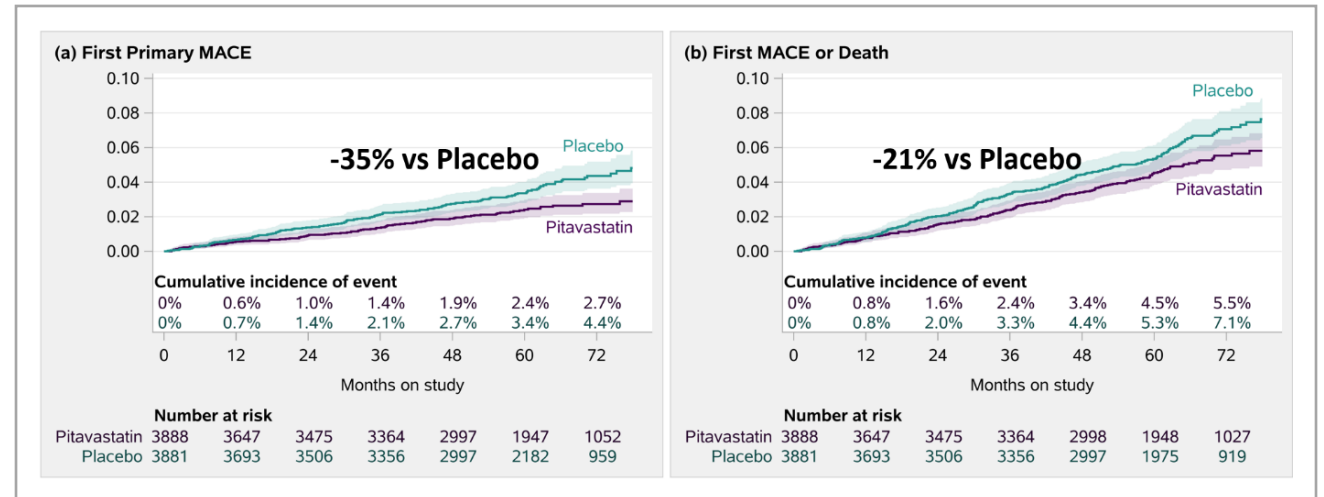
Effects of statins

- ▶ REPRIEVE enrolled 7,769 people living with HIV aged 40 to 75 (median age 50).
- ▶ 100+ sites in North and South America, Europe, Africa and Asia.
- ▶ Participants were randomly assigned to daily pitavastatin (4mg) or placebo.
- ▶ Median follow-up time was 5 years.



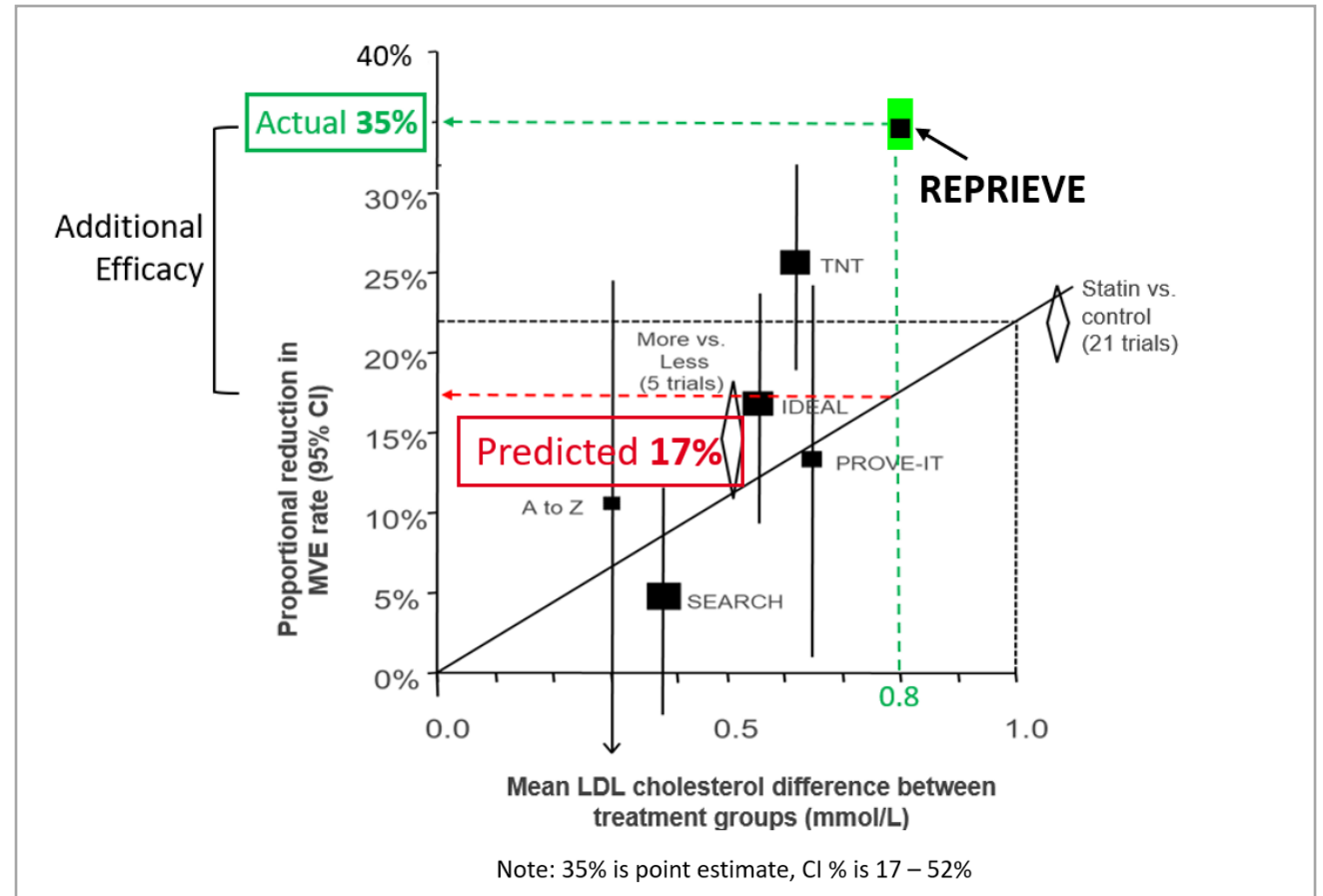
REPRIEVE trial design

- ▶ Significant benefits were observed in the pitavastatin arm:
  - 35% reduction in the incidence of major cardiovascular events (MACE) compared with the placebo arm
  - 21% reduction in the incidence of MACE or death compared with the placebo arm



Primary and key secondary endpoints

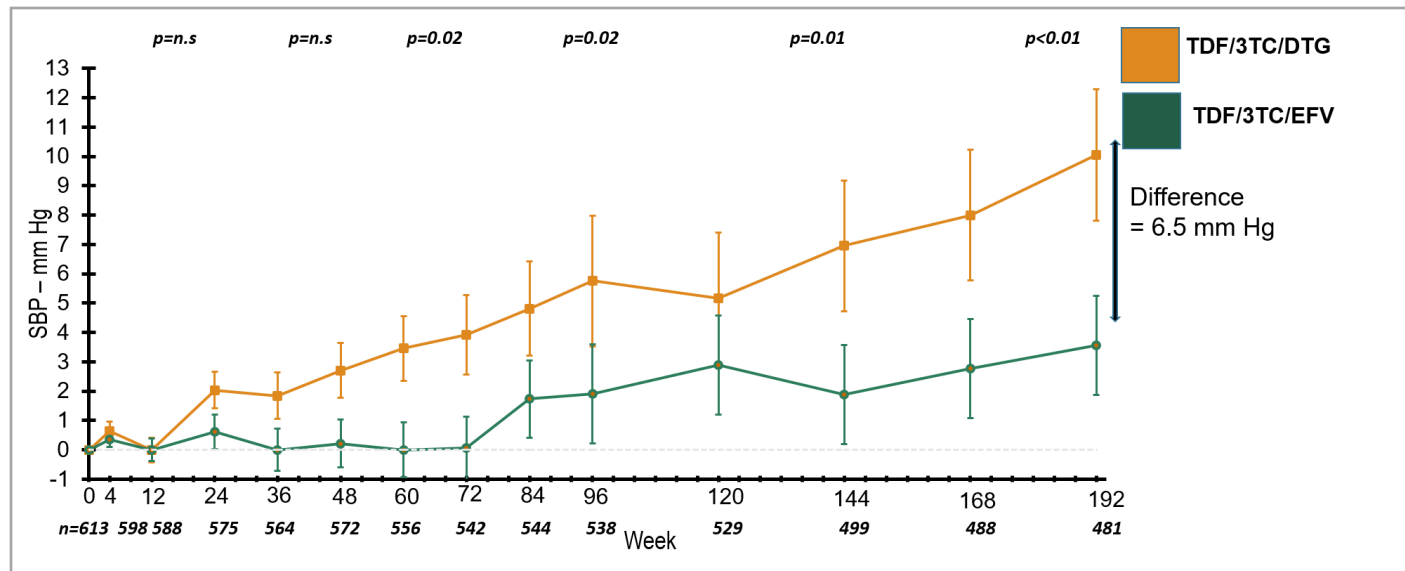
- ▶ Low-density lipoprotein (LDL) was lowered by 30% in the pitavastatin group.
- ▶ The reduction in cardiovascular events was similar for people with high or low LDL cholesterol at baseline, indicating that benefits go beyond lowering LDL.
- ▶ This effect is as yet unexplained, but the researchers are exploring inflammation biomarkers.



Effect larger than lowering of LDL

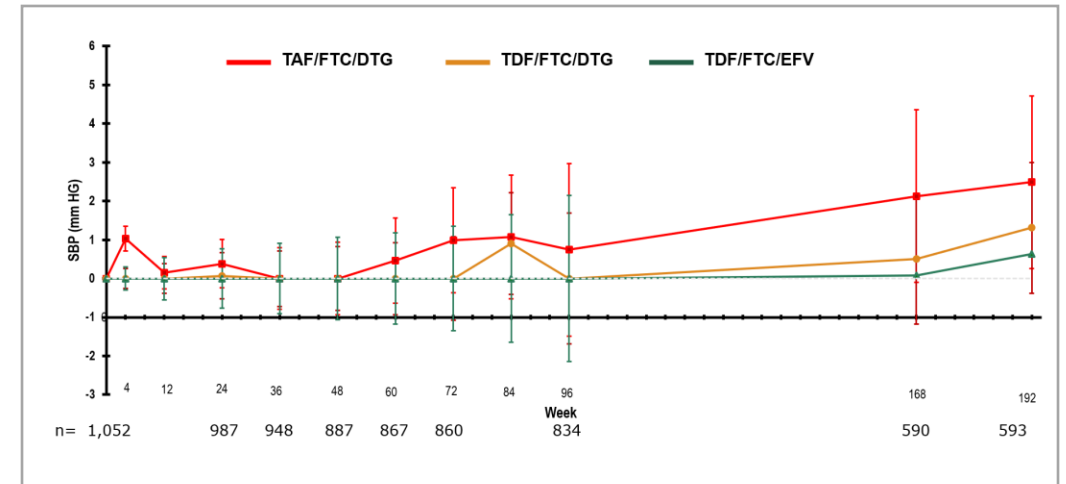
## Hypertension and HIV

- ▶ In the NAMSAL study, 613 people living with HIV in Cameroon were randomized to either dolutegravir or lower-dose efavirenz (400mg) combined with tenofovir disoproxil and lamivudine.
- ▶ Very few participants (less than 1%) were given antihypertensives.
- ▶ Blood pressure rose in both study arms, with significantly greater increases in the dolutegravir arm.



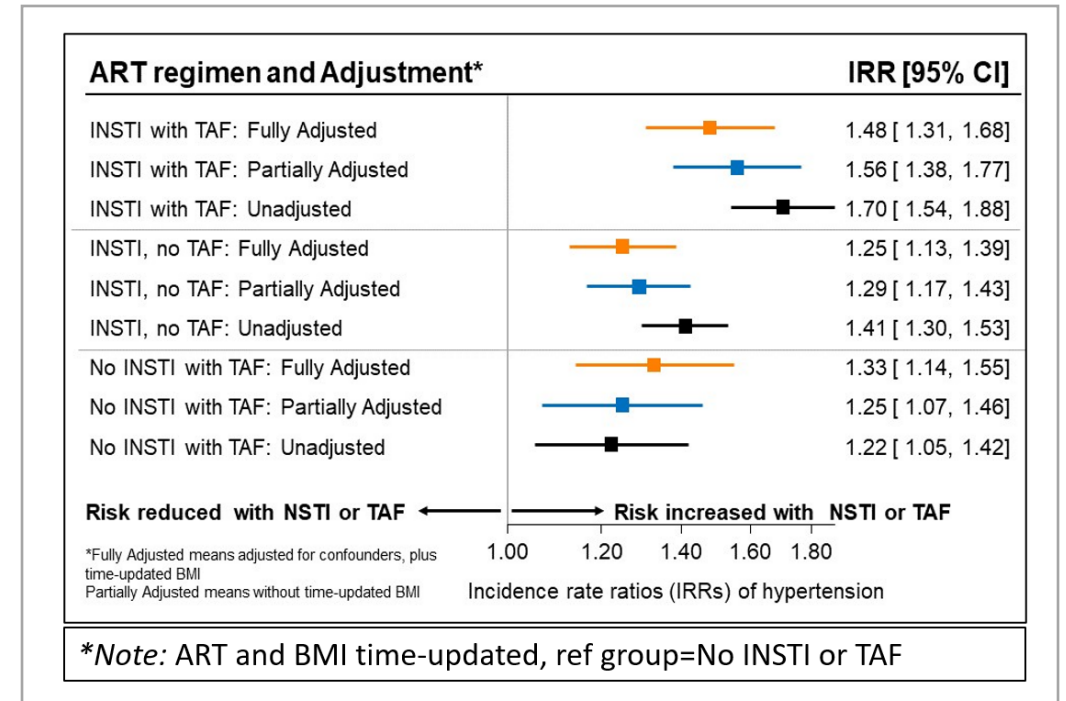
NAMSAL blood pressure change over time

- ▶ In the ADVANCE trial, 1,053 people in South Africa were randomized to: dolutegravir, TAF and emtricitabine; dolutegravir, TDF and emtricitabine; or efavirenz (600mg), TDF and emtricitabine.
- ▶ Participants developing Grade 1 hypertension were offered antihypertensives.
- ▶ By week 192, there was no significant difference in mean systolic blood pressure or Grade 1 hypertension between arms.



ADVANCE blood pressure change over time

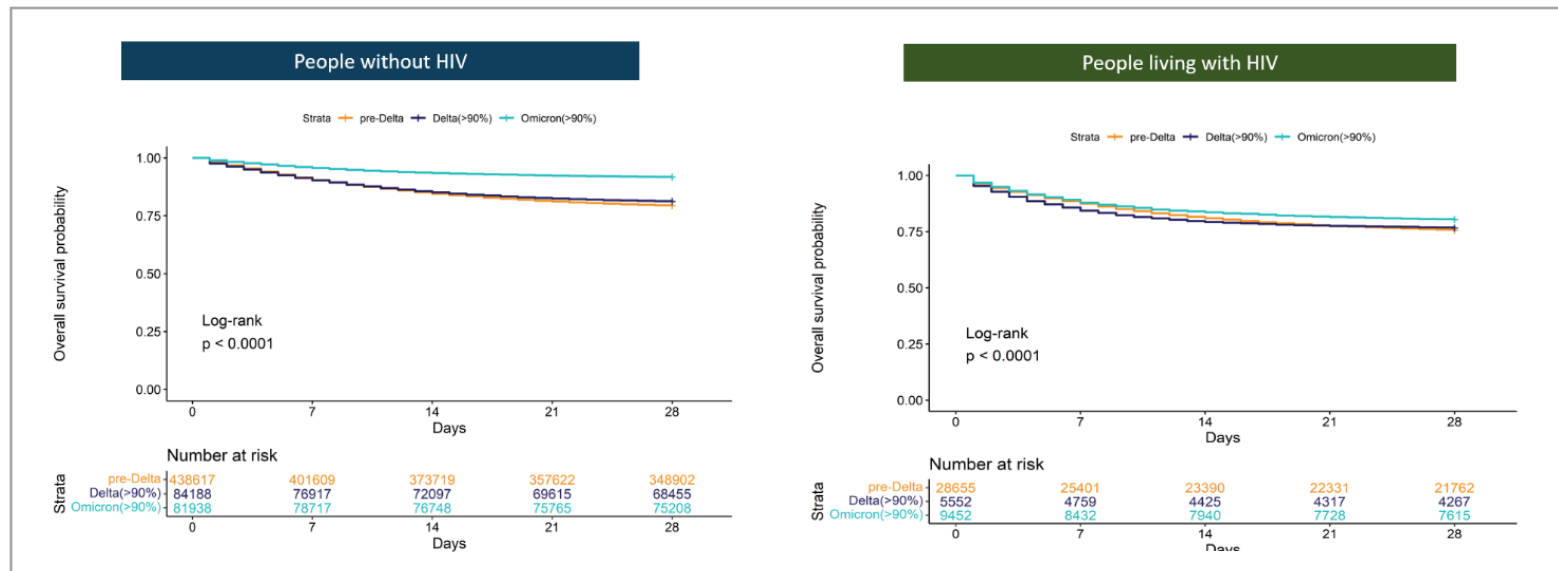
- ▶ A further analysis examined the relationship between ART, weight and blood pressure in 13 observational cohorts in Europe and Australia.
- ▶ 30% of 9,704 participants developed hypertension during 39,993 person-years of follow-up.
- ▶ Those taking both an integrase inhibitor and TAF had a 48% higher rate of hypertension after adjusting for body mass index (BMI) and other confounding factors.



Incidence rate ratios of hypertension

## COVID-19 and HIV

- ▶ Using data from 821,331 hospitalized people, a study found people living with HIV have an increased risk of death from COVID-19 than other people.
- ▶ While the mortality rate among HIV-negative people declined from 22% (Delta wave) to 9.8% (Omicron wave), the reduction among people living with HIV was modest (from 23.4% to 19.6%).



Mortality among patients hospitalized with COVID-19

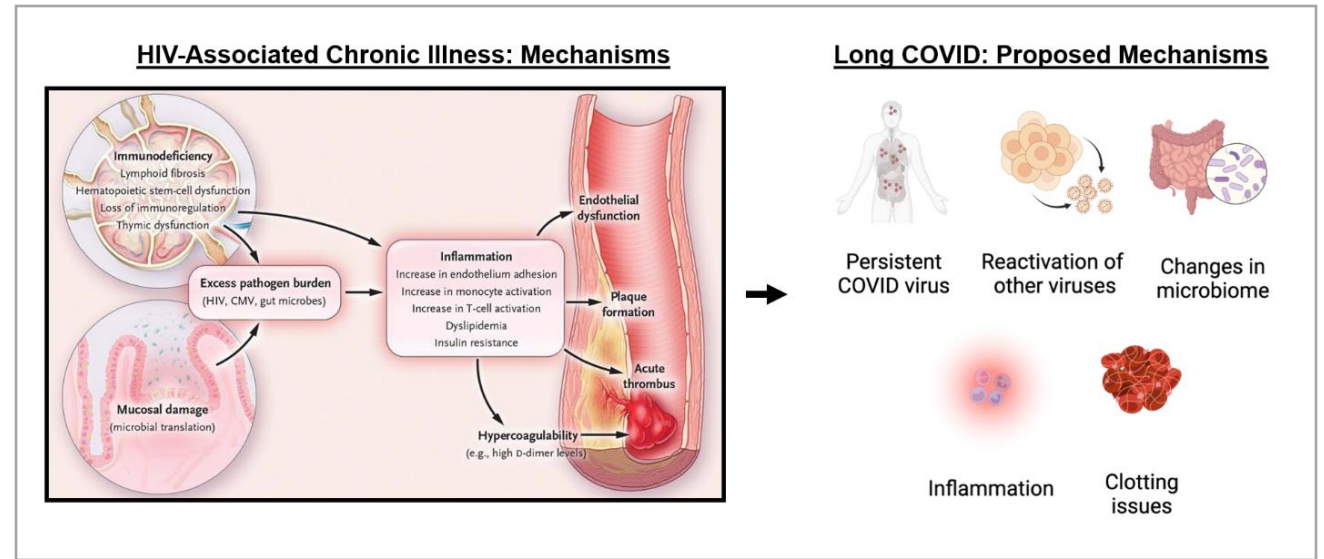
- ▶ People with unknown HIV status were also at higher risk of mortality than people without HIV.
- ▶ A low CD4 count was also associated with mortality.
- ▶ Vaccination reduced the risk of death by almost 40% in people living with HIV during the Delta and Omicron waves.
- ▶ The findings highlight the importance of booster vaccines for people living with HIV.

Characteristic	aHR (95% CI)		
	Pre-delta	Delta	Omicron
Severe/critical COVID-19 at hospital admission	2.17 (1.91-2.47)	1.95 (1.46-2.59)	1.97 (1.65-2.35)
CD4 <200 cells/ $\mu$ L	1.64 (1.45-1.89)	1.52 (1.15-1.96)	1.79 (1.45-1.96)

Risk factors across all waves

- ▶ Another study looked at effectiveness of COVID-19 vaccination in people living with HIV who inject drugs.
- ▶ The analysis included 2,700 people living with HIV and 375,043 matched HIV-negative individuals, of whom 40.7% and 4.3% respectively had a history of injection drug use.
- ▶ Vaccine effectiveness was lower among people living with HIV who had a history of injection drug use (65.8%) than among people living with HIV who did not (80.3%).
- ▶ Lower vaccine effectiveness among people with a history of injection drug use was also seen in the HIV-negative cohort but was less pronounced.

- ▶ There are parallels between HIV and long COVID.
- ▶ Treated HIV is associated with excess risk of multiple morbidities, including cardiovascular disease and cancer.
- ▶ Acute and persistent HIV can lead to chronic inflammation, which in turn can cause vascular disease.
- ▶ Proposed mechanisms of long COVID are the same.



Disease mechanisms

- ▶ HIV seems to be a risk factor for long COVID, although this is not consistent across all studies.
- ▶ There are various possible reasons why people with HIV might be at increased risk for long COVID, such as chronic co-morbidities, socioeconomic factors, or baseline inflammation.
- ▶ Early COVID treatment appears to reduce long COVID risk.
- ▶ Inflammation is consistently identified in long COVID.
- ▶ Microbial translocation may drive inflammation.
- ▶ Like HIV, long COVID may be a generation-defining challenge.

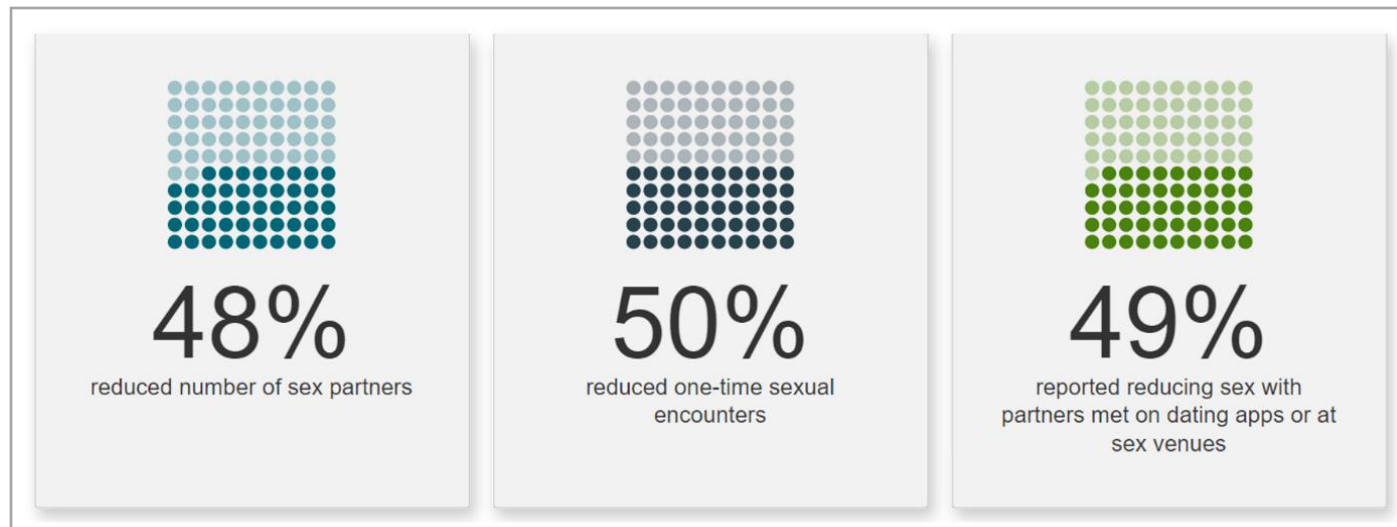
## Mpox and HIV

- ▶ A year on from the mpox outbreak, there have been 87,972 confirmed cases, including 147 deaths.
- ▶ The mpox outbreak has been contained, but with ongoing transmission beyond historically affected countries.
- ▶ There has been significant progress in understanding mpox, including viral evolution, clinical presentation and transmission.
- ▶ Neither natural nor vaccine-induced immunity appear to be lifelong.



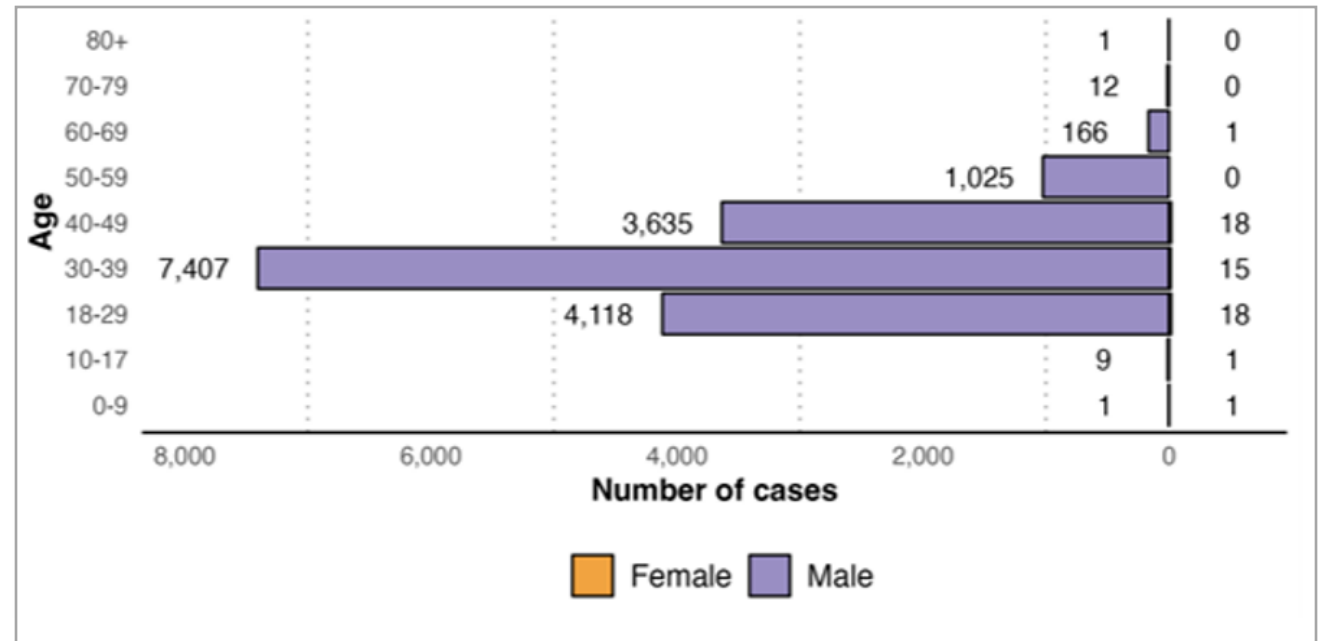
Mpox in figures

- ▶ Communities vulnerable to mpox were quickly identified.
- ▶ There were sincere efforts to engage communities at increased risk, which contributed to significant behaviour change.
- ▶ Vaccines were rapidly deployed, and a treatment identified: tecovirimat (TPOXX).
- ▶ Of concern, mpox presents in a severe form in people with advanced HIV.
- ▶ Mortality in people living with HIV with a CD4 under 100 was around 30%.



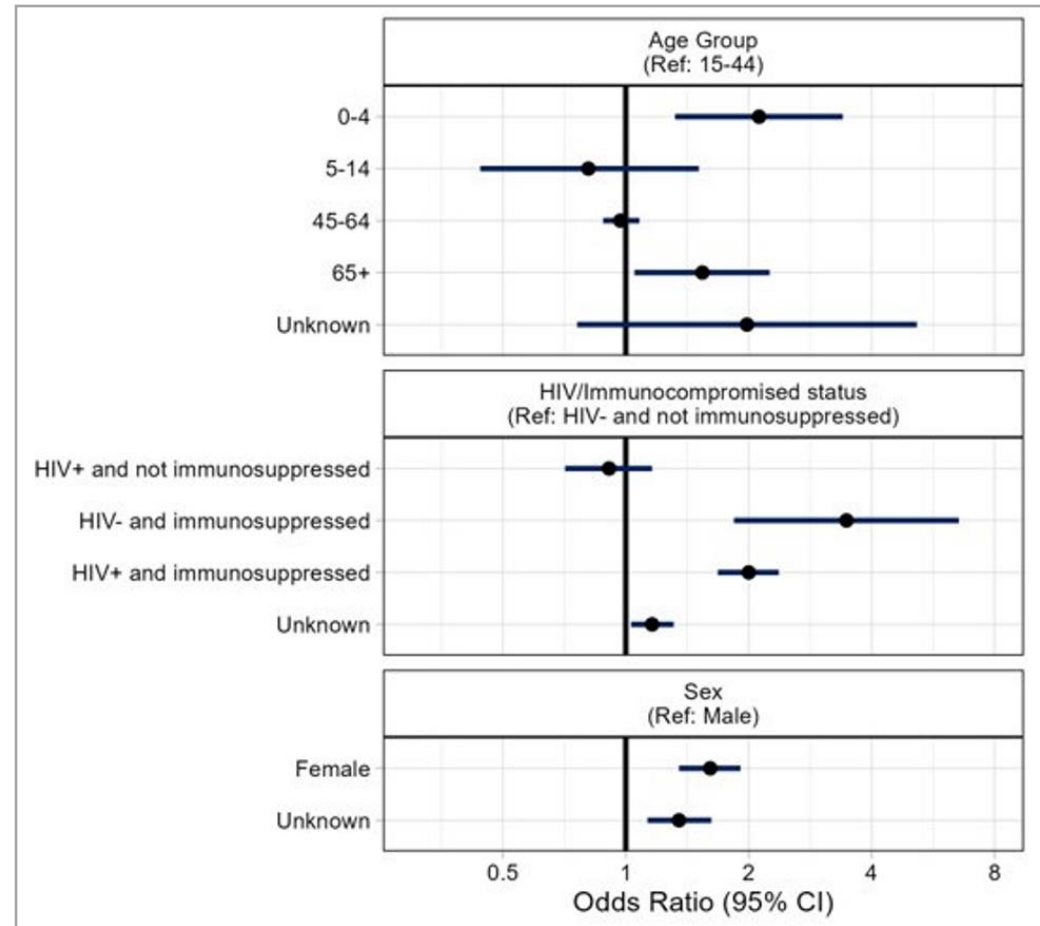
Behaviour change

- ▶ An analysis examined 80,843 cases reported in 2022 to the WHO mpox global surveillance system.
- ▶ Information on HIV status was available for 44% of reported cases. Of these, 52% were people living with HIV.
- ▶ Immunosuppression, concurrent STIs and mortality were higher in people living with HIV.



Mpox cases among people living with HIV

- ▶ Immunosuppressed people living with HIV were at higher risk of hospitalization, as were those who were immunosuppressed and HIV negative.
- ▶ The risk of hospitalization for people living with HIV with an adequate CD4 count was similar to that of HIV-negative people without immune suppression.



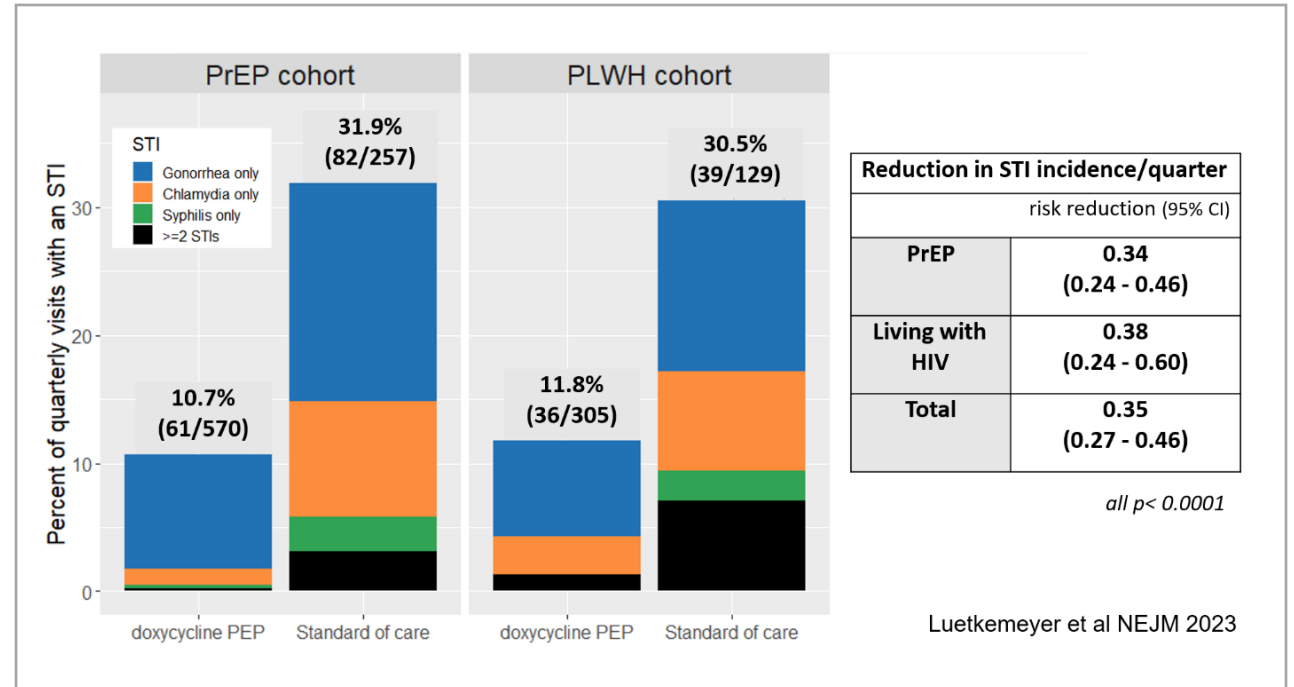
Risk of hospitalization

- ▶ In New York City, the RESPND-MI study team (RST) was established to gather actionable data on mpox.
- ▶ In May 2022, it began a study on sexual activity and mpox symptoms among those most vulnerable to mpox.
- ▶ RST organized an online community forum and weekly cross-sector calls.
- ▶ Its website hosted community-generated information on vaccination, testing and treatment services.
- ▶ Educational materials and policy recommendations were adopted by city, state, and federal public health agencies.
- ▶ Community-led research efforts can provide useful data in public health emergencies.
- ▶ Facilitating spaces for community members to discuss challenges can yield creative solutions.

## Doxycycline PEP: Is it time for implementation?

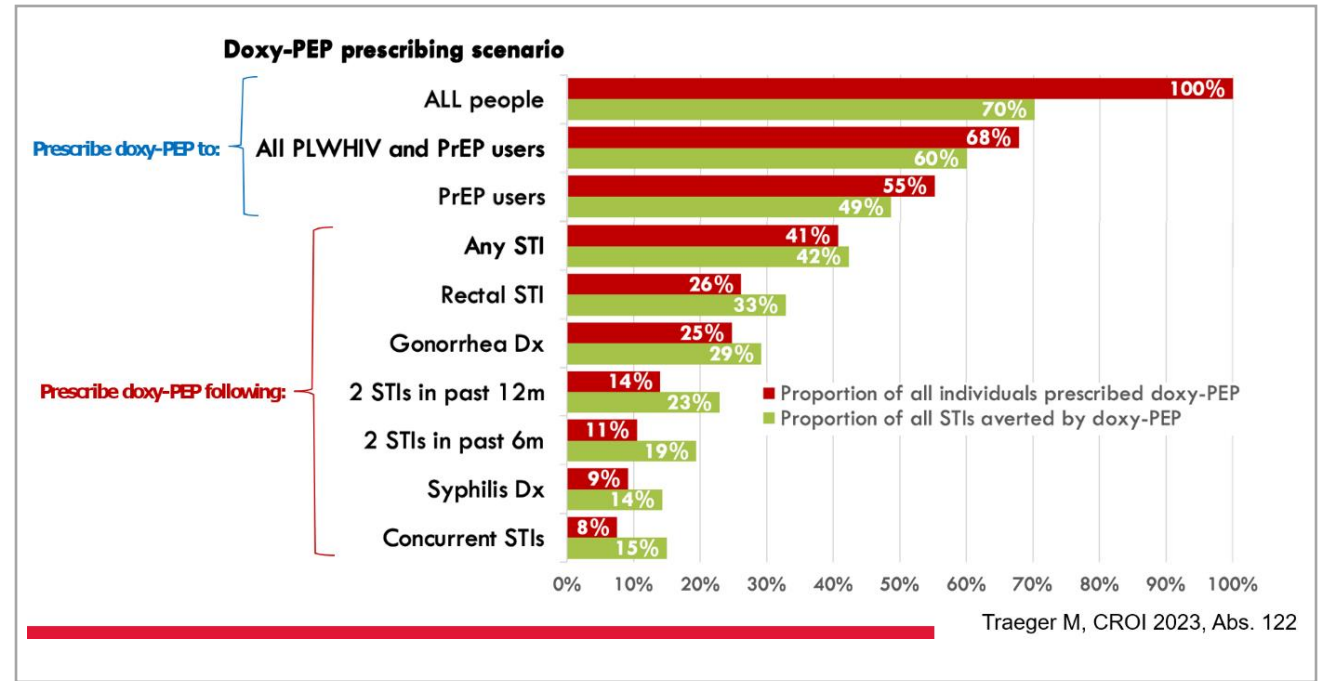
- ▶ There has been a dramatic increase in bacterial sexually transmitted infections (STIs) in recent years.
- ▶ Prevention tools available include promoting condom use, regular testing and treatment and vaccines (where available).
- ▶ Offering antibiotics to prevent bacterial STIs is not a new strategy, and there are concerns about drug resistance, particularly with gonorrhoea.
- ▶ Antibiotic strategies have included daily doxycycline, monthly azithromycin, mass treatment by location, and post-exposure prophylaxis (PEP).
- ▶ PEP for syphilis is already recommended in the US.

- ▶ The first randomized French study of doxycycline PEP found a 47% reduction in STIs in those offered PEP.
- ▶ The US DoxyPEP trial confirmed a significant impact on chlamydia and syphilis, and also showed a nearly 50% reduction in gonorrhoea diagnoses.
- ▶ The French DOXYVAC trial also reported a significant impact of PEP (nearly 80% reduction) on chlamydia and syphilis.



DoxyPEP trial: STI incidence per quarter

- ▶ There are concerns that using antibiotics as PEP may create drug resistance.
- ▶ One study modelled how best to use doxyPEP to limit exposure to antibiotics while preventing the most STIs.

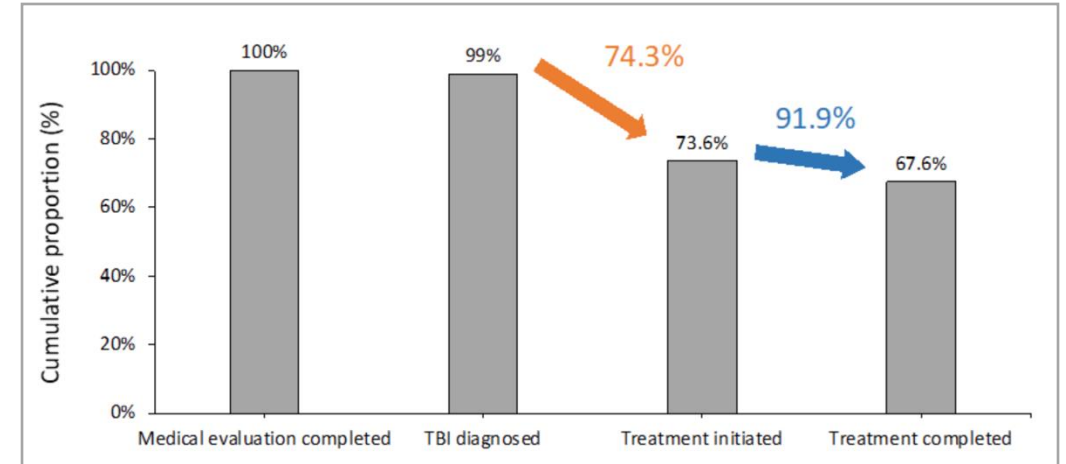


Doxy PEP use vs STIs averted in a US clinic

- ▶ Molina recommended targeted doxyPEP use for gay men and other men who have sex with men and trans women:
  - Who have sex with casual sexual partners without regular use of condoms
  - Who have had more than one or two STIs in the past year
  - Who have tested negative for gonorrhoea, chlamydia and syphilis before starting PEP
  - Who have no contraindications for doxyPEP use
- ▶ DoxyPEP would be given as a single dose of 200mg monohydrate, no later than 72 hours after condomless sex, and no more than three times per week.
- ▶ Monitoring should include STI testing at least every three months.

## Latent TB and HIV

- ▶ People living with HIV are at an increased risk of reactivation of latent tuberculosis (TB) compared to those not living with HIV .
- ▶ Previous research shows gaps in the TB care cascade in Taiwan, especially before starting latent TB treatment.
- ▶ Rifapentine-based regimens for latent TB have a higher completion rate than others; however, rifapentine may reduce plasma concentrations of integrase inhibitors.



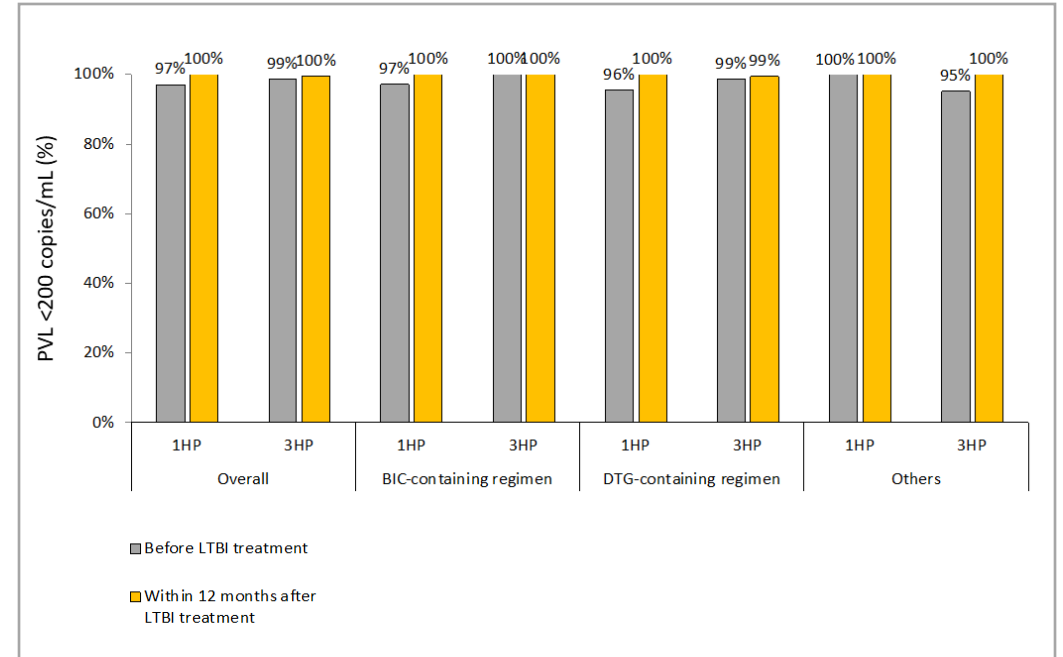
Latent TB care cascade in Taiwan

- ▶ In a study from Taiwan, people testing positive or indeterminate for interferon-gamma release assay (IGRA) were advised to receive directly observed therapy for latent TB (after excluding active TB).
- ▶ They received either 3HP or 1HP.

	1HP regimen (n=205)	3HP regimen (n=274)	P
Age, median (IQR), years	43 (34-51)	43 (35-51)	0.417
Male sex, n (%)	193 (94.1)	260 (94.9)	0.722
Risk factor, n (%)			
Male-to-male sex	155 (75.6)	158 (57.7)	<0.001
Heterosexual sex	22 (10.7)	23 (8.4)	0.386
Illicit drug use	28 (13.7)	94 (34.3)	<0.001
Incarceration, n (%)	8 (3.9)	32 (11.7)	0.002
HBsAg positivity, n (%)	24 (11.7)	14 (5.1)	0.008
Anti-HCV positivity, n (%)	38 (18.5)	73 (26.6)	0.037
Baseline CD4 count, median (IQR), cells/mm <sup>3</sup>	658 (503-878)	636 (487-814)	0.186
Baseline PVL, median (range), log <sub>10</sub> copies/mL	UD (UD-4.74)	UD (UD-4.15)	0.383
ART during LTBI treatment, n (%)			<0.001
BIC-containing regimen	142 (69.3)	38 (13.9)	
DTG-containing regimen	46 (22.4)	214 (78.1)	
Others	17 (8.3)	22 (8.0)	

Clinical characteristics

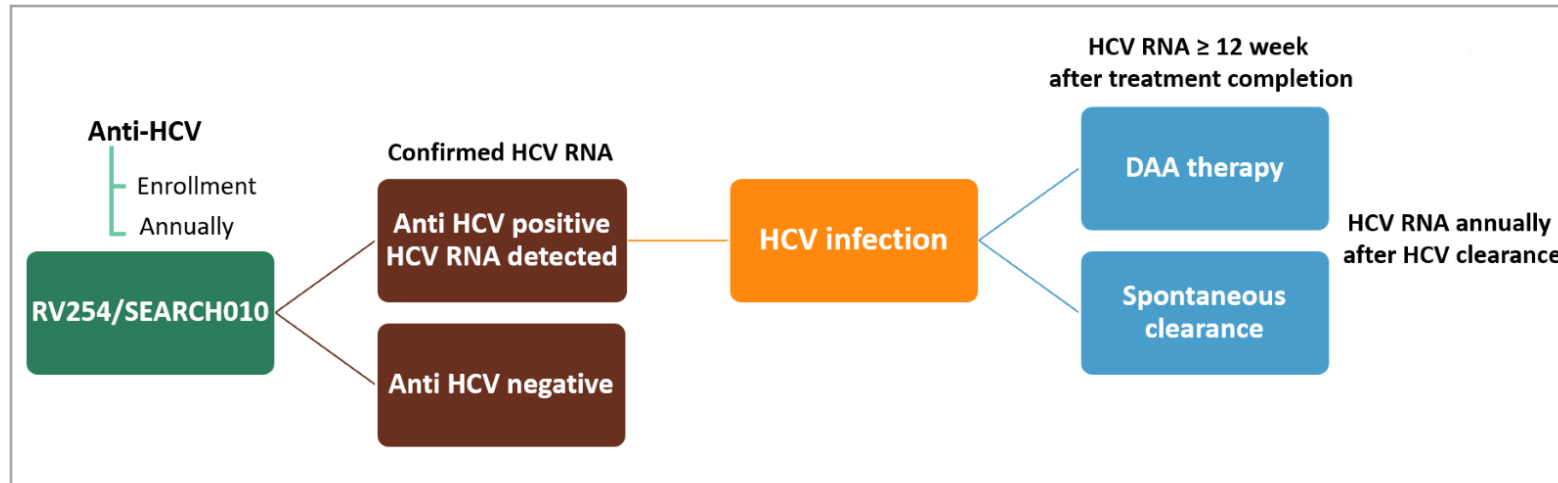
- ▶ Completion rates were similar in the 1HP and 3HP groups (92.7% vs 90.0%).
- ▶ After excluding those who did not complete TB treatment or who were lost to follow-up, only one person did not achieve viral suppression, due to poor adherence.
- ▶ The authors conclude that combinations of integrase inhibitor-containing regimens and rifapentine-based regimens both had good safety profiles and maintained viral suppression.



Viral suppression in per protocol analysis

## Hepatitis C and HIV

- ▶ Direct-acting antivirals (DAAs) are associated with high hepatitis C virus (HCV) cure rates, but re-infection can occur.
- ▶ A study reviewed results of participants diagnosed with HCV in the RV254/SEARCH010 study, which enrolled people with acute HIV in Thailand, between 2009 and 2022.



HCV management

- ▶ Between 2009 and 2022, 694 HCV seronegative participants were enrolled.
- ▶ 98 (14.1%) acquired HCV.
- ▶ Of 72 participants who completed treatment, 68 achieved sustained virologic response (SVR).
- ▶ Additionally, 10 participants spontaneously cleared HCV.
- ▶ HCV re-infection occurred in nine people: Three re-infections occurred after spontaneous clearance and six after SVR.
- ▶ The authors conclude that post-clearance follow-up with harm reduction measures is essential to identify and minimize HCV re-infection.

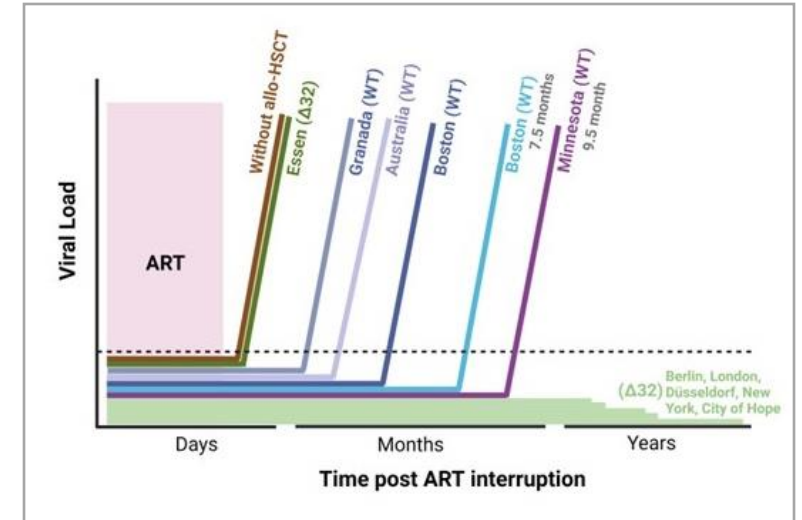
# Remission and cure

- [67](#) The "Geneva patient"
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- [77](#) Germline targeting
- [83](#) BH3 mimetics

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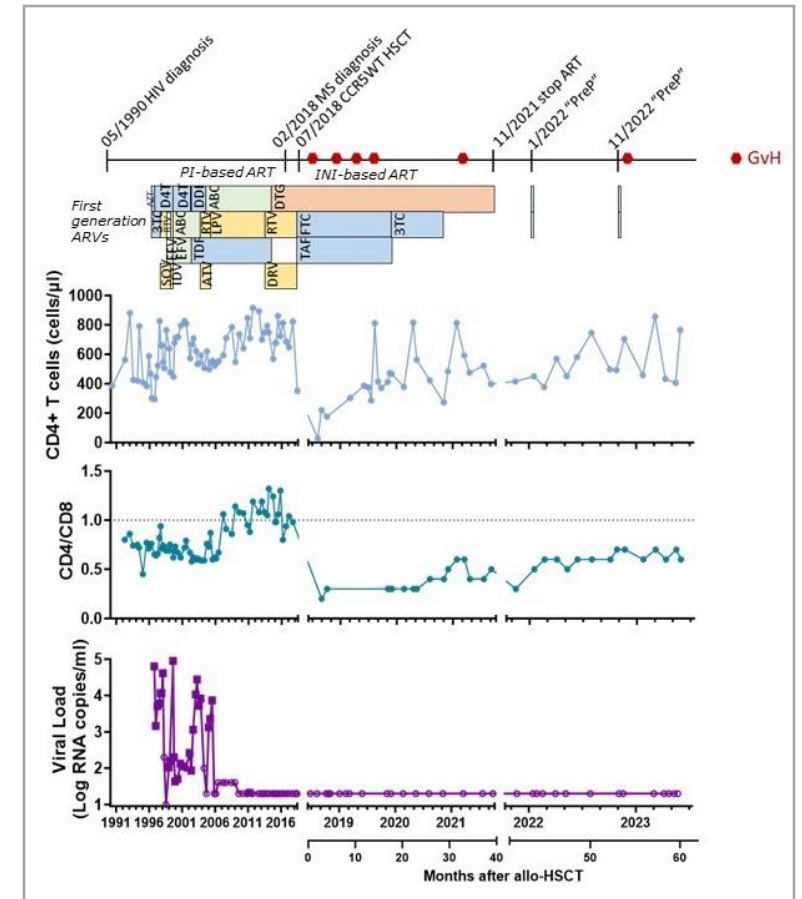
## The “Geneva patient”

- ▶ This is the first person in long-term HIV remission following a transplant from a donor not immune to HIV.
- ▶ The man, known as the “Geneva patient”, is in his mid-50s, has been living with HIV since 1990 and started ART in 2005.
- ▶ He developed rare solid white-cell cancer; the prognosis is usually poor.
- ▶ He received a stem cell transplant for cancer in July 2018. A donor with homozygous CCR5- $\Delta$ 32 mutation (immune to HIV) could not be found.
- ▶ Prolonged remission of HIV was unexpected; similar patients have only had remissions of months.



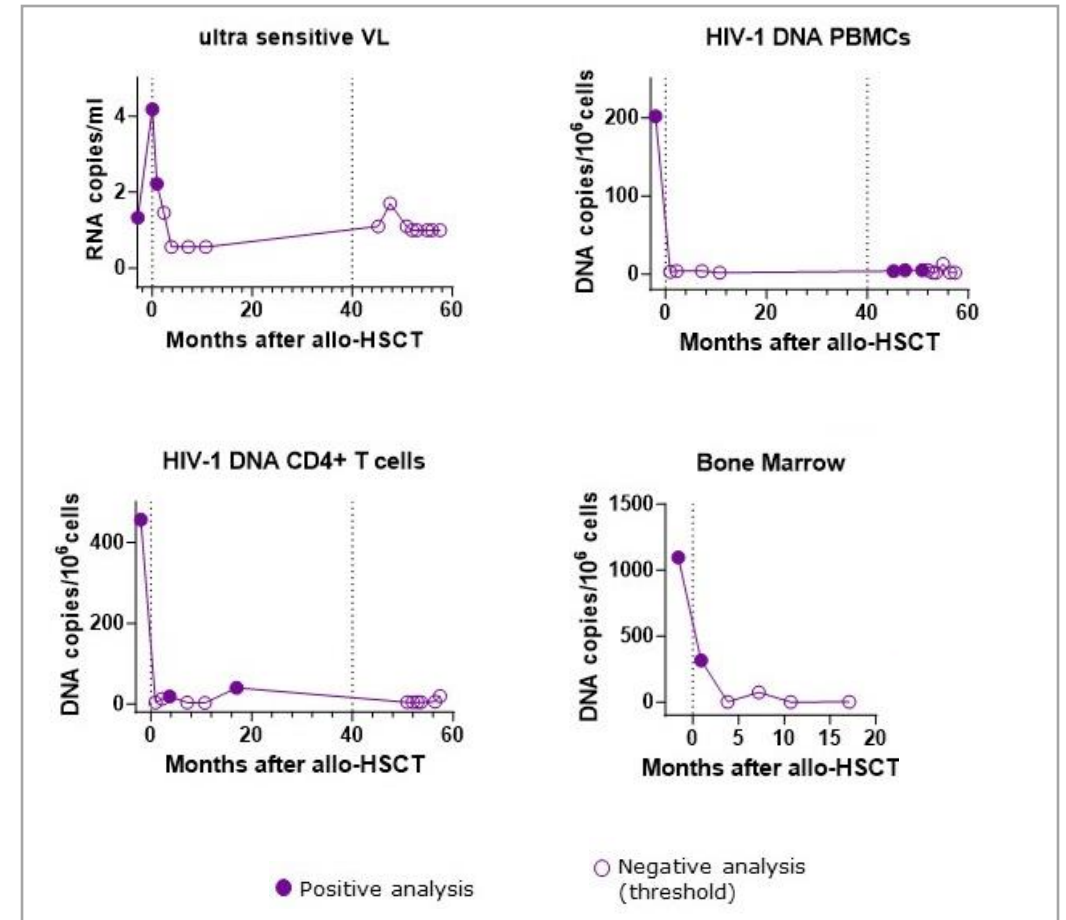
Viral rebound after ART interruption in other people who received allo-HSCT

- ▶ He received intensive chemotherapy and radiotherapy to delete the host immune system.
- ▶ Within a month, he received full chimerism, i.e., all host immune cells were replaced by the donor’s.
- ▶ The “Geneva patient” had multiple episodes of acute and chronic graft-versus-host disease (GVHD).
- ▶ GVHD was managed with immune suppressants, especially ruxolinitib (*Jakavi*).
- ▶ ART was gradually tailed off, ending in November 2021 (analytical treatment interruption – ATI).



20 months of undetectable viremia without ART after CCR5WT allo-HSCT

- ▶ Is this remission – or cure?
- ▶ The “Geneva patient” has an undetectable viral load in ultrasensitive tests; it has now been 20 months since the ATI.
- ▶ Only defective HIV DNA can be found, including in the gut.
- ▶ HIV cannot be induced from his CD4 cells.
- ▶ CD8 cells are not sensitive to HIV.
- ▶ HIV antibodies are gradually declining, suggesting there is no HIV to react to.

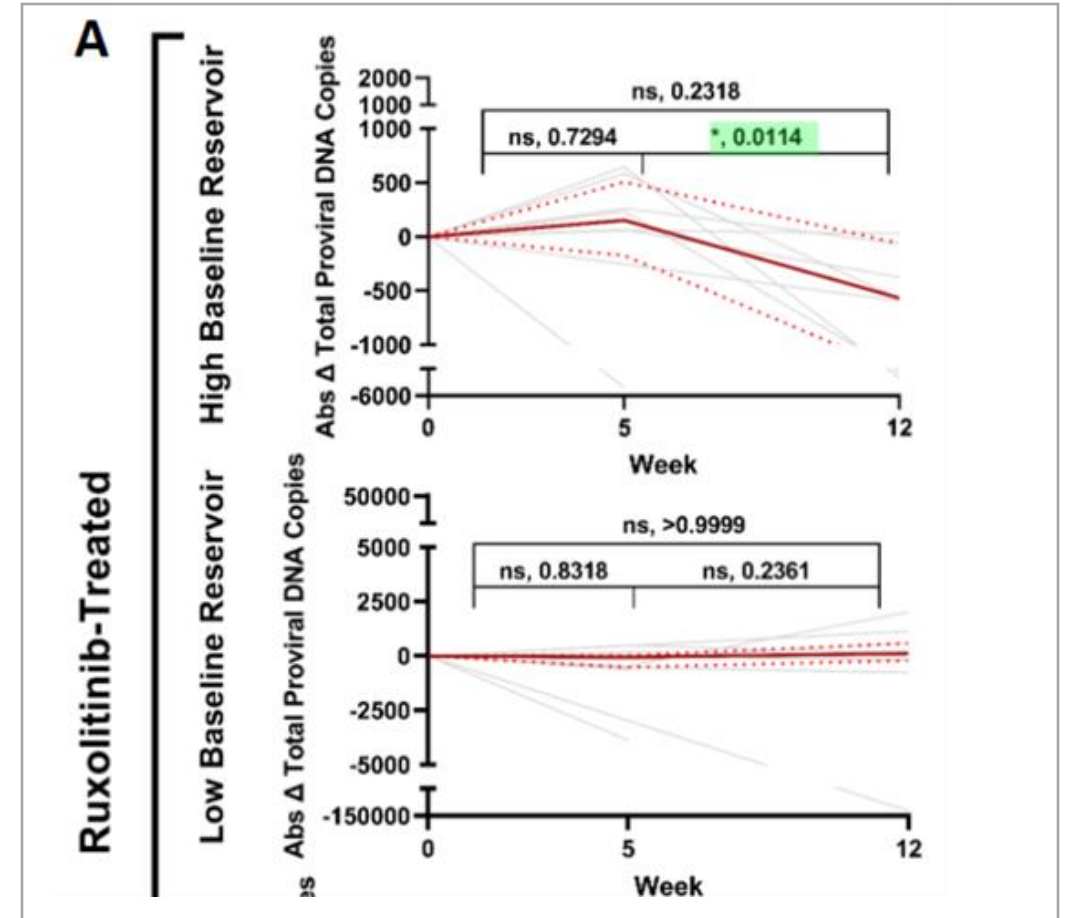


Drop in markers of HIV persistence

- ▶ What contributed to the Geneva patient’s remission?
- ▶ GVHD – when donor cells attack remnant host cells. This was a factor in Timothy Ray Brown’s cure.
- ▶ NK (natural killer) cells – these distinguish self proteins from foreign proteins. The host’s NK subtype was capable of suppressing HIV replication in vitro.
- ▶ Ruxolitinib, a medication taken to manage GVHD (see next slide).
- ▶ “Viral rebound is still a concern in this patient as he lacks the safety net of CCR5-deleted cells other recipients have had. If there is any HIV left in his system, the mechanisms controlling it may be more transient. But the longer his remission lasts, the more secure it will feel.” – Asier Sáez-Cirión

## Ruxolitinib (*Jakavi*)

- ▶ Ruxolitinib is an anti-inflammatory and anti-proliferative drug (JAK/STAT inhibitor) used to treat cancer.
- ▶ Another study at IAS 2023 showed that ruxolitinib suppressed HIV replication and contributed to reducing the size of the HIV DNA reservoir.
- ▶ This effect, however, was only seen in people who had lots of cells containing replication-competent HIV. It did not reduce size of smaller reservoirs.



Reservoir decay

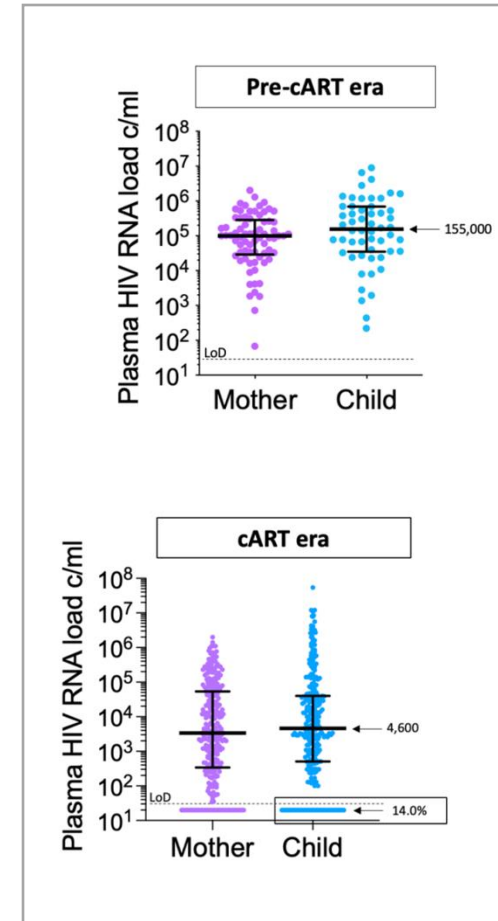
## South African post-treatment controllers

- ▶ Young children are good candidates for cure/viral control since:
  - The date of acquisition is known.
  - They start ART very early.
  - They have fewer of the CD4 memory cells that become reservoir cells.
- ▶ Previous cases include the “South African child”: undetectable viral load maintained for 14 years following analytical treatment interruption.



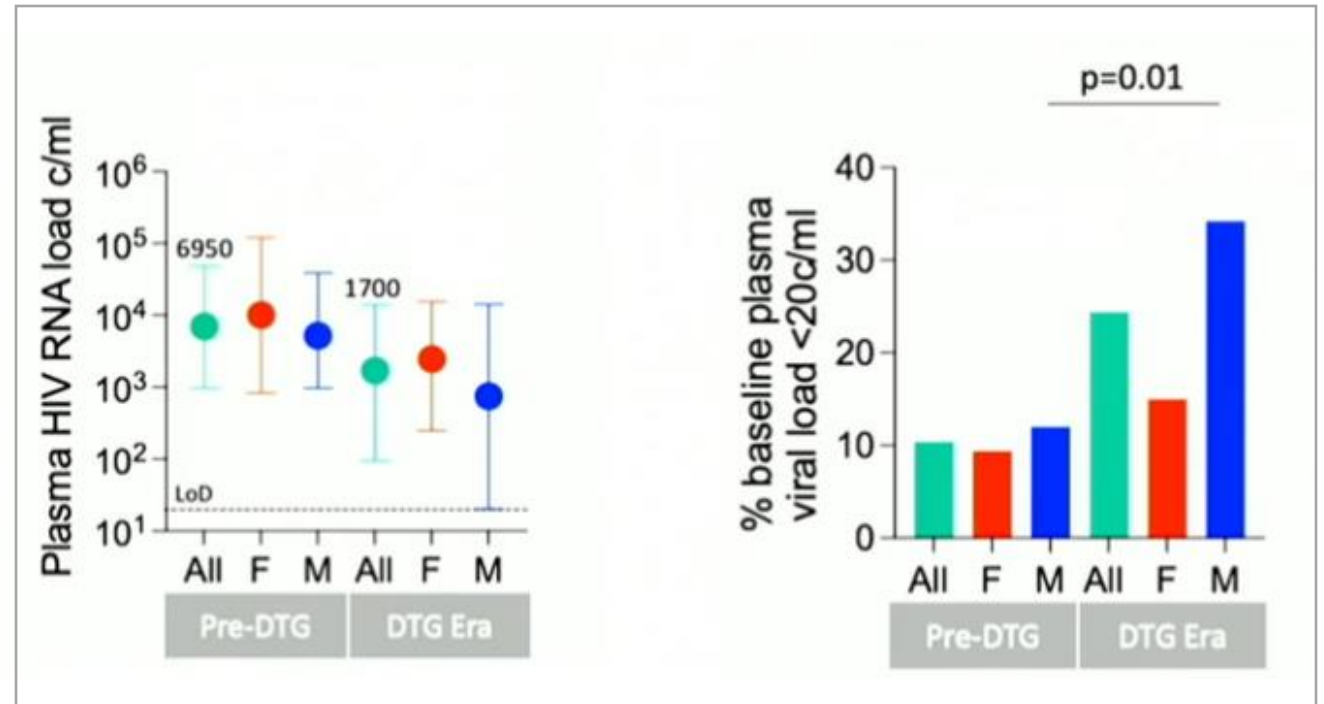
Reports of post-treatment control/functional cure  
in early cART-treated children

- ▶ The South African cohort had 281 mother-baby pairs; all infants were born with HIV.
- ▶ Two-thirds of the mothers were diagnosed when pregnant, some during labour.
- ▶ All babies were given ART at birth and 92% received pre-natal ART via placenta.
- ▶ Before ART programmes started in South Africa in 2005, the average viral load of newborns was 155,000 copies/mL.
- ▶ In years following universal ART for pregnant women in 2013, the average viral load of newborns was 4,600 copies/mL.



Low baseline viral loads,  
cART beginning pre-birth

- ▶ 10% of babies were born with baseline viral loads below 20 copies/mL.
- ▶ This was more common in males:
  - 8% of females and 12% of males exposed to lopinavir
  - 16% of females and 33% of males exposed to dolutegravir
- ▶ 36 months after birth, 37% were lost to follow-up.
- ▶ Of those retained, 63.5% had viral load <20 copies/mL.



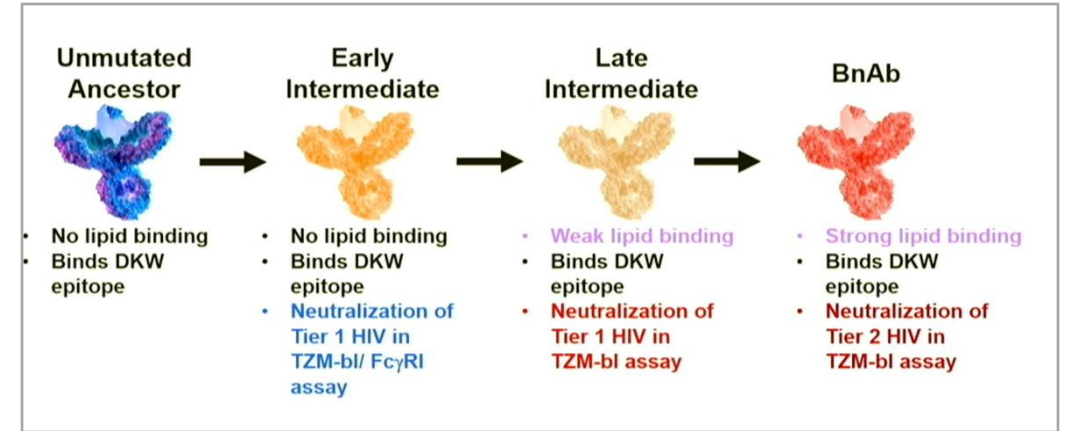
Lower baseline viral loads with dolutegravir-based regimens

- ▶ Five males (no females), had viral load <20 copies/mL throughout follow-up despite not receiving ART from <2 months after birth.
- ▶ Male children made up 40% of the cohort.
- ▶ One male had not received ART since just after birth. Clinicians told mother he need no longer required ART at age 40 months. Now aged 5, he is still undetectable, though HIV antibodies appeared at month 37.
- ▶ Three of the other four males are now in treatment interruption studies.

- ▶ The cohort highlights sex differences in viral response.
- ▶ Males are less likely to vertically acquire HIV.
- ▶ Viruses in females were less sensitive to type 1 interferons and had low replicative capacity.
- ▶ Viruses in male children were more sensitive to type 1 interferons and had higher replicative capacity – except in five post-treatment controllers, whose viruses had low replicative capacity.
- ▶ Hypothesis:
  - Females produce more type 1 interferon, so more CD4 cells are sensitized to be targets for HIV.
  - Only viruses which are non-sensitive to interferon get through but when they do, they find a more permissive environment.
  - Males: all viruses get through, but less virulent ones die off.
- ▶ “Points to pivotal importance of interferons in control of HIV” – Gabriela Cromhout

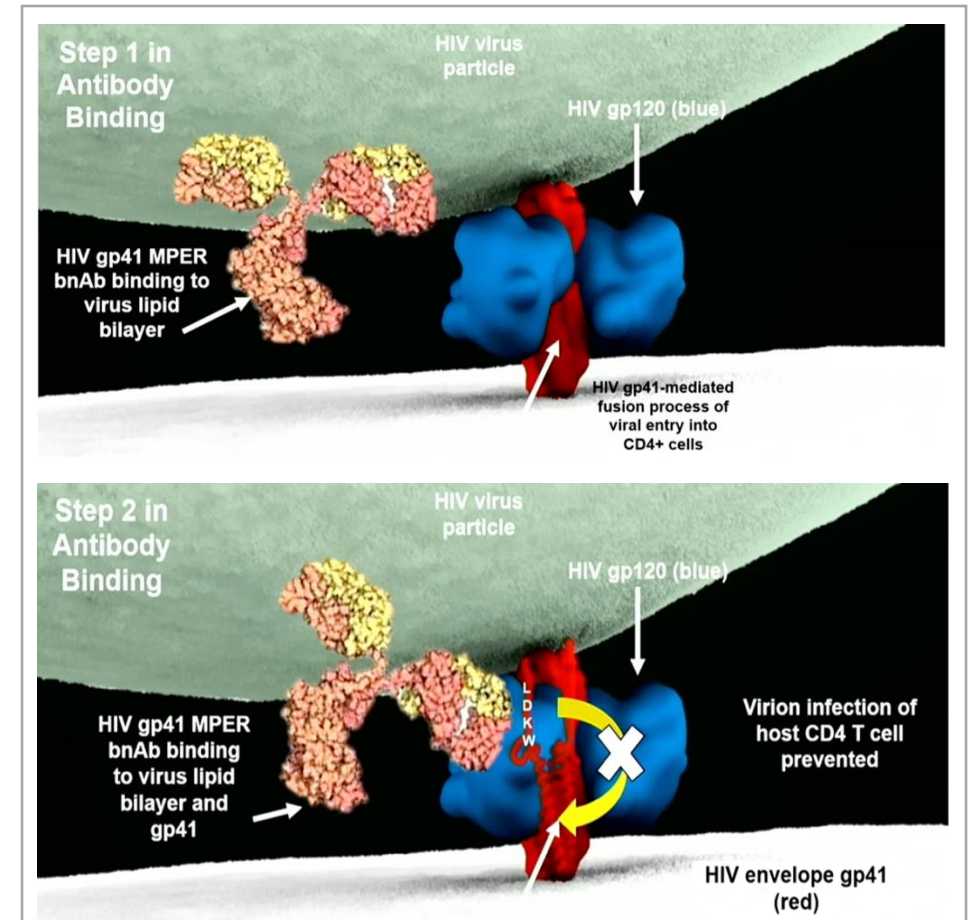
## Germline targeting

- ▶ The HVTN133 study is testing a vaccine designed to push the immune system into developing B cells that can produce broadly neutralizing antibodies (bnAbs).
- ▶ It uses the “germline targeting approach” that guides the B cells that make antibodies, from unmodified precursor cells that react to part of HIV but do not produce neutralizing antibodies, to cells that can generate bnAbs fully capable of neutralizing hard-to-neutralize tier 2 viruses.



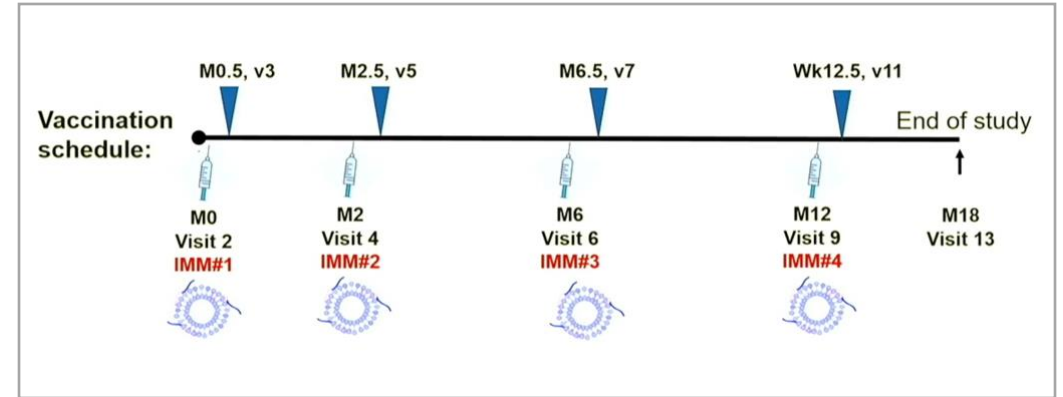
Degree of proximal-MPER BnAb lineage maturation induced by Gp41 MPER-peptide liposomes in humans

- ▶ The vaccine is designed to stimulate production of bnAbs that bind to two parts of the virus.
- ▶ The main target is the membrane proximal target region (MPER): part of the gp41 "spike" that is closest to CD4 cell surface during entry.
- ▶ But MPER is only exposed for a brief period, especially in tier 2 viruses.
- ▶ So the bnAb must bind to the viral lipid membrane first, then await attempted cell entry and rapidly block the MPER.



MPER broad neutralizing antibody site of action

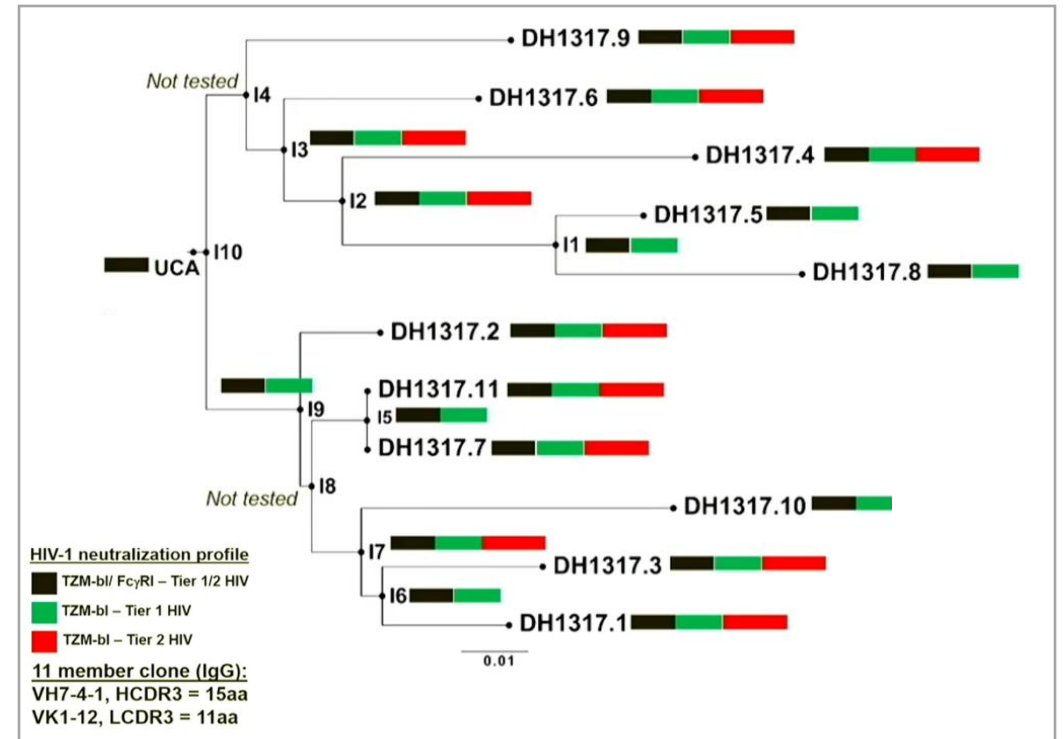
- ▶ The vaccine consists of lipid nanoparticles (fat droplets) bearing the most immunogenic amino acid sequences in MPER and the viral membrane.
- ▶ The original schedule was four injections (20 vaccine, 4 placebo) at months 0, 2, 6, 12.
- ▶ The study stopped at month 6: one person had an anaphylactic reaction to polyethylene glycol, commonly used as a carrier in vaccines. By then, 20 participants had had two vaccinations, and five had had three.



Immunization schedule for HVTN133 human clinical trial that studied Gp41 MPER-peptide liposomes

- ▶ Reactivity after two immunizations (n=20):
  - Crucial 'DKW' amino acid sequence in MPER was recognized by 13 recipients.
  - B cells producing antibodies were reactive to MPER in 7 recipients: 0.03% of B cells capable.
- ▶ Reactivity after three immunizations (n=5):
  - 87 individual cells that produced bnAbs with high affinity for MPER.
- ▶ By analysing the most potent antibodies, they found 38 B cell genetic sequences:
  - 24/38 cells could produce "early neutralizing" bnAbs.
  - 14/38 cells could make "intermediate neutralizers", that neutralized tier 1 viruses.
  - 2/38 cells could make fully mature bnAbs that neutralized tier 2. One such cell was called DH1317.

- ▶ The researchers looked at the B cells and their genetic relatedness in the two best responders (out of the five who had had three immunizations).
- ▶ Gene sequencing traced lineages of bnAb-producing B cells as they developed during study.
- ▶ Found 11 sequences capable of producing bnAbs: 8/11 turned out to have DH1317 lineage.
- ▶ Evidence of proliferation of different bnAb responses: exactly what you'd want to see.



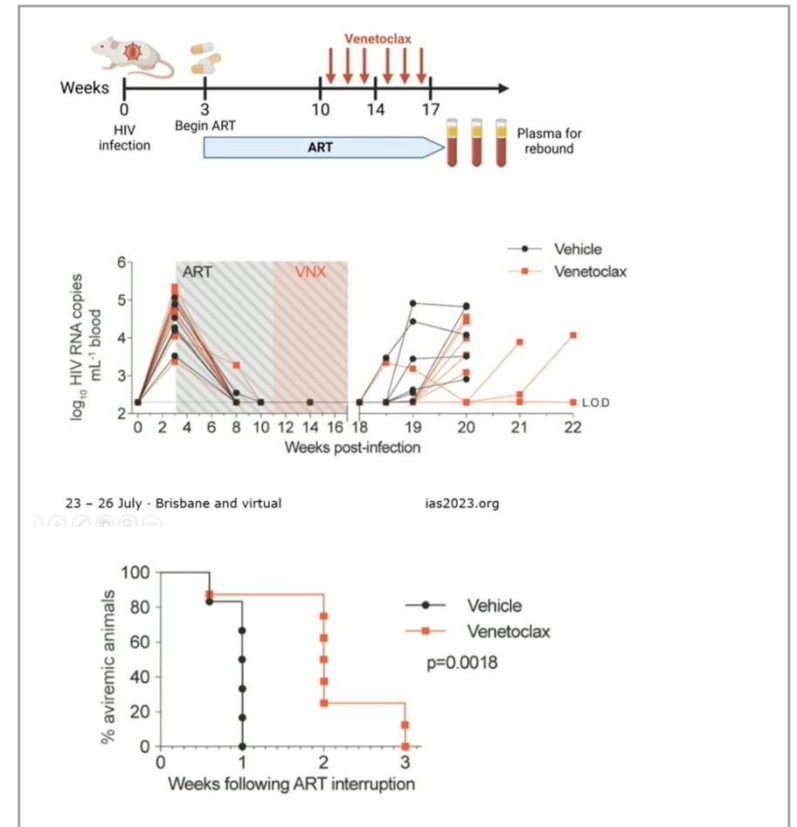
Progression of neutralization capacity in HVTN133 vaccine-induced heterologous HIV-1 neutralizing B cell clonal lineage, DH1317; late intermediates/early bnAbs

- ▶ “Never been reported before” – Wilton Williams. But there are cautions...
- ▶ Genetic development is promising, but bnAbs from cells with DH1317-4-1 lineage (one of the two most promising) only neutralized 15% of multiclade viruses, compared to 35% of clade B viruses.
- ▶ They did not neutralize clades A and C (predominant in Africa), but evidence was found in genes that sequences capable of neutralizing them were developing.
- ▶ The next step is to repeat the study with PEG-free formulation and  $\geq 4$  immunizations.
- ▶ “Lack of additional breadth is due to insufficient antibody affinity maturation, and insufficient recognition of HIV sequence diversity” – Wilton Williams

## BH3 mimetics

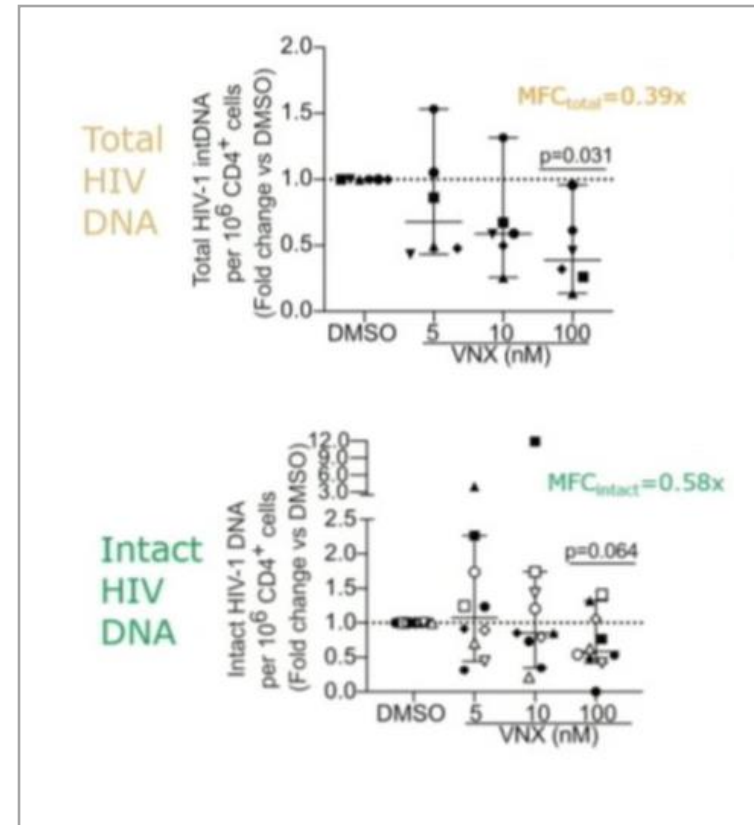
- ▶ HIV reservoir cells may persist because they produce anti-apoptotic proteins such as BCL-2 and MCL-1 that have also been seen to be overactive in leukaemia and lymphoma cancer cells. These prolong cellular life by evading apoptotic mechanisms.
- ▶ BAX and related proteins are pro-apoptotic proteins that join on to BCL-2 and MCL-1 and moderate their effects. But BCL-2 is so overproduced in cancer cells that BAX cannot counteract it.
- ▶ BH3 mimetics (also called BCL-2 inhibitors) are small molecules that "slot into" the same active site on BCL-2 as BAX. They restore the immune system's ability to kill off disordered cells.
- ▶ BCL-2 inhibitor venetoclax (*Venclexta*) was licensed in 2016 to treat some types of leukaemia and lymphoma.

- ▶ Study in mice: venetoclax was given to eight mice "humanized" to have CD4 cells receptive to HIV.
- ▶ The drug was given for six weeks while the mice were still on ART, then treatment was interrupted.
- ▶ Humanized mice normally have viral rebound within a week off ART.
- ▶ The average time to rebound more than doubled in mice on venetoclax.
- ▶ Adding in a second investigatory drug, S63845 (inhibits MCL-1, a different anti-apoptotic protein), extended the average rebound time to three weeks.



Venetoclax significantly delays viral rebound in humanized mice by up to 2 weeks

- ▶ In human cells, venetoclax only killed off cells containing intact HIV DNA.
- ▶ Lymphocytes were donated by 10 people with HIV.
- ▶ They were cultured in a lab dish with venetoclax (or DMSO placebo).
- ▶ The total HIV DNA significantly reduced in a dose-dependent manner by 42%.
- ▶ *Intact* HIV DNA also reduced, though not quite significantly ( $p = 0.064$ ). There was no decline in defective HIV DNA.



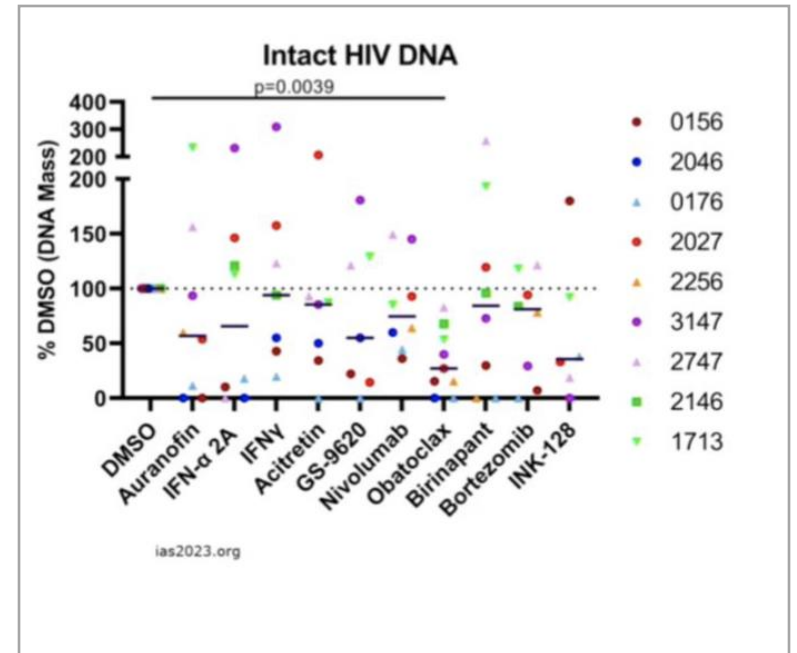
Venetoclax reduces levels of total and intact HIV DNA in CD4 T cells from people living with HIV on ART *ex vivo*

- ▶ A separate study included obatoclax (GX15-070, a BH3 mimetic), which inhibits both BCL-2 and MCL-1.
- ▶ Lymphocytes from nine donors with HIV were cultured in a lab dish with 10 drugs known to have immunological properties, including obatoclax, or DMSO placebo.

Drug tested	Dose*	Mechanism	Human use
Auranofin	20nM-5uM	inhibits redox enzymes; modulates p53	FDA-approved
Interferon alpha 2A	2ng/ml	antiviral	FDA-approved
Interferon gamma	200pg/ml	antiviral	FDA-approved
Acitretin	5uM	retinoid; induces RIG-I	FDA-approved
GS-9620 (vesatolimod)	50nM	TLR7 agonist	Phase2+
Nivolumab	0.2-7nM	PD-1 blocker	FDA-approved
Obatoclax	5-50nM (500 x1)	Bcl-2 inhibitor	Phase 3
Birinapant	20nM (100nM x1)	XIAP/cIAP1 inhibitor	Phase 2
Bortezomib	0.5-10nM	proteasome inhibitor	FDA-approved
INK-128 (sapanisertib)	25nM (125nM x1)	mTOR (TORC1/2) inhibitor	Phase 2

Drugs tested

- ▶ Obatoclox was the only drug to reduce intact HIV DNA in all donors.
- ▶ The average reduction in intact DNA: 83% at 5-50 nM (cf 42% on 100nM with venetoclax).
- ▶ There was no significant reduction in total or defective DNA.
- ▶ Caution: some cell toxicity was seen; the dose was reduced, but without affecting efficacy.
- ▶ Conclusion from the two studies: human trials in BH3 mimetics are warranted. Other BH3 mimetics (e.g., navitoclax) exist and may have additive effects.



Obatoclox (Bcl-2 inhibitor) reduced intact HIV DNA

# Community-led interventions

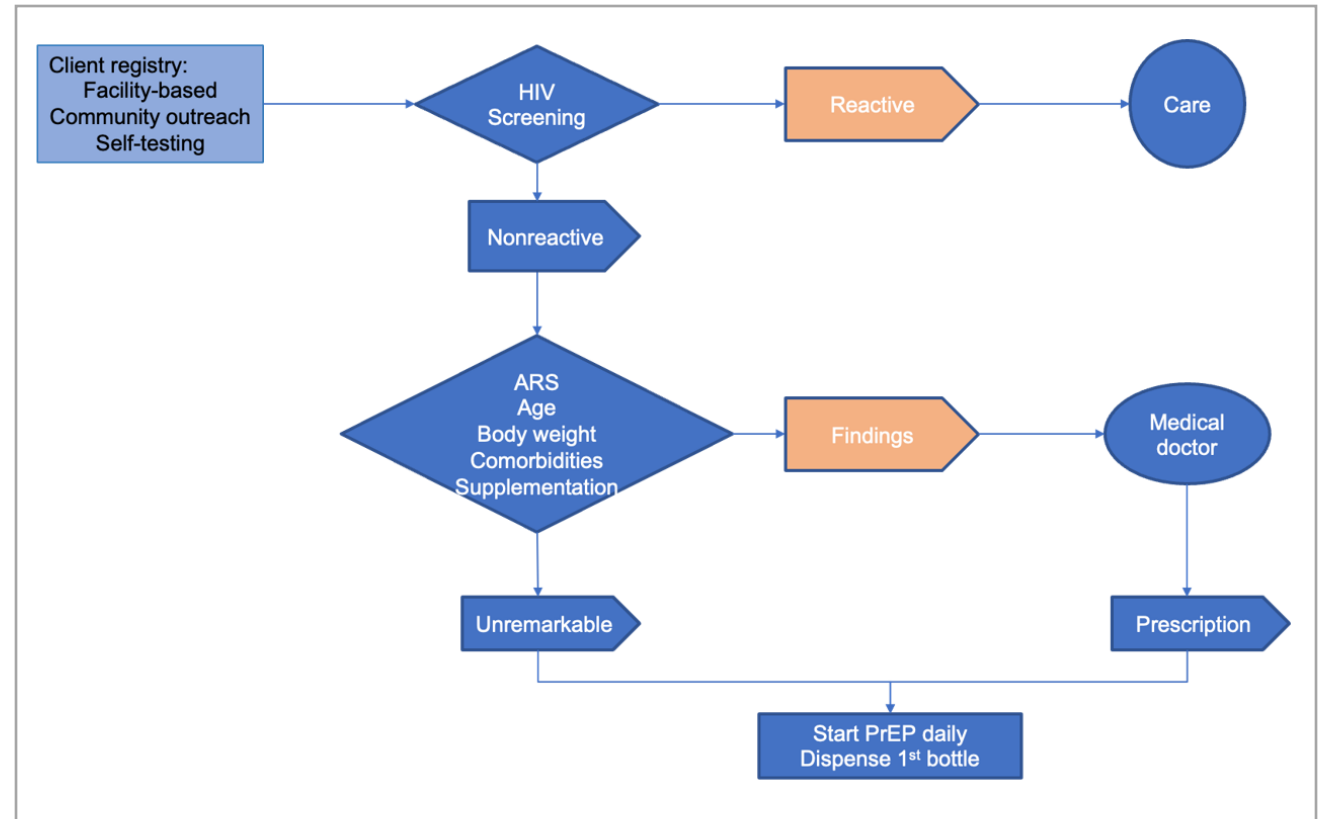
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## All-virtual, community-led PrEP

- ▶ HIV incidence is increasing in the Philippines, with 50 new diagnoses every day (up from 6 in 2011).
- ▶ Removing barriers to PrEP access is an important part of the country's HIV prevention response.
- ▶ The e-PrEPPY online service offers PrEP to clients (men who have sex with men) who participate in an HIV self-testing programme and report an HIV-negative result.
- ▶ A blood-based self-test kit is delivered, followed up with a self-assessment tool to determine sexual behaviour and any indicators that PrEP would not be suitable.
- ▶ Information is validated by trained community peers, and PrEP information and counselling is available by phone.

- ▶ Once assessed, the client is sent PrEP, another HIV self-test kit, and a QR code for refill instructions.
- ▶ Between August 2022 and April 2023, 230 clients started PrEP, 10.44% of those invited via the HIV self-testing programme.



e-PrEP service algorithm

## Key population-led same-day ART

- ▶ An implementation trial piloted same-day ART initiation following counselling and testing at two key population-led services in Bangkok.
- ▶ Aim was to reduce loss to follow-up.
- ▶ Trained key population lay providers led counselling, laboratory testing, opportunistic infection screening, and ART dispensing under physician supervision primarily via telehealth.
- ▶ Participants were followed up at 2-4 weeks, referred to a long-term ART facility, and supported for 12 months by lay providers.
- ▶ Between October 2021 and March 2023, 587 individuals registered.
- ▶ 97.9% started ART – 52% on the day of HIV diagnosis.
- ▶ At month 12, of 210 participants with viral load data available, 94.3% had undetectable viral load.

## Community-led monitoring in Asia

- ▶ Community-led monitoring (CLM) is an approach where communities:
  - Identify concerns
  - Monitor implementation and experiences of services
  - Compile and analyse data
  - Review, advocate and co-create solutions to improve health services
- ▶ It focuses on indicators that are relevant to communities to improve services.
- ▶ To build an evidence-base for CLM, a programme in Asia developed a toolkit on sustainable CLM for key populations.

► Toolkit framework:

- Eight core indicators to monitor availability, accessibility, acceptability, and quality of services
- Five indicators to measure and ensure follow-up for those experiencing stigma, discrimination, and/or violence

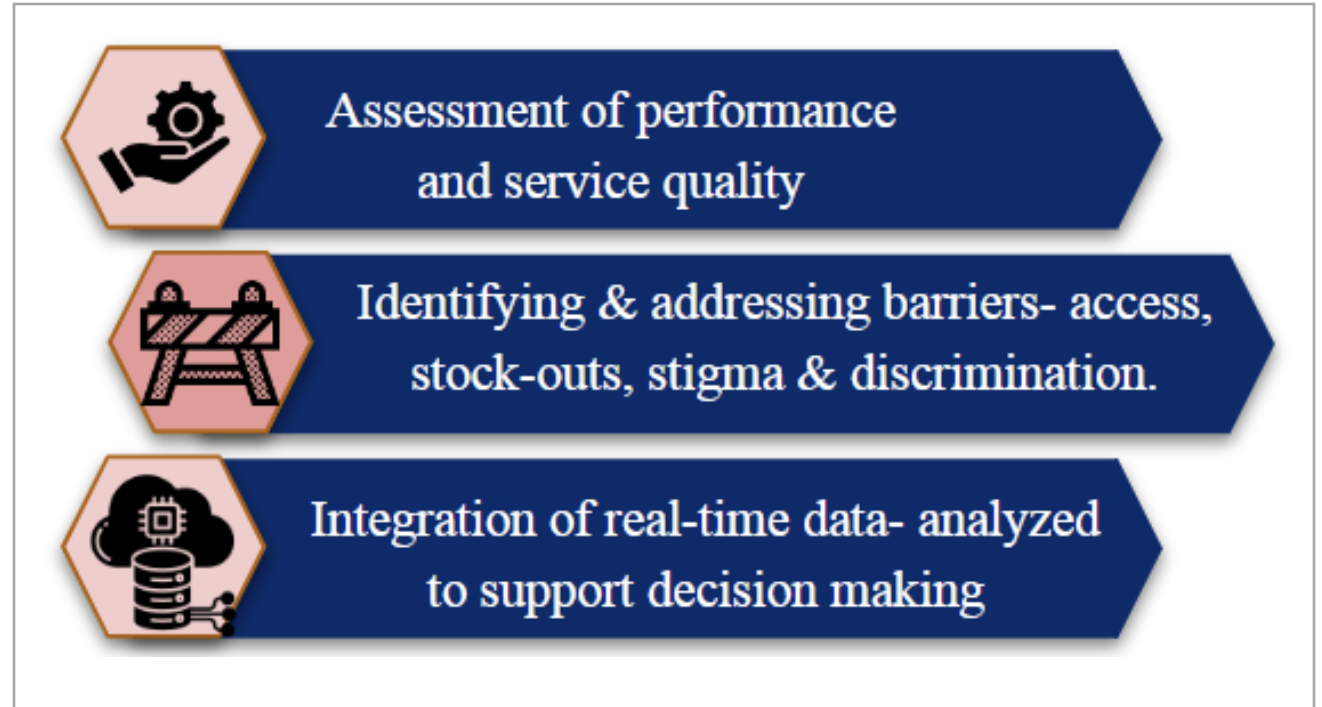


CLM indicators

- ▶ The toolkit was piloted in Mongolia, Bhutan and Sri Lanka with key population groups.
- ▶ It helped identify the type of healthcare settings where stigma and discrimination were more prevalent, supporting targeted efforts to reduce these.
- ▶ Engaging government staff and healthcare providers helped to improve sustainability and reach.
- ▶ The process identified the type of services with the least availability of CD4 count and viral load testing.
- ▶ The authors advise paying particular attention to how data are presented, so data are accessible to community groups.

## Community-led monitoring in India

- ▶ CLM was piloted in the three, high HIV burden states of Maharashtra, Delhi and Telangana from May 2020 to September 2022.
- ▶ Two rounds of CLM were completed, with 240 community champions trained, 445 action points identified based on community feedback and 208 action points resolved.



Aspects of CLM

## Community-led monitoring in South Africa

- ▶ The Ritshidze CLM programme monitored PrEP access among key populations in seven provinces of South Africa.
- ▶ Recruitment was between July and September 2022 using community-based snowball sampling.
- ▶ 5,060 (55% of those surveyed) indicated they accessed public health facilities.
- ▶ Knowledge of PrEP, ever having been offered PrEP, and PrEP satisfaction were highest among trans people and sex workers, followed by gay, bisexual and other men who have sex with men.
- ▶ People who use drugs gave the lowest scores in all categories.
- ▶ Less than a third of HIV-negative key population respondents had ever been offered PrEP.

## Community-led monitoring of community engagement in DSD

- ▶ A differentiated service delivery (DSD) approach should ensure that HIV services are tailored for recipients of care.
- ▶ Advocates developed a tracking tool defining community engagement in shaping DSD policy and programming.
- ▶ The tool was used in seven countries in Africa to collect data in 2022.
- ▶ 55% of community groups were engaged in DSD policy and programming at policy level, 51% at programme level and 59% at community level.
- ▶ Community engagement varied by area: 65% at design, 51% at implementation and 45% at monitoring and evaluation.

# HIV care, integration and service delivery

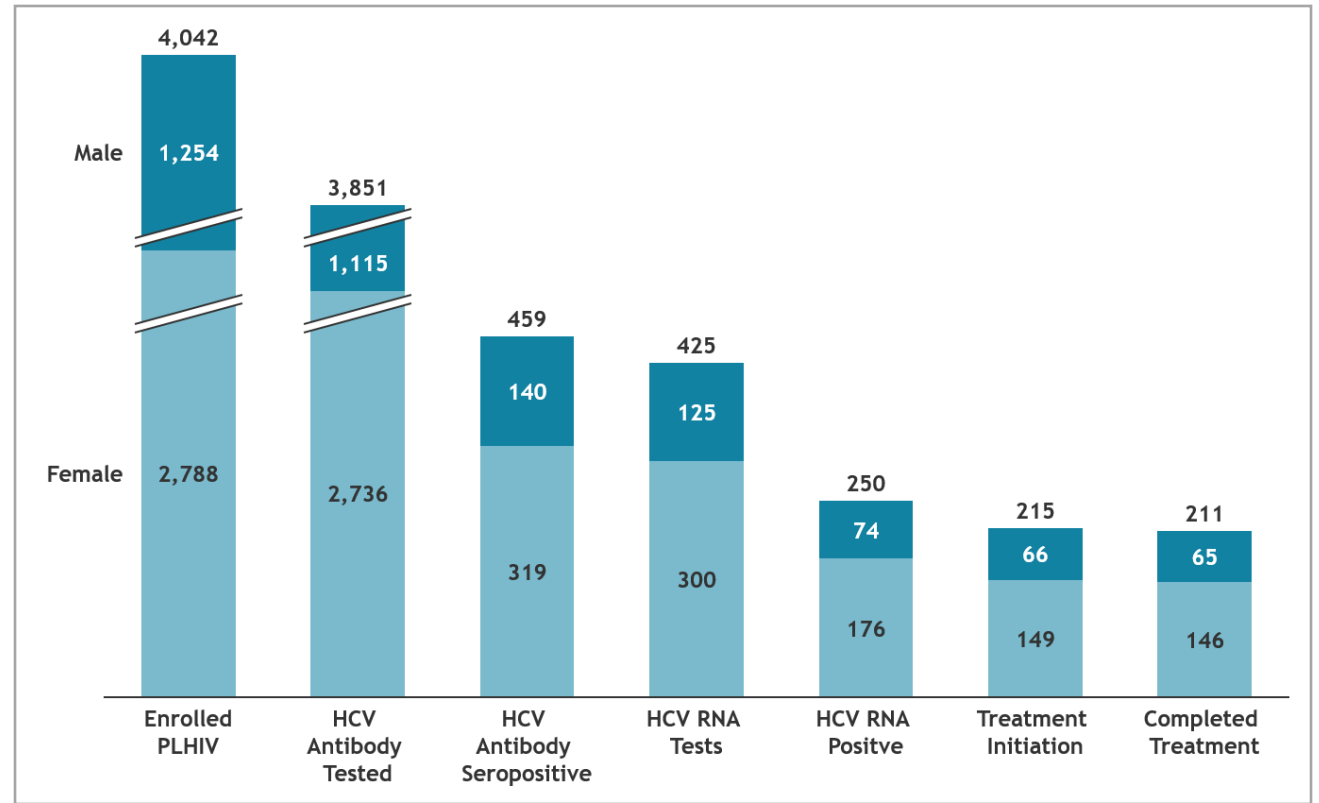
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## Hepatitis C services in ART clinics

- ▶ Nasarawa state has the highest HCV prevalence in Nigeria and is focusing on HCV elimination in people living with HIV.
- ▶ Limited access to HCV services for people living with HIV was identified as a critical gap, e.g., no routine HCV screening.
- ▶ A pilot programme in four ART clinics, from July 2020 to December 2022, trained healthcare workers, provided HCV screening, and linked people to HCV care.
- ▶ New clients received HCV screening as part of their initial appointments and existing clients were contacted for screening.
- ▶ People testing positive for HCV were linked to viral load testing and treatment.

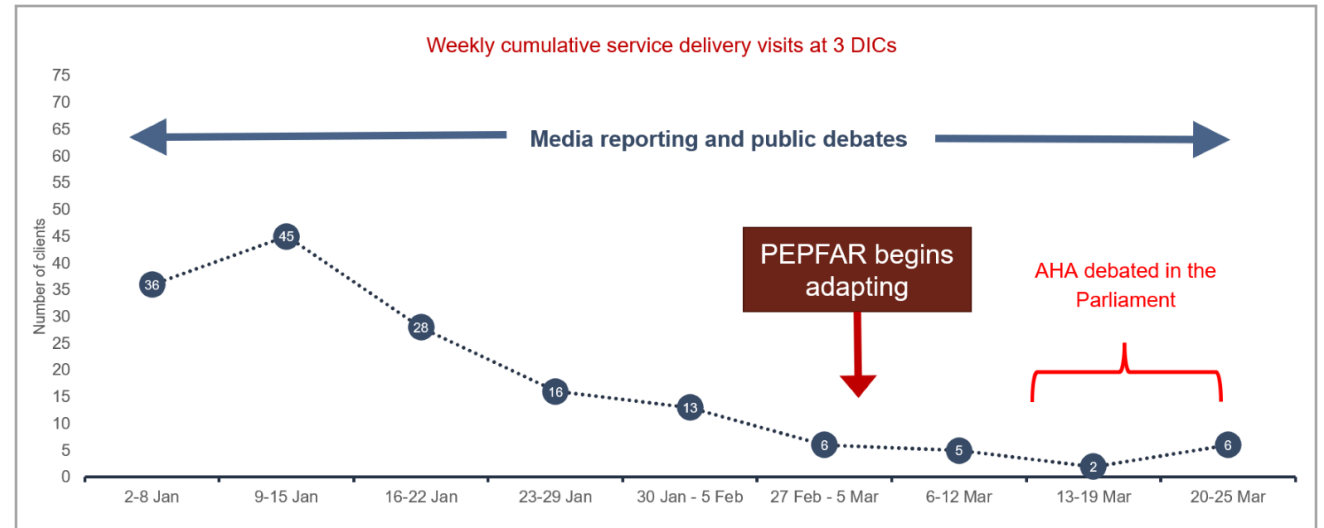
- ▶ An average of 70% of people living with HIV were linked to care across the HCV treatment cascade.
- ▶ The authors conclude that service integration was a successful strategy to expand HCV screening and treatment for people living with HIV.



Results of the integration pilot

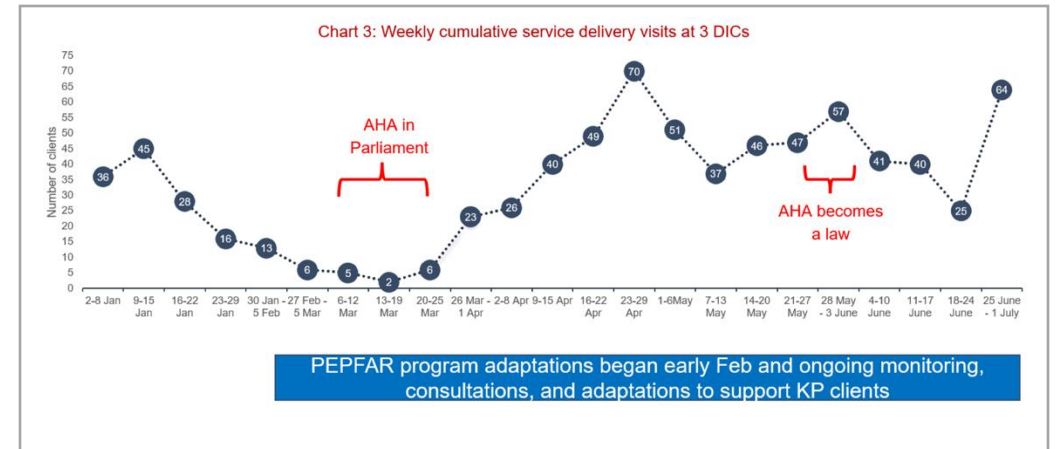
## Key population services in Uganda

- ▶ The hostile environment created by the Anti-Homosexuality Act in Uganda has led to reduced access to services for key populations.
- ▶ PEPFAR supports over 80 drop-in centres providing HIV services for key population clients.
- ▶ In an analysis of three drop-in centres, weekly data show a steady decrease in client visits.



Impact of Anti-Homosexuality Act on PEPFAR HIV drop-in centres

- ▶ The centres adapted their services: home delivery of ART, condoms and PrEP; extra safety measures at centres; more multi-month dispensing; and paralegal peers offering legal support for clients.
- ▶ These supportive measures led to an increase in key population clients accessing HIV services at these three centres by April 2023.
- ▶ 20 other drop-in centres have not seen a rebound in client attendance despite adaptations.

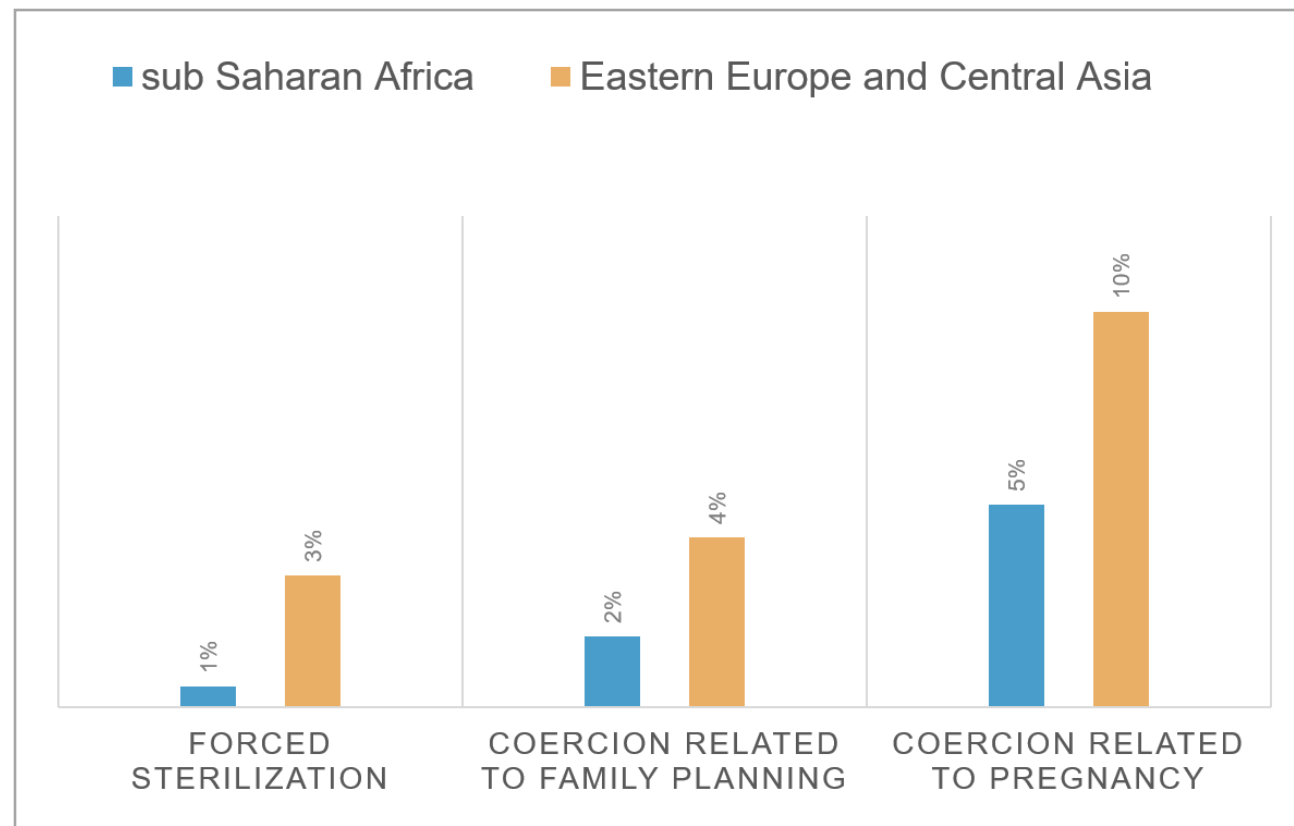


Impact of Anti-Homosexuality Act and adaptations

## Reproductive coercion

- ▶ Information was collected from interviewer-administered questionnaires on reproductive coercion among 12,794 cisgender women living with HIV.
- ▶ Data was collected as part of the People Living with HIV Stigma Index 2.0. This is a socio-behavioural survey led by networks of people living with HIV.
- ▶ Data came from 16 countries in eastern Europe, central Asia and central, eastern, western and southern Africa between 2020 and 2022.
- ▶ Reproductive coercion was categorized as coercive experiences in the last 12 months relating to: sterilization; contraception and family planning; and pregnancy and feeding practices.

- ▶ Forced sterilization (3% vs. 1%), coercion related to family planning (4% vs. 2%) and coercion related to pregnancy (10% vs. 5%) were more prevalent among respondents from eastern Europe and central Asia compared to those from central, eastern, western and southern Africa.



Experiences of reproductive coercion in past 12 months

- ▶ In central, eastern, western and southern Africa, women with a history of drug use and migrant women disproportionately experienced coerced family planning, pregnancy and sterilization from healthcare professionals.
- ▶ Migrants were 7 times more likely to experience coerced sterilization and women with a history of drug use 3 times more likely.
- ▶ In eastern Europe and central Asia, sex workers and women with a history of drug use were at increased risk of coercion related to contraception by healthcare professionals (1.5 and 1.77 times).
- ▶ Young women were at increased risk for coercion related to pregnancy (1.75 times).

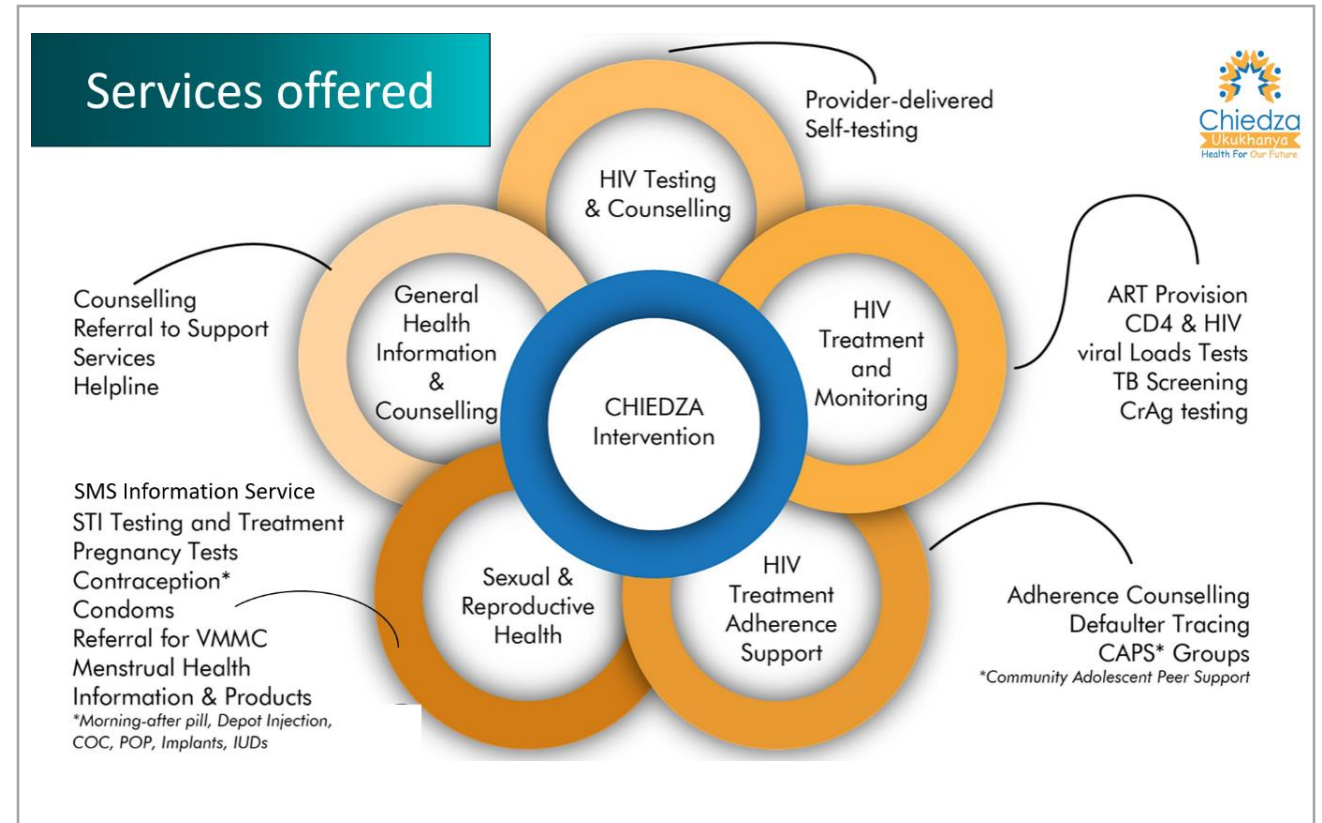
## Pharmacy-based PrEP refills

- ▶ In many settings, PrEP is delivered from HIV clinics, which can create barriers to access due to long waiting times.
- ▶ Researchers in Kenya worked with four HIV clinics with established PrEP services: two intervention clinics and two controls (standard of care).
- ▶ In the intervention clinic, a clinic navigator helped people move quickly to HIV self-testing and the pharmacy for their PrEP refill, usually without needing to see a testing counsellor or clinician.
- ▶ 746 clients were enrolled: 338 in standard of care and 380 in intervention clinics.
- ▶ 57% were female, median age was 33, and 58% were in serodifferent partnerships.

- ▶ 80 clients participated in a time and motion study to determine client time in the clinics.
- ▶ Visit time was 35% shorter in intervention clinics than standard-of-care clinics:
  - Median 33 minutes vs 51 minutes
- ▶ PrEP continuation was significantly higher in the intervention clinics than control clinics:
  - Month 1: 45% vs 33%
  - Month 3: 35% vs 25%

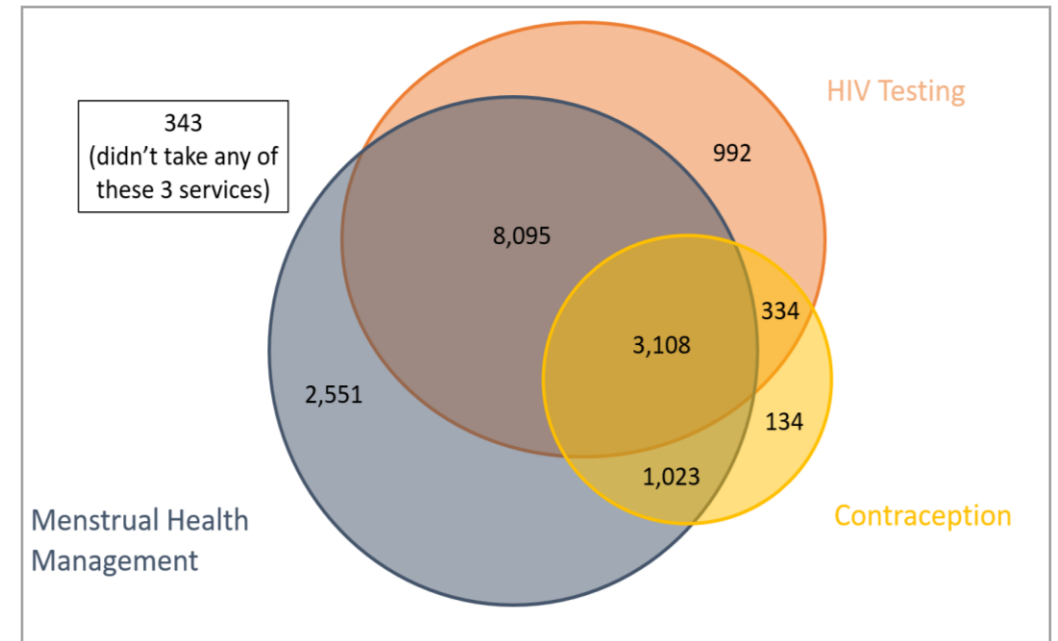
## Integrated HIV and SRH services

- ▶ Young people have lower rates of HIV testing, treatment and viral suppression than adults.
- ▶ In Zimbabwe, the Chiedza trial involved young people in the design and delivery of community-based integrated HIV and sexual and reproductive health (SRH) services.



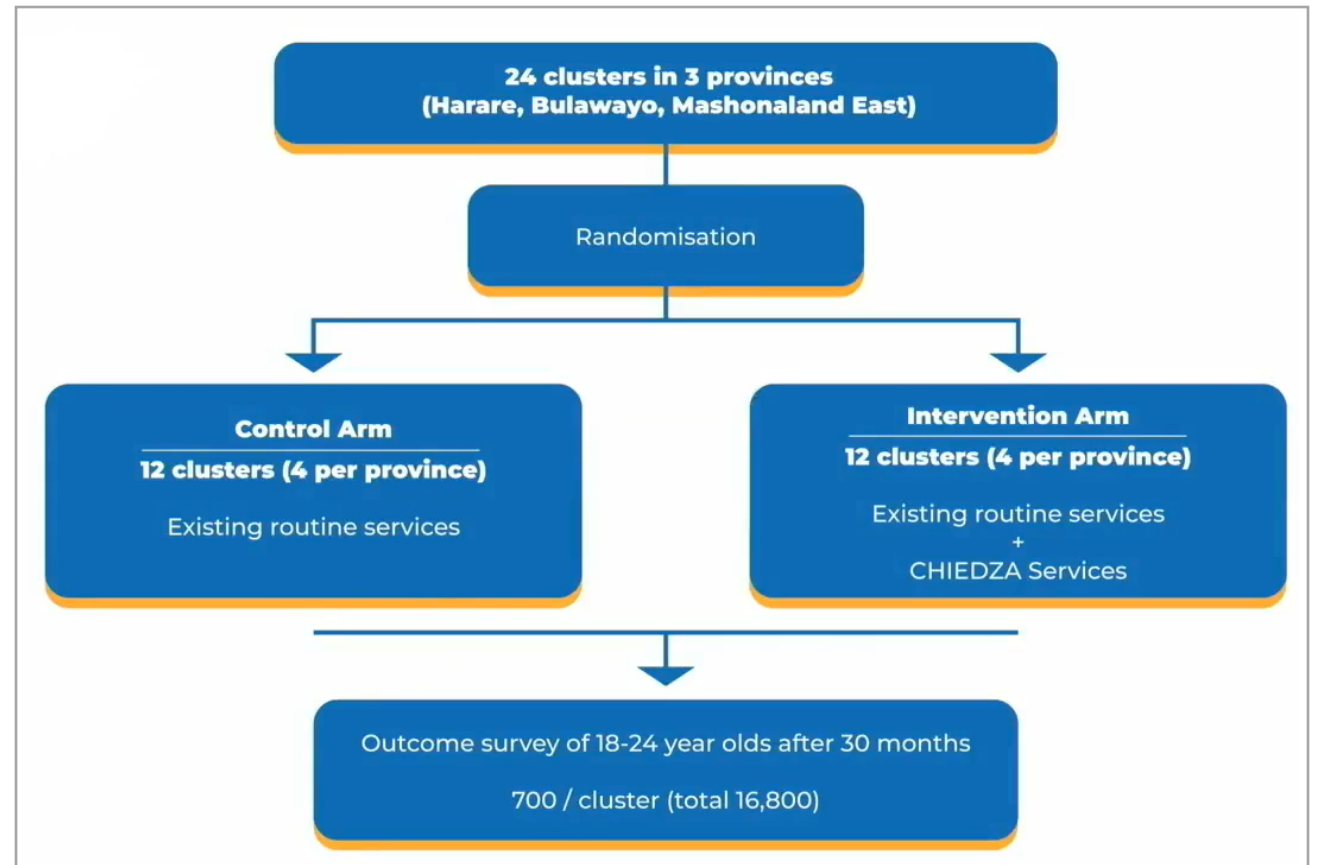
Services offered through the Chiedza trial

- ▶ 36,991 young people attended health services (78,810 visits in total).
- ▶ The most popular services for young women were menstrual hygiene products (taken up by 96.5%), HIV testing (83.7%) and period pain management (59.9%).
- ▶ For young men, the most popular were condoms (93.9%), HIV testing (85.6%) and text messages on SRH (67.1%).
- ▶ Of those newly diagnosed with HIV, 90% achieved undetectable viral load.



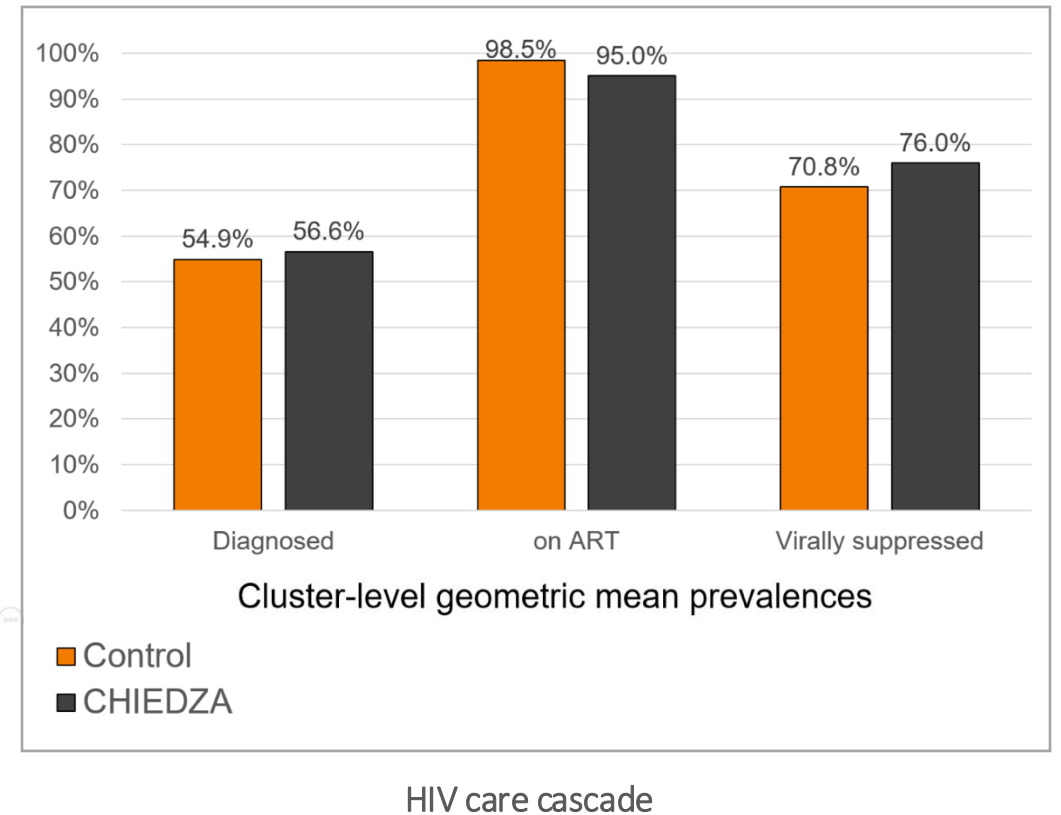
Overlap of services (women)

- ▶ The primary outcome for the Chiedza cluster randomized control trial were improvements in the UNAIDS 95-95-95 targets among young people, 18-24 years of age.
- ▶ A population-level outcome survey was designed to target 700 young people in each of the geographical clusters.



Overview of study design

- ▶ Overall, there was no difference in the primary outcomes between the control and intervention clusters.
- ▶ The proportion of people who knew their HIV status was especially low.
- ▶ Nonetheless, youth-friendly services were very popular among participants.
- ▶ At the session, speakers explored whether a trial is the most effective way to test whether interventions work and whether success should be defined by communities, instead of researchers.



- ▶ In a Chiedza sub-study, 1 in 5 young people had a sexually transmitted infection.
- ▶ The risk of gonorrhoea was 43% lower in the intervention arm compared to the standard of care arm (1.7% prevalence in the intervention vs. 2.9% in the control).

Outcome type	Outcome	Cluster-level geometric mean prevalence		Risk ratio (95% CI)	Test
		STICH (N=8)	Control (N=8)		
Primary	CT/NG/TV	19.1%	20.0%	0.92 (0.78-1.09)	0.34
Secondary	CT	12.9%	12.9%	0.96 (0.84-1.11)	0.57
Secondary	NG	1.7%	2.9%	0.57 (0.34-0.96)	0.036
Secondary	TV	7.1%	6.2%	1.08 (0.73-1.60)	0.67

Sexually transmitted infections (STIs)

# Cost, financing and sustainability

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## Long-acting PrEP for young women

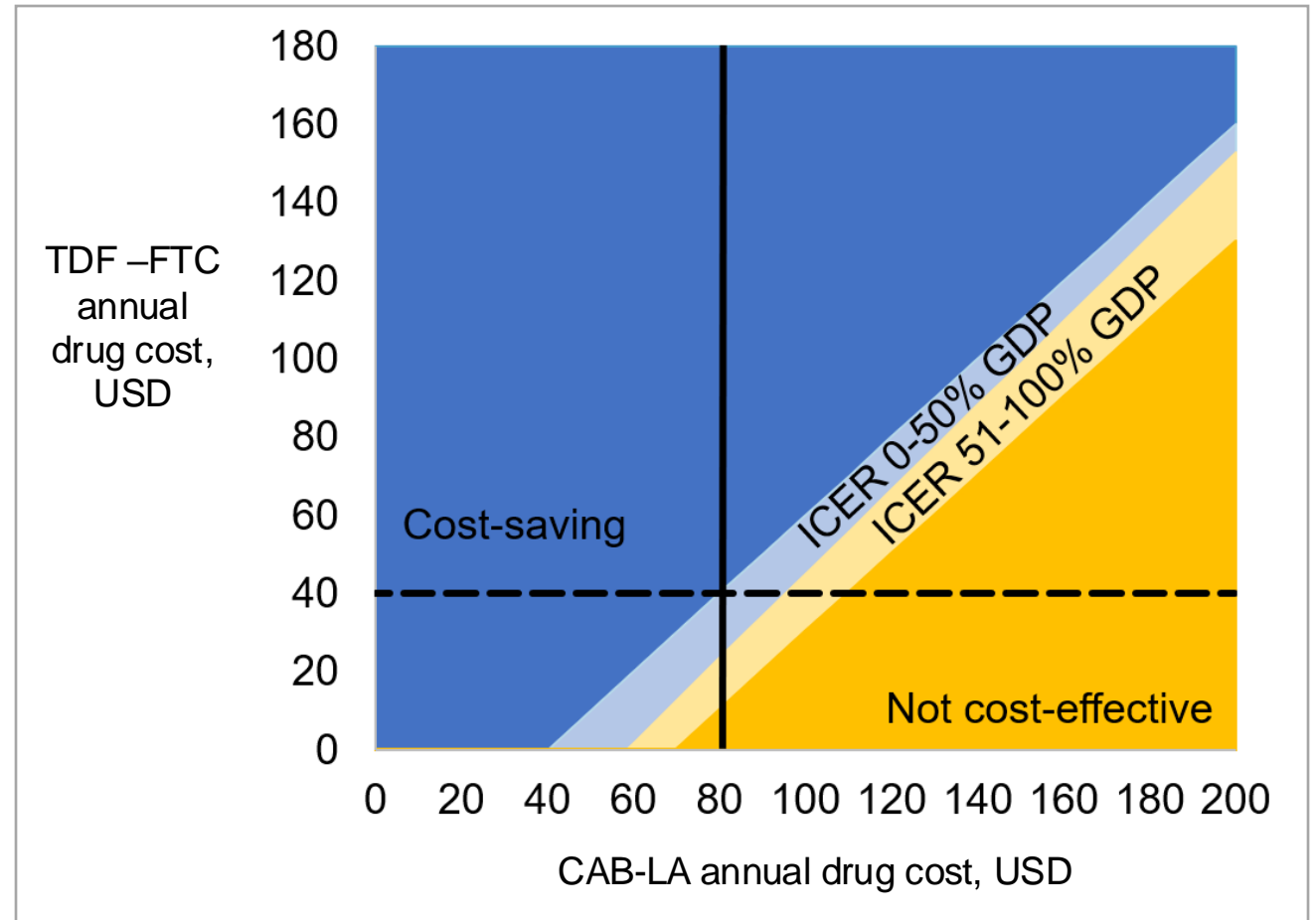
- ▶ HIV incidence among adolescent girls and young women in South Africa is high (3-7 per 100 person-years).
- ▶ Long-acting injectable cabotegravir (CAB-LA) is more effective than daily oral tenofovir/emtricitabine (TDF-FTC) as PrEP in cisgender women.
- ▶ However, implementing CAB-LA as PrEP is expected to be expensive.
- ▶ An analysis aimed to identify the price at which CAB-LA remained cost-effective in South Africa.
- ▶ Using microsimulation modelling, two PrEP strategies were examined over 10 years for 10,000 young women (15-30): daily oral TDF-FTC and injectable CAB-LA.

- ▶ Annual costs factored into the model included:
  - The cost of the PrEP drug and the programme to provide it (TDF-FTC: USD 6.6 million, CAB-LA: USD 7.1 million)
  - The cost of ART and HIV-related care
- ▶ Assumed cost-effectiveness threshold of USD 3500 a year per life-year saved; 50% of South Africa’s per capita GDP.

<b>Adolescent girls and young women ONLY (n = 10,000)</b>						
<b>Strategy</b>	<b>Incident infections</b>	<b>Life-years</b>	<b>Incremental life years</b>	<b>Costs, millions USD</b>	<b>ICER (\$/LY)</b>	<b>CAB-LA max price premium (absolute price)</b>
<i>TDF-FTC</i>	1,980	85,800		6.6	-	-
<i>CAB-LA</i>	1,080	85,950	+150	7.1	3,440	+\$40 (\$80)

10-year projected outcomes

- ▶ Over ten years, 1,980 women would acquire HIV in the TDF/FTC scenario, but only 1,080 with CAB-LA.
- ▶ If costs associated with HIV acquired by male partners were included, CAB-LA became cost-saving at just under USD 80 a year.
- ▶ The authors conclude that CAB-LA should be priced at less than twice the cost of TDF-FTC to be cost-effective.

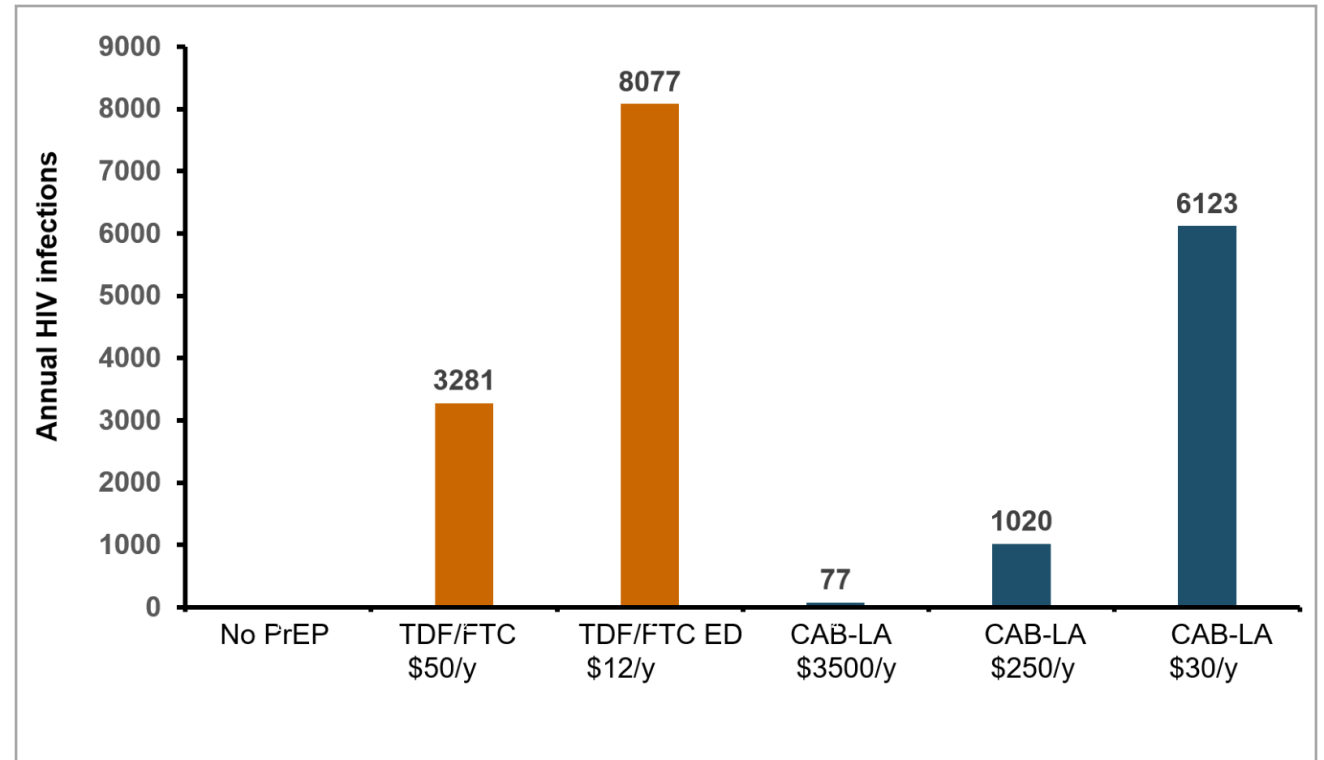


Sensitivity analysis: drug prices

## Long-acting PrEP in Brazil

- ▶ TDF/FTC is available as generic PrEP in most countries, costing USD 48/year for daily use.
- ▶ CAB-LA costs USD 22,200/year in US, USD 9,000 in the UK.
- ▶ A voluntary licensing scheme will permit generic producers to sell CAB-LA at low prices in some countries, estimated at USD 250/year.
- ▶ Brazil has a fast-growing HIV epidemic but is not included in the licensing scheme.
- ▶ The HIV prevention budget in Brazil is USD 6 million per year.
- ▶ A model looked at how many people in Brazil could access PrEP under different cost scenarios.

- ▶ Including all annual costs, Brazil can afford to provide event-driven TDF/FTC to 230,769 people (preventing 8,077 new HIV acquisitions).
- ▶ However, it could only provide CAB-LA to 1,707 people at the price of USD 3,500 (preventing 77 new HIV acquisitions).
- ▶ CAB-LA would only lower overall HIV rates if it cost less than USD 30/year.



HIV acquisitions prevented in different scenarios

## Differentiated service delivery models in Mozambique

- ▶ In 2018, Mozambique’s Ministry of Health launched a guideline to implement 8 differentiated service delivery (DSD) models to optimize HIV service delivery, improve retention in care, and reduce cost to the health system.
- ▶ A cost-effectiveness analysis and a budget impact analysis compared these DSD models to conventional services.

	Cost-effectiveness		Budget impact
<b>Analysis</b>	Primary	Secondary	Primary
<b>Time horizon</b>	2019-2021	2019-2021	2022-2024
<b>Perspective</b>	MISAU	Societal	MISAU
<b>Costs</b>	Economic 1. Start-up and training 2. Antiretrovirals 3. Laboratory tests 4. Service provision interactions	Economic 1. Start-up and training 2. Antiretrovirals 3. Laboratory tests 4. Service provision interactions 5. Opportunity cost	Financial 1. Antiretrovirals 3. Laboratory tests 4. Service provision interactions
<b>Effectiveness</b>	12-month retention in treatment measured through an Interrupted time series analysis		

Study design

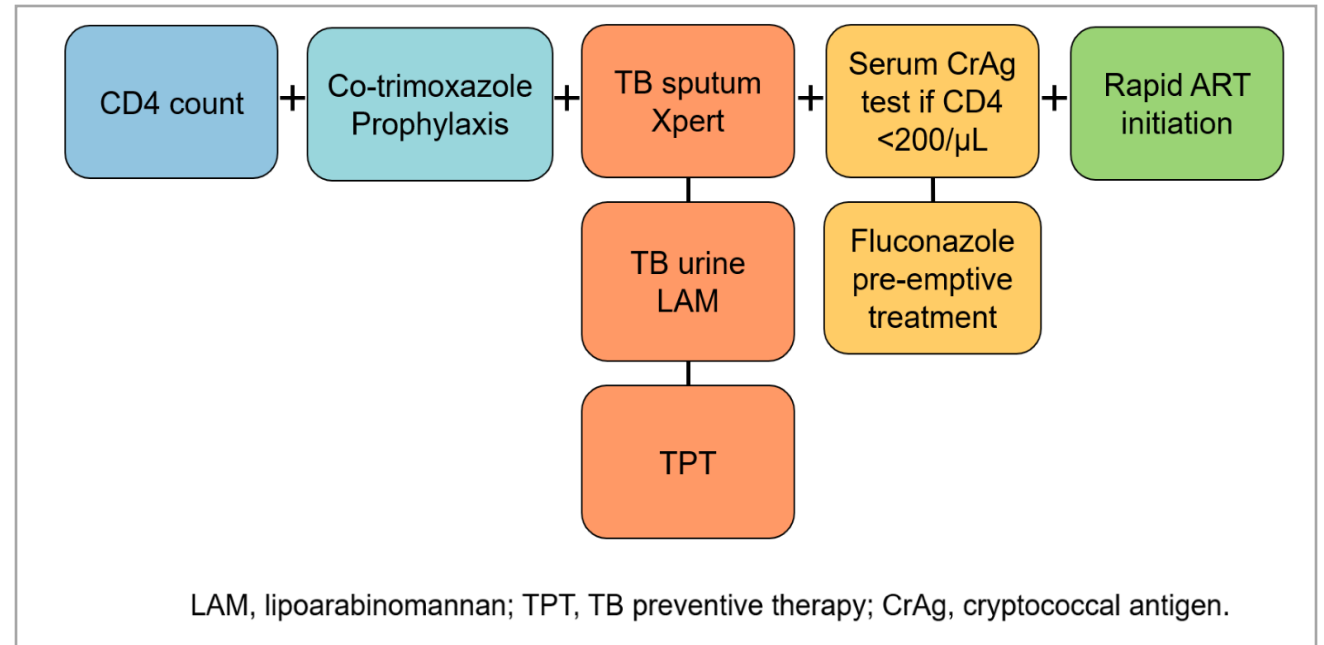
- ▶ The fast-track model with 3-month dispensing was the least expensive model. One-stop shop and conventional care models were the most expensive.
- ▶ DSD models were also more effective in retaining clients 12 months after ART initiation.
- ▶ DSD models were estimated to have saved the health system USD 14 million from 2022 to 2024.

Model of care	Cost per US\$ per perspective	
	Health System	Societal
Conventional care	174	<b>251</b>
One-stop shop maternal and child health	<b>187</b>	245
One-stop shop tuberculosis	<b>187</b>	245
Family approach	179	218
Community adherence group	144	165
Fast-track	134	162
Adherence club	129	153
Fast-track plus three months dispensing of ARVs	<b>120</b>	<b>138</b>

Cost per client per year

## Advanced HIV care package in Malawi

- ▶ WHO recommends a package of care to reduce mortality from advanced HIV disease.
- ▶ A modelling study assessed the clinical outcomes, costs, and cost-effectiveness of the package of care in Malawi.
- ▶ Additionally, it examined elements of the package singly or in combination.



WHO-endorsed AHD package of care

- ▶ The model simulated a cohort of adults with HIV starting ART in an outpatient setting.
- ▶ Mean age was 37, 51% were female, mean CD4 was 362 (19% had CD4 under 200).
- ▶ All strategies modelled would improve clinical outcomes and increase costs.
- ▶ The full package of care would result in the greatest life expectancy and be cost-effective.

Strategy	Undisc. QALYs	Discounted QALYs*	Lifetime costs (\$)*	ICER (\$/QALY)
<i>ART only</i>	12.81	9.00	1,010	-
<i>+Xpert</i>	17.79	11.69	1,330	120
<i>+Xpert+LAM</i>	18.04	11.83	1,350	150
<i>+Xpert+LAM+TPT</i>	18.15	11.89	1,370	170
<i>+Xpert+LAM+TPT+CrAg</i>	18.15	11.89	1,370	300
<i>Full AHD Care Package</i>	18.42	12.05	1,420	360

Results

## Demand-side financing in HIV self-testing

- ▶ From November 2021 to October 2022, a demand-side financing (DSF) pilot for HIV self-testing was implemented in Nigeria.
- ▶ It aimed to scale up and sustain HIV self-testing through private sector pharmacies.
- ▶ DSF involves generating demand from customers by lowering the cost of kits (lessening the risk for private sector providers by ensuring demand).
- ▶ Pharmacists in 166 private retail pharmacies were trained and given reporting tools and promotional materials.
- ▶ A “buy 1, get 3 free” model was used to stimulate demand and gradually costs were transferred to customers in two phases.
- ▶ Customers redeemed vouchers to receive kits.

- ▶ Voucher redemption dropped initially from 91% in the free phase to 60% in the first cost transfer phase, before increasing to 72% in the second cost transfer phase.
- ▶ 2,920 HIV self-testing kits (USD 10,000 value) were purchased by 166 pharmacies within 3 months of the first and second cost transfers.
- ▶ The DSF initiative was effective in sustaining a market for fee-based HIV self-testing in Nigeria.
- ▶ Since the pilot, additional investments of USD 32,000 have been made by pharmacies in scale-up states, via pooled procurement.

# Thank you

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