Highlights of 12th IAS Conference on HIV Science

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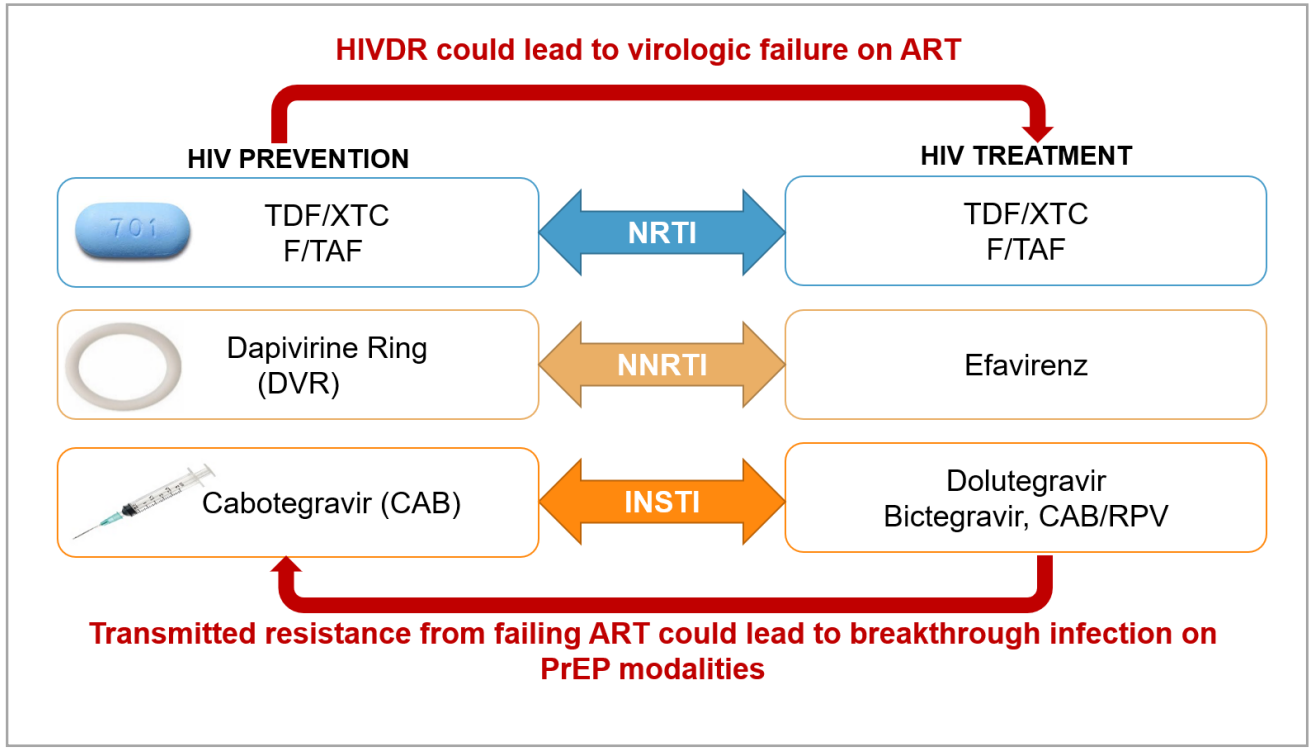
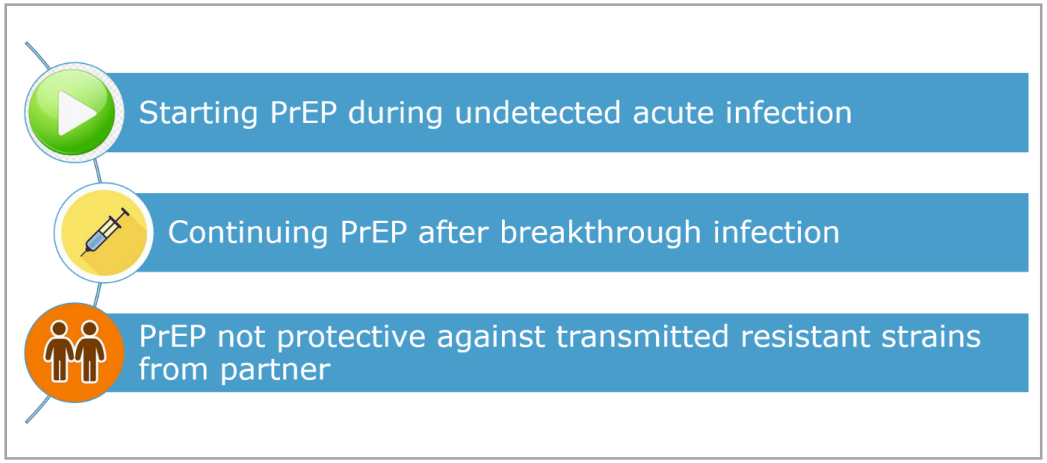
HIV testing and long-acting PrEP

- Evidence from oral PrEP shows the risk of drug resistance can occur when PrEP is started during undiagnosed acute infection.
- Using the same drug classes means drug resistance from prevention could lead to treatment failure; and transmitted resistance from treatment could lead to prevention failure.



Same drug classes for treatment and prevention

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



Resistance risk on PrEP

- In HPTN 083, 14 participants acquired HIV when their last CAB-LA injection was more than six months ago. In this group: no integrase inhibitor resistance; one case of delayed HIV seroconversion.
- 18 participants acquired HIV within six months of their last injection. In this group: 10 cases of integrase inhibitor resistance; 14 cases of delayed HIV seroconversion.

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

Updated HPTN 083 analysis of participants who acquired HIV

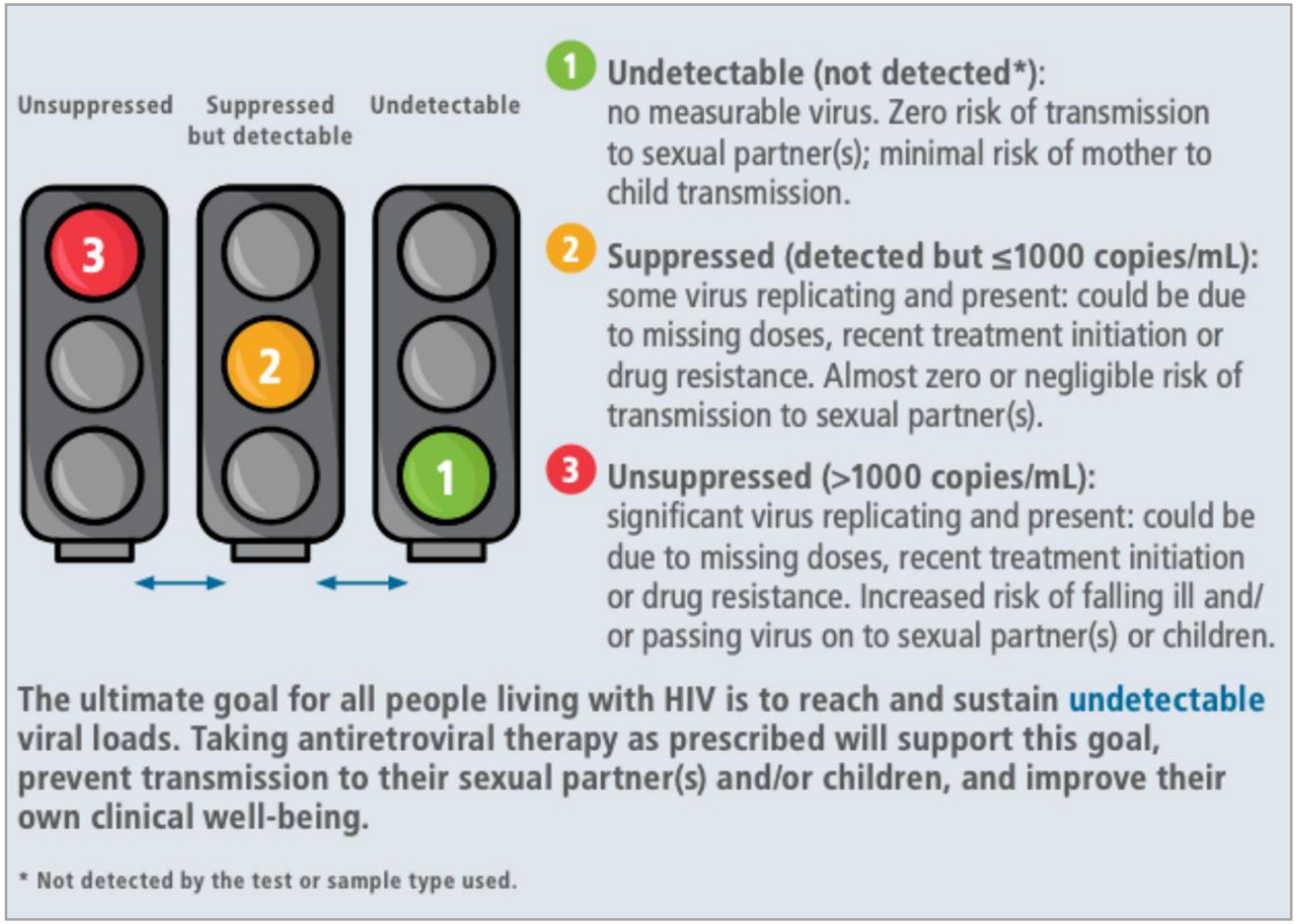
- In the era of CAB-LA, need to consider delayed immune response due to low levels of nucleic acid. This may lengthen the window period.
- In HPTN 083, most cases could have been detected earlier with HIV RNA testing.
- In some cases, HIV RNA levels were too low to have been detected.

SPECIFICATIONS	3rd Gen	4th Gen	5th Gen
Detects	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
Sensitivity	>99.5	99.5	99.5
Specificity	>99.5	>99.8	100%
Window period	2-3 weeks	2 weeks	2 weeks
Result produced	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

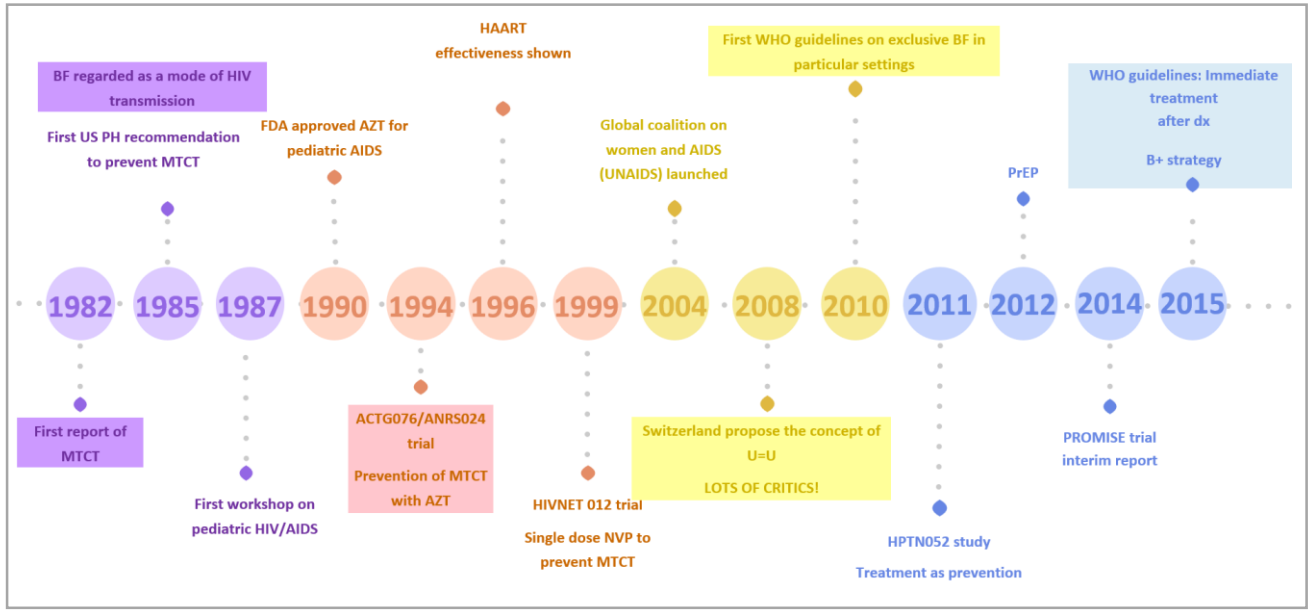
- WHO launched a policy brief on the role of HIV viral suppression in improving individual health and reducing transmission.
- The brief distinguishes between three categories of viral load:
  - undetectable;
  - suppressed; and
  - unsuppressed.



- The third, 'suppressed' category is important because some tests can detect HIV at viral loads below 1000, but cannot come up with a specific figure.
- Viral load testing is important for clinical management of HIV, but guidance is needed for this category.
- A viral load in the high hundreds is often transient: either falling (new to treatment) or rising (through adherence problems or treatment failure).
- WHO recommends enhanced adherence counselling, and a repeat viral load test at three months. If the result is still suppressed but detectable, then the regimen should be changed.

U=U in pregnancy and breastfeeding

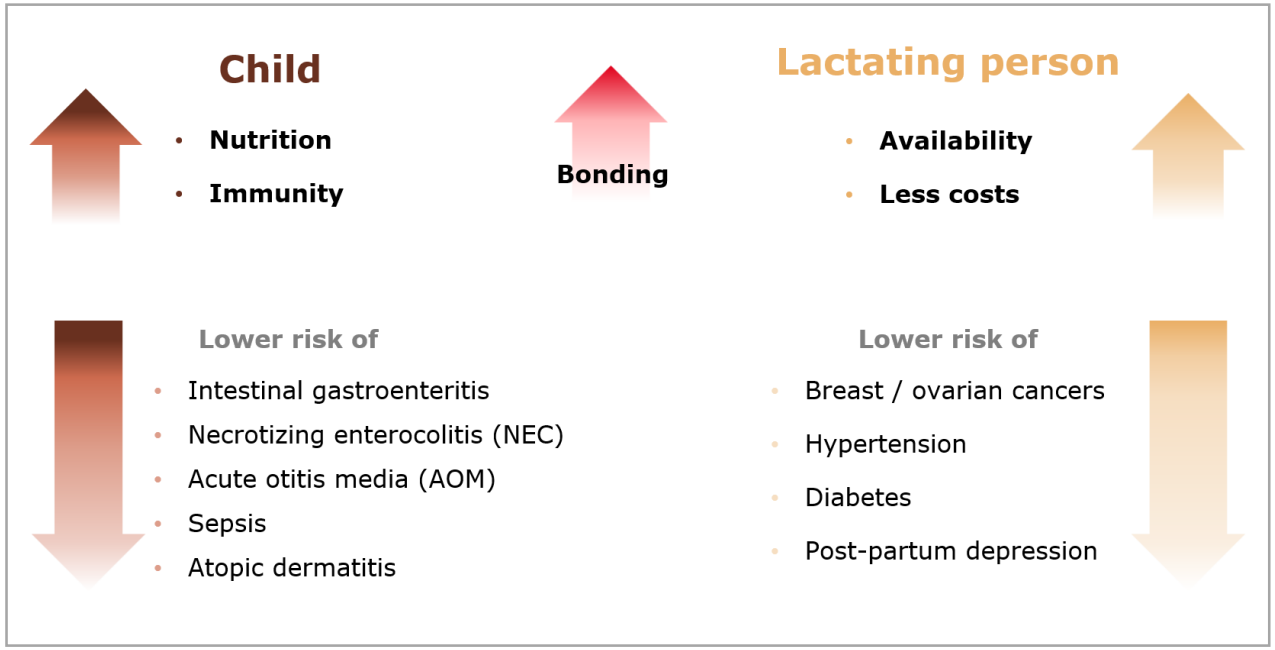
- Early in the epidemic, breastfeeding was understood to be a mode of HIV transmission.
- In 2008, the concept of U=U was proposed for sexual transmission, but there are evidence gaps on breastfeeding.
- In 2023, US guidelines began to include breastfeeding options for people living with HIV on ART.



Timeline

- If a mother starts ART before conception and maintains undetectable viral load, risk of transmission during pregnancy and delivery is zero.
- However, all infants in this scenario would receive neonatal post-exposure prophylaxis (neoPEP).
- There is increasing evidence regarding shorter or no neoPEP.
- In 2019, Swiss recommendations changed – they do not recommend neoPEP for infants of people with maintained undetectable viral load.
- Although breastfeeding has not been recommended for women living with HIV, there is plenty of evidence that people choose to do it.
- There have been some studies looking at breastfeeding, but they are very varied.

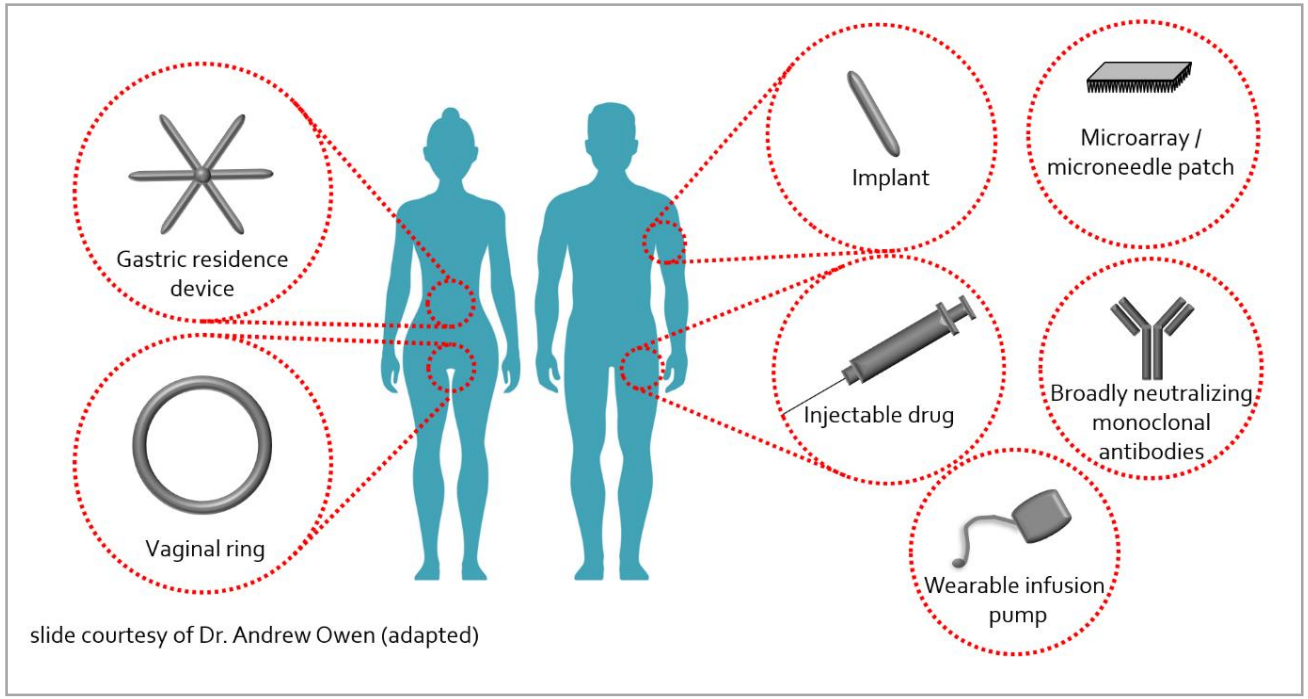
- The Swiss HIV Cohort published a study this year, in which infants were not given neoPEP and there were no transmissions.
- Guidelines in high-income countries are changing – some recommend breastfeeding; others do not recommend it but support those who choose it.
- There continues to be gaps in the evidence and individual factors for clinicians to discuss with people in their care.



Benefits of breast/chest feeding

Overview of long-acting ART

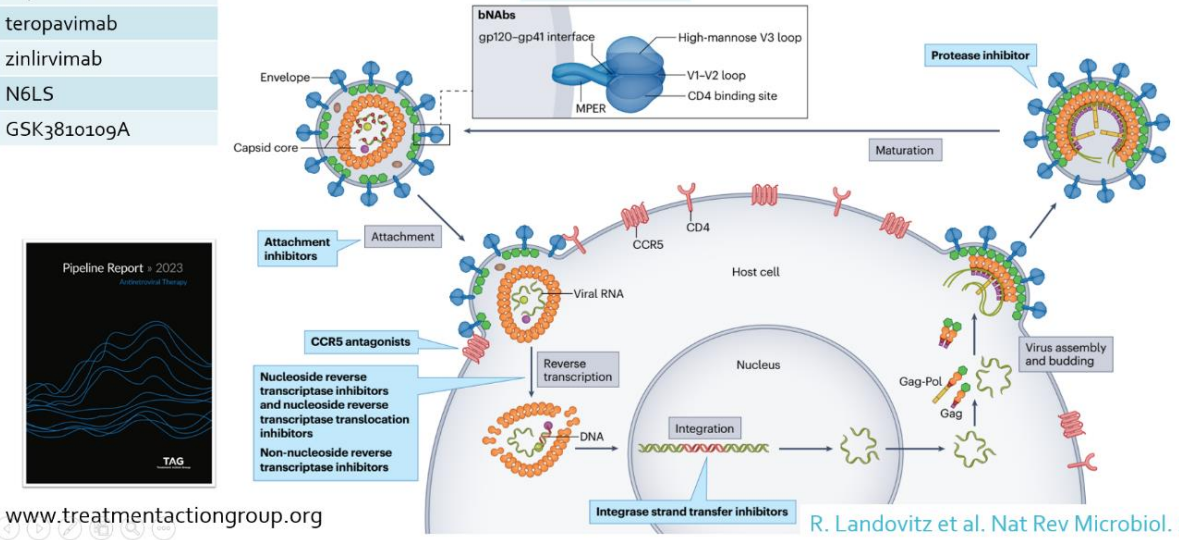
- Claudia Cortes set out the opportunities and challenges associated with long-acting antiretroviral therapy (ART).
- "Long-acting" means oral medications that are dosed once a week or less; injectable treatments dosed once a month or less; or implants, dosed twice a year or less.



Drug delivery systems and long-acting technologies

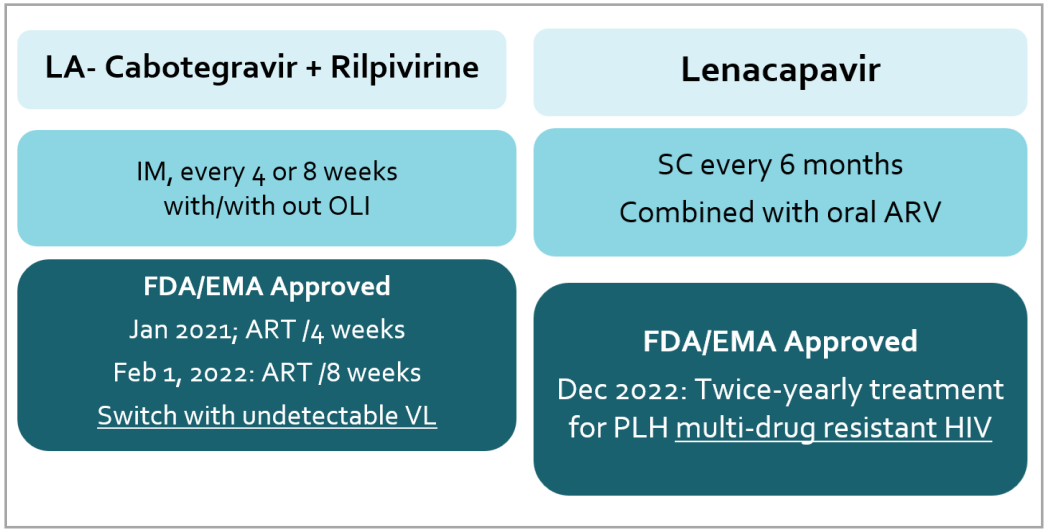
- There are long-acting antiretrovirals in development that target different parts of the HIV lifecycle.

bNAb	Entry inhibitor	NRTI NRTTI	NNRTI	INI	PI	Capsid inhibitor	Maturation inhibitor
Leronlimab (PRO-140)	Alburtide	TAF implant	Elsufaviride	S-365598	-	**Lenacapavir**	GSK937
Semzuvolimab	Cenicriviroc	Islatravir	Depulfaviride	**Cabotegravir**			
VRC 01-07/LS			**Rilpivirine**				
Elipovimab							
teropavimab							
zinlirvimab							
N6LS							
GSK3810109A							



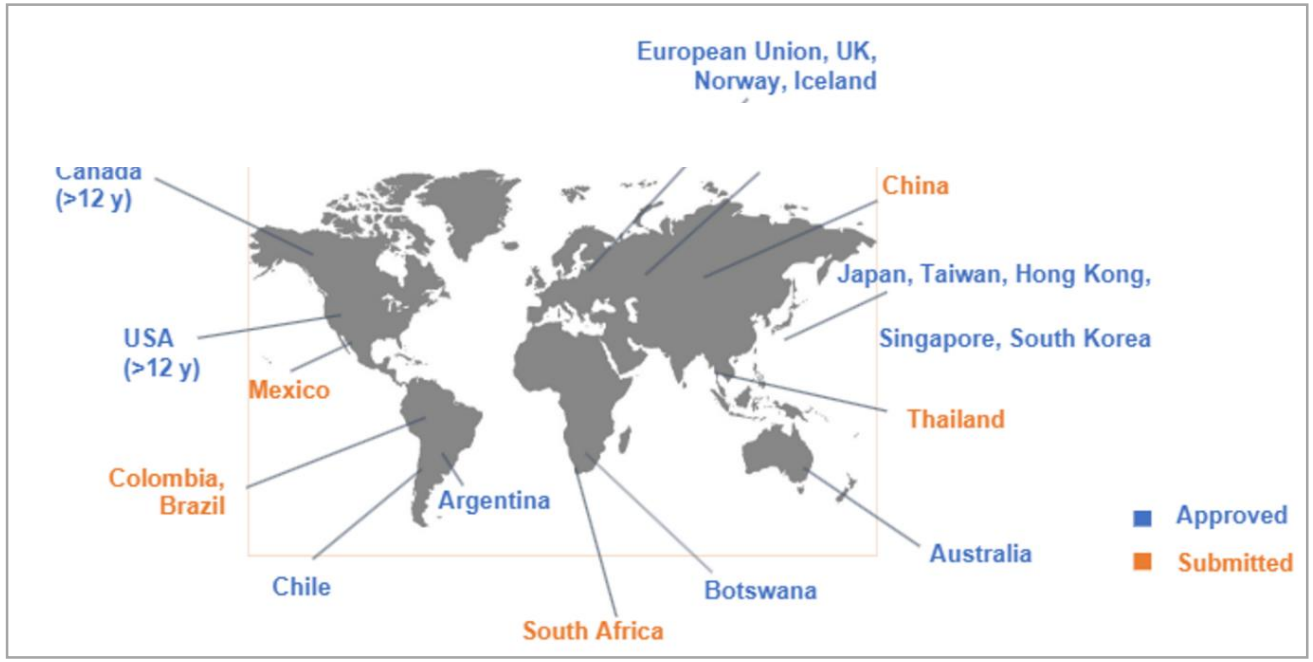
Long-acting ART pipeline

- Two long-acting antiretrovirals are approved:
  - long-acting cabotegravir and rilpivirine, given by injection every 4 or 8 weeks, approved for people with undetectable viral load;
  - lenacapavir, given by injection every six months, but which must be combined with oral antiretrovirals. Approved for people with multidrug-resistant HIV.
- Many other long-acting antiretrovirals are in development.



Approved long-acting and extended-release ARVs

- Cortes believes that long-acting ART is a “game-changer” for HIV care and treatment.
- However, these drugs are only available in a handful of countries.

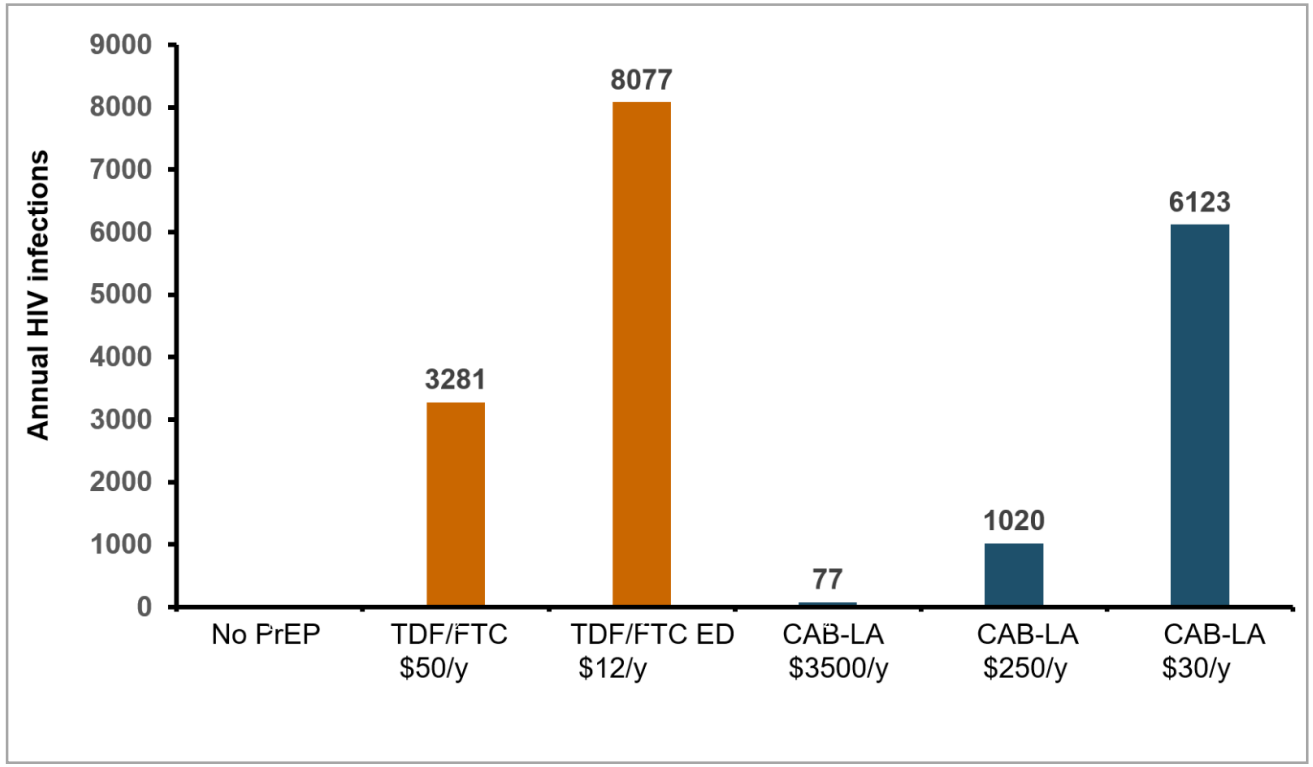


Long-acting cabotegravir and rilpivirine approvals

Long-acting PrEP in Brazil

- TDF/FTC is available as generic PrEP in most countries, costing $48/year for daily use.
- CAB-LA costs $22,200/year in US, $9000 in the UK.
- A voluntary licensing scheme will permit generic producers to sell CAB-LA at low prices in some countries, estimated $250/year.
- Brazil has a fast-growing HIV epidemic, but is not included in the licensing scheme.
- The HIV prevention budget in Brazil is $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 8077 new HIV acquisitions).
- However, it could only provide CAB-LA to 1707 people at the price of $3500 (preventing 77 new HIV acquisitions).
- CAB-LA would only lower overall HIV rates if it cost less than $30/year.



HIV acquisitions prevented in different scenarios

Questions?
Comments?

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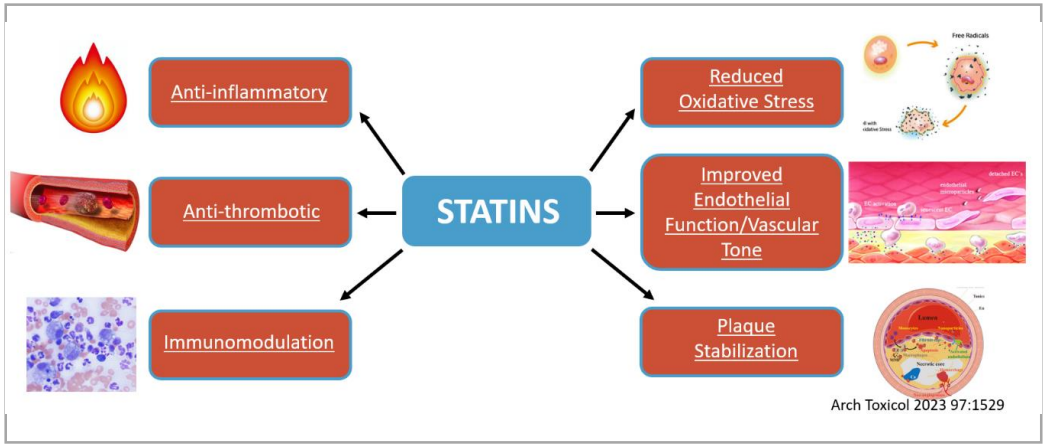
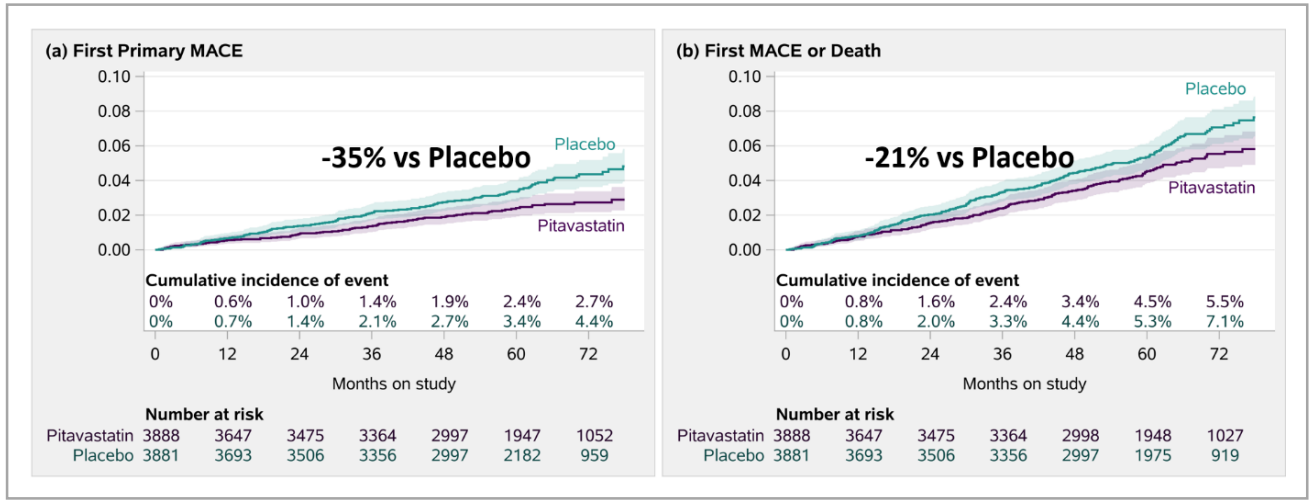
Statins and HIV

- People living with HIV are twice as likely to develop cardiovascular disease, 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, who would not typically be prescribed statins.



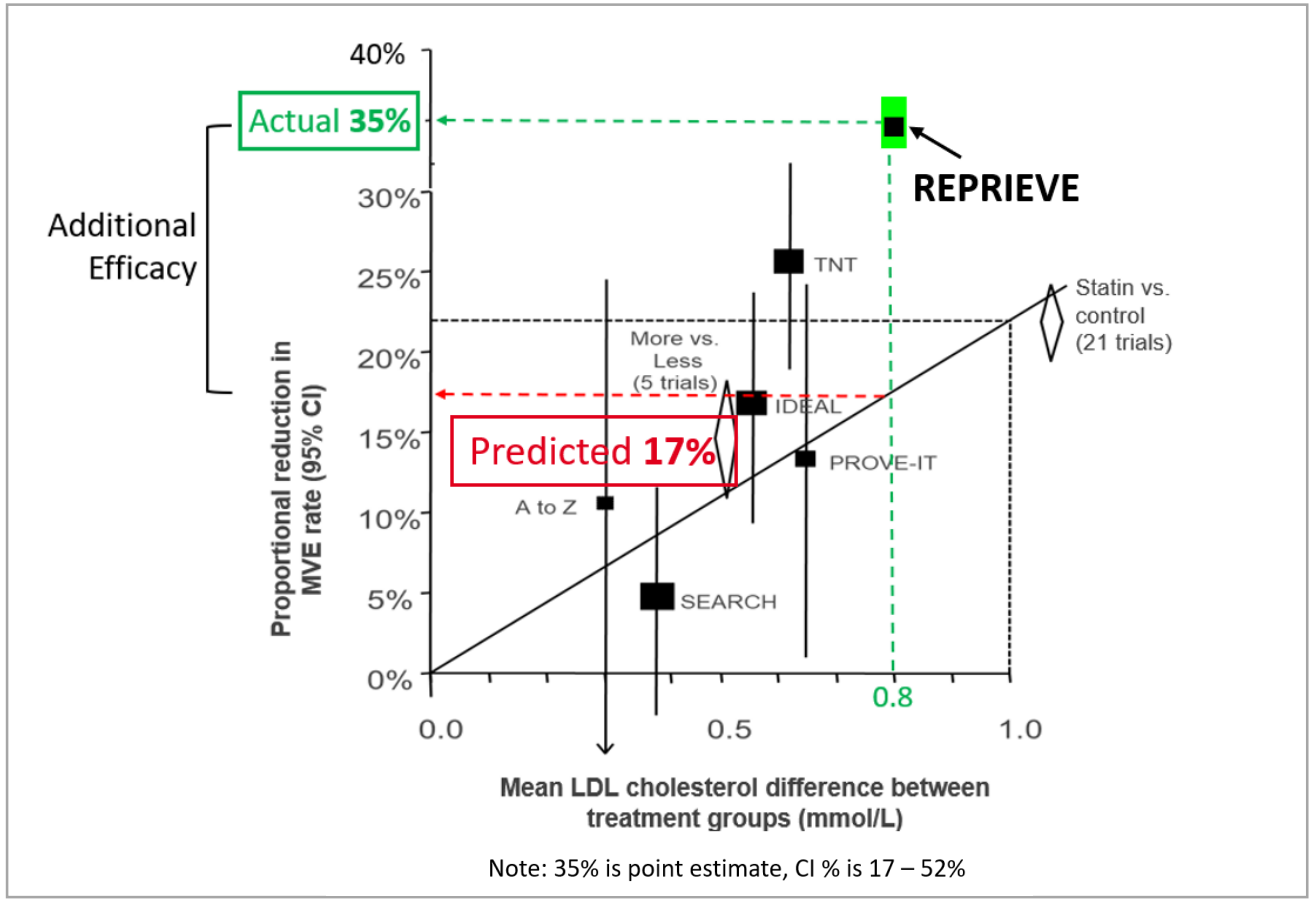
Effects of statins

- Median follow-up time was 5 years.
- The rate of major cardiovascular events was 35% lower in the pitavastatin arm compared with the placebo arm.
- The risk of cardiovascular events or death from any cause was 21% lower with pitavastatin.



Primary and key secondary endpoints

- LDL was lowered by 30% in the pitavastatin group.
- However, 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.

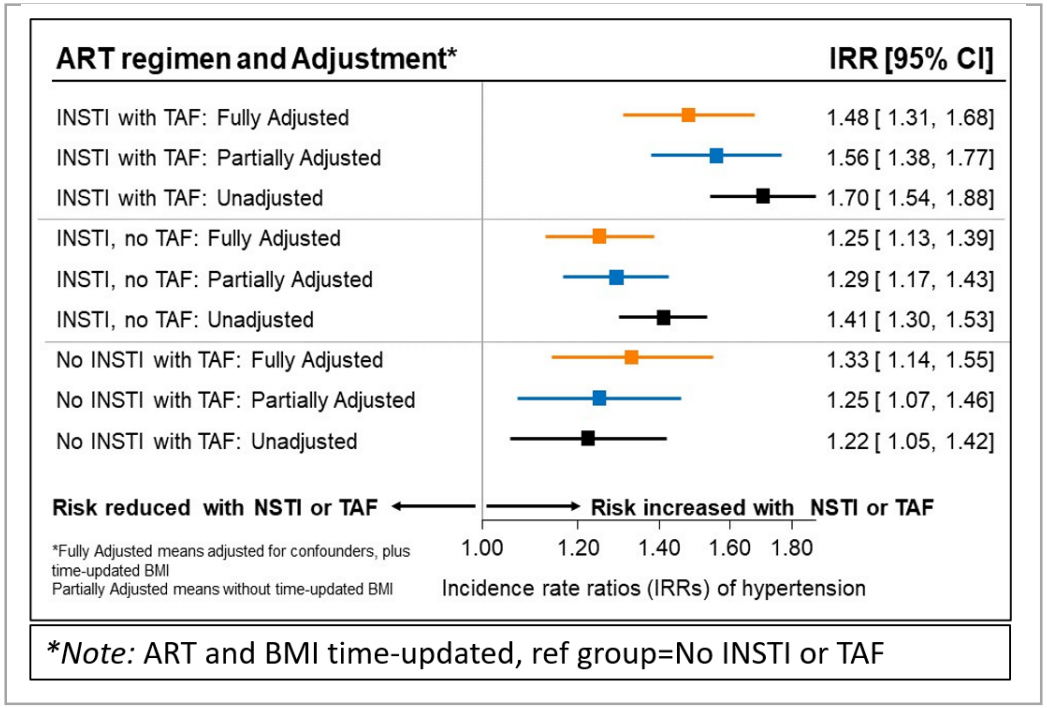


Effect larger than lowering of LDL

- What are the implications of the study?
- REPRIEVE has shown that statin therapy will prevent major cardiovascular events in people with HIV at low to moderate risk.
- Grinspoon said that statin therapy with lifestyle counselling should be considered for people with HIV, even for those with low to moderate risk.
- Decision to take a statin should be individualized.
- All relevant factors should be considered, including drug interactions and patient preferences.
- Conversations about risk should emphasis heart healthy lifestyle factors, including diet, smoking and blood pressure.

Hypertension and HIV

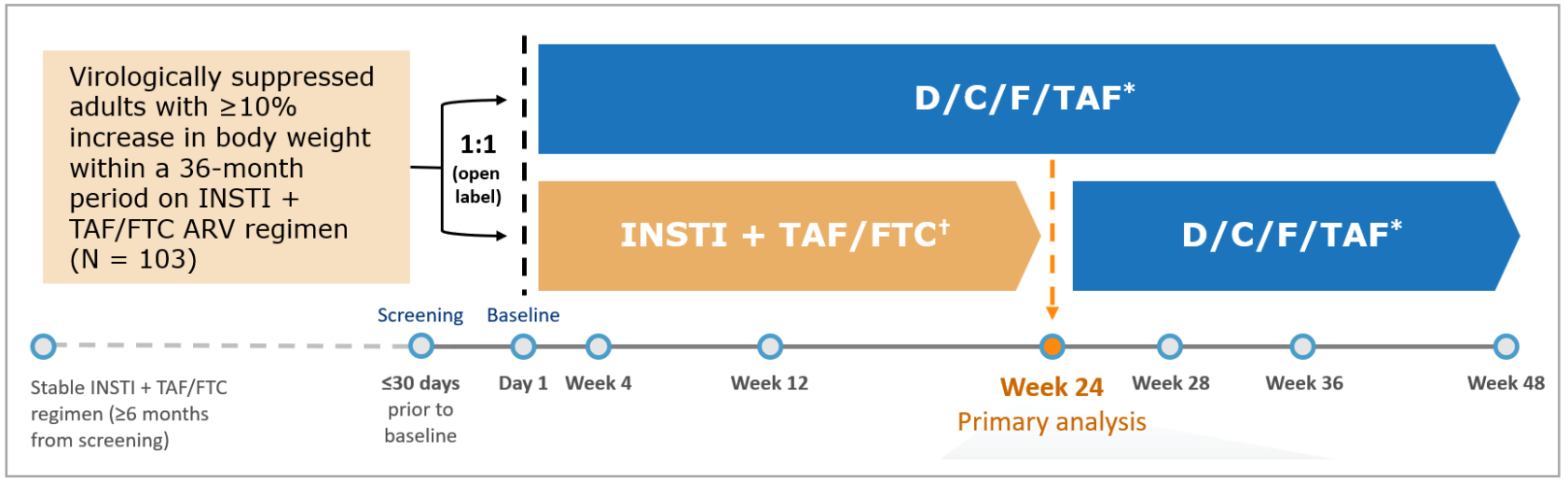
- An analysis examined the relationship between ART, weight and blood pressure in 13 observational cohorts in Europe and Australia.
- 30% of 9704 participants developed hypertension during 39,993 person-years of follow-up.
- Those taking both an integrase inhibitor and TAF had a 48% higher rate of hypertension after adjusting for BMI and other confounding factors.



Incidence rate ratios of hypertension

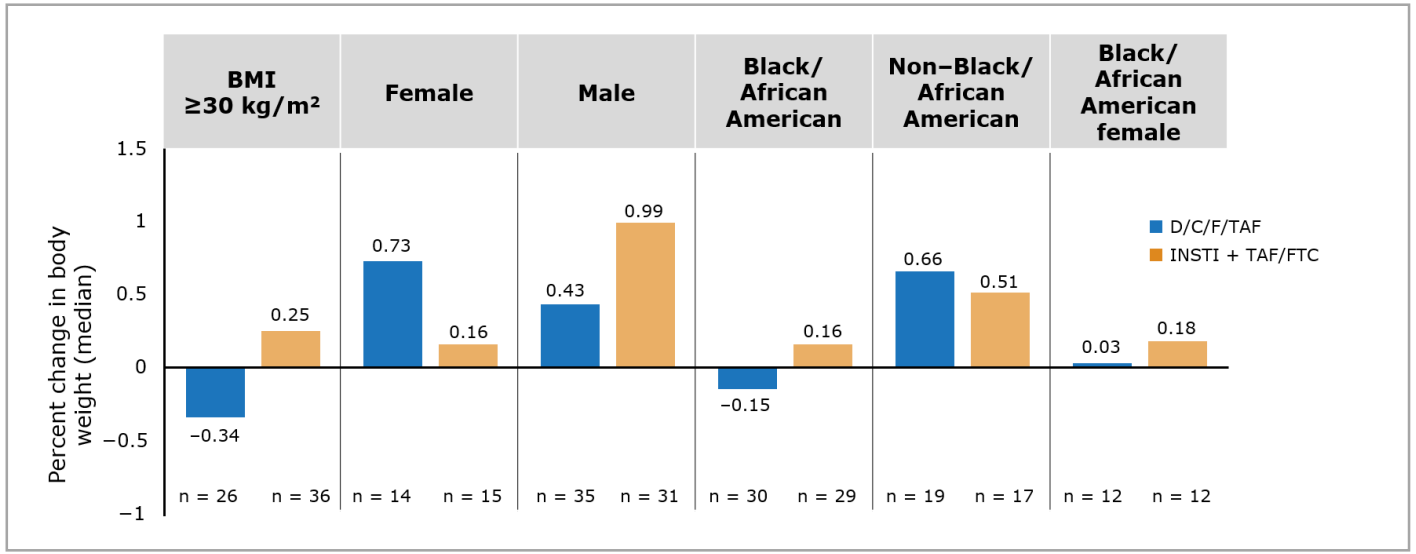
Integrase inhibitors and weight gain

- In the DEFINE study in the US, people who had gained at least 10% of body weight on an integrase inhibitor-based regimen either stayed on it (50 people) or switched to a darunavir-based regimen (53 people).
- 30% of participants were female and 61% were Black. Median weight was 100kg, and median weight gain 14%.



DEFINE study design

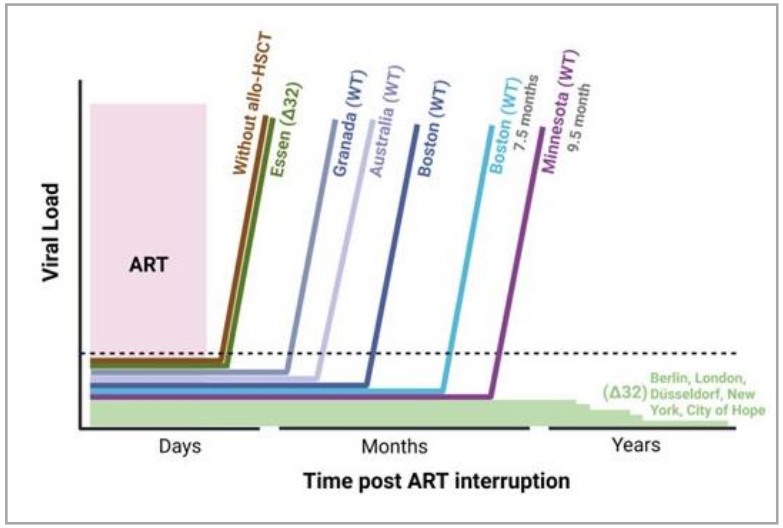
- There was no significant difference in percentage change in body weight between the study arms at week 24.
- Weight increased by 0.63% in the switch arm and decreased by 0.24% in the integrase inhibitor arm.
- The study is ongoing, but these results suggest INSTI-related weight gain may not be reversible by changing treatment.



Changes in body weight across subgroups at week 24

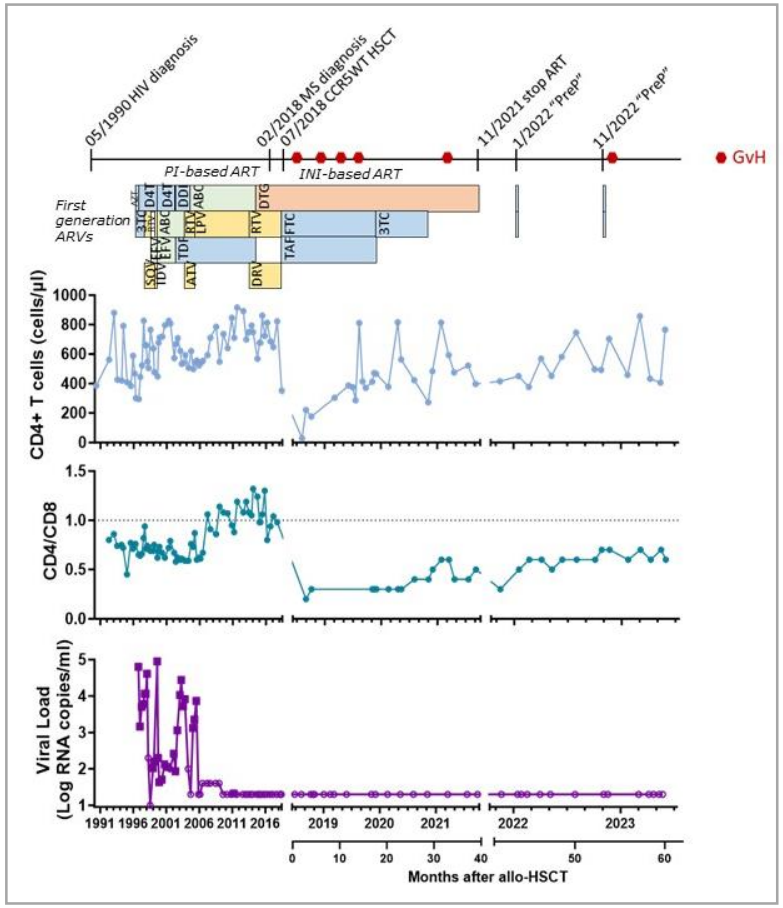
The Geneva patient

- The first person to apparently be cured of HIV with 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: prognosis is usually poor.
- The man received a stem cell transplant for cancer in July 2018. A donor with homozygous CCR5-Δ32 mutation (immune to HIV) could not be found.
- Prolonged remission of HIV was unexpected; similar patients have only had remissions of months.



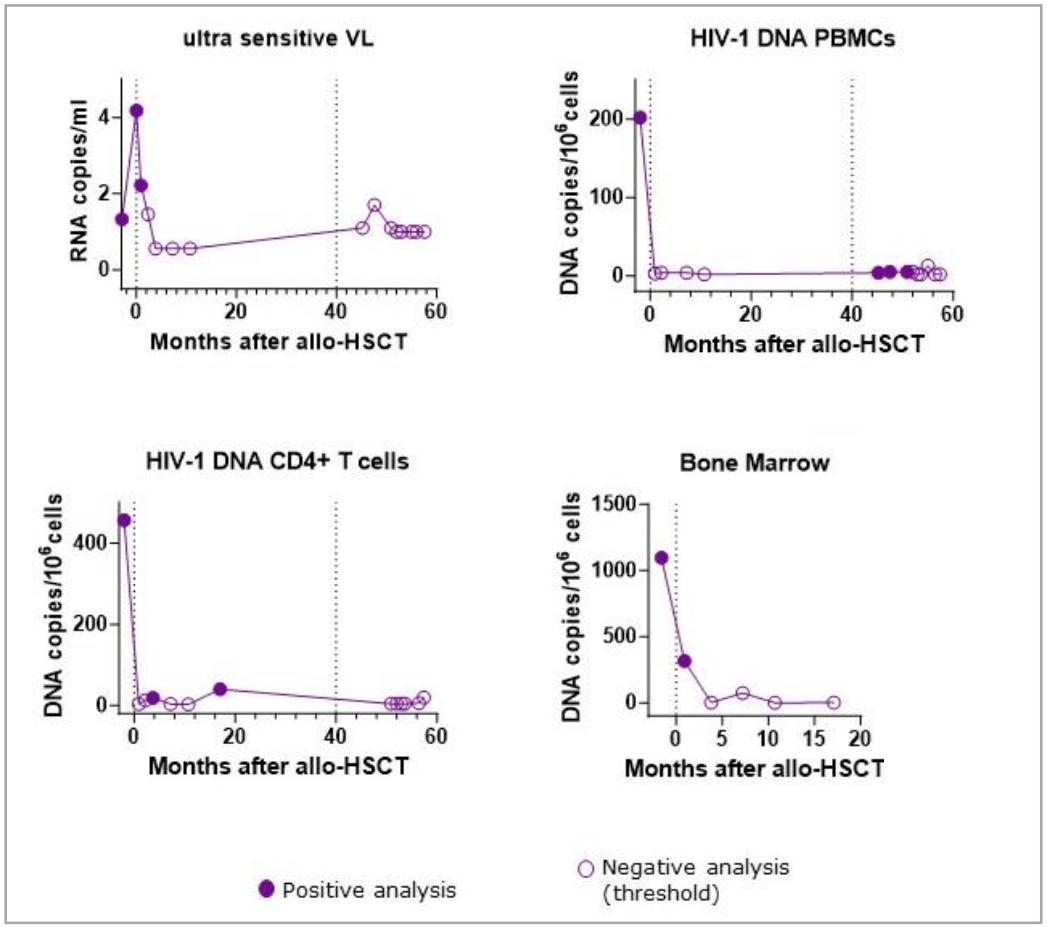
Viral rebound after ART interruption in other people who received allo-HSCT

- The man received intensive chemotherapy and radiotherapy to delete the host immune system.
- He achieved full chimerism within a month, i.e. all host immune cells were replaced by donor's.
- The man 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: it ended in November 2021 (analytical treatment interruption – ATI).



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

- Is this remission – or cure?
- The man has 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.

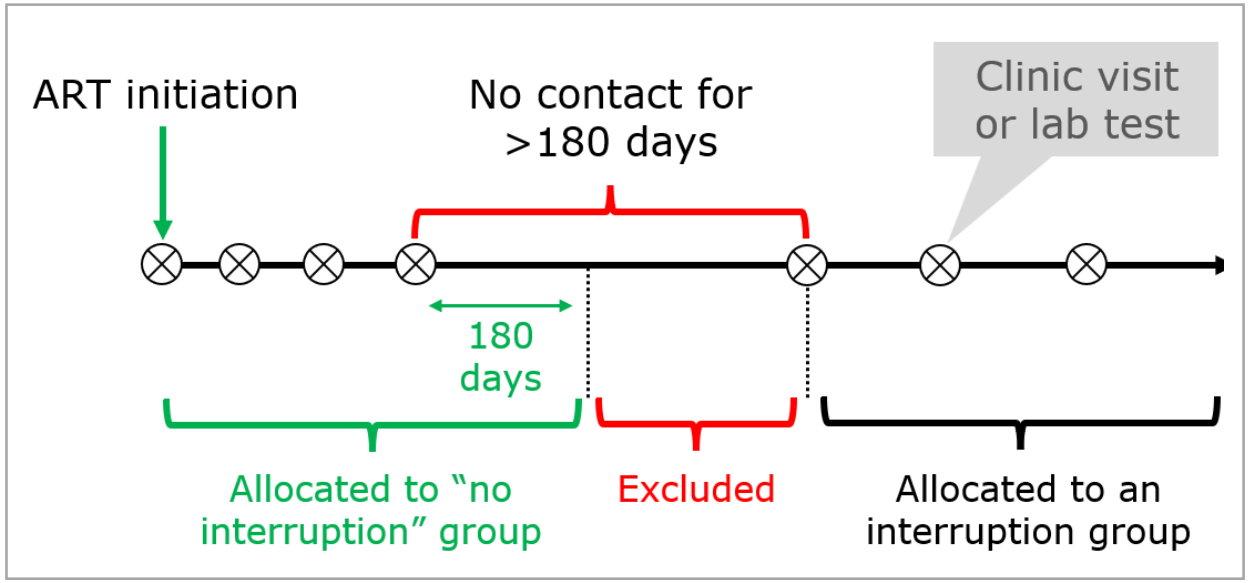


Drop in markers of HIV persistence

- 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 Saéz-Cirión

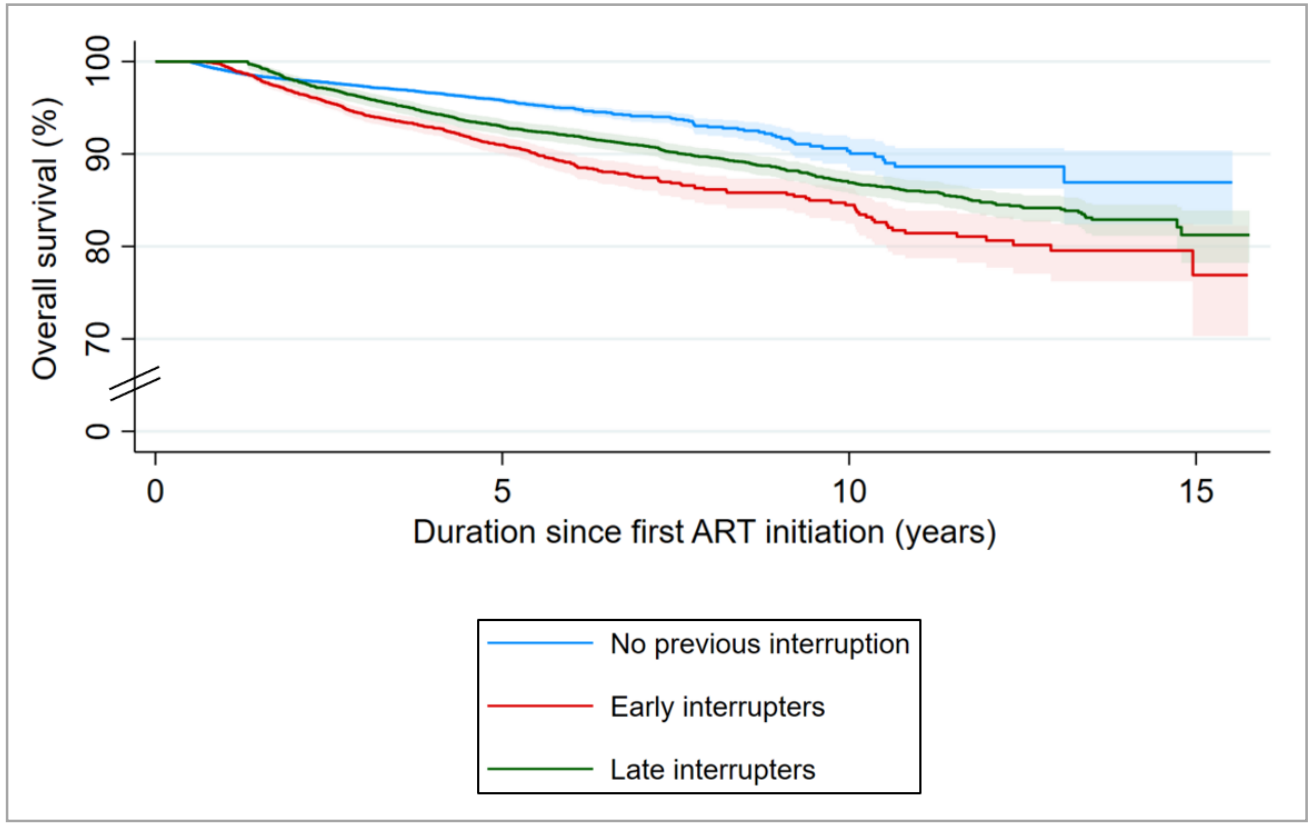
Unplanned treatment interruptions

- Study included data from 44,386 adults with HIV starting ART between 2014 and 2019 in South Africa.
- Care interruptions were defined as a gap in contact longer than 180 days.
- Grouped based on whether interruption was before or after 6 months of ART.
- 12,601 people interrupted care, of whom 7038 interrupted within the first 6 months of ART.



Allocating observation time

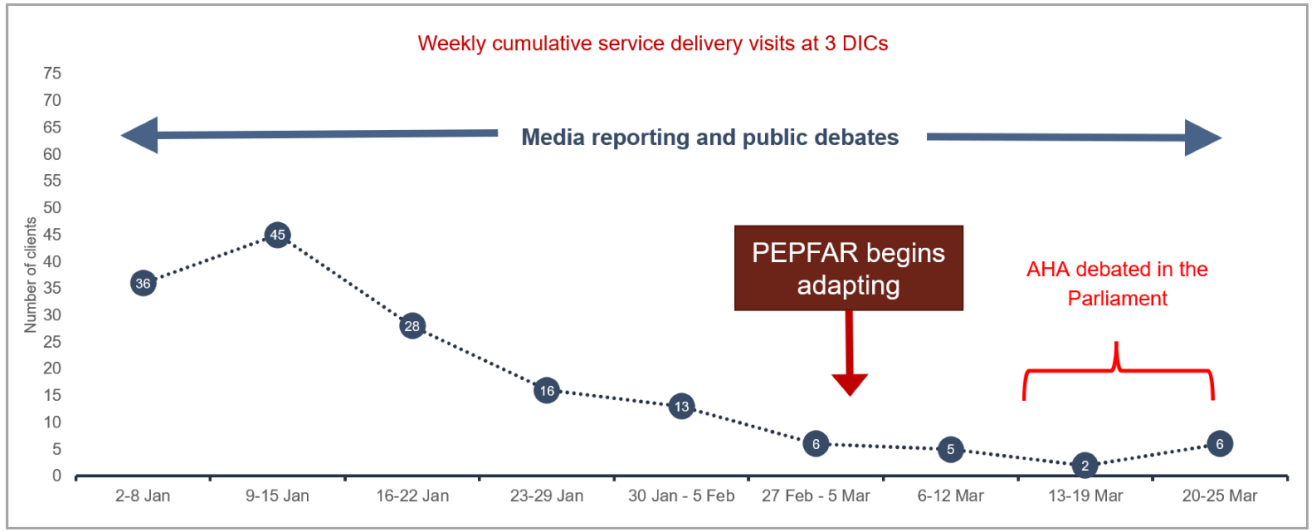
- Those resuming ART experienced increased mortality compared to those without an interruption.
- Within 6 months of starting ART: 208% increase in mortality; after 6 months: 147% increase.
- This highlights the need to prioritize and support retention in care, particularly during the first 6 months of ART.



Survival curves by interruption group

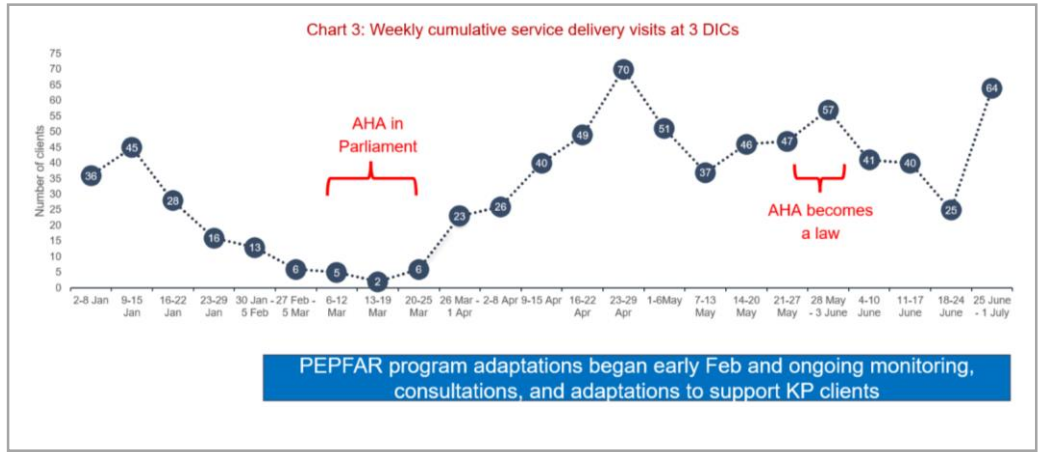
Key population services in Uganda

- 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.
- 20 other centres have not seen a resurgence of clients despite interventions.



Impact of Anti-Homosexuality Act and adaptations

Questions?
Comments?

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