# CROI 2022 highlights

Produced by NAM aidsmap

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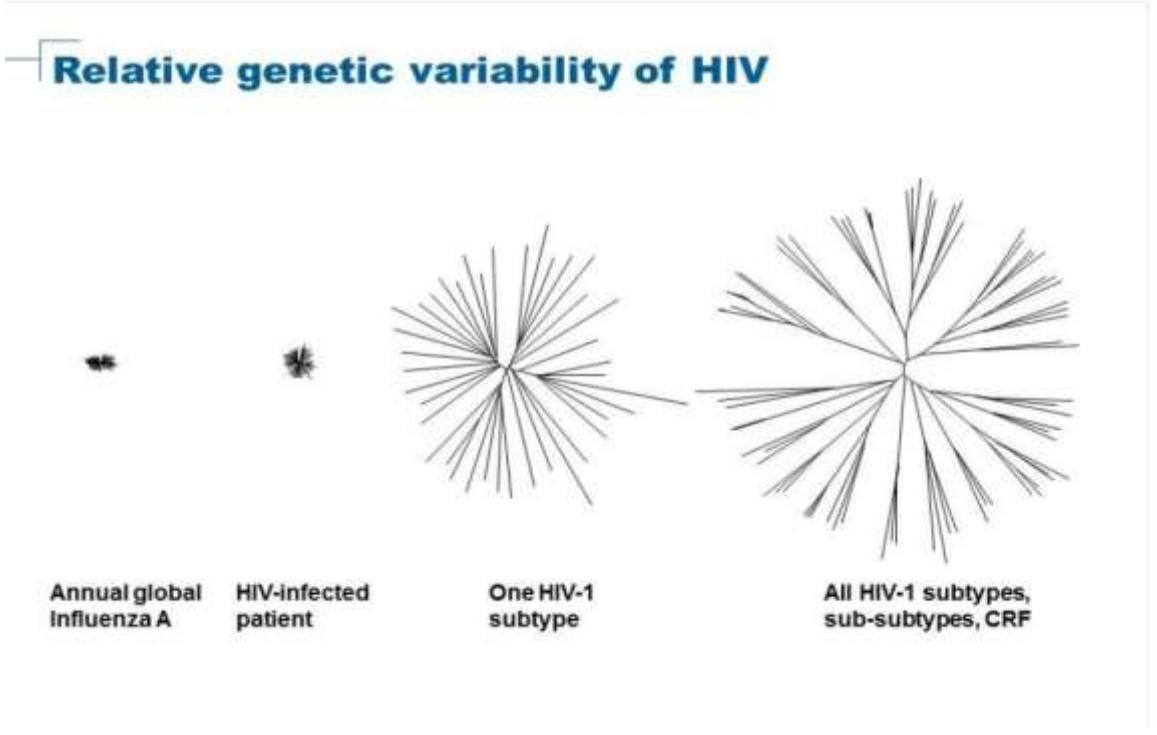
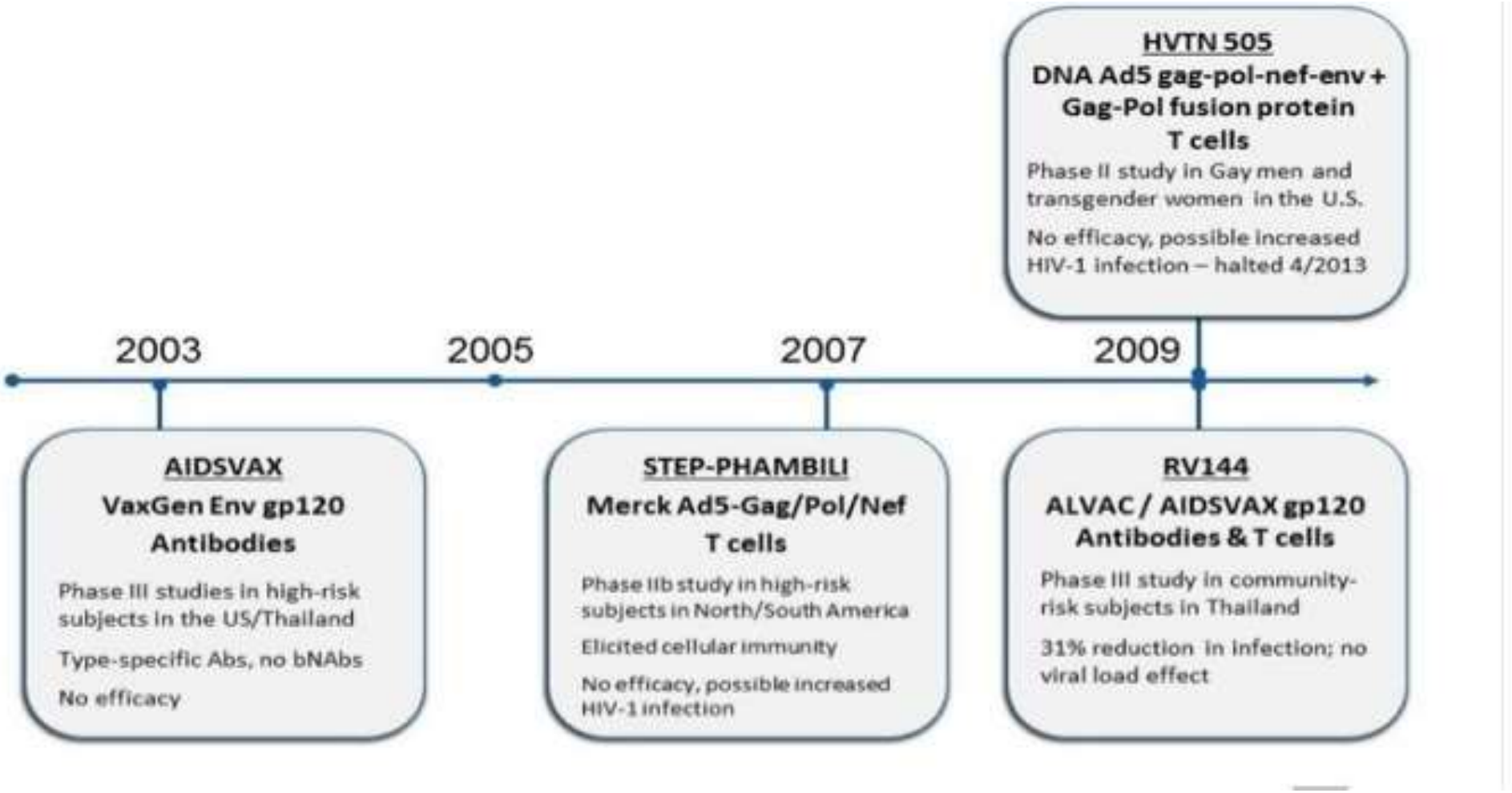
HIV PREVENTION ENGLAND

# Why is HIV so hard to vaccinate against?

- It is **SILENT**. HIV naturally does not provoke an effective immune response. Antibodies are made (and are detected in tests) but they are too late/too specific to stop infection.
- It is **SHIFTY**. It changes all the time – much faster than flu or COVID. This means by the time antibodies have developed, it has mutated beyond them and they are uselessly specific.
- It is SUBVERSIVE. Remember the commanding role of the T-helper cells? They are exactly the cells HIV infects. The more activated they are by HIV, the more cells there are to infect.

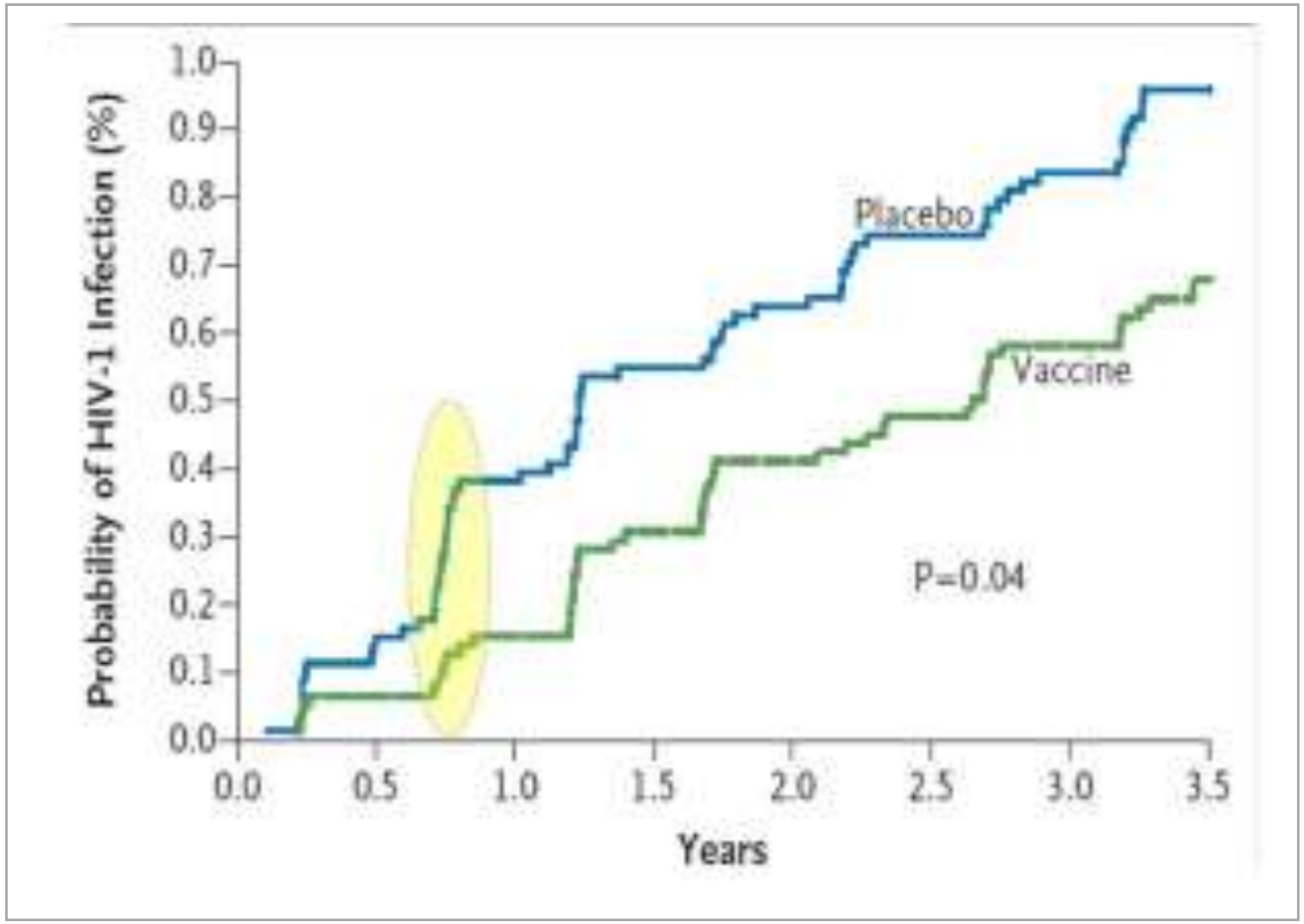


# Large vaccine trials up to 2009…



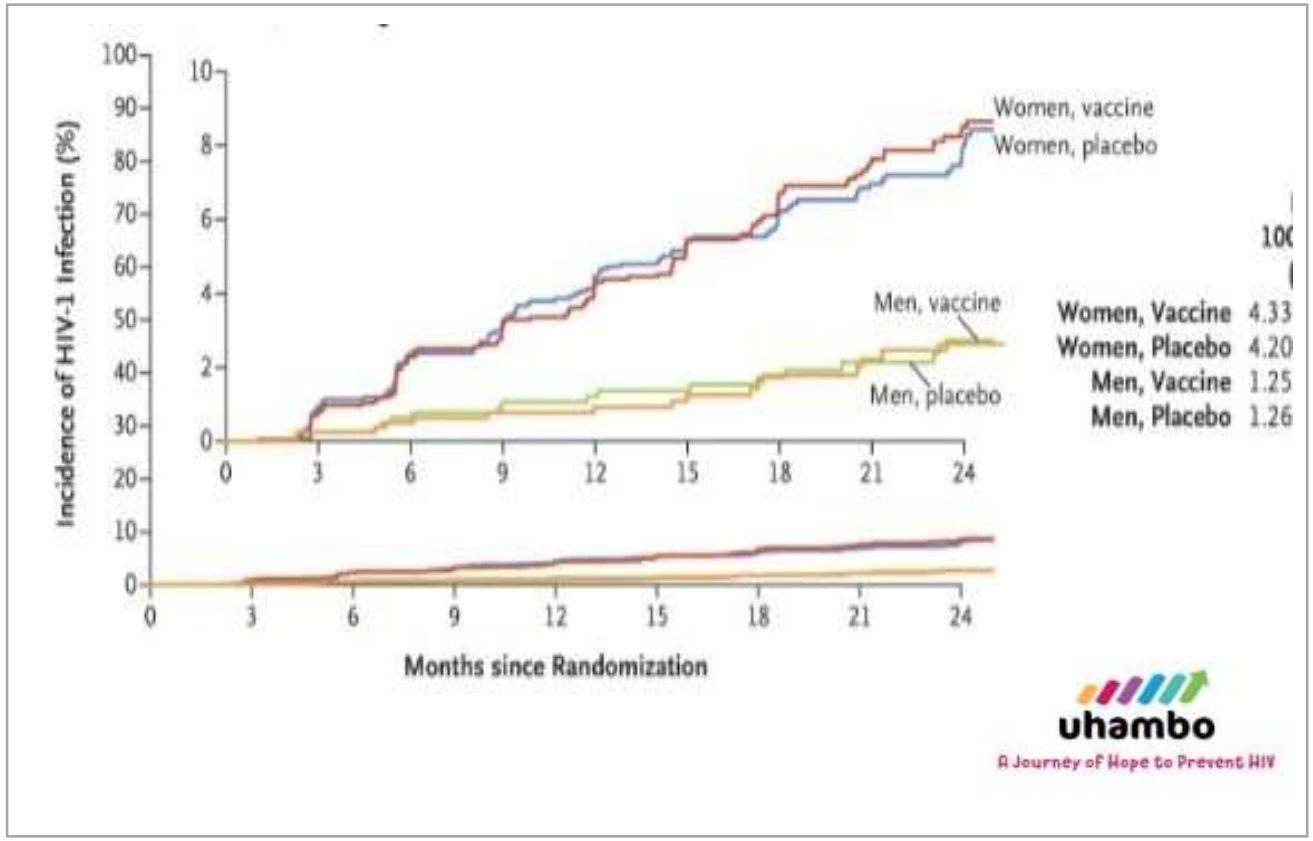
# 2009: RV144: the vaccine that WORKED (a bit)

- Surprise; it used AIDSVAX, which hadn't worked before + vector
- 31% efficacy after 3 years: only just statistically significant
- Only against the weakest 'tier 1' viruses: low-risk population
- HIV escaped the vaccine: at none months, there was 60% efficacy
- Strong antibody response to a specific part of the env protein
- This in turn recruited a strong innate – immunity response



# Flash forward to 2020 – UHAMBO didn't work

- ►Lengthy development process
- The vaccine expected to work hadn't; the vaccine not expected to work did
- ►Similar design to RV 144 but adapted for S African viral subtypes
  - 5407 men and women in S Africa
- ►Why didn't it work?
  - Appears it was overwhelmed by far higher incidence and viral variety in S African context



# 2021– IMBOKODO also didn't work

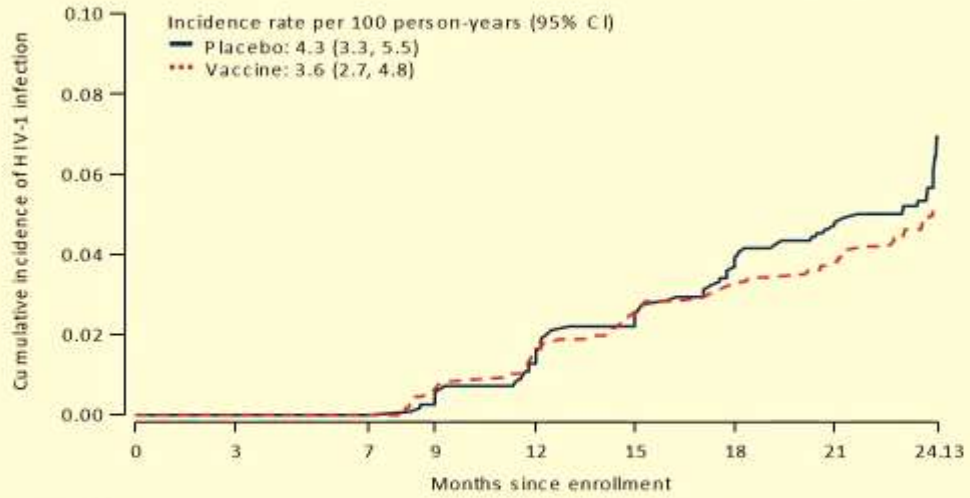
- Women-only trial: 2637 in five southern African countries.
- Vector vaccine containing 'mosaic' of antigens from different viruses and viral proteins
  - Designed to overcome over-specific immune response
- A hint of an effect: 25% fewer infections in vaccine arm
  - But not statistically significant

# CROI 2022 – IMBOKODO efficacy

## Primary efficacy endpoint

IMBOKODO

**Cumulative incidence of HIV-1 infection over Months 7-24 in the PP cohort**




| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 1109 | 1109 | 1100 | 1092 | 1068 | 1049 | 1031 | 1007 | 161 |
| Vaccine | 1079 | 1079 | 1065 | 1054 | 1036 | 1014 | 993 | 977 | 156 |
| **Cumulative HIV-1 infections** | | | | | | | | | |
| Placebo | 0 | 0 | 0 | 3 | 18 | 28 | 42 | 51 | 63 |
| Vaccine | 0 | 0 | 0 | 6 | 17 | 27 | 34 | 40 | 51 |

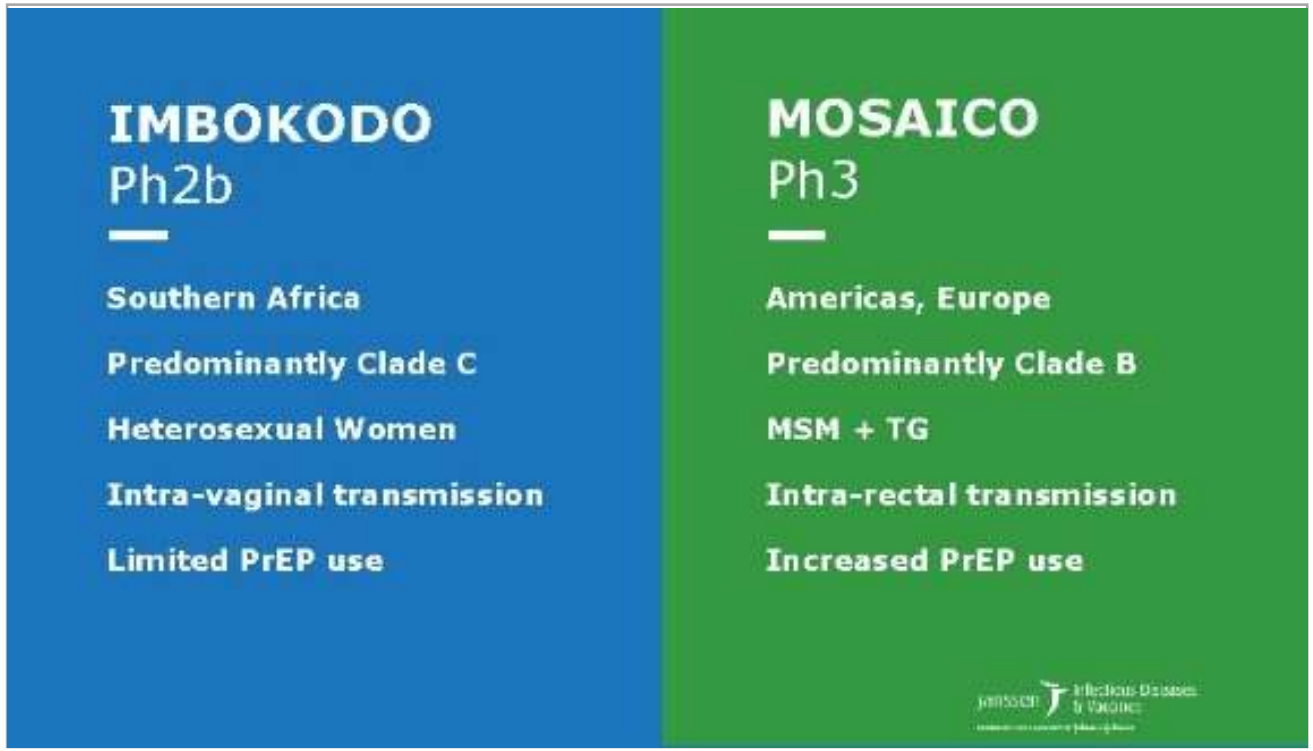
VE(7-24) was 25.2% (95% CI: −10.5 to 49.4); $P = 0.14$[a]

[a]Two-sided α = 0.05 level Wald-based hypothesis test evaluating equality of the log cumulative hazard functions at 24.13 months.

8 CI, confidence interval; HIV, human immunodeficiency virus; PP, per-protocol; VE, vaccine efficacy.

# MOSAICO – only current phase III trial

- Same design as IMBOKODO, adapted for HIV subtype B
- Aims to recruit 3800 gay and bi men and trans women in US/Latin America/Europe
- Started Oct 2019
  - Recruitment paused under COVID
- Planned completion March 2024

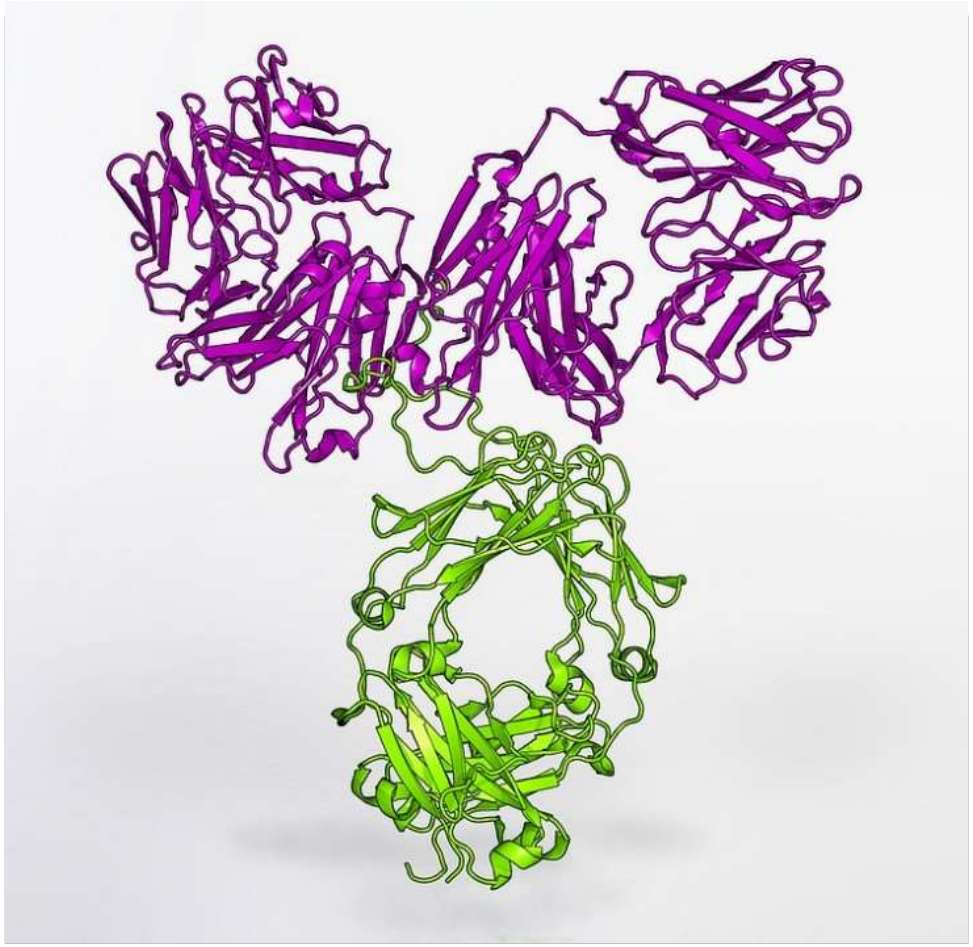


# If MOSAICO fails, what then?

- Fundamental issue in HIV is that the virus outruns the body's immune response against it
  - Same with the immune response created by a vaccine
- Body also 'prefers' to make less effective, non-neutralising antibodies ('immunodominance')
- We need to turbocharge the immune system with a vaccine so by the time an HIV infection comes along, it will meet a response *that has already won*

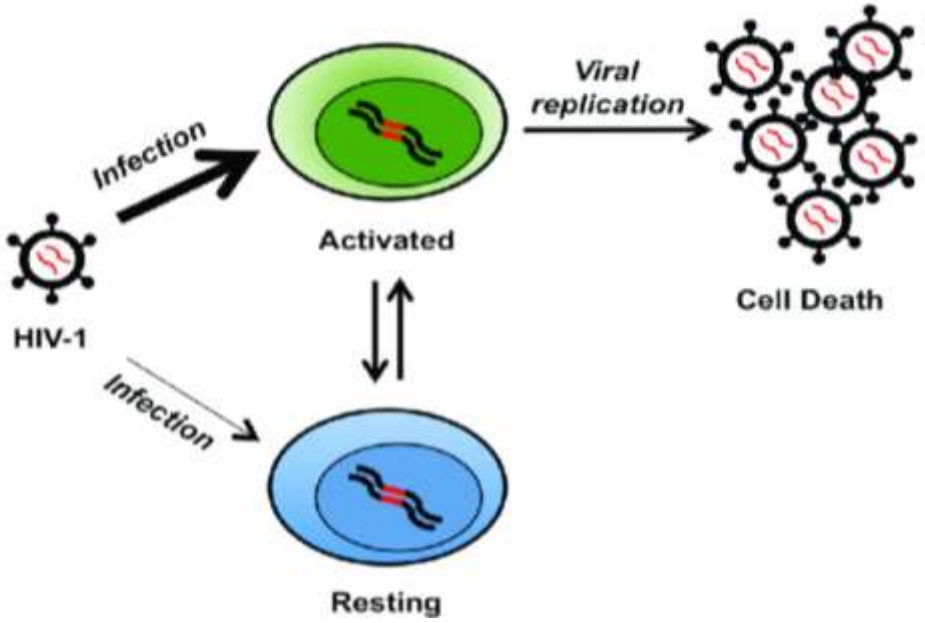
# Broadly Neutralising antibodies (bNAbs)

- Weird, hyper-evolved antibodies to indispensable 'conserved' areas of HIV
  - Eventually develop after years of infection in 10-30% of adults
- If a vaccine could induce the body to make them in advance of HIV infection, it could win the race
  - 5407 men and women in S Africa
- Other approaches
  - Broad T-cell immunity via replicating vectors (e.g. Ebola vaccine)
  - mRNA vaccine (e.g. COVID vaccines)



# Why is HIV so hard to cure?

- It is SILENT, SHIFTY, SUBVERSIVE… and SECRET
- It splices its proviral DNA into the DNA in your immune cells: it becomes part of their genes
- In active infection, most immune cells die. But some become memory cells. Their job is to recognise new infections.
- They would normally stay ‘asleep’ till a new infection arrives (that’s how vaccines work)
- But cells containing HIV DNA stay ‘on’ unless stopped by antiretroviral therapy. Stop that, you wake up the virus along with the cell
- Your immune system is HIV’s fuel…
  …it is also its disguise.
  You’ll hear the silently-infected immune cells called…
  THE HIV RESERVOIR



# Five people who were cured (now maybe 6,7*)

- Two men cured by medical science (bone-marrow transplants with cells immune to HIV)
- Three women who cured themselves
  - Two without any treatment
  - One after standard ART

Adam Castillejo

Loreen Willenberg

The ‘Buenos Aires patient’

Timothy Ray Brown

The ‘Esperanza patient’

**At least. And there may be others cured who don’t even know it themselves*

# CROI 2022 biggest story: 'The New York Patient'

- Mixed-race woman. HIV 2013, leukaemia 2017.
- Needed stem cell* transplant for leukaemia
  - Progenitor immune-system cells. In bone marrow in adults, but also in placental/umbilical cord blood in newborns.
- Aim: stem cells replace immune system ('engraftment')
- With Timothy/Adam, was replaced with cells immune to HIV (CCRΔ32 mutation) - very rare in non-white people
- So mix of CCRΔ32 cord cells + non-immune bone marrow cells from relative used, to support engraftment
- 100% replacement of immune system with CCRΔ32 cells in 100 days
- Now been off ART 14 months with no sign of HIV

The New York Times

**A Woman Is Cured of H.I.V. Using a Novel Treatment**

She's the third person ever to be cured. Researchers announced that the new approach holds the potential for curing more people of racially diverse backgrounds.

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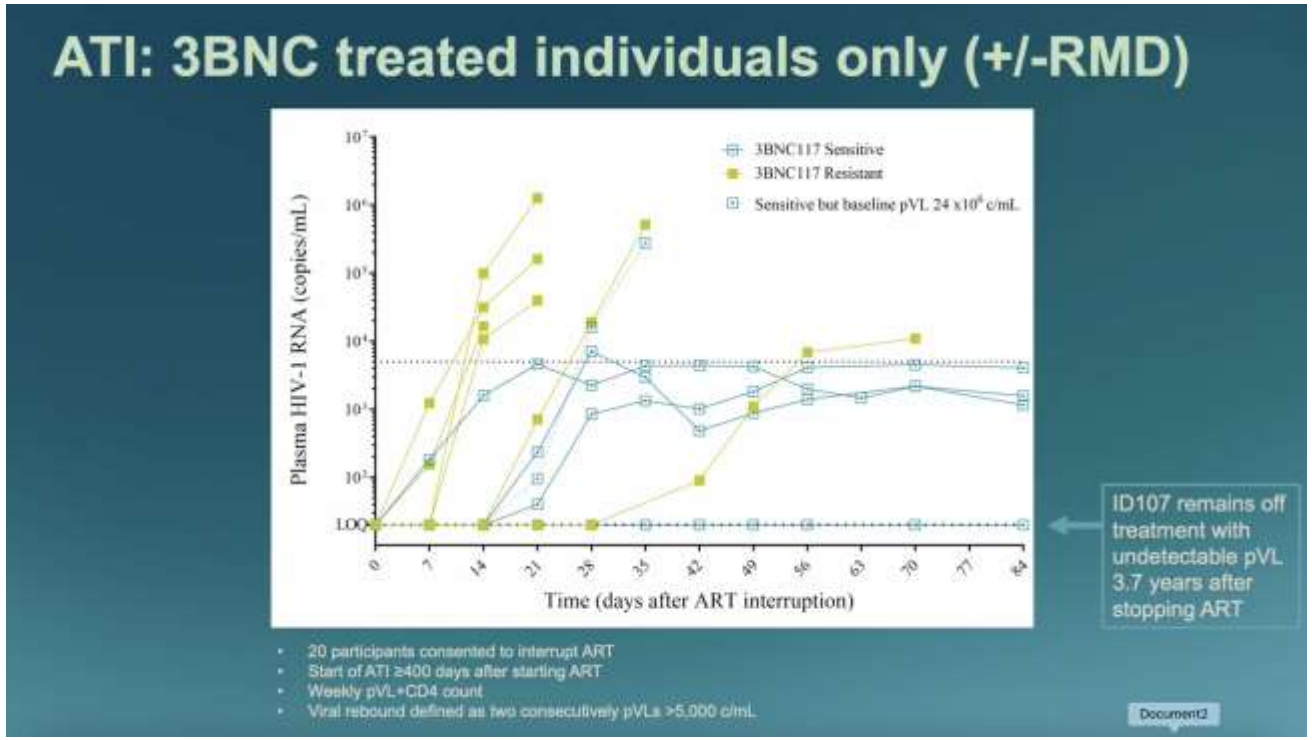
A colored scanning electron micrograph of H.I.V. particles, in yellow, infecting a host cell. The patient received cord blood from a donor with the mutation that blocks H.I.V.'s entry into cells. Thomas Deerinck, NCMIR/Science Source

# Even bigger? 3.5 years off ART with no rebound

- 60 people in trial of immune booster (to wake up HIV+ cells) + broadly neutralizing antibody (to help kill them)
- 15 had bNAb alone, 15 both therapies
  - In people having both, CD4 cells expressing HIV increased– but so did cell-killing CD8 cells
- After 400 days from start of study, people asked if they wanted to stop ART. 20 did.
- Seven stayed off ART for 3m without having to restart ART
- One stayed undetectable and as of now is 3.5 years off therapy



# Two different concepts of cure

## Elimination

*[Misleading term: "sterilising cure"]*

- **Removal of every HIV+ cell in the body**
- **How?**
  - Bone-marrow transplant
    - *Risky (not for non-cancer patients)*
    - *Expensive*
  - Genetic engineering – snip out the HIV DNA
    - *Has been done - for other diseases*
    - *Unbelievably expensive*

## Remission

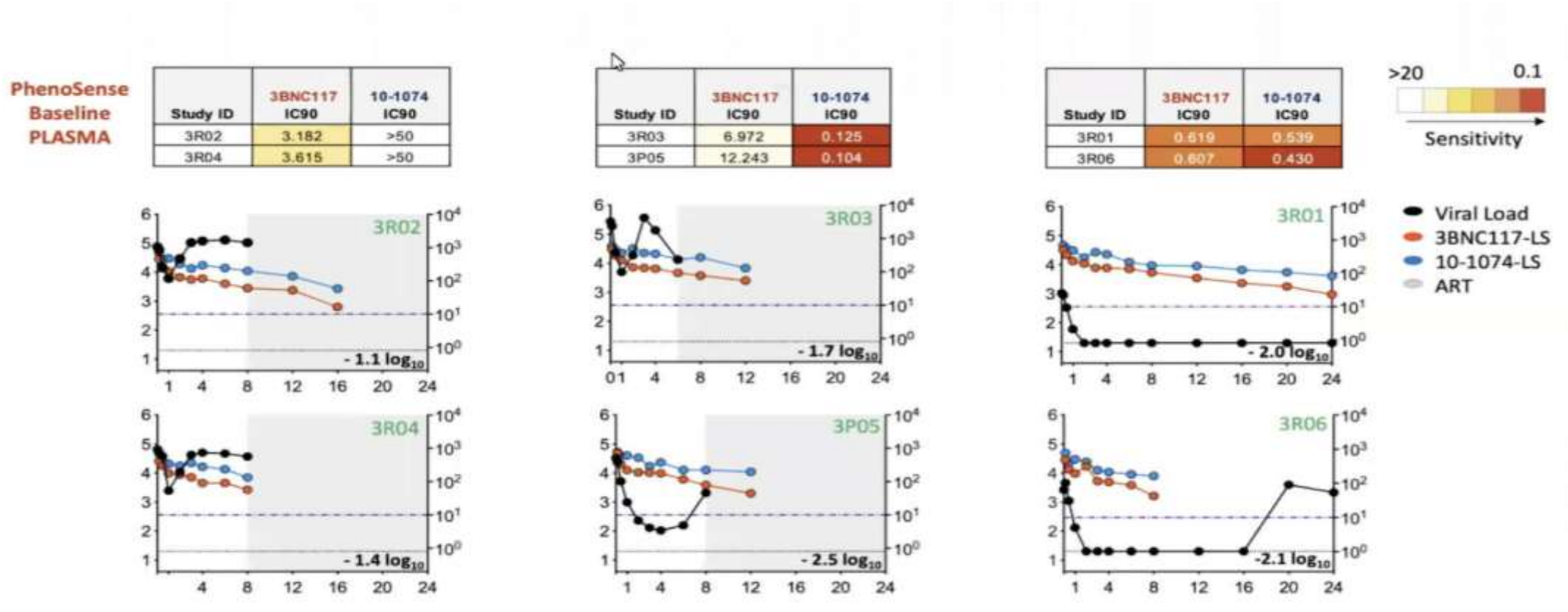
*[Misleading term: "functional cure"]*

- **Drive down levels of HIV so far that immune system contains it**
- **How?**
  - Very early treatment?
  - Early treatment +antibodies? Or a T-cell vaccine?
    - *Some people have done it naturally*
    - *Maybe others we don't know about*
    - *Less risky and expensive … **BUT***
  - May not last (when is a remission a cure?)
  - Pre-existing antibody resistance

# Pre-existing antibody resistance

White: resistant HIV. Red: sensitive HIV. Black line: viral load. Red & blue lines: bNAB levels.

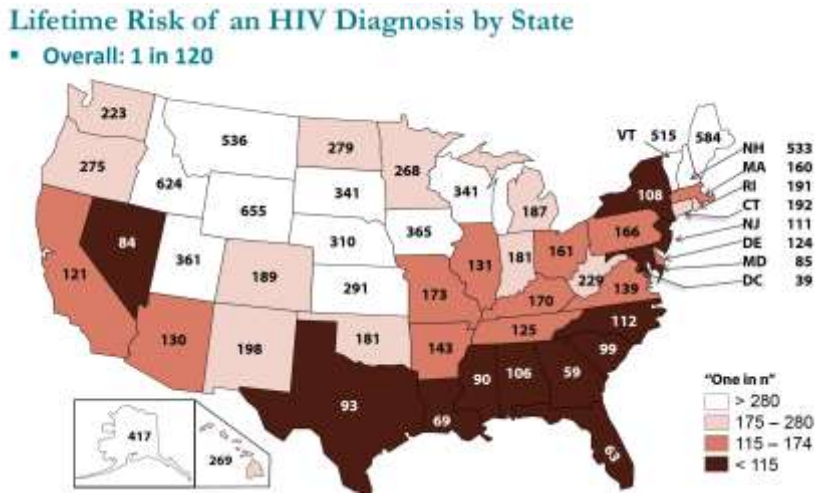
3R01 (top right) stayed off ART and undetectable for 8 months



# Q&A

# HIV lifetime risk in the US

- Approximately, 1.2 million people living with HIV in the US, around 37,000 new diagnoses in 2019.
- Overall lifetime risk of receiving an HIV diagnosis in the US has decreased by 11% when comparing 2010-2014 to 2017-2019.
- New estimate for lifetime risk: 1 in 120
- No improvement in lifetime HIV risk for groups such as Latinx, American Indians, and White females.
- Lifetime risk is much higher for some racial groups:
  - Black males have a 6 times higher lifetime risk than White males
  - Black females have a nearly 12 times higher risk than White females
  - Risk differs dramatically based on location: from a high of 1 in 39 in Washington DC down to 1 in 655 in Wyoming.

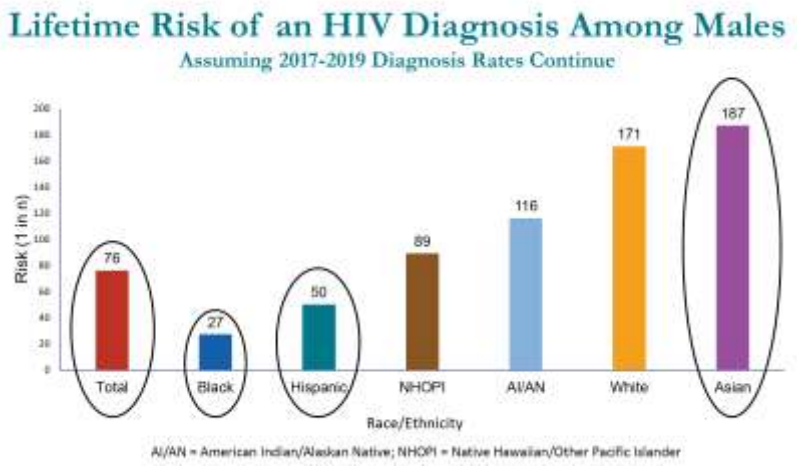


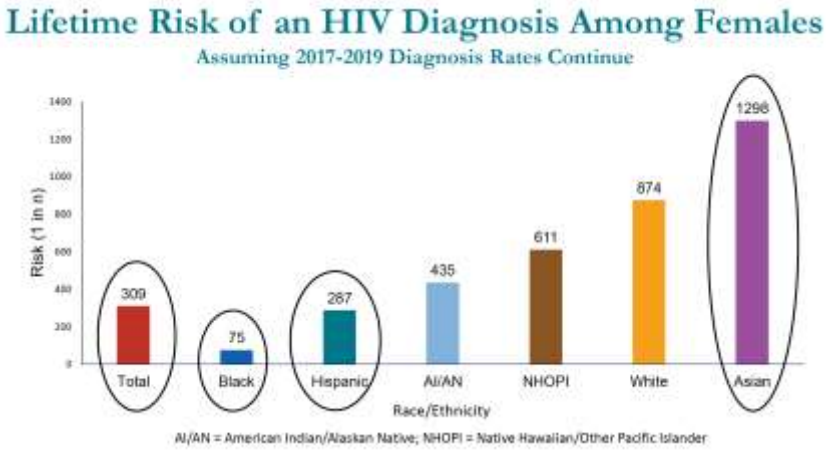

*Research from the 2014 Gay Men's Sex Survey indicated that Black MSM in the UK were more likely to be diagnosed with HIV overall (adjusted OR 1.53) and in the year prior to the survey (adjusted OR 2.57).*

# HIV lifetime risk in the US

## Sex and race

- Overall lifetime risk is much higher for males (1 in 76) than for females (1 in 309).
- **Males**: highest among Black (1 in 27) and Latino (1 in 50) males; lowest in White (1 in 171) and Asian males (1 in 187).
- **Females**:  highest among Black (1 in 75) and Latina (1 in 287) females; lowest among Asian (1 in 1298) and White (1 in 874) females.
- **Changes since 2010-2014:** larger reduction for White males (was 1 in 140), no change for Latino males and a slight reduction for Black males (from 1 in 22). While there has been a reduction in risk for Black females (from 1 in 54), it has increased for White females (was 1 in 941)

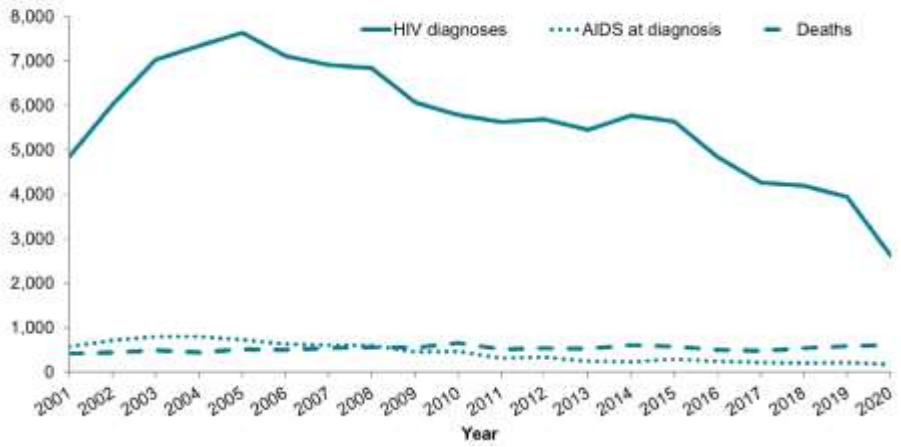


# HIV diagnoses in England

- In the UK, an estimated 106,890 people living with HIV, 97,740 in England.
- Approximately 4,660 undiagnosed people in England in 2020.
- Overall, 33% decrease in the number of new diagnoses from 3,950 in 2019 to 2,630 in 2020.
- MSM: 41% decrease from 1,500 in 2019 to 890 in 2020. Less apparent for MSM living outside London and those of Black, Asian, Mixed or Other ethnicity groups, and those born abroad.
- Only a small decline in testing: this reflects an actual change in the incidence trend.
- Heterosexuals: 23% decrease from 1,320 in 2019 to 1,010 in 2020.
  - 40% decline among White and Black Caribbean
  - 25% among Black Africans
  - 17% among Asians
  - Very large decline in testing in 2020

**Figure 6. New HIV diagnoses, AIDS at diagnosis, and all-cause deaths in people with HIV: England, 2001 to 2020**



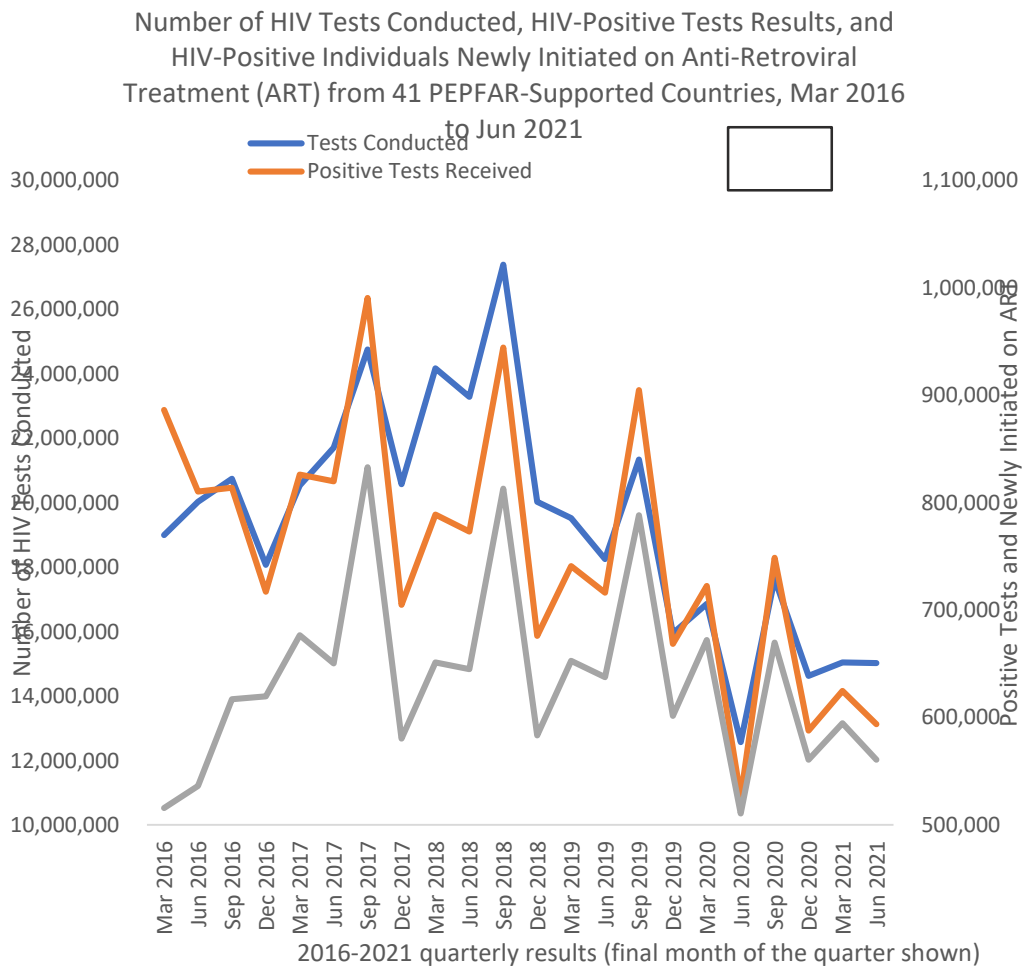
## HIV diagnoses in England

- 95:95:95 targets: 95% of all people diagnosed, 99% of those in care on treatment and 97% of those receiving treatment being virally suppressed in both the UK and England.

- 91% of all people living with HIV in care were virally suppressed.

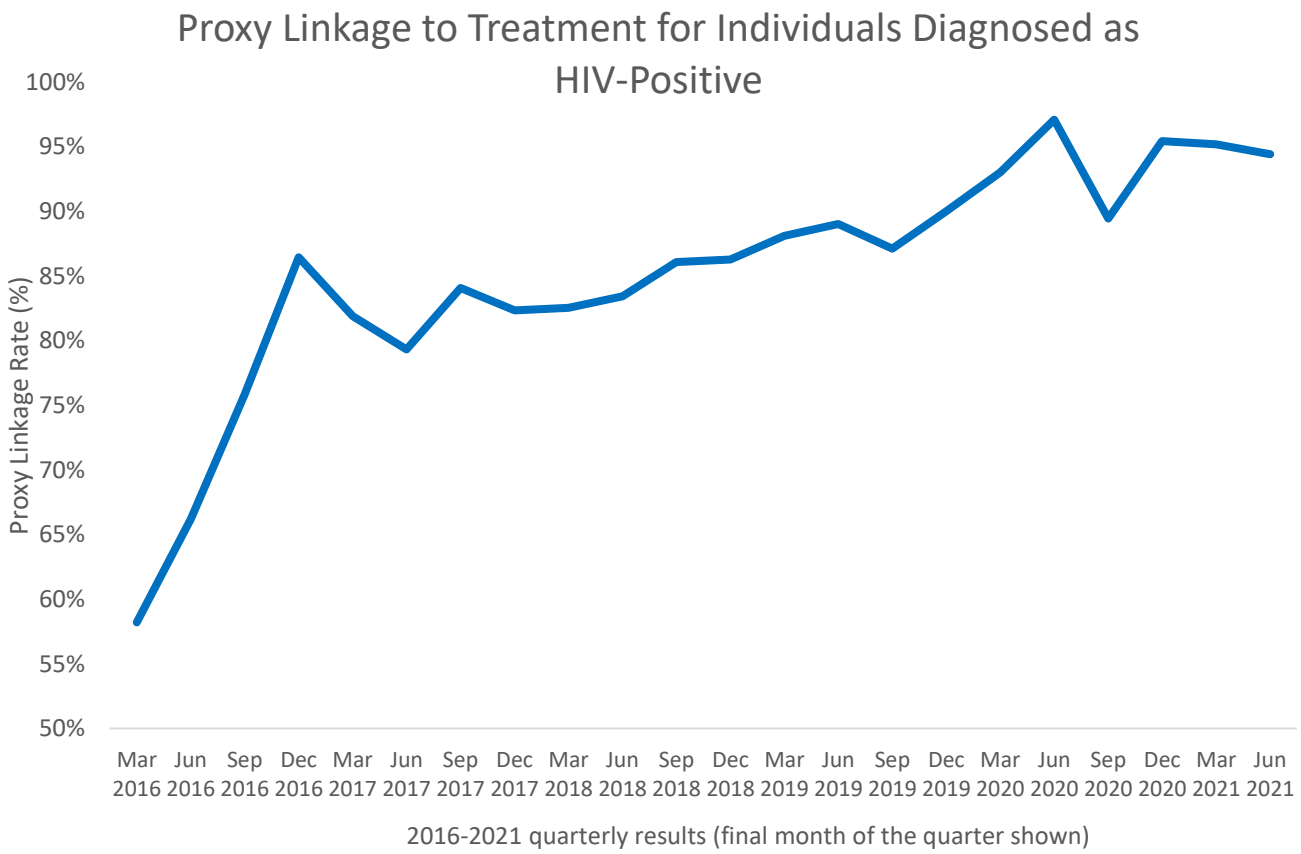
# HIV testing in PEPFAR countries

- PEPFAR is active in 55 countries globally.
- Change in testing guidelines in 2019.
  - Move from universal HIV testing to more targeted testing.
  - Index testing, case finding and the use of algorithms to determine risk profiles.
  - Some controversy over this decision: will more people go undiagnosed?
- Data from 41 PEPFAR countries for 2016-2021, for those aged 15 and older. Africa (22), Asia (10), Caribbean (6), Central and South America (2), Europe (1).
- 443 million tests for this period, with 17.5 million positive tests.



# HIV testing in PEPFAR countries

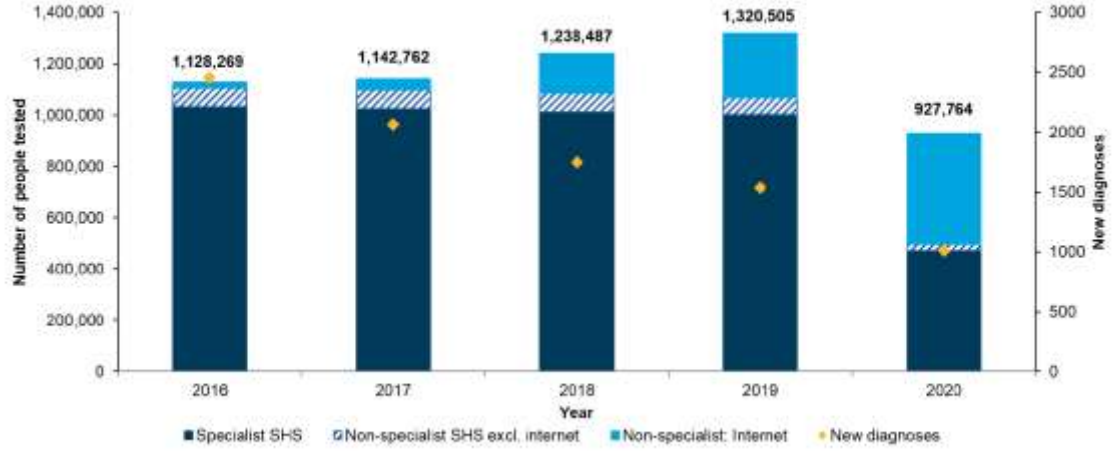
- Number of people starting treatment: increased from around 500,000 in March 2016 to 800,000 in Sep 2017.
- This decreased to 600,000 in June 2021, reflecting the reduction in the number of people being diagnosed with HIV.
- Linkage to care: the percentage of people testing positive who started ART increased from a low of 66% in March 2016 to 94% in June 2021.
- COVID-19 had an impact by lowering this figure during 2020.



# HIV testing in England

- Between 2019 and 2020, the number of people testing for HIV in any sexual health services fell by 30% from 1,320,510 to 927,760. Nearly half of all these tests were online.
- This drop was more pronounced from some groups:
  - For men who have sex with men testing at SHS fell by 7% (higher than in 2018; number of frequent testers remained high).
  - For heterosexuals, this fell more sharply: 33% (Black African heterosexuals, 34% for men and 24% for women and White heterosexuals 43% and 30%, respectively).
- There was a rise in the percentage of tests conducted by non-specialists, such as GPs, community nurses and via self-testing.

Figure 2. Number of attendees tested for HIV and new diagnoses at all SHS by SHS type: England, 2016 to 2020



## HIV testing in England

- Undiagnosed HIV (15 to 74) decreased from 11,600 in 2013 to 5,900 by 2019.
- A halving in undiagnosed HIV prevalence from 0.29 to 0.14 per 1000 people for this period.
- Absolute numbers of undiagnosed infections and prevalence for each subgroup:
- Men who have sex with men, from 7,100 to 2,900; 13.9 to 5.4 per 1000.
- Black African heterosexuals from 2,200 to 1,200; 3.3 to 1.7 per 1000.
- All heterosexuals from 4,300 to 2,900; 0.1 to 0.07 per 1000
- People who inject drugs from 70 to 50; 0.7 to 0.5 per 1000

# What has contributed to the decline in HIV incidence among MSM in England?

- Around 670 new HIV infections in gay and bisexual men in 2021. In 2011, this figure was around 3000. This 75% reduction was due to combination prevention.

Combination prevention led to a very large reduction in HIV incidence among GBM in the UK from around **2,600 in 2011** to around **670 in 2021**. Condom use, the PrEP strategy, a boost in HIV testing and ART played a key role.

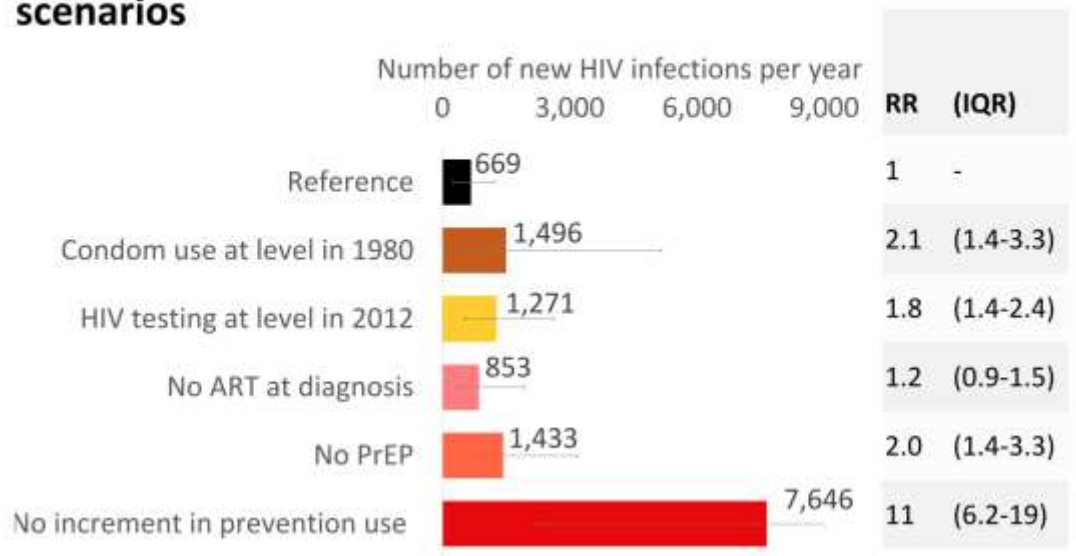
Continuation of current prevention policies is likely to lead **virtual elimination** (defined as <1/1000 person-years) **of HIV transmission** among GBM in the UK in **~25 years time**.

# What has contributed to the decline in HIV incidence among MSM in England?

**Different counterfactual scenarios from 2012 onwards:**

- If condom use had not increased beyond 1980 levels (only 10%), there would be 1496 new infections in 2021, or 115% more.
- If the number of gay men testing for HIV remained the same as in 2012, there would be 1271 infections, or 80% more.
- If condom use, testing and PrEP stay at today's levels, but treatment was only started at CD4 counts below 350, as in 2012, there would be 853 infections in 2021, or 25% more.
- If PrEP had never been introduced, if condom use, testing and treatment were all at 2021 levels, then there would be 1433 new infections in 2021, or 100% more.
- With none of these interventions there would have been 7646 new infections in 2021.

**Figure 1. Median (and 90% range) annual number of new HIV infections in 2021 under the different counterfactual scenarios**



# Q&A

## Anal cancer

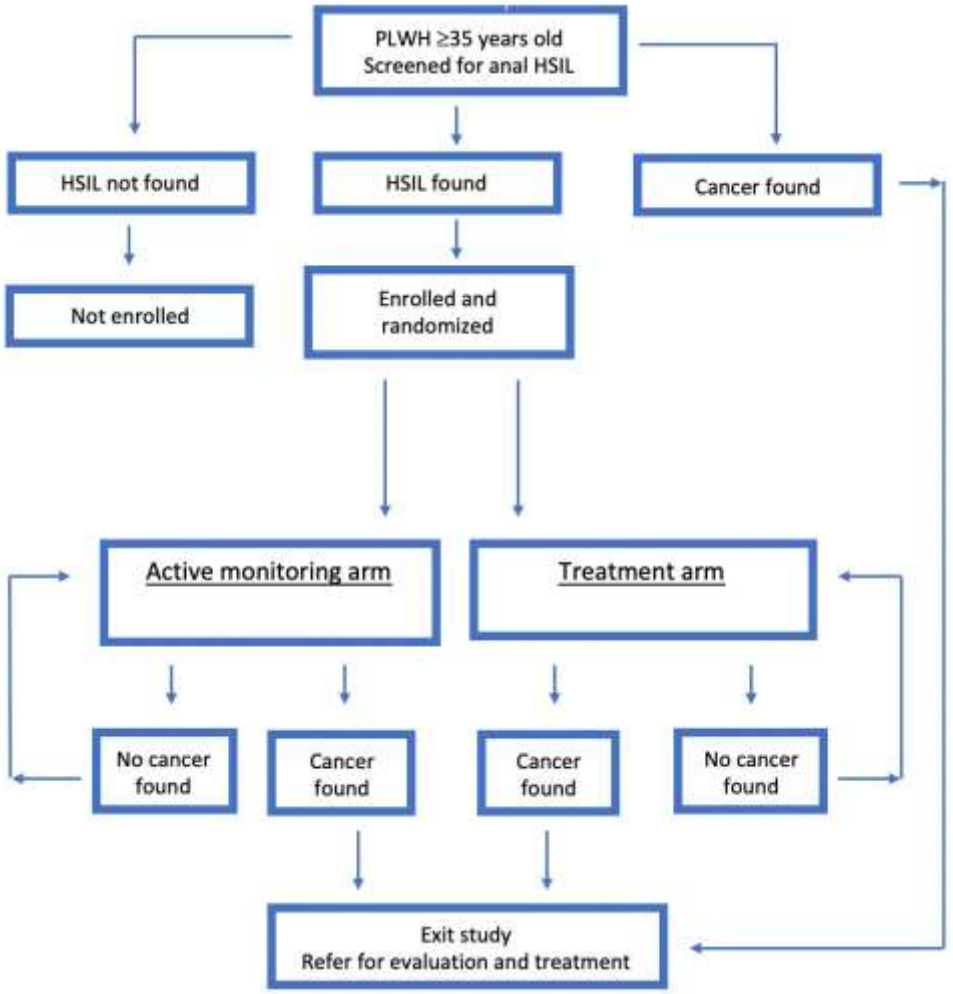
- Uncommon in the general population, but high rates in people with HIV
  - Especially gay and bisexual men and older people with HIV
- A similar disease to cervical cancer
  - Human papilloma virus (HPV) >> pre-cancerous lesions (HSIL) >> anal cancer
  - Cervical screening helps prevent cervical cancer
  - But, until now, no clear evidence that anal screening helps prevent anal cancer

# Why anal screening and treatment of lesions might not work

- Many people with HIV have multiple, large lesions
  - These have higher risk of treatment failure
- Screening is difficult to do well – some lesions may be missed
- Clinicians may inadequately treat lesions
- New lesions often arise after treatment – “anal whack-a-mole”

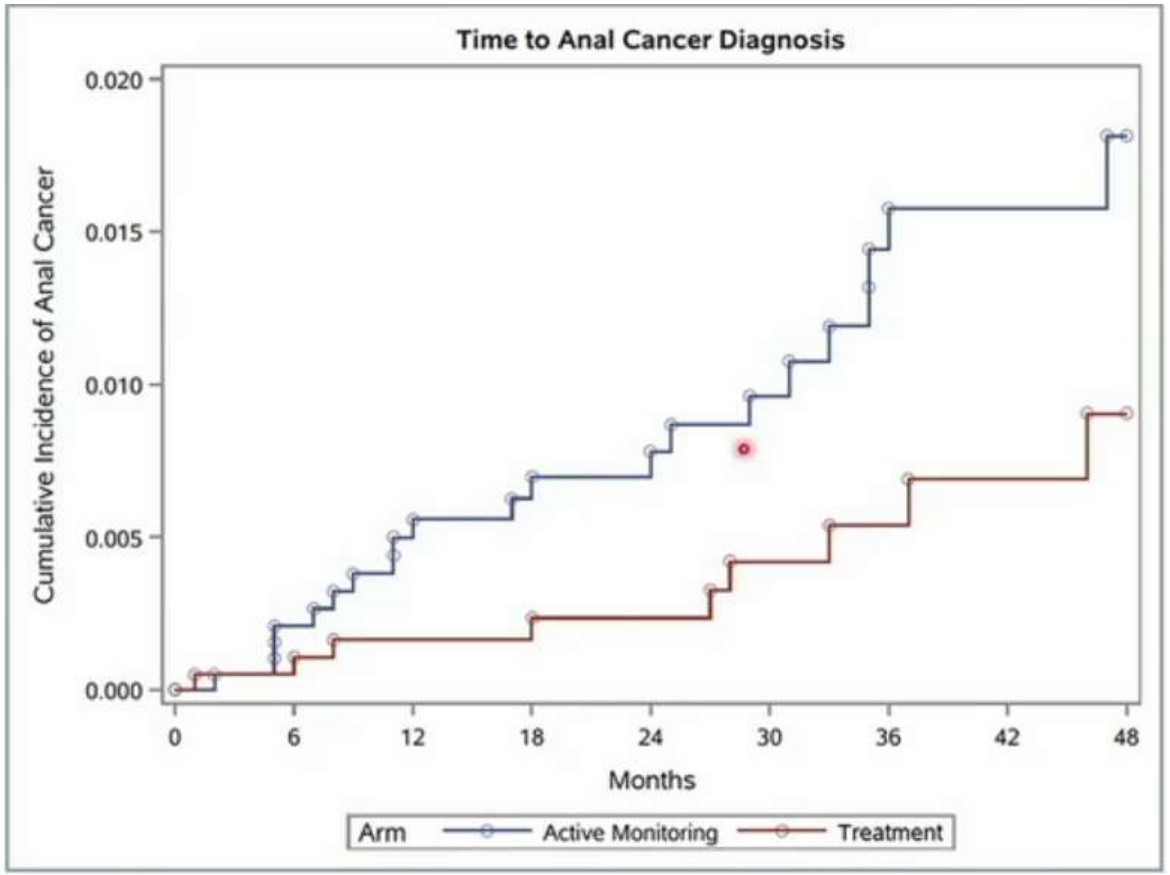
# ANCHOR randomised clinical trial – study design

- Over 10,000 people with HIV screened
  - Aged 35+
  - Anal cytology (Pap smear) + high-resolution anoscopy (small magnifying device)
- Those with HSIL randomly allocated to:
  - Immediate treatment of lesions, OR
  - Active monitoring (follow-up screening every six months)
- Everyone with anal cancer immediately treated
- Primary outcome: new cases of anal cancer



# ANCHOR randomised clinical trial – results

- ANCHOR randomised clinical trial – results
- At screening, high rates of HSIL
  - 53% of men
  - 46% of women
  - 63% of transgender people
  - 17 people (0.16%) had anal cancer at screening
- Median follow up 26 months
- 9 cases anal cancer in immediate treatment arm
- 21 cases anal cancer in active monitoring arm




*Kaplan-Meier curve of time-to-confirmed cancer cases*

the ANCHOR study

## Implications

- Regular anal screening and immediate treatment may be recommended for people with HIV aged 35+
- Challenge – not enough trained clinicians for anoscopy
- Digital rectal example is simple, cheap
- Prioritise people with possible symptoms (lumps, pain, bleeding)
- Prioritise older people and those with low CD4 counts

## Implications

- Prevention better than cure – HPV vaccination
  - Recommended for 12 and 13 year olds
  - BHIVA recommends for adults with HIV. (Women up to 40 years, gay & bisexual men up to 40 years, heterosexual men up to 26 years).
  - HIV-negative gay and bisexual men up to 45 years.

# Vertical HIV transmission in France

- Data from 2000 to 2017, 14630 infants
- HIV transmission rate of 0% among women who:
  - started HIV treatment before conception,
  - had an undetectable viral load at childbirth, and
  - did not breastfeed
- HIV transmission rate of 0% among women who:
  - had an undetectable viral load in first trimester, and
  - did not breastfeed

**CONCLUSIONS**

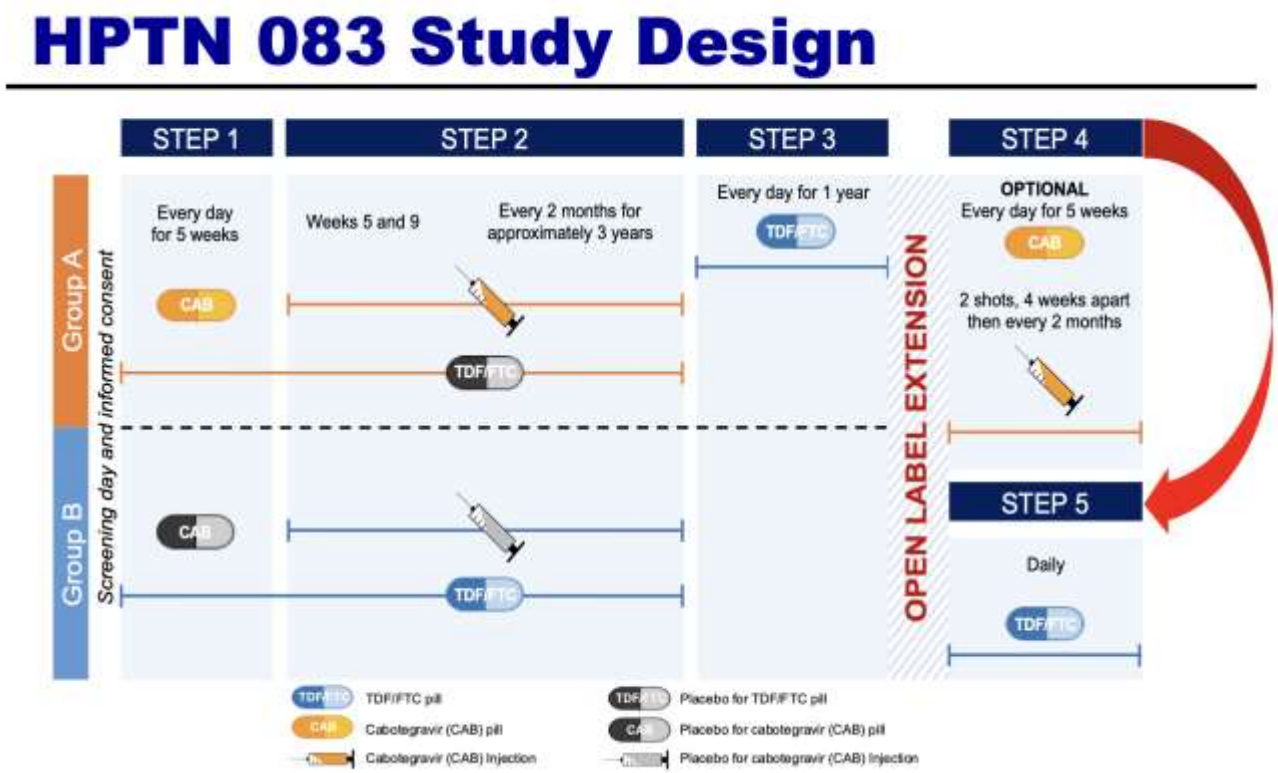
In the absence of breastfeeding, and in the French context of free access to ART and monthly pVL assessment suppressive ART initiated before pregnancy and continued throughout the pregnancy can eliminate perinatal transmission of HIV.

# Vertical HIV transmission in France

- Overall transmission rate among non-breastfed infants decreased from 1.1% to 0.2%
- Risk factors:
  - No treatment
  - Starting treatment later
  - Higher viral load
  - Premature delivery

# PrEP: HPTN 083: injections vs pills

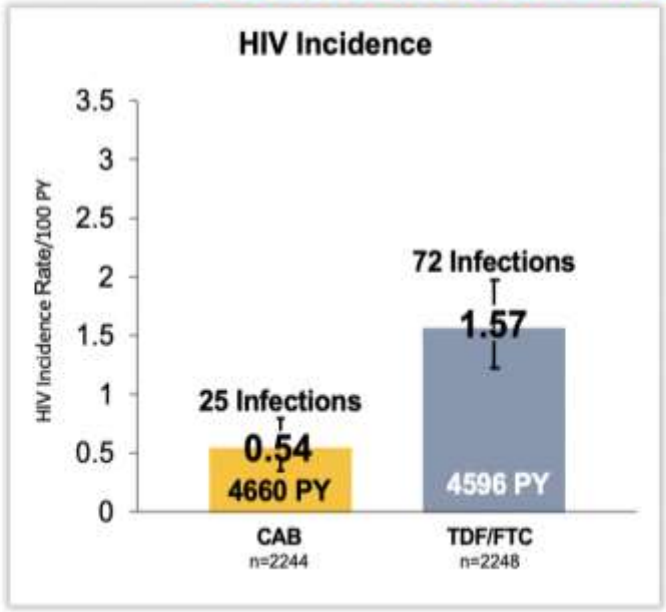
- 4566 gay and bisexual men and trans women (12.5%)
- Randomised to 2-monthly cabotegravir injections + placebo pills or TDF/FTC + injected placebo
- Data now from 1 more year of open label use

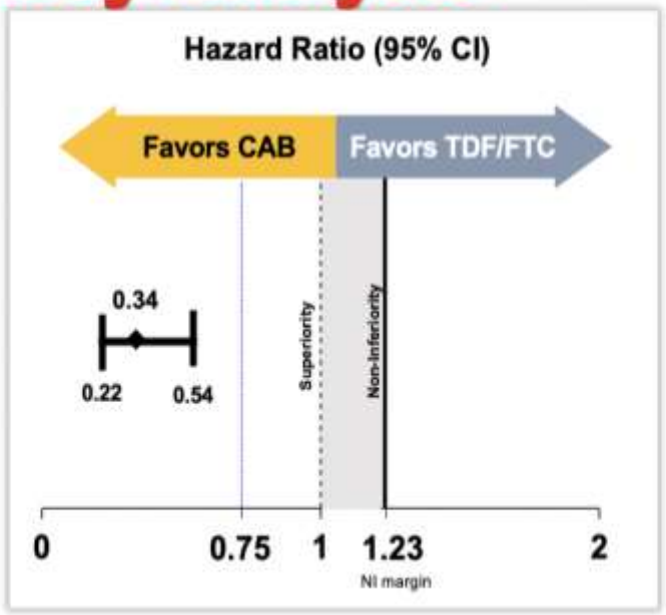


## Injections stop two-thirds more infections than pills

# HIV Incidence: CAB vs. TDF/FTC

## Combined Efficacy Analysis



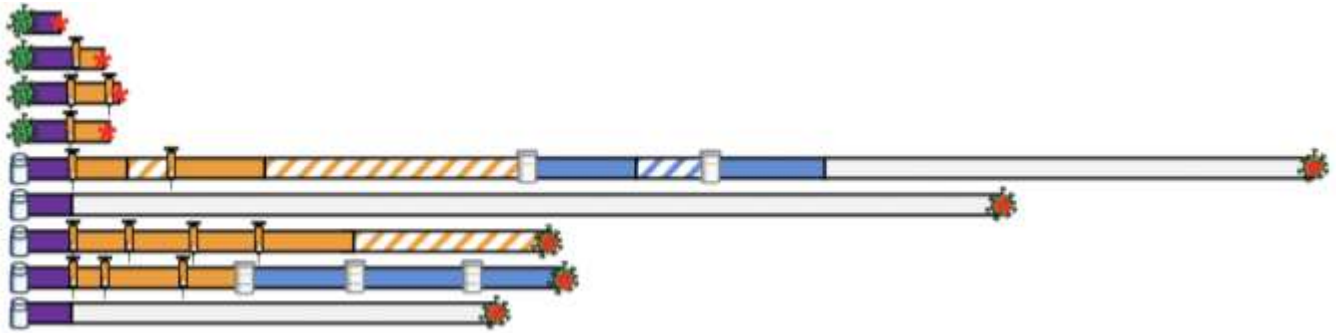



# There were some infections on the injections

## Cabotegravir Arm infections

These 4 already had HIV at the start

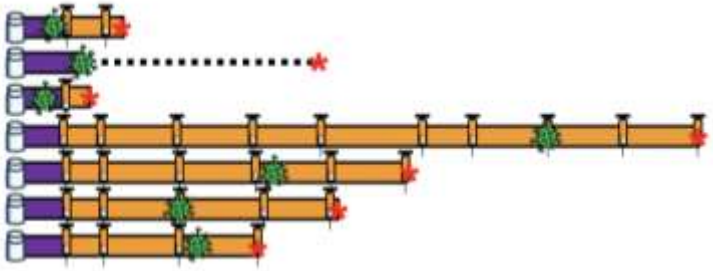
These 5 stopped or switched



These 3 were on the pills (prior to injections)

These 4 caught it despite good adherence to the injections. We don't know why

- But we could have detected their infections sooner using PCR ( = viral load) tests



# Q&A

# Thank you

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