



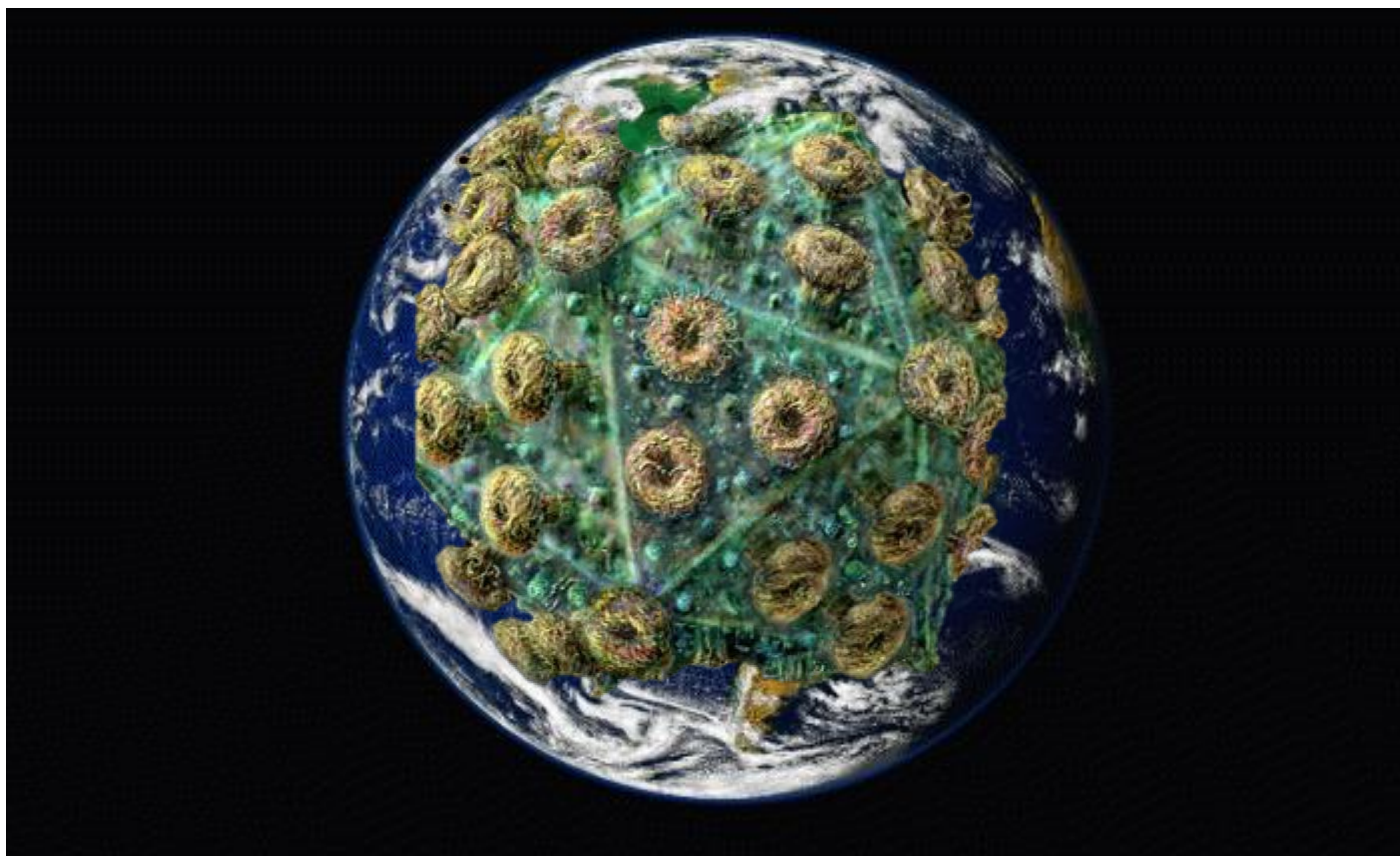
AMP

STUDY

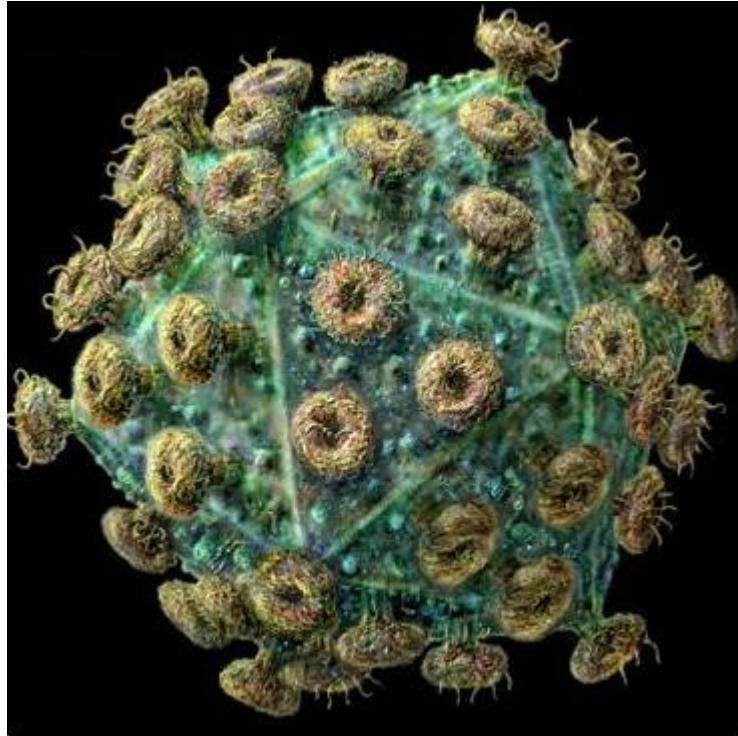
The HIV Prevention Toolbox: More Tools Needed

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**78 million people infected,
39 million people dead**



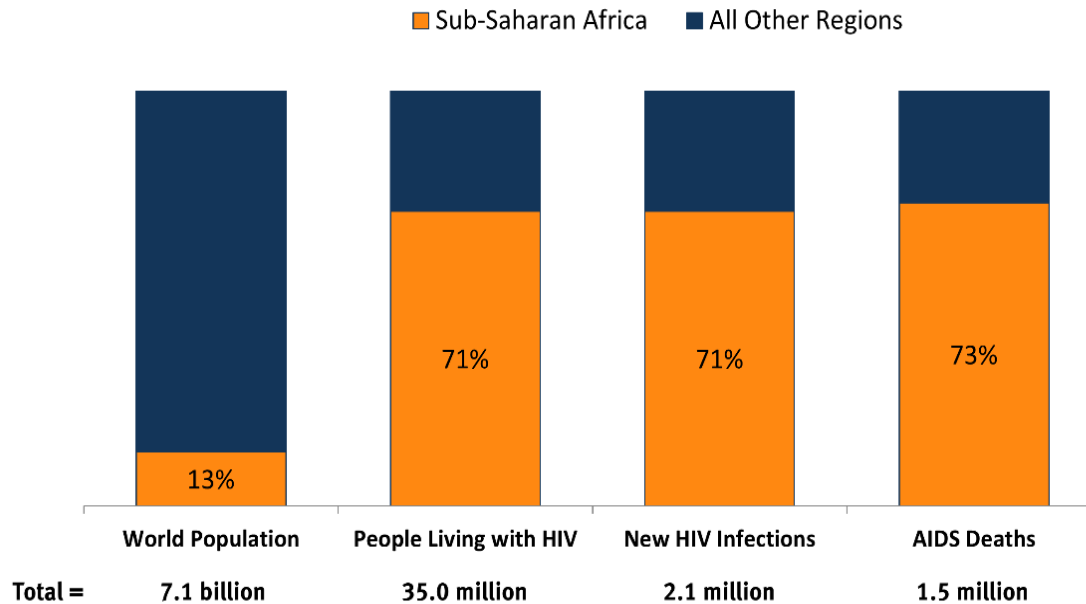
Worldwide 37m living with HIV today



SSA has 70% of this burden, in most SSA countries close to 60% of people living with HIV are women

Global Picture vrs SSA HIV burden

Sub-Saharan Africa as Share of Global HIV Prevalence, Incidence, and Deaths Compared to Share of World Population, 2013



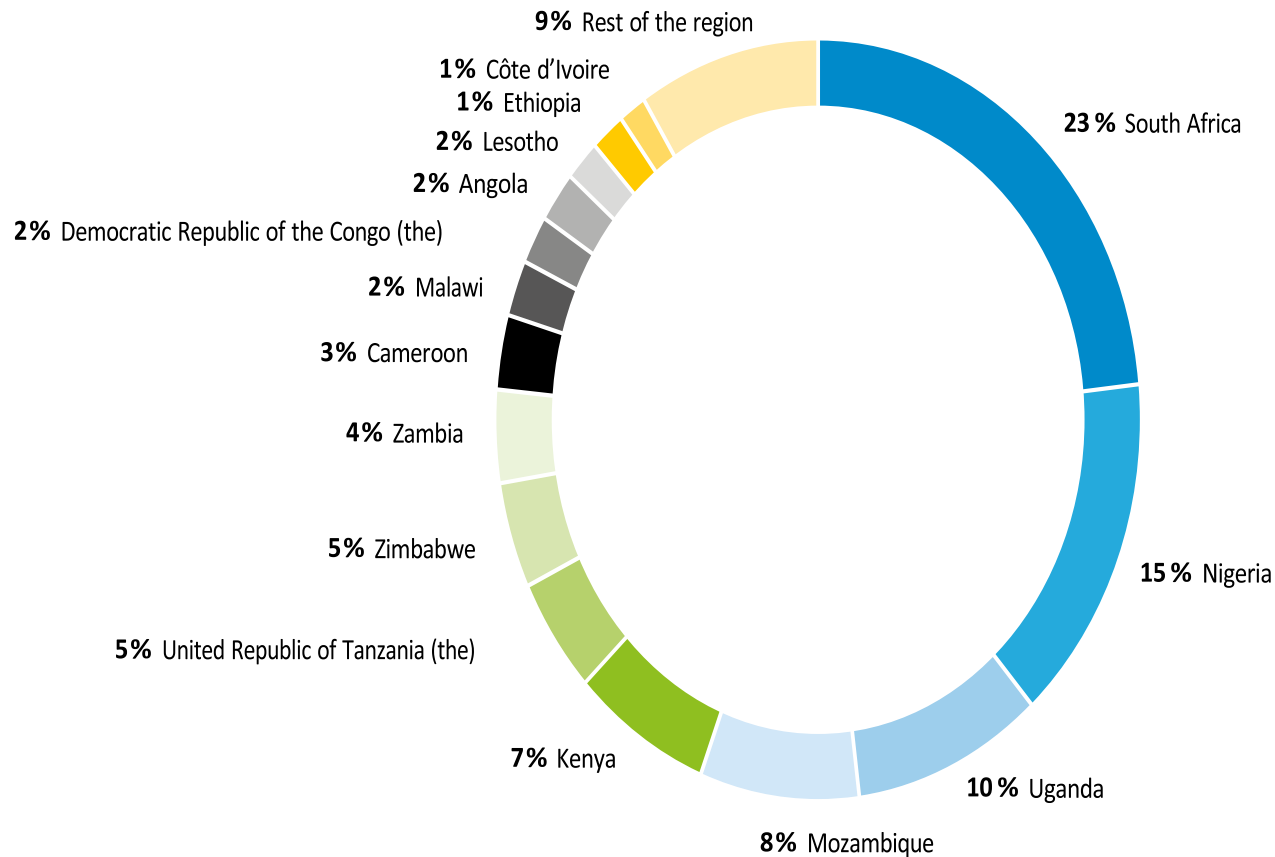
SOURCE: Kaiser Family Foundation, based on UNAIDS, Gap Report; 2014 and Population Reference Bureau, 2013 World Population Data Sheet; 2013.



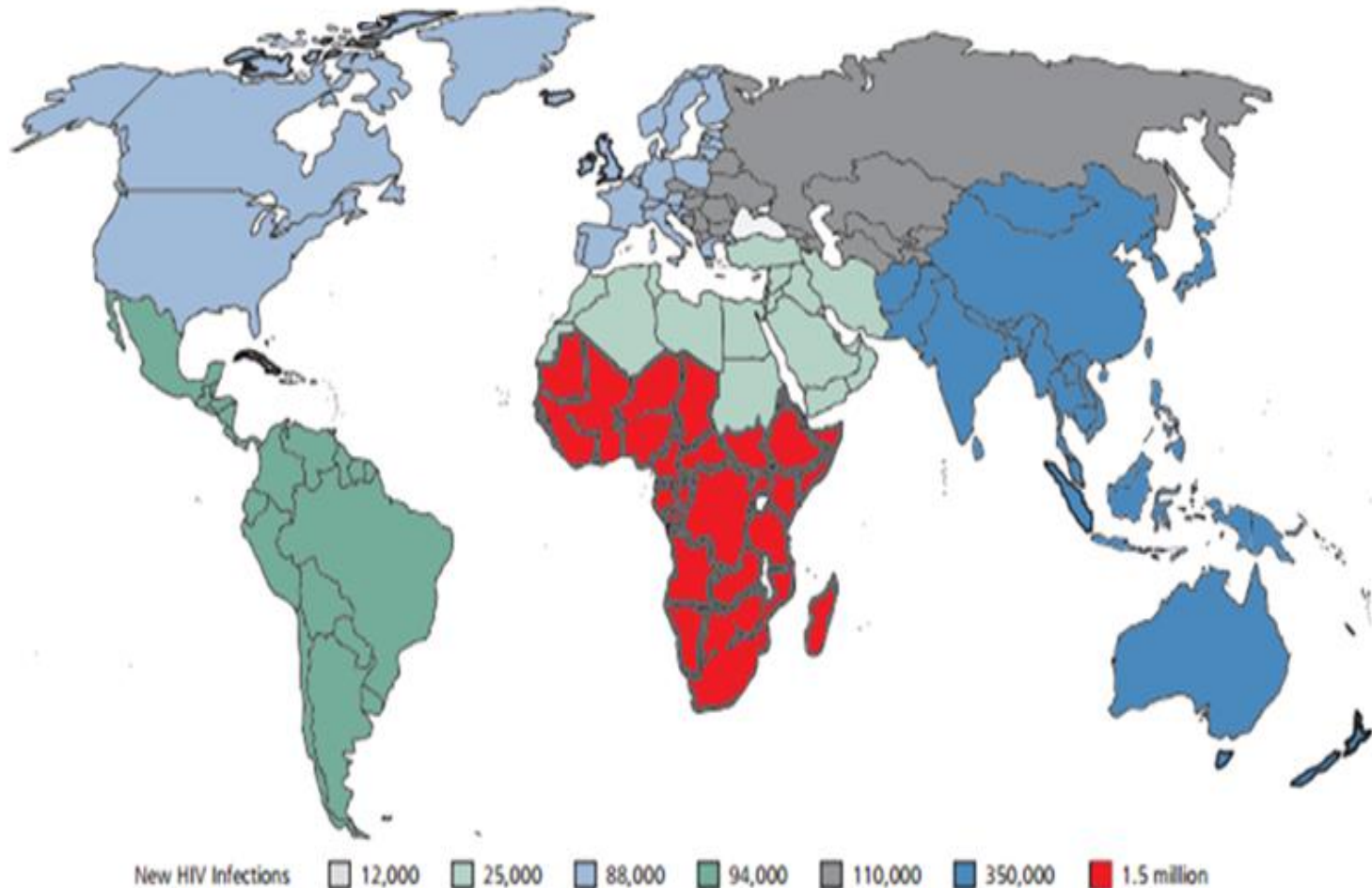
Burden of HIV in SSA AMP Countries

Country	People living with HIV/AIDS	Adult (15-49 yr) Prevalence	Women with HIV/AIDS	Children with HIV/AIDS	AIDS Deaths
Botswana	300 000	23.4	160 000	15 000	4 200
Kenya	1, 600 000	6.2	800 000	220 000	62 000
Malawi	910 000	10.0	430 000	170 000	44 000
Mozambique	1, 400 000	11.3	750 000	200 000	74 000
SA	5, 600 000	17.3	2, 900 000	460 000	270 000
Tanzania	1, 800 000	5.6	760 000	230 000	84 000
Zimbabwe	1,200 000	14.9	600 000	200 000	58 000

New HIV infections in sub-Saharan Africa, 2013



Annual New HIV Infections in 2013



About half of all new HIV infections in 2014 occurred in 8 ESA countries

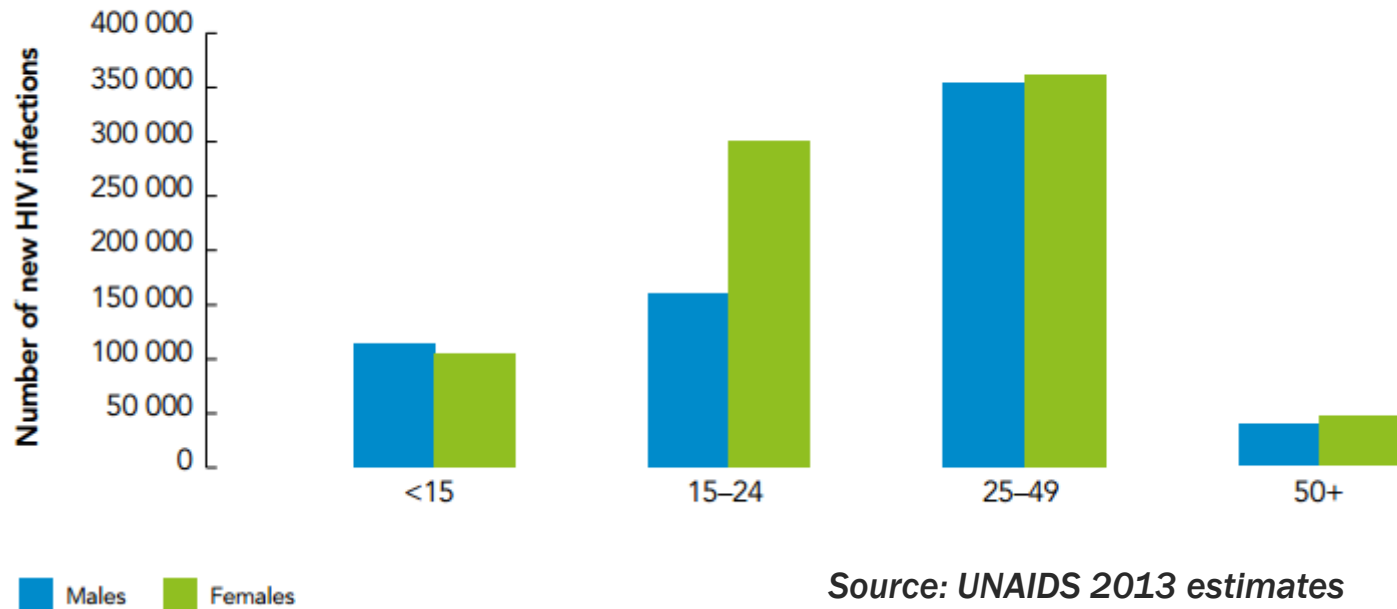
Country	Number of new HIV infections in 2014
South Africa	340 000
Uganda	100 000
Mozambique	88 000
Zimbabwe	64 000
UR Tanzania	62 000
Kenya	56 000
Zambia	56 000
Malawi	42 000

60% new infections occurred in women
Over all Decline of 32% between 2005-2013



HIV in SSA: the Epidemic Among Women

New HIV infections in sub-Saharan Africa, by age and sex, 2013

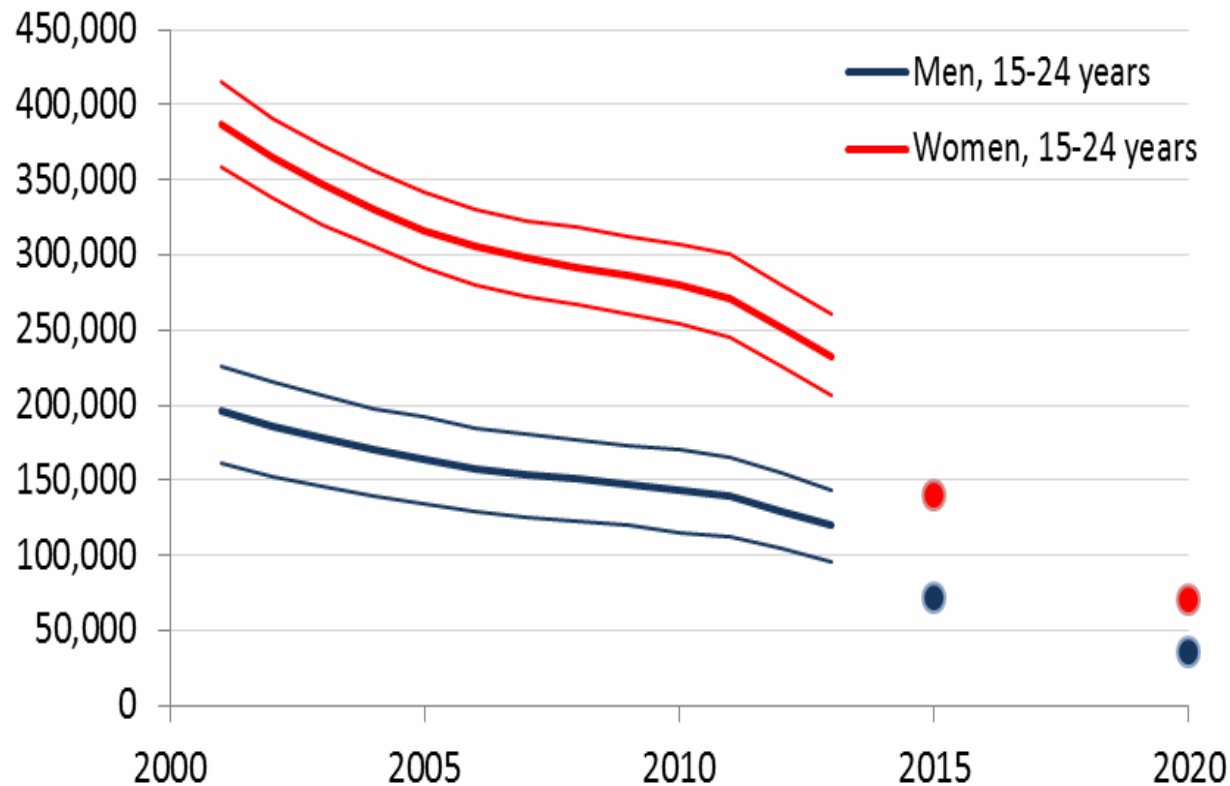


Source: UNAIDS 2013 estimates

- In 2013, of the 24.7 million people HIV infected in SSA >50% were women
- Young women are twice as likely to be infected as young men
- Women have fewer HIV prevention options than men

UNAIDS Gap Report, 2014

Eastern and Southern Africa: New HIV infections among young people aged 15-24 years



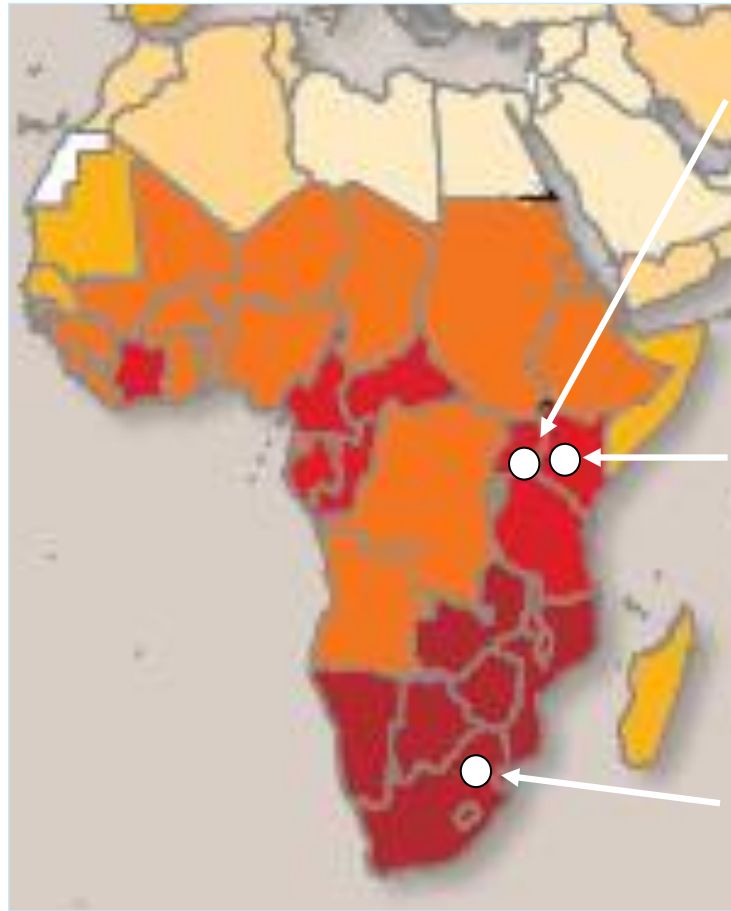
Pleased to notice a decline but burden of disease twice as high in F than M



Controlling HIV Epidemic

- Despite widespread promotion of behavioral modification that include abstinence, correct and persistent use of M or F condom the HIV epidemic continuous to cause enormous burden in SSA particularly in evolving key populations
- A new HIV prevention tool kit that has effective biomedical interventions will help control the epidemic

Randomised controlled trials of medical male circumcision to reduce HIV infection



Rakai, Uganda

Gray *et. al.* (2007) Lancet; 657 – 66%

Kisumu, Kenya

Bailey *et. al.* (2007) Lancet; 643 – 56%

Orange Farm, South Africa

Auvert *et. al.* (2005) PLoS Med; e298 – 61%



U.S. Department of Health and Human Services

NIH News

National Institutes of Health

National Institute of Allergy and Infectious
Diseases (NIAID)

<http://www.niaid.nih.gov/>

FOR IMMEDIATE RELEASE

Thursday, May 12, 2011

Treating HIV-infected People with Antiretrovirals Significantly Reduces Transmission to Partners

Achieved Complete and Sustained Virological Suppression

- **96% reduction in HIV transmission when ART started in HIV-infected partner at CD4 count of 350-550 compared to <250**



HPTN

HIV Prevention
Trials Network



**HIV VACCINE
TRIALS NETWORK**

The Washington Post

May 10, 2012

FDA Panel Recommends Approval of Drug to Prevent HIV Infection

By Brian Vastag

For the first time in the 30-year battle against the HIV epidemic, a panel of experts has recommended that the Food and Drug Administration approve a drug to give to healthy people to protect against the infection.



What is the Ideal drug for PrEP?

- **Drug must be safe, potent, easy to use and acceptable**
- **High barrier to resistance**
 - Ideally, no effect on future ART options
- **Adequate concentrations and activity at all vulnerable sites of infection**
 - Vagina, cervix, rectum, bloodstream
- **Available & affordable**

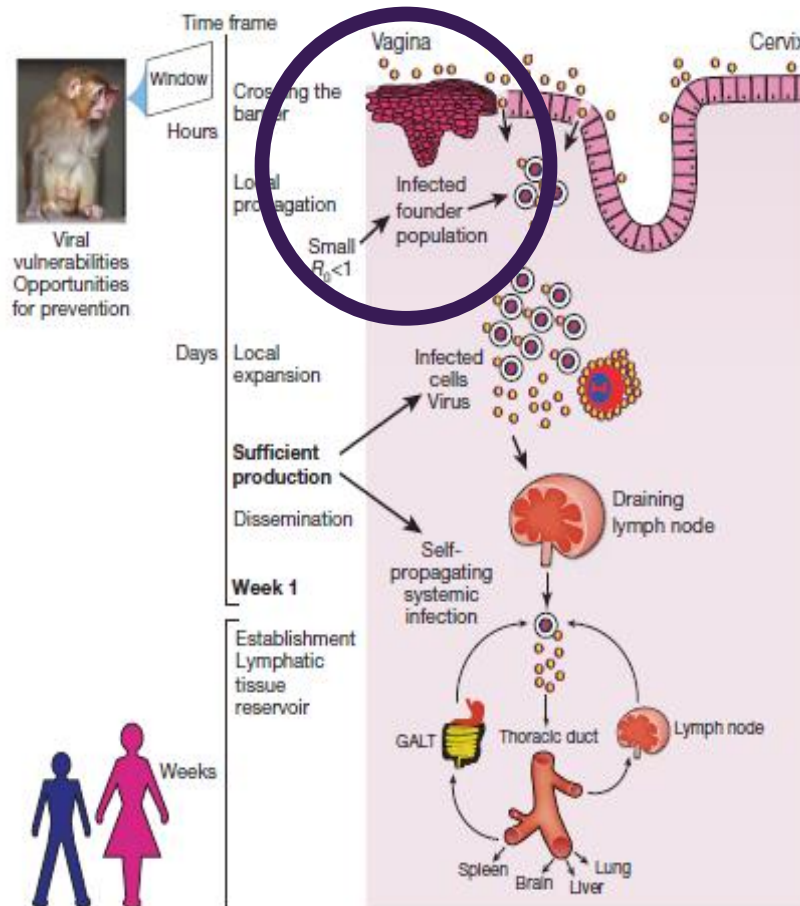
Controlling HIV Epidemic

- Despite widespread promotion of behavioral modification that include abstinence, correct and persistent use of M or F condom the spread of new HIV infections continues mostly in high risk populations.
- High risk populations: **discordant couples, MSM, sex workers, cross-border traders, truck drivers, refugees**

Biomedical Interventions: Focusing on HIV prevention options for women

- **What have we done to combat HIV prevention in women?**
- **Firs attempt was development of a microbicide since 1992 has been long, tortuous, with at least 41,000 women from ESA volunteering in these trials**
- **For a product to be effective, it must get to right place, right time, right dose, high barrier to develop resistance**
- **Available & affordable**

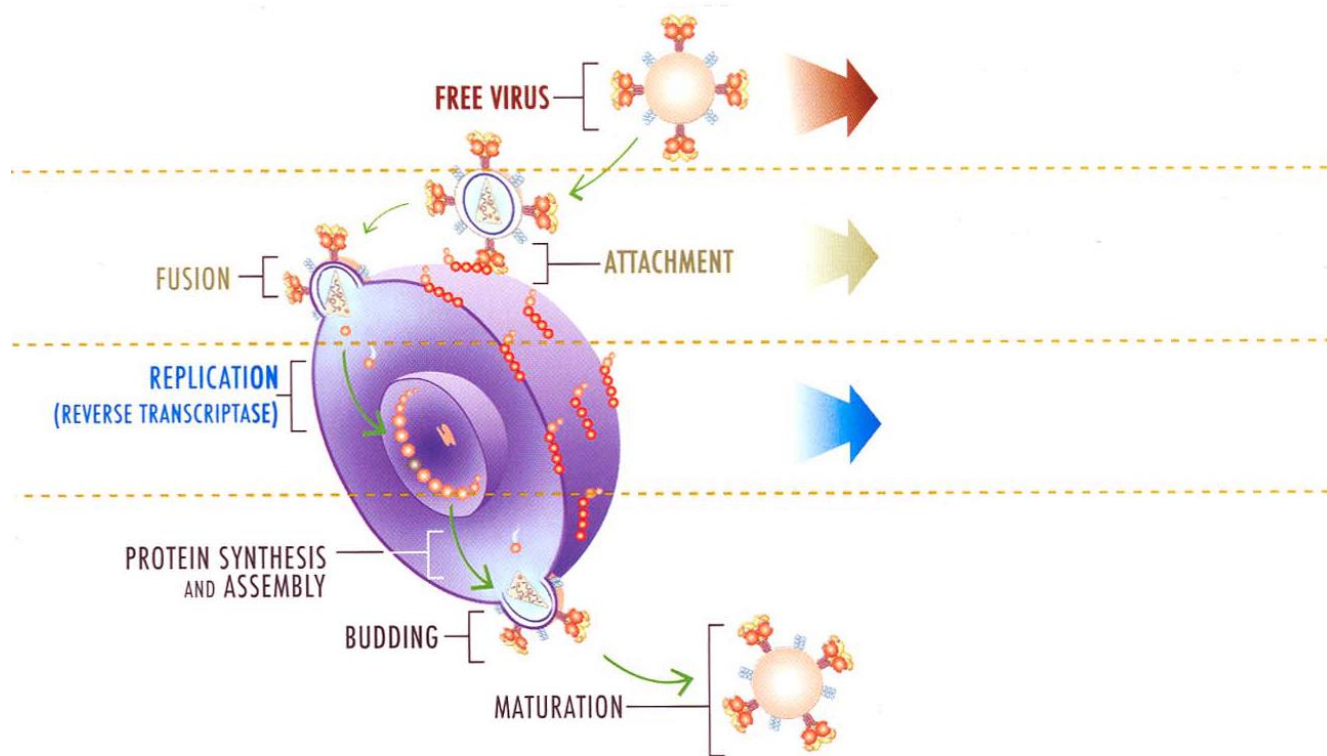
A Model of HIV Entry Into Female Genital Tract



Epithelial Disruption that allows viral entry

Hassey, Nature 2010

Progression in the product pipeline



In past 6 yrs we have seen pivotal, proof of concept PrEP trials



- **Oral pre-exposure prophylaxis (PrEP)**
Involves taking an ARV tablet by mouth Truvada (combination of tenofovir and emtricitabine) tested in 6 studies



- **Vaginal topical products**
1% tenofovir gel tested in CAPRISA 004, VOICE, FACTS



- Vaginal ring containing dapivirine tested in ASPIRE and ongoing RING Study

End of TFV gel development for HIV prevention in women?

- **At CROI March 2013, VOICE study reported no protection of HIV infection among women using TFV gel as daily regimen**
- **At CROI Feb 2015, FACTS 001 reported no protection of HIV infection among women using TFV gel BAT regimen used in CAPRISA**
- **Clearly tenofovir gel was not acceptable for these women as evidenced by low levels (<25%) of detectable tenofovir in swabs collected from genital tract**

Conclusions

- Incidence of HIV substantially higher than anticipated
- No study drug significantly reduced risk of HIV acquisition
- Adherence to study products was low, especially among younger, unmarried women
- **Results consistent with Fem-PrEP**
 - Consider PrEP agents / delivery systems that are long acting and require minimal daily adherence
- **Understanding HIV risk perception and biomedical, social and cultural determinants of adherence in this high-risk population urgently needed**

What was Impact of VOICE Study

- VOICE was “Game-changer” – removed any reliance on self-reported adherence
- Surprisingly, HIV risk perception was clearly not their greatest concern, particularly in young women < 25yrs
- Objective measurements(PK) of adherence are now obtained during the trial and results discussed with participants as unblinded data across CRS

On the Horizon (ASPIRE and RING Study Results are encouraging

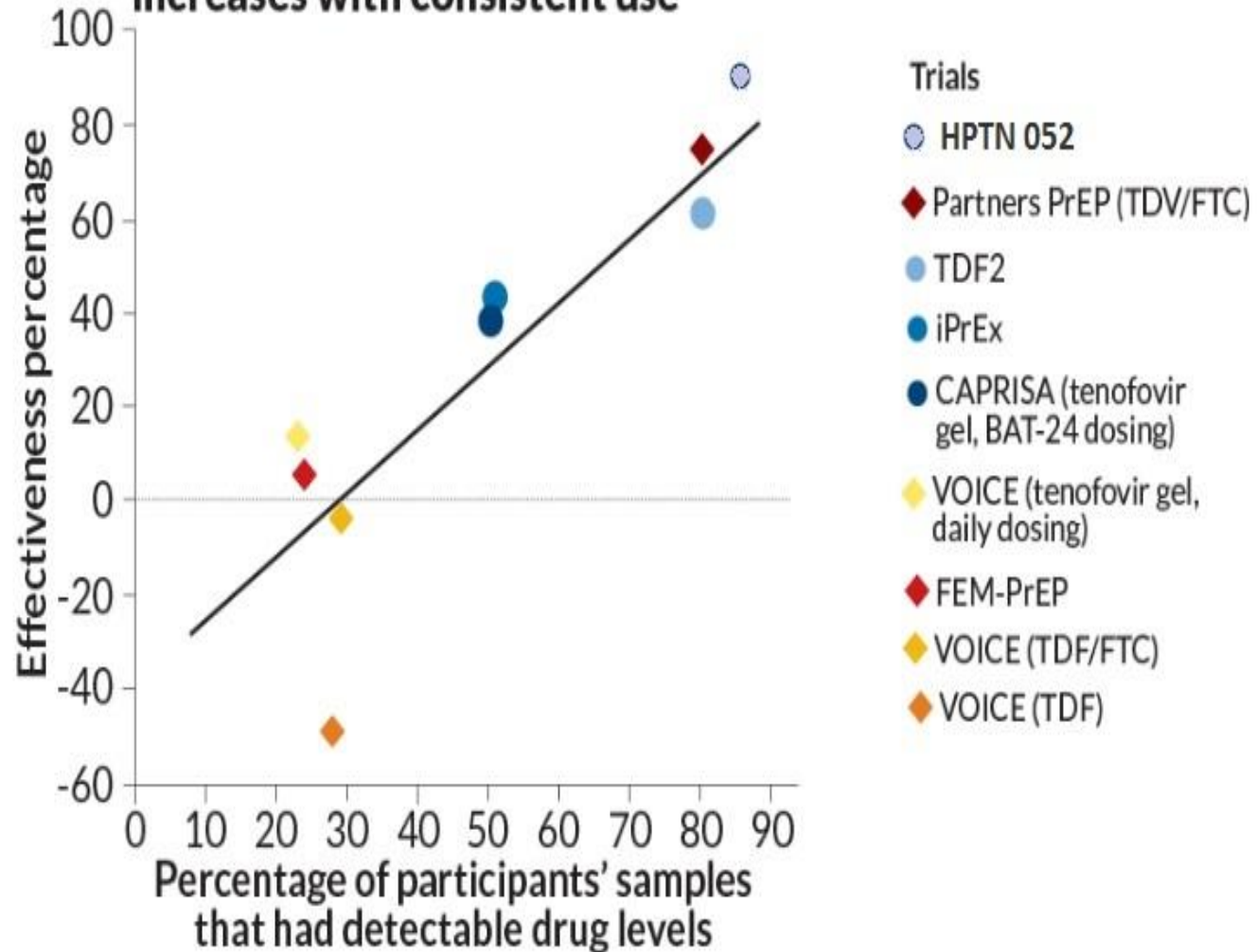


- Phase III safety and effectiveness trial of a vaginal ring containing the ARV dapivirine, replaced every 4 weeks.

high level of protection (56% in ASPIRE) women > 21yrs

- Lower adherence and no protection women 18-21 yrs

Effectiveness of tenofovir-based preventions increases with consistent use



Long Acting (LA) PrEP for Women: New Opportunity

- To overcome adherence changes observed in many PrEP trials, new ARV based 8 week IM formulations are early testing phases
- LA form of oral Rilpivirine (TMC278 LA) an NNRTI and GSK126744 LA an Integrase Inhibitor

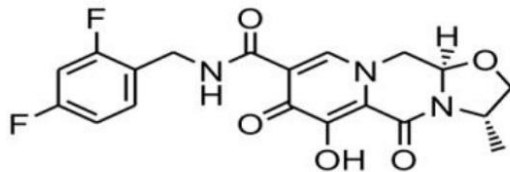
HPTN 076

- To evaluate the safety and acceptability of the injectable product, TMC278 LA, in healthy, 132 HIV-uninfected women.
- Enrolled 136 women (Harare 52, Capetown 48 and US 36)
- Results expected by 2017

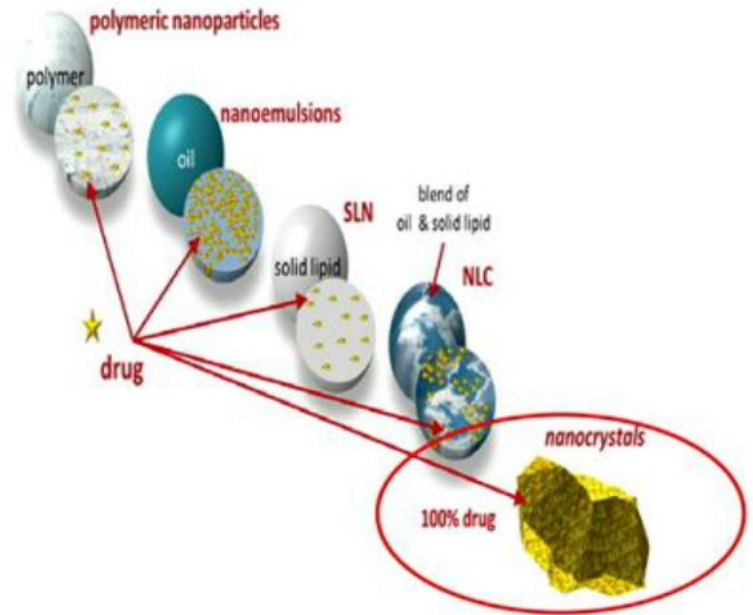
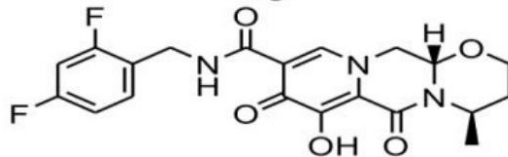


CABOTEGRAVIR: GSK126744 Long Acting (744LA)

GSK1265744
(GSK744)



Dolutegravir



Favorable attributes for PrEP:

- High genetic barrier to resistance
- PK profile – half life of 21-50 days -- allows once-daily oral or 1-3 month injectable dosing using nanosuspension formulation

Muller *et al*, European Journal of Pharmaceutics and Biopharmaceutics, 2011
Spreen, 7th IAS, 2013; Min, ICAAC, 2009
Taoda, International Congress on Drug Therapy in HIV Infection, 2012

Long Acting PrEP: Concerns

- **Tolerance of two injections (4 ml)**
- **Safety, as drug “removal” is not possible**
- **Managing discontinuation (the tail)**
 - **subtherapeutic levels of ART threaten resistance if HIV is acquired**

Long Acting PrEP Opportunity: WOMEN

First Signal of Efficacy in an HIV Vaccine Clinical Trial



The
New England
Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

Volume 361

December 3, 2009

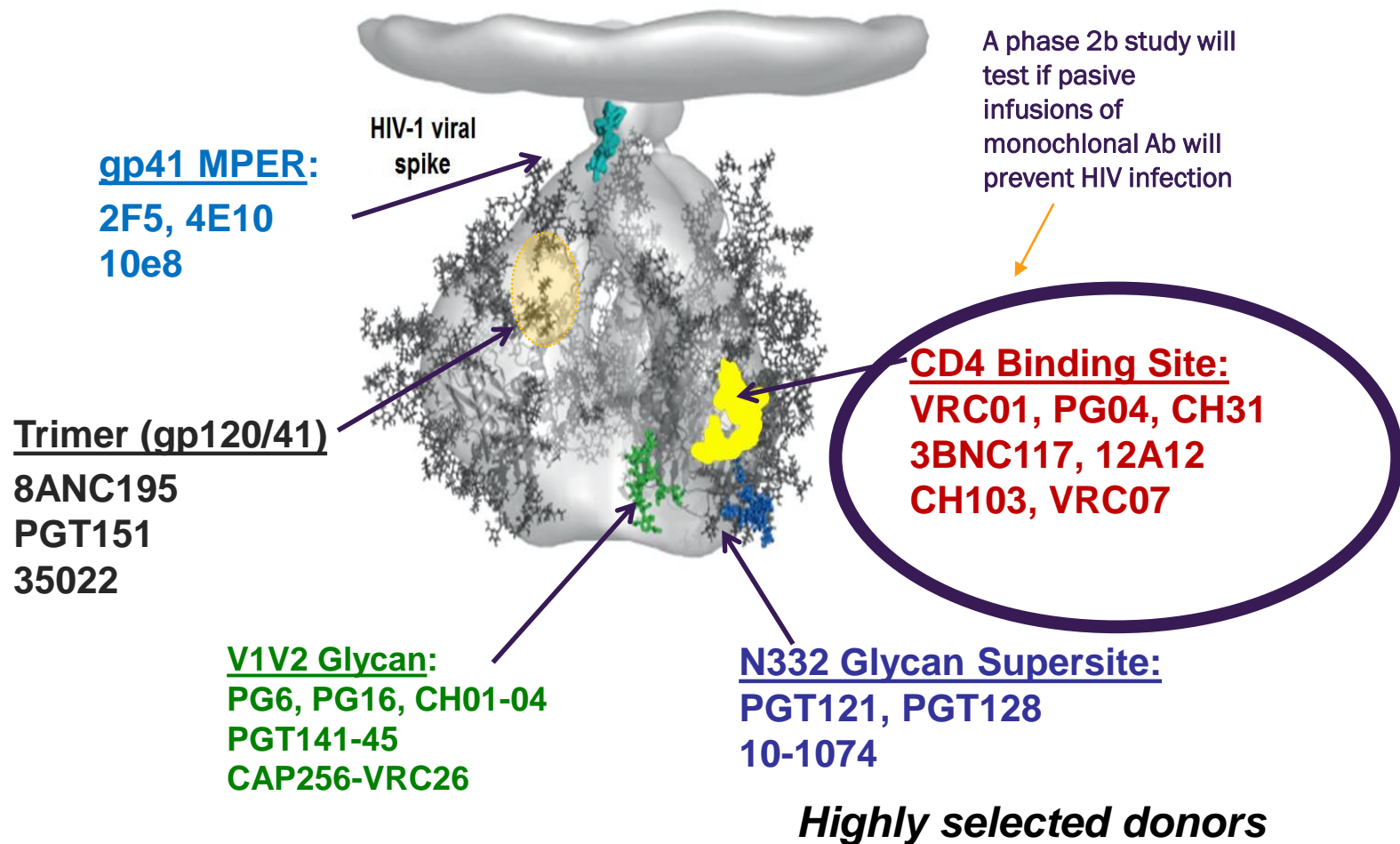
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Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

**S Rerks-Ngarm, JH Kim, NL Michael et al. for the
MOPH-TAVEG Investigators**

Modest (31%) protection vaccine recipients in Thai study correlates with neutralizing Abs to a conserved region Region of HIV Envelope

Neutralizing Antibody Epitopes on Native Trimer (since 2009)



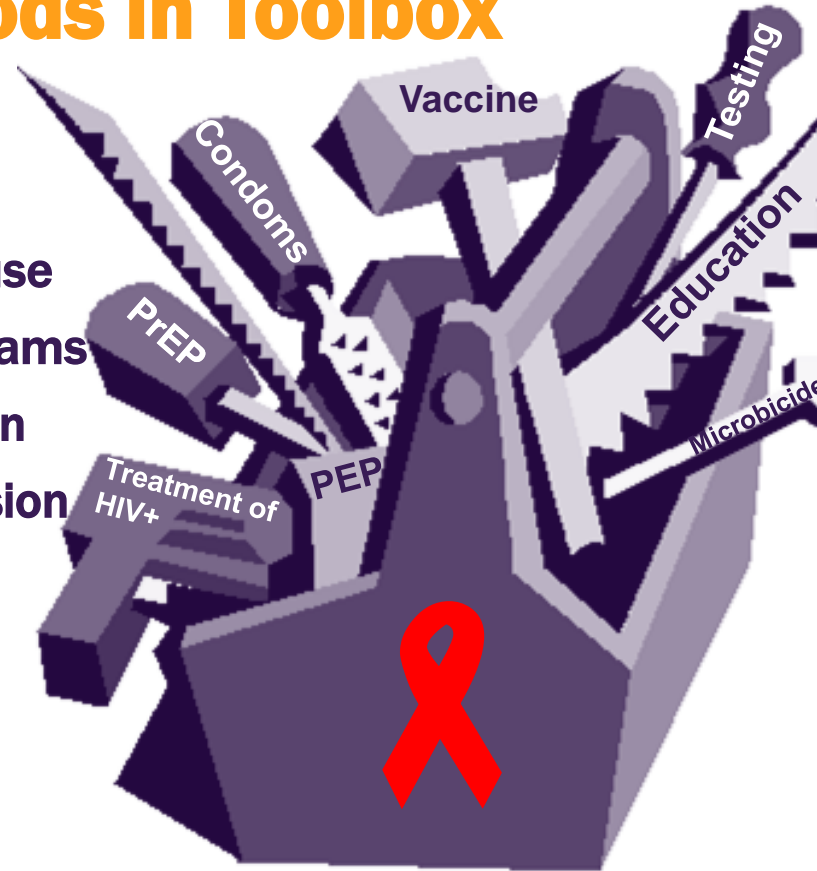
The HVTN 703/HPTN 081 AMP Study: Filling the Gap

AMP = Antibody Mediated Prevention

This is the idea of using an **antibody** made by scientists and giving it to people directly, i.e. using an intravenous (IV) **infusion**, to **prevent** HIV infections.

HIV prevention Methods in Toolbox

- Education and behavior modification
- Condoms, and other barrier methods
- Treatment/prevention of drug/alcohol abuse
- Clean syringes, i.e. needle exchange programs
- Interruption of mother-to-child transmission
- Circumcision for female-to-male transmission
- HIV/STI Testing
- Antiretroviral treatment as prevention
- Post-exposure prophylaxis (PEP)
- Pre-exposure prophylaxis (PrEP)*
- **Topical microbicides[‡]**
- **Intra vaginal rings[‡]**
- **Vaccination[‡]**



*Daily Truvada®; alternate regimens still in research

[‡]Still in research

With thanks to Carl Dieffenbach & Jeff Schouten

Scientists need to test novel prevention modalities to fill the prevention gap

