

The Prevention Landscape for Women: Yesterday, Today and Tomorrow

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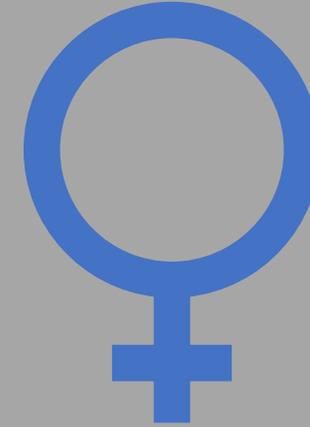
(MBChB, MMed)

MTN Regional Meeting

September 25, 2018



- Despite global progress in the last decade, women still bear a disproportionate burden of HIV.
- **Young women** twice as likely to be infected as young men.
- Biological factors that may increase the susceptibility of young women to HIV infection:
 - genital mucosa immaturity or inflammation,
 - other sexually transmitted infections,
 - hormonal effects,
 - high partner HIV viral loads.
- Unprotected heterosexual intercourse - leading mode of HIV-1 transmission in **women in communities with generalized epidemics.**

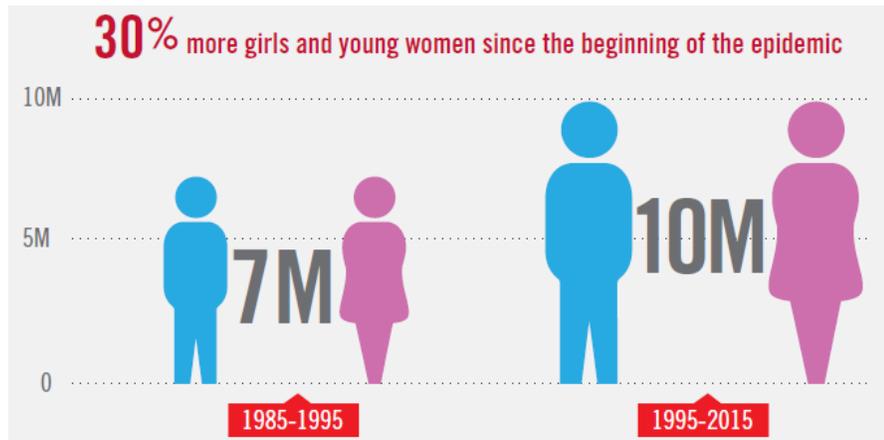


State of the Epidemic in Women

Rate of decline in new HIV infections is far too slow to reach the Fast-Track Target of <500 000 new infections per year by 2020.
(UN General Assembly –2016)

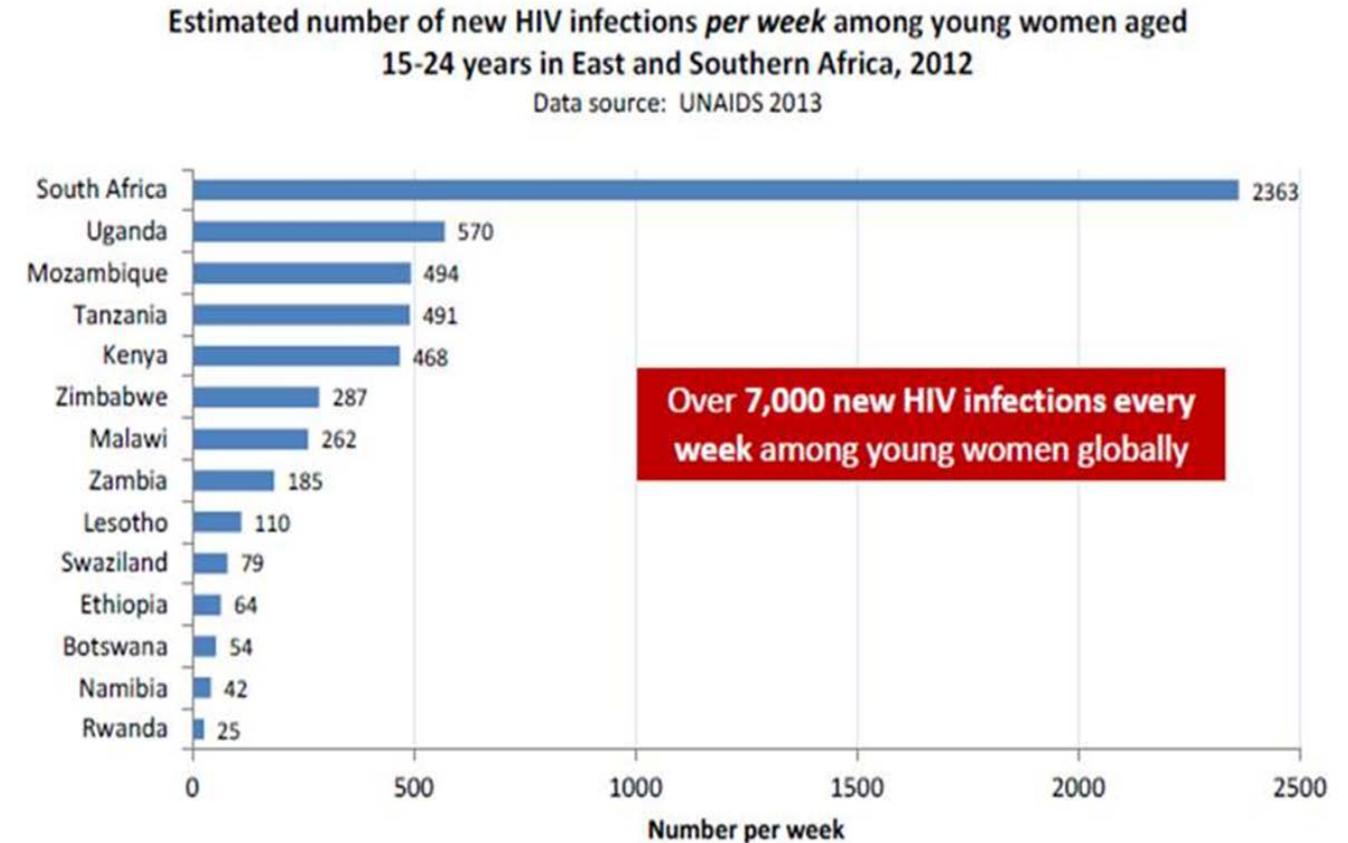
The Youth Bulge

Most pronounced in sub-Saharan Africa



HIV Incidence among Young Women

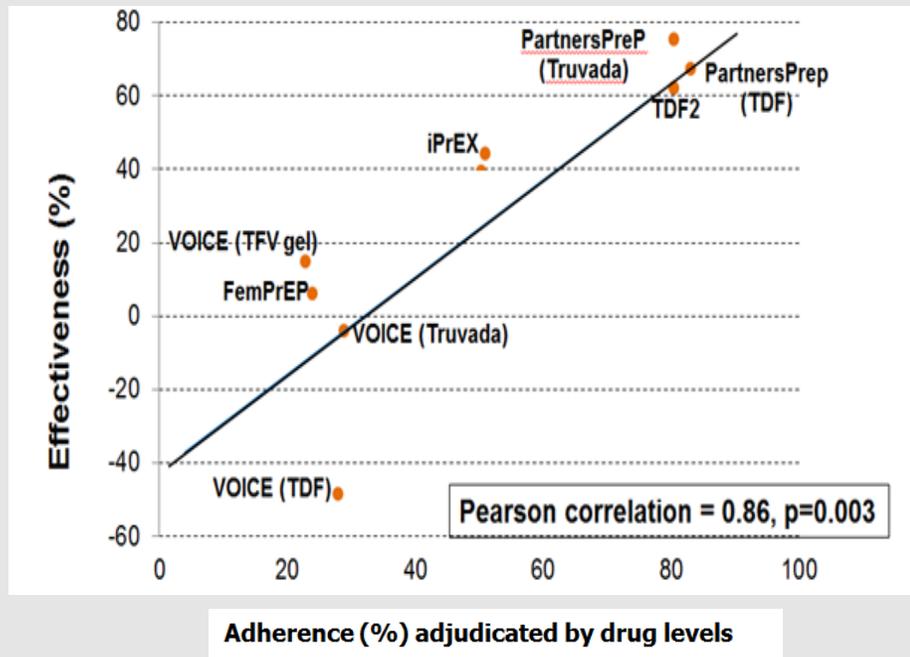
More than 1/3 New HIV Infections Globally Occur among Young Women in Africa



- High rates of HIV in young women remain unchecked.
- If prevention isn't effectively targeted to this population, early gains in the fight against the epidemic will come to naught.

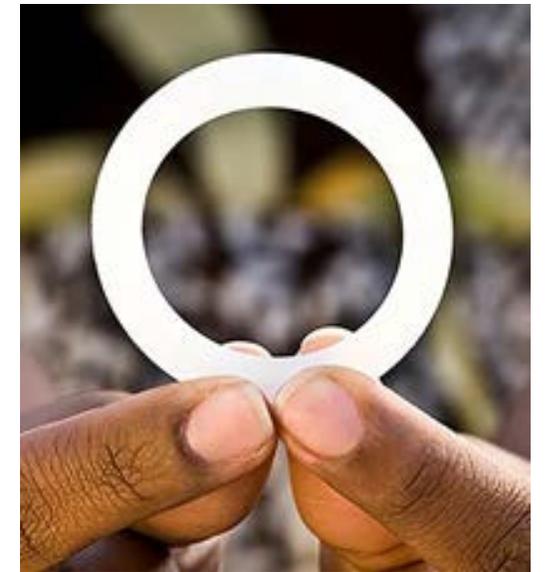
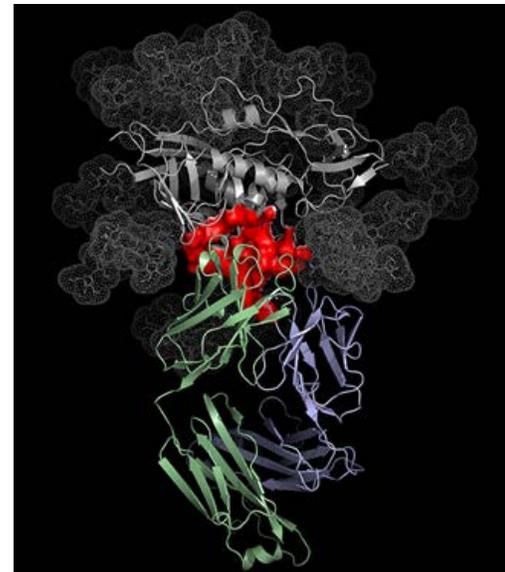
Oral PrEP

- Shows a clear dose-response relationship of protection and adherence.
- Protection modelled to be 99% when taken 7 days per week as prescribed.
- Modelled data suggest some forgiveness of missed doses for protection against rectal exposures
- Protection against vaginal exposures is modelled to be much less forgiving of missed doses.
- Urgent need for PrEP agents that have more convenient dosing schedules.



Long-Acting Formulations

- Topical Intravaginal ring (topical)
- Injectable
 - Cabotegravir
 - Broadly neutralizing antibodies
- Implantable



The AMP Studies

- Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults?
- Placebo controlled trial of VRC01 mAb (IV), given on Q2 month schedule
- Two cohorts:
 - 2,700 MSM + TG in North & South America
 - 1,900 Women in sub-Saharan Africa
- Powered to detect 60% efficacy; and to associate VRC01 plasma level with protection



HIV VACCINE
T R I A L S N E T W O R K

AMP SSA Study Updates

As of Sep 20, 2018



- Protocol opened May 9, 2016
- First participant enrolled: May 17, 2016
- **Accrual is complete!** - 1901 enrolled, **100%**
- Retention - **96%** of 23,001 clinic visits
- Adherence - **99%** of 11,600 infusions
- Study end – Q3/Q4, 2020
- HIVR4P – Retention and Baseline Findings posters



bNAbs – Next steps

- Recently, a new generation of highly potent and broadly neutralizing HIV-1 antibodies has been identified.
- To optimize the chance of success, such antibodies can be modified to improve their potency, breadth, and half-life.
- HIV-1 exhibits genetic diversity and viral escape mechanisms - Prudent to consider using a combination approach.
- Like antiretroviral therapy, combinations of mAbs may reduce the likelihood of viral escape, and increase neutralization breadth.

Vaginal Rings - Next Steps



- Long-acting PrEP formulated as a flexible silicone ring that slowly releases the antiretroviral dapivirine.
- MTN-025/HOPE and IPM-032/DREAM have shown **increased adherence**, sustained the **safety** profile and HIV-1 risk was **reduced by 54%** in both open-label studies.
- Ongoing and completed studies are evaluating the Dapivirine vaginal ring among: **Adolescents, pregnant women, lactating women and women >45 years of age.**
- Next-phase product development
 - Longer-acting rings (3-month product in Phase I) - **increased convenience, lower yearly costs**
 - Multipurpose rings - (levonorgestrel + dapivirine, in Phase I studies) **for pregnancy + HIV protection together**
- **Preparing for delivery**



Poised for Success



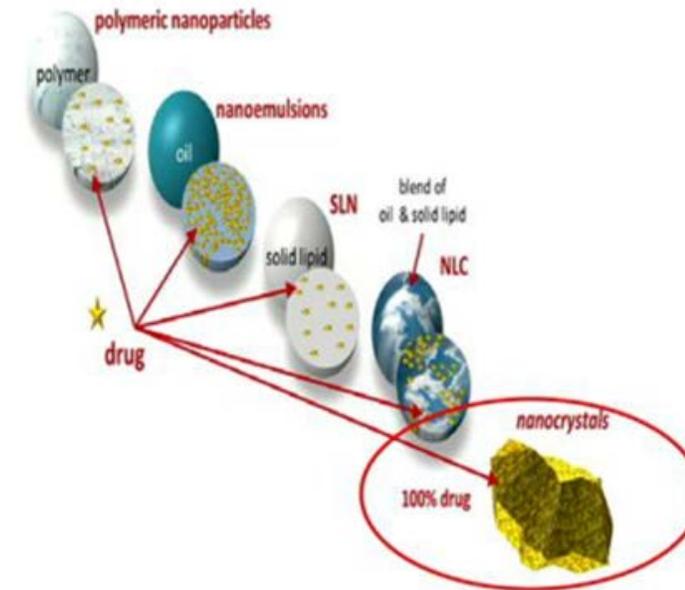
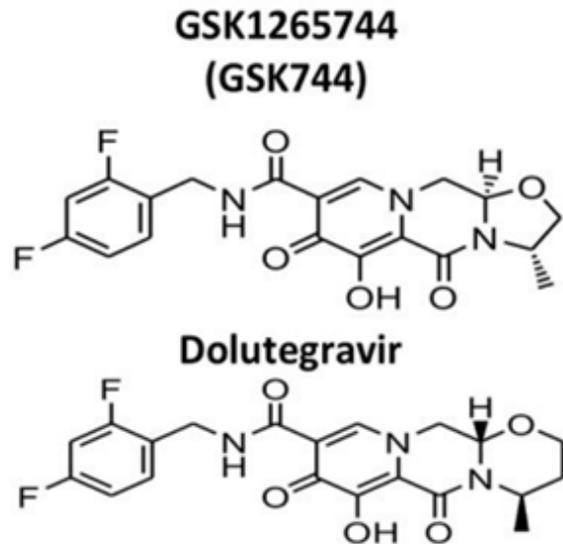
Long-Acting Injectable PrEP in HIV-1 Prevention

Advantages

- Injection every 1-3 months could address adherence issues.
- Different drug, not used heavily for treatment
 - > less concern for resistance/cross-resistance
- People are familiar with injections - highly acceptable
- Women have talked about how injections are more discreet and private than pills or rings.



Cabotegravir - GSK126744 Long Acting (744LA)



Favorable attributes for PrEP:

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

HPTN-084

- To evaluate the relative safety and efficacy of CAB vs. daily oral TDF/FTC for HIV prevention.
- Phase 3 superiority trial comparing once daily oral PrEP (Truvada®) to oral/injectable PrEP (Cabotegravir)
- Randomized, Double Blind, Double Dummy
- All study volunteers receive one active and one inactive product
- Oral run-in (5 weeks) to confirm tolerance before long-acting injection
- 20 sites in 7 countries in sub-Saharan Africa
- 3,200 women
- Results - 2023



Will CAB LA cause Neural Tube Defects (NTDs)?

- We do not know if CAB increases the risk of NTDs.
- CAB LA has a **good safety record** in women.
- Women in Africa remain at risk of becoming infected with HIV and they need prevention options now!
- Effective contraception was always a requirement for women in HPTN-084.
- Now even more stringent - injectable contraception, implant or intrauterine systems
- In the unlikely event that a woman falls pregnant:
 - CAB LA will be stopped,
 - She will be transitioned to open label FTC/TDF and
 - She will be referred for obstetric care which now includes **USS**.
- Pregnancies will be managed per site SOPs .



Long-Acting Injectable PrEP in HIV-1 Prevention



Disadvantages

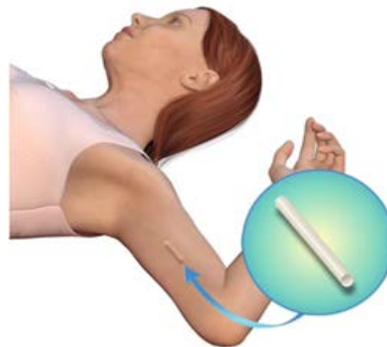
- IM injection cannot be removed once given
 - Toxicity
 - Desire to stop PrEP
- Confirmation of tolerance before long-acting injection:
 - Oral lead in phase
- Long pharmacologic tail after last injection (up to 48 weeks) → safety and resistance if recipient becomes HIV infected.
- IM dosing **every** 4 to 8 weeks
- A product that can be **removed** would **not need**:
 - An oral lead-in phase
 - Cover for the tail phase

Implants: Advantages and Disadvantages



Pros

- Consistent and predictable drug release
- Long-acting (months to years)
- May remain in place for up to 5 years
- Simple insertion or removal
- May be (non) – biodegradable
- Palpable
- Radiography/USS tracking?
- PrEP + contraception?

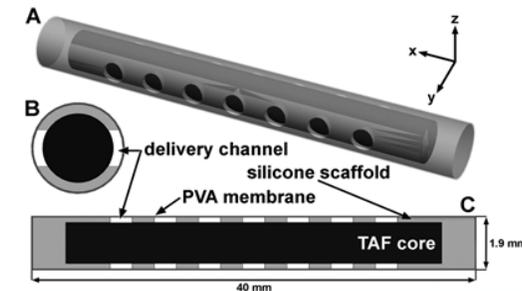


Cons

- Sterile procedure required for insertion or removal
- Expired *in situ* implants
- Scarring?
- Complicated regulatory environment

Current development

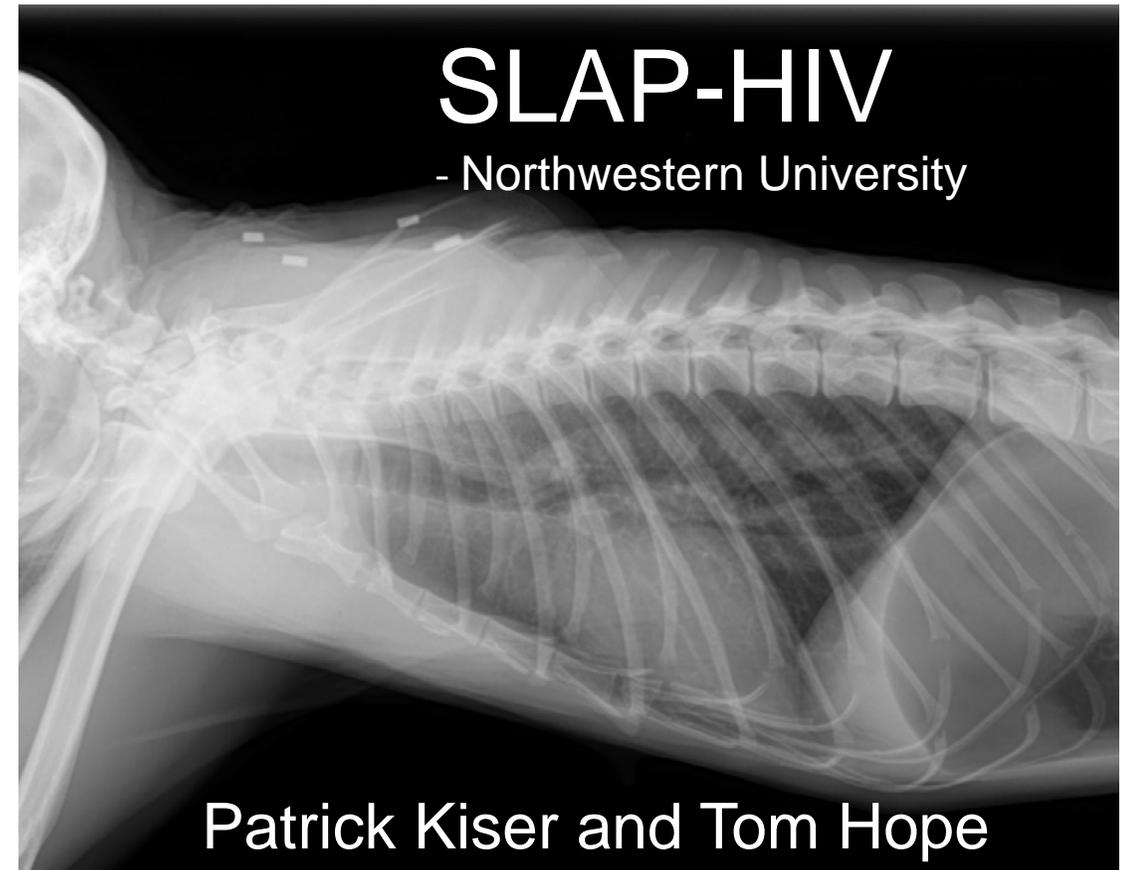
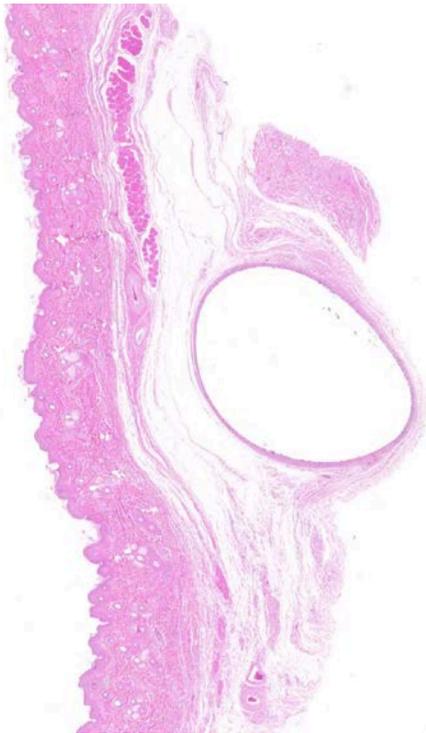
- TAF, CAB, EFdA (MK-8591)



Schlesinger, et al, *Pharm Res* 2016; Gunawardana, et al., *AAC* 2015, Flexner C. *Curr Opin HIV AIDS* 2018.

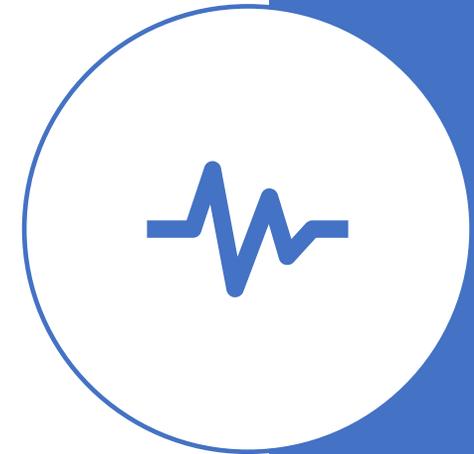
Sustained Long-Acting Protection Against HIV

The National Institutes of Health (NIH)- funded The SLAP HIV program is an interdisciplinary project that aims to invent, develop and test an implantable drug delivery system to protect high-risk individuals from HIV infection for up to a year at a time.



Summary: The PrEP Landscape

- Improved delivery methods to allow long-acting products may prove revolutionary to the PrEP landscape for women
- When we complete current and future studies we should have:
 - A long-acting PrEP agent
 - Advanced bNAbs for prevention of HIV infection
- These products will expand product choice and help bridge the prevention gap
- But we must learn from history, recent findings and from nature ...





Brunfelsia pauciflora

- The Yesterday, Today and Tomorrow plant is a tropical plant native to Brazil.
- Its lush green foliage is accented with unique blooms that change colour.
- The flowers bloom first as a purple or violet bloom - **Yesterday**.
- A day later, that same bloom is pale lavender - **Today**
- And the next day it is a brilliant white - **Tomorrow**.



Lessons Learnt from Oral PrEP

- *“We must learn from oral PrEP implementation in order to catalyze implementation of other prevention tools (injections, rings, bnabs, vaccine) so they will be delivered better and faster in the future.”*
- Post-approval studies were not all designed to address decision-maker questions.
- Data from research was not well timed to inform decision making at global or country level.
- Complex, fragmented stakeholder landscape.
- Approval pathway for new HIV prevention drug can be more complex than for a drug already approved for treatment .

Lessons Learnt from Dolutegravir (DTG)

- Current DTG discussions and anxiety.
- Recommend concurrent or near-concurrent data collection of pregnancy and lactation safety
 - For oral PrEP – data are still being collected.
 - For dapivirine vaginal ring there are good research plans to get that information.
 - For CAB LA there are also good research plans to get that information.
 - For dolutegravir, - we should gather as much information as possible.



Why I do this work



Roselyne Sachiti : Features Editor

Mary Moyo, a woman from Zimbabwe's capital Harare, was just 18 when she married her 27-year-old husband Mike Moyo in 2013. When she fell pregnant the following year, both Mary and Mike were tested for HIV when they visited their gynaecologist. Mary tested negative on three different times, while her husband was positive. "This strained our relationship. He could not take any of it. He was in denial despite being counselled before we took the test," she said. Following the tests, their gynaecologist advised them to practise safe sex by consistently and correctly using condoms.

"This was not to be. Mike refused to use condoms. He said he paid lobola (bride price) to my parents and would not take any of that. He would assault me each time I refused to have unprotected sex. One day he beat me up before he became intimate with me. I was afraid," she said.

Mary eventually left the marriage after endless beatings. She is currently single but hopes to meet someone "new".



obrigado

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Merci

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спасибо

Grazie

Thank
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Takk

Gracias

Dziękuję

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Kiitos