The MTN Journey with the Dapivirine Ring

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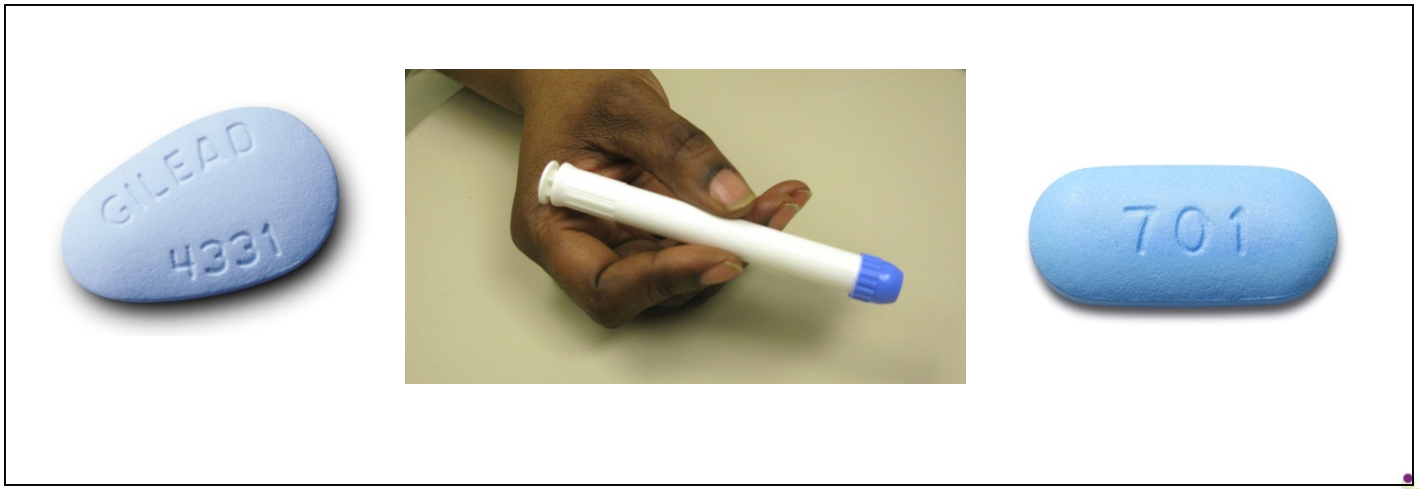
it's about the journey
not the destination.

Think back in time……

- The MTN was funded
- Several studies of oral PrEP were ongoing
- The CAPRISA 004 study was underway.
- We had proposed to do a study comparing tenofovir gel, oral tenofovir and Truvada in our application.
- We believed that both oral and topical products would work…… and we wanted to help prove it!
- Our goal was to take a product to licensure

The VOICE Study: Launched in 2009

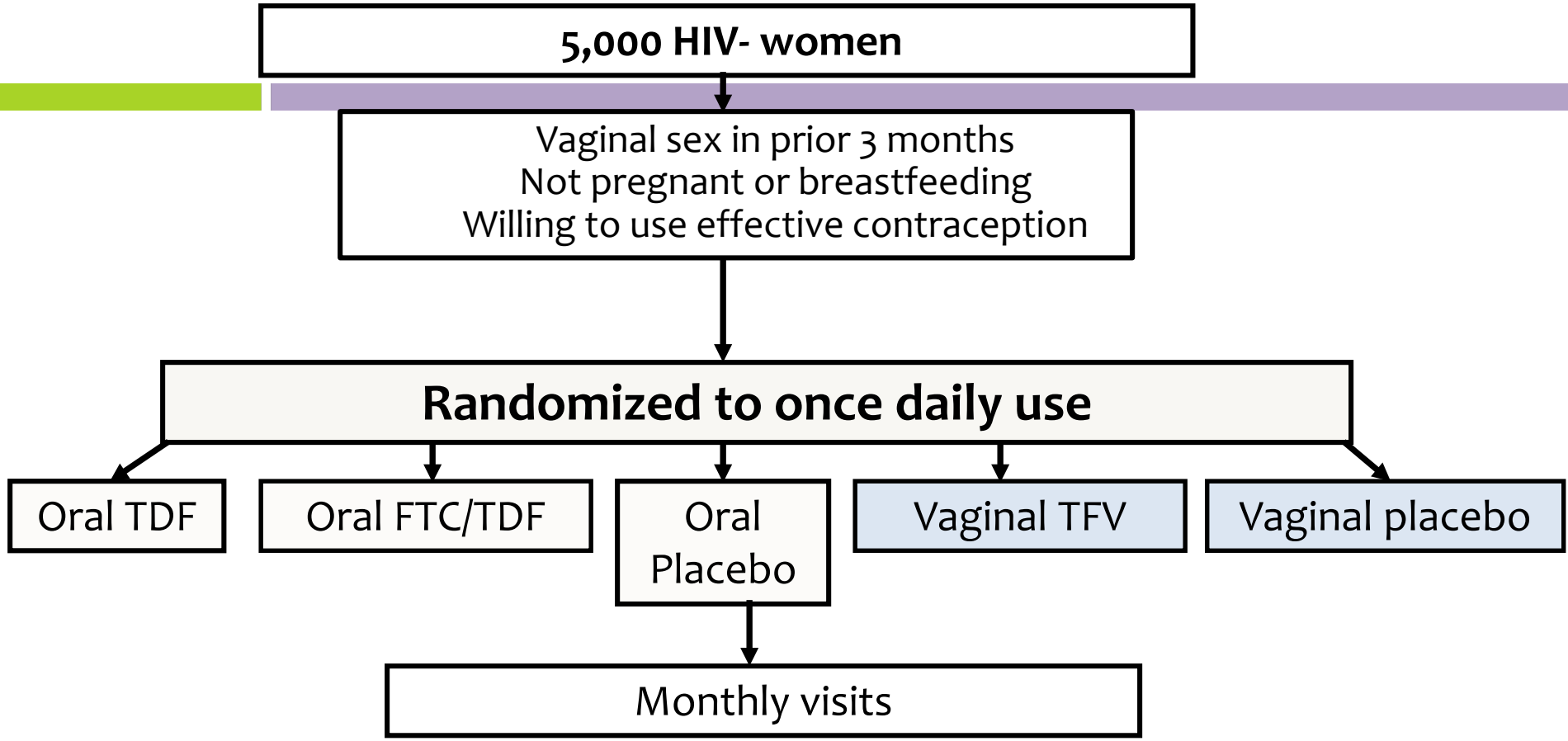
- Phase 2B, randomized, double-blind, placebo-controlled, five-arm trial of daily use of the following for prevention of HIV acquisition in women:
  - Vaginal tenofovir (TFV) 1% gel (40 mg)
  - Oral tenofovir (TDF, 300 mg)
  - Oral tenofovir / emtricitabine (TDF / FTC; 300 mg / 200 mg)



VOICE
VAGINAL + ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC

MTN
microbicide trials network

VOICE Design



Comprehensive HIV prevention counseling, condoms, contraception, STI evaluation & treatment, provision of study product

1° endpoints: HIV infection, safety

While VOICE was enrolling…

- July 2010: CAPRISA 004 study: tenofovir gel used around the time of sex reported to be 39% effective

- Dec 2010: iPrEX: oral Truvada in MSM 40% effective

- March 2011: FemPrEP study of oral Truvada stopped for futility

Different messages to the IRBs and study participants every 3 months …

And different reactions from the communities and the IRBs with each announcement……

July 2010:

"The gel arms of VOICE should be stopped because the gel worked in the CAPRISA study!"

December 2010

"The oral Truvada arm of VOICE should stop because **Truvada worked** in men who have sex with men!"

Different messages to the IRBs and study participants every 3 months …

And different reactions from the communities and the IRBs with each announcement……

March 2011:

"The oral Truvada arm of VOICE should be stopped because **it did not work** in women enrolled in FemPrEP"

But We Also Started to Work on the Dapivirine Ring

- January-March 2011: First discussions with IPM about doing a phase 3 trial of the dapivirine ring; protocol development and site selection initiated
- May 2011: DAIDS approved ASPIRE to go forward
- May 2011: DAIDS approved the "CHOICE" protocol, the open label extension study for VOICE

Committed to Having Options for Interventions to Control the Epidemic

CHOICE

- Nyaradzo Mgodi, MBChB
- Gita Ramjee, PhD
- Sharon Riddler, MD, MPH

The Prevention Landscape Seemed to Change Every Day

- The VOICE study started enrollment in 2009 and completed enrollment in June of 2011
- During that time, outcomes in other trials required new materials for study participants- confusing, because the different studies were not in agreement
- Phone calls and face to face meetings were held with the IRBs to answer questions
- Some international IRBs wanted to know what the DSMB was seeing during the VOICE reviews……

And then… one month after completing VOICE enrollment

- July 2011: oral Truvada and tenofovir 65-75% effective in reducing HIV
  - Partners PrEP study
  - CDC Botswana study

Some people said: "The oral arms of VOICE should be stopped because **tenofovir and Truvada were shown to be effective in preventing HIV transmission in couples enrolled in the Partners PrEP study**

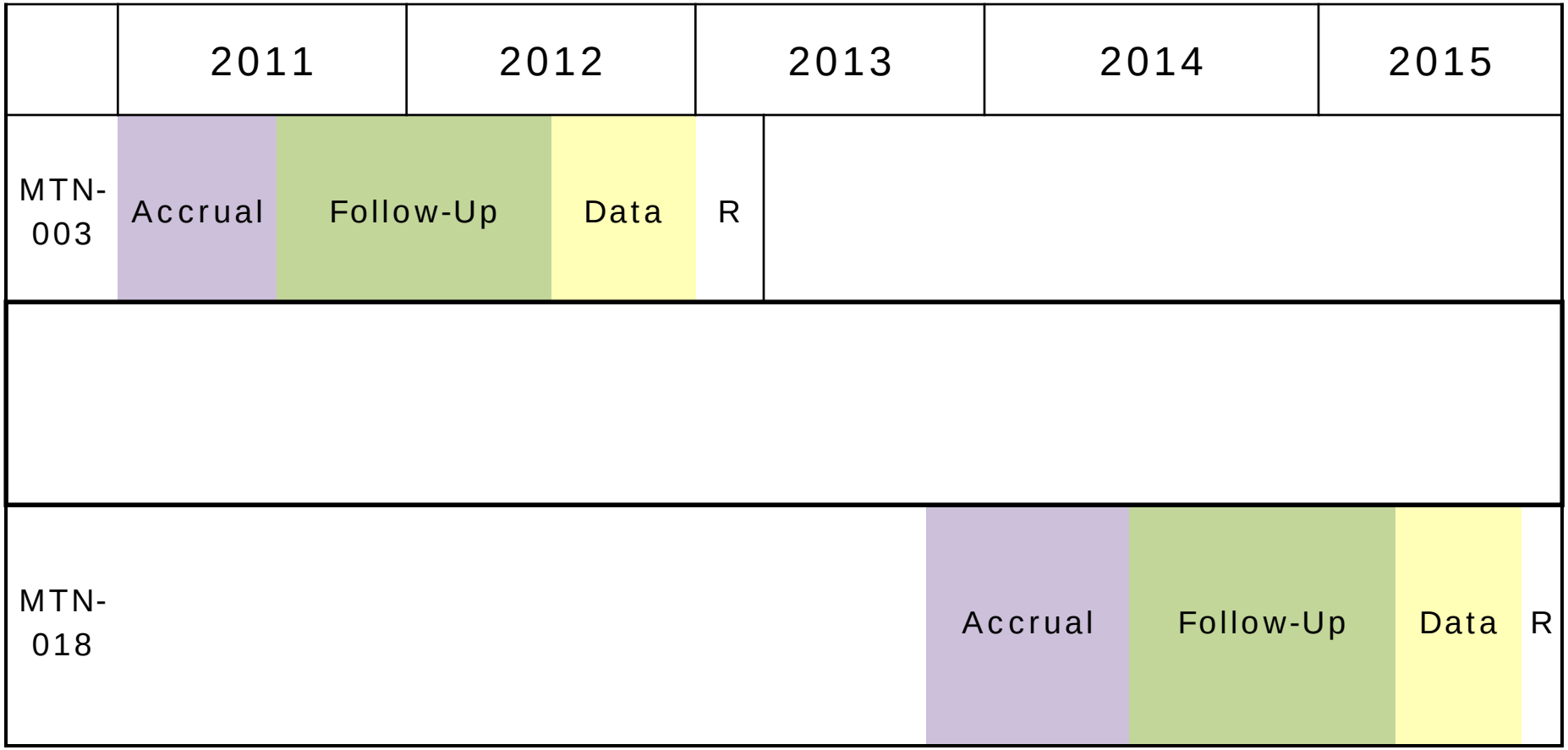
Lots of questions…

- Was it still ethical to do a placebo-controlled trial of the dapivirine ring (still in the planning stages)?
- Was there any way for the MTN to execute the ASPIRE trial when it was expected that we would have to move from VOICE to MTN-018 (CHOICE)?

What We Thought Would Happen

- VOICE would continue on schedule
  - Accrue adequate endpoints by June 2012
  - Demonstrate efficacy of one or more arms
  - Data analysis complete Q4 2012
- MTN-020 was planned to be conducted between the end of VOICE in 2012 and accrual into CHOICE in 2013-2014

VOICE, MTN-020, and CHOICE Plan from 2011



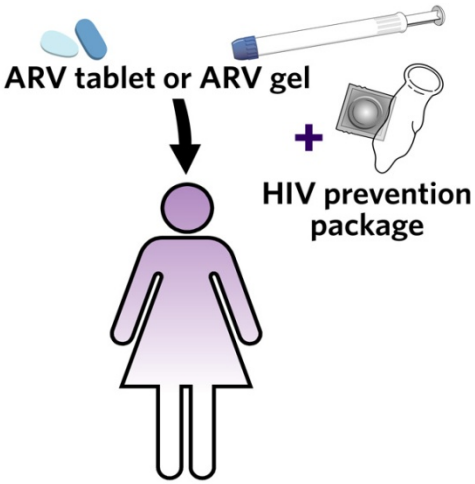
But we Also Planned for Other Possible Outcomes

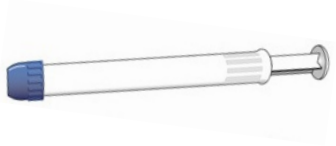
- VOICE study could be stopped early by DSMB due to futility, safety, or efficacy considerations
  - Oral PrEP arms and/or tenofovir gel arm stopped
- Impact on timelines on ASPIRE and CHOICE
  - Depends on the reason for stopping study
    - **Futility**: CHOICE would not proceed
    - **Efficacy**: CHOICE might start earlier & impact MTN-020

MTN microbicide trials network

But they call it research because we don't know the answer……

After a 16 September 2011 interim review of study data, the DSMB stopped tenofovir tablets were not found to be effective in VOICE.





5,000 Women

Tablet (3,000)

Vaginal Gel (2,000)

Truvada (1,000)

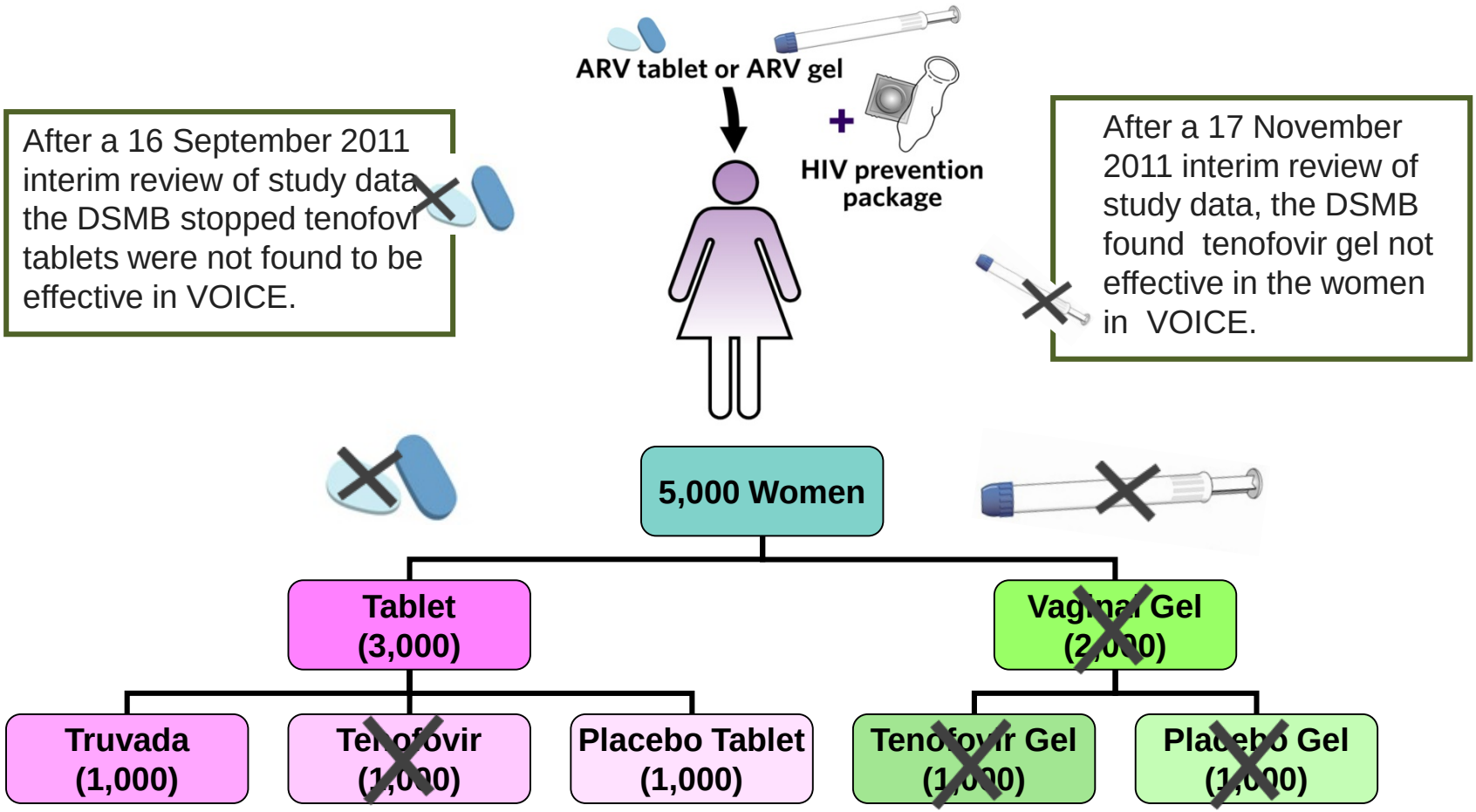
Tenofovir (1,000)

Placebo Tablet (1,000)

Tenofovir Gel (1,000)

Placebo Gel (1,000)

They call it research because we don't know the answer……



What Happened Next?

- The VOICE Study continued with the oral tenofovir/emtricitabine arm until the planned end of the study in September 2012.
- ASPIRE also launched in July 2012
- Results of VOICE were presented at CROI in 2013
  - None of the products was better than placebo because adherence to all of the products was very low

What Else Happened Next?

- CHOICE disappeared
- We worked really hard, really quickly to understand what happened in VOICE
- ASPIRE was already enrolling (588 women already enrolled by the end of 2012)
  - We did everything we could do to make sure that all lessons from VOICE were applied in real time to the execution of ASPIRE
  - That also meant that we needed to catch a "moving train"

What Women Told Us

- They highly value the reproductive health services which we provide: Contraception, STI and HIV screening, Cervical cancer screening
- The youngest women were the least able to balance investigational product risks vs benefits, and are the most susceptible to peer advice regarding safety of products
- Having a placebo leads to greater uncertainty about whether or not to adhere to study products
- There was stigma associated with use of ARVs
  - Even for a vaginal product it can be difficult to explain to a partner or family member what it is and why it is being used

Would All of These Issues Be Addressed by Using a Ring?

- Use of a monthly ring would address one of the issues associated with daily use products
- BUT not the issues
  - –with concerns about product safety
  - –with placebo
  - –with special adherence challenges with youngest women

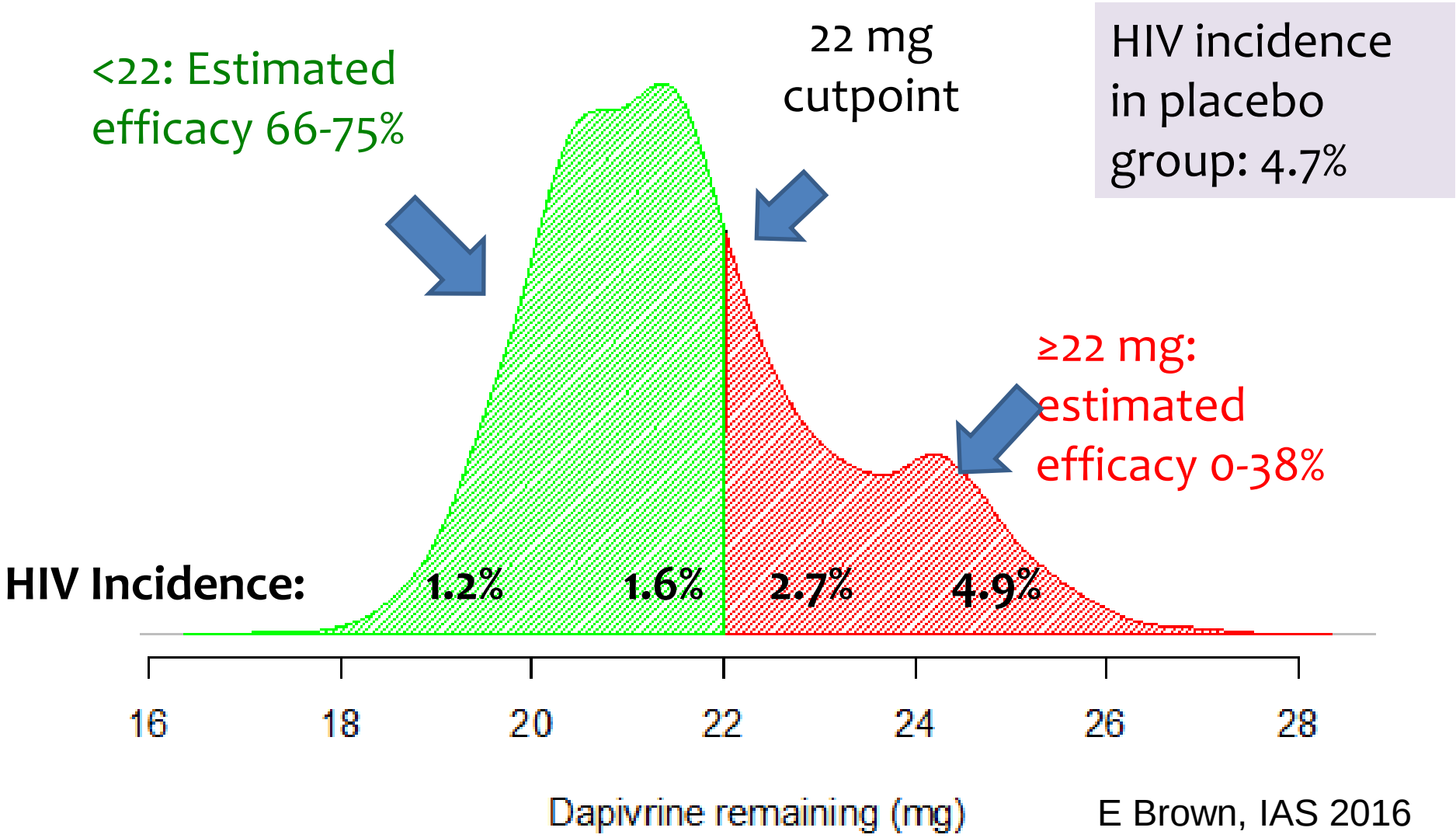
HIV Prevention in ASPIRE and Ring

ASPIRE

THE RING STUDY
Developing HIV Prevention for Women

But a 60% reduction in HIV among women >25 years of age

Distribution of Residual Dapivirine in Used Rings



E Brown, IAS 2016

Limitations of These Secondary Analyses

- Returned rings not tested at all visits for entire cohort – leading to this sub-cohort
- Unknown potential confounding – although we did adjust for two significant predictors of adherence and risk: age and site
- Misclassification remains due to variability in manufacturing and testing
- Does not identify a threshold for HIV protection

Dapivirine Ring Dossier Was Submitted to EMA for Rview

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

IPM's Application for Dapivirine Vaginal Ring for Reducing HIV Risk in Women Now Under Review by European Medicines Agency

Product would offer women at high risk the first long-acting HIV prevention option

SILVER SPRING, Md. (July 13, 2017) — The nonprofit International Partnership for Microbicides (IPM) is pleased to announce that its application for the monthly dapivirine vaginal ring, designed to reduce the risk of HIV-1 infection via vaginal intercourse in HIV-negative women in combination with safer sex practices, has been validated and is now under review by the European Medicines Agency (EMA). IPM designed the ring, which releases an antiretroviral drug (ARV) called dapivirine over the course of one month, to offer a discreet and long-acting HIV prevention method for women, who insert and replace it themselves.

So What Are We Learning from the Open Label Extension Studies?

HOPE
HIV Open-label Prevention Extension
Out of ASPIRE, there is HOPE

DREAM

1. Uptake of the ring is very high
2. Adherence to the ring is higher than in the placebo controlled studies
3. HIV incidence is low- supporting a protective benefit of more than 50%

So if the dapivirine ring is effective…now what?

- New data in US adolescents (15-17 year olds) show that the ring is very safe and acceptable (Bunge et al, IAS 2017)
- New data in lactating women show that exposure to ARVs about 100-1000X lower for dapivirine ring vs oral PrEP (Noguchi et al, IAS 2017)
- Planned studies of adolescents (MTN-034 REACH and pregnant women (MTN-042) in S Africa, Zimbabwe, Uganda, Kenya, Malawi

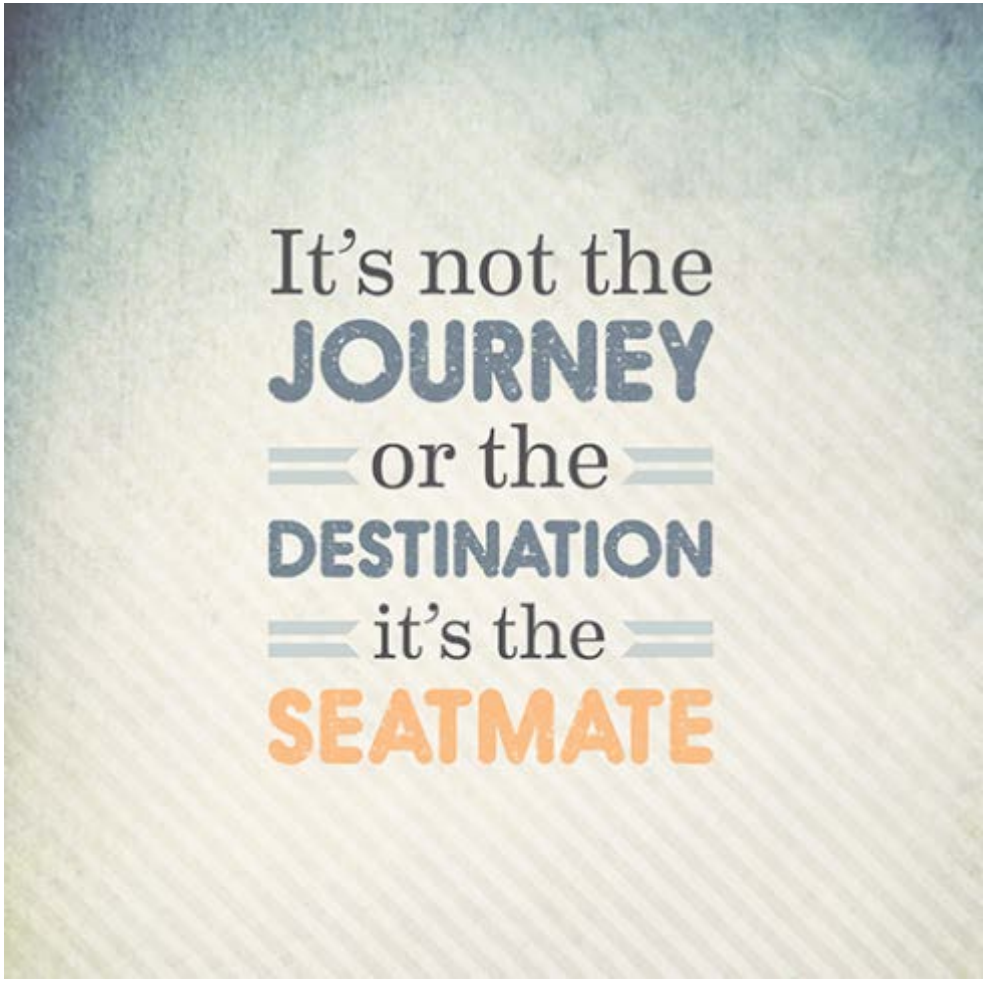
It's About the Journey Not the Destination

- The MTN planned to help take tenofovir gel to possible licensure AND to contribute to the body of data showing that PrEP works in women

- That was not our **destination**

- The **journey** taught us many lessons which prepared us to do ASPIRE, and to take those lessons so that we could do HOPE with success.

Good bye to One of Our Favorite "Seat Mates" in the MTN



What is Loss?

loss

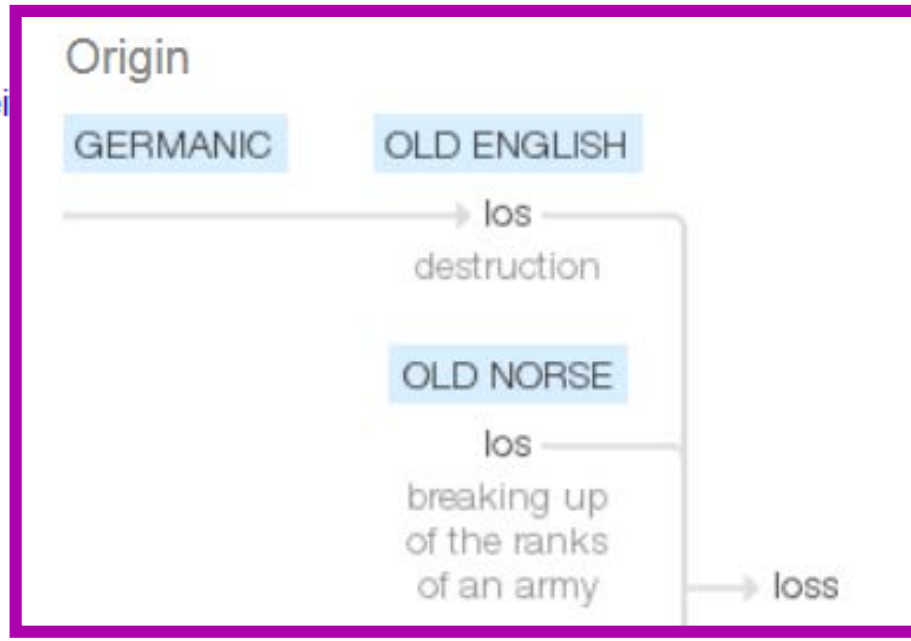
/lôs,läs/

noun

noun: **loss**; plural noun: **losses**

the fact or process of losing something or someone.
"avoiding loss of time"
synonyms: mislaying, misplacement, forgetting More

- deprivation, disappearance, privation, forfei
  depletion



Charlene is still with us in spirit

Lessons from Charlene

1. Keep smiling
2. Have fun every day
3. Keep focused on the important work we do
4. Take time to be kind and welcoming to the people who have joined us on this journey