AVAC

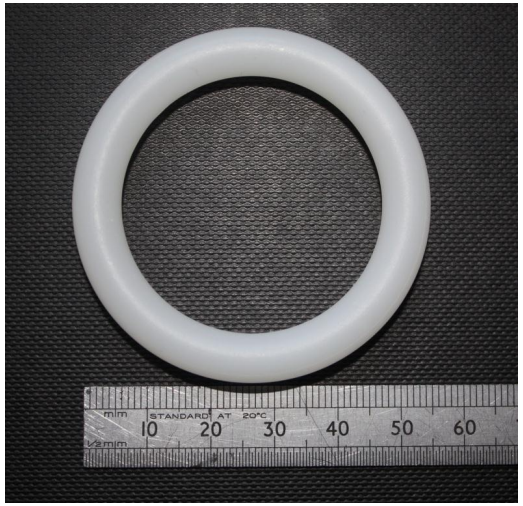
Global Advocacy for HIV Prevention

The Dapivirine Ring: What's the Story?

Rebekah Webb
AVAC

The Dapivirine Ring

- Flexible ring of elastic silicone
- Inside vagina, ring releases dapivirine (NNRTI) slowly over time
- Two Phase III trials of 4-week vaginal dapivirine ring
  - ➢Modest HIV protection shown



IPM Ring Study

- 1950 women
- South Africa and Uganda
- 31% protection
- DREAM OLE *(not PEPFAR)*

MTN ASPIRE Study

- 2629 women
- Malawi, South Africa, Uganda, Zimbabwe
- 27% protection
- HOPE OLE

THE RING STUDY
Developing HIV Prevention for Women

ASPIRE
A Study to Prevent Infection with a Ring for Extended Use

Study	The Ring Study (IPM 027) International Partnership for Microbicides	ASPIRE (MTN-020) Microbicide Trials Network
Study design and enrollment		
Objectives	Long-term safety and effectiveness	Safety and effectiveness
Study design	Double-blind randomized placebo controlled with 2:1 randomization (active: placebo)	Double-blind randomized placebo controlled with 1:1 randomization (active: placebo)
Enrollment	Total: 1959 women, ages 18-45; Active arm: ~1300	Total: 2629 women, ages 18-45; Active arm: ~1325
Regulatory requirement	3000 women on dapivirine ring for at least 1 year follow-up; 1500 women on dapivirine ring for 2 year follow-up	
Participant follow-up	2 years + 6 weeks following ring discontinuation	Minimum 1 year + 4 weeks following ring discontinuation
Research sites	7 IPM research center partners in South Africa and Uganda	15 MTN research centers in Malawi, South Africa, Uganda, Zimbabwe
Results		
Overall results	31% effective, confidence interval 1-51	27% effective, confidence interval 1-46
Secondary analysis that excluded data from 2 sites with lower retention and adherence		37% effective, confidence interval 12-56
Results by age stratification (post hoc analysis)		
Women over 21 years of age	37% effective, confidence interval 3.5-59	56% effective, confidence interval 31-71
Women 18-21 years of age	No statistically significant effect	No stastistically significant effect
HIV incidence		
Overall	4.1% among women in active arm 6.1% among women in placebo arm	3.3% among women in active arm 4.5% among women in placebo arm

Results announced at CROI 2016

Questions for today

- Why were the ring results greeted with disappointment by some and joy by others?
- Why were the results different for younger women?
- What plans are there to introduce the ring into prevention programmes and how will it sit within the roll-out of PrEP?
- What role can/should such biomedical tools play within the overall response to HIV?

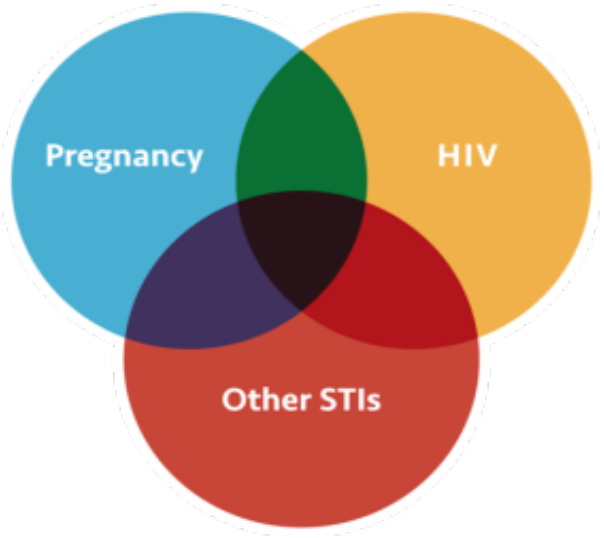
Introduction to microbicides

- 1990s: Deep frustration with male condoms presented as a solution to feminisation of HIV
- Scientists confirm it is theoretically possible
- No funding available and no pharma interest
- Advocacy groups start up (e.g. Global Campaign for Microbicides founded 1998)
- First generation products looked at existing compounds including spermicides and thickening agents
- Trials of oral PrEP and daily gels have mixed results
- Recognition of women's needs for longer-acting, discreet methods of protection

Why a vaginal ring?

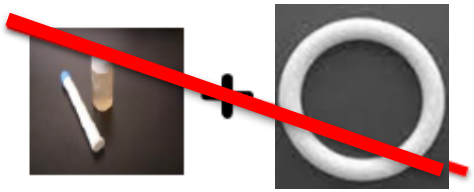
- Currently available options often unrealistic for many women
- Existing methods (male and female condoms) have to be used at the time of sex and rely on male co-operation
- Adherence to a daily gel/daily pill can be challenging
- Established method of contraception/hormone replacement
- Do not interfere with sexual pleasure
- Low side effects (non-systemic)
- Giving drug topically delivers drug:
  - where it is needed in genital tissue
  - closer to when it is needed as absorption is local
  - at a much higher level (10-100x) than an oral pill

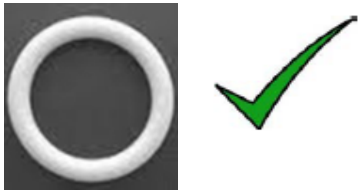
Multipurpose Prevention Technologies (MPTs)



CAMI COALITION ADVANCING MULTIPURPOSE INNOVATIONS *http://www.cami-health.org*

A single product, configured for at least two SRH prevention indications:
Pregnancy, STI, and/or HIV
Could be different combinations:
Drug:Drug Drug:Device Vaccine





- Greater efficiency in terms of cost, access and delivery of SRH prevention products
- Capitalize on the demand in populations using one product type to achieve uptake and use of a second "product"

Ring Results Reactions

“Research on women from Africa, especially, keeps coming back with low adherence…”

“I think it a serious concern that even after both these studies there is no indication of the likely level of protection for someone using this ring. Given that oral PrEP now has close to 100% efficacy for someone taking it, these results raise ethical issues about the proposal to ask women in the study to continue using this ring for several years longer”

“When they announced at our ASPIRE site that the IPM Ring Study participants would all be offered the active ring, they applauded and cheered --- they cheered for their sisters at other sites and in other communities that would be offered this new prevention product”

- Deborah Baron, Wits RHI

Mixed reactions due to…?

- High expectations (of product development timeframes and comparisons with PrEP)
- Obsession with #% effectiveness
- Assumption that rings would be acceptable to young women
- Dismissal of women-specific products
- Lack of awareness of microbicide history
- Assumption that microbicide research is Pharma/profit/Dr driven
- Suspicion of biomedical approaches

Adherence in young women

Interviewer: We have spoken about so many things today, before we finish, I would like to ask if maybe you have anything you would like to understand, or share?

Participant: *Yes, what I have noticed is that, most of the younger people, let me say those who are younger than me, they are not using the ring because they are saying it's just for the money; others that it's just a waste of time; they take it off when they get home and put it back again …during the week they are coming. So that is something that they need to look at.*

Source: Jared Baeten & Thesla Palanee-Phillips

"We now face what we all knew from the start, that technology alone will never be enough to help women to protect themselves"

- Dr Lori Heise, founder of the Global Campaign for Microbicides

What next?

- Only a few rings have been manufactured
- Rings can only be made available in research settings until they are approved
- Open-label studies provide real-world patterns of use and acceptability – participants know what they are getting
- How will women use the ring now they know it is safe and modestly effective?
- First countries to have access to the ring will be those with highest HIV incidence among women globally

From Research to Rollout

Post-trial access

- Intervention provided to trial participants and, sometimes, their communities, after trial & before product is available for widespread use

Open label extensions

- Intervention made available in follow-on protocol in which participants from previous RCT know they are receiving active intervention
- Gather information about how product use in people who are now aware of potential benefit

Open label/ Implementation studies

- Research protocols similar to above but enrolling new participants

Demonstration projects

- "Road test" use of new option in real-world settings – not in trial site
- Can address both infrastructure needs to deliver intervention and ways individuals integrate it into daily activities and decision making.
- Can help answer core questions about for whom and how

Product introduction

- Complex process of formally making new options widely available. Can include meeting regulatory requirements, WHO prequal, various country-specific requirement, logistical challenges

Scale-up

- Ramping up access to new options for all who need them – mobilization of resources for procurement, distribution, delivery, worker training and other costs associated with rollout; quick ID and resolution of bottlenecks

HOPE and DREAM

- HOPE (MTN)
- Approval and funding from NIH
- HOPE due to start this summer

- DREAM (IPM)
- Approval from SA MCC
- Awaiting funding and approval
- All participants will transition to DREAM

- Both research teams will combine and analyse the data further to understand challenges to adherence
- HOPE and DREAM won't generate information on younger women as all participants will be over 21 – other studies will look at this

When will the ring be available?

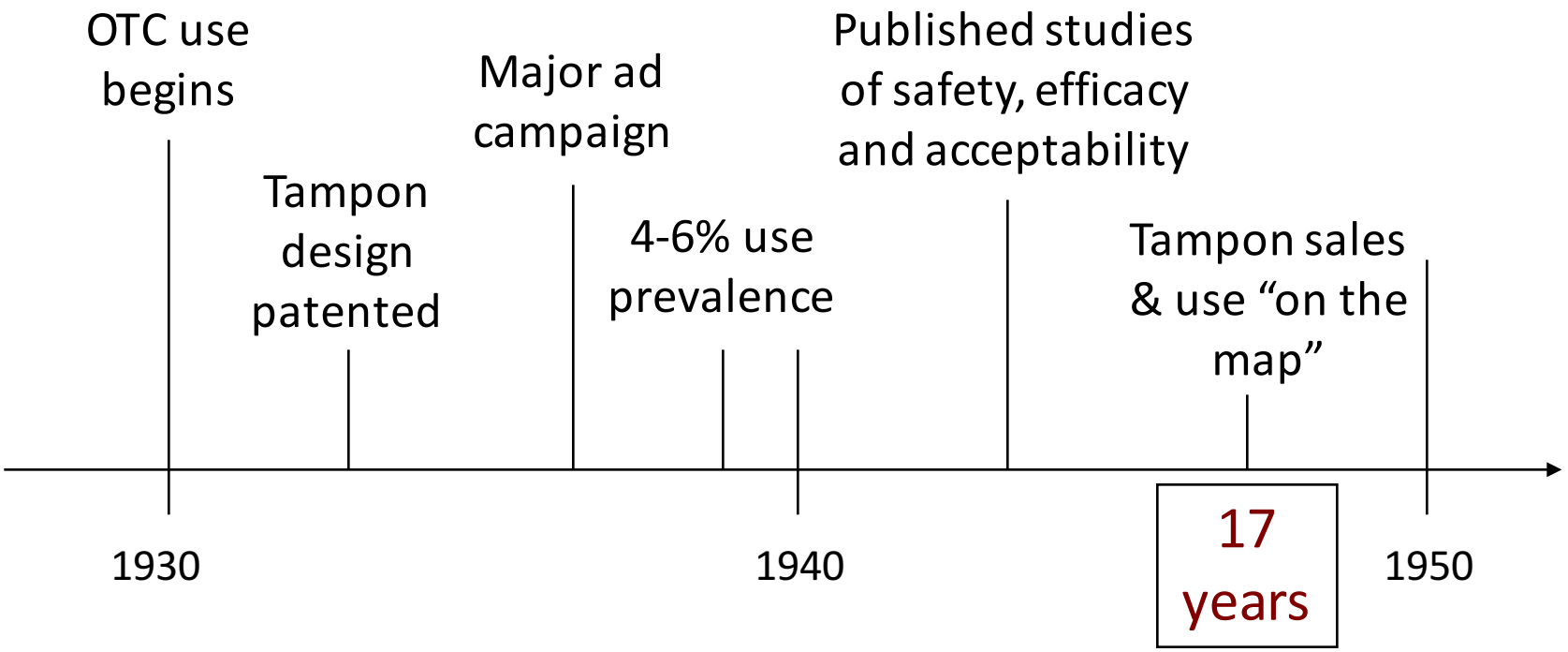
- IPM plans to prepare and submit a dossier of evidence in Q1 2017
- Countries need to approve it for their contexts
- WHO guidance will be needed
- 2019 is the most optimistic timeframe for access
- In the meantime, provide oral PrEP

The "Science of Delivery"

- "The problem is we don't really invest as much time and energy into thinking about how to deliver these tools. We're creating a stockpile of tools that never get to the poorest people.
- "This is just as complicated as developing new tools, and we should take it just as seriously.
- "We should bring the same kind of rigorous approach and scientific thinking to actually delivering these tools for health that we bring to creating them."

- ***A Q&A with the other banker to the poor, World Bank Prez Jim Kim,*** 12 Sep 2013, http://www.humanosphere.org/2013/09/a-qa-with-the-other-banker-to-the-poor-world-bank-prez-jim-kim/
- Also, ***Redefining global health-care delivery***, Jim Yong Kim, Paul Farmer, Michael E Porter, *Lancet,* May 20, 2013

The Tampon in America



Source: Latka, Journal of Urban Health, 2001

Prevention Paradigm 2016 & beyond

Different Strokes for Different Folks		
Method	Contraception	HIV Prevention
Behaviour	✓	✓
Barrier Methods	✓	✓
Gels	✓	?
Rings	✓	✓ – ?
Oral pill	✓	✓
Injectables	✓	
Implants	✓	
Surgical procedures	✓	✓
Treatment		✓

“It’s not just about putting pills in peoples’ mouths!”

- Dr Marie Laga, Be-PrEP-ared study

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