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CAPRISA IS A UNAIDS COLLABORATING CENTRE FOR HIV PREVENTION RESEARCH

Doing studies of ARV based microbicides what's different, what's the same?

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VOICE Trial

OVERVIEW

- Brief historical overview of microbicide trials
- Differences between polymer and ARV microbicide
- What's the same?
- What's different?
- Conclusions

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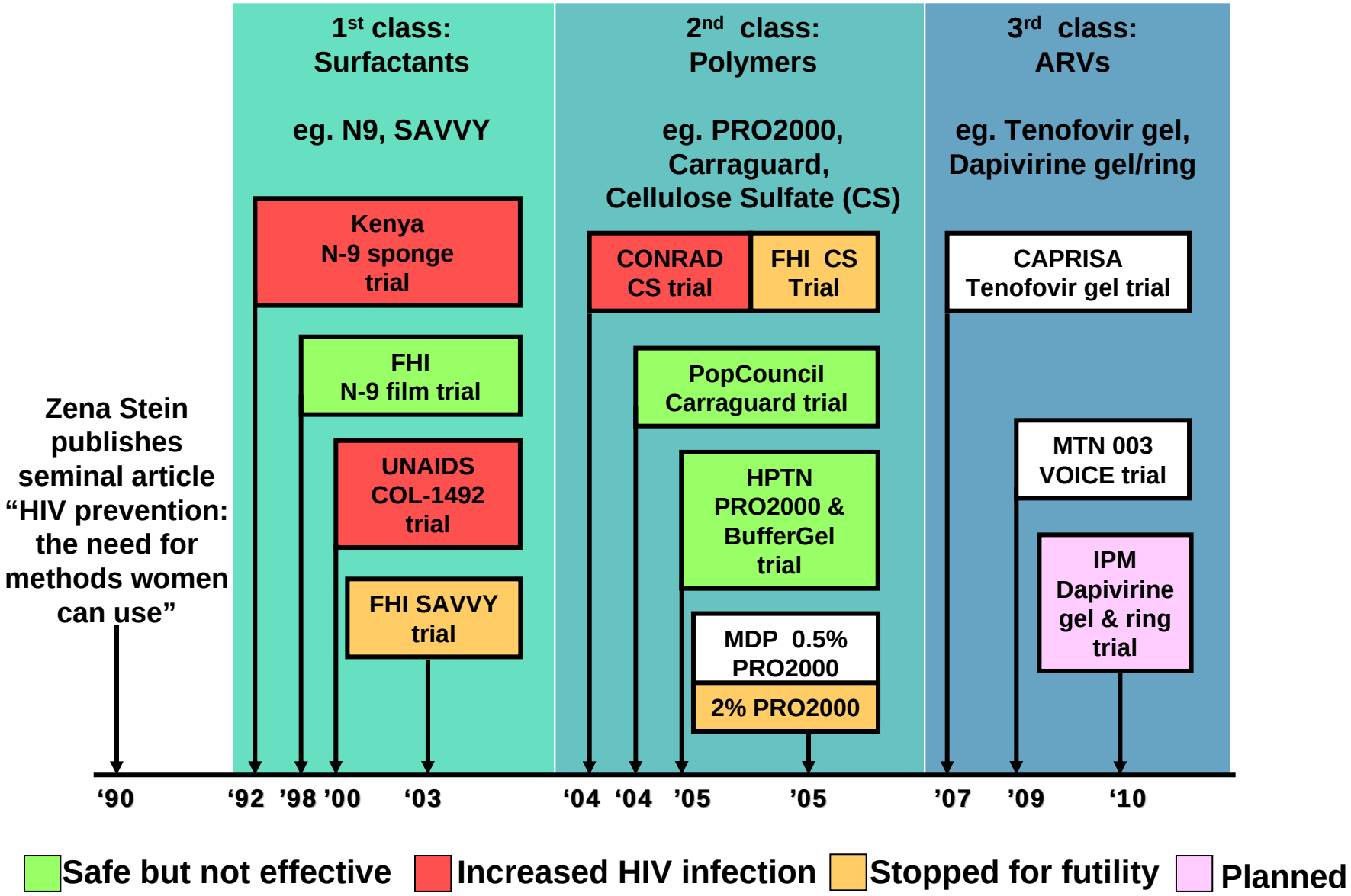
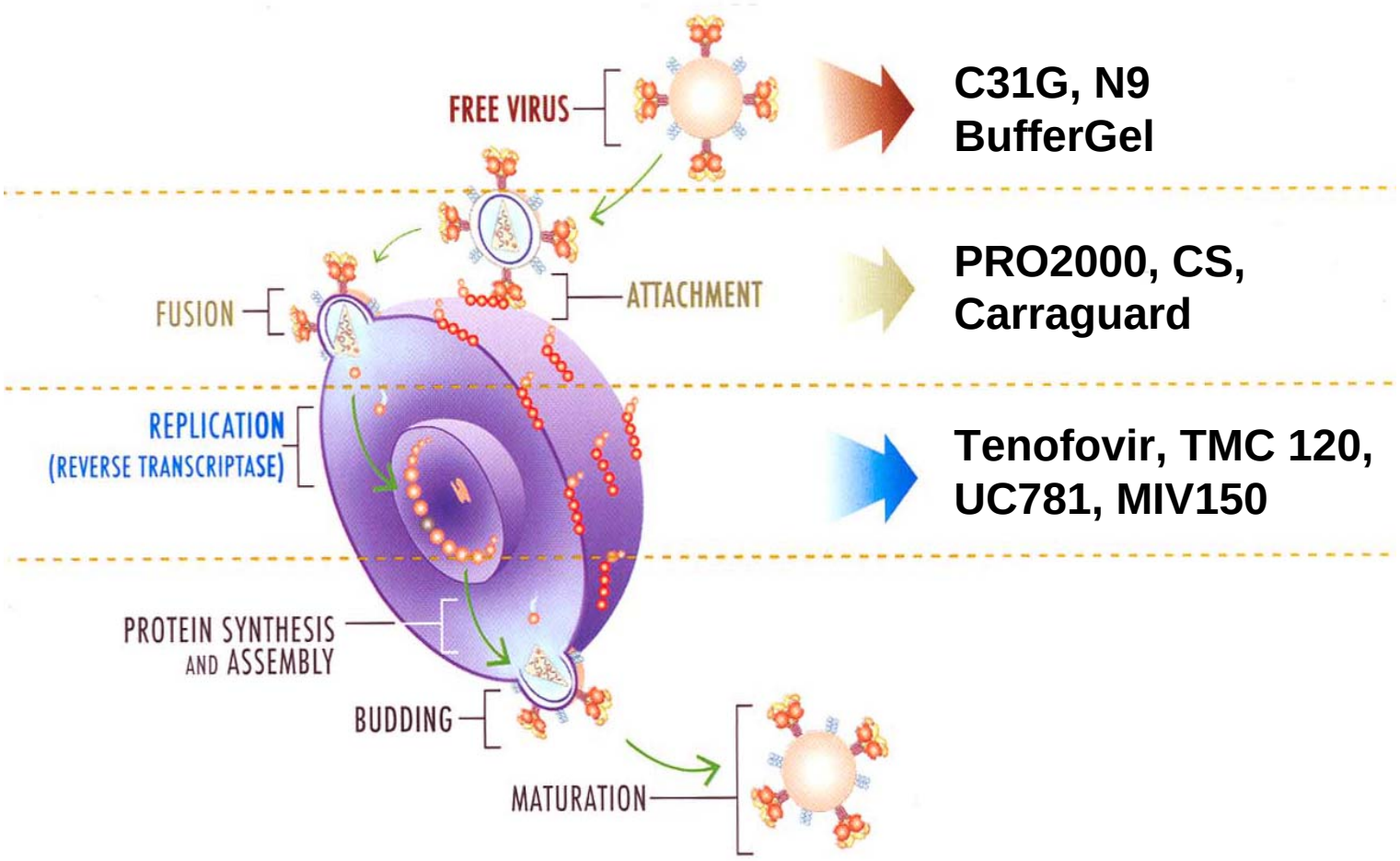
PAST & CURRENT MICROBICIDE CLINICAL TRIALS



PROGRESSION IN THE PRODUCT PIPELINE



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ARV BASED MICROBICIDES

- **Why antiretroviral agents as microbicides?**
  - **Effective as treatment – suppresses HIV replication**
  - **Proven concept as prevention in:**
    - PMTCT
    - Needle stick injury PEP
    - Animal challenge studies
  - **Oral TDF results in equal/higher concentration of ARVS in genital tract in comparison to plasma**

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DIFFERENCES BETWEEN PRO 2000 & TENOFOVIR

PRO 2000 Gel	Tenofovir Gel
Over-the-counter product (non contraceptive)	By prescription – Tenofovir is schedule 4 (non-contraceptive)
No systemic absorption – local genital action only	Due to systemic absorption, during use, will need regular: HIV testing (to reduce resistance), pregnancy testing and HBV testing
No concern about: HIV status ARV resistance – though HIV may mutate to bypass PRO2000 action HBV infection	Concerns about: Development of ARV resistance HBV resistance HBV flares
Used 1 hour before sex	Used coitally related or daily (not only within an hour of sex)

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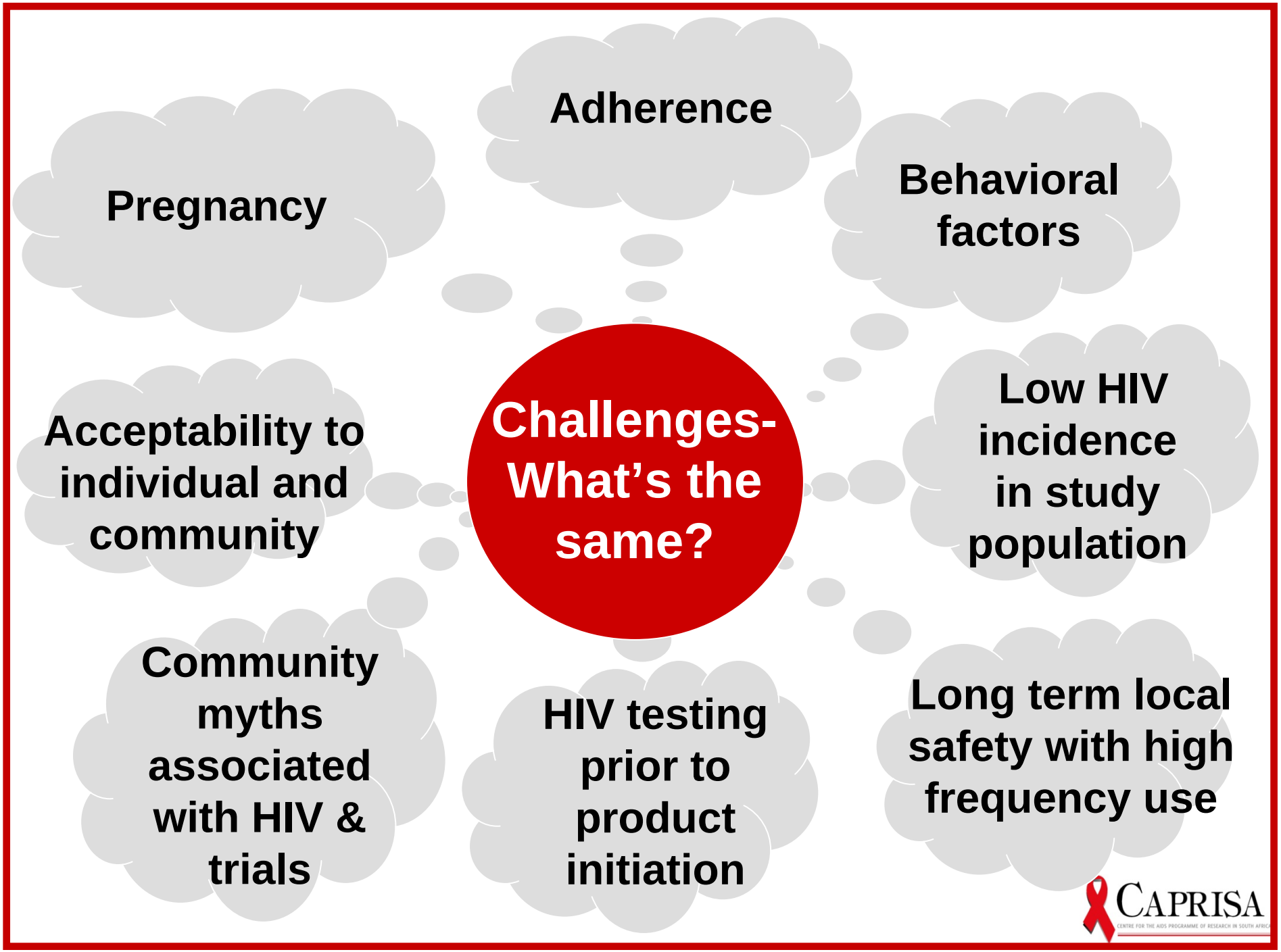
Adherence
Pregnancy
Behavioral factors
Challenges- What's the same?
Acceptability to individual and community
Low HIV incidence in study population
Community myths associated with HIV & trials
HIV testing prior to product initiation
Long term local safety with high frequency use
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ACCEPTABILITY BY THE COMMUNITY

- Trials generally carried out in high risk populations/high HIV incidence – developing countries.
- Potential for “exploitation of vulnerable populations”.
- However, trials are being conducted throughout the world – under high ethical and care standards
- Acceptability also dependent on dispelling community myths associated with HIV and trials

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ACCEPTABILITY BY THE INDIVIDUAL

- **Success of a microbicide linked to long term adherence**

- **Adherence maybe compromised:**
  - **In the event of mild side effects**
  - **If the timing of product use is inconvenient and several applications are required in one day**
  - **Partner opposition to use**
  - **If it interferes with normal sexual practices**

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ACHIEVING HIGH ADHERENCE AND MEASURING ADHERENCE

- Testing the efficacy of microbicides is dependant on high adherence and accurate measurement of adherence
- Direct observation is impossible, self report - sometimes unreliable
- Respondent independent methods – more objective, but assumptions are made

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BEHAVIOURAL DISINHIBITION

- **Will a more efficacious intervention be abandoned for a less efficacious one?**
- **Mathematical modeling suggests that effect of PrEP maybe diminished by behavioral disinhibition**
- **Ghana PrEP Study- no increase in risky sexual behaviour**
- **Other behavioural factors**
  - Use of intra vaginal substances
  - Prevalence of anal sex

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HIV INCIDENCE IN STUDY POPULATIONS

- Trials conducted in populations with high risk of acquiring HIV infection.
- Low HIV incidence – a challenge in effectiveness trials.
- A Multicentre study – unable to establish effectiveness of TDF secondary to low HIV incidence in the study population.

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PREGNANCY

- High rates of pregnancy experienced amongst several microbicide trials
- Product discontinuation in event of pregnancy
- Seroconversion amongst pregnant women regarded as microbicide “failure”
- Effect of pregnancy on outcome – decreases the effect of the intervention

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Systemic safety – renal, bone

Multiple formulations incl. oral

Many options for dosing

Breastfeeding

Challenges- What's different?

Logistic challenges

Does not offer protection against other STI's

HBV infection & resistance

HIV resistance

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DEVELOPMENT OF HIV RESISTANCE MUTATIONS

- Drug resistance could possibly develop with continuous product use following HIV seroconversion
- Future treatment options could be compromised if prophylaxis fails
- Phase II trial of tenofovir gel – no resistance mutations detected in plasma and cervico vaginal lavage

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HEPATITIS B INFECTION

- Development of resistance to nucleoside/nucleotide analogues for treatment of Hepatitis B infection

- Risk of hepatitis B “flares” on withdrawal of Tenofovir

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SYSTEMIC SAFETY

- The effect of PrEP on renal and hepatic function and bone mineral density

- The phase 2 TDF PrEP trial showed no significant differences in safety patterns between participants receiving TDF and the control group

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BREASTFEEDING

- Could levels of ARVS in breast milk have any beneficial or toxic effect on infants?
- Could exposure to sub therapeutic levels of drug lead to resistance in the infant?
- Animal models- suggested that concentration of TDF unlikely to be toxic or to select for resistance

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EFFECT ON OTHER SEXUALLY TRANSMITTED INFECTIONS

- A high prevalence of *C. trachomatis* and *T. vaginalis* was reported in the Carraguard trial
- Reported behavioral change showed no effect on overall STI incidence rate
- This is of concern since ARV based microbicides will confer no protection against other STI's
- However, HPTN 059, showed no significant STI acquisition

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LOGISTIC AND FINANCIAL CHALLENGES

- **Hepatitis B and renal function testing required for Tenofovir based PrEP-**

- **In addition to laboratory costs, programmatic and drug costs need to be considered**

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So, what is the three most important similar or different challenges?

1. **Adherence**

Achieving high adherence is the highest priority regardless of product:

- Need high retention
- Practical and proven adherence support programmes
- Ongoing support and guidance to maintain adherence
- Need a dedicated and knowledgeable team supporting adherence at the site – needs to include medical, pharmacy and counselling team members

Measuring adherence accurately

- Need much more than self-report

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So, what is the three most important similar or different challenges? Cont….

2. **Systemic toxicity is as important as genital toxicity:**
   - In trials of polymers, systemic toxicity was minor concern
   - In ARV based microbicides, it is a major concern due to systemic absorption of product

3. **Interaction with HIV treatment now a substantial concern as we want to preserve future treatment options**

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