

Anticipating New Tools for HIV Prevention: Understanding Clinical Trial Results Over the Next 5 Years

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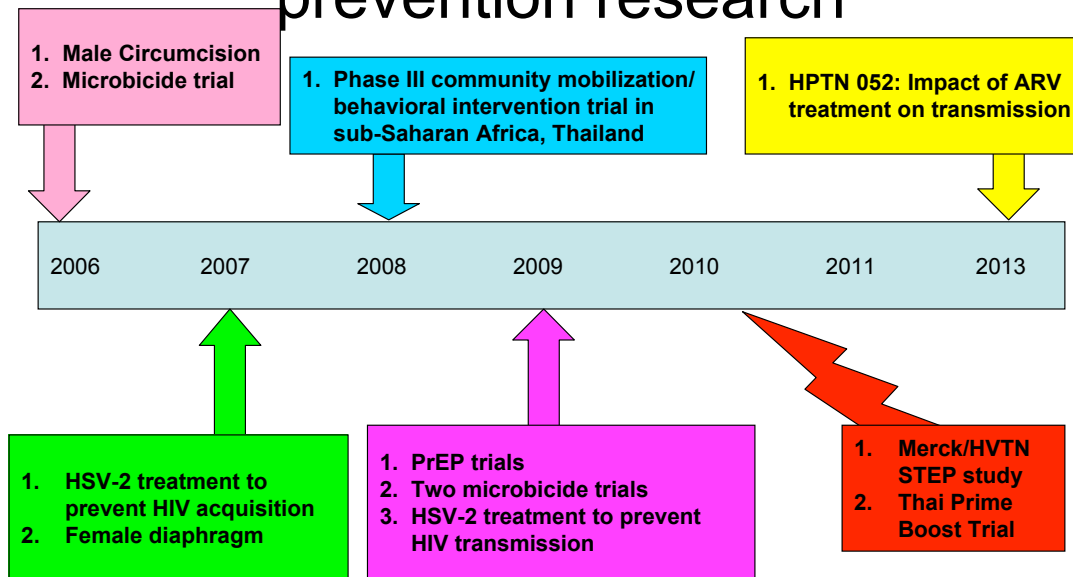
HIV PREVENTION RESEARCH: A COMPREHENSIVE TIMELINE*



| 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
|--|---|---|---|--|------|--|
| Phase II trial of the vaginal microbicide Carraguard for the prevention of HIV infection in women | Study of different risk-reduction interventions for HIV vaccine trials (Project UNITY) | Large-scale trial of a broadly neutralizing antibody to prevent HIV infection in heterosexual men and women | Large-scale trial of a broadly neutralizing antibody to prevent HIV infection in high-risk HIV-uninfected men who have sex with men | Test-of-concept trial of Marck's adenovirus preventive HIV vaccine candidate (Step 1/2) | | Phase III trial to determine the effectiveness of two antiretroviral treatment strategies in preventing the sexual transmission of HIV in HIV-serodiscordant couples |
| Phase III trial of the female dapivirgin to prevent HIV infection in women | Large-scale trial to evaluate the safety of male circumcisions and to potential selective effect for HIV infection in a partner of HIV-infected or HIV-serodiscordant males | Phase III trial of HSV-2 suppression in serodiscordant couples | Phase III trial of a pre-exposure (PrEP) combination preventive HIV vaccine | Test-of-concept trial of Marck's adenovirus preventive HIV vaccine candidate (Phase III) | | |
| FHI Phase II trial of the vaginal microbicide Cellulose Sulfate gel for the prevention of HIV infection in women [Trial stopped early, January 2007] | Large-scale trial of a broadly neutralizing antibody to prevent HIV infection in injecting drug users | Phase III trial of the vaginal microbicide PRO 2000 for the prevention of HIV infection in women | | | | |
| CONRAD Phase III trial of the vaginal microbicide Cellulose Sulfate gel for the prevention of HIV infection in women [Trial stopped early, January 2007] | Phase III trial of community mobilization, mobile testing, same-day results, and post-test support for HIV | Phase IIIb trial of the vaginal microbicides BufferGel and 0.5% PRC2000-5 Gel (P) for the prevention of HIV infection in women | | | | |
| | Phase III trial of abacavir for the reduction of HIV infection in high-risk, HIV-uninfected, HSV-2 seropositive individuals | Large-scale trial to test the clinical and behavioral safety of a once-daily dose of tenofovir among HIV-uninfected men who have sex with men | | | | |

*The trial end dates listed in this table are estimates. Due to the nature of clinical trials the actual dates may change. We will continue to monitor the trials' progress and will update the timeline accordingly. If you have any questions regarding the information presented here please contact us at www.avac.org

Results from advanced prevention research



The New York Times

December 13, 2006

Circumcision Halves H.I.V. Risk, U.S. Agency Finds

Circumcision appears to reduce a man's risk of contracting [AIDS](#) from heterosexual sex by half, United States government health officials said yesterday, and the directors of the two largest funds for fighting the disease said they would consider paying for circumcisions in high-risk countries.

Male Circumcision

- Researchers have been conducting clinical trials to see if medically-provided male circumcision can reduce the risk of an HIV negative man from getting infected through heterosexual intercourse.
- Rationale:
 1. The foreskin has a high concentration of cells that HIV likes to infect
 2. Researchers have observed that areas where male circumcision is common generally have lower incidence
- We have had news from three trials...

Male Circumcision Data

(Stopped Trials)

| | Kenya | South Africa | Uganda |
|------------------|---|---|---|
| Sponsor | NIH and Canadian Institute of Health Research | ANRS (French Government) | NIH |
| Start/Stop Dates | Feb 2002 - Dec 2006 | July 2002 - July 2006 | Aug 2003 - Dec 2006 |
| Question | Does circumcision reduce female-to-male HIV transmission through sex? 2784 men | Does circumcision reduce female-to-male HIV transmission through sex? 3274 men | Does circumcision reduce female-to-male HIV transmission through sex? 4996 men |
| Results | 53% reduction | 61% reduction | 48% reduction |

Male Circumcision

(Ongoing Trial)

| | Uganda |
|------------------|--|
| Sponsor | John's Hopkins University and Bill and Melinda Gates Foundation |
| Study Population | 800 HIV positive men and 1000 men who decline to know their status 5000 women partners of men enrolled in the Ugandan studies |
| Question | Does circumcision reduce female risk of infection by HIV positive, circumcised partners? |
| Results | Trial is still on-going... |

HSV-2 (Herpes) Treatment to Prevent HIV Infection

- Researchers have been conducting clinical trials to see if treating Herpes can reduce the transmission of HIV.
- Rationale:
 1. We know people infected with HSV-2 are up to three times more likely to become infected with HIV
 2. HSV-2 appears to accelerate HIV replication and shedding - this might make them more infectious
- There are two trial currently underway...

HSV-2 Treatment to Prevention HIV Transmission

| | Africa, Latin America and US | Africa |
|------------------------|--|---|
| Question | Does treating Herpes decrease one's risk of becoming HIV infected? | Does treating Herpes decrease one's ability to pass HIV on to others? |
| Study Population | HSV infected men and women who do not have HIV | HSV discordant couples in which one partner is infected with both HIV and HSV-2 and the other is not HIV infected |
| Number of Participants | 3227 men and women | 3000 heterosexual couples |
| Results Expected | 2007 | 2009 |

Cervical Barriers (Female Diaphragm)

- Researchers have been conducting clinical trials to see if using a female diaphragm can reduce a woman's risk of becoming infected with HIV.
- Rationale:
 1. The cervix has a high concentration of cells that HIV likes to infect
 2. Research suggests that most HIV infections in the female genital tract occur in the cervix and endocervix
- There is a trial currently underway...

Female Diaphragm MIRA

| | |
|------------------|--|
| | South Africa and Zimbabwe |
| Question | Does use of a latex female diaphragm and a condom reduce HIV infection more than using a condom alone? |
| Study Population | 5045 women |
| Results Expected | 2007 |

Microbicides

- Researchers have been conducting clinical trials to develop a safe and effective microbicides that prevent HIV infection.
- Proposed Strategies:
 1. Disable HIV
 2. Provide a barrier between HIV in semen and vaginal or rectal tissue
 3. Interfering with the process by which HIV enters cells and establishes infection
 4. Strengthening the body's natural defenses against HIV
- There are three products in advanced stage trials currently underway...

Microbicides

| | BufferGel* | Pro2000 | Carraguard |
|------------------|---|--|--------------|
| Trial sites | Malawi, South Africa, Tanzania, Zambia, Zimbabwe and US | 1. Malawi, South Africa, Tanzania, Zambia, Zimbabwe and US* 2. South Africa, Tanzania, Uganda, Zambia, Zimbabwe | South Africa |
| Study Population | 3220 women | 1. 3220 women 2. 10,000 women | 6299 women |
| Expected Results | 2009 | 2009 | 2009 |

Cellulose Sulfate Trials Close

- At the end of January 2007, the Data Safety and Monitoring Boards (DSMB) of CONRAD met and based on a review of preliminary data, recommended that the Phase III trial of the candidate microbicide Cellulose Sulfate (CS) in Benin, India, Uganda and South Africa be discontinued.
- Early data suggest that CS may be contributing to an increased risk of HIV infection. Scientists are struggling to figure out exactly what this means given that 11 earlier safety trials had not revealed any safety concerns.
- Erring on the side of safety, the Family Health International DSMB recommended that the CS trial underway in Nigeria be closed as well, although review of the Nigerian data by that trial's DSMB found no evidence of increased risk.
- The Global Campaign for Microbicides (GCM) and the African Microbicides Advocacy Group (AMAG) have been collecting questions from advocates and seeking answers from site investigators, sponsors, microbicide experts and information publicly available about the trials.

Vaccines

- Researchers have been conducting clinical trials to develop a safe and effective vaccines for HIV/AIDS.
- Proposed Strategies:
 1. Stimulate cellular immune response
 2. Using other viruses or bacteria as “vectors”
 3. Prime-Boost models
 4. Stimulate antibody response
- There are two advanced stage trials currently underway...

Vaccines

| | Thai Prime Boost Study | STEP Study | Phambili |
|-------------------|---------------------------------------|---|--|
| Trial Sites | Rural Thailand (Rayong and Chun Buri) | Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, and US | Soweto, Cape Town, Klerksdorp, Medunsa and Durban - South Africa |
| Study Populations | 16,000 men and women | 3,000 men and women | 3,000 men and women |
| Products Tested | Prime: ALVAC Boost: AIDSVAX | Merck Adenovirus 5 | Merck Adenovirus 5 |
| Expected Results | 2010 | 2010 | 2011 |

WHAT'S THE T?
a study for men who have sex with men.

IF I PARTICIPATE:

- Free Rapid HIV testing and counseling
- Free STD testing
- Free Physical Exam and Lab tests
- Compensation for your time
- Study visits every 3 months for 2 years

WHO CAN PARTICIPATE:

- HIV Negative men, 18 or older, who have sex with men

HOW CAN I GET INVOLVED?

CALL: 404.876.2317

ARCA
AIDS Research Center at Emory

TENOFOVIR
is an approved medicine for persons with HIV/AIDS

Maurice Cook (EM Designs Group, Inc.)

Therapy Prevents Maternal to Child Transmission

Transmission Proportion

- No therapy 20-40%
- Monotherapy 4-8%
- Combination ART 0-1.5%

More suppressive therapy for the mother is more effective prevention and prevents drug resistance

Basis for nPEP recommendations

- Non-human primates
 - Tenofovir PEP was protective
- Single dose NVP to Mother/Infant was protective
 - Not enough time to lower VL in mother
 - So drugs may have been primarily active in infant
- PEP after needlestick
 - Associated with lower risk in HCW
 - Compared with *external* controls
- Clinicians/patients were using PEP anyway
- Conclusion :“nPEP might sometimes reduce the risk for HIV infection after nonoccupational exposures”
- Result: PEP access is variable

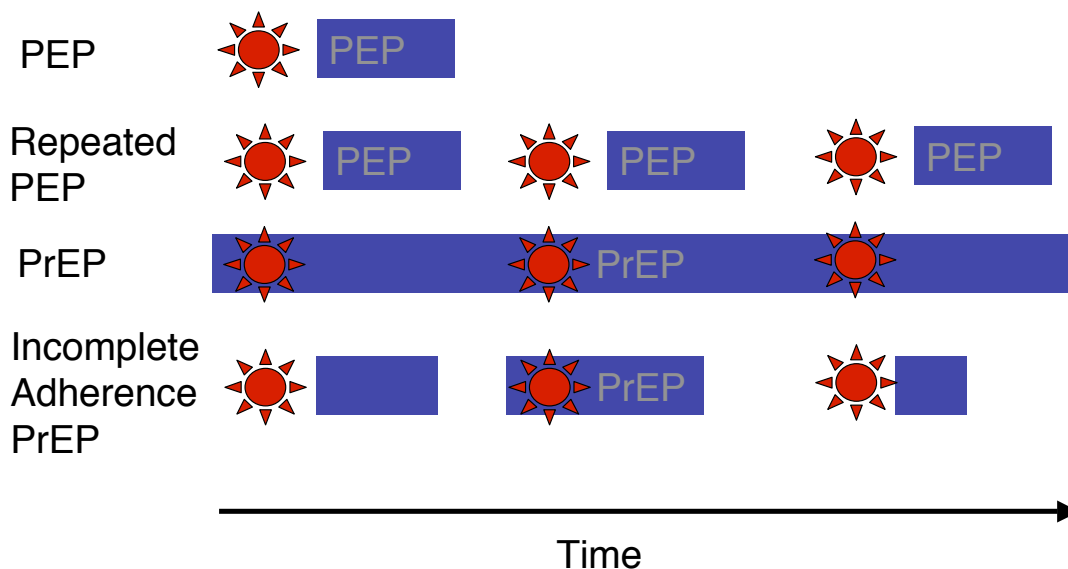
MMWR 2005

Goals of the PREP Program

- To learn what is needed to guide and promote prevention program implementation
 - Not settle for “clues” and “recommendations”
 - Level of Efficacy Matters
 - 0 vs 30% vs 70%
 - Minimum lab monitoring required for safety
- Inclusion of many risk groups
 - Women, Men, Heterosexual, MSM, IDU

PEP and PrEP:

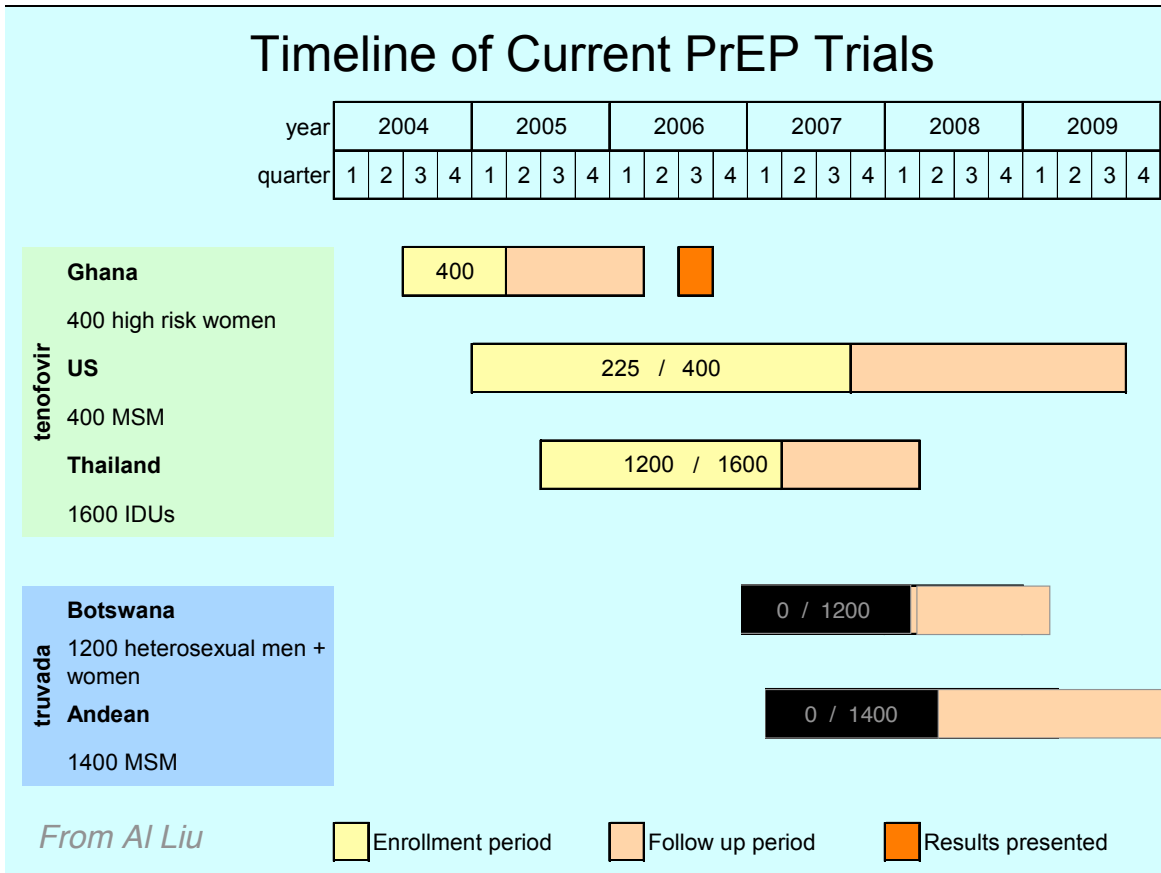
”Between the idea and the reality
Between the motion and the act” T.S. Eliot



PEP fails if it is not used

- PEP (AZT/3TC) 4 day starter pack
 - Followed by 28 day course
- N=200 high risk men
 - Followed over 24.2 months
- 68 used PEP 109 times
- HIV incidence 2.9 100py overall
 - 10 in those who did not use PEP (N=132)
 - Thought partner was HIV-,
 - Did not appreciate risk of that contact
 - 1 in a PEP user (N=68)
- *Risk Behavior decreased*

Timeline of Current PrEP Trials



Behavioral Change and Biomedical Prevention

- Will Lower Risk Per Partner Beget
 - More Partners
 - Less Condom Use

Or ...

- Would Effective Oral Prevention:
 - Serve As A Daily Reminder Of Imminent Risk?
 - Foster A Vision For An Aids-free Life?
 - And Investment In Future Health?
 - De-stigmatize “At Risk” Groups?
 - And Build Communities?
 - Stabilize Sexual Relationships?
 - For Example, By Protecting Those Desiring Pregnancy.

Risk Behavior Declined With Open-Label Post-Exposure Prophylaxis and Counseling

Martin et al., *AIDS* 2004
 also observed by Schecter et al., *JAIDS* 2004

Postexposure prophylaxis against HIV Martin et al.

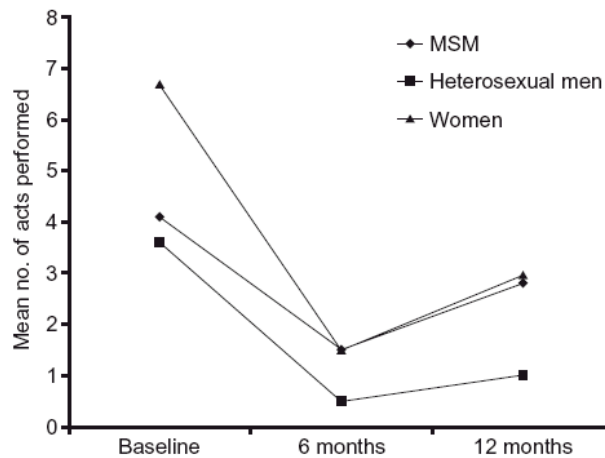


Fig. 1. Effect of postexposure prophylaxis (PEP) on high-risk sexual acts. Mean number of times participants engaged in either unprotected receptive or insertive anal or vaginal intercourse, or oral intercourse with receipt of ejaculate with high-risk partners in the 3-month period prior to receipt of PEP (baseline) and in the 3-month period prior to the 6- and 12-month visits following receipt of PEP.

Sexual Behavior

| | Screening | Follow-up |
|----------------------------------|-----------|-----------|
| Number of partners (30 days) | 21 | 14 |
| Number of new partners (30 days) | 11 | 6 |
| Number of sex acts (7 days) | 12 | 15 |
| Condom use (last act) | 52% | 94% |

Strong Communities Help by

- Setting the Agendas
- Fostering Public Discussion (Even Controversy)
 - Helps if it makes us talk, think, and improve
 - Hurts if it infringes on the right to know
- Finding Those at High Risk
 - High risk partly because they are hidden
 - Overcoming stigma and disorganization
- Using (or not) what is found
 - Prevention tools fail if not used
 - Practical (operational) knowledge is key
- Better Theories of Behavior

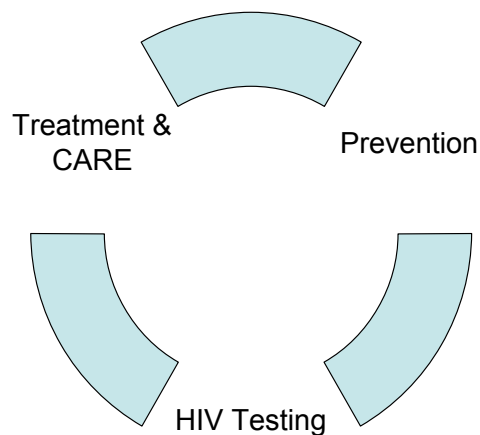
What are the implications?

- Evaluate our knowledge
 - Need to conduct more research & make better research agendas (for non conclusive data)
 - Need to make decisions based on conclusive data
- Implementation
 - How do we utilize new knowledge and interventions? Where, when, how and with whom?
 - How do you talk about partial efficacy/disease modulation/reduction of infectiousness?
- Future research
 - Trial design (size, location and incidence rate)
 - Standard of care

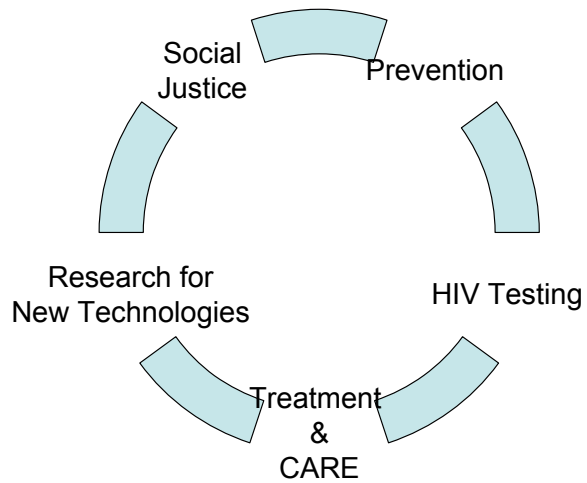
Community Involvement

- No intervention will be useful if communities do not use them.
- Communities have to be aware of, involved with and accepting of any interventions
- Communities need to help determine what are the best prevention/treatment packages for them.

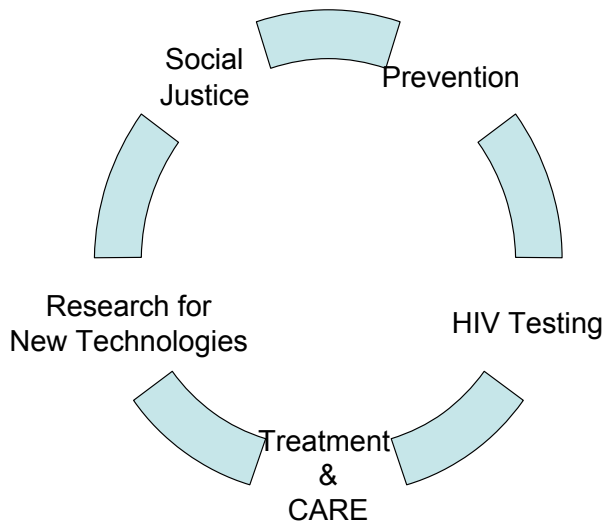
Continuum of care...



Comprehensive Response

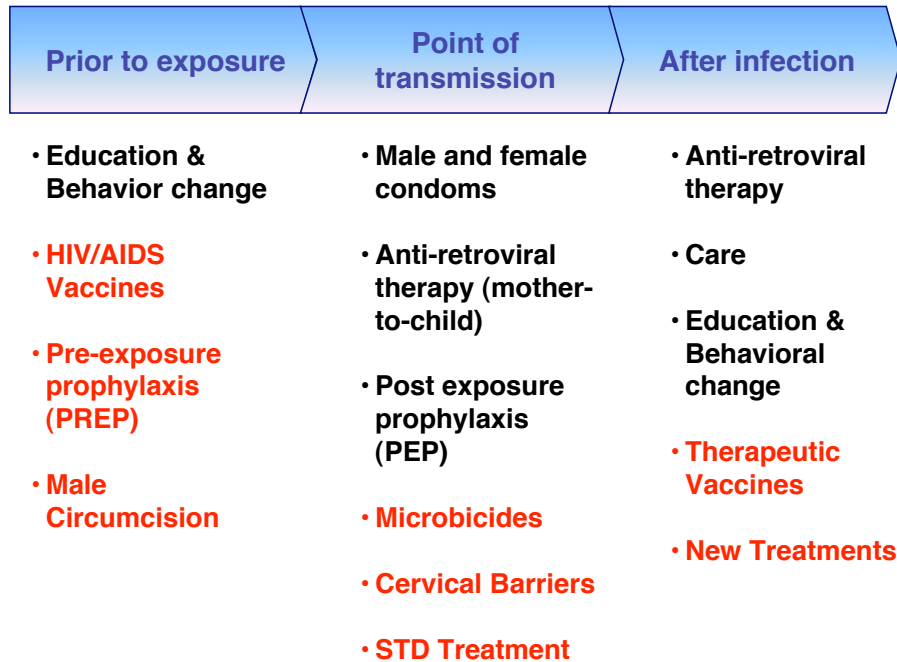


New Technologies

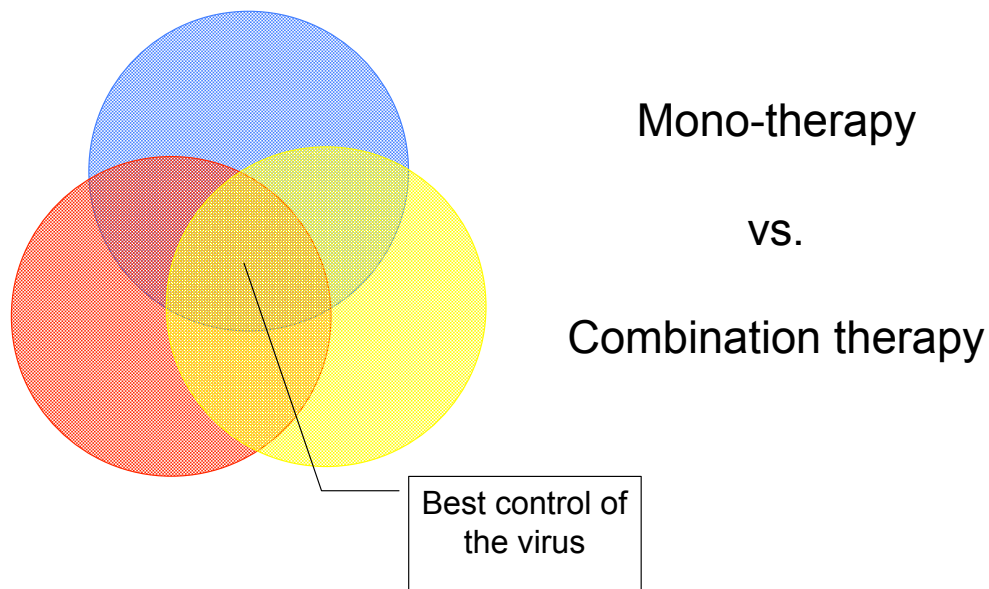


- New Treatments
- Vaccines
- Microbicides
- Male Circumcision
- PrEP
- STD Prevention
- Cervical Barriers

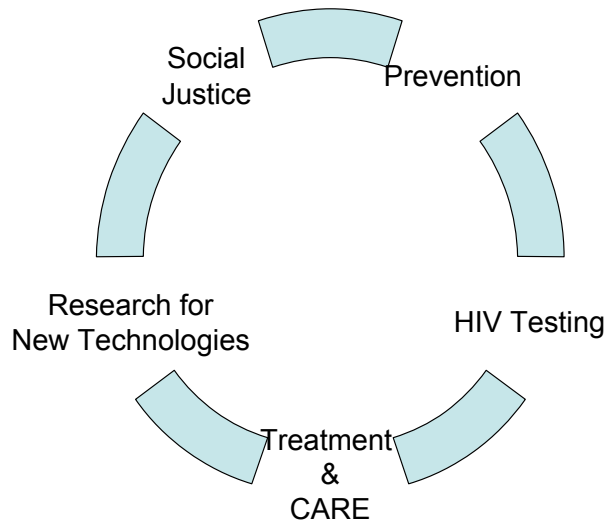
HIV/AIDS Tool Kit



Treatment Analogy



Social Justice



- HIV/AIDS is driven by the same socio-economic factors that put marginalized groups at risk and without needed resources
- The poor, people of color, women, drug users, sex workers, minorities, youth, etc
- Stigma for PLWHA