

The Moving Prevention Landscape and Embracing Combination HIV Prevention

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PreventionRX Study

HIV Prevention at the Cross-Roads

- Critically need evidence-based prevention strategies
- Behavior change can be effective
 - Increased condom use among serodiscordant couples
 - Need to understand role of & interventions for multiple, concurrent partnerships
- Biomedical interventions that have partial efficacy
 - Male circumcision of HIV-negative heterosexual men (clinical trial data)
 - ART (based on observational & ecologic data)
- New biologic interventions being tested for efficacy
 - PrEP, microbicides (tenofovir gel), HIV vaccines, ART at higher CD4 (HPTN 052)
- No single strategy will work alone
 - Multi-component, integrated, partially effective biomedical & behavioral interventions
- Evidence-based approach to design of combination HIV prevention & testing effectiveness of a package



Principles of Combination HIV Prevention

1) Important to “know one’s HIV epidemic”

- HIV prevalence & incidence
- Populations at highest risk
- Whether they know they’re at risk & their HIV serostatus
- Modifiable risk factors (community & individual levels)
- Evidence for different prevention interventions

2) To slow HIV epidemic ($R_0 < 1$), need interventions with demonstrated efficacy to reduce infectiousness & susceptibility

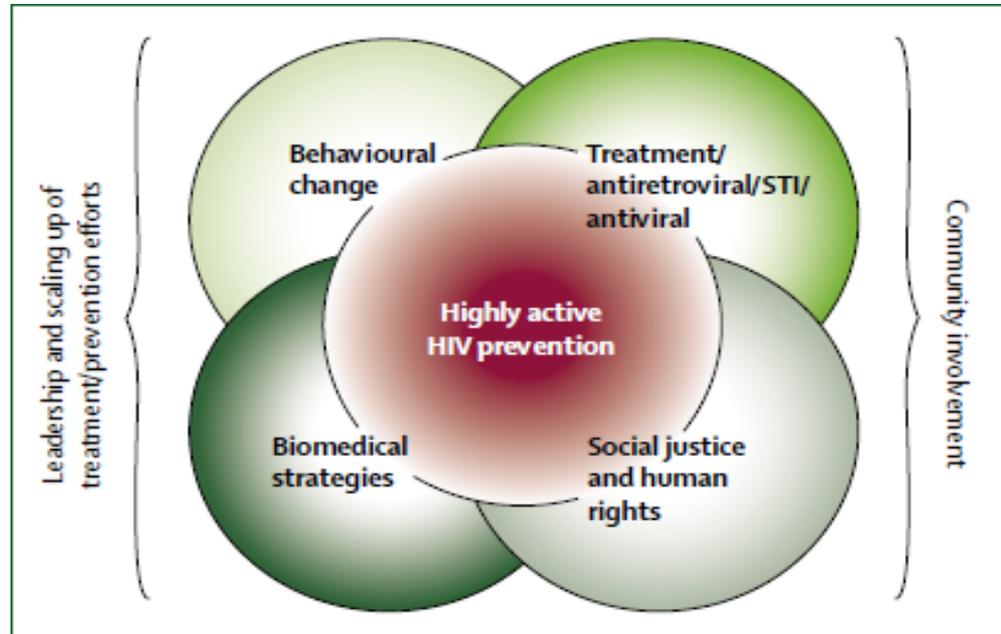
- ART for HIV+, MC for HIV- men at high risk (eg., in discordant couples)
- Consider synergy, redundancy & antagonism when combine interventions

3) Consider coverage, efficacy & cost-effectiveness in ‘scaling up’ interventions



“Highly Active HIV Prevention” (aka HARP), or Combination, multi-component HIV prevention

Should be evidenced-based, targeted & integrated...



... and yet, not “kitchen sink” with all possible interventions

Research Agenda for Combination HIV Prevention:

NIH Methods for Prevention Packages ('MP3')

Description:

This project will support collaborations between **behavioral and biomedical clinical scientists, epidemiologists, and clinical trial design specialists** to:

- (1) **devise** optimal HIV **“prevention packages”** (combination interventions) for specific populations
- (2) **design clinical studies** to rigorously examine the safety and efficacy of these “packages” in the target population
- (3) **demonstrate** that the proposed **prevention package** is **acceptable** to the target population and the **study design** is **appropriate** and **feasible**.



MP3 Grantees: Population & approaches

1) PUMA (Buchbinder - Americas)

- MSM
- Participants self-select menu items
- iRCT of 'menu' of interventions vs SOC

2) Prevention Rx (Celum – Uganda)

- Heterosexual men and women
- Home-based VCT (HBCT) platform, targeted facilitation of MC, ART,...
- cRCT or RCT in discordant couples or demonstration project

3) Mochudi (Essex, DeGruttola – Botswana)

- Entire community
- HBCT, test and treat (using PVL), contact tracing, sequencing
- cRCT or demonstration project

Six MP3's – what and where?

4) Acute HIV Infection (Miller, Pettifor – Malawi)

- Heterosexual men and women with acute infection
- ART, behavioral counseling
- Eventual trial ? (cRCT or RCT in discordant couples)

5) IDUs (Des Jarlais – Estonia)

- IDUs
- Needle exchange, methadone, community support - coverage and targeting
- cRCT (stepped wedge design)

6) EPIC (El-Sadr – Lesotho)

- Discordant couples identified through PMTCT
- MC, ART, couples counseling
- Eventual trial? (RCT in discordant couples)

Developing & evaluating a combination HIV prevention package

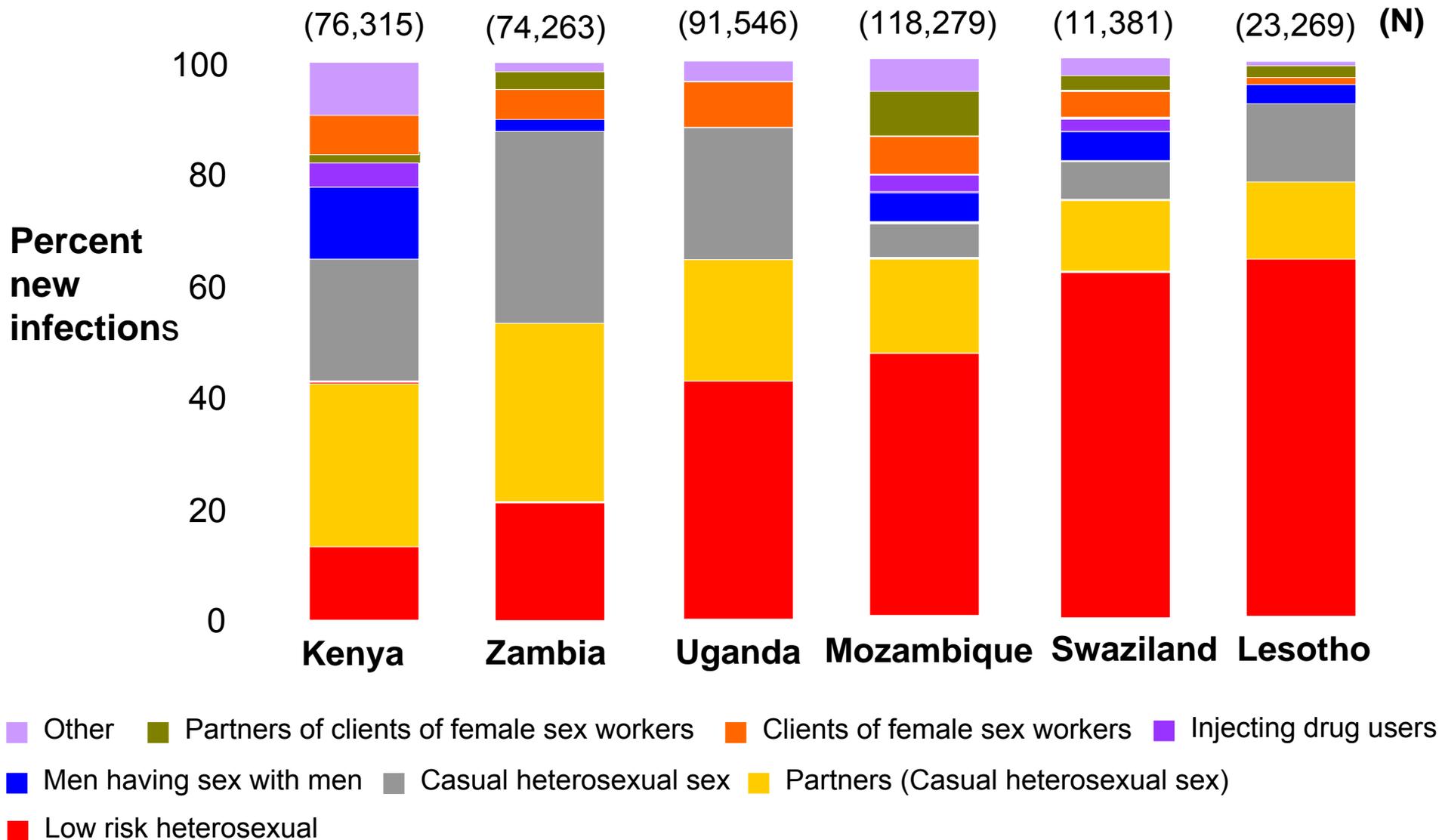
Uganda case study: PreventionRx

1. “Know Your Epidemic”
2. “Know Your Response”
3. Design evidence-based combination prevention package & evaluate population-level impact on HIV

“Know Your Epidemic”

- Stage of HIV epidemic (nascent, concentrated, larger concentrated epidemic)
- Proportion of new infections in different populations (CSWs, stable partnerships, MSM, IDU)
- “Drivers” of HIV epidemic in different populations (eg., lack of male circumcision)
- Which drivers are modifiable and have effective, ‘scaleable’ interventions

Incidence by Modes of Transmission



Sources: Draft results from Know your Epidemic project

Uganda: Key demographic indicators

Demographic data	Year	Estimate	Source
Total population (thousands)	2007	30 884	UN Population Division
Population aged 15-49 (thousands)	2007	13 370	UN Population Division
Female population aged 15-24 (thousands)	2007	3 149	UN Population Division
Annual population growth rate (%)	2005-2010	3.6	UN Population Division
% of population in urban areas	2007	13	UN Population Division
Crude birth rate (births per 1000 pop.)	2007	46.6	UN Population Division
Crude death rate (deaths per 1000 pop.)	2007	13.6	UN Population Division
Maternal mortality ratio (per 100 000 live births)	2005	550	WHO, UNICEF, UNFPA and The World Bank, 2007
Life expectancy at birth (years)	2006	50	World Health Statistics 2008, WHO
Total fertility rate (per woman)	2006	6.6	WHO Statistical Information System (WHOSIS)
Infant mortality rate (per 1000 live births)	2006	78	World Health Statistics 2008, WHO
Under 5 mortality rate (per 1000 live births)	2006	134	World Health Statistics 2008, WHO

High population growth >> continued expansion of the HIV epidemic

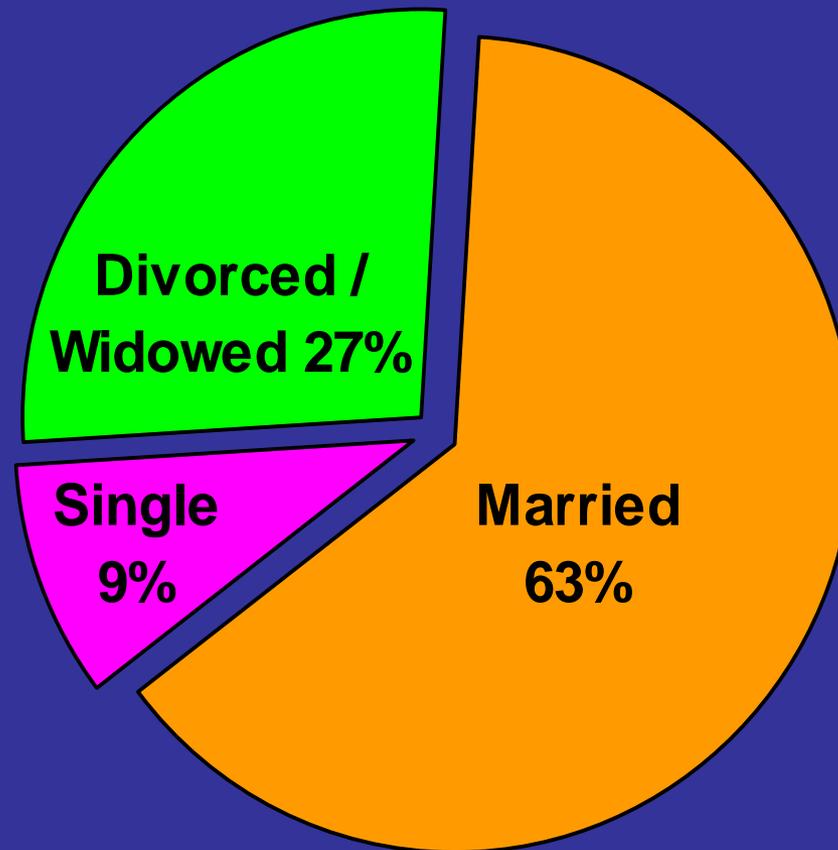
Source: UNAIDS

How is HIV mostly spreading in Uganda?

1. Discordant stable partnerships
2. Multiple concurrent partnerships
3. Mother-to-child transmission
4. Most At Risk Populations:
 1. Commercial sex
 2. MSM
 3. Drug use

Source: Modes of Transmission Study, 2008 & Mathematical projections

Incident HIV infections by marital status



“Married” status: Not all transmissions within married partners

- ~1/2 of recent infections observed where spouses were HIV-negative

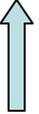
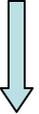
HIV transmission risk behavior among HIV-infected adults in Uganda: results of a nationally representative survey

Rebecca Bunnell^a, Alex Opio^b, Joshua Musinguzi^b, Wilford Kirungi^b, Paul Ekwaru^a, Vinod Mishra^c, Wolfgang Hladik^a, Jessica Kafuko^d, Elizabeth Madraa^b and Jonathan Mermin^a

- 77% sexually active
- 40% have HIV-uninfected spouse
- Only 21% had tested previously (2005)
 - 3x more likely to use condoms
- Only 9% knew their partner's HIV status
 - 2.3x more likely to use condoms

Trends in HIV-Related Behaviors and Knowledge in Uganda, 1989–2005: Evidence of a Shift Toward More Risk-Taking Behaviors

Alex Opio, MB ChB, MSc, PhD, Vinod Mishra, MStat, MA, MPH, PhD,† Rathavuth Hong, MD, DrPH,†
Joshua Musinguzi, MB ChB, MPH,* Wilford Kirungi, MB ChB, MPH,* Anne Cross, MA,†
Jonathan Mermin, MD, MPH,‡ and Rebecca Bunnell, PhD‡*

- Men: multiple sexual partnerships
 - 2005: 29% 
 - 2001: 24%
- Men aged 15-24 yrs: Condom use at last non-spousal sex
 - 2005: 55% 
 - 2001: 65%

What puts people at risk for HIV acquisition in Uganda?

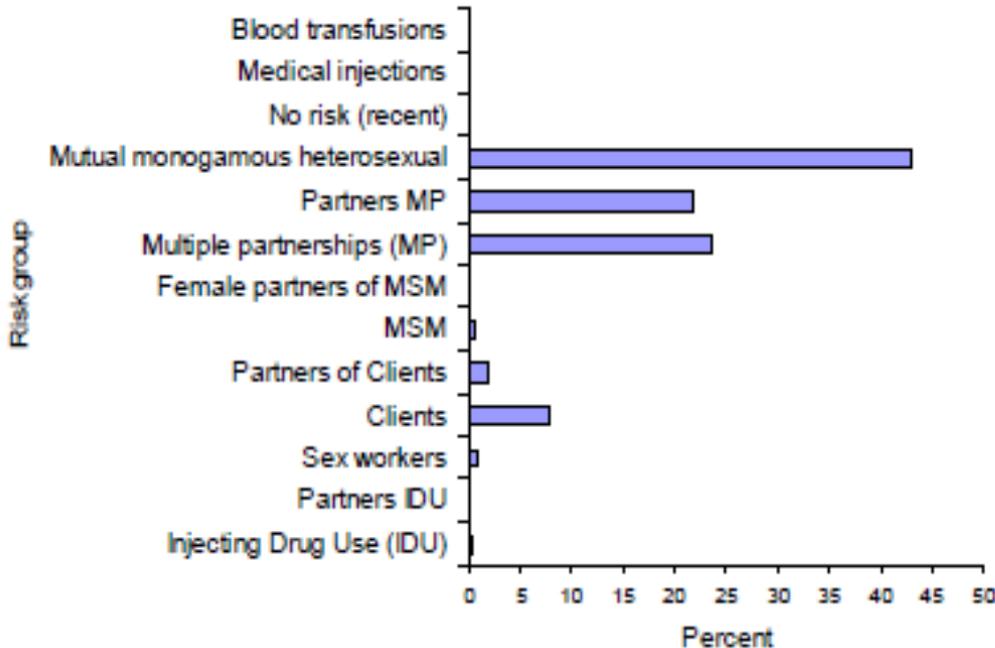
- Multiple partners: 2.5 ↑ risk
- HSV-2 infection: 3.9 ↑ risk
- STD in last year: 1.7 ↑ risk
- Not circumcised: 2.5 ↑ risk (males)
- Not using condoms: 3.3 ↑ risk

UGANDA

HIV Prevention Response and Modes of Transmission Analysis

“Know your epidemic”

Figure 5: Distribution of new infections by mode of exposures



“Know your response”

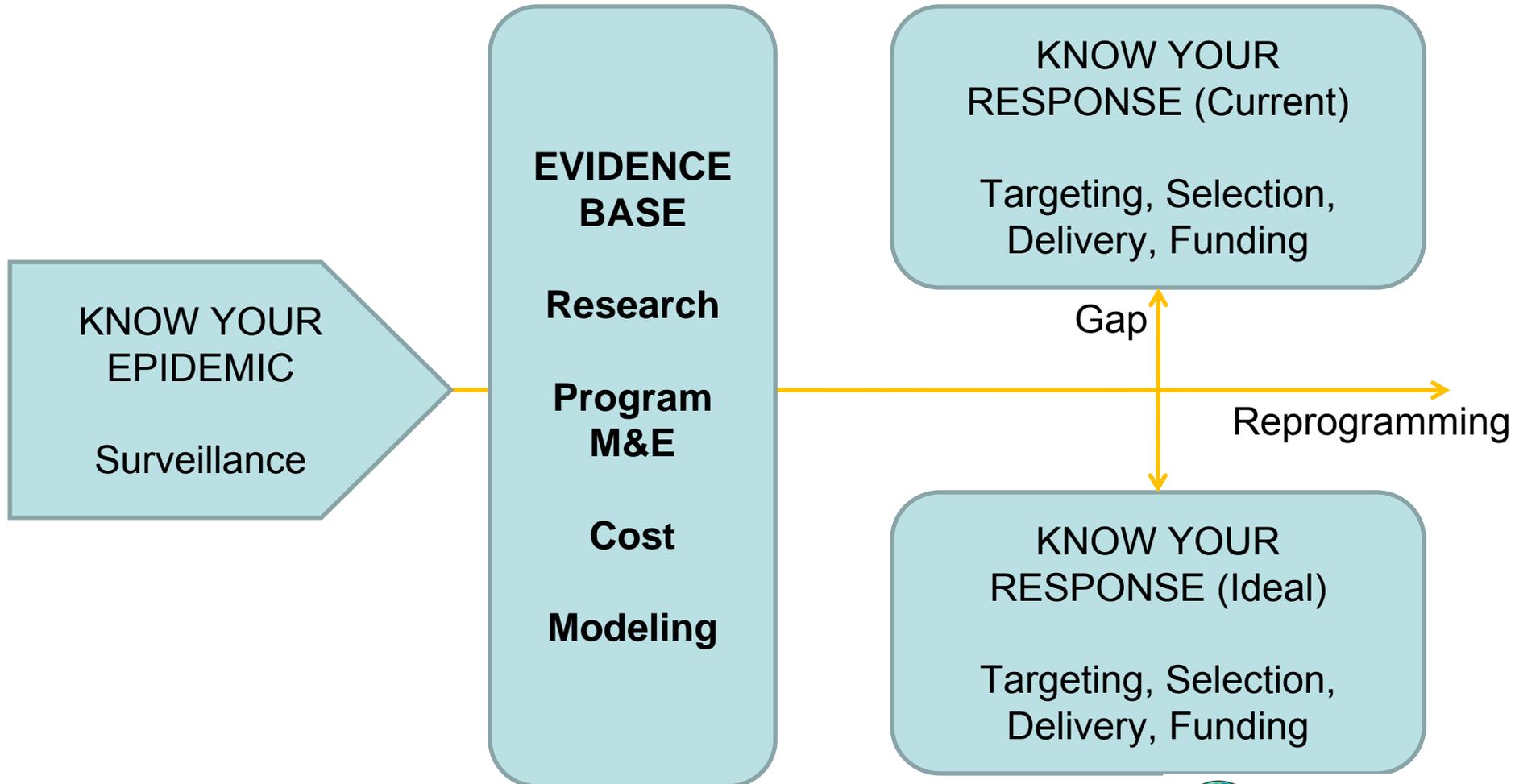
- Increase knowledge of HIV status & links to prevention
- Scale up safe, medical male circumcision
- Scale up couples counselling
- Strengthen prevention for:
 - Cohabiting couples
 - HIV + persons (prevention beyond ART & care)
 - Persons with multiple partners
 - Populations at higher risk of exposure (eg fishing communities, MSM)



Uganda AIDS Commission



Programmatic methodology of “Know Your Response”



Evidence for “what works” for HIV prevention

- Individual RCTs measure direct effects of individual interventions (e.g. RCTs of male circumcision in African heterosexual HIV- males)
- Often do not have RCT data (e.g. condom use, effect of VCT & knowledge of serostatus, serosorting among MSM)
- Seldom have data on population effectiveness (direct & indirect effects) of interventions, feasibility and scalability
- Difficult to know synergy of interventions



What Works for HIV Prevention (strong observational evidence & RCT data)

Intervention	Target	Evidence	Effect for HIV prevention	Comment
Male circumcision	HIV- men	3 RCTs; >30 observational studies	58% reduction	Population-level reduced HIV risk for women in mathematical modeling studies

- **MP-3 grants:** Use math modeling to estimate *targeting*, *coverage*, *time* to see a population-level impact on HIV from medical MC programs in specific settings



What Should Work for HIV Prevention

(observational or preclinical data; clinical trials ongoing)

Intervention	Target	Evidence	Effect for HIV prevention	Comment
PrEP	HIV- men and women	6 RCTs ongoing	First data end of 2010	High efficacy in animal model studies
ART provided to HIV+ persons, including "early" treatment at higher CD4 counts	HIV+ men and women	1 RCT ongoing; observational studies in context of CD4<200	observational studies 79-100% reduction	Mathematical modeling:potentially high population effect
Knowledge of serostatus / VCT	HIV- & HIV+, men & women	1 RCT ongoing	unknown	One RCT demonstrated behavior change with VCT
Treatment of malaria, helminths	HIV+, men & women (pre-ART)	Short-term treatment studies	unknown	Treatment reduces plasma HIV

Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings

Peter J. Dodd, Geoff P. Garnett and Timothy B. Hallett

AIDS 2010, 24:729–735

- Depends on epidemiologic context, including sexual networks
- Cost-effective approach: testing every 3-5 yrs?
- Need empiric data: HPTN 052 to determine effect of ART at higher CD4 counts & over longer duration

Treatment of co-infections to reduce Plasma and/or genital HIV RNA

Intervention	Study Population	N	Estimate of Effect (95% CI)
Co-trimoxazole for prophylaxis of malaria & bacterial infections	Uganda (adults)	509	Δ plasma HIV RNA (\log_{10})= -0.6 (-0.97 to -0.13)
Malaria treatment	Meta-analysis of studies from China, Malawi, Nigeria, Uganda, Zambia (adults)	363	Δ plasma HIV RNA (\log_{10})= -0.4 (-0.7 to -0.1)
Albendazole for treatment of helminths	Kenya (adults)	208	Δ plasma HIV RNA (\log_{10})= -0.5 (-1.2 to 0.1)
Tuberculosis treatment	Meta-analysis of studies from Côte d'Ivoire, England, Ethiopia, Ghana, India, So Africa, Uganda, Ukraine, US (adults)	521	Δ plasma HIV RNA (\log_{10})=-0.01 (-0.14 to 0.12)
HSV-2 suppression (Acyclovir 400 mg bid x 2 yrs)	East and south African adults	3408	HIV Transmission HR 0.92 (0.6-1.4); Plasma HIV RNA=-0.25 \log_{10} (-0.22 to 0.29)
Bacterial STI treatment	Ethiopia, Kenya, Malawi (adults)	110 men; 124 women	<u>Men</u> : $\Delta \log_{10}$ seminal HIV RNA = -0.4 (trich); -0.5 (urethritis) <u>Women</u> : $\Delta \log_{10}$ cervicovag HIV RNA = -0.4 (GUD/discharge); -0.6 (trich);-0.7 (GC); -0.8 (cervicitis); -1.0 (CT)

What Probably Works for HIV Prevention (strong observational evidence)

Intervention	Target	Evidence	Effect for HIV prevention	Comment
Condom use	HIV- & HIV+, men & women	Multiple observational studies	estimated 80% reduction with consistent use	Less evidence for female condoms
HIV testing as a couple & ongoing couples counseling	HIV serodiscordant couples	Observational cohorts	>50% reduction in HIV incidence	Limited data to quantify efficacy

Defining Package for Multi-Component HIV Prevention in Uganda

- Community Interventions
 - HBCT to massively increase knowledge of HIV serostatus
- Biomedical Interventions
 - Male circumcision to prevent HIV in men (age criteria, men in discordant couple)
 - ART for HIV+ persons for HIV prevention
 - ART at national guidelines: CD4 250 (need data to justify higher CD4 ie, 'test & treat'?)
- Behavioral Interventions
 - Condoms
 - Couples counseling for serodiscordant couples (needs piloting)
 - Risk reduction counseling, inc. partial efficacy of male circumcision
 - Adherence & risk reduction counseling in HIV+ persons
- Possible components, pending data
 - PrEP? Treatment of co-infections in HIV+?
 - Intervention for multiple, concurrent partnerships?



HBCT Results from Bushenyi District, Uganda, 2005-6

VCT RESULTS

	N (%)
Eligible for HIV Testing	296,431
Tested for HIV	264,966 (89.4%)
Received HIV Results	264,953 (99.9%)
HIV Positive	11,359 (4.3%)
Individuals in HIV-Discordant Partnerships	1,785

Dr. Elioda Tumwesigye,
Integrated Community Based Initiatives (ICOBIs)
CROI 2008

Components of Basic Care Package (BCP) delivered to HIV+ persons

Safe water vessel



Chlorine



Filter for H2O



Condoms



Bednet



Cotrimoxazole Prophylaxis



IEC materials



- ~80% of Ugandan HIV+ on TMP-sulfa prophylaxis through BCP

HBCT Platform for Delivery of Multi-Component, Combination HIV Prevention

- Massively increase knowledge of HIV serostatus
 - Home-based VCT
- Coupled with electronic data capture for risk stratification
 - HIV seropositive individuals & HIV concordant + couples
 - Pregnant HIV+ women
 - HIV serodiscordant couples (DCs)
 - High-risk HIV- uncircumcised men (in DC couples, multiple SP, age <35)
 - HIV- men & women with multiple SP in past 12 mos (including CSWs & clients)
- Knowledge of HIV serostatus and triage to target & increase coverage: **‘PreventionRx’**
 - *Example of PreventionRx for a Discordant Couple: 1) Couples counseling, 2) HIV+ female: Basic Care Pkg & Refer for ART & 3) HIV- male for MC*
 - Facilitated referral to ART for HIV+ and HIV- to prevention services
 - Follow-up to ensure high uptake

Empiric data needed on interventions to reduce HIV infectiousness as part of combination HIV prevention

- Measure behavioral & cost impact of HBCT to identify HIV+ persons unaware of their status
- Among HIV+ identified through HBCT, POC CD4 effective triage to:
 - CD4<250 (or national guidelines): ART with enhanced referral
 - CD4>250: prevention and treatment of co-infections
 - Malaria (bednets, TMP/Sx), helminths (albendazole), bacterial infections/PCP (TMP/Sx)
- Provide risk reduction & adherence counseling to all HIV+
- Effect on *community viral load & risk behaviors*

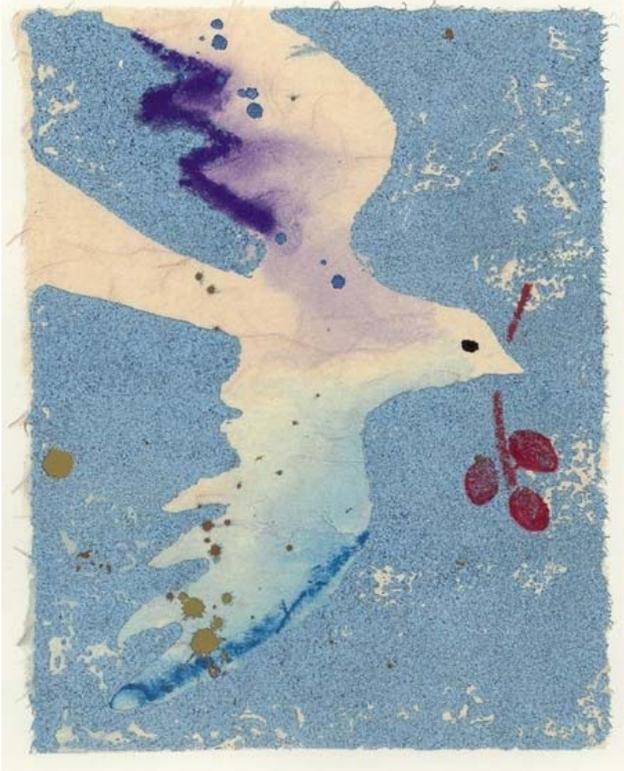


Evaluation of Combination HIV Prevention: Design Issues (Sept 2009 MP-3 meeting)

- Goals & specific situation dictate design
- HIV incidence is ultimate endpoint of interest
 - Need lab method for estimating incidence from cross-sectional samples
 - Nested cohorts to directly measure HIV incidence
 - Proximal surrogates of impact on HIV incidence (community viral load?)
- RCT of individuals, communities vs discordant couples?
 - Direct effects vs community level effects?
 - Direct effects: Transmission (discordant couples) vs acquisition?
- RCT vs phase II or demonstration project?
 - To evaluate modest effects, need an RCT to avoid confounding
 - If see a “homerun” in pilot or phase II, RCT may not be necessary
 - If the sole issue is to establish ‘scaleability’ of proven intervention(s), conduct demonstration project rather than RCT



Combination HIV Prevention: Needs, Challenges & Opportunities



*If you want to go fast, go alone.
If you want to go far, go together.*
– African proverb



Thanks to the 'PreventionRx' MP-3 Team

Epidemiology/Modeling Core

Connie Celum, Laith Abu-Raddad, Jared Baeten, Tim Hallett, Martina Morris, Judy Wasserheit, Helen Weiss

Intervention Core

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