Combination prevention for HIV

How to evaluate whether it works?

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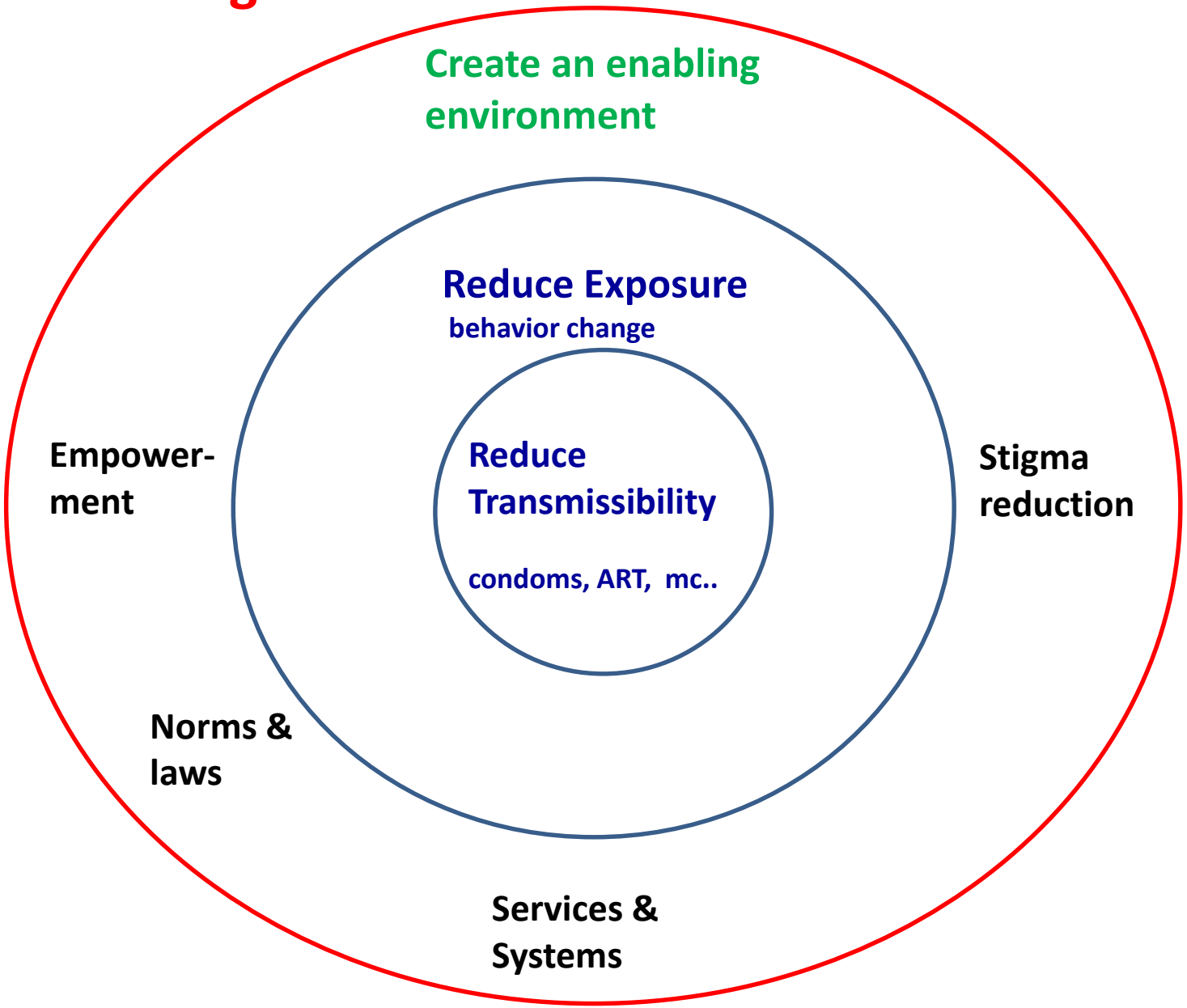
Preventing HIV includes…



HIV prevention: human behaviour at the center

- **Negotiating and using** condoms
- **Adopting** safer sex
- **Accepting** to be tested for HIV
- **Adhering** to ART , PrEP or condom use
- **Seeking** health care for Male circumcision
- **Overcoming stigma** to seek care

UNAIDS (2010) provides the following definition of *combination HIV prevention*:

"The strategic, simultaneous use of different classes of prevention activities (biomedical, behavioral, social/structural) that operate on multiple levels (individual, relationship, community, societal), to respond to the specific needs of particular audiences and modes of HIV transmission, and to make efficient use of resources through prioritizing, partnership, and engagement of affected communities" .

The biomedical approaches robust RCT evidence

Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial

Bertran Auvert et al, Plos 2005

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Robert M. Grant, M.D., M.P.H., Javier R. Lama, M.D., M.P.H., Peter L. Anderson, Pharm.D., Vanessa McMahan, B.S., Albert Y. Liu, M.D., M.P.H., Lorena Vargas, Pedro Goicochea, M.Sc., Martín Casapía, M.D., M.P.H., Juan Vicente Guanira-Carranza, M.D., M.P.H., María E. Ramírez-Cardich, M.D., Orlando Montoya-Herrera, M.Sc., Telmo Fernández, M.D., Valdilea G. Veloso, M.D., Ph.D., Susan P. Buchbinder, M.D., Suwat Chariyalertsak, M.D., Dr.P.H., Mauro Schechter, M.D., Ph.D., Linda-Gail Bekker, M.B., Ch.B., Ph.D., Kenneth H. Mayer, M.D., Esper Georges Kallás, M.D., Ph.D., K. Rivet Amico, Ph.D., Kathleen Mulligan, Ph.D., Lane R. Bushman, B.Chem., Robert J. Hance, A.A., Carmela Ganoza, M.D., Patricia Defechereux, Ph.D., Brian Postle, B.S., Furong Wang, M.D., J. Jeff McConnell, M.A., Jia-Hua Zheng, Ph.D., Jeanny Lee, B.S., James F. Rooney, M.D., Howard S. Jaffe, M.D., Ana I. Martínez, R.Ph., David N. Burns, M.D., M.P.H., and David V. Glidden, Ph.D., for the iPrEx Study Team*

Science

Science **329**, 1168 (2010)

Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

Quarraisha Abdool Karim,[1,2]*† Salim S. Abdool Karim,[1,2,3]* Janet A. Frohlich,[1] Anneke C. Grobler,[1] Cheryl Baxter,[1] Leila E. Mansoor,[1] Ayesha B. M. Kharsany,[1] Sengeziwe Sibeko,[1] Koleka P. Mlisana,[1] Zaheen Omar,[1] Tanuja N. Gengiah,[1] Silvia Maarschalk,[1] Natasha Arulappan,[1] Mukelisiwe Mlotshwa,[1] Lynn Morris,[4] Douglas Taylor,[5] on behalf of the CAPRISA 004 Trial Group‡

“ What works” in Behaviour change or Community Empowerment ?

Community RCTs on impact of multi-component behavioral Interventions : no effect on HIV incidence

- **Cowan** et al. (2010). The Regai Dzive Shiri Programme : results of a randomized trial of a of an HIV prevention intervention for youth . *AIDS 24: 2541-52*
- **Jewkes** et al. (2008). Impact of Stepping Stones on incidence of HIV and HSV-2 and sexual behaviour in rural South Africa : a cluster randomized controlled trial. *BMJ* 337: a506.
- **Ross** et al. (2007): Biological and behavioural impact of an adolescent sexual health intervention in Tanzania: a community-randomized trial. *AIDS* 21:1943-1955.
- **Gregson** et al. (2007). Impact and process evaluation of integrated community and clinic-based HIV-1 control: a cluster-randomised trial in eastern Zimbabwe. *PLoS.Med.* 4:e102.
- **Pronyk** et al. (2006). Effect of a structural intervention for the prevention of intimate partner violence and HIV in rural South Africa: a cluster RCT. *Lancet* 368:1973-1983.
- **Kamali** et al. (2003): Syndromic management of sexually-transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: a community randomised trial. *Lancet* 361:645-652.

Possible Explanations for flat results in c-RCT ?

- Control group: *Compared to what*?
- The intervention too "weak" ? *The trial design lead to fit the intervention to the trial*
- The power to detect an effect? *HIV rare event*
- Low or heterogeneous "uptake" of the interventions ?
- Long and complex pathway between interventions and endpoint ?
- Context specificities

Is intervention truly ineffective or evaluation method inappropriate?

The evidence dilemma

- "Scientific rigour =good quality RCT" require tightly defined interventions, preferebly with a short impact pathway, which tends to limit HIV prevention to biomedical approaches only

- Combination prevention including **also** social movements, advocacy, education, social mobilisation, arelikely to be more powerfull , but impractical to prove evidence , because less-well-defined and longer more complex impact pathway

The Evidence dilemma

- C-RCT : gold standard for evaluation of combination prevention programs?

- Absence of evidence does not mean absence of effectiveness

- More negative trials add to the “confidence crisis in HIV prevention”

- Balance cost of prevention trials versus cost of preventing infections

- Alternative methods to obtain “ rigorous evidence” ?

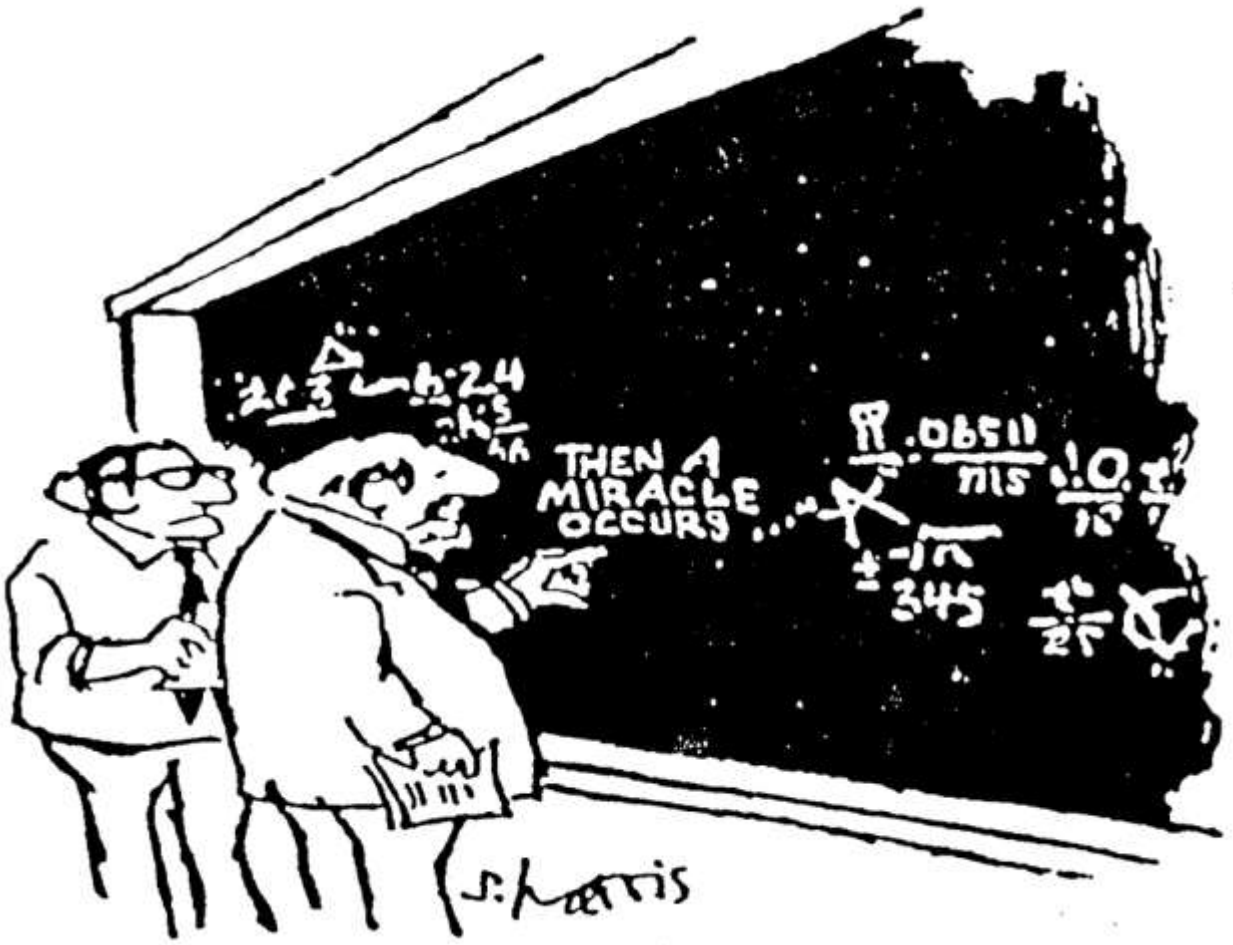
Evaluating HIV prevention effectiveness: the perfect as the enemy of the good

Marie Laga[a], Deborah Rugg[b], Greet Peersman[c] and Martha Ainsworth[d]

There is a need to better understand the effectiveness of HIV-prevention programs. Cluster randomized designs have major limitations to evaluate such complex large-scale combination programs. To close the prevention evaluation gap, alternative evaluation designs are needed, but also better articulation of the program impact pathways and proper documentation of program implementation. Building a plausible case using mixed methods and modeling can provide a valid alternative to probability evidence. HIV prevention policies should not be limited to evidences from randomized designs only.

AIDS 2012, **26**:779–783

Dealing with “complexity”

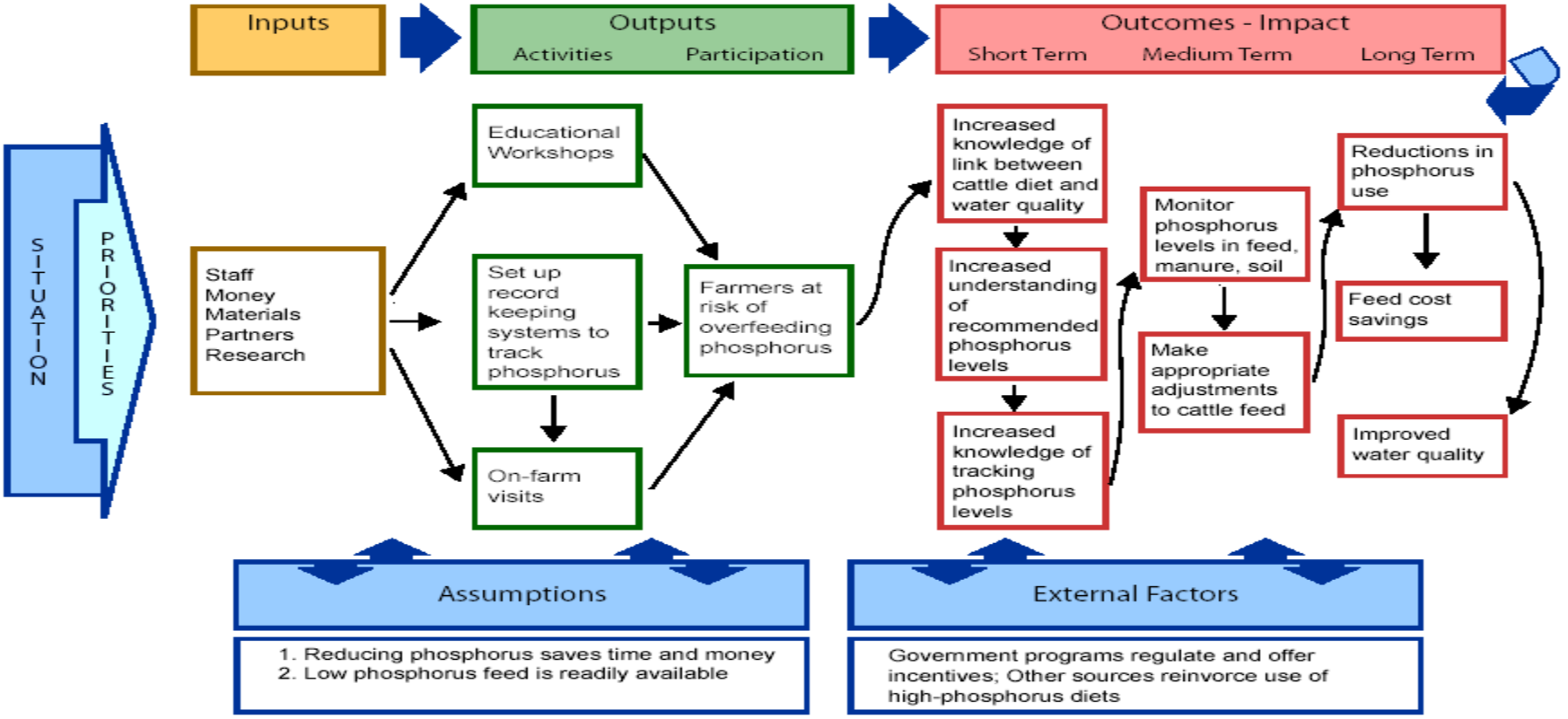


Need for Program Theory or Logic

- Spelling out the different steps
- Makes the connections explicit

- More work needed here to desentangle steps and components of HIV prevention programs!

Example: Water quality



Levels of Evidence in public health program evaluation

Type of evidence	Type of statement	Compared to what
Adequacy	The expected change occurred (but no causality)	-No control group -Predefined criteria, or absolute or incremental value
Plausibility	Program seemed to have effect over & above external influences *based on a step by step ruling out of other confounding factors*	-A non-random control group (historical, external, internal, simulated)
Probability	-The program has an effect -(P<x% that the difference between program & non-program were due to confounding / bias)	Randomised control group or cluster

from Habicht et al

Effectiveness by "Plausible attribution"

- Triangulation of data sources : survey's, surveillance, program data, context
- Mixed methods needed
- Causality considerations: Bradford Hill criteria
- Modelling to simulate control groups and predict impact

Has Prevention worked?

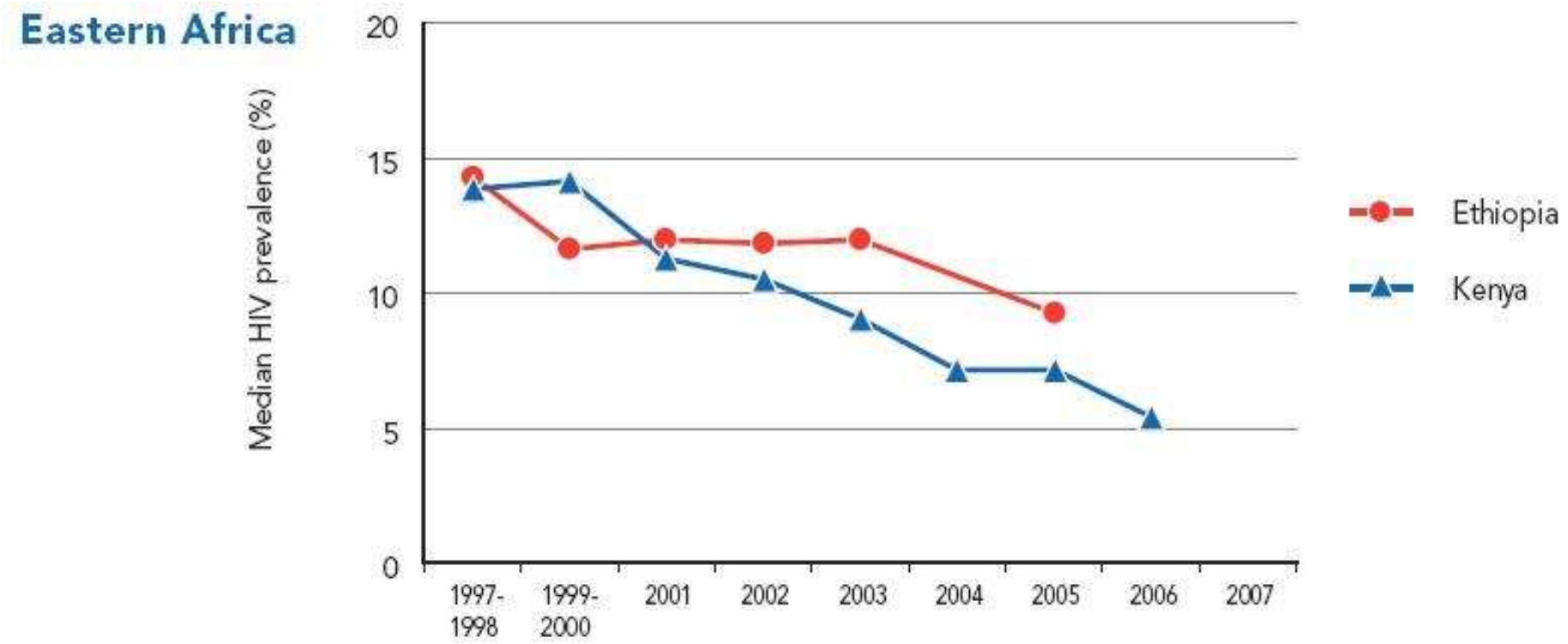
Working backwords

- Making sense of national trends
- Showing effectiveness of ongoing, real life programs programs

Prospective Evaluations

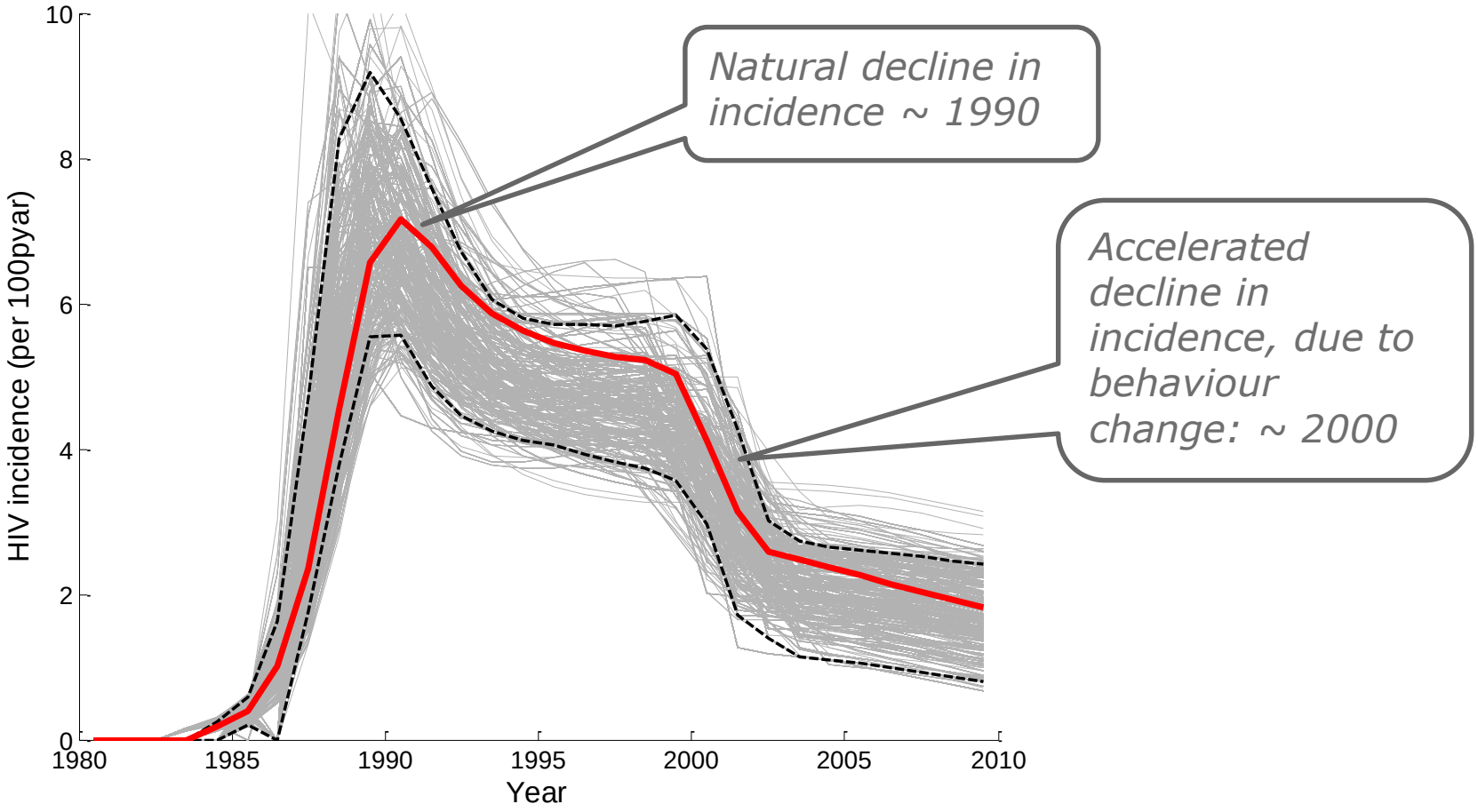
- Evaluating “new programs”

Declining HIV prevalence trends observed in many African countries: what does it mean?



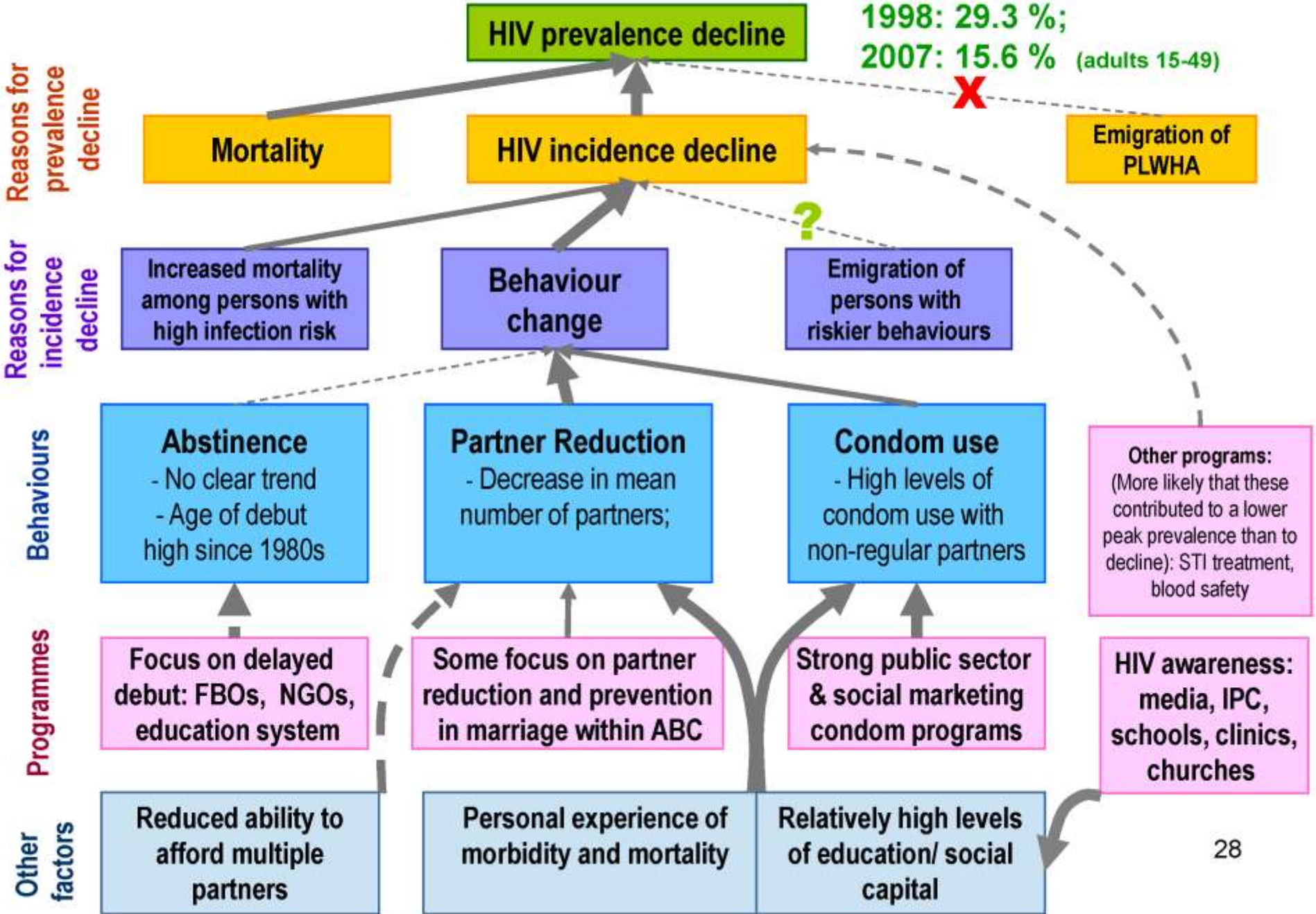
Understanding National Trends: Impact of Prevention

The example of Zimbabwe



Ref Halett T et al, 2010

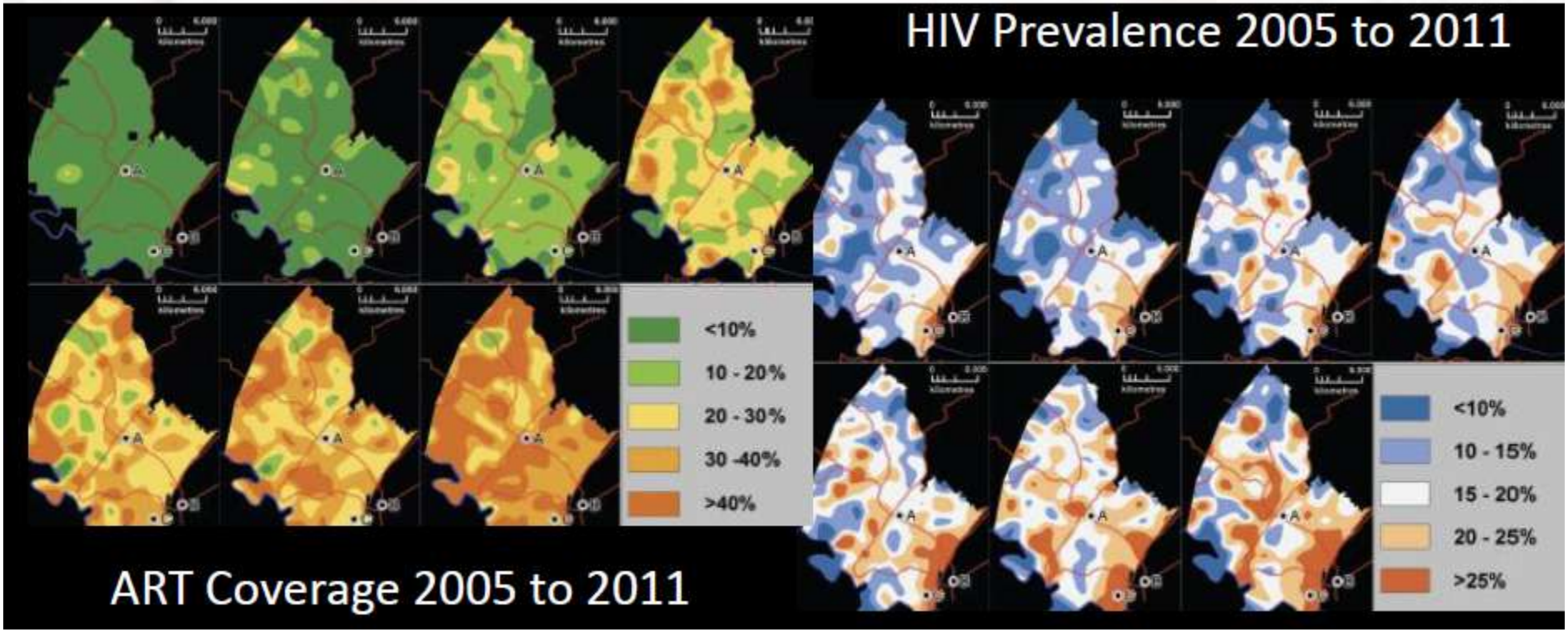
Declining HIV incidence/prevalence in Zimbabwe



High Coverage of ART Associated with Decline in Risk of HIV Acquisition in Rural KwaZulu-Natal, South Africa

Frank Tanser,[1*] Till Bärnighausen,[1,2] Erofili Grapsa,[1] Jaffer Zaidi,[1] Marie-Louise Newell[1,3]

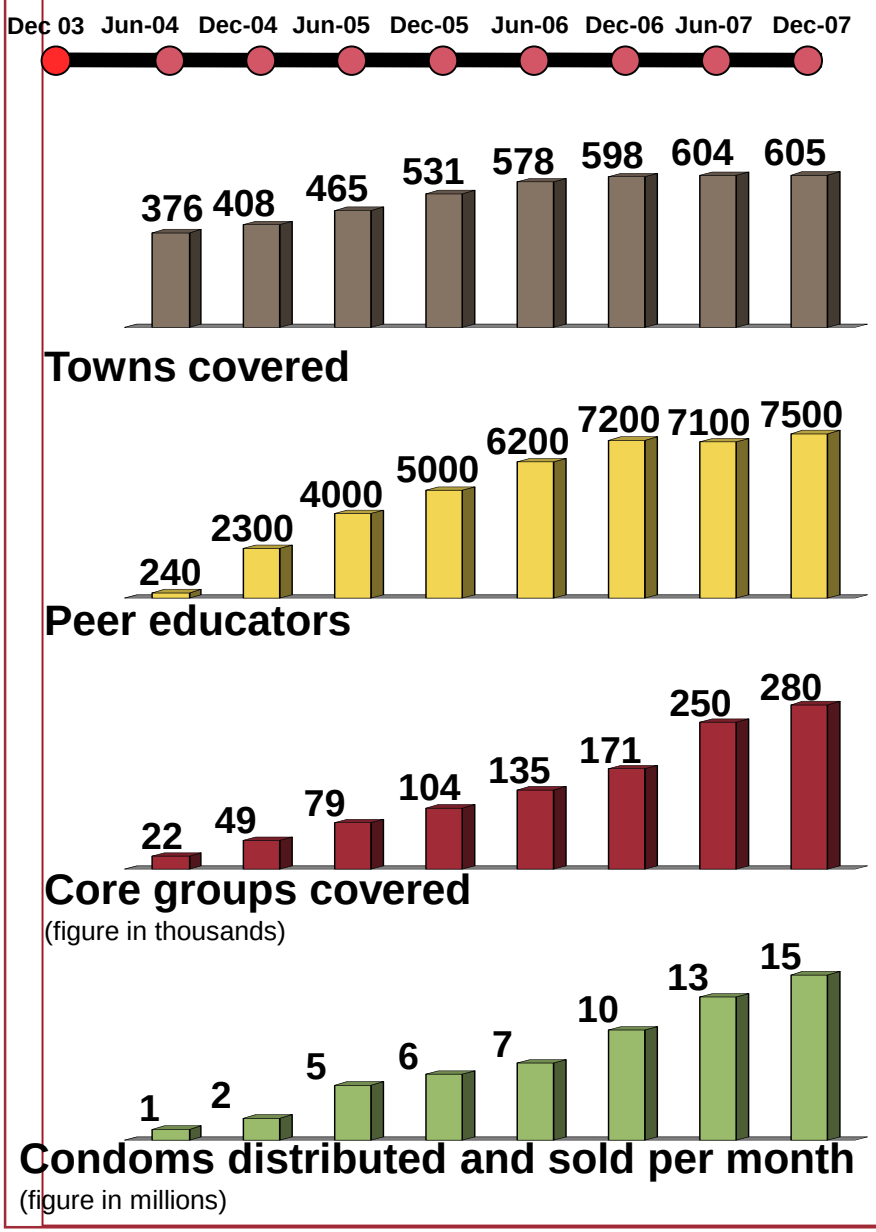
SCIENCE VOL 339 22 FEBRUARY 2013



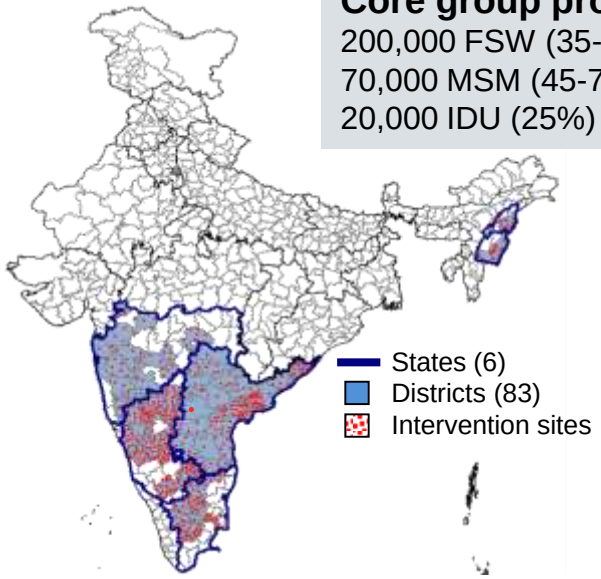
Avahan case study

A prospective impact evaluation using “ plausibility “ design

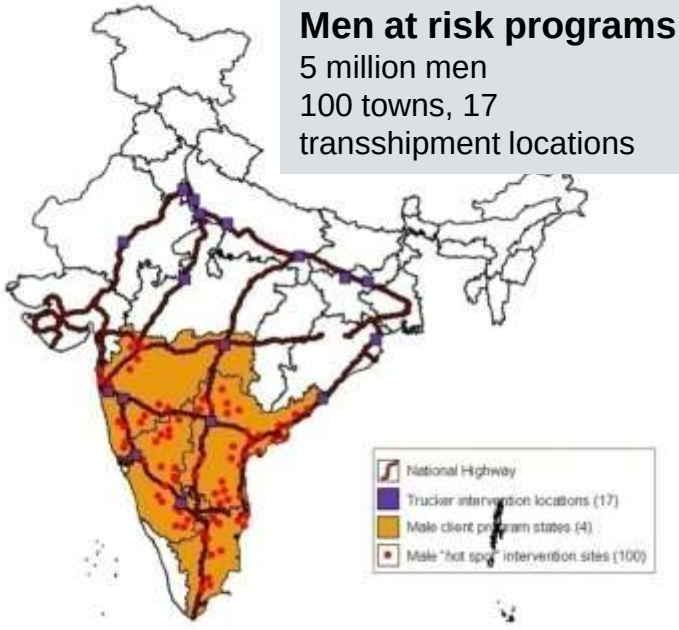
Avahan footprint, coverage, services in first 5 years..



Core group programs
200,000 FSW (35-45%)
70,000 MSM (45-70%)
20,000 IDU (25%)

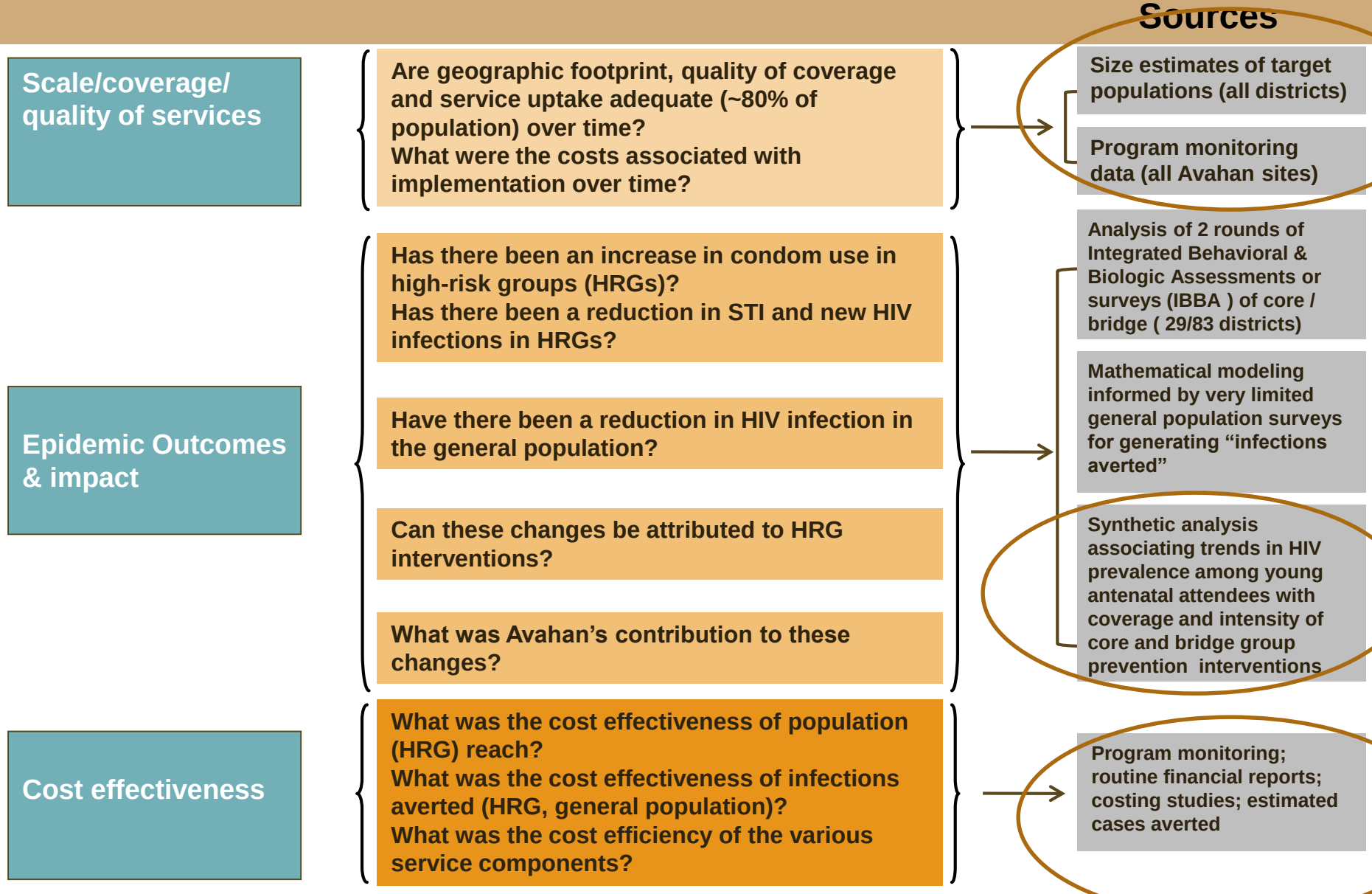


Men at risk programs
5 million men
100 towns, 17 transshipment locations



Source: Avahan routine monitoring data

Avahan Evaluation Design – Questions, Methods, Data Sources



Assessment of the population-level effectiveness of the Avahan HIV-prevention programme in South India: a preplanned, causal-pathway-based modelling analysis

Michael Pickles, Marie-Claude Boily, Peter Vickerman, Catherine M Lowndes, Stephen Moses, James F Blanchard, Kathleen N Deering, Janet Bradley, Banadakoppa M Ramesh, Reynold Washington, Rajatashuvra Adhikary, Mandar Mainkar, Ramesh S Paranjape, Michel Alary

Summary

Background Avahan, the India AIDS initiative of the Bill & Melinda Gates Foundation, was a large-scale, targeted HIV prevention intervention. We aimed to assess its overall effectiveness by estimating the number and proportion of HIV infections averted across Avahan districts, following the causal pathway of the intervention.

Methods We created a mathematical model of HIV transmission in high-risk groups and the general population using data from serial cross-sectional surveys (integrated behavioural and biological assessments, IBBAs) within a Bayesian framework, which we used to reproduce HIV prevalence trends in female sex workers and their clients, men who have sex with men, and the general population in 24 South Indian districts over the first 4 years (2004–07 or 2005–08 dependent on the district) and the full 10 years (2004–13) of the Avahan programme. We tested whether these prevalence trends were more consistent with self-reported increases in consistent condom use after the implementation of Avahan or with a counterfactual (assuming consistent condom use increased at slower, pre-Avahan rates) using a Bayes factor, which gave a measure of the strength of evidence for the effectiveness estimates. Using regression analysis, we extrapolated the prevention effect in the districts covered by IBBAs to all 69 Avahan districts.

Findings In 13 of 24 IBBA districts, modelling suggested medium to strong evidence for the large self-reported increase in consistent condom use since Avahan implementation. In the remaining 11 IBBA districts, the evidence was weaker, with consistent condom use generally already high before Avahan began. Roughly 32 700 HIV infections (95% credibility interval 17 900–61 600) were averted over the first 4 years of the programme in the IBBA districts with moderate to strong evidence. Addition of the districts with weaker evidence increased this total to 62 800 (32 000–118 000) averted infections, and extrapolation suggested that 202 000 (98 300–407 000) infections were averted across all 69 Avahan districts in South India, increasing to 606 000 (290 000–1 193 000) over 10 years. Over the first 4 years of the programme 42% of HIV infections were averted, and over 10 years 57% were averted.

Interpretation This is the first assessment of Avahan to account for the causal pathway of the intervention, that of changing risk behaviours in female sex workers and high-risk men who have sex with men to avert HIV infections in these groups and the general population. The findings suggest that substantial preventive effects can be achieved by targeted behavioural HIV prevention initiatives.

Funding Bill & Melinda Gates Foundation.

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See **Comment** page e243

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Evaluation of Combination Prevention Conclusions

- Redefine meaning of "What works in Combination prevention?" Evidence based Prevention programming cannot rely solely on RCT evidence
- Lower expectations about need for probability evidence; When and why is precise estimate of impact needed ?
- Plausibility designs , improved program data and mixed methods and mathematical models get us a long way to provide answers on "whether, why and how?.."
- Shift towards analyzing National Program Successes, and real-time program evaluation
- Clear need for collaboration and cross fertilization between Researchers, Evaluators and Program Implementers