Combination prevention: Public health and human rights imperatives

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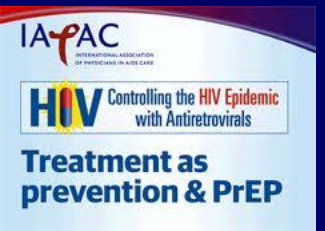
HIV/AIDS Department
WHO, Geneva

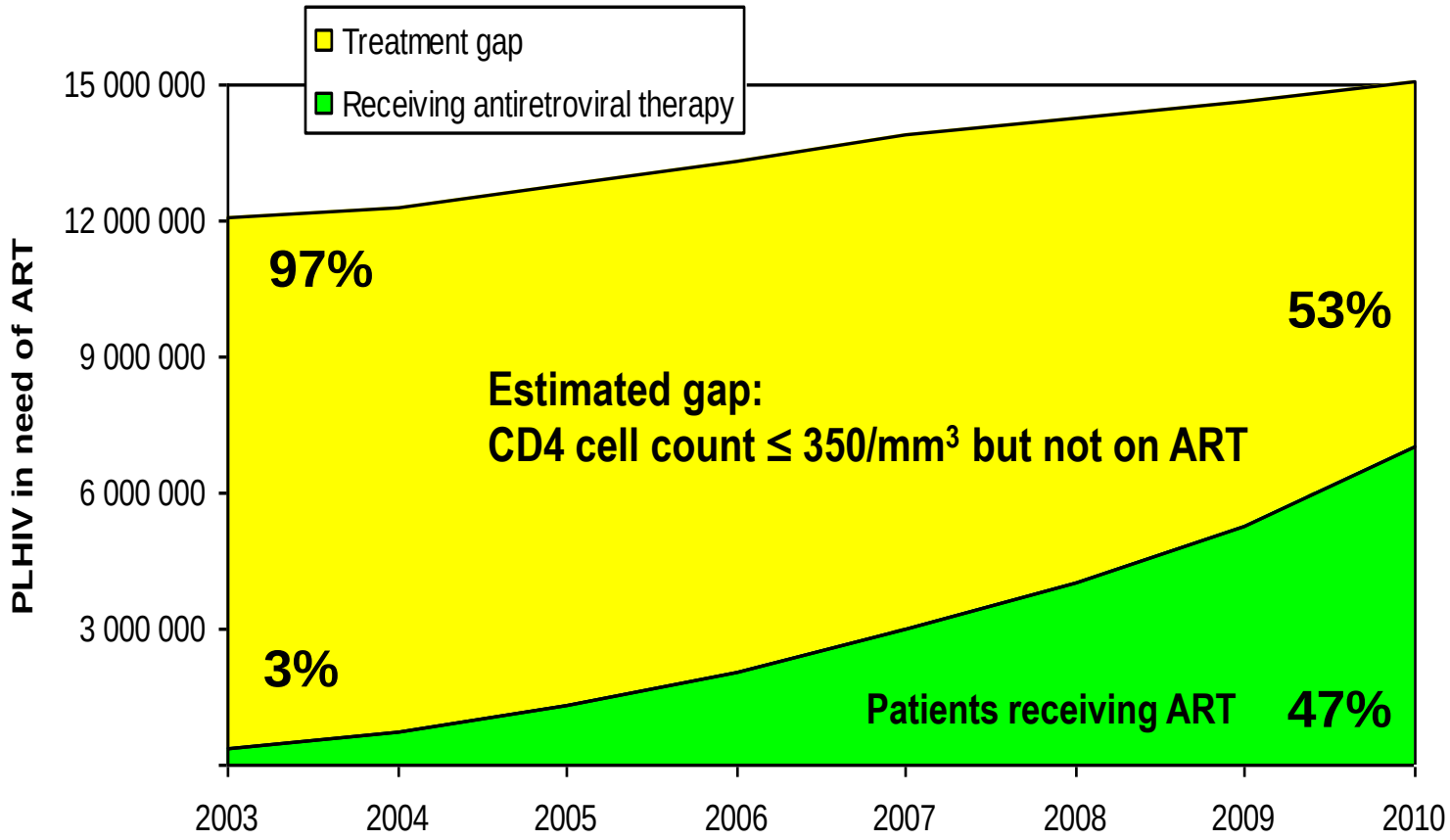
London, June 11, 2012



Outline

- The epidemic and response
- What is combination prevention?
- The role of ARVs in prevention: TasP and PrEP
- Implementation and research challenges
- WHO's approach and guidance
- Human rights and ethical considerations

Still a long way to go to reach 15 million on ART



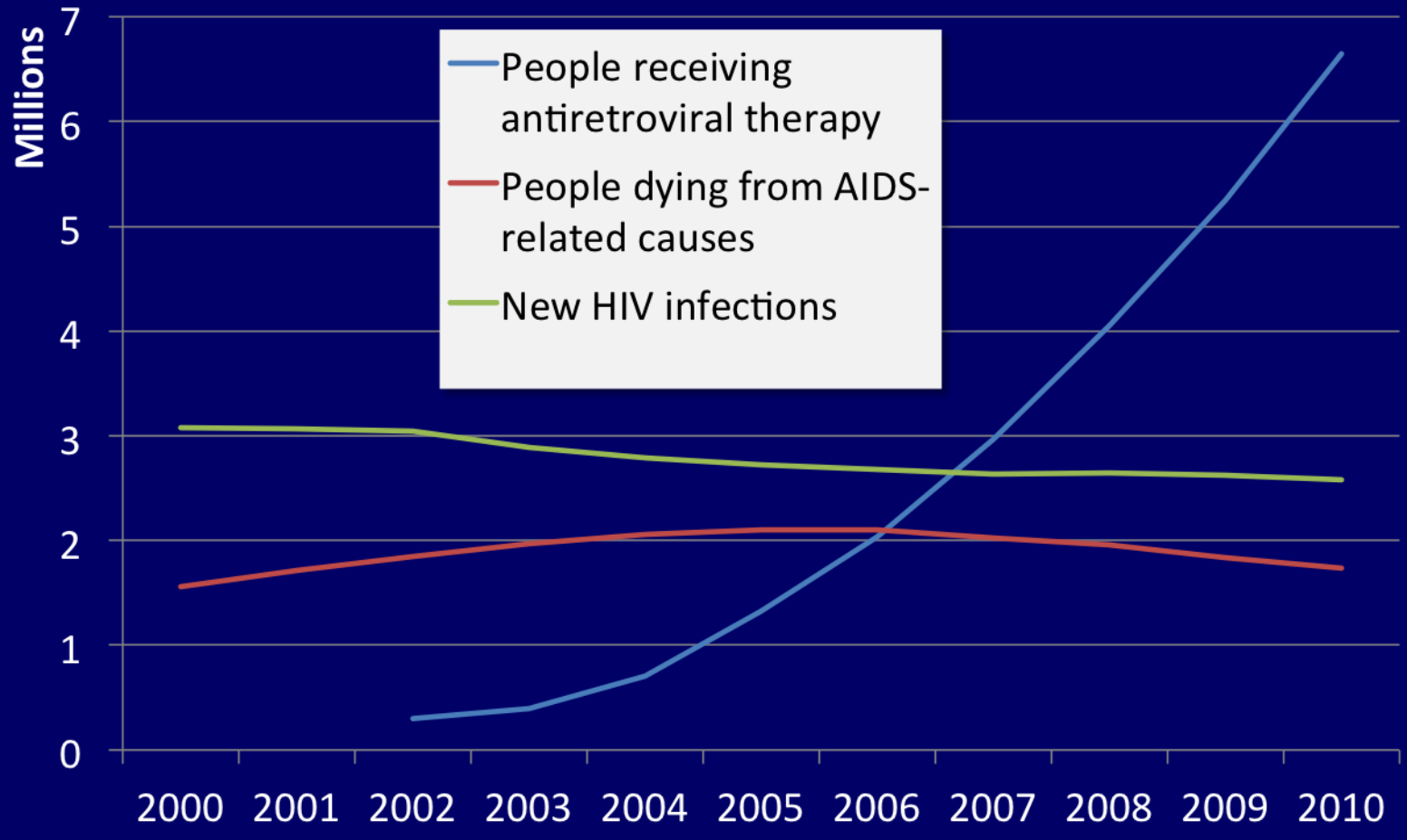
WHO, 2011

Major inequities persist in access to treatment and prevention

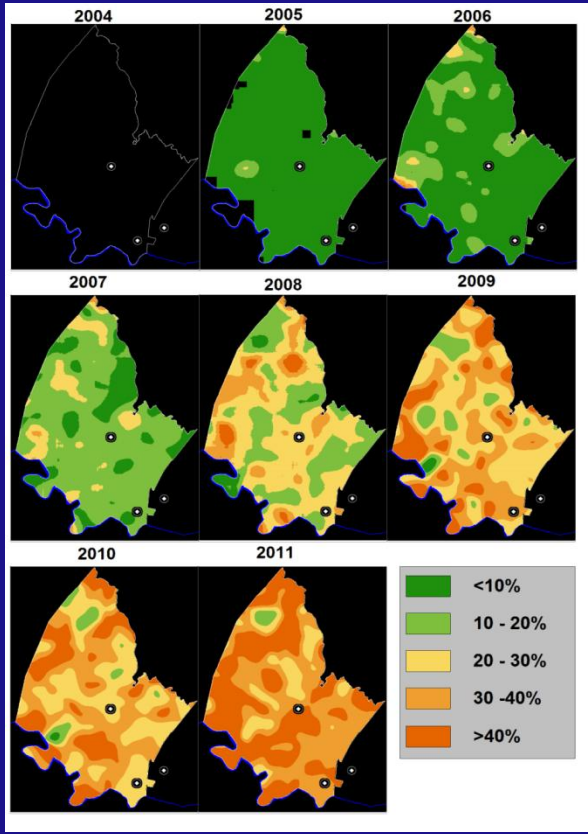
PROPORTION OF PEOPLE WHO INJECT DRUGS RECEIVING ART IN LOW AND MIDDLE INCOME COUNTRIES IN EECA REGION 2002-10	2002	2005	2006	2010
Number of reporting countries among 26 low- and middle-income countries surveyed	17	21	23	19
HIV cases among people who inject drugs (% among cumulative reported HIV cases with a known transmission route)	46,052 (71%)	221,849 (77%)	249,982 (77%)	185,565 (62%)
People who inject drugs receiving antiretroviral therapy (% among the total reported people receiving ART with a known route of transmission)	130 (20%)	4,670 (26%)	5,275 (26%)	7,646 (22%)

Source: Global HIV/AIDS Response. Epidemic update and health sector progress towards Universal Access. Progress Report 2011. WHO/UNAIDS/UNICEF. Table 6.9, p. 137.

Number of people with access to antiretroviral therapy and dying from AIDS-related causes, low- and middle-income countries, 2000–2010



ART coverage significantly decreased individual risk

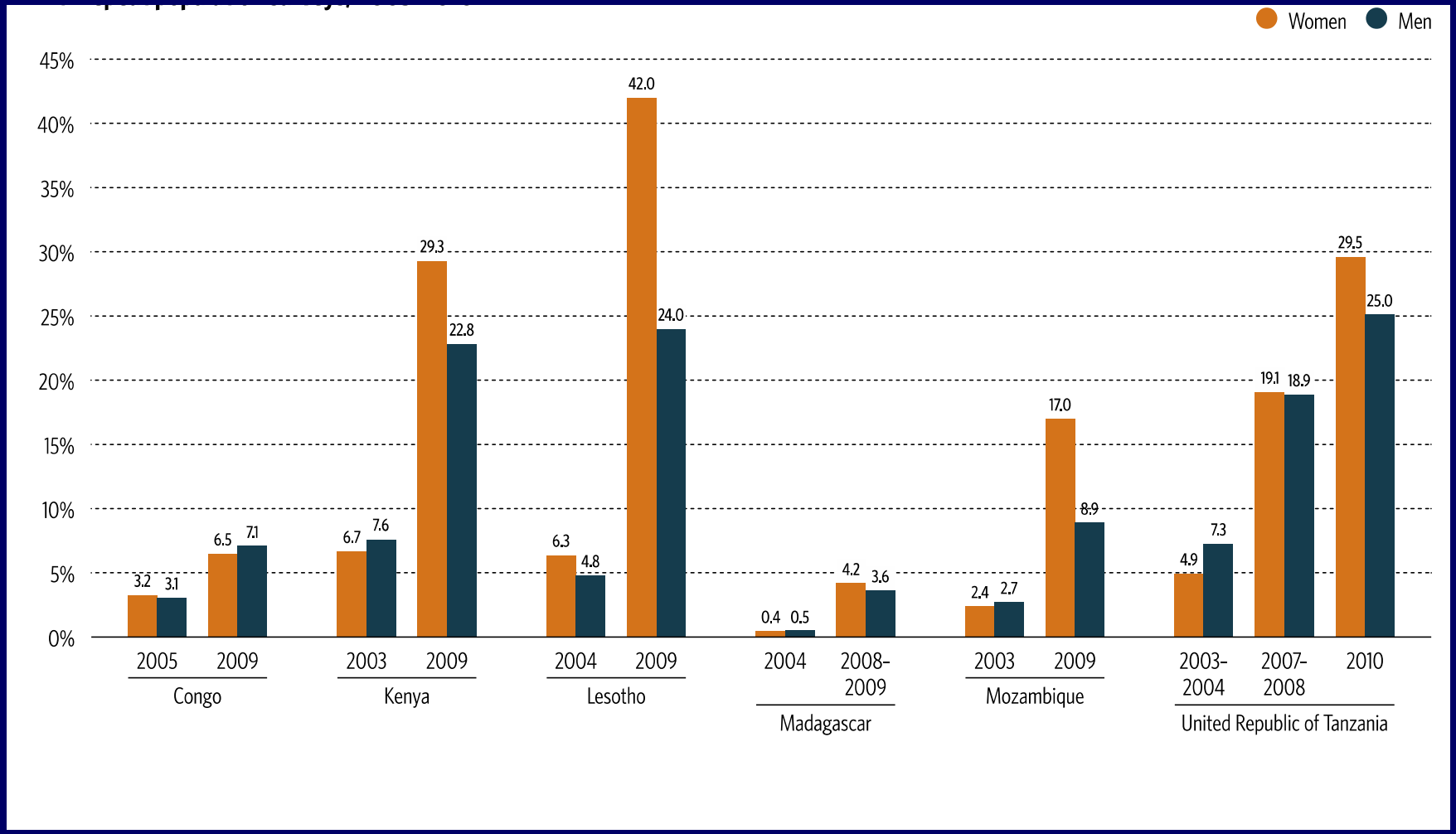


Maps showing the estimated percentage of HIV⁺ adults (≥15 years of age) on ART across the Africa Centre's surveillance area (2004 to 2011)

- AfricaCentre longitudinal surveillance cohort with community and individual data
- Between 2004 and 2011, 1395 HIV seroconversions and over 53,042 person-years of observation (crude HIV incidence rate of 2.63 (95% C.I. 2.50 to 2.77) per 100 person-years
- **Every percentage point increase in ART coverage among all HIV⁺ adults in a community, was associated with a 1.7% decline in the hazard of HIV acquisition** (*p* <0.001)

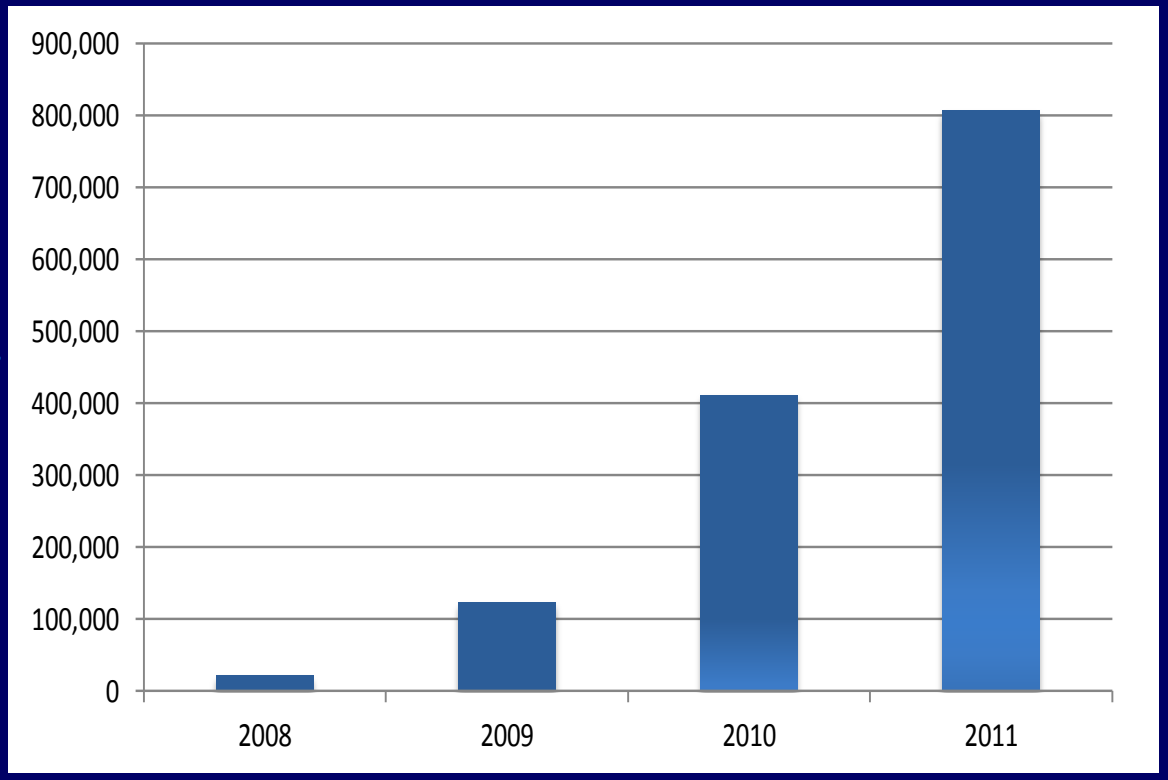
Paper #136LB, CROI Seattle 2012: Effect of ART Coverage on Rate of New HIV Infections in a Hyper-endemic, Rural Population: South Africa
Frank Tanser et al. Africa Ctr for Hlth and Population Studies, Univ of KwaZulu-Natal, South Africa;

Knowledge of HIV status remains insufficient



Percentage of women and men who received an HIV test and test results in last 12 months, 2003–2010 (WHO/UNAIDS)

Effective prevention interventions have not been brought to scale



Male circumcisions performed annually in 14 priority countries in eastern and southern Africa

Goal:

~ 20 million by 2016

Total MCs through 2011:

~1.35 million, 6.5%

of target

Source: WHO

Treatment and prevention gap…..

End 2010:

- 6.65 million were receiving ART
- ~7.4 (53%) million in need (CD4 <350)
- ~2.7 million new infections annually
- Bottom line:
  - Everyone HIV+ will need ART to survive
  - For every one person placed on treatment around 2.5 are infected
  - Need for sustained efforts combined with innovative approaches to decrease prevention gap

Outline

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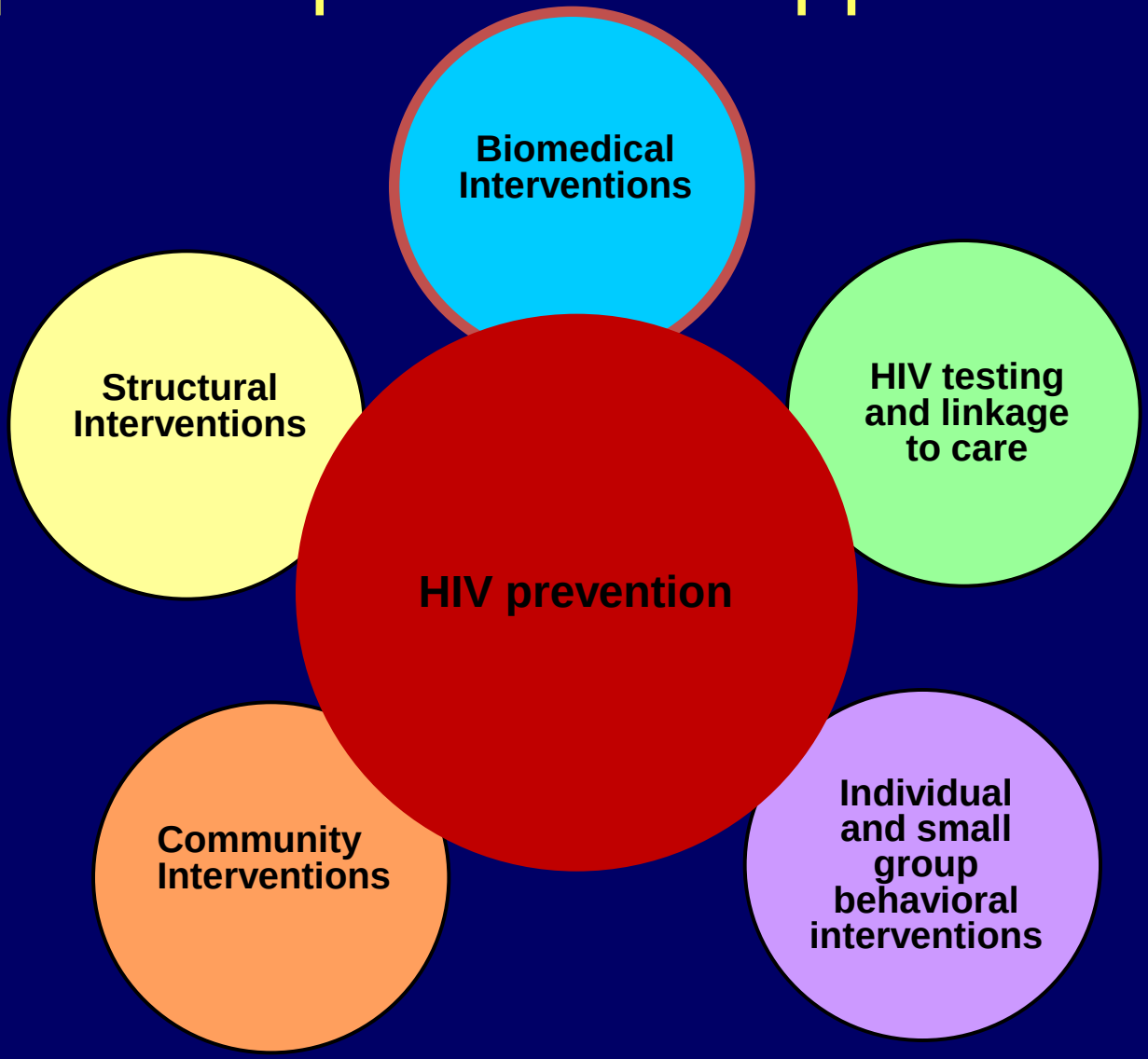
What is combination prevention?

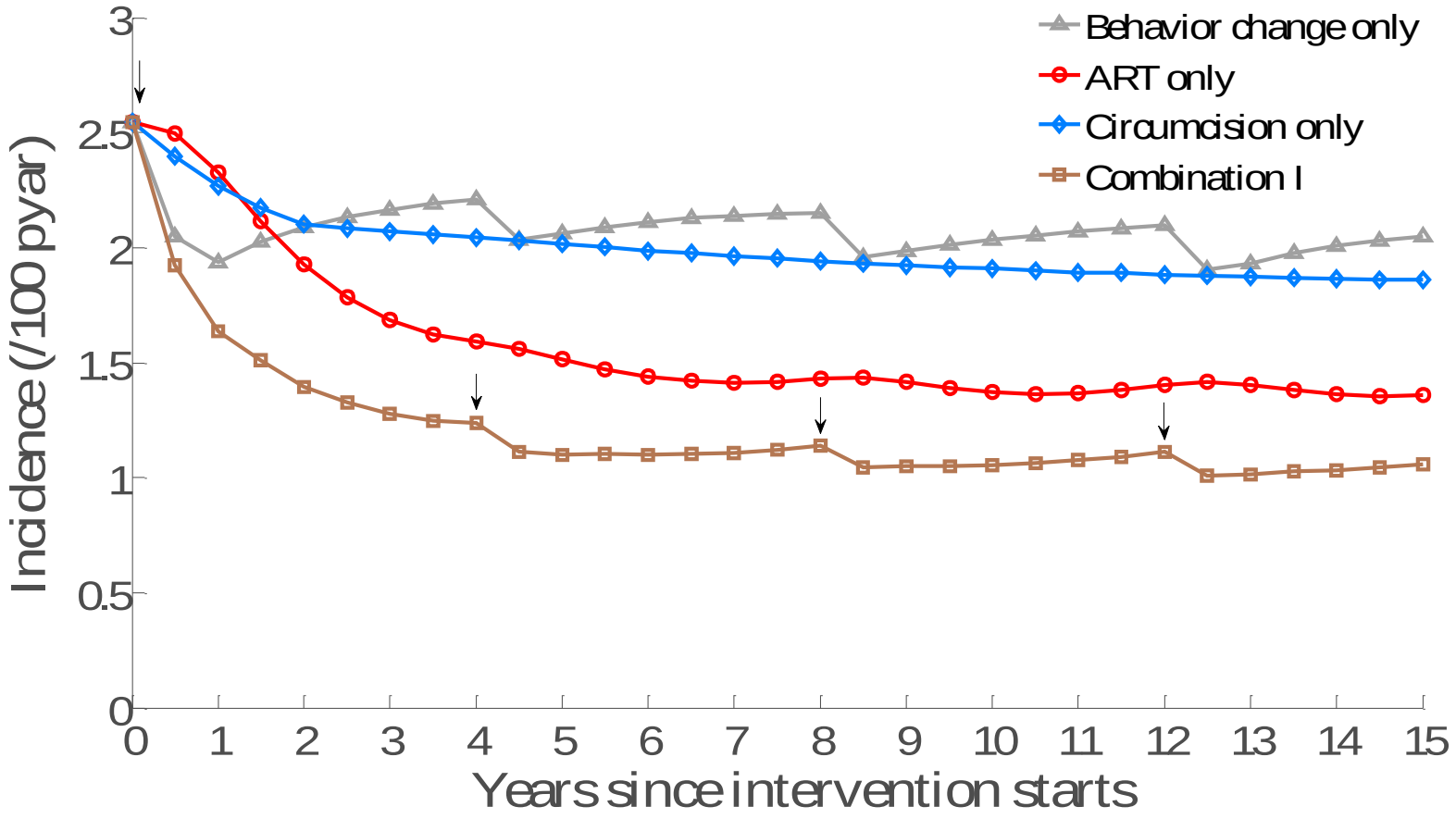
- Mix of biomedical, behavioral, and structural interventions
- Targets the prevention needs of different populations based upon epidemiological and demographic data
- Includes non-ARV based prevention (condoms, male circumcision, behavior change, etc.) as well as maximizing new prevention opportunities of ARVs

Combination prevention involves multiple disciplines and approaches



Adapted from Coates T

A combination of interventions has more impact than the interventions delivered alone



Source: Tim Hallett, personal communication

Opportunities for biomedical interventions

34 million

YEARS	HOURS	72 HOURS	YEARS
Prior to exposure	Exposure (pre-coital/coital)	Exposure (post-injury/-coital)	After infection
• Male circumcision • PMTCT • Harm reduction for IDU • Oral PrEP (daily TDF or TDF/FTC) • Topical PrEP (gels or intra-vaginal rings (microbicides) • Preventive HIV vaccine	• Oral intermittent PrEP • Coitally dependent topical PrEP (microbicides)	• Oral post exposure prophylaxis (PEP)	• ART ≤ 350 • ART ≤ 500 • "Incremental" TasP (SD couples, pregnant women, key populations, TB) • "Test and Treat"

All have important behavioral components

Adapted from R. Shattock 2011

Outline

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New evidence = rapidly changing field

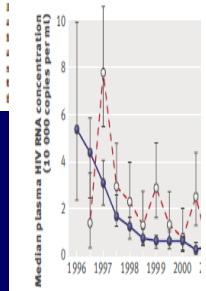
MAJOR ARTICLE

Expanded Access to Highly Active Antiretroviral Therapy: A Potentially Powerful Strategy to Curb the Growth of the HIV Epidemic

Viviane D. Lima,[1,a] Karissa Johnston,[2,a] Robert S. Hogg,[1,3] Adrian R. Levy,[2] P. Richard Harrigan,[1,3] Aranka Anema,[1] and Julio S. G. Montaner[1,4]

[1]British Columbia Centre for Excellence in HIV/AIDS and [2]Centre for Health Evaluation and Outcome Sciences, St. Paul's Hospital, and [3]Department of Health Care and Epidemiology and [4]Department of Medicine, Faculty of Medicine, University of British Columbia, Vancouver, and [5]Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia, Canada

We developed a mathematical model us
of the expansion of highly active antire



Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

Reuben M Granich, Charles F Gilks, Christopher Dye, Kevin M De Cock, Brian G Williams

Summary

Background Roughly 3 million people worldwide were receiving antiretroviral therapy (ART) at the
an estimated 6·7 million were still in need of treatment and a further 2·7 million became infected w
Prevention efforts might reduce HIV incidence but are unlikely to eliminate this disease. We investig
strategy of universal voluntary HIV testing and immediate treatment with ART, and examined the
which the HIV epidemic could be driven towards elimination.

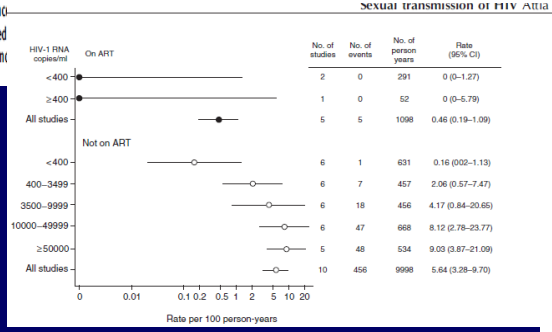
Methods We used mathematical models to explore the effect on the case reproduction number (stoch
long-term dynamics of the HIV epidemic (deterministic transmission model) of testing all people
community (aged 15 years and older) for HIV every year and starting people on ART immediate
diagnosed HIV positive. We used data from South Africa as the test case for a generalised epidemi
that all HIV transmission was heterosexual.

Findings The studied strategy could greatly accelerate the transition from the present endemic phas
adults living with HIV are not receiving ART, to an elimination phase, in which most are on ART, w
could reduce HIV incidence and mortality to less than one case per 1000 people per year by 2016, o
of full implementation of the strategy, and reduce the prevalence of HIV to less than 1% within 50 ye
that in 2032, the yearly cost of the present strategy and the theoretical strategy would both be US$1·7
after this time, the cost of the present strategy would continue to increase whereas that of the the
would decrease.

Interpretation Universal voluntary HIV testing and immediate ART, combined with present preven
could have a major effect on severe generalised HIV/AIDS epidemics. This approach merits furth
modelling, research, and broad consultation.

Sexual transmission of HIV Attia *et al.*

Estimated community plasma HIV-1 RNA
confidenc
estimated
assess in



Open access, freely available online PLOS MEDICINE

Randomized, Controled Intervention Trial of Male Circumcision for Reduction of HIV on Risk: The ANRS 1265 Trial

[2,3,4*], Dirk Taljaard[5], Emmanuel Lagarde[2,4], Joëlle Sobngwi-Tambekou[2], Rémi Sitta[2,4], Adrian Puren[6]

e, Assistance Publique—Hôpitaux de Paris, Boulogne, France, 2 INSERM U 687, Saint-Maurice, France, 3 University Versailles Saint-Quentin, Versailles, f, France, 5 Progressus, Johannesburg, South Africa, 6 National Institute for Communicable Disease, Johannesburg, South Africa

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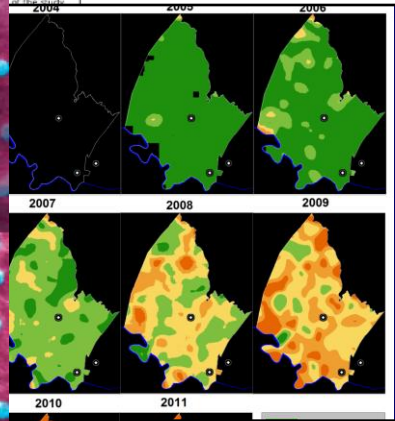
ABSTRACT

Background

Observational studies suggest that male circumcision may provide protection against HIV-1 infection. A randomized, controlled intervention trial was conducted in a general population of South Africa to test this hypothesis.



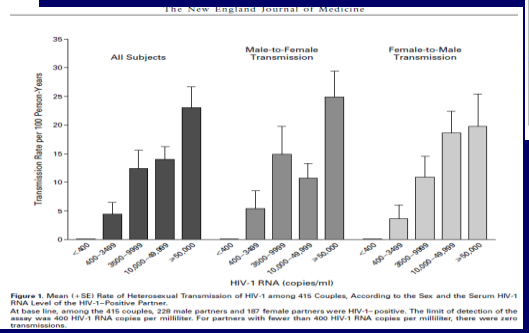


Figure 1. Mean (+SE) Rate of Heterosexual Transmission of HIV-1 among 415 Couples, According to the Sex and the Serum HIV-1 RNA Level of the HIV-1–Positive Partner.
At base line, among the 415 couples, 228 male partners and 187 female partners were HIV-1–positive. The limit of detection of the assay was 400 HIV-1 RNA copies per milliliter. For partners with fewer than 400 HIV-1 RNA copies per milliliter, there were zero transmissions.

The 2012 TIME 100 Poll

Voting for inclusion in the TIME 100 issue is now closed. The final list, selected by our ed be revealed on Wednesday, April 18th

Story | All Best and Worst Lists

Robert Grant

By TIME STAFF Thursday, Mar. 29, 2012

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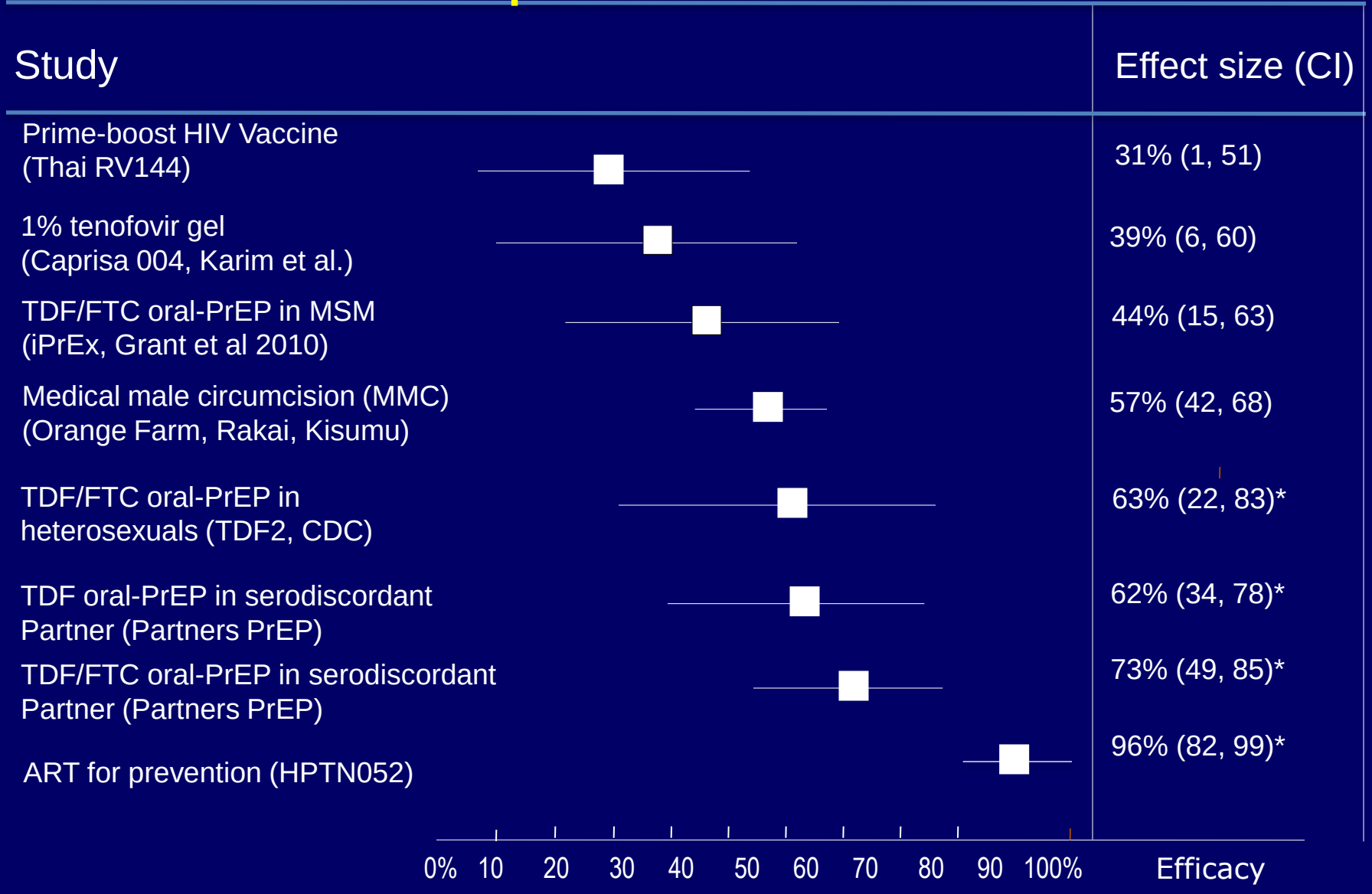
Age: 52
Occupation: AIDS researcher, Gladstone Institutes

Ask anyone with AIDS awareness about the latest groundswell for controlling HIV, and most will mention Grant. In the early 2000s, he pushed to test antiviral drugs to protect healthy, uninfected people at high risk of becoming HIV-positive. It was a tough sell, but he was right. Not only can treating uninfected individuals protect them from getting HIV, but also, giving newly infected patients antivirals can lower their risk of developing AIDS. Some say these breakthroughs are a turning point in the epidemic.

View the full list for "The 2012 TIME 100 Poll"

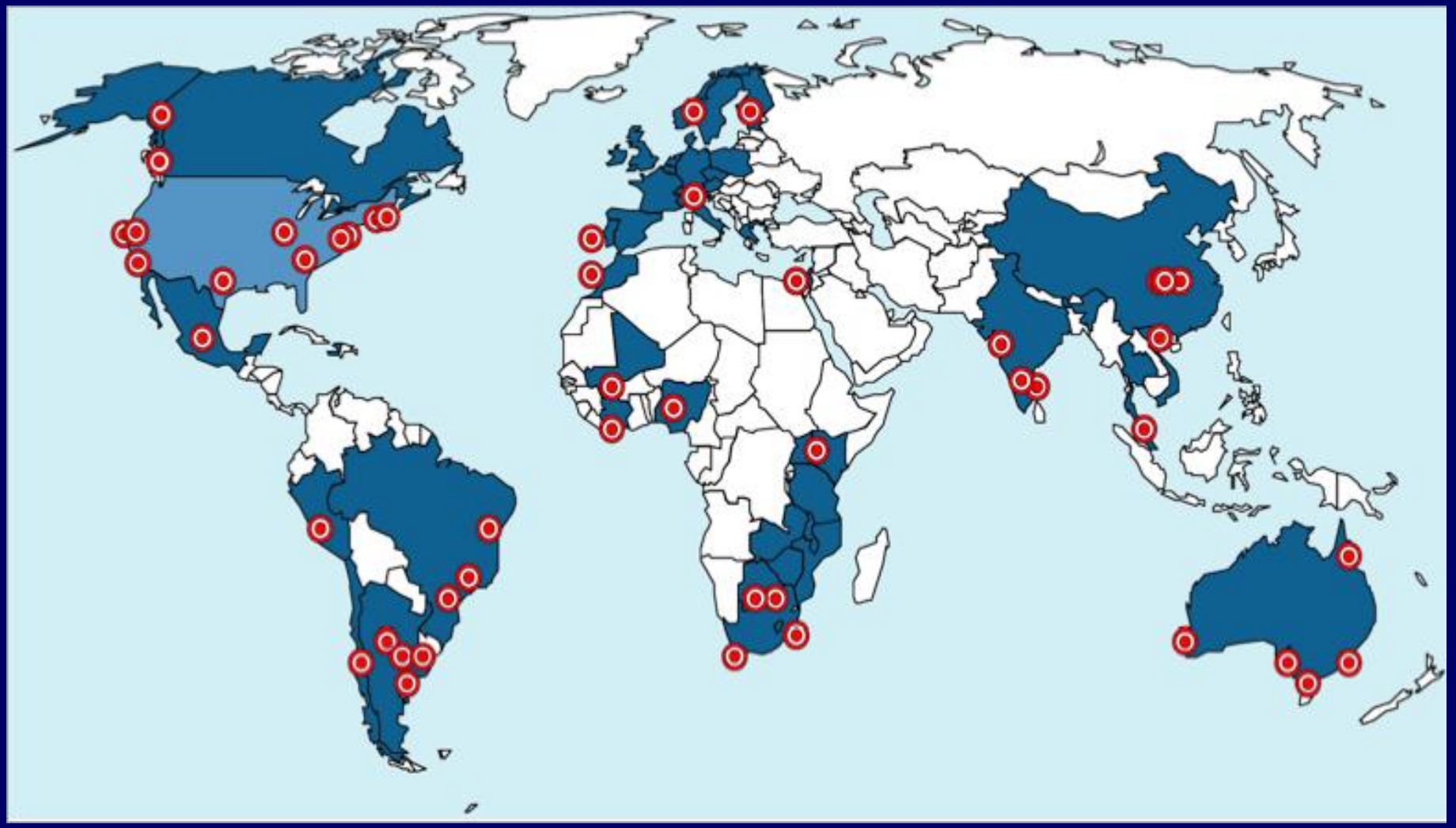
LACY ATKINS / SAN FRANCISCO CHRONICLE / CORBIS

Biomedical HIV prevention trials



Adapted from Abdool Karim SS, et al. Lancet. 2011

More evidence on the way: 2011 ART for prevention studies



Current HIV Research, 2011, *9*, 355-366

HPTN 052: HIV transmissions

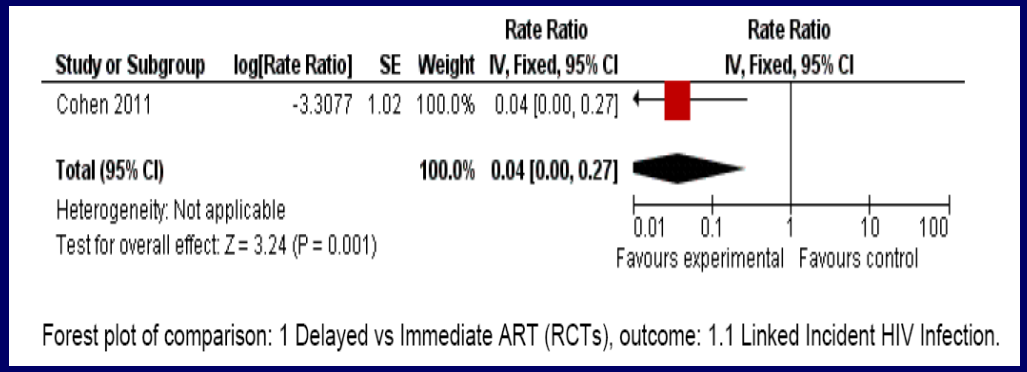
Total HIV-1 Transmission Events: 39

Linked Transmissions: 28

Immediate Arm: 1

Delayed Arm: 27

p < 0.001



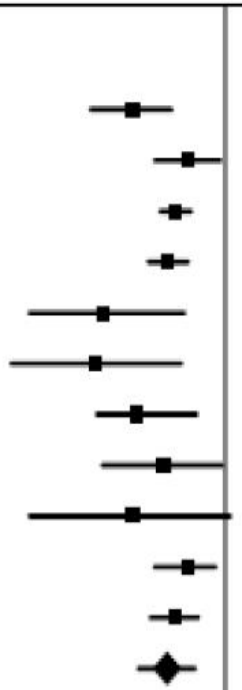
Forest plot of comparison: 1 Delayed vs Immediate ART (RCTs), outcome: 1.1 Linked Incident HIV Infection.

96% reduction in HIV transmission

Early ART also reduces risk of TB transmission…

	ART		Control		IRR (95% CI)
	TB cases	PY at risk	TB cases	PY at risk	
All baseline CD4 counts					
Badri (2002)	9	375.1	82	848.2	0.19 (0.09 - 0.38)
Cohen (2011)	17	1661.9	33	1641.8	0.51 (0.28 - 0.91)
Golub (2007)	221	11627	155	3865	0.41 (0.31 - 0.54)
Golub (2009)	44	952	200	2815	0.36 (0.25 - 0.51)
Jerene (2006)	6	162.6	9	80.9	0.11 (0.03 - 0.48)
Lannoy (2008)	-	-	-	-	0.10 (0.02 - 0.45)
Miranda (2007)	-	-	-	-	0.20 (0.10 - 0.60)
Samandari (2011)	-	-	-	-	0.33 (0.11 - 0.94)
Santoro-Lopes (2002)	1	-	42	-	0.19 (0.03 - 1.09)
Severe (2010)	18	-	36	-	0.50 (0.28 - 0.83)
Zhou (2009)	57	5186	40	985	0.40 (0.26 - 0.61)
All studies					**0.35 (0.28 - 0.44)**

Effect: Z = 9.19, p < 0.001; Heterogeneity: I^2 = 31% (22% - 44%) , p = 0.151



Suthar et al 2012,PlosMed, in press

Providing ART for PLHIV prevents TB up to 65%

What is PrEP?

- Pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs by uninfected people to avoid HIV acquisition
  - Trials have typically evaluated either oral TDF/FTC or TDF alone; studies of other drugs are starting
  - Topical TDF has also been tried as vaginal microbicide
  - Four trials have completed; one was stopped

Demonstrated efficacy of oral PrEP in serodiscordant couples, and men who have sex with men

Study	Population	N	Intention to treat[b]		
iPrEx	MSM	2499	44% (15-63%)		
Partners PrEP	Heterosexual HIV discordant couples	4758 couples	All 75% (55-87%)	Men 84% (54-95%)	Women 66% (28-84%)
TDF2	Heterosexual men and women		All 62% (21-83%)	Men 80% (25-97%)	Women 49% (-21-81%)
Fem-PrEP	Heterosexual women	2056	NS		

[a] restricted to trials of oral TDF/FTC only as this guidance does not address use of other antiretroviral regimens

[b] excluding only those enrolled participants later found to be infected at randomization and those with no follow-up visit/HIV test

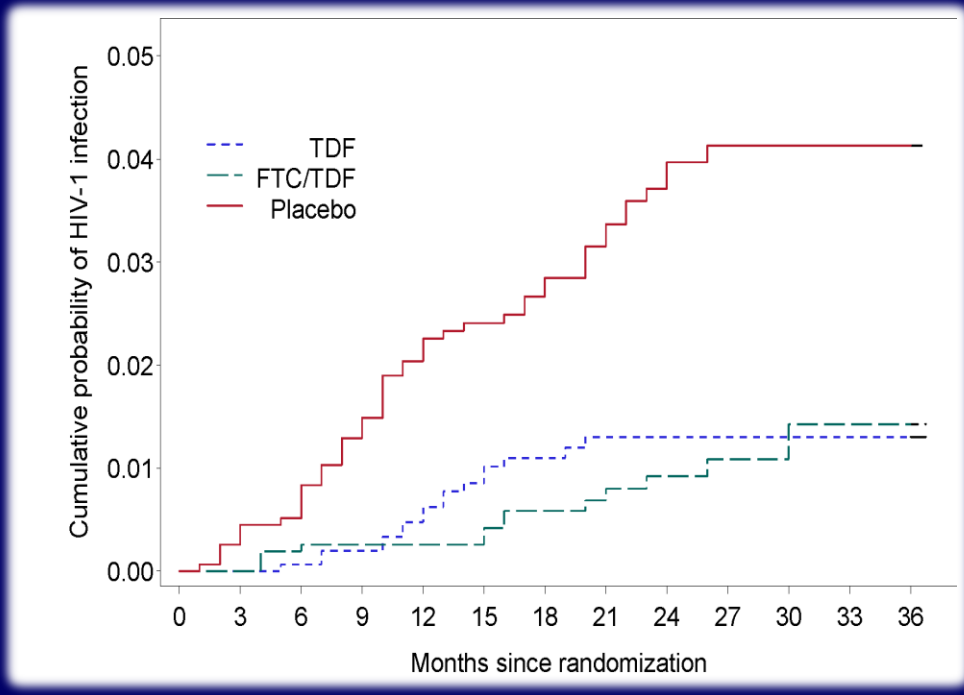
[c] NS= finding not statistically significant

Partners' PrEP: PrEP among heterosexual men and women

4758 couples, in which HIV+ partner not yet eligible for ART, randomized 1:1:1 to daily oral TDF or FTC/TDF vs placebo

82 HIV infections

17 TDF | **13 FTC/TDF** | **52 placebo**



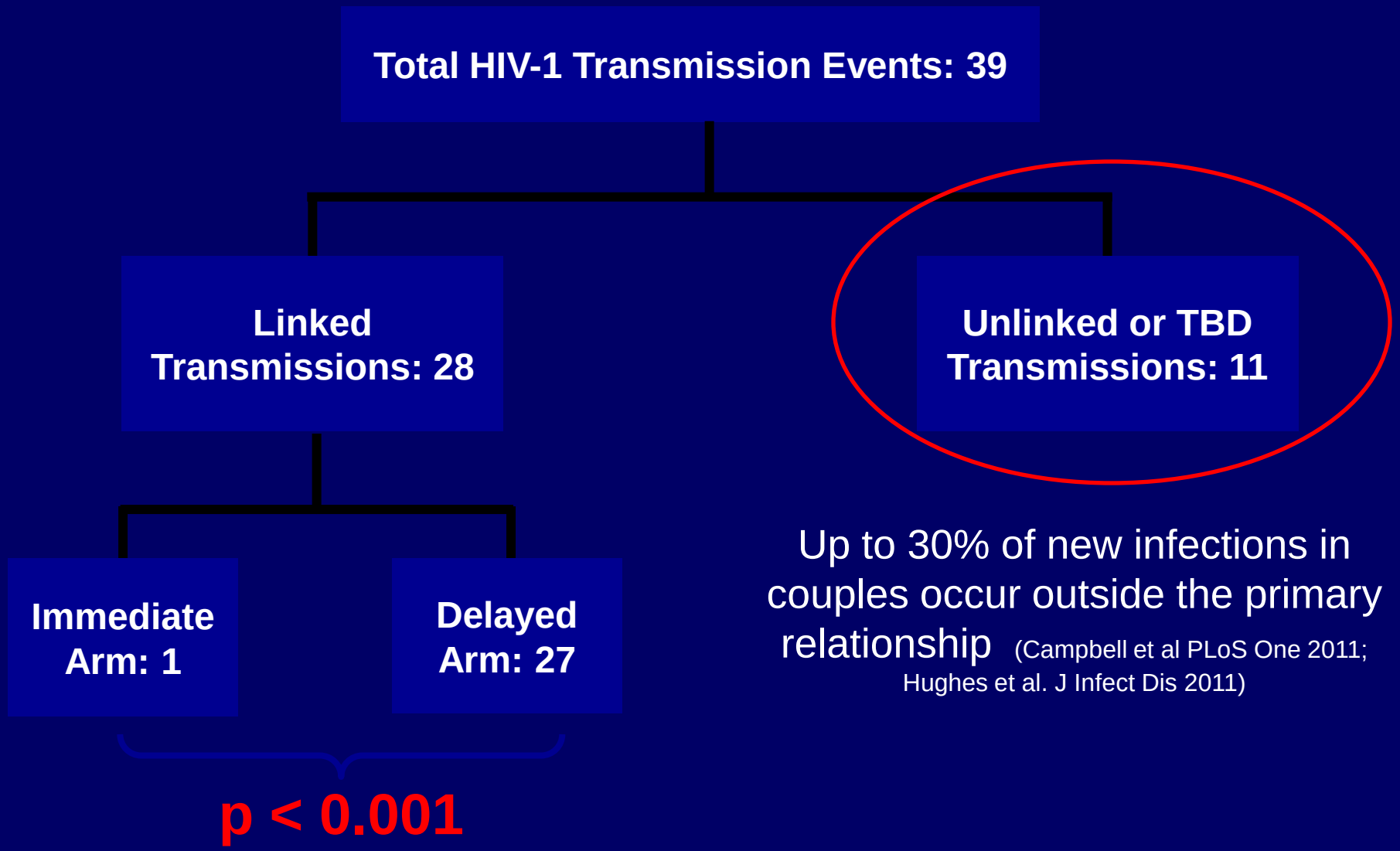
Reduction in HIV acquisition:

TDF = 67% (95% CI 44%-81%)

FTC/TDF = 75% (95% CI 55%-87%)

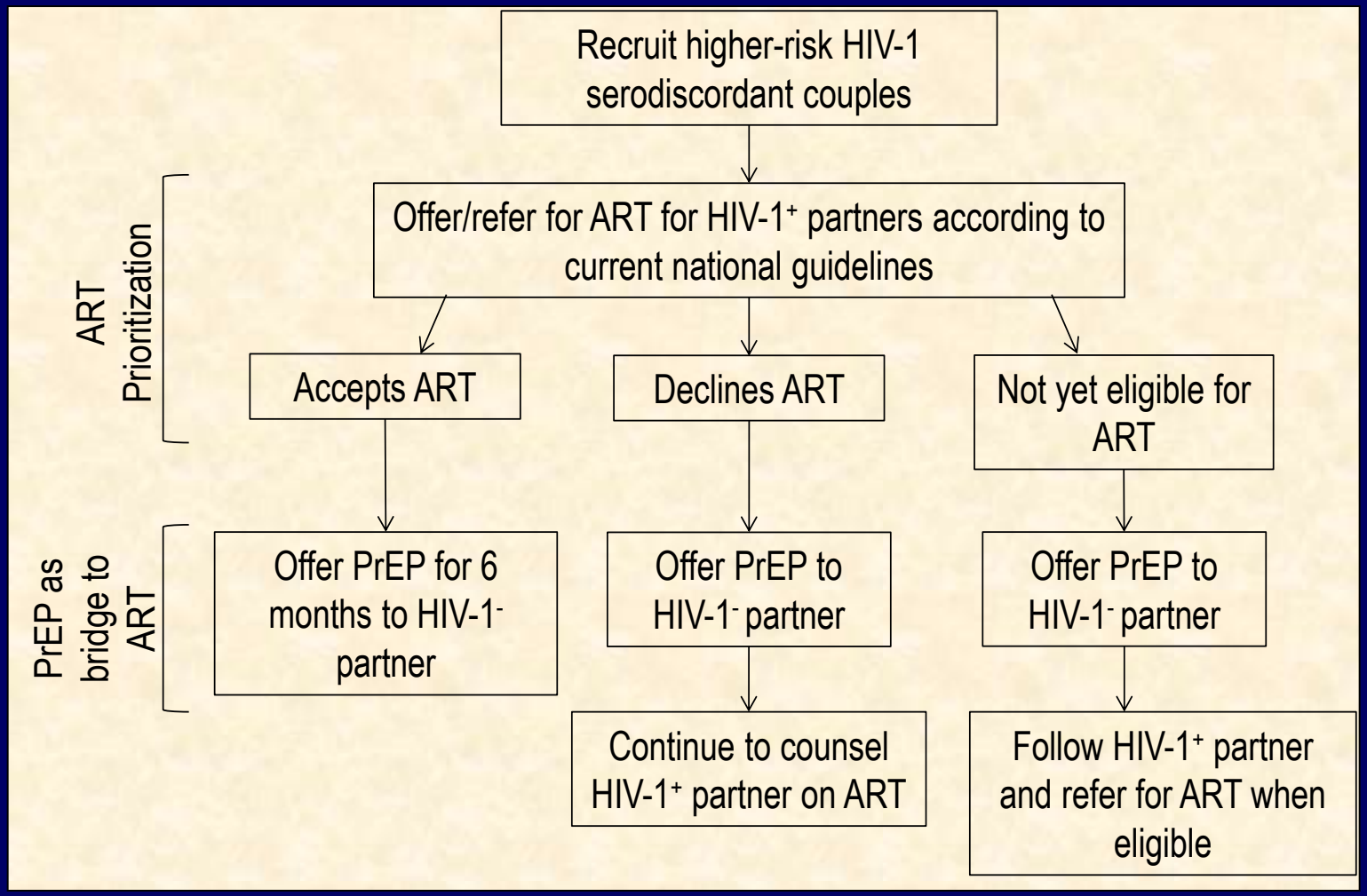
Combining TasP and PrEP?

HPTN 052: HIV transmissions



Up to 30% of new infections in couples occur outside the primary relationship (Campbell et al PLoS One 2011; Hughes et al. J Infect Dis 2011)

PrEP as a "niche" intervention? e.g., as bridge to early ART in couples



Source: Baeten & Celum

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Challenges for implementing TasP / PrEP

- How to optimally combine interventions to achieve best health and prevention impact?
- Can we extrapolate the study results to other groups?
- How to balance benefits and risks? e.g. health and prevention gains vs possible long term effects such as toxicity and resistance
- What threshold of early treatment is needed to achieve viral suppression for population level impact?

Challenges (contd.)

- Using the same drugs in HIV + and in HIV – is problematic. Should drugs can be “reserved” for PrEP? Which ones?

- Repeat testing required for PrEP?

- How to optimize adherence?

- Is a combination approach needed in highly adherent ART users / those with maximum viral suppression?

Examples of planned implementation research in Asia

	Thailand	Indonesia	Cambodia	Vietnam	China
Population	MSM FSW	MSM FSW	All SD couples FSW ++	All SD couples IDU++	All SD couples MSM
Goal	To guide future national policy & strategy on earlier ART for MSM and/or FSW		To guide future national policy & strategy on earlier ART for SD couples, FSWs, MSM and/ or people who inject drugs		Improve **existing policy & strategy**
Primary objective	Feasibility of repeat testing, immediate ART	New HTC approaches & uptake Adherence immediate ART	Feasibility of identifying partner (network approach), early ART, repeat testing	Feasibility improved implementation cascade from KAP HTC to couple FU	Programme strengthening
ART criteria	Irrespective CD4 TDF-based	Irrespective CD4 TDF-based	Irrespective CD4	Irrespective CD4 TDF-based (possibly FDC)	Irrespective CD4 TDF
Enrollment	Outreach internet peers	NGO and public services for MSM and FSW	VCCT/TI sites Pre ART	HTC Methadone sites Pre ART	HTC Pre ART

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WHO ART guidance: 2012/13

- 2012 – ART as prevention in sero-discordant couples
- 2012 – Programmatic update on operational aspects of ARVs for PMTCT (A, B, B+)
- 2012 – Treatment as Prevention programmatic update (9 June 2012)
- 2012 – PrEP rapid advice (July, IAC)
- 2013 WHO consolidated guidance will combine all ARV related guidance for the first time, including use for treatment and prevention

WHO guidance on ART for treatment and prevention in serodiscordant couples

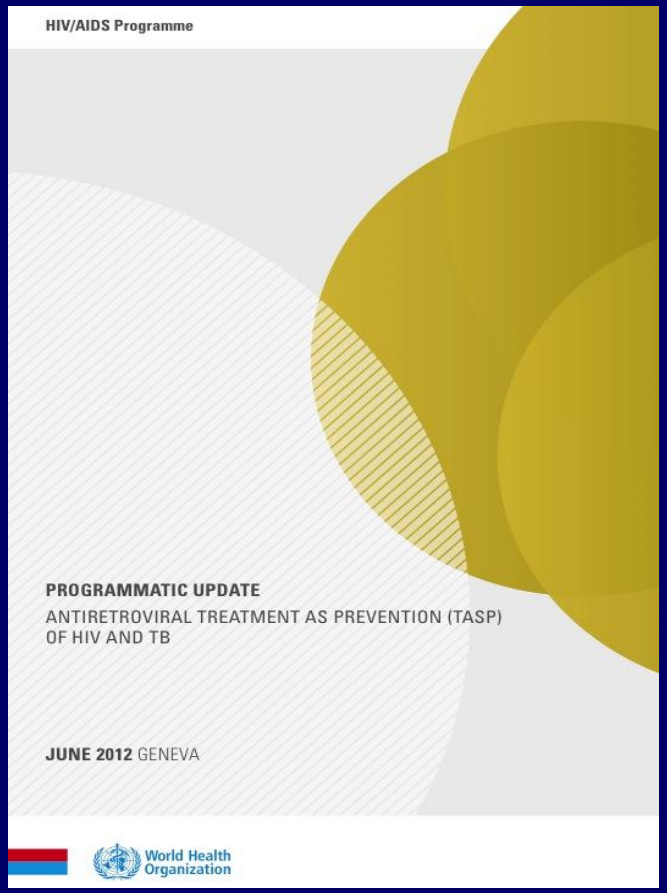
- First formal WHO TasP guidance
- Strongly recommends couples counseling
- Strong recommendation for offering ART in a serodiscordant couple irrespective of CD4 count
- Operational issues are also addressed

ART initiation for serodiscordant couples

ART INITIATION CRITERIA	NUMBER OF COUNTRIES	COUNTRIES
Irrespective of CD4 count	8	United States, Canada, Zambia, Europe, Venezuela Argentina (>500) Nigeria (>350), Thailand*(>350)
ART irrespective of CD4 count in practice	2	China, Rwanda
350 - 500	1	Mexico
Others	2	Malawi – Lifelong ART irrespective of CD4 count for pregnant women, rationale includes improving health of mother, preventing vertical transmission and preventing of HIV transmission in discordant relationships Burundi – ART irrespective of CD4 count if partners of HIV-negative pregnant women are HIV-positive

* Expert consultation is recommended

WHO TasP programmatic update, 2012



Outlines WHO's strategy for TasP:

1. Intensify and scale up ART for those with CD4 < 350

2. Identify additional opportunities for

TasP ("incremental approach") in specific populations

- Recommended for serodiscordant couples

-Move towards offering ART to all pregnant women (option B+)

- Explore feasibility in key affected populations

Ethical and human rights issues

- How to prioritize use of ART in absence of universal access: First come, first served? Treat the sickest? Use for TasP? Provide drugs to uninfected persons (PreP)?
  - WHO to hold consultation on ethics of ARV use in the absence of universal access
- Ensuring that testing and treatment remain voluntary, informed, are not coercive and do not inappropriately "target" or stigmatize
- Promoting community-based and driven models of service delivery

In conclusion…

The strategic use of ARVs is a key element of combination HIV prevention with a view to ending the HIV epidemic.

Imperatives are to:

- Accelerate and scale-up treatment programmes (CD4 below 350)
- Proactively optimize prevention benefits of ART (TasP)
- explore possible use of Prep as niche interventions (demonstration projects in countries)
- Scale up other interventions of known effectiveness, including male circumcision, condom use, behavioural
- Address important ethical and human rights issues in programme design and planning – requires close community participation

WHO will issue consolidated ARV guidance (2013) and support implementation research

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