17TH ANNUAL CONFERENCE OF THE BRITISH HIV ASSOCIATION (BHIVA)

British HIV Association BHIVA

Professor Thomas Quinn

Johns Hopkins Center for Global Health, Maryland, USA

6-8 April 2011, Bournemouth International Centre

17TH ANNUAL CONFERENCE OF THE BRITISH HIV ASSOCIATION (BHIVA)

British HIV Association BHIVA

Professor Thomas Quinn

Johns Hopkins Center for Global Health, Maryland, USA

COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Thomas C Quinn M.D.:	None declared
Date	1 April 2011

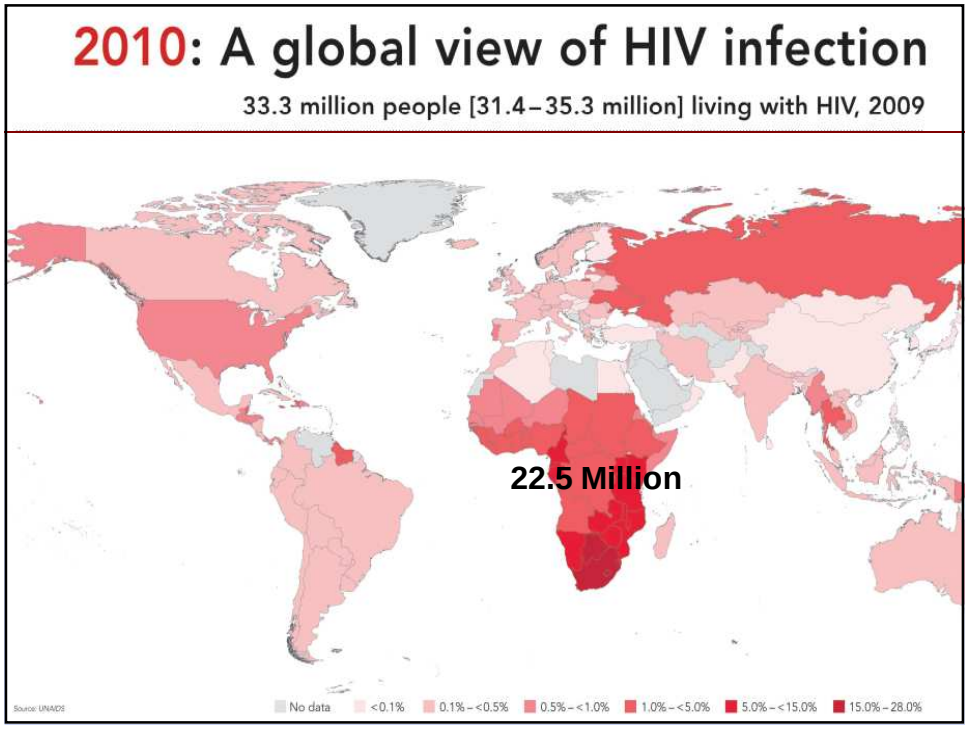
6-8 April 2011, Bournemouth International Centre

HIV, STIs and Transmission; An Update in Biomedical Prevention

Thomas Quinn, M.D., M.Sc.

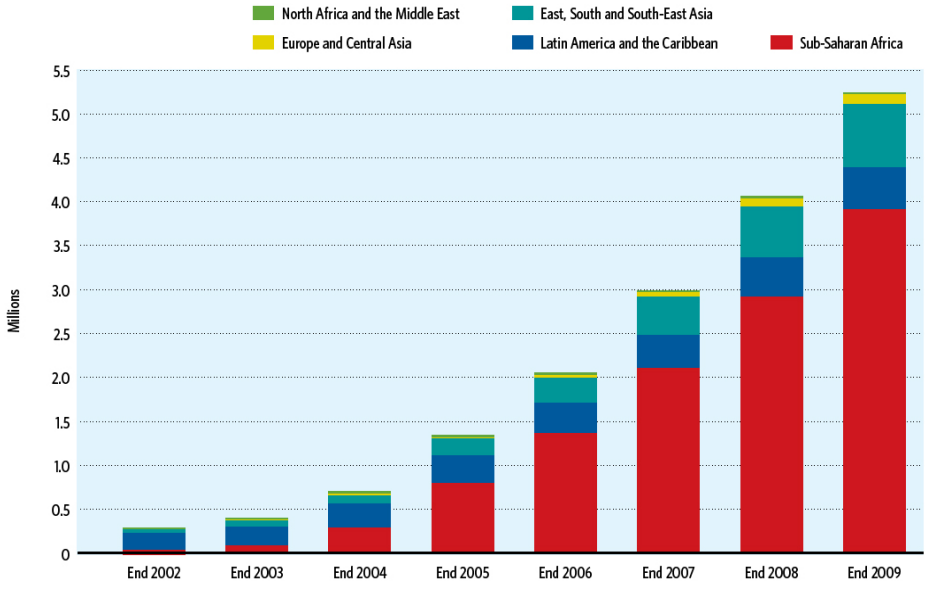
Director & Professor of Global Health, Johns Hopkins Univ.
Associate Director for International Research, NIAID

30 Years of AIDS, 30 Million Deaths and 33 Million Infected

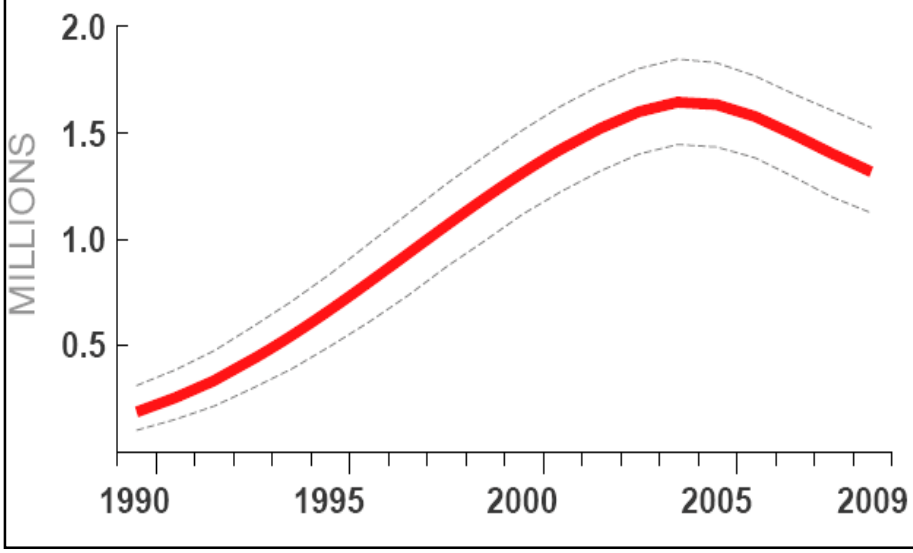

2010: A global view of HIV infection
33.3 million people [31.4–35.3 million] living with HIV, 2009
22.5 Million
No data
<0.1%
0.1%–<0.5%
0.5%–<1.0%
1.0%–<5.0%
5.0%–<15.0%
15.0%–28.0%


2000: The International Response

Number of people receiving antiretroviral therapy in low- and middle-income countries, by region, 2002–2009



Sub-Saharan Africa



For Every Person Put on Antiretroviral Therapy in Africa, Two People are Newly Infected with HIV

Biomedical Interventions to Prevent HIV

HIV Sexual Transmission

Transmission Dynamics Model

$$R_0 = ß \times c \times D$$

R_0 = Case reproduction rate

ß = Efficiency of transmission
(infectiousness of pathogen, prophylaxis)

C = Mean number of contacts per time
(acts, partners)

D = Duration of infectiousness
(natural hx of pathogen, treatment)

HIV treatment reduces viral load and heterosexual transmission

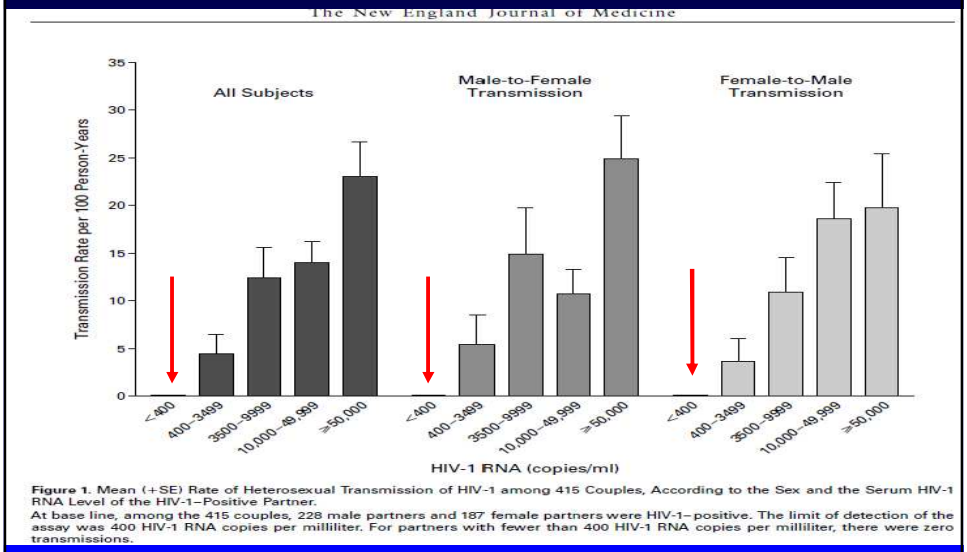


Figure 1. Mean (+SE) Rate of Heterosexual Transmission of HIV-1 among 415 Couples, According to the Sex and the Serum HIV-1 RNA Level of the HIV-1–Positive Partner.
At base line, among the 415 couples, 228 male partners and 187 female partners were HIV-1–positive. The limit of detection of the assay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

Quinn et al. NEJM. 2009;342(13):921-929.

Biological Factors That Affect HIV Sexual Transmission (Infectiousness)

- Level of Blood Viral Load
- Genital Viral Load
- Acute Infection and Advanced Disease
- Immunosuppression
- Genital ulcerations
- Inflammatory STDs
- Cervical ectopy
- Viral Subtype and phenotype X4/R5
- Antiretroviral therapy ↓

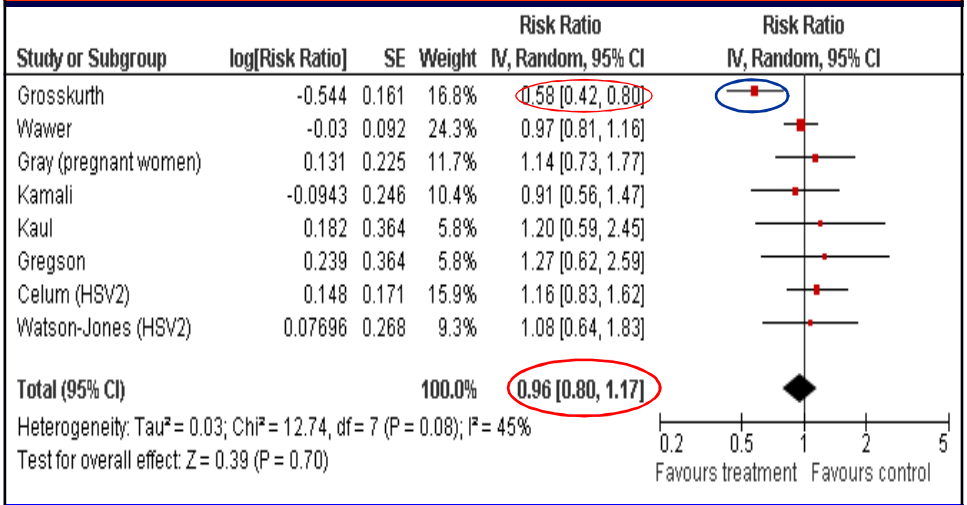
Biological Factors That Affect Susceptibility To HIV (Acquisition)

- Viral Load in the Infected Index Case
- Genital ulcers
- Inflammatory STDs
- Cervical ectopy
- Uncircumcised
- HLA Haplotype
- Chemokines/Cytokines

9 Trials of STI Control for HIV Prevention

- Control of Curable STIs:
  - Syndromic management or presumptive therapy
  - 5 community randomized trials
    - Grosskurth Lancet 2005, Wawer Lancet 1999, Gray Am J Ob Gynecol 2001, Kamali Lancet 2003, Gregson PLos 2007
  - 1 individually randomized trial
    - Kaul JAMA 2004
- HSV-2 suppression in HIV-negative participants
  - 2 randomized trials of acyclovir
    - Watson Jones NEJM 2007, Celum Lancet 2008
- HSV-2 suppression in HIV-positive participant
  - 1 randomized trials of acyclovir
    - Celum et al NEJM 2010

Trials of STI Control for Prevention of HIV Acquisition

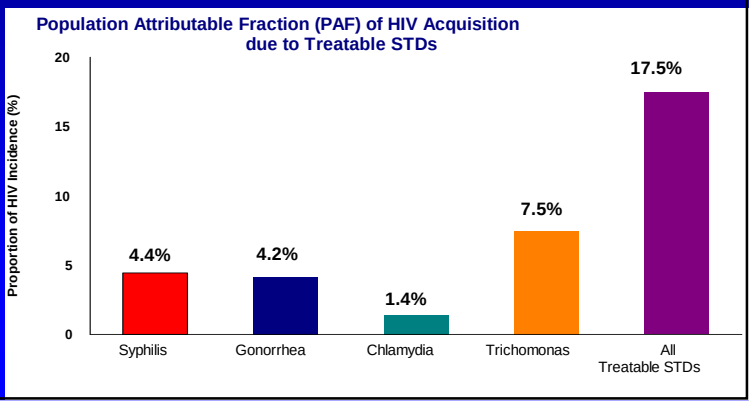


7 negative trials; One RCT showed efficacy in a low HIV incidence/prevalence setting (Mwanza)

Why were Bacterial STI RCTs largely negative?

- **Population Attributable fraction of HIV due to STIs**
  - STIs play a modest role in HIV acquisition at a population level?
  - Trials were not powered to detect modest effects

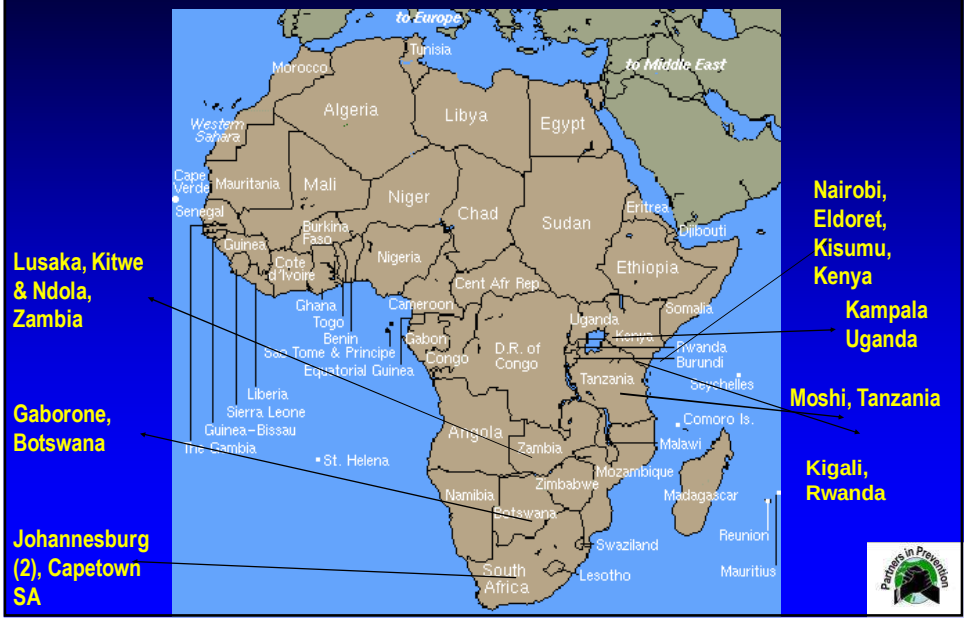
(Gray and Wawer Lancet 2008)



HSV-2 Suppression in HIV+ co-infected persons to prevent transmission

- **4 RCTs with Intermediate end points**
  - HIV shedding, genital and plasma viral load
  - Ouedraogo AIDS 2006, Zuckerman JID 2007,NaGOT nejm 2007, Baeten JID 2008, Zuckerman AIDS 2009
- **One RCT with a HIV end point:**
  - (Celum et al, NEJM 2010)

14 Sites for HSV-HIV Transmission Trial



HSV-2 Suppression in HIV+ Co-infected Partners in Serodiscordant couples

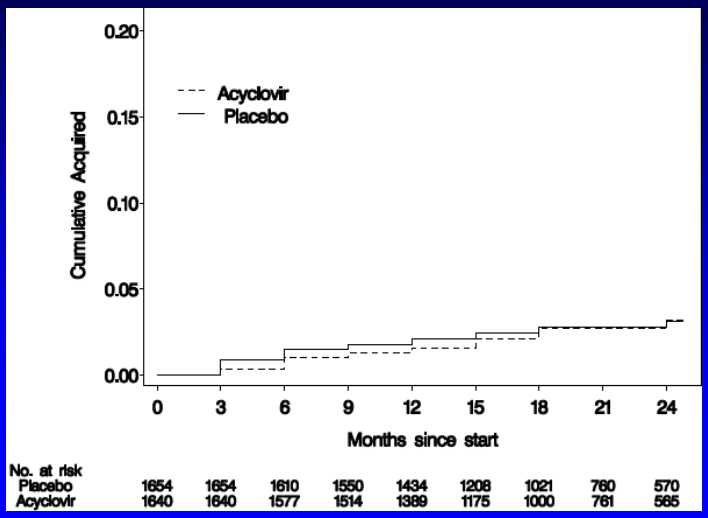
- 3408 HIV-serodiscordant couples
- Co-infected HIV+ partners treated with acyclovir 400mg bid
- Primary endpoint HIV transmission

Results

- HIV transmission: HR = 0.92 (0.60-1.41)^{ns}
- HSV-2 GUD: HR = 0.27 (0.20-0.36) $^{<0.001}$
- Plasma viral load: -0.25 $\log_{10}$ cps/mL $^{<0.001}$

(Celum et al NEJM 2010.)

Kaplan-Meier Curve for mITT analysis (Linked Transmissions)



HR* 0.92 (95% CI 0.60-1.41); p=0.70

*HR stratified by site

What about…"The STD Paradox"?

Only 1/9 STD intervention RCTs have led to reduced transmission of HIV

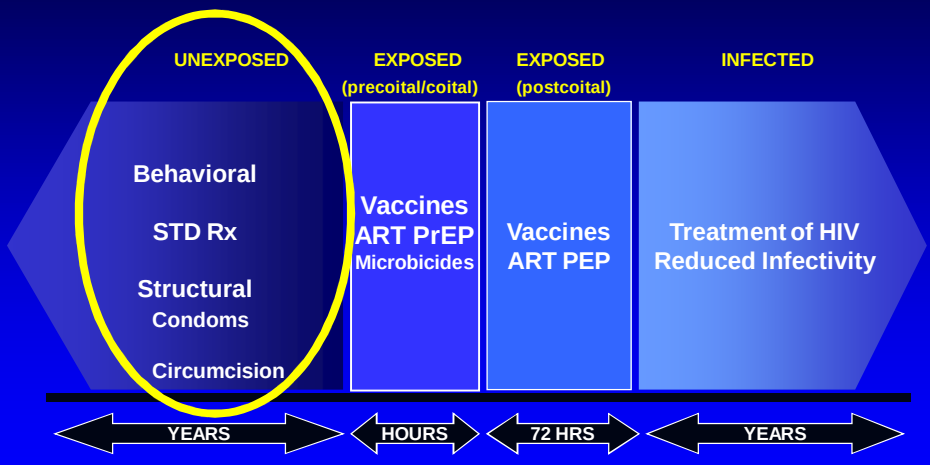
So… either STDs do not "amplify" HIV transmission OR (MORE LIKELY) the interventions were inadequate??

BUT Successful intervention requires that…..

- ✓ **The "RIGHT" STD(S) are treated**
- ✓ **At JUST the right time**
- ✓ **In JUST the right people (HIV positive or negative)**
- ✓ **With VERY EFFECTIVE drugs(s)**
- ✓ **For the RIGHT duration of time**

And treating STDs has a benefit far BEYOND the effects of HIV prevention

Four Prevention Opportunities

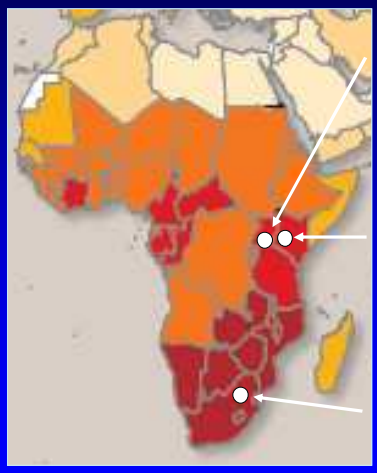


Cohen et al. JCI 2008; Cohen. IAS 2008

23

The Effect of Circumcision on Acquisition and Transmission of HIV and STIs

Randomised controlled trials of male circumcision to reduce HIV infection (>50% Effectiveness)



Rakai, Uganda
Gray *et. al.* (2007) Lancet; 657 – 66

Kisumu, Kenya
Bailey *et. al.* (2007) Lancet; 643 – 56

Orange Farm, South Africa
Auvert *et. al.* (2005) PLoS Med; e298

HIV incidence during and after the RCT in Trial Participants

	Circumcised HIV/100 py	Uncircumcised HIV/100 py	IRR (95%CI)
Trial (N=4,996)	0.47	1.14	0.41 (0.25-0.68)

Gray et al Lancet 2007

26

HIV incidence during and after the RCT in Trial Participants

	Circumcised HIV/100 py	Uncircumcised HIV/100 py	IRR (95%CI)
Trial (N=4,996)	0.47	1.14	0.41 (0.25-0.68)
Post-Trial Period			
All Men	0.54	1.66	0.33 (0.18-0.59)

Post-trial effectiveness ~ 67%

Kong et al CROI 2011

27

HIV incidence during and after the RCT in Trial Participants

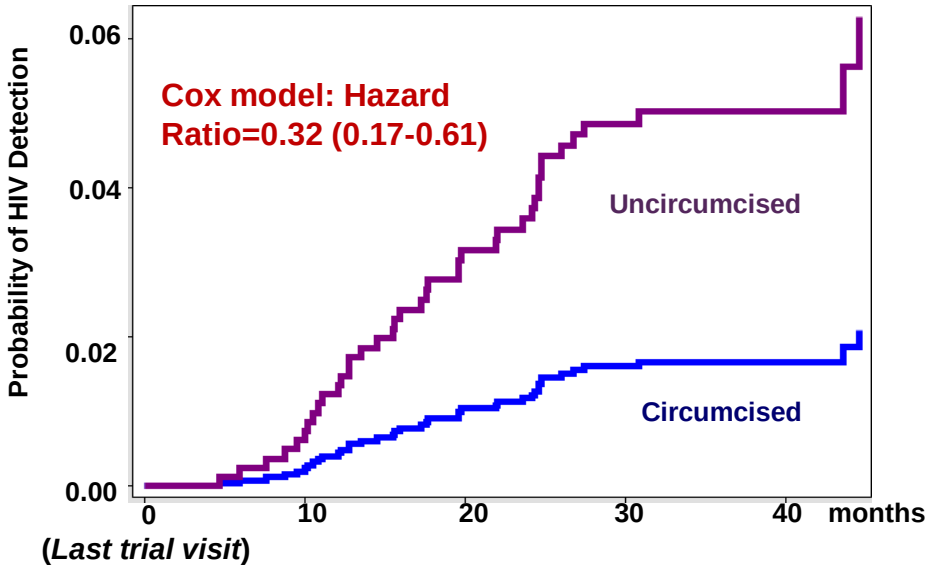
	Circumcised HIV/100 py	Uncircumcised HIV/100 py	IRR (95%CI)
Trial (N=4,996)	0.47	1.14	0.41 (0.25-0.68)
Post-Trial Period			
All Men	0.54	1.66	0.33 (0.18-0.59)
Control Arm Men	0.53	1.65	0.32 (0.15-0.65)

Post-trial effectiveness ~ 67%

Kong et al CROI 2011

28

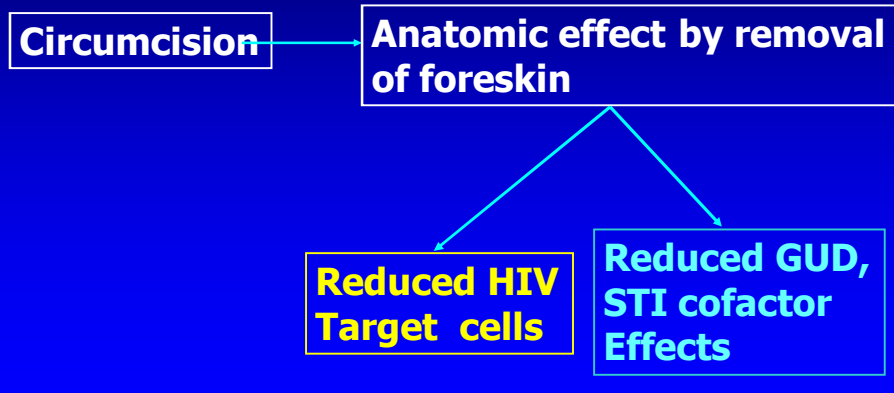
MC Effect on HIV Incidence Post Trial



Kong et al CROI 2011

29

Potential Biologic Mechanisms of Protection In Circumcised Males



Protective Efficacy of MC for STIs

MEN

- GUD
  - RR = 0.53 (0.43-0.64)
- HSV-2
  - RR = 0.72 (0.56-0.92)
- Pro-inflam anaerobes
  - RR = 0.28 (P=0.014)
- HPV
  - RR = 0.65 (0.46-0.90)

Gray et al Lancet 2007; Am J Obstet Gynecol 2008; Tobian et al NEJM 2009; Price et al Plos One 2010; Tobian et al Lancet Jan 7, 2011

31

Protective Efficacy of MC for STIs

MEN

- GUD
  - RR = 0.53 (0.43-0.64)
- HSV-2
  - RR = 0.72 (0.56-0.92)
- Pro-inflam anaerobes
  - RR = 0.28 (P=0.014)
- HPV
  - RR = 0.65 (0.46-0.90)

FEMALE PARTNERS

- GUD
  - RR = 0.78 (0.63-0.97)
- Trichomonas
  - RR = 0.52 (0.05-0.98)
- Severe BV
  - RR = 0.39 (0.24-0.64)
- HPV
  - RR = 0.72(0.60-0.85)

Gray et al Lancet 2007; Am J Obstet Gynecol 2008; Tobian et al NEJM 2009; Price et al Plos One 2010; Tobian et al Lancet 2011

32

33

Antiretroviral Therapy as HIV Prevention

- Prevention of mother-to-child transmission
- Post-exposure prophylaxis
- Pre-exposure prophylaxis
- Treatment of chronic infection

34

The Impact of ART on HIV Transmission

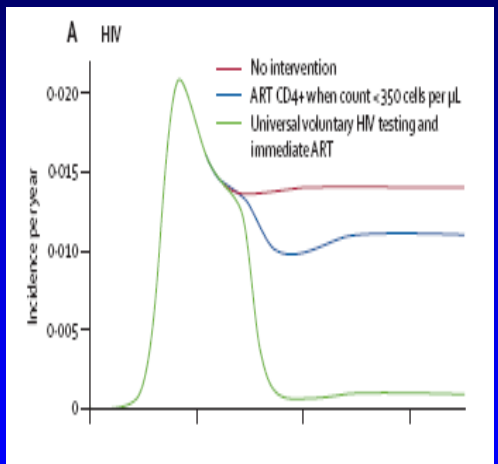
- ART offered in 7 African countries (part of the Partners in Preventions trial on ACV)
- 3381 HIV serodiscordant couples followed
- 349 "index cases" receiving ART (median CD4=198)
- In spite of counseling, 103 seroconversions occurred, but only 1 seroconversions were with partner on ART (18 days after starting ARVs)
- **ART leads to 92% reduction in HIV transmission**

Donnell D, et al Lancet May 27, 2010

Mathematical Modeling Universal Test and Treat

Utopian Assumptions

- High uptake of annual testing by all individuals >15 year old
- Treat all HIV+
- 99% decrease in infectiousness
- High adherence and low failure with 1st line ART



Is it practical; is it affordable; what about resistance

Granich P et al Lancet 2009; 373:48-57

Slide #37

Antiretroviral Therapy as HIV Prevention

- Prevention of mother-to-child transmission
- Post-exposure prophylaxis
- Pre-exposure prophylaxis
- Treatment of chronic infection

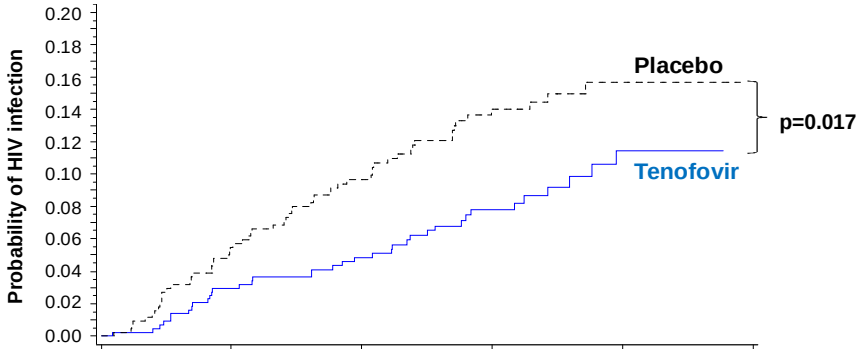
37

CAPRISA 004: Urban and Rural sites

CAPRISA Vulindlela Clinic
KwaZulu-Natal Midlands

CAPRISA eThekwini Clinic
Durban City Centre

HIV infection rates in the tenofovir and placebo gel groups: Kaplan-Meier survival probability

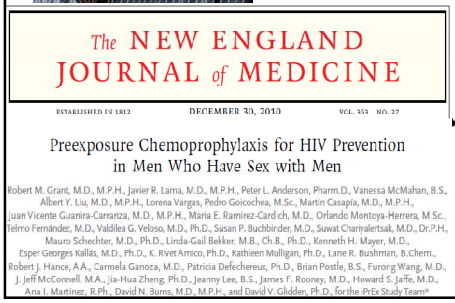


Months of follow-up	6	12	18	24	30
Cumulative HIV endpoints	37	65	88	97	98
Cumulative women-years	432	833	1143	1305	1341
HIV incidence rates (Tenofovir vs Placebo)	6.0 vs 11.2	5.2 vs 10.5	5.3 vs 10.2	5.6 vs 9.4	5.6 vs 9.1
Effectiveness (p-value)	**47% (0.069)**	**50% (0.007)**	**47% (0.004)**	**40% (0.013)**	**39% (0.017)**

Impact of adherence on effectiveness of tenofovir gel

	# HIV	N	HIV incidence		Effect
			TFV	Placebo	
High adherers (>80% gel adherence)	36	336	4.2	9.3	**54%**
Intermediate adherers (50-80% adherence)	20	181	6.3	10.0	**38%**
Low adherers (<50% gel adherence)	41	367	6.2	8.6	**28%**

2010: A landmark year for oral PrEP for HIV-1 prevention with iPrEx



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 30, 2010 VOL. 363 NO. 27

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., Martin Casapía, M.D., M.P.H., Juan Vicente Guanira-Carranza, M.D., M.P.H., Maria E. Ramirez-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. Martinez, R.Ph., David N. Burns, M.D., M.P.H., and David V. Glidden, Ph.D., for the iPrEx Study Team*

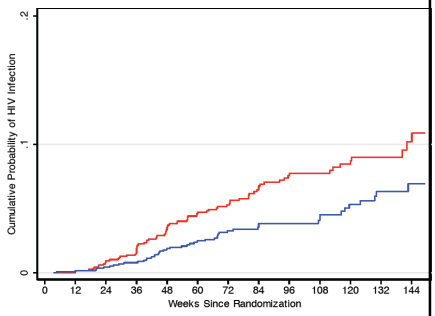
- ✓ **2499 MSM,** randomized 1:1 daily oral FTC/TDF vs placebo
- ✓ **11 sites** (Brazil, Ecuador, Peru, South Africa, Thailand, US)
- ✓ **Young high risk MSM**:
  - 50% <25 yrs
  - Median 18 partners in 12 wks prior to enrollment
- ✓ **Completed 2010; excellent safety profile**
  - ↑ nausea 1st month
  - Small decrease in bone mineral density (Mulligan CROI 94LB)[12]

Updated iPrEx Efficacy

131 infections after randomization

48 on FTC/TDF

83 on placebo



Updated efficacy estimate (mITT): 42% reduction in HIV acquisition (95% CI 18%-60%)

No reduction in HSV-2 acquisition (Lama, CROI 1002)

- **TDF-DP drug levels in blood << EC_{50} for HSV**

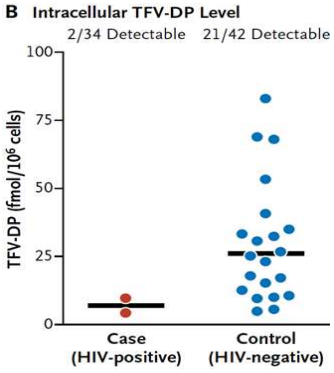
iPrEx: Adherence is critical to efficacy

Efficacy by as-treated analysis
(data as of Feb 21, 2011)

High (≥ 90% adherence; 49% of visits)
68% efficacy

Intermediate (50-90% adherence; 33% of visits)
34% efficacy

Low (< 50% adherence;18% of visits)
16% efficacy



- **9% of seroconverters had detectable drug at first HIV+ visit vs 51% of nonseroconverters**

Grant et al, NEJM 2010

Slide 43

t1 I split the text into different boxes so it would be easier to manipulate

got better photo from article
tmaddox, 09/02/2011

Investigation:
Ongoing PrEP efficacy studies

Location	Sponsor/ Funder	Population	N	PrEP Agent	Status
Thailand *Bangkok Tenofovir Study*	CDC	IDU	2400	TDF	Fully enrolled Results 2012
Kenya, Uganda *Partners PrEP Study*	UW / BMGF	HIV discordant couples	4758	TDF, FTC/TDF	Fully enrolled Results 2012
Kenya, South Africa , Tanzania, Zimbabwe *FEM-PrEP*	FHI / USAID & BMGF	Women	3900	FTC/TDF	49% enrolled Results 2013
South Africa, Uganda, Zimbabwe *VOICE / MTN 003*	MTN / NIH	Women	5000	TDF, FTC/TDF, Vaginal tenofovir gel (daily)	65% enrolled Results 2013

Safety, efficacy, resistance & costs of TDF & FTC-TDF will inform choice of drugs for PrEP roll-out

Key challenges in future implementation of PrEP: impact on study design

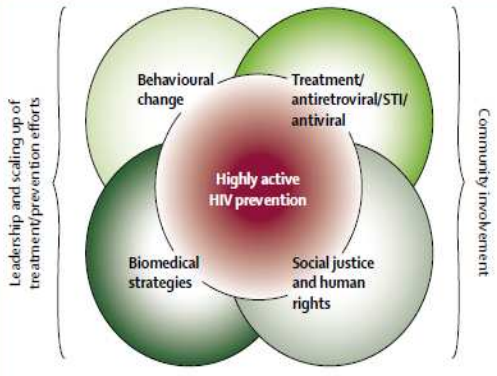
- Is it safe to give ARV drugs to healthy people?
- Will those who get infected have HIV that is resistant to the PrEP antiretrovirals? Will this affect their subsequent care and choice of ARV treatment?
- Will healthy people be willing to take medication everyday or at the time of sex for long periods?
- Is this an affordable and practical HIV prevention strategy for scale-up if it is efficacious?
- Will there be behavioral disinhibition / risk compensation?

Successes In Prevention

- ARVs for PMTCT (>90%)
- ARVs for Discordant Couples (>90%)
- Male Circumcision (>68% and lifelong)
- PrEP (42%) (up to 73% if >90% adherent)
- Microbicide (39%, but >54% if 80% adherent)
- Thai vaccine (31%)

Combination, high impact HIV prevention

Should be evidenced-based for a given population, targeted, integrated & achieve…



- **Synergies** of partially effective interventions from combining interventions that
  - Reduce HIV infectiousness (eg ART), and
  - Reduce HIV susceptibility (eg male circumcision, PrEP, vaccine)
- **High coverage**

Coates, Lancet 2008