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Lebanese AIDS Society
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Pre Exposure Prophylaxis The Future of HIV Prevention?

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Disclosures

- No financial interest in any pharmaceutical company
- Served as a speaker and/or as a consultant to several pharmaceutical companies (by alphabetical order):
  - Aventis
  - BMS
  - Cipla
  - GSK
  - MSD
  - Pfizer.

HIV prevention

- Behavioral intervention
- Voluntary counselling and testing
- Testing and treatment of genital infections
- Cervical barriers
- Condoms
- Male circumcision
- HSV 2 suppressive therapy
- Microbicides
- Immunization, vaccines

What is PrEP?

- Pre-exposure prophylaxis (PrEP) is a novel HIV-prevention strategy that would use antiretrovirals (ARVs) to protect HIV-negative people from HIV infection. In this strategy, people would take the medications before they were exposed to HIV, in the hope that it would lower their risk of infection.

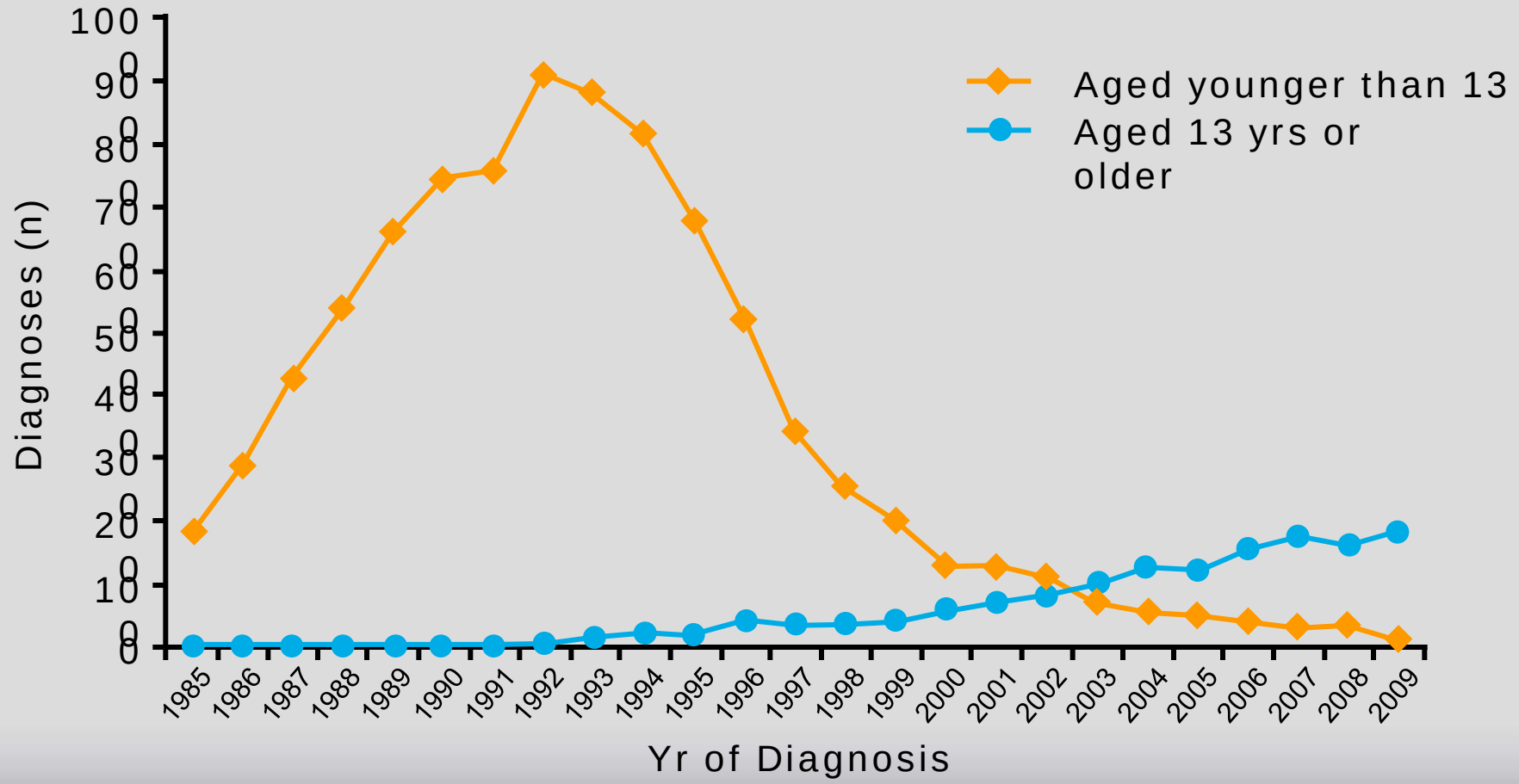
PrEP

- Long term exposure to a prophylactic treatment of a disease prior to exposure to the cause of that disease

PrEP: Proof of Concept

- Malaria
- Prevention of mother to child transmission of HIV

AIDS Diagnoses Among Perinatally Infected Persons in US: 1985-2009



CDC 2010.

Possible drawbacks

- Divert resources
- Who will get it?
- Who will pay for it?
- Would it be more effective to help people use other interventions instead, like condoms?
- Who will decide who gets it?
- How will it be distributed?
- What would be the consequences of a proportion (high risk) of the HIV-negative population being on antiretrovirals?
- Which drugs should we use?

Possible drawbacks

- Are we confident that we have *any* antiretrovirals whose safety is sufficiently well established to allow them to be given to HIV-negative people for a number of years as a preventative measure?
- What is the potential for drug resistance, given that it will be almost impossible to ensure that people who are seroconverting never take PrEP?

Possible drawbacks

- What are the cost implications, not just of the drugs, but of viral load and other tests, which are implied in order to make sure we give PrEP to as few seroconverters as possible?
- The usefulness of a new prevention technology will vanish if people abandon other proven, and possibly safer, measures, such as condoms, in favour of the new idea. If PrEP is not 100% effective, how will that be explained to vulnerable populations?

Why the interest in tenofovir and tenofovir/emtricitabine?

- Potent drugs and combination
- Safe
- Few side effects
- Single daily dose
- Prolonged duration of action
- Little resistance generated
- Encouraging animal data
- Low local and systemic toxicity from intravaginal tenofovir
- Generics

Ethical concerns

- What are the obligations of governments and industry to provide such prophylaxis?
- How should resources be distributed between research, treatment, counselling, testing, primary prevention, PrEP and PEP?
- Who should have priority for prophylaxis?

More questions

- Which settings would be appropriate?
- What level of efficacy would warrant widespread use?
- Which populations would benefit most?

Mathematical scenarios

- An optimistic scenario in which PrEP was assumed to be effective 90% of the time and used by 75% of the sexually active population. In this case, there was a significant public health benefit with a reduction of new HIV infections by 74%.
- A neutral scenario in which PrEP was effective 60% of the time and used by 50% of the sexually active population. This gave a 25% reduction in infections.
- A pessimistic scenario in which PrEP was effective 30% of the time and used by 25% of the sexually active population. A 3.3% reduction was found.

Cost effectiveness

- Questionable
- Continuous adherence to program is needed
- Cost effective down to 46% efficacy ($50,000 per QALY saved)

Impact on HIV prevalence

- PrEP programme targeting 25% of the highest-risk gay men could prevent between 4% and 23% of the infections that would otherwise happen in the next five years. The cost was estimated at $31,970 per quality-adjusted year of life saved.

PrEP: Key Challenges

- Implications of breakthrough infections with resistant viruses for future therapy options
- Level of adherence required
- Monitoring for adverse events
- Acceptability of chronic medication for healthy people ?
- Potential for abuse of PrEP among those who cannot/will not use condoms

Concerns about PrEP: Drug resistance

- When HIV replicates in a person not on effective therapy, resistance can emerge
- Accidental mutations
- Selection of resistant mutant
- Risk of exposure to single drug
- Risk of transmission of resistant virus

Concerns about PrEP: Partial effectiveness

- No 100% protection
- Need for the other strategies
- Educational challenge

Concerns

- Irregular use
- Reduction of condom use
- Non prescription

Concerns about PrEP: Riskier behaviour

- Less vigilance
- More complacency
- Disinhibition (the magic pill)

Concerns about PrEP: Stigma

- Misunderstanding of why someone is taking PrEP
- Also might destigmatize since it implies the understanding of prevention

Questions about PrEP

- Intermittent dosing?
- Other drugs?
- Other groups: pregnant women, adolescents
- Availability and distribution
- Guidelines
- Medical monitoring: side effects, resistance development, periodic HIV testing

LARGE SAFETY AND EFFICACY STUDIES OF ORAL AND TOPICAL TENOFOVIR FOR HIV PREVENTION, JULY 2011

Location	Sponsor/ Funder	Population	Agent	Status
Ghana, Nigeria, Cameroon *FHI safety study* *(phase II study)*	FHI	936 high-risk women	Oral TDF	**Results published 2007. Safety demonstrated**
US *CDC Extended Safety Study* *(phase II study)*	CDC	400 MSM	Oral TDF	**Results reported July 2010. Safety demonstrated**
Thailand *Bangkok Tenofovir Study*	CDC	2400 IDU	Oral TDF	Fully enrolled Results 2011-2012
Botswana *TDF2 Study*	CDC	1200 women and men	Oral FTC/TDF	**Results anticipated July 2011**
South Africa *CAPRISA 004* *(phase II study)*	CAPRISA / USAID	889 women	Vaginal tenofovir gel (coital use)	**Vaginal tenofovir gel reduced HIV risk by 39% (95% CI 6-60%, p=0.02)**
Brazil, Ecuador, Peru, S. Africa, Thailand, US *iPrEX*	UCSF/ NIH&BMGF	2499 MSM	Oral FTC/TDF	**Oral FTC/TDF PrEP reduced HIV risk by 42% (95% CI 15-63%, p=0.005)**
Kenya, South Africa, Zimbabwe *FEM-PrEP*	FHI / USAID& BMGF	1951 high-risk women	Oral FTC/TDF	**Early closure 2011** **No evidence of protection against HIV**
Kenya, Uganda *Partners PrEP Study*	UW / BMGF	4758 HIV discordant couples	Oral TDF Oral FTC/TDF	**Oral TDF PrEP reduced HIV risk by 62% (95% CI 34-78%, p=0.0003)** **Oral FTC/TDF PrEP reduced HIV risk by 73% (95% CI 49-85%, p<0.0001)**
South Africa, Uganda, Zimbabwe *VOICE / MTN 003*	MTN / NIH	5000 women	Oral TDF, Oral FTC/TDF Vaginal tenofovir gel (daily use)	Fully enrolled Results late 2012

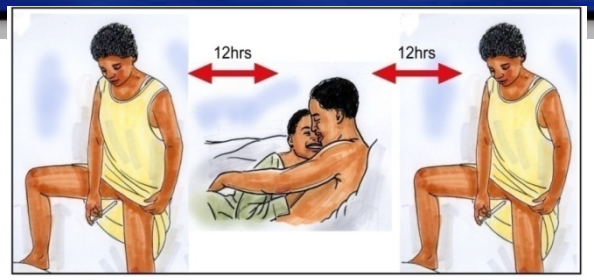
Completed trial - 2005
Nigeria, Ghana, Cameroon (FHI)

- 859 women
- Tenofovir v/s placebo
- No safety or toxicity problems
- 2 infections in TDF group and 6 in the placebo group
- Not statistically significant

Studies

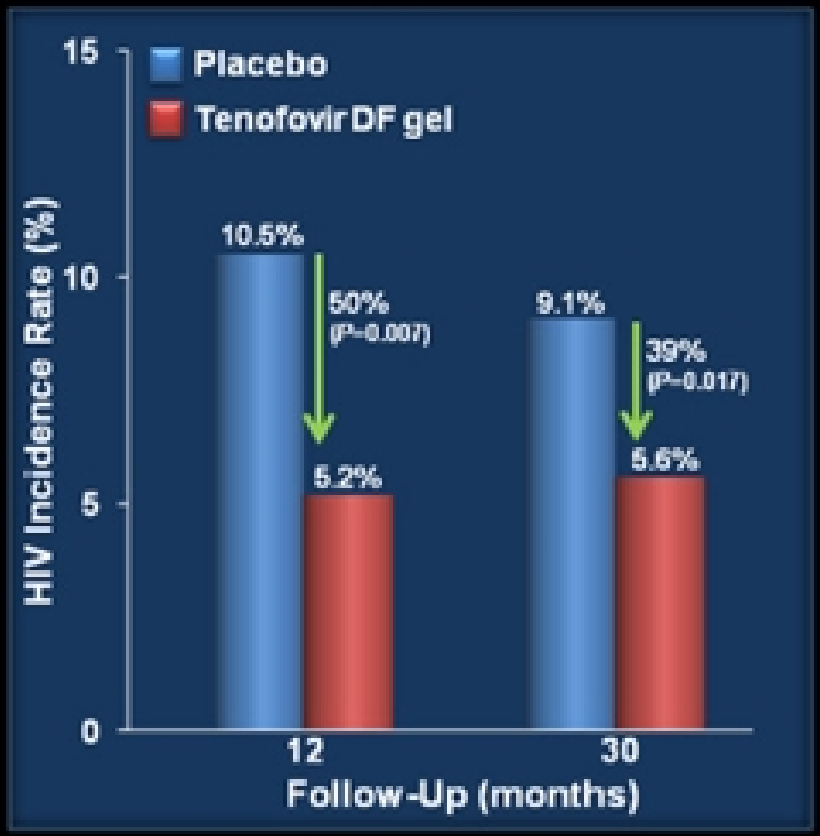
- MTN 001: Adherence and pharmacokinetics study of oral and vaginal preparations of tenofovir
- MTN 003: Safety and effectiveness study of tenofovir 1% gel, TDF tablet and TDF/FTC tablet for the prevention of HIV infection in women
- CDC 4940: Safety and efficacy of daily oral antiretroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana and South Africa

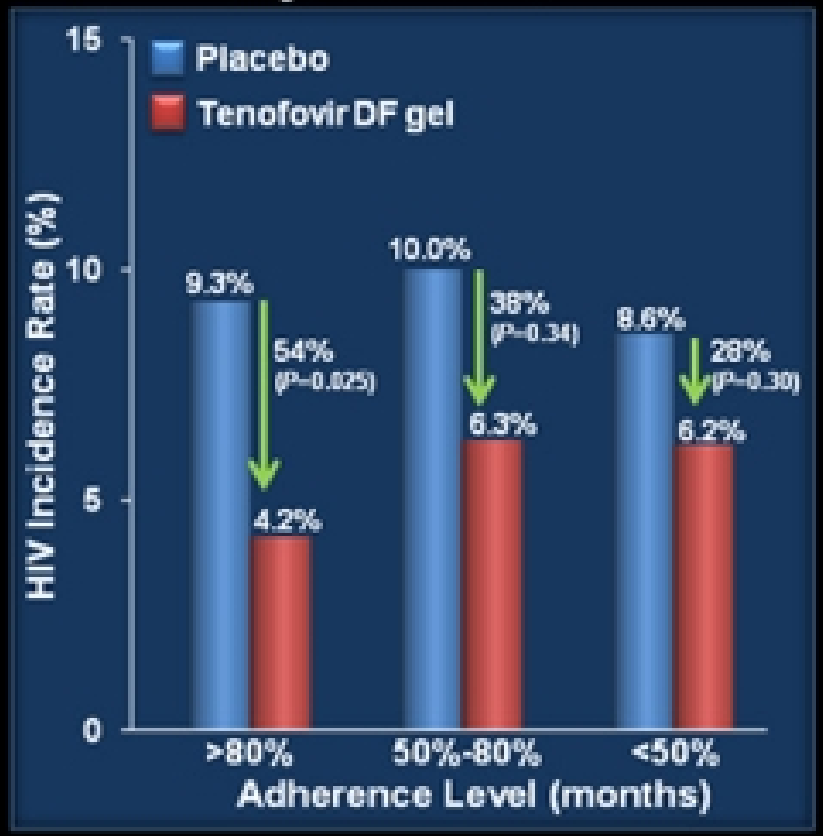
CAPRISA 004: HIV infection rates in the tenofovir and placebo gel groups: Kaplan-Meier survival probability



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)**

CAPRISA 004 Results: HIV Incidence





Abdool Karim Q, et al. *Science*. 2010;329:1168-1174.

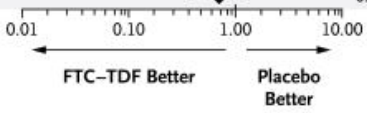
PrEP studies

- Efficacy:
  - PrEP
  - iPrEx study
  - Partners PreP
  - TDF2 study
- Lack of efficacy:
  - FemPrEP
  - VOICE

Grant RM et al. *PrEP, N Eng*l Jour Med 363(27):2587-2599, 2010; Baeten J Partners *PrEP Study.* IAS 2011; Thigpen M et al. TDF2 *study. IAS* 2011; Family Health International :*FEM-PrEP.* 2011; Microbicides Trial Network *MTN 2*011

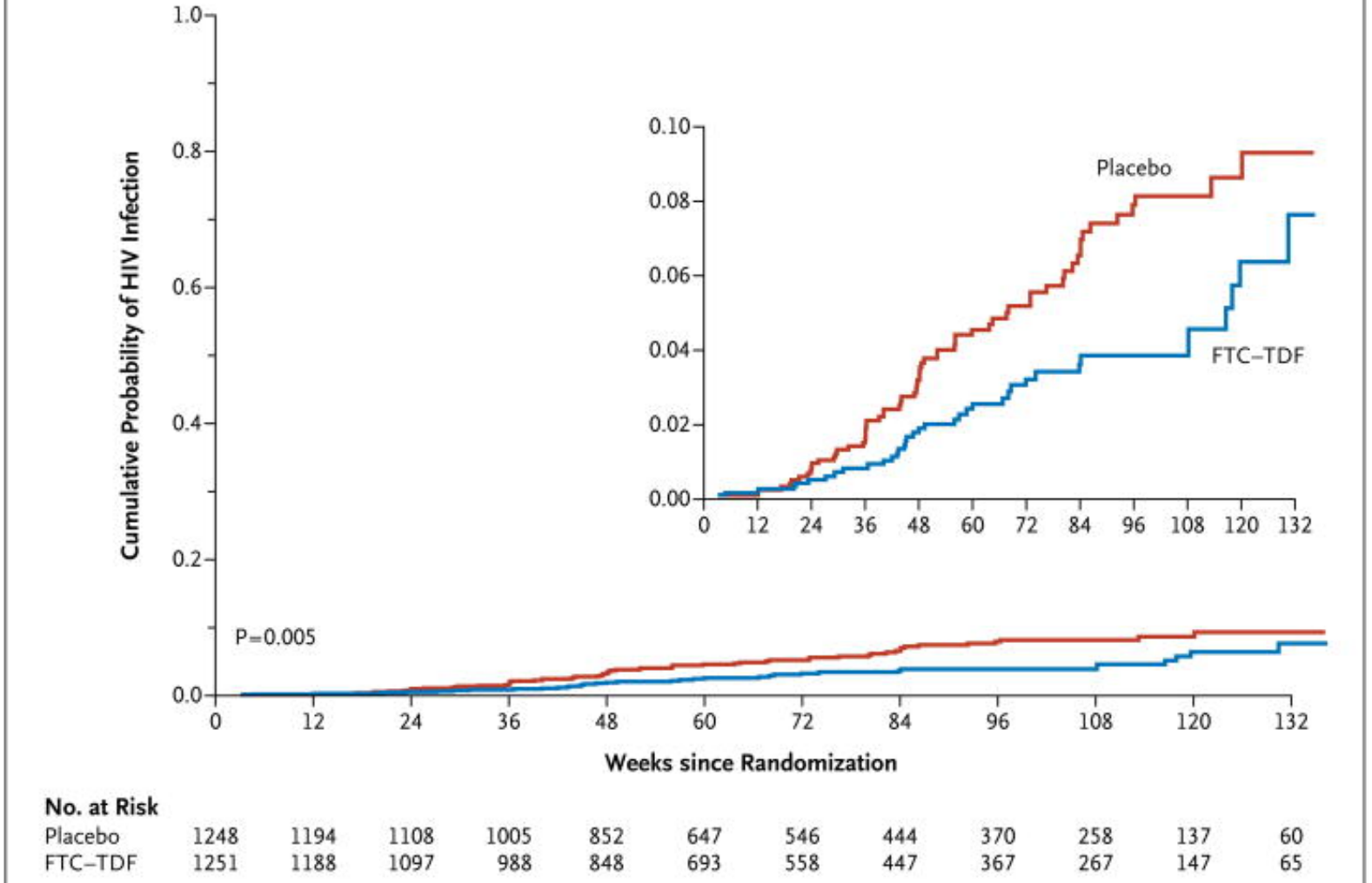
Preexposure chemoprophylaxis for HIV prevention in men who have sex with men.
Grant et al, NEJM 363:2587-2599,2010

Subgroup	FTC–TDF	Placebo	FTC–TDF	Placebo	Hazard Ratio (95% CI)	P Value
	no. of patients		*no. of events*			
Analysis						
Intention-to-treat	1251	1248	38	72	0.53 (0.36–0.78)	0.001
Modified intention-to-treat	1251	1248	36	64	0.56 (0.37–0.85)	0.005
As treated						0.48
<50% Pill use	NA	NA	13	17	0.68 (0.33–1.41)	
≥50% Pill use	NA	NA	23	47	0.50 (0.30–0.82)	
Pill use						0.02
<90% Pill use	NA	NA	28	34	0.79 (0.48–1.31)	
≥90% Pill use	NA	NA	8	30	0.27 (0.12–0.59)	
Age						0.36
<25 yr	591	662	22	37	0.67 (0.40–1.14)	
≥25 yr	660	586	14	27	0.41 (0.24–0.87)	
Education						0.16
<Secondary education	279	244	12	12	0.89 (0.40–1.98)	
≥Secondary education	955	992	23	52	0.46 (0.28–0.74)	
Ethnic group						0.79
Non-Hispanic	351	342	4	8	0.48 (0.14–1.60)	
Hispanic	900	906	32	56	0.57 (0.37–0.89)	
Region						0.62
Andean	850	850	32	55	0.59 (0.38–0.91)	
Non-Andean	401	398	4	9	0.43 (0.13–1.39)	
Risk at screening						0.01
URAI	732	753	23	56	0.42 (0.26–0.68)	
No URAI	519	495	13	8	1.59 (0.66–3.84)	
Daily alcohol use						0.38
0–4 Drinks	554	529	15	32	0.43 (0.23–0.80)	
≥5 Drinks	666	687	19	32	0.63 (0.36–1.11)	
Circumcised						0.22
No	1085	1074	34	55	0.62 (0.40–0.95)	
Yes	162	170	2	9	0.23 (0.05–1.06)	
HSV-2 at screening						0.32
Negative or indeterminate	783	813	17	38	0.46 (0.26–0.82)	
Positive	458	430	19	26	0.70 (0.39–1.2)	



Preexposure chemoprophylaxis for HIV prevention in men who have sex with men.

Grant et al, NEJM 363:2587-2599,2010



iPrEx

- Once-daily oral FTC–TDF provided 44% additional protection from HIV among men or transgender women who have sex with men who also received a comprehensive package of prevention services.
- The protective effect of FTC–TDF was significant but not as high as originally hypothesized during the design of the study.

Partners PrEP study

- Through 31 May 2011, a total of 78 HIV infections occurred in the study: 18 among those assigned TDF, 13 among those assigned FTC/TDF, and 47 among those assigned placebo.
- Thus, those who received TDF had an average of 62% fewer HIV infections (95% CI 34 to 78, p=0.0003) and those who received FTC/TDF had 73% fewer HIV infections (95% CI 49 to 85, p<0.0001) than those who received placebo. PrEP reduced HIV risk in both women and men.

Partners PrEP

- **Pre-exposure prophylaxis (PrEP) is an important strategy to prevent HIV infection.**
- **The Partners PrEP study found high safety and significant efficacy of both TDF and FTC/TDF in reducing HIV acquisition risk in heterosexual African men and women.**

Partners PrEP Study: Tenofovir Levels Correlate with HIV Protection

- Case cohort study of 30 seroconverters in active arms vs. 200 uninfected subjects randomly selected from active arms
- Plasma TDF levels at months 1, 3, 6, 12, 18, 24, 30, 36 + seroconversion visit

Subjects with Detectable Tenofovir Levels and Risk Reduction

	Cases (TDF = 17, FTC/TDF = 12)				Cohort (N=198)	
	Visits prior to seroconversion		Seroconversion visits		All visits	
TDF	35/63	56%	6/17	31%	363/437	83%
FTC/TDF	20/36	56%	3/12	25%	375/465	81%

- Relative risk reduction associated with detectable tenofovir
  - TDF arm: 86% (95% CI: 57%, 95%)
  - FTC/TDF arm: 90% (95% CI: 56%, 98%)

Donnell D, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 30.

TDF2 trial

- Setting: Botswana
- Participants: 1200 heterosexual men and women
- Method: Placebo controlled
- Design: 601 individuals received tenofovir/emtricitabine (TDF/FTC) and 599 received placebo.

- 9 infections (/601) in the treatment group and 24 (/599) infections in the placebo group
- 62.6% reduction in infections
- After excluding individuals who did not adhere to treatment, 77.9 % reduction
- Efficacy in men 80% (2 v/s 10 infections)
- Efficacy in women 49% (7 v/s 14 infections)

TDF 2 Study Botswana

		Total	Men (663) HIV infections	Women (557) HIV infections	HIV infections
Total	TDF/FTC	601	2	7	9
	Placebo	599	10	14	24
	Reduction		80.1%	49.4%	62.6%
Individuals with good adherence	TDF/FTC		1	3	
	Placebo		6	13	
	Reduction		82%	75.5%	77.9%

FEM-PrEP study

- 1951 HIV-negative women aged 18 to 35 at risk of HIV infection in South Africa, Kenya and Tanzania were randomised to receive daily oral *Truvada* (tenofovir and FTC in one pill) or placebo. On average, participants took the study drug for 12 months and attended study visits for 14 months.
- Approximate annual rate of new HIV infections was 5% per year, and a total of 56 new infections had been recorded up to February 2011. These were equally distributed between the *Truvada* and placebo groups (28 in each arm)

FEM-PrEP (Feb 2011)

Screened: 3752 (21% HIV-positive)

- **Enrolled: 1951 (50%)**
  - Bondo, Kenya 739
  - Pretoria, SA 764
  - Bloemfontein, SA 432
  - Arusha, Tanzania 16
- **Retention: ~90%**
- **Person-years of follow-up: 1100**

FEM-PrEP Main Findings

- **HIV incidence: 5.1 per 100 person years**
- **HIV infection endpoints: 56 (78% of 72)**
  – Truvada arm: 28
  – Placebo arm: 28

- **Pregnancies: 9 per 100 person years**
  – Higher among women in Truvada arm compared with placebo arm

Hypotheses for HIV Outcome

- **Adherence too low to show effectiveness**
- **Biological (next slide)**
- **Product sharing**
- **Chance**
- **Combination of factors**

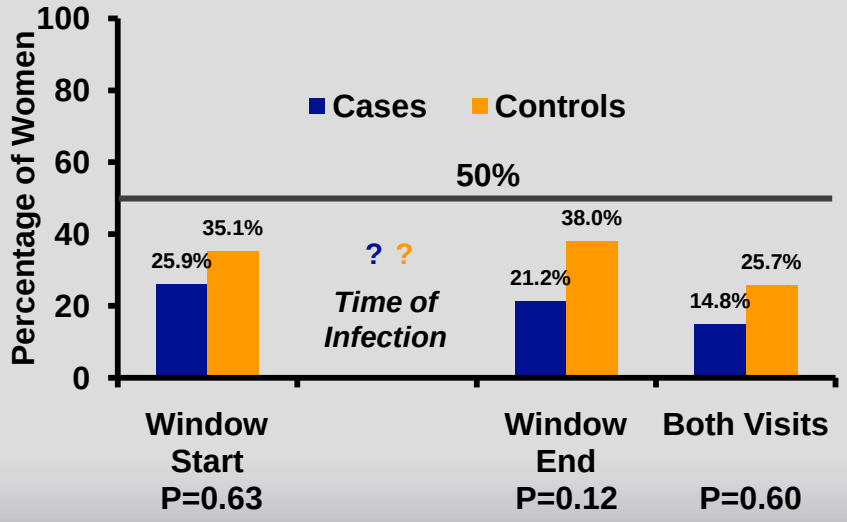
Possible Biological Explanations

- **Penetration of tenofovir and/or emtricitabine in female genital tract inadequate to provide protection**
  - Differential distribution to rectum and the female genital track
- **High drug levels required at site of HIV entry**
  - These levels may not be achieved in female genital tract with a single daily dose
- **Contraceptive hormones**
  - May interfere with effectiveness of Truvada (TDF-FTC)
- **Truvada side effects**
  - May have resulted in decreased adherence to study drug

FEM-PrEP: Failure of TDF/FTC as PrEP Related to Nonadherence

- FEM-PrEP: Placebo controlled trial of TDF/FTC as PrEP for heterosexual women in South Africa, Kenya, and Tanzania
- DSMB stopped trial for futility
- TDF levels indicate nonadherence played significant role in trial failure

Subjects with TDV ≥10 ng/mL



Efficacy Analyses

Primary Efficacy Analysis		
	TDF/FTC N=1024	PLC N=1032
HIV infections	33	35
Incidence	4.7/100 PY	5.0/100 PY
HR = 0.94 (0.59, 1.52) p=0.81		
Efficacy: Censored for Available Drug		
HIV infections	27	34
Incidence	4.2/100 PY	5.0/100 PY
HR = 0.82 (0.49, 1.36) p=0.44		

Van Damme L, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 32LB.

HPTN 052: Immediate vs Delayed ART for HIV Prevention in Serodiscordant Couples

HIV-infected, sexually active serodiscordant couples; CD4+ cell count of the infected partner: 350-550 cells/mm^3 (N = 1763 couples)

Immediate HAART
Initiate HAART at CD4+ cell count 350-550 cells/mm^3
(n = 886 couples)

Delayed HAART
Initiate HAART at CD4+ cell count ≤ 250 cells/mm^3*
(n = 877 couples)

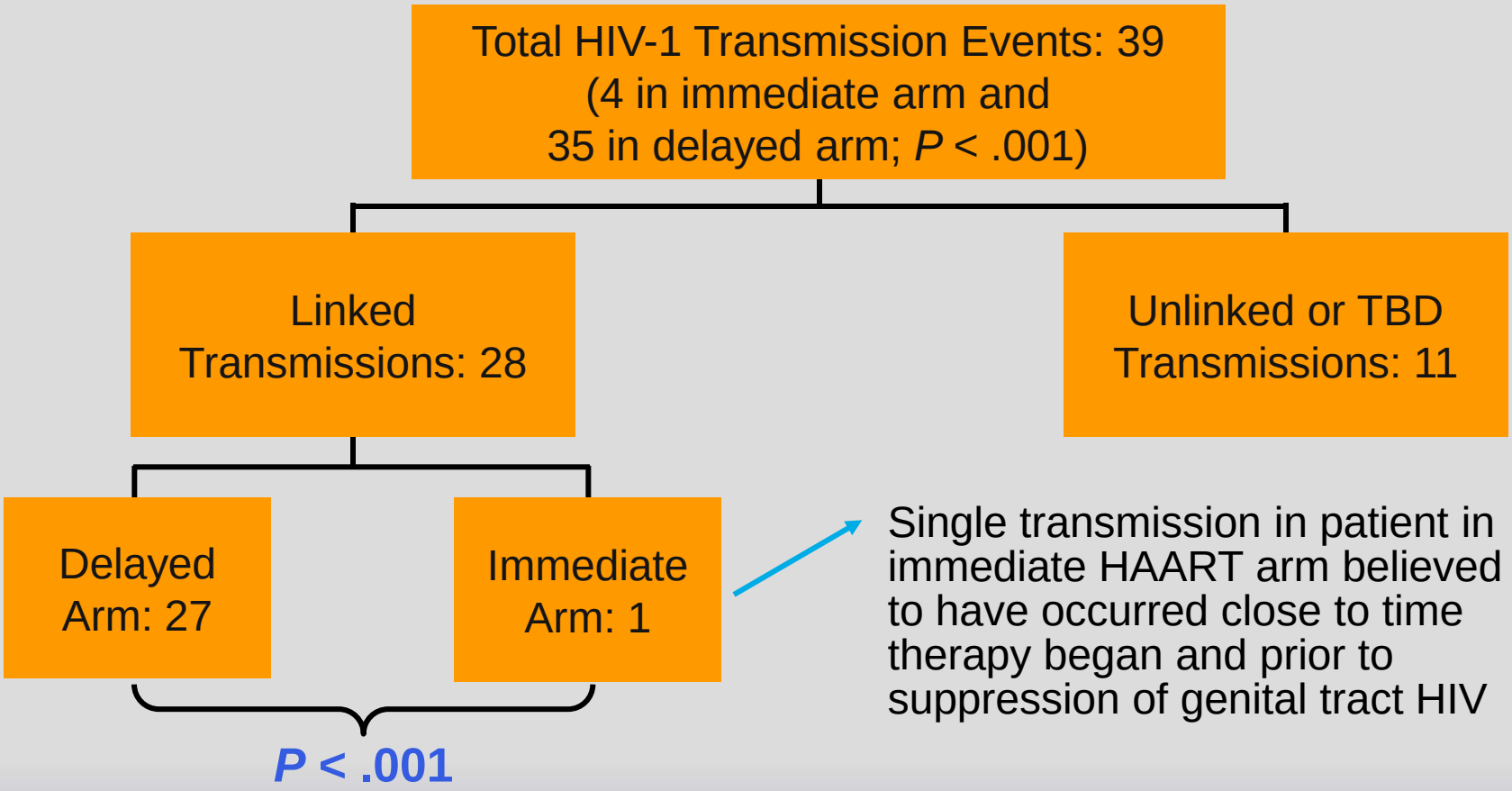
*Based on 2 consecutive values ≤ 250 cells/mm^3.

- Primary efficacy endpoint: virologically linked HIV transmission
- Primary clinical endpoints: WHO stage 4 events, pulmonary TB, severe bacterial infection and/or death
- Couples received intensive counseling on risk reduction and use of condoms

DSMB recommended release of results as soon as possible following April 28, 2011, review; follow-up continues but all HIV-infected partners offered ART after release of results

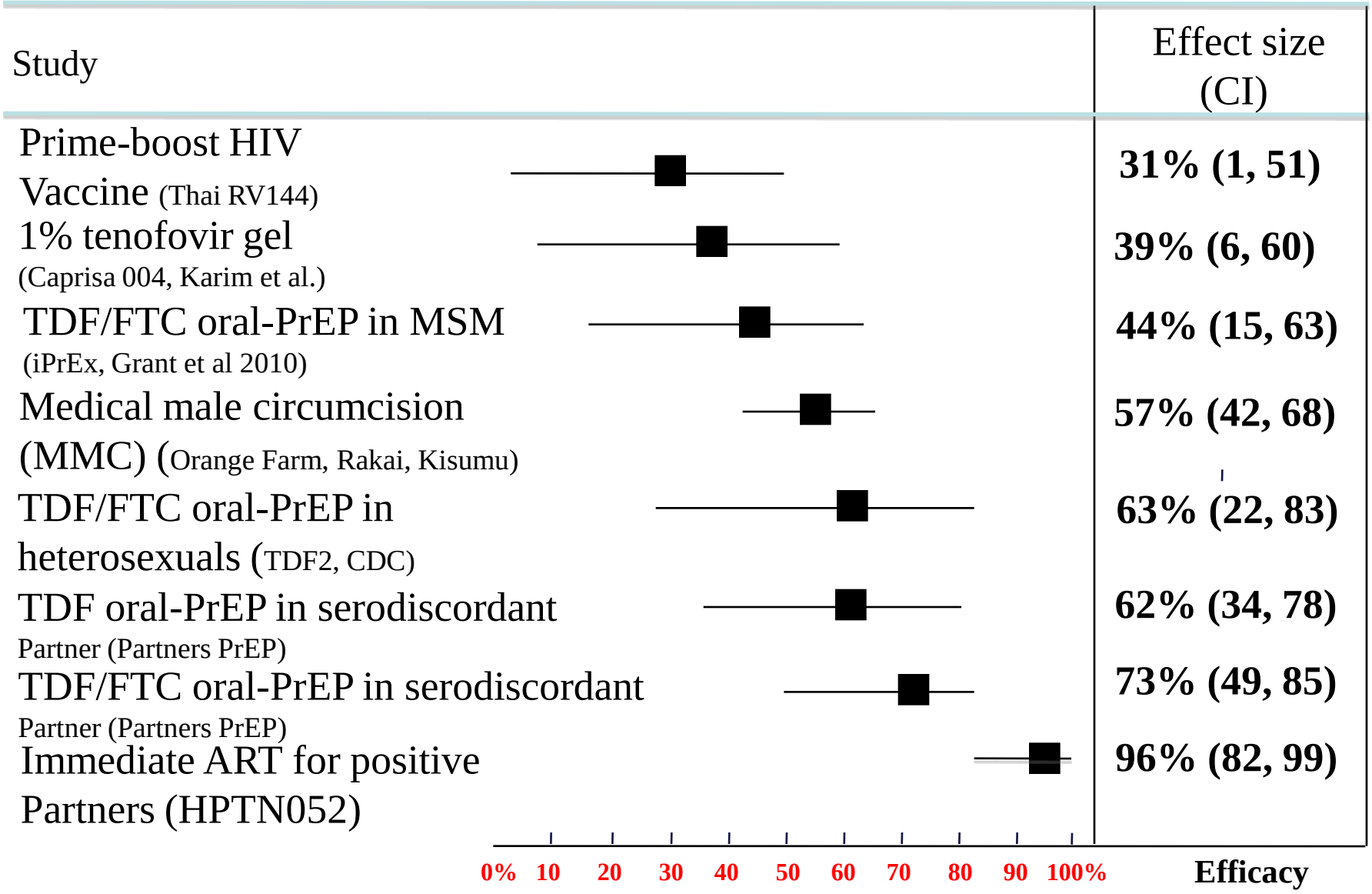
Cohen MS, et al. N Engl J Med. 2011;365:493-505.

HPTN 052: HIV Transmission Reduced by 96% in Serodiscordant Couples

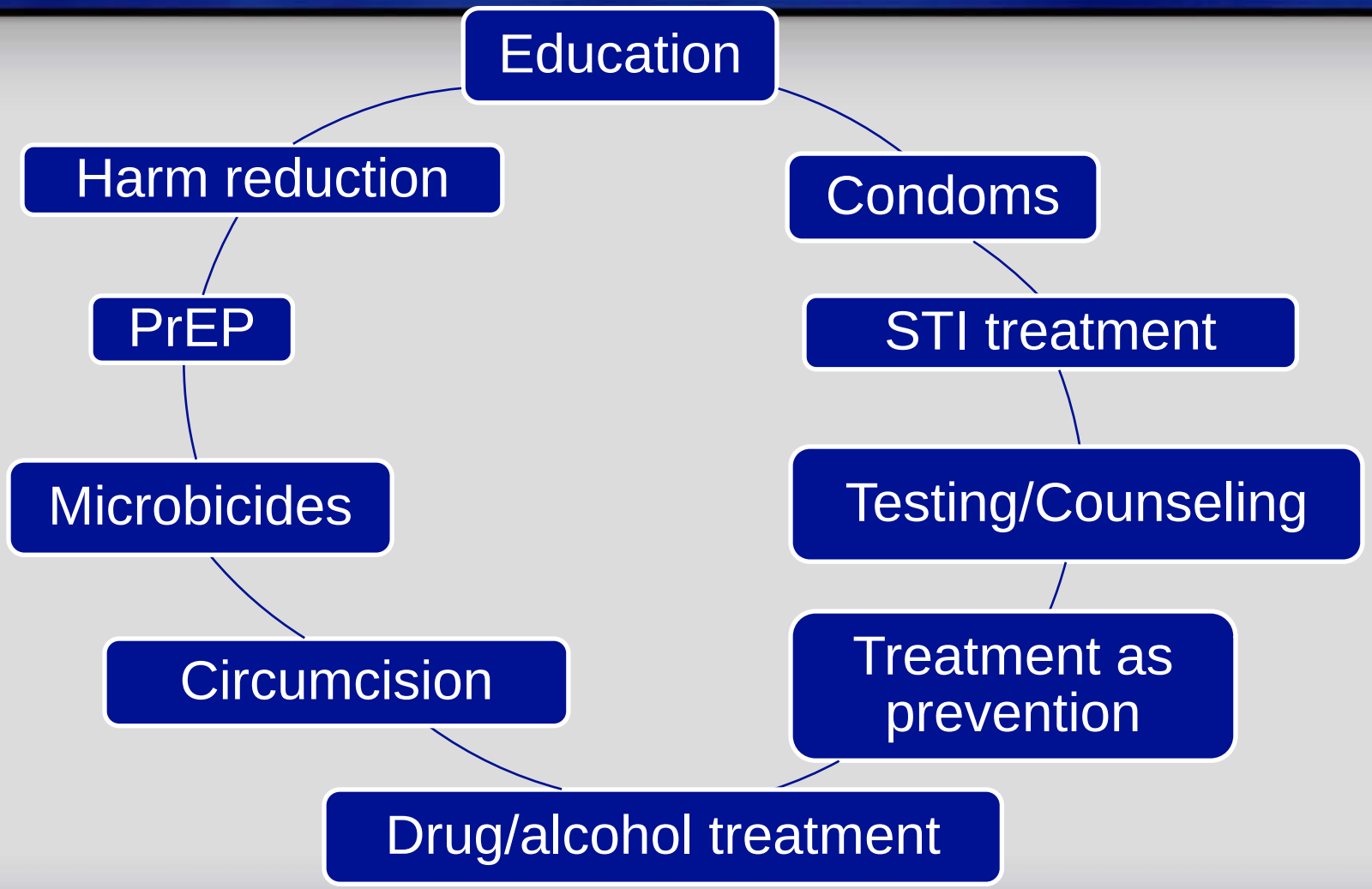


Cohen MS, et al. N Engl J Med. 2011;365:493-505.

Biomedical intervention strategies



Combination HIV Prevention



Conclusion

- Preventive therapy of pregnant women effective in prevention transmission to child
- Treatment of HIV-infected partners effective in preventing transmission to partner
- Daily TDF-based PrEP regimens effective in preventing HIV acquisition in MSM (iPrEx), serodiscordant couples (Partners PrEP), and young men and women (TDF2)

Conclusion

- Inconclusive results in high-risk women
- Pregnant and breastfeeding women excluded from PrEP trials
- The approach to HIV prevention is a combination effort
- Further evaluation needed

Thank you

LEBANESE AIDS SOCIETY