Results and Controversies Surrounding the Use of Antiretroviral Drugs in HIV Pre-Exposure Prophylaxis (PrEP)

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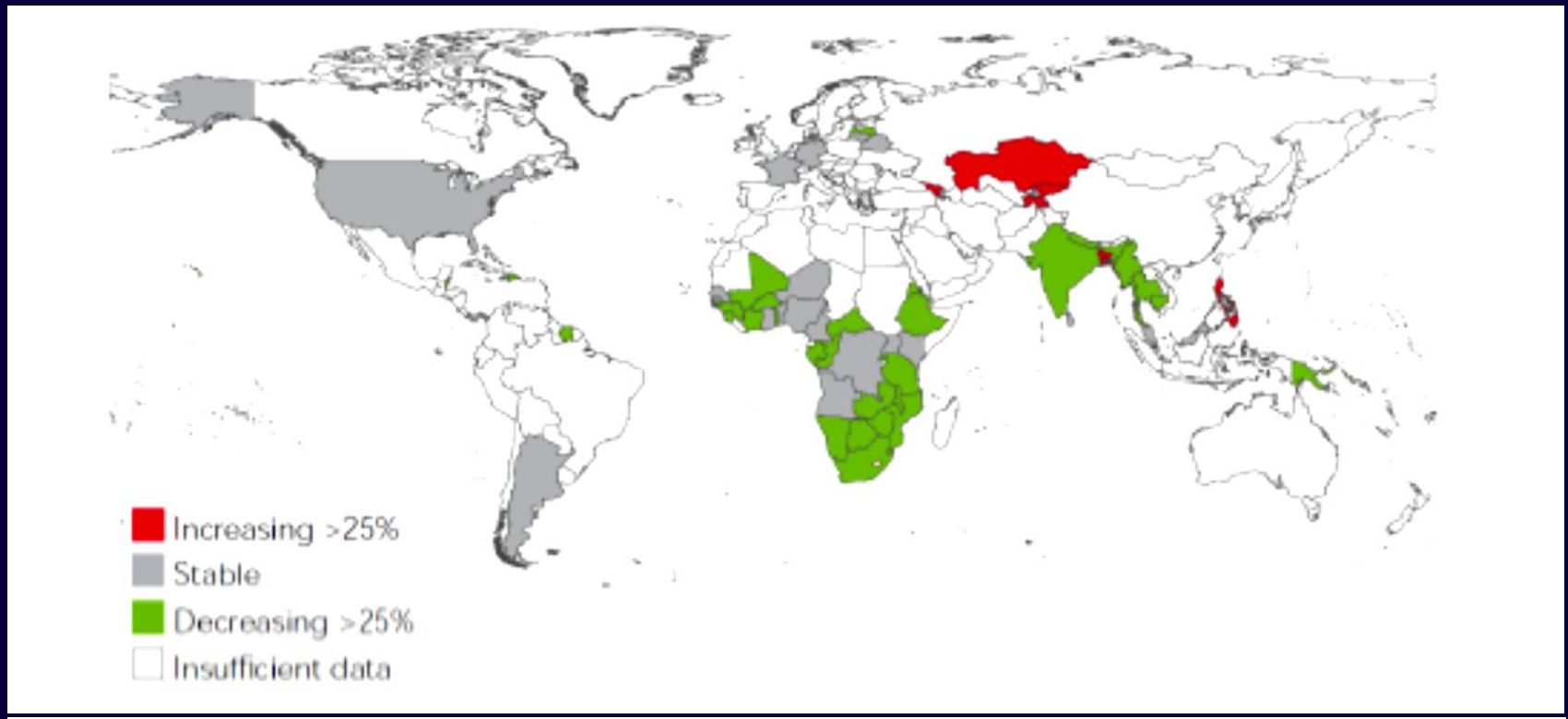
Current Prevention Methods

- Information and Education
- Regular use of condoms
- Change in sexual behavior
- Male circumcision
- Treatment of the HIV-infected partner
- Microbicides
- Vaccination

2.6 Millions New HIV Infections in 2009

Globally the number of new HIV infections had fallen 19% from 2001 to 2009, but there is resurgence of HIV in several high income countries among MSM



World Health Organization

UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
UNHCR UNICEF WFP UNDP UNFPA UNODC ILO UNESCO WHO WORLD BANK

PreP : Pre-Exposure Prophylaxis

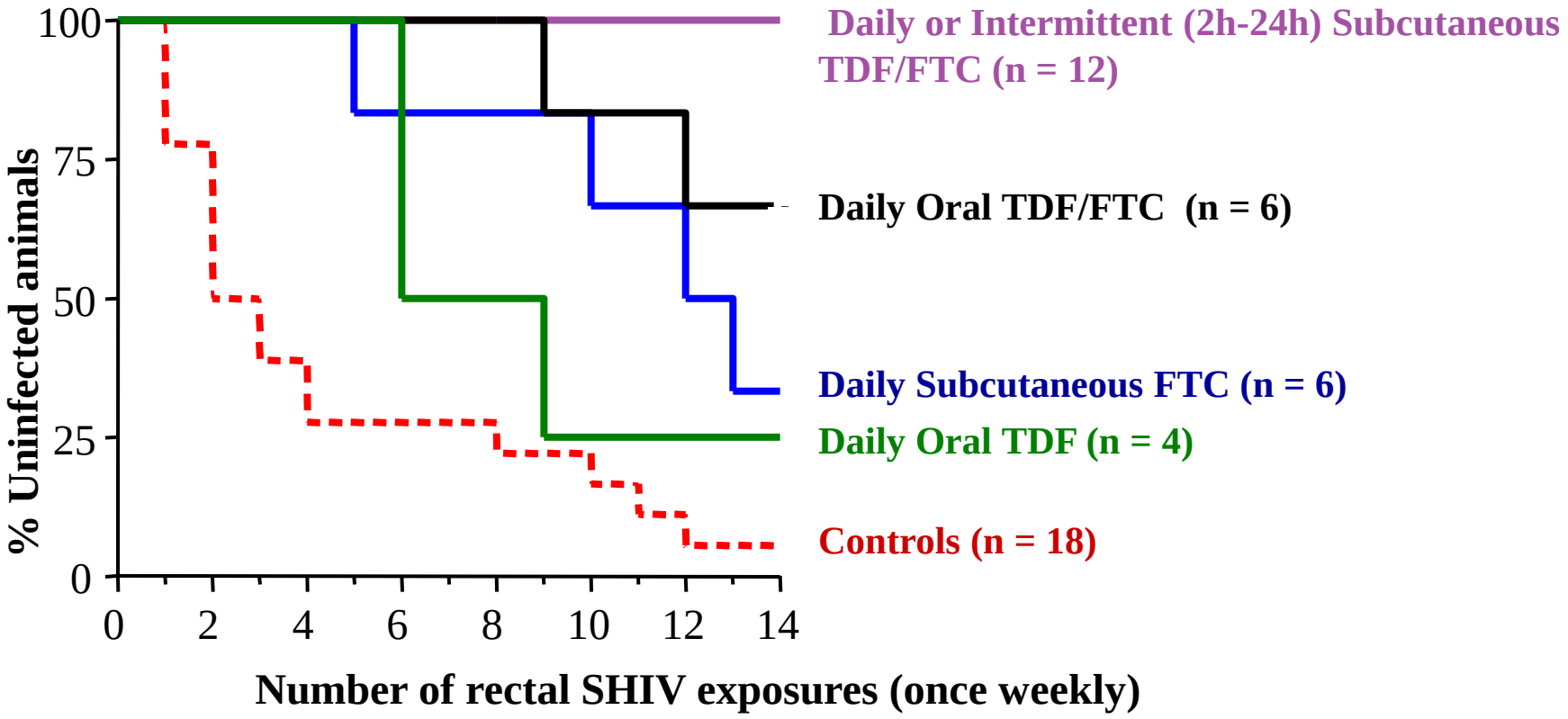
- Will the use of antiretroviral drugs before sexual exposure prevent HIV acquisition ?
- The success of the prevention of mother to child transmission of HIV : < 1% in France
- Antibiotic prophylaxis to prevent surgical site infections
- Prevention of Malaria:
  - Mosquito-nets and repellents
  - Anti-malarial drugs: before exposure, during exposure and after the end of exposition
- In vitro efficacy in tissue culture and animal data

Prevention of Vaginal Transmission of SHIV in Macaques using TDF or TDF/FTC gel

Full protection with 1 % TDF gel with/without FTC
30 mn before vaginal inoculation

Parikh UM J Virol. 2009 83:10358-65.

Prevention of Rectal Transmission of SHIV using Daily TDF or TDF/FTC



Garcia-Lerma , PLoS Medicine 2008

Results of Human PrEP Trials

- Six efficacy trials
  - Caprisa 004 trial in South African women (KwaZulu-Natal)
  - iPrex trial in MSM in the Americas, Thailand and South Africa
  - Fem-PrEP in women in Sub-Saharan Africa
  - Partners Prep in men and women in Kenya and Uganda
  - TDF-2 in men and women in Botswana
- All treatment strategies assessed TDF or TDF/FTC vs PCB
- No study in Europe…

CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

CAPRISA 004

Effectiveness & safety of vaginal microbicide 1% tenofovir gel for prevention of HIV infection in women

Quarraisha & Salim S Abdool Karim

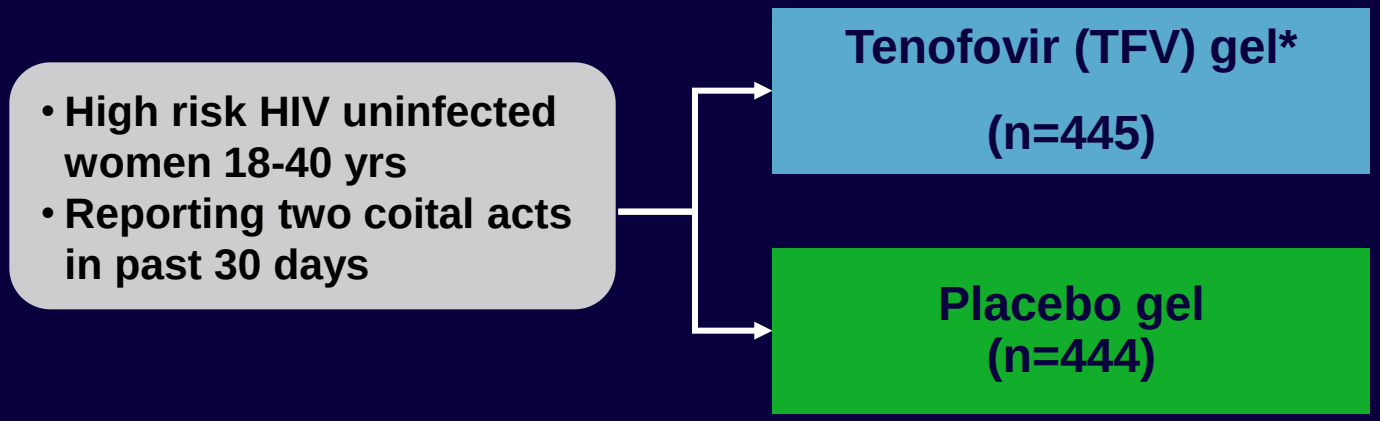
on behalf of the

CAPRISA 004 Trial Group

CAPRISA 004

Study Design

Proof of concept double-blinded, randomized, placebo-controlled trial



2160 screened to enroll 1085 (prevalence of HIV-infection : 24%)

Mean age 24 years, 30% always used a condom

Primary endpoint: HIV infection

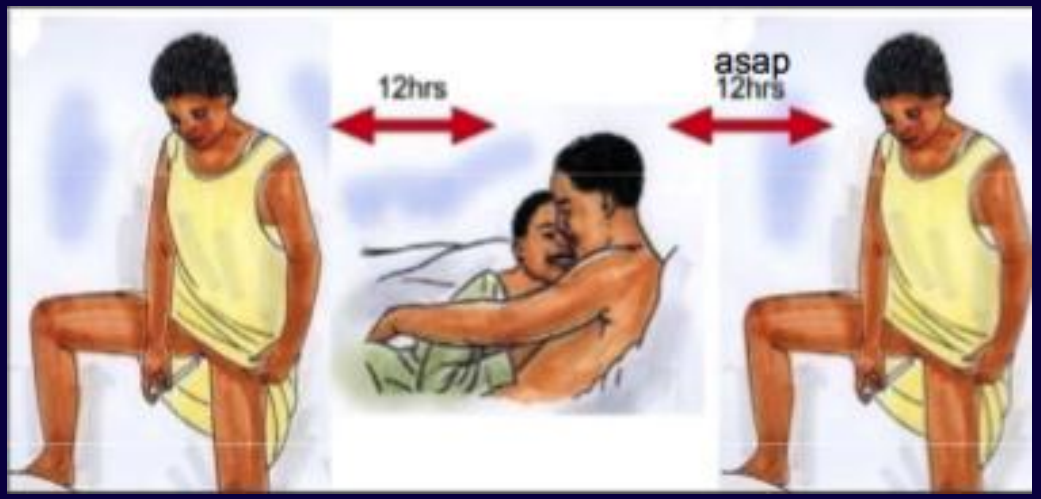
Endpoint driven trial : participants followed until 92 HIV infections

Median follow-up : 18 months

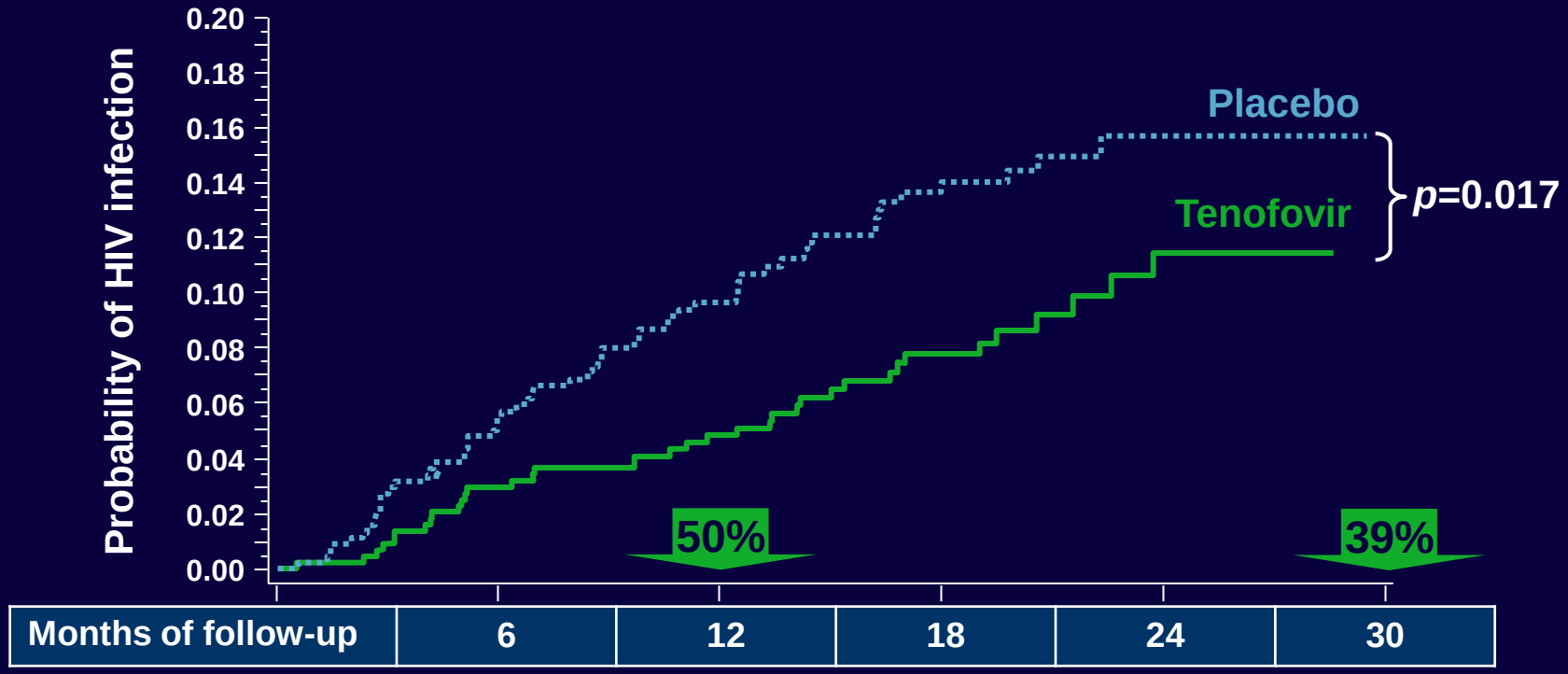
Abdool Karim Q, et al. Sciencexpress July 19, 2010.

CAPRISA 004 Assessed the Safety and Effectiveness of 1% Tenofovir Gel

- BAT 24 coitally-related gel use
  - Insert 1 gel up to 12 hours Before sex,
  - insert 1 gel as soon as possible within 12 hours After sex,
  - no more than Two doses in 24 hours



CAPRISA 004: HIV Infection Rates in the Tenofovir and Placebo Gel Groups

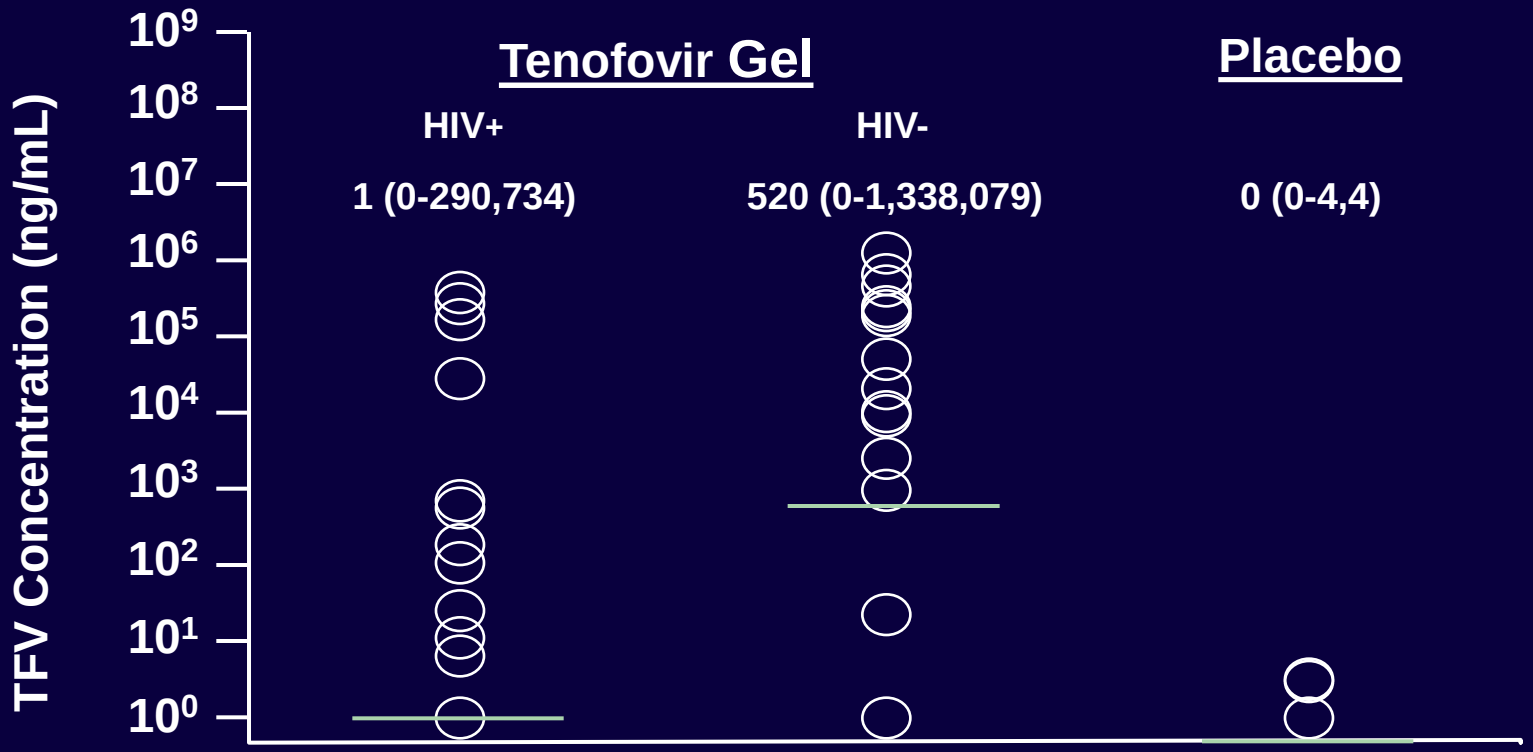


Gel Adherence	Effect
>80%	54%
50-80%	38%
<50%	28%

39% protection (CI: 6%-60%)
38 vs 60 HIV-infections : 22 avoided
80% reported using condoms

Abdool Karim Q, et al. Sciencexpress July 19, 2010.

CAPRISA 004: TDF Cervicovaginal Fluid Concentrations



	Tenofovir Gel HIV+	Tenofovir Gel HIV-	Placebo
Proportion with Detectable Concentrations	45%	96%	7%
Time post reported gel use (days)	4.5 (1-24)	4.5 (2-28)	6 (1-34)

Kashuba A, et al. 18th IAC; Vienna, July 18-23, 2010 Abst. TUSS0503.

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., 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*

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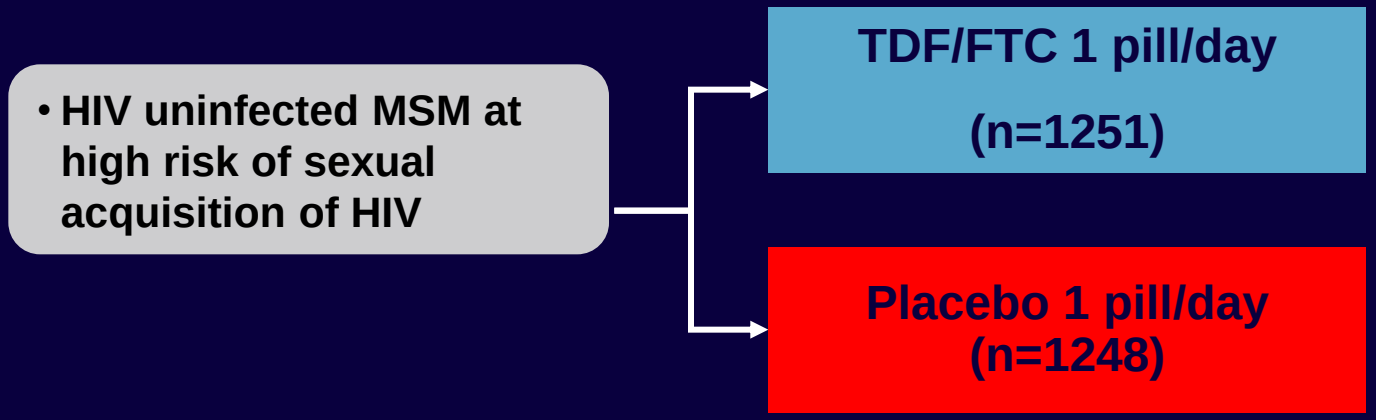
iPREX
Study Design

Proof of concept double-blinded, randomized, placebo-controlled trial



- High risk defined as having in the 6 months prior to screening : anal sex with > 4 partners, STI, transactional sex, condomless anal sex (HIV prevalence at screening : 8%)
- Events driven trial : 85 events yield a power of 80% to reject the null hypothesis of efficacy of < 30% if the true efficacy is > 60%
- Rapid HIV testing at every 4 weeks visit, with drug dispensation and adherence counseling

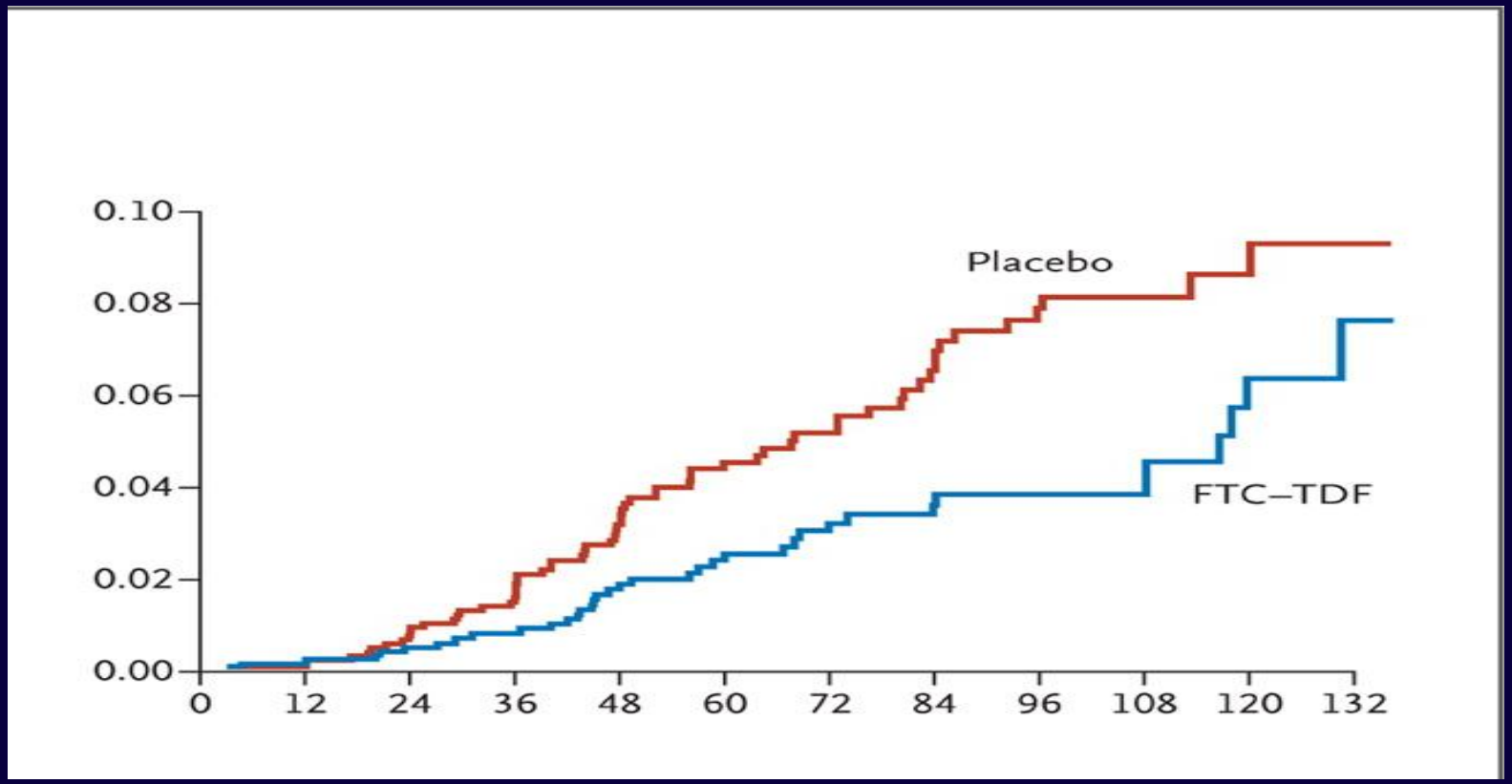
Grant RM et al N Engl J Med, Nov 23, 2010.

iPREX
Baseline Characteristics

- 50% of participants were < 25 years
- 54% had ≥ 5 alcoholic drinks per day
- 73% enrolled in South America (Peru, Ecuador, Brazil)
- Median number of partners in last 12 weeks : 18
- 60% had unprotected receptive anal intercourse in past 12 weeks
- 41% had transactional sex in past 6 months

Grant RM et al N Engl J Med, Nov 23, 2010.

iPREX : KM Estimates of Time to HIV Infection (mITT Population)



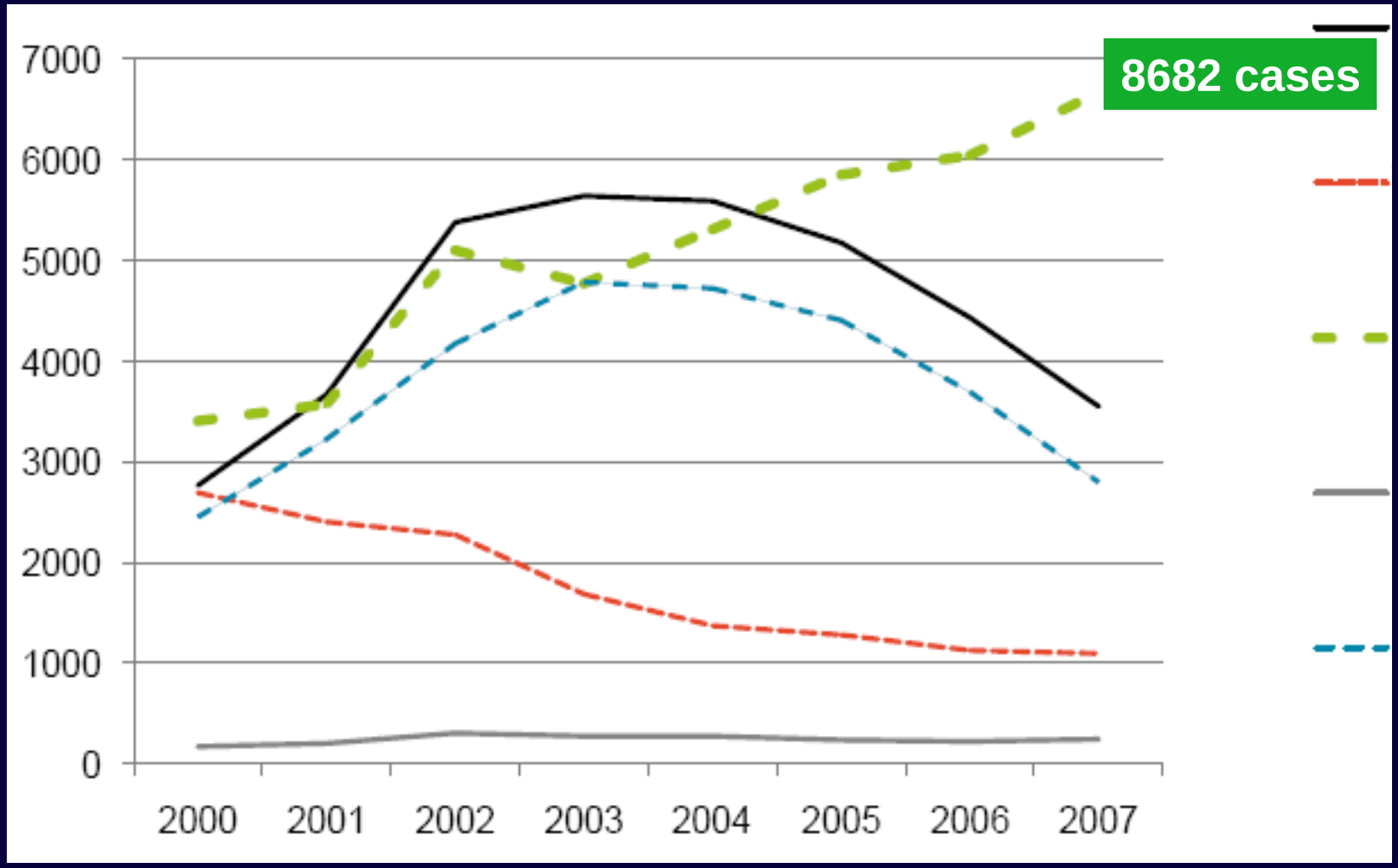
After a median follow-up of 14 months, 100 subjects became infected, 36 in the TDF/FTC arm and 64 in the placebo arm :

44% reduction in the incidence of HIV (95% CI : 15-63, p=0.005)

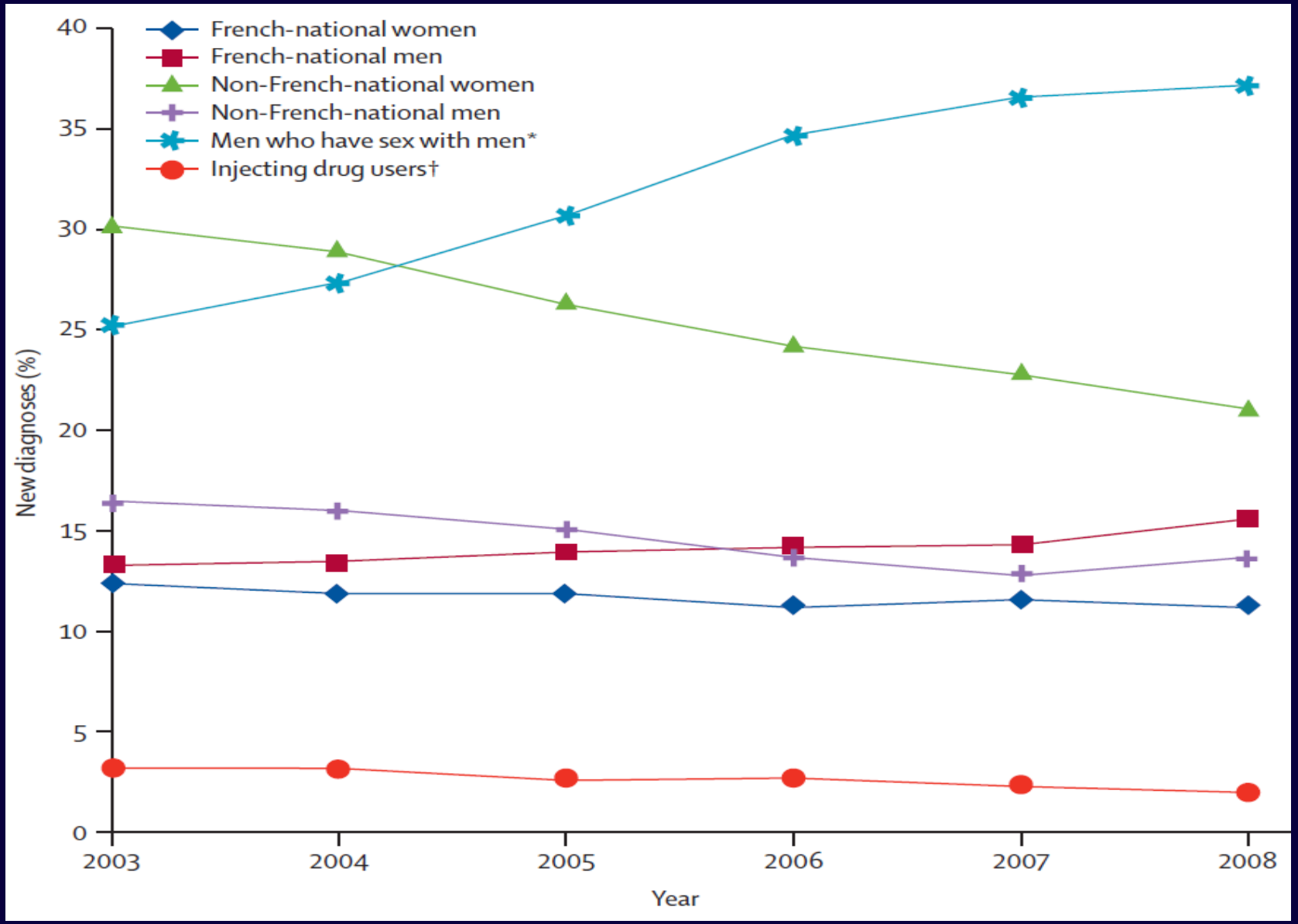
Update at CROI 2011 : 42% at 144 weeks

Grant RM et al N Engl J Med, Nov 23, 2010.

Increase in the Number of New Diagnoses of HIV-infections in MSM in Europe (2000-2007)



New HIV Diagnoses in France (2003-8)



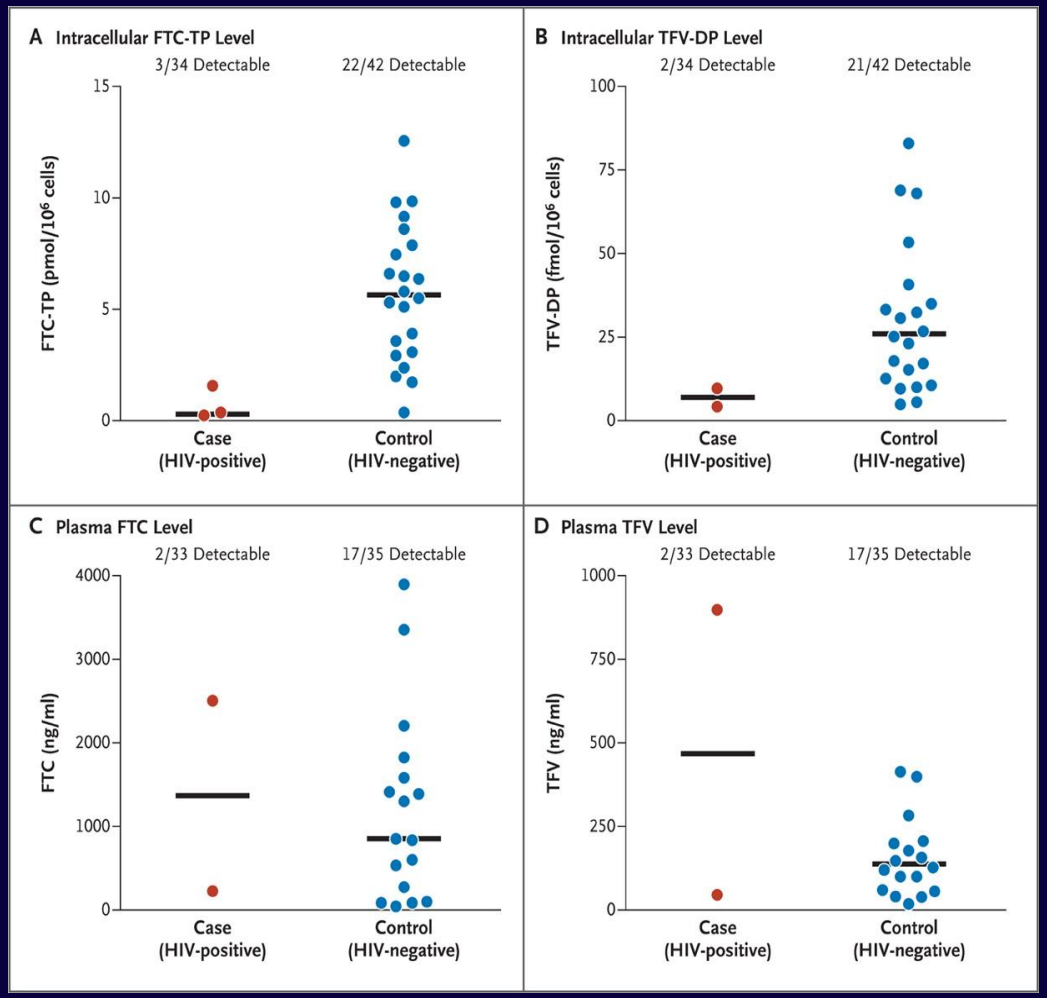
Le Vu S et al, Lancet Infect Dis 2010

Inconsistency of Prep Results

- Iprex : 44% reduction in the incidence of HIV (95% CI : 15-63) after a median follow-up of 14 months, and 42% afer 144 weeks
- Failure to reach the primary endpoint : trial was designed to exclude a strategy with < 30% of protection
- 5 trials using oral Prep have reported results : 2/5 could not show a benefit
- Oral TDF and TDF/FTC failed to prevent HIV-infection in heterosexual women in Sub-Saharan Africa (VOICE, Fem-Prep)
- Oral TDF and TDF/FTC prevented new HIV-infections in heterosexual individuals (TDF-2 : 62.6%) and discordant couples (Partners Prep : 75% TDF/FTC and 67% TDF)
- Will efficacy be better/worse outside placebo-controlled trials ?
- Efficacy of Prep could be different from its effectiveness
- Open-label extension if Iprex (Iprex-OLE) could answer this question

Is a high level of adherence required with daily Prep achievable ?

Iprex : Levels of Study-Drugs in Blood of Subjects Receiving TDF/FTC



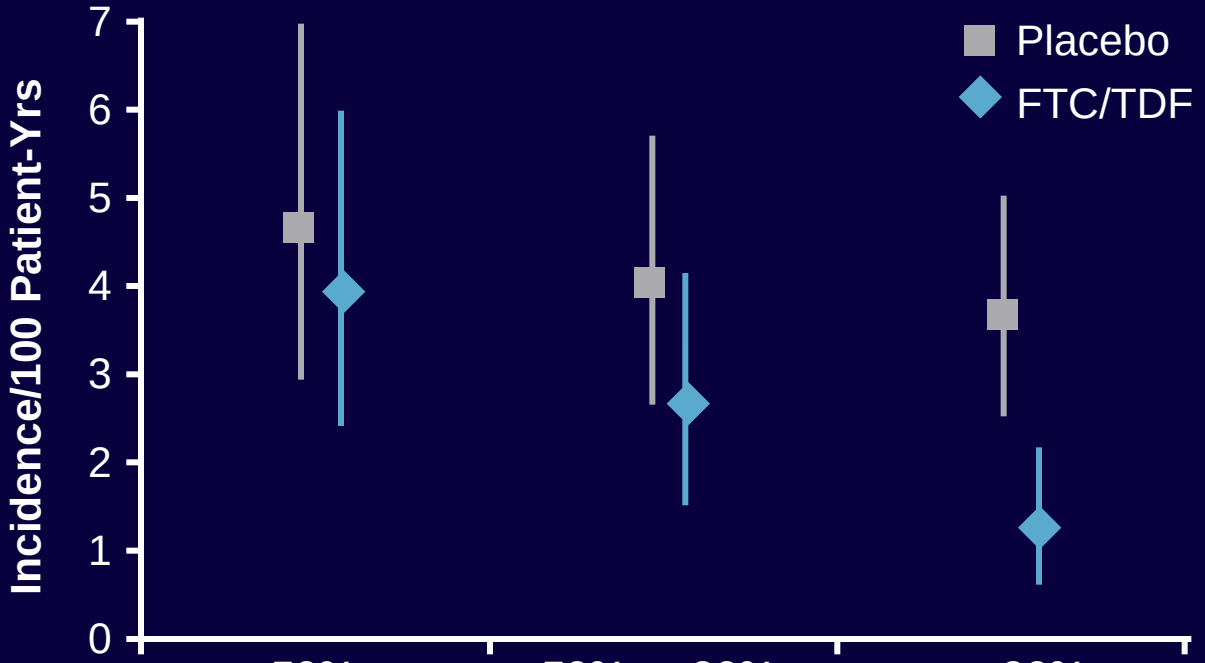
- The study drug was detected in 22/43 (51%) of seronegative subjects and 3/34 (9%) of HIV-infected subjects
- In the TDF/FTC group among those with detectable level, odds of HIV lower by a factor 12.9, corresponding to a relative protection of 92%
- Detectable levels strongly correlated with prophylactic effect

TDF/FTC Limit of detection in plasma : 10 ng/ml

Grant RM et al. N Engl J Med 2010.

iPrEx: Recorded Adherence and Efficacy

Recorded Adherence (Pill Use) and Efficacy



	< 50%	50% to 90%	> 90%
Efficacy	**16%**	**34%**	**68%**
95% CI	-54% to 54%	-20% to 64%	36% to 84%

Grant R, et al. CROI 2011. Abstract 92

Adherence in Other Prep Trials ?

- Highest levels of adherence (97% doses taken, 82% with drugs detectable) achieved in Partners Prep with higher efficacy (75% for TDF/FTC and 67% for TDF - > 44%)
- Targeted population might be critical: discordant couples face dilemma of avoiding infection but preserving the relationship: Prep can be seen as a solution (Ware et al, JAIDS in press)
- In other studies adherence to daily Prep was low, probably because the strategy is not convenient, especially for long-term use
- Will adherence improve in open label studies with the knowledge of Prep efficacy ?
- Can other Prep regimens be associated with better adherence and therefore better efficacy ?

The major concern in regard to PrEP is:

1. Development of drug resistance by people who become infected while on PrEP

2. PrEP being taken by people who are infected but don’t know it

The occurrence of drug resistance to either FTC (M184I/V) or TDF (K65R) does not appear to be a problem in all the studies conducted until now.

Additional point:

It is an advantage that all of the drugs being considered in PrEP are approved by regulatory agencies and have well-described and manageable toxicity profiles.

Final thought: PrEP should not re-allocate resources from people who need treatment to people who are not infected. We must prioritize both of these groups in our society.

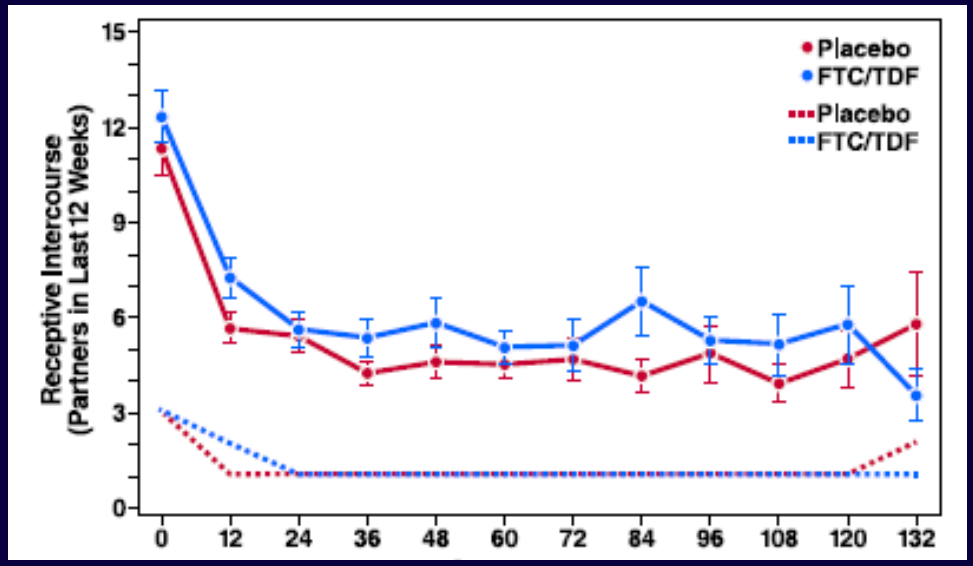
NRTI resistance in Oral Prep Trials

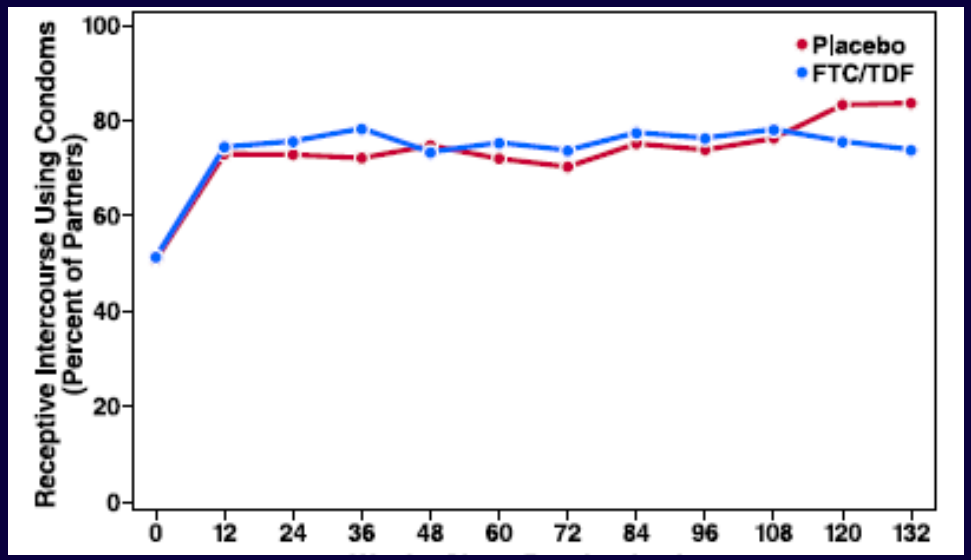
- Iprex: no emerging resistance but lack of resistance may be underestimated (0/36 :higher bound 95%CI : 9.5%)
- Iprex: the two patients already infected at baseline and who started daily Prep developed 3TC resistance (M184I/V)
- Partners Prep : 2/8 already infected at baseline developed K65R (1) and M184V (1) and TDF-2 : one participant with acute infection at BL developed K65R + M184V + A62V
- Fem-Prep : 4/35 acquired M184V/I resistance in TDF/FTC arm
- Critical to exclude acute infection before starting Prep
  - Frequency of HIV testing : monthly (in real world ?)
  - Type of assay used to detect infection : Rapid tests, serologic assays, combined assays (Ab- Ag), RNA assays ?
- Unknown consequences of spread of resistant viruses

Is there a risk of change in behavior that could off-set the benefit of Prep ?

iPREX

Sexual Practices





- Sexual practices were similar in the two groups at all time points
- Number of partners with receptive anal intercourse decreased
- Percentage of partners using a condom increased
- More than 500 cases of syphilis in each arm: 40% incidence !

Grant RM et al N Engl J Med, Nov 23, 2010.

Is Oral Prep safe enough ?

iPREX: Adverse Events

Adverse Event	FTC–TDF (N=1251)		Placebo (N=1248)		P Value†
	no. of patients (%)	*no. of events*	*no. of patients (%)*	*no. of events*	
Any adverse event	867 (69)	2630	877 (70)	2611	0.50
Any serious adverse event	60 (5)	76	67 (5)	87	0.57
Any grade 3 or 4 event	151 (12)	248	164 (13)	285	0.51
Grade 3 event	110 (9)	197	117 (9)	225	0.65
Grade 4 event	41 (3)	51	47 (4)	60	0.57
Elevated creatinine level	25 (2)	28	14 (1)	15	0.08
Headache	56 (4)	66	41 (3)	55	0.10
Depression	43 (3)	46	62 (5)	63	0.07
Nausea	20 (2)	22	9 (<1)	10	0.04
Unintentional weight loss (≥5%)	27 (2)	34	14 (1)	19	0.04
Diarrhea	46 (4)	49	56 (4)	61	0.36
Bone fracture	15 (1)	16	11 (<1)	12	0.41
Death	1 (<1)‡	1	4 (<1)	4	0.18
Discontinuation of study drug					
Permanently	25 (2)	26	27 (2)	33	0.82
Permanently or temporarily	79 (6)	99	72 (6)	92	0.49

10 subjects (7 TDF/FTC and 3 placebo discontinued stuy drugs because of creatinine elevations). All elevations resolved after study drug discontinuation.

Grant RM et al. N Engl J Med 2010

Safety of TDF or TDF/FTC in other Trials

- Evidence for safety must be particularly strong for healthy persons
- Nausea (p=0.04) and vomiting (p<0.001) more frequent in the TDF/FTC arm in Fem-Prep
- Elevated ALT more frequent in the TDF/FTC arm (p=0.03), but no difference in grade 3+ in Fem-Prep
- No difference in creatinine and phosphorous in Partners Prep
- Safety assessments could have been biased due to low adherence
- Data are lacking in some groups (adolescents, pregnant women)
- Unknown safety beyond 1-3 years of use

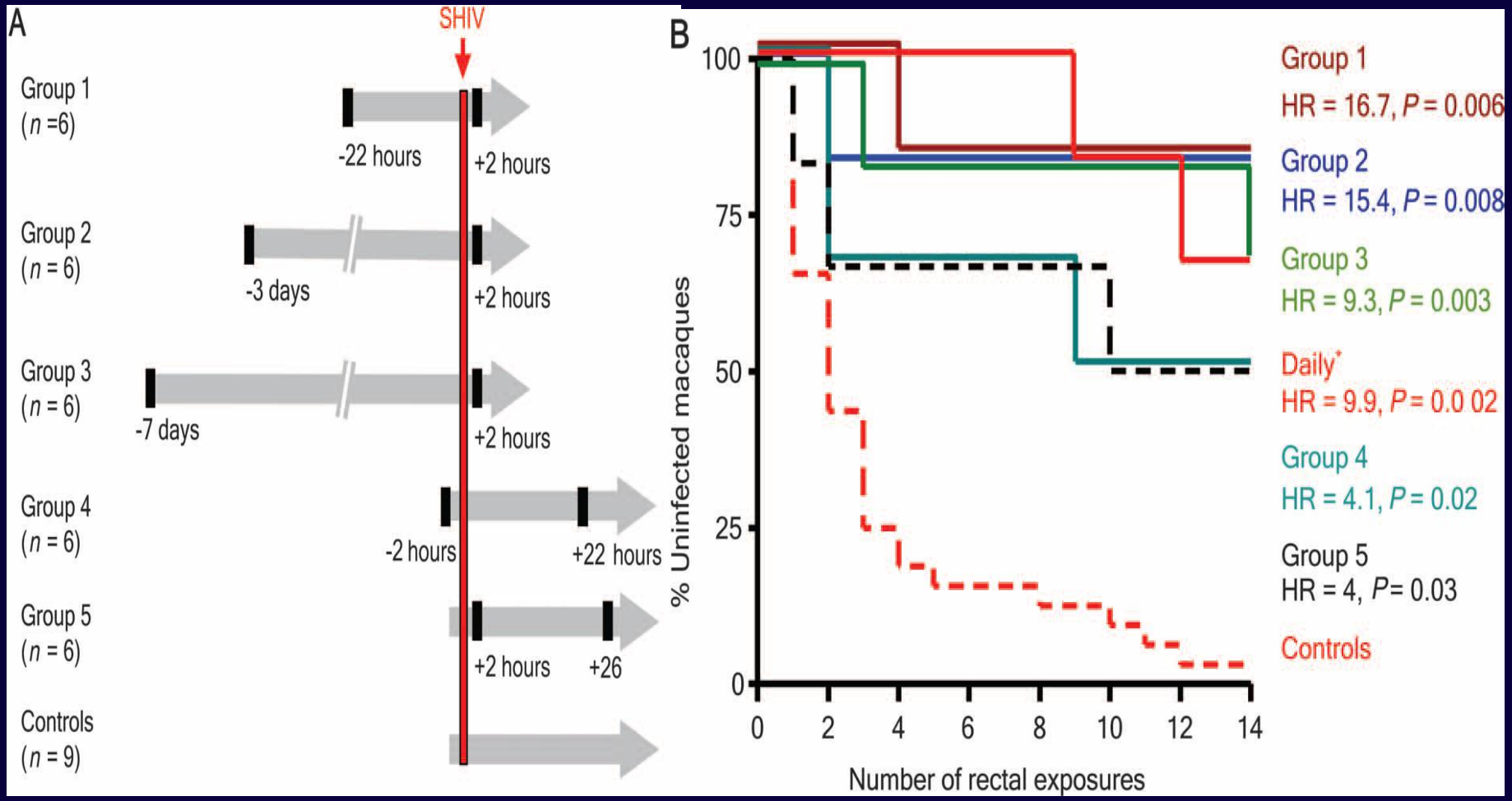
Cost-Effectiveness Analyses

- Iprex : Need to treat 44 subjects during one year to prevent 1 HIV-infection
- Cost of 44 years of TDF/FTC would not be so different from 44 years of TDF/FTC/EFV in a 30-year old MSM who will become infected despite Prep
- Take 1 pill a day to prevent the use of 1 pill a day….
- Who will pay for Prep ?
- 3 major factors to assess cost-effectiveness
  - Incidence of HIV-infection in the targeted population
  - Level of effectiveness
  - Cost of antiretroviral drugs

Interest in Intermittent PrEP

- Data from animal models support this strategy
- A more convenient treatment strategy to assess
- Better adherence to this type of strategy is likely with a potentially better efficacy/safety ratio
- Intermittent use of TDF gel was effective in Caprisa 004 whereas daily TDF gel was ineffective in VOICE
- Could be more cost-effective
- Sexual activity is not permanent, and is usually concentrated during week-ends and pre-planned

Efficacy of Intermittent Oral Truvada in the SHIV/Macaque model



IPERGAY
Study Design

Proof of concept of "on demand" Prep

Randomized placebo-controlled trial

- High risk MSM
- Condomless anal sex with ≥ 2 partners

→ **Full prevention services* TDF/FTC before and after sex (n=950)**

→ **Full prevention services* placebo before and after sex (n=950)**

- *Counseling, testing for STI, condoms, HBV and HAV vaccination, PEP
- Primary endpoint : HIV infection, 64 events expected
- Incidence of HIV-infection: 3% / yr in the control arm, assessing a 50% efficacy of Prep and a two-year follow-up : need to enroll ~ 2000 individuals

Why Such a Trial ?

- A single trial with modest efficacy in MSM is unlikely to be sufficient to gain approval for TDF/FTC use for PrEP in Europe
- A trial comparing daily to intermittent PrEP
  - Seems unrealistic since 20.000 participants required
  - Could lead to behavioral changes
  - Results difficult to interpret in an open-label design
- A placebo-controlled trial seems the “best” way to assess intermittent PrEP
- 2,000 participants is an achievable goal
- Participants will not know if they are receiving an active drug and there will therefore be less risk of disinhibition / pill sharing than in an open-label trial

ART to Prevent Sexual Transmission of HIV

- Post-exposure Prophylaxis (PEP)???
- Pre-exposure prophylaxis (PrEP) ????
- Treatment of the infected person ???

Treatment as Prevention
"The Four Questions"

1) Do ART drugs prevent HIV transmission?

2) What do we tell infected people?

3) Can we reduce population HIV incidence ?

4) Barriers to "Treatment as Prevention"?

HPTN 052 Study Design

Stable, healthy, serodiscordant couples, sexually active
CD4 count: 350 to 550 cells/mm^3

Primary Transmission Endpoint

Virally linked transmission events

Primary Clinical Endpoint

WHO stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death

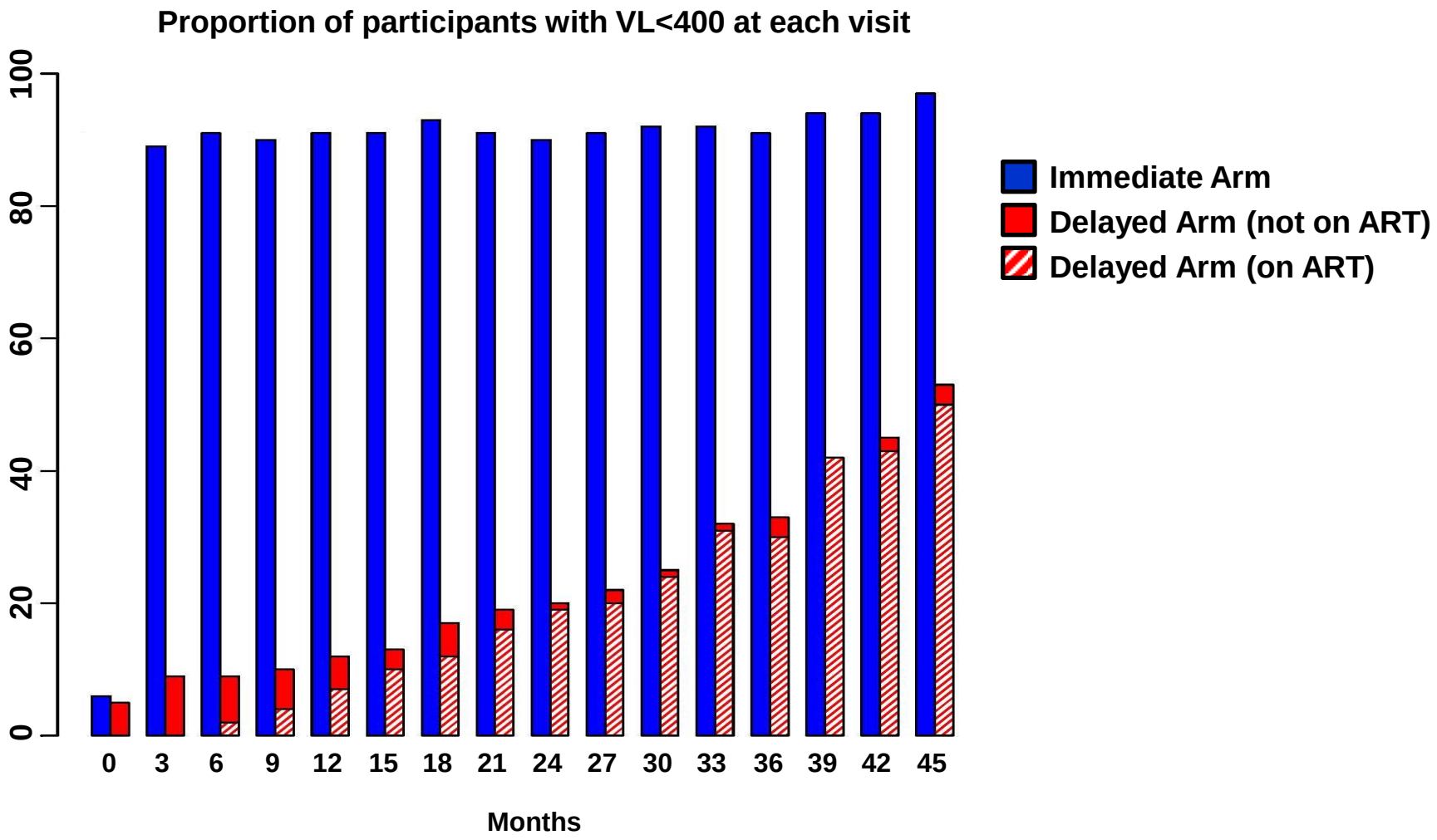
96%

Results of the HPTN052 trial announced on 12 May 2011 show that if an HIV-positive person adheres to an effective antiretroviral therapy regimen, the risk of transmitting the virus to their uninfected sexual

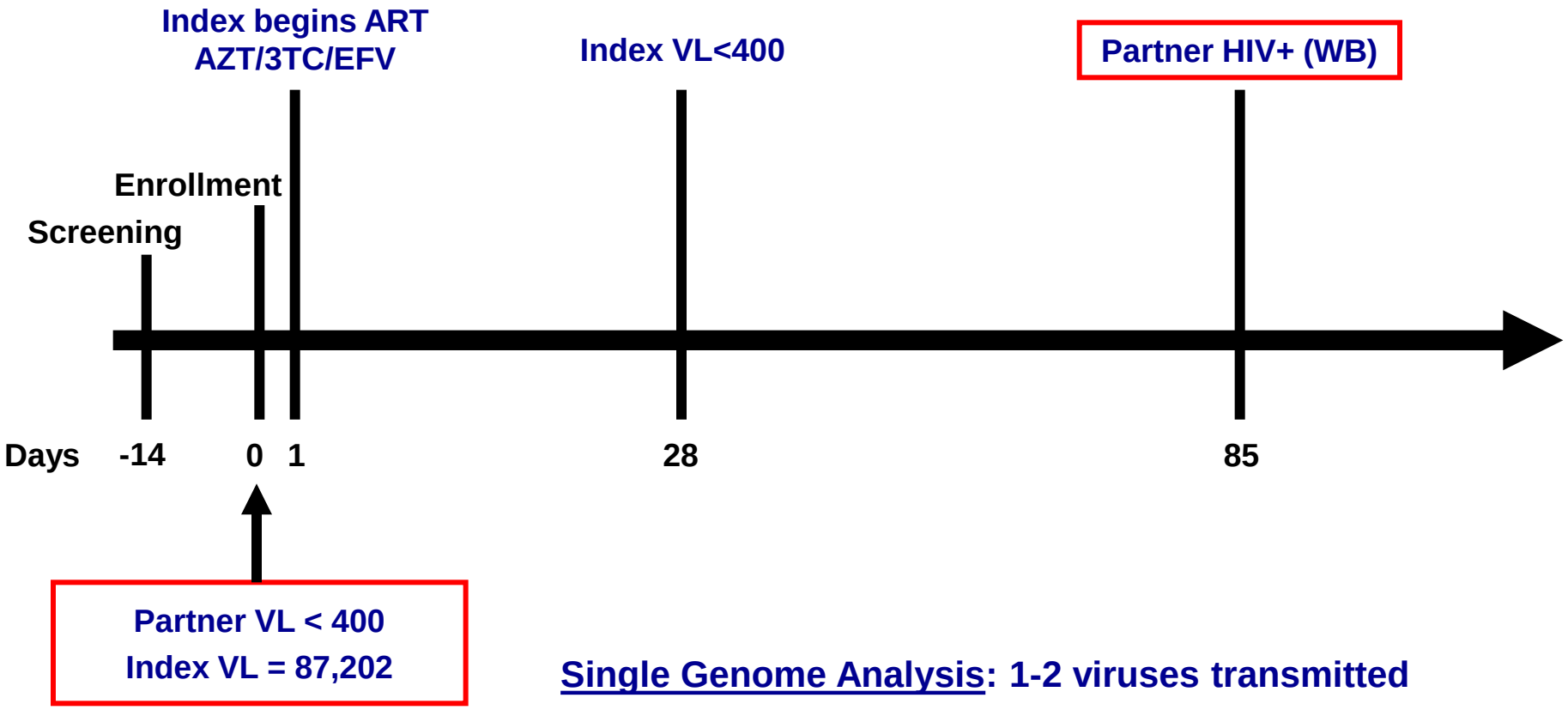
“Treatment for prevention is a game changer”.

Michel Sidibe
Executive Director of UNAIDS

HPTN 052: ADHERENCE MATTERS



One Transmission Event on ART



Single Genome Analysis: 1-2 viruses transmitted

Analysis of Transmission: >50 days earlier (84 – 190 days)

The Economist

HPTN 052: What's Happened Next

- All HIV infected subjects offered ART
- Continued follow-up in HPTN 052

-1682 index cases /1763 (96% retention)

-1502 discordant couples (85% retention)

-1561/1682 index cases are NOW on ART

DURABILITY OF PREVENTION?
DELAYED ART & CLINICAL OUTCOMES?

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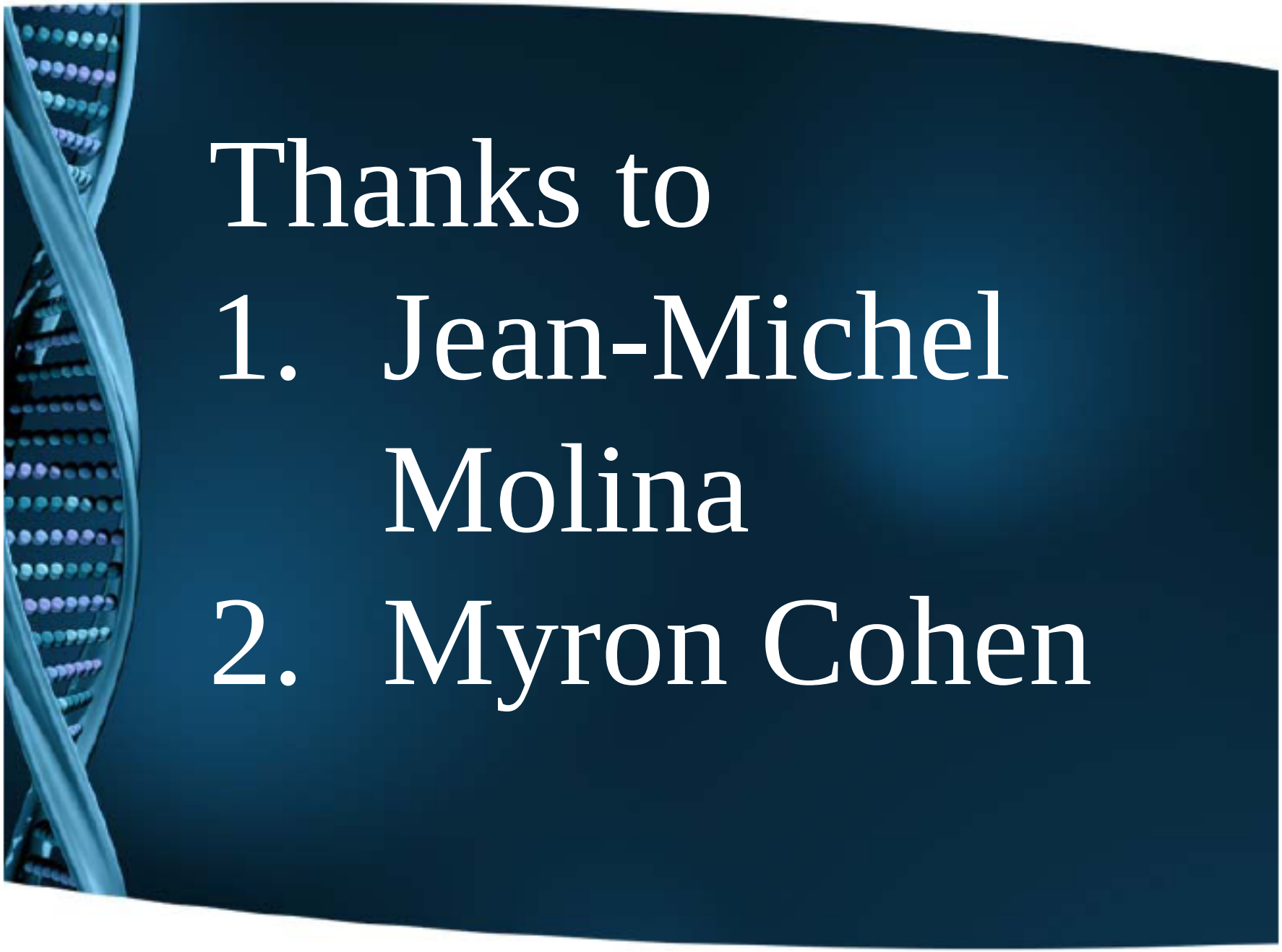
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