



**Sede y alojamiento**  
• Hotel Zenit Coruña.  
c/ Comandante Fontanes, 19.  
DP 15003 , A Coruña

## **VII CURSO AVANCES EN INFECCION VIH Y HEPATITIS VIRALES**

**A Coruña  
1 y 2  
de Febrero  
2013**

# Profilaxis Antiretroviral para la Prevención de la Infección VIH



- TAR precoz HIV + en pareja discordante
- Profilaxis pre exposición (PrEP)

# TAR precoz de la persona VIH en parejas “mixtas”

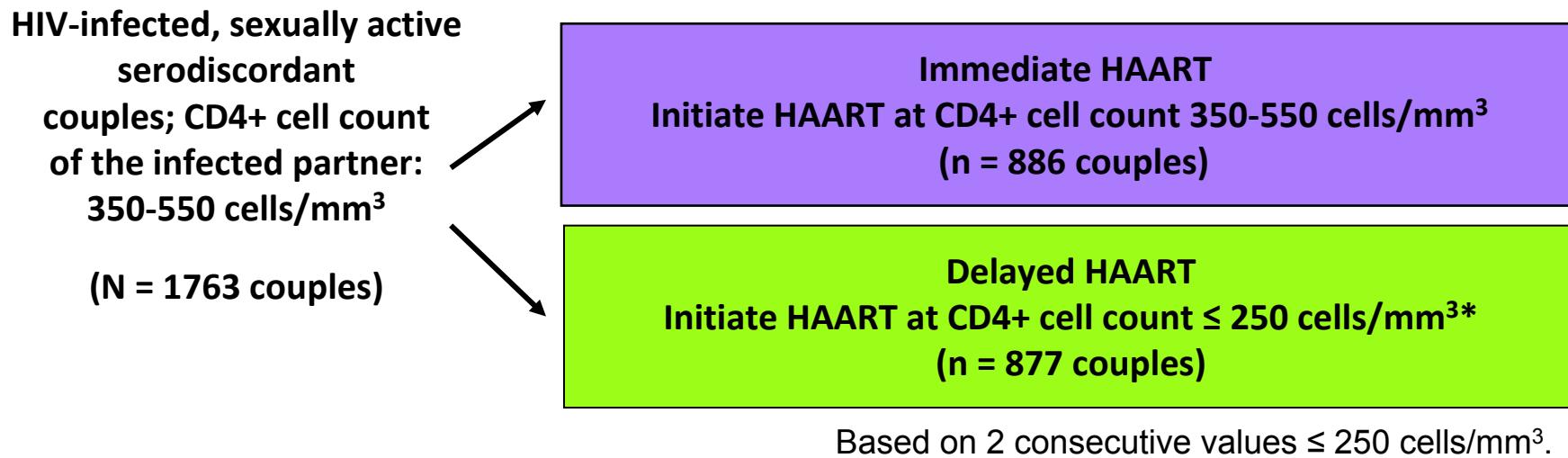


Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Estudio HPTN 052



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



- 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**

# HPTN 052 Study: Key Finding



1,763 sero-discordant couples (97% heterosexual)  
HIV infected partners: 890 men, 873 women

+ 39 HIV Transmissions

28 linked HIV  
transmissions

11 unlinked

Single transmission in patient in immediate HAART arm  
believed to have occurred close to time therapy  
began and prior to suppression of genital tract HIV

Immediate ART:  
1 transmission

Deferred ART:  
27 transmissions



96% Protection

## HPTN 052: What Happened Next

### NIH DSMB Nov 9, 2012

- All HIV infected subjects offered ART
  - 1682 index cases/1763 (96% retention)
  - 1502 discordant couples (85% retention)
  - 1561/1682 index cases are NOW on ART

DURABILITY OF PREVENTION?  
ADVERSE EVENTS?  
DELAYED ART & CLINICAL OUTCOMES

# What Do These Results Mean for Others?

Likely that ART prevents transmission in others, although

- Only 2 couples HPTN 052
- Other routes of transmission and clades
  - needles, anal intercourse
  - HIV subtypes
  - may have different transmission biology
- No protection for mixed clade partnerships
  - 28% of infections





Guidelines for the Use of Antiretroviral Agents in  
HIV-1-Infected Adults and Adolescents



JAMA®  
Online article and related content  
current as of September 6, 2010.

Antiretroviral Tr  
Recommendatio  
Society USA Pa  
Melanie A. Thompson  
JAMA. 2010;304(3):321-3



- Effective ART also has been shown to prevent transmission of HIV from an infected individual to a susceptible partner.

## TODAS LAS DIRETRICES CONSIDERAN LA DISCORDANCIA SEROLOGICA

### RAZON “SUFICIENTE” PARA INICIO DE TAR

sintomaticos la cifra de linfocitos CD4, la CVP, la edad y las comorbilidades son los factores que determinan el inicio. Las estrategias terapéuticas deben ser individualizadas para conseguir en cualquier circunstancia el objetivo de CVP indetectable.

# PrEP-CONTROVERSIA



# PrEP Studies Published in The NEW ENGLAND JOURNAL of MEDICINE



## Partners PrEP



### Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women

J.M. Baeten, D. Donnell, P. Nsama, N.R. Maggi, J.D. Campbell, J. Wang, et al.

The use of antiretroviral medications to prevent the transmission of HIV type 1 (HIV-1) to reduce the spread of HIV-1. Antiretroviral treatment for persons infected with HIV-1 provides important clinical benefits and substantially

reduces the risk of transmission, data analysis, or manuscript preparation. All authors contributed to the completeness and accuracy of the data presented.

#### when submitted

From July 2006 through November 2009, we re-



## TDF2

### Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana

Michael C. Thigpen, M.D., Polokwane M. Kekwaletla, Ph.D., M.P.H., et al.

Homosexual transmission of human immunodeficiency virus (HIV) remains limited.<sup>1</sup> In animal models, preexposure prophylaxis with tenofovir disoproxil fumarate (TDF) or with the combination of TDF and emtricitabine (TDF-TDF) can prevent infections with HIV or inhibit transmis-

sion. For complete details of the study conduct, see the preprint, available with the full text of this article at NEJM.org.

**study and study design:** In 2009, the study investigators initiated the TDF1 study to evaluate the safety and efficacy of preex-

## FEM-PrEP



### Preexposure Prophylaxis for HIV Infection among African Women

Lut Van Damme, M.D., Amy Coates, Ph.D., Khanya Ahmed, M.Med., et al.

RECENT EFFORTS HAVE SHOWN THAT

participants attended clinic visits at the time of screening and enrollment and at 6-week intervals thereafter for up to 96 weeks (52 weeks of taking the study drug, followed by 4 weeks off the study drug).

**when submitted**

from December 2007 to January 2009.

## iPrEX:HSH

DECEMBER 30, 2010

VOL. 363 NO. 27

## Editorial

### Preexposure Prophylaxis for HIV — Where Do We Go from Here?

Marcus S. Cohen, M.D., and Lindsay R. Baden, M.D.

Transmission of the human immunodeficiency virus (HIV) continues at a staggering rate in many areas of the world. The rate of HIV acquisition in young, healthy adults (mostly women) was 2 to 6 per 1000 transmissions in most trials, and this

was found, yet the FEM-PrEP study was discontinued early because of a lack of promotion. Inconsistency in this area of study is not unique. Tenoviro gel used during intercourse by women in the Centre for the AIDS Programme of Re-

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

# Estudio iPrEXP

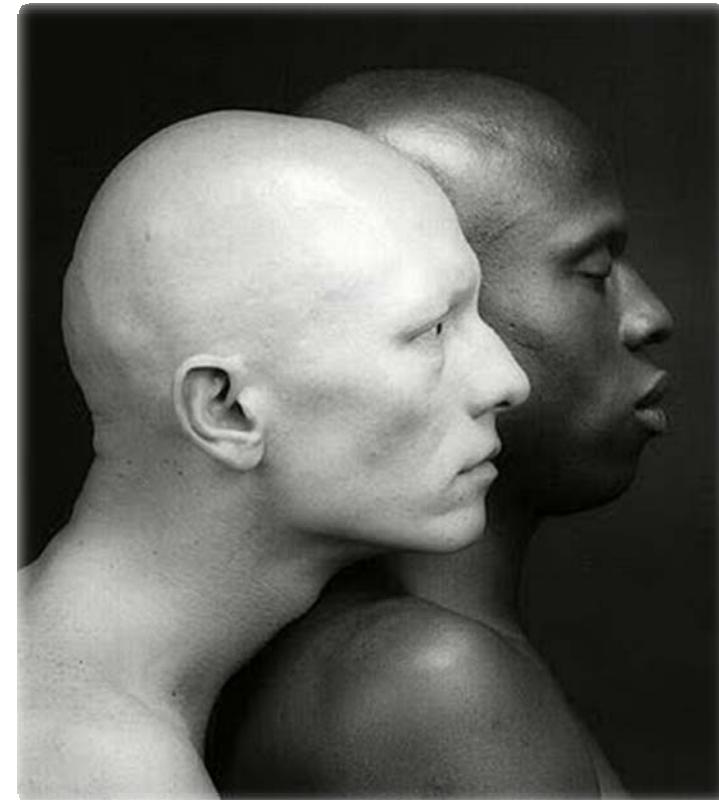


ESTABLISHED IN 1812

DECEMBER 30, 2010

VOL. 363 NO. 27

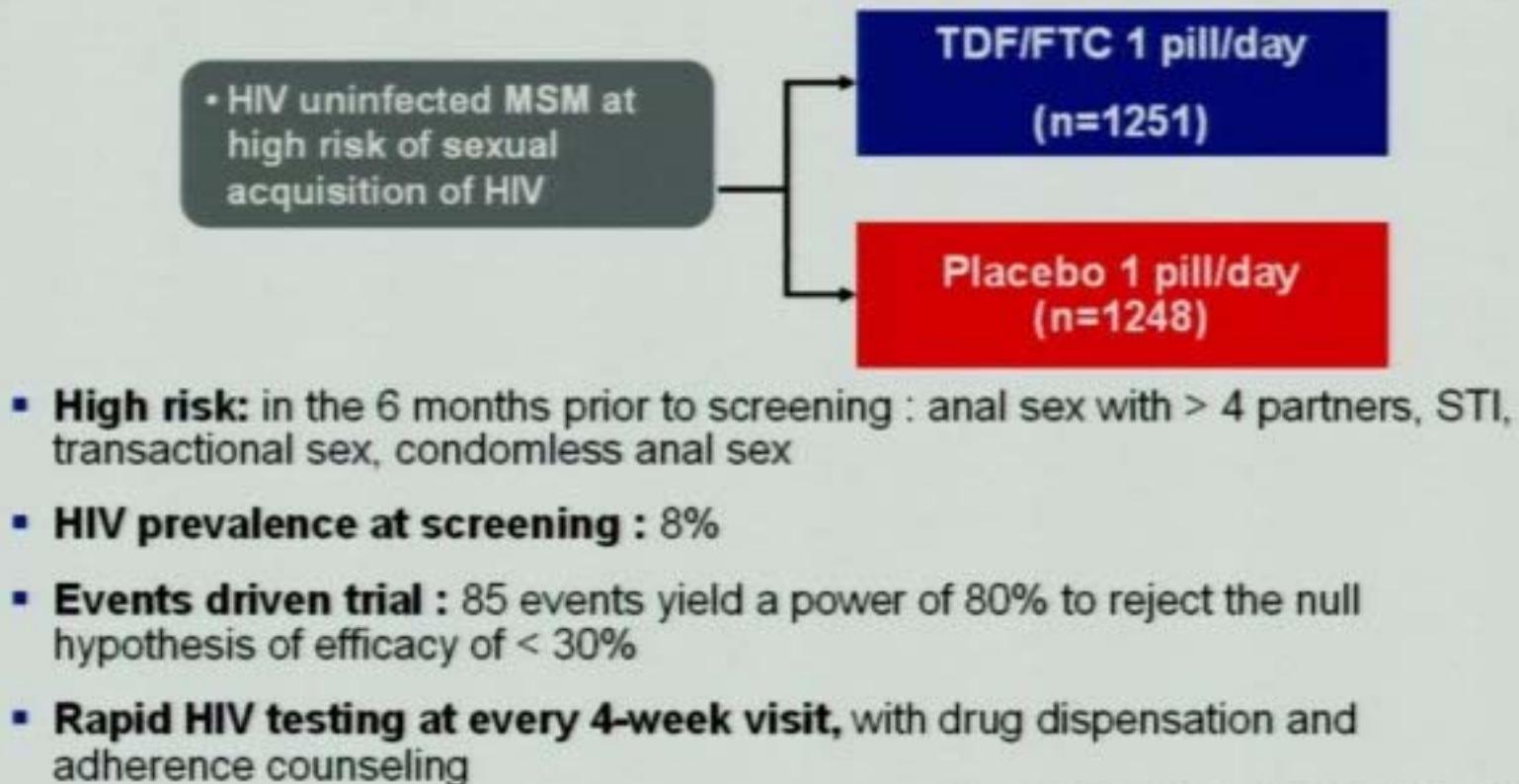
Preexposure Chemoprophylaxis for HIV Prevention  
in Men Who Have Sex with Men





# iPREX Study Design

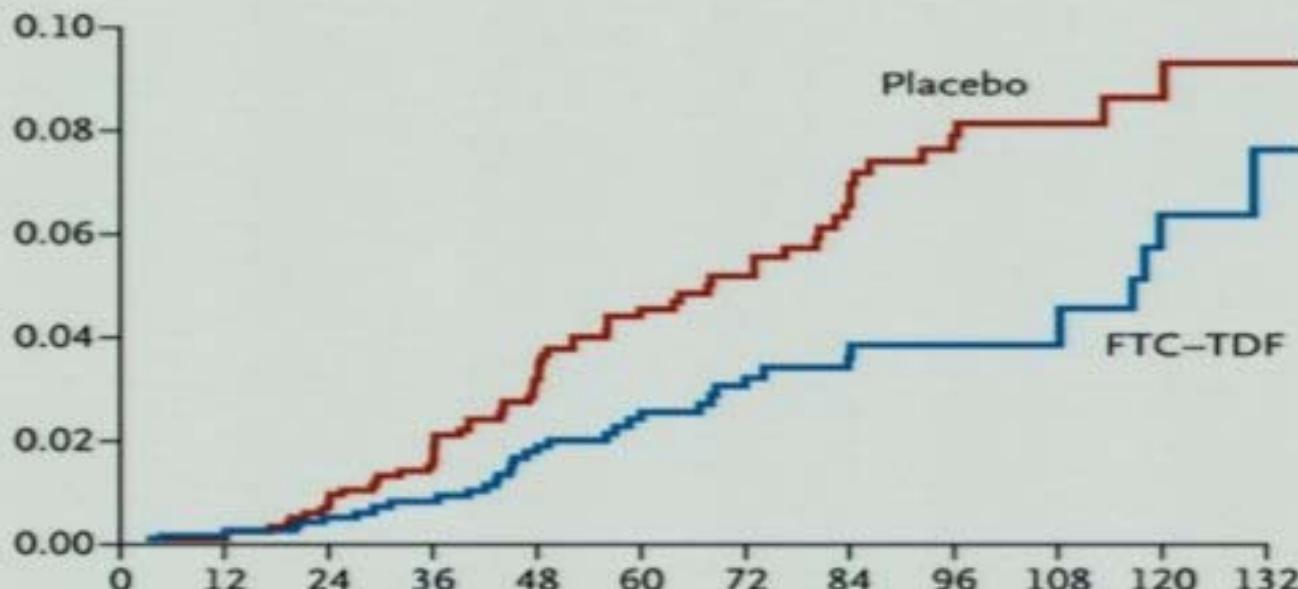
Double-blinded, randomized, placebo-controlled trial



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.

## Limitations of Current Data

- **Only ~ 10% of iPrEx population from the US**
  - Arguably, prevention benefit should not differ by geography
- **Long-term adherence and adherence at time of HIV exposure unknown** (in those who became infected)
- **Long-term health effects of TDF/FTC in HIV negative and HIV seroconverters unknown**
- **Adherence, risk behavior, PrEP interest likely to be different now that results are known compared with clinical trial population**

*The* NEW ENGLAND  
JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 2, 2012

VOL. 367 NO. 5

Antiretroviral Prophylaxis for HIV Prevention in Heterosexual  
Men and Women

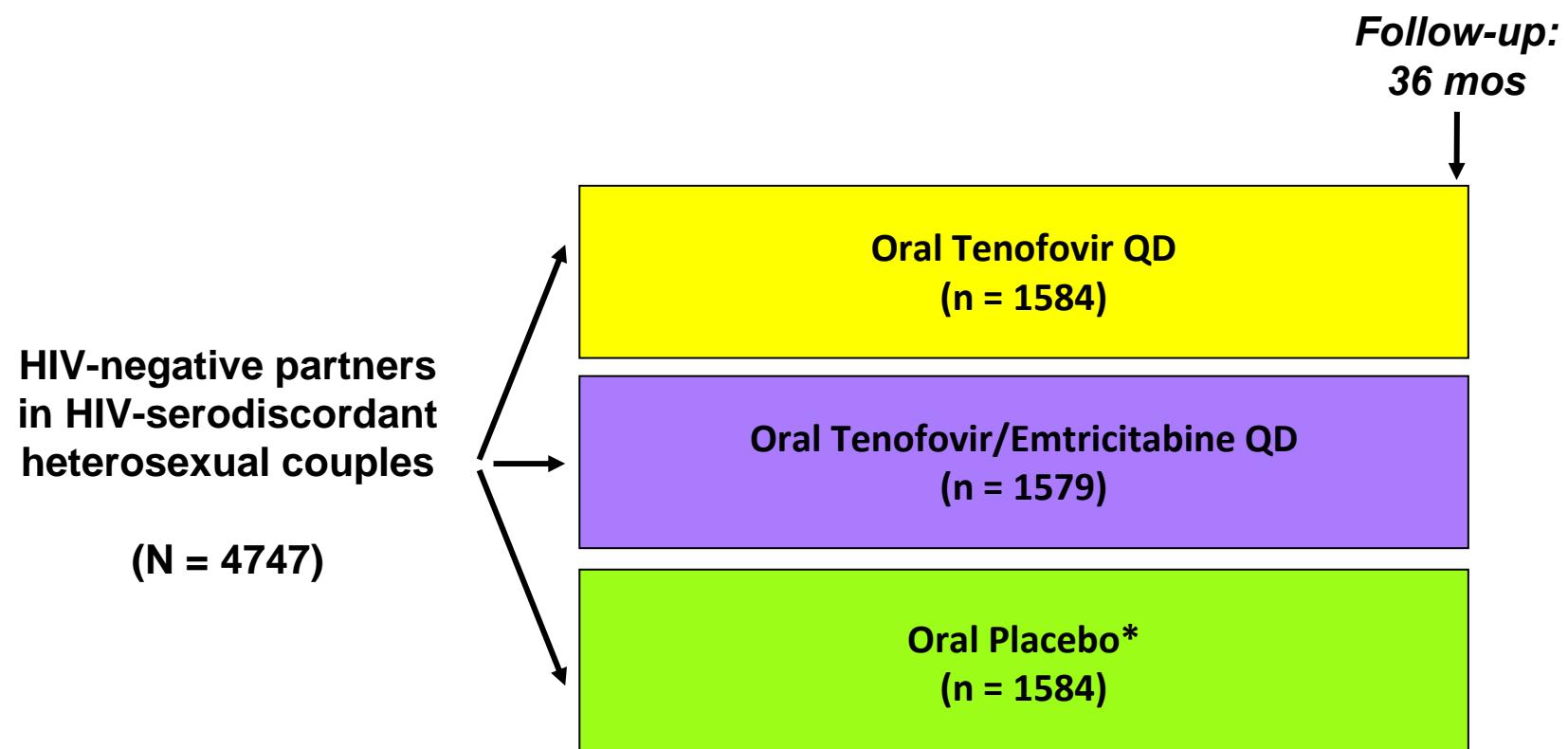
**ESTUDIOS:**  
**\*Partners PrEP**  
**\*TDF 2**

ORIGINAL ARTICLE

Antiretroviral Preexposure Prophylaxis for  
Heterosexual HIV Transmission in Botswana



# Partners PrEP: TDF vs TDF/FTC vs Placebo in HIV-Serodiscordant Couples



\*Placebo arm terminated early on July 10, 2011, by data and safety monitoring board.

Baeten JM, et al. N Engl J Med. 2012;[Epub ahead of print].



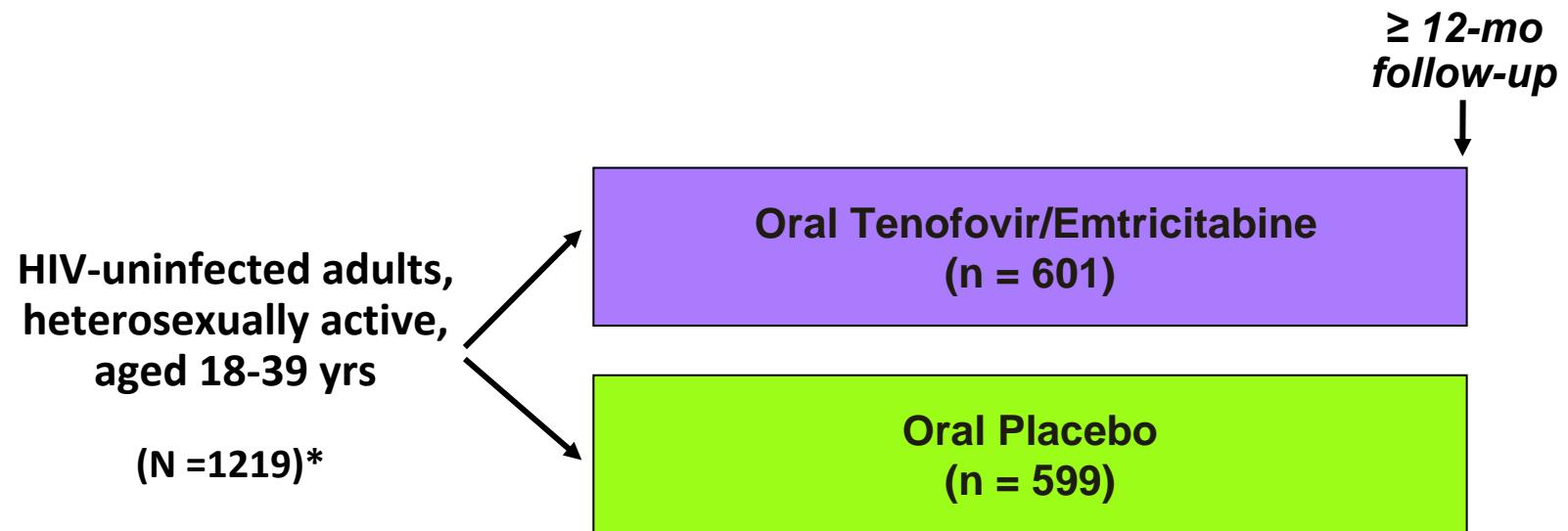
## Partners in PreP: K-M Estimates of HIV-1 Infections in the mITT analysis (4758 discordant couples)



No. at risk:	1572	1559	1547	1498	1350	1223	1062	902	735	510	287	108	15
TDF	1568	1557	1546	1493	1371	1248	1059	901	743	525	291	114	16
FTC/TDF	1568	1557	1544	1487	1347	1224	1061	902	744	523	295	120	18
Placebo													

Baeten et al., N Engl J Med 2012, 367: 411-22

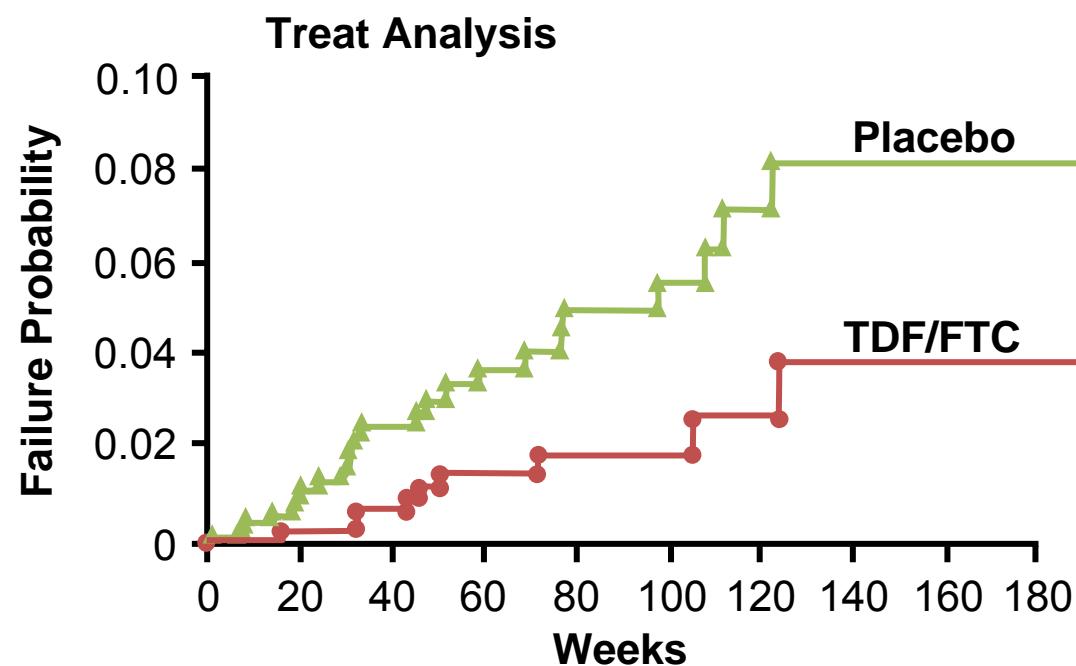
# TDF2: PrEP With TDF/FTC in HIV-Negative Heterosexuals in Botswana



\*n = 19 patients excluded for failure to start study medication or HIV infection.

# TDF2: PrEP With TDF/FTC Significantly Reduces HIV Acquisition

- 9 vs 24 patients seroconverted in TDF/FTC vs placebo arms, respectively
- Overall protective efficacy of TDF/FTC: 62.2% (95% CI: 21.5-83.4; P = 0.03)
- Reduction in HIV acquisition with TDF/FTC observed in both men and women  
*underpowered to demonstrate sex-based differences in outcomes*



Thigpen MC, et al N Engl J Med. 2012;[Epub ahead of print].

ORIGINAL ARTICLE

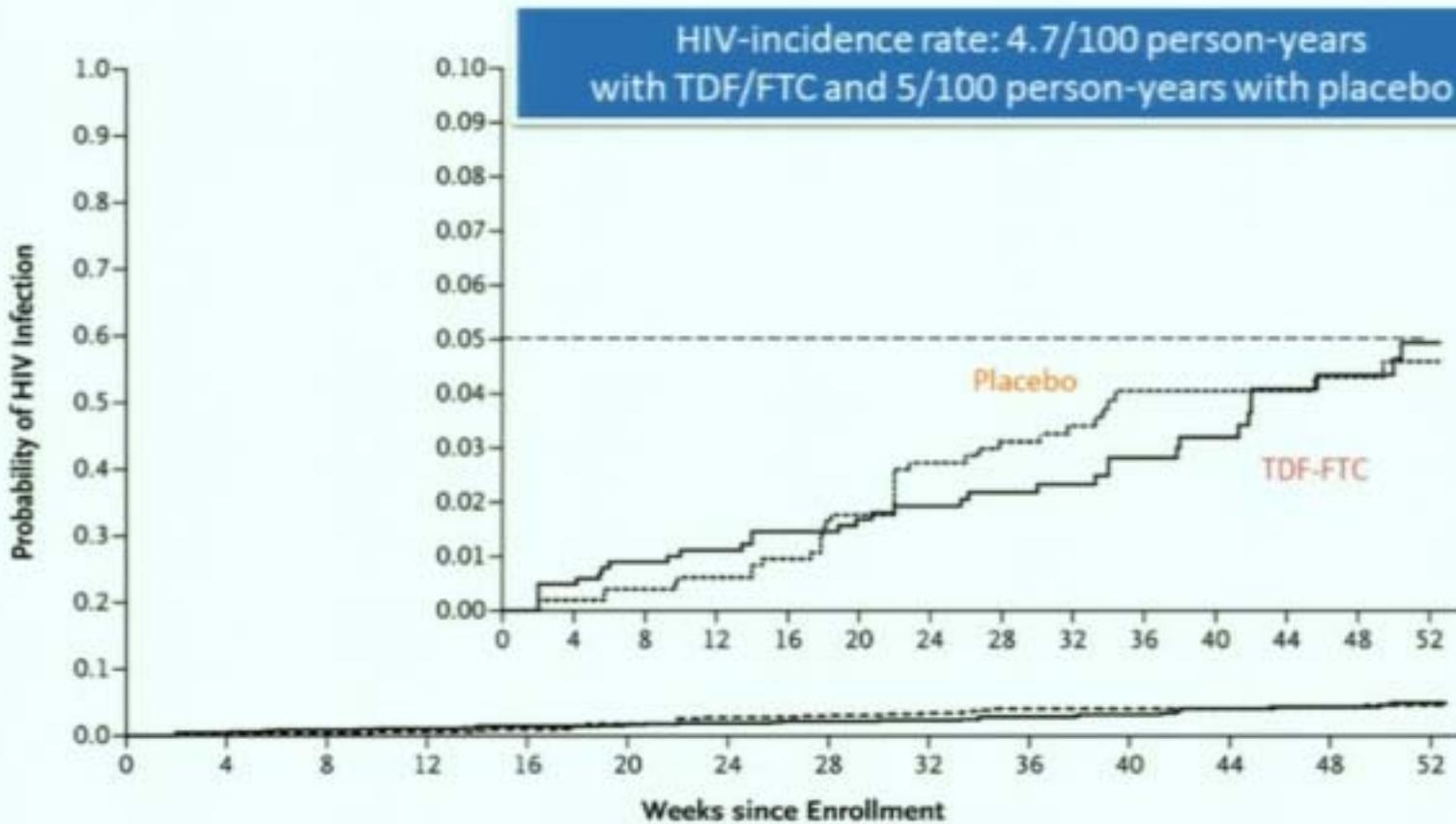
## Preexposure Prophylaxis for HIV Infection among African Women



### Estudio FEM-PrEP



## FEM-PrEP: Lack of Efficacy of TDF/FTC to Reduce HIV-infection (N:2120)



### No. at Risk

Placebo	1032	1019	963	917	864	841	799	736	659	565	491	420	360	229
TDF-FTC	1024	1008	953	904	860	844	811	733	663	569	486	418	356	212

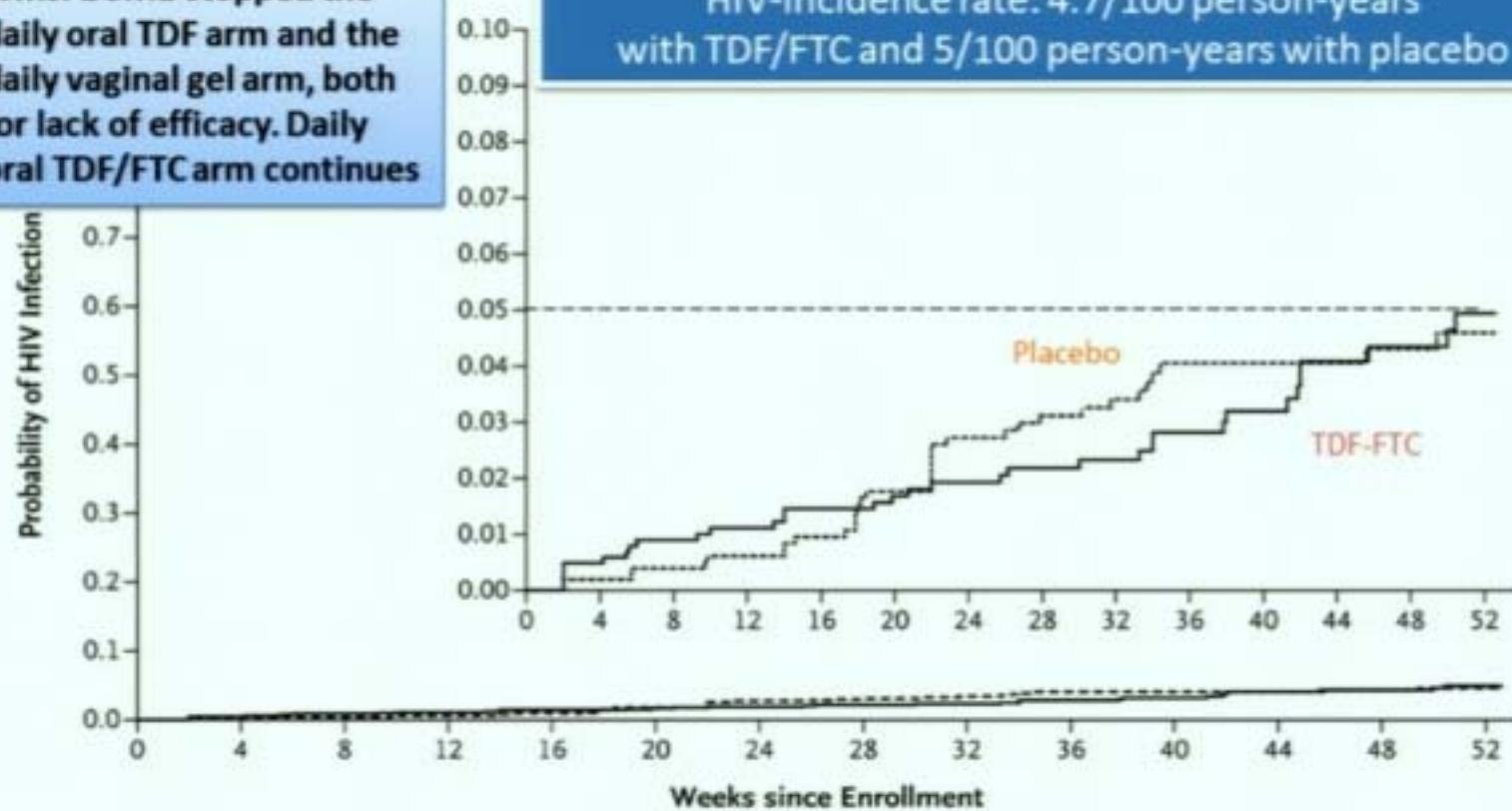
Van Damme et al., N Engl J Med 2012, 367:399-410



## FEM-PrEP: Lack of Efficacy of TDF/FTC to Reduce HIV-infection (N:2120)

VOICE: > 5,000 women, 3 arms. DSMB stopped the daily oral TDF arm and the daily vaginal gel arm, both for lack of efficacy. Daily oral TDF/FTC arm continues

HIV-incidence rate: 4.7/100 person-years with TDF/FTC and 5/100 person-years with placebo



### No. at Risk

Placebo	1032	1019	963	917	864	841	799	736	659	565	491	420	360	229
TDF-FTC	1024	1008	953	904	860	844	811	733	663	569	486	418	356	212

Van Damme et al., N Engl J Med 2012, 367:399-410

# Disappointing Results of PrEP in Women: FEM-PrEP and VOICE

- **FEM-PrEP:**
  - Phase III study of oral TDF/FTC
  - high-risk women in Africa
  - 2120 randomized
    - Announced April 18, 2011, that study was ended early because of lack of efficacy
    - 35 vs 33 new HIV infections in the placebo and TDF/FTC arms<sup>[1]</sup>
    - TFV blood levels suggest that use was too low (< 40%) to assess efficacy
    - 4 vs 1 patient with M184V/I in the TDF/FTC and placebo arms
- **VOICE:**
  - Phase IIB
  - placebo-controlled trial
  - > 5000 women
  - in South Africa, Uganda, and Zimbabwe<sup>[2]</sup>
    - Daily oral TDF; daily oral TDF/FTC; daily vaginal TFV 1% gel
    - DSMB stopped 2011:
      - the **daily oral TDF arm**
      - the **daily vaginal gel arm, both for lack of efficacy**
    - **Daily oral TDF/FTC arm** continues

1. Van Damme L, et al N Engl J Med. 2012 Jul 11.

# Questions That Arise From These Data

- Why were there differences between these studies and the other TDF-based studies?
  - Adherence?
  - Penetration of drug in vaginal tissue?
    - But data on oral PrEP in women in Partners (TDF and TDF/FTC) and TDF2 (TDF) trials
  - Degree of HIV exposure?
  - Genital inflammation?

## The Reality: Conflicting Results with Oral PrEP Trials

Study	Population	N	Results
<b>iPrEx</b> Brazil, Ecuador, Peru, South Africa, Thailand, US	MSM	2499	44% efficacy TDF/FTC
<b>Partners PrEP Study</b> Kenya, Uganda	Heterosexual couples	4758	67% efficacy TDF 75% efficacy TDF/FTC
<b>TDF2 Study</b> Botswana	Young men women	1219	62% efficacy TDF/FTC
<b>FEM-PrEP</b> Kenya, South Africa, Tanzania	Young Women	2120	TDF/FTC = no efficacy
<b>VOICE</b> South Africa, Uganda, Zimbabwe	Young Women	5029	TDF = no efficacy TDF/FTC = ongoing

## Adherence and Detection of Drugs in Patients Assigned to TDF/FTC or TDF

Study	Self reported adherence	Pill count	% Infected with Drugs*	% Uninfected Pts with Drugs*	Efficacy in trials
Partners PrEP					
PrEP	ND	97%	31% (n=29)	82% (n=198)	75%
CDC TDF2					
TDF2	94%	84%	50% (n=2)	80% (n=69)	62%
iPrEx					
iPrEx	95%	91%	9% (n=34)	51% (n=42)	44%
FEM-PrEP					
FEM-PrEP	95%	86%	21% (n=33)	37% (n=95)	6%

\* drug detected = plasma levels > 10 ng/ml

# What Do Physicians Think about PrEP for HIV Prevention ?

- ✓ A 46-year old MSM from NYC with multiple sexual encounters and a recent negative HIV test, asks whether he should receive PrEP ?
- ✓ Which one of the following approaches would you find appropriate for this patient ?
  1. Recommend initiating PrEP
  2. Do not recommend initiating PrEP

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL DECISIONS  
INTERACTIVE AT NEJM.ORG

Preeexposure Prophylaxis for HIV Prevention

Interactive clinical case NEJM August 2, 2012

## What Do Physicians Think about PrEP for HIV Prevention ?

- ✓ A 46-year old MSM from NYC with multiple sexual encounters and a recent negative HIV test, asks whether he should receive PrEP ?
- ✓ Which one of the following approaches would you find appropriate for this patient ?
  1. Recommend initiating PrEP
  2. Do not recommend initiating PrEP
- ✓ 1115 votes from 85 countries
- ✓ 51% of respondents favored initiation of PrEP
- ✓ Readers in favor of PrEP think difficult to alter sexual behavior; PrEP should be embraced as an additional tool
- ✓ Readers against PrEP concerned about risky sexual behavior, resistance, low effectiveness because of low adherence

# DIRETRICES OMS

GUIDANCE ON PRE-EXPOSURE ORAL PROPHYLAXIS (PrEP)  
FOR SERODISCORDANT COUPLES, MEN AND TRANSGENDER  
WOMEN WHO HAVE SEX WITH MEN AT HIGH RISK OF HIV:  
Recommendations for use in the context of demonstration projects

July 2012



World Health Organization

## **3. RECOMMENDATIONS**

### **3.1 Use of PrEP by serodiscordant couples<sup>1</sup>**

#### **Recommendation 1:**

In countries where HIV transmission occurs among serodiscordant couples, where discordant couples can be identified and where additional HIV prevention choices for them are needed, daily oral PrEP (specifically tenofovir or the combination of tenofovir and emtricitabine) may be considered as a possible additional intervention for the uninfected partner.

*Conditional recommendation, high quality of evidence*

### **3.2 Use of PrEP by men and transgender women who have sex with men**

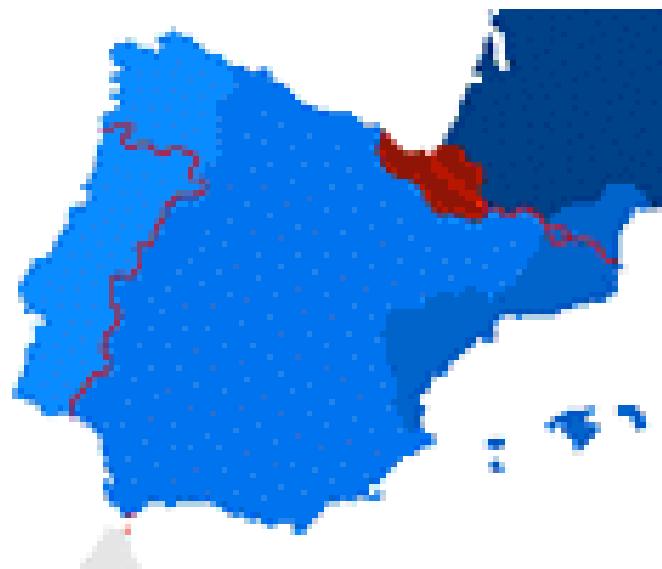
#### **Recommendation 2:**

In countries where HIV transmission occurs among men and transgender women who have sex with men and additional HIV prevention choices for them are needed, daily oral PrEP (specifically the combination of tenofovir and emtricitabine) may be considered as a possible additional intervention.

*Conditional recommendation, high quality of evidence*

### **3.3 Use of PrEP by other groups**

# ¿Es necesario implementar EL PrEP en Europa?

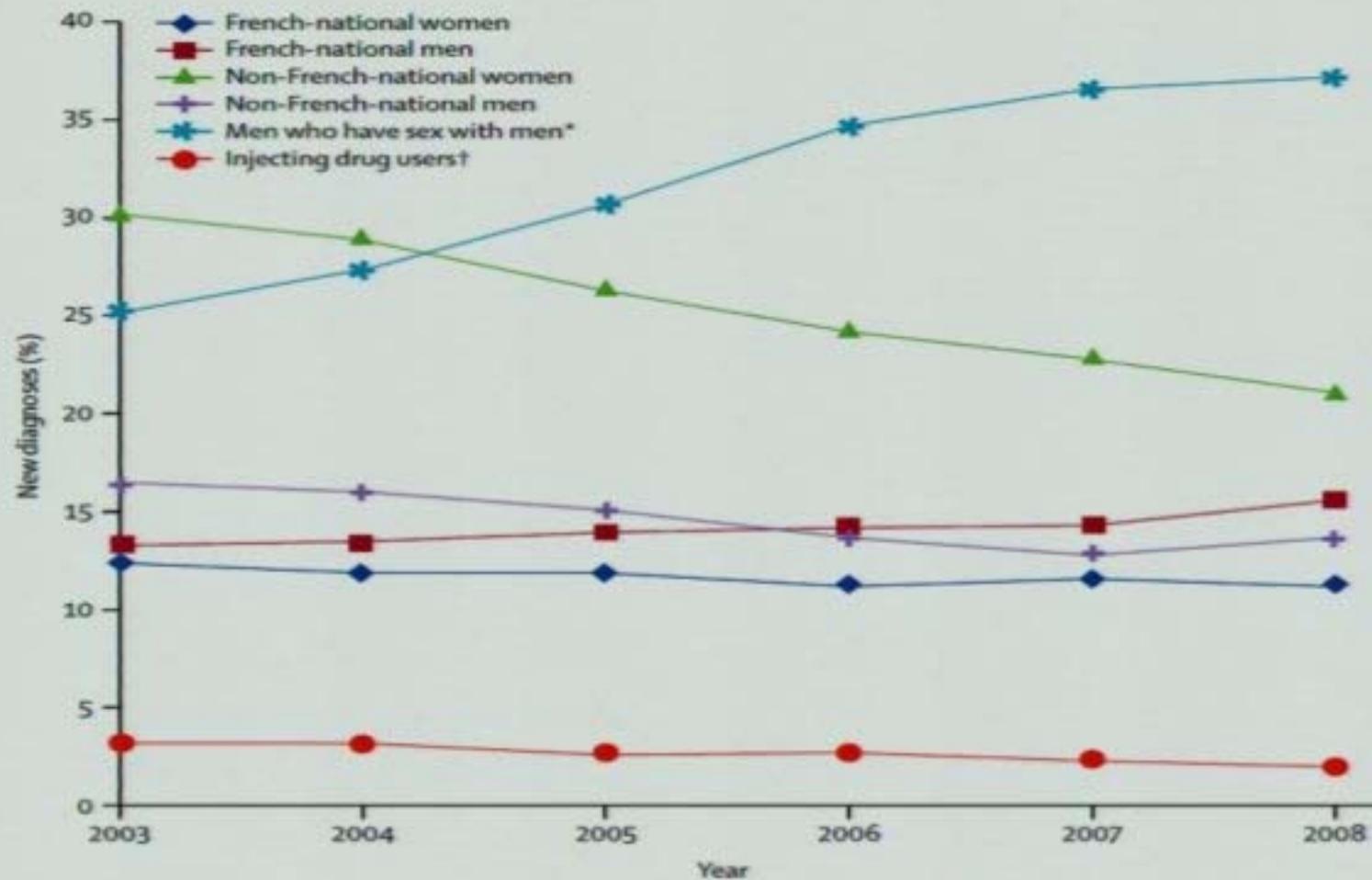


¿Y en España?

## **Will We Implement PrEP in Europe ?**

- FDA approval of TDF/FTC for PrEP in the US
  - REMS : ensure safe proper use / benefits outweigh risks
- Issues to be addressed before approval and roll-out
  - Is there a need for Prep in Europe ?
  - Do we have enough confidence in PrEP effectiveness ?
  - Is the high level of adherence required achievable ?
  - What is the risk of selecting NRTI resistance ?
  - Is oral Prep safe enough ?
  - What is the cost-effectiveness of Prep ?
  - Is there a risk of behavior change that could offset benefit ?

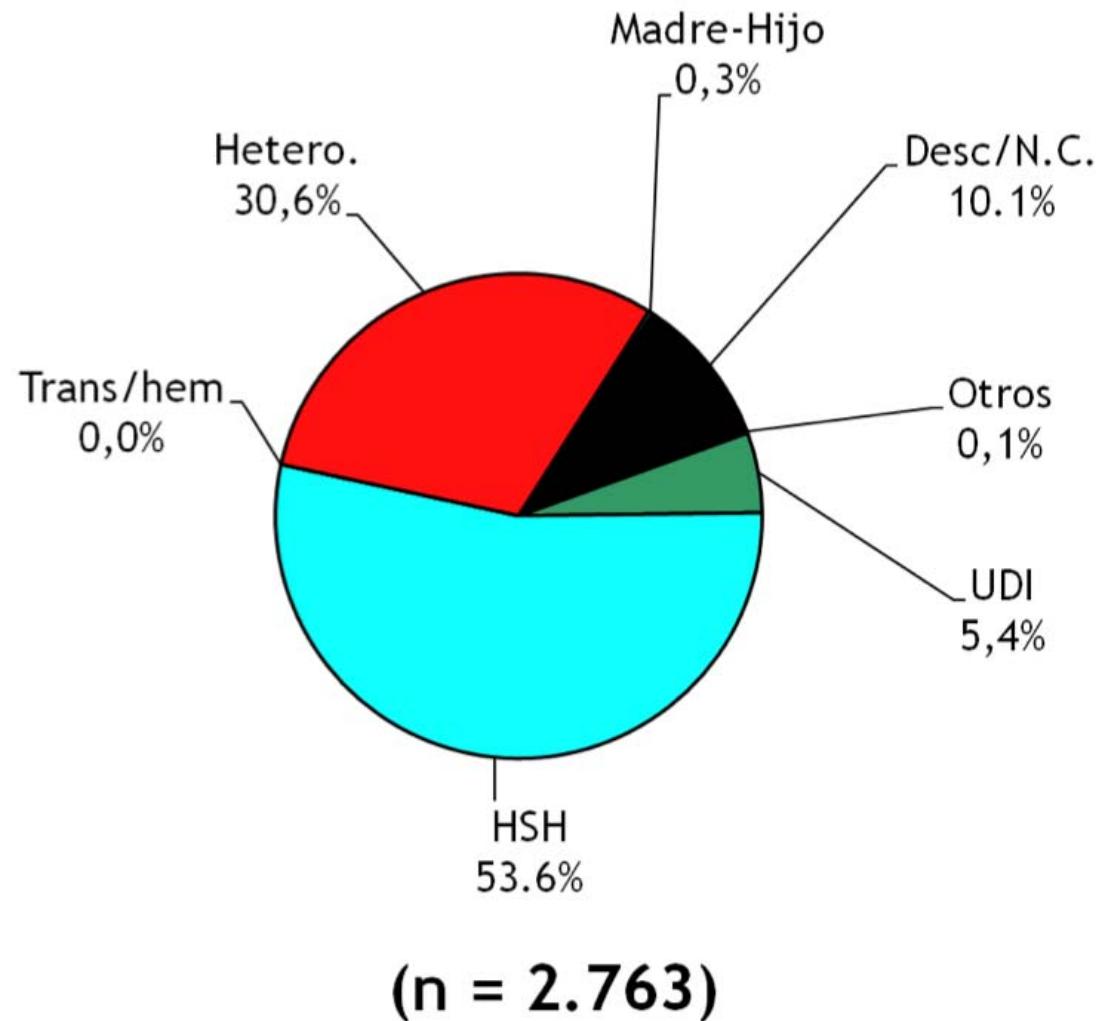
## New HIV Diagnoses in France (2003-8)



Le Vu S et al, Lancet Infect Dis 2010

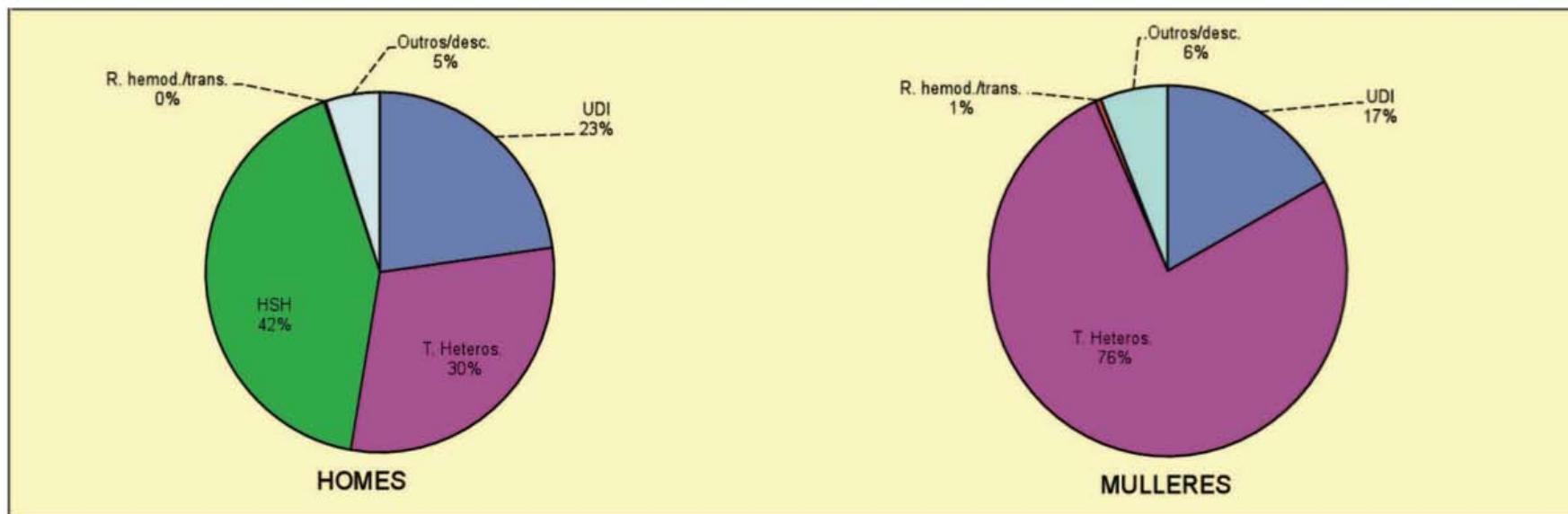
Figura 2

Nuevos diagnósticos de VIH. Categoría de transmisión  
España. Datos de 17 CCAA\*. Año 2011



185  
140  
45

**Gráfico 14:** Categorías de transmisión dos diagnósticos VIH+ por sexos. Galicia 2004-2011.



(DXIXSP: datos o 31 de decembro de 2011)

Se describimos todas as categorías de transmisións nos homes, obsérvase que as infeccións asociadas aos HSH representan a primeira categoría de transmisión do período (en claro ascenso), por riba dos casos das categorías heterosexuais e UDI (estes últimos en claro descenso).

## Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention

EDITORIAL



### Preexposure Prophylaxis for HIV — Where Do We Go from Here?

By Jonathan S. Jav, JD, MA

## Antiviral agents and HIV prevention: controversies, conflicts, and consensus

ONLINE FIRST

## Ethical Challenges of Preexposure Prophylaxis for HIV

Jonathan S. Jav, JD, MA

At a health system level, com

# Nuevos fármacos PrEP en EC



# Next PreP

- A maraviroc based regimen (HPTN 069)
- An injectable long acting ART
  - TMC 278LA (rilpivirine)
  - S-GSK1265744LA (an integrase inhibitor)
- Monoclonal antibodies
  - Ibaluzimab (TMB-355)
  - VRC01-7
- Vectored immunoprophylaxis (VIP),

# ARVs for Prevention

## What do these studies tell us?

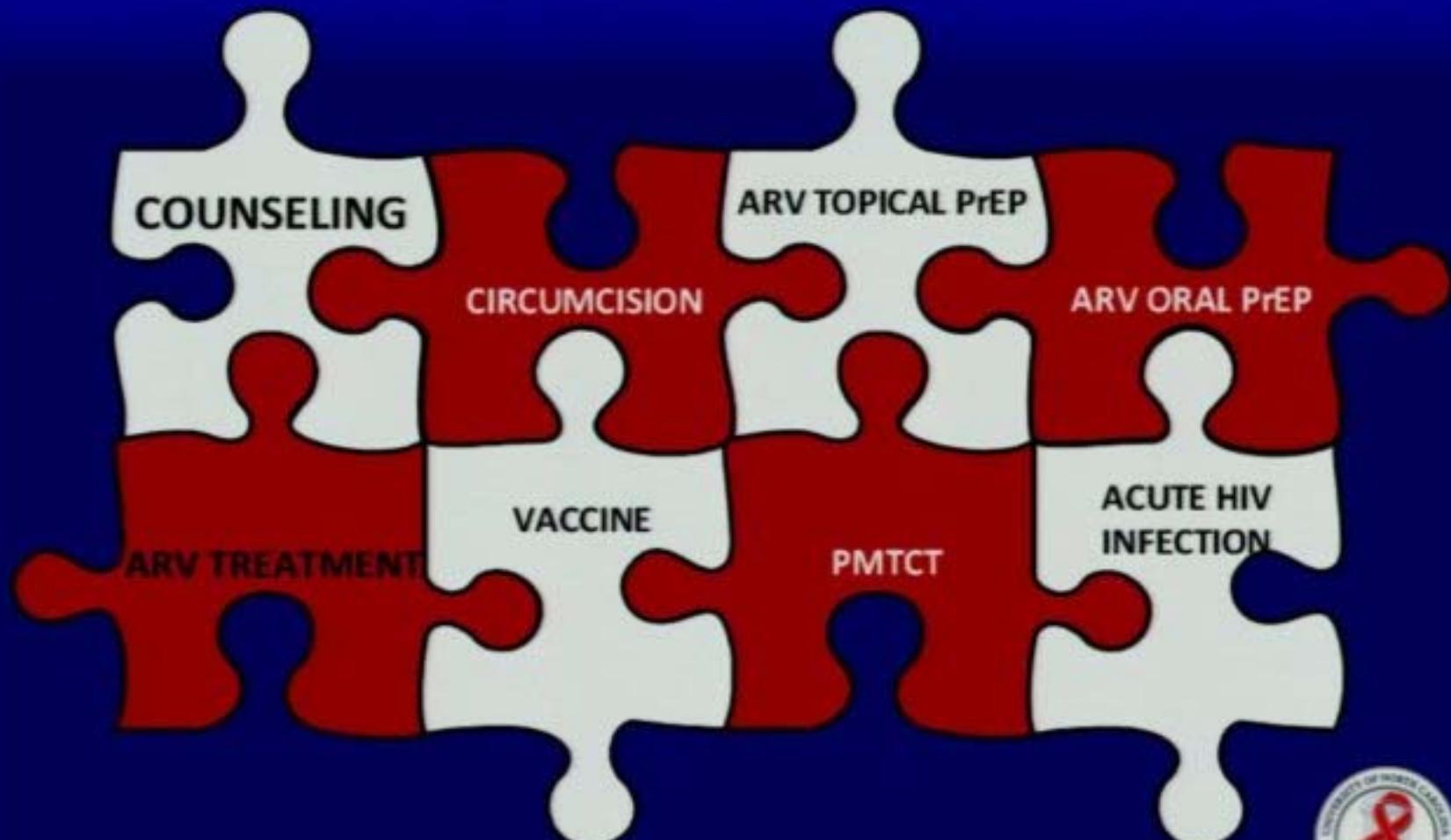
### PreP :

- Efficacy in clinical trials has ranged from 0-75%.
- Physiologic and behavioral differences between at-risk populations
- Different rates of adherence:  
Detectable levels of TDF in uninfected FEM-PrEP : 37%;  
Partners PrEP and TDF2 >80%
- Route of HIV entry and TDF/FTC PK

## Take home messages

- TasP: ARVs work for prevention, at least in serodiscordant HTS couples
- PreP: Research questions:
  - Drug exposure in mucosal tissues
  - Adherence optimization
  - Safety
  - Selection of drug resistance
  - Cost-effectiveness
  - Impact on risk behaviour
  - ARVs are biomedical prevention tools, to be used together with behavioral interventions

# HIV Prevention 2012



# CONCLUSIONES

**Son necesarios nuevos estudios con diferentes/adecuados:**



- **Diseños**
- **Poblaciones**
- **Evaluación**
  - Largo plazo seguridad
  - Métodos adherencia
  - Cambios en las practicas de riesgo
  - Fármacos
  - Tto intermitente

# The New York Times

Early H.I.V. Therapy Sharply Curbs Transmission

By Michael J. KEEGAN, M.D.

Published: May 12, 2005

On Thursday, Dr. F.

from th

EDITORIAL

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The disease AIDS virus and nations troubling is

The Economist

## The end of AIDS?

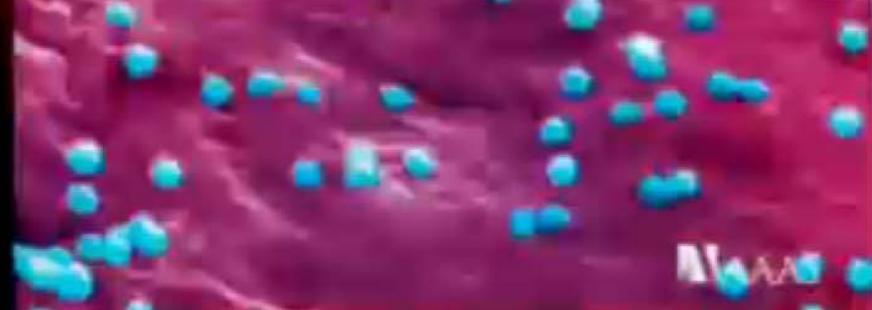


How 5 million lives have been saved, and a plague could now be defeated

# Science

## BREAKTHROUGH OF THE YEAR

HIV Treatment as Prevention



**¡GRACIAS POR SU ATENCION!**

