

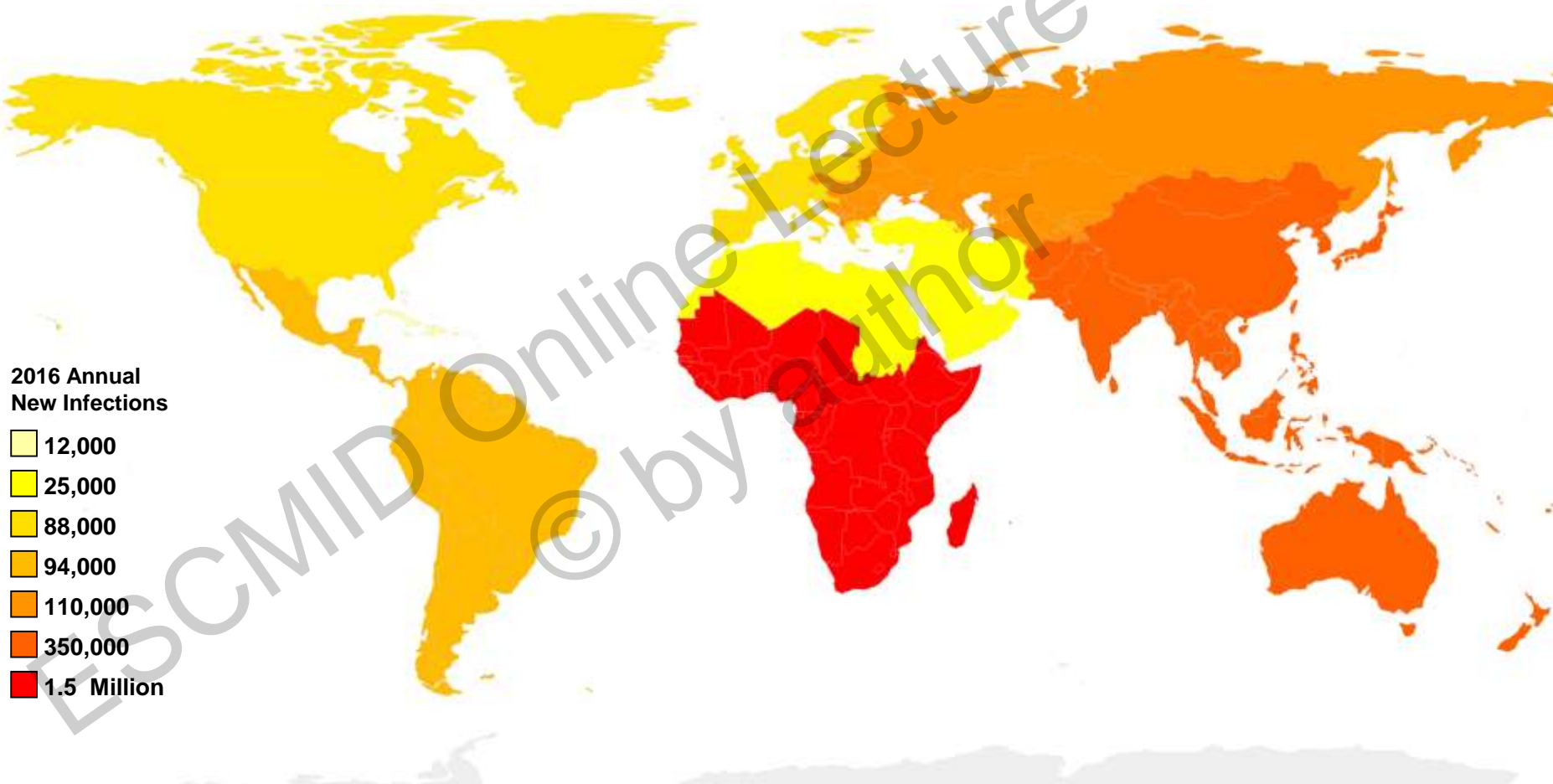
The Evidence and Experience of PrEP

Jean-Michel Molina

Saint-Louis Hospital, University of Paris Diderot,
Inserm U941, Paris, France

**ECCMID Annual Congress
22-25 April 2017, Vienna**

2.1 M Newly Diagnosed HIV Infections in 2015 6,000 New Infections each Day



Prevention of HIV/AIDS

- **Condoms:** 70-80% risk reduction of HIV sexual transmission (observational studies)
- **Male Circumcision :** 60% risk reduction of HIV transmission from women to men (2005 ANRS 12126 randomized trial)
- **Use of Antiretroviral Drugs in HIV Prevention**
 - ✓ Prevention of mother to child transmission: 67.5% reduction with AZT monotherapy (1994 ACTG 076 randomized trial)
 - ✓ Post-Exposure Prophylaxis: 80% risk reduction with 4 weeks of AZT in health care workers (1997 case-control study USA/France)
 - ✓ Treatment of HIV-infected individuals: 93% risk reduction of HIV transmission to HIV-uninfected partner (2016 RCT HPTN 052 trial)
 - ✓ Pre-Exposure Prophylaxis (PrEP)

PrEP is Changing HIV Prevention

SWALLOW THIS

This pill is changing HIV prevention.
Take it once a day
to stay HIV negative.

Is PrEP for you?

HARLEM UNITED
HarlemUnited.org/PrEP

What is PrEP ?

- Use of antiretroviral drugs started before sexual exposure and continued after exposure to reduce the risk of HIV acquisition in high risk individuals
- PrEP has shown efficacy in the macaque model
- 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

Different PrEP Modalities



Pills



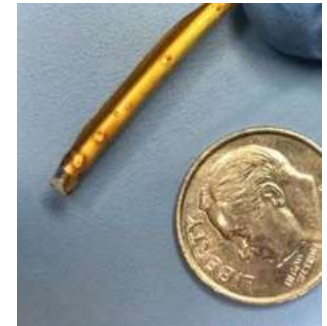
Vaginal/Rectal Gel



Vaginal Ring



Injections



Implants

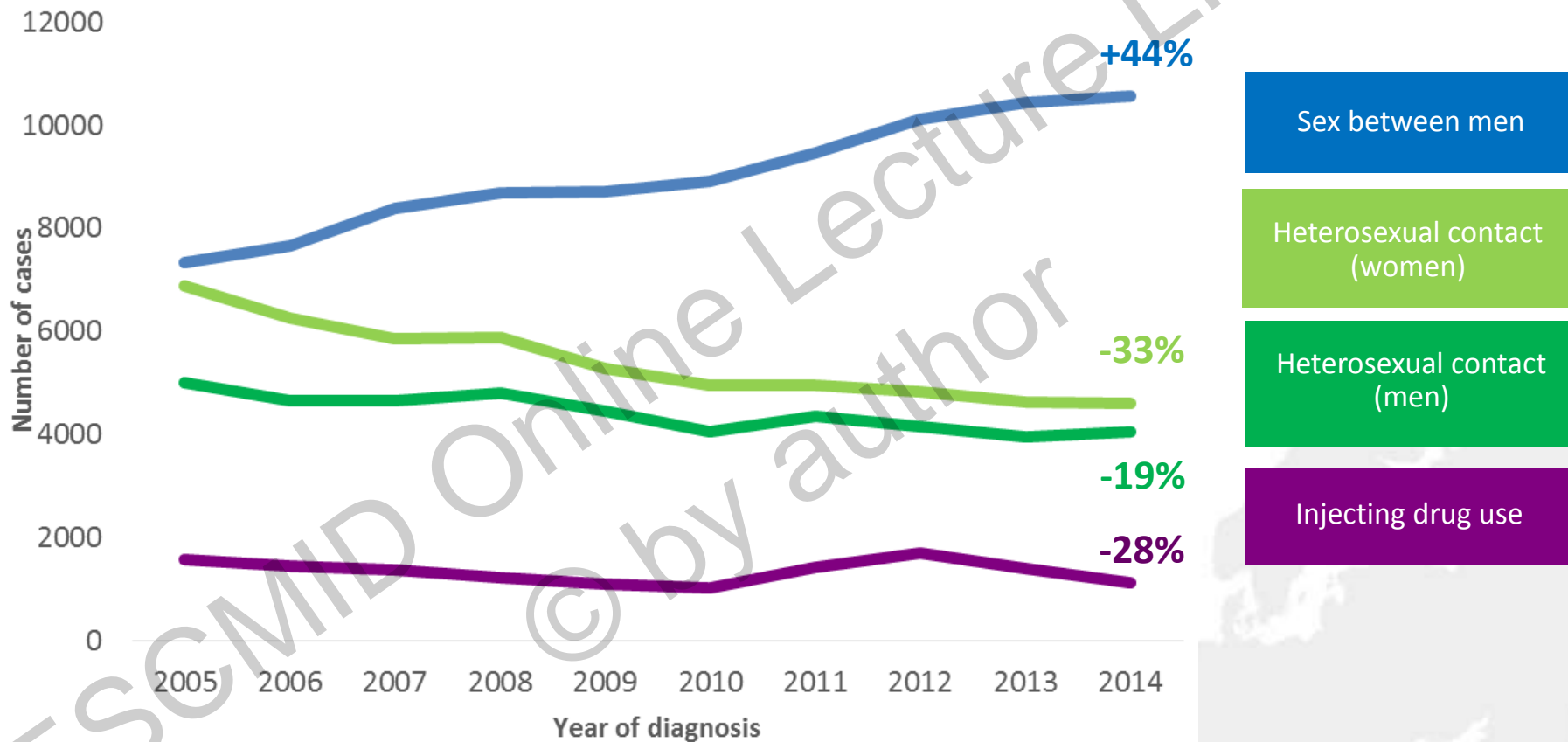
- ✓ Ideally: high efficacy, safety and tolerability, conveniency, low cost
- ✓ Multiples choices to accommodate everyone
- ✓ Combination of drugs and/or contraceptives

Is There a Need for PrEP in Europe ?



HIV diagnoses, by mode of transmission

2005-2014, EU/EEA



Data is adjusted for reporting delay. Cases from Estonia and Poland excluded due to incomplete reporting on transmission mode during the period; cases from Italy and Spain excluded due to increasing national coverage over the period.

**Do We Have Enough
Confidence in PrEP
Effectiveness ?**



iPrEX Study Design

Double-blinded, randomized, placebo-controlled trial

• HIV uninfected MSM at high risk of sexual acquisition of HIV

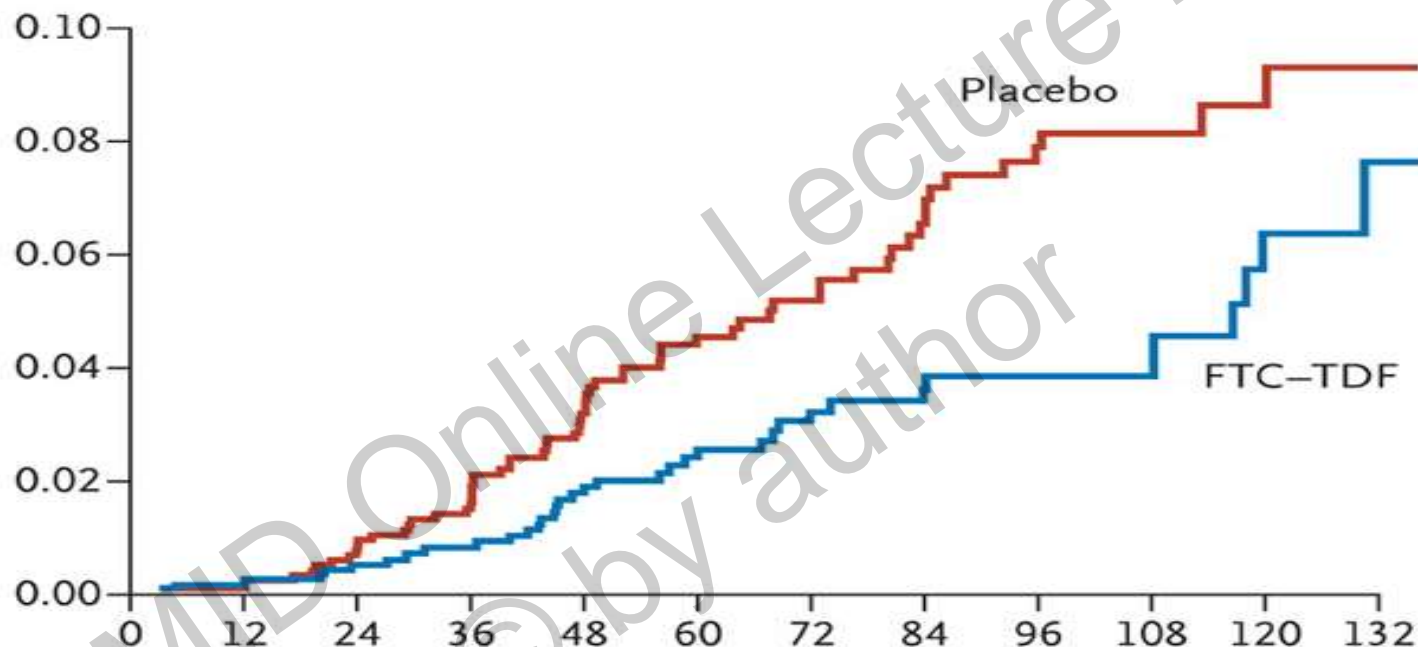
**TDF/FTC 1 pill/day
(n=1251)**

**Placebo 1 pill/day
(n=1248)**

- High risk: 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



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



Partners PrEP Design



4758 HIV-1 serodiscordant couples
(HIV-1 seropositive partner **not yet medically eligible for ART**)



Randomize HIV-1 seronegative partners
(normal liver, renal, & hematologic function and no HBV-infection)



Placebo once daily

FTC/TDF once daily

TDF once daily

All receiving comprehensive

HIV-1 prevention services



Follow couples monthly for up to 36 months

1° endpoint: HIV-1 infection in the HIV-1 **seronegative** partner
Co-1 ° endpoint: Safety

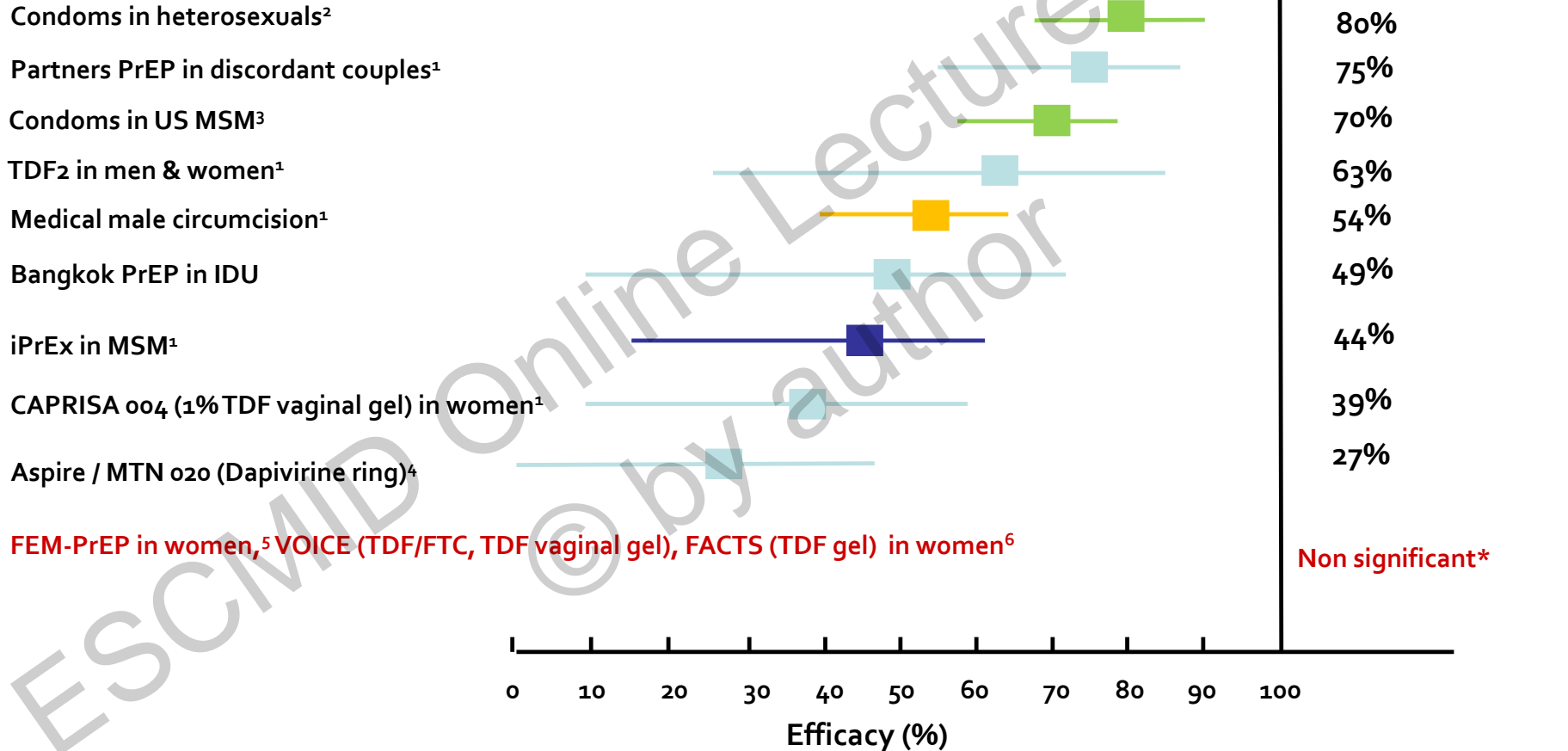


Primary efficacy results

	TDF	FTC/TDF	Placebo
Number of HIV- infections	17	13	52
HIV-1 incidence, per 100 person-years	0.65	0.50	1.99
HIV-1 protection efficacy, men & women	67%	75%	
95% CI	(44-81%)	(55-87%)	
P-value	<0.0001	<0.0001	
HIV-1 protection efficacy, men	63%	84%	
95% CI	(20-83%)	(54-94%)	
P-value	0.01	<0.001	
HIV-1 protection efficacy, women	71%	66%	
95% CI	(37-87%)	(28-84%)	
P-value	0.0002	0.005	

Relative Efficacy of Prevention Strategies

Studies



1. Adapted from Karim SS and Karim QA. Lancet 2011;378:e23-25; 2. Weller S and Davis K. Cochrane Database Syst Rev 2002:CD003255; 3. Smith DK et al. JAIDS 2015;68:337-344; 4. Baeten et al NEJM 2016; 5. van Damme L et al. NEJM 2012;367:411-422; 6. Marrazzo JM et al. NEJM 2014, Rees H, CROI 2015, Abs. 26LB



The PROUD Trial

Multi-center Open-label randomized trial in GUM clinics

HIV-negative Gay Men
and transgender women
reporting unprotected anal
intercourse with a man
within last 90 days



Immediate Daily Oral TDT/FTC
(n = 275)

Deferred Daily TDF/FTC by 12 months
(n = 269)

- **Primary endpoint:** Time to accrual of 500 participants and retention
- **From June 2014:** HIV-infection in first 12 months
- **Other outcome measures:** safety, adherence, risk compensation
- All participants will be offered a risk reduction package : regular HIV testing, diagnosis and treatment of STIs, support to reduce high risk behavior including condoms, PEP.
- Visits every 3 months with HIV testing using ELISA or rapid tests

Efficacy of Daily PrEP in MSM in the UK



Group	No. of infections	Follow-up (PY)	Incidence (per 100 PY)	90% CI
Overall	23	465	5.0	3.5–6.9
Immediate	3	243	1.2	0.4–2.9
Deferred	20	222	9.0	6.1–12.8

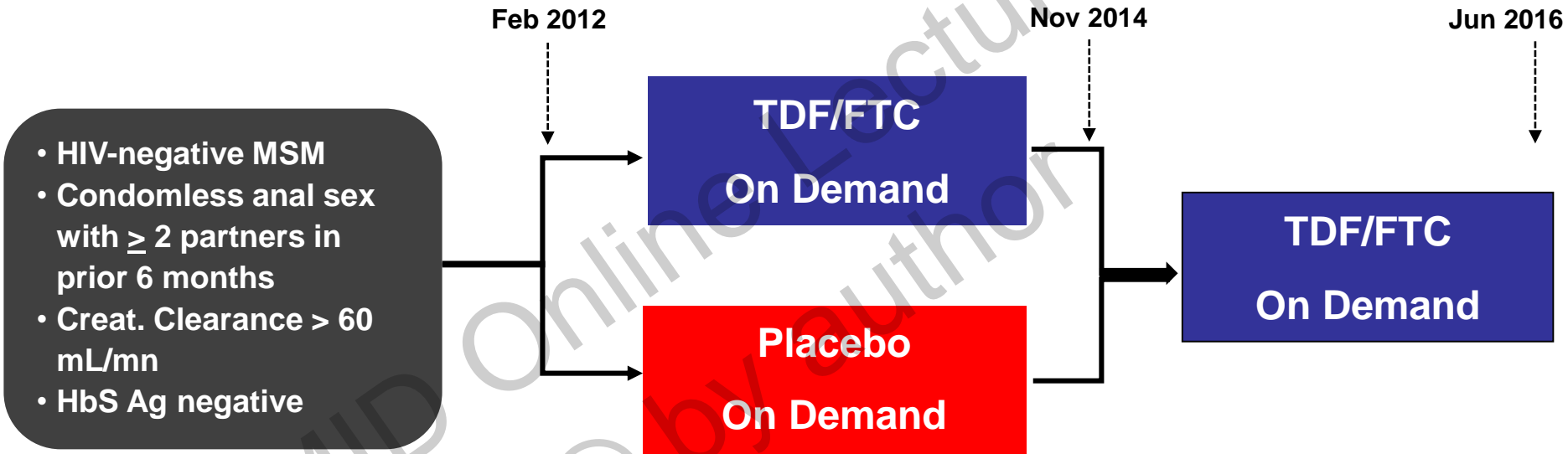
Efficacy = **86%** (90% CI: 64-96%)

P-value = 0.0001

Number Needed to Treat = 13 (90% CI: 9 – 23)

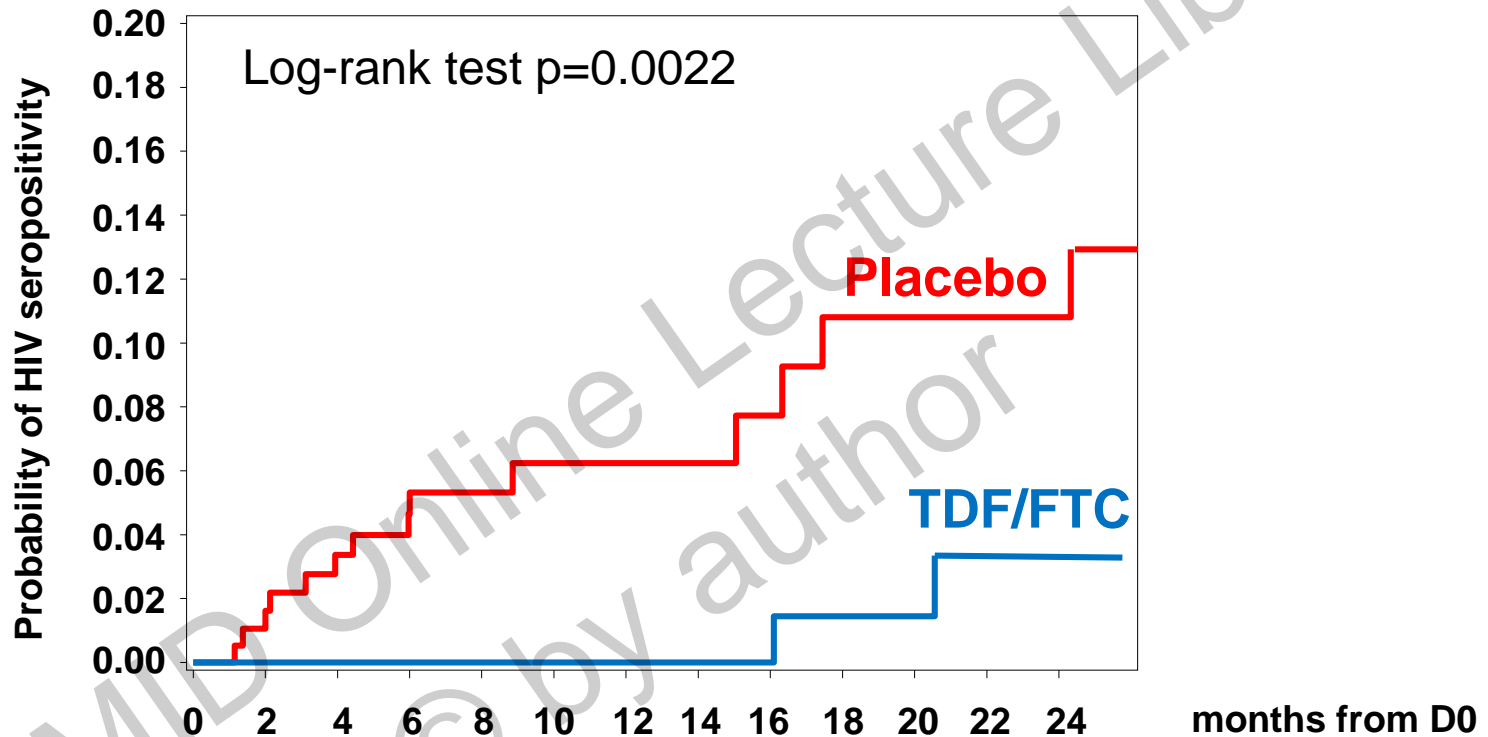
Study Design

Randomized Double-Blinded vs. Placebo then Open-Label Extension



- Condoms, gels, tests for HIV (using 4th generation assays) and STIs, vaccinations for Hepatitis A and B, and **peer counseling on risk reduction and adherence**
- Follow-up every two months

KM Estimates of Time to HIV-1 Infection (mITT Population)



Mean follow-up of 12 months: 16 subjects infected (**14 placebo, 2 in TDF/FTC**)

Incidence: **6.6 /100 PY** overall but **9.17 in Paris** (and 2.45 in other cities)

86% relative reduction in the incidence of HIV-1 (95% CI : 40-98, p=0.002)

NNT to avert one HIV-infection: 18 (95% CI: 11-50)

HIV Incidence (mITT Analysis)

Treatment	Follow-Up Pts-years	HIV Incidence per 100 Pts-years (95% CI)
Placebo	212	6.60 (3.60-11.1)
TDF/FTC (double-blind)	219	0.91 (0.11-3.30)
TDF/FTC (open-label)	515	0.19 (0.01-1.08)

Median Follow-up in Open-Label Phase 18.4 months (17.5-19.1)

97% relative reduction vs. placebo

Is Oral PrEP Safe Enough ?

ESCMID Online Lecture Library
© by author

Adverse Events

Nb Participants (%)	TDF/FTC n=199	Placebo n=201	TDF/FTC n=362
All AEs	186 (93)	181 (90)	353 (98)
Severe AEs	20 (10)	17 (8)	40 (11)
Grade 3 or 4 AEs	19 (10)	15 (7)	40 (10)
AEs leading to Rx D/C	1	0	3*
GI-related AEs	28 (14)	10 (5)	48 (13)
Nausea/vomiting	16	2	14
Abdominal pain	13	3	9
Diarrhea	8	6	25

**Decrease in plasma creatinine clearance to 48, 71 and 76 ml/mn

PrEP and HIV Resistance

- Resistance rare in clinical trials of PrEP
- Resistance mutations assessed: K65R, K70E (TDF) or M184V/I (FTC)
- Resistance with oral PrEP in PHI: 8/29 (27.5%)

Number of HIV Seroconverters on Active PrEP Arms With HIV Resistance*		
Trial	N mITT (oral drug)	HIV Infected After Enrollment, Resistant / Seroconverters
iPrEx	1224	0/36
Partners PrEP*	3140	4/51
TDF2	601	0/10
FEM-PrEP*	1024	4/33
VOICE	1978	1/113
PROUD	275	1/3
IPIRGAY	199	0/2
TOTAL	8441	10/248 (4%)
Modified Total§	8441	10/8441(0.1%) of exposed

* For 454 sequencing, resistance levels >1% of variants

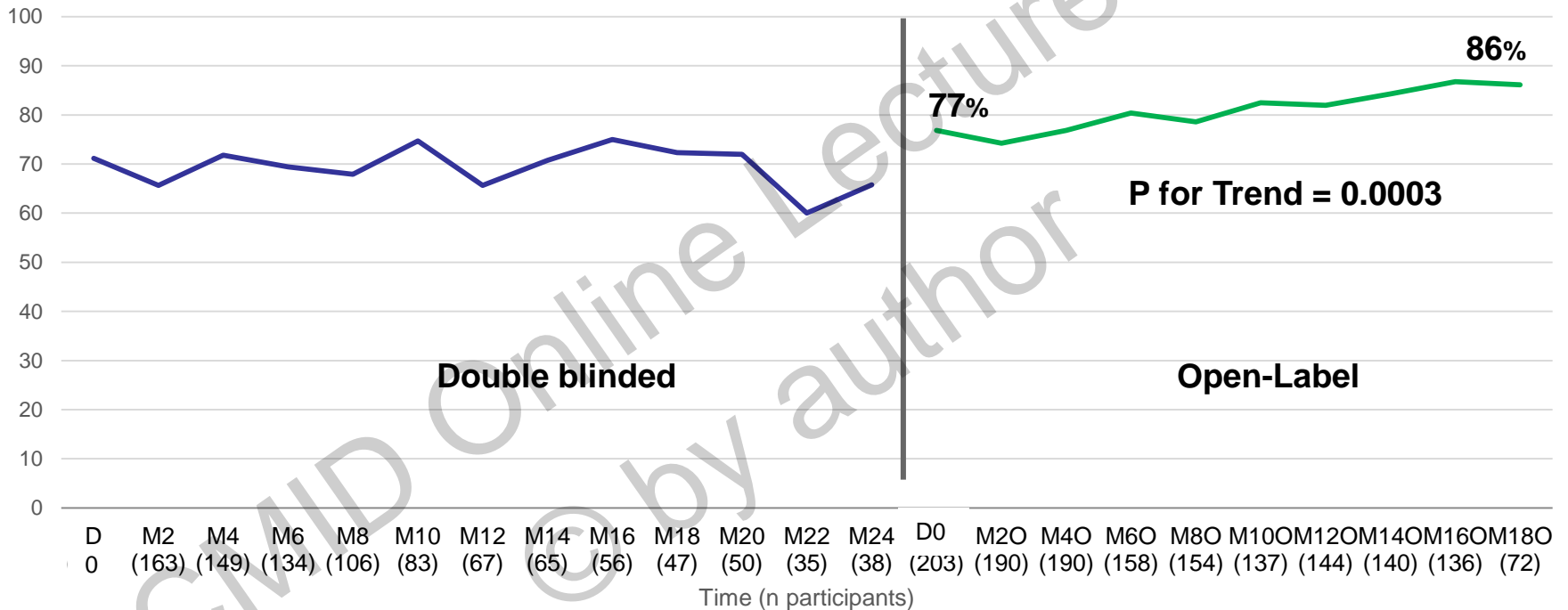
§After exclusion of resistance likely to be transmitted

What Impact of PrEP on Sexual Behavior ?

ESCMID Online Lecture Library
© by author

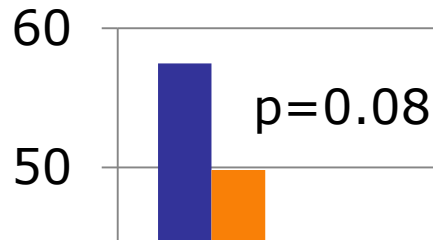
Sexual Behavior

Proportion Pts with Condomless Sex for Last Receptive Anal Intercourse



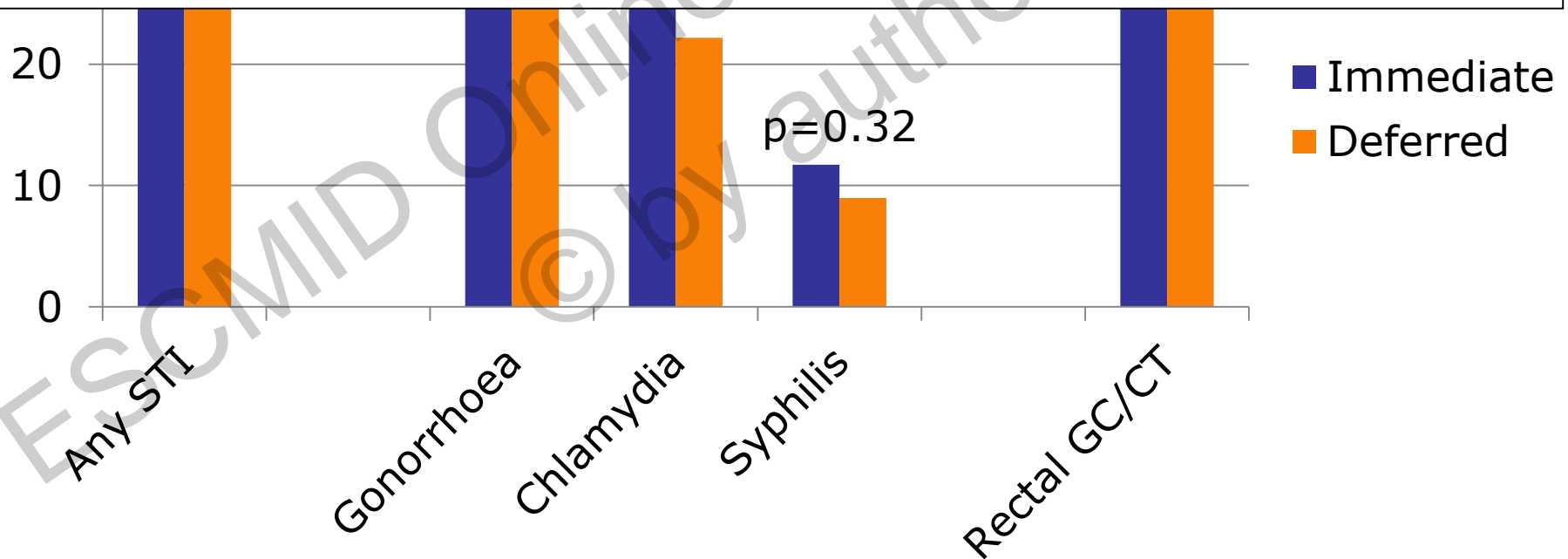
- **No significant change in median Nb of partners or sexual acts during the open-label phase (P= 0.42 and P= 0.12)**

STIs During Follow-up in PROUD



Caveat

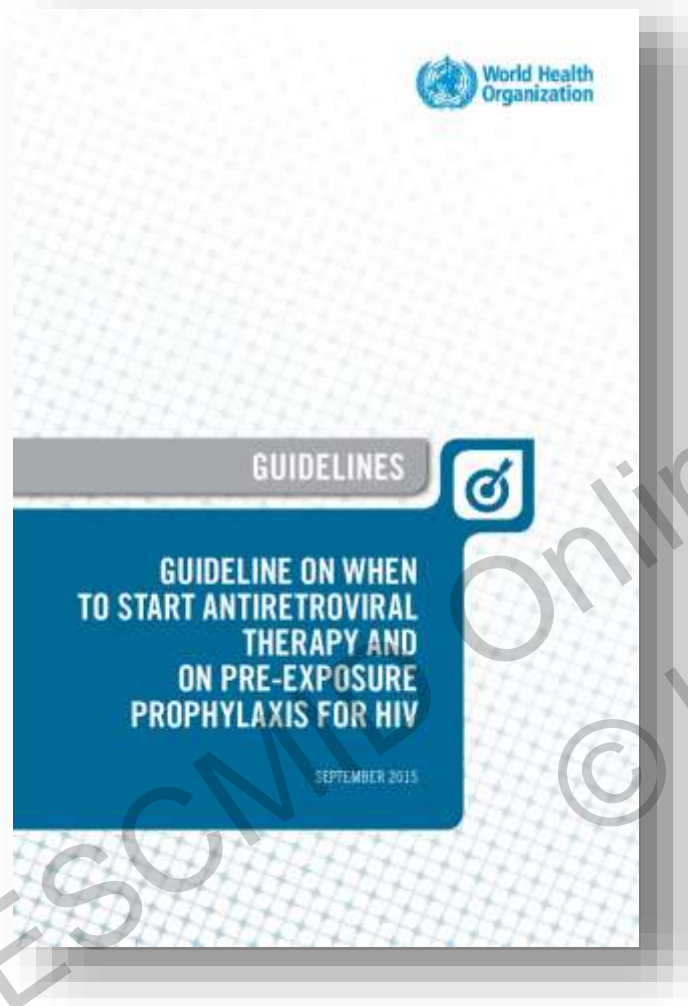
Number of screens differed between the groups:
e.g. Rectal gonorrhoea/chlamydia
974 in the IMM group and 749 in the DEF



Summary of Findings

- High incidence of HIV infection in high risk MSM in France, UK and Canada
- Daily and On Demand PrEP with oral TDF/FTC both highly effective in high risk MSM
- Low condom use did not undermine efficacy
- Safety of PrEP was good
- PrEP improved satisfaction and removed fear during sexual activity

WHO 2015 guidelines



Oral PrEP should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches

Defining “substantial risk”: Substantial risk of HIV infection is provisionally defined as HIV incidence greater than 3 per 100 person–years in the absence of PrEP. HIV incidence greater than 3 per 100 person–years has been identified among some groups of men who have sex with men, transgender women in many settings and heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection.

<http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/>

Experience with PrEP in France

ESCMID Online Lecture Library
© by author

Temporary Recommendation for Use (RTU) for Truvada for PrEP

- Specific French procedure to **secure and regulate off-label** indication of a medicine for unmet medical needs
- ASM and Gilead set up an RTU to allow the use of TDF/FTC for PrEP on January 4, 2016
- **Adults (> 18 years) at high risk of sexual HIV acquisition**
- **Daily or On Demand PrEP (for MSM)**
- Subject registration mandatory
 - Data collected by physicians on a Gilead website
 - PrEP initiation, HIV seroconversion, AEs, pregnancy
 - Data analyzed by Gilead and reported to ANSM every 3 months
 - Prescription for 1 month, then every 3 months

High Risk of Sexual HIV Acquisition

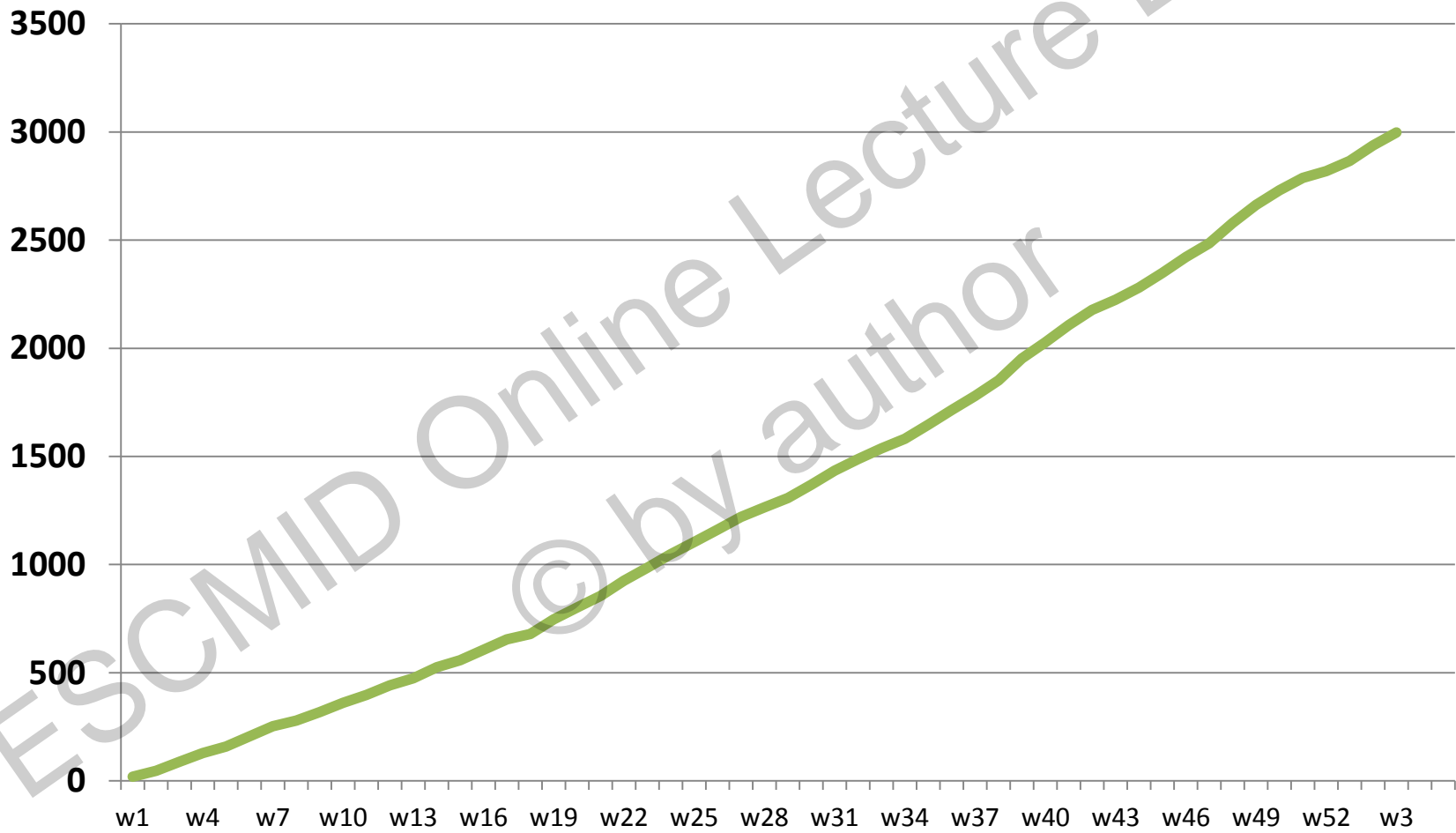
- **MSM or transgender individuals with:**
 - Condomless anal sex with at least two different partners over the last 6 months
 - Episodes of STIs (syphilis, chlamydiae, gonorrhea, HBV, HCV) over the last 12 months
 - Multiple PEP treatments in the last 12 months
 - Use of drugs during sexual intercourse (cocaine, GHB, MDMA, etc...)
- **Other persons at high risk of HIV acquisition on a case by case basis:**
 - Sex workers exposed to condomless sex
 - Vulnerable persons exposed to condomless sex with people from a group with a high prevalence of HIV
 - Person from areas/countries of high HIV prevalence
 - Person with multiple sexual partners
 - IVDU

Places where PrEP can be Prescribed and Delivered in France

- Hospitals (80%) HIV specialists
- STI clinics (21%)
- GP will be able renew prescriptions in 03/2017
- Drugs are delivered in hospital and private pharmacies.



Cumulative Nb of Individuals Enrolled Jan 2016 - Jan 2017



Number of Subjects Registered per Region



Subjects Registered up to January 2017

Patients (Median, range) or (%)

N= 2998

Age

37 (18-84)

French

88.9%

Men

97.8%

Women

0.7% (n=20)

Transgender

0.7% (n=19)

MSM

97.4%

Chemsex

19.9%

STIs in prior 12 months

30.6%

PrEP in prior 12 months

10.9%

PrEP on demand

59%

2 HIV seroconversion with 1100 person-years of FU (0.17/100 PY)

Challenges with PrEP Roll-Out

- **Dedicated PrEP clinic** to provide information/appointment
- PrEP guide with prescription for tests for HIV and STIs sent by email
- Organize outpatient clinic to meet the demand
- PrEP usually started at first visit and persons seen at Month 1 and every 3 months
- Adapt outpatient clinic for STI treatment (injections)
- **Peer-counseling by the community (AIDES):** PrEP adherence, risk reduction

Lessons Learned in France

- Close partnership with the community and strong political support have led to PrEP approval
- Increase PrEP awareness among doctors and people at risk (MSM, transgender, and heterosexual migrants)
- Define best models of care and access points (hospitals, sexual health clinics, GP)
- Monitor and evaluate PrEP implementation
- High risk people self-select for PrEP: HIV-infection detected at screening or soon after PrEP initiation

National Prevention Campaign for MSM



POUR LA VIE
POUR UN WEEK-END
POUR UNE FOIS

Les situations varient.
Les modes de protection aussi.

Sexe entre hommes : trouvez vos modes de protection sur sexosafe.fr

PRÉSÉRVATIFS / DÉPISTAGES / PROF / EPE / TROP



COUP DE Foudre
COUP D'ESSAI
COUP D'UN SOIR

Les situations varient.
Les modes de protection aussi.

Sexe entre hommes : trouvez vos modes de protection sur sexosafe.fr

PRÉSÉRVATIFS / DÉPISTAGES / PROF / EPE / TROP



S'AIMER
S'ÉCLATER
S'OUBLIER

Les situations varient.
Les modes de protection aussi.

Sexe entre hommes : trouvez vos modes de protection sur sexosafe.fr

PRÉSÉRVATIFS / DÉPISTAGES / PROF / EPE / TROP



AVEC UN AMANT
AVEC UN AMI
AVEC UN INCONNU

Les situations varient.
Les modes de protection aussi.

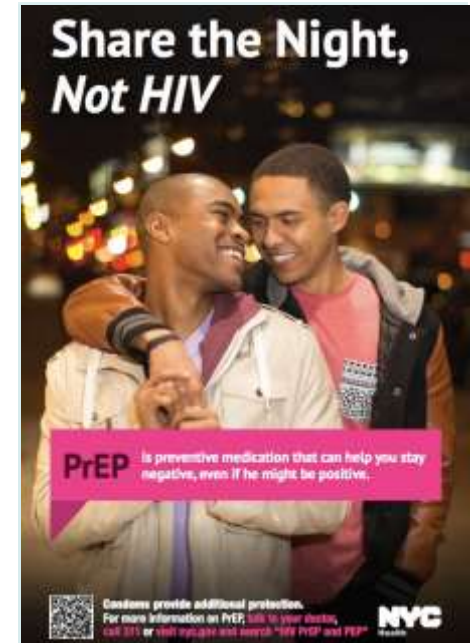
Sexe entre hommes : trouvez vos modes de protection sur sexosafe.fr

PRÉSÉRVATIFS / DÉPISTAGES / PROF / EPE / TROP

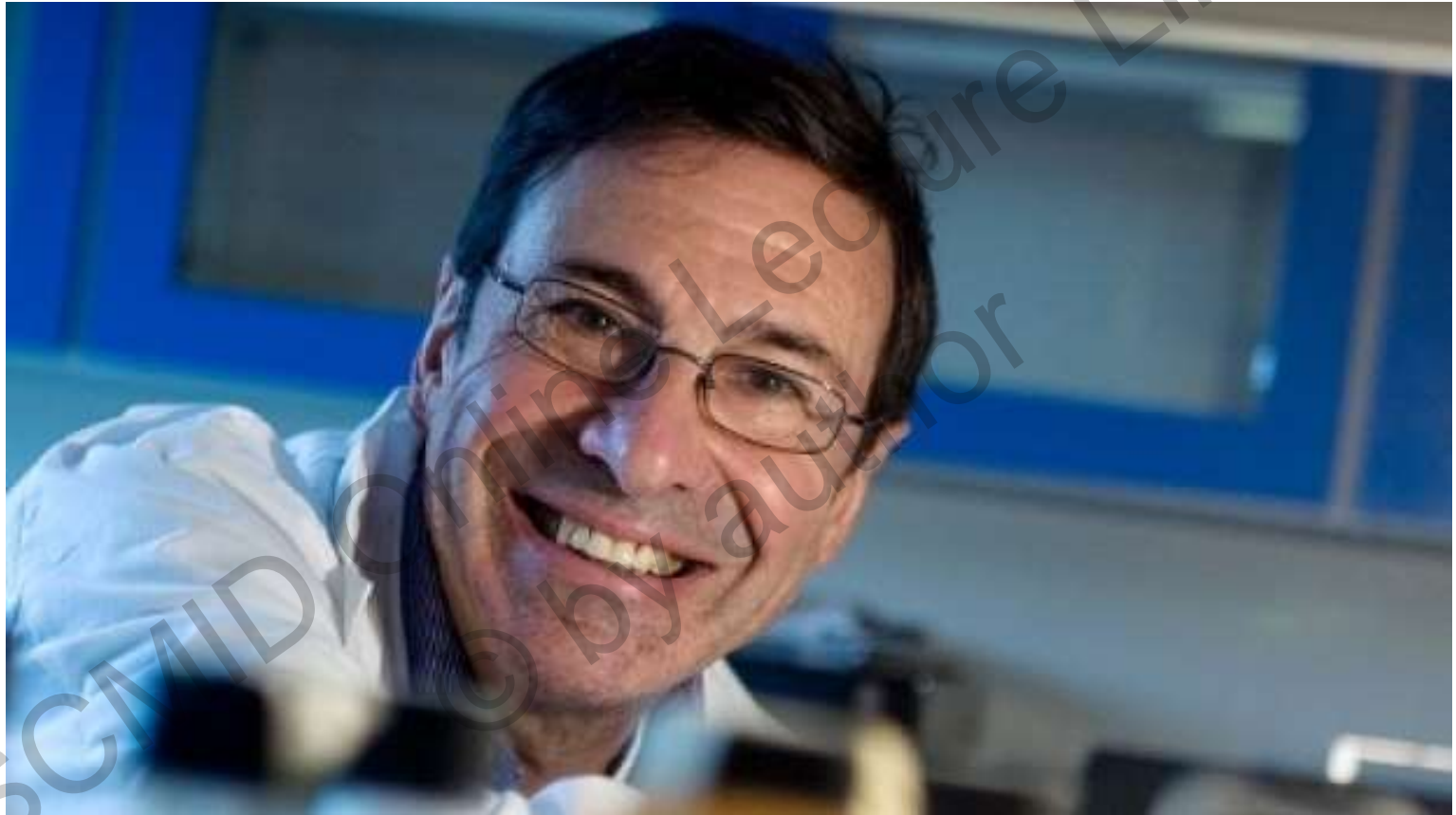


Summary

- Current efforts to reduce STI/HIV incidence among MSM in Europe are failing
- While countries figure out whether or not to implement PrEP, demand is increasing
- An increasing number of countries in Europe are considering implementing PrEP demonstration projects
- PrEP is an additional tool to prevent HIV-infection, and people at risk of HIV-acquisition should have access to PrEP
- PrEP is a unique opportunity to change the course of the HIV epidemic



In Memoriam



Prof. Mark Wainberg