Evidències científiques de la profilaxi pre-exposició (PrEP) en la prevenció de l'HIV

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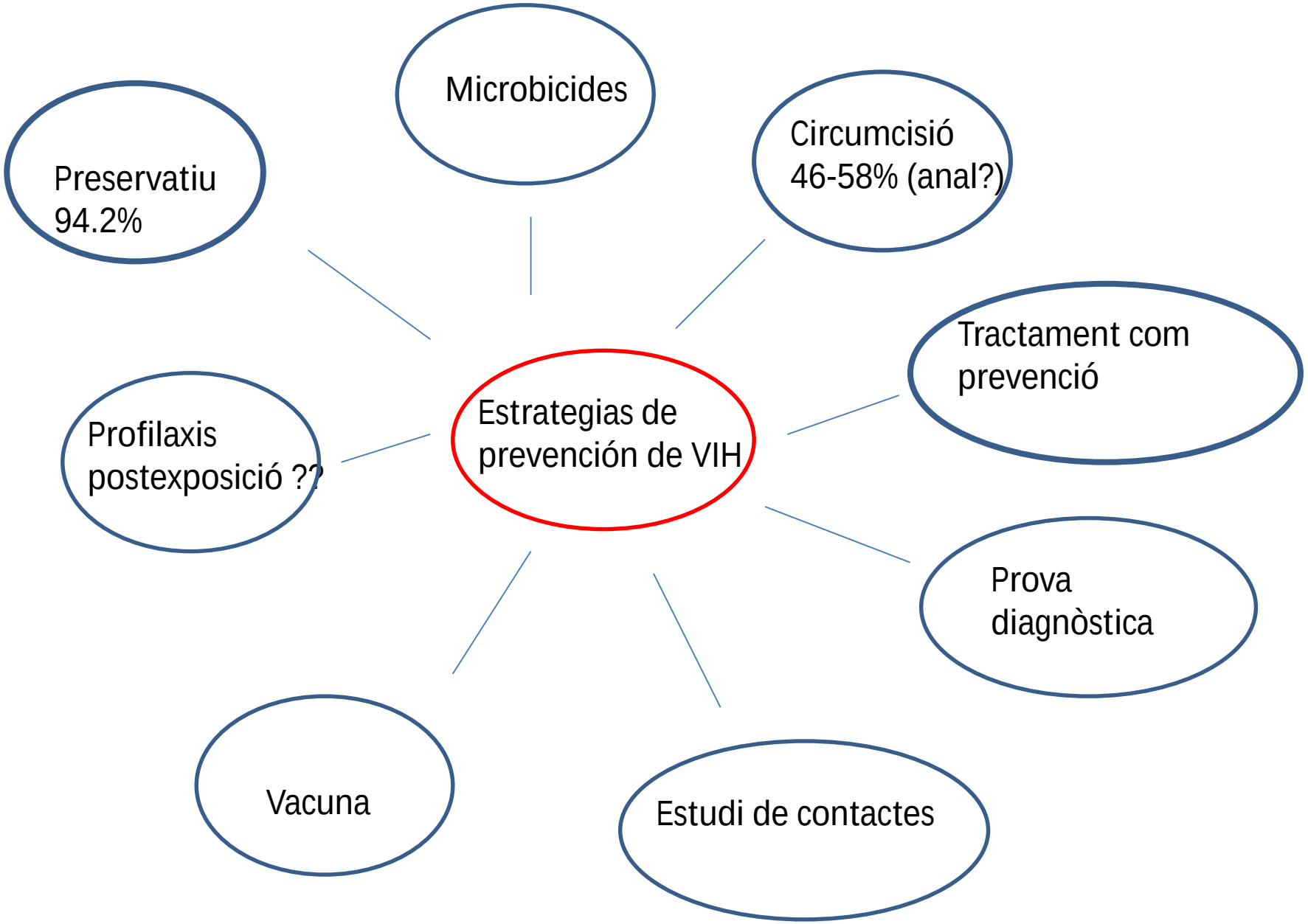

Estrategias de prevención de VIH
Microbicides
Preservatiu 94.2%
Circumcisió 46-58% (anal?)
Tractament com prevenció
Profilaxis postexposició ??
Prova diagnòstica
Vacuna
Estudi de contactes

HIV prevention

Combination HIV prevention refers to a combination **of behavioural, biomedical and structural** approaches to HIV prevention to achieve maximum impact on reducing HIV transmission and acquisition.

- Epidèmia descontrolada
- 15% de HSH de Bcn/Cat
- Alt nivell de transmissió a la 1ª fase de la infecció

O-25 An epidemiological analysis of men who have sex with men who are prescribed HIV post-exposure prophylaxis: implications for wider pre-exposure prophylaxis policy

Holly Mitchell, Martina Furegato, Gwenda Hughes, Nigel Field, Hamish Mohammed and Anthony Nardone
Public Heath England, UK

HIV incidence was higher among those receiving PEPSE (adjusted hazard ratio¼1.18, 95% CI: 1.03–1.35).

PrEP may be beneficial for high-risk MSM receiving PEPSE and also avoid the need for repeat PEPSE prescriptions.

International Journal of STD & AIDS 26(11) Supplement

P008 High rates of repeat post-exposure prophylaxis and HIV incidence among men who have sex with men prescribed post-exposure prophylaxis in London, UK

Gary Whitlock, Jennifer Fearnley, Chris Mccormack and Alan Mcowan
NHS, UK

P082 High proportion of newly diagnosed HIV-positive men who have sex with men had previous HIV test in Germany – is testing used as prevention strategy?

Bartmeyer Barbara, Schönerstedt-Zastrau Kerstin, Hofmann Alexandra, Kollan Christian, Voss Lieselotte, Osamah Hamouda and Viviane Bremer
Robert Koch Institute, Germany

What if there were a pill that could help prevent HIV?

There is.

Ask your doctor if PrEP is right for you.

Pre-exposure prophylaxis: A daily pill to reduce risk of HIV infection

www.cdc.gov/hiv/basics/prep.html

HIV prevention

PrEP: Oral PrEP of HIV infection is the use of ARV drugs by HIV-uninfected people before the potential exposure to block the acquisition of HIV

Cost?
Toxicitat?
Resistències?
Compensació de risc?

PrEp and ART evidence to come: Summary of status of relevant PrEP and ART effectiveness trials including those underway

	CAPRISA 004(8)	iPrEx(6)	FEM-PREP(10)	Partners in PrEP(4)	CDC-TDF2(7)	HPTN 052(21)	CDC 370(5)
Population	889 women from urban and rural settings in Kwazulu Natal, South Africa	2499 MSM or transgender men in South America, the US and South Africa	1,950 Women at high risk in Kenya, South Africa and Tanzania	4,758 Sero-discordant couples in Kenya, Uganda,	1,219 young adults in Botswana	1,750 Sero-discordant couples in Uganda, Kenya, , Brazil, India, Thailand	2, 413 male and female Injecting drug users in Bangkok, Thailand
Intervention	Before and after sex 1% tenofovir vaginal gel applied	Daily Oral Truvada	Daily Oral Truvada	Daily Oral tenofovir or Truvada	Daily Oral Truvada	ART for positive partner when enrols vs standard	Daily Oral tenofovir
Trial status	Reported Jul 2010	Reported Nov 2010	Reported Apr 2011	Reported Jul 2011	Reported Jul 2011	Reported Aug 2011	Reported Jul 2013

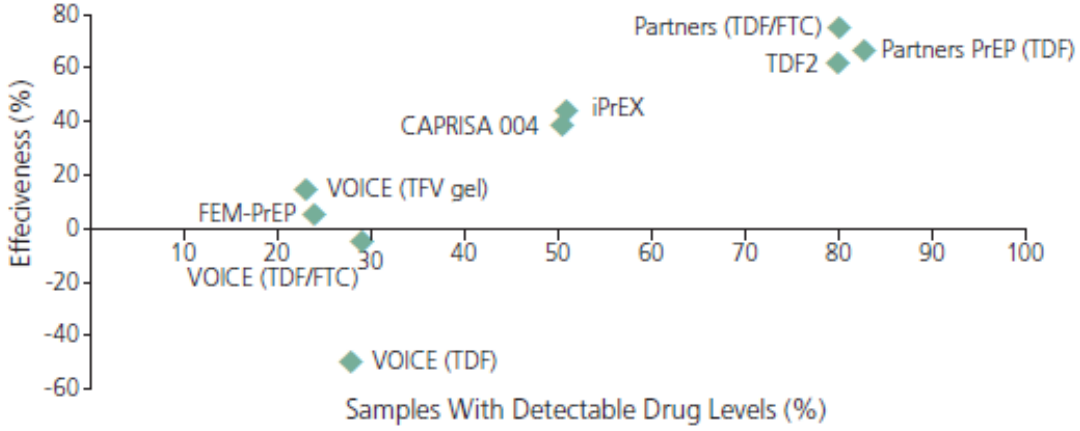


Figure 2. Relationship between effectiveness and adherence in preexposure prophylaxis (PrEP) and microbicide trials (Pearson correlation, 0.86; $P = .003$). CAPRISA indicates Centre for the AIDS Programme of Research in South Africa; FEM-PrEP, Preexposure Prophylaxis Trial for HIV Prevention Among African Women; FTC; emtricitabine; iPrEx, Chemoprophylaxis for HIV Prevention in Men; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; VOICE, Vaginal and Oral Interventions to Control the Epidemic. Adapted from AIDS Vaccine Advocacy Coalition (AVAC).[36]

PrEp and ART evidence to come: Summary of status of relevant PrEP and ART effectiveness trials including those underway

VOICE(11)	FACTS-001(9)	IPERGAY(2)	PROUD(1)	IPM 027/ The Ring Study	MTN20/ Aspire
5,000 Women from urban and rural settings in South Africa, Uganda, Zimbabwe	2059 women from urban and rural settings in South Africa,	413 MSM in France and Canada	545 MSM in England	1950 Women from urban and rural settings in South Africa, Uganda	3476 Women from urban and rural settings in Malawi South Afria, Uganda, Zimbabwe
Daily Oral tenofovir or Truvada or 1% tenofovir vaginal gel	Before and after sex 1% tenofovir vaginal gel applied	Before and after sex Oral Truvada	Dailu Oral Truvada	Continuous Dapivirine, released from a vaginal ring	Continuous Dapivirine, released from a vaginal ring
Reported Feb 2015	Reported Feb 2015	86% Costo-efect		In follow-up to report 2016	In follow-up to report 2016

Eficàcia →

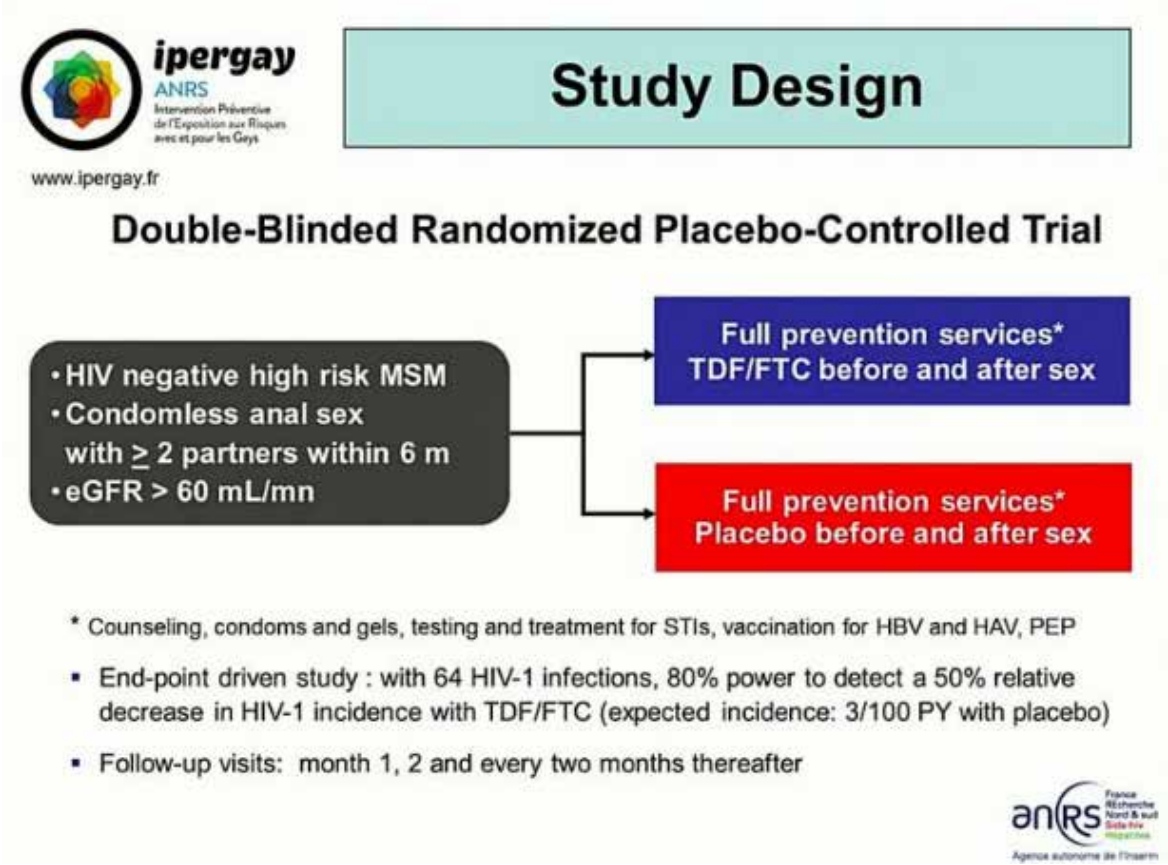
Updated BHIVA-BASHH Position Statement on PrEP in the UK

PrEP Systematic review results

Analysis	No. of studies	Sample Size (N)	Risk Ratio (95% CI)	p-value	I^2	P-value (meta-regression)
RCTs comparing PrEP to placebo						
Overall	10	17424	0.49 (0.33-0.73)	0.001	70.9	--
Adherence						
High (>70%)	3	6150	0.30 (0.21-0.45)	<0.0001	0.0	<0.0001
Moderate (41-70%)	2	4912	0.55 (0.39-0.76)	<0.0001	0.0	0.009
Low (≤40%)	2	5033	0.95 (0.74-1.23)	0.70	0.0	*ref*
Mode of Acquisition						
Rectal	4	3167	0.34 (0.15-0.80)	0.01	29.1	0.36
Vaginal/penile	6	14252	0.54 (0.32-0.90)	0.02	80.1	
Biological sex[1]						
Male	7	8706	0.38 (0.25-0.60)	<0.0001	34.5	0.19
Female	6	8716	0.57 (0.34-0.94)	0.03	68.3	
Age[2]						
18 to 24 years	3	2997	0.71 (0.47-1.06)	0.09	20.5	0.29
≥25 years	3	5129	0.45 (0.22-0.91)	0.03	72.4	
Drug Regimen						
TDF	5	4303 active	0.49 (0.28-0.86)	0.001	63.9	0.88
FTC/TDF	7	5693 active	0.51 (0.31-0.83)	0.007	77.2	
Drug Dosing						
Daily	8	17024	0.54 (0.36-0.81)	0.003	73.6	0.14
Intermittent	1	400	0.14 (0.03-0.63)	0.01	0.0	
RCTs comparing PrEP to no PrEP						
Overall	2	720	0.15 (0.05-0.46)	0.001	0.0	NA

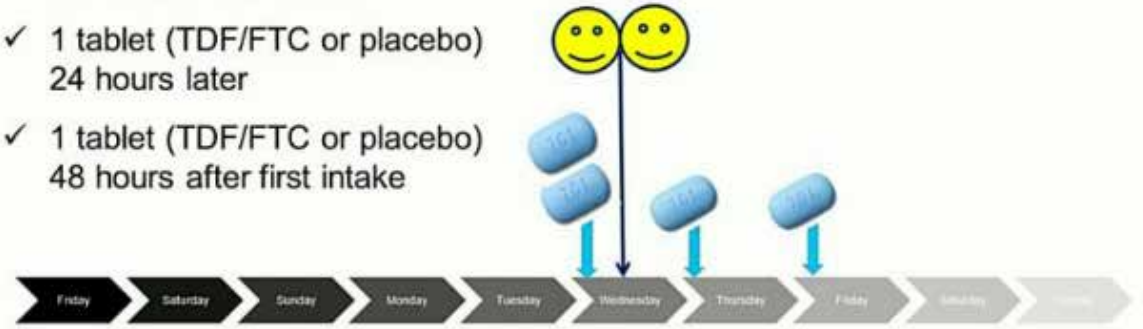
[1] The iPrEx trial included 313 (13%) transgender women. [2] Includes only studies that stratified age by <25 and ≥25.

On Demand PrEP With Oral TDF-FTC in MSM: Results of the ANRS Ipergay Trial



Ipergay : Event-Driven iPrEP

- ✓ 2 tablets (TDF/FTC or placebo) 2-24 hours before sex
- ✓ 1 tablet (TDF/FTC or placebo) 24 hours later
- ✓ 1 tablet (TDF/FTC or placebo) 48 hours after first intake



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ipergay
ANRS
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

Baseline Characteristics

Characteristics (Median, IQR) or (n, %)	TDF/FTC n = 199	Placebo n = 201
Age (years)	35 (29-43)	34 (29-42)
White	190 (95)	184 (92)
Completed secondary education	178 (91)	177 (89)
Employed	167 (85)	167 (84)
Single	144 (77)	149 (81)
History of PEP use	56 (28)	73 (37)
Use of psychoactive drugs*	85 (44)	92 (48)
Circumcised	38 (19)	41 (20)
Infection with NG, CT or TP**	43 (22)	59 (29)
Nb sexual acts in prior 4 weeks	10 (6-18)	10 (5-15)
Nb sexual partners in prior 2 months	8 (5-17)	8 (5-16)

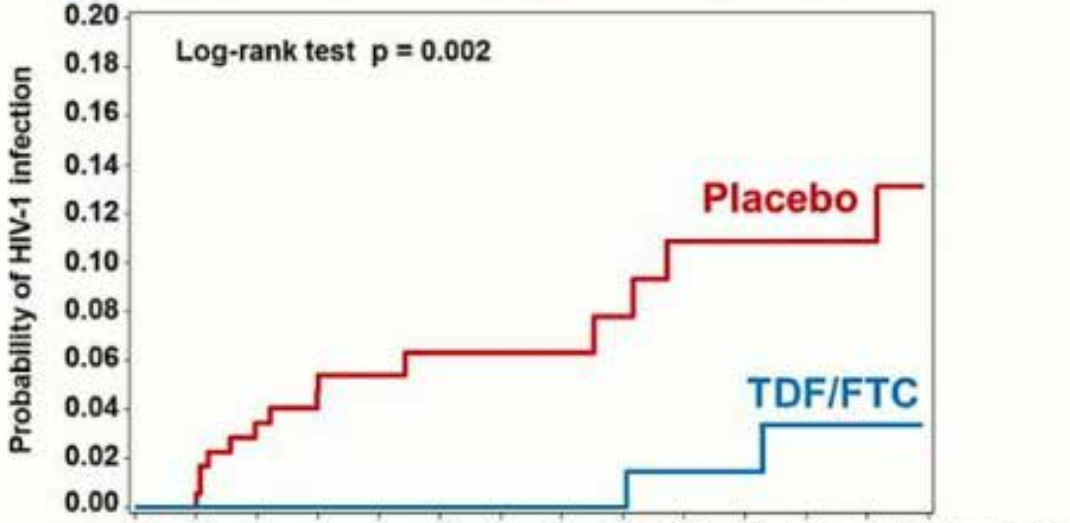
* in last 12 months: ecstasy, crack, cocaine, crystal, speed, GHB/GBL
** NG: Neisseria gonorrhoeae, CT: Chlamydia trachomatis, TP: Treponema pallidum

anrs
Agence autonome de l'Inserm

Jean-Michel Molina, CROI 2/25/2015

ipergay
ANRS
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

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



Mean follow-up of 13 months: 16 subjects infected

14 in placebo arm (incidence: 6.6 per 100 PY), **2 in TDF/FTC arm** (incidence: 0.94 per 100 PY)

86% relative reduction in the incidence of HIV-1 (95% CI: 40-99, p=0.002)
NNT for one year to prevent one infection : 18

anrs France Recherche Nord & sud Sida-hiv Hepatites
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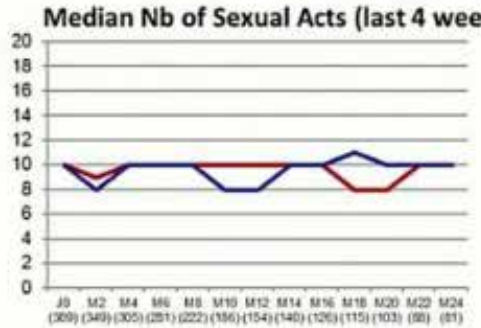
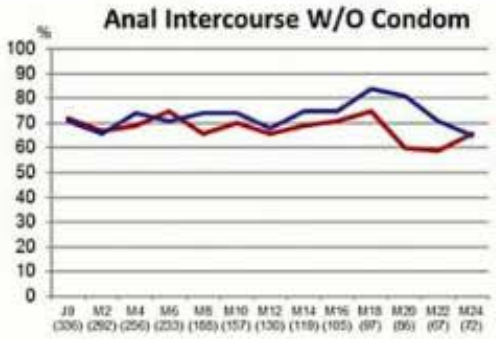
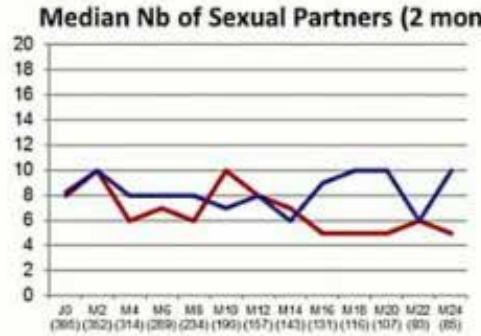
Sexual Behavior

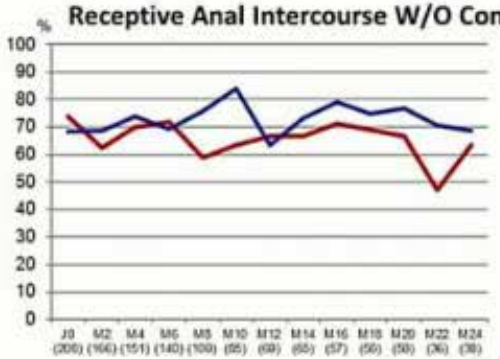




TDF/FTC

Placebo





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Sexually Transmitted Infections

- 276 STIs were diagnosed in 141 participants

	TDF/FTC n=199		Placebo n=201		P value
	Nb Pt (%)	Nb Events	Nb Pt (%)	Nb Events	
Chlamydia	43 (22)	61	34 (17)	48	0.23
Gonorrhoeae	38 (19)	50	45 (22)	67	0.42
Syphilis	19 (10)	19	19 (10)	25	0.98
HCV	3 (<2)	3	3 (<2)	3	1.00
Any STI	76 (38)	133	65 (32)	143	0.22

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Adherence Assessed by CASIs

PrEP use during the last sexual intercourse

1212 sexual intercourses assessed in 319 participants

% PrEP Use (min-max)	TDF/FTC n = 649 acts	Placebo n = 563 acts	Total % (min-max)
Correct use*	45 (36-57)	40 (22-49)	43 (35-51)
Suboptimal use	27 (14-35)	31 (18-44)	29 (20-38)
No PrEP	27 (15-37)	29 (24-44)	28 (20-38)

* According to the protocol, or at least one pill before and one pill after sex

- **Median number of pills/month (IQR):** 16 pills (10-23) in the placebo arm and 16 pills (12-24) in the TDF/FTC arm (p=0.84)
- **48 participants (12%) received PEP**
  25 (13%) in the TDF/FTC arm and 23 (11%) in the placebo arm (p=0.73)

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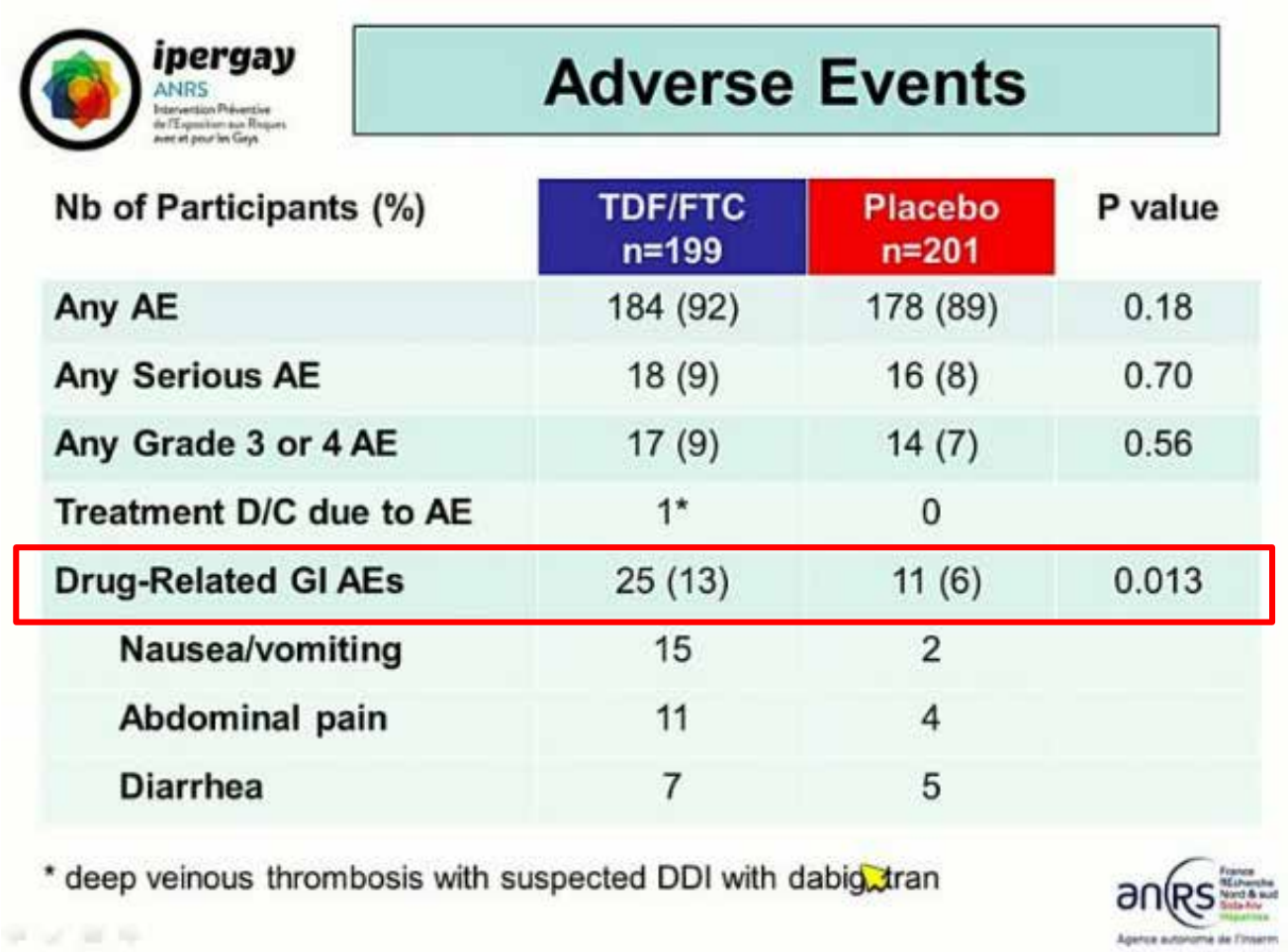

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Lab Abnormalities

Nb of Participants (%)	TDF/FTC n=199	Placebo n=201	P value
Grade 1 Creatinine	28 (14%)*	15 (7%)	0.042
Proteinuria ≥ 2+	10 (5%)	9 (5%)	0.83
Glycosuria ≥ 2+	1 (1%)	0 (0%)	1.00
All Grades ALAT	33 (17%)	26 (13%)	0.37
Grade 3 or 4 ALAT	1 (1%)**	4 (4%)***	0.36

* 2 Participants in the TDF/FTC arm had a transient creatinine clairance < 60 ml/mn
** Acute HCV infection
*** Acute HCV infection in 3 and syphilis in one

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Conclusions

- In this population of high risk MSM, incidence of HIV-1 infection in the placebo arm was higher than expected
- "On Demand" oral PrEP with TDF/FTC was very effective with a 86% (95% CI: 40-99) reduction in HIV-incidence
- Adherence to PrEP was good supporting the acceptability of "on demand" PrEP
- Safety of "on demand" TDF/FTC was overall similar to placebo except for gastrointestinal AEs
- No evidence of risk compensation
- On demand PrEP: attractive alternative to daily PrEP in high risk MSM who do not use condoms consistently

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Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial

Sheena McCormack, David T Dunn*, Monica Desai, David I Dolling, Mitzy Gafos, Richard Gilson, Ann K Sullivan, Amanda Clarke, Iain Reeves, Gabriel Schembri, Nicola Mackie, Christine Bowman, Charles J Lacey, Vanessa Apea, Michael Brady, Julie Fox, Stephen Taylor, Simone Antonucci, Saye H Khoo, James Rooney, Anthony Nardone, Martin Fisher, Alan McOwan, Andrew N Phillips, Anne M Johnson, Brian Gazzard, Owen N Gill*

www.thelancet.com **Published online September 10, 2015** **http://dx.doi.org/10.1016/S0140-6736(15)00056-2**

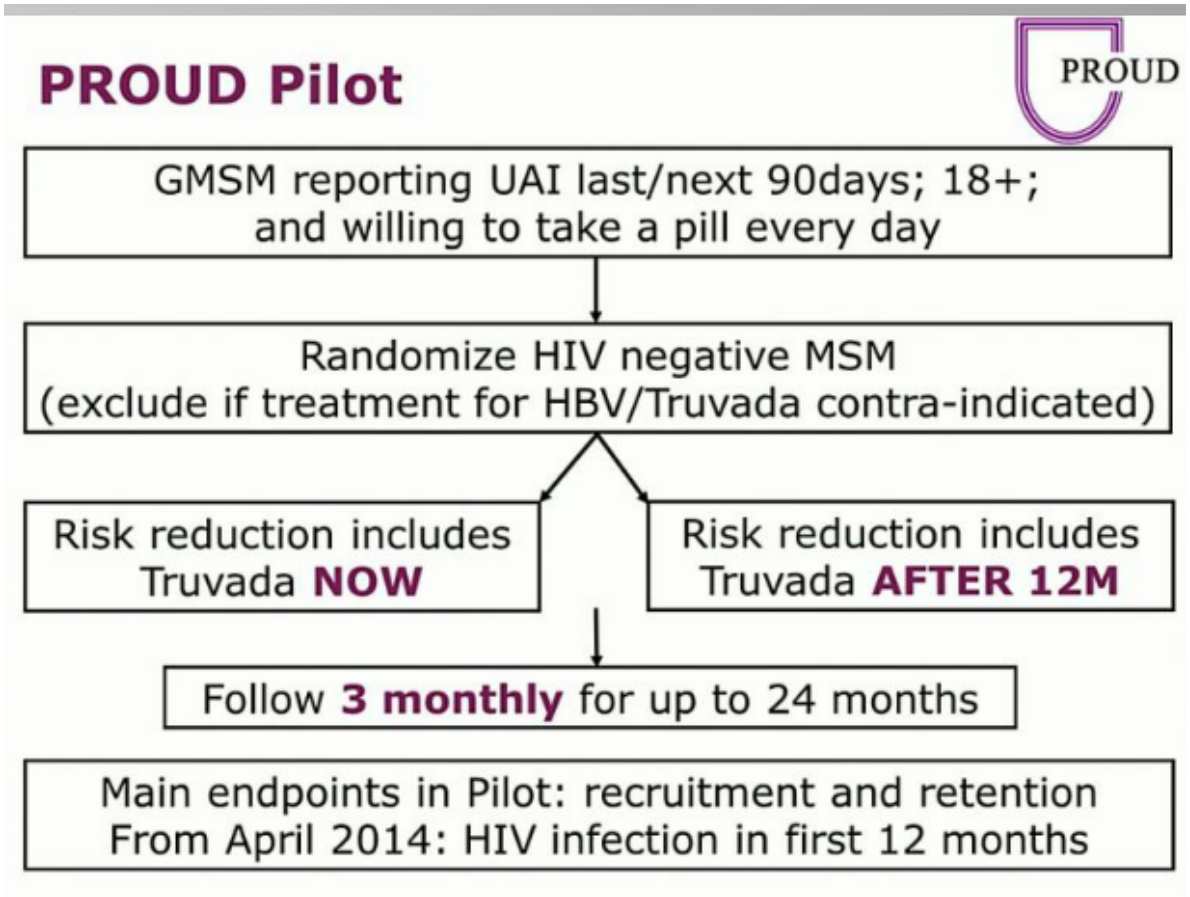
Rationale

- **To determine whether PrEP worked as well as iPrEx in this setting (44% reduction in HIV)**

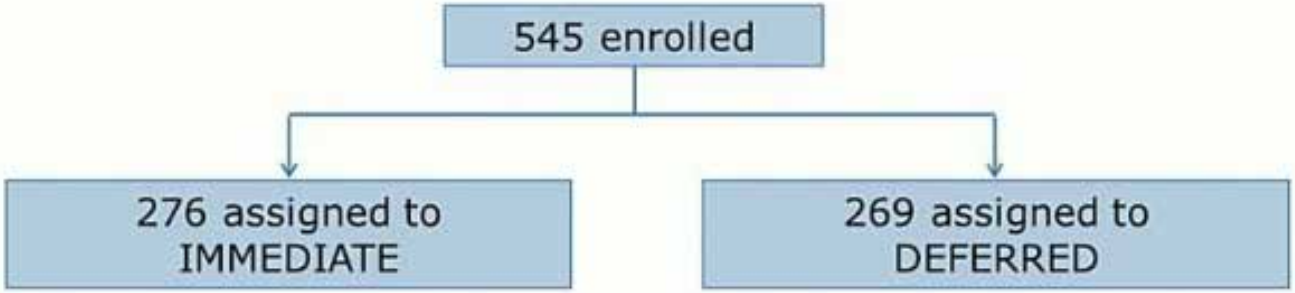
- **Why might effectiveness be less in real world?**
- Adherence less
  - trial schedules monthly
  - well resourced for adherence support

- Behaviour riskier
  - participants constantly reminded that they could be on placebo, and that effectiveness was unknown
  - well resourced for behaviour change interventions

PROUD Pilot


PROUD
GMSM reporting UAI last/next 90days; 18+;
and willing to take a pill every day
Randomize HIV negative MSM
(exclude if treatment for HBV/Truvada contra-indicated)
Risk reduction includes
Truvada NOW
Risk reduction includes
Truvada AFTER 12M
Follow 3 monthly for up to 24 months
Main endpoints in Pilot: recruitment and retention
From April 2014: HIV infection in first 12 months

Participant randomization



Baseline demographics[1]

Characteristics		Immediate	Deferred
Age, median (IQR)		35 (30 – 43)	35 (29 – 42)
Ethnicity	White	80%	82%
Born UK	No	40%	40%
Education	University	59%	60%
Employment	Full-time	70%	73%
Sexuality	Gay	96%	94%
Current relationship	No	53%	55%
Recreational drug use[2]	Yes	76%	64%

[1] 539/545 (99%) questionnaires returned
[2] in the last 90 days

HIV Incidence

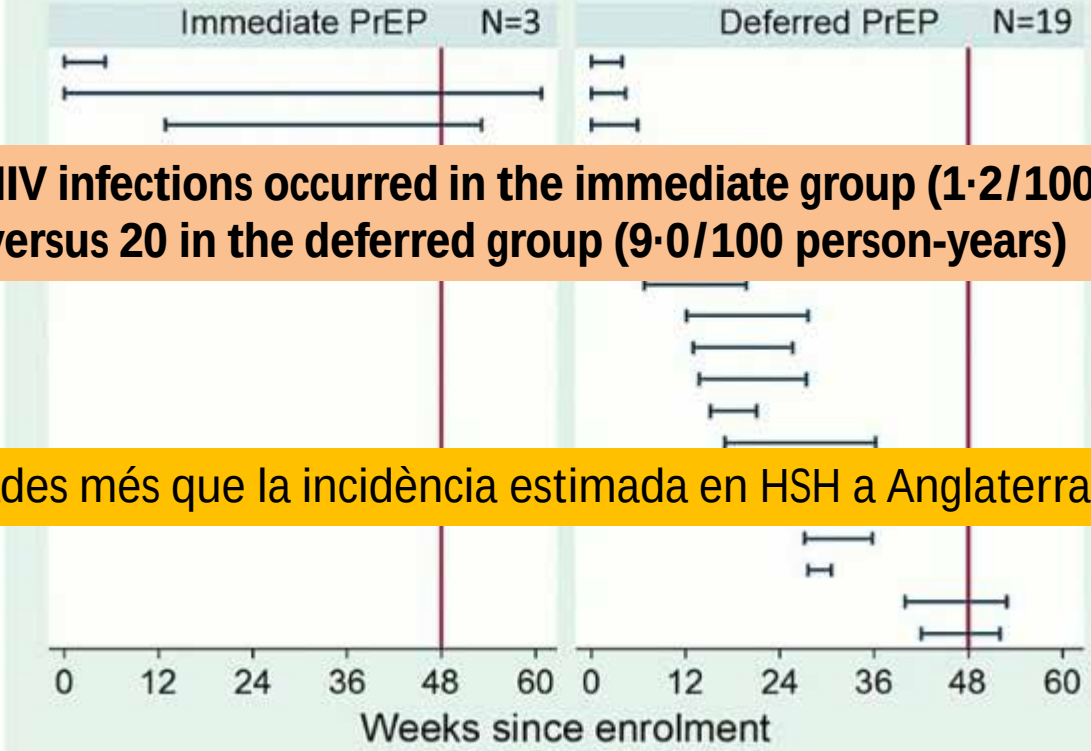
Group	No. of infections	Follow-up (PY)	Incidence (per 100 PY)	90% CI
Overall	22	453	4.9	3.4–6.8
Immediate	3	239	1.3	0.4–3.0
Deferred	19	214	8.9	6.0–12.7

Efficacy =86% (90% CI: 58 – 96%)
P value =0.0002

Rate Difference =7.6 (90% CI: 4.1 – 11.2)
Number Needed to Treat

13 men (90% CI 9–23) would need access to 1 year of PrEP to avert one HIV infection.

Individual incident HIV infections



Three HIV infections occurred in the immediate group (1·2/100 person-years) versus 20 in the deferred group (9·0/100 person-years)

18 vegades més que la incidència estimada en HSH a Anglaterra.

No serious adverse drug reactions; 28 adverse events, most commonly nausea, headache, and arthralgia, resulted in interruption of PrEp.

PrEP interruptions for medical event

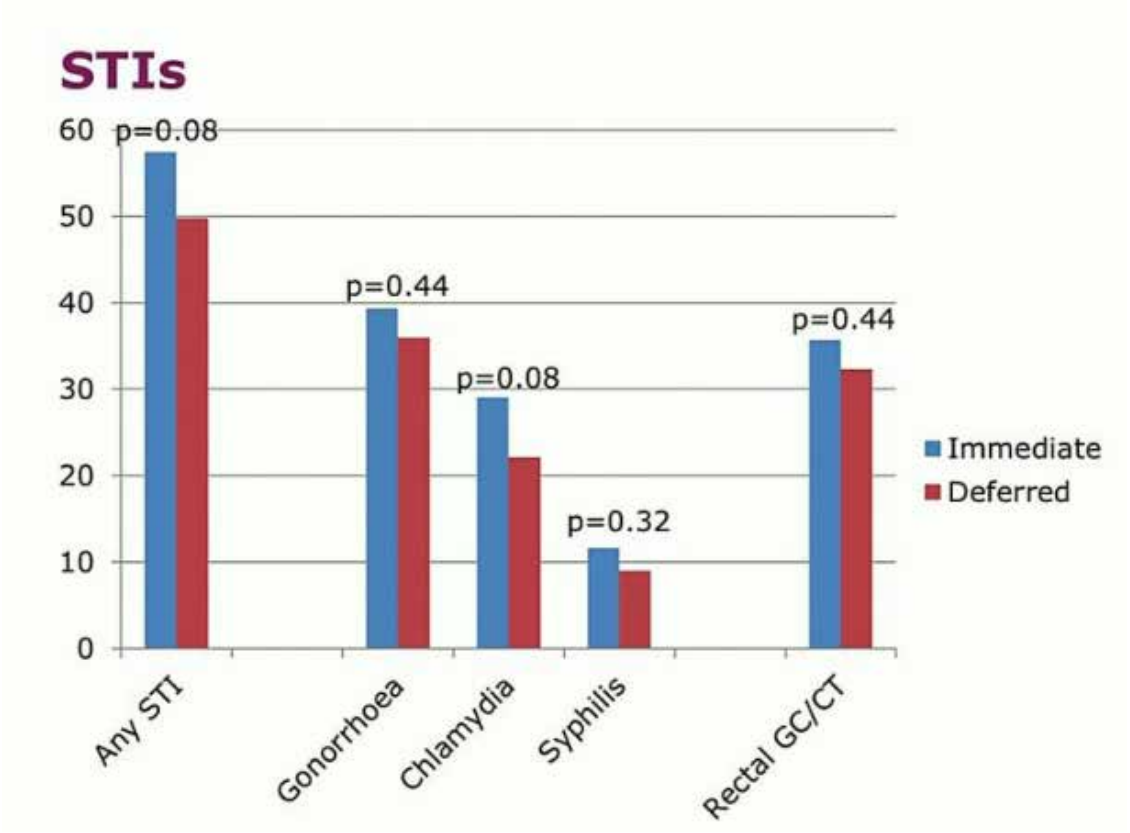
- **PrEP interrupted** by 28 participants (**both groups**) but only **13** had events considered related to drug:
  - nausea alone or with diarrhoea/abdominal pain/aches and fatigue (n=5)
  - decline in creatinine clearance (n=2)
  - headache (n=2)
  - joint pain, with fatigue in one case (n=2)
  - sleep disturbance (n=1)
  - flu-like illness (n=1)
- **PrEP re-started** by 11 of 13 participants above

Drug Resistance

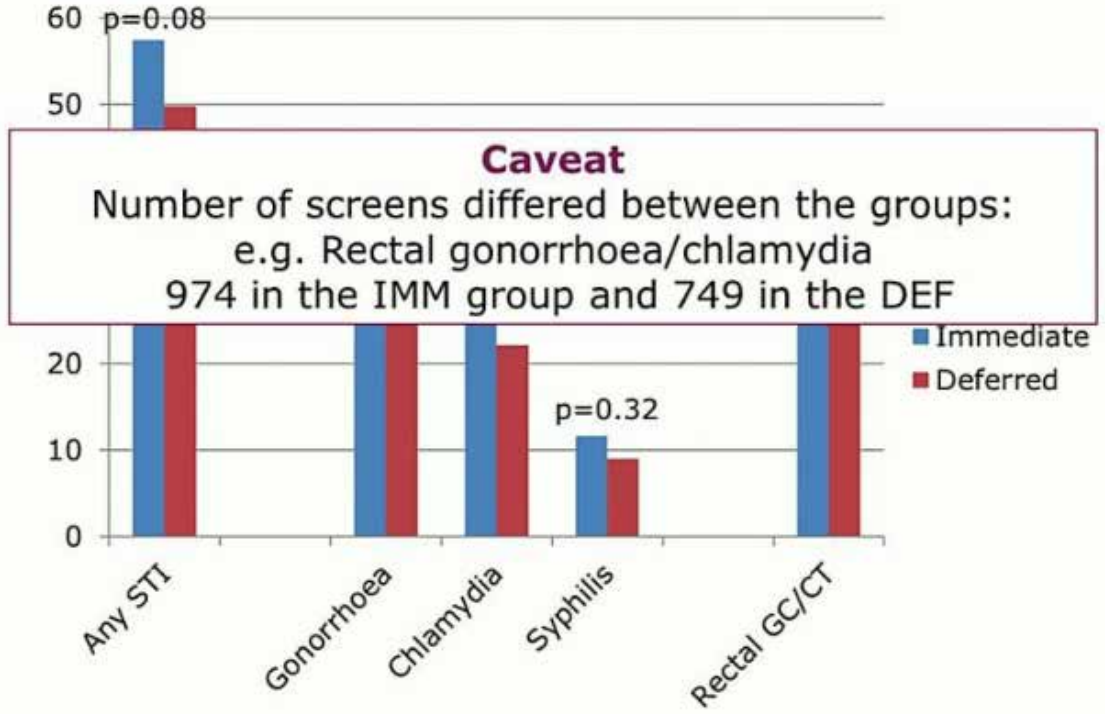
- **3** of **6** individuals who were seroconverting around baseline (immediate group) or month 12 (deferred group) developed **M184V/I** mutations (as a mixture with wild type)

- **K65R** was not detected

No difference in the occurrence of sexually transmitted infections



STIs



Caveat

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

Reported sexual behaviour (preliminary)

Anal sex partners in last 90 days **BASELINE n=539**	**Immediate** Median (IQR)	**Deferred** Median (IQR)
Total number of partners	10.5 (5-20)	10 (4-20)
Condomless partners, participant receptive	3 (1-5)	2 (1-5)
Condomless partners, participant insertive	2.5 (1-6)	3 (1-7)

A suggestion of risk compensation among some PrEP recipients.

Conclusions

- HIV incidence in the population who came forward to access PrEP was much higher than predicted based on all MSM attending sexual health clinics
- Despite extensive use of PEP in the deferred period
- Our concerns about PrEP being less effective in the real world were unfounded

- MSM incorporated PrEP into existing risk reduction strategies which continued to include condom use
- There was no difference in STIs, which were common in both groups

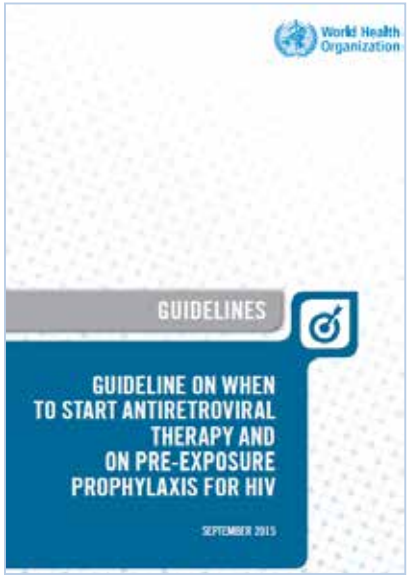
- Clinics were able to adapt routine practice to incorporate PrEP

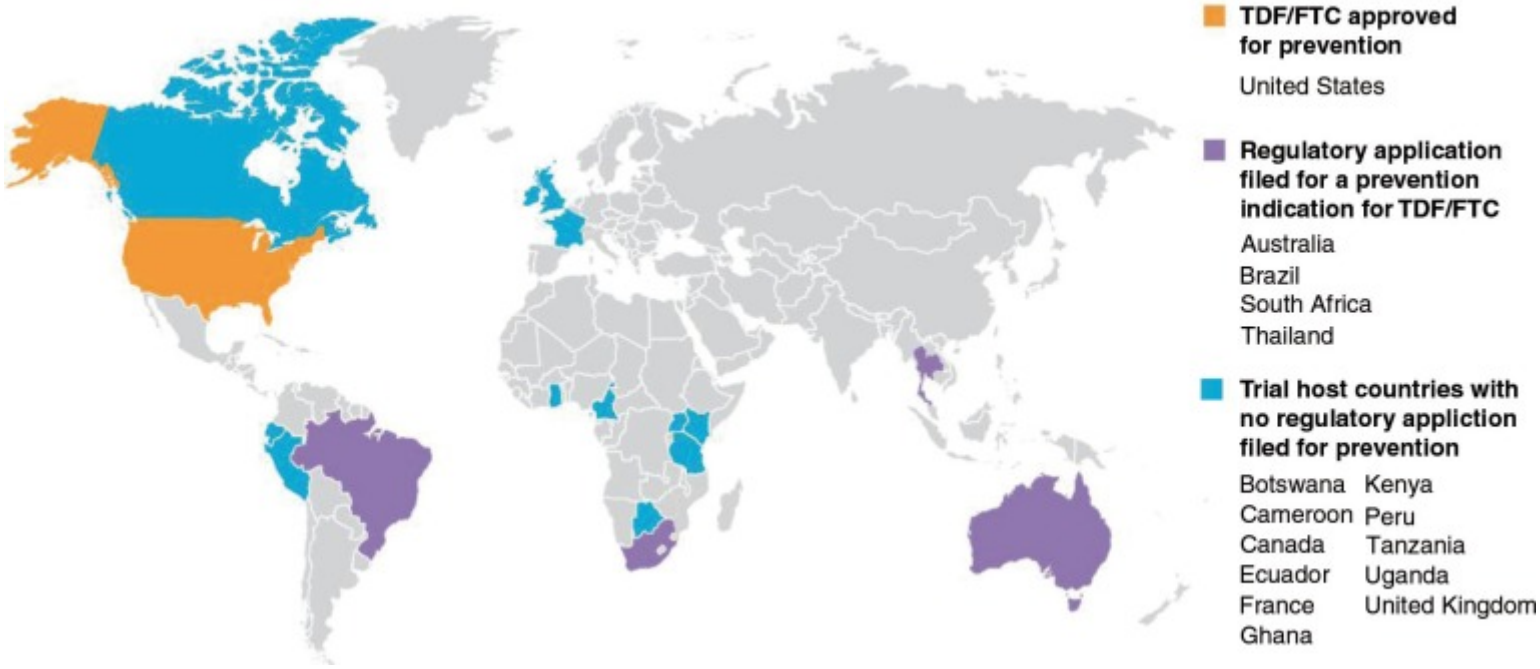
Cost-efectivitat

- Cost-efect en HSH
- “A demanda” 1/2 dosis
- Fin patenteTruvada: 2018
  - Autoritzat en cARV
  - Ús *off label* en PPE

Recommendation 2: Oral pre-exposure prophylaxis to prevent HIV acquisition			
Target population	**Specific recommendation**	**Strength of the recommendation**	**Quality of the evidence**
HIV-negative individuals at substantial risk of HIV infection[b]	Oral PrEP (containing TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches	*Strong*	*High*

NEW





Hankins C et al. *Journal of the International AIDS Society* 2015, **18**(Suppl 3):19973
http://www.jiasociety.org/index.php/jias/article/view/19973 | http://dx.doi.org/10.7448/IAS.18.4.19973

PrEP in USA

- FDA appoved the use of tenofovir/emtricitabine (Truvada™) for PrEP in July 2012, but clinicians have been slow to implement its use in clinical practice.

- The CDC and the USPHS released the first official clinical practice guidelines on the use of PrEP in May, 2014

the WHITE HOUSEPRESIDENT BARACK OBAMA

The White House
Office of the Press Secretary
For Immediate Release
July 30, 2015

FACT SHEET: The National HIV/AIDS Strategy: Updated to 2020

Goal 1: Reducing New HIV Infections
Goal 2: Increasing Access to Care and Improving Health Outcomes for People Living with HIV
Goal 3: Reducing HIV-related Disparities and Health Inequities
Goal 4: Achieving a More Coordinated National Response

HIV prevention

Substantial risk of HIV infection is defined by an incidence of HIV infection in the absence of PrEP that is sufficiently high (>3% incidence) to make offering PrEP potentially cost-saving (or cost-effective).

Offering PrEP to people at substantial risk of HIV infection maximizes the benefits relative to the risks and costs.

People at substantial risk of HIV infection are present in most countries, including some (but not all) people identified with key and vulnerable populations and some people not so identified.

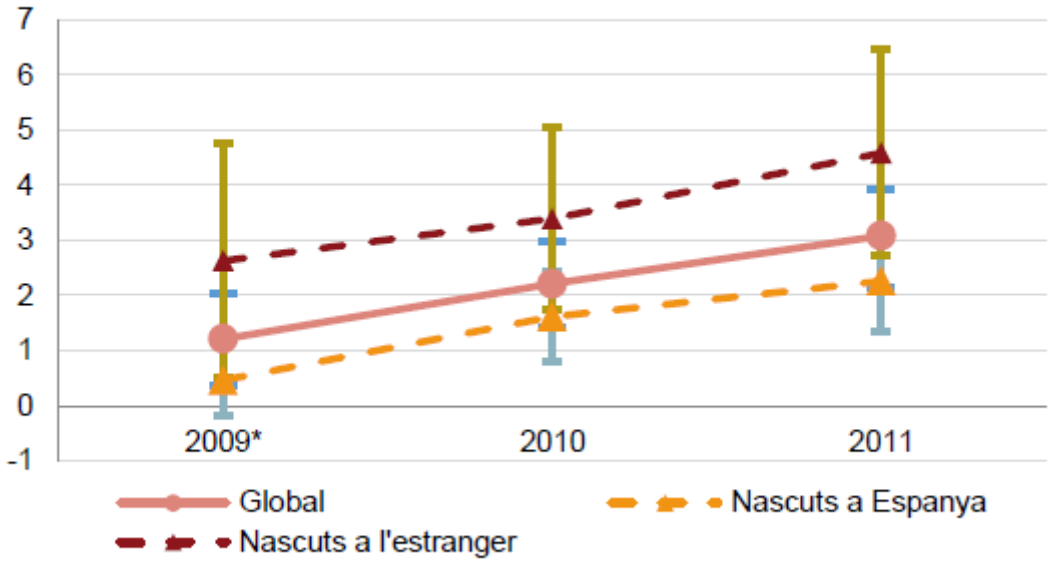
OMS 2015

HIV incidence rate in people undergoing HIV testing, by different variables, EPI-VIH Study, Spain, 2000–09 (n=30,679)

Variable	Number of persons tested	Number of seroconversions	Person-years	Incidence rate[a] (95% CI)
Sex				
Male	15,672	601	34,086.2	1.8 (1.6 to 1.9)
Female	14,840	36	29,588.1	0.1 (0.09 to 0.2)
Transgender women	167	5	429.8	1.2 (0.5 to 2.8)
Age group (years)				
<20	1,193	14	1,051.2	1.3(0.8 to 2.3)
20–24	6,899	88	9,595.1	0.9 (0.7 to 1.1)
25–29	8,071	163	15,886.3	1.0 (0.9 to 1.2)
30–34	6,304	163	14,737.5	1.1 (1.0 to 1.3)
35–39	4,065	132	10,826.6	1.2 (1.0 to 1.5)
40–44	2,126	50	6,178.0	0.8 (0.6 to 1.1)
45–49	1,015	19	2,974.2	0.6 (0.4 to 1.0)
>50	1,006	13	2,855.2	0.5 (0.3 to 0.8)
Region of birth				
Spain	15,970	423	33,340.2	1.3 (1.2 to 1.4)
Western[b]/Eastern Europe	1,912	29	3,224.5	0.9 (0.6 to 1.3)
Latin America	9,796	121	19,999.2	0.6 (0.5 to 0.7)
Sub-Saharan/ North Africa	1,132	8	1,901.6	0.4 (0.2 to 0.8)
Other	167	6	250,4	2.4 (1.1 to 5.3)
HIV transmission category				
PWID or ex-PWID	884	32	2,016.1	1.6 (1.1 to 2.2)
MSM	8,492	529	21,181.0	2.5 (2.3 to 2.7)
Heterosexual men and women	10,500	23	17,914.2	0.1 (0.09 to 0.2)
Female sex worker	9,808	16	21,027.9	0.1 (0.05 to 0.1)
MSM sex worker	549	39	1,311.0	3.0 (2.2 to 4.1)

Díez M et al, Euro Surveill. 2014;19(47):pii=20971.

Figura 1.13. Incidència global i per origen en HSH. Cohort ITACA, desembre de 2008 - desembre de 2011



* Inclou dades de desembre 2008

93.8% casi siempre o siempre usan preservativo

SIVES 2015

Cohort saunes. ASPB

- HSH
- 2007-
- Incidència (2014): 2.7 casos/100 persones-any (IC 1.8-3.8)

P079 Knowledge and willingness to use pre-exposure prophylaxis among men who have sex with men in Spain

Laia Ferrer Serret[1], Cinta Folch[1], Percy Fernández-Dávila[1], Josefina Belda[2], Antonio Susperregui[3], Adriana Morales[4] and Jordi Casabona[1]

[1]CEEISCAT, Spain; [2]UPS-ITS, Spain; [3]ADHARA, Spain; [4]STOP SIDA, Spain

866 MSM HIV-negatives aged18 years

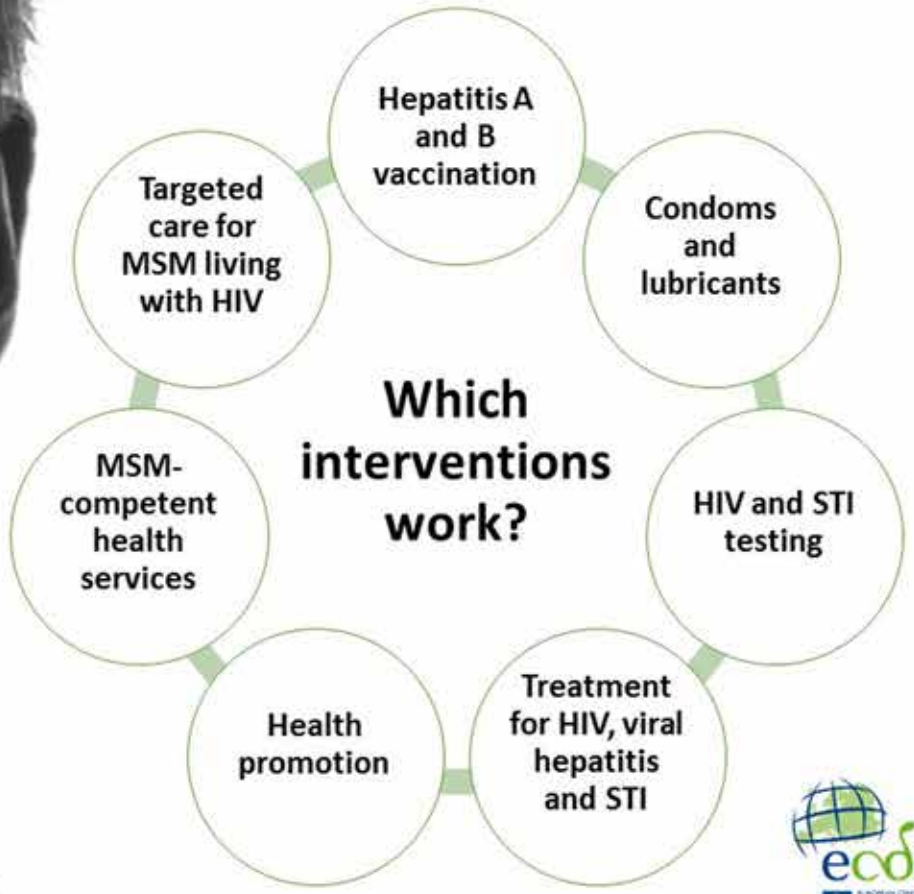
Paper-and-pencil and online version of a questionnaire

29% of men knew PrEP, 57.6% intent to use it, 16.6% did not intent and 26% hesitated

Men knowing about PrEP had more doubts about its use.

Having access to VCT centres was associated with knowledge of PrEP

ECDC Guidance: HIV and STI prevention among men who have sex with men



ecdc

EACS guidelines, Octubre 2015

- Recommended in HIV-negative men who have sex with men (MSM) and transgender individuals who are inconsistent in their use of condoms with casual partners or with HIV-positive partners who are not on treatment. A recent STD or use of post-exposure prophylaxis may be markers of increased risk for HIV acquisition.
- May be considered in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and likely to have HIV positive partners who are not on treatment.

PrEP regimen

TDF/FTC 300*/200 mg 1 tablet qd. For MSM with high-risk sexual behavior PrEP may be dosed 'on demand' (double dose of drug 2-24 hours before each sexual intercourse, followed by two single doses of drug, 24 and 48 hours after the first drug intake). If dosed 'on demand', the total dose per week should not exceed 7 tablets.

- No estem preparats
- Cóm integrar-lo amb la resta de serveis: ¿final del sexe segur?
- Cost: fàrmacs, analítiques, DMO, cribratges ITS, professionals...¿és assumible per Salut Pública?
- Durada? Cada dia? Intermitent? Abans de relació de risc?

Queda pendent

- Com: implementació
- On i qui: Atenció Primària? UVIH? UITS? ONG?
- Amb quins recursos

Conclusió

- Alt nivell d'evidència de la eficàcia de PrEP en població d'alt risc i adherent
- Bona tolerància, baix risc de resistències i no compensació de risc
- Manca d'explorar nous fàrmacs i formulacions
- Pendent definir i avaluar la implementació al nostre entorn
- Pendent avaluar la eficiència a a llarg termini a la vida real