BASHH
British Association for Sexual Health and HIV

ANNUAL CONFERENCE 2019

PrEP Update

Sheena McCormack
MRC Clinical Trials Unit at UCL
56 Dean Street, CWH
Imperial College

Disclosures

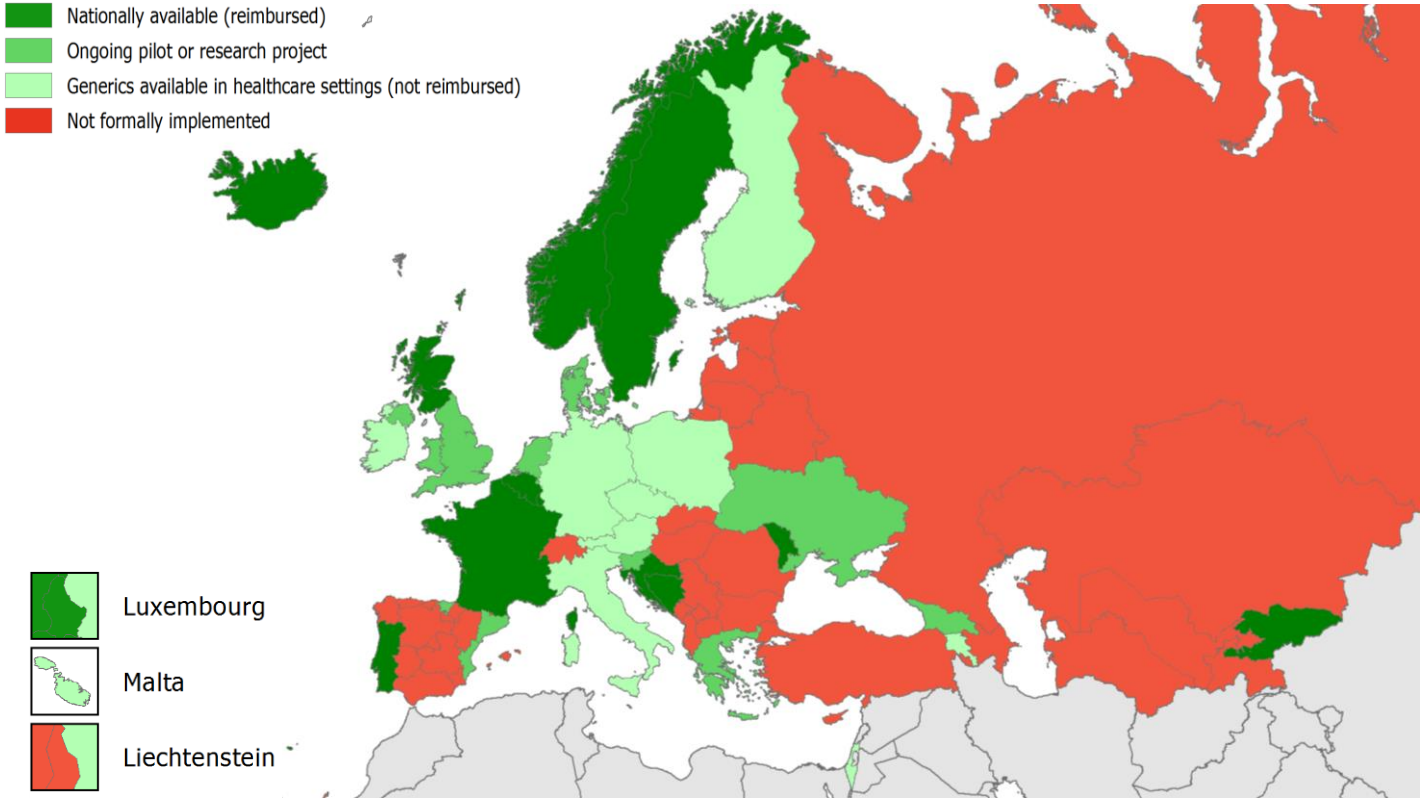
- Grant support from EU2020, EDCTP, NIHR and Gilead Sciences, and Gilead provided drug for PROUD (during and after)
- None through employment, stocks, patents, consultancy, speaking engagements (money to UCL for my time)

Outline

- TDF/FTC penetration and emerging themes
- Choice and the PrEP pipeline
- PrEP Impact, and current issues

Status of formal PrEP implementation in Europe

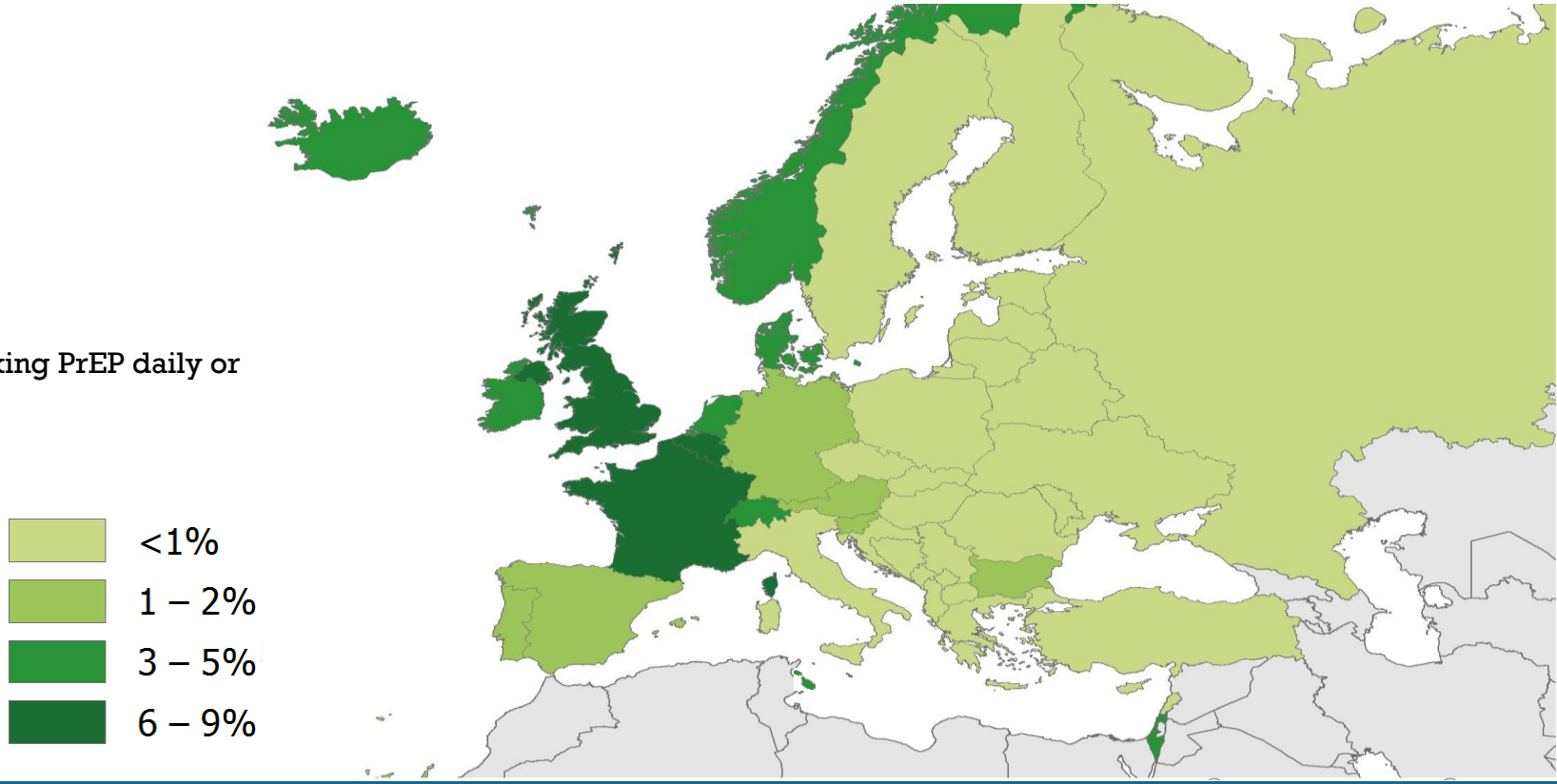
June, 2019



Source: ECDC. Dublin Declaration monitoring 2019; validated unpublished data.

DDM 3.29
Use of PrEP

Percentage taking PrEP daily or on demand.

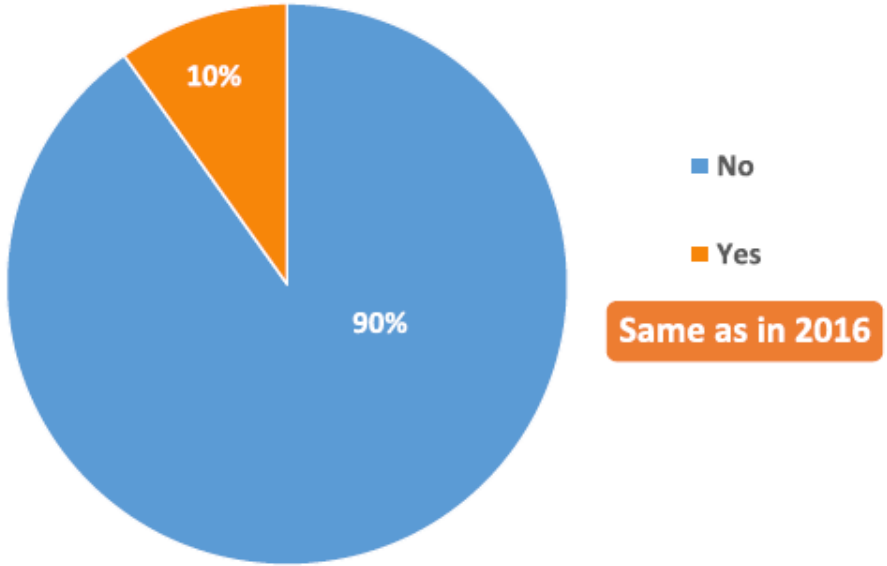


Citation: **The EMIS Network: 2018 Dublin Declaration Monitoring indicators for men-who-have-sex-with-men in Europe. LSHTM/RKI, London/Berlin 2018.**
Primary Funding: **EU Health Programme 2014-2020 for Europe.** **www.esticom.eu** **www.emis2017.eu**

Hornet survey 2016, 2017

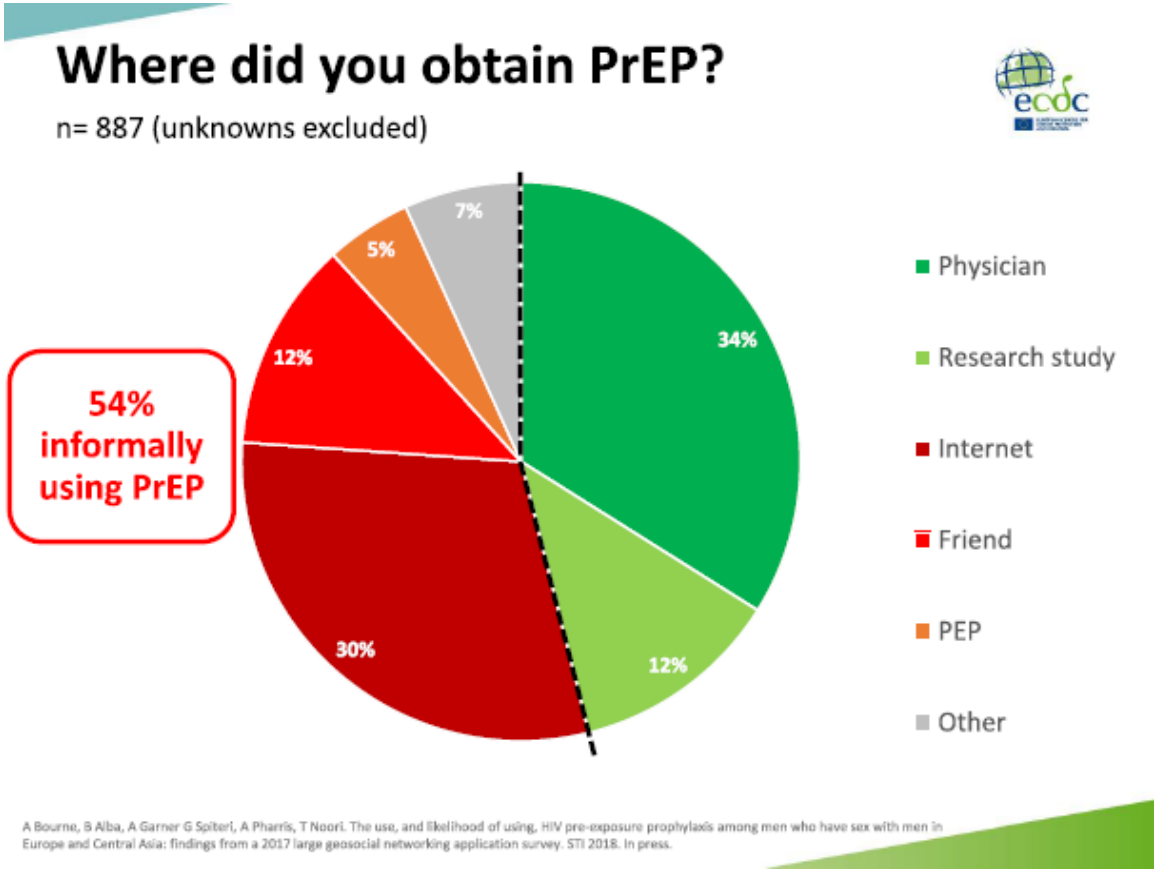
Are you currently taking PrEP?

n= 10,562 (excludes HIV-positive respondents and non-responders)

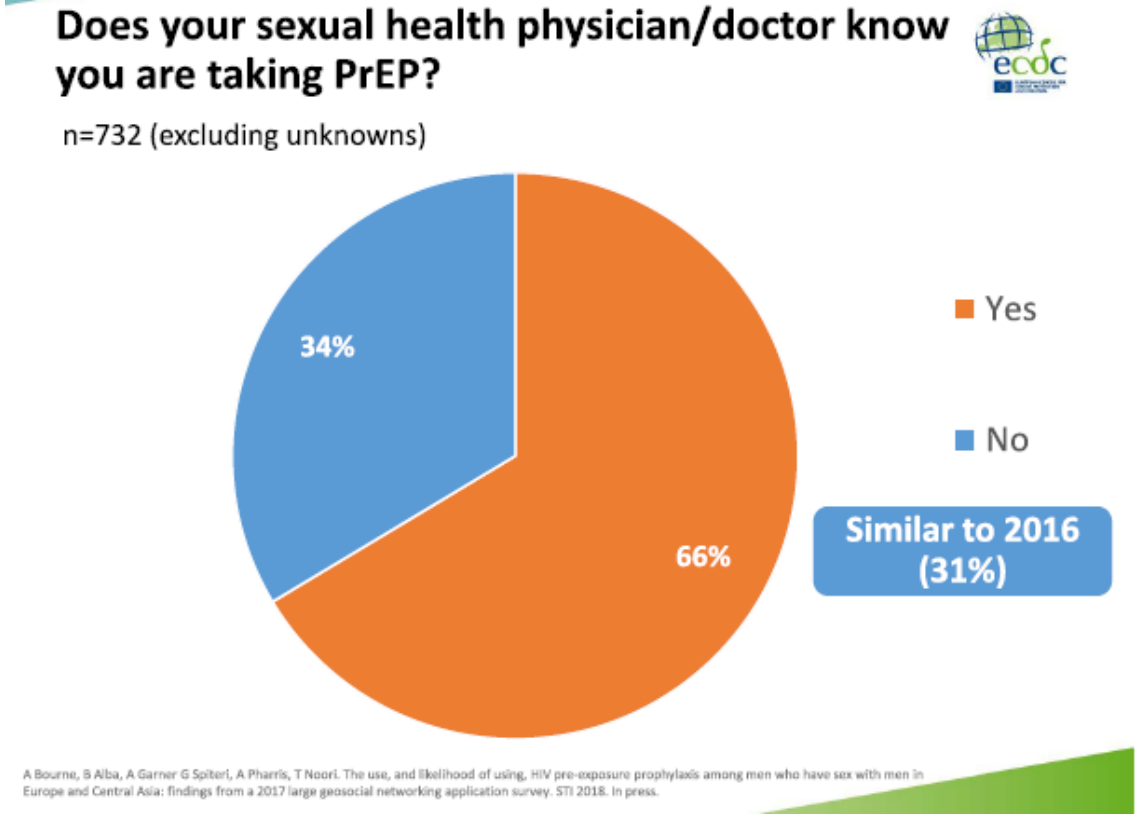


A Bourne, B Alba, A Garner G Spiteri, A Pharris, T Noori. The use, and likelihood of using, HIV pre-exposure prophylaxis among men who have sex with men in Europe and Central Asia: findings from a 2017 large geosocial networking application survey. STI 2018. In press.

Hornet survey 2016, 2017



Hornet survey 2016, 2017



A Bourne, S Alba, A Garner G Spiteri, A Pharris, T Noori. The use, and likelihood of using, HIV pre-exposure prophylaxis among men who have sex with men in Europe and Central Asia: findings from a 2017 large geosocial networking application survey. STI 2018. In press.

What has worked well in Europe?

- Partnership with government and community to deliver services and embed evaluation eg France, Scotland, Norway
- Partnership with community to support those purchasing drug online eg England, Spain
- We embraced event-driven/on-demand, which underscored the fact that PrEP is not for life (EACS, French and BASHH/BHIVA guideines)

Prévenir ANRS

HIV Incidence (ITT Analysis)

Treatment	Follow-Up Pts-years	HIV Incidence per 100 Pts-years (95% CI)
TDF/FTC (Daily)	443	**0** (0-0.8)
TDF/FTC (On Demand)	506	**0** (0-0.7)

Mean Follow-up in this Open-Label Study: 7 months (SD: 4)

Incidence of study discontinuation:
3.3/100 PY including 1.5/100 PY who discontinued PrEP

85 HIV-infections averted*

Emerging themes

Persistence on daily is challenging

- Average duration on PrEP in many populations is relatively brief in US
  - MSM 38% - 57% at 6 months; 43% - 63% at 1 year
  - Women 37.5% at 6 months
- HIV infections high if stop PrEP
  - 18 seroconversions in San Francisco STD clinic
  - 3.9/100 py in Montreal
  - 0.95/100py vs. 0.25 in those remaining on PrEP in Los Angeles

Blackstock, AIDS Care 2017;29:866-9
Greenwald, CROI 2018, Abstract #1038
Liu, JAMA Intern Med 2016;176:75-84
Rusie, CID 2018;67:283-7
Chan, JIAS 2016;19: 20903
Hojilla, AIDS and Behav; 2018:22:1096-9
Montgomery PLOS One 2016;11:e0157742
Shover, CROI 2018, Abstract #1009

Biomedical Interventions and Risk Compensation

Jean-Michel Molina
Saint-Louis Hospital, University of Paris Diderot,
ANRS (National Agency for AIDS Research)
Inserm U941, Paris, France

STI 2018
Understanding and Adressing the HIV and STI syndemics

Amsterdam, July 21-22, 2018

STIs increasing - maybe

- Studies plagued by methodological challenges such as temporal, selection and detection bias
- PROUD randomized - but rates very high at start
- Partners, not PrEP/condom use, drive STI rates
- PrEP users in European Hornet survey more likely to be tested for STIs than those not using PrEP
- PrEP is an opportunity for STI control, not a threat

Choice should improve uptake and adherence

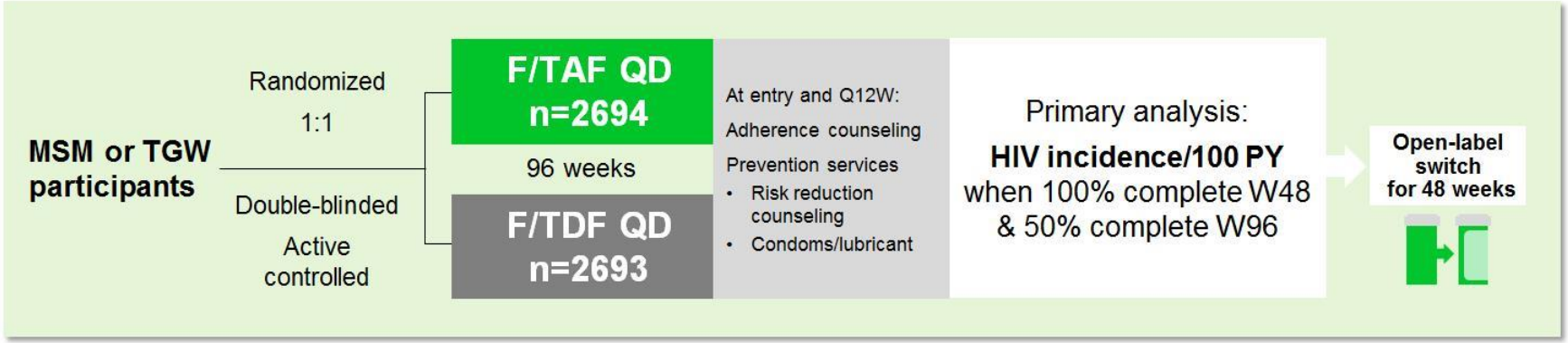
People want a Choice

Monthly Dapivirine Ring

- Flexible silicone vaginal ring developed by IPM
- Woman-initiated
  - Self-inserted monthly
  - Discreet
- Slowly releases ARV dapivirine
- Reduced women's HIV-1 risk by ~30% in two Phase III trials
- Modelling in 2 open-label trials estimates reduced risk by 54%
- Under regulatory review with EMA, and WHO next

Nel A et al. NEJM 2016
Baeten J et al. NEJM 2016
Baeten J et al. CROI 2018, #143LB
Nel A et al. CROI 2018, #144LB

DISCOVER: A Randomized, Noninferiority Trial of F/TAF for PrEP



Eligibility required high sexual risk of HIV

- 2+ episodes condomless anal sex in past 12W **or** rectal gonorrhea/ chlamydia, syphilis in past 24W
- HIV & HBV negative, eGFR ≥60 mL/min
- Prior use of PrEP allowed

Study conducted in NA, EU in cities/sites with high HIV incidence

- 94 sites in 11 countries
- Participants: US, 60%; EU, 34%; Canada, 7%

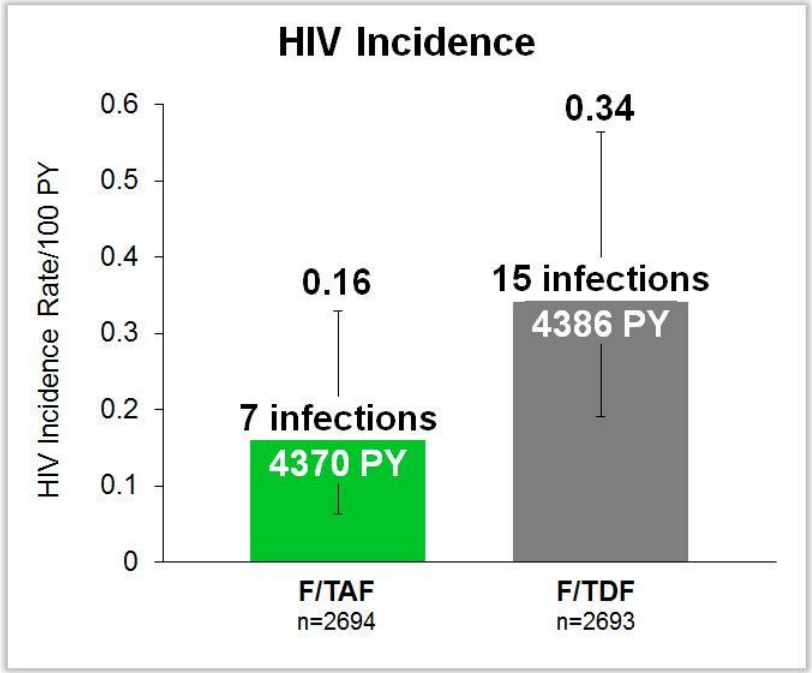
Primary efficacy endpoint: HIV incidence

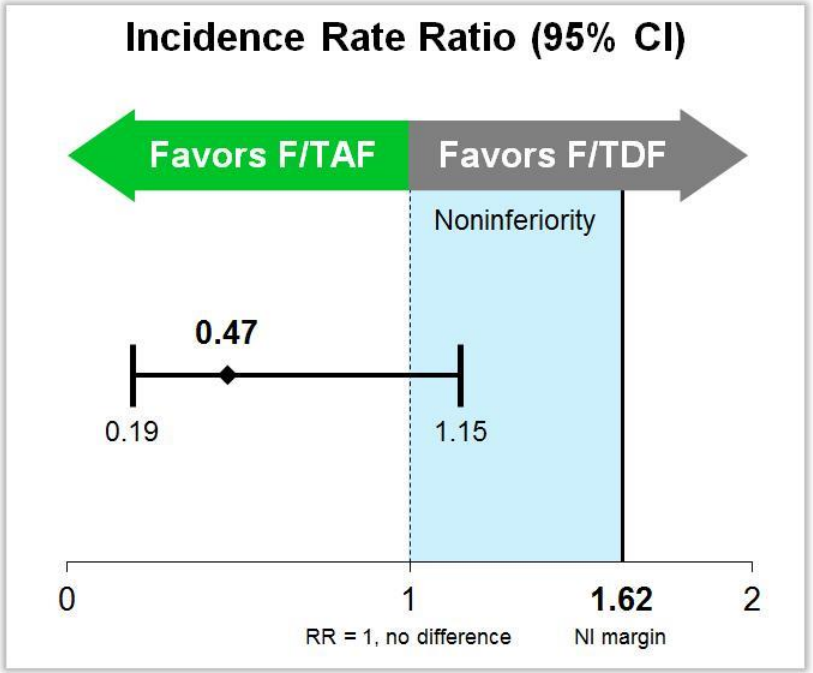
- Evaluated by rate ratio with noninferiority (NI) margin <1.62
- Expected incidence of 1.44/100 PY based on pooled studies: iPrEx, PROUD, IPERGAY

F/TAF dose: 200/25 mg; F/TDF dose: 200/300 mg. eGFR, estimated glomerular filtration rate.

DISCOVER Primary Endpoint Analysis: HIV Incidence

22 HIV infections in 8756 PY of follow-up





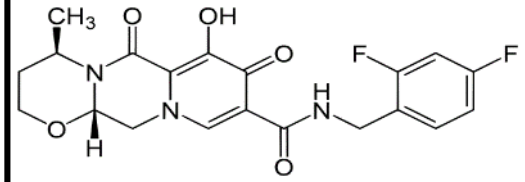
F/TAF is noninferior to F/TDF for HIV prevention

CI, confidence interval; RR, rate ratio.

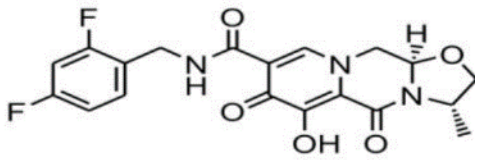
Long-acting Injectables: Cabotegravir

- **Cabotegravir LA is a long-acting suspension for delivery via IM injection** (Currently in advanced development for Maintenance of virologic suppression [with RPV LA] and PrEP-monotherapy)
- **Agent class:**
  Strand-transfer integrase inhibitor
- **Half-life:**
  Oral: 40 hours
  Injectable: 40-65 days

DOLUTEGRAVIR

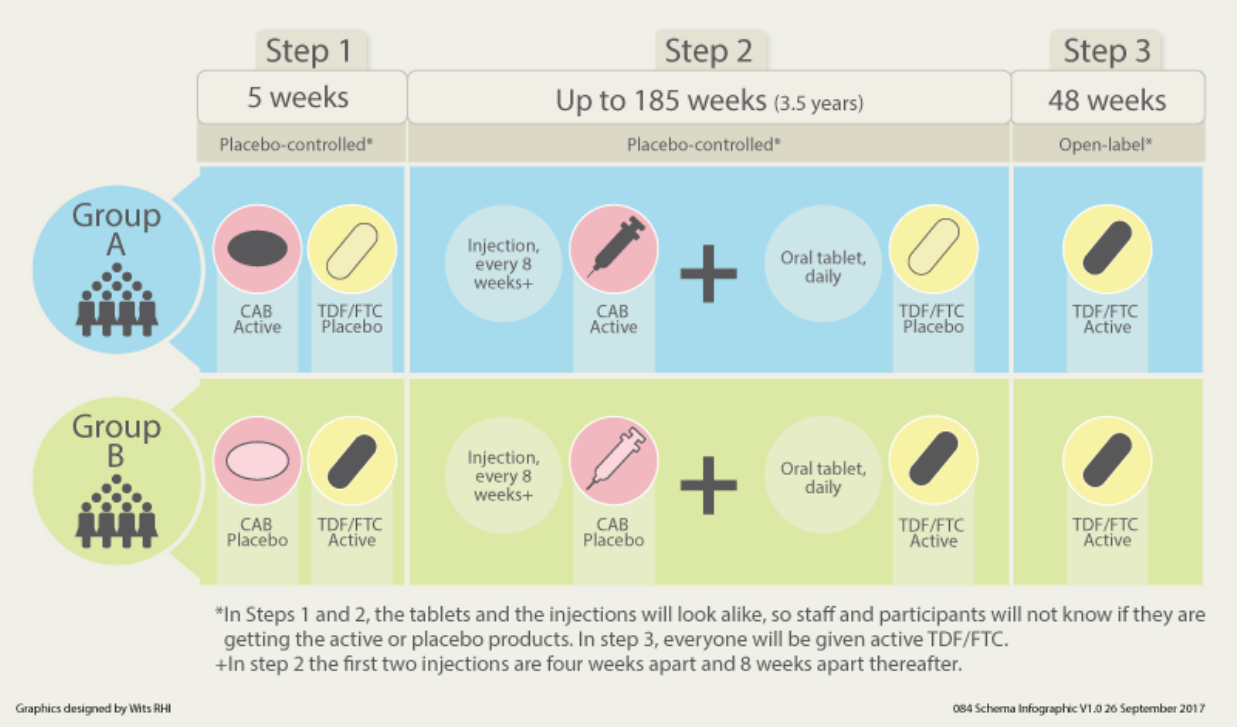


CABOTEGRAVIR



HPTN 083 and 084: Phase 3 for CAB LA PrEP

Objective: To evaluate the safety and efficacy of CAB LA compared to TDF/FTC for PrEP in HIV uninfected MSM/TGW (083) and cisgender women (084)



Implantable Devices

- Reversible with removal
- Long-acting (months to years)
- Potential for Multi-purpose
- Current development
  - TAF, CAB, EFdA
  - Others

Schlesinger, et al, Pharm Res 2016
Gunawardana, et al., AAC 2015

PrEP Impact and current issues

Public Health England

PrEP Impact Trial: What is it?

? Non-interventional, non-randomised trial of PrEP implementation

13,000 (26,000) participants over 3 years

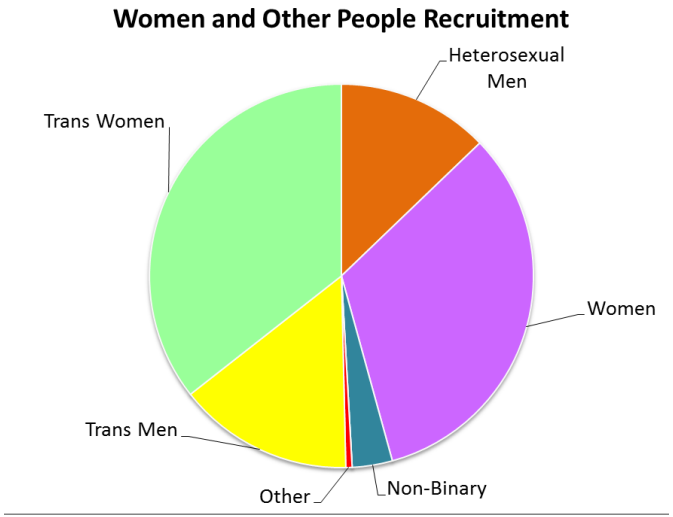
✓ Eligibility criteria developed by policy proposition stakeholder group

Uses existing systems for data collection, including the yellow card system

Public Health England

Impact trial progress (24th June 2019)

13,231 participants



PrEP Impact Trial

A pragmatic health technology assessment of PrEP and implementation

Home | The PrEP Impact Trial | FAQs | Join the Trial | Trial Site Resources

Well done you!

Public Health England

Trial objectives

1. To measure eligibility, uptake, duration of eligibility and duration of use among GUM clinic attendees
2. To determine whether or not incident HIV infections in trial participants are due to non-adherence or biological failure
3. To measure change over time in HIV diagnoses and incidence rate in those at high HIV risk
4. To measure change over time in bacterial STI diagnoses and incidence rate in those at high HIV risk
5. To measure the PrEP prevention care continuum by clinic throughput and in different regions

Safety not an objective

- Serious adverse events do not need to be reported unless they merit a yellow card
- Two reasons you might send in a yellow card
  - An unexpected event clearly linked to drug in time (usually moderate-severe)
  - A recognised event that is more severe than expected, for example one that led to a *clinical* decision to discontinue PrEP

How to judge expectedness

https://www.medicines.org.uk/emc/product/9028/smpc#UNDESIRABLE_EFFECTS

emc

HOME | MEDICINES | COMPANIES | LATEST UPDATES | ABOUT EMC | HELP | SIGN UP | LOG IN

4.8 Undesirable effects

Summary of the safety profile

HIV-1 infection: The most frequently reported adverse reactions considered possibly or probably related to emtricitabine and/or tenofovir disoproxil were nausea (12%) and diarrhoea (7%) in an open-label randomised clinical study in adults (GS-01-934, see section 5.1). The safety profile of emtricitabine and tenofovir disoproxil in this study was consistent with the previous experience with these agents when each was administered with other antiretroviral agents.

Pre-exposure prophylaxis: No new adverse reactions to emtricitabine/tenofovir disoproxil were identified from two randomised placebo-controlled studies (iPrEx, Partners PrEP) in which 2,830 HIV-1 uninfected adults received emtricitabine/tenofovir disoproxil once daily for pre-exposure prophylaxis. Patients were followed for a median of 71 weeks and 87 weeks, respectively. The most frequent adverse reaction reported in the emtricitabine/tenofovir disoproxil group in the iPrEx study was headache (1%).

Tabulated summary of adverse reactions

The adverse reactions considered at least possibly related to treatment with the components of emtricitabine/tenofovir disoproxil from clinical study and post-marketing experience in HIV-1 infected patients are listed in Table 3, below, by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) or rare (≥ 1/10,000 to < 1/1,000).

Table 3: Tabulated summary of adverse reactions associated with the individual components of emtricitabine/tenofovir disoproxil based on clinical study and post-marketing experience

Frequency	Emtricitabine	Tenofovir disoproxil
Blood and lymphatic system disorders:		
Common:	neutropenia	
Uncommon:	anaemia[2]	
Immune system disorders:		
Common:	allergic reaction	
Metabolism and nutrition disorders:		
Very common:		hypophosphataemia[1]
Common:	hyperglycaemia, hypertriglyceridaemia	

1. Name of the medicinal product
2. Qualitative and quantitative composition
3. Pharmaceutical form
4. Clinical particulars
4.1 Therapeutic indications
4.2 Posology and method of administration
4.3 Contraindications
4.4 Special warnings and precautions for use
4.5 Interaction with other medicinal products and other

4.8 Undesirable effects

5.1 Pharmacodynamic properties
5.2 Pharmacokinetic properties
5.3 Preclinical safety data
6. Pharmaceutical particulars
6.1 List of excipients
6.2 Incompatibilities
6.3 Shelf life
6.4 Special precautions for storage
6.5 Nature and contents of container
6.6 Special precautions for disposal and other handling
7. Marketing authorisation holder

Renal scenarios

- Baseline eGFR abnormal, or significant decline
  - Check for evidence of body building (creatinine/protein supplements, high protein diets, steroids)
  - ➢ Can repeat after 48hrs interruption of supplements
  - Check other factors (diabetes, blood pressure, age, etc)
  - ➢ At next visit if eGFR ≥60, but inform individual
  - ➢ On the phone if eGFR <60, and recall for early repeat
  - ➢ eGFR <45 need to interrupt PrEP safely (2 or 7 days after last risk) and repeat 4 weeks later

Renal scenarios

- UPCR >30
  - Check no STI and that urine not too dilute (creatinine will be low but best to ask duty biochemist)
  - Check most recent eGFR
  - ➢ eGFR >90 check other factors at next visit and repeat after modifying these if possible
  - ➢ eGFR 60-90 call to check other factors and judge recall accordingly, repeat on early morning specimen and consider ACR at the same time, if available

Starting safely

- 2 pills for men 2-24hrs before sex, unless injecting drugs

- 7 pills each of 7 days for everyone else including injecting drugs

Stopping safely

- 2 pills each of 2 days for men after the last sex act, unless injecting drugs

- 7 pills each of 7 days for everyone else including injecting drugs

Testing safely

- 2:1:1 more vulnerable to missed pills so an extra HIV test advisable if miss any pills

- 7 pills each of 7 days less vulnerable, but an extra test advisable if miss 2 in a row

Missed pills

- 2:1:1 – take the double dose after sex if missed before, and continue for 2 days
- Concern linked to how late 1st dose is
  - Within 12hrs means one active drug 16hrs after sex ~second cycle replication
  - Beyond 12hrs moving into PEP territory so a reasonable solution is to complete the 28 days
  - Not clear how late it has to be for integrase inhibitor

Public Health England

Other progress/ plans

- Release of further trial spaces
- Full trial analysis end or 2020
- Commission planning underway: led by sub-group of Programme Oversight Board with all stakeholders including community
- Community Advisory Board sub-group exploring ways to increase awareness amongst women

EPIC-NSW STUDY

CLICK TO ACCESS YOUR TOOLKIT

A targeted, high-risk approach to PrEP roll-out

Overall HIV incidence in gay men in Sydney is 0.9/100py

High Risk behaviour in last 6 months	Incidence per 100py*	95% CI
Regular partner of an HIV-positive man, at least some condomless sex	5.4	2.8-10
Receptive condomless sex with any casual HIV-positive/status unknown partner	2.3	1.5-3.6
Rectal gonorrhoea	7.0	2.3-21
Rectal chlamydia	3.6	1.3-9.5
Methamphetamine use	1.9	1.3-2.8

*Incidence from the Health in Men cohort study, Sydney 2001-07

http://arv.ashm.org.au/images/Australian_National_PrEP_Guidelines.PDF

Andrew Grulich, R4P 19Oct2016

Added value of PrEP

Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study

Andrew E Grulich, Rebecca Guy, Janaki Amin, Fengyi Jin, Christine Selvey, Jo Holden, Heather-Marie A Schmidt, Iryna Zablotska, Karen Price, Bill Whittaker, Kerry Chant, Craig Cooper, Scott McGill, Barbara Telfer, Barbara Yeung, Gesalit Levitt, Erin E Ogilvie, Nila J Dharan, Mohamed A Hammoud, Stefanie Vaccher, Lucy Watchirs-Smith, Anna McNulty, David J Smith, Debra M Allen, David Baker, Mark Bloch, Rohan I Bopage, Katherine Brown, Andrew Carr, Christopher J Carmody, Kym L Collins, Robert Finlayson, Rosalind Foster, Eva Y Jackson, David A Lewis, Josephine Lusk, Catherine C O'Connor, Nathan Ryder, Emanuel Vlahakis, Phillip Read, David A Cooper*, for the Expanded PrEP Implementation in Communities New South Wales (EPIC-NSW) research group

Summary

Background HIV pre-exposure prophylaxis (PrEP) is highly effective in men who have sex with men (MSM) at the individual level, but data on population-level impact are lacking. We examined whether rapid, targeted, and high-coverage roll-out of PrEP in an MSM epidemic would reduce HIV incidence in the cohort prescribed PrEP and statewide in Australia's most populous state, New South Wales.

Lancet HIV 2018

Published Online October 17, 2018

http://dx.doi.org/10.1016/S2352-3018(18)30215-7

- 90-90-90 goals met before study began without decline
- 20% of MSM in the study area had initiated PrEP by the end of follow-up

- 25.1% reduction overall
- 31.5% decline in recent infections

- 49% decline in Australia-born
- 52% in gay suburbs of Sydney

EPIC decline in recent infections

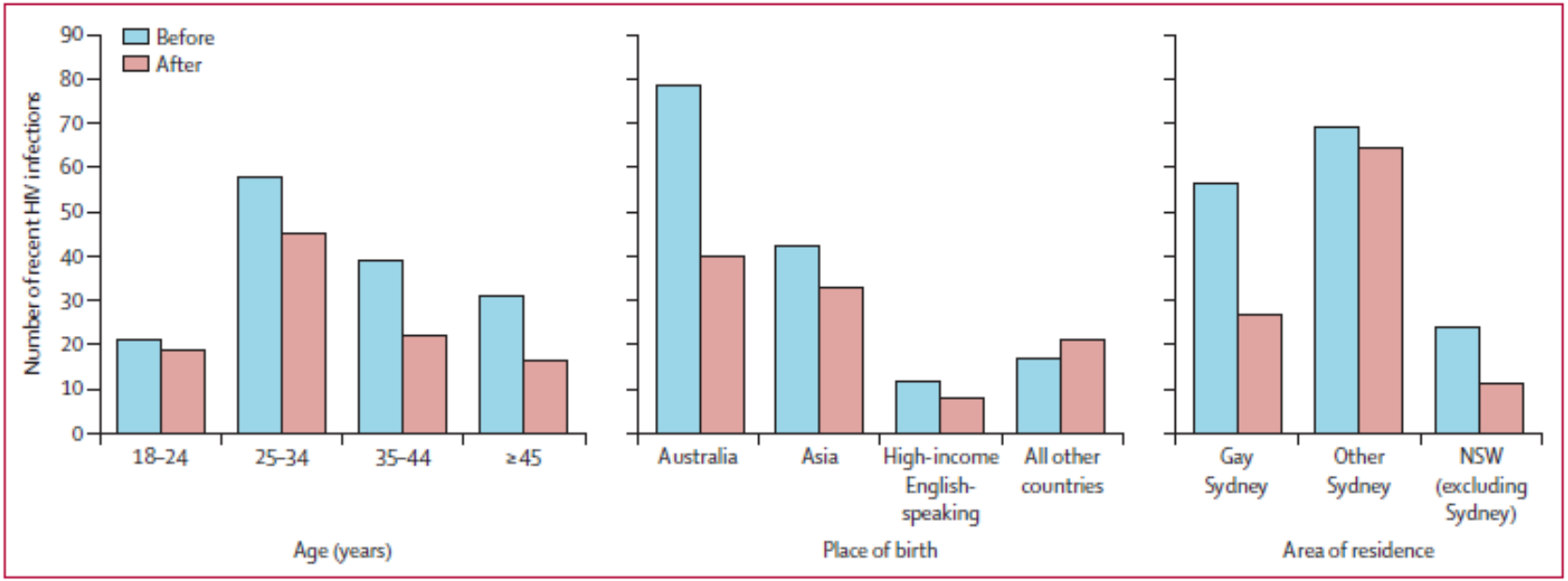


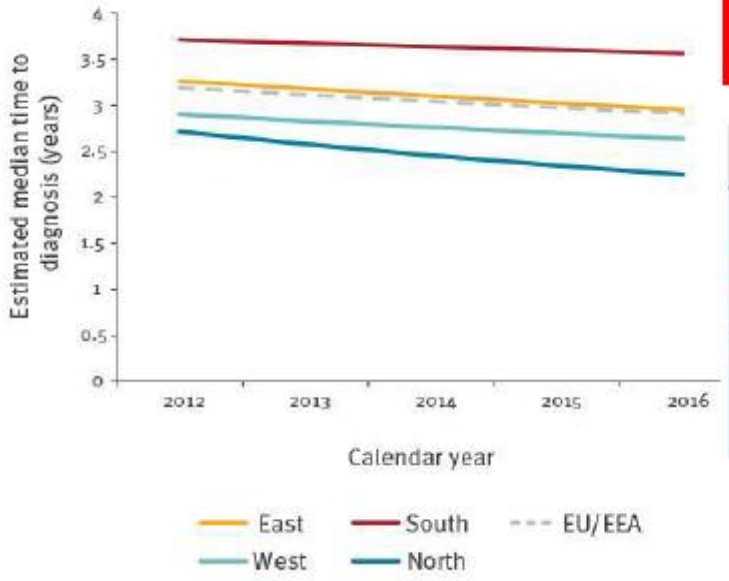
Figure 2: **Number of recent HIV infections in New South Wales**

Figure shows data for the 12 months before commencement of recruitment to EPIC-NSW (n=149, "before") and the 12 months after the 3700th EPIC-NSW participant was recruited (n=102, "after") by age, country or region of birth, and area of residence. NSW=New South Wales.

Work to be done on testing

- Behaviours include not testing at all, and not testing frequently enough
- Stigma a barrier to visiting clinics/GPs/ pharmacies – could self-testing address this?
- Access to clinics decreasing and often inconvenient or time-consuming

Decreasing estimated time from infection to diagnosis in the EU/EEA



Median time from infection to diagnosis is 2.9 years

Source: van Sighem Ard, Pharris Anastasia, Quinten Chantal, Noori Teymur, Amato-Gauci Andrew J. Reduction in undiagnosed HIV infection in the European Union/European Economic Area, 2012 to 2016. Euro Surveill. 2017;22(48):pii=17-00771.

At clinic level in Soho, London

Lancet HIV 2017
Published Online
October 20, 2017
http://dx.doi.org/10.1016/S2352-3018(17)30181-9

80% decline in HIV cases since 2015

56 DEAN STREET

DEAN STREET express

Scrutiny of missed chances

- Gay man, mid-thirties
- 51 HIV tests in 20 months
- Multiple STIs including rectal GC, rectal CT and secondary syphilis
- Was on PrEP, missed the chance to get on the Impact study, advised where and how to buy PrEP

Opportunities

- Gay man, early twenties, multiple partners, inconsistent with condoms
- Never had an HIV test or been to a clinic
- Came to clinic as a contact of GC
- Had not heard of hep A, B, C or HPV
- Had heard of PrEP and thought it was a good idea!

Conclusions

- Population effectiveness not impacted by resistance or STIs – appropriate uptake and persistence the dominant factors
- We need to be clearer about stopping and starting safely
- A minority need a safety net
- Disparities exist everywhere and the reasons are complex
- Demand creation required – **for testing as well as PrEP, and testing more critical to address in some populations**
- Peers do a great job (they know who needs testing/PrEP), and public services benefit from considering them an equal partner
- PrEP is well on its way, but surveillance at risk of lagging behind

With thanks

Teymur Noori (and Axel Schmidt)
Jean-michel Molina, David Dunn and Ellen White
Jared Baeten, Scott McAllister and Raphy Landowitz

PrEP Impact participants and participating clinic teams
Ann Sullivan and trial teams at CWH and PHE
Monica Desai, Laura Waters, Cecilia Priestley, Kaveh Manavi and John Saunders

Andrew Grulich
Dean Street


BASHH
Birmingham 2019
Greg Owen
Tribute to Mags Portman
#BASHH2019


BASHH
Birmingham 2019
BASHH Symposium
Current challenges U=U
Sponsored by an educational grant from ViiV
#BASHH2019