

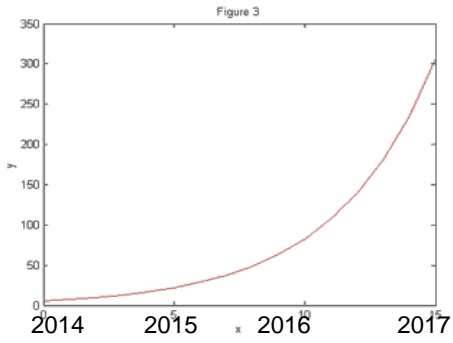
# Maximising the population-level impact of PrEP

Andrew Grulich,  
HIV Epidemiology and Prevention Program,  
Kirby Institute, UNSW  
November 2017



- 
- State of PrEP science
  - State of PrEP implementation
  - Measuring population-level impact of PrEP
  - Challenges in maximising the population-level impact

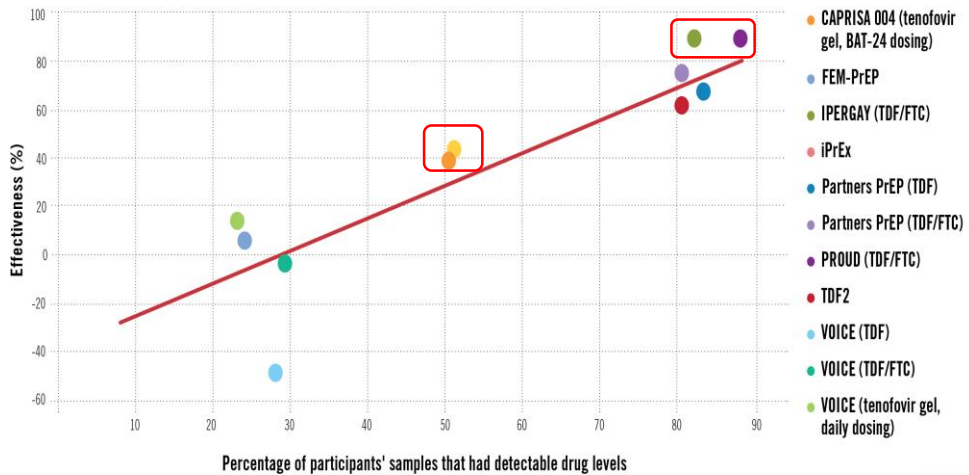
### ASHM conference presentations on PrEP by year



### State of PrEP science



### PrEP Works if You Take It — Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention

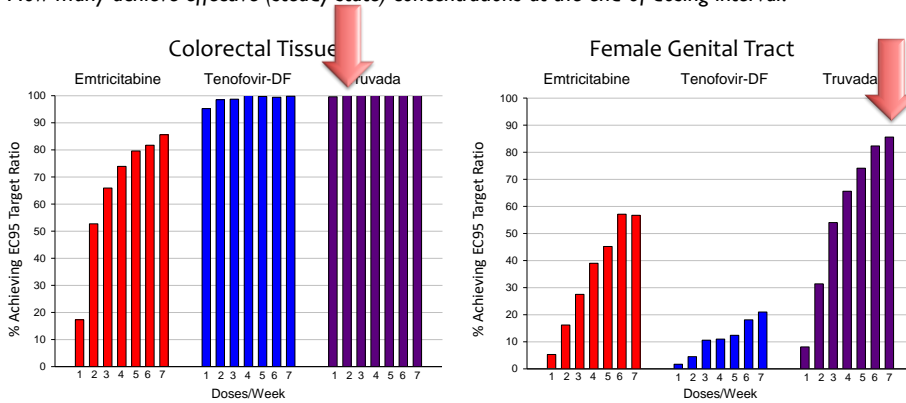


## The Right Concentration

Cottrell et al J Infect Dis. 2016 Jul 1;214(1):55

### Estimating Efficacy With Various Doses/Week

How many achieve effective (steady-state) concentrations at the end of dosing interval?



Anderson et al. Sci Transl Med Sep 12, 2012; 4(151): 151ra125.

Donnell D et al. JAIDS. 2014;66(3):340-348.;



### PrEP efficacy: summary

- Oral TDF/FTC PrEP is extremely effective in adherent individuals
- Oral TDF/FTC PrEP works best in the rectum
  - The regimen is forgiving for missing up to 3 pills/week
  - However, daily adherence is required for vaginal protection
- Daily TDF/FTC PrEP is close to 100% effective in adherent gay men
  - Case reports of failure in adherent individuals are rare (<5)
    - Drug resistant HIV in at least two of these



### 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

## Intermittent PrEP?

- 86% reduction in HIV risk in the placebo controlled randomised phase
- 97% reduction in open label extension, including in infrequent users

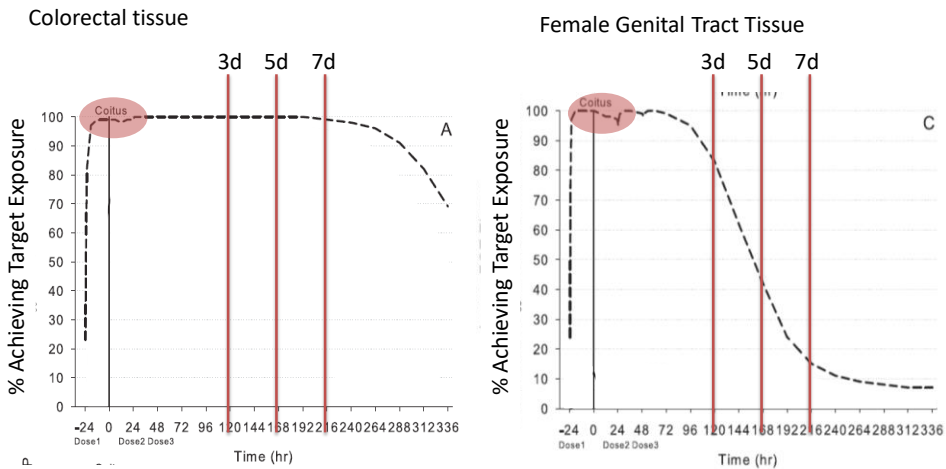
**Intermittent PrEP, with a loading dose, is extremely effective in gay men**

*JM Molina et al, New Engl J Med 2015; Lancet HIV 2017.*

#IAS2017 | @IAS\_conference







## The Right Time

*Estimating Truvada Efficacy With Ipergay Dosing Strategy*



*A Kashuba et al, IAS 2017.*

## The near future: PrEP agents in phase 3 trials

Strategy	Trial	Product	Number participants	Population	Status start-end	Location
 Antibody	HVTN 704/ HPTN 085	VRC01 antibody, infused every two months	2,700	Men and transgender persons who have sex with men	Ongoing Apr 2016–June 2020	Brazil, Peru, Switzerland, US
	HVTN 703/ HPTN 081		1,500	Sexually active women	Ongoing May 2016–Jan 2020	Botswana, Kenya, Malawi, Mozambique, Tanzania, South Africa, Zimbabwe
 Preventive HIV vaccine	HVTN 702	ALVAC/gp120 MF59 adjuvant boost, five doses over 12 months	5,400	Sexually active heterosexual women and men	Ongoing Nov 2016–End 2020	South Africa
 Oral PrEP	Discover	Daily F/TAF	5,000	Men and transgender women who have sex with men	Ongoing Q4 2016–End 2020	Canada, Denmark, Germany, Ireland, Italy, Netherlands, Spain, UK, US
 Long-acting injectable	HPTN 083	Cabotegravir injections every two months	4,500	Men and transgender persons who have sex with men	Ongoing Q4 2016–June 2020	Brazil, Peru, South Africa, Thailand, US
	HPTN 084		3,200	Sexually active women	Planned start in late 2017	Botswana, Kenya, Malawi, South Africa, Swaziland, Uganda, Zimbabwe
 Preventive HIV vaccine	HPX2008/ HVTN705	Ad26 Mosaic + gp140	2,600	Sexually active women	Planned start in late 2017/early 2018	Malawi, Mozambique, South Africa, Zambia, Zimbabwe
 Vaginal ring/ Oral PrEP	REACH/ MTN 034/ IPM 045	Dapivirine ring and oral TDF/FTC	300	Sexually active women	Planned start in late 2017	Kenya, South Africa, Uganda, Zimbabwe

## DISCOVER study

### Oral F/TAF versus F/TDF for PrEP

- 5,400 men and transgender women who have sex with men
  - reporting condomless anal sex with  $\geq 2$  partners, or
  - recent syphilis or rectal gono/CT
- Primary outcome is HIV infection
- Secondary outcomes
  - Bone mineral density (hip and spine)
  - Renal biomarkers
- Results in 2020



## The near future: PrEP agents in phase 3 trials

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## HPTN 083: long acting cabotegravir 600mg

To Prevent HIV Acquisition in MSM and TGW

Landovitz and Grinsztejn, *Protocol Chairs*

Step 1	Daily oral CAB and TDF/FTC placebo	TDF/FTC and oral CAB placebo
Step 2	CAB LA at two time points 4 weeks apart and every 8 weeks thereafter and TDF/FTC placebo	TDF/FTC and injectable placebo at two time points 4 weeks apart and every 8 weeks thereafter
Step 3	Open-label TDF/FTC to cover the PK tail	Open-label TDF/FTC to Cover the PK tail



**Primary Objective: Reduce HIV Incidence (non-inferiority, double blind, double dummy design)**

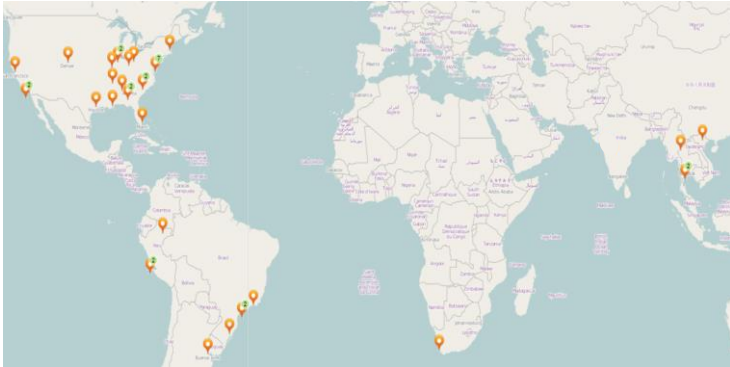
N=4500; Study duration: Enrollment **24-30 months**; follow-up ~ 4.5 years

Enrollment goals:

- Minimum 50% of US enrollment Black MSM (~ 950)
- Overall minimum 10% TGW (~ 450)
- Overall > 50% under age 30



## HPTN 083 Research Sites 44 Sites in 7 Countries

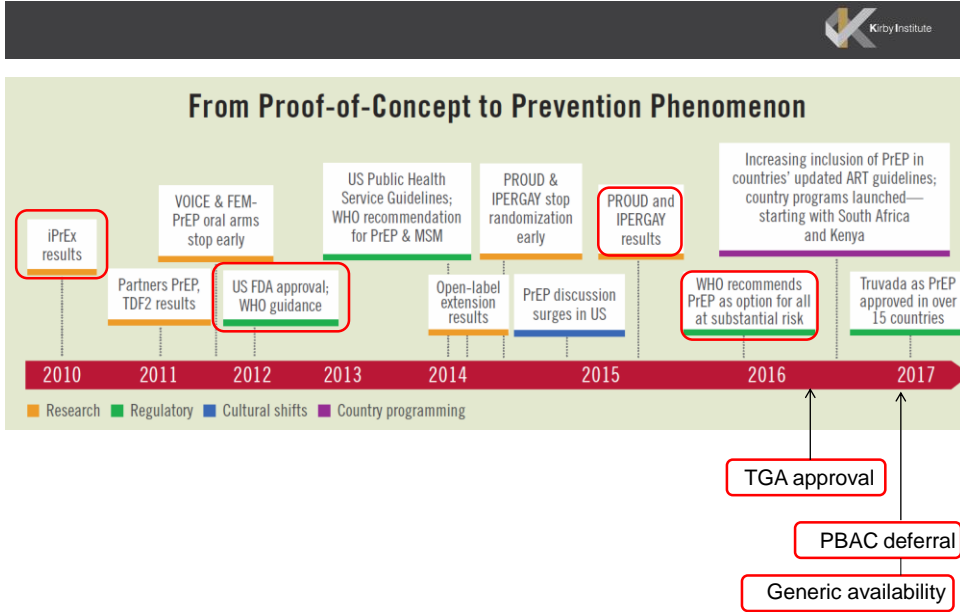


Study started in December 2016 in U.S.  
350 enrolled as of July, 2017

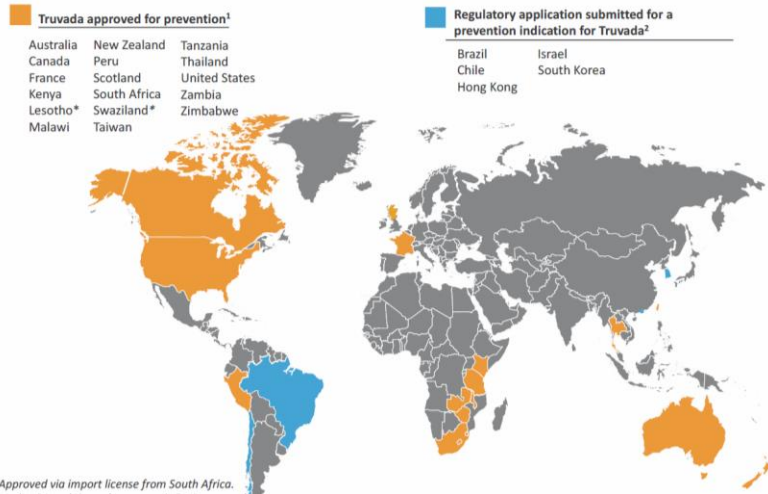
## State of PrEP implementation







## Global licensing of TDF/FTC PrEP, 2017

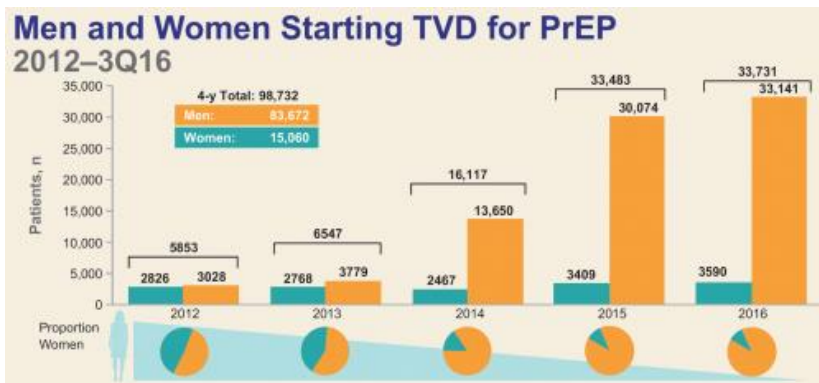


## PrEP roll-out, USA, 2012-2016



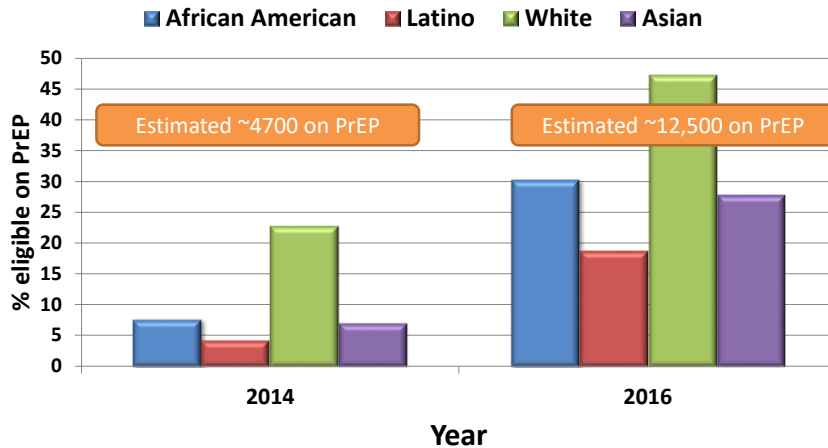
R Mera et al, IAS 2017.

## PrEP roll-out, USA, 2012-2016



R Mera et al, IAS 2017.

## PrEP use in MSM in San Francisco, 2014-2016



2014 data from NHBS; 2016 data extrapolated from STOP AIDS data 2015  
 Snowden STI 2016 NHBS; Jen Hecht (personal communication)



## PrEP implementation, France

- The French Medicines Agency approved and funded PrEP use in November 2015 (temporary mechanism)
- 3405 registered, 2774 prescribed PrEP over first 13 months
- 80% of PrEP initiated in hospitals
- >90% male, mix of intermittent (60%, MSM only) and continuous PrEP



## PrEP implementation, UK

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### PrEP Impact Trial

- PrEP is not funded by the NHS
  - Funded in Scotland from mid 2017 for high-risk (mainly gay men)
- 10,000 places on the Public Health England Impact trial implementation study, launched in October 2017
  - Targeted at high-risk
  - Recruited over 3 years
  - Up to 230 genitourinary medicine clinics
  - Very high initial demand



## PrEP Implementation, Australia

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- Demonstration projects in Victoria, NSW and Qld, 2014-2016
  - Enrolled approximately 500 participants
- First large scale implementation project (EPIC-NSW) announced on December 1 2015
  - CTN framework, using donated drug and imported generic
- PrEP approved by TGA May 2016
- Implementation trials in all states and territories except NT



## PrEP implementation projects, Australia

	NSW	Vic	QLD	SA	ACT	Tas	WA
	EPIC-NSW	PrEPX	QPrepd	PrEPX-SA	EPIC	PrEPX-Tas	PrEPIT-WA
Start date	3/2016	7/2016	11/2016	5/2017	9/2017	9/2017	11/2017
Estimated eligible (2016)	9600	7800	6300	2300	550	700	3750
Target	All high risk	3800	3000	500	315	100	2000
Current	7699	3661	2001	468	153	53	0

*EPIC investigators, PrEP-IT investigators, Edwina Wright, Darren Russell, Charlie Gilks*

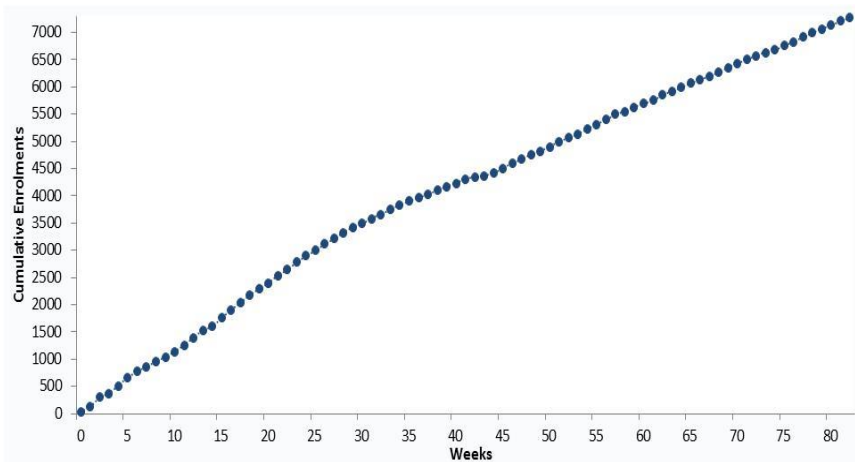
## PrEP Activism



- PrEP as an urgent issue
- Education and demand building
- Advocacy for widespread availability
- Facilitation of personal importation



## EPIC-NSW: recruitment as at 30 September



## Demographics of EPIC participants to September 30

Characteristic	%
<b>Gender</b>	
Male	98.9
Female	0.1
Transgender, male-to-female	0.8
Transgender, female-to-male	0.2
Other	0.1
<b>Sexual identity</b>	
Gay/Homosexual	93.8
Bisexual	5.1
Heterosexual	0.5
Other <sup>£</sup>	0.6
<b>Age at enrolment (years)</b>	
< 20	1.2
20-29	28.3
30-39	34.8
40-49	22.0
≥50	13.7
Total*	100.0

Slight under-recruitment of aged < 30

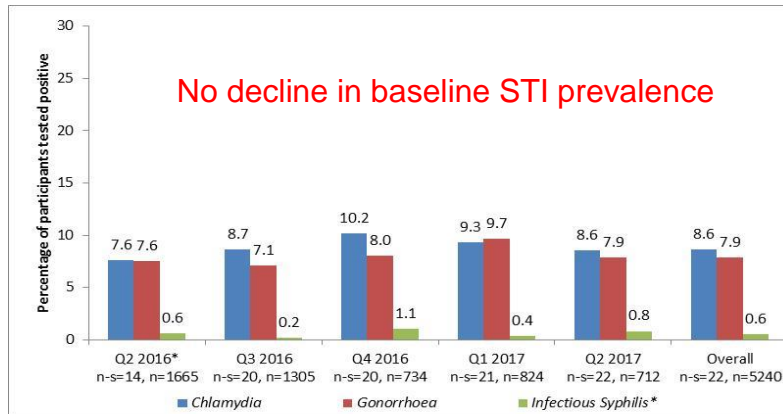
## Demographics of EPIC participants to September 30

Characteristic	%
<b>Aboriginal /Torres Strait Islander status</b>	
Non-Indigenous	98.3
Aboriginal/Torres Strait Islander	1.7
<b>Country/Region of birth</b>	
Australia	61.0
Oceania	4.0
Asia	13.9
Northern America	2.9
South/Central America, Caribbean	3.6
Europe	11.3
Middle East	1.6
Africa	1.9
<b>Area of residence</b>	
Major cities	94.2
Inner Regional	5.3
Outer Regional	0.4
Remote	0.1

Under-recruitment of Asian gay and bisexual men

## STI prevalence at baseline

EPIC-NSW continues to enrol high-risk participants



<http://www.health.nsw.gov.au/endinghiv/Documents/>

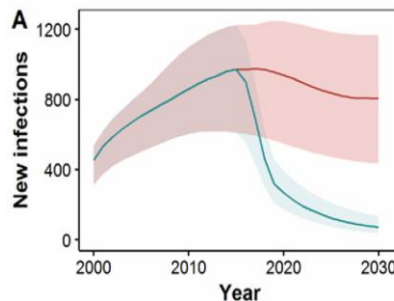
Measuring population-level  
impact of PrEP



## What population-level impact do we expect?

Mathematical modelling suggests it will be maximised if...

- Targeted to ***high-risk*** gay men
- With ***high coverage*** (90%)
- Rolled out ***quickly*** (1-2 years)
  
- Lower levels of roll out lead to much lower reductions in incidence
  
- **Herd protection** is a critical part of the population-level effect



R Gray et al, Wednesday 230pm Royal Theatre

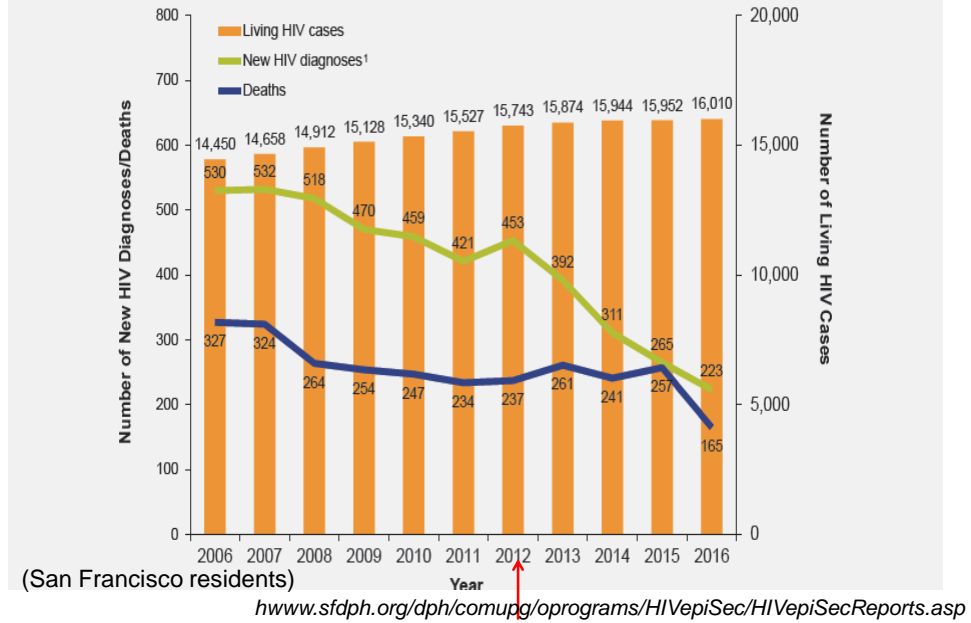
## High level coverage is required for population level effectiveness

Two places where highest level of coverage attained

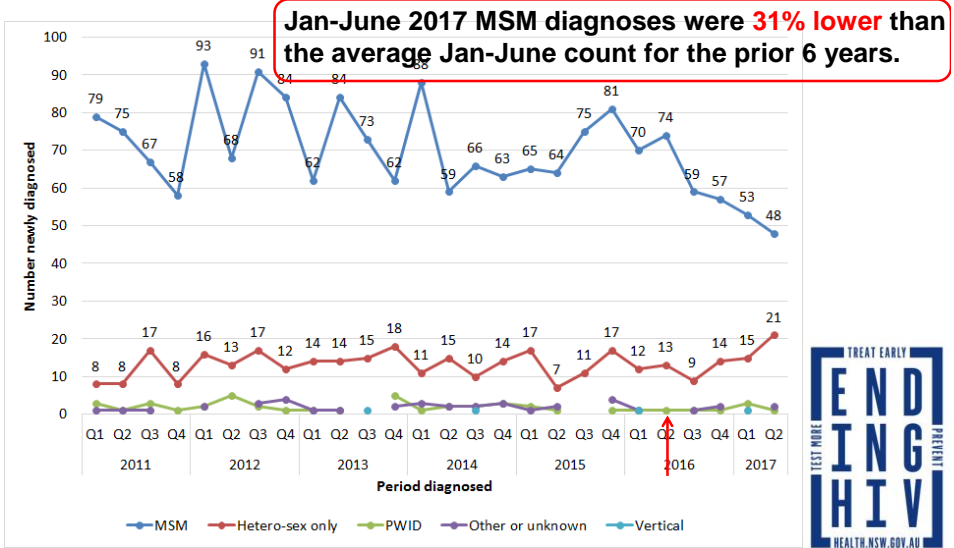
- San Francisco
  - Gradual uptake since 2012
  - Now > 12,500 on PrEP in a city of < 1 million
  
- NSW
  - Little PrEP prior to 2016
  - Rapid uptake: >7,700 initiated since March 2016
  - About 70% of estimated high-risk gay men are on PrEP
  - No caps to eligibility, so that all eligible men who present to one of the 30 clinics can receive PrEP



Figure 1.2 New HIV diagnoses, deaths, and prevalence, 2006-2016, San Francisco

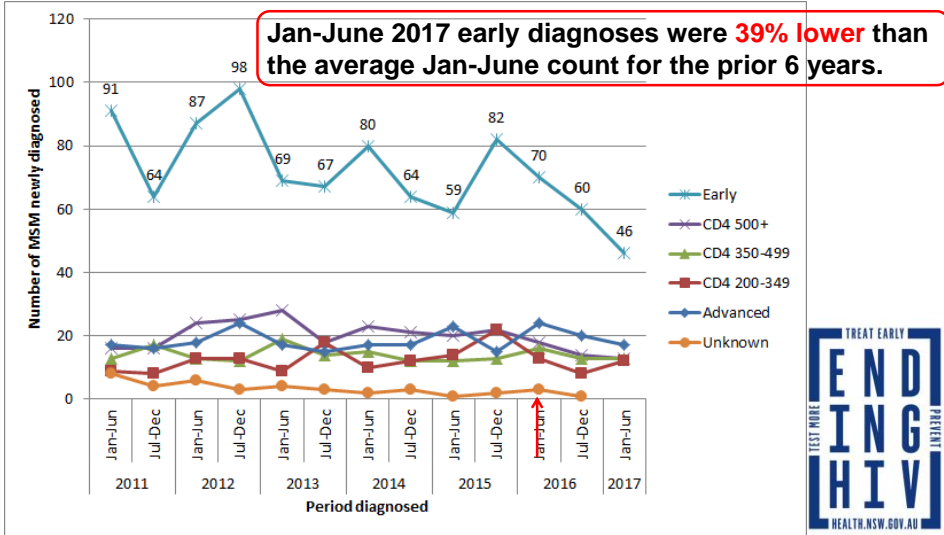


### Number of NSW residents newly diagnosed Jan 2011 - Jun 2017 by reported HIV risk exposure



NSW Notifiable Conditions Information System - 7 Aug 2017 C Selvey et al, Tuesday 1220, Bradman theatre NSW Health

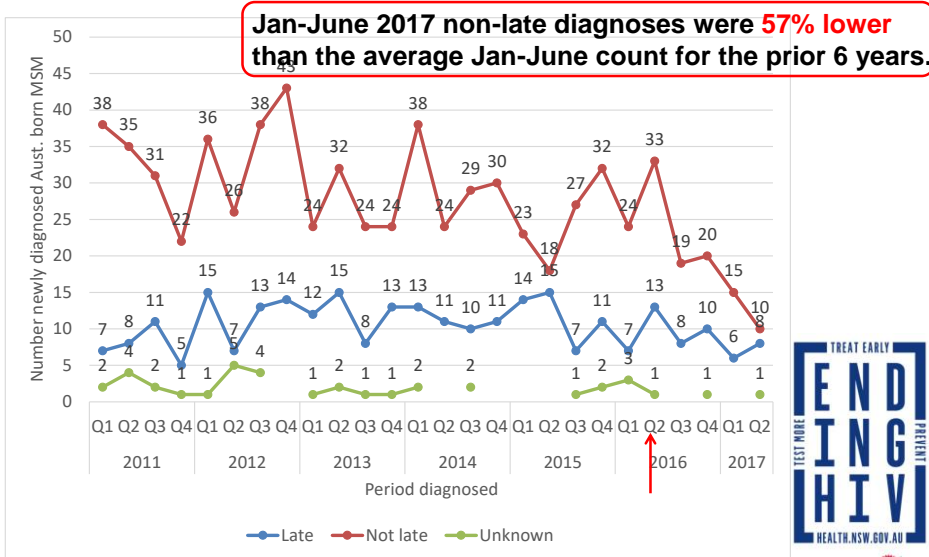
## NSW new diagnoses Jan 2011 - Jun 2017 in MSM, by stage of infection at diagnosis



NSW Notifiable Conditions Information Management System – extract 7 Aug 2017



## NSW new diagnoses Jan 2011 - Jun 2017 in Australian born MSM by evidence of late diagnosis



C Selvey et al, Tuesday 1220, Bradman theatre



# Challenges in maximising the population-level impact of PrEP



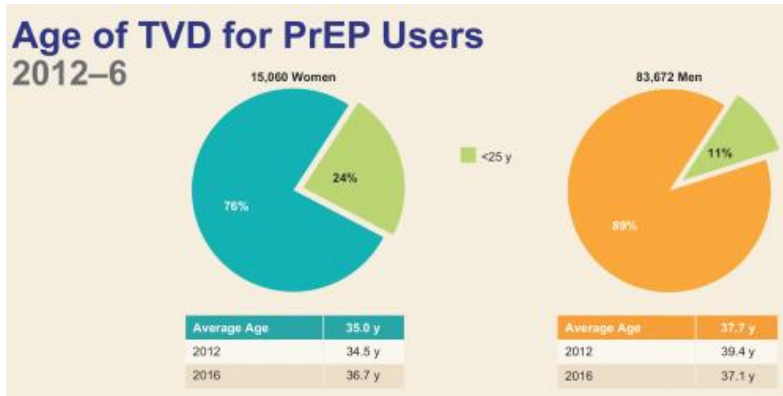
## **Some challenges we are facing now**

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- Providing equitable access to PrEP
- Increasing condomless anal intercourse and STIs
- Public funding of PrEP

## PrEP roll-out, USA, 2012-2016

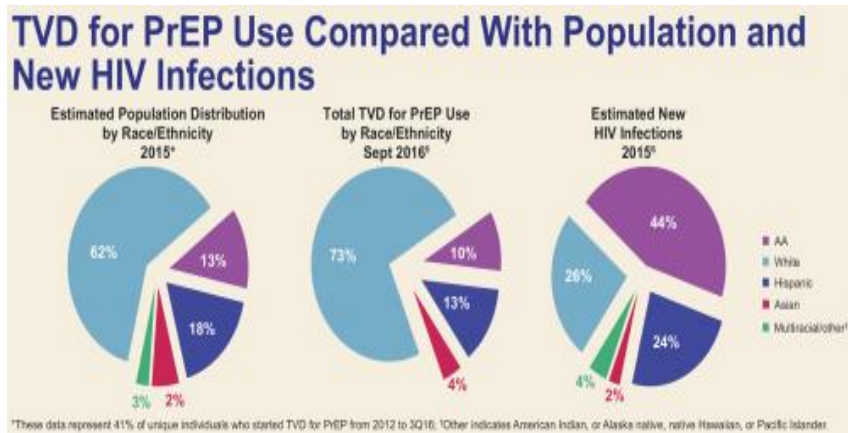
Under-recruitment of young people



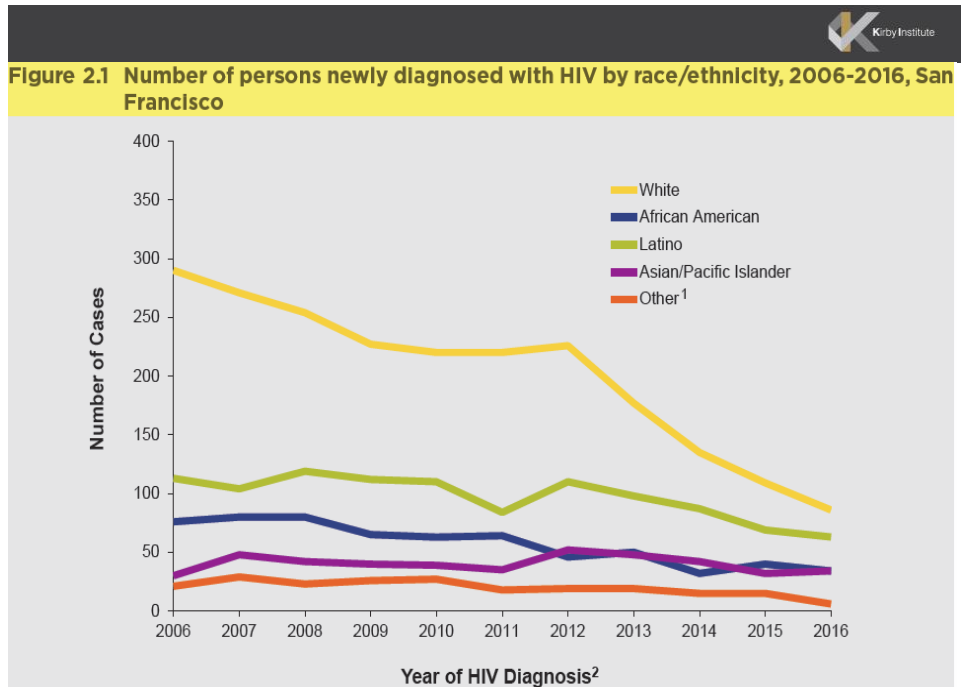
R Mera et al, IAS 2017.

## PrEP roll-out, USA, 2012-2016

Under-recruitment of ethnic minorities



R Mera et al, IAS 2017.



<http://www.sfdph.org/dph/comupg/oprograms/HIVepiSec/HIVepiSecReports.asp>

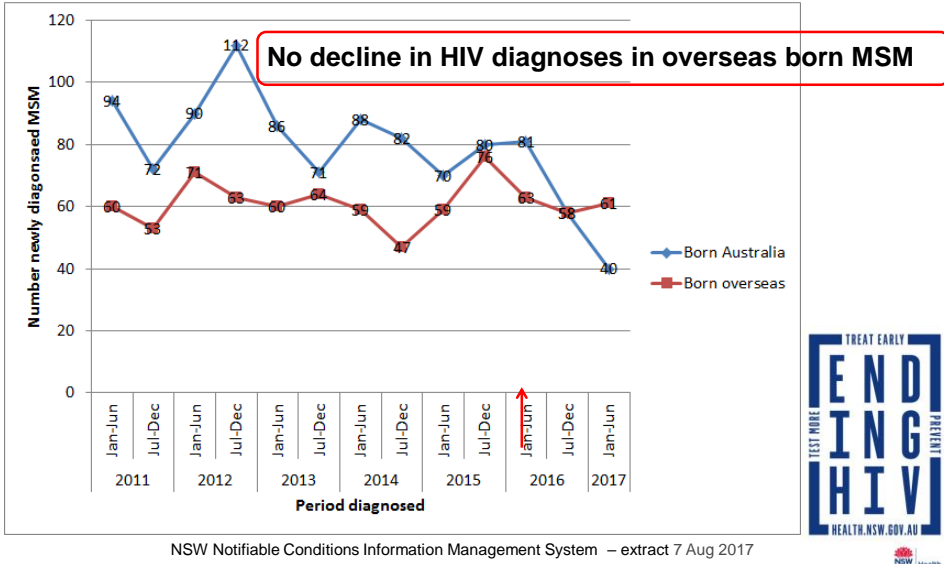
## Equity of PrEP access, EPIC-NSW participants

Compared to 2015 HIV notifications in MSM, EPIC-NSW participants are

- Less likely to be born in NE or SE Asia
  - However a sector-side response is leading to substantial increases in enrolment in the most recent quarter
- Less likely to be aged < 30 (slightly)
- No different in indigenous status, non-Sydney residence

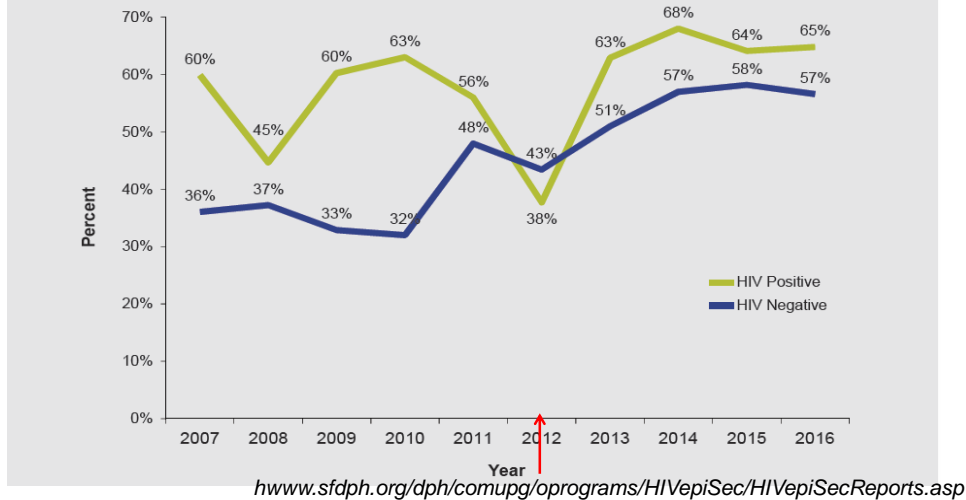
*R Guy et al, Monday 1615, Bradman theatre*

## NSW new diagnoses Jan 2011 - Jun 2017 in MSM, by place born



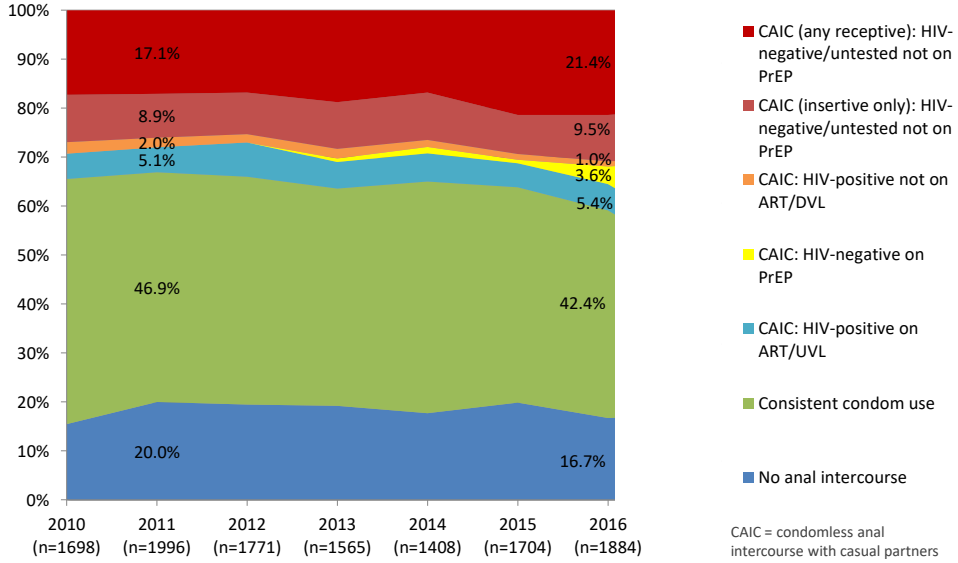
## Increasing condomless anal intercourse

Figure 7.2 Percent of MSM reporting condomless anal intercourse in the last six months by self-reported HIV status, the STOP AIDS Project, 2007-2016, San Francisco



### Gay men with casual partners, Sydney/Melbourne Periodic surveys, 2011-17

Arts & Social Sciences  
Centre for Social Research in Health

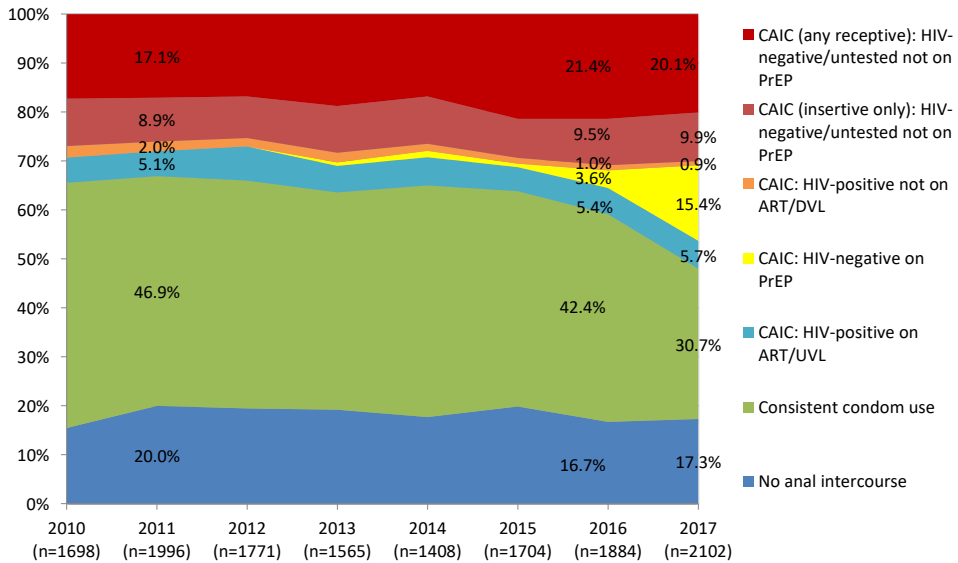


Source: [Sydney Gay Community Periodic Survey 2017](#)

M Holt et al, Monday 1600, Royal Theatre

### Gay men with casual partners, Sydney/Melbourne Periodic surveys, 2011-17

Arts & Social Sciences  
Centre for Social Research in Health



Source: [Sydney Gay Community Periodic Survey 2017](#)

M Holt et al, Monday 1600, Royal Theatre





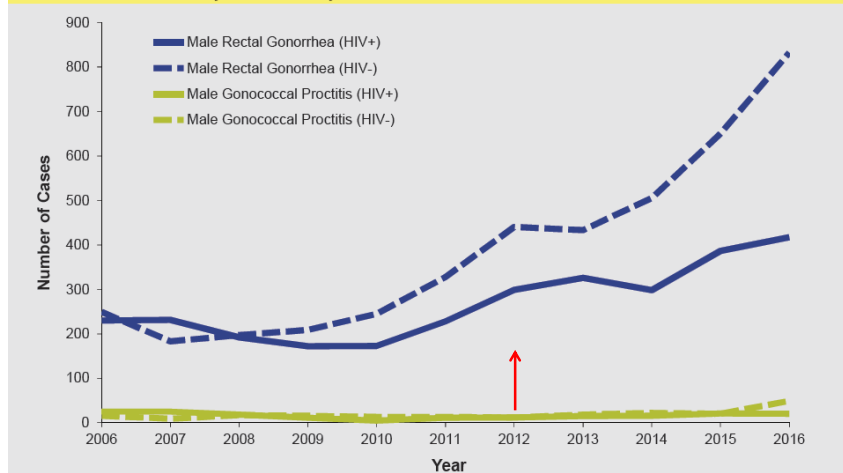
## “Risk compensation” or “increased CLAI”?

- Increasing condomless anal intercourse with casual partners has accompanied PrEP roll-out in San Francisco and in Australia
- Mathematical modelling suggests that this will have little impact on population-level HIV prevention impact provided there are high levels of uptake and adherence in those at high-risk
- Increase in STI risk
  - Overall epidemic effect will be counter-balanced by increased testing and shortened duration of infection
  - An increased number of infections related to increased STI testing can definitely be anticipated



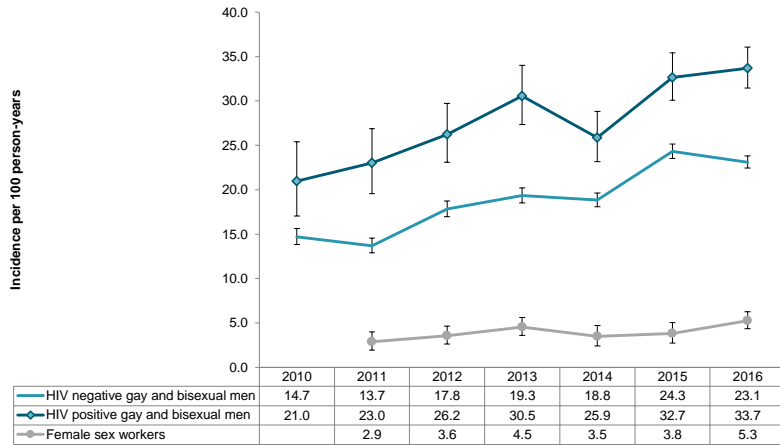
## Increasing STIs, San Francisco

**Figure 7.3 Male rectal gonorrhea and male gonococcal proctitis among MSM by HIV serostatus, 2006-2016, San Francisco**



[www.sfdph.org/dph/comupg/oprograms/HIVepiSec/HIVepiSecReports.asp](http://www.sfdph.org/dph/comupg/oprograms/HIVepiSec/HIVepiSecReports.asp)

## Increasing gonorrhoea, Australia



Annual Surveillance Report of HIV, Viral Hepatitis, STIs 2017



## How the HIV-prevention drug could break the NHS

Ross Clark



### Public funding of PrEP

- PrEP can be highly cost-effective
- However, it will always be much less cost effective than ART for HIV therapy
- Countries which fund drugs based on cost-effectiveness will offer **lower prices for ART as a preventive** than prices offered for ART as treatment
- For the pharma industry, the counterbalance is **substantially larger markets than for treatment**

Substantial price reductions, guided by cost-effectiveness analyses, are required for PrEP to be publically-funded in Australia and similar countries



## Maximising PrEP effectiveness: summary (1)

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- PrEP Implementation can lead to rapid, substantial declines in HIV infection if it is rapidly targeted to saturation of high-risk groups
- Systems for monitoring **recent** infection are required to monitor population-level efficacy
- Equitable PrEP promotion is essential for maximal effect
  - Roll-out should reflect the epidemic
  - Increased use by Asian-born gay and bisexual men is a pressing need in Australia



## Maximising PrEP effectiveness: summary (2)

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- Increasing CLAI occurs, but will not compromise effectiveness provided those at high risk are on PrEP
  - HIV outbreaks in the 20% of gay men with casual partners who do not always use condoms are still possible
  - Multi-faceted HIV risk reduction, including condom use, in this group remains critical
  - In a casual sex setting, everybody needs to protect themselves
- “Prevention” PrEP pricing must be resolved urgently
  - Prevention therapeutics is a different field of health economics
  - For pharma, lower drug prices are balanced by substantially larger markets

## PrEP is part of Combination Prevention



### The EPIC-NSW Research team



Kirby Institute	NSW Ministry of Health	Site investigators	Site investigators (cont)
David Cooper	Jo Holden	Debbie Allen	Nathan Ryder
Andrew Grulich	Christine Selvey	David Baker	David Smith
Rebecca Guy	Heather-Marie Schmidt	Mark Bloch	Emanuel Vlahakis
Jeff Jin	Dale Halliday	Katherine Brown	Don Smith
Janaki Amin	Kerry Chant	Christopher Carmody	Nick Doong
Iryna Zablotska	Bill Whittaker	Andrew Carr	David Townson
Barbara Yeung	<b>Community Organisations</b>	Kym Collins	Bradley Forssman
Ges Levitt	Nic Parkhill	Robert Finlayson	Daniel Chanisheff
Erin Ogilvie	Craig Cooper	Rosalind Foster	Gia Han Thai
Mo Hammoud	Levinia Crooks	Eva Jackson	Sarah Martin
Denton Callender	Matt Vaughan	David Lewis	Tuck Meng Soo
Lucy Watchirs-Smith	Karen Price	Josephine Lusk	Ben Anderson
Stefanie Vaccher		Anna McNulty	
Daminda Weerasinghe		Catherine O'Connor	
Nila Dharan		Phillip Read	

The EPIC-NSW study team thanks the over 7700 participants. EPIC-NSW is funded by the NSW Ministry of Health. We thank Gilead for providing a donation of Truvada for use in EPIC-NSW. Study drug is also purchased from Mylan pharmaceuticals.

## The EPIC-NSW Site Coordinators



EPIC-NSW Site	Site Coordinator
Albury & Wagga Sexual Health Clinics	Alison Kincaid
Canberra Sexual Health Centre	Shannon Woodward
Clinic 16	Brett Hadlow
Coffs Harbour Sexual Health Clinic	Nives Houlihan
Crown St Medical Centre	Airisse Cortez
Dr Doong's Surgery	Shane Hewitt
East Sydney Doctors	Melissa Benson
Fountain Street General Practice	Anne Maree O'Brien
Green Square Health	Christina Van Prehn
Holden Street Clinic	Michael Williamson
Holdsworth House Medical Practice, Sydney	Annabelle Caspersz
Illawarra Sexual Health Clinic	Jodie-Lee Little
Interchange General Practice	Philip Habel
Kirketon Road Centre	Karen Chronister
Lismore Sexual Health Centre	Andrew Buggie
Liverpool Sexual Health Clinic	Almario Mangaran
Nepean Hospital & Blue Mountains Sexual Health Clinics	Adriana Trujillo
Newcastle Community Health Centre	Nathan Ryder (PI)
Macleay Street Medical Practice	David Townson (PI)
Orange & Dubbo Sexual Health Clinics	Roisin Dyer
Royal Prince Alfred Sexual Health	Brett Sinclair
Short Street Clinic	Damien Brown
St Leonards Medical Centre	Ben Andersen (PI)
St Vincent's Hospital	John McAllister
Sydney Sexual Health Centre	Ruthy McIver
Taylor Square Private Clinic	Phuoc Loc Le
The Albion Centre	Raghib Ahmad
Western Sydney Sexual Health Centre	Melissa Power



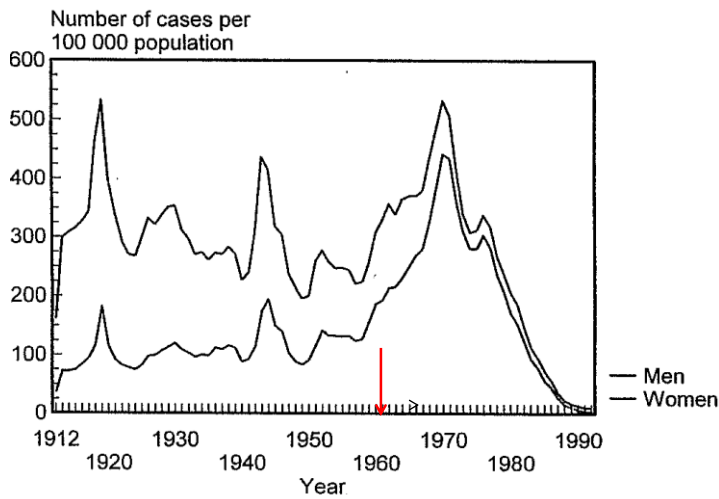

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Charlie Gilks	University of Queensland
Martin Holt	Centre for Social Research in Health, UNSW
Darren Russell	Cairns Sexual Health
Barbara Telfer	NSW Ministry of Health
Edwina Wright	Alfred Health, Monash University, Burnet Institute

Déjà vu?



Gonorrhoea incidence, Sweden, 1912-1995



## Gonorrhoea incidence, US, 1941-1997

