



HIV Pre-Exposure Prophylaxis (PrEP)

A Crash Course For General Practitioners

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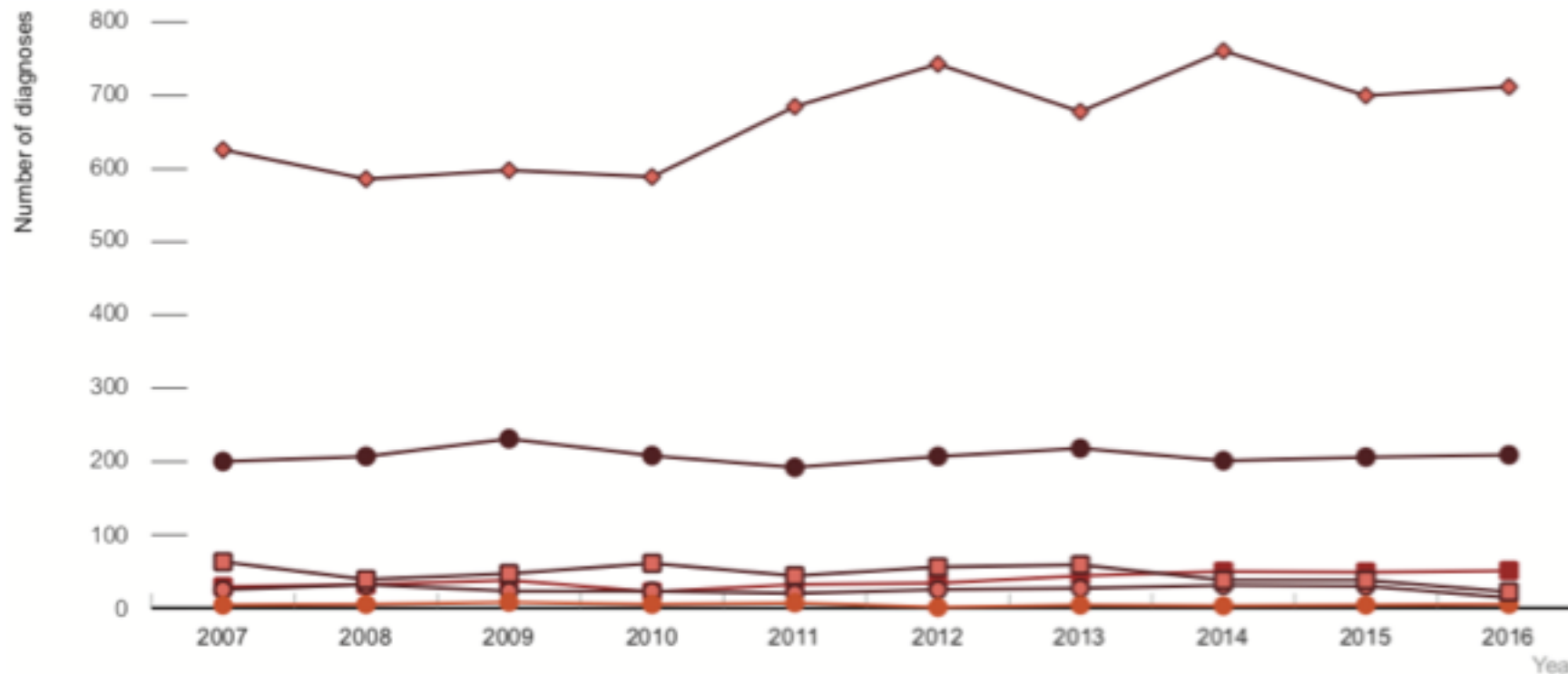
DISCLOSURES

- Speaker's fees and conference assistance from Gilead Sciences
- Speaker's fees from Merck Sharp & Dohme
- Advisory board fees from ViiV Healthcare.
- Co-investigator on VicPrEP trial, with study drug supplied by Gilead.
- Co-investigator on PrEPX trial, with study drug supplied by Mylan.

LEARNING OUTCOMES

1. Discuss HIV epidemiology in Australia
2. Assess a patient's HIV risk
3. Describe potential contraindications to starting PrEP
4. Be able to prescribe PrEP
5. Implement a system for appropriate ongoing monitoring for a patient in PrEP.

Figure 1.1.10 Number of new HIV diagnoses, 2007–2016, by exposure category



◆ Male-to-male sex

626	586	598	589	685	743	678	761	700	712
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■ Male-to-male sex and injecting drug use

29	32	38	22	32	34	44	50	49	51
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● Injecting drug use

25	32	23	23	20	25	27	31	30	14
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● Heterosexual sex

200	207	231	208	192	207	218	201	206	209
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● Mother with/at risk of HIV infection

4	5	8	5	7	1	4	3	4	5
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■ Other/undetermined

63	39	47	61	44	56	59	38	38	22
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New HIV diagnoses in Australia.
Annual Surveillance Report 2017
The Kirby Institute, UNSW

WHAT IS PrEP?

- Use of daily HIV medication on an ongoing basis, to prevent HIV in people who have ongoing HIV risk.
- TDF/FTC (tenofovir DF 300mg, emtricitabine 200mg)
- cf PEP, which is used after a HIV exposure
- Very effective at reducing HIV risk if done properly
- Does not protect against other STIs (except HBV)

Body System ANTINFECTIVES FOR SYSTEMIC USE > ANTIVIRALS FOR SYSTEMIC USE > DIRECT ACTING ANTIVIRALS

► **Note**

▼  Authority Required (STREAMLINED)

7580

Pre-exposure prophylaxis (PrEP) against human immunodeficiency virus (HIV) infection

Clinical criteria:


- The treatment must be for patients at medium to high risk of HIV infection, as defined by the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) Guidelines.

AND

- Patient must have a negative HIV test result prior to treatment with PBS-subsidised therapy with this drug.

Population criteria:

- Patient must be 18 years or older.

Code & Prescriber	Medicinal Product Pack (Name, form & strength and pack size)	Max qty packs	Max qty units	No. of repeats	DPMQ	Max Safety Net	General Patient Price
11276L  	TENOFOVIR + EMTRICITABINE tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg tablet, 30 (PI, CMI)	1	30	2	\$249.99	\$39.50	\$39.50
Available brands							
 Truvada							

A BRIEF HISTORY OF PREP FOR MSM

PrEP Pre-History:

- 1988: PEP for healthcare workers (USA)
- 2005: WHO and US DHHS recommend nPEP for sexual exposure to HIV.
- August 2005: Victorian nPEP service established at The Alfred Hospital

iPrEx trial

PrEP on PBS

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iPrEx (Iniciativa Profilaxis Pre-Exposición)

Recruitment:

- USA: Boston & San Fran (9%)
- South America: Ecuador, Peru, Brazil (82%)
- Thailand (5%)
- South Africa (4%)
- 2,499 HIV-negative participants (86% MSM, 14% trans women)
- Median age of 24 years



iPrEx (Iniciativa Profilaxis Pre-Exposición)

Study design:

- 1:1 randomisation to TDF/FTC or placebo. Take one pill per day.
- Median follow-up time of 1.2 years
- 4-weekly study visits for HIV testing, drug dispensing, pill counting, adherence counselling, risk reduction counselling, treatment of symptomatic STIs
- 24-weekly asymptomatic STI screening



1. Grant et al. NEJM 2010, 363(27):2587-2599.
2. Anderson et al. Sci Transl Med 2012, 4(151):151ra125.

iPrEx (Iniciativa Profilaxis Pre-Exposición)

Results:

- 100 HIV infections during study: 36 in TDF/FTC group, 64 in placebo group.¹
- 44% risk reduction (95% CI 15 to 36; $p = 0.005$).¹
- BUT: only 9% of seroconverters in TDF/FTC group had detectable blood tenofovir.¹
- Participants with detectable tenofovir had 92% HIV risk reduction.¹
- Pharmacokinetic analysis² showed HIV-1 risk reduction of:
 - 76% for 2 doses per week,
 - 96% for 4 doses per week,
 - 99% for 7 doses per week



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iPrEx trial

PROUD trial (UK)

PrEP PBS

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PROUD

PRe-exposure **O**ption for reducing HIV in the **U**K:
an open-label randomisation to immediate or
Deferred daily TDF/FTC for HIV negative gay men

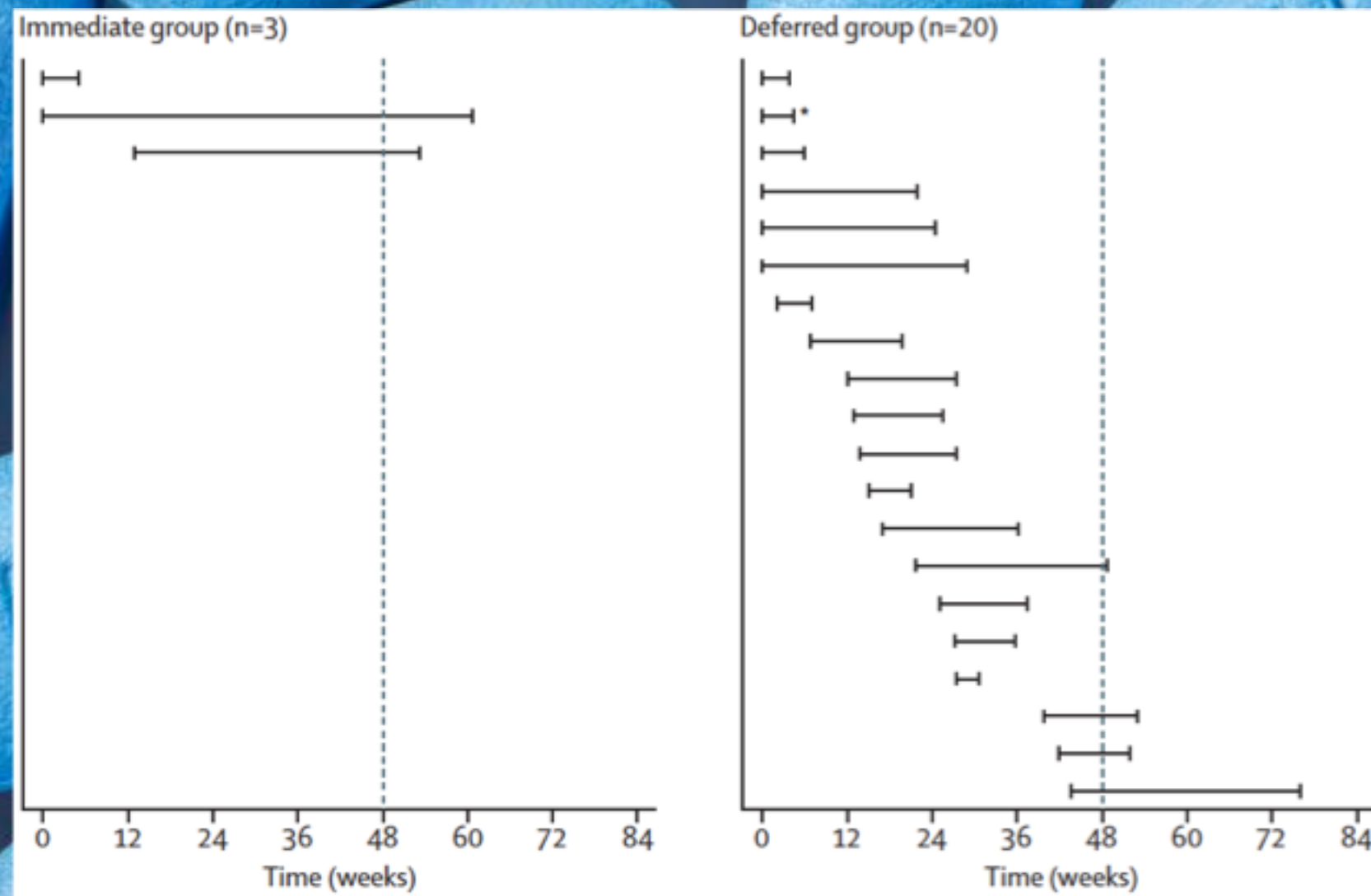


PROUD

Study Design:

- 544 high-risk MSM in London
- Open label with 1:1 randomisation:
 - 275 started PrEP (TDF/FTC) immediately, take one pill per day
 - 269 to defer starting PrEP by 1 year
- Follow-up designed to imitate envisaged real-world scenario: 3 monthly.





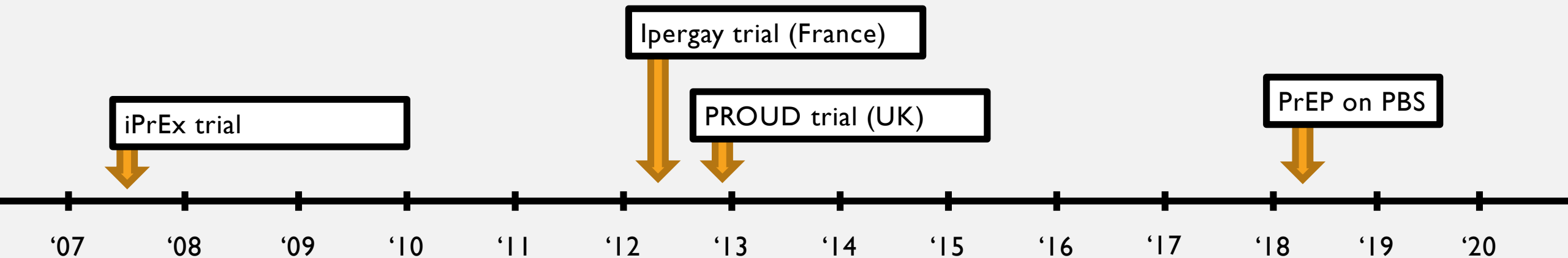
Relative risk reduction: 86%
(90% CI 64-96; $p = 0.0001$)
NNT = 13



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IPEGAY

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

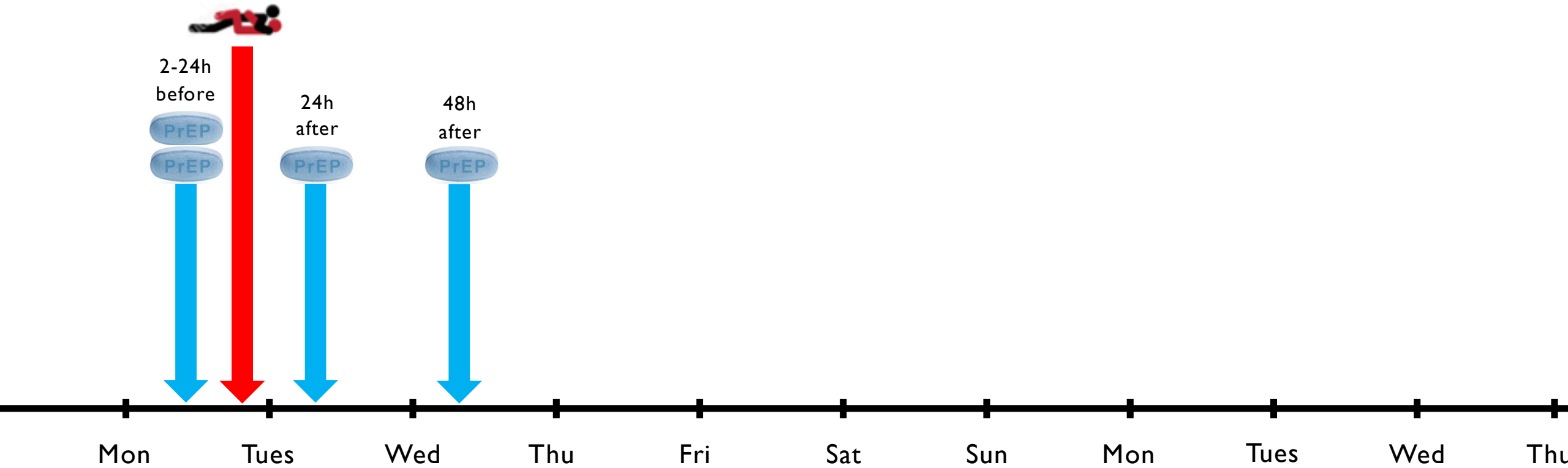
Question: Is PrEP effective if it's just taken around the time of HIV exposure, rather than every day?

IPIRGAY

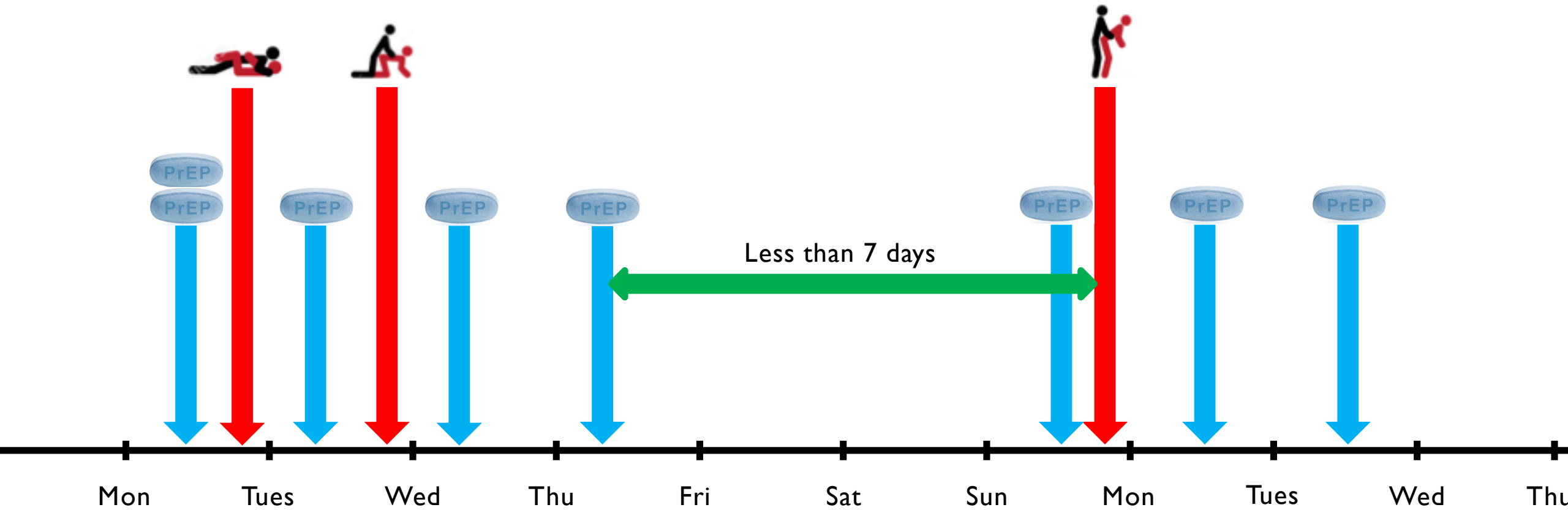
Study design:

- 414 MSM in France, who reported condomless anal sex.
- 1:1 randomisation (TDF/FTC or placebo)
- “Event-based” dosing rather than daily dosing.
- Study visits every 8 weeks

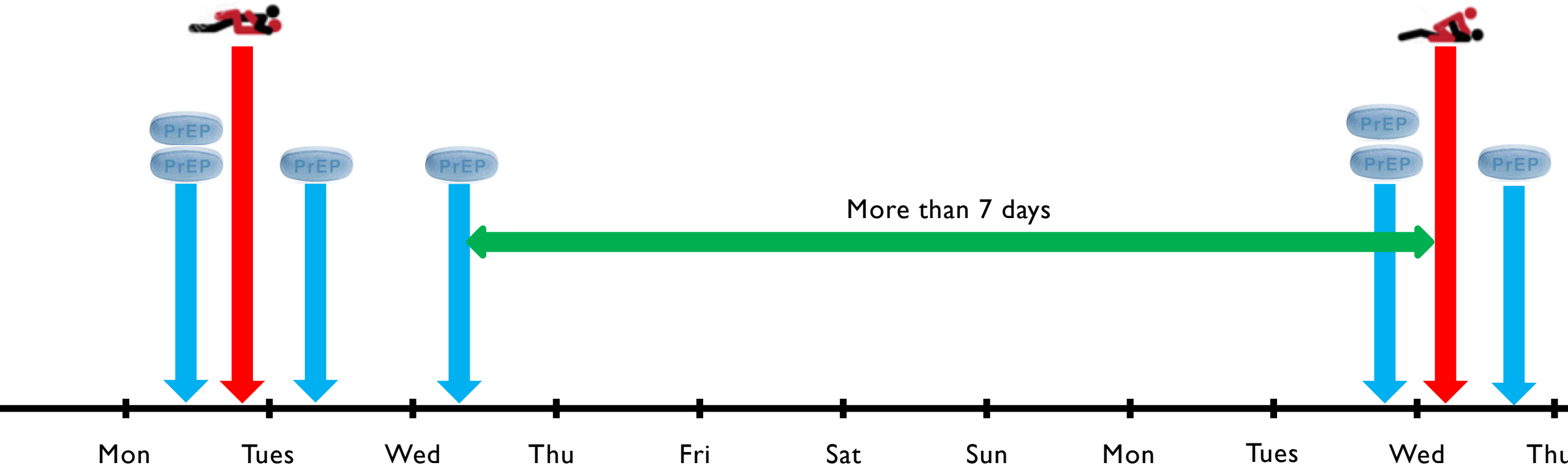
IPERGAY – EVENT-BASED DOSING



IPERGAY – EVENT-BASED DOSING



IPERGAY – EVENT-BASED DOSING



1. Molina et al. NEJM 2015, 373(23):2237-2246.
2. Molina et al. Conference presentation at AIDS 2016, Durban (not yet published).
3. Antoni et al. Conference presentation at IAS 2017, Paris (not yet published).

IPERGAY

Results:

- 16 HIV infections during follow-up:
 - 2 in TDF/FTC group
 - 14 in placebo group
- Relative risk reduction of 86% (95% CI 40 to 98; P = 0.002).¹
- IPERGAY-OLE: 95% risk reduction.²
- But, participants used an average of 15 pills per month.¹
- 6 HIV infections among participants using < 15 pills per month:³
 - 0 in TDF/FTC group (RRR 100%; 95%CI 20-100)
 - 6 in placebo group

PREP FOR WOMEN

- **Partners PrEP**, conducted in Uganda and Kenya
- 4758 serodiscordant couples, where HIV+ partner was not on ARV Rx
- For 38% the HIV- partner was female
- Median follow-up of 23 months
- Randomised: TDF vs TDF/FTC vs placebo
- 82 new HIV infections during the trial
- TDF: 67% RRR (95% CI 44 to 81; $P < 0.001$)
- TDF/FTC: 75% RRR (95% CI 55 to 87; $P < 0.001$)
- If detectable plasma tenofovir: 90% RRR for TDF/FTC

PrEP for transgender women

Results:

- iPrEx included 339 transgender women.
- More transactional sex, more receptive CLAI, more partners.
- 11 HIV infections in TDF/FTC group
- 10 HIV infections in placebo group
- In the TDF/FTC group, drug was detected in none of the women at the seroconversion visit.
- Among MSM, those with the highest risk were also most adherent. Among transgender women, this linkage did not exist.
- Conclusion: Barriers to adherence among transgender women, particularly among those most at risk. But PrEP seems effective when taken.



Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine HIV pre-exposure prophylaxis: clinical guidelines. Update April 2018

Edwina Wright^{1–3*}, Andrew Grulich⁴, Katy Roy⁵, Mark Boyd^{4,6}, Vincent Cornelisse^{1,7}, Darren Russell^{8,9}, Darryl O'Donnell¹⁰, Bill Whittaker¹¹, Levinia Crooks^{5,12,13†} and Iryna Zablotska^{4†}

“Trans and gender diverse individuals have rarely been included in PrEP studies. As a result, limited data are available for these individuals.”

“Trans and gender diverse people who are at high risk of acquiring HIV on the basis of their sexual history are eligible to access PrEP.”

PREP FOR PWID

- Bangkok Tenofovir Study
- RCT among PWID, 2005-2012.
- 2413 people (80% men), 9665 PY of follow-up
- 49% HIV risk reduction overall, 84% for those with at least 97.5% adherence
- Factors associated with lower adherence: men, younger, incarcerated, meth use

PREP FOR PWID

- PrEP should be part of a comprehensive harm minimisation package.
 - Safe injecting rooms
 - Needle exchange
 - Opioid substitution
 - Mental health support
 - Vaccinations
- PWID may also experience sexual exposure to HIV.



POSSIBLE RISKS OF PREP

RISKS OF PrEP

- Renal toxicity
- Bone density loss
- Risk of resistance to antiretroviral medication
- Risk of hepatitis B flare

Group	# of visits	% ≥ 1 visit with CrCl falling ≤ 70 ml/min over a year on PrEP [*]	Relative risk	p-value
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Table 2a: All iPrEx OLE participants

Overall	7198	2.6% (1.9 to 3.4%)		
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Baseline renal function

Baseline CrCl ≥ 90 ml/min	6583	0.7% (0.4 to 1.3%)	Ref	
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Baseline CrCl < 90 ml/min	615	20.4% (15.1 to 27.2%)	31.2 (16.2 to 60.1)	<0.001
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Age at initiation of PrEP

Age <40	5686	0.5% (0.2 to 1.0%)	Ref	
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Age 40–50	973	6.4% (3.9 to 10.2%)	13.4 (5.5 to 32.5)	<0.001
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Age ≥ 50 years	539	16.3% (11.3 to 23.3%)	36.2 (15.6 to 83.9)	<0.001
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Relative risk of participant experiencing creatinine clearance fall to ≤ 70 ml/min over the first year on PrEP in the entire iPrEx cohort.

(Ghandi et al. Lancet HIV. 2016 Nov; 3(11): e521–e528.)

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“Creatinine, eGFR and urinary PCR should be evaluated at baseline, 3 months after commencing PrEP then 6 monthly thereafter, while they receive PrEP.”

“However, based on currently available evidence, more intensive monitoring may be warranted in individuals under the age of 25 years or over the age of 40 years, and in those with a baseline eGFR of less than 90 mL/min/1.73 m².”

“A patient with an eGFR of less than 60 mL/min/1.73 m² should not be prescribed PrEP.”

FURTHER RECOMMENDATIONS?

- Not much data on PrEP for older people, including renal safety.
- Prudent to screen for renal risk factors prior to initiating PrEP:
 - Check BP
 - Check fasting glucose and lipids
 - Review medications for nephrotoxins (including OTC and herbal)
 - Review smoking, alcohol, drugs

DXA Substudy Schema

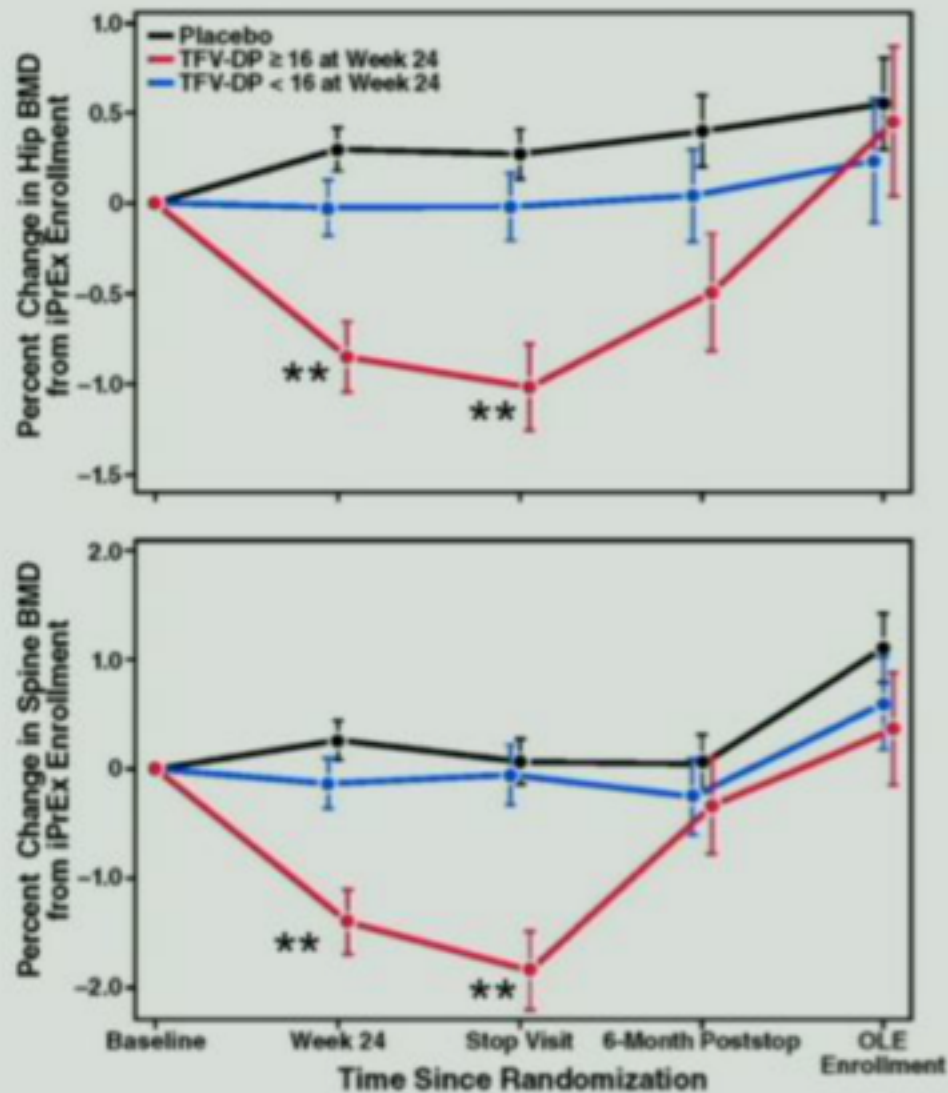


Mulligan et al. (2015)
CID, 61(4):572–580

- DXA scans of hip and spine at...
 - Baseline and every 24 weeks during PrEP/Placebo use,
 - 24 weeks after stopping PrEP/Placebo,
 - At enrollment in Open Label Extension (OLE).
- Drug concentrations in vPBMCs collected in all DXA participants at...
 - Week 24 concentrations used to stratify analysis of BMD,
 - Strong predictor of consistent drug detection at subsequent visits.



Recovery of Hip and Spine BMD by PrEP Use



HIP BMD
average annualized
recovery rates
after stopping PrEP were
 $1.13 \pm 0.27\%$
($P=0.002$ vs. placebo)

Spine BMD
average annualized
recovery rates
after stopping PrEP were
 $1.81 \pm 0.36\%$
($P=0.01$ vs. placebo).

Mulligan et al. (2015)
CID, 61(4):572–580

US CDC PREP STUDY

- 10% of HIV-negative MSM had low BMD at baseline.
- No increased rate of pathological fractures from TDF use, but concluded that larger studies over a longer period of time were needed to assess this further.
- Other factors associated with low BMD (Z score < -2.0):
 - Amphetamine use (Univariate OR 5.86, 95% CI 1.7 to 20.2; $p < 0.01$)
 - Inhalant use (Univariate OR 4.57, 95% CI 1.32 to 15.8; $p = 0.02$)
- Participants who took vitamin D, calcium or multivitamins had a lower risk of reduced bone density (Univariate OR 0.26, 95% CI 0.1 to 0.7; $p < 0.01$)

Recommendations?

“DEXA scans or other assessments of bone health are not recommended before the initiation of PrEP or for the monitoring of persons while taking PrEP. However, any person being considered for PrEP who has a history of pathologic or fragility bone fractures or who has significant risk factors for osteoporosis should be referred for appropriate consultation and management.”

- 2014 CDC PrEP guidelines

... but is there any harm in doing a FRAX assessment?

... and maybe check vitamin D?

ARV resistance in iPrEx HIV at enrolment

- 2 participants had unrecognised HIV at enrolment and were randomised to TDF/FTC.
- Both had M184V/I mutations, conferring resistance to FTC.
- 1 of 2 participants had confirmed wild-type HIV at study entry.
- No TDF resistance mutations

ARV resistance in iPrEx HIV during study

- 48 participants in TDF/FTC group infected with HIV during study.
- Only 8 had detectable drug levels at or within 90 days before their seroconversion visit.
- No mutations detected on standard genotype and pheno type tests.
- 2 participants had minor variant M184I on ultra-sensitive testing.
- Conclusion: No clinically-significant drug resistance.

PrEP and hepatitis B: Why worry?

- PrEP contains tenofovir
- Tenofovir is active against hepatitis B, and used as treatment for HBV.
- Stopping HBV treatment can result in a flare of HBV, causing liver damage.
- So, stopping PrEP can theoretically be dangerous for someone with HBV.
- Poor adherence to PrEP could also result in antiviral resistance in HBV.

Prep and hepatitis B – is it safe?

- iPrEx: 2499 participants
- 12 (0.5%) cases of chronic HBV; 6 randomised to TDF/FTC
 - No hepatitis B flares, even after TDF/FTC discontinuation
- 4 cases of acute hepatitis B; 2 randomised to TDF/FTC
 - One developed immunity (HBsAb)
 - One lost HBsAg, but left study before evidence of immunity
- No TDF or FTC resistance in HBV genotypes





HOW TO PROVIDE PREP

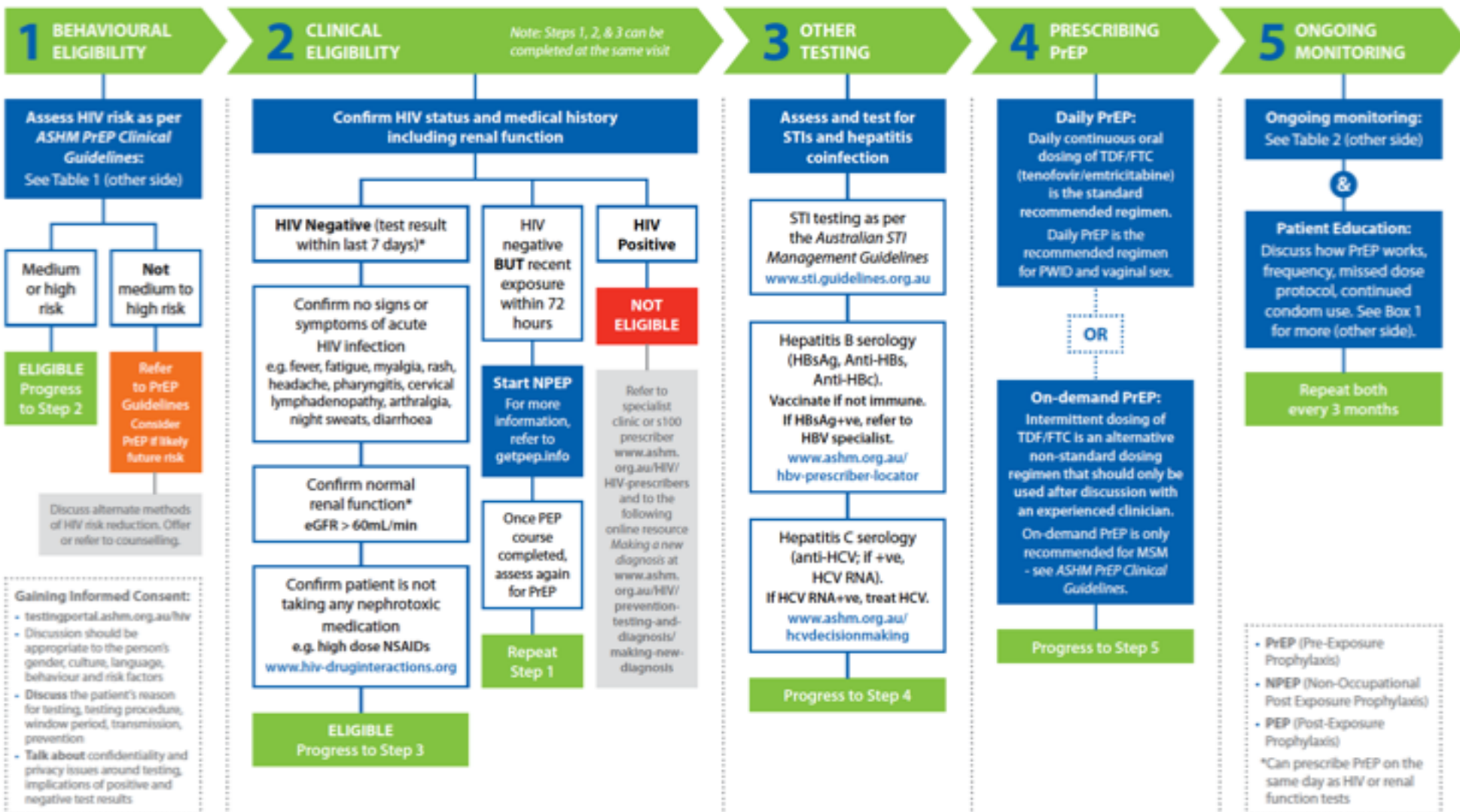


Table 1: Behavioural eligibility criteria for PrEP

RISK CRITERIA FOR MSM		RISK CRITERIA FOR TRANS & GENDER DIVERSE PEOPLE		RISK CRITERIA FOR HETEROSEXUAL PEOPLE		RISK CRITERIA FOR PWID	
High Risk – Recommend PrEP		High Risk – Recommend PrEP		High Risk – Recommend PrEP		High Risk – Recommend PrEP	
Last 3 months	Next 3 months*	Last 3 months	Next 3 months*	Last 3 months	Next 3 months*	Last 3 months	Next 3 months*
<ul style="list-style-type: none"> • CLAI with a regular HIV+ partner (not on treatment and/or detectable viral load) • Receptive CLAI with any casual HIV+ male partner or a male partner of unknown status • Rectal gonorrhoea, rectal chlamydia or infectious syphilis diagnosis • Methamphetamine use 	<ul style="list-style-type: none"> • Multiple episodes of CLAI with or without sharing intravenous drug equipment 	<ul style="list-style-type: none"> • Regular sexual partner of an HIV+ person (not on treatment and/or detectable viral load) with inconsistent condom use • Receptive CLAI with any casual HIV+ partner or a male partner of unknown status • Rectal or vaginal gonorrhoea, chlamydia or infectious syphilis diagnosis • Methamphetamine use 	<ul style="list-style-type: none"> • Multiple episodes of anal or vaginal CLJ with or without sharing intravenous drug equipment 	<ul style="list-style-type: none"> • A regular sexual partner who is HIV+ (not on treatment and/or with detectable viral load) with inconsistent condom use • Receptive anal or vaginal CLJ with any casual HIV+ partner, male homosexual or bisexual partner of unknown status • A female patient in a serodiscordant heterosexual relationship, who is planning natural conception in the next 3 months 	<ul style="list-style-type: none"> • Multiple episodes of CLJ with or without sharing intravenous drug equipment 	<ul style="list-style-type: none"> • Shared injecting equipment with an HIV+ individual or with a gay or bisexual man of unknown HIV status 	<ul style="list-style-type: none"> • Multiple events of sharing injecting equipment with an HIV+ individual or a gay or bisexual man of unknown HIV status • Inadequate access to safe injecting equipment
Medium Risk – Consider PrEP		Medium Risk – Consider PrEP		Medium Risk – Consider PrEP			
Last 3 months	Next 3 months*	Last 3 months	Next 3 months*	Last 3 months	Next 3 months*		
<ul style="list-style-type: none"> • Anal intercourse when proper condom use was not achieved (e.g. condom slipped off) where the serostatus of partner was not known, or was HIV+ and not on treatment or with a detectable viral load • If patient uncircumcised: more than one episode of insertive CLAI where the serostatus of partner was not known, or was HIV+ and not on treatment or with a detectable viral load 	<ul style="list-style-type: none"> • Multiple episodes of CLAI with or without sharing intravenous drug equipment 	<ul style="list-style-type: none"> • 1+ episodes of anal or vaginal intercourse when proper condom use was not achieved (e.g. condom slipped off) and where the serostatus of partner was not known, or was HIV+ and not on treatment or with a detectable viral load • If patient uncircumcised: 1+ episodes of insertive CLAI where the serostatus of partner was not known, or was HIV+ and not on treatment or with a detectable viral load 	<ul style="list-style-type: none"> • Multiple episodes of anal or vaginal CLJ with or without sharing intravenous drug equipment 	<ul style="list-style-type: none"> • CLJ with a heterosexual partner, not known to be HIV+, from a country with high HIV prevalence 	<ul style="list-style-type: none"> • Multiple episodes of CLJ with or without sharing intravenous drug equipment 	<ul style="list-style-type: none"> • PWID (People Who Inject Drugs) • CLJ (Condomless Intercourse) • CLAI (Condomless Anal Intercourse) <p>*Is the patient likely to behave like this in the next 3 months (indicates a sustained risk)</p>	

Table 2: Laboratory evaluation & clinical follow-up of individuals who are prescribed PrEP

Test	Baseline	±30 days after initiation (optional)	90 days after initiation	Every 90 days on PrEP	Other frequency (minimum)
HIV testing and assessment for signs or symptoms of acute infection	✓	✓	✓	✓	n/a
Assess side effects	n/a	✓	✓	✓	n/a
Hepatitis B serology	✓	n/a	n/a	n/a	n/a
Hepatitis C serology	✓	n/a	n/a	n/a	Every 12 mths
STI (i.e. syphilis, gonorrhoea, chlamydia) as per Australian STI Management Guidelines	✓	n/a	✓	✓	n/a
eGFR ± urine albumin: creatinine ratio (ACR) at 3 mths and then every 6 mths	✓	n/a	✓	n/a	Every 6 mths
Pregnancy test (women of child-bearing potential)	✓	✓	✓	✓	n/a

Box 1: Patient Education

- Discuss HIV-risk behaviours
- Discuss combination HIV/STI prevention, including the central role of condoms
- Discuss safer injecting practices if applicable
- Check mental health and recreational drug use
- Discuss the importance of medication adherence at every visit
- Patients need to take a daily dose of PrEP for 7 days to achieve high levels of protection, 20 days to achieve maximum protection
- If stopping PrEP – patients on daily PrEP should continue PrEP for 28 days following exposure
- Ongoing monitoring every 3 months is required – see Table 2; discuss potential side effects include early e.g. headache, nausea and long term e.g. renal injury, lowered bone density;
- Ask about medications that can affect renal function, eg regular use of NSAIDs

australian STI MANAGEMENT GUIDELINES FOR USE IN PRIMARY CARE

Standard
asymptomatic check-up

STIs

Syndromes

Populations
& situations

Resources

How to use these Guidelines?

All STIs can cause disease without producing symptoms. Please refer to Populations & Situations for asymptomatic screening recommendations, Syndromes for guidance about managing specific clinical scenarios and to STIs for specific management of a diagnosed infection.

Latest Update

2017/18: Annual Critical Review
Complete - what's changed?

Guidelines index

STI

- Chancroid
- Chlamydia
- Donovanosis
- Ectoparasites
- Genital warts
- Gonorrhoea

SYNDROME

- Ano-genital Lumps
- Ano-genital Ulcers
- Ano-rectal Syndromes
- Cervicitis
- Epididymo-orchitis
- PID - Pelvic inflammatory

POPULATIONS & SITUATIONS

- Aboriginal and Torres Strait Islander People
- Adult Sexual Assault
- MSM - Men who have sex with men
- People in correctional facilities

WHAT IF NO MEDICARE CARD?

- TGA's personal importation scheme
- Insurance may cover consultations and pathology
- <https://www.tga.gov.au/personal-importation-scheme>
- PrEP ACCESS NOW – pan.org.au
- PrEP'd for Change – prepdforchange.com