

Guidelines on the use of pre-exposure prophylaxis (PrEP)

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On behalf of the BHIVA/BASHH PrEP guideline writing committee

Disclosures

I have no disclosures

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Outline

- Development and structure of the guidelines
- Main PrEP guideline recommendations
- Challenges and controversies
- National context

Guidelines developed based on process in the BHIVA Guidelines Development Manual



Mar
2016

GRADE training undertaken by all group members

POPULATIONS: HIV negative
INTERVENTION: PrEP
COMPARISON: No specific comparators applied to ensure all picked up in search
OUTCOME: HIV, STIs, adverse events, risk behaviours or risk compensation (condom use, number of sexual partners), adherence

Search strategy: Jan 2004 to May 2016. Medline, Embase and Cochrane. Only papers in English included, animal studies excluded. Relevant evidence between May 2016 -July 2017 also included

Abstracts reviewed and sifted to identify relevant papers

Sections allocated to small teams to draft guideline chapters

Writing group review draft and discuss content and recommendations

Update and reiteration of guideline sections, finalise content and recommendations

Public consultation then review by BHIVA/BASHH guideline subcommittee and EC

Aug
2018

Published with appendix of comments and responses

Community Consultation

- Yusef Azad (NAT)
- Takudzwa Mukiwa (THT)
- Will Nutland (Prepster)
- Greg Owen (I Want PrEP Now)
- Michelle Ross (CliniQ)
- Sophie Strachan (Sophia Forum)
- Marc Thompson (Prepster/Black Out UK)
- George Valiotis (HIV Scotland)



Thank you for consultation feedback

- Abraham Kowo
- Sanjay Bhagani
- Frances Keane
- Sophie Forsyth
- Amy Evans
- David White
- Nurul Huda
- Mohamad Fadzillah
- Emma Wainwright
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Guidelines Structure

Section 1-3: Objectives, Methods, Summary Recommendations

Section 4: Detailed evidence review (including Efficacy, Adherence, Safety, Risk behaviour, Timelines for Starting and Stopping PrEP):

(i) Men who have sex with men; (ii) Heterosexual populations; (iii) PWID; (iv) Trans people; (v) Young people

Sections 5-7: Practical guidance to support risk assessment, starting PrEP, on-going management and stopping PrEP

Section 8. Buying generic PrEP (GPP)

Section 9. Cost effectiveness of PrEP in high income countries

Section 4: PrEP efficacy

Randomised Controlled Trials

IPEGAY (on-demand TDF/FTC in MSM)

PROUD (daily TDF/FTC in MSM)

Partners PrEP (daily TDF or TDF/FTC serodifferent HT couples)

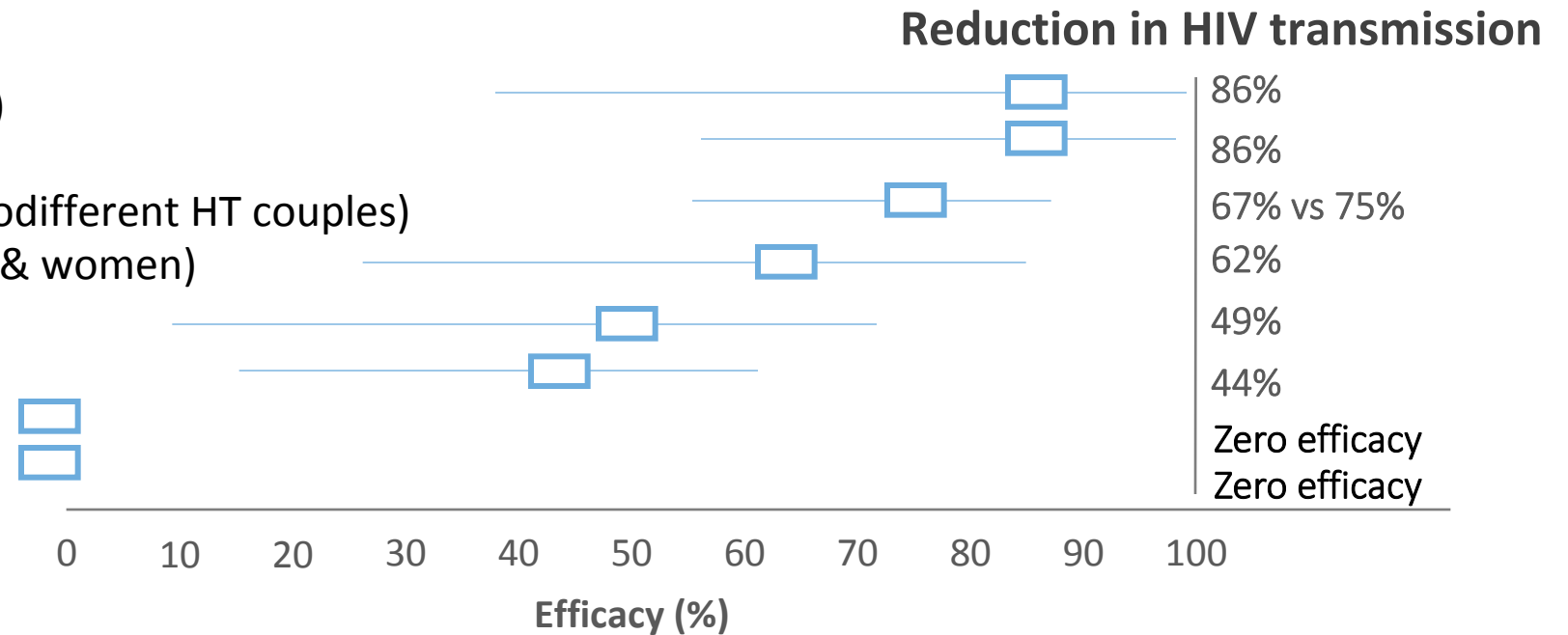
TDF2 (daily TDF/FTC heterosexual men & women)

Bangkok PrEP in PWID (daily TDF)

iPrEx (daily TDF/FTC MSM/TGW)

VOICE (daily TDF, TDF/FTC, TFV vag gel)

FEM-PrEP (daily TDF/FTC)

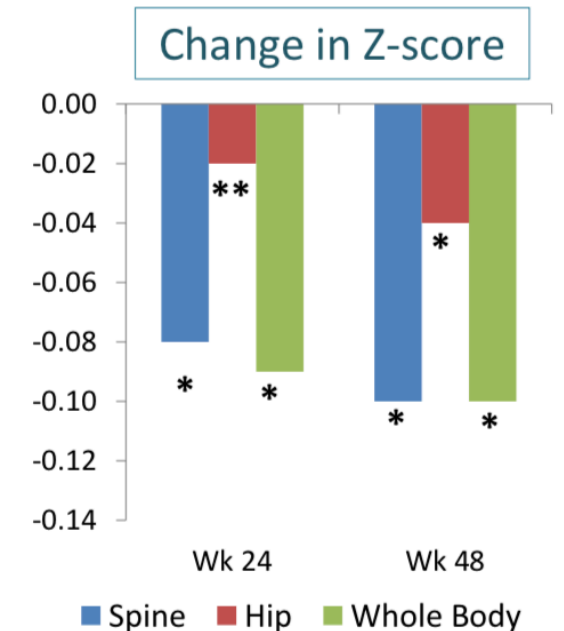
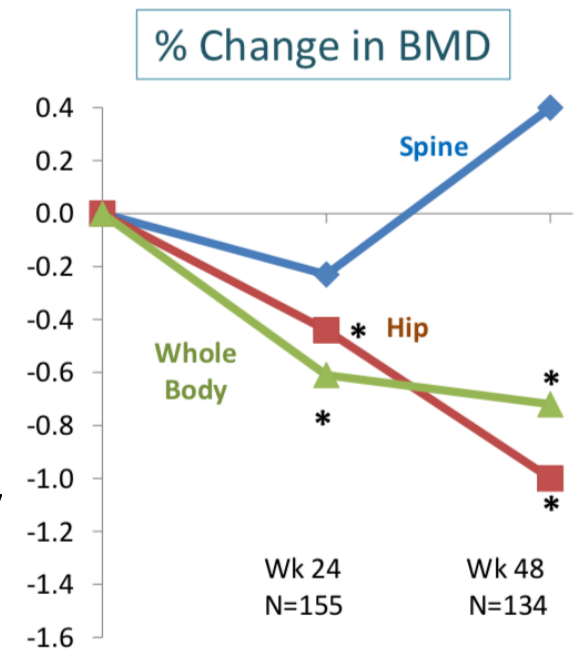


Open label extension studies

- iPrEx-OLE: Daily TDF-FTC. No seroconversions if drug levels compatible with \geq four pills/week
- IPEGAY-OLE: 97% reduction in risk compared to the placebo arm of the IPEGAY randomised phase
- TDF2 OLE: No new HIV infections during the 12 month F/U. 87% women and 96% men had detectable drug levels at visits
- PREVENIR: Ongoing cohort, n=1435, 99% MSM at risk of HIV. Daily PrEP (44%, 302 PYFU): On-demand (53%, 261 PYFU). No seroconversions.

Section 4: Safety in Young People

- Peak bone mass is achieved during early adulthood
- Project PrEPare 2 (ATN 110)¹, 200 young MSM (18-22yrs), 46% Black ethnicity, baseline Z scores below normal in spine, hip & total body
- 48 weeks daily TDF-FTC significantly reduced hip (-1.4%), whole body (-0.6%) BMD, but not spine. Z scores significantly less than baseline
- Greater loss in BMD (3% difference in hip) if TFV-DP levels in protective range compared to low drug exposure group (ATN 117)²
- TDF-FTC discontinuation in YMSM (n=70) who lost BMD during 48 weeks PrEP, generally led to BMD recovery over 48-weeks FU
- But, persistently **lower Z scores in the spine remained** (-0.164, $P < 0.001$) compared to baseline
- Suggests that TDF PrEP is a risk for adolescents during a critical period for attainment of peak bone mass.



Safety in Young People

Recommendation: Routine BMD scanning in young people initiating PrEP is not recommended. (1D)

Good Practice Point: A discussion about side effects including impact upon bone density in young people should be held at PrEP initiation and maintenance visits.

General GPP for Bone Health

- Patients should be informed of the risk of reduction in BMD of around 1.5–2% at the hip and spine following 48 weeks of treatment.
- Routine monitoring of BMD is not recommended in individuals taking TDF for PrEP with no other risk factors for reduced BMD.
- In those with risk factors for reduced BMD, the FRAX tool could be undertaken, to indicate the need for a DEXA scan and potential treatment for reduced BMD.

Section 4: Safety in Pregnancy

- Systematic reviews and observational studies show TDF to be safe in pregnancy¹
- A BMJ clinical practice guideline² (2017) made a “weak recommendation” that AZT/3TC should be used preferentially over TDF/FTC in pregnant women, because of the lower number stillbirths and early neonatal deaths reported in the PROMISE RCT³
- The BHIVA pregnancy guidelines writing group issued a full critical response to this article and BHIVA recommendation remains to use TDF plus 3TC/FTC as required⁴
- The PrEP guidelines writing group agree with the BHIVA response that the PROMISE data should not influence the use of TDF-FTC for PrEP in women of child-bearing potential



Safety in Pregnancy: Recommendation

We suggest that if an individual is pregnant when starting PrEP or becomes pregnant while on PrEP, that they continue PrEP during pregnancy or breastfeeding if there is an on-going risk of HIV acquisition, after discussing the potential risks of TDF-FTC (2B)



Section 4: Safety/Efficacy in Trans People

- Trans women form a minority of PrEP RCT participants.
- No data at all for trans men
- iPrEX and iPrEx-OLE subgroup analysis: minimal effectiveness TDF-FTC as PrEP in trans women, linked to lower adherence and drug concentrations.
- Concerns persist in trans women about potential DDI (FHT and PrEP), which may hamper uptake/adherence
- Interaction between TDF-FTC and feminising hormones or androgen preparations is thought unlikely due to differing metabolism and clearance www.hiv-druginteractions.org

		HIV drugs with no predicted effect
Estrogens		RPV, MVC, DTG, RAL, NRTIs (ABC, ddl, FTC, 3TC, d4T, TAF, TDF, ZDV)
Estradiol oral	Starting dose	2 mg/day
	Average dose	4 mg/day
	Maximum dose	8 mg/day
Estradiol gel (preferred for >40 y and/or smokers)	Starting dose	0.75 mg twice daily
	Average dose	0.75 mg three times daily
	Maximum dose	1.5 mg three times daily
Estradiol patch (preferred for >40 y and/or smokers)	Starting dose	25 µg/day
	Average dose	50-100 µg/day
	Maximum dose	150 µg/day
Conjugated estrogen†	Starting dose	1.25-2.5 mg/day
	Average dose	5 mg/day
	Maximum dose	10 mg/day
Ethinylestradiol	Starting dose	No interaction expected, but not recommended due to thrombotic risks
	Average dose	
	Maximum dose	
Androgen Blockers		RPV, MVC, DTG, RAL, NRTIs (ABC, ddl, FTC, 3TC, d4T, TAF, TDF, ZDV)
Spironolactone	Starting dose	50 mg/day
	Average dose	150 mg/day
	Maximum dose	400 mg/day
Finasteride	Starting dose	2.5 mg/day
	Average dose	2.5 mg/day
	Maximum dose	5 mg/day
Cyproterone acetate	Starting dose	50 mg/day
	Average dose	150 mg/day
	Maximum dose	150 mg/day
Goserelin	Starting dose	3.6 mg/month
	Average dose	3.6 mg/month
	Maximum dose	3.6 mg/month
Leuprorelin acetate	Starting dose	3.75 mg/month
	Average dose	3.75 mg/month
	Maximum dose	3.75 mg/month
Triptorelin	Starting dose	3.75 mg/month
	Average dose	3.75 mg/month
	Maximum dose	3.75 mg/month

† Conjugated estrogen is associated with high thromboembolic risk and therefore should be avoided.

Section 4: Safety/Efficacy in Trans People

TUPDX0107LB: *iFACT* Study¹

- Daily TDF/FTC in 20 trans women
- No significant changes in PK parameters for FHT levels with and without PrEP
- TDF exposure 13% lower AUC with estradiol.

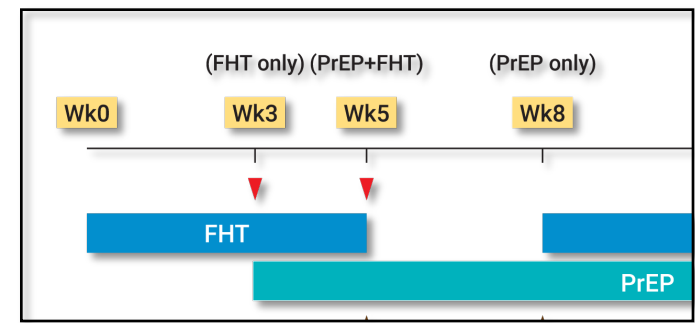


Table 1 Summary of E2 pharmacokinetic parameters; data are presented in geometric mean (%CV)

E2 PK parameter	Week 3 (FHT)	Week 5 (PrEP+FHT)	GMR (95%CI)	p-value
AUC ₀₋₂₄ (pg*h/mL)	775.13 (26.2)	782.84 (39.6)	1.01 (0.89 - 1.15)	0.88
C _{max} (pg/mL)	51.47 (26.9)	55.76 (32.9)	1.08 (0.94 - 1.24)	0.25
C ₂₄ (pg/mL)	15.15 (42.0)	14.32 (67.4)	0.95 (0.75 - 1.19)	0.63
Half-life (h)	11.25 (32.6)	11.83 (50.9)	1.05 (0.87 - 1.27)	0.60

TUPDX0106: Cottrell et al²

- Compared intracellular drug levels rectal tissue in 4 TGW, 4CGW and 2CGM.
- TDF-dp:dATP ratio 7-fold lower in TGW, but absolute TFV-dp levels similar.
- Clinical implications not clear. Need for further studies



Figure 1. No significant difference in rectal tissue intracellular nucleotide concentrations of TGW compared to CGW or CGM

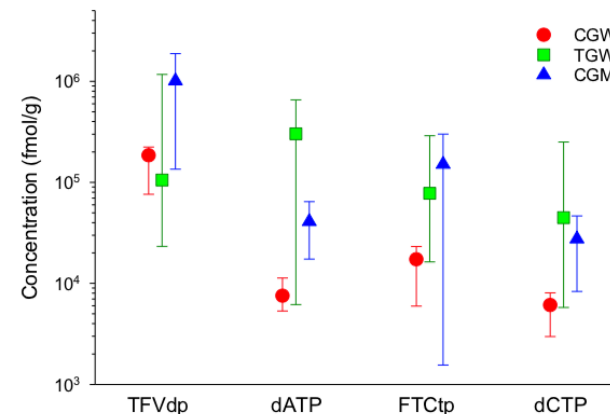
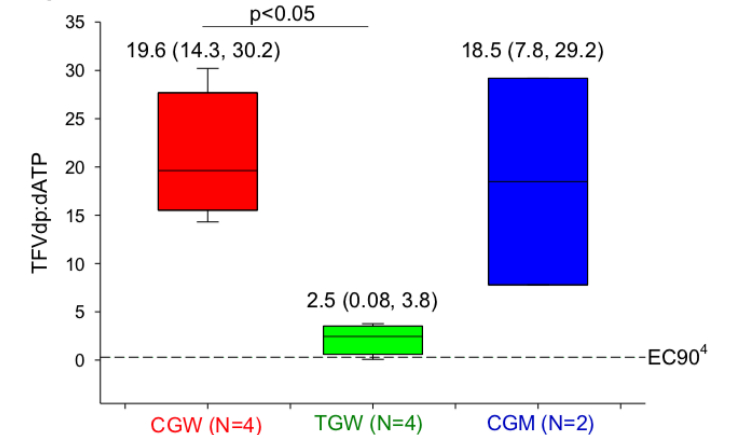


Figure 2. Median rectal TFVdp:dATP ↓ by ~10-fold among TGW compared to CGW or CGM



1. Hiransuthikul A et al. *Drug-drug interactions between the use of feminizing hormone therapy and pre-exposure prophylaxis among transgender women: the iFACT study.*, abstract TUPDX0107LB, 2018. 2. Cottrell ML et al. Altered TDF/FTC pharmacology in a transgender female cohort: Implications for PrEP. TUPDX0106.

Section 4: Safety/Efficacy in Trans People

Recommendation: We recommend that PrEP with daily oral TD-FTC should be offered to HIV-negative trans women who are identified as being at elevated risk of HIV acquisition through condomless anal sex in the previous 6 months and ongoing condomless sex. (1A)

Good Practice Points:

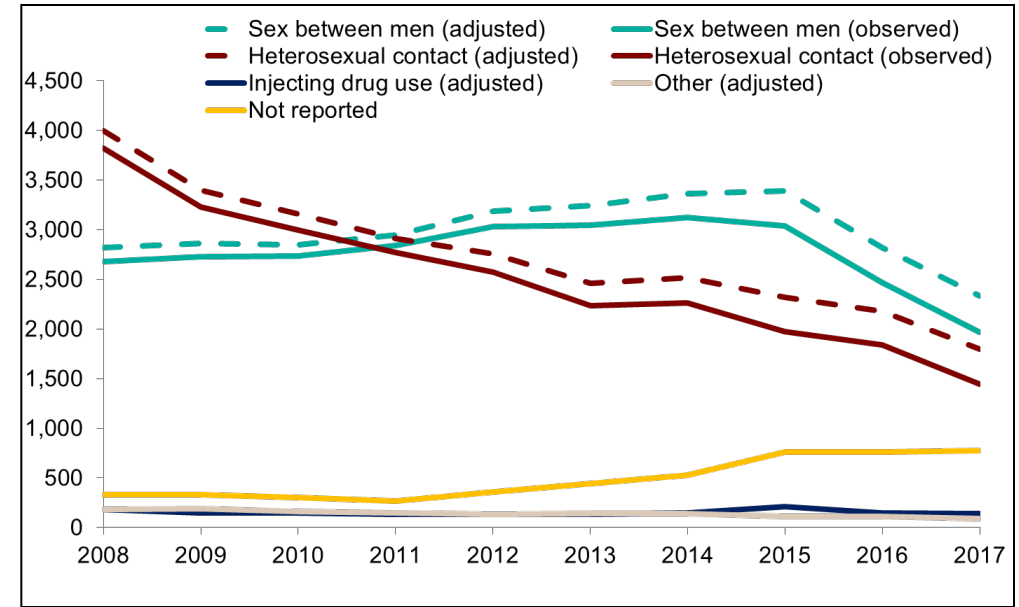
- PrEP could be considered on a case-by-case basis in trans women and trans men with current factors other than condomless anal sex that may put them at increased risk of HIV acquisition
- For both trans women and trans men a discussion should be had regarding unknown PrEP efficacy for frontal (vaginal) sex.
- A discussion should be had, both at PrEP initiation and maintenance visits, that there are no known interactions between TD-FTC and feminising or masculinising hormones.

General GPP (Section 6): Robust adherence support is required. Some individuals may require more extensive counselling and support. This may be particularly relevant to some trans people, some young people and some heterosexual men and women to ensure PrEP literacy and maximise adherence.

Section 4: PWID

- No UK data on efficacy of PrEP in PWID
- One RCT (TDF vs placebo) in PWID in Bangkok: 49% reduction in HIV incidence.
- Efficacy was strongly linked to adherence.
- Overall, the number acquiring HIV through IDU in the UK remains low, though outbreak among PWID in Glasgow is ongoing
- Chemsex and slamming (the act of injecting the drugs used in chemsex) are more commonly seen in MSM and are associated with risk behaviours for HIV acquisition.

Number of people newly diagnosed with HIV by exposure category: UK 2008 to 2017



(HIV in the United Kingdom, 2018, Public Health England)



Section 4: PWID

Recommendations:

- We suggest that PrEP is not recommended for people who inject drugs where needle exchange and opiate substitution programmes are available and accessed by the individual. (2C)
- We recommend that existing harm-reduction strategies such as needle exchange and opiate substitution programmes should be encouraged for people who inject drugs. (1D)

Good practice points

- Consider PrEP on a case-by-case basis in people who inject drugs in an outbreak situation or with other factors that put them at increased risk of HIV acquisition.
- Interventions for chemsex should be encouraged for people who are identified as being at elevated risk of HIV acquisition through report of injecting drug use during chemsex (slamming).

Section 5: Eligibility - Recommendations

We recommend that

- PrEP with daily or on-demand oral TD-FTC is offered to MSM, and daily oral TD-FTC is offered to trans women, at elevated risk of HIV acquisition through recent (6 months) and on-going condomless anal sex. (1A)
- PrEP with daily oral TD-FTC is offered to HIV-negative people having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A)

We suggest that

- PrEP with daily oral TD-FTC (or TDF alone if FTC contraindicated) should be offered on a case-by-case basis to heterosexual men and women with current factors that may put them at increased risk of HIV acquisition (2B)

Good Practice Point

- Consider PrEP with daily oral TD-FTC on a case-by-case basis in people with current factors other than condomless anal sex that may put them at increased risk of HIV acquisition

Section 5: Eligibility – Good Practice Point

Consider PrEP with daily oral TD-FTC on a case-by-case basis in people with current factors other than condomless anal sex that may put them at increased risk of HIV acquisition

Consider PrEP on a case-by-case basis	
PrEP may be offered on a case-by-case basis to HIV-negative individuals considered at increased risk of HIV acquisition through a combination of factors that may include the following:	
Population-level indicators <ul style="list-style-type: none"> • Heterosexual black African men and women • Recent migrants to the UK • Transgender women • People who inject drugs • People who report sex work or transactional sex 	Clinical indicators <ul style="list-style-type: none"> • Rectal bacterial STI in the previous year • Bacterial STI or HCV in the previous year • Post-exposure prophylaxis following sexual exposure (PEPSE) in the previous year; particularly where repeated courses have been used
Sexual behaviour/sexual-network indicators <ul style="list-style-type: none"> • High-risk sexual behaviour: reporting condomless sex with partners of unknown HIV status, and particularly where this is condomless anal sex or with multiple partners • Condomless sex with partners from a population group or country with high HIV prevalence (see UNAID definitions [1]) • Condomless sex with sexual partners who may fit the criteria of ‘high risk of HIV’ detailed above • Engages in chemsex or group sex • Reports anticipated future high-risk sexual behaviour • Condomless vaginal sex should only be considered high risk where other contextual factors or vulnerabilities are present 	Drug use <ul style="list-style-type: none"> • Sharing injecting equipment • Injecting in an unsafe setting • No access to needle and syringe programmes or opioid substitution therapy Sexual health autonomy Other factors that <i>may</i> affect sexual health autonomy <ul style="list-style-type: none"> • Inability to negotiate and/or use condoms (or employ other HIV prevention methods) with sexual partners • Coercive and/or violent power dynamics in relationships (e.g. intimate partner/domestic violence) • Precarious housing or homelessness, and/or other factors that may affect material circumstances • Risk of sexual exploitation and trafficking

PrEP and renal function

- A good renal safety profile for TDF demonstrated across all PrEP trials, safety data for HIV-negative persons with reduced renal function not available.
- Mild progressive renal impairment seen in PrEP studies, reversed on stopping study medication
- Assess the risk of CKD at baseline. Factors that may increase risk include older age, concomitant nephrotoxic medication or comorbidities such as HT and DM
- Prior to initiating PrEP, clinicians should discuss possibility of kidney disease if pre-existing risk factors. Thorough medication history obtained regarding concomitant nephrotoxic drugs or drugs that have interactions with TDF-FTC.
- Serum creatinine, eGFR and urinalysis should be performed at baseline.
- PrEP may be started immediately, but results should be reviewed as soon as possible.

PrEP and renal function

- In PROUD¹, three participants interrupted drug due to elevated creatinine concentrations
- In IPERGAY², 18% of active drug participants experienced (mild and transient) elevated creatinine levels compared to 10% of placebo group (P=0.03).
- In iPrEx³, TDF-FTC use was associated with a mild non-progressive decrease in estimated creatinine clearance (CrCl) of 2.4% from baseline, which was reversible.
- Creatinine elevations of greater than 1.1 ULN were similar between active (2.6%) and placebo arms (2.2%). RR: 1.35, 95% CI 0.80–2.3.

1. McCormack S, Dunn DT, Desai M et al. 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. *Lancet* 2016; 387 : 53–60.

2. Molina JM, Capitant C, Spire B et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med* 2015; 373 : 2237–2246.

3. Grant RM, Lama JR, Anderson PL et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; 363 : 2587–2599

4. Baeten JM, Donnell D, Ndase P et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; 367 : 399–410

PrEP and renal function

- In iPrEX, proteinuria by dipstick was detected regularly (12% dipsticks), but there was no between group difference in the proportion of participants ever positive for proteinuria
- PPV of proteinuria in predicting creatinine elevation was poor at 0.7%
- In Partners PrEP⁴ the overall mean decline for those receiving PrEP compared to placebo was estimated to be 2–3mL/min/1.73 m² ($p \leq 0.01$).
- The proportions of participants with a confirmed >25% decline in eGFR from baseline by 12 and 24 months were 1.3% and 1.8% for TDF, 1.2% and 2.5% for TDF-FTC, and 0.9% and 1.3% for placebo (not statistically significant)
- Sub-group analysis (n=1,549) found no difference in markers of tubulopathy between the TDF-FTC and placebo group over a median of 2 years' follow-up

1. McCormack S, Dunn DT, Desai M et al. 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. *Lancet* 2016; 387 : 53–60.

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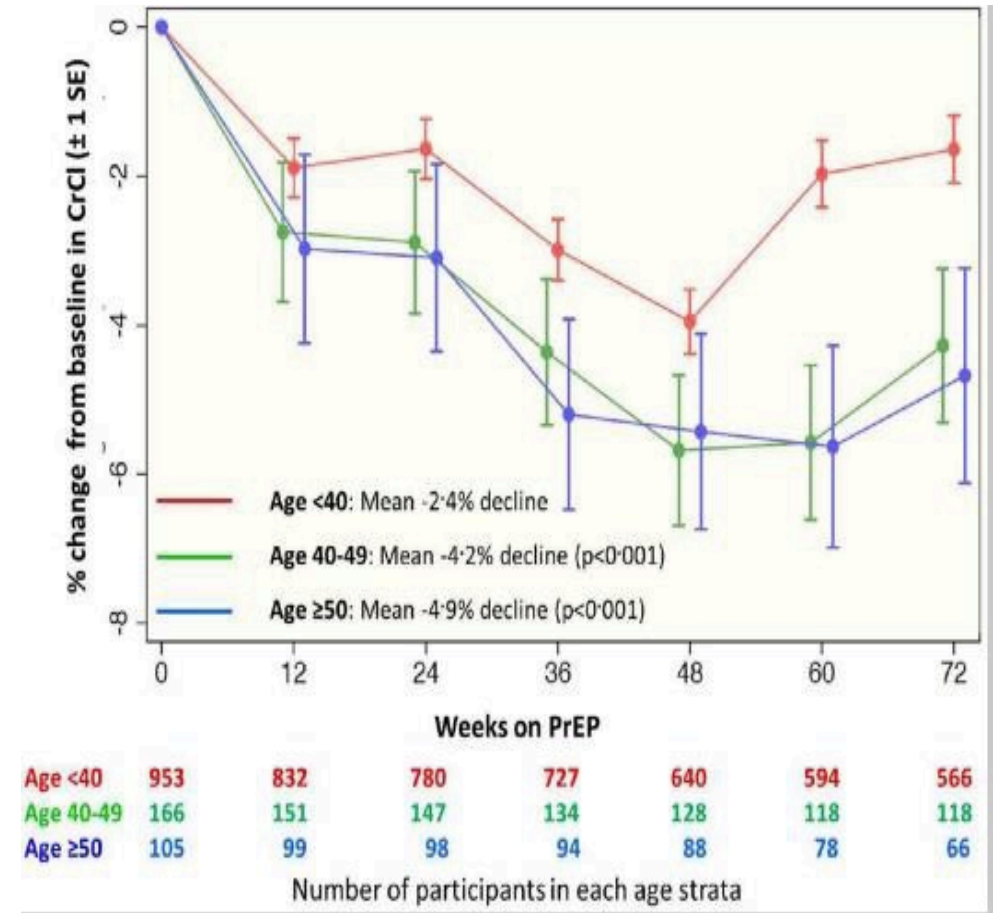
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4. Baeten JM, Donnell D, Ndase P et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; 367 : 399–410

PrEP, renal monitoring and age

- In iPrEx-OLE the probability of CrCl falling to ≤ 60 mL/min was more likely when participants started PrEP at older ages (>40 years) or with a starting CrCl ≤ 90 mL/min
- No participants under 40 years of age experienced a CrCl drop to ≤ 60 mL/min indicating that annual monitoring of renal function should be sufficient.

- Being aged >40 years or with a lower baseline creatinine clearance (≤ 90 mL/min) at PrEP initiation independently associated with a risk of CrCl falling ≤ 60 mL/min.
- CrCl fell to ≤ 60 ml/min in 9 individuals (0.1%). All 9 of the drops occurred in participants who started PrEP at CrCl < 90 ml/min and 8/9 occurred in participants starting PrEP ≥ 50 years of age
- More frequent renal monitoring on PrEP may be required in older PrEP users (>40 years) and in those with marginal renal function at baseline, even if there are no other concomitant risk factors for renal disease.



PrEP and renal function - Recommendations

Section 6 – Baseline Assessment

- We recommend that baseline renal function is assessed with a serum creatinine, eGFR and urinalysis but PrEP can be commenced while waiting for the results. (1A)
- We suggest that the eGFR for individuals starting TDF is >60 mL/min/1.73 m². (2A)
- We suggest that individuals with eGFR <60 mL/min/1.73 m² should be started on PrEP only on a case-by-case basis and after a full assessment and discussion with the patient of the risk and benefits and obtaining specialist renal advice (2B).

Section 7 - Monitoring on PrEP

- If eGFR >90 mL/min/1.73 m² at baseline (and follow up) and the person is aged <40 years then annual eGFR should be conducted. (1A)
- If eGFR 60–90 mL/min/1.73 m², aged >40 years or concomitant risk factors for renal impairment, more frequent monitoring of renal function at physician discretion is recommended, but should be at least 6 monthly. (2B)
- If eGFR <60 mL/min/1.73 m², the risks and benefits of continuing PrEP should be assessed on a case-by-case basis. Specialist renal input should be obtained to determine further investigations and frequency of monitoring. (1C)

Section 6: Initiating PrEP

Date of visit:

Age:

Gender: Male (including trans) Female (including trans) Other

Is this the same as the gender at birth? Yes No

Medical history

Past medical history (including renal, bone, diabetes, hypertension):

Regular medications:

Nephrotoxic medication:

Allergies:

Any symptoms of HIV seroconversion in past 4/52? Yes No *(If yes, defer PrEP until HIV infection is excluded)*

Hepatitis B vaccination in past? No *Screen for HBV and commence vaccination course*

Yes *Send anti-HBS*

Where relevant: LMP:

Contraception:

Sexual history:

Date of most recent sexual intercourse: ___/___/___ Condom used? Yes No

Gender of partner: Partner country of origin:

Any HIV positive partners? Yes No Unknown

If HIV positive, on ART for 6 months with VL < 200 copies/mL? Yes No

Type of condomless sex in previous 6/12 (tick all that apply):

Receptive anal Insertive anal Receptive vaginal Insertive vaginal Other

Total number of condomless sex partners in the last 6 months:

STI/HIV screen

Date of last STI screen: ___/___/___ All STI diagnosis in last 12 months:

Date of last HIV test: ___/___/___ HIV test result:

Risk factors

Recommend PrEP

MSM or trans woman reporting condomless anal sex in previous 6 months: Yes No

Reporting condomless sex with HIV positive partners not on ART for 6 months with viral load < 200 copies/mL: Yes No

Consider PrEP on case-by-case basis if a combination of factors applies:

Population-level indicators (tick all that apply)

Heterosexual black African men and women Recent migrants Trans women People who inject drugs

Sexual behaviour/sexual-network indicators (tick all that apply):

Condomless sex partners (especially anal/multiple) of: (i) unknown HIV status and/or (ii) population group with high HIV prevalence

Chemsex or group sex Reports anticipated future high-risk sexual behaviour Sex work or transactional sex

Clinical indicators (tick all that apply):

Rectal bacterial STI in the previous year Bacterial STI or HCV in the previous year

PEPSE in previous year; particularly repeated courses

Drug use indicators (tick all that apply):

Sharing injecting equipment Injecting in an unsafe setting (outside safe injection facilities)

No access to needle and syringe or opiate substitution programmes

Sexual health autonomy (tick all that apply):

Coercive and/or violent power dynamics in relationships Inability to negotiate and/or use condoms with sexual partners

Eligibility for PrEP

Based on above risk factors (tick one only)

(1) Eligible as high risk

(2) Eligible on a combination of factors

(3) Not eligible

Baseline clinical tests

HIV POCT/ELISA result today (if available): Reactive* Non-reactive

**If reactive do not commence PrEP – send 4th generation HIV test to confirm diagnosis*

Baseline tests	Tick if sent	Results
HIV testing with combined antigen/antibody serology test		
Hepatitis B screening		
Hepatitis C screening		
Syphilis serology		
CT/GC testing: Genital Rectal Pharyngeal		
Renal function		Creatinine (plus units): _____ eGFR: _____ How was eGFR calculated: (i) Cockcroft-Gault <input type="checkbox"/> (ii) CKD-EPI <input type="checkbox"/> (iii) Lab estimate <input type="checkbox"/> Abnormal renal function? Yes <input type="checkbox"/> No <input type="checkbox"/> Results baseline urinalysis: Action taken: _____
Pregnancy test (if indicated)		

Patient counselling

Importance of adherence to dosing schedule discussed: Yes No

Patient information given and adherence support provided as appropriate

Importance of regular HIV testing, STI screening and monitoring of renal function discussed: Yes No

Discussed risk of decrease in bone density: Yes No

Counselled on importance of condom use to prevent other STIs while on PrEP: Yes No

Referred to specialist chemsex or alcohol or drug services if applicable: Yes No

Discussed daily PrEP dosing/on demand dosing (OD): Yes No

Dosing schedule decided: Daily On demand*

**Only recommended for anal sex*

Discussed lead-in times (see table below) until PrEP effective: Yes No

	Anal sex	Vaginal sex
Time to steady state	Two tablets 2–24 hours before condomless sex	7 days

Information given to patient on where to purchase PrEP online/private prescription given: Yes No

Follow up

Date next appointment due: ___/___/___ Booked today? Yes No

PrEP prescription given/further medication purchased online: Yes No

Section 6: How to Start

- Heterogeneity across PK studies, but consensus that time to protection for TDF and FTC is shortest in lower GI tract, followed by PBMCs and FGT
- Concentrations in genital and colonic tissues probably most important in averting infection and may differ from protective levels in PBMCs

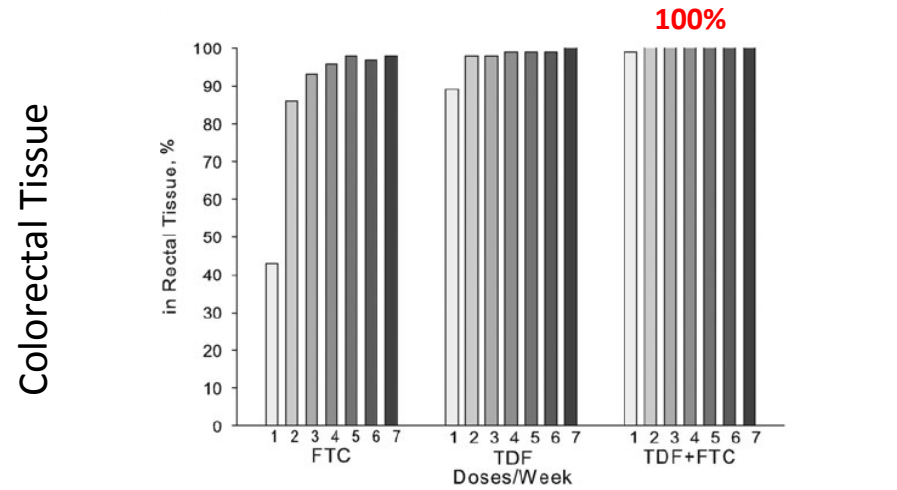
Anal Sex

- Double dose 2-24 hours before sex
- FTC plays important role (active within 4hrs)
- Time to clinical protection for anal sex evaluated in IPERGAY

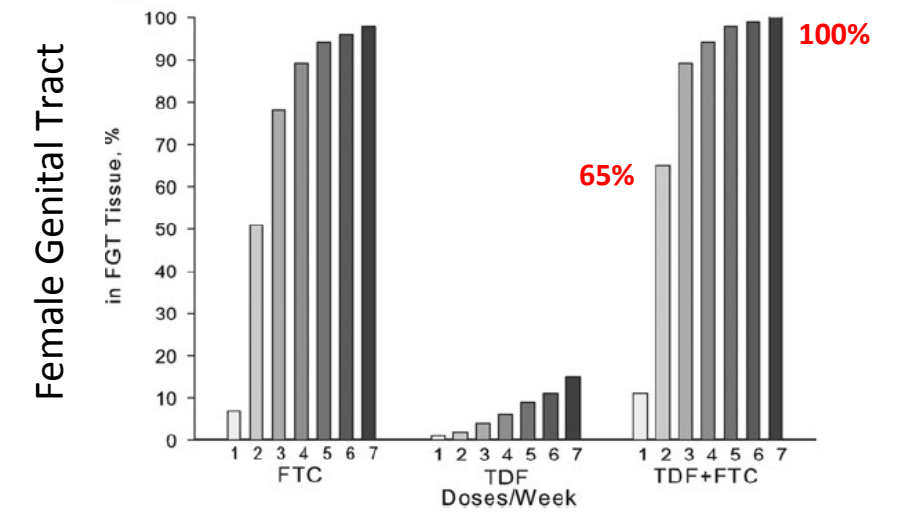
Vaginal Sex

- The time to clinical protection for vaginal sex extrapolated from PK studies of TDF-FTC
- Expert consensus (compromise) of 7 days daily TDF-FTC
- FTC could play an important role – higher levels quicker

ESTIMATING EFFICACY WITH VARIOUS DOSES/WEEK



iPrEx OLE= ↓ HIV incidence by 90% with 2 Truvada doses per week



Partners PrEP= ↓ HIV incidence by 90% with 7 Truvada doses per week

Section 7: How to stop

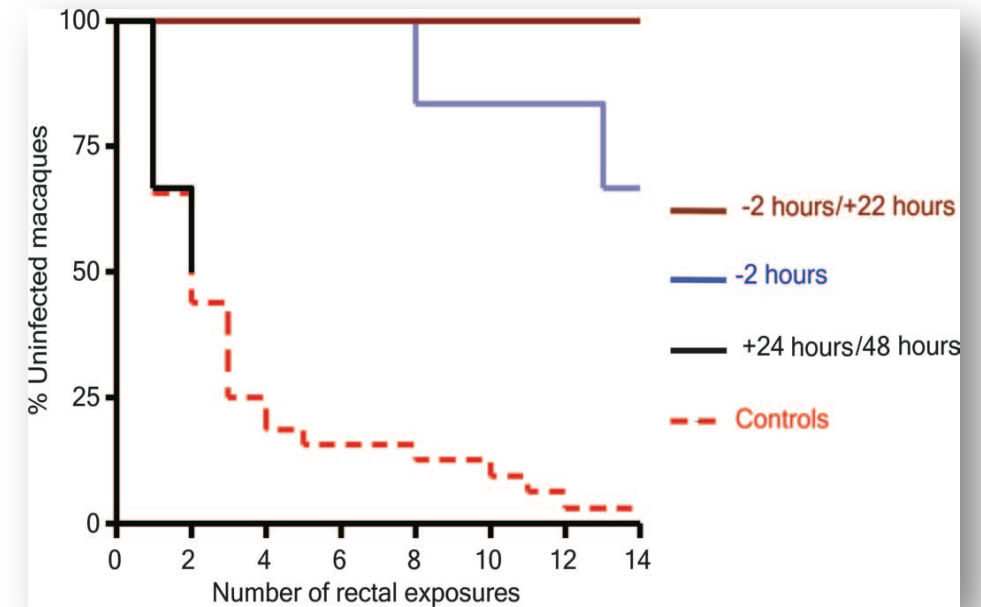
Anal sex

- Daily for 2 days after the last risk
- Data from IPERGAY demonstrated dosing can be stopped when an oral dose taken 24 hours and 48 hours after last potential exposure.
- Supported by animal and pharmacokinetic studies, but fewer data for foreskin and urethra.

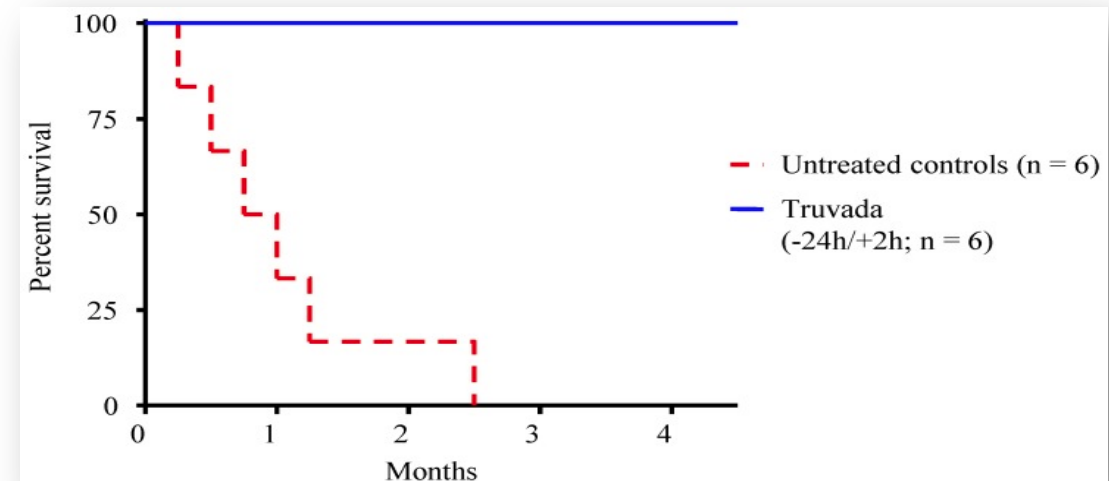
Vaginal sex

- Data from Cottrell *et al.* suggest drug concentrations quickly drop (particularly FTC-DP) in vaginal tissue, suggesting a longer duration of needed following vaginal exposure
- To date, expert consensus is 7 days of daily TDF-FTC required after the last potential exposure

Cottrell ML, Yang KH, Prince HM *et al.* A translational pharmacology approach to predicting outcomes of preexposure prophylaxis against hiv in men and women using tenofovir disoproxil fumarate with or without emtricitabine. *J Infect Dis* 2016; **214**: 55–64.



Garcia-Lerma et al. *Sci Transl Med.* 2010.2(14):14ra4



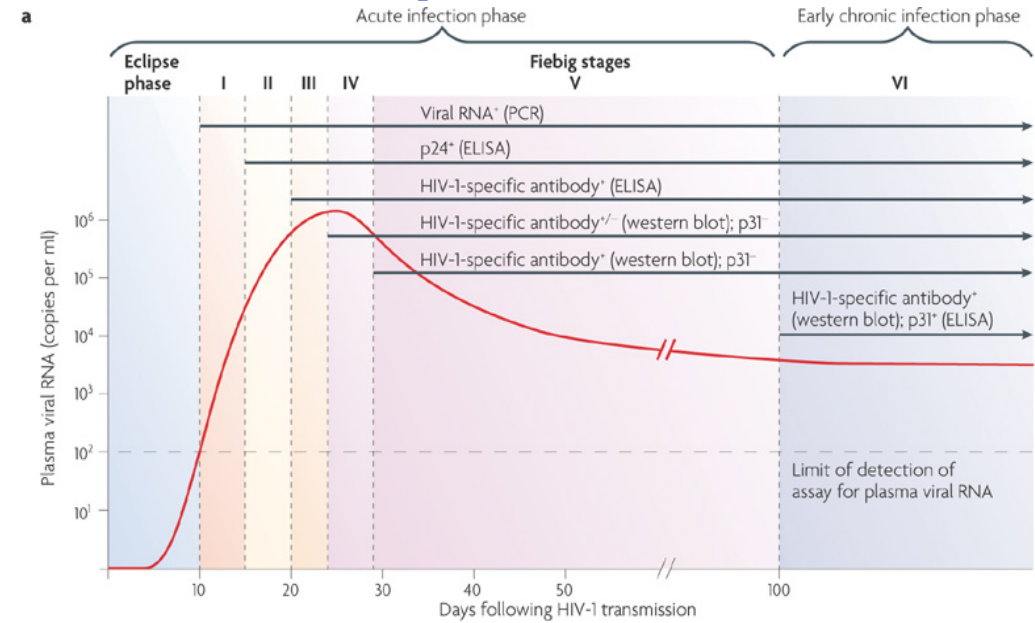
Radzio et al. *PLoS One.* 2012;7(12):e50632

Recommendations: Timelines for Starting and Stopping PrEP

- We recommend that, if the risk of HIV acquisition is through anal sex, PrEP can be started with a double dose of TD-FTC taken 2–24 hours before sex and continued daily until 48 hours after the last sexual risk. (1B)
- We recommend that if PrEP for anal sex has been interrupted and it is less than 7 days since the last TD-FTC dose then PrEP can be re-started with a single dose of TD-FTC. (1B)
- We recommend that if the risk of HIV acquisition is through vaginal sex, PrEP should be started as a daily regimen 7 days ahead of the likely risk and continued daily for 7 days after the last sexual risk. (1C)

Section 7: HIV Testing During Follow Up

- Taking PrEP during AHI can blunt anti-HIV-1 response. Both non-reactive HIV serology and non-progressive Fiebig profiles seen, and undetectable virus in blood.
- DR-HIV is unusual in context of PrEP (5.9% in 308 SC in 8 RCT), but higher rates observed in “missed” acute HIV infections during PrEP use
- 12 HIV seroconversions on PrEP in HPTN 067 ADAPT RCT; n=8 in context of PrEP use; n=7 with infrequent dosing or suboptimal use.
- Acute infections missed by 3rd gen POCT (n=8) and non reactive 4th gen assays (n=7). POCT also missed n=3 at subsequent study visits
- PrEP continued due to failure to detect HIV infection (n=8); developed DR mutations (n=3); HIV VL <400 copies at acute HIV infection (n=4)



BOX 1: Atypical HIV results: what to look for

1. Low signals near to cut off in screening assays (including either just below or below cut-off).
2. Sero-reversion on follow up specimens.
3. Discrepant results between assays.
4. Slow development of antibody/antigen signal in subsequent samples.
5. Weak and/or incomplete banding patterns on Innolia or Western blot.

BOX 2: HIV Reference Laboratory Services at PHE Colindale

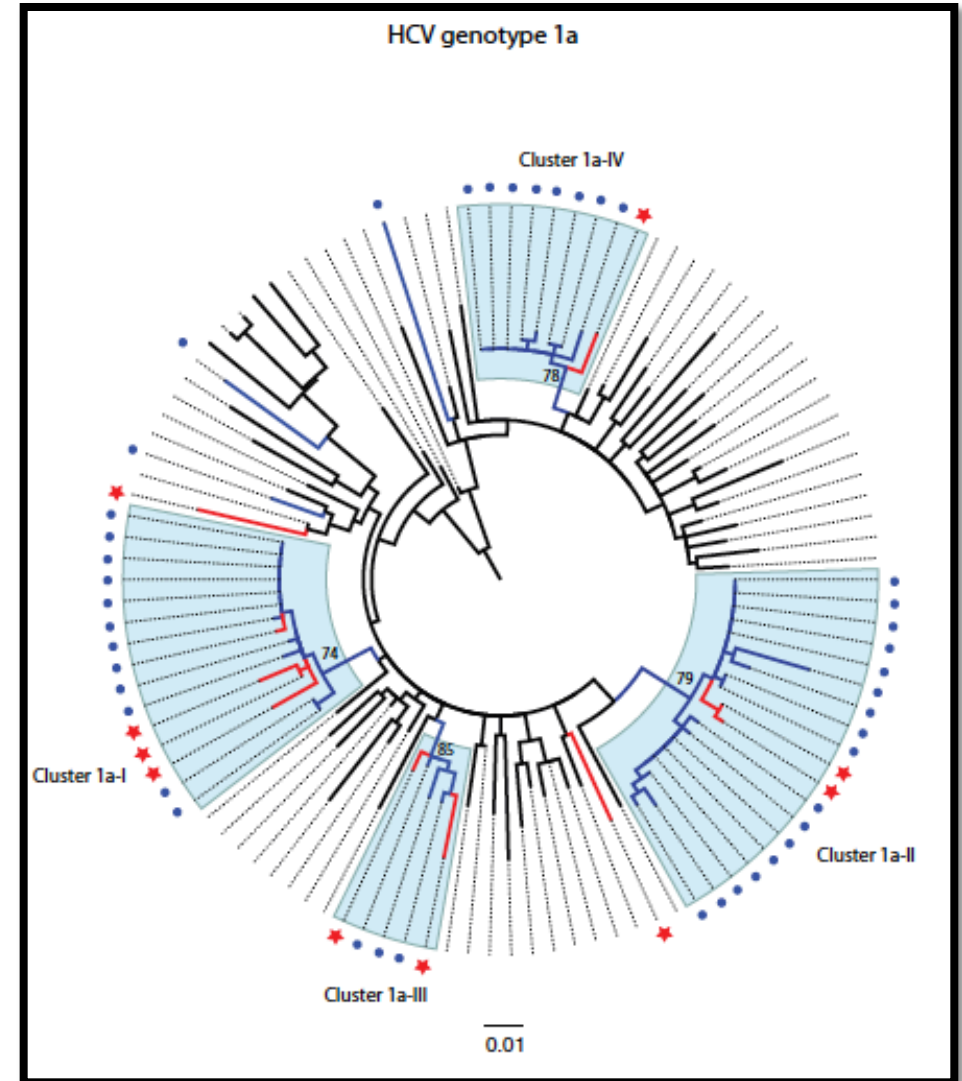
1. Wide range of assays (non-standard commercial and in-house ELISAs, proviral DNA, novel sequencing).
2. Western blot to determine antibody specific responses.
3. Collation of test results from a variety of platforms to determine PrEP interference with particular assays.
4. Referral to clinic specialising in atypical serological responses to HIV infection (difficult diagnoses).

Recommendations: HIV testing during follow up

1. We recommend HIV testing should be undertaken every 3 months with a laboratory combined HIV antigen/antibody test (1A) or a blood-based POCT. (1B)
2. We recommend that patients with symptoms suggestive of seroconversion should be investigated with a combined HIV antigen/antibody test and HIV viral load. Atypical testing results should be discussed with a regional expert. (1C)
 - Atypical testing results include: (a) unchanging reactivity on two or more consecutive samples that do not fit pattern usually associated with positivity; and (b) discrepant reactivity that changes over time. We recommended that the BASHH/EAGA 'high-risk' testing window should be used for follow-up testing, i.e. retest at both 4 and 8 weeks following discontinuation of PrEP.
 - The Antiviral Unit of PHE Colindale should be informed (csuqueries@phe.gov.uk); will liaise with regional experts, provide expert advice, and collate events.
 - Laboratory request forms should contain information on PrEP use or other ART, AHI symptoms, HIV testing history
 - If seroconversion suspected on PrEP, the writing group recommends current best practice is to intensify ART while investigations on-going.
 - If an atypical result detected off PrEP, it is advised that no further PrEP prescribed until expert consensus reached regarding the HIV status.
3. We recommend that in confirmed primary HIV infection, baseline resistance testing should be undertaken. (1B)

Hepatitis C

- Since 2000, HCV emerged as STI among HIV + MSM
- HIV negative men remained largely unaffected
- High HCV prevalence of 4.8% (95%CI: 3-8%) in HIV negative MSM starting PrEP in Amsterdam in 2015-16 compared to 0.6% (2007-2010)
- All reported chemsex and 23% slamming
- High degree of phylogenetic clustering between HIV positive and HIV negative MSM on PrEP suggests shared transmission networks
- Further report from France in 2018 highlighted clusters and networks of HCV transmission between HIV-positive and HIV-negative MSM.
- High HCV reinfection rates seen in HIV neg MSM on PrEP in Amsterdam (25.5/100 py)



Hepatitis C virus NS5B fragment phylogenetic tree for HCV subtypes 1a, comparing sequences from HIV-negative MSM starting PrEP (red branches and red stars) with sequences obtained from HIV-positive MSM (blue branches and blue dots) and unrelated hepatitis C virus-positive people other than MSM (black branches) in the Netherlands.

Section 6 and 7: HCV Testing

Section 6: We recommend that baseline screening for hepatitis C should be undertaken in MSM and other groups at risk of HCV. (1B)

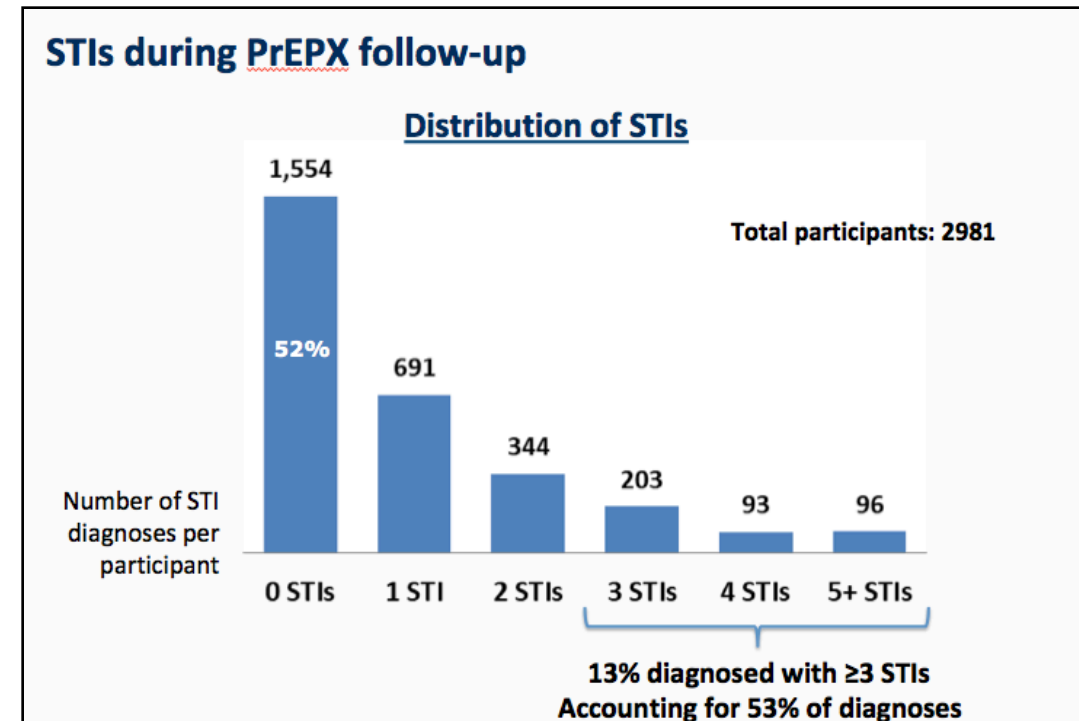
Section 7: We recommend 3-monthly HCV testing in MSM, trans women and others at on-going risk of HCV. (1B)

- If anti- HCV is positive then HCV RNA should be tested and, if positive, the patient referred to specialist services for consideration of early DAA treatment.
- For anti-HCV positive individuals who have previously cleared HCV, HCV testing would need to be with HCV RNA or HCV-cAg testing.

Follow up: STI testing

- STI rates (gonorrhea, chlamydia and syphilis) increasing prior to the introduction of PrEP
- Incidence of STIs increases during PrEP use (PrEPX 69/100 py pre PrEP, 98/100py during) – partly explained by increased testing frequency
- Over half not diagnosed with an STI. STIs were highly concentrated among PrEP users experiencing repeat infections, driven by number of partners and group sex
- High screening rates reduce duration of infection and may lead to an overall decrease in population-level STI incidence
- PrEP use must be combined with regular STI testing

STI Incidence in PROUD			
	Immediate	Deferred	Adjusted RR
Any STI	57%	50%	1.07 (0.78-1.46)
Gonorrhea	39%	37%	0.86 (0.62-1.2)
Chlamydia	30%	22%	1.27 (0.89-1.8)
Syphilis	11%	9%	1.29 (0.79-2.1)



Section 6 and 7: STI Testing

- Section 6: We recommend a full STI screen at baseline including syphilis serology and NAAT testing for gonococcal and chlamydial infection at sites of exposure (genital, rectal, pharyngeal) (1A)
- Section 7: We recommend 3-monthly screening for bacterial STIs (chlamydia, gonorrhoea and syphilis) in all taking PrEP (1B)

Section 8: Generics/online

Prepster

- The MHRA advise it is legal to buy up to 3 months medicines from outside the EU for personal use. There is no requirement for a certificate or authorisation
- Information in this section mostly drawn from conference presentations, personal communication with members of the writing group, BASHH MSM Special Interest Group, Clinicians PrEP Support Group and Community Group consultation.
- Supported by advice from GMC, Medical Defence Unions and Imperial College Ethics Committee



Section 7: Generics - Good Practice Points

- Clinicians should discuss PrEP, including buying online, if deemed to be at high risk for HIV.
- Clinicians should sign post to [IWantPrEPnow](#) if unable to access PrEP on the NHS as this site at least offers support and advice and ability to source generic drug as safely as possible.
- The discussion of sourcing PrEP online needs to be fully informed including risks and benefits
- Generic PrEP users buying TD-FTC online should order from a manufacturer listed by the US FDA and order in advance in case of delays
- Clinicians should ensure that people buying generic PrEP are taking medication that is labelled as containing both tenofovir and FTC and are taking PrEP correctly.
- Generic PrEP users should be advised to have regular STI (including HCV if at risk) and HIV tests and renal monitoring in line with the monitoring schedule in this guideline.
- Clinicians should offer full support, including renal monitoring, to patients who are taking PrEP sourced online.
- Therapeutic drug monitoring is not required for those taking generic PrEP.
- Clinicians should fully investigate any possible HIV seroconversions and refer to specialist HIV services.

Thanks for listening