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Module 4:
Pre-Exposure Prophylaxis (PrEP)

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Faculty Disclosure

- **Faculty:** Dr. Mark Hull

- **Relationships with commercial interests:**
  - **Grants/Research Support:** none to disclose
  - **Speakers Bureau/Honoraria:** Gilead Sciences Canada Inc., Merck Canada Inc.
  - **Consulting Fees:** Gilead Sciences Canada Inc., Merck Canada Inc.,
  - **Other:** none to disclose

Disclosure of Commercial Support

- This program has not received any financial or in-kind commercial support.

- **Potential for conflicts of interest:**
  - Dr. Hull has received payment or funding from Gilead Sciences Canada Inc., Merck Canada Inc.
  - No commercial organization has supported this program.

Mitigating Potential Bias

- All grants, research support, honoraria, and consulting fees are received by the institution (BC-CfE) and not Dr. Hull
- The content of the presentation is consistent with guidelines developed by the BC-CfE Pre-Exposure Prophylaxis (PrEP) sub-committee of the Committee for Drug Evaluation and Therapy (CDET)
- Generic names of medications are used in place of brand names

Learning Objectives

On completion of this module, participants will develop an understanding of:

- Pre-Exposure Prophylaxis (PrEP)
- HIV risk and potential benefits of PrEP
  - Evidence for use in MSM and other populations
- The safety of PrEP
- Complex components of PrEP prescribing and monitoring

MSM, men who have sex with men

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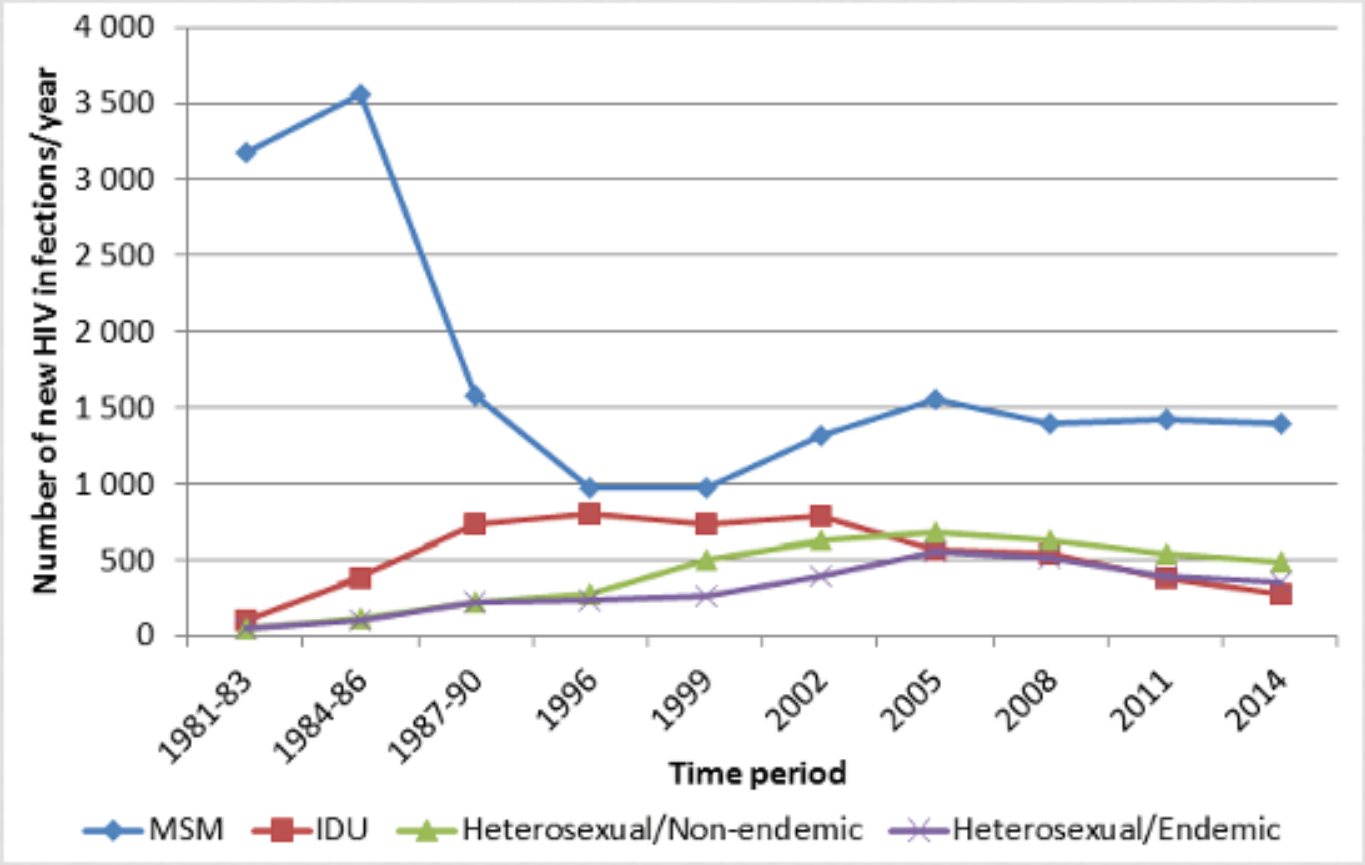
Why are we focusing on MSM as a priority target for PrEP?

MSM, men who have sex with men

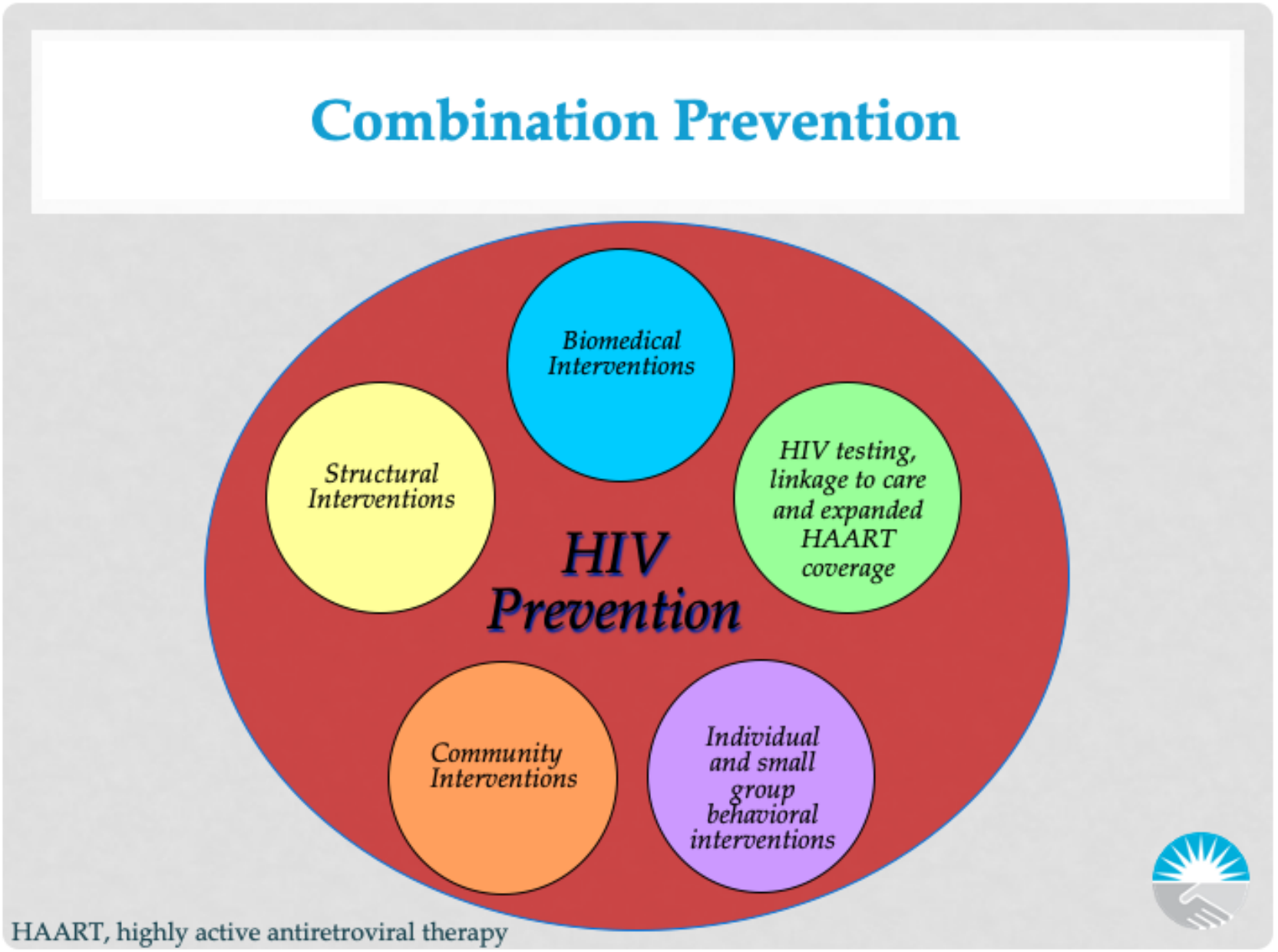
MSM Continue to Experience Highest Rates of New Diagnoses in Canada



MSM, men who have sex with men; IDU, injection drug users

Men who have sex with men continue to make up the majority of new diagnoses in Canada – just over half of all cases in 2011.

Source:
PHAC, 2015



The current model for HIV prevention interventions: structural possibilities include reducing stigma and barriers to care for marginalized groups. Treatment as Prevention® through expanded testing and engagement in ART has been shown to have significant reductions in HIV infection.
We will be focusing on biomedical interventions: post-exposure prophylaxis, and, for this module, pre-exposure prophylaxis.

Source:

Figure adapted from: Coates T, et al. Lancet. 2008;372(9639):669-84.

What is Pre-Exposure Prophylaxis (PrEP)?

- A biomedical prevention intervention
- Provision of two antiretroviral agents in combination to prevent HIV infection PRIOR to (and after) high risk exposure
  - Usually in an ongoing daily fashion, when timing of the risk event could occur at any time
  - Contrasts to post-exposure prophylaxis, where standard three drug antiretroviral therapy is provided only AFTER a distinct episode with high risk exposure

PrEP: Therapy

- Current medication in use for PrEP: tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC)
  - Fixed dose combination tablet
  - Both components have long intracellular half life
  - High concentrations achieved within the genital tract
  - Initial pharmacokinetic studies suggest 7 days to effective concentrations in anal and likely also in vaginal tissues when used daily

Sources:
Cohen MS, et al. Ann Intern Med. 2007;146(8):591-601.
Hendrix CW, et al. AIDS Res Hum Retroviruses. 2016;32(1):32-43.
Seifert SM, et al. AIDS Res Hum Retroviruses. 2016;32(10-11):981-91.
Cottrell ML, et al. J Infect Dis. 2016;214(1):55-64.

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Strategies to identify at risk MSM for PrEP

MSM, men who have sex with men

Clinical Risk Score for Calculating HIV risk

HIRI-MSM Risk Index*			
1	How old are you today (yrs)?	<18 years	score 0
		18–28 years	score 8
		29–40 years	score 5
		41–48 years	score 2
		≥49 years	score 0
2	How many men have you had sex with in the last 6 months?	>10 male partners	score 7
		6–10 male partners	score 4
		0–5 male partners	score 0
3	In the last 6 months, how many times did you have receptive anal sex (you were the bottom) with a man?	1 or more times	score 10
		0 times	score 0
4	How many of your male sex partners were HIV positive?	>1 positive partner	score 8
		1 positive partner	score 4
		<1 positive partner	score 0
5	In the last 6 months, how many times did you have insertive anal sex (you were the top) with a man who was HIV positive?	5 or more times	score 6
		0 times	score 0
6	In the last 6 months, have you used methamphetamines such as crystal or speed?	Yes	score 5
		No	score 0
7	In the last 6 months, have you used poppers (amyl nitrate)?	Yes	score 3
		No	score 0
		Add down entries in right column to calculate total score	Total score†

- HIRI-MSM risk score
- Score >10 had sensitivity of 84% for incident HIV infection; specificity of 45%
- Subsequent versions of the HIRI-MSM no longer include item 7.

Original HIRI-MSM, HIV incidence risk index for men who have sex with men

When we look at introducing PrEP, our goal is to ensure that individuals at highest risk for subsequent HIV seroconversion are offered PrEP. How we identify individuals who are at risk for HIV infection has not been always readily apparent. Investigators in the U.S. developed a simple risk calculator that is relatively sensitive for predicting incident HIV infection in MSM populations. **This has now been updated to remove the final question (Popper use) in updated versions.**

Source:
Smith DK, et al. J Acquir Immune Defic Syndr. 2012;60(4):421-7.

Other predictors of HIV risk in MSM

- Antecedent STI is a good indicator risk for HIV
- Data shows recent syphilis infection is a relatively good predictor of subsequent HIV seroconversion.
  - 2,805 men from 2000 – 2010
  - Risk of HIV following secondary syphilis: 5% in the following year
    - 1 in 20 men diagnosed with HIV in the year after a syphilis diagnosis
  - With syphilis and another bacterial STI: 7.89% in the following year

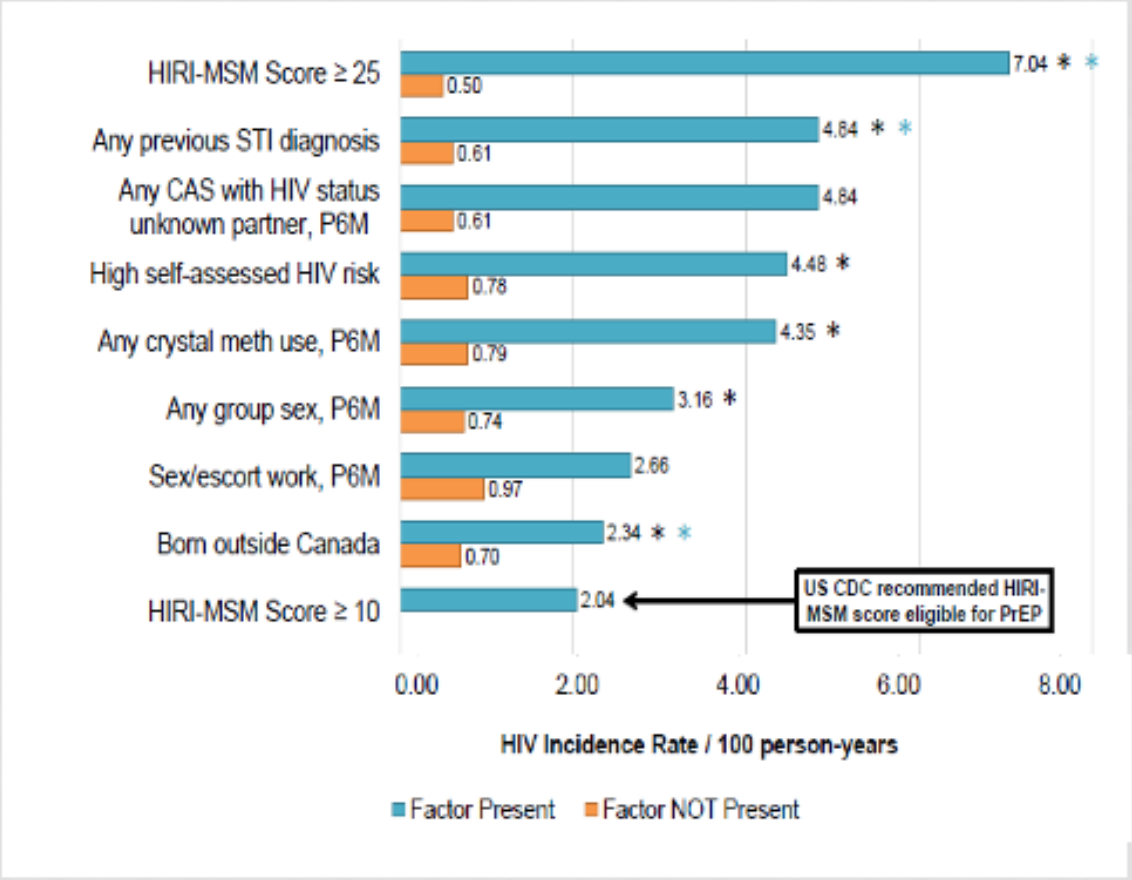
Similar data exists for prior rectal bacterial STI such as gonorrhea and chlamydia with the same group of researchers having validated these as markers in another earlier publication.

Sources:
Pathela P, et al. Clin Infect Dis. 2013;57(8):1203 -9.
Pathela P, et al. Clin Infect Dis. 2015;61(2):281-7.

momentum
moving men's health research forward

The Momentum Study: Use of HIRI and prior STI diagnosis in a BC context

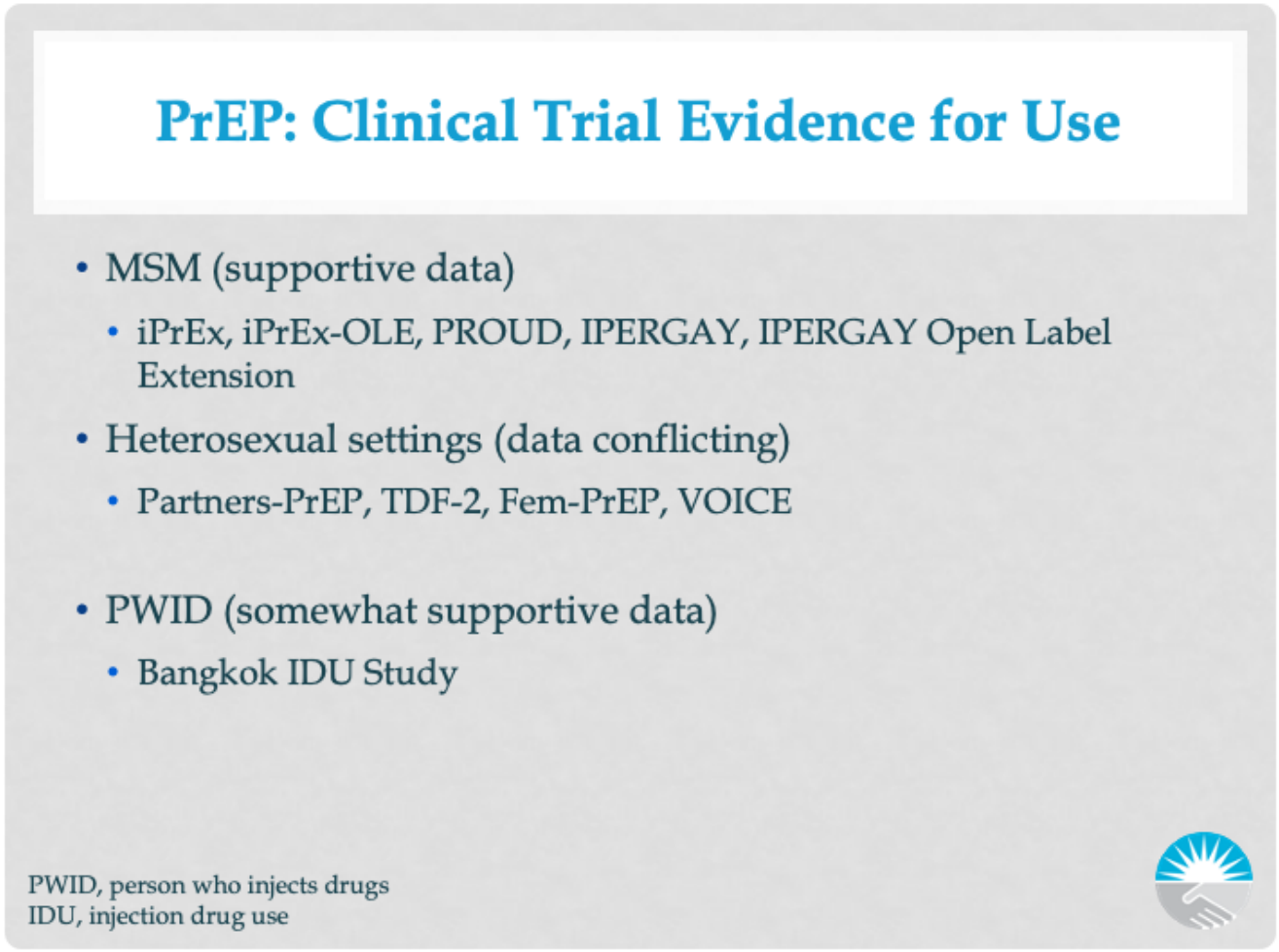
- HIV incidence among general MSM in Vancouver is **1 per 100 person-years** of follow-up
- Among particular individuals reporting specific behaviours incidence is much higher



* Univariable statistical significance at p<0.05;
P6M, previous 6-month period;
CAS, condomless anal sex

The HIRI-MSM score of >10 can predict a doubling of HIV risk. HIV incidence in those with a score of 25 was 7.04/100 person-years: a very high incidence in North America. No HIV seroconversion was seen in those with a score <10. Similarly, prior STI diagnosis was associated with increase in HIV incidence to 4.84/100 person-years.

Source:
Lachowsky N, et. al. CAHR; 2016; Winnipeg, Manitoba.

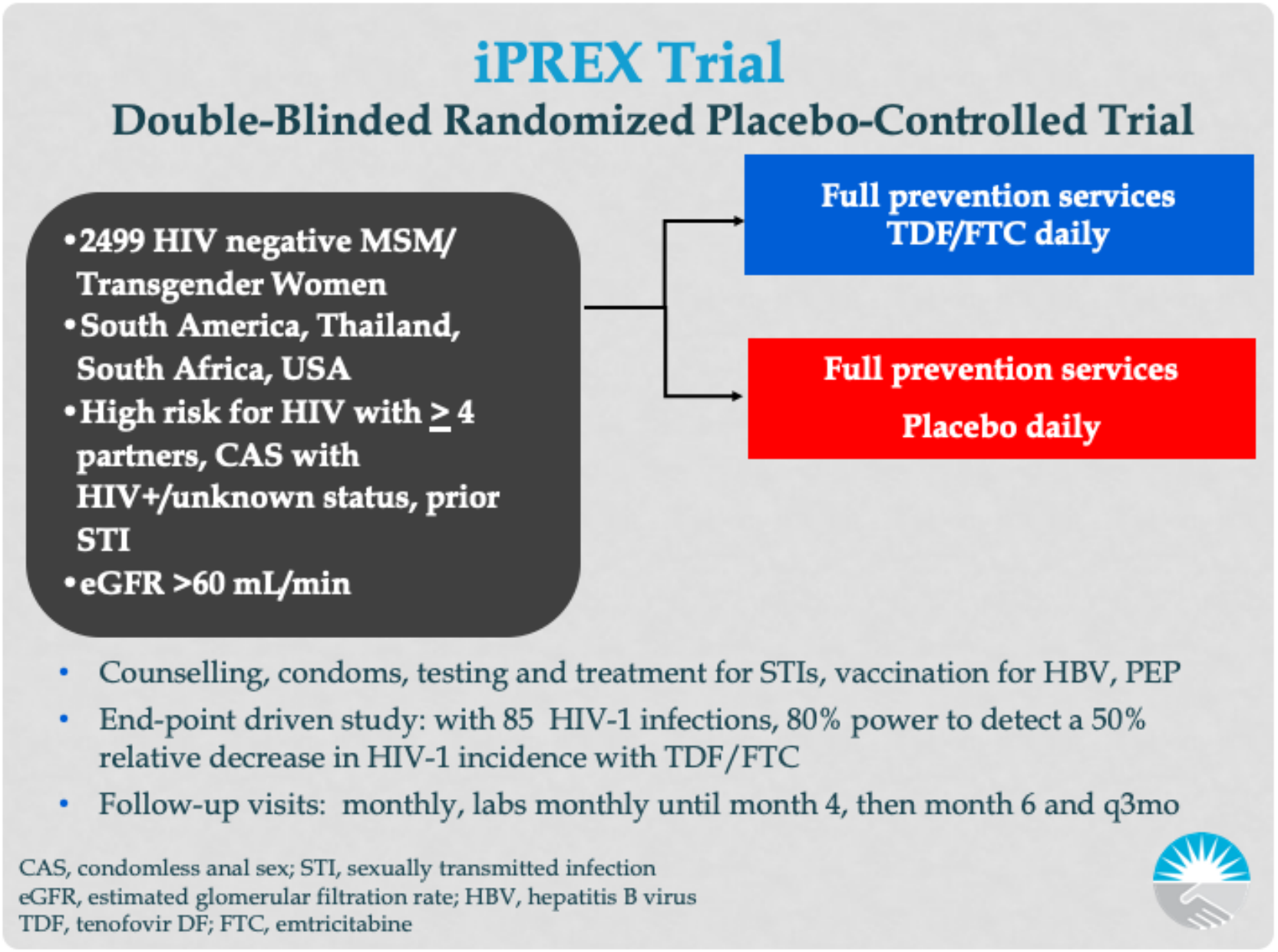


Data from studies in heterosexual settings (either high endemic settings or sero-discordant studies) found differing results with Partners-PrEP and TDF-2 studies finding supportive data, and no benefit seen in Fem-PrEP and VOICE.

In the PWID study, only tenofovir was used as a single agent for PrEP.

Sources:

Grant RM, et al. N Engl J Med. 2010;363(27):2587-99.
McCormack S, et al. Lancet. 2016;387(10013):53-60.
Molina JM, et al. N Engl J Med. 2015;373(23):2237-46.
Baeten J, et al. N Engl J Med. 2012;367:399-410.
Thigpen M, et al. N Engl J Med. 2012;367:423-434.
Corneli A, et al. J Acquir Immune Defic Syndr. 2014;66(3):324–331.
Marrazzo J, et al. Engl J Med. 2015;372(6):509-18.
Choopanya, K, et al. Lancet. 2013;381(9883):2083-90.



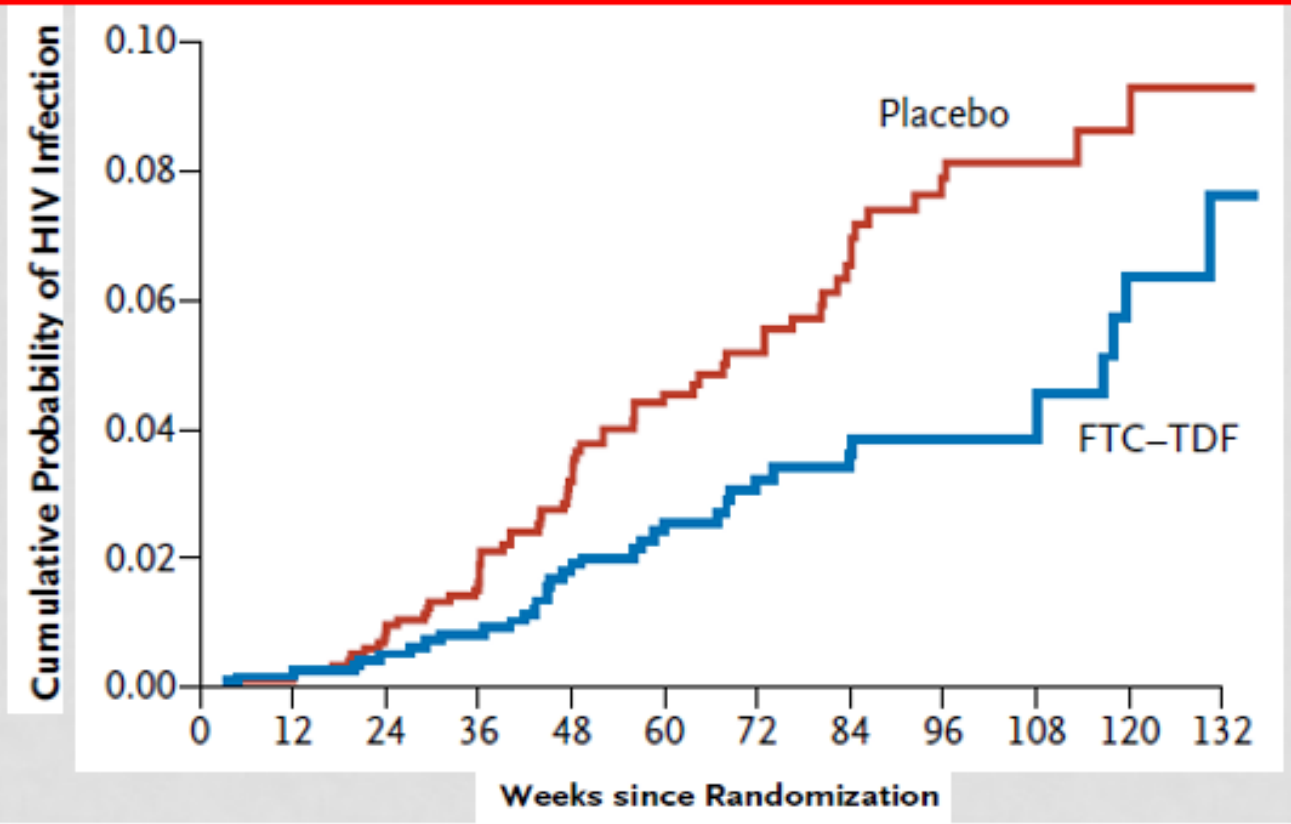
The iPrEX study was the first large PrEP trial published. It also included a subset of Transgender Women and did not exclude hepatitis B co-infection (these were exclusionary criteria in other trials). Individuals were randomized to DAILY TDF/FTC or standard of care prevention interventions.

Source:
Grant RM, et al. N Engl J Med. 2010;363(27):2587-99.

iPrEX: Results

Overall 44% Risk Reduction (95% CI 15 – 63) in HIV incidence

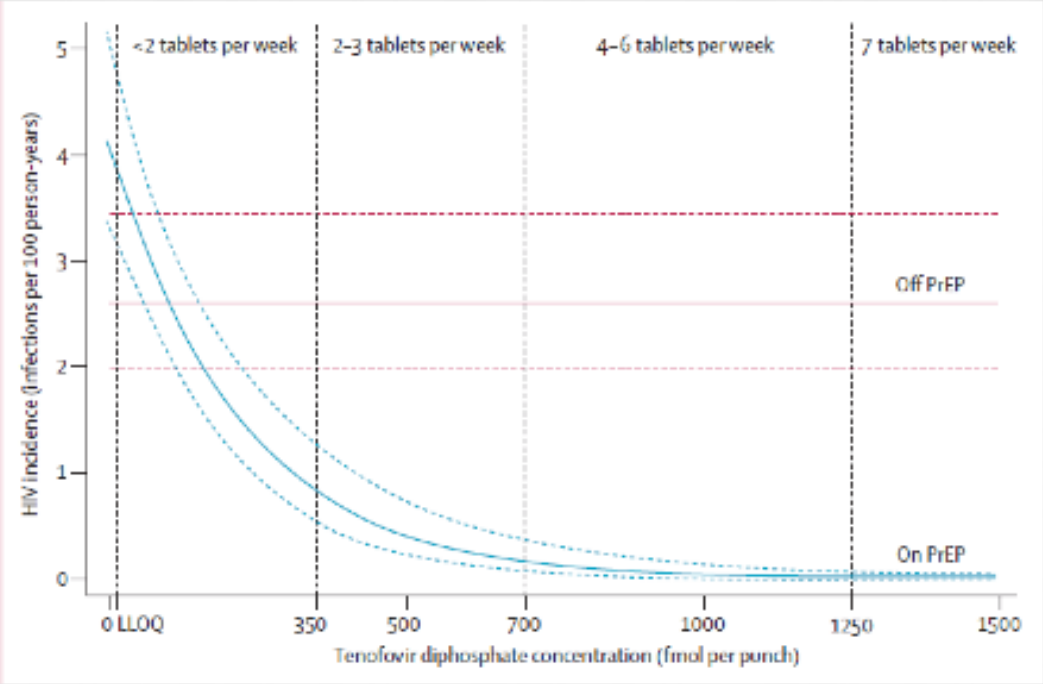
92% risk reduction if detected drug levels



The overall reduction in HIV incidence was 44%, however in a post-hoc analysis accounting for non-adherence, the risk reduction was over 90% in those who had detectable TDF levels on dried blood spot testing.

Source:
Grant RM, et al. N Engl J Med. 2010;363(27):2587-99.

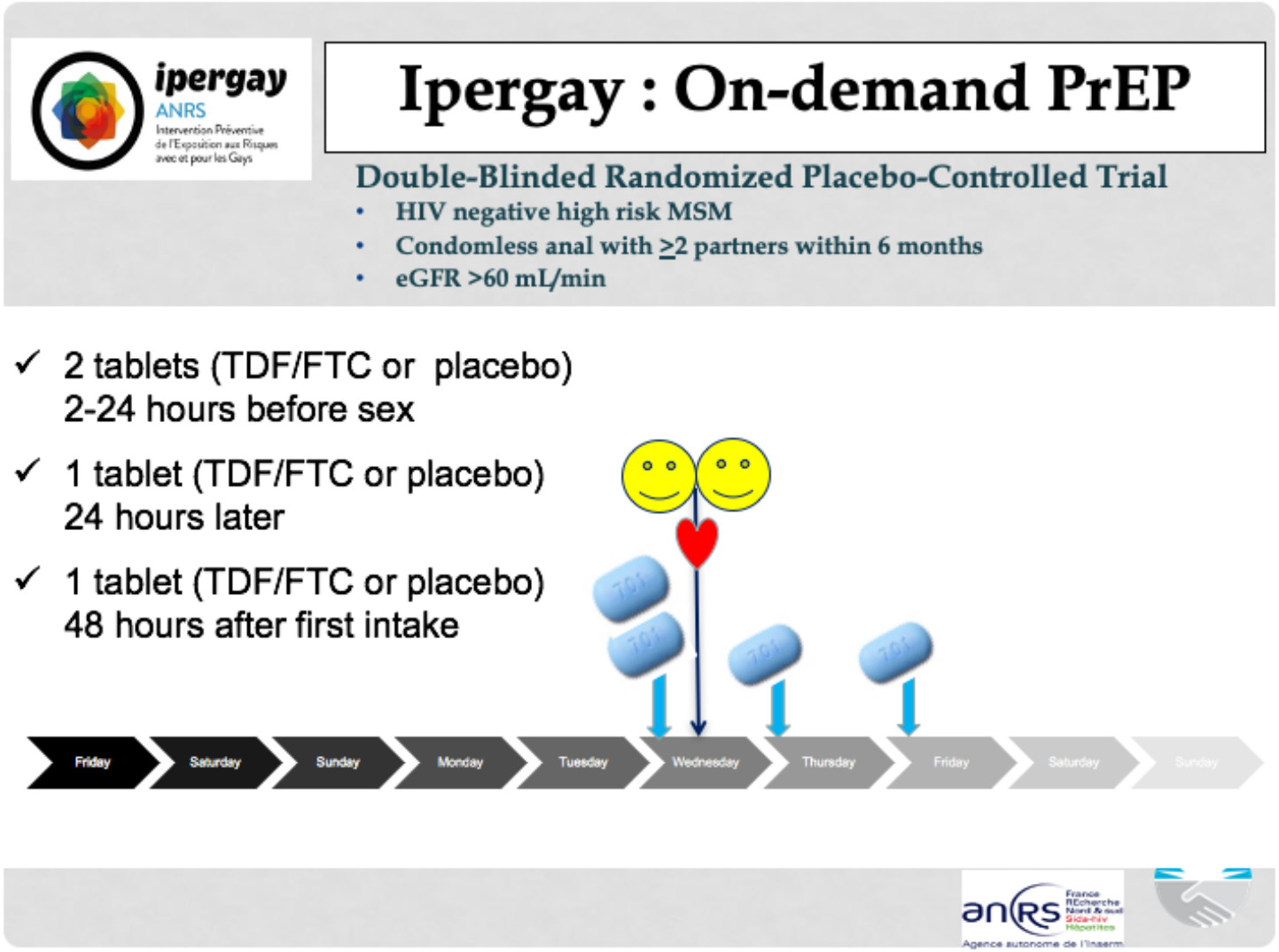
iPrEx OLE: Results



- **HIV incidence 4.7/100 PY if no drug detected**
- **HIV incidence 2.3/100 PY if <2 tablets/week**
- **HIV incidence 0.6/100 PY if 2-3 tablets/week**
- **HIV incidence 0.0/100 PY if >4 tablets/week**

In the Open-label extension of iPrEx all individuals received TDF/FTC and reported on use or no use of therapy. A clear dose response curve for protective effect was seen based on adherence determined by concentration of tenofovir in dried blood spot tests. A minimum of 4/7 days of coverage appeared to provide 100% protection against HIV infection.

Source:
Grant RM, et al. N Engl J Med. 2010;363(27):2587-99.

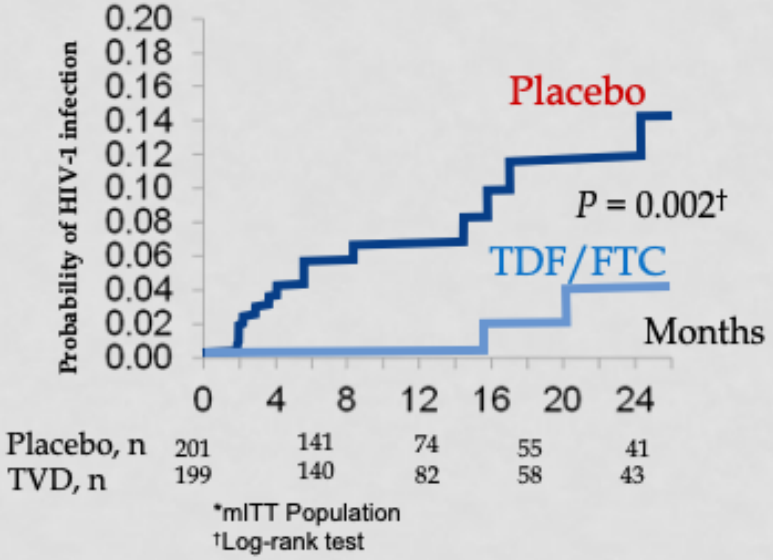


MSM in France and Montreal were enrolled in the Ipergay trial. Here a different strategy of PrEP use was evaluated: that of on-demand PrEP in conjunction with standard prevention services. Individuals were randomized to either on-demand PrEP or placebo. This data therefore cannot be extrapolated to other populations such as heterosexuals or transgender individuals as no similar studies have been undertaken in these populations. Dosing schedule for on-demand PrEP consisted of a loading dose taken 24 hours to 2 hours before sex, then a pill daily during sex and a tablet daily for 48 hours post sex (in the study graphic shown in the slide, first take intake dose and sex occurred on the same day).
Note: On-demand TDF/FTC is off-label use in Canada (compared to daily use).

Source:
Molina JM, et al. N Engl J Med. 2015;373(23):2237-46.

IPERGAY: Results

- **16 subjects infected**
  - Placebo arm =14 (incidence: 6.6/100 PY)
  - PrEP arm =2 (incidence: 0.94/100 PY)
- Mean follow-up = 13 months
- Average 16 pills/month



86% (95% CI: 40-99, *p*=0.002)
reduction in MSM at high risk of HIV infection who took on-demand PrEP

The placebo arm was stopped early due to high protective benefit seen in MSM PrEP users. A similar 86% protective benefit was seen. Long term follow-up suggests similar rates of risk reduction as daily PrEP : 97% risk reduction. Seroconversions were again seen only in those who were not using PrEP at the time of sexual exposure. (Note: On-demand PrEP is considered off-label use in Canada)

Sources:

Molina JM, et al. N Engl J Med. 2015;373(23):2237-46.
Molina JM, et al. Lancet HIV. 2017;4(9): e402-e10.

When to consider On-demand vs. Daily PrEP for MSM

Criteria	Daily	On-demand
MSM	Yes	Yes
TGW, heterosexual risk	Yes	No
Predicted frequency of sexual exposure	Regular (ie. Daily to weekly)	Irregular (usually > once a week, otherwise daily dosing would result)
Can they predict when sex will occur?	No – daily use better	Yes – absolutely required in order to achieve timing for loading dose
Able to adhere to 2:1:1 schedule	No	Yes

Source:

BC Centre for Excellence in HIV/AIDS. PrEP Guidelines, 2019. Available from: http://www.cfenet.ubc.ca/publications/centre-documents/guidance-use-pre-exposure-prophylaxis-prep-prevention-hiv-acquisition

Real World Uptake: San Francisco

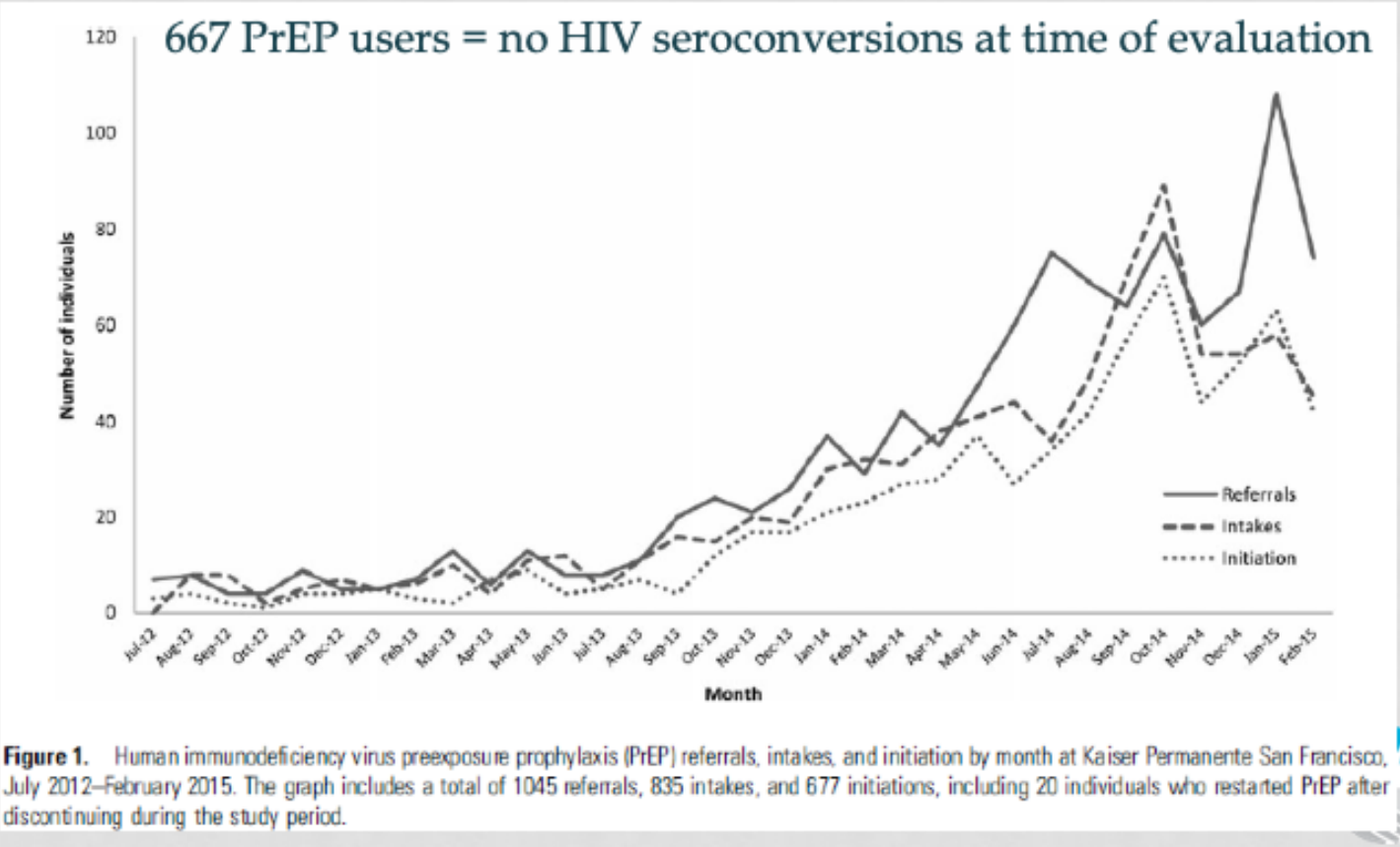


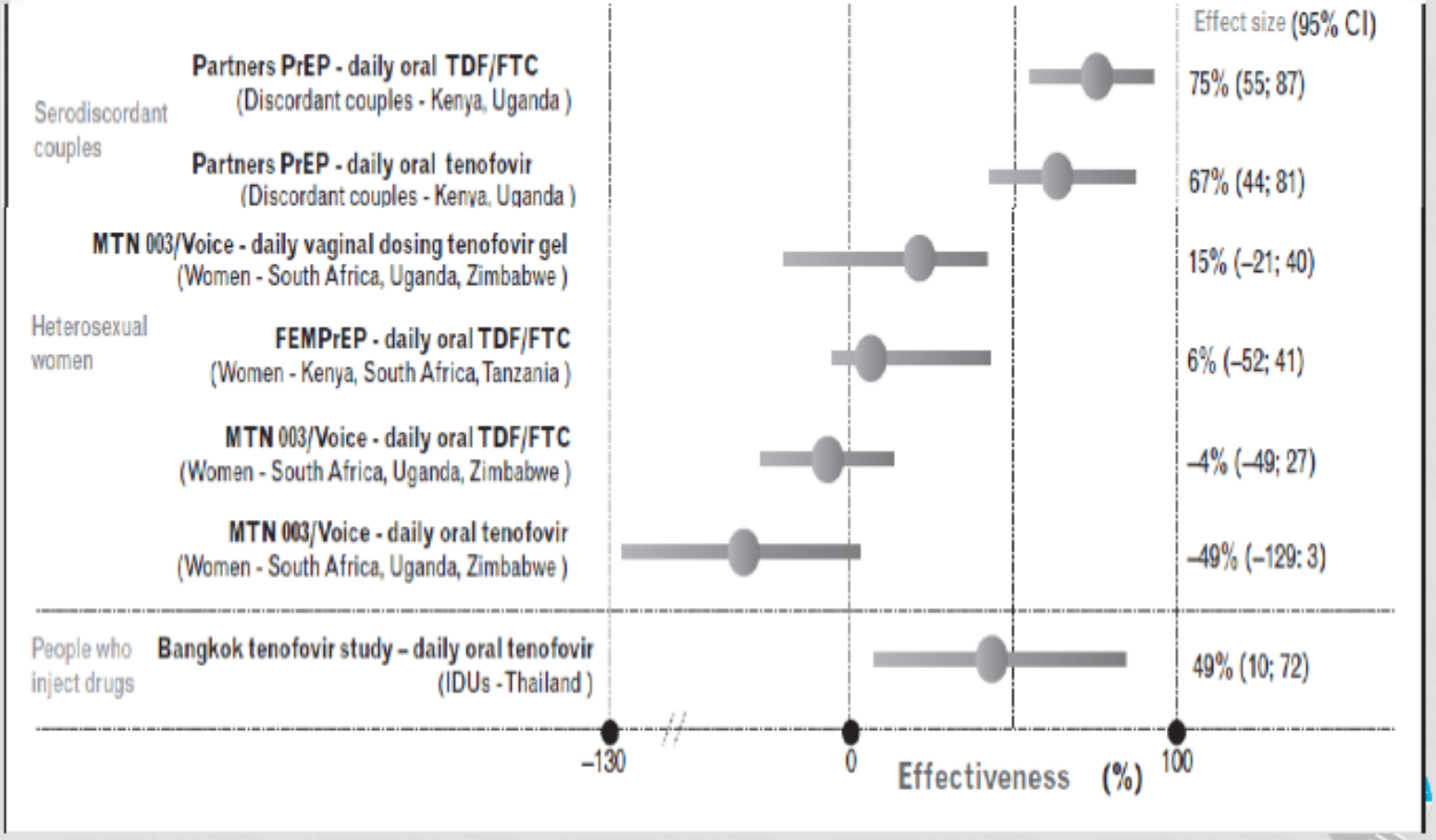
Figure 1. Human immunodeficiency virus preexposure prophylaxis (PrEP) referrals, intakes, and initiation by month at Kaiser Permanente San Francisco, July 2012–February 2015. The graph includes a total of 1045 referrals, 835 intakes, and 677 initiations, including 20 individuals who restarted PrEP after discontinuing during the study period.

Data from Kaiser Permanente in San Francisco showed high protective benefit of PrEP use. In this study 50% of men had a sexually transmitted infection (STI) during observation, suggesting that risk behaviours continued. Longer term follow-up of the same cohort showed ongoing high rates of STI diagnoses and no HIV seroconversions. Seroconversions occurred only in two individuals who had discontinued PrEP due to cost reasons.

Sources:

Volk JE, et al. Clin Infect Dis. 2015;61(10):1601-3.
Marcus J, et al. JAIDS. 2016;73(5):540 – 46.

PrEP Benefit in Other Populations



This figure summarizes PrEP trials in serodiscordant trials, studies in heterosexual women in high HIV endemic countries, and a single trial of tenofovir for PrEP in PWID. Outcomes for these trials varied, with adherence likely being primarily responsible for the lack of benefit seen in most of these studies. Decisions to use PrEP in these populations in British Columbia must also take into consideration the low rates of transmission currently seen.

Source:
Mayer KH, Ramjee G. Current opinion in HIV and AIDS. 2015;10(4):226-32.

PrEP Benefit in Other Populations

- As present access to harm reduction services and scale-up of HIV treatment has significantly reduced new infections amongst PWID.
- BC PrEP guidelines therefore recommend PrEP only for those individuals who are sharing equipment/paraphernalia with an individual who is known to be HIV positive without full viral load suppression.
- Similarly, for heterosexuals in BC, current guidelines recommend PrEP only for those individuals in a serodiscordant relationship with a partner with HIV where viral load suppression has not been achieved/documented.

Source:

BC Centre for Excellence in HIV/AIDS. PrEP Guidelines, 2019. Available from: http://www.cfenet.ubc.ca/publications/centre-documents/guidance-use-pre-exposure-prophylaxis-prep-prevention-hiv-acquisition

Adherence

- **Adherence to PrEP is vital for effectiveness.**
- In IprEx OLE dose response curve was observed with no HIV infections seen in those with those high levels of adherence.
- In the PROUD study, in those who had acquired infection in the immediate PrEP arm, all seroconversions occurred when use of TDF/FTC could not be verified.
- In heterosexual studies VOICE and FEM-PrEP overall adherence was less than 30% at all study visits where drug levels were determined, and no protective benefit of PrEP could be observed.
- Adherence to PrEP needs to be stressed at baseline and reviewed at subsequent visits.

Sources:

Grant RM, et al. N Engl J Med. 2010;363(27):2587-99.

McCormack S, et al. Lancet. 2016;387(10013):53-60.

Marrazzo J, et al. Engl J Med. 2015;372(6):509-18.

Corneli A, et al. J Acquir Immune Defic Syndr. 2014; 66(3):324–331.

BC Guidelines for PrEP in MSM

- PrEP can be considered in any MSM reporting condomless anal sex
- **PrEP recommended for:**
  - HIRI score >10
  - Prior diagnosis of rectal STI or syphilis within last 12 months
  - Recurrent PEP use
  - HIV positive sexual partner who is not receiving ART or without a pVL<200 copies/mL

STI, sexually transmitted infection;
pVL, plasma viral load

Source:

BC Centre for Excellence in HIV/AIDS. PrEP Guidelines, 2019. Available from: http://www.cfenet.ubc.ca/publications/centre-documents/guidance-use-pre-exposure-prophylaxis-prep-prevention-hiv-acquisition

BC Guidelines for Other Populations

PrEP is recommended for heterosexual men and women at high risk of acquiring HIV infection

High risk is defined as reporting:

- Condomless vaginal or anal sex **and** meeting the following additional criteria:
  - Ongoing sexual relationship with an HIV-positive partner who is not receiving stable ART **and/or** does not have an HIV viral load <200 copies/mL

PrEP is recommended for PWID who are at high risk of acquiring HIV infection

High risk is defined as reporting:

- Sharing injection equipment **and** meeting the following additional criteria:
  - Having an HIV-positive injecting partner who is not receiving stable ART **and/or** does not have an HIV viral load <200 copies/mL.
- All PWID who report these risk behaviours should be actively referred to harm reduction services

PWID, person who injects drugs

Source:

BC Centre for Excellence in HIV/AIDS. PrEP Guidelines, 2019. Available from: http://www.cfenet.ubc.ca/publications/centre-documents/guidance-use-pre-exposure-prophylaxis-prep-prevention-hiv-acquisition

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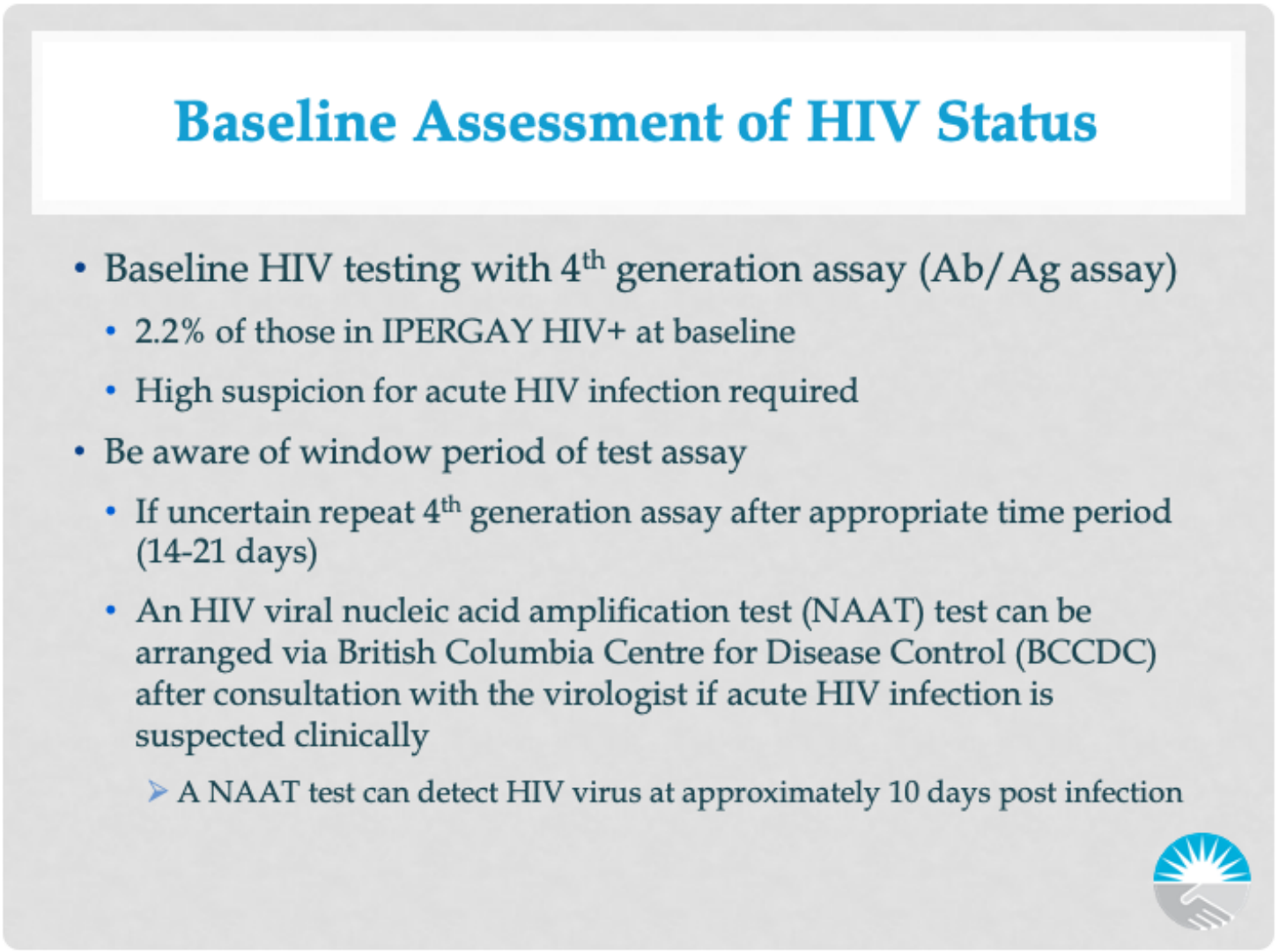
Laboratory Assessment prior to PrEP



The 4th generation assay is recommended for determining HIV status prior to starting PrEP as it detects both host antibody and viral p24 antigen – giving it the shortest window period of available HIV tests. The window period is approximately 14-21 days, and as long as just over 40 days in some studies. As such, it is very important to consider the test result in terms of last potential risk exposure, and be sure that the test is outside of the window period. The reason for concern is to ensure the individual remains HIV negative prior to the institution of PrEP. **IF** the individual is HIV positive, exposure to only two drug therapy may increase risk for HIV drug resistance.

Source:

BC Centre for Excellence in HIV/AIDS. PrEP Guidelines, 2019. Available from: http://www.cfenet.ubc.ca/publications/centre-documents/guidance-use-pre-exposure-prophylaxis-prep-prevention-hiv-acquisition

Baseline Laboratory Assessment for PrEP

- Baseline sexually transmitted infection (STI) screens
  - Throat/rectal/urine NAT tests for GC/CT, vaginal testing where appropriate
- Baseline renal panel
  - Creatinine, urinalysis, urine ACR
  - Pregnancy screens for female patients of child-bearing potential
- Baseline hepatitis screens
- Vaccinations:
  - Hepatitis A and B
  - Human papilloma virus (HPV) vaccine to eligible individuals

ACR, albumin to creatinine ratio

STI screens: syphilis testing and gonorrhea and chlamydia testing from all sites.

Source:

BC Centre for Excellence in HIV/AIDS. PrEP Guidelines, 2019. Available from: http://www.cfenet.ubc.ca/publications/centre-documents/guidance-use-pre-exposure-prophylaxis-prep-prevention-hiv-acquisition

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PrEP Safety and Monitoring During Use

Safety

- Well established safety profile in the setting of HIV therapy
- Common side effects: GI upset in first 4 weeks (2% vs < 1% p.004 in iPrEx, 14% vs. 5% in IPERGAY)
- Minor bone mineral density changes seen on imaging in iPrEX and TDF-2 studies
  - Not clinically apparent
  - Reversible upon discontinuation

eGFR, estimated glomerular filtration rate

In a meta-analysis of PrEP studies, very limited signal for renal toxicity was seen.
There was a minor signal for increased risk, but this was related to relatively small changes in serum creatinine versus serious renal insult.
As individuals stay on PrEP for longer periods, renal issues may, however, become more apparent.

Sources:
Liu AY, et al. PLoS One. 2011;6(8):e23688.
Kasonde M, et al. PLoS One. 2014;9(3):e90111.
Yacoub R, et al. J Acquir Immune Defic Syndr. 2016;71(4):e115-e18.

Safety: Renal

- Renal
  - TDF associated with renal toxicity (usually proximal tubular defects) in setting of HIV therapy
  - On-label PrEP use only for those with eGFR >60 mL/min
  - No significant renal deterioration seen in original PrEP trials
    - Two meta-analyses have found no significant elevations in serum creatinine in PrEP users in the trials
      - One study found association with mild grade I elevations in creatinine values only
  - Open-label follow-up has suggested higher risk for renal decline in those starting PrEP at older age

Sources:

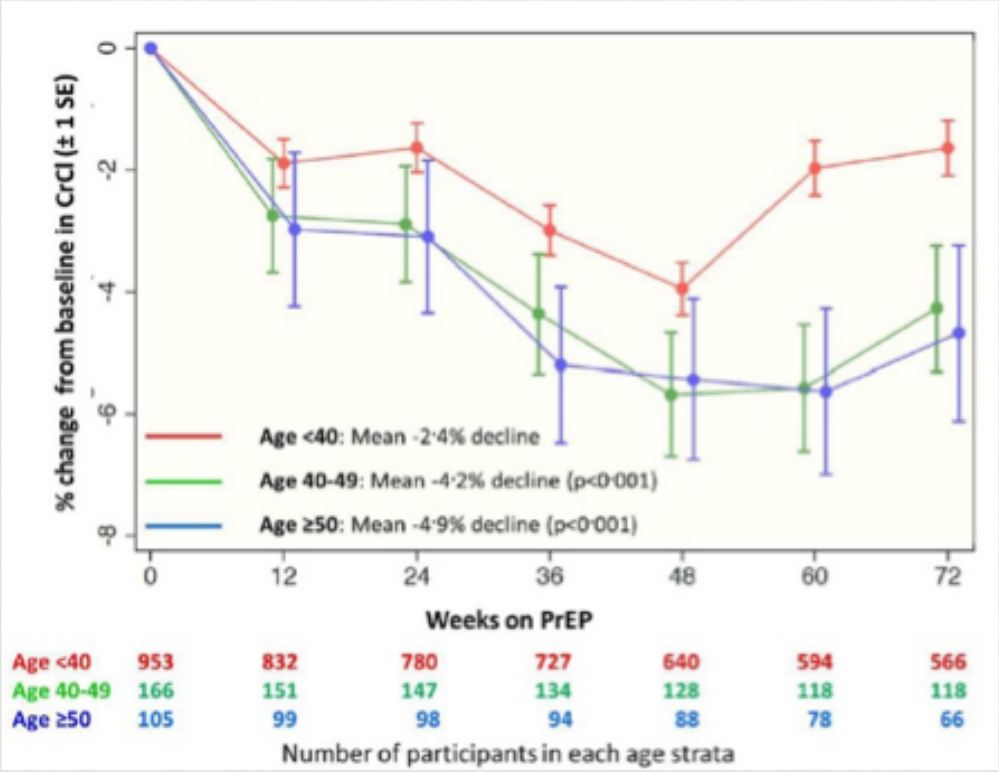
Meta-analyses:

Yacoub, R. et al. J Acquir Immune Defic Syndr. 2016;71(4): e115–e118.

Pilkington, V. et al. Journal of Virus Eradication 2018;4(4):215–24.

Safety: Renal

iPrEx OLE Renal Follow-up



Renal follow-up in the iPrEx OLE trial identified more significant declines in eGFR in those starting at ages over 40 years, supporting the need for regular follow-up in this population. The rate of CrCl falling to ≤60 ml/min (which was a protocol-defined criterion for stopping PrEP) was low at 0.1% overall in the cohort across all visits (9 of 7198 visits), but occurred in those starting age > 50, and with baseline GFR < 90.

Source:

Gandhi, M Lancet HIV 2016;3(11): e521-e28.

Safety: Renal

- Very few discontinuations of PrEP due to renal concerns in real world studies
  - In an evaluation of 525 individuals starting PrEP in a clinic in Sydney, Australia found at baseline 1.5% had GFR < 70 mL/min
  - Further 6.5% had drop to GFR < 70 mL/min over 18 months
    - Associated with age > 40 at PrEP start
    - Only 2 patients (0.4%) discontinued PrEP

Source:

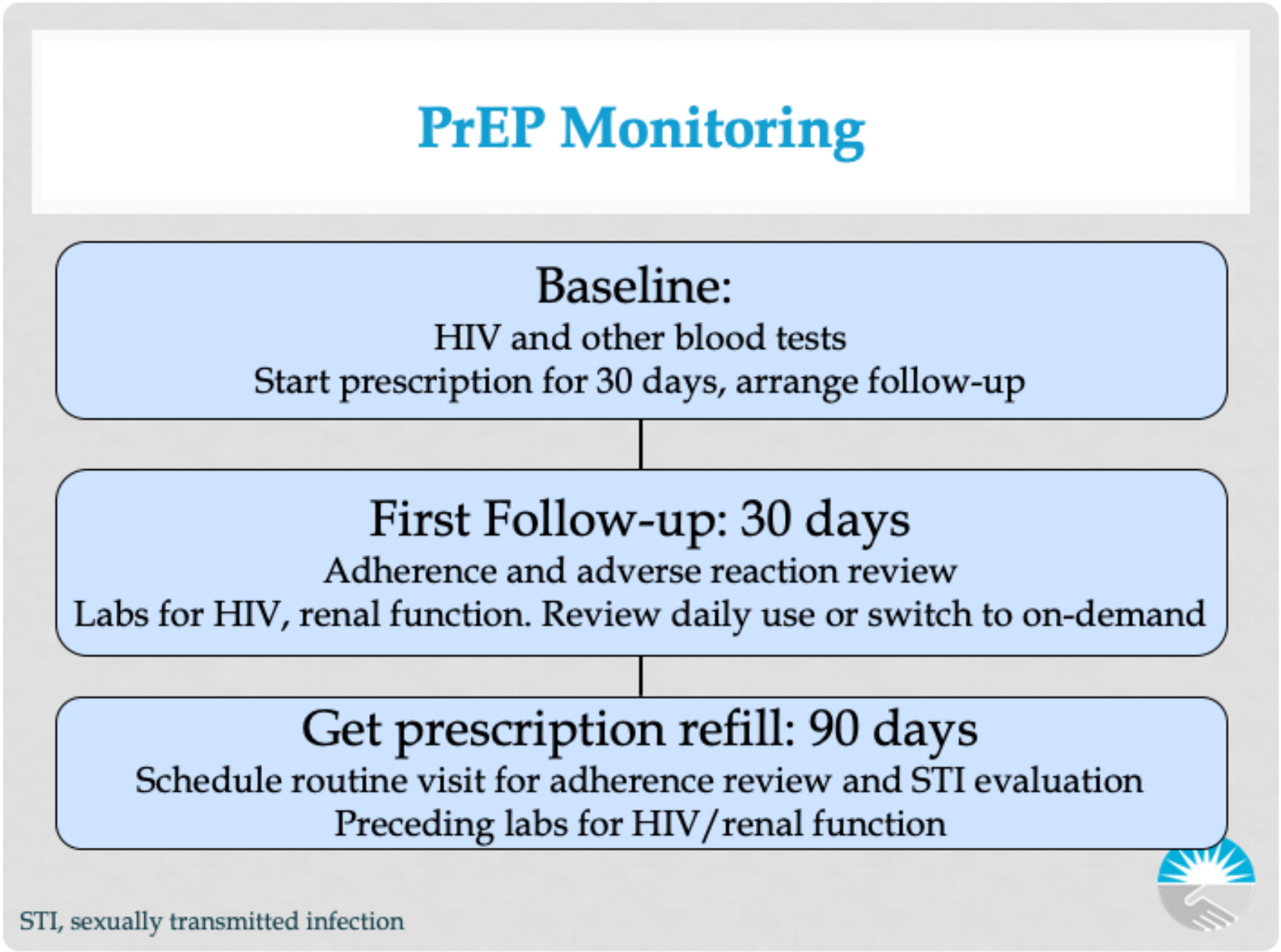
Drak D, et al. PLOS One. 2019;14(1):e0210106.

Safety: Hepatitis B

- Both TDF and FTC are active against HBV
  - Important to be aware of HBV status at baseline
  - Risk of flare if HBV+ individual discontinues PrEP as TDF/FTC active against HBV
    - Need ALT/AST/HBV DNA monitoring post-discontinuation
  - However, no flare was seen in 5/6 HBV patients treated in iPrEX Trial who then discontinued TDF/FTC

HBV, hepatitis B virus
TDF, tenofovir DF; FTC, emtricitabine
ALT, alanine transaminase test; AST, aspartate aminotransferase

Source:
Solomon MM, et al. J Acquir Immune Defic Syndr. 2016;71(3):281-6.



Note: On-demand PrEP is off-label use in Canada (compared to daily use).

Source:

BC Centre for Excellence in HIV/AIDS. PrEP Guidelines, 2019. Available from: http://www.cfenet.ubc.ca/publications/centre-documents/guidance-use-pre-exposure-prophylaxis-prep-prevention-hiv-acquisition

STI Screening Every 3 Months

- USA PrEP demonstration project:
  - 50.9% experienced STI during follow-up
- If screening only semi-annually or based on symptoms, the following cases would have been missed:
  - 62 (34.3%) of participants with gonorrhea
  - 86 (41.0%) of participants with chlamydia
  - 11 (20.4%) of participants with syphilis

STI, sexually transmitted infection

This study demonstrated the importance of performing STI screens every 3 months as a high proportion of individuals had asymptomatic infections that would have been missed with less frequent testing.

Source:
Cohen SE, et al. CROI; 2016; Boston, Massachusetts.

HIV Drug Resistance During PrEP (Rare)

- Drug resistance is predominantly seen in those with undocumented HIV infection at baseline who are then put on dual therapy
  - Highlights need to ensure accurate baseline HIV testing
  - Rare cases of lamivudine resistance were observed in heterosexual PrEP trials
- There are additional rare cases of an individual failing PrEP due to exposure to multidrug resistant (MDR) HIV strain now reported

Sources:

Knox DC, et al. NEJM. 2017;376(5):501-02.
Markowitz M, et al. JAIDS. 2017;76(4):e104-e6.

Stopping PrEP

- No clear guidelines for stopping PrEP
- IPERGAY data suggests 48 hrs post last sexual exposure sufficient for MSM only, at least 7 days for vaginal exposure
- Ensure the patient is HIV negative after stopping
  - Re-check at 4-6 weeks
- Be aware of HBV status

HBV, hepatitis B virus

There is no consensus on how best to stop PrEP. In individuals who have been using it long-term, the Ipergay trial data likely can apply: 48 hours after last sexual exposure for MSM. Data is absent for women and transgender individuals, at minimum 7 days however some experts have recommended more of a PEP-type approach and give a 28 day course after last exposure.

Sources:
Molina JM, et al. N Engl J Med. 2015;373(23):2237-46.
Seifert SM, et al. Clin Infect Dis. 2015;60(5):804-10.

Tenofovir Alefenamide (TAF) for PrEP

- Use of TAF for ART is associated with lower plasma tenofovir levels and less renal and bone toxicity
- Use of TAF for PrEP has been evaluated in the DISCOVER trial
  - N = 5387 randomized to TDF vs. TAF for PrEP
    - Included small subset of TG women
  - Primary outcome showed non-inferior outcome for HIV prevention (HIV incidence rate/100 PY: 0.16 with FTC/TAF, 0.34 with FTC/TDF, IRR 0.47 95% CI 0.19 – 1.15)
  - Fewer renal adverse events, changes in eGFR and other renal markers in those receiving TAF

However, cost-effectiveness analysis has shown that while TAF for PrEP would avert 25 cases of renal failure over 5 years, it was not a cost-effective intervention compared to current availability of generic TDF.

Sources:

Hare C. CROI; 2019; Seattle, Washington.

Mills A, et al. IDWeek; 2019; Washington, DC.

Wohl D, et el. IDWeek; 2019; Washington, DC.

Walensky R, et al. Ann Intern Med. 2020;172(9):583-90.

Conclusions

- Overall the use of HIV Treatment as Prevention® has reduced HIV infections in BC and Canada
- MSM constitute a key population in the ongoing epidemic
- Biomedical prevention strategies are an important tool to further reduce transmission in the setting of combination prevention interventions

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