RCT
Potential PURL Review Form
PURL Jam Version
Version #11 October 29, 2009

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

1. Citation	Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, Tremblay C, Le Gall JM, Cua E, Pasquet A, Raffi F, Pintado C, Chidiac C, Chas J, Charbonneau P, Delaugerre C, Suzan-Monti M, Loze B, Fonsart J, Peytavin G, Cheret A, Timsit J, Girard G, Lorente N, Préau M, Rooney JF, Wainberg MA, Thompson D, Rozenbaum W, Doré V, Marchand L, Simon MC, Etien N, Aboulker JP, Meyer L, Delfraissy JF; ANRS IPERGAY Study Group. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med. 2015 Dec 3;373(23):2237-46.
2. Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/pubmed/26624850
3. First date published study available to readers	12/03/2016
4. PubMed ID	26624850
5. Nominated By	Other Other: Josh Merok
6. Institutional Affiliation of Nominator	Other Other:
7. Date Nominated	12/13/2015
8. Identified Through	Other Other: TOC
9. PURLS Editor Reviewing Nominated Potential PURL	Kate Rowland Other:
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12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	Debra Stulberg
14. Reviewer Affiliation	Other Other: University of Chicago
15. Date Review Due	04/07/2016
16. Abstract	BACKGROUND: Antiretroviral preexposure prophylaxis has been shown to reduce the risk of human immunodeficiency virus type 1 (HIV-1) infection in some studies, but conflicting results have been reported among studies, probably due to challenges of adherence to a daily regimen.

METHODS:
We conducted a double-blind, randomized trial of antiretroviral therapy for preexposure HIV-1 prophylaxis among men who have unprotected anal sex with men. Participants were randomly assigned to take a combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) or placebo before and after sexual activity. All participants received risk-reduction counseling and condoms and were regularly tested for HIV-1 and HIV-2 and other sexually transmitted infections.
RESULTS:
Of the 414 participants who underwent randomization, 400 who did not have HIV infection were enrolled (199 in the TDF-FTC group and 201 in the placebo group). All participants were followed for a median of 9.3 months (interquartile range, 4.9 to 20.6). A total of 16 HIV-1 infections occurred during follow-up, 2 in the TDF-FTC group (incidence, 0.91 per 100 person-years) and 14 in the placebo group (incidence, 6.60 per 100 person-years), a relative reduction in the TDF-FTC group of 86% (95% confidence interval, 40 to 98; P=0.002). Participants took a median of 15 pills of TDF-FTC or placebo per month (P=0.57). The rates of serious adverse events were similar in the two study groups. In the TDF-FTC group, as compared with the placebo group, there were higher rates of gastrointestinal adverse events (14% vs. 5%, P=0.002) and renal adverse events (18% vs. 10%, P=0.03).
CONCLUSIONS:
The use of TDF-FTC before and after sexual activity provided protection against HIV-1 infection in men who have sex with men. The treatment was associated with increased rates of gastrointestinal and renal adverse events. (Funded by the National Agency of Research on AIDS and Viral Hepatitis [ANRS] and others; ClinicalTrials.gov number, NCT01473472.).

17. Pending
PURL Review
Date

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer if needed]

1. Number of patients starting each arm of the study?	206 in the intervention group, 208 in the placebo group
2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?	Inclusion: 18 years or older; male or transgender female; sexually active with men; HIV-negative; at high risk for acquiring HIV, defined as unprotected anal sex with 2 or more partners in the past 6 months. (Presumably "high risk for HIV" also included men with a partner known to be HIV positive, but they don't state this in the inclusion criteria section) Exclusion: current Hep B, Hep C, kidney or liver dysfunction Summary of participants: recruited from Montreal and 5 cities in France; median number of sexual partners in past 2 months = 8; >25% had STI at initial screening; >43% use recreational drugs. 8% were in a couple with an HIV+ partner.
3. Intervention(s) being investigated?	Fixed dose combo pill: 300 milligrams of tenofovir disoproxilfumarate (TDF) and 200 milligrams of emtricitabine (FTC) (Truvada). "On demand" use, meaning take it when you have sex, rather than every day. Instructions to study participations: loading dose of 2 pills to be taken 2-24 hours before sex; take a 3rd pill 24 hours after the loading dose; take a 4th pill 24 hours later.
4. Comparison treatment(s), placebo, or nothing?	placebo. Both groups received preventive counseling, free condoms, and HIV and STI testing at every study visit: weeks 4 and 8 after enrollment then Q8 months.
5. Length of follow up? Note specified end points e.g. death, cure, etc.	Primary endpoint was development of HIV-1. The study aimed to enroll 1900 particpants and follow them 12-36 months. The placebo arm was discontinued early when the data safety monitoring board found a significant benefit to the study drug during its first unblinded review. The study is now continuing with an open-label design. This paper presents results from the double-blind placebo controlled portion of the trial, i.e. the first 2.5 years of enrollment. Total person-years observed = 431. Median follow-up of subjects is 9.3 months (interquartile range: 4.9 - 20.6).
6. What outcome measures are used? List all that assess	Primary outcome = infection with HIV-1 (by either ELISA or PCR). Adherence was measured through self-report (standardized questions), pill counting, and serum assays to test for presence of the study drug

effectiveness.

7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.

Intervention group: 0.91 new infections per 100 person-years
Placebo group: 6.60 new infections per 100 person-years
Relative reduction in incidence: 86% (95% CI 40-98%, p=0.002). These results are using the authors' modified intention to treat analysis, which excluded particpants after randomization if they tested positive for HIV-1 before receiving any study drug (n=7 from placebo group and n=7 from intervention group). In the unmodified intention to treat protocol, the relative reduction in incidence was 82% (95% CI 36-97%, p=0.002).
Adherence data showed that the 2 participants in the intervention group who acquired HIV-1 were non-adherent: they returned 58/60 and 60/60 pills and had no drug detectable in their serum.
No NNT is reported. Seeing an absolute reduction of 5.69 cases of HIV per 100 person-years, I treated this as a 5.69% absolute risk reduction which gives an NNT of 17.6. In other words, we would have to treat 17.6 people for a year to prevent 1 new case of HIV.

8. What are the adverse effects of intervention compared with no intervention?

GI side effects were more common in the intervention vs. placebo group (14% vs. 5%, p=0.002). No difference in serious adverse effects. No deaths. One participant discontinued when he developed a recurrent DVT which was attributed to the study drug interacting with the dabigatrin he was on. There were no significant differences in sexual risk behavior between the two groups.

9. Study addresses an appropriate and clearly focused question - ***select one***

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable

Comments:

10. Random allocation to comparison groups

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

11. Concealed allocation to comparison groups

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

12. Subjects and investigators kept “blind” to comparison group allocation

☐ Well covered
☒ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

12. Comparison groups are similar at the start of the trial

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

14. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes,

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments: The only significant different was 89 vs 94% of the participants were white. i don't see this as affecting the study's validity in any way.

please indicate whether the differences are a potential source of bias.	
15. Were all relevant outcomes measured in a standardized, valid, and reliable way?	☒ Well covered ☐ Adequately addressed ☐ Poorly addressed ☐ Not applicable Comments:
16. Are patient oriented outcomes included? If yes, what are they?	The primary outcome is infection with HIV-1, which I would consider patient-oriented. They also assessed adherence to study protocol (self-reported and by pill counts and serum assays), and sexual risk behaviors.
17. What percent dropped out, and were lost to follow up? Could this bias the results? How?	12% total: n=23 dropped out in the intervention group, and n=26 in the placebo group. I don't see this as a source of bias.
18. Was there an intention-to-treat analysis? If not, could this bias the results? How?	Yes, they present both a "pure" intention to treat, and a modified intention to treat analysis exluding 7 people in each arm who were diagnosed with HIV before receiving any study drug (i.e. they were randomized but did not receive study study, so they were excluded after randomization).
19. If a multi-site study, are results comparable for all sites?	Not discussed. There's no reason to think the results would vary by site.
20. Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?	Funding appears unbiased, except the study drug was provided by the manufacturer. The authors state the manufacturer had no role in data collection, analysis, or manuscript preparation.
21. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.	Men who have sex with men who are HIV negative and are at high risk for acquiring HIV (2 or more partners in past 6 months, or in a couple with a HIV+ partner)
22. In what care settings might the findings apply, or not apply?	Primary care or HIV/ID clinic. In primary care settings, we would need to make sure we're taking routine sexual histories in order to screen for eligibility for this intervention.
23. To which clinicians or policy makers might the findings be relevant?	Anyone who takes care of men who have sex with men.

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions

For UpTo Date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS as editor & current year as publication year.

EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:

1. DynaMed excerpts

Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at: http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009.{search date}

- preexposure prophylaxis (PrEP) refers to the use of antiretroviral agents by HIV-uninfected but at-risk individuals to prevent the acquisition of HIV infection
- tenofovir 300 mg/emtricitabine 200 mg (TDF-FTC, Truvada) 1 tablet orally once daily is only drug FDA approved for PrEP
- Centers for Disease Control and Prevention (CDC) recommends PrEP as one option for HIV prevention in the following populations(1)
  - adult men who have sex with men (MSM) at substantial risk of HIV acquisition (CDC Grade A, Level I)
  - adult heterosexually active men and women who are at substantial risk of HIV acquisition (CDC Grade A, Level I)
  - adult injection drug users at substantial risk of HIV acquisition (CDC Grade A, Level I)
- several randomized trials evaluating PrEP efficacy support these recommendations
  - PrEP with TDF-FTC reduces incidence of HIV infection in men who have sex with men (level 1 [likely reliable] evidence)
  - PrEP with tenofovir alone or in combination with emtricitabine reduces risk of HIV infection in serodiscordant heterosexual couples (level 1 [likely reliable] evidence)
  - PrEP with oral tenofovir reduces HIV infection in high-risk heterosexual adults (level 1 [likely reliable] evidence), uncertain if addition of emtricitabine increases efficacy in heterosexual adults
  - PrEP with TDF-FTC may prevent HIV infection in sexually active heterosexual adults (level 2 [mid-level] evidence)
  - PrEP with tenofovir may reduce incidence of HIV infection in adults who use injection drugs (level 2 [mid-level] evidence)
  - PrEP with TDF-FTC may not be associated with reduced risk of HIV infection in high-risk African women (level 2 [mid-level] evidence) but adherence in the studied population was low
- nausea is a common side effect of PrEP with oral tenofovir or tenofovir-emtricitabine
- serious adverse effects have been rare to date and, in clinical trials, were not more common with PrEP than with placebo
- antiretroviral resistance is rare, but has been detected in patients with undiagnosed HIV infection at time of PrEP initiation

PrEP Regimens

- tenofovir-emtricitabine (tenofovir 300 mg plus emtricitabine 200 mg, TDF/FTC, brand name Truvada) orally once daily has been approved for PrEP in the United States by the FDA (FDA News Release 2012 Jul)
- fixed-dose tenofovir-emtricitabine (tenofovir 300 mg plus emtricitabine 200 mg, TDF/FTC, brand name Truvada) orally once daily is the only regimen approved by the FDA and is recommended for those who meet criteria (CDC Grade A, Level I)
- tenofovir (TDF, brand name Viread) alone can be used as an alternative regimen for injection drug users and heterosexually active adults but not for men who have sex with men, among whom its efficacy has not been studied (CDC Grade C, Level I)
- no other medication or dosing schedules have been shown to be safe or effective for the prevention of HIV acquisition(1)
  - do not use other antiretroviral medications in place of TDF/FTC or TDF (CDC Grade A, Level III)
  - oral PrEP for coitally timed or other noncontinuous daily use is not recommended (CDC Grade A, Level III)

	• when starting PrEP(1) o discuss all options for HIV prevention and likelihood of patient adherence • consistent condom use is associated with decreased risk of HIV acquisition in heterosexual couples • condoms may be used concurrently with PrEP, particularly if condom use is likely to be inconsistent • see HIV prevention for additional information o educate patients about the medication and provide support for adherence o provide HIV risk-reduction support and prevention services or service referrals o provide effective contraception to women who do not wish to become pregnant o monitor patients for HIV infection, medication toxicities, and levels of risk behavior, and make changes in strategies as needed to support long-term health • consider prescribing no more than a 90-day supply to help ensure that patients do not take PrEP continuously without repeat HIV testing(1)
2. DynaMed citation/access date	Title. Preexposure prophylaxis (PrEP) for HIV Author. Kevin Ard In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated: 3/21/16. Accessed 4/4/16
3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)	Same as above. Of note, DynaMed currently says "coitally timed or other noncontinuous daily use is not recommended" so this article would definitely be a change from DynaMed's current reccomendation
4. UpToDate excerpts	For HIV-uninfected adults who are at high risk for HIV and are committed to medication adherence and close follow-up, we suggest offering pre-exposure prophylaxis with tenofovir-emtricitabine (Grade 2B). Specific high-risk populations include the following (see 'Candidates for pre-exposure prophylaxis' above): •Men who have unprotected anal sex with men and have multiple or anonymous sex partners •Heterosexual individuals who have multiple sex partners in areas of high HIV prevalence •Partners of HIV-infected individuals who have not achieved viral suppression •Injection drug users in drug treatment ●Prior to initiation of pre-exposure prophylaxis, all patients should have HIV testing to be certain that they do not have unsuspected HIV infection. If a patient has had symptoms of acute HIV infection, and/or a recent high-risk exposure in the last four weeks, additional testing for HIV RNA should be performed. (See 'Evaluation prior to initiating pre-exposure prophylaxis' above.) ●Routine baseline laboratories include serum creatinine and urinalysis, hepatitis B serologies, and pregnancy testing. (See 'Evaluation prior to initiating pre-exposure prophylaxis' above.) •We do not prescribe Pre-exposure prophylaxis for patients with an estimated creatine clearance <60 mL/min/1.73m2 •For patients with evidence of chronic HBV infection (ie, anti-HBs negative, HBsAg-positive), the decision to initiate pre-exposure prophylaxis depends, in part, upon whether or not the patient requires treatment for HBV. •For pregnant women, the risk of acquiring HIV must be weighed against the risk of using antiviral medications during pregnancy. In general, tenofovir and emtricitabine (both category B) are felt to be safe for use in pregnancy. ●Tenofovir-emtricitabine for pre-exposure prophylaxis should be administered once daily for as long as the risk of infection persists. (See 'Regimen for pre-exposure prophylaxis' above.) ●Routine monitoring for adherence and safety is important for patients who use pre-exposure prophylaxis. This includes regular HIV antibody/antigen testing, STD screening, as well as monitoring of renal function. (See 'Patient monitoring' above.)

5. UpToDate citation/access date

Always use Basow DS as editor & current year as publication year.
Title. Pre-exposure prophylaxis against HIV infectionAuthor. Kenneth Mayer In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: March 20, 2015. Accessed4/4/16

6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

PreP should be offered for high risk MSM (unprotected anal sex with multiple or anonymous partners), injection drug users in drug treatment, partners of HIV-infected individuals who have not achieved viral suppression, and anyone who has mulitple sex partners in areas of high HIV prevalence.

7. PEPID PCP excerpts
www.pepidonline.com
username: fpinauthor
pw: pepidpcp

8. PEPID citation/access data

Author. Title. In: PEPID [database online]. Available at: http://www.pepidonline.com. Last updated: . Accessed

9. PEPID content updating

1. Do you recommend that PEPID get updated on this topic?
☒ Yes, there is important evidence or recommendations that are missing
☐ No, this topic is current, accurate and up to date.
If yes, which PEPID Topic, Title(s):
HIV infection is discussed only under "fever in immunocompromised" and in "AIDS: Needle stick/blood exposure." There s no content on HIV prevention that I could find.

2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon ( ) that should be updated on the basis of the review?
☐ Yes, there is important evidence or recommendations that are missing
☐ No, this topic is current, accurate and up to date.
If yes, which Evidence Based Inquiry(HelpDesk Answer or Clinical Inquiry), Title(s):
There's one on POST exposure prophylaxis. A new HelpDesk Answer on PRE exposure prophylaxis would be great!

10. Other excerpts (USPSTF; other guidelines; etc.)

CDC practice guideline: recommends PreP in patients consistent with those described above in UpToDate excerpt

From WikiPedia: "The drug has been approved in the USA for pre-exposure prophylaxis against HIV infection. The Food and Drug Administration approved it for prophylactic use on July 16, 2012.[1] In studies, tenofovir reduced the incidence of HIV infection, especially in high-risk individuals (by 42% in MSM in the iPrEx study), but produced conflicting results in other studies (notably the FEM-PrEP study in heterosexual African women). One study estimated through mathematical modeling that daily intake of Truvada could potentially achieve a 99% of risk reduction of contracting HIV in high risk individuals.[2] Another study, iPrEX OLE, showed overall PrEP effectiveness of 50% rising to 100% when participants took the drug four or more times per week.[3] A Cochrane review found that both tenofovir alone, as well as the tenofovir/emtricitabine combination, decreased the risk of contracting HIV by 51% (RR 0.51; 95% CI 0.30 to 0.86; 8918 participants).[4]"

11. Citations for other excerpts

CDC practice guideline on PreP: http://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf

https://en.wikipedia.org/wiki/Tenofovir/emtricitabine

12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

Standard care should already include offering PreP to high risk men who have sex with men, and to some non-MSM patients who are at high risk for other reasons (e.g. injection drug use, or in a relationship with an infected or high-risk partner, or regular unprotected sex with partner(s) at high risk). The change in practice here is offering the "on demand" dosing to high risk MSM. The current study also shows a higher efficacy than previous studies. The authors explain this as follows: it may be that stopping the study early led to an exaggerated estimate of efficacy due to initial higher adherance. It may also be that "on demand" dosing is easier to adhere to and therefore people in this study took the drugs as prescribed at a higher rate than in earlier studies.

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity?

Give one number on a scale of 1 to 7
(1=extremely well; 4=neutral; 7=extremely poorly)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians?

Give one number on a scale of 1 to 7
(1=extremely well; 4=neutral; 7=extremely poorly)
☐1 ☐2 ☒3 ☐4 ☐5 ☐6 ☐7

4. If 4.3 was coded as 4, 5, 6, or 7, lease provide an explanation.

5. Practice changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice?

Give one number on a scale of 1 to 7
(1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

7. Applicability to a Family Medical Care Setting: Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention?

Give one number on a scale of 1 to 7
(1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.

9. Immediacy of Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market?

Give one number on a scale of 1 to 7
(1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)
☐1 ☐2 ☒3 ☐4 ☐5 ☐6 ☐7

10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

This should be a fairly easy intervention to implement: prescribe the med following the protocol in the study. I do think there are some barriers related to how comfortable family physicians may be counseling patients on HIV prevention and giving a med they perceive as an HIV treatment med. Also, it's important to test for HIV frequently, because a person on this med who develops HIV needs to stop taking it and get on a combo regimen in order to prevent developing resistance.

11. Clinical meaningful outcomes or patient oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented?

Give one number on a scale of 1 to 7
(1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

12. If you coded 4.11 as a 4, 5, 6, or 7 please explain why.

13. In your opinion, is this a Pending PURL?
Criteria for a Pending PURL:

- Valid: Strong internal scientific validity; the findings appears to be true.
- Relevant: Relevant to the practice of family medicine
- Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
- Applicability in medical setting:
- Immediacy of implementation

Give one number on a scale of 1 to 7
(1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

14. Comments on your response in 4.13

The caveats listed above under "Immediacy of implementation" are my only concern, but I think the benefits of recommending this are clear.
Also of note: I suspect many family physicians are not currently prescribing HIV PreP (or post-exposure prophylaxis either). In some ways, the practice change we are writing up may be, "you can do this, it's not so scary!" Even though the real change in evidence with this study is only the difference between daily

dosing vs. on-demand dosing.