**TITLE:** Benefits of PrEP as an adjunctive method of HIV prevention during attempted conception between HIV-uninfected women and HIV-infected male partners

**TARGET JOURNAL:** Journal of Infectious Diseases

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Abstract presented at IAS, Kuala Lumpur, Malaysia, July 2013-footnote?

Running Title?

Major Article: 3500 words, 50 references, 7 figures or tables in print, 3 figures or tables online

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**ABSTRACT (200 words)**

***Background:*** Data on the effectiveness of pre-exposure prophylaxis (PrEP) for HIV-1-uninfected women attempting to conceive with infected male partners are limited to small observational studies.

***Methods:*** We developed a model to estimate the annual probability of a woman remaining HIV-1-uninfected and having a child via unprotected sex with an HIV-1-infected male, to explore the potential benefits of antiretroviral therapy (ART) and/or PrEP. The likelihoods are dependent on parameters that define HIV-1 infectivity (transmissibility, ART, number of sex acts, and age-specific female fertility) and assume STIs are treated. The model simulated two scenarios: 1. *Optimal* –unprotected sex acts limited to the window of ovulation (3-12/month) 2. *Suboptimal* –unprotected sex acts not limited to the window of ovulation (1-60/month).

***Results:* In both optimal and suboptimal scenarios, the HIV-1-infected partner being on ART has the greatest influence on HIV-1 transmission. The probability of the female remaining uninfected and conceiving is most influenced by female age (<30 years), followed by ART. On average, the annual probability of remaining HIV-uninfected and having a child increases with ART from 29.5% to 33.3% in the optimal case and from 16.5% to ~31.7% in the suboptimal case. PrEP increases the probability in the optimal case from 29.5% to 31.3%, and in the suboptimal from 16.5% to 22.3%.**

***Conclusions:* In our model, PrEP provides little added benefit when the HIV-1-infected male partner is on ART, unprotected sex is limited to the window of ovulation, and other modifiable transmission risks are optimized. Younger female age reduces the risk of transmission by decreasing the number of unprotected sexual acts required for conception.**

**KEYWORDS (3 minimum)*:*** *Safer conception; mathematical model; pre-exposure prophylaxis; PrEP; antiretroviral therapy*

**INTRODUCTION**

* Globally, HIV infection is estimated to affect over 34 million individuals, with 2/3 of infections heterosexually acquired
* 20-75% desire to conceive
* Serodiscordant couples engage in transmission-risk behavior in order to conceive
* Protection against HIVE transmission during conception among serodiscordant couples remains challenging. Options include self insemination or assisted reproduction. Optimal procedures are often prohibitive due to cost and lack of widespread availability (e.g., sperm washing+adjunctive)
* Less costly menu of options include: timing of intercourse, STI treatment, PrEP, ART for positive partner)
* The aim of this paper is two pronged: (1) to explore the relative benefits of ART and PrEP solely and in combination across many simulated clinical scenarios and (2) to evaluate the impact of maternal age on annual successful conception/HIV non-transmission.
* While the model produces results for five different outcomes, the outcome of interest is the HIV-woman remaining HIV-uninfected and successfully conceiving and delivering a child.

Pre-exposure prophylaxis with combination tenofovir-emtricitabine has proven to be efficacious in a variety of clinical studies, including with men who have sex with men and men and women in heterosexual relationships [REFS]. Despite promising efficacy data and guidelines for the use of PrEP for HIV prevention [REFS], concerns remain regarding optimization of dosing strategy, issues related to differential biologic activity in women, cost, toxicity, risk compensation, and risk of HIV resistance in those who may seroconvert on therapy. Additionally, while there are multiple studies of PrEP in the United States and developing countries for men who have sex with men and heterosexual men and women, there are limited data on the use of PrEP in the setting of conception in serodiscordant couples with an HIV-infected male partner, with publications limited to small case series or observational studies [rEFS?].

Randomized data has confirmed the benefit of antiretroviral therapy (ART) as an effective method for the prevention of HIV transmission [REF 052 and transmission data from CROI in Europe cohort]. In this setting, the additive benefit of PrEP has not been well described. PreP is attractive because of desire to minimize transmission to provide an extra measure of protection, and this is particularly salient for an HIV-uninfected woman who engages in unprotect sex with an HIV-infected male partner in order to conceive. Given the high cost of sperm washing and assisted reproduction such as intra-uterine insemination, in vitro fertilization, and/or intracytoplasmic injection, interest in PrEP for improving safety of conception is high, both for benefits to the woman as well as the child. However, in many settings, particularly in resource-limited countries, the use of PreP is also cost prohibitive. Data to shed light on the additive benefit of PreP for conception could be helpful both for individual men and women making decisions about safer conception, as well as for countries planning policies around the availability of PrEP in a variety of circumstances in which a public health approach must take into account how to provide maximal benefit with a limited amount of funding.

Given the complexity and ethical dilemmas presented by answering the question about the efficacy of PrEP for safer conception in a randomized clinical trial, we used a mathematical model to examine the additive benefit of PrEP for serodiscordant couples desiring natural conception when the male partner is HIV-infected and evaluating a variety of clinical scenarios, including male partner ART status, frequency of intercourse, timing of intercourse, sexually transmitted infections (STIs), and maternal age. We modeled scenarios with a desired outcome of successful conception and delivery of an HIV-uninfected baby.

**METHODS**

**Model Structure**

We develop a probabilistic model to predict the likelihood of possible outcomes defined in terms of HIV infection and successful pregnancy of uninfected women that engage in unprotected sex with infected partners. The estimates depend upon the number of sex acts and on biological parameters that define HIV infectivity, such as the male being on treatment, and age-based female fertility. The outcomes are evaluated under situations where the male is receiving and not-receiving ART and when the female does and does not use PrEP[[1]](#footnote-1). The estimated probabilities are computed per sexual act and then summarized at an annual level. All modeling construction was implemented in the open-source statistical software R.

The mathematical model examines possible HIV-infection and conception[[2]](#footnote-2) outcomes for women aged 18 to 49 across the following five instances:

1. Female stays HIV negative, and becomes pregnant and is successful in giving birth. This occurs with a given probability of

2. Female becomes HIV positive, and becomes pregnant and is successful in giving birth to an HIV negative infant.

This occurs

3. Female becomes HIV positive, and becomes pregnant and gives birth to an HIV+ infant.

4. Female stays HIV negative, and does not become pregnant.

5. Female becomes HIV positive, and does not become pregnant.

For each unprotected sex act each of the five outcomes occurs with a probability from zero to one, where the sum of outcome probabilities is one.

**Model Parameters**

Tables See here for how table needs to be formatted: http://www.oxfordjournals.org/our\_journals/jid/for\_authors/table\_guidelines.pdf

* Discuss model parameters and ranges – update from before
* Include a table for multiplicative impact

Table 1 provides parameter values, their ranges, their sampling pdf and the reference to literature used to quantify these. Similarly table 2 provides the values of the probability of conception and delivery as a function of age and how these change with age a of the female as given by Van Noord-Zaadstra et. at. [1]. The values for late stage treatment were obtained using values given by another modeling paper by Smith et. al. [2] as given by their table S2 in the supplementary material. These values were estimated by analyzing viral load data and using relationships obtained by Quinn et.al.[3] that link viral load to probabilities of transmission. The multiplicative value for treatment (i.e., ART) was estimated by a recent and exciting finding of a 96% overall reduction in HIV transmission in discordant heterosexual couples randomized to early HIV treatment [4]. This study provides strong evidence for the dramatic effectiveness of antiretroviral therapy (ART) in reducing HIV infectiousness. The value for hPrEP is based on two seperate studies: the first by Quarraisha Abdool Karim et. al. showed that Tenofovir Gel reduced transmission to 39% when used as an aniviral microbicide for the preventionof HIV infection in women [5]; the second is the IPREX study by Myers et. al. where PrEP was shown to have efficacy ranges from 15.4% to 87.5% with peak at 43.8% (Note: hPrEP = 1 􀀀 \_PrEP , where \_PrEP represents efficacy) [6]. The value of pMTCT was found based on a study by Conner et. al. [7] and on a study by Cock et. al. on the prevention of Mother-to-Child HIV transmission (MTCT) in resource-poor countries [8]. The value for the reduction factor in MTCT hTxMTCT was found based on the same study by Conner et. al. [7] and on the study by Zutlevics et. al. that showed risks fall to 1 to 2%. Therefore, when compared to the Cock et. al. this indicates that the multiplicative reduction factor that multiplies the MTCT probability is between 0.05 and 0.2.

**Outcomes and Evaluation**

* Outcome of interest
* Optimal versus suboptimal scenario
* Aggregation from sex-act to annual estimate

**Uncertainty Analyses**

* Latin Hypercube Sampling
* Impact of holding parameters at the mean

**Sensitivity Analyses**

* Influential Variables
* Random Forest Analysis and CART

**RESULTS**

*Modeling the optimal scenario when unprotected sex is limited to the window of ovulation*

Figure X shows the annual probability the female partner remaining HIV-uninfected, becoming pregnant, and delivering and HIV-uninfected infant in each of four scenarios in the optimal scenario when the serodiscordant couple limits unprotected sex to the window of ovulation (range of 0-12 sex acts with peak sampling around 3) and sexually transmitted infections are identified and treated: (1) Male partner not on ART and female not on PrEP (27.6%) (2) Male partner not on ART and female on PrEP (29.5%) (3) Male partner on ART and female partner not on PrEP (30.6%), and (4) Male partner on ART and female partner on PrEP (30.7%). There was no significant difference between the probability of the desired outcome with the male partner on ART versus use of ART with PrEP added to the female (29.5% versus 30.7%, p=XXX). All other pairwise comparisons in this scenario were significant suggesting in this modeling scenario that PrEP has an added benefit above no intervention in either partner (29.5% versus 27.6%, p<0.0001) and as expected, ART has an added benefit above the use of PrEP alone and above no intervention (30.6% versus 29.5% and 30.6% versus 27.6%, respectively, p<0.0001 for both comparisons).

Utilizing the model to evaluate the ‘worst case scenario’ outcome of “Female HIV-infected and unsuccessful pregnancy, in the optimal scenario the annual probability of this occurring is 7.4% with neither ART nor PrEP, 2.9% with PrEP along, 0.6% with treatment alone, and 0.2% with ART plus PrEP. [Amber, are these statistically significant?]. Figure X [we created this figure for the IAS talk]

*Modeling the suboptimal scenario when unprotected sex occurs continuously throughout the menstrual cycle*

Figure X shows the annual probability the female partner remaining HIV-uninfected, becoming pregnant, and delivering and HIV-uninfected infant in each of four scenarios in the suboptimal scenario when the serodiscordant couple does not limit unprotected sex to the window of ovulation (0-60 sex acts sampled most frequently around 15). This scenario assumes sexually transmitted infections are identified and treated and reveals the following probabilities: (1) Male partner not on ART and female not on PrEP (17.6%) (2) Male partner not on ART and female on PrEP (24.1%) (3) Male partner on ART and female partner not on PrEP (29.3%), and (4) Male partner on ART and female partner on PrEP (30.3%). In this scenario, all pairwise comparisons were significant. Notably, there was a significant but small difference between the probability of the desired outcome with the male partner on ART versus use of ART with PrEP added to the female (29.3% versus 30.3%, p < 0.0001). PrEP had an added benefit above no intervention in either partner (24.1% versus 17.0%, p < 0.0001) and as expected, ART has an added benefit above the use of PrEP alone and above no intervention (29.3% versus 24.1% and 29.3% versus 17.0%, respectively, p < 0.0001 for both comparisons).

One again, utilizing the model to evaluate the ‘worst case scenario’ outcome of “Female HIV-infected and unsuccessful pregnancy, in the suboptimal scenario the annual probability of this occurring is 31.1% with neither ART nor PrEP, 15.1% with PrEP alone, 3.5% with treatment alone, and 1.3% with ART plus PrEP. [Amber, are these statistically significant?]. Figure X [we created this figure for the IAS talk]

*Comparing optimal to suboptimal: the role of the number of unprotected sex acts in determining probabilities*

When superimposing the results of both the optimal and suboptimal scenarios and looking at the outcome of the annual probability of the woman remaining HIV-uninfected and having a successful pregnancy, the comparisons within each of the four scenarios are statistically significant (p < 0.0001for all) highlighting the important impact of number of sex acts in determining the probability of the outcome of the woman remaining HIV-uninfected and delivering an infant, particularly when there is no intervention for either partner (27.6% in the optimal versus 17.0% in the suboptimal) or PrEP alone for the uninfected woman (29.5% in the optimal versus 24.1% in the suboptimal). Although the difference in the absolute probabilities was very small for the ART (1.3%) and ART+PrEP (0.4%), these differences were statistically significant (both p-values < 0.0001).

Utilizing this same strategy to compare optimal and suboptimal scenarios for the “worst-case” outcome of the female becoming HIV-infected without conceiving and delivering an infant, the powerful role of number of sex acts is again apparent. The comparisons within each of the four scenarios are statistically significant (p < 0.0001for all). Figure X Compared to modeling the outcome of the woman remaining HIV-uninfected and having a successful pregnancy, there are more notable differences in the annual probabilities for the ART group (2.9%) and ART+PrEP (1.1%).

*The role of maternal age in the probability of remaining HIV-uninfected and successful pregnancy*

Given the importance of age on probability of conception and delivery, we utilized CART analysis to evaluate age in the optimal and suboptimal scenarios. In the optimal scenario with unprotected intercourse limited to the window of ovulation, age was the most influential factor in the probability of achieving the desired outcome (woman remaining HIV-uninfected and delivering an infant) (FIGURE?). However, in the suboptimal scenario, [Amber, I have “for women <40 ART is the next most important-is age still the most important?].

Additionally, if we use the suboptimal model and vary only age while the male partner is off ART and no PrEP is used (and all continuous variables are set to the median values), the younger the age the greater the probability of the desired outcome of the woman remaining HIV-uninfected and conceiving and delivering an infant. The probability of this outcome steadily declines as age increases. After age 30, the most likely outcome is that the woman remains HIV-uninfected but does not conceive and deliver a child (Figure 2 From model?). Evaluating the probability of an outcome at 20 years versus 30 years versus 40 years (varying other variables and keeping the age constant), causes the most likely outcome to change from the woman remaining HIV-uninfected and successful pregnancy at age 20 to the female remaining HIV-uninfected with an unsuccessful pregancny by age 30 being more common, to being HIV-uninfected with unsuccessful pregnancy domination the outcomes at age 40 [there is a really complicated set of figures in the model draft-could we simplify and create one figure with panels to show the difference between 20, 30 and 40?].

**Influential Variable Results**

**Relative ranking of influential variables across optimal and suboptimal scenarios- I’m not sure what data this refers to**

**DISCUSSION**

* Public Health Implications
  + What does this mean for PrEP?
  + How does it relate to cost (Treatment vs PrEP)?
  + How does this change the age at which serodiscordant couples are targeted?
* How could a practitioner use this information? …the prototype tool
* Shortcomings
  + Simple model limited by input data
  + Using estimates based upon per sex-act
  + STIs optimized
* Future work
  + Very large range for STIs difficult to evaluate
  + Location specific parameters

CONCLUSIONS AS SEPARATE SECTION?

* Based upon our inputs to our model, PrEP provides little added benefit when all are true:
  + The HIV-infected male partner is on ART
  + Unprotected intercourse is limited to the period of ovulation
  + STIs are diagnosed and treated in both partners
* In the timing-optimized scenario, there is little absolute difference between any of the 4 strategies
* In the non-timing optimized scenario, ART treatment of the HIV+ male partner drives the differences between strategies
* The model highlights that younger age is associated with the desired outcome
* These data are reassuring that patients can have desired results without the addition of PrEP if they are motivated to optimize other modifiable risk factors (provided ART is available)

FOOTNOTE PAGE

* A conflict of interest statement
* A funding statement
* Mention of any meeting(s) where the information has previously been presented
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**ACKNOWLEDGEMENTS?**

**REFERENCES**

Major Articles are limited to 50 references

1. The model is also able to incorporate whether a partner has other STIs. However, according to academic and clinical studies, the multiplicative effect of this situation has an exceptionally large range. [↑](#footnote-ref-1)
2. The conception outcome includes both becoming pregnant and delivering the child. [↑](#footnote-ref-2)