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

**Journal:** Journal of Infectious Diseases

**Abstract**

***Background:*** *The estimated additive impact of pre-exposure prophylaxis (PrEP) in the absence of antiretroviral therapy (ART) and combined with*

***Methods:*** *A probabilistic mathematical model that explores the additive impact of PrEP by predicting the likelihood of outcomes defined in terms of HIV infection and successful pregnancy in a simulated serodiscordant setting.*

***Results:***

***Conclusions:***

***Keywords (3 minimum):*** *HIV transmission; HIV epidemic; serodiscordant conception; mathematical model; pre-exposure prophylaxis; PrEP; antiretroviral therapy*

***Intro***

* 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.

**Methods**

**Model Structure**

A probabilistic model is developed 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. These likelihoods depend on 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.

The mathematical model examines possible HIV-infection and conception[[1]](#footnote-1) 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.

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

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.

**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**

For Figure construction see this: <http://www.oxfordjournals.org/for_authors/figures.html>

**Optimal Scenario Results**

* No intervention compared to PrEP and Treatment along
* Combining PrEP with Treatment

**Suboptimal Scenario Results**

* No intervention compared to PrEP and Treatment along
* Combining PrEP with Treatment

**Optimal versus Suboptimal**

**Influential Variable Results**

**Relative ranking of influential variables across optimal and suboptimal scenarios**

**Impact of Age and Fertility**

**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

**Funding (Separate Section)**

 The sentence should begin: “This work was supported by …”

 The full official funding agency name should be given, i.e., “the National Cancer Institute at the National Institutes of Health” or simply “National Institutes of Health” not “NCI” (one of the 27 subinstitutions) or “NCI at NIH.” [Please go to this Web site for a full RIN-approved list of UK funding agencies](http://www.rin.ac.uk/our-work/research-funding-policy-and-guidance/acknowledgement-funders-journal-articles).

 Grant numbers should be complete and accurate and provided in brackets as follows: “[grant number ABX CDXXXXXX]”

 Multiple grant numbers should be separated by a comma as follows: “[grant numbers ABX CDXXXXXX, EFX GHXXXXXX]”

 Agencies should be separated by a semicolon (plus “and” before the last funding agency)

 Where individuals need to be specified for certain sources of funding the following text should be added after the relevant agency or grant number “to [author initials].”

An example is given here: “This work was supported by the National Institutes of Health [P50 CA098252 and CA118790 to R.B.S.R.] and the Alcohol & Education Research Council [HFY GR667789].”

**Acknowledgements**

Acknowledgments and details of non-financial support must be included at the end of the text before references and not in footnotes. Personal Acknowledgment should precede those of institutions or agencies. Please note that acknowledgment of funding bodies and declarations regarding conflict of interest should be given in separate "Funding" and "Conflict of Interests" sections, respectively.

**References**

Major Articles are limited to 50 references, and Brief Reports are limited to 15 references. Only works that have been published or accepted for publication can be included in the reference list. Unpublished observations by the authors (authors' unpublished data), personal communications (J. L. Searle, personal communication), and manuscripts submitted for publication (H. Chapin and G. Miller, submitted) should be mentioned parenthetically in the text. Please note that all personal communication must be confirmed in writing by the person mentioned. Please number references in order of appearance; those cited only or first in tables or figures are numbered according to the order in which the table or figure is cited in the text. Example: If table 2 is cited in the text after reference 25, a new reference cited in table 2 will be reference 26.

References must follow the National Library of Medicine format as used in [MEDLINE](http://www.nlm.nih.gov/tsd/serials/lji.html) and [Uniform Requirements](http://www.icmje.org/). Provide all authors' (or editors') names when there are fewer than 7; for 7 or more, list the first 3 and add "et al." Titles of journals not listed in MEDLINE should be spelled out in full. Reference to a doctoral dissertation should include the author, title, institution, location, year, and publication information, if published. For online resources, include a URL and date accessed. Accuracy of references is the responsibility of the authors.

Examples of the proper format are as follows:

**Journal Article**  
  
Uherova P, Connick E, MaWhinney S, Schlichtemeier R, Schooley RT, Kuritzkes DR. In vitro effect of interleukin-12 on antigen-specific lymphocyte proliferative responses from persons infected with human immunodeficiency virus type 1. J Infect Dis **1996**; 174:483-9.

**Book chapter**  
  
McIntosh K. Diagnostic virology. In: Fields BN, Knipe DM, Chanock RM, et al., eds. Fields virology. 2nd ed. Vol 1. New York: Raven Press, **1990**:411-40.

**Conference program**  
  
Lyon DJ, Cheng AFB, Norrby SR. Mechanisms of cefotaxime resistance in blood culture isolates of Enterobacter high prevalence of extended-spectrum β-lactamases [abstract C43]. In: Program and abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington, DC: American Society for Microbiology, **1995**:47.

**Internet site**  
  
Public Health Service Task Force. Recommendations for the use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. Available at: http://www.hivatis.org. Accessed 24 April 2002.

1. The conception outcome includes both becoming pregnant and delivering the child. [↑](#footnote-ref-1)