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Cost-Effectiveness of Pre-Exposure Prophylaxis for HIV Prevention for Conception in the United States

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INTRODUCTION

Marking a major paradigm shift in public health, the “Undetectable = Untransmittable” (“U=U”) initiative was launched in 2016 to recognize the effectiveness of combination anti-retroviral therapy (cART) to prevent the transmission of HIV [1–5]. The U.S. Department of Health and Human Services (DHHS) and the Centers for Disease Control and Prevention (CDC) have since endorsed this message, including in recent guideline changes for interventions to reduce perinatal HIV transmission in the United States [6–9].

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It is now advised that for couples with same or differing HIV status that are trying to conceive (there is an estimated half a million serodiscordant couples in the United States [10,11], cART alone for the infected partner is a sufficient prevention option [6–9]. Another option includes daily medication of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) for pre-exposure HIV prophylaxis for the uninfected partner. Approved by the FDA in 2012 under the brand Truvada®, the FDA approved a generic version of the medication in 2017, which could reduce its cost by up to 80% [12,13]. PrEP, however, is still more costly than cART alone with additional pill burden and side effects [14]. It also adds marginal benefit when the partner living with HIV is on suppressive therapy [15–17]. The revised DHHS/CDC perinatal recommendations advise the use of PrEP in cases when the partner living with HIV has not been able to achieve viral suppression or when the viral suppression status is not known [6–9].

These recommendations also advise the consideration of assisted reproduction for couples comprised of an HIV-uninfected woman and HIV-infected male partner [7,8]. Prior to PrEP, couples in this position did not have many options for safer conception apart from either sperm wash with intrauterine insemination (SW-IUI) or in-vitro fertilization (IVF) [18–20]. For IUI, processing of sperm to remove HIV includes density gradient centrifugation with an additional swim-up step in addition to PCR testing of the washed sperm fraction. Couples with reversed serodiscordancy (HIV-infected woman and HIV-uninfected male partner) alternatively do not need sperm preparation techniques; their options for safer conception are less restricted [8]. While these technologies are costly and infrequently available for HIV couples [21,22], cost-effectiveness analysis can establish the tradeoff among care options by determining the cost incurred per unit health gain for each intervention compared to an alternative. Therefore, it is important to evaluate whether, as society, we *should* invest in these services.

While “U=U” is an important public health message that is generally applicable given the accumulated evidence on HIV transmission, a single guideline cannot address real-world heterogeneity of experiences and does not speak to nuances that could make U=U inappropriate. Specifically, the “U” of undetectable is not always certain. Notwithstanding variations in pregnancy planning preferences among couples affected by HIV, with inclined preference towards additional protective barriers [23,24], the female partner might not be in a position to negotiate their partner’s cART use, or protected intercourse. PrEP offers women autonomy and empowerment to make personal decisions affecting their health [25,26].

We therefore sought to investigate the value of PrEP for conception in the U.S. and to identify scenarios in which U=U may not be sufficient, and rather, PrEP or assisted reproduction would improve outcomes. We constructed a Markov model to investigate long-term outcomes, costs, and cost-effectiveness of strategies for HIV prevention for couples comprised of an HIV-uninfected woman and HIV-infected male partner in the U.S. seeking to conceive.

METHODS

Overview

We developed a Markov cohort simulation model and conducted both deterministic and probabilistic sensitivity analyses (PSAs), to estimate the incremental benefits and cost-effectiveness of PrEP compared to alternative risk reduction strategies for HIV serodiscordant couples in the U.S. who seek to conceive. Outcomes included lifetime risk of HIV infection to both women and infants, maternal life expectancy, discounted quality-adjusted life years (QALY), discounted lifetime medical costs, and incremental cost-effectiveness ratios (ICERs). Since our goal is to quantify the value of PrEP for HIV-uninfected women who want to conceive with their HIV-infected male partners, our model includes outcomes for women and babies only.

The base case analysis assumed the most optimal scenario of HIV RNA suppression in the male partner. We then relaxed this assumption and present results varying the probability that the male partner was HIV suppressed. We modeled six strategies (Table 1):

1. cART alone, intercourse *not* limited to ovulation
2. cART alone, intercourse *limited* to ovulation
3. cART + generic TDF/FTC for PrEP, intercourse *not* limited to ovulation
4. cART + generic TDF/FTC for PrEP, intercourse *limited* to ovulation
5. cART + SW-IUI
6. cART + IVF

In natural conception strategies (options 1–4 above), we assumed that women attempt conception for 12 months either with or without effort to restrict unprotected intercourse to peak fertility times. We calculated these ICERs two ways – with ovulation only and without to represent situations in which women are not empowered to make such choices. Of those women who are not pregnant after 12-months, some initiated a course of up to three cycles of SW-IUI and if unsuccessful, up to six cycles of IVF. In states where coverage of infertility treatment is mandated, the most generous coverage limits do not exceed six cycles of IVF. In assisted reproduction strategies, women began the simulation in SW-IUI or IVF, and we accounted for drop-out probabilities after each cycle [19].

We constructed the model and performed analyses in TreeAge Pro 2016 software. The model assumed a monthly time cycle, lifetime horizon, and a healthcare sector perspective on costs. We discounted costs and benefits using a 3% annual discount rate. Using the US Bureau of Labor Statistics consumer price index (CPI), we converted all cost data into 2016 USD.

Model structure

Demography and cohort characteristics: We initiate a cohort of nulliparous women (start age of 33) who are HIV uninfected and seeking to become pregnant (HIV-/pregnancy-). This age corresponds to the observed average age of women representative of

this population in the literature; however, we vary this parameter in our sensitivity analyses [27]. In every simulation month, the cohort experiences non-HIV mortality that is a function of age. Because the racial demography of HIV-infected persons in the U.S. does not match that of the general population, we used standard mortality ratios (SMRs) and HIV surveillance data to adjust non-HIV mortality in the model to reflect the population at high-risk for HIV [28–30].

Conception and HIV infection among women: In each month of pregnancy attempts, the probability of pregnancy is a function of age and method of conception [19,20,31]. Due to declining fertility after the age of 40, women in our model cannot attempt conception after this age. Among women attempting conception through unprotected intercourse, the risk of HIV infection is a function of the estimated risk per unprotected sexual act [3] and the number of sexual acts each month [32]. To model the difference between sex limited versus not limited to ovulation, we reduce the number of condomless sex acts per month [3,32]. In PrEP strategies, women start PrEP one month prior to their first conception attempt and continue until pregnancy [7,8]. To model the effect of PrEP, we multiply the probability of HIV infection from a condomless sex act by the relative risk of HIV infection observed among heterosexual couples in PrEP clinical trials [3,4,33,34].

Women in our model have a risk of HIV transmission after conception, if unprotected intercourse continues throughout pregnancy. Whether a seroconversion occurs before or after conception, women transition from an “HIV-uninfected” health state to an “HIV-infected” health state accordingly.

Teratogenic effects of PrEP: TDF/FTC falls under FDA pregnancy category B with no known harmful effects related to pregnancy, fetal development, parturition, or postnatal development [8,35]. We, however, do not model PrEP during pregnancy and thus do not incorporate potential fetal risk or safety of TDF/FTC.

HIV simulation: When women in the model are diagnosed with HIV, they initiate cART. HIV infection results in decreased life expectancy and quality of life and increased costs related to both cART and chronic medical care.

HIV infection in baby: During conception attempts, women are tested for HIV at least every three months [8,9]. During pregnancy, women are tested during the first trimester (at week five) and again in the third trimester [9]. Every month an HIV-infected woman is pregnant, there is a risk of vertical transmission that is reduced when a woman is taking cART [36].

Adding the baby to the analysis: To incorporate the impact of HIV on child outcomes, we focus on the incremental loss of QALY and increase in lifetime medical cost attributable to a baby born with HIV [37,38]. Whenever a baby is born with HIV infection, we subtract the present value of the expected QALY losses attributable to the baby being born with HIV from the total population life expectancy and add the present value of excess cost. As a result, ICERs appropriately include incremental costs and benefits of PrEP related to preventing vertical transmission.

Model data

We used randomized clinical trials, meta-analyses, and observational cohort studies to inform base-case parameters. See Table 2 for specific values and sensitivity ranges.

Conception and HIV infection among women: For pregnancy and spontaneous abortion (SAB) outcomes, we parameterized rates based on age and prevention method [31]. For HIV transmission parameters, we used data from the PARTNER Study Group on the HIV transmission rate among serodiscordant couples during condomless sex when the HIV-infected partner had HIV RNA <200 copies/ml [3]. While there were no phylogenetically linked transmissions that occurred in this study, our baseline input value of 0.0018 falls on the lower end of the 95% CI of within-couple HIV transmission [3]. To determine the additive effect of PrEP, we used the hazard ratio of TDF/FTC versus placebo from the Partner's PrEP Study (0.34) (95% CI: 0.16–0.72) (adherence rate: 92.1%) and multiplicatively applied this figure to the monthly probability of HIV infection [3,33].

Due to the rarity of seroconversion using assisted reproductive technologies, we estimated the one-month transmission rate for IUI to be 0.0000001 and for IVF to be 0.000000001 [16,39].

HIV infection in baby: We used data from the pre-cART era to inform estimates of vertical transmission without cART and used in utero transmission data during the era of highly active antiretroviral therapy when women initiated cART [36].

Costs related to HIV risk reduction strategies: Costs related to HIV risk reduction strategies were derived from clinical protocols, AMA 2016 Clinical Diagnostic Laboratory Fee Schedule, Medicare Physician Fee Schedule, Veterans Affairs Federal Supply Schedule (FSS), and Micromedex Red Book 2016® wholesale price index [6–8,40–43]. Our base case represents the estimated 80% reduction in cost when generic PrEP becomes available [13]. We used Truven Health Analytics MarketScan® Commercial Claims and Encounters database for price estimates for sperm isolation with complex prep [44]. We included the National Infertility Association's average procedural cost estimates for IUI and IVF [45].

Lifetime non-HIV and HIV costs: Healthcare costs for HIV uninfected individuals are informed by the Medical Expenditure Panel Survey's (MEPS) average medical costs stratified by age and sex [46]. To calculate medical costs for HIV-infected individuals, we took the undiscounted lifetime costs saved of preventing an HIV infection in the U.S. (\$400,000) and amortized it evenly over the remaining life expectancy for persons who became HIV infected at age 35 [47]. We added these costs to the medical costs incurred among a non-HIV infected MEPS cohort.

Quality of life data: Health state utilities combined independent estimates of quality of life based on age and HIV Status. We used age-based utility weights, derived from EQ-5D index scores from a nationally representative U.S. sample, to reflect increased comorbidity over time [48]. We assumed cART suppression and asymptomatic HIV infection for seroconverted women and used previously published estimates of utility with

asymptomatic HIV. We used a multiplicative assumption to combine age-based and HIV-related utility functions [37,38].

Analyses

We simulated the lifetime progression of a cohort of women in each safer conception strategy. We recorded outcomes and calculated ICERs as the ratio of marginal cost and marginal QALY gained. We considered as dominated any strategy that had higher cost and lower QALY than another strategy, as well as strategies that had lower QALY at a higher cost/QALY gained than an alternative strategy (extended dominance). We interpreted cost-effectiveness conclusions using the commonly cited U.S. willingness to pay threshold (WTP) at \$100,000/QALY gained [49].

Varying the probability of male virologic suppression

To identify scenarios in which PrEP provides value, we modeled scenarios in which HIV RNA suppression in the male partner was less than perfect [50]. We conducted four analyses: The probability that the HIV-infected male partner was virologically suppressed at 75%, 50%, 25%, and 9% [3,4] (See Supplementary Appendix).

Sensitivity analyses

We performed one- and two-way deterministic sensitivity analyses characterizing uncertainty in our assumptions and tested the extent to which the level of uncertainty influenced our findings. Parameters of particular interest included the cost of PrEP and its efficacy, HIV transmission rates, perinatal HIV transmission, and the probability that the HIV-infected male partner was virologically suppressed. We further performed PSAs (second-order Monte Carlo simulation) to investigate the robustness of results to parameter uncertainty (Figure 2). We defined probability density functions around HIV transmission parameters, which are the key parameters differentiating risk reduction strategies, using the beta distribution. When data were inadequate to inform a beta distribution, we assumed a uniform distribution between high and low feasible ranges.

RESULTS

Base case

In general, strategies that limit unprotected intercourse to the ovulatory period provided better outcomes at a lower cost per QALY gained compared to strategies that did not limit unprotected intercourse. PrEP with limited unprotected intercourse prevented two maternal and 0.04 infant HIV infections per 10,000 women treated compared to cART alone, extended quality-adjusted life expectancy by 0.02 discounted quality-adjusted life months, and had a discounted, incremental cost of \$1,159 per person. As a result, when the male was consistently on suppressive therapy, PrEP was not economically attractive compared to cART alone (ICER = \$725,960/QALY gained) (Table 3) [49], resulting in an estimated \$723,950,000 per HIV positive pregnancy averted.

SW-IUI and IVF both had better protective effects than PrEP strategies, preventing six maternal and up to 0.11 infant HIV infections per 10,000 women treated, both extending

quality-adjusted life expectancy by 0.04 discounted quality-adjusted life months. However, both interventions were expensive (discounted, incremental cost of \$18,275 and \$28,845 per person, respectively) and neither had an appealing ICER compared to the next best alternative (SW-IUI compared to PrEP ICER= \$5,296,000; IVF compared to SW-IUI ICER = \$237,800,000) (Table 3) [49]. SW-IUI resulted in an estimated \$250,869,000 per HIV positive pregnancy averted compared to PrEP, while IVF resulted in \$17,363,500,000 per HIV positive pregnancy averted compared to SW-IUI.

If we remove conception strategies that rely on condom use, our base case conclusions do not change; however, the ICER for PrEP decreased since the medication would be tackling a larger risk (See Supplementary Table 10).

Identifying scenarios in which PrEP provides value

Compared to cART alone, we found that PrEP was cost-effective, and potentially cost-saving, in scenarios in which the probability of male partner HIV suppression was low and we assumed generic pricing of PrEP. In fact, PrEP was a favorable method even at higher than generic pricing when the male partner was not suppressed. As cART adherence decreased, PrEP's value increased (Figure 1). Even when the male partner was virologically suppressed 75% of the time, PrEP was cost-effective compared to cART alone (\$50,600/QALY) at the estimated generic price of \$200/month and cost-saving below this price. In cases when the probability of male partner suppression was 50%, the ICER of PrEP compared to cART alone was \$4,168/QALY. When the male partner's probability of suppression was either 25% or 9%, PrEP was the preferred prevention strategy compared to cART alone.

While SW-IUI provided a better protective effect than PrEP, this strategy was not considered cost-effective at the \$100,000/QALY threshold at any male suppression level (Figure 1). IUI only dominated PrEP above the \$900/month threshold when the male partner had a low chance of viral suppression (Figure 1) (See Supplementary Tables 1–4).

Sensitivity analyses

While the cost of PrEP affected cost-effectiveness ratios, we found that only reductions in cost beyond the estimated generic price would change the base-case conclusions. Only when the cost of TDF/FTC fell below \$40/month did the ICER of PrEP compared to cART alone fall below the threshold of \$100,000/QALY gained (Supplementary Table 5) [13,42,49]. Alternating other parameters did not change our conclusions. For example, while increasing transmission risk to the child made all preventive strategies appear *more* attractive than in the base case, PrEP was still not cost-effective compared to cART alone (Supplementary Table 7). Increasing the efficacy of PrEP also made PrEP look more attractive, but still not cost-effective when the male was virologically suppressed (Supplementary Table 8).

In PSAs for the optimal baseline scenario (Figure 2), cART with intercourse limited to ovulation was preferred in 65% of 10,000 simulations, assuming a societal WTP threshold \$100,000/QALY. With a significantly higher societal WTP (\$1,000,000/QALY), PrEP with intercourse limited to ovulation was the preferred strategy in 40% of 10,000 simulations.

DISCUSSION

With the availability of PrEP, the reproductive landscape has changed and priorities have shifted for serodiscordant couples seeking conception. While revised clinical recommendations recognize the marginal added value of PrEP when the partner living with HIV is consistently on cART, our study speaks to situations in which PrEP for conception provides value and is an important tool for HIV prevention [6–9]. With up to half of HIV medications in the U.S. not taken as directed [51], our study quantifies instances in which PrEP should be considered for conception. When a male partner is either not reliably suppressed or *not* on cART, PrEP prevents more infections and has an appealing ICER. When a male partner is likely not on cART, PrEP is cost-saving (Figure 2). Moreover, when power dynamics are imbalanced, and women cannot negotiate protected sex, PrEP's ICER reduces; however, our base case conclusions stayed the same. While PrEP is not a high-value intervention for *all* women seeking to conceive a baby with an HIV-infected male partner, it is a cost-effective, and potentially cost-saving, option in scenarios in which partners are not reliably on cART.

While we found PrEP to marginally reduce the risk of sexual transmission when the partner living with HIV is on suppressive therapy, it was not enough to support the cost of PrEP, even when we assumed generic pricing. If, in reality, HIV viral suppression eliminates all HIV transmission, then PrEP adds no value and is not cost-effective under any circumstance. More likely, however, is that at the population level, there is some low level of viral transmission that cannot be observed in a clinical trial, even a large trial. Therefore, despite no phylogenetically linked HIV transmissions found in the PARTNER Study Group trial [3], our analyses reflect this residual risk.

This analysis extends the findings of previous cost-effectiveness and simulation studies comparing PrEP to cART and other risk reduction options [15–17,54,55]. While former studies evaluating conception strategies for HIV serodiscordant couples varied in context and model assumptions, the general conclusions were the same [15–17]. This study adds to the existing literature by considering a wider spectrum of conception options, less than perfect condom use, inconsistent cART use, the timing of HIV testing, generic pricing for PrEP, and by incorporating infant outcomes in the analysis (who could potentially lead an entire life being HIV-infected). Previous papers were written at a time when there was resistance to U=U. Former work was thus important in revising clinical guidance and universally recognizing the strength of this message. Our research makes clear, however, that this slogan should not serve as universal guidance and suggests a more nuanced policy that will better serve the needs of women in the real world.

This analysis has limitations. First, we assumed a healthcare sector perspective and therefore did not consider out-of-pocket costs to patients or differences in coverage for PrEP versus assisted reproduction. Second, our analysis did not consider the potential value of PrEP in terms of psychological reassurance, or the agency of the woman (i.e. her capacity and freedom to make her own choices). PrEP is the first HIV prevention strategy that offers women agency over their sexuality. Were we to incorporate PrEP benefits beyond HIV prevention, its economic value would likely increase.

CONCLUSIONS

This decision analysis reveals that from a U.S. healthcare sector perspective, cART with condomless intercourse limited to peak ovulation is the sound economic choice of HIV prevention among women seeking to conceive with HIV-infected partners who they know is HIV-suppressed. However, we also demonstrate a clear role for PrEP in common scenarios of women wishing to conceive with partners who are not reliably on cART, and we can now quantify this. Cost-effectiveness analysis is an important tool that should be incorporated as one of many factors to inform comprehensive care guidance for serodiscordant couples desiring conception.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points:

From the perspective of the U.S. healthcare sector, our study speak to situations in which PrEP for conception does provide good value and is an important tool for HIV prevention.

Figure 1: Two-way analysis on cost of TDF/FTC PrEP and likelihood that the male partner is HIV suppressed.

This two-way analysis varies the efficacy of each risk reductive strategy based on scenarios in which HIV RNA suppression in the male partner was less than perfect (suppression probabilities: 100%, 75%, 50%, 25%, 9%) and the cost of PrEP varied between \$100 to \$900/month. We eliminated strategies that had higher cost and lower QALY than other strategies (i.e. dominated by another strategy). cART= Combination antiretroviral therapy for the male positive partner; IUI = Intrauterine insemination.

Figure 2: Cost-effectiveness acceptability curve for risk reductive strategies for HIV serodiscordant couples seeking conception

The acceptability curve presents the results of base case probabilistic sensitivity analysis in which we performed 10,000 iterations of the cost-effectiveness simulation. For each iteration, we drew strategy efficacy parameters from defined probability density functions. The vertical axis represents the percentage of the simulations in which a given strategy was “preferred” from a cost-effectiveness perspective at a given societal willingness-to-pay. The horizontal axis represents various societal willingness-to-pay thresholds. cART = Combination antiretroviral therapy for the male positive partner; IUI = Intrauterine insemination; IVF = In vitro fertilization.

Table 1:

Risk reductive strategies considered in cost-effectiveness analysis of HIV Serodiscordant couples seeking conception

Strategy	Specific elements within each strategy
cART suppression alone ^a	(a) Intercourse <i>not</i> limited to ovulation (b) Intercourse limited to ovulation
cART suppression + generic TDF/FTC for PrEP ^b	(a) Intercourse <i>not</i> limited to ovulation (b) Intercourse limited to ovulation
cART + IUI ^c	Maximum of 3 cycles before transitioning to IVF
cART + IVF ^d	Maximum of 6 cycles

^a cART=Combination antiretroviral therapy for the male-infected partner;

^b TDF = Tenofovir disoproxil fumarate; FTC= emtricitabine;

^c IUI = Intrauterine insemination;

^d IVF = In vitro fertilization

Table 2:

Model inputs

Variable	Base Case Value	Range Evaluated in Sensitivity Analyses	Sources
Cohort characteristics			
Start age (years) of HIV-negative woman in serodiscordant couple desiring child	33	28–37	[27]
Life expectancy of women aged 33 years in US population (weighted)	44 (77 from age 0)	47–37	[30]
Life expectancy at birth (49.6% male & 50.4% female)	75.75	72.5 – 77 (Boy – Girl)	[28,30]
Life expectancy for HIV+ patients from 24 weeks after the start of HAART	62.5	61 – 64 (Man – Woman)	[(30,56)]
HIV transmission			
Monthly risk of HIV transmission without condom and male on suppressive cART (condomless sex acts: IQR 15–71 per year)	0.000152 (1/548 couple years of follow-up)	0 – 0.01	[3]
Transmission rate per sex act	0.0000278 (1/36,000)	--	[3]
Transmission rate, 3 sex acts/month during peak ovulation	0.0000833 (1/36,000)*3	0.0000556 (2x/month) – 0.000167 (6x/month)	[3,32]
Effectiveness of PrEP, Hazard ratio (PrEP vs. Placebo)	0.34	0.16 – 0.72	[33]
Relative risk of transmission, PrEP	0.0000517 (0.000152*0.34)	0.00002432905036 (0.000152*0.16)	[3,33]
HIV transmission per safer conception strategy			
Strategy: cART suppression alone; (a) Intercourse NOT limited to ovulation <i>Transmission risk from male to female partner; cART only (VL<200 copies/ml)</i>	0.00015 (1/548 couple years of follow-up)	0 – 0.01	[3]
Strategy: cART suppression alone; (b) Intercourse limited to peak ovulation <i>Targeting fertile days with urine ovulation test, cART only</i>	0.0000833 (3x/month)	0–0.0006	[3,32]
cART suppression + Truvada® for PrEP; (a) Intercourse NOT limited to ovulation <i>Transmission risk with PrEP, using Hazard ratio of 0.34 to determine additive effect of PrEP when on cART</i>	0.00005	0 – 0.0035	[3,33]
cART suppression + Truvada® for PrEP; (b) Intercourse LIMITED to ovulation <i>Transmission risk with PrEP, using Hazard ratio of 0.34 to determine additive effect of PrEP when on cART * probability of targeting fertile days without PrEP</i>	0.00003 (3x/month)	0 – 0.0002	[3,32,33]
Strategy: cART + SW-IUI <i>Transmission risk, sperm wash with density gradient centrifugation/swim-up/PCR + IUI Max # of cycles: 3</i>	9×10 ⁻⁷ per cycle [39]	1×10 ⁻⁶ [16] – 4.5×10 ⁻⁴ [19,20]	[16,19,20,39]
Strategy: cART + IVF <i>Transmission risk, IVF; Max # of cycles: 6</i>	9×10 ⁻⁹ per cycle [39]	1×10 ⁻⁸ [16] – 1×10 ⁻⁵ [20]	[16,19,20,39]
Mother-to-child HIV transmission risks			
Mother-to-child transmission; In utero, mother is <i>not</i> on cART <i>(Not aware of HIV status)</i>	0.005 (19/(385*9))	0.0033 – 0.0085	[36]
Mother-to-child transmission; In utero, mother on cART <i>(Aware of HIV status)</i>	0.001 (4/(312*9))	0.0004 – 0.0036	[36]
Pregnancy outcomes			
Pregnancy rate, natural conception (<i>Ages 30–34</i>)	0.25174	0.146 [16] – 0.252 [31]	[31]
Pregnancy rate, natural conception (<i>Ages 35–39</i>)	0.197	0.181 – 0.197	[31]

Variable	Base Case Value	Range Evaluated in Sensitivity Analyses	Sources
<i>Average pregnancy monthly probability, natural conception (Ages 30–39)</i>	0.225	0.146 [16] – 0.252	[31]
Pregnancy rate per cycle, IUI (<i>Ages 29–40</i>)	0.156 [19]	0.139 [19] – 0.271 [16]	[16,19,20]
Pregnancy rate, IVF (<i>Ages 29–40</i>)	0.259 [19]	0.221 – 0.295 [19]	[19,20]
SAB, natural conception (<i>Ages 30–34</i>), under the assumption that 80% of women with SABs in recognized pregnancies were hospitalized	0.029 (Overall risk: 15%)	0.020 – 0.039	[19]
SAB, natural conception (<i>Ages 35–39</i>)	0.048 (Overall risk: 24.6%)	0.039 – 0.058	[57]
<i>Average SAB monthly probability, natural conception (Ages 30–39)</i>	0.039	0.020 – 0.058	[57]
SAB, IUI (<i>Ages 29–38</i>)	0.030 (Overall risk: 15.5%)	0.026 – 0.035	[57]
SAB, IVF (<i>ages 30–40</i>)	0.035 (Overall risk: 17.7%)	0.027 – 0.043	[57]
IUI dropouts, per cycle (<i>Among HIV-positive men</i>)	0.095	0.010 – 0.229	[19]
IVF dropouts per cycle (<i>Among HIV-positive men</i>)	0.113	0.049 – 0.189	[19]
Natural conception, post 12M probability of “keeps trying”	.44	.34 – .54	[58]
Costs considered in each strategy			
New office/outpatient visit ^a	\$155	\$77.5 – 232.5	[41]
Established office/outpatient visit ^a	\$101	\$50.5 – 151.5	[41]
84703 (Gonadotropin, chorionic (hCG) qualitative test, urine)	\$10.24	\$5.12 – 15.36	[40]
84702 (HCG quantitative), blood	\$20.51	\$10 – \$30.8	[40]
Costs related to cART and PrEP			
TDF + FTC (300mg/200mg; 30 days) (pkg size: 30) ^b	\$200	\$100 – \$300	[13,42,43]
Total clinical test costs (see breakdown under component costs)	\$438.18	\$219.09 – \$657.27	[43]
Component costs:			
Urinary LH testing	\$20.25		[32]
87389 (HIV Antigen & Antibody, 4th gen screen)	\$32.8		[40]
86701 (HIV-1/2 Antibody Differentiation - HIV-1)	\$12.11		[40]
86702 (HIV-1/2 Antibody Differentiation - HIV-2)	\$18.41		[40]
87535 (DNA/RNA; HIV 1; amplified probe)	\$47.8		[40]
86360 (CD4/T-Helper Cell Profile (Lymphocyte Subset Panel 4); test includes: WBC/T Lymphs, CD4, CD8, CD4/CD8 Ratio	\$64.01		[40]
87536 (HIV-1 RNA, Quantitative PCR)	115.92		[40]
86780 (Syphilis Antibody Cascading Reflex)	\$18		[40]
87491 (Chlamydia trachomatis, amplified probe technique)	\$48		[40]
87591 (Neisseria Gonorrhoeae, amplified probe technique)	\$48		[40]
82575 (Creatinine clearance) - for PrEP; M3 & M9	\$12.88		[40]
Costs related to insemination strategies			
89261 Sperm isolation; simple prep (e.g., sperm wash and swim-up) for insemination or diagnosis with semen analysis	\$142.18	\$71.09 – \$213.27	[44,59]
Sperm wash with density gradient centrifugation/swim-up/PCR + IUI	\$1,000	\$500 – \$1,500	unpublished data

Variable	Base Case Value	Range Evaluated in Sensitivity Analyses	Sources
89343 Storage costs (per year) for sperm/semen	\$110.24	\$55.12 – \$165.36	[44,59]
Average cost of an IUI cycle	\$865	\$432.5 – \$1,297	[45]
IUI: Letrozole (2.5–5 milligrams; 5 days) (pkg size: 30; for 5 days)	\$69.74	\$34.87 – \$104.61	[43]
Average cost of an IVF cycle using fresh embryos	\$8,158	\$4,079 – \$12,237	[45]
Total clinical test/medical costs for IVF (see breakdown under component costs)	\$2,580	\$1,290 – \$3,870	[43]
Component costs (IVF):			
IVF: Leuprolide 5 mg/1 ml) 2 week administration subcutaneous KIT	\$110.88		[43]
IVF: Insulin Syringe for Lupron, Qty: 24	\$20.54		[43]
IVF: Gonal F RFF 900 iu/1.5ml Subcutaneous (Form: SOL); (Pkg size: 1.5ml)	\$1,396		[43]
IVF: Needle 30g 0.5 in N/A - N/A Qty: 2	\$0.20		[43]
IVF: Pregnyl 10000 iu - Qty: 1; (Form: PDS)	\$77.64		[43]
IVF: Syringe 3cc 22g 1.5 in. Qty: 2	\$0.54		[43]
IVF: Crinone 8 % - Applicator (Gel) Qty: 30	\$661.52		[43]
IVF: Estradiol Patch 0.1 mg - Dots Qty:16	\$286		[43]
IVF: Oral contraceptive (21 days) - Sprintec	\$27		[43]
Costs related to HIV positive status of woman; pregnant and non-pregnant ^b			
TDF + FTC (300mg/200mg; 30 days) (pkg size: 30) ^b	\$200	\$100 – \$300	[13,42,43]
Raltegravir BID (400mg; 2 capsules daily; pkg size: 60) ^b	\$1,190	\$595 – \$1,785	[42,43]
Costs related to HIV transmission			
Lifetime (undiscounted) costs for non-HIV care if a woman stays HIV-negative	\$293,677	\$146,838 – \$440,515	[46]
Lifetime (undiscounted) costs for HIV care if woman became infected during conception attempts or during pregnancy	\$794,053	\$397,026 – \$1,191,079	[46,47]
Lifetime (undiscounted) costs for HIV care if baby born infected	\$1,044,582	\$522,291 – \$1,566,873	[46,47]
Discount rate	.03 annual (-00247 monthly)	0.0015 – 0.045	
Quality of life			
HIV-negative	0.922 – 0.736	0.461 – 1.104	[48]
HIV-positive	0.733 – 0.585	0.3665 – 0.8775	[37,60]

Note: all costs are in 2016 US dollars

IVF= In Vitro Fertilization; IUI= Intrauterine Insemination; SAB= Spontaneous Abortion

^a Costs for new office/outpatient visits and established office/outpatient visits were derived from the Medicare Physician Fee Schedule [41]. For new office visits, we calculated a weighted cost of 80% level four visit (CPT code: 99204, 45 minutes) and 20% level three visit (CPT code: 99203, 30 minutes), which yielded a cost of \$154.67. For established office visits, we also calculated a weighted cost of 80% level four visit (CPT code: 99214, 25 minutes), and 20% level three visit (CPT code: 99213, 15 minutes), which yielded a cost of \$101.18.

^b We estimated the generic cost of TDF/FTC (300mg/200mg; 30 days) based on an 80% predicted price reduction from a base cost between \$981.51 (VA's FSS) and \$1,355/month (AWP pkg price with a 23% Medicare reduction) and therefore ranged this reduction in our sensitivity analyses. For women in the model who become HIV-positive, the cost of treatment included the estimated monthly cost of TDF/FTC plus Raltegravir BID (400mg; 2 capsules daily; pkg size: 60) with a 23% Medicare reduction, which totaled \$1,189.70 [43]. We also ranged this latter value to reflect the VA's FSS price of \$1,166.7 [42].

Table 3:

Effectiveness, cost, and cost-effectiveness of reproductive strategies for HIV serodiscordant couples; (Base case: Estimated cost of generic Truvada® \$200/30-day; 100% probability of male VL suppression)

Risk reductive strategy	Pregnancy	HIV women / 10,000	HIV babies / 10,000	Life expect. (undisc.) (years)	QALM	Lifetime costs (disc.)	ICER (QALY)
cART (b) intercourse limited to ovulation	1-2	10	0-16	42-68	239-47	\$143,631	--
cART (a) non-targeted ovulation	1-2	14	0-21	42-68	239-45	\$143,733	abs. dominated
cART + PrEP (b) intercourse limited to ovulation	1-2	8	0-12	42-68	239-49	\$144,790	\$725,960
cART + PrEP (a) non-targeted ovulation	1-2	9	0-13	42-68	239-48	\$144,824	abs. dominated
cART + IUI	0-77	1-5	0-017	42-69	239-53	\$163,065	\$5,296,000
cART + IVF	0-75	1-4	0-009	42-69	239-53	\$173,635	\$237,800,000

^aQALM = Quality-Adjusted Life Months