HIV Reproductive Health: Conception Options in the Era of PrEP

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38 y/o HIV(+) ♂, h/o past IVDU, CD4 390,
On ART x 2 years; HVL undetectable
Has 28 y/o ♀ partner x 3 years, HIV(-)
Couple desires child of their own
Fertility desires among HIV+ adults

1998

US HIV Cost & Services Utilization Survey
2,864 HIV+ in care:
29% wanted to have children

2007

Cross-sectional US data; HIV(+)women on HAART:
61% felt could bear children with appropriate medical care
Of those who desired children: 46% of the females; 51% of the males had negative partners
Serodiscordant Heterosexual Couples US

1.2 million HIV-infected in US

240,000 heterosexuals of reproductive age

>140,000 Serodiscordant couples

Estimated to be > 70,000 serodiscordant couples desiring children in US

Positive influencing factors:
- Younger age
- Better health
- Perceived partner desire for children
HIV-infected Serodiscordant Couples are Willing to Have Unsafe Sex to Conceive

20% of couples seeking Assisted Reproduction Services in NY clinic reported engaging in unprotected intercourse to achieve pregnancy at some point in the past.

40% would have unprotected intercourse to conceive if no alternatives.

92% had discussed the risk of transmission to their partner.

Klein et al Obstet Gynecol 2003;101:987094
Options for Safe Conception

- Sperm-washing + IVF-ICSI
- Sperm-washing + IUI
- ARV (HIV+)
- PrEP/PEP (HIV-)

Cost vs. Effectiveness?
Heterosexual HIV Transmission
Mean (+SE) Rate of Heterosexual Transmission of HIV-1 Among 415 Couples (Rakai Project Study Group)

Male-to-Female Transmission

Transmission Rate per 100 Person Years

<400 | 400-3,499 | 3,500-9,999 | 10,000-49,999 | >50,000

Female-to-Male Transmission

HIV-1 RNA (copies/ml)
Genital HIV-1 RNA Predicts Risk of Heterosexual HIV-1 Transmission

Baeten et al, Sci Transl Med 2011;3:77ra29

Male-Female Transmission
Transmission Risk to Uninfected Partner

- Female → Male: 0.04–0.38%/unprotected sexual act
- Male → Female: 0.08–0.3%/unprotected sexual act

With HVL < 700, risk estimates 1/10,000 per unprotected sexual act

**More recent analysis, on cART > 6 months- <13/100,000**

Boily Lancet Inf Dis 2009, Hughes CROI 201Supervie CID 2014
Options for Safe Conception

- Sperm-washing + IVF-ICSI
- Sperm-washing + IUI
- ARV (HIV+)
- PrEP/PEP (HIV-)

Adoption, sperm donation, not having children
Assisted Reproduction Techniques
HIV does not attach to motile viable sperm
Gradient-Swim Up Method

Discontinuous Density Gradient

47% Separation Medium

Seminal Plasma

Nonmotile Sperm, Immature Germ Cells, WBCs

90% Separation Medium

Motile Sperm

Wash Pellet

Swim-up

Motile Sperm for Insemination

Sperm Wash Medium
Safety and Efficacy of Sperm Wash
CREAThE Network

**CREAThE**: Multicenter European consortium to pool knowledge & improve reproductive services for serodiscordant couples

1,036 serodiscordant couples, 3,390 assisted cycles
- 2,840 IUI, 107 IVF, 394 ICS
- 533 pregnancies, 410 deliveries, 463 live births
- HIV testing of female known in 967/1,036 women
  - 100% negative 6 months post-procedure

Bujan et al, AIDS. 2007;21(14):1909-1914
Barriers to Assisted Reproduction Services

Accessibility

• 80% US Fertility Clinics not supporting services for HIV-affected couples (estimated 70,000 couples in US)

• Per Perinatal HIV Hotline only 6 fertility clinics in US offering sperm wash-IUI

Prohibitive Advisories/Regulations

Cost Limitations
## Sperm Wash/Intrauterine Insemination in Serodiscodant Couples

8200 IUI cycles  
1200 IVF cycles  
HIV transmission: 0%  
**estimates 4.5 transmissions per 10,000 IUI cycles**

<table>
<thead>
<tr>
<th>Study</th>
<th>Couples (N)</th>
<th>Median age, women</th>
<th>Median age, men</th>
<th>Cycles (N)</th>
<th>Pregnancy per cycle (%)</th>
<th>Pregnancy cumulative (%)</th>
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</thead>
<tbody>
<tr>
<td>Sempri et al., 1992 (5)</td>
<td>29</td>
<td>30.0</td>
<td>31.0</td>
<td>59</td>
<td>30.7</td>
<td>30.7</td>
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<td>Marina et al., 1998 (9)</td>
<td>63</td>
<td>28.8</td>
<td>31.9</td>
<td>101</td>
<td>20.6</td>
<td>50.0</td>
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<td>Veiga et al., 1999 (14)</td>
<td>64</td>
<td>30.4</td>
<td>33.6</td>
<td>155</td>
<td>27</td>
<td>27</td>
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<td>Lee et al., 2001 (20)</td>
<td>16</td>
<td>35.3</td>
<td>44.0</td>
<td>27</td>
<td>25.3</td>
<td>25.3</td>
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<td>Manna et al., 2002 (23)</td>
<td>233</td>
<td>—</td>
<td>33.7</td>
<td>458</td>
<td>25.3</td>
<td>42.7</td>
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<tr>
<td>Bujan et al., 2004 (18)</td>
<td>56</td>
<td>36.9</td>
<td>36.9</td>
<td>213</td>
<td>17.4</td>
<td>66.1</td>
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<tr>
<td>van Leeuwen et al., 2005 (35)</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>76</td>
<td>13.0</td>
<td>50.0</td>
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<tr>
<td>Kowalska et al., 2005 (19)</td>
<td>13</td>
<td>—</td>
<td>—</td>
<td>48</td>
<td>14.3</td>
<td>53.8</td>
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<tr>
<td>Manigart et al., 2006 (22)</td>
<td>25</td>
<td>—</td>
<td>—</td>
<td>68</td>
<td>14.7</td>
<td>40.0</td>
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<tr>
<td>Savasi et al., 2007 (15)</td>
<td>581</td>
<td>33.9</td>
<td>38.0</td>
<td>2400</td>
<td>19.0</td>
<td>78.0</td>
</tr>
<tr>
<td>Bujan et al., 2007 (12)</td>
<td>84</td>
<td>33.2</td>
<td>32.3</td>
<td>294</td>
<td>18.0</td>
<td>68.1</td>
</tr>
</tbody>
</table>
Barriers to Assisted Reproduction Services

Accessibility

Prohibitive Advisories/Regulations

- As of 2006 ASRM “endorses” sperm wash; reversing 1994 advisory against sperm wash
- As of 2014, DHHS Guidelines support use of sperm wash
- In 1990, CDC advised against sperm wash due to one isolated case of transmission when current standard sperm wash protocol not employed
- Some states still have prohibitive legislation

Cost Limitations
Barriers to Assisted Reproduction Services

Accessibility

Prohibitive Advisories/Regulations

Cost Limitations
Reproductive Options Comparison

<table>
<thead>
<tr>
<th>Variable</th>
<th>IUI with SW</th>
<th>IVF with SW</th>
<th>ICSI with SW</th>
<th>Self-insemination</th>
<th>Intercourse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average number of cycles</td>
<td>2.8</td>
<td>1.4</td>
<td>0.6</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Average cost/cycle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without PrEP&lt;sup&gt;50&lt;/sup&gt;</td>
<td>$1,265</td>
<td>$12,513</td>
<td>$15,128</td>
<td>$30 (kit)</td>
<td>$0</td>
</tr>
<tr>
<td>With PrEP&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>$2,195</td>
<td>$13,443</td>
<td>$16,058</td>
<td>$960</td>
<td>$930</td>
</tr>
<tr>
<td>Average cost/live birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without PrEP&lt;sup&gt;50&lt;/sup&gt;</td>
<td>$12,635</td>
<td>$41,132</td>
<td>$46,256</td>
<td>$30</td>
<td>$0</td>
</tr>
<tr>
<td>With PrEP&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>$16,835</td>
<td>$42,062</td>
<td>$47,156</td>
<td>$5,145</td>
<td>$5,115</td>
</tr>
<tr>
<td>Pregnancy rate/procedure&lt;sup&gt;48,49c&lt;/sup&gt;</td>
<td>19%&lt;sup&gt;29&lt;/sup&gt;</td>
<td>38.1%&lt;sup&gt;51&lt;/sup&gt;</td>
<td>23%&lt;sup&gt;29&lt;/sup&gt;</td>
<td>20%</td>
<td>20%&lt;sup&gt;51&lt;/sup&gt;</td>
</tr>
<tr>
<td>Risk of HIV transmission&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.1-0.5%&lt;sup&gt;52&lt;/sup&gt;</td>
<td>0-0.4%</td>
<td>0-0.09%</td>
<td>0.03-0.14%&lt;sup&gt;50,51&lt;/sup&gt; or 0.1-0.5%&lt;sup&gt;53&lt;/sup&gt;</td>
<td>0.03-0.14%&lt;sup&gt;50,51&lt;/sup&gt; or 0.1-0.5%&lt;sup&gt;53&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Natural Conception
Options for Safe Conception

Cost

Effectiveness?

PrEP/PEP (HIV-)

ARV (HIV+)

Sperm-washing + IUI

Sperm-washing + IVF-ICSI
Prevention of HIV-1 Infection with Early Antiretroviral Therapy


ABSTRACT

BACKGROUND

Antiretroviral therapy that reduces viral replication could limit the transmission of human immunodeficiency virus type 1 (HIV-1) in serodiscordant couples.

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Cohen at the University of North Carolina.
Stable, healthy, serodiscordant couples, sexually active
CD4+ count: 350 to 550 cells/mm³

HPTN 052 Study Design

Randomization

Immediate ART
CD4 350-550

Delayed ART
CD4 ≤250

Primary Transmission Endpoint
Virologically-linked transmission events
HPTN 052: HIV-1 Transmission Breakdown

Total HIV-1 Transmission Events: 39

Linked Transmissions: 28
- Immediate Arm: 1
- Delayed Arm: 27

Unlinked or TBD Transmissions: 11

96% efficacy (p < 0.001)
HAART/Natural Conception

- Natural pregnancies: serodiscordant couples on ARV
  - Inclusion criteria (3 centers in Spain):
    - Undetectable plasma viremia on HAART
  - Outcomes: 62 couples
    - 22 HIV+ females (mean CD4 522)
    - 40 HIV+ males (mean CD4 629)
    - 76 natural pregnancies; 68 children
    - HIV seroconversion in uninfected partners = 0
    - Perinatal HIV transmission = 1

Barreiro et al 2006
Number of Acts of Unprotected Intercourse to Conceive

Avg number of acts to achieve pregnancy
general population: 3-10

Risk of seroconversion
0.1% per pregnancy

**If risk per act 1/10,000

Vandermelen Hum Repro 2010
Why isn’t HAART alone enough for Safe Conception?
Discordance of Genital and Plasma HVL

- Well-documented evidence that HIV RNA can be detected in genital secretions despite undetectable plasma HVL
- Prospective study, 25 men starting HAART, despite undetectable HVL plasma, 48% had intermittent shedding, no STIs
- 5% of 145 men on HAART seeking ART services found to have detectable genital HIV despite negative plasma HVL x 6 months, no documented STIs

(Sheth et al AIDS 2009; Marcelin et al AIDS 2008)
- 88 HIV (+) males on ART, >6 mo undetectable plasma HVL
- 306 semen samples
- HIV RNA detected in semen of 17/88 (19%) males
- Tendency towards higher risk of detectable semen HVL in males on PI regimen; PIs diffuse poorly into genital tract
Intermittent Semen HIV-1 RNA Shedding

Figure 1. Pattern of HIV-1 shedding in the semen of 17 patients with at least one detectable seminal plasma viral load. Each horizontal line represents the data for one subject. Seminal plasma viral loads are represented by circles coloured as follows: white, undetectable; dark grey, detectable. The viral loads (copies/ml) of detectable samples are annotated near the dark grey circles. Two juxtaposed circles represent samples provided at a one-hour interval.
Options for Safe Conception

Cost

Effectiveness?

- PrEP/PEP (HIV-)
- ARV (HIV+)
- Sperm-washing + IUI
- Sperm-washing + IVF-ICSI

Sperm-washing + IVF-ICSI
Pre-exposure Prophylaxis
PrEP
Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women

Partners PrEP Study

4758 HIV serodiscordant couples
(HIV+ partner not yet medically eligible for ART)

Randomize HIV- partners
(normal liver, renal, hematologic function)

TDF once daily
FTC/TDF once daily
Placebo once daily

All receiving comprehensive HIV prevention services

Follow couples for up to 36 months

Primary endpoint: HIV infection in HIV- partner
Co-1° endpoint: Safety
**Partners PrEP**

**Primary efficacy results**

<table>
<thead>
<tr>
<th></th>
<th>TDF</th>
<th>FTC/TDF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of HIV infections</strong></td>
<td>18</td>
<td>13</td>
<td>47</td>
</tr>
<tr>
<td><strong>HIV incidence, per 100 person-years</strong></td>
<td>0.74</td>
<td>0.53</td>
<td>1.92</td>
</tr>
<tr>
<td><strong>HIV protection efficacy, vs placebo</strong></td>
<td><strong>62%</strong></td>
<td><strong>73%</strong></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(34-78%)</td>
<td>(49-85%)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0003</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Z-score, vs. H₀=0.7</td>
<td>-2.17</td>
<td>-2.99</td>
<td></td>
</tr>
</tbody>
</table>

Excludes infections present at randomization (3 TDF, 3 FTC/TDF, 6 Placebo)
### Efficacy and Adherence

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median Age</th>
<th>Married/Stable partner</th>
<th>Efficacy</th>
<th>Adherence (as per drug levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP 004 *</td>
<td>24</td>
<td>88%</td>
<td>TFV gel: 39% [CI = 6-60%]</td>
<td>50.5%</td>
</tr>
<tr>
<td>iPrEx *</td>
<td>27</td>
<td></td>
<td>Oral TDF/FTC: 42% [CI = 18-60%]</td>
<td>51%</td>
</tr>
<tr>
<td>Partners PrEP **</td>
<td>36</td>
<td>98%</td>
<td>Oral TDF: 67% [CI = 44-81%] Oral TFD/FTC: 75% [CI = 55-87%]</td>
<td>83% 81%</td>
</tr>
<tr>
<td>TDF-2 **</td>
<td>25</td>
<td>6%</td>
<td>Oral TDF/FTC: 62% [CI = 22-83%]</td>
<td>80.5%</td>
</tr>
<tr>
<td>FEM-PrEP **</td>
<td>24</td>
<td>31%</td>
<td>Oral TDF/FTC: No HIV Protection</td>
<td>24%</td>
</tr>
<tr>
<td>VOICE **</td>
<td>25</td>
<td>21%</td>
<td>TFV gel: No protection Oral TDF: No protection Oral TDF/FTC: No protection</td>
<td>23% 28% 29%</td>
</tr>
</tbody>
</table>

* Measured adherence based on self-reported use and counts of returned used (for gel) and unused (pill and gel) product

** Measured adherence based on drug levels in blood.
Options for Safe Conception

- PrEP/PEP (HIV-)
- ARV (HIV+)
- Sperm-washing + IUI
- Sperm-washing + IVF-ICSI

Cost

Effectiveness?
Preexposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child

Pietro L. Vernazza\textsuperscript{a}, Irma Graf\textsuperscript{b}, Ulrike Sonnenberg-Schwan\textsuperscript{c}, Maria Geit\textsuperscript{d} and Anja Meurer\textsuperscript{c}

Many HIV-discordant couples express a strong wish to conceive a child. Insemination with processed semen is offered to these couples in many countries. Given the very low level of transmission risk during fully suppressive antiretroviral therapy, we offered timed intercourse combined with preexposure prophylaxis to further reduce the transmission risk. In 53 cases, natural conception was attempted using the proposed method. Pregnancy rates were high and reached a plateau of 75\% after six cycles. Advanced age in the female partner was a predictor for infertility in these couples.

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Prep and Timed Intercourse for Conception

Male partner on HAART with undetectable HIV-RNA in plasma (<50 copies/ml)
No current symptoms of genital infections
Urine LH-test to determine the optimal time of conception (36 h after LH-peak)
Administration of PrEP (tenofovir po). First does at LH-peak-Second 24 hours later
After 6 unsuccessful attempts, fertility evaluation recommended

(Vernazza et al, AIDS 2011)
PrEP for Conception

Outcomes: March 2004 – 2007
- 46 serodiscordant couples
- 75% became pregnant: 50% after 3 or fewer attempts
- 0 seroconversions or adverse events

PrEP-C as a Risk Reduction Strategy in HIV(+) Men and HIV(-) Women in the UK

HIV-positive men & HIV-negative women desiring conception

Median Ages:
- Males: 41
- Females: 31

Contraindications:
- Co-infection with HBV/HCV
- Detectable HIV viral load in plasma and/or semen
- Sub-fertility and high anxiety regarding possible HIV transmission

(Wetham, J. AIDS Care 2014)
PrEP for Conception in the UK

Discussion
- Advice only
- Sperm washing
- PrEP-C
- Adoption
- Rationale of using ARVs to decrease infectiousness
- Swiss Statement
- Current data
- No blame
- Worst-case scenario
- Timed ovulation

Female Investigations
- HIV tests 1-3 monthly
- Day 2-3 FSH/LH/Oestradiol
- Day 21 Progesterone
- TFTs
- Prolactin
- Transvaginal ultrasound pelvis
- Hyserosalpingogram
- STI screening syphilis and hepatitis serology

Male Investigations
- Semen analysis
- Baseline seminal viral load
- STI screening syphilis and hepatitis serology

Intervention
- Tenofovir/emtrictabine vs Tenofovir 1-2 doses 24-36 hours prior to unprotected intercourse
- Further dose within 2 hours of intercourse
- Repeated on sequential days-maximum 3 days

Wetham, J. PrEP-C as a risk reduction strategy in HIV-positive Men and HIV-negative women in the UK AIDS Care 2014
Table 1. Data on 32 couples considered for PrEP-C protocol.

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Brighton data to October 2012</th>
<th>Birmingham data to October 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Couples referred for PrEP-C protocol</td>
<td>N=32</td>
<td>N=14</td>
<td>N=18</td>
</tr>
<tr>
<td>Couples declining after consultation</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Couples not suitable following fertility investigations</td>
<td>9</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Couples not suitable because of transmission risk</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Couples progressing through PrEP-C Protocol</td>
<td>15</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Couples who have taken at least one cycle of PrEP-C</td>
<td>13</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Pregnancies</td>
<td>11</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Live births</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Ongoing pregnancy</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Miscarriages</td>
<td>4</td>
<td>2 (6/40, 10/40 same woman)</td>
<td>2 (5/40; and 1 twin 17/40, other twin live birth)</td>
</tr>
<tr>
<td>Number of attempts per pregnancy, median (range)</td>
<td>2.5 (1-5)</td>
<td>3 (1-5)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>Switch to sperm-washing</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PrEP-C discontinuations due to AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HIV transmissions</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: aOne couple conceived before PrEP-C; one couple about to start PrEP-C.
US FDA Approves First Drug for Reducing Risk of Sexually Acquired HIV Infection

From: US Food & Drug Administration

When: 16 July 2012

For: Gilead Sciences oral TDF/FTC in the US

What: Regulatory approval in the US for daily oral TDF/FTC (Truvada) for PrEP in HIV-negative adults
Initial Preconception Counseling with serodiscordant couple reviewing risks and options for reduced-risk conception completed:

**Female Partner:**
- Confirm HIV negative
- Calculated creatinine clearance $\geq$ 60 mL per minute by the Cockcroft-Gault formula
- STI testing and treatment
- A second HIV test (4th Generation preferable) on day PrEP medication prescribed If any signs, symptoms of acute HIV are present at the time a viral RNA test should be sent
- Provide medication adherence, risk-reduction counseling and condoms
PrEP for Conception Protocol-BMC

Male Partner

- Undetectable plasma viral load
- Stable ART regimen for six months or longer
- STI testing
- Semen analysis suggested
- Provide risk-reduction counseling and condoms
PrEP for Conception BMC

• Oral tenofovir disoproxyl fumarate- emtricitabine (Truvada), daily
• Female partner should be on PrEP x 30 days minimum prior to first unprotected exposure
• The couple should engage in unprotected sex on the day of a positive urine ovulation predictor as well as on the subsequent day
• If pregnancy achieved and any concern for inconsistent condom use, continuing tenofovir disoproxyl fumarate/emtricitabine until delivery should be considered
• The tenofovir disoproxyl fumarate-emtricitabine regimen should be continued for a minimum of 28 days after the last episode of unprotected sexual intercourse, taking one pill per day.
QUESTIONS??