Outcomes from the first assisted reproduction program for HIV-serodiscordant couples in Australia

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About 33 million people worldwide are living with HIV, the majority of whom are of reproductive age.1 The introduction of combination antiretroviral therapy (ART) has led to a significant reduction in morbidity and mortality for HIV-positive individuals. This has dramatically changed the approach many countries take towards reproductive choices for HIV-positive people.

HIV-positive individuals may wish to have children.2-6 Options to achieve pregnancy for HIV-serodiscordant couples (where one partner has HIV infection and the other does not) include unprotected sexual intercourse, self-insemination, intrauterine insemination and in-vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI). The principal considerations when evaluating these methods for couples affected by HIV include risk of horizontal transmission of HIV to the uninfected partner, efficacy of achieving pregnancy, access to treatment, coexisting subfertility, and personal choice.

In 2008, the Swiss Federal Commission for HIV/AIDS stated that, in the absence of other sexually transmitted infections, HIV-positive people who were using effective ART were not infectious.7 In response to this controversial statement, some national public health bodies reasserted the need for consistent condom use,8 as did researchers from Australia who applied mathematical modelling to conclude that the risk of transmission in heterosexual partnerships in the presence of effective treatment is low but not zero.9

Here, we report the outcomes for HIV-serodiscordant couples attending an assisted reproduction program between 2003 and June 2010 in Australia.

Methods

Assisted reproductive techniques have been offered to HIV-positive men with HIV-negative female partners at the Royal Women’s Hospital in Melbourne since 2003, and to HIV-positive women since 2006. Details of the program have previously been published,10 as have details of the laboratory process and semen HIV testing.11

To participate in the program, HIV-positive men must have a plasma viral load below the detection limits of the assay (< 50 copies/mL) for a minimum of 2 months before providing two semen samples that undergo HIV RNA quantification.

Once the HIV-positive man’s two semen samples are cleared (ie, with undetectable HIV RNA), he provides further semen samples that are cryopreserved, tested for HIV RNA and HIV DNA and used for future clinical treatment. The HIV proviral DNA assay is performed on the pellet that results from centrifugation of 400 µL of semen diluted with Tyrode’s solution (JRH Biosciences, Lenexa, Kan, USA).

Semen analysis12 is performed for all male clients attending the program and measures volume, sperm count, motility, velocity and morphology.

The choice of treatment offered (intrauterine insemination or IVF/ICSI) depends on the woman’s age, reproductive history, results of fertility investigation, and the quality of the prepared sperm. After treatment, HIV testing is performed at 14 days, 6 weeks, 12 weeks, and 6 months if not pregnant or 32 weeks’ gestation and at birth of the baby if pregnant.

Ethics approval was not required for this study as it was a retrospective audit.

Statistical analysis

We made statistical comparisons between the HIV-positive men in our study group and a control group of recipient-recruited sperm donors. The continuous variables of age and semen characteristics were compared using the non-parametric Kolmogorov–Smirnov two-sample test. Statistical analysis was performed using Statgraphics, version 5 (Statistical Graphics Corp, Warrenton, Va, USA).

Results

As of June 2010, 39 HIV-positive clients had proceeded to assisted reproduction after the initial consultation in the program. There were 162 completed cycles, with 26 pregnancies (clinical pregnancy rate per cycle, 16.2% for HIV-positive men with an HIV-negative partner, and 15.4% for HIV-positive women). Of all 222 tested semen samples, 18 (8%) had HIV RNA detected despite these men receiving antiretroviral therapy and having an undetectable HIV viral load in plasma. Sperm velocity was significantly lower in HIV-positive clients receiving combination antiretroviral therapy than in a control group of recipient-recruited sperm donors (P = 0.01); there were no other significant differences in sperm quality between the two groups. No HIV transmission to babies or HIV-negative partners occurred.

Conclusion: Our findings show detectable HIV in 8% of semen samples from men with an undetectable HIV viral load in plasma, but confirm the safety of assisted reproduction for HIV-serodiscordant couples within a program with strict protocols for HIV treatment and testing of all semen before use.

Abstract

Objective: To describe the clinical outcomes for all HIV-serodiscordant couples attending an assisted reproduction program.

Design, setting and participants: Retrospective review of demographic, clinical and outcome data for all HIV-serodiscordant couples who attended an assisted reproduction program at a tertiary hospital in Melbourne, between its commencement in 2003 and June 2010.

Main outcome measures: Pregnanacies, miscarriages, births, HIV transmission to the HIV-negative partner, semen quality and detection of HIV (HIV RNA and HIV DNA) in semen.

Results: As of June 2010, 39 HIV-positive clients had proceeded to assisted reproduction after the initial consultation in the program. There were 162 completed cycles, with 26 pregnancies (clinical pregnancy rate per cycle, 16.2% for HIV-positive men with an HIV-negative partner, and 15.4% for HIV-positive women). Of all 222 tested semen samples, 18 (8%) had HIV RNA detected despite these men receiving antiretroviral therapy and having an undetectable HIV viral load in plasma. Sperm velocity was significantly lower in HIV-positive clients receiving combination antiretroviral therapy than in a control group of recipient-recruited sperm donors (P = 0.01); there were no other significant differences in sperm quality between the two groups. No HIV transmission to babies or HIV-negative partners occurred.

Conclusion: Our findings show detectable HIV in 8% of semen samples from men with an undetectable HIV viral load in plasma, but confirm the safety of assisted reproduction for HIV-serodiscordant couples within a program with strict protocols for HIV treatment and testing of all semen before use.

As of June 2010, 39 HIV-positive clients had proceeded to assisted repro-
**1 Semen analysis for HIV-positive men and control group of recipient-recruited sperm donors**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 114)</th>
<th>HIV group (n = 29*)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man’s age (years)</td>
<td>38.8 (23.4–64.8)</td>
<td>36.7 (26.6–51.9)</td>
<td>0.37</td>
</tr>
<tr>
<td>Abstinence (days)</td>
<td>3.5 (1–10)</td>
<td>4.0 (1–28)</td>
<td>0.06</td>
</tr>
<tr>
<td>Delay to testing (hours)</td>
<td>0.7 (0.3–1.7)</td>
<td>0.5 (0.3–1.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Semen volume (mL)</td>
<td>3.2 (0.3–9.9)</td>
<td>3.4 (1.4–5.2)</td>
<td>0.44</td>
</tr>
<tr>
<td>Sperm count (10⁶/mL)</td>
<td>84 (13–750)</td>
<td>62 (17–313)</td>
<td>0.20</td>
</tr>
<tr>
<td>Sperm motility (%)</td>
<td>49 (20–84)</td>
<td>50 (14–77)</td>
<td>0.86</td>
</tr>
<tr>
<td>Sperm velocity (µ/sec)</td>
<td>42 (22–66)</td>
<td>35 (17–59)</td>
<td>0.01</td>
</tr>
<tr>
<td>Morphology (% abnormal)</td>
<td>83 (46–98)</td>
<td>78 (61–95)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

* * Morphology data missing for one man, sperm velocity missing for two men.

**2 Clients and outcomes of assisted reproduction program, 2003 – June 2010**

<table>
<thead>
<tr>
<th></th>
<th>HIV-positive man with HIV-negative female partner</th>
<th>HIV-positive woman with HIV-negative male partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients*</td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td>Completed cycles</td>
<td>136</td>
<td>26</td>
</tr>
<tr>
<td>Pregnancies with an outcome</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>Miscarriages</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Babies born</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Ongoing pregnancies</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Clinical pregnancy† rate per cycle</td>
<td>16.2%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Clinical pregnancy† rate per number of patients</td>
<td>81.5%</td>
<td>50%</td>
</tr>
</tbody>
</table>

* Those with complete data who proceeded with treatment. † Fetal heartbeat at 6 weeks after embryo transfer or intrauterine insemination.

**Discussion**

Although we found detectable HIV viral load in 8% of semen samples from men who were receiving combination ART and had an undetectable HIV viral load in plasma, our study confirms the safety of assisted reproduction for HIV-serodiscordant couples within a program with strict protocols for HIV treatment and testing of all semen before use.

The clinical pregnancy rate per cycle in our study was 16.2% for HIV-positive men with an HIV-negative partner and 15.4% for HIV-positive women. In comparison, the clinical pregnancy rate from 61 929 assisted reproductive technology treatment cycles undertaken for HIV-negative couples in Australia and New Zealand in 2008 was 22.6%. 13

For HIV-positive men, there are few options for biological parenthood that carry no risk of HIV transmission to their HIV-negative partners. Recent experience with assisted reproductive technology from Europe and the United States reports 3390, 14 2683 15 and 42016 cycles of treatment with no seroconversions among women with 6-month follow-up HIV testing data. These figures suggest that the risk of HIV transmission occurring would be less than 1/6000 with assisted reproduction, which is lower than the estimated risk of sexual transmission per single act of penile–vaginal intercourse (1/1000). 17

A meta-analysis reported an overall HIV transmission rate of 0.46 per 100 person-years (irrespective of viral load), based on five episodes of HIV seroconversion. 18 There were no data on viral load available for these five seroconversions, which occurred despite receipt of ART, and insufficient data to calculate rates according to condom use, sexually transmitted...
infections or for female–male and male–female transmission.  

When comparing overall transmission rates between patients who were and were not receiving ART, heterosexual transmission was reduced by 92% in those receiving ART. However, despite this reduction, there are case reports of HIV transmission occurring between serodiscordant individuals where the HIV-positive partner is receiving combination ART.  

Previous studies have reported abnormalities in semen parameters of HIV-positive men, including reduced volume,  

concentration and motility, and changes in morphology.  

There have been conflicting reports of the effect of combination ART on semen parameters, but many studies are small, and teasing out the effect of HIV and/or the effect of antiretroviral drugs can be difficult. In our study, the only significant difference in sperm quality between HIV-positive clients receiving combination ART and the control group was in sperm velocity. Numbers in our study were too small to draw meaningful conclusions about any relationship between the specific combination ART regimen and semen abnormality. We also had no control group of HIV-positive men not receiving ART with whom to compare semen quality.  

The relative contributions that HIV infection and ART make to semen quality remain unclear. Even if combination ART is found to be the major contributing factor to semen abnormality, the relative reduction in semen quality must be weighed against the potential benefit of reducing infectivity by reducing HIV viral load in semen. Along with the evidence of discordant HIV results between semen and plasma in men receiving combination ART, the observation of significantly impaired sperm velocity in our HIV-positive group supports a recommendation that serodiscordant couples attempting to conceive naturally should undergo semen analysis, and HIV-negative women should be educated regarding cycle tracking to maximise the chance of success.

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Competing Interests: No relevant disclosures.

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7 Vernazza P, Hirschel B, Bernasconi E, Flepp M. [HIV infected people free of other STDs are sexually not infectious on effective antiretroviral therapy] [German]. Schweiz Arzteztg 2008; 89: 165-169.