HIV: FERTILITY, SUB-FERTILITY, INFERTILITY

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Outline

1. Fertility: A critical question
2. Sub-fertility: impact of HIV infection and HAART
   - Female fertility
   - Male fertility
3. Infertility: role of infertility clinic
   - Failed ‘home plan’
   - Sperm washing for HIV + men
   - Management of HIV positive infertile couples

HAART: antiretroviral therapy
ART: Assisted reproductive techniques (IUI/IVF/ICSI)
A Critical Question
Is this couple fertile?

- Compromised fertility
  - History of PID, ectopic pregnancy, tubal surgery
  - Irregular menstruation
  - Clinical examination suggesting pathology
  - Infertility: failure to conceive after 1 year regular unprotected intercourse

- Reasons for concern
  - High background rate of infertility
  - Impact of HIV on fertility
  - Risks of unprotected intercourse without benefit
HIV and Fertility
HIV: Female fertility and fecundity

- Pelvic inflammatory disease
- Ovarian dysfunction
  - Ovulatory dysfunction
  - Secondary amenorrhea
  - Reduced ovarian reserve
- Coital frequency
- Pregnancy loss
- Neonatal / infant death

Correlate with CD4 count and disease severity
Meta-analysis
31 Studies: 1983-1996

HIV INFECTED WOMEN VERSUS HIV UNINFECTED WOMEN

- Spontaneous abortion
- Stillbirth
- Fetal abnormality
- Perinatal mortality
- Neonatal mortality
- Infant mortality
- Growth retardation
- Low birth weight
- Pre-term delivery

Peto Odds Ratio (95% CI)

HIV infected women at lower risk
HIV infected women at higher risk

Brookehurst 1998, BJOG, 105:836
HIV and male fertility

- Male hypogonadism: reduced testosterone
- Reduced libido, ejaculatory dysfunction
- Abnormal spermatogenesis

Correlate with CD4 count and disease severity

Table 3 Published studies comparing semen parameters between HIV patients and controls

<table>
<thead>
<tr>
<th>Study</th>
<th>HIV patients</th>
<th>ART (%)</th>
<th>Control</th>
<th>Group</th>
<th>Volume (ml)</th>
<th>Concentration</th>
<th>Motility</th>
<th>Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krieger [30]</td>
<td>21</td>
<td>50</td>
<td>40</td>
<td>Sperm donors</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
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<tr>
<td>Crittenden [31]</td>
<td>39</td>
<td>48</td>
<td>51</td>
<td>Sperm donors, hemophiliacs</td>
<td>n.s.</td>
<td>n.s.</td>
<td>Reduced</td>
<td>Not done</td>
</tr>
<tr>
<td>Dondero [35]</td>
<td>21</td>
<td>76</td>
<td>30</td>
<td>Donors, healthy men</td>
<td>n.s.</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Dulious [33]</td>
<td>189</td>
<td>95</td>
<td>79</td>
<td>PWTI</td>
<td>Reduced</td>
<td>n.s.</td>
<td>Reduced</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diehl [32]</td>
<td>31</td>
<td>77</td>
<td>7</td>
<td>Healthy men</td>
<td>Not done</td>
<td>n.s.</td>
<td>n.s.</td>
<td>Not done</td>
</tr>
<tr>
<td>Nicopoulos [29]</td>
<td>106</td>
<td>55</td>
<td>234</td>
<td>PWTI</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Cardona-May [39]</td>
<td>16</td>
<td>0</td>
<td>16</td>
<td>No data</td>
<td>n.s.</td>
<td>n.s.</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Pavili [36]</td>
<td>31</td>
<td>100</td>
<td>31</td>
<td>Healthy men</td>
<td>n.s.</td>
<td>Not done</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

PWTI partner of women with tubal infertility, ART antiretroviral therapy, n.s. no significant changes between HIV group and control group
HAART and Fertility

Multicountry study:

- 4531 HIV+ women in sub-Saharan Africa
- HAART: Pregnancy Hazard ratio 1.74 (1.19-2.54)
- Behavioural and biomedical factors

Myer, 2012, PLOS Medicine
Fertility assessment of HIV + couples

Cross-sectional study, 1998 – 2005, Spain

- 130 HIV+ women; 121 male partners (38 HIV+)
- HAART: 74% women, 84% men
- No history of infertility
- Pre-conception infertility investigations
  - High rate of HSG pathology (15.2%)
  - Abnormal semen analysis: 83.4% vs 41.7%

Role of the Infertility Unit

- Failed “home plan”
- Sero-discordant couple, HIV + male
- HIV + infertile couple
Initial evaluation

- CD4 count and viral load
- Screening for
  - Haemoglobin or full blood count
  - HIV test partner
  - Rubella, syphilis, cervical dysplasia
  - In resource-rich environments:
    - Hep A/B/C, CMV, Herpes simplex, toxoplasma
    - Genital secretions: gonorrhea, chlamydia, trichomonas, bacterial vaginosis
- Routine infertility investigations:
  - Semen analysis, “D 21” progesterone, hysterosalpingography
Infertility Management

- Subject to underlying pathology
- Couple fully counselled
- No STDs or significant co-morbidity
- Adequate social circumstances
- Stable CD4, low viral load
- HAART: access, teratogenicity
- Appropriate facilities
  - Trained staff – multi-disciplinary team
  - Dedicated laboratory

Informed consent: risk reduction not risk free
Ethical Considerations

- HIV positive, infertile couple:
  - Physician has responsibility towards offspring
  - Withholding of treatment justified if reproduction considered to cause serious harm

- HIV positive, non-infertile couple
  - Able to procreate
  - Physician’s role: Risk reduction only, moral obligation
  - No responsibility for adverse pregnancy outcome
  - Withholding of assistance unethical

Sero-discordant couple, man HIV+

- Sperm detoxification procedure
  - Separate semen from sperm
- Assess viral load in aliquot of post-wash sperm (~100µl) : < 25 copies/ 10^6 sperm
- Intra-uterine insemination
- Intra-cytoplasmic sperm injection (ICSI)
Intracytoplasmic sperm injection (ICSI)

Indication

- 2nd line treatment
- Infertility management
- Controversial: 1st line treatment
  - Spermatozoa appear to be free of HIV-1
  - Increased safety? : reduced exposure to sperm
  - Increased risk? : accidental injection of free viral particle into oocyte
  - More expensive and invasive than IUI
Effectiveness and safety of ART

- Systematic review
- HIV sero-discordant couples, HIV + male
- With/ without infertility factors
- 17 publications
- 3900 IUI cycles
  - Median pregnancy rate per cycle: 18.1%
  - Median miscarriage rate: 15.6%
  - Cancellation rate: 5-9%

Vitorino, 2011 Fertil Steril, 95(5):1684
<table>
<thead>
<tr>
<th>IVF/ICSI 748 cycles</th>
<th>Cycles</th>
<th>PR/cycle %</th>
<th>Misc. Rate %</th>
<th>Seroconversion</th>
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<tbody>
<tr>
<td>Veiga, 1999</td>
<td>16</td>
<td>26.6</td>
<td>0</td>
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<tr>
<td>Marina, 2002</td>
<td>58</td>
<td>49.7</td>
<td>18.5</td>
<td>No</td>
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<tr>
<td>Sauer, 2002</td>
<td>55</td>
<td>45.4</td>
<td>20.6</td>
<td>No</td>
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<tr>
<td>Pena, 2003</td>
<td>113</td>
<td>38.1</td>
<td>25.7</td>
<td>No</td>
</tr>
<tr>
<td>Garrido, 2004</td>
<td>-</td>
<td>40.1</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>Chu, 2005</td>
<td>146</td>
<td>34.6</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>Chu, 2006</td>
<td>-</td>
<td>47.0</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>Manigart, 2006</td>
<td>62</td>
<td>17.7</td>
<td>33.3</td>
<td>No</td>
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<tr>
<td>Savasi, 2007</td>
<td>288</td>
<td>23.0</td>
<td>-</td>
<td>No</td>
</tr>
</tbody>
</table>

Median PR 38.1%
# Reproductive Medicine Unit, GSH 2010-2012

## IUI
### HIV pos women: n=16
- **No. inseminations:** 31
- **No. pregnancies:** 4 (Incl. 1 miscarriage)
- **Pregnancy rate:** 12.9% per insemination, 25% per patient

## IVF/ICSI
### HIV pos men: n=13
- **No. ICSI cycles:** 18 (All virus free)
- **No. embryo transfers:** 16
- **No. pregnancies:** 3
- **Pregnancy rate:** 18.7% per ET, 23% per patient
Summary

- Critical question
- Risk of sub-fertility in HIV infected individuals
- HAART: many benefits, some adverse effects

- Collaboration between HIV physicians and infertility specialists

- Barriers
  - Access to care
  - Additional laboratory requirements
  - Cost