Systematic review of HIV transmission between heterosexual serodiscordant couples where the HIV-positive partner is fully suppressed on antiretroviral therapy

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Background

Swiss Statement
• January 2008, the Swiss National AIDS Commission deemed an HIV-positive individual as “sexually non-infectious” if (3) criteria fulfilled:
  (1) Adherence to ART with regular monitoring by physician
  (2) Absence of STIs
  (3) Undetectable plasma VL for 6 months or more

WHO and UNAIDS Response
• Risk of HIV transmission reduced but not eliminated
• More research is needed on the:
  (1) degree to which plasma VL predicts HIV transmission risk
  (2) association between viral load in blood and viral load in semen and vaginal secretions
  (3) other factors contributing to HIV transmission
Background

Biological studies report plasma and genital VL discordance
(1) In 2008, Marcelin et al. (French group)
  • 5% of 145 HIV-infected men in ART program with undetectable plasma VL had detectable HIV-RNA in semen
(2) In 2009, Sheth et al. (Toronto group)
  • 25 men on ART rapidly suppressed virus in plasma and semen; but over time, 48% had semen HIV shedding more than once and 16% had semen VL > 5,000 copies/mL

What is missing from the systematic reviews on horizontal HIV transmission published to date
(1) Power et al. (2008) – did not consider ART
(2) Boily et al. (2009) – did not consider ART
(3) Attia et al. (2009) – 3/5 inclusions were conference abstracts
(4) Anglemyer et al. (2011) – did not consider VL, only CD4 count

2. Sheth et al. AIDS 2009; 23(15):2050-4
Study Objective

• To systematically review observational studies and randomized controlled trials evaluating rates of sexual HIV transmission between heterosexual serodiscordant couples when the HIV-positive partner has full suppression on cART
## Literature Search Strategy

- Citations systematically retrieved from these sources
- 2 reviewers independently searched articles at each stage and 3rd party settled disagreements

### Electronic Databases (1950-2012): MEDLINE, Embase, CINAHL, Web of Science

### Journals/conferences (June 2010 to November 2012)

### Reference lists of identified and included articles

### Authors contacted as needed

### Data Extraction

<table>
<thead>
<tr>
<th>References</th>
<th>Abstracts</th>
<th>Full-Texts</th>
<th>Data Extraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Obvious relevance</td>
<td>2) Two or more inclusion criteria • sexual contact • HIV+ partner on cART • confirmed suppressed VL at HIV transmission • HIV infection rates in HIV- partner • Peer-reviewed publications</td>
<td>3) All inclusion criteria</td>
<td>4) Extract • Descriptive variables • Quality data • Outcomes • Incidence of transmission per 100-person years • Incidence of transmission per act • Incidence of transmission on ART; without ART</td>
</tr>
</tbody>
</table>
Data Analysis

Risk of bias assessment
• New Castle-Ottawa scale used for observational studies
• Cochrane risk of bias tool for RCTs

Meta-Analysis
• The $I^2$ statistic was used to assess heterogeneity
• 2 meta-analyses were carried out using Comprehensive Meta-analysis®
  • Rate of transmission per 100 person-years using a fixed-effects Poisson regression model (** insufficient reports of rate per sexual)
  • Pooled odds ratio of HIV transmission on cART vs. no cART with 95% CI
• Sensitivity analysis
  • Overall HIV transmission rate per 100 person-years with 95% CI using random-effects model
Results

Citations retrieved from electronic database search (26396); hand search (20); bibliography (2)

Duplicates removed (6,166)

Total potential citations (20252)

Citations excluded due to non-relevant studies (19957)

(150) Abstracts excluded due to lacking the following data:
- ART (134)
- seroconcordant couples (1)
- new HIV infection (1)
- undetectable viral load (9)
- single case studies (5)

Potentially relevant abstracts screened (295)

(134) Full-texts excluded due to lacking the following data:
- non-original data (10)
- suppressed viral load, ART (70)
- discordant couples, suppressed viral load, ART (12)
- discordant couples and new HIV infection (1)
- new HIV infection, suppressed viral load, ART (5)
- discordant couples, new HIV infection, suppressed viral load, ART (7)
- all criteria (14)
- suppressed viral load (12)
- unprotected sex, new HIV infection, suppressed viral load, ART (3)

Full-text articles assessed for eligibility (145)

Articles included in systematic review (11)

Articles included in primary review (5)

Articles included in system review (3)

Articles included in 2y analysis (6)

* 2 articles on same study population for each of 3 studies

Articles included in 2y analysis (3)

* 3 articles repeat same population
<table>
<thead>
<tr>
<th>Studies</th>
<th>Method/type of study</th>
<th>Study setting</th>
<th>Enrolment Period</th>
<th>Age</th>
<th>Gender/sexual orientation of HIV+ partner</th>
<th>Type of cART</th>
<th>Freq. of HIV test</th>
<th>Freq. of VL measur</th>
<th>VL limit of detection (copies/ml)</th>
<th>VL (copies/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melo 2008</td>
<td>Retrospective/prospective cohort</td>
<td>Single centre in Spain</td>
<td>Feb 2000 – Jan 2006</td>
<td>Not reported</td>
<td>Heterosexual 67 (72%) women, 26 (28%) men</td>
<td>Zidovudine, lamivudine, nelfinavir, efavirenz</td>
<td>6 months</td>
<td>Not reported</td>
<td>50</td>
<td>Median: 24082 for transmitter 4583 for non-transmitter All undetectable on ART</td>
</tr>
<tr>
<td>Del Romero 2010</td>
<td>Cross sectional and prospective cohort</td>
<td>Single centre in Brazil</td>
<td>1989-2008</td>
<td>Median: Women 29, Men 32</td>
<td>Heterosexual 113 (17%) women, 535 (83%) men</td>
<td>Not reported</td>
<td>6 months</td>
<td>Not reported</td>
<td>500 until 1999, 50 thereafter</td>
<td>Median: 6402 for non ART, 5367 for mono/dual therapy, Not detectable for combined treatment</td>
</tr>
<tr>
<td>Reynolds 2011</td>
<td>Retrospective cohort</td>
<td>Multi mobile clinics in Uganda</td>
<td>2004-2009</td>
<td>HIV-partner: 5% 15-19 18% 20-24 29% 25-29 48% 30+</td>
<td>Heterosexual 105 (42%) women, 145 (58%) men</td>
<td>Not reported</td>
<td>12 months</td>
<td>6 months</td>
<td>400</td>
<td>6mo: 71%&lt;400, 29%&lt;2000 12mo: 85%&lt;400, 15%&gt;2000 24mo: 100%&lt;400</td>
</tr>
</tbody>
</table>
## Table 1b. Characteristics of included prospective cohort studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Method/ type of study</th>
<th>Study setting</th>
<th>Enrolment Period</th>
<th>Gender/ sexual orientation of HIV+ partner</th>
<th>Type of cART</th>
<th>Freq. of HIV test</th>
<th>Freq. of VL measure</th>
<th>VL limit of detection (copies/ml)</th>
<th>VL (copies/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donnell 2010</td>
<td>Prospective cohort</td>
<td>Multi-Centre in Africa</td>
<td>Nov 2004 – Apr 2007</td>
<td>Median (IQR): HIV+: 32 (26-38) HIV-: 33 (28-40)</td>
<td>Heterosexual 2284 (68%) women, 1097 (32%) men</td>
<td>Stavudine, lamivudine, nevirapine (61%); zidovudine, lamivudine, nevirapine (13%); Protease inhibitor-containing regimen (3%); Other (16%); Insufficient information to establish full regimen (7%)</td>
<td>3 months</td>
<td>Baseline, months 3, 6, 12 and final study visit</td>
<td>240 Median: 4.1 log10 copies per ml. 241 (70%) achieved virological suppression at the final visit</td>
</tr>
<tr>
<td>Apondi 2011</td>
<td>Prospective cohort</td>
<td>Single centre in Africa</td>
<td>May 2003 – Dec 2007</td>
<td>Median: Women 37 Men 41</td>
<td>Not reported</td>
<td>Not reported</td>
<td>12 months</td>
<td>50 36 months: 97.5%&lt;1700 2.5%&gt;1700</td>
<td></td>
</tr>
<tr>
<td>Cohen 2011</td>
<td>Randomized controlled trial</td>
<td>Multi-Centre in Africa, India, Thailand, USA, and Brazil</td>
<td>Jun 2007- May 2010</td>
<td>18%-18-25 61% 26-40 21% 40+ 97% heterosexual 873 (50%) women, 890 (50%) men</td>
<td>Zidovudine, lamivudine, efavirenz in 72% of participants (Other study drugs: atazanavir, nevirapine, tenofovir, emtricitabine, zidovudine, didanosine, stavudine, lopinavir and ritonavir)</td>
<td>Quarterly</td>
<td>Not reported</td>
<td>400 Median: 4.4 log10 copies per ml</td>
<td></td>
</tr>
</tbody>
</table>
### Table 2. Risk of bias assessment of included observational studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Representativeness of exposed cohort</th>
<th>Selection of non-exposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Demonstration</th>
<th>Comparability</th>
<th>Assessment of outcome</th>
<th>Follow-up long enough</th>
<th>Adequacy of follow-up</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melo 2008</td>
<td>Somewhat representative *</td>
<td>Same community *</td>
<td>Secure record *</td>
<td>Yes *</td>
<td>No</td>
<td>Medical record *</td>
<td>Yes</td>
<td>4 of non-ART were lost *</td>
<td>7</td>
</tr>
<tr>
<td>Del Romero 2010</td>
<td>Somewhat representative *</td>
<td>Same community *</td>
<td>Structured interview *</td>
<td>Yes *</td>
<td>No</td>
<td>Medical record *</td>
<td>Yes</td>
<td>65% with follow up</td>
<td>6</td>
</tr>
<tr>
<td>Reynolds 2011</td>
<td>Truly representative*</td>
<td>Same community *</td>
<td>Secure record</td>
<td>Yes *</td>
<td>Study control for behaviour</td>
<td>Medical record *</td>
<td>Yes</td>
<td>Not reported</td>
<td>7</td>
</tr>
<tr>
<td>Donnell 2010</td>
<td>Somewhat representative *</td>
<td>Same community *</td>
<td>Secure record</td>
<td>Yes *</td>
<td>Study control for time on study and CD4 cell count</td>
<td>Medical record *</td>
<td>Yes</td>
<td>4% person-years were lost *</td>
<td>8</td>
</tr>
<tr>
<td>Apondi 2011</td>
<td>Somewhat representative *</td>
<td>No non-exposed cohort</td>
<td>Secure record</td>
<td>Yes *</td>
<td>No</td>
<td>Medical record *</td>
<td>Yes</td>
<td>82% had data at 36 months, 10% died *</td>
<td>6</td>
</tr>
</tbody>
</table>

### Table 3. Risk of bias assessment of included RCT

<table>
<thead>
<tr>
<th>Studies</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other sources of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen 2011</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Table 3a. Data reported in included studies

| Studies   | Total enrollment | Analyzed | Follow-up duration | Total follow-up (person-years) | Male circumcision of HIV+ partner | Male circumcision of HIV- partner | condom use | Index case on cART | HIV transmission on cART | HIV transmission not on cART | HIV transmission rate |
|-----------|------------------|----------|--------------------|--------------------------------|-----------------------------------|-----------------------------------|------------|---------------------|---------------------------|---------------------------|----------------------|------------------------|
| Melo 2008 | 93               | 93       |                    | 196.4                         | No men in the cohort were circumcised | No men in the cohort were circumcised | Interview 37 couples, 8/24 female index case (21.6%) reported no condom use and 13 of 13 men interviewed reported regular condom use | 41       | 0                   | 6                          | 3.1 (1.4-6.5)             | 0 (0-4.1) 5.7 (2.6-11.8) | Not reported |
| Del Romero 2010 | 648           | 648   | Not reported       | 1355                          | Not reported                      | Not reported                       | For patients without ART, 86% had always used condoms | 149      | 0                   | 5                          | 0.4 (0.1-0.9)             | 0 (0-1.1) 0.6 (0.2-1.4) | 0.2 (0.1, 0.6) |
| Reynolds 2011 | 250            | 250   | Median: 1.57 year before ART, 1.54 year after ART | 459.3 before ART, 53.6 after ART | 20%                              | 19.3%                             | Consistent condom use: 14.3% prior to ART, 53.7% after ART | 32       | 0                   | 42                         | 8.2 (6.1-10.9)            | 0 (0-6.7) 9.2 (6.59, 12.36) | Not reported |

### Confirmed Viral Load

- **Melo 2008**
  - Median: 25.5 mo transmitter; 22.34 mo non-transmitter
  - Median: 25.5 mo transmitter; 22.34 mo non-transmitter

- **Del Romero 2010**
  - 20% Consistent condom use: 14.3% prior to ART, 53.7% after ART

- **Reynolds 2011**
  - Median: 1.57 year before ART, 1.54 year after ART

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**HIV transmission rate**

<table>
<thead>
<tr>
<th></th>
<th>Per 100 person-years (Overall)</th>
<th>Per 100 person-years (on cART)</th>
<th>Per 100 person-years (Not on cART)</th>
<th>Per 1000 sex acts (Overall)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melo 2008</td>
<td>3.1 (1.4-6.5)</td>
<td>0 (0-4.1)</td>
<td>5.7 (2.6-11.8)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Del Romero 2010</td>
<td>0.4 (0.1-0.9)</td>
<td>0 (0-1.1)</td>
<td>0.6 (0.2-1.4)</td>
<td>0.2 (0.1, 0.6)</td>
</tr>
<tr>
<td>Reynolds 2011</td>
<td>8.2 (6.1-10.9)</td>
<td>0 (0-6.7)</td>
<td>9.2 (6.59, 12.36)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Studies</td>
<td>Total enrollment</td>
<td>Analyzed</td>
<td>Follow-up duration</td>
<td>Total follow-up (person-years)</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------</td>
<td>----------</td>
<td>--------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Donnell 2010</td>
<td>3408</td>
<td>3381</td>
<td>Median: 8.2 months after ART</td>
<td>4558 for those not on ART, 273 for ART</td>
</tr>
<tr>
<td>Apondi 2011</td>
<td>62</td>
<td>62</td>
<td>3 years</td>
<td>Not reported</td>
</tr>
<tr>
<td>Cohen 2011</td>
<td>1763</td>
<td>1775</td>
<td>Median: 1.7 years</td>
<td>1585.3* in early therapy group; 169.5* delayed-therapy group who started ART; 1397.7* for delayed-therapy group when not on ART</td>
</tr>
</tbody>
</table>

Table 3b. Data reported in included studies

Unconfirmed Viral Load

- Donnell 2010: Median: 8.2 months after ART.
- Apondi 2011: 3 years follow-up.
- Cohen 2011: Median: 1.7 years.
Transmission rate of ART-treated patients when VL was confirmed = 0 per 100-person years (95% CI: 0-0.5)

Transmission rate of ART-treated patients when VL was confirmed and unconfirmed = 0.14 per 100-person years (95% CI: 0.4-0.31)
4 Unconfirmed VL Transmissions

Donnell et al. (2010)
- 1/103 F to M genetically-linked; HIV+ F had 302 CD4 cells /μL at enrolment; 201 cells /μL at 6-month; started ART 18 days earlier than 9-month visit; M partner tested neg HIV-1 at 9 months; at 12-month visit, M tested pos HIV-1

Apondi et al. (2010)
- 1/62 F to M genetically-linked; seroconversion occurred in year 1 but VL not reported at 12 months in this study, only at 36 months

Cohen study et al. (2012)
- Mastro et al. (2011) - HIV-1 transmission event occurred within 3 months index partner was on ART
- Eshleman et al. (2011) - 1 extra transmission on ART in delayed therapy group 4 weeks after the start of ART

4 transmissions all occurred within 6 months of starting ART; VL likely not suppressed.
Removing these transmissions via sensitivity analysis to be c/w Swiss Statement requirements.
The transmission rate excluding the 4 transmissions when VL was not confirmed = 0 per 100-person years (95% CI: 0-0.1)
Conclusions

Limitations included lack of data
- same-sex couples, type of sexual intercourse (vaginal vs. anal), frequency of sexual exposure, direction of HIV transmission, exact viral load at the time of transmission, sexually transmitted infections (STI) rates, and extent of condom use.

Implications
- Minimal risk of sexual HIV transmission for heterosexual serodiscordant couples when the HIV-positive partner has full viral suppression on cART with caveats regarding information on sexual intercourse type, STIs, and condom use
- Pertinent counseling tool for serodiscordant couples on sexual and reproductive health
- More research is needed to explore HIV transmission risk between same-sex couples

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