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

Michelle Letchumanan[1,3], Wei Wu[1], Lise Bondy[2], Tony Antoniou[3,4], Shari Margolese[1], Yimeng Zhang[2], Sergio Rueda[4,5], Frank McGee[6], Ryan Peck[7], Louise Binder[8], Patricia Allard[9], Sean Rourke[4,5], Paula Rochon[1,2,3], Mona R. Loutfy[1,2,3,4]

1 Women's College Research Institute, 2 Faculty of Medicine, University of Toronto, 3 Institute of Health Policy, Management and Evaluation, University of Toronto, 4 St. Michael's Hospital, 5 Ontario HIV Treatment Network, 5 CDC-Uganda, National Center for HIV, STD and TB Prevention, Center for Disease Control and Prevention, Entebbe, Uganda, 6 AIDS Bureau, Ontario Ministry of Health and Long Term Care, 7 HIV & AIDS Legal Clinic Ontario, 8 Canadian Treatment Action Council, 9 Canadian HIV/AIDS Legal Network.

3rd International Workshop on Women and HIV
January 14th, 2013

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

1.Vernazza *et al.* Bulletin des médecins suisses 2008; 89:165-169.
2. UNAIDS/WHO (2008) Statement: Antiretroviral therapy and sexual transmission of HIV

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

1. Marcelin *et al.* AIDS 2008; 22: 1677-1679
2. Sheth *et al.* AIDS 2009; 23(15):2050-4
3. Powers *et al.* Lancet Inf Dis 2008; 8:553-563
4. Boily *et al.* Lancet Inf Dis 2009; 9:118-129
5. Attia *et al. AIDS*2009; 23:1397-1404.
6. Anglemyer *et al.* The Cochrane Library 2011; 5:1-42.

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

Reference lists of identified and included articles

Journals/conferences (June 2010 to November 2012)

Authors contacted as needed

References → **Abstracts** → **Full-Texts** → **Data Extraction**

1) Obvious relevance

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

3) All inclusion criteria

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

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

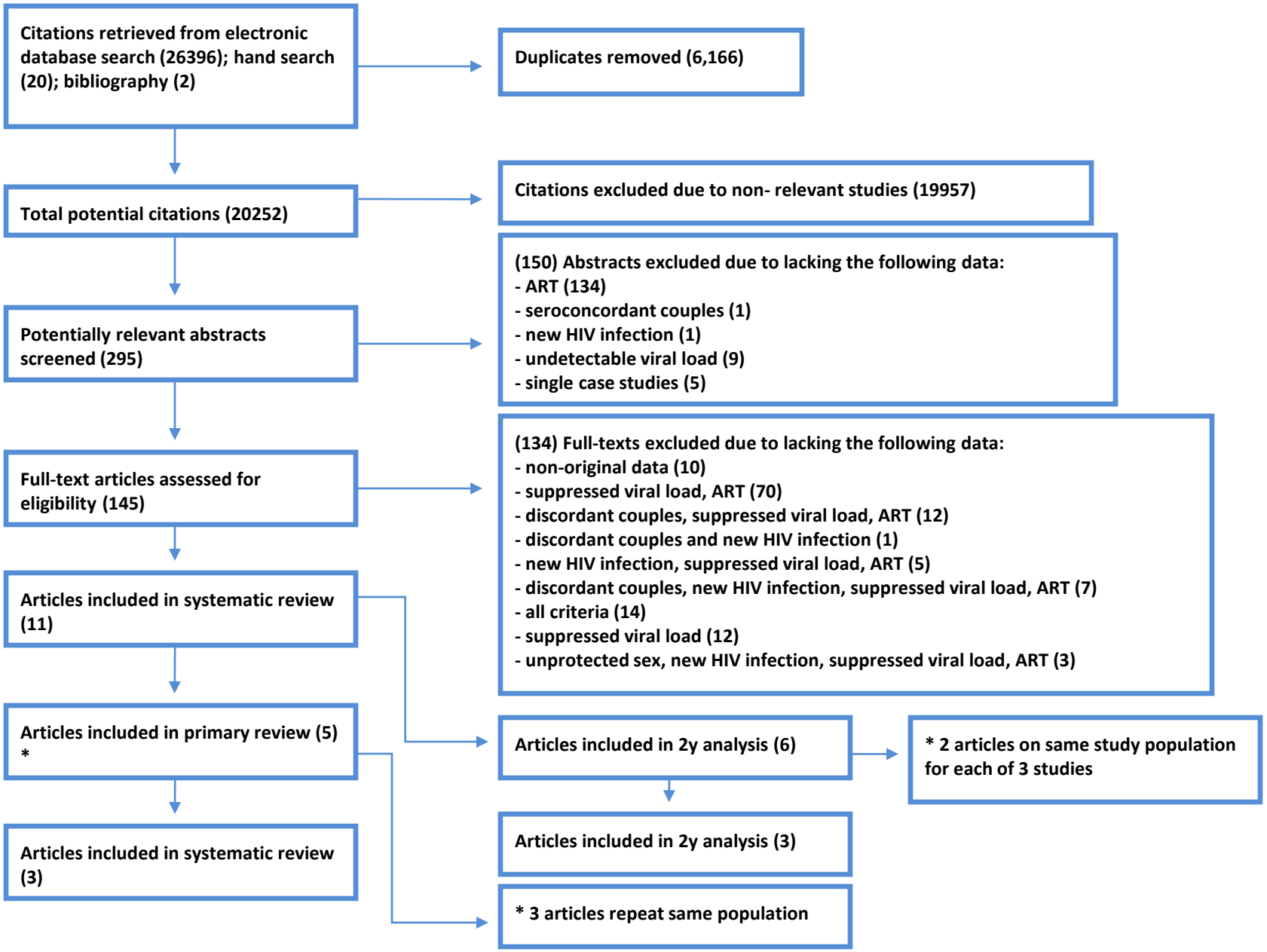

Citations retrieved from electronic database search (26396); hand search (20); bibliography (2)
Duplicates removed (6,166)
Total potential citations (20252)
Citations excluded due to non- relevant studies (19957)
Potentially relevant abstracts screened (295)
(150) Abstracts excluded due to lacking the following data:
- ART (134)
- seroconcordant couples (1)
- new HIV infection (1)
- undetectable viral load (9)
- single case studies (5)
Full-text articles assessed for eligibility (145)
(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)
Articles included in systematic review (11)
Articles included in primary review (5) *
Articles included in 2y analysis (6)
* 2 articles on same study population for each of 3 studies
Articles included in 2y analysis (3)
Articles included in systematic review (3)
* 3 articles repeat same population

Table 1a. Characteristics of included prospective cohort studies

Studies	Method/ type of study	Study setting	Enrol-ment Period	Age	Gender/ sexual orientation of HIV+ partner	Type of cART	Freq. of HIV test	Freq. of VL measur e	VL limit of detect-ion (copies /ml)	VL (copies/ ml)
Confirmed Viral Load										
Melo 2008	Retrospective/ prospective cohort	Single centre in Spain	Feb 2000 – Jan 2006	Not reported	Heterosexual 67 (72%) women, 26 (28%) men	Zidovudine, lamivudine, nelfinavir, efavirenz	6 months	Not reported	50	Median: 24082 for transmitter 4583 for non-transmitter All undetectable on ART
Del Romero 2010	Cross sectional and prospective cohort	Single centre in Brazil	1989-2008	Median: Women 29 Men 32	Heterosexual 113 (17%) women, 535 (83%) men	Not reported	6 months	Not reported	500 until 1999, 50 thereafter	Median: 6402 for non ART, 5367 for mono/dual therapy, Not detectable for combined treatment
Reynolds 2011	Retrospective cohort	Multi mobile clinics in Uganda	2004-2009	HIV-partner: 5% 15-19 18% 20-24 29% 25-29 48% 30+	Heterosexual 105 (42%) women, 145 (58%) men	Not reported	12 months	6 months	400	6mo: 71%<400, 29%<2000 12mo: 85%<400, 15%>2000 24mo: 100%<400

Table 1b. Characteristics of included prospective cohort studies

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

Table 2. Risk of bias assessment of included observational studies

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

Table 3. Risk of bias assessment of included RCT

Studies	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Cohen 2011	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes

Table 3a. Data reported in included studies

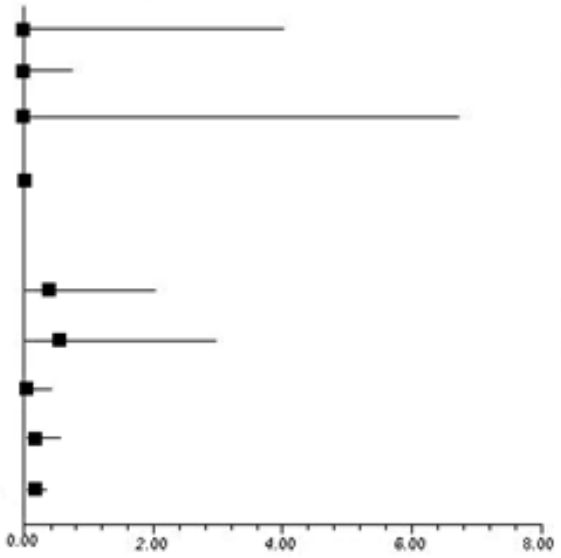
Studies	Total enrollment	Analysed	Follow-up duration	Total follow-up (person-years)	Male circumcision of HIV-partner	Male circumcision of HIV+ partner	Condom use	Index case on cART	HIV transmission on cART	HIV transmission not on cART	HIV transmission rate			
											Per 100 person-years (Overall)	Per 100 person-years (on cART)	Per 100 person-years (Not on cART)	Per 1000 sex acts (Overall)
Confirmed Viral Load														
Melo 2008	93	93	Median: 25.5 mo transmitter; 22.34 mo non-transmitter	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

Table 3b. Data reported in included studies

Studies	Total enrollment	Analysed	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			
											Per 100 person-years (Overall)	Per 100 person-years (on cART)	Per 100 person-years (Not on cART)	Per 1000 sex acts (Overall)
Unconfirmed Viral Load														
Donnell 2010	3408	3381	Median: 8.2 months after ART	4558 for those not on ART, 273 for ART	55%	34%	No condom use: 6.2% prior to ART, 3.7% after ART	349	1	102	2.13 (1.76-2.58)	0.37 (0.09-2.04)	2.24 (1.84-2.72)	Not reported
Apondi 2011	62	62	3 years	Not reported	Not reported	Not reported	Condom use: 74% with discordant set, 55% with unknown and 46% with concordant set	62	1	Not applicable	0.5(0.01-3.0)	0.5(0.01-3.0)	Not applicable	Not reported
Cohen 2011	1763	1775	Median: 1.7 years	1585.3* in early therapy group; 169.5* delayed-therapy group who started ART; 1397.7* for delayed-therapy group when not on ART	19% of early therapy group and 14% in delayed therapy group	19% of early therapy group and 14% in delayed therapy group	Among HIV infected participants, 96% early-therapy group and 95% delayed-therapy group reported 100% condom use	893	2	27	0.9 (0.6-1.3)	0.1 (0.0-0.4)	2.1 (1.5-3.1)	Not reported

Figure 2a. Forest plot of HIV transmission rates per 100 person-years of confirmed and unconfirmed viral loads

Study name	Event / person years	Rate	Lower limit	Upper limit
Confirmed viral load				
Melo 2008	0 / 90	0.00	0.00	4.02
Del Romero 2010	0 / 492	0.00	0.00	0.75
Reynolds 2011	0 / 53	0.00	0.00	6.72
Subtotal		0.00	0.00	0.05
Unconfirmed viral load				
Donnell 2010	1 / 273	0.36	0.01	2.02
Apondi 2011	1 / 185	0.54	0.01	2.97
Cohen 2011	2 / 1755	0.11	0.01	0.41
Subtotal		0.18	0.05	0.40
Total		0.14	0.04	0.31



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; seroconverion 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

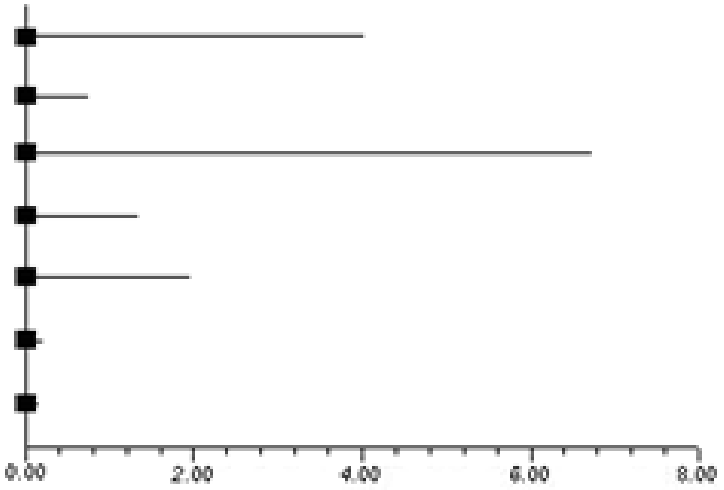
4 transmissions all occurred within 6 months of starting ART; VL likely not suppressed.

Removing these transmissions via sensitivity analysis to be c/w Swiss Statement requirements.

1. Donnell et al. Lancet 2010; 375:2092-2098.
2. Apondi et al. AIDS 2010; 25(10):1317-27.
3. Mastro et al. AIDS 2011; 25: 2049–2051
4. Eshleman et al. J Infect Dis 2011; 1918-1926

Figure 2b. Forest plot of HIV transmission rates per 100 person-years, excluding unconfirmed viral loads

Study name	Event / person years	Rate	Lower limit	Upper limit
Melo 2008	0 / 90	0.00	0.00	4.02
Del Romero 2010	0 / 492	0.00	0.00	0.75
Reynolds 2011	0 / 53	0.00	0.00	6.72
Donnell 2010	0 / 273	0.00	0.00	1.34
Apondi 2011	0 / 185	0.00	0.00	1.97
Cohen 2011	0 / 1755	0.00	0.00	0.21
Total		0.00	0.00	0.01



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

**** Accepted for publication in PLOS ONE ****

Acknowledgements

Search strategy librarian

• Angela Eady

Citation reviewer

• Elena Ivanova

York University

• Eric Mykhalovskiy, PhD

Canadian AIDS Treatment Information Exchange

• James Wilton

Canadian HIV/AIDS Legal Network

• Cecile Kazatchkine