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EVIDENCE BRIEF

Human immunodeficiency virus (HIV) Sexual Transmission Risk with Bacterial Sexually Transmitted Infection (STI) Co-infection

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Key Messages

- Co-infection with chlamydia, gonorrhea or syphilis may result in transient increases in viral load (VL), but these increases are not statistically significant in individuals who are on antiretroviral therapy (ART) and virally suppressed.
- Co-infection with chlamydia, gonorrhea or syphilis in individuals who are on ART and virally suppressed has not resulted in HIV sexual transmission events in published studies of serodiscordant couples.
- Future research is needed to address the sexual transmission risk of HIV in the context of a bacterial STI co-infection under scenarios of varying adherence to ART and varying VL levels that may be more applicable to the general population.

Issue and Research Question

Risk of sexual transmission of HIV with bacterial STI co-infection

Evolving evidence on the risk of sexual transmission of HIV has led to recent statements from both Canada and the United States (US) in 2017 asserting that people living with HIV who are both consistently taking antiretroviral therapy (ART) and virally suppressed have effectively no risk of transmitting HIV to their sexual partners.[1,2] A 2018 Canadian systematic review reported a "negligible risk of sexual transmission of HIV when an HIV-positive sex partner adheres to antiretroviral therapy and maintains a suppressed viral load (VL) of less than 200 copies/mL measured every 4-6 months."[3]

Previous similar statements, however, had further qualified the negligible risk of HIV transmission associated with appropriate treatment and viral suppression with a third condition that there were no other sexually transmitted infections (STIs) as studies had shown increases in HIV VL with STI co-infection, and particularly with syphilis co-infection.[4-6] Despite the removal of this STI co-infection caveat in the 2017 Canadian and US statements, other jurisdictions, such as New York, continue to recommend that contacts of an HIV-STI co-infected case be followed-up for both HIV and STIs, regardless of the viral suppression status of the case.[7] Public health practitioners need to understand the evidence on the risk of sexual transmission of HIV in the context of co-infection with a bacterial STI, and how to apply that evidence in order to appropriately assess and manage sexual contacts of co-infected individuals. Public Health Ontario (PHO) conducted a literature synthesis on the impact of bacterial STI co-infection on the sexual transmission risk of HIV.

> **This evidence brief answers the question: "What is the evidence regarding the impact of reportable bacterial STIs (Chlamydia trachomatis [Ct], Neisseria gonorrhoeae [Gc], and infectious syphilis [Tp]) on the risk of sexual transmission of HIV from individuals on ART?"**

Issues that were out of scope for this evidence brief included: i) the legal context of HIV case management (both criminal and public health law); and ii) the impact of non-reportable STIs (e.g., herpes simplex virus, human papillomavirus [HPV]), as public health would not receive notification of such infections.

Background

HIV case and contact management in Ontario

In Ontario, each board of health is required to provide public health management of HIV cases and contacts in accordance with the Ontario Public Health Standards.[8] Instructions on how to implement these requirements are outlined in the *Sexual Health and Sexually Transmitted/Blood-Borne Infections Prevention and Control Protocol*, 2018.[9] Case and contact management in the Protocol includes providing disease-specific education and general preventive sexually transmitted and blood-borne infection (STBBI) counseling.

In addition, the Council of Ontario Medical Officers of Health HIV Workgroup developed the *Public Health Approach to HIV Case Management* to provide additional guidance to Medical Officers of Health (MOHs) on the management of HIV cases.[10] This management guide also describes situations that may require consultation with the MOH or Associate MOH, including co-infection with a STI or blood-borne infection.[10]

Prevalence and risk of STIs among people with HIV

In Ontario, in 2015, there were an estimated 16,110 diagnosed people living with HIV, and of those people, it was estimated that 87% were linked to care, 81% were on ART, and 80% were virally suppressed.[11] Co-infection with both HIV and STI is not uncommon, and such individuals may or may not be virally suppressed despite engagement in care and being on treatment. A 2011 systematic review of studies measuring STI co-infection among people living with HIV found a median point prevalence estimate of 12.4% for any STI, and median prevalence estimates of 5.0% for Ct, 9.5% for Gc, 9.5% for Tp.[12] These overall STI prevalence estimates were similar in studies comparing HIV-infected individuals on ART and those not on ART.[12] A 2018 US study involving an HIV clinic-based cohort (6,762 participants attending for routine care and on ART) found cumulative incidence rates of 1.8, 1.7, and 0.8 per 100 person-years for Ct, Gc and Tp, respectively.[13] Of those with at least one STI episode, 41.8% had a detectable VL within one month before or after the STI diagnosis, and 14.6% had a VL ≥ 1500 copies/mL.[13]

Methods

Our strategy for identifying peer-reviewed journal articles for inclusion in this evidence brief was modelled after the search methods used in a 2015 systematic review and meta-analysis by Champredon et al. on the effect of STIs on HIV VLs in individuals on ART.[14] However, we broadened the search strategy used by Champredon et al. by including additional relevant subject headings and keywords. Using the modified search strategy, we searched for primary studies published after the search conducted by Champredon et al. (August 12, 2014). We also used this expanded search term strategy to retrieve review articles published prior to August 2014, without date limitation to validate and supplement the findings of the 2015 systematic review.

Five databases (MEDLINE, Embase, CINAHL, Cochrane Library, and PubMed) were searched by PHO Library Services on July 30th and August 1st, 2018. The search strategies included terms related to antiretroviral therapy, human immunodeficiency virus, seroconversion, viral load, and bacterial sexually transmitted infections (specifically Ct, Gc and Tp). A search of the grey literature was conducted by PHO Library Services on August 27th, 2018, using a simplified version of the database search strategy described above and custom search engines for Canadian and International public health organizations, as well as Google. A detailed description of the database and grey literature search strategies are available upon request from PHO.

Identified articles were eligible for inclusion if they: a) were published in English; b) evaluated sexual transmission of HIV in the context of a reportable STI co-infection; and c) reported either HIV VL

measurements around the time of STI diagnosis or HIV transmissibility among serodiscordant couples. Articles that exclusively focused on HIV in terms of non-reportable STIs (e.g., herpes simplex virus, HPV) and studies that focused on the effectiveness of pre- or post-exposure prophylaxis (PrEP/PEP) were excluded.

Two reviewers independently screened titles and abstracts to identify articles for full-text review which were subsequently retrieved and reviewed. Consensus on inclusion of full text articles was achieved through discussion. Relevant information was extracted from each article by the same two reviewers.

The reference lists of included studies were reviewed to identify additional eligible publications. Finally, based on known on-going studies of serodiscordant couples that had final results pending publication, we manually searched for study-specific articles published after our literature search.

Two reviewers independently conducted quality appraisal of the included full-text articles. PHO's Meta Quality Appraisal Tool (MetaQAT) was used to assess the relevancy, reliability, validity, and applicability of the articles. Discrepancies in quality appraisal outcomes between the reviewers were resolved by consensus. More information on quality appraisal is available upon request.

Main Findings

Search results

The primary literature search identified 1,787 peer-reviewed journal articles. After duplicates were removed, 1,550 remained, of which 660 were published since August 2014; the remainder were review articles published between 1988 and 2014. Title and abstract screening identified 42 articles for full-text review, of which three met the inclusion criteria (two primary studies[15,16] and one review[17]).

The grey literature search identified one article[24] and two conference proceedings[23,25] that met the inclusion criteria. A review of reference lists identified one additional study[22] that met the inclusion criteria. These papers were not retrieved by database searches because they did not contain keywords related to STI co-infection, nor were they indexed with subject headings related to STIs other than HIV. However, upon full text review, these studies were found to include discussions of STI co-infection within the full text.

Systematic review and meta-analysis on the impact of STIs on HIV transmission risk among individuals on ART

A 2015 systematic review and meta-analysis by Champredon et al. summarized 14 studies that assessed sexually active HIV-positive individuals on ART with and without bacterial STI co-infections (Ct, Gc and Tp).[14] The reviewed studies evaluated HIV VLs measured from three different body sites (i.e., blood plasma, cervicovaginal, and semen) among a total of 2,835 participants from the US, Brazil, Australia, France, Denmark, Kenya, Italy and the United Kingdom.

Results of the meta-analysis showed a non-significant increase in the VL of HIV-positive individuals with any bacterial STI co-infection compared to those without an STI. Individual average effect-sizes by STI and anatomical site for Ct, Gc and Tp all showed non-significant increases in VLs.

Limitations of this systematic review and meta-analysis: lack of assessment of gender effects, the exclusion of studies that measured rectal VL, and inclusion of studies that did not assess adherence to ART. The number of VL measurements included in the meta-analysis was highest for Tp (660) compared to Ct (18), and Gc (20). The authors concluded that it is unlikely for an STI to change the suppressed VL of an HIV-infected individual on ART, but could not rule out the possibility that certain bacterial STI co-infections (or certain combinations of bacterial STIs and anatomical site) may have a larger impact.

Other evidence on the impacts of STIs on HIV viral load levels

Chun et al. conducted a narrative review in 2013 on the effect of STIs on HIV transmission.[17] The 2013 review identified primary studies (four on Tp, one on Ct and Gc) that were not included in the 2015 systematic review and meta-analysis described above. Results from the primary studies described by Chun et al. included:

Syphilis:

Palacios et al**.** found that among 44 patients with an undetectable VL before Tp infection, 11 (25%) had an increase in plasma VLs (mean HIV VL increase of 1.46 $\log_{10}$, interquartile range: 0.32-3.21 $\log_{10}$). However, among all 76 participants with both detectable and undetectable initial VLs, those on ART were significantly less likely to demonstrate an increase in their HIV VL while co-infected with Tp compared to those not on ART (p=0.01).[18]

Buchacz et al. found that, among all 36 HIV-infected individuals with Tp co-infection, there was an overall statistically significant increase in VL from before to during co-infection (mean increase 0.21 $\log_{10}$, p=0.02); among the 10 individuals with undetectable VL prior to Tp co-infection, two had non-significant increases in VL (p=0.5) and among the 21 individuals on ART, seven had non-significant increases in VL (p=0.19).[4]

Two small studies found no effect of Tp on HIV VL.[19,20]

Gonorrhea and Chlamydia:

Kelley et al. found that among 80 men who have sex with men (MSM), rectal Ct or Gc infections were not significantly associated with increased HIV VLs in rectal secretions.[21]

A 2018 retrospective Canadian study by Lang et al. described 194 patients with positive Tp results among 2,448 HIV positive clinic patients with Tp testing results, of whom most were MSM.[15] Routine Tp serology and HIV VL measurements were conducted every four months; a supressed VL was defined as having <40 copies/mL. Comparison of HIV VL measurements at Tp diagnosis and at follow-up appointment after treatment of Tp showed no significant change in HIV VL (p=0.47), regardless of the

stage of Tp infection. Other potential clinical and behavioural factors were not explored due to the retrospective nature of the study and the fact that data collection was limited to chart reviews.

A cross-sectional study by Storim et al. published in 2018 evaluated rectal inflammation and HIV-RNA rectal shedding in patients with and without Ct and Gc infections; 112 HIV-positive MSM enrolled clinic patients, presenting for either asymptomatic high-resolution anoscopy or with an acute proctological problem, were offered testing for rectal Ct/Gc.[16] The majority (90.9%; 100/110) of participants were on ART; of these, 88.0% (88/100) were virally supressed (<40 copies/mL). Rectal HIV RNA shedding was observed in 2.4% (2/83) of all individuals with suppressed plasma VL at <40 copies/mL at presentation, but none of the 13 individuals with Gc or Ct co-infection and suppressed plasma VL had a detectable rectal VL. The authors acknowledged that this population had a high rate of STIs and therefore other non-investigated STIs could have had unknown effects on the results.

Impact of bacterial STIs from HIV transmission studies

Two major observational cohorts of serodiscordant couples assessed the risk of sexual transmission of HIV, including during episodes of STI co-infection in the positive partner. The findings of these studies are described below.

THE PARTNERS OF PEOPLE ON ART – A NEW EVALUATION OF THE RISKS (PARTNER)

PARTNER was a prospective observational cohort study involving HIV serodiscordant couples (548 heterosexual and 340 MSM) recruited from 75 clinical sites in 14 European countries. The goal of the study was to evaluate the cumulative incidence of within-couple HIV transmission "during periods of sex without condoms and when the HIV-positive partner had HIV-1 RNA load less than 200 copies/mL".[22]

In the 1,238 couple-years of follow-up, there was one episode of Gc in the HIV-positive male partner of a heterosexual couple, and 20 episodes of Gc in HIV-positive partners of MSM couples. Less than five Ct co-infections and zero Tp co-infections were reported. There were 11 non-linked seroconversions (i.e., new HIV infection in the previous HIV-negative partner that was confirmed to be unrelated to the HIV virus of the HIV-positive partner by phylogenetic comparison) and zero linked seroconversions (i.e., there were no identified transmissions from the HIV-positive partner to their HIV-negative partner). The rate for linked transmission through any condomless sex with the HIV-positive partner taking ART with VL <200 copies/ml was zero, with upper confidence limit of 0.3 per 100 couple-years. Based on reported sexual encounters, the authors calculated an upper confidence limit of 2.2 transmissions per 100 couple-years from condomless receptive anal sex with ejaculation.

While the study did not describe whether the reported STIs occurred at the same time as sexual activities with higher transmission risk, there were no linked transmissions of HIV despite occurrences of Gc and Ct in HIV-positive partners. The HIV-positive study participants were motivated individuals with a median of 7.5 years on ART (>90% self-reported >90% adherence) who maintained a suppressed VL.

PARTNER 2 – EXTENSION STUDY

To further elucidate the risk of sexual transmission of HIV from MSM couples only, the PARTNER study continued with 783 MSM couples. Preliminary unpublished results of this extension study (PARTNER 2) were presented at the 2018 International AIDS Conference.[23]

During 1.6 years of follow-up, there were 15 unlinked seroconversions in the HIV-negative partners and zero linked seroconversions. The overall upper limit of the 95% confidence interval for acquiring HIV in this extension study was 0.23 per 100 couple-years. During this period, 23% of HIV-negative and 27% of HIV-positive partners were diagnosed with an STI (unspecified types), corresponding to 135 couple-years of observation with an STI and no linked HIV seroconversions. The upper 95% confidence limit for HIV transmission from any sexual activity while co-infected with an STI was 2.74 per 100 couple-years. This is ten-fold higher than the overall upper confidence limit (0.23 per 100 couple-years) and is likely due to the lower number of couple-years of follow-up time with an STI co-infection included in the study.

OPPOSITES ATTRACT

Opposites Attract was a prospective observational cohort study involving 358 homosexual male serodiscordant couples who were recruited from clinics in Australia, Bangkok, and Rio de Janeiro and followed from 2012 to 2016 to evaluate within-couple HIV transmission risk.[24]

Based on preliminary data released at the 2017 International AIDS Society Conference on HIV Science (and available at the time of our literature search), among HIV-positive partners at baseline, 80% (274/343) were on ART and 78% (267/343) had a VL <200 copies/ml. The STI prevalence (unspecified types) was 14.3% in HIV-positive partners and 11.7% in HIV-negative partners.[25]

Final results from Opposites Attract were published after our library literature search date, but obtained through manual searching and included in our review.[24] There were three unlinked HIV seroconversions observed and zero linked seroconversions during the study period. Based on 16,889 acts of condomless anal intercourse among couples, including periods when the HIV-positive partner had an STI co-infection, the overall incidence of linked HIV transmissions per 100 couple years of follow-up was 0 (95% confidence interval (CI) 0-0.62).[24]

There were 115 diagnoses of any bacterial STIs (including infectious Tp, rectal and urethral Gc, and rectal and urethral Ct) in the HIV-positive partner and 85 diagnoses in the HIV-negative partner.[24] There were 56.4 couple-years of follow-up with any STI diagnosed in the HIV-positive partner, which included 1391 condomless anal intercourse acts, with zero linked transmissions (upper limit of one-sided 95% CI for HIV incidence = 6.55 per 100 couple-years of follow-up).[24] However, over the study, 32.1% of HIV-negative partners had taken daily PrEP at some point, affecting their HIV transmission risk. Given the high rate of PrEP use among the HIV-negative partners in the study, sub-analysis of incidence was conducted for periods when PrEP was not used (HIV-negative partner), VL <200 copies/mL (HIV-positive partner), and with any STI diagnosed in the HIV-positive partner. Here, there were zero linked transmissions over 15.4 couple-years of follow-up (upper limit of one-sided 95% CI for HIV incidence = 23.97 per 100 couple-years of follow-up). [24]

Discussion and Conclusions

Summary of evidence of VL measurements around the time of STI co-infection

For evidence on HIV VL measures with bacterial STI co-infection, we included one systematic review and meta-analysis[14], one summary of primary studies described in a narrative review[15], and two primary studies[15,16] published after the systematic review was conducted. The overall and STI by site estimates in the 2015 systematic review and meta-analysis showed non-significant increases in VL in the presence of Ct, Gc or Tp co-infection; however, VL measurements from Gc or Ct co-infection studies were limited, and no studies measured rectal VL levels.[14] It is unclear whether the addition of rectal VL measurements would change their findings, as the studies by Kelley et al. and Storim et al. did not find a relationship between rectal bacterial STIs (Gc or Ct) and rectal VL among men on ART.[16,21]

Results from two of the four syphilis studies included in the 2013 narrative review by Chun et al.,[15] that were not included in the 2015 Champredon et al review, demonstrate that it is possible for individuals who were previously virally suppressed to have a detectable VL in the context of Tp co-infection. However, overall findings from both studies also found that the increases in VL were not statistically significant among individuals on ART.[4,18] More recent evidence from Canada did not find any significant increases in plasma VL with syphilis co-infection when individuals were on ART and virally suppressed.[15] Additional high quality evidence that systematically measures VL (plasma and genital/rectal secretions) before, during, and after Ct, Gc and Tp co-infections with HIV, in the context of adherence to ART over that time, are needed.

Summary of evidence of sexual transmission from couples studies

From the studies of two cohorts of serodiscordant couples assessing HIV transmission, no linked HIV transmissions occurred despite STI coinfections in the HIV-positive partner during their follow-up periods.[22-24] While no transmissions occurred, higher levels of risk cannot be excluded given the higher upper limit 95% CIs for estimates during STI co-infection.

Syphilis co-infections were only documented in the Opposites Attract study. Therefore, sexual transmission risk among heterosexual serodiscordant couples with Tp co-infection is lacking, but is unlikely to be higher than among MSM couples. Additionally, the prevalence of STIs in the PARTNER study was lower than described in other studies.[22] Therefore, results from PARTNER may not be representative of the actual risk in individuals who are less closely monitored, less adherent, and/or have more frequent STI co-infections. Sub-analysis results from Opposites Attract with no PrEP use and suppressed viral load address the high usage of PreP in the cohort, but significantly reduce the couple-years of follow-up for analysis, increasing the upper limit 95% CI for HIV incidence.

Limitations

The most definitive data on the risk of sexual transmission of HIV in the context of STI coinfection would ideally be from prospective cohort studies. However, only two such cohorts were available for inclusion, of which only one addressed heterosexual serodiscordant couples, and only one addressed co-infection with infectious syphilis. Both cohorts had limited couple-years of follow-up while the HIV-positive partner had an STI and neither cohort was powered to detect a reduction in incidence in the context of a bacterial STI. As well, study participants in both cohorts may not be generalizable to the broader population in terms of having high adherence to monitoring and treatment. Research from other studies has shown that individuals with HIV who are engaged in care and on treatment may not necessarily be virally suppressed and may have VLs in ranges associated with an increased risk of transmission.[13,26] Additionally, two recent studies demonstrate that high-risk sexual activity is not uncommon amongst individuals who are not virally suppressed, and that particularly for youth, STIs were more likely to occur when individuals were not taking their prescribed ART and when they had increases in their VL.[27,28] Future research is needed to address the sexual transmission risk of HIV in the context of a bacterial STI co-infection under these scenarios of varying adherence to ART and varying VL levels that may be more applicable to the general population.

Our search strategy was adapted from the methods used by Champredon et al. which involved including their STI key terms in our search strategy; however, a number of relevant studies were excluded from our search results because the studies did not use STI key terms in their indexing even though the paper discussed STI co-infection. Some relevant studies that were missed in our peer-reviewed literature search were subsequently identified in our grey literature search, review of conference proceedings and manual searching. However, it is possible there are other relevant studies that were not included in our results.

Implications for Practice

- The Ontario *Sexual Health and Sexually Transmitted/Blood-borne Infections Prevention and Control Protocol* provides guidance to public health units on follow-up of reported cases of STIs in HIV-infected individuals, which includes assessment of the individual's HIV care history as part of case and contact management.[9]

- Working with the HIV-infected individual and their health care providers, a review of VL testing history and results is important for routine bacterial STI case investigations. Information on VL testing history around the time of STI diagnosis informs the overall risk assessment for HIV sexual transmission risk. Other factors that affect the overall transmission risk include condom use, the presence of other (non-reportable) genital infections, and sexual practices.

- When HIV-infected individuals have received regular testing and treatment, and are consistently virally suppressed, evidence from two cohort studies of serodiscordant couples suggests that any increases in VL associated with Ct, Gc or Tp co-infection do not appreciably increase the HIV sexual transmission risk as no linked transmission events were observed despite bacterial STI co-

infections. Based on this evidence, contacts of an individual with consistently suppressed VL and with Ct, Gc or Tp co-infection would generally not be considered contacts of HIV, however further data are needed.

- In general, public health unit follow-up of individuals with an STI aims to ensure that all contacts receive preventive counseling regarding all STBBIs, including HIV, and an explanation of testing and treatment options.

- Because contact tracing for STIs is often a shared responsibility involving health care providers, the patient and public health units, it is important to ensure knowledge dissemination also occurs to those outside of public health with respect to HIV transmission risks in the context of bacterial STI co-infections.

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Specifications and Limitations of Evidence Brief

The purpose of this Evidence Brief is to investigate a research question in a timely manner to help inform decision making. The Evidence Brief presents key findings, based on a systematic search of the best available evidence near the time of publication, as well as systematic screening and extraction of the data from that evidence. It does not report the same level of detail as a full systematic review. Every attempt has been made to incorporate the highest level of evidence on the topic. There may be relevant individual studies that are not included; however, it is important to consider at the time of use of this brief whether individual studies would alter the conclusions drawn from the document.

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