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The effect of sexually transmitted co-infections on HIV viral load among individuals on antiretroviral therapy

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A large body of evidence suggests that antiretroviral therapy (ART), particularly with newer treatment regimens, markedly reduces the risk of sexual transmission of HIV(1). This inspired the idea of ART as prevention: aggressive programs that identify and treat HIV-positive individuals could substantially reduce HIV incidence at the population level, by reducing the infectiousness of HIV-infected individuals (2). However, increased infectiousness when treated individuals are co-infected with one or more other sexually transmitted infections (STIs) could potentially undercut the effectiveness of treatment as prevention programs.

Indeed, many STIs have been associated with higher risks of both HIV acquisition and sexual transmission. Increased HIV transmission may be underpinned by higher HIV viral load resulting from larger concentration of HIV-infected immune cells in genital secretions induced by an inflammatory response and/or additional pathways caused by genital ulcers. Similarly, inflammatory STIs, by recruiting immune cells, may provide additional targets for HIV virions, increasing HIV acquisition risk. Ulcerative STIs may present additional entry points for HIV infection.

In the past, studies on HIV-STI interactions have been conducted mostly on individuals *not* receiving ART(3). However, less is known about the impact of STI co-infections on HIV shedding from individuals who are on ART. STI prevalence is high among HIV-infected individuals (4) and the proportion of these individuals on ART is quickly rising, from less than 500,000 in 2003 to nearly 13 million worldwide in 2013 (5). Thus, any potential increase of HIV infectiousness due to STI co-infections among treated individuals could have important epidemiological consequences as treatment as prevention becomes more widespread.

Our goal was to review and synthesize all published scientific evidence to assess the impact of STIs co-infection on HIV infectiousness among patients on ART (6). To that end, we systematically reviewed all the scientific literature and searched for studies that published data relevant to HIV infectiousness for individuals on ART in presence of another STI co-infection. We included STIs commonly discussed in the context of HIV transmission: *Chlamydia trachomatis*, chancroid, any type of Human Papilloma Virus, Herpes Simplex Virus 2, *gonorrhoeae*, syphilis and Trichomoniasis. We also included bacterial vaginosis and candidal vaginitis, although these are not known to result directly from sexual transmission, and urethritis, which can be associated with more than one STI.

This search retrieved 3,020 potential studies, but only 14 had data that passed all our selection criteria. All 14 studies provided HIV infectiousness data in the form of HIV viral load change (none considered sexual transmission within sero-discordant partnerships) and represented 4,607 visits from 2,835 unique individuals. Hence, we estimated the difference of HIV viral load between patients only infected with HIV and patients who were co-infected with another STI. These data were incorporated in a statistical model in order to summarize across all 14 studies the overall effect of STI co-infections on HIV infectiousness among patients on ART.

Impact of STIs co-infection on HIV infectiousness ART patients

We found that, on average, HIV viral load of an individual on ART was 30% higher in the presence of an STI co-infection (the credible interval of this statistical result spans from a reduction of HIV VL of 75% to an increase by 6.8 times).

Disentangling the many interacting factors at play is challenging because of several effects that :

- HIV viral load response to ART is specific to both the drugs regimen and also to patient's gender;
- Numerous , and not necessarily consistent, methods are used to sample and quantify HIV viral load;
- HIV viral load measurements can vary between anatomical sites (blood, genital secretions, etc.) within an infected individual;
- HIV viral loads exhibit substantial temporal variation.

Our statistical model coherently takes into account this complexity, but this comes at the price of requiring a large amount of data in order to have a small uncertainty attached to its estimates (and hence have a more definitive conclusion).

So, one of the main conclusion of our study was that there is not enough published data to really ascertain the impact of STI co-infections on HIV infectiousness for a patient on ART.

Although our study provided some evidence for a small effect of STI co-infection on viral loads, we could not rule out the possibility of no effect, or the possibility of a moderately large effect (the upper credible interval states nearly a 7 times increase of HIV viral load). Importantly, we were also not able to rule out the possibility that certain STIs (or certain combinations of STIs and anatomical site) have a much larger effect. Nonetheless, based on our analysis, we cautiously posited that ART manages—on average—to sustain its effectiveness at keeping HIV viral loads low during STI co-infection episodes, at the anatomical sites considered in this review (blood plasma, semen and cervicovaginal), and thus would be expected to maintain its effectiveness at preventing transmission.

There are several limitations to our results:

- Not all studies tested for all STIs, hence we may have misclassified some co-infected individuals (for example, a patient infected with syphilis enrolled in a study testing only for chlamydia and gonorrhea would be considered as HIV infected only)
- Adherence to ART was rarely reported or measured in the studies we used. Hence we may have wrongly attributed increase of HIV viral load to a co-infection whereas it could have been caused by non-adherence to HIV treatment.
- Most HIV viral load observations included in this meta-analysis were measured in blood plasma, not in genital secretions, which may limit the interpretation of our effect size to actual sexual transmission risk. Indeed, while plasma and genital HIV viral loads are correlated, evidences of HIV compartmentalization in some treated patients where viral loads as measured in genital secretions remain compatible with a non-negligible risk of transmission despite very low blood plasma viral loads.

In conclusion, our findings suggest that, on average, ART maintains its effectiveness at controlling HIV viral load during STI co-infections. However, with currently available data, we cannot rule out the possibility that certain STI co-infections have a larger effect. More high-quality studies specifically aimed at investigating the impact of STI co-infection on HIV sexual transmission from individuals on ART are needed.

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