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Are associations between HIV and HPV transmission due to behavioural confounding or biological effects?

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The human immune deficiency virus (HIV) and human papillomavirus (HPV) are two heavy hitting sexually transmitted infections (STIs). HIV has crippled the social structures and economies of countries in Sub-Saharan Africa and has led to an unprecedented response in research and fund raising. The prevalence of HIV worldwide has mostly stabilised with the widespread availability of antiretrovirals, but the number of new infections that occur yearly is still unacceptably high. HPV is the most common STI globally, the necessary cause of cervical cancer and also leads to genitals warts and other male and female genital cancers. As expected, because of the common mode of transmission, co-infection rates are high. It has also been easy to show empirically that HIV co-infected individuals are more likely to have persistent HPV infections and are more likely to progress to HPV related disease.

Associations between prevalence of the one infection and incidence of the other have also been estimated empirically. Meta-analyses of the association between HPV prevalence and HIV acquisition and the association between HIV prevalence and new HPV detection have estimated a two-fold increased risk in both directions, after adjusting for individual-level behavioural factors such as marital status and the number of recent sexual partners. The studies argue that biological mechanisms may be responsible for these increased risks and hence primary prevention of the one infection may reduce incidence of the other, but they also concur that residual confounding due to behaviour at the sexual network level cannot be ruled out. We used an individual based model to shed some light on the matter.

We adapted an existing HIV-STI model, MicroCOSM (1), to include infection with 13 oncogenic HPV types (2). The model population represented the South African population by age and sex and there was individual level variation in sexual behaviour. The model was fitted to HIV and type-specific HPV prevalence data using a Bayesian approach. The model world represented the null hypothesis that infection with HIV does not increase susceptibility to or infectiousness of HPV, and vice versa.

Using 500 parameter combinations from the posterior distributions of the parameters for each HPV type, we simulated 500 cohorts similar in design to the studies that estimated transmission associations between HIV and HPV: individuals were tested for HIV and HPV every three months for three years. We used these simulated cohorts to perform statistical analyses similar to those conducted in the empirical studies. For example, the Cox proportional hazards model was used to calculate hazard ratios (HRs) to assess association. A HR of 1 means that there is no association between the 'exposure' and the 'outcome'. A HR of greater than one means that the 'exposure' increases the risk of the 'outcome'. Since these two STIs have the same mode of transmission, we expected the HR to be greater than one. We then controlled for the sexual behaviour indicators that most of the empirical studies adjusted for – age, marital status and number of new sexual partners in the preceding 6 months. As stated earlier, there were no direct biological effects on transmission of one infection in presence of the other in our model world. Hence, we expected the HRs after controlling for sexual behaviour to become closer to one.

The mean of the unadjusted HRs from the 500 cohorts for the association between HPV prevalence and HIV acquisition was 2.6 (95% CI 2.2-3.1). After adjusting, the HR remained significantly greater than one: HR=1.8 (95% CI 1.3-2.2). The mean unadjusted HR for the association between HIV prevalence and new HPV detection was 2.5 (95% CI 2.2-2.8) and also remained significantly greater than one after adjustment: HR=2.0 (95% CI 1.8-2.3). These adjusted estimates are very similar to the adjusted estimate of association found in meta-analyses and led us to the conclusion that direct biological effects on transmission are not necessary to reproduce the empirical estimates.

In our simulated data, we can calculate measures of network level effects. For example, we can calculate the size of each individual's sexual network by counting all individuals linked to each other at one point in time. This measure is extremely difficult to accurately obtain in observational studies. Also adjusting for this measure brought the associations much closer one, thus confirming the importance of network-level effects. These findings were consistent in multiple sensitivity analyses. We also included direct biological effects in our model world, and although simulated measures of association were greater than in the model world without these effects, they still compared well to empirical estimates.

To get back to our question: are associations between HIV and HPV transmission due to behavioural confounding or biological effects? We cannot rule out the possibility of biological mechanisms of increased transmission of one infection in presence of the other, but observed associations can be explained entirely by network-level effects that observational studies cannot account for.

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