Herpes simplex virus type 2: a key role in HIV incidence

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Many epidemiological studies have found a strong association between HSV-2 infection and HIV infection, including longitudinal studies in which it was known that the HSV-2 infection preceded the HIV infection [1]. However, two recent trials of suppressive therapy of HSV-2 with acyclovir (400 mg b.i.d) showed no reduction in HIV incidence [2,3]. Although this may simply reflect the difficulty of adequately suppressing HSV-2 reactivations with the drug regimen used, the results have led some to challenge the importance of HSV-2 infection as a risk factor for HIV [4].

In this issue, Tobian *et al.* [5] use data from the Rakai male circumcision trial to assess the effect of prevalent and incident HSV-2 infection on HIV incidence. They found that prevalent HSV-2 infection increased HIV incidence three-fold, and that men who acquired HSV-2 during follow-up had a six-fold risk of HIV incidence, in analyses adjusted for sexual behaviour.

These results are very similar to those found in a systematic review [1]. This included cohort and nested case–control studies up to 2004, and identified 18 that were adjusted for age and sexual behaviour. We have re-run the meta-analysis including more recent studies that fit the same criteria (Fig. 1). Six additional studies, as well as that by Tobian *et al.* [5], are included: one in men from the circumcision trial in South Africa [6]; two in women in the general population, in Uganda and Zimbabwe [7]; two in female sex workers in Kenya [8] and Tanzania [9]; and one in men who have sex with men (MSM) in the US [10]. Summary estimates of the relative risk (RR) show a strong and consistent association of prevalent HSV-2 and incident HIV after adjusting for age and measures of sexual behaviour [$RR_{women} = 3.4$, 95% confidence interval (CI) 2.4–4.8; $RR_{men} = 2.8$, 2.1–3.7; $RR_{sex\ workers} = 1.5$, 0.75–3.0; $RR_{MSM} = 1.6$, 1.2–2.0). In addition, a cohort study in Uganda found an adjusted rate ratio of 8.7 (1.1–67.2) for men and women combined [11].

The observational epidemiological evidence is strong, but Tobian *et al.* [5] question whether the association between HSV-2 and HIV is causal. Whereas confounding by sexual risk behaviour is likely in these studies, the effect persists after adjusting for sexual behaviour, and in their analysis this adjustment makes very little difference. In fact the association may be underestimated: some studies adjust for genital ulceration, which lies on the causal pathway between HSV-2 and HIV infection; and tests for HSV-2 lack specificity [12], which would also tend to bias the RR towards one.

The association between recent HSV-2 infection and HIV incidence is generally stronger than the association with prevalent HSV-2 infection [1,6–8,10]. This is biologically plausible as clinical and subclinical reactivations are most common shortly after HSV-2 infection [13]. However, results are difficult to interpret since, unless repeat testing is very frequent, most seroconversions for both infections occur within the same follow-up interval. It is therefore impossible to know which came first and therefore to distinguish HIV-2 infection increasing susceptibility to HIV from coinfections from the

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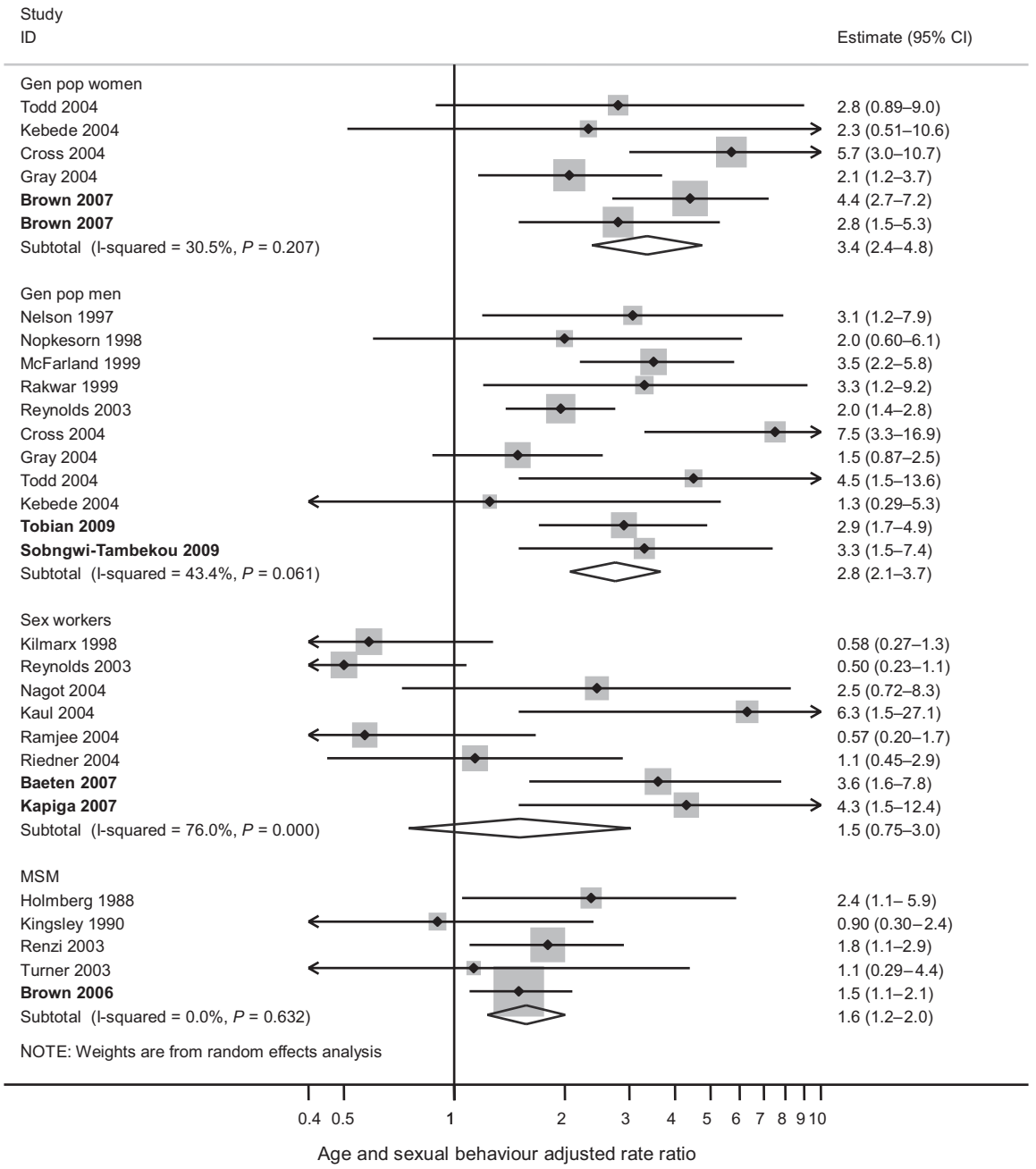

Fig. 1. Meta-analysis of the effects of prevalent HSV-2 on incident HIV infection. Studies from the previous meta-analysis are shown in normal type (see [1] for details). Additional studies are shown in bold. For each study the relative risk and 95% CI are shown. The size of the squares reflects the weight of the study. The summary relative risks are shown as diamonds.

same source. In the study by Tobian *et al.*, HSV-2 preceded HIV in three individuals, but the relative timing was unknown in nine. Some studies include all who seroconvert, even when the timing is unknown, which is likely to overestimate the association. Others exclude those for whom the timing is unknown, but this is also biased, since it excludes some who do acquire HIV, and none who do not, so is likely to underestimate the association. In Zimbabwe and Uganda, where the proportion excluded was small, recent HSV-2 infection was associated with a 4–8-fold increase in HIV incidence [7].

That prior HSV-2 infection increases susceptibility to HIV is thus well supported epidemiologically, and is also biologically plausible. However, the effect of HSV-2 on increasing susceptibility to HIV is only part of the story of their interaction, as genital ulceration and HSV-2

infection also increase HIV plasma load, HIV shedding, and hence transmissibility [14–16], and HIV infection increases the risk of acquisition of HSV-2, and the frequency and severity of reactivations [16]. Randomized controlled trials of HSV suppressive therapy with valacyclovir or high-dose acyclovir (800 mg b.i.d) have shown a significant reduction in genital and plasma HIV-1 RNA levels [17–20], although trials using lower-dose acyclovir (400 mg b.i.d) have tended to find less of an effect [21–23]. Recently announced results from the Partners in Prevention trial, which assessed the effect of suppressive therapy with lower-dose acyclovir on HIV transmission in discordant couples, showed no reduction in transmission [24].

HSV-2 is a common infection, with an estimated 536 million prevalent infections and 23.6 incident infections in 15–49-year-olds worldwide [25]. It is particularly prevalent in sub-Saharan Africa, reaching 70% in women and 55% in men [25]. If the association between HSV-2 infection and HIV is causal, then the proportion of HIV infections attributable to HSV-2 infection is high, estimated at 25–35% in Africa [26], and higher further into the epidemic [27]. It may both help explain the variable distribution of HIV in Africa [26], and provide one of our best hopes in prevention. Whereas to date it has not been possible to suppress HSV-2 adequately to prevent HIV acquisition or transmission, this may be possible with alternative drug regimens, or with a prophylactic HSV-2 vaccine, and such a vaccine could have substantial impact on HIV incidence [28]. The failures of the suppressive therapy trials, far from undermining the hypothesis, make the case for investment in a prophylactic HSV-2 vaccine even stronger.

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