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Sexual networks, HIV, race and bacterial vaginosis

In their recent article, Buvé et al. [1] argue that the higher HIV prevalence in ‘black populations’ is due, in large part, to racial differences in the vaginal microbiome. They base this argument on two findings. Firstly, bacterial vaginosis (BV) prevalence tends to be higher in black populations. Secondly, a number of studies have found an increased incidence of HIV following the diagnosis of BV.

We would like to advance a sexual network based explanation that we believe provides a better fit to the observed patterning of BV, sexually transmitted infections (STIs), sexual behaviour and race. We illustrate our argument by way of an analogy with John Snow’s insights into the forces underpinning cholera transmission in London in 1854. Snow [2] showed that persons whose houses were supplied by the water-pipes from the Southward water company had nine times the cholera-related mortality of those supplied by the Lambeth company. He argued that this was likely due to Lambeth, unlike Southward, drawing its water upstream from the sewage contamination. Facecal contamination of Southward’s water network put the Southward supplied houses at a high risk for exposure to entero-pathogens, including cholera and other faecal-oral transmitted illnesses such as typhoid. It is also possible that there could have been an association between typhoid and cholera infections at an individual level. However, the higher prevalence of cholera in Southward, together with the association between typhoid and cholera, would have best been explained by their common source (a contaminated water network) rather than by typhoid potentiating the transmission of cholera.

In a similar vein, black as opposed to white populations in the USA, UK and South Africa have been found to have higher prevalences of BV, HIV and other STIs [3–5]. The most parsimonious explanation in each case is that the black populations in these countries have more connected sexual networks [3,4,6]. This results from a number of factors, including the higher prevalence of partner-concurrency observed in black populations in each of these countries [3–5]. A more connected sexual network represents a higher risk network for all STIs entering the network [3].

These network-level properties could in turn explain a part of the observed higher prevalence of STIs in black populations in these countries. Network factors could also explain the observed association between different STIs at an individual level. Persons who contract one STI are by virtue of this more likely to be connected to a high-risk part of the sexual network and therefore more likely to contract other STIs. This effect is very difficult to control for in individual-level analyses [3]. Just as in the case of entero-pathogens in the Lambeth versus Southward populations, it would not be appropriate to assume that an association between STIs represented a causal relationship.

This sexual network-level explanation is supported by a variety of types of evidence. Studies at both individual [7,8] and ecological levels [9] have found an association between partner-concurrency and BV prevalence. BV prevalence is not just increased in blacks but in a range of nonblack populations such as Greenland, Aboriginals in Canada and Aymara speakers in Peru [10–12]. In each of these cases, the populations with a high BV prevalence had markers of higher-risk sexual behaviour such as a high prevalence of other STIs [10–12]. This is commensurate with the findings of a systematic review and meta-analysis of the relationship between sex and BV that found that various forms of multiple partnering were associated with an increased incidence of BV [13].

A further crucial problem for hypothesis by Buvé et al. [1] is that the available data suggest that black populations with low-risk behaviour and low prevalence of other STIs have a low BV prevalence. In our systematic review of the global epidemiology of BV, we found that Burkina Faso, which has a relatively low prevalence of HIV and other STIs [14], has a very low prevalence of BV, 6.4% and 7.9% according to two large, high-quality studies [15]. This fits with findings from studies from other sub-Saharan African countries that find considerable differences between HIV and STI prevalence between different black ethnic groups that is strongly associated with differences in sexual behaviour [5,6,16].

We have enough evidence to conclude that the vaginal microbiome varies considerably according to a myriad of factors considered at the levels of individuals, couples and sex networks. Longitudinal studies that sample the genital microbiomes of women and their partners from the time of sexual-debut and in multiracial communities are required to assess whether any of these variations can be attributed to race.

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Conflicts of interest

There are no conflicts of interest.
In response to the letter by Kenyon and Osbak [1], we first would like to clarify that we did not argue that the higher HIV prevalence in African populations is ‘in large part’ due to racial differences in the vaginal microbiota. We hypothesized that there may be differences in per sex act transmission probability of HIV between different populations that may in part be explained by differences in the composition of the vaginal microbiota [2]. We used the following line of argument in support of this hypothesis. Bacterial vaginosis and intermediate vaginal flora have been shown to increase the risk of HIV acquisition in women. When reviewing data on the prevalence of bacterial vaginosis, there seems to be a pattern of higher prevalence of bacterial vaginosis in African women and women of African descent, populations that are hard hit by HIV. The question is why there are these variations in prevalence of bacterial vaginosis. Many risk factors for bacterial vaginosis have been identified and there is still uncertainty whether bacterial vaginosis is a sexually transmitted infection (STI). In our review [2], we presented both pros and cons for this argument. However, there are data emerging that suggest that the composition of the vaginal microbiota in balance varies by ethnic group, hence differences in the prevalence of bacterial vaginosis between different ethnic groups might originate in differences in the ‘healthy’ vaginal microbiota.

Kenyon and Osbak [1] are right in pointing out that a pattern of high prevalence of bacterial vaginosis associated with certain ethnic groups does not necessarily mean that ethnicity is an independent risk factor for bacterial vaginosis. The association between ethnicity and bacterial vaginosis may be confounded by numerous risk factors. So far, very few studies have explored whether differences in bacterial vaginosis prevalence between different ethnic groups may be explained by differences in the distribution of known risk factors for bacterial vaginosis. The study by Ness et al. [3] among women in the USA failed to find an explanation for the differences in bacterial vaginosis prevalence between Afro-American and white women, but it is clear that we need more such studies.

Kenyon and Osbak [1] advance sexual networking as an alternative explanation for variations in prevalence of bacterial vaginosis, which would at the same time explain the association between different STIs at the individual level. However, this explanation also reduces a complex...
interplay of many risk factors to one factor, that is concurrent partnerships. For instance, in their own study from Kenya, Kenyon et al. [4] found several factors that were correlated with higher HIV prevalence in certain ethnic groups, including not only sexual behavioural factors but also male circumcision. Lagarde et al. [5] found that a measure of concurrency could not discriminate between cities in sub-Saharan Africa with high HIV prevalence and cities with lower prevalence. They attributed the lack of correlation to other behavioural and biological factors that play a role in the spread of HIV. It is not unreasonable to think that also for bacterial vaginosis concurrent partnerships would not be the sole factor explaining differences in prevalence.

Furthermore, the explanation why high levels of concurrent partnerships lead to very rapid spread of HIV is that the virus ‘does not waste any time’. On the basis of this logic, there needs to be a sexually transmitted pathogen in order for concurrent partnerships among men to cause high levels of bacterial vaginosis. The problem is that, so far, no such pathogen has been identified and there is even no consensus whether bacterial vaginosis is an STI or a ‘sexually enhanced disease’. Some have suggested that Gardnerella vaginalis is the pathogen that causes bacterial vaginosis but we argued in our review that G. vaginalis has also been detected in women who did not suffer from bacterial vaginosis. Concurrent partnerships, however, could increase the incidence and prevalence of bacterial vaginosis indirectly by increasing the spread of HIV (and possibly other STIs), which enhance the risk of developing bacterial vaginosis. It is also conceivable and important to study whether multiple concurrent sexual partnerships among women may alter the physiologic vaginal inflammatory response to semen and through ‘sexually enhanced inflammation’ predispose to bacterial vaginosis [6].

Lastly, concurrent partnerships are not needed to explain the association at the individual level between bacterial vaginosis and STIs. There is fairly good evidence from longitudinal studies that bacterial vaginosis enhances the susceptibility to STIs and that STIs enhance the risk of bacterial vaginosis, which we have reviewed in our study.

But we agree with Kenyon and Osbak [1] that more research is needed on the vaginal microbiota and the factors that cause disturbances. Longitudinal studies are warranted, but we would also suggest that comparative studies are done on the vaginal microbiota of adolescent girls who have not yet initiated sexual activity. These studies would tell us whether there are indeed differences in the vaginal microbiota that cannot be explained by sexual activity.

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References


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How does weight influence tenofovir disoproxil-fumarate induced renal function decline?

We read with interest the single-center cohort study of Nishijima et al. [1] evaluating the effects of tenofovir disoproxil-fumarate (TDF) on estimated glomerular filtration rate (eGFR) decline in HIV-positive Japanese patients. They observed high adjusted odds ratios (ORs) on eGFR decline in their lightweight population (median 62.9 kg) on TDF, particularly in patients below 70 kg, compared with patients on abacavir. These observations
may also be relevant for lightweight Caucasian HIV patients. However, the described methods and results raise questions in light of previous studies and our own experience.

First, Nishijima et al. [1] used a 70 kg cut-off and found a strikingly higher OR of 2.5 ($P < 0.001$) on eGFR decline above 10 ml/min in patients below 70 kg compared to an OR of 1.7 ($P = .15$) in patients above 70 kg. The choice for a 70 kg cut-off seems surprising because even the interquartile range (IQR) upper border of the weight in the patients on TDF was below 70 kg. The use of the median would be more rational. The largest effect would be expected in the lowest-weight categories and different cut-off points could have altered results. The authors should explain this choice and also why the methods and results of their present study are different from their two previously published studies that also evaluated long-term renal effects of TDF in similar populations [2,3]. The weight cut-off points in these studies were at 60 and 68 kg. No significant associations were observed between eGFR changes and patients weighing 61–68 kg or above 68 kg. Weight was also included as continuous variable in models of the present study to evaluate dichotomized eGFR declines of more than 10 ml/min, above 25%, and the occurrence of less than 60 ml/min during follow-up. Weight per 1 kg increase was not significantly associated with eGFR changes in these models. In contrast to the present study, the authors found highly significant associations in their own previous studies between lower body weight as continuous variable and eGFR declines in multivariable models. The authors should clarify the use of different cut-off points, elucidate the discrepancies between the analysis of weight as continuous and dichotomized variable, and explain why the results are different between their present and previous studies.

Furthermore, Nishijima et al. [1] should mention which boosted protease inhibitors were used because an additional effect of atazanavir and lopinavir with TDF on eGFR is reported [4]. Also, the present models did not include age to prevent overadjustment because age was not associated with TDF use and it was already included in the eGFR equation. However, larger cohort studies, including populations with comparable median BMI (19.7 kg/m$^2$) as well, adjusted for age and identified older age as predictor for eGFR decline [4,5]. The authors mention that age and TDF use were not associated. However, age could still be a confounder in the association between weight and eGFR, especially since older patients had lower baseline eGFR in this study. Notably, the authors acknowledge the effect of an age-related eGFR decline in their references [6]. Age was also included in the models of the authors’ previous studies and was identified as an independent risk factor for eGFR decline. In these models, eGFR (not age) was excluded based on its multicollinearity with sex, age, and creatinine. These inconsistencies and the above mentioned differences in outcomes and applied methods between the present and previous studies by the same authors remain unexplained.

To elucidate the issues stated above, we conducted a cross-sectional study in a different setting. Included were 329 consenting HIV-1-suppressed, predominantly Caucasian men on TDF-containing regimens, with cumulative 1435 patient-years of follow-up. We assessed eGFR decline greater than 10 ml/min in logistic regression models. Patients were median 45 years (IQR 36–52), weighed 76 kg (IQR 68–87), and had eGFR (Cockcroft–Gault) of 115 ml/min (IQR 98–136) at TDF initiation. Patients had median 11.2 ml/min eGFR decline during median 47 months (IQR 16–81) TDF exposure. We did not find an association between weight below 70 kg and eGFR decline greater than 10 ml/min during follow-up [OR 1.8, 95% confidence interval (CI) 0.9–3.5, $P = 0.07$]. When weight was included as continuous variable, a highly significant lower OR per 1 kg increase on eGFR decline was observed (OR 0.95, 95% CI 0.92–0.97, $P < 0.001$). Both models were adjusted for age, ethnicity, baseline eGFR, CD4$^+$ cell count, time on TDF, boosted atazanavir or lopinavir use, nephrotoxic medications, diabetes, cardiovascular disease, and chronic hepatitis C.

In conclusion, the evidence points towards additional TDF-related renal toxicity in slimmer HIV patients. In our opinion, the precise effect of weight and the identification of patients at highest risk are yet unclear. Also, the possibility of racial genetic differences in altering primary TDF efflux transporters activity could be of interest [7,8]. The authors’ recommendation on regular and long-term renal monitoring should therefore apply to all HIV patients initiating TDF-containing regimens, not only to those with lower body weights, as long as these issues remain.

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**Conflicts of interest**

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References


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Reply to ‘How does weight influence tenofovir disoproxil-fumarate induced renal function decline?’

We appreciate Rokx’s [1] interest in our article that examined the effect of long-term tenofovir disoproxil fumarate (TDF) use on renal function among the cohort of lightweight (median 63 kg) Japanese patients with HIV-1 infection [1,2]. Low body weight has been identified as a risk factor for TDF-related nephrotoxicity not only in clinical studies [3,4], but also in in-vitro and pharmacokinetic studies [5,6]. In fact, we have been interested in this issue and published a series of studies [2,4,7].

In the present study [2], a cut-off value of 70 kg was used for subgroup analysis, which investigated the effect of body weight on TDF-related renal dysfunction. We used this cut-off, rather than 63 kg (the median of the study population), because having this cut-off value allowed generalization of the results to include the people in North America and Western Europe, who are characterized by a larger body weight relative to Asians [4,8]. Selection of a cut-off value of 63 kg would have resulted in the inclusion of a small number of patients with less than 63 kg body weight in such regions. For reference, the following data are the results of analyses using 63 kg as the cut-off value; the odds ratio (OR) for more than 10 ml/min/1.73 m\(^2\) decrement in estimated glomerular filtration rate (eGFR) was higher in the less than 63 kg group [adjusted OR 2.3, 95% confidence interval (CI) 1.48–3.54, \(P<0.001\)] than the at least 63 kg group [adjusted OR 2.0, 95% CI 1.34–3.08, \(P=0.001\)].

Rokx [1] also pointed out that a lower body weight as a continuous variable was significantly associated with renal dysfunction in one of our previous studies [4], but not in the present study [2]. The two cited studies from our group [2,4] included two totally different study populations; one of our previous studies [4] included only patients who initiated TDF and investigated the effect of weight on renal function, whereas the present study [2] included patients who initiated TDF or abacavir-containing antiretroviral therapy and compared renal function between the two groups [2]. This difference in study population should explain the lack of reproducibility. The design of another previous study [7] was similar to that of the present study [2]. However, the latter was much better designed; including longer follow-up period, larger study population, evaluating three renal outcomes [2] compared to just one [7], and calculating eGFR with the equation developed by the Japanese Society of Nephrology (JSN) [9] and CKD–EPI (Chronic Kidney Disease Epidemiology Collaboration) equation adjusted for the Japanese coefficient [10], whereas the previous study [7] used the MDRD (Modification of Diet in Renal Disease Study) [11] and Cockcroft–Gault equation [12]. These advantages in the design of the present study can explain the differences in the results, if any.

The number of patients who started each ritonavir-boosted protease inhibitors (PI/r) was 198 for ritonavir-boosted lopinavir, 227 for ritonavir-boosted atazanavir, 197 for ritonavir-boosted darunavir, and 49 for ritonavir-boosted fosamprenavir. Unfortunately, due to the small number of patients on each PI/r, we could not perform meaningful statistical analysis to look at the TDF-related renal effects in terms of each PI/r use.
We agree with the comment by Rokx [1] that age could be an important confounding factor for the association between eGFR decrement and TDF use. However, we did not add age to the logistic regression model to avoid overadjustment because the equation for eGFR calculation already includes age, and because baseline age was not associated with TDF use \((t\text{ test } P = 0.24)\). We checked the baseline data again and observed higher baseline age was still associated with eGFR decline, which was calculated with the equation containing age (linear regression, \(P < 0.0001\)). In this case, age is just a predictive variable for eGFR decline, which corresponds to C4 in the Causal Diagram No. 5 in the study by Schisterman et al. [13]. They stated: ‘although adjustment for predictive covariates in classic linear regression can result in either increased or decreased precision, adjustment by logistic regression will result in loss of precision’. This is the reason for not adding age to the model. Just for reference, the results were very similar when age was added to the model \((>10\text{ ml/min/1.73 m}^2\text{ decrement, adjusted OR 2.1, 95\% CI 1.4–2.8} < 0.001)\) \((>25\% \text{ decrement, adjusted OR 2.1, 95\% CI 1.4–2.89, } P < 0.001)\) \((eGFR <60\text{ ml/min/1.73 m}^2, \text{adjusted OR 4.2, 95\% CI 1.6–10.4, } P < 0.001)\). The cumulative mean eGFR loss relative to the control after 5 years of TDF exposure reached \(-10.0\text{ ml/min/1.73 m}^2\).

In conclusion, only a few studies, including ours, have investigated the effect of long-term TDF use on renal function among patients with HIV-1 infection [2, 14]. We agree with Rokx and colleagues in that uncertainty remains for long-term renal safety of TDF, especially among patients with low body weight.

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References


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