Higher risk behaviour and rates of sexually transmitted diseases in Mwanza compared to Uganda may help explain HIV prevention trial outcomes

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Objective: To determine to what extent the higher impact of treatment for sexually transmitted diseases (STD) on HIV incidence in Mwanza, Tanzania than in Rakai and Masaka, Uganda might be explained by baseline differences between the trial populations.

Design: A re-analysis of baseline data from the three trial populations comparing demography, sexual risk behaviour and HIV/STD epidemiology.

Methods: Data were compared after age-standardization and adjustments for sample selection where necessary. STD rates were also adjusted for the sensitivities and specificities of the diagnostic techniques used.

Results: Demographic patterns were similar across populations, apart from effects of AIDS on fertility and mortality (including widowhood) in Uganda. Higher sexual risk behaviours, including younger age of sexual debut, higher numbers of recent partners and lower frequency of condom use, were apparent in Mwanza compared to Masaka and Rakai. High-titre serological syphilis, gonorrhoea, chlamydia infection and trichomoniasis were all more prevalent in Mwanza, except for chlamydia infection in males. There was little difference between sites in the seroprevalence of Herpes simplex virus type-2. Age patterns in the prevalence of short-duration STD and current risk behaviours were similar across sites but all-titre serological syphilis was more prevalent among older participants in Rakai and Masaka than Mwanza.

Conclusions: Differences between trial populations included higher reported risk behaviour and higher rates of curable STD in Mwanza compared to Rakai and Masaka. These differences probably relate to previous reductions in risk behaviour in Uganda and may explain, at least in part, the contrasting results of these trials.

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See also p. 2661

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Introduction

Sexually transmitted diseases (STDs) enhance HIV transmission, and this effect is especially important in populations where STDs are highly prevalent [1]. STD treatment as an intervention to prevent HIV transmission has been evaluated in three large-scale community randomized trials in East Africa. In Mwanza, Tanzania syndrome STD case management reduced HIV incidence by 38% [95% confidence interval (CI) 15–55%] in the general population suggesting that the treatment of genital ulcer and discharge syndromes could be an effective HIV control strategy in African populations [2,3]. However, trials of STD mass treatment in Rakai, Uganda, and of a behavioural intervention in conjunction with syndromic STD treatment in Masaka, Uganda showed little or no effect on HIV incidence [4,5]. The contrasting results of these trials have led to confusion regarding the role of STD treatment in HIV prevention.

Several hypotheses have been put forward to explain the contrasting results of the Mwanza and Rakai trials including differences between the interventions, differences in the stage of the epidemic and differences in the populations [6–11]. Continuous provision of syndromic treatment (ST) in Mwanza, was postulated to have resulted in higher coverage of cofactor STD than periodic mass treatment in Rakai, because ST targets symptomatic STD which may exert stronger cofactor effects than asymptomatic STD [7]. This hypothesis is now less plausible given the subsequent observation of no impact of ST on HIV in Masaka [5].

Given the lack of impact of either STD treatment intervention on HIV incidence in the two Ugandan populations, differences between the epidemics or in the study populations now seem more likely explanations for the differing trial outcomes. Several factors may have resulted in the lower population attributable fraction of HIV infections due to curable STDs in Uganda compared to Mwanza [9,10]. At the time of the trial, Uganda was at a later stage of the HIV epidemic than Mwanza. As a result, relatively less HIV transmissions would have taken place in core groups in which STD prevail, and the average HIV viraemia was likely to be higher in Uganda due to more incident HIV infections and more persons with advanced HIV disease [12]. Apart from the stage of the HIV epidemic, the populations may have differed in sexual risk behaviour resulting in differing STD and HIV epidemiology. However, comparison of data from the three trials regarding demographic characteristics, sexual behaviour and epidemiology is not straightforward due to differences in data collection methods and definition of indicators.

The objective of the study presented here was to determine to what extent differences in the trial outcomes might be explained by differing STD epidemiology, sexual risk behaviour and demographic risk factors in the three populations. This was accomplished by comparing baseline data from the Mwanza, Rakai and Masaka trial populations using standardized indicators and definitions after taking account of differences in data collection methods.

Methods

Data collection and collation

Detailed data collection methods for each trial have been described previously [5,13,14]. Data on demographic surveillance population in nearby Kisera ward, Mwanza Region. The migration-defining population was smaller in Rakai (average n = 654) than in Masaka (average n = 2072) and Mwanza (average n = 1500) and no adjustment was made for this difference between the sites. Upwards adjustment was made to the Rakai migration rates (× 24/20) to account for the shorter follow-up period in Rakai (20 months) compared to Mwanza and Masaka (24 months). Quantitative comparison of short-term circulation rates was not possible due to lack of data.

Migration rates were calculated using trial census data for Rakai and Masaka. For Mwanza, all-age trial census data from the follow-up round were not available so we used census data from the rural stratum of a demographic surveillance population in nearby Kisera ward, Mwanza Region. The migration-defining population was smaller in Rakai (average n = 654) than in Masaka (average n = 2072) and Mwanza (average n = 1500) and no adjustment was made for this difference between the sites. Upwards adjustment was made to the Rakai migration rates (× 24/20) to account for the shorter follow-up period in Rakai (20 months) compared to Mwanza and Masaka (24 months). Quantitative comparison of short-term circulation rates was not possible due to lack of data.

Sexual behaviour data were available from structured questionnaire surveys administered by trained interviewers in all three sites [3–5]. We compared self-reported age of sexual debut, proportion married, numbers of recent and lifetime sex partners, age mixing between partners and condom use for the three populations. In Rakai, sexual behaviour data were available for all participants but for purposes of comparison with Masaka and Mwanza the data presented here are restricted to those who had lived in the study community for at least 6 months and were enrolled at round 1 (minimum n ≈ 11 600). Participants followed up in round 3 provided data on lifetime partners.
Comparison of Mwanza, Rakai and Masaka trial populations

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(minimum n ≈ 9000). In Masaka, sexual behaviour data were available for a 50% random sample of the cohort enrolled at round 1 (minimum n ≈ 5900). In Mwanza, sexual behaviour data were collected for a random sample of the cohort in the context of a nested case–control study which took place several months after the main baseline survey (minimum n ≈ 1100) [20,21]. Age of debut was derived from the proportion of the youngest study participants (15–24 years) who reported any lifetime sex partners (all three sites) and from the age of first sex reported by the entire cohort (Mwanza and Masaka only). Regarding condom use, we analysed the proportion reporting consistent ‘always’ condom use in casual relationships (Mwanza and Rakai), and the proportion reporting condom use during the last casual sexual contact (Masaka and Rakai) among those who reported a casual partner.

Serum, urine and genital swabs were collected to measure STD prevalence using methods described previously [3–5]. Prevalences were adjusted for differences in diagnostic methods between the trials and for differences in eligibility criteria and populations sampled. These adjustments are described elsewhere and the adjusted data are presented here [22]. We analysed the prevalences of HIV, Neisseria gonorrhoeae (NG), Chlamydia trachomatis (CT), Trichomonas vaginalis (TV), all titre serological syphilis [Treponema pallidum hemagglutination assay (TPHA+) and rapid plasma reagin (RPR) titre ≥ 1 : 2], hightitre serological syphilis (TPHA+ and RPR ≥ 1 : 8) and Herpes simplex virus type-2 (HSV-2) seropositivity. We also compared data on these STD by mobility status depending on whether participants were lost to follow-up between the first and subsequent survey rounds.

Statistical methods
For comparisons between summary measures that included all ages, data were age-standardised based on five-year age group tabulations and a standard population composition derived as the average of the three populations based on national census data [15,16]. Comparisons were restricted to age ranges for which data were available from all sites. For outcomes for which trial data were not available from one site, comparisons were limited to the remaining two sites. Life-table methods were used to determine the median age of sexual debut for the entire cohorts in Mwanza and Masaka.

Results

Demography
Rural census data indicated that the age and sex composition of the three populations from which the trial samples were selected were similar (Table 1).

These data are typical of rural African populations with high growth rates. Females slightly outnumbered males in all three areas and growth rates were similar. The total fertility rate (TFR) was slightly higher in rural Uganda than in rural Tanzania. Mortality rates for HIV-negatives were similar in the three populations.

All three populations showed similar all-age net out-migration rates of around 1–2% per year (data not shown). Slightly higher out-migration and in-migration rates were observed in Rakai in comparison with Masaka and Mwanza. The higher rates in Rakai are in part due to the smaller migration defining population used. Both in-migration and out-migration were concentrated in the young in all sites. All-age in- and out-migration rates peaked in women aged 15 to 24 years. Peak male migration rates occurred at slightly older ages, 20–24 years and 20–34 years for out-migration and in-migration, respectively (data not shown).

Sexual behaviour
The age of sexual debut among males was younger in Mwanza than in Rakai and Masaka according to either of the indicators (Table 1). In Rakai and Masaka, but not in Mwanza, the age of debut was older in males than females so the difference with Mwanza was especially marked for males. Data from Masaka suggest the age of debut has increased recently as it was older for the youngest study participants than for the entire cohort. The age patterns in the proportions currently married indicate that males married at older ages than females in all sites (Fig. 1). Proportions married among the young were similar across sites and as a result the period of premarital sex for men was longest in Mwanza. Among older men and women, higher proportions were married in Mwanza than in Rakai and Masaka probably due to higher AIDS-related widowhood in the Ugandan sites. The proportion of men in polygamous marriages was similar in Mwanza and Rakai (Table 1).

Regarding recent sexual behaviour, the most partners in the past year were reported in Mwanza whereas similar numbers of partners were reported in Rakai and Masaka (Table 1). Among men, the proportion reporting five or more partners was 9.6% in Mwanza, 2.1% in Masaka and 1.4% in Rakai. A similar differential between trials was apparent for women. Comparing numbers of lifetime partners, the most partners were reported in Mwanza but the difference with the Ugandan sites was less extreme than for recent partners. The proportion of males with no lifetime partners was higher for the Ugandan sites relative to Mwanza, consistent with the site difference in age of sexual debut.

The age patterns in the proportion of males and females reporting two or more recent partners were examined...
The patterns were similar across the sites but more partners were reported in Mwanza than in Rakai and Masaka, especially for older participants. The age difference between partners provides some insight into mixing patterns for Mwanza and Rakai. In both sites, males were on average older than their female partners (Table 1). The median age difference between males and their spouses was around 5 years. In general, the age differences reported for casual partners were less than for spouses in both sites. Age differences were similar across the sites for both stable and casual partnerships.

Much higher condom use was reported in Rakai and Masaka than in Mwanza for casual partnerships (Table 1). Condom use was similar in Masaka and Rakai with about 25% of males and 15% of females reporting condom use during the last casual contact. For ‘always using condoms’ with a casual partner, proportions were much lower among males in Mwanza (2%) than Rakai (20%). In all sites, among those with casual partners, the proportion reporting condom use decreased with age (data not shown). In both Mwanza and Rakai where data were available for different types of partners, frequency of condom use was higher for casual than for stable partnerships. In all sites reported condom use was higher for males than females (Table 1).

### STD and HIV epidemiology

HIV epidemiology at the start of the three trials showed major differences between the sites. HIV prevalence was highest in Rakai (16.5%), somewhat

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**Table 1. Demographic indicators, sexual behaviour characteristics and adjusted sexually transmitted disease (STD) prevalences for the Mwanza, Rakai and Masaka trial populations at baseline.**

<table>
<thead>
<tr>
<th></th>
<th>Rakai M</th>
<th>Rakai F</th>
<th>Masaka M</th>
<th>Masaka F</th>
<th>Mwanza M</th>
<th>Mwanza F</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic indicators</strong></td>
<td></td>
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<tr>
<td>Population composition, % &lt; 15 years</td>
<td>50.0</td>
<td>48.4</td>
<td>51.2</td>
<td>49.6</td>
<td>47.9</td>
<td>46.7</td>
</tr>
<tr>
<td>All-age sex ratio (M : F)</td>
<td>0.98</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>TFR (number live births per woman, 15–49 years)</td>
<td>7.7</td>
<td>7.5</td>
<td>6.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-negative mortality (/1000 py, 15–54 years)</td>
<td>5.0</td>
<td>5.0</td>
<td>5.6</td>
<td></td>
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</tr>
<tr>
<td>Inmigration (annual % moved into area, 15–54 years)</td>
<td>14.1</td>
<td>14.1</td>
<td>11.0</td>
<td>12.2</td>
<td>9.2</td>
<td>13.3</td>
</tr>
<tr>
<td>Outmigration (annual % moved out of area, 15–54 years)</td>
<td>18.2</td>
<td>17.1</td>
<td>13.7</td>
<td>15.3</td>
<td>10.3</td>
<td>14.8</td>
</tr>
<tr>
<td><strong>Sexual behaviour characteristics</strong></td>
<td></td>
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<tr>
<td>Age of debut (years), estimates based on</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>One or more lifetime partners (median, 15–24 years)</td>
<td>17.4</td>
<td>15.8</td>
<td>17.7</td>
<td>16.4</td>
<td>15.0</td>
<td>15.3</td>
</tr>
<tr>
<td>Reported age of debut in cohort (median, 15–54 years)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>17.0</td>
<td>15.0</td>
<td>15.6</td>
<td>15.4</td>
</tr>
<tr>
<td>% Males in polygamous marriages (15–54 years)</td>
<td>2 spouses</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>3+ spouses</td>
<td>1.3</td>
<td>n.a.</td>
<td>1.2</td>
<td></td>
<td></td>
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<tr>
<td>Number of recent partners, %, 15–54 years</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0–1</td>
<td>72.6</td>
<td>95.9</td>
<td>79.6</td>
<td>96.4</td>
<td>46.8</td>
<td>88.5</td>
</tr>
<tr>
<td>2–4</td>
<td>25.8</td>
<td>4.0</td>
<td>18.2</td>
<td>3.7</td>
<td>43.5</td>
<td>10.6</td>
</tr>
<tr>
<td>5+</td>
<td>1.4</td>
<td>0.1</td>
<td>2.1</td>
<td>0</td>
<td>9.6</td>
<td>1.0</td>
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<tr>
<td>Number of lifetime partners, %, 15–54 years</td>
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<td></td>
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</tr>
<tr>
<td>0–1</td>
<td>22.4</td>
<td>38.8</td>
<td>27.5</td>
<td>39.1</td>
<td>8.6</td>
<td>33.1</td>
</tr>
<tr>
<td>2–4</td>
<td>28.4</td>
<td>50.6</td>
<td>29.9</td>
<td>46.4</td>
<td>21.6</td>
<td>48.5</td>
</tr>
<tr>
<td>5–9</td>
<td>14.7</td>
<td>7.5</td>
<td>18.3</td>
<td>11.0</td>
<td>24.6</td>
<td>15.3</td>
</tr>
<tr>
<td>10+</td>
<td>34.4</td>
<td>3.1</td>
<td>24.3</td>
<td>3.5</td>
<td>45.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Age difference between partners (M–F, years)</td>
<td></td>
<td></td>
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<tr>
<td>Spouses (median)</td>
<td>5.2</td>
<td>5.0</td>
<td>n.a.</td>
<td>n.a.</td>
<td>5.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Casual partners (median)</td>
<td>2.5</td>
<td>3.0</td>
<td>n.a.</td>
<td>n.a.</td>
<td>5.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Condom use, %, 15–54 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always/consistent with steady partner</td>
<td>20.3</td>
<td>5.9</td>
<td>n.a.</td>
<td>n.a.</td>
<td>2.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Always/consistent with casual partner</td>
<td>21.0</td>
<td>11.5</td>
<td>27.7</td>
<td>14.9</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Last casual contact</td>
<td></td>
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<tr>
<td>STD prevalence (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV (15–54 years)</td>
<td>13.9</td>
<td>19.0</td>
<td>10.7</td>
<td>13.2</td>
<td>3.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Gonorrhoea (15–39 years)</td>
<td>1.1</td>
<td>1.9</td>
<td>0.9</td>
<td>1.8</td>
<td>2.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Chlamydia (15–39 years)</td>
<td>2.7</td>
<td>3.2</td>
<td>2.2</td>
<td>1.6</td>
<td>2.3</td>
<td>13.0</td>
</tr>
<tr>
<td>Trichomoniasis (F only, 15–49 years)</td>
<td>7.7</td>
<td>7.2</td>
<td>4.5</td>
<td>3.9</td>
<td>7.3</td>
<td>8.9</td>
</tr>
<tr>
<td>Serological syphilis – TPHA+/RPR &gt; 1 : 2 (15–54 years)</td>
<td>2.3</td>
<td>1.4</td>
<td>1.2</td>
<td>0.7</td>
<td>5.6</td>
<td>6.3</td>
</tr>
<tr>
<td>High-titre syphilis – TPHA+/RPR &gt; 1 : 8 (15–54 years)</td>
<td>21.0</td>
<td>42.8</td>
<td>16.8</td>
<td>44.2</td>
<td>13.3</td>
<td>47.4</td>
</tr>
</tbody>
</table>

*From national censuses - rural district strata for Rakai and Masaka, rural region strata for Mwanza. From national censuses - district strata for Rakai and Masaka, region strata for Mwanza. From trial censuses for Rakai and Masaka, from rural Kisesa Demographic Surveillance System for Mwanza. Sample from antenatal clinics. M, male; F, female; n.a.; not available; py, person-years; TFR, total fertility rate, age range is 15–54 years unless otherwise noted; TPHA+, *Treponema pallidum* hemagglutination assay; RPR, rapid plasma reagin. STD prevalences have been adjusted for differences in test diagnostics and sampled populations [21].

(Fig. 1). The patterns were similar across the sites but more partners were reported in Mwanza than in Rakai and Masaka, especially for older participants. The age difference between partners provides some insight into mixing patterns for Mwanza and Rakai. In both sites, males were on average older than their female partners (Table 1). The median age difference between males and their spouses was around 5 years. In general, the age differences reported for casual partners were less than for spouses in both sites. Age differences were similar across the sites for both stable and casual partnerships.

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HIV incidence (as measured in the comparison arm of the trials) was 1.5 per 100 person-years in Rakai (rounds 1–2, 2–3 and 1–3 pooled), 1.1 per 100 person-years in Masaka (rounds 1–2, 2–3 and 1–3 pooled), and 1.0/100 person-years in Mwanza leading to higher prevalence/incidence ratios in the Ugandan sites (over 10) compared to Mwanza (3.8). Other features of the epidemics suggest a more mature epidemic in the Ugandan sites compared to Mwanza: the female/male prevalence ratios were higher in Rakai (1.4) and Masaka (1.2) compared with Mwanza (1.1) and the proportion of married couples with HIV that were concordantly positive was higher in the Ugandan sites (> 40%) compared with Mwanza (28%) [23–25].

Age and sex patterns of HIV prevalence were similar across sites apart from differences in overall levels (Fig. 2). Prevalences were higher in females than males, peaking between 25–29 years for females and 30–34 years for males. Age peaks were somewhat younger in Mwanza compared with the Ugandan sites. This finding is consistent with the relatively young epidemic in Mwanza, where the majority of prevalent cases have been infected recently.

Prevalences of NG, CT and TV were higher in Mwanza than in Masaka and Rakai apart from CT in males (Table 1). CT prevalence was higher in females than males in Mwanza and Rakai. Apart from the higher overall prevalence in Mwanza, age and sex patterns in NG prevalence were similar across the sites (Fig. 2). Prevalences peaked around age 20–24 years, and at a slightly younger age in women than in men. NG prevalence was higher in females than males in the Ugandan sites. Prevalences of all-titre serological syphilis (TPHA+/RPR > 1 : 2) were similar in Mwanza and Rakai and slightly lower in Masaka. The prevalence of high-titre serological syphilis (TPHA+/RPR > 1 : 8) was considerably higher in Mwanza than in Rakai and Masaka. Prevalence of high-titre serological syphilis and all-titre serological syphilis increased more rapidly with age in Mwanza than in the Ugandan sites, with peak ages between 20 and 39 years for Mwanza but above 35 years in Rakai and Masaka (Fig. 3). For high-titre active syphilis, Mwanza had a higher prevalence than the Ugandan sites for all age groups. However, for serological syphilis, prevalence in Rakai and Masaka exceeded that for Mwanza in the oldest study participants. Seroprevalence of HSV-2 was similar in all three sites and higher in females than males in all sites.

For HIV, prevalence was higher in males lost to follow-up in Mwanza (4.1%) compared with those followed (2.8%). For females, HIV prevalence was higher in those lost to follow-up in all sites (20, 15 and 4.8% in Rakai, Masaka and Mwanza, respectively) compared to females followed up (15, 12 and 3.4%).
These data suggest the trial surveys may have underestimated HIV prevalence and incidence in the study populations in all sites. HIV and serological syphilis were less associated with mobility in Rakai and Masaka as compared with Mwanza (data not shown). A reason could be that mobility was highest among the young in all sites, whereas in Rakai and Masaka, serological STD markers were concentrated in older age groups, and reflected past rather than recent infection.

Discussion

Several hypotheses have been put forward to explain the contrasting results of the Mwanza, Rakai and Masaka STD treatment trials. By comparing demography, sexual behaviour and STD/HIV epidemiology across these trial populations at baseline we have identified several important differences between these populations which could help explain the observed trial outcomes.

The populations were similar with respect to population composition (proportion young and sexually active), male–female sex ratios, growth rates and migration. Furthermore, age and sex patterns in sexual behaviour, age mixing between partners and age and sex patterns in STD epidemiology were broadly similar across sites as was HSV-2 seroprevalence.

A clear difference was between the mature stage of the HIV epidemic in Rakai and Masaka, and the earlier stage epidemic in Mwanza. In contrast with this, short duration, curable STDs were more prevalent in Mwanza than in Rakai and Masaka. The latter difference was consistent with higher rates of reported risky sexual behaviours in Mwanza relative to Rakai and Masaka as suggested by younger age of sexual debut, higher partner change rates and lower frequency of condom use in Mwanza compared to Rakai and Masaka (Table 1). The difference in risk behaviour in Mwanza compared to Rakai and Masaka was less marked for lifetime partners than for recent partners (Table 1). Thus, most differences between the sites related to markers of recent risk rather than past risk, suggesting that behavioural risk may have decreased in Uganda in the recent past. Supporting this inference, the analysis showed that high-titre serological syphilis, reflecting recent risk behaviour, was more prevalent in Mwanza than the Ugandan sites, but all titre serological syphilis, a long-term marker of past risk behaviour, was more prevalent among older individuals in Uganda (Fig. 3).

This comparative analysis is subject to a number of limitations. Data on sexual behaviour were based on self-reported survey data and these data are subject to both selection and reporting biases. In Mwanza, sexual behaviour data were available for a random sample of the baseline cohort collected several months after the baseline survey. As a result, the behavioural survey under-sampled the more mobile individuals in the trial population. Among participants enrolled at baseline those lost to follow-up in Mwanza had higher rates of HIV and serological syphilis. Hence, the under-representation of more mobile individuals in the sexual behaviour survey most likely underestimated the true excess in risk behaviour in Mwanza relative to the Ugandan sites may have been even larger.

Reporting bias may also be evident in the data in the form of recall bias (eg. forgetting to mention past partners) or ‘social desirability’ bias (reporting the norm rather than true behaviour). Although we might expect recall bias to be similar across the sites, effective health education and HIV/AIDS awareness in Uganda has led to a shift in what is viewed as desirable behaviour which could cause under-reporting of the number of sex partners in Uganda. This may partly explain the higher reported partner change rates in Mwanza compared to the Ugandan sites. However, it seems more likely that partner change rates were truly lower and condom use truly higher in Rakai and Masaka compared to Mwanza given the lower prevalence of short duration STD observed in the Ugandan sites (Table 1).
While STD rates are not sensitive to population-specific reporting biases, these data are influenced by diagnostic limitations and biases due to selected population sampling. We attempted to adjust for these biases so that the presented comparisons are more likely to be valid [22]. Even when taking into account uncertainties in the sensitivity and specificity of the diagnostic tests and samples selected, short duration STD prevalences appeared to be higher in Mwanza compared with Rakai and Masaka. In addition, a substantial site difference was found for high-titre serological syphilis for which no adjustments were required.

The more severe HIV epidemic in Uganda probably reflects earlier introduction of HIV into this region and higher risk behaviour in Uganda in the past. Higher population mobility and frequency of casual sexual contacts during the years of civil unrest in Uganda between 1979 and 1986 probably contributed to an explosive spread of HIV when it was introduced in Rakai and Masaka [26–28]. The lower levels of curable STDs in Uganda at the baseline of the trials suggest risk behaviour may have declined in Uganda after 1986 to levels lower than observed in Mwanza in the 1990s. Behavioural surveys conducted in Rakai and Masaka between 1989 and 1998, suggest reductions in risky sexual behaviour, including decreases in partner change rates and prostitution and increases in condom use [29–33]. These observations in the Ugandan sites probably reflect true reductions in risk behaviour relating to three factors: (1) the normalization of sexual risk exposure following the end of the civil war; (2) heightened HIV and AIDS awareness because most Ugandans had lost relatives, friends or neighbours to AIDS; and (3) effective health education campaigns [31,34]. Selective mortality among high risk groups due to AIDS may also have contributed, although simulations of the Rakai epidemic suggest this only made a minor contribution to the reduction in risk behaviour and STD prevalence [28]. Differences between Uganda and Mwanza in the stage of the epidemic and risk behaviour at the time of the trials may explain the lack of impact of STD treatment in Uganda.

HSV-2 seroprevalence was similar in the three populations. Herpetic ulceration due to HIV-related immuno-suppression may have occurred more frequently in Uganda, but this was not explicitly measured in the trials. Our comparison of the populations at baseline does not shed light on hypotheses relating to the effectiveness of the interventions such as treatment efficacy and coverage or the role of random error in the measurement of HIV incidence. Therefore, we are unable to determine how much of the difference in trial impacts was due to population differences at baseline and how much was due to other factors.

Our findings of higher risk sexual behaviour and STD prevalences in Mwanza than in Rakai and Masaka may help to explain why STD reductions reduced HIV incidence in Mwanza, but had little effect in Rakai or Masaka. We would theoretically expect a larger impact of STD treatment interventions and behavioural interventions in populations in which reductions in risky sexual behaviour have not yet taken place and in which prevalences of curable STD are high. For generalized epidemics in which behavioural change may have already occurred, interventions to prevent HIV transmission in stable relationships become much more important. Such interventions might include voluntary counselling and testing with disclosure to partners, vaginal microbicides, consistent condom use by HIV-discordant couples, male circumcision, HSV-2 suppression, vaccines and antiretroviral therapy.

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