Public health

Transmission of HIV-1 infection in sub-Saharan Africa and effect of elimination of unsafe injections

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During the past year, a group has argued that unsafe injections are a major if not the main mode of HIV-1 transmission in sub-Saharan Africa. We review the main arguments used to question the epidemiological interpretations on the lead role of unsafe sex in HIV-1 transmission, and conclude there is no compelling evidence that unsafe injections are a predominant mode of HIV-1 transmission in sub-Saharan Africa. Conversely, though there is a clear need to eliminate all unsafe injections, epidemiological evidence indicates that sexual transmission continues to be by far the major mode of spread of HIV-1 in the region. Increased efforts are needed to reduce sexual transmission of HIV-1.

In the 1980s, WHO[1] estimated that unsafe injections and the use of other inadequately sterilised skin-piercing instruments caused 1·6% of HIV-1 infections in Africa. More recent estimates[2] have put the proportion at 2·5% of all infections in sub-Saharan Africa. Gisselquist and colleagues[3,4] argue, however, that unsafe injections are a major if not the main mode of transmission in the region, causing 20–40% of HIV-1 infections, and they question the orthodox epidemiological interpretations about the lead role of unsafe sex in transmission. There are few policy makers who would not agree that unsafe injections should be eliminated. However, the way in which Gisselquist and co-workers downplay the importance of sexual transmission could hinder efforts to control the sexual transmission of HIV-1 in sub-Saharan Africa. For example, the US Senate Committee on Health, Education, Labor, and Pensions has held hearings to establish whether HIV/AIDS funds should be devoted to programmes that target unsafe injections. Here, we review what we believe are Gisselquist and colleagues' main arguments (table 1) to ascertain whether they provide convincing evidence against the prevailing view among epidemiologists that sexual intercourse is by far the most important route of transmission of HIV-1 in sub-Saharan Africa.

Frequency of unsafe injections

The number of injections administered for health reasons has been estimated at an average of 3·4 per person per year in low-income and middle-income countries.[5] Of these, about 39% are given with unsafe injection equipment—ie, equipment that is reused without first being sterilised.[6] Injections given with reused equipment are more common in the Middle East and south Asia than in sub-Saharan Africa, where the results of population-based surveys indicate that an estimated 2·1 injections are given per person per year, of which about 18% (approximate 95% CI 13–23) are given with reused equipment. This proportion is considerably less than the 50% of injections cited by Gisselquist and colleagues,[7] and results in a mean of 0·4 potentially unsafe injections per person per year.[6]

Most injections in sub-Saharan Africa are given intramuscularly, and blood contamination of needles after use for intramuscular injection is infrequent. A threshold value of 0·0015 μL is thought by some to be the minimum amount needed to transmit HIV-1.[8] The likelihood of encountering blood in syringes or needles that have been used for medically indicated intramuscular injection of HIV-1-infected patients in the USA has been estimated by PCR (with a mean limit of sensitivity of 0·09 μL to detect viral DNA from white blood cells) and enzyme immunoassay (with a mean limit of sensitivity of 0·00084 μL to detect antibodies to HIV-1).[9] In one study,[10] none of 184 syringes or needles tested positive for blood with the PCR assay, and only ten (5%) tested positive when the enzyme immunoassay was used. Furthermore, none of the needles or syringes was positive for HIV-1 DNA, as judged by an assay sensitive enough to detect proviral DNA with single-copy sensitivity. In a subsequent study[10] of 80 needles or syringes tested with a nested PCR assay capable of detecting two infectious units of viral RNA, 66 of which had been used for intramuscular injection and 14 for subcutaneous injection, three (4%) were positive. However, the identification of HIV-1 RNA means only that the equipment is potentially infectious, since the assay does not identify whether the nucleic acid is from whole, or viable, virus. Moreover, findings of studies in health-care workers suggest that simple exposure to even viable virus, particularly in low concentrations, seldom results in transmission. A careful distinction should, therefore, be made between injections with needles and syringes that might not be sterile and those that are capable of transmitting HIV-1, with the latter being a fraction of the former.

Additionally, in health-care practice, procedures are commonly used that, though not guaranteeing the safety

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Unsafe injections are a predominant mode of HIV-1 transmission in Africa: the main arguments of Gisselquist and colleagues	Sexual transmission is a predominant mode of HIV-1 transmission in Africa: main arguments against Gisselquist and colleagues
Unsafe injections are common	Unsafe injections are not sufficiently common to play a dominant part in HIV-1 transmission in Africa
HIV-1 transmission efficiency for injections is high, in the range of 2·3% or greater	Transmission efficiency of HIV-1 for injections in African health-care settings is overestimated and is far less than 2·3%
There is a strong association between having a history of injections and HIV-1 infection in studies of adults in sub-Saharan Africa	Analyses to assess the association between a history of injections and HIV-1 infection do not adequately take into account reverse causality and confounding
There are unexpectedly high rates of infections in individuals in whom sexual transmission is unlikely—eg, children and adolescents who have never had sex	Apart from mother-to-child transmission, HIV-1 infection is rare in children. The age and sex distribution pattern of HIV-1 infection cannot be explained by injection patterns, but is similar to that of other STIs
There is only a weak association between sexual behaviour and HIV-1 infection in studies of adults in sub-Saharan Africa	The analyses are oversimplified and do not consider issues related to measurement of exposure
	Prevalence of HSV-2 is high and follows a pattern by sex and age similar to that of HIV-1
	The South African epidemic has developed in the absence of unsafe injections with much data indicating sexual transmission is the cause

Table 1: **Route of transmission of HIV-1: main arguments for and against unsafe injections**

of the injection from HIV-1 contamination, will nevertheless further reduce the likelihood of contamination. Washing or, possibly, rinsing or soaking of syringes or needles will dilute any blood that might have contaminated the equipment. Experimentally, a single flush of a syringe or needle with water leads to an approximate 70% decrease in the proportion that contain sufficient HIV-1 to replicate in culture, while two flushes decrease that proportion by 95%.[11] Furthermore, heating in water at 60–65°C will inactivate HIV-1 within seconds.[12,13] Although the proportion of syringes or needles that are washed or heated is unknown, findings of several studies[8,14–16] indicate that reused equipment is often sterilised or boiled. Storage of syringes or needles at room temperature also results in a decline in viral titre.[17,18] Results of a survey[15] of 16 rural health centres in Ethiopia showed that, although 12% of injections were given with reused equipment, the equipment had been boiled, steam-sterilised (although not always in accord with WHO standards), or heated with burning alcohol—HIV-1 RNA was not detected in any of 212 needles tested (approximate HIV-1 prevalence, 8·3%), with an assay capable of detecting 150 copies/mL.

Transmission efficiency via unsafe injections

The best data on transmission efficiency via injections come from studies of health-care workers, among whom findings of longitudinal studies[19] indicate an estimated risk of HIV-1 infection after direct percutaneous exposure of 0·3%. This summary estimate is an average of different risk estimates taken from studies of different exposure categories (0·2%—ie, one seroconversion in 497 exposures—if one uses only needlestick-puncture exposures).[19,20]

Gisselquist and colleagues use two arguments to arrive at their much higher estimated risk of transmission efficiency of 2·3%.[7] A case-control study[21] on occupational risk of HIV-1 infection identified several factors that increase the risk of infection, including deep injury, visible blood on the device, any procedure involving drawing blood from an artery or vein in the source patient, and terminal illness of the source patient. Gisselquist and colleagues used the proportion of cases and controls in the study that reported a deep injury to estimate the risk after a deep injury as 2·3%. They argued that this transmission risk is applicable to unsafe injections in health-care settings in Africa, but they neglected important factors in the study—namely, that 73% of exposures had venous or arterial blood as a source (compared with 31% of controls), that visible blood on needles was common, and that most patients probably had high viral loads. These factors, also with significant odds ratios, are unlikely to be present in typical African health-care settings, where intramuscular injections are most common, a cleaning procedure is likely before reuse of equipment, and source patients are less likely to have terminal illness—all these factors will lessen the calculated transmission efficiency of 2·3%. Furthermore, washing and heating of needles and syringes will greatly diminish even this lower transmission efficiency.

The second method Gisselquist and co-workers used for estimating the transmission probability relied on data from nosocomial outbreaks in Russia, Romania, and Libya.[7] Even if one accepts their calculations and assumptions, unusual outbreaks are likely to have higher than usual transmission efficiency. The Russian outbreak was a result of a combination of intramuscular and intravenous (catheter and possibly transfusion) exposures;[22] the Romanian outbreak involved the sequential, immediate use of large-bore needles in children; and there are few epidemiological data from the Libyan outbreak. To believe that their calculated risk of 2–7% can be generalised to the African setting is, therefore, erroneous.

Population attributable fractions (PAFs)

Based on the findings of various studies, Gisselquist and colleagues[4] calculate the PAFs (causal fractions) associated with injections and conclude that, "Many studies show 20%–40% of HIV infections in African adults associated with injections (though direction of causation is unknown)". Furthermore, in analyses of data from the 1980s, Gisselquist and co-workers[3] report that, "Overall, crude PAFs from general population studies through 1988 suggest that medical exposures were responsible for more African HIV than sexual exposures".

The association of unsafe injections with prevalent HIV-1 infection has been examined in at least 19 cross-sectional studies. The results of most of these studies have shown an association between injections and HIV-1 infection, and relative risks are 1·16–2·96 (Seguy N, US Centers for Disease Control and Prevention, personal communication). In those studies that have adjusted for confounding, the adjusted relative risks were generally smaller than the unadjusted ones, indicating that other factors—in particular

	Age of participant (years)				
	≤4	5–14	15–44	≥15	≥45
Location of study population (year)					
Cameroon (1985–87)[32]	0%	0%	0% (0 of 375)	0% (0 of 375)	ND
Cameroon (1987)[32]	0%	0%	0·3% (1 of 335)	0·3% (1 of 335)	ND
Central African Republic (1986–87)[32]	0%	0%	7·8% (30 of 383)	7·8% (30 of 383)	ND
Gabon (1986–87)[32]	0%	0%	1·8% (7 of 383)	1·8% (7 of 383)	ND
Gabon (1986–87)[32]	0%	0%	0·2% (1 of 385)	0·2% (1 of 385)	ND
Rwanda (urban) (1987)[33]	10·1% (15 of 148)	4·2% (10 of 238)	23·6% (234 of 993)	20·7% (307 of 1484)	14·9% (73 of 491)
Rwanda (rural) (1987)[33]	0% (0 of 109)	1·7% (2 of 115)	2·0% (7 of 346)	1·5% (8 of 518)	0·6% (1 of 172)
Tanzania (urban) (1987)[34]	7·1% (10 of 140)	1·9% (4 of 215)	24·4% (128 of 525)	24·1% (133 of 551)	19·2% (5 of 26)
Tanzania (rural) (1987)[34]	1·4% (8 of 552)	0·2% (2 of 985)	5·3% (80 of 1502)	4·9% (86 of 1739)	2·5% (6 of 237)
Malawi (1987–89)[35]	0% (0 of 590)	0·03% (2 of 6511)	2·0% (164 of 8033)	1·7% (188 of 11 309)	0·7% (24 of 3276)
Uganda (1989–93)[36]	1·7% (24 of 1378)	0·4% (10 of 2500)	ND	8·2% (343 of 4183)	ND
Ethiopia (1994)[37]	0·8% (2 of 242)	0·2% (2 of 1145)	7·0% (161 of 2313)	6·8% (168 of 2466)	4·6% (7 of 153)

ND=not done. Data are % (number positive/number studied). Age limits vary slightly from one study to another: Rwanda=0–5, 6–15, 16–40, ≥16; Malawi=1–4; Uganda=5–12 and ≥13; Ethiopia=45–49; Tanzania 45–54.

Table 2: **Prevalence of HIV-1, according to age[32–37]**

a history of sexually transmitted infections (STIs)—confound the association. Additionally, four published longitudinal studies[23–26] have examined the association of incident HIV-1 infections with a history of injections. The results of two studies from Kinshasa, Democratic Republic of Congo,[23] and Rakai, Uganda,[24] noted no association between injections and risk of HIV-1 infection, whereas those of a third,[25] from Rwanda, indicated no association after adjustment for other variables. The findings of the fourth study,[26] from Masaka, Uganda, in which study participants were interviewed, on average, a year after seroconversion, showed a significant association in men but not women. Unpublished data from a longitudinal study in Mwanza Region, Tanzania, indicate a non-significant association between injections and HIV-1 seroconversion in men (p=0·08) and women (p=0·40) (Todd J, London School of Hygiene and Tropical Medicine, personal communication).

Potential reverse causality and residual confounding hamper the interpretation of these results on PAF. Because people with HIV-1 infection are more likely to be sick than those not infected, injections might have been given for the treatment of primary HIV-1 illness or complications of the infection. This notion is confirmed by data from a population-based study in Mwanza, where initially HIV-1-positive adults reported receiving nearly twice as many injections as HIV-1-negative people during 2 years of follow-up (Todd J, personal communication). Injections might also have been given for the treatment of STIs, which are a marker of unprotected sex and an important cofactor for HIV-1 transmission. STIs are, therefore, an important confounding factor that distorts the association between injections and HIV-1 infection. Not all studies have adjusted for STIs and, even if they have, STI episodes are imperfectly measured in retrospective observational studies.[27] Even in longitudinal studies, reverse causality is a problem because the intervals between the last seronegative and first seropositive result are usually a year or more.

Furthermore, the PAF is calculated from the prevalence of the risk factor in the population and the relative risk associated with the risk factor. If measurement of the prevalence or the relative risk is inaccurate, the PAF will also be inaccurate. Data on sexual behaviour are notoriously imprecise and tend to be underestimates of true risk.[28–30] For example, in one sub-Saharan Africa study,[31] 23 (2·3%) of 980 women aged 15–24 years who reported never having had sex were infected with HIV-1, but 15 (1·6%) of 958 of these same women were also pregnant. Underestimation of sexual exposure results in an underestimation of the relative risk of the association between risky sexual behaviour and HIV-1 infection and, thus, of the corresponding PAF. Data on the history of injections, on the other hand, are not affected by the same social desirability bias and should, therefore, be more accurate.

Finally, PAFs should be used with great care for epidemic infectious diseases. If they are taken to mean the proportion of infections in the population that occurs because of a risk factor, then the standard PAF calculations will give incorrect results. Infectious disease epidemics are dynamic, so that the proportion of infections in each risk group changes over time as the epidemic develops, and risk is a community effect, so that an increase in risk of infection for one individual increases the risk for all their subsequent contacts. The use of PAFs can be especially misleading for risk behaviour measured over a short time with respect to duration of infection. For example, the risk associated with sexual partners or injections over 1 year is not particularly informative of risk over a much longer period.

Age and sex patterns of infection

One of the most consistent features of the HIV-1 epidemic in sub-Saharan Africa is its distribution by age and sex.[31] We identified six population-based studies[32–37] of the prevalence of HIV-1 infection in sub-Saharan Africa that included children. The findings of these studies showed that the prevalence of infection in children aged 5–14 years (an age-range in which they are less likely to have acquired the

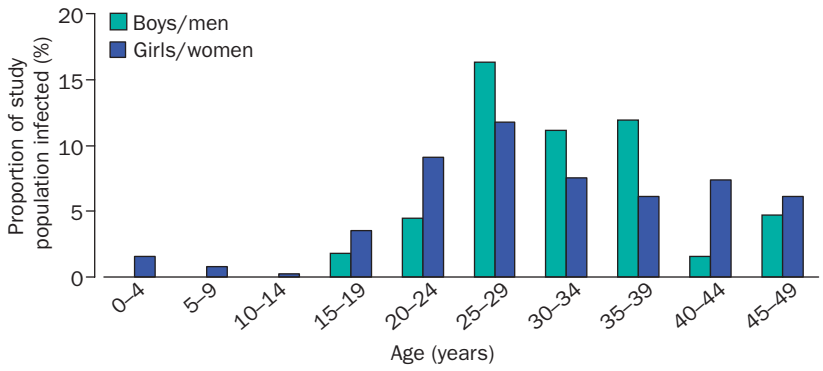

Figure 1: **HIV prevalence by age and sex in Addis Ababa, Ethiopia, 1994[37]**

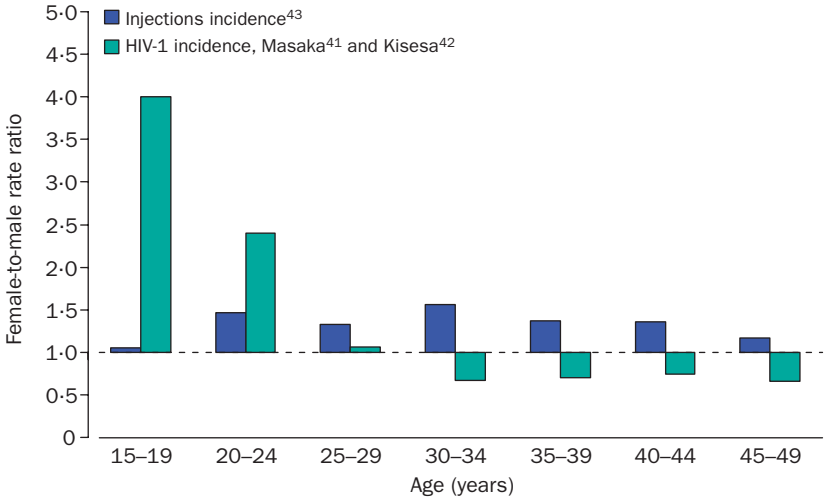

Figure 2: **Female-male rate ratio of HIV-1 and injections received by age[41–43]**

infection from their mother) was much lower than the prevalence in adolescents and adults aged 15 years or older (table 2, figure 1). If injections were a major mode of transmission, a much smaller discrepancy between HIV-1 prevalence in children and adults would be expected, since there is no evidence to suggest that children receive substantially fewer injections than adolescents and adults.

Even the low prevalence in the 5–14-year-old age group cannot be ascribed to unsafe injections because it includes some children infected by mother-to-child transmission, who have long survival times, or by transfusion. One study,[36] in Masaka, Uganda, explored the modes of transmission in children. Of ten HIV-1-infected children aged 5–12 years, six had a mother who was infected or who had died from AIDS, one was probably infected through a blood transfusion, one possibly through unsafe injections, and in the remaining two the route of transmission remained unclear. Also, the findings of a study[38] of mother-child pairs in Cote d'Ivoire showed that, of 20 infected children aged 15 months or older, 16 had an infected mother and the remainder had received a blood transfusion.

Results of longitudinal studies suggest that seroconversion in uninfected children is rare. In Uganda,[39] for example, of 5451 HIV-1-negative infants aged 0–12 years followed-up for 8596 person-years, only one seroconversion occurred (0·12 seroconversions per 1000 person-years), and in Cote d'Ivoire,[40] none of the children born to 266 persistently HIV-1-negative mothers seroconverted over a period of up to 48 months.

Another consistent feature of HIV-1 epidemics in Africa is the age and sex distribution in adolescents and adults. Female prevalence climbs during the teens and early twenties and peaks in the late twenties or early thirties, whereas male prevalence follows a similar pattern with a 5–10-year age delay (figure 1). The differences in prevalence between men and women in different age-groups cannot easily be explained by injections, unless wide variations in the frequency of injections by age and sex are assumed.

There are distinct patterns of injections by age and sex. However, they differ from patterns of HIV-1 infection. Several national demographic and health surveys undertaken in sub-Saharan Africa during 1999–2001 have included questions about number of injections in the past 3 months. Data from these surveys show that women receive more injections than men at all ages, with the difference being largest in the early twenties. Differences in the incidence of HIV-1 infection in women and men, however, are greatest at ages before those at which injection differences are large. Figure 2 shows the age patterns of the female-to-male ratio for HIV-1 incidence from two rural community cohort studies[41,42] in Uganda and Tanzania, and the incidence of injections (from national demographic and health surveys in Uganda in 2000).[43] Sexual transmission is the most likely explanation for the pronounced incidence of HIV-1 infection among women following the years of sexual debut. Thus, a more plausible explanation for the observed patterns is sexual transmission and sexual mixing between different age-groups—eg, young women have sex with older men who are more likely to be infected with HIV-1.

Sex as primary mode of HIV-1 transmission

Figure 3 shows that infection with herpes simplex virus type 2 (HSV-2)—a common STI that often has no signs or symptoms (similar to HIV)—follows a similar pattern in sub-Saharan Africa to that of HIV-1 in the first 10–15 years after individuals reach the age of sexual maturity, lending further support to the notion that HIV-1 is frequently transmitted by sex.[44,45] That sub-Saharan Africa has the highest rates of HSV-2 seroprevalence in the world,[46] and that Africa has the highest burden of STIs

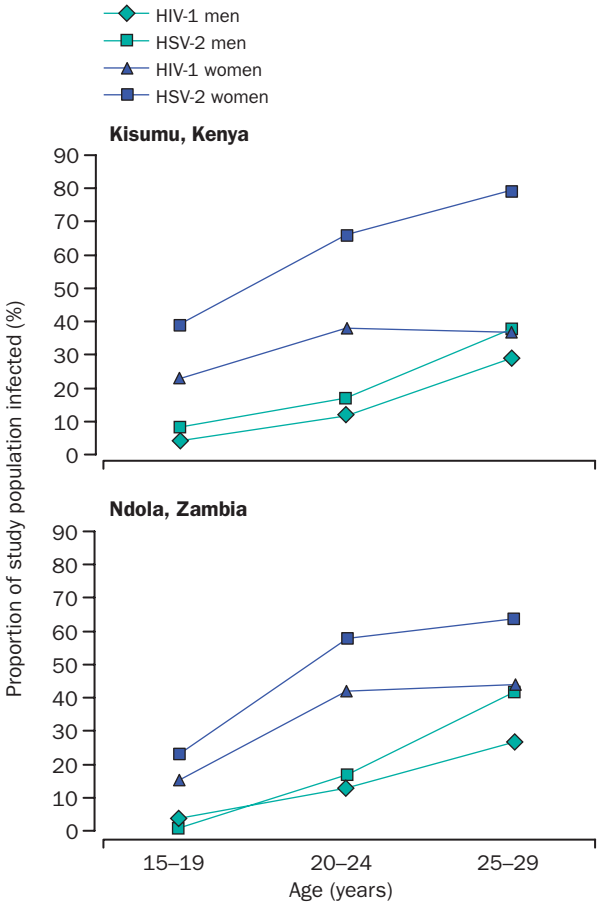

Figure 3: **Prevalence of infection with HIV-1 and HSV-2 by age and sex in two African regions[44]**

in the world,[47] lends biological validity to conclusions about both frequency of sexual transmission of HIV-1 and of risky sexual behaviour in sub-Saharan Africa.

HIV-1 is effectively transmitted by sex, as shown by high rates of infection among couples.[48–50] Furthermore, concordant infections among couples, when examined in the context of a household, allow an examination of the contribution of sexual transmission to total numbers of infections. If injections were a frequent mode of transmission, infections clustered exclusively among adults in a household would be unexpected. Hira and colleagues[48] studied 228 families in each of which one adult had HIV-1: of 150 men, 92 (61·3%) had infected wives; of 78 infected women, 57 (73·1%) had infected husbands; of 144 children aged younger than 5 years, 36 (25%) were infected and all had infected mothers; and of 120 children aged 5–10 years, three were infected (mother's serostatus not reported). Unless there are huge disparities in injection practices between children and adults, only sexual transmission can explain the seroprevalence differences by age. The logical conclusion is that sexual transmission of HIV-1 is responsible for most infections not transmitted from mother to child.

Last, male circumcision has a consistent and significant protective effect against HIV-1 acquisition, with the findings of 21 of 27 studies showing a protective effect and an adjusted summary rate ratio of 0·42 (95% CI 0·34–0·54).[51] Rates of HIV-1 in Africa are also inversely correlated with circumcision status.[52,53] The findings of one longitudinal study[50] showed a startling seroconversion rate of 16·7 per 100 person-years in 137 uncircumcised men compared with 0 of 50 circumcised men. In this study, acquisition of HIV-1 was not affected by an incident STI in the man, in particular, a genital ulcer or syphilis. This finding is important because, although an injection history was not reported, the seroconversions would not have occurred as a result of injections being given for treatment of an STI, as has been argued.[3]

South Africa

South Africa provides an example of a country for which the hypothesis that unsafe injections are the primary mode of HIV-1 transmission does not stand. The South African HIV-1 epidemic has reached enormous proportions; prevalence among women attending sentinel surveillance antenatal care clinics reached 26·5% in 2002.[54] However, South Africa has the most highly developed health-care system in sub-Saharan Africa and their blood-transfusion system is of developed-world standard.[55] Unfortunately, there is no database of injection safety practices within South Africa. However, a year 2000 survey[56] of 106 randomly-selected clinics in its neighbouring country, Zimbabwe, also hard-hit by the HIV-1 epidemic, showed safe injection practices in immunisation and, probably, other practice situations. Furthermore, our own personal communication with ten South African health-care authorities in March, 2003, indicated that all believed injection practices had been safe, with possible rare exceptions, since the HIV-1 epidemic began 10 years earlier.

The results of a national survey[57] of South African children and adults, which indicated a prevalence rate of HIV-1 infection of 5·6% among 2–14 year-olds, were hence totally unexpected, and led to the charge by Brody and colleagues,[58] in multiple writings, that the findings provided ignored evidence of iatrogenic transmission to hundreds of thousands of children. There are, however, questions about the exact validity of the survey findings—many were discussed by the report's authors, but

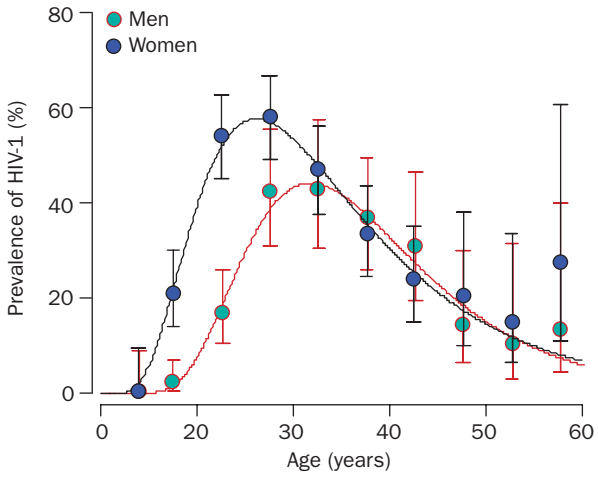

Figure 4: **HIV-1 infection rates by age and sex in Carletonville, South Africa[61]**

seemingly ignored by Brody and co-workers. There was, for instance, no increase in prevalence of infection in children by age (making iatrogenic infection an unlikely explanation, even considering deaths at early ages from infections acquired via mother-to-child transmission). Furthermore, the non-response rate in the survey was high because 29% of listed visiting points (mostly households) did not participate nor did 37% of eligible respondents in the remaining households, the test strategy may have been suboptimal, prevalence among children by race is the opposite of what other surveillance and death-registration data indicate, and the HIV-1 pattern by provinces in the survey was inconsistent with surveillance and previous research. Also, there is no evidence that AIDS is nearly as important a cause of mortality among children and teenagers as the survey numbers would suggest.[59]

Conversely, many sets of data point to unsafe sex as the cause of the epidemic in South Africa.[60] For example, the findings of a 1998 survey[61] in Carletonville—a community with considerable medical research capabilities and good quality medical care—indicated that the prevalence of HIV-1 among women was greater than 57%. Yet, of118 children aged 13 and 14 years, none was seropositive. Sexual activity commenced at a later age than this, with a mean age of sexual debut of 15·9 years for men and 16·3 years for women. Consistent with these ages, the acquisition of HIV-1 in men and women began at age 15 years and escalated sharply, with men following women (figure 4). The curve mirrors that noted in a Zimbabwe community.[62] Consistent with sexual transmission, acquisition of HIV-1 closely paralleled acquisition of HSV-2.[45]

Conclusion

Reinterpretation of studies published by Gisselquist and colleagues provides no compelling evidence that unsafe injections are a dominant mode of HIV-1 transmission in sub-Saharan Africa. We agree, however, that unsafe injections are an unacceptable practice and that efforts should be increased to reduce exposure of patients to bloodborne infections in health-care settings. At the same time, improved data are needed to identify these risks. We believe that research should focus not just on the formal health-care system (both public and private), but also on the informal health-care system and possibly additional practices—eg, circumcision—where even fewer data are available. Meanwhile, epidemiological evidence indicates that sexual transmission continues to be the major mode of spread of HIV-1 in Africa.

Contributors

G P Schmid, A Buvé, G P Garnett, G Calleja, R J Hayes, R Heimer, and J T Boerma conceived and designed the report. G P Schmid, A Buvé, P Mugyenyi, R J Hayes, P D Ghys, R Heimer, and J T Boerma acquired the data; which was analysed and interpreted by G P Schmid, A Buvé, B G Williams, R J Hayes, K M De Cock, J A Whitworth, S H Kapiga, C Hankins, B Zaba, and J T Boerma. The article was drafted by G P Schmid, A Buvé, G P Garnett, J Calleja, P D Ghys, and J P Boerma, and revised by G P Schmid, A Buvé, P Mugyenyi, B G Williams, R J Hayes, K M De Cock, J A Whitworth, S H Kapiga, P D Ghys, C Hankins, B Zaba, R Heimer, and J T Boerma. G P Schmid and J A Whitworth provided the study materials, and G P Garnett and B G Williams the statistical advice.

Conflict of interest statement

None declared.

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