MEASURE *Evaluation*

HIV, STDs and Infertility: Key Issues

Digest of a MEASURE *Evaluation*/UNAIDS/CDC meeting held in Arlington, Virginia, December 14-15, 1998

Introduction

The interaction between sexually transmitted diseases, HIV and infertility is complex and presents challenges when it comes to disentangling cause and effect. The three are independently associated with one another, and interactions between them are behavioural as well as biological.

This tangle of associations complicates the monitoring of trends in prevalence of infertility and STDs, including HIV. It may also frustrate efforts to evaluate programmes designed to reduce the prevalence of STDs and the incidence of infertility and HIV.

This document describes key issues raised by researchers working to illuminate the relationship between these three elements of sexual health. It is based on a research meeting held in Arlington, Virginia in December 1998 which was organized by MEASURE *Evaluation* at the University of North Carolina at Chapel Hill, in collaboration with UNAIDS and CDC. The meeting was sponsored by the Africa Bureau/SD of USAID (through the Measure *Evaluation* project) and UNAIDS. Although several of the observations and conclusions are generalizable to other less-developed countries, the primary focus was on sub-Saharan Africa.

Infertility: a public health concern in its own right

In recent decades, population policy has focused on fertility control; infertility remained largely neglected by public health officials. For the general public, however, infertility is a major issue. This is especially true in many of the Sub-Saharan African cultures where the prevalence of infertility is highest but where a woman's status may be determined by her ability to bear children. In this context protection against infertility is as much a ticket to social rights as it is to health.

It was not until the Cairo conference of 1994 that infertility was put on the public health agenda, and that the association between STDs and infertility became a major area of concern. Indeed in cultures where fertility is highly prized, infertility data can motivate governments to provide services to prevent and cure STDs.

Infertility is of particular importance in monitoring the HIV epidemic for three reasons:

- Most infertility is caused by STDs, which are a cofactor for HIV infection.
- Infertility may lead to marital instability and encourage multiple partnerships which increase the risk of contracting and passing on HIV.
- An association between HIV and infertility affects estimates of HIV prevalence based on data collected at antenatal clinics. It also affects estimates of pediatric AIDS and orphanhood.

Patterns of infertility

Worldwide, it is estimated that around three percent of women are infertile from birth. Beyond that, however, the prevalence of primary infertility (in women who have never borne a child) and secondary infertility (in women who have borne a child but who are unable to bear further children) varies enormously.

The prevalence of infertility is exceptionally high in Sub-Saharan Africa, where it is largely associated with reproductive tract infections (RTIs) that lead to the formation of scar tissue and the blockage of the fallopian tubes. It is estimated that over three-quarters of infertility in Sub-Saharan Africa is related to tubal damage, compared with around one-third in developed countries. Most RTIs are the result of STDs, although septic abortions, poor IUD insertions and poor obstetric practices also contribute. Since infertility, STDs and HIV are all most prevalent in Sub-Saharan Africa, the meeting focused on that region.

There is only limited evidence of the role of postpartum infections in causing secondary infertility. Postpartum infections may be related to poor obstetric practices and to increased risk of RTI/STD (e.g., through biological vulnerability of the female reproductive system or sexual behaviour of the husband). Data from Zimbabwe indicating that birth by Caesarean section may be associated with subsequent infertility give cause for concern. C-section delivery has been shown in industrialised countries to reduce the likelihood of transmission of HIV from mother to child, but the risk of subsequent infertility should be considered when recommending a C-section delivery.

Historical data from Africa have shown very high levels of infertility in a zone across Central Africa. But also in other parts of Africa infertility was very common and about one in 10 African women remained childless in the early 1950s. Analysis of survey data in Africa show that, on the whole, both primary and secondary infertility have fallen dramatically from the late 1940s or even earlier in some populations. Time trend analysis, a few intervention studies and micro-simulations show that the main part of the decline in infertility is associated with the introduction of antibiotics to treat STDs. In addition, long-term sexual behaviour changes in adolescence (a later age at first sex relative to the menarche) and host resistance to STDs and their sequelae may have contributed to the decline.

Issues in the measurement of infertility

There is no standardised definition of what constitutes infertility. Working definitions range from one to seven years of sexual activity without conception, though the intensity of sexual exposure is never specified. There is an urgent need to standardise definitions of infertility. Clinical diagnosis of infertility is invasive, expensive and impractical in countries where the prevalence of infertility is highest. Most estimates of the prevalence of infertility rely on extrapolating from data collected in birth histories or fertility surveys such as Demographic and Health Surveys (DHS), and as such focus exclusively on effects measured in females.

Extrapolations from survey data need to take into account contraceptive use. While some women using contraception will be infertile, contracepting women will, on the whole, be more likely to be fertile than non-contracepting women. In any case, as contraceptive use increases it will become increasingly difficult to estimate infertility from survey data. Some DHS provide calendar data, which could greatly improve analysis of exposure to pregnancy, infecundity, terminations and foetal wastage, giving much better estimates of infertility. Currently, the measures developed by Ulla Larsen present the best methods to estimate infertility from survey data.

The addition of a standardised question about efforts to conceive may improve estimates of infertility derived from survey data (a suggested question: "Have you been trying to become pregnant for at least the last x months?") Socially, infertility is only a burden when it is undesired, although the absolute prevalence of infertility remains important when considering interactions with STDs and HIV.

Infertility is not a viable marker for the burden of STDs

While the measurement of infertility is a worthwhile activity in its own right, it was generally agreed that it is not useful as marker for the burden of STDs for the following reasons:

- Infertility has several causes besides STDs.

- Infertility data tell us nothing about which STDs may have been responsible for the condition, and therefore are of limited value in planning service provision.
- Infertility is associated with past rather than current STD infection and is therefore of limited value in monitoring or evaluating the impact of current STD prevention or treatment programmes.
- Survey data are subject to strong survival bias. Infertility is strongly associated with STDs and HIV, and HIV is strongly associated with early death. So infertile women are disproportionately likely to have died before their infertility can be recorded in a survey and associated with STDs in the subsequent analysis.
- Infertility data only measure STD outcome for females.

Other ways of measuring STDs

The research meeting agreed that direct measurement of STDs was far more useful than indirect estimation based on infertility.

Diagnostic techniques for many of the pathogens causing STDs have improved markedly in recent years. However, many of them remain far too expensive for routine use in developing countries; even if increased demand pushes costs down. And, the need for highly trained technicians will limit their use. They have, however, proved to be viable in well-funded research projects in rural communities in developing countries.

RPR testing for syphilis among pregnant women at antenatal clinics is likely to remain the cornerstone of STD surveillance for some time. In theory, syphilis screening of pregnant women is a precursor to treatment and partner referral where indicated. Surveillance data are supposed to be an added bonus to this cost-effective intervention. However, sometimes the syphilis screening does not take place at all; where it does, the results are rarely fed into a national STD surveillance system. Yet this type of surveillance remains the most viable source of data on STD prevalence among women.

Syphilis screening among pregnant women provides an indication of the success of STD prevention and treatment programmes (WHO Prevention Indicator 8). Behavioural data, such as trends in consistent condom use provide other useful indicators of the success of such programmes.

While tests for current STD infection continue to improve, tests for past infection remain unreliable. Since infertility is a consequence of past rather than current STD infection, STD data are of limited use in assessing the burden of infertility.

The interaction between STD, HIV and fertility

It has long been known that STDs can cause infertility. The link between STD infection and HIV transmission is also well established. More recently, a clear association has been established between HIV infection and reduced fertility. This exists independently of other STDs or of behavioural modifications, although these may increase the magnitude of the association.

In a recent study in the United States, HIV positive women were significantly less likely to bear children than HIV negative women at every age, although no difference was detected in foetal loss by HIV status. The difference in fertility increased with the progression from initial infection to AIDS. This study did not provide a way of determining the relative contributions of biology and behaviour in reducing births among the HIV-infected. It is reasonable to assume, however, that with easy access to contraception, near universal HIV testing in pregnancy and access to safe abortions, U.S. women diagnosed as HIV positive may choose not to bear a child. In a number of studies in Africa, however, knowledge of HIV status has had only limited effect on subsequent efforts to conceive.

In a Ugandan study, significantly higher foetal losses were recorded among HIV-infected women. There was also a strong association between HIV and infertility. Regardless of whether or not they had syphilis, HIV-infected women were less than half as likely to become pregnant as those who were free of syphilis and HIV after adjusting for age, marital status and other potential confounders. Syphilis had an independent effect in reducing fertility, and was more common in HIV positive women.

Many of these studies were designed to detect infertility caused by HIV, rather than the reverse causal association. Given the importance of childbearing in establishing social position and securing access to family resources in Africa, however, it is not unreasonable to posit that infertile women may be more likely to have multiple partners, increasing their risk of HIV. A sero-incidence study in Uganda looked at pregnancy and sero-conversion in women with evidence of existing sub-fertility (women who were in the lowest 25 percent gravidity for their age group). The study found a strong association between subfertility prior to sero-conversion and subsequent infertility. In fact, pre-existing subfertility accounted for around half of all infertility in sero-positive women. In other words, the study results suggest that a large proportion of the reduced fertility in HIV-positive women is due to subfertility prior to HIV infection.

The behavioural consequences of infertility are clearly indicated in a Tanzanian study, where infertile women were more likely than fertile women to be divorced (often more than once) and to have multiple sex partners. The study also found that infertility was far higher in women working in bars than in the general population. In the study context, bar workers often offered sex on a commercial basis. HIV prevalence in the rural female population was 8 percent among fertile women and 22 percent in infertile women.

The cohort data from the four studies illustrate the difficulty in ascertaining the direction of the relationships between infertility and STDs. In almost all Sub-Saharan African data sets analysed, infertility is higher in urban than in rural areas. This may be because STDs are more common in urban areas. However, it may also reflect the fact that infertile women from rural areas are likely to be rejected by their families and communities and may have to move to urban areas in search of new partners or economic opportunities.

- In summary, HIV and infertility are related in four principle ways:
- Infertility leads to high risk behaviour and HIV infection
- Concurrent STDs such as syphilis independently reduce fertility and are more common in HIV positive women
- HIV has a direct biological effect on fertility
- Knowledge or suspicion of HIV status may lead to behaviour change and reduced exposure to pregnancy

Making better use of ANC data

Most HIV surveillance data, particularly in Africa, come from tests performed on pregnant women attending public antenatal clinics (ANC). These data are often extrapolated to create estimates for the entire adult population. However, pregnant women at public clinics ANC differ from the entire female population (not to mention the male population) in many ways, and some of these differences may introduce serious biases into national estimates derived from ANC.

Some of these biases can be corrected for by improving sentinel site selection and by collecting basic socio-demographic information from ANC attendees so that they can be compared with women in the general population and adjustments can be made for systematic differences.

The link between HIV and infertility introduces one potentially serious bias. Since HIV positive women are less likely to become pregnant than the HIV negative, they will be less likely to attend ANC and to be included in HIV surveillance samples. And since infertility increases with the length of infection, this bias may increase over time.

There are now several countries where population based sero-surveys can be compared with ANC-based surveillance figures. They show a remarkably consistent pattern. ANC data tend to overestimate infection in the youngest age group in the general population by about 40%, since these age groups include large numbers of women who are not sexually active and therefore not at risk of either HIV infection or pregnancy. In older age groups, they tend to underestimate infection by about the same magnitude. A summary prevalence figure for all ANC women aged 15-49 is usually 20% to 30% lower than the equivalent figure for women derived from population based studies. This bias may vary over time and affects assessments of trends.

Adjusting ANC data to correct for reduced fertility

A technique to adjust ANC data to reflect likely infection levels among women at risk of HIV but not of pregnancy (because of current sexual inactivity, contraceptive use and infertility) has been developed. The method uses survey data to determine the proportion of women in the general population in various risk categories of exposure to pregnancy. It then uses community-based sero-surveys to estimate the relative risk of HIV infection in each of these groups. The observed HIV prevalence in ANC women is multiplied by the appropriate relative risk measure and applied to the fraction of the female population 15-49 in each risk group. Sub-fertility in HIV-positive women still capable of becoming pregnant is allowed for by weighting by birth interval. This last refinement improves estimates but has a relatively small impact on the overall adjustment.

The major drawback of this method is that it requires relatively reliable estimates of relative prevalence in women in various risk groups in the general population. Given the diversity of the HIV epidemic, it is not clear how accurately the relative risk of infection between risk groups in one community will reflect the relative risks in any other population. In particular, relative risks measured in low contraceptive use populations may not be appropriate for more developed populations with high levels of contraceptive use.

Reporting HIV prevalence: age or parity?

Biases associated with infertility and mortality are unlikely to be pronounced in the early years of sexual activity. UNAIDS and its partners therefore recommend concentrating surveillance activities on the youngest age groups, where such biases are limited and where prevalence most closely reflects incidence.

There are, however, large variations in sexual activity in the late teens and (to a lesser extent) in the early 20s, so changes in the age structure of samples in these age groups may seriously distort prevalence estimates from year to year. Data collection by single year of age would overcome this difficulty, but is unlikely to be practical in all but the highest-turnover sentinel sites, since numbers of mid-teen pregnancies tend to be relatively small.

One approach, suggested to reduce artificial fluctuations in surveillance data designed to reflect incidence as closely as possible, is to report ANC prevalence by parity or gravidity rather than by age. (Parity is less prone to misreporting and would probably prove the more practical of the options.) Parity is more directly indicative of sexual activity than age, and prevalence at low parities would more accurately reflect changes in incidence among those newly exposed to unprotected sex than prevalence reported by age.

Micro-simulation shows that parity-based reporting of HIV prevalence among ANC women may offer a more robust guide to changes in HIV incidence in the general population than age-based reporting.

If a shift towards parity-based reporting is encouraged, careful thought needs to be given to continuity in data reporting and to constructing national estimates of HIV infection that are comparable with past estimates. The data on young women by parity (or age) would complement rather than replace the estimates based on all women.

Estimating HIV prevalence among men

While the proposed adjustment techniques and changes to ANC reporting methods may improve estimates of HIV prevalence and incidence for women in the general population, they do little to improve the accuracy of estimates for men. In most countries, surveillance data for men are non-existent or confined to high-risk groups such as clients at STD clinics. Virtually all national estimates in countries with generalised epidemics are based on the assumption that the sex ratio of infection is 1:1. In most of these countries, reported AIDS cases are roughly equal by sex, and a systematic gender bias in AIDS case reporting has been considered unlikely. It has also been assumed that most women are infected by their regular partners, and that HIV-related mortality is similar between the sexes. All of these assumptions are open to question.

Increasingly, community-based sero-surveys record somewhat higher levels of overall infection in women than in men. While higher non-response among men may introduce some bias, it is unlikely to account for observed differences in infection across the 15-49 age range of up to 50 percent. The difference is in part because women become infected younger than men, so higher proportions of the relatively larger younger age cohorts are HIV positive. There is also evidence that people infected young survive longer with the virus, which would increase overall prevalence among women.

Evidence of systematic differences between male and female prevalence remains relatively limited, but is certainly sufficient to question the basic assumption that for every infected woman in a population there will be one infected man. In a small but growing number of community-based sero-surveys, very similar patterns are seen between male and female infection rates: very distinctive age patterns with the mean age infection among women about five years younger than among men and somewhat higher prevalence among women compared to men. It may be possible to begin to develop standard adjustments to improve the extrapolation of ANC data to the overall population, although the often higher non-response rates among men in surveys pose a problem for adjustments.

A note on data use

As always, researchers and public health officials should consider the end users of their data before launching into cohort studies or modelling programmes. As noted, existing ANC data so far give a fairly robust summary figure of prevalence levels, but trend assessments are more problematic, as biases are likely to change over time. For the purposes of advocacy, this may well already provide more information than a government is willing to act on. Improving the accuracy of the estimate by a few percentage points would in this case be futile.

Where a government is actively involved in responding to the epidemic, and particularly in planning care and support for those affected, single summary figures are not good enough. It will be important to look at geographic variability (e.g. urban versus rural), adults versus children and men versus women. Reliable projections of paediatric AIDS and orphanhood (both affected by the HIV-fertility link) will also be important.

The most accurate data are needed to assess the progress and the impact of prevention and care programmes. More accurate data can be obtained by good quality, standardized data collection and laboratory testing procedures and by a well-designed sample of facilities with adequate geographic representatation. At present, the best low-cost option is HIV prevalence among young ANC women by age and/or parity. Indeed, small improvements in the accuracy of regular surveillance figures can be a major help in monitoring and evaluating the success or failure of the national response.

Unanswered questions

The research meeting identified several areas where more information is needed to improve understanding of STDs, HIV and infertility, and particularly of the relationship between the three. Some of these areas are listed here, in no particular hierarchy of importance:

- Standard operational definitions of infertility are needed. These should include consideration of the difference between desired and undesired infertility.
- It is clear that bacterial vaginosis (BV) is extremely prevalent in many African populations (recorded at 50 percent in one Ugandan study). However little is known about its relationship with pelvic inflammatory disease, gonorrhoea and chlamydia.
- More work is needed on male infertility, the possible contribution of STDs and HIV to male infertility and links with risk behaviour.
- The association between unsafe delivery practices (especially Caesarean section) and subsequent infertility needs investigation.
- Ethically sound methods of collecting community-based HIV and STD data need development. The feasibility of integrating sample collection into existing surveys such as DHS should be investigated. Particular attention should be paid to the potential for increased refusal bias to jeopardise the quality of overall survey data.
- DHS-type surveys may also be expanded to include data on service use to help identify possible biases in sentinel site data.

- Although not strictly related to the STD/HIV/infertility triangle, the meeting identified a clear need for more information on the relationship between male and female infection levels in high prevalence epidemics. Differential susceptibility and the possibility of different survival times with HIV infection should be investigated.

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