
GLOBAL
PROGRAMME
ON AIDS
AND
PROGRAMME
OF STD

REPORT OF THE CONSULTATION
ON SEXUALLY TRANSMITTED DISEASES
AS A RISK FACTOR FOR HIV TRANSMISSION

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1. INTRODUCTION

The Global AIDS Strategy has three objectives: (1) to prevent the transmission of the human immunodeficiency virus (HIV)¹; (2) to reduce the personal and social impact of HIV infection; and (3) to unify national and international efforts against AIDS. The World Health Organization and the United Nations General Assembly have called upon all countries to establish national AIDS prevention and control programmes in conformity with the Global AIDS Strategy.

Epidemiological studies document only three routes of HIV transmission: through sexual intercourse (heterosexual or homosexual), exposure to blood, blood products or donated organs and semen; and from infected mother to child. Sexual transmission is the most predominant of these routes of transmission. Information regarding biological factors which may influence the sexual transmission of HIV are therefore of crucial importance. Recent studies have suggested that sexually transmitted disease (STD), particularly those which cause genital ulceration (GUD)², may facilitate the transmission of HIV-1.

To review available information on STD as a risk factor for HIV transmission, the World Health Organization's (WHO) Global Programme on AIDS (GPA) and Sexually Transmitted Disease Programme (VDT) convened a Consultation in Geneva from 4 to 6 January 1989. A total of 32 participants from 21 countries participated, in the three-day meeting including experts in public health, epidemiology, biomedical research and social science aspects of AIDS and STD.

The Consultation had the following objectives:

1. to review and assess the available data regarding STD as a risk factor for HIV transmission;
2. to identify future research priorities and methodologies for better understanding of the biological interactions between HIV and STD;
3. to consider strategic and programmatic implications of the results of discussion on objectives 1 and 2.

Dr D. Heymann, Acting Chief, Epidemiological Support and Research Unit (ESR), GPA, called the Consultation to order and Dr J. Mann, Director, GPA, and Dr A. Meheus, Programme Manager, VDT, welcomed the participants. Dr P. Piot (Belgium), chaired the meeting, and Dr M. Melbye (Denmark) acted as rapporteur.

¹ HIV is used throughout this document unless the data are specific for HIV-1 or HIV-2.

² Herein referred to as genital ulcer disease (GUD) although some of these ulcerations may not be clinically evident.

The Consultation began with an overview of STD and HIV epidemiology to ensure the necessary background information. Methodologies and the results of specific studies which examined STD as a risk factor for HIV transmission were then presented and discussed.

Three working groups were then established to consider the following specific issues regarding STD as a risk factor for HIV transmission: research evaluation (chaired by Dr R. Ancelle), research needs (chaired by Dr R. Greenblatt) and programme implication (chaired by Dr R. Coutinho). The Consultation summarized the discussion, then drafted and approved a Consensus Statement.

2. STUDIES ON STD AS A RISK FACTOR FOR HIV TRANSMISSION

The following studies were presented and discussed along with other previously published studies not included in the presentations. All studies were discussed in the following format:

1. Study design
2. Measurements conducted/definitions used
3. Potential source(s) of bias
4. Presence of confounding variables
5. Potential interactions of results
6. Sample size
7. Populations studied

The discussions included a careful evaluation of the following criteria:

1. Temporal sequence
2. Consistency among studies
3. Strength of association
4. Biological gradient
5. Specificity of the effect
6. Biological plausibility.

2.1 Europe

A total of 197 female sexual partners of HIV seropositive men from six European countries were analysed for HIV status in a European Multicentre Study. Females reporting sexual contacts other than the HIV seropositive partner were excluded. Histories of genital infections within the past five years from both males and females were compared to the HIV status of the female partners. Multivariate analysis was used to control for sexual behaviour, clinical status of the male index case and other characteristics of the couples, and results were presented.

2.2 Kenya

A cohort of HIV seronegative female prostitutes was followed over a period of 30 months, with reassessment of HIV status at six monthly intervals.

Six monthly interviews were conducted which included: Physical examination, including genital examination; culture for *N. gonorrhoeae*, *C. trachomatis*, *H. ducreyi*; serology for syphilis; and interviews regarding sexual practices. HIV seroconversion was compared to the presence of STD using univariate and multivariate analysis with adjustment for the number of sexual partners per day.

A cohort of HIV seronegative men were followed for several months. These men had presented to an STD clinic and had a history of recent sexual exposure to prostitutes who lived in a low income district of Nairobi. At varying intervals during the follow-up period, the type of STD at the time of enrolment in the cohort was compared to HIV serostatus, using both univariate and multivariate stepwise logistic regression analysis; reports of these studies were presented.

2.3 Netherlands

A cohort of 748 male homosexuals had been studied in Amsterdam since late 1984-early 1985. Members of the cohort have been interviewed every three months and asked to provide a blood sample for virological and immunological analyses. Multiple linear regression analysis was performed on eight significant univariate variables which correlated with HIV seropositivity including syphilis serology, sexual practices and previous history of GUD. Results of this analysis were presented.

A sample of 117 intravenous drug-using female prostitutes attending an STD clinic in Amsterdam between 1985 and 1987 was studied. History of STD during the preceding six months was determined from clinic records for each of the women and the women were requested to provide blood samples for syphilis testing. History of STD and its relationship to HIV seropositivity was subjected to both univariate and multivariate logistic regression. Preliminary results of the analysis were presented.

2.4 Uganda

Results from a national serosurvey to determine the seroprevalence of HIV infection were reported, and HIV seropositivity was compared to reported history of STD at any time prior to the survey. Data from a national surveillance system for AIDS were reported and the presence of AIDS was compared to reported history of previous STD. Preliminary results of a study of 1 300 patients were presented in which the clinical diagnosis of STD was compared to HIV-seropositivity. Clinical diagnosis of STD was not confirmed by microbiological or serological studies. HIV testing was performed using a competitive ELISA; repeat ELISA testing was used for confirmation in most instances.

2.5 USA

The relationship of self-reported STD to HIV seropositivity was examined in two study populations of homosexual men, one recruited in the neighbourhood surrounding the San Francisco General Hospital, the other from the hospital STD clinic. Multivariate analysis was used to control for the number of lifetime sexual partners.

A cohort of 1 600 homosexual men, randomly selected from 6 700 men who attended the city STD clinic and participated in a study of hepatitis B, has been studied in San Francisco since the late 1970s. Serial blood specimens from a subgroup of 62 HIV-seronegative men were tested at the Centers for Disease Control for a variety of infectious agents including HIV and herpes simplex virus type 2 (HSV-2). HSV-2 serostatus was compared among men who remained HIV seronegative and those who seroconverted to HIV.

A prospective examination of discordant heterosexual pairs in which the males were HIV seropositive was conducted in the California partner study group. Several factors in males were examined including lifetime number of STD, serology for HSV, and serology for syphilis. HSV and syphilis serology, and cultures for N. gonorrhoeae and C. trachomatis were performed on HIV seronegative female partners at regular intervals. Results of laboratory tests were compared to the HIV status of the women and logistic regression analysis was performed for significant univariate correlations.

Two populations of homosexual men were studied in Seattle. One group included 200 attendees of an STD clinic who had symptoms of acute rectal or gastrointestinal infection (proctitis-enteritis group); the other included 111 men who sought HIV serologic testing and counselling (AIDS prevention project group).

Syphilis, HSV and HIV serologic testing were performed on blood specimens collected from both groups. Present and prior history of STD and history of sexual practices were obtained in the proctitis-enteritis group. History of sexual practices was also obtained for men in the AIDS prevention group. Results of serologic testing, of history of sexual practices (among the proctitis-enteritis group) and sexual behaviour were compared to HIV serology using logistic regression to adjust for sexual activity. Results of all these studies were presented.

Data on the prevalence of genital ulcer-causing infections in the US were presented from the Centers for Disease Control (CDC) surveillance reports. The incidence of primary and secondary syphilis is as high as 64.3 per 100 000 among 20-24 year old males, and is higher among subgroups of the population. Approximately 5 000 cases of chancroid were reported to the CDC in 1987. Those geographic regions and subpopulations in the US which have the highest rates of HIV infection also have the highest incidence of syphilis and chancroid. In addition, antibody to HSV-2 is present in approximately 20% of persons over the age of 30 years, but the proportion of these persons who develop recurrent genital ulcer is not known. The presentation dealt in depth with the methodologic problems associated with calculation of the attributable risk of GUD in the acquisition of HIV infection.

A recent decrease in the incidence of gonorrhoea and syphilis in Sweden with a paradoxical simultaneous increase in the incidence of chlamydia, was also reported. This may be explained by an increased use of laboratory tests for diagnosis of chlamydial infection. The sex ratio for gonorrhoea in Sweden is approaching unity and reflects a similar pattern seen for syphilis in the US. Attention was drawn to a change in the ethnic distribution of patients with gonorrhoea in the US, with an overall decline among whites and an increase in blacks. A newly identified epidemic of syphilis among inner city minority populations, where sex is exchanged for drugs, was discussed.

2.6 Zambia

Among attendees at four STD clinics in Lusaka HIV seroprevalence was compared to clinical ulcerative and non-ulcerative STD diagnosed in the clinics. In order to determine the incidence of HIV, a subgroup of attendees who were HIV seronegative were followed for a two year period. Incidence of HIV among this subpopulation was compared to the HIV incidence among women attending antenatal clinics; results of these comparisons were presented.

2.7 Zaire

Physical examination for clinical evidence of STD, confirmed by direct microscopy, culture and/or serology, was conducted on 761 female prostitutes who were recruited from hotels, homes and streets in Kinshasa. Blood specimens were also tested for HIV. Results of HIV testing were compared to the previous history of STD as reported by the women and to physical presence of STD at the time of blood testing.

Interviews conducted with employees and spouses at a textile factory and a bank in Kinshasa, included a physical examination and the provision of a blood specimen for HIV testing. Results of HIV testing were compared to prior history of STD, in particular genital ulcer disease. Reports of both of these studies were presented.

2.8 Zimbabwe

The wives of 270 HIV seropositive men provided blood specimens for HIV testing. A history of STD during the preceding two years was obtained from the men and compared to the HIV status of the wife; results of this comparison were presented.

3. CONSENSUS STATEMENT¹

The Consultation developed the following consensus statement:

A. STD as a risk factor for HIV transmission

1. While HIV-1 is transmitted sexually in the absence of other STD, the weight of the evidence for genital ulcer disease (GUD) as a risk factor for HIV-1 transmission is sufficiently strong that GUD intervention may contribute to prevention of sexual transmission of HIV-1.
2. Several studies in developing countries have shown that GUD is associated with HIV-1 infection in heterosexuals. A few studies have shown an association of antibody to herpes simplex virus type 2 (HSV-2) and to Treponema pallidum (the major causes of genital and anorectal ulcers in industrialized countries) with HIV-1 infection in homosexual men, and in heterosexual men and women.
3. Evidence for these associations is consistent in most studies, but because GUD and HIV-1 are both sexually transmitted it is necessary to examine only studies that have attempted to measure and adjust for confounding and bias, primarily involving sexual behaviour.
4. The evidence is strongest for GUD in Africa where prospective studies have been done which have given consistent results. There is also evidence for a temporal association between GUD and HIV-1 infection which further suggests that GUD facilitates transmission of HIV-1.

¹ Weekly Epidemiological Record, Z: 46-48 (1989)

5. Sero-epidemiological studies which have examined the relationship of HIV-1 with HSV-2 and T. pallidum have demonstrated a consistent association of the two with HIV-1 infection. Some evidence in homosexual men suggests that a temporal association exists for HSV-2 and HIV-1.
6. While some studies have found an association between other STD pathogens or STD syndromes and HIV-1 infection, the available data are inconsistent and insufficient to assess their role as risk factors for HIV-1 transmission.
7. It is biologically plausible for all STD pathogens that cause genital ulcers or inflammation to be risk factors for increased infectiousness or increased susceptibility to HIV-1 infection.
8. In general, it is not possible from available data to distinguish an effect on increase of susceptibility to HIV-1 infection in an HIV-seronegative person with an STD, from an effect on increased infectiousness of HIV-1 in a HIV-seropositive person with an STD.
9. The importance of genital ulcers on increasing transmission at the population level (population attributable risk), as opposed to the individual level, has been calculated in only one study of prostitutes and STD clinic patients and cannot be generalized. Therefore, the proportion of sexually transmitted HIV-1 infections which can be attributed to GUD has not yet been defined for the general population.
10. Intervention trials have not yet been done, the results of which may further support GUD as a risk factor in increasing HIV-1 transmission: such trials would further be helpful in assessing the effectiveness of GUD control in reducing the sexual transmission of HIV-1.

B. Research priorities

The main needs identified for further research are:

1. Effectiveness of GUD control in reducing sexual transmission of HIV-1 (intervention trials).
2. The effects of STD on HIV-1 transmission. Although a large volume of data is available in this area, few cohort studies have been performed and rigorously controlled for microbiologic etiology of the STD and the sexual behaviour of the participants. In addition, statistical methodology to examine the effects and interactions of two highly related events need to be refined and standardized. The two specific questions that need to be examined in female-to-male, male-to-female, and male-to-male sexual relations are: (1) Among individuals not infected with HIV-1, do STD increase susceptibility to HIV-1 infections? (2) Among those infected with HIV-1, do STD increase the likelihood of HIV-1 transmission to their uninfected sexual partners? Important factors to be included in any study are controlling for sexual behaviour, attempting to quantify HIV-1 exposure risk, examining with reliable methods all potentially important STD, with appropriate consideration being given to sample size and methods of analysis. Other factors to be considered in study design and analysis are circumcision, contraception, social class, duration of HIV-1 infection and stage of disease.

3. There is an urgent need for innovative strategies for control of GUD.
4. Studies of epidemiology and biology of STD as pertains to HIV-1 transmission and the effect of HIV-1 on STD. A better understanding of the epidemiology of some STD, such as chancroid, is required. Better assessments of population prevalence and incidence of STD are needed for determining population-attributable risk and for monitoring changes in sexual behaviour. Appropriate diagnostic techniques for many STD, especially GUD, need to be developed or improved, especially for field conditions. The effect of HIV-1 infection on manifestations, recurrence, diagnosis and therapy of STD needs to be clarified. These studies need to take into account the effects of sexual orientation, gender and geographical setting on this interaction.
5. Basic research is needed on techniques for assessing sexual behaviour. In addition, it is important to collect systematic information on the sexual behaviours of different populations in all areas of the world.
6. The effect of STD on the natural history of HIV-1 infection in individuals.
7. Biology of the sexual transmission of HIV-1 and STD. Basic science studies should include immunopathology of STD, genital shedding of HIV-1 with and without STD, the effects of mechanical damage to the genital epithelium and study of potential target tissues in the genital tract. Animal models may be useful to simulate sexual transmission of HIV-1.
8. As all previous studies have evaluated the association of HIV-1 and STD, it is also important to obtain information on the interaction of STD and HIV-2.
9. The Consultation also identified three priority areas for action:
 - (a) development of study design and statistical methods best adapted to examining the interactions between two highly related events, such as STD and HIV infections;
 - (b) promotion of exchange of information and discussion among investigators in this field;
 - (c) development of intervention studies on control of GUD and on the effects of GUD control on HIV transmission.

C. Strategic and programmatic implications

1. The global importance of STD, including complications and sequelae particularly in women and newborns, as well as the emergence of the HIV pandemic, mandate the development and strengthening of STD control programmes, in all countries and at all levels. For example, in countries where effective STD control does not yet exist, STD interventions should be established and integrated into already existing primary health care infrastructures.
2. The AIDS pandemic further emphasizes the urgent need for increased support for broad programmes of STD prevention, control and research. At the national and international level, STD and AIDS prevention and control programmes should work together to develop strategies and effective means of programme interaction and mutual support. In addition, it is essential that STD and AIDS researchers collaborate in areas of common interest.

3. As modes of transmission are similar, primary prevention of either STD or sexual transmission of HIV will help to reduce transmission of the other. For example, behavioural interventions including condom promotion will help reduce both STD and sexual transmission of HIV, and persons at high risk for HIV infection can be reached through STD services for preventive intervention.
4. STD and AIDS programmes need to take into account the emerging evidence on GUD and HIV-1, as early and adequate management of GUD may contribute to reducing HIV-1 transmission.
5. The World Health Organization is requested to consider coordinated action to address the policy, programmatic and research issues discussed in this document.

ANNEX 1

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