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THE EPIDEMIOLOGY OF HIV INFECTION AND AIDS

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ABSTRACT

The current state of knowledge on the epidemiology of HIV infection and AIDS is reviewed, with extensive references to the medical literature. The particular focus is on those aspects of the epidemiology of HIV infection which are of interest in the formulation of models for projecting the future spread of the virus and its impact in terms of numbers of cases of AIDS and deaths from AIDS.

KEYWORDS

AIDS; Epidemiology; HIV

1. THE ORIGINS OF HIV

1.1 In June 1981 Gottlieb and colleagues reported the occurrence of *pneumocystis carinii* pneumonia in 4 previously healthy homosexual men in Los Angeles (C.D.C., 1981). This was regarded as unusual because opportunistic infections of this type rarely occurred in the absence of immunosuppressive therapy. The conclusion was drawn that the observed syndrome represented a potentially transmissible immune deficiency (Gottlieb *et al.*, 1981).

1.2 A report also appeared in June 1981 in the United States Centers for Disease Control (C.D.C.) Morbidity and Mortality Weekly Report of cases of *pneumocystis carinii* pneumonia and Kaposi's sarcoma, which had been observed in 11 homosexual men and drug abusers between July 1979 and April 1981 (C.D.C., 1981a). This suggested a possible underlying infection resulting in cellular immune deficiency (Masur *et al.*, 1981).

1.3 These cases, together with another report of 4 homosexual men with severe perianal ulceration (Siegal *et al.*, 1981) were presented in the *New England Journal of Medicine* on 10 December 1981, accompanied by an editorial (Durack, 1981).

1.4 Following these initial reports, the C.D.C. established a task force to undertake surveillance and to carry out further investigations. This led to the identification of 159 documented cases of Kaposi's sarcoma, *pneumocystis carinii* pneumonia and other serious opportunistic infections reported to the C.D.C. between 1 June and 10 November 1981 (C.D.C. Task Force on Kaposi's sarcoma and opportunistic infections, 1982).

1.5 The condition became known as the acquired immune deficiency syndrome or AIDS. A case definition was drawn up by the C.D.C. for

surveillance purposes (see § 3.2) and was subsequently endorsed by the World Health Organization (W.H.O.).

1.6 The viral agent which is thought to be responsible for causing AIDS was identified by Barre-Sinoussi *et al.* (1983) and Gallo *et al.* (1984). Gallo had isolated HTLV-I, the first human retrovirus, which was associated with adult human T-cell leukaemia, in 1978, although retroviruses had been known to cause leukaemias, lymphomas and immune deficiency conditions in animals for over 50 years. In 1982 Gallo postulated that the cause of AIDS was likely to be a new human retrovirus. Further development work by Montagnier, Barre-Sinoussi and others at the Pasteur Institute in Paris and by Gallo and Essex at Harvard Medical School resulted in the identification of a virus which the American team named human T-cell lymphotropic virus type III (HTLV-III) and the French team lymphadenopathy-associated virus (LAV) (Wong-Staal & Gallo, 1985; Gallo, 1987).

1.7 At this stage it had not been demonstrated that the viruses, which were subsequently shown to be different strains of the same virus, were in fact the cause of AIDS. In late 1983 Gallo *et al.* were able to grow significant quantities of the new virus and also to demonstrate that the virus was present in a group of AIDS patients, but not in a control group of healthy heterosexuals (Gallo *et al.*, 1984; Popovic *et al.*, 1984). The International Committee on the Taxonomy of Viruses subsequently recommended that the new virus should be known as HIV, the human immunodeficiency virus (Coffin *et al.*, 1986).

1.8 Tests on stored serum samples suggest that American homosexuals and haemophiliacs first became infected with HIV in 1977/78 (Jaffe *et al.*, 1983; Melbye, 1986). Some evidence suggests earlier cases in Central Africa (Brun-Vézinet *et al.*, 1984; Melbye, 1986; Nahmias *et al.*, 1986; McClure & Schulz, 1989). The origins of HIV remain a mystery, but it has been suggested that there may be some connection with similar retroviruses found in certain species of monkey in Central Africa (Penny, 1988; McClure & Schulz, 1989). Another possibility is that HIV evolved from a non-pathogenic human virus. Flahault & Valleron (1988) have shown that the current global distribution of HIV infection is consistent with the hypothesis of a central African origin in the 1950s, taking into account the role of air transport movements around the world. The virus could, in fact, have existed for many years prior to this in isolated communities in Central Africa, only spreading more widely as a result of social changes in the 1950s and 1960s and key population movements, such as those involving large numbers of people from Haiti going to Zaire to work in the 1960s and then returning to Haiti (Chuffart, 1988).

1.9 Although the vast majority of AIDS experts accept that HIV is what causes AIDS, there are a few dissenting voices (Duesberg, 1987, 1988, 1989; Adams, 1989; Stewart 1989). There is much that is not yet fully understood about the transmission of HIV and about what triggers the development of AIDS, but for the moment it seems reasonable to accept the hypothesis that AIDS is the direct result of infection with HIV.

2. THE NATURE OF HIV

2.1 The virus has been described by Gallo (1987). HIV has RNA as its genetic material and when it enters a host cell the RNA is used as a template to assemble a molecule of DNA. The DNA travels to the cell nucleus and, in appropriate circumstances, replicates itself and infects other cells, whilst at the same time destroying the originally infected cell. HIV can infect various different types of cell, but a favourite host is a T4 lymphocyte, a white blood cell which has a key role in regulating the body's immune system.

2.2 The long incubation period associated with the development of AIDS seems to arise because the virus can remain latent within infected cells for many years before a secondary infection stimulates the process of viral replication. Until this happens, there may be little evidence of illness in the infected person and very low levels of antigen in the blood. The initial infection will normally have stimulated the creation of antibodies to HIV and these will be present, to a greater or lesser extent, in the infected person's blood. A number of studies have shown, however, that formation of antibodies, known as seroconversion, may take place some time after the initial infection, in some cases up to 3 years later (Salahuddin *et al.*, 1984; Ranki *et al.*, 1987; Imagawa *et al.*, 1989). Although antibodies usually develop eventually in someone infected with HIV, they do not seem to offer sufficient protection from the subsequent development of AIDS.

2.3 Once the virus starts to replicate actively and to infect other cells, the number of T4 lymphocytes in the blood can soon be dramatically reduced. Two of the indicators of progression towards AIDS are a reduction in the number of T4 lymphocytes and a reduction in the ratio of T4 helper cells to T8 suppressor cells (Quinn *et al.*, 1987: Redfield *et al.*, 1986; Redfield & Tramont, 1989).

3. DIAGNOSIS OF AIDS

3.1 HIV infection does not manifest itself in any single illness or progression of symptoms. The infected person may remain asymptomatic for many years. At some stage various symptoms begin to appear, in particular swelling of the glands (lymphadenopathy), weight loss, sweating and diarrhoea. As the infection takes hold and the body's immune system is progressively impaired, other minor infections are less readily brought under control than would usually be the case. Other symptoms may include progressive dementia, sometimes called HIV disease or AIDS dementia complex (Black, 1985; Price *et al.*, 1988; Jakobsen *et al.*, 1989).

3.2 The original case definition for AIDS established by the C.D.C. in the United States of America was:

(a) a reliably diagnosed disease that is at least moderately indicative of an underlying cellular immune deficiency. For example, Kaposi's sarcoma in a patient aged less than 60 years, or opportunistic infection, and

(b) no known underlying cause of the cellular immune deficiency nor any other cause of reduced resistance reported to be associated with the disease.

3.3 This original definition was extended in June 1985 (C.D.C., 1985) and, again, in the summer of 1987 (C.D.C., 1987). It was anticipated that the new definition, which came into effect in the United Kingdom from the beginning of 1988, would result in an increased number of cases and there was evidence from the U.S.A. that the number of cases covered by the new definition could be up to 10% higher (Kirn *et al.*, 1988; Robertson, 1988; Rutherford *et al.*, 1988; Stehr-Green *et al.*, 1988). However, many of the additional cases in the U.S.A. have been amongst drug users and, with the currently fairly low proportion of U.K. AIDS cases in this category, it is not thought that the change of definition has had a major effect of AIDS reporting in the U.K.

3.4 Once AIDS has been diagnosed, the body's immune system is severely compromised, leading to opportunistic infections. The range of diagnoses can be quite wide, but by far the commonest conditions in patients with AIDS are *pneumocystis carinii* pneumonia and Kaposi's sarcoma.

4. SURVIVAL WITH AIDS

4.1 The inability of the person with AIDS to withstand infection means that survival times are relatively short. National AIDS surveillance data are generally in a suitable form for investigating survival, although the necessary detail regarding both date of diagnosis and date of death may not be included on publicly available databases.

4.2 There are problems also with ensuring that all deaths of AIDS cases have been reported and linked to the AIDS case data. Deaths of people with AIDS are not in general attributed to AIDS (Bobby *et al.*, 1988; King, 1989). McCormick (1988) found 95 conditions which might be given on the death certificate for deaths of people infected with HIV.

4.3 The Communicable Disease Surveillance Centre (C.D.S.C.), which is responsible for monitoring AIDS cases in the U.K., relies on medical staff in hospitals and clinics around the country to report cases where AIDS has been diagnosed. The subsequent death of an AIDS case may not be reported, sometimes because the person with AIDS may have moved to a different area before death, or simply because there is less incentive to report a death. Deaths which are identified from death certificates as possible deaths from AIDS are checked against the records of people with AIDS, but many deaths can be expected to be missed by this procedure. However, the C.D.S.C. has begun an annual follow-up exercise of all people with AIDS who have been reported, but who are not known to have died. This has resulted in a number of additional deaths being identified and should ensure that any survival analysis based on followed-up data is reasonably reliable.

4.4 Overton *et al.* (1988) described an analysis of all cases of AIDS reported in the U.K. up to September 1987 and found a median survival time of about 10 months. A similar result has been obtained by analysis of a more recent data set which has been subject to a follow-up exercise. For cases of AIDS reported in the U.K. up to December 1988, our own analysis pointed to an overall median survival time of 11 months. About 46% have survived for 1 year, 21% for 2 years and 13% for 3 years. Survival probabilities are higher for the younger age-groups and, generally, for later years of diagnosis.

4.5 Marasca & McEvoy (1986) examined the survival times of the first 1978 cases of AIDS reported to the C.D.S.C. (including cases in Scotland reported to the Communicable Diseases (Scotland) Unit (C.D.S.U.)) up to 1 June 1985, but without any follow-up of cases to check whether any had subsequently died without this being reported. They found a median survival time of 13·5 months, with a standard error of 1–2 months. Three-quarters of the patients were dead after 28 months.

4.6 Marasca & McEvoy also looked at differences in survival time for patients with different modes of presentation of AIDS. Cases with Kaposi's sarcoma exhibited the highest probabilities of survival, with a median survival time of 21 months, and 44 months elapsing before three-quarters of the patients were dead. Patients with *pneumocystis carinii* pneumonia had a median survival time of 12·5 months and three-quarters of the patients were dead after 22 months. Among those presenting with both Kaposi's sarcoma and *pneumocystis carinii* pneumonia the median survival time was 6·6 months; three-quarters of these patients were dead after only 10 months.

4.7 Some similar findings have been described by Rothenburg *et al.* (1987), based on a cohort of 5,833 people with AIDS in New York City, diagnosis of AIDS having been made up to 31 December 1985. In this study, 48·8% survived for one year, 28·3% for 2 years and 22% for 3 years. This is not very different from the results presented by Marasca & McEvoy (1986). However, the much larger data set in Rothenburg *et al.* (1987) permitted a more detailed analysis of survival probabilities by different variables. This showed higher survival probabilities for males than females, for the age-group 30–34 as compared with other age-groups, for homosexuals than intravenous drug users and for AIDS cases presenting with Kaposi's sarcoma as compared to other diagnoses. However, the results of this study are not entirely satisfactory, since it was not possible to follow up all the cases.

4.8 Survival experience in other populations of people with AIDS has been similar (Greco *et al.*, 1988; Whyte *et al.*, 1988; Chang *et al.*, 1988; Hassig *et al.*, 1988), but there is evidence that cases of AIDS diagnosed in more recent years are exhibiting longer survival times (Lemp *et al.*, 1988; NH & MRC Special Unit, 1989). This could be due to the influence of drug treatment now being made available to many people with AIDS, in particular zidovudine. It may, on the other hand, reflect earlier diagnosis and reporting of AIDS cases as physicians become more familiar with the diagnosis of AIDS. Redfield & Tramont (1989)

report that the average survival time of people with AIDS is now almost 2 years, whilst a recent report from Australia shows a similar picture, with over 70% of cases diagnosed in the last 2 or 3 years surviving for 1 year (NH & MRC Special Unit, 1989).

4.9 Fischl, Richman *et al.* (1987) reported on the original double-blind placebo-controlled trial of zidovudine (then called AZT or azidothymidine), which was halted because early evidence from the trial suggested that the drug was having a significant beneficial effect on those receiving it and it was thought improper to withhold the treatment from those receiving only a placebo. Richman *et al.* (1987), however, drew attention to the adverse side effects resulting from treatment with zidovudine.

4.10 In a follow-up study of 297 patients from the original double-blind, placebo-controlled study who continued taking zidovudine, Richman *et al.* (1988) showed that 85% of those taking zidovudine throughout the trial had survived for 52 weeks since entry, compared to 67% of those originally given a placebo and transferred to zidovudine after 17 weeks. Too few patients who had never taken zidovudine remained under observation at 52 weeks to give a reliable comparative figure, but only 54% of this group survived to 36 weeks.

4.11 More recently, there have been a number of reports of the beneficial effect on the survival experience of people with AIDS after being treated with zidovudine (Dournon *et al.*, 1988; Creagh-Kirk *et al.*, 1988; Williams *et al.*, 1989; Stambuk *et al.*, 1989). Bach (1989) and Larder *et al.* (1989, 1989a) have drawn attention to the limits of the efficacy of zidovudine when treatment is continued for a long period, suggesting that HIV becomes resistant to the drug after a while (Marx, 1989). The different studies have been reviewed by Fischl (1989).

4.12 Others have suggested that zidovudine can be used to good effect in the treatment of people infected with HIV in order to delay the onset of AIDS (*Lancet* editorial, 1989; Tersmette *et al.*, 1989; Henderson & Gerberding, 1989) and first results of trials on asymptomatic patients have confirmed this (Weller, 1989).

4.13 Other drugs will no doubt become available in the next few years, out of the large number of potential candidates currently being considered or undergoing trial, and further improvements in the survival prospects of people with AIDS can be expected. Pentamidine has been used from the beginning of the AIDS epidemic in the treatment of *pneumocystis carinii* pneumonia (C.D.C. Task Force on Kaposi's sarcoma and opportunistic infections, 1982). More recently there has been considerable interest in the use of pentamidine aerosol and combined therapies involving pentamidine and zidovudine (Girard *et al.*, 1989) and other combinations. Few people believe, however, that with any of these treatments it will be possible to do more than delay death from AIDS by a few months, or at most a few years.

5. TESTING FOR HIV

5.1 Most of the tests commonly used to establish the presence of HIV infection seek to detect antibodies to HIV. Direct testing for HIV antigen is possible, but is a more expensive and difficult process. HIV antibodies normally develop in the blood soon after infection with HIV takes place, but the delay in seroconversion is thought to be rather variable. As mentioned in § 2.2, some studies have suggested that antibodies could take up 3 years to form in some cases (Ranki *et al.*, 1987; Imagawa *et al.*, 1989; Horsburgh *et al.*, 1989).

5.2 The standard test for HIV antibodies is the enzyme-linked immunosorbent assay test (ELISA), which is quick to perform and relatively cheap (Weiss *et al.*, 1985). It detects antibodies to whole and partial virus and measures the total amount of antibodies present in serum, the liquid part of blood. A different type of test, known as the Western Blot, uses electrophoretic separation of virus proteins and glycoproteins to give a profile of bands characteristic of HIV when antibodies to the major individual proteins that make up HIV are present. A person who registers a positive result from an appropriate series of tests is described as HIV-positive (C.D.C., 1985a; Nishanian *et al.*, 1987). Western Blot is often used as the main confirmatory test, but some have suggested that a wider range of tests should be employed (Oldham *et al.*, 1987).

5.3 The studies of latency to which reference has already been made (see § 5.1) have used either more sophisticated antibody tests (Ranki *et al.*, 1987) or have isolated HIV and tested the cultured virus directly using the reverse transcription assay (Imagawa *et al.*, 1989). More recently there have been some developments in the use of a test known as polymerase chain reaction (PCR). This is a very sensitive test, which amplifies proviral sequences of HIV using DNA (Ou *et al.*, 1988). Several studies have shown how HIV can be identified by means of PCR in patients registering as negative by the standard tests for antibodies (Wolinsky *et al.*, 1988; Pezzella *et al.*, 1989; Imagawa *et al.*, 1989; Rogers *et al.*, 1989).

5.4 The accuracy of tests for HIV is a matter of considerable public concern. There would be particular concern over false positives since these cases would be wrongly identified as having HIV infection, which could give rise quite unnecessarily to tremendous psychological and social pressures (Meyer & Pauker, 1987). False negatives are of less concern from this point of view, but if the tests are imperfect in this respect, they may be unsatisfactory for screening blood donations. Ward *et al.* (1988) discuss the extent to which the blood supply is still contaminated with HIV, in spite of screening for HIV antibodies.

5.5 In a testimony to a U.S. Congress Subcommittee in October 1987, Lawrence Miike, of the Office of Technology Assessment, showed how, even with extremely accurate tests for antibodies to HIV, a major proportion of positive results may be false positives if the prevalence of the virus is very low in the population being tested (Miike, 1987). Both sensitivity (the proportion of infected people correctly identified as infected) and specificity (the proportion of

people who are not infected who are correctly identified as not infected) are, in principle, very high for the ELISA and Western Blot tests. Miike quotes the tests' capabilities as being 99·6% sensitivity in both cases and specificity of 99·0% for the ELISA and 99·5% for the Western Blot. Using these figures, and assuming a population in which 10% are infected with HIV, 8·3% of all positive results would, in fact, be false positives. However, this assumes only one test, which is not the case in practice.

5.6 In a population in which 1% are infected with HIV, the above calculation shows that 49·8% of all positive results would be false positives. In such circumstances, relying on a single test would clearly be highly unsatisfactory. The result would be even worse if testing a very low prevalence population, such as in any general screening of the U.K. population, where the proportion of false positives could be as high as 95%.

5.7 Miike uses this as an argument against widespread testing. His arguments have been espoused by others who would like to prevent insurance companies from testing for HIV. However, the argument's main strength is in relation to testing using a single ELISA or Western Blot test. The use of a second test reduces the proportion of false positives to less than 1% with a 1% prevalence population. The use of a protocol, such as might be used in insurance applications, of, for example, two ELISA tests followed by a Western Blot, reduces the percentage of false positives to 0·005%, or 0·1% in the context of a very low prevalence population (0·05% HIV positive), such as the overall U.K. population. This would mean 27 cases falsely identified as HIV positive if the entire U.K. population of around 55 million were tested.

5.8 The more that combinations of tests are devised to minimise the number of false positives, the higher the number of those who really are infected who cannot be confirmed as such by the test protocol. This rises to over 1% of the total number of HIV positive in any tested population, which could imply around 300 HIV positive cases missed if the whole U.K. population were tested. In practice, this is likely to be much less of a problem than failing to identify people who are already infected with HIV, but who are not yet antibody positive. Different strategies are appropriate for different purposes (Mortimer, 1989).

5.9 In practice, it is alleged that tests may not perform to the sensitivity and specificity targets of which they are capable. Miike (1987) quotes values of 99·4% and 98·3% respectively for the ELISA test and 90·7% and 95·3% respectively for the Western Blot, based on a proficiency testing programme run by the College of American Pathologists. The C.D.C., on the other hand, has estimated that currently licensed ELISA tests have a sensitivity and a specificity of around 99% (C.D.C., 1985a).

5.10 In the U.S.A. programme of screening military recruits, the testing protocol involves two ELISA tests followed by a Western Blot and then a second confirmatory Western Blot using an entirely new blood sample (Burke *et al.*, 1987). When applied to a very low prevalence population, this procedure

identified 15 HIV positive cases out of 135,187 tested (Burke *et al.*, 1988). Retesting on two different Western Blot methods confirmed 14 out of these 15 as unequivocally positive and 1 as apparently negative.

5.11 On the whole, therefore, the tests available for HIV antibodies are remarkably good if used properly (Mortimer, 1988). They are, however, likely to remain controversial, both in relation to whether or not it is ethical to test anonymously for epidemiological reasons or without consent for the benefit of health workers, and in relation to the attitude of insurance companies to testing. The arguments on the former aspects are exercising the medical and legal professions (Kennedy & Grubb, 1989; Dyer, 1988; Bayer, 1989; Miller & Pinching, 1989); those on the latter are concerning politicians (Social Services Committee, 1989) and the insurance industry.

6. INCUBATION PERIOD

6.1 It has already been observed that there may be a long period between infection with HIV and diagnosis of AIDS. Indeed, it is still too early to say whether all those infected with HIV will ultimately progress to AIDS, or whether only a proportion will. Proper analysis of the distribution of incubation times for people infected with HIV can only be carried out by studying groups where the date of infection is known, or can be accurately estimated, and observing them over a long period, probably for 20 years or more.

6.2 In the relatively early stages of the HIV epidemic in which we are now, knowledge of the shape of the incubation time distribution is limited. However, various studies have been carried out, or are still in progress, and a number of models have been constructed.

6.3 Goedert *et al.* (1986) investigated the incidence of AIDS from 1982 to 1985 in 5 separate cohorts of people infected with HIV. The proportion developing AIDS over the course of the 3 years, for those HIV positive at the start, ranged from 29·5% (13 out of 44) for Manhattan homosexuals to 4·2% (1 out of 24) for drug-users in Queens, New York. It was considered that a possible reason for the variation could be in the duration since infection, which, it was surmised, may have been longer in the case of the Manhattan homosexuals.

6.4 Polk *et al.* (1987) studied a large group (almost 5,000) of homosexual and bisexual men from 4 cities of the U.S.A. over the period from April 1984 to December 1985. By the end of this period AIDS had been diagnosed in 59 participants, all of whom were seropositive for HIV when they were enrolled into the study. This represented 3·2% of the 1,835 participants who were initially seropositive, over an observation period which varied from 9 to 20 months, with a median of 15 months. The percentage progressing to AIDS varied from 2·6% for those with no symptoms on enrolment, through 3·2% for those initially with lymphadenopathy, to 8·6% of those with AIDS-related complex at the first time of observation. The study identified factors correlated with early progression to

AIDS, such as decreased numbers of T helper lymphocytes (T4 cells), an increased level of T suppressor lymphocytes (T8 cells) and a low level of antibody to HIV.

6.5 Redfield *et al.* (1986) had also noted the fall in T4 lymphocytes and a reduction in the ratio of T4 helper-cells to T8 suppressor cells as being markers of progression to AIDS and had used this in the Walter Reed classification of stages in HIV infection (see also Redfield & Tramont, 1989). An alternative classification has been suggested by Justice *et al.* (1989), but it is generally recognised that there are a number of indications of the progressive development of HIV infection.

6.6 Brodt *et al.* (1986) showed that, although AIDS developed in only a modest proportion of cases in Frankfurt (6 out of 31 (19·4%) observed for 24 to 36 months), about 80% of all the observed cases of people infected with HIV showed some deterioration in the period under observation. The authors used five stages of progression from at risk but HIV antibody negative to diagnosed as having AIDS. In this they largely followed the Walter Reed classification described by Redfield *et al* (1986). Brodt *et al.* extrapolated their results to suggest that 50% of symptomless HIV carriers would develop AIDS within 5 years and 75% within 7 years.

6.7 In a follow-up article on the Frankfurt study, Helm *et al.* (1987) reported that 28·8% of one group of patients observed for some $4\frac{1}{2}$ years had developed AIDS. They confirmed that a tendency towards a decline in the state of health was observable in patients at whatever stage of the disease they were.

6.8 Moss *et al.* (1988) followed a cohort of homosexual men in San Francisco for periods of up to 44 months from 1983. Of 288 who were seropositive for HIV at enrolment to the study 17% (50) progressed to AIDS during the follow-up period. Progression rates were calculated as 5% after 1 year, 11% after 2 years and 22% after 3 years (95% confidence interval after 3 years: 16% to 30%). These corresponded with 3-year progression rates in Goedert *et al.* (1986) of 34% for the Manhattan homosexual cohort and 17% for the Washington cohort. A further 19% in the San Francisco study had progressed to AIDS-related condition (ARC) in 3 years.

6.9 It was estimated by Moss *et al.* (1988), that the median date of infection of the cohort they were studying was about the middle of 1981, or about 3 years before the median date of enrolment into the study. Thus the 22% who had progressed to AIDS after 3 years in the study might approximate to the proportion with AIDS at about 6 years from infection. The authors used the progression data for those who had not yet developed AIDS to extrapolate the progression to AIDS, predicting a 50% progression rate 9 years from infection and an ultimate figure of at least 75%.

6.10 In another study of a cohort of 75 homosexual men with generalised lymphadenopathy at enrolment in 1982–83 in Atlanta, a cumulative incidence of AIDS of 38% was observed after 6 years (Kaplan *et al.* 1987, 1988). However, the

risk of progressing to AIDS appeared to increase with duration since infection. No estimate was made of the mean duration since infection of this cohort when enrolled into the study, but the criterion that they should already have generalised lymphadenopathy may suggest that the effective duration since infection, to which the 58% progression rate relates, could be of the order of 8 years.

6.11 Eyster *et al.* (1987) studies a group of 84 seropositive haemophiliacs for whom the date of seroconversion could be approximately determined from frozen blood samples. Ten patients developed AIDS at durations varying from 24 to 95 months after seroconversion, leading to an estimated 6-year progression rate of 18%, with a standard error of 7%. In a more recent study of a cohort of 154 haemophiliacs (over 20 years of age) in the U.S.A. with known or estimated date of HIV seroconversion, Goedert *et al.* (1988) reported that 2·3% had progressed to AIDS after 3 years, 10·9% after 5 years, 27·4% after 7 years and 42·3% after 9 years. The progression rate amongst 1,201 seropositive haemophiliacs in the U.K. was 3% after 3 years and 7% after 5 years (Darby *et al.*, 1989). However, progression varied strongly by age, with only 4% of under 25s developing AIDS during 5 years from seroconversion, 6% of 25- to 44-year olds and 19% of over 45-year olds.

6.12 In a study of the progression to AIDS amongst 98 seropositive haemophiliacs in Sweden, Giesecke *et al.* (1988) reported a 6-year progression rate of only 9%, with a standard error of 4%, based, however, on a mere 7 patients who had progressed to AIDS. They also studied 48 people infected with HIV as a result of blood transfusions. These people were identified from amongst 180 survivors of patients who had been given blood transfusions taken from donors who were subsequently found to be HIV seropositive. Ten of the 48 developed AIDS, giving a 6-year progression rate of 29%, with a standard error of 22%. This estimate is subject to downwards bias, since a number of recipients of infected blood had died before the study began and it was not possible to determine whether they had progressed to AIDS. Thus it is likely that some further allowance should be made for progression at early durations since infection.

6.13 An important source of data for studying the incubation time of HIV is provided by the cases of AIDS arising from transfusion-associated infection in the U.S.A. In many such cases, it is possible to determine accurately the date of exposure to HIV through an infected blood transfusion. Lui *et al.* (1986) analysed 100 cases of transfusion-associated AIDS in the U.S.A. and showed that the mean interval between exposure to HIV and diagnosis of AIDS was 2·6 years. However, the analysis was based only on cases where AIDS had already been diagnosed, which were by definition the cases with short incubation periods.

6.14 Unlike the Swedish study (Giesecke *et al.*, 1988), it is not possible to obtain data on U.S. transfusion-associated cases of infection, which have not yet

progressed to AIDS. Further analysis can only be carried out by assuming a parametric form for the distribution of incubation times (Kalbfleisch & Lawless, 1988). Lui *et al.* (1986) fitted a Weibull distribution to the data and estimated the mean incubation period for transfusion-associated AIDS to be 4·5 years, with a 90% confidence interval ranging from 2·6 to 14·2 years.

6.15 More recent analysis of the C.D.C. data set of transfusion-associated AIDS cases has been carried out by Medley *et al.* (1987, 1988). The analysis was based on the 297 cases of transfusion-associated AIDS known to have been diagnosed in the U.S.A. before 1986 and for whom date of transfusion and date of diagnosis of AIDS were known. Assuming exponential growth in the number of infected individuals and a Weibull distribution for the incubation time, Medley *et al.* estimated a mean incubation time of 8·23 years for adults (5 to 59 years old), with a lower mean of 5·50 years for elderly patients (60 years and older) and a very low mean of 1·97 years for children (0 to 4 years old at infection).

6.16 The danger of drawing conclusions about the mean or median of the distribution of incubation times has been emphasised by Kalbfleisch & Lawless (1988), since the estimates in Medley *et al.* (1987, 1988) depend fundamentally on the assumptions regarding the form of the distribution and the rate of increase of cases of transfusion-associated infection.

6.17 Medley *et al.* (1988a) have repeated the analysis on 560 cases of transfusion-associated AIDS reported to the C.D.C. up to February 1988, with a resulting estimated mean incubation time for all adults (over 12 years old) of 7·59 years. They assumed an exponential increase in the number of new infections by transfusion up to early 1985, when routine screening of donated blood was introduced, and a constant number of new infections since then. The distribution of incubation times was assumed to follow a Weibull distribution. The calculations were also carried out using a gamma distribution, but this pointed to a much higher rate of new infections since the introduction of screening than seemed likely, so the Weibull results were to be preferred.

6.18 Further details of the analysis of transfusion-associated AIDS cases reported to the C.D.C. up to February 1988 were given in Anderson & Medley (1988). This shows that 7·4% of cases are estimated to be diagnosed during the first 3 years of infection, 23·3% during the first 5 years, 45·2% during the first 7 years and 76·1% during the first 10 years.

6.19 The parametric estimates described in the previous paragraphs rely on making assumptions about the pattern of development of new infections and about the form of the distribution of incubation times. The AIDS cases diagnosed at time t are the result of the combined effect of infections at each past time s and the corresponding proportions progressing to AIDS for each of the respective durations $(t-s)$. An alternative approach, based on this same relationship, is to use direct estimates of the numbers of new infections and to use these to make non-parametric estimates of the form of the distribution of

incubation times. Bacchetti & Moss (1989) use this method of analysis on data for male homosexuals in San Francisco from 1978 to 1988.

6.20 The assumed pattern of HIV infections involved a very steep increase in 1979 to 1981, a steadier increase from 1981 to 1983 and then a dramatic fall to 1984, continuing to fall away almost to zero thereafter. The results of the analysis suggested a rather slow initial progression to AIDS, with about 15% diagnosed as having AIDS in the first 5 years and 50% in the first 10 years.

6.21 Costagliola *et al.* (1989) have analysed the French transfusion-associated cases of AIDS, postulating a Weibull distribution for the incubation period, and have estimated a mean (and median) incubation time of 5·3 years, with a 90% confidence interval of 4·4 to 8·9 years. Lui *et al.* (1988) used the Weibull distribution, again with data from 84 homosexual men in the San Francisco City Clinic Cohort (see § 6.25 ff.) and estimated a mean incubation period for AIDS of 7·8 years.

6.22 Rees (1987) modelled the incubation period using a normal distribution, obtaining a 15-year mean and consequently rather high estimates of the numbers currently infected with HIV. Barton (1987) and Beal (1987) challenged the data analysis of Rees and suggested that the mean should be around 5 years.

6.23 Panjer (1987) modelled the progression to AIDS and subsequent death of people infected with HIV using 3 exponential distributions to represent different phases of development. Salzberg *et al.* (1989) have used a similar approach with 4 exponentially distributed states. They suggest that this may fit the observed data better than a single Weibull distribution, which tends to show too fast a progression after the first few years.

6.24 Weyer (1987) assumed that the proportion of infected cases who had not yet progressed to AIDS at each duration, could be described by a negative exponential. Combining this assumption with an exponential growth rate for the incidence of new infections, he estimated the mean of the incubation time distribution as 11 years and showed that data from the first 7 years after infection would produce an observed mean incubation time of 5·3 years.

6.25 Another estimate of the incubation time distribution, based on more than 10 years' longitudinal data from the San Francisco City Clinic Cohort of homosexual and bisexual men, has been given by Hessol *et al.* (1988). Out of 6,709 homosexual and bisexual men enrolled in the study between 1978 and 1980, originally with the intention of studying the prevalence and incidence of hepatitis B, 1,007 had developed AIDS by May 1988, roughly 20% of those known to be infected with HIV. Detailed follow-up investigations were carried out on a subset of the original cohort. From 90 men estimated to have seroconverted between 1977 and 1980, 31 (34%) had developed AIDS, over a follow-up period which averaged 7·3 years.

6.26 An exposed-to-risk analysis based on duration since seroconversion (described as Kaplan-Meier analysis in the medical literature), gave rise to the following proportions having progressed to AIDS at successive durations:

Duration from seroconversion	% having progressed to AIDS
1	0
2	2
3	5
4	10
5	15
6	23
7	33
8	37
9	40
10	48

The 10-year progression rate of 48% is stated as having a 95% confidence interval of 31% to 65%. In a further update on this study, presented by Rutherford at the Vth International Conference on AIDS in Montreal in June 1989, the 9-year proportion with AIDS had risen to 43% and the 10-year figure to 54% (*The Times*, 8 June 1989).

6.27 Apart from the 34% of those estimated to have seroconverted in 1980 or earlier who had progressed to AIDS by May 1988, 16% had AIDS-related conditions and a further 27% had generalised lymphadenopathy. Only 23% were still free of symptoms. In another study, based on the same cohort of homosexual and bisexual men, Hessol *et al.* (1988a) investigated possible cofactors associated with more rapid progression of HIV infected persons to AIDS. They showed that earlier progression was associated with the use of certain drugs (e.g. hallucinogens) and with infection with certain sexually transmitted diseases (e.g. gonorrhoea). A study of the progression to AIDS amongst haemophiliacs suggested that cytomegalovirus infection is associated with more rapid development of symptoms of disease (Webster *et al.*, 1989).

6.28 Differences in observed rates of progression to AIDS are to be expected, given differences in study design, uncertainties about estimating dates of infection, relatively short follow-up periods and, in many cases, relatively small numbers included in the study population. Frösner (1988) and Anderson & Medley (1988) have reviewed some of the large number of abstracts presented to the IVth International Conference on AIDS in Stockholm in June 1988 on this subject. Most studies show relatively low rates of progression to AIDS in the first 2 or 3 years after seroconversion, and increasing rates of progression thereafter. Jason *et al.* (1988) compared progression rates for infected male homosexuals and haemophiliacs and found no significant difference. Parametric methods have similarly produced estimates of a similar order for the mean incubation time, based on data for transfusion-associated infection and male homosexuals (Medley *et al.*, 1987, 1988, 1988a; Lui *et al.*, 1988).

6.29 Non-parametric methods use only the information available from the observed data, but cannot therefore provide estimates of the progression to

AIDS at durations greater than have been observed. The San Francisco City Clinic Cohort Study (Hessol *et al.*, 1988) and the Hershey haemophiliac study (Goedert *et al.*, 1988) provide the longest observed series of data. Both show around 40% to 45% having progressed to AIDS after 9 years.

6.30 Parametric methods require assumptions to be made about the form of the distribution of the incubation period. In general, there is insufficient data available to be sure that the distribution chosen is appropriate and very different results can be obtained using different distributions (Medley *et al.*, 1988). However, it is sometimes possible to use the chosen distribution to make estimates of other outcomes which can be checked for reasonableness (Medley *et al.*, 1988a). Parametric methods provide estimates of rates of progression to AIDS at durations greater than have yet been observed, although such estimates depend heavily on the assumed form of the distribution and estimates of the parameters.

7. INFECTIVITY

7.1 An important concern when it comes to preventing the spread of HIV infection, and in considering transmission models to project the future incidence of infections, is whether people infected with HIV remain equally infectious throughout the incubation period. Studies of transmission between HIV-infected patients and their sexual partners have shown great variability in the transmission of infection. Whilst there could be a number of reasons for this, a possible contributing factor may be variability in infectiousness according to duration from infection, or according to the clinical state of the HIV-infected person.

7.2 Studies of the presence of antibodies to HIV and of HIV antigenaemia suggest considerable variation in the concentrations that can be observed (Imagawa *et al.*, 1989). An increased level of p24 antigen is associated with progression to AIDS, as is a reduction in the number of T4 helper cells (Moss *et al.*, 1988). Detectable antigen increases rapidly in the period immediately after infection, reaching a peak within a few months, after which antigenaemia falls to a low level. Antibodies become less easily observable and antigenaemia increases markedly as the infected person progresses to AIDS (Biggar *et al.*, 1985; Lange *et al.*, 1986; Gaines *et al.*, 1987; Goudsmit *et al.*, 1986; Pedersen *et al.*, 1987).

7.3 It has been suggested that the pattern of two peaks in antigen concentration in the serum of infected persons may be mirrored in a pattern of variable infectiousness with similar peaks (Blythe & Anderson, 1988; Anderson & Medley, 1988). Evidence for a correlation of this nature has been observed in the context of other diseases. Albert *et al.* (1988) have shown that low levels of antigen in the serum may be correlated with a low level of infectiousness. Vertical transmission from mother to unborn children seems most likely to occur if the mother already has ARC or AIDS (Tricoire *et al.*, 1988).

7.4 The considerable variability of the incubation period between individuals, and differences in antigenaemia and antibody response, make it difficult to

demonstrate variable infectivity conclusively unless studies are very carefully designed. It does, however, seem possible, from the available evidence, that variations in infectivity may be much more important in determining whether HIV is transmitted than some other factors, such as frequency of sexual contact.

7.5 The impact of variable infectivity on the possible future spread of HIV infection could be considerable (Blythe & Anderson, 1988; Hyman & Stanley, 1988; Institute of Actuaries AIDS Working Party, 1989). The initial stages of the epidemic would be determined by the early phase of infectiousness and some levelling out could be expected before increasing numbers of infections begin to occur as a result of the second phase of infectiousness. This pattern will tend to be blurred by the variability in the incubation period, but the general effect will be to slow down the rate of new infections after the initial surge. Whether or not a further increase in new HIV infections will be observed as a result of more people entering the second phase of infectiousness will depend on whether or not behavioural change is sustained.

8. TRANSMISSION OF HIV

8.1 The principal modes of transmission of HIV have been reviewed by Friedland & Klein (1987). The virus is associated with bodily fluids, in particular blood, semen and mucus, and cannot survive for long other than in these fluids. It can readily be transmitted through the transfer of infected blood into the blood of an uninfected person, rather less readily through semen in sexual intercourse and probably rarely, if at all, through other bodily fluids.

Blood transfusion

8.2 Although transmission through blood can occur with relative ease, only a small proportion of infected persons in the U.K. have been infected in this way. Three principal types of infection through blood have occurred. The first is through the transfusion of infected blood. Curran *et al.* (1984) identified 18 cases out of the 2,157 people with AIDS who had been reported to the C.D.C. up to August 1983, where the patient had received a blood transfusion within the last 5 years, and where no other known risk factors for AIDS appeared to be present. Increased awareness of the risk of infection through transfusion led to screening of all donated blood for HIV in industrialised countries and to the discouragement of those perceived as being most at risk for HIV infection from donating blood.

8.3 The efficiency of blood transfusion as a mode of transmission has been demonstrated by Ward *et al.* (1987) and by Giesecke *et al.* (1988). Unfortunately, although the risk of transmission by this route has been dramatically reduced in industrialised countries by screening, some cases of infection by transfusion are still occurring, largely because of the presence of virus in blood screened as negative for HIV antibodies (Ward *et al.*, 1988). The extremely low risk should, however, be kept in perspective, since the risk of what may happen if a

transfusion is not given, is usually very much greater (Zuck, 1988). Infected blood transfusions remain a serious threat to public health in many developing countries because facilities are not available to screen donated blood (Quinn *et al.*, 1986; Piot *et al.*, 1988; N'Galy *et al.*, 1988). The risk of HIV transmission from an HIV seronegative unit collected between March 1985 and February 1987 in the U.S.A. has been estimated as 1 in 68,000 (Kleinman & Secord, 1988).

Blood products

8.4 The second principal type of infection with HIV through blood arises through concentrated blood products, in particular Factor VIII and IX, which are administered to haemophiliacs (Evatt *et al.*, 1984). Because of the large number of blood donations which are needed to produce a single dose of factor concentrate, the probability of a dose being infected is very much higher than for a single blood transfusion. Since many countries also import factor concentrate from the U.S.A., contamination of the blood supply there in the early 1980s has resulted in a high percentage of haemophiliacs becoming infected with HIV in many industrialised countries. In Japan this is still the major mode of transmission for reported cases of AIDS.

8.5 In the U.K., out of 2,830 cases of AIDS reported to 31 December 1989, 47 are attributed to the receipt of an infected blood transfusion and 169 are haemophiliacs who have received infected factor concentrate. A total of 1,114 haemophiliacs were reported, as at 31 December 1989, as having been infected with HIV. This can be expected to represent a high proportion of the true figure, since all haemophiliacs have been tested for HIV, although some are thought to have been wrongly classified.

Needle-sharing

8.6 The third major route of infection through blood is by the sharing of needles amongst intravenous drug users. This is a major mode of transmission in the U.S.A., accounting for over 25% of cases of AIDS reported to date, whilst in Italy and Spain around two-thirds of reported cases of AIDS are attributed to intravenous drug use. In the U.K. only 118 cases of AIDS had been reported amongst intravenous drug users up to 31 December 1989, but 1,819 reports of HIV positive intravenous drug users had been received. A large proportion of these have been reported in Edinburgh where a substantial level of infection (at least 50% seropositive) has developed amongst the population of intravenous drug users (Robertson *et al.*, 1986; Brettle *et al.*, 1987; Hart *et al.*, 1989).

8.7 The prevalence of HIV infection amongst intravenous drug users in some parts of the U.S.A. has lead to a serious public health problem (Weinberg & Murray, 1988). In parts of New York, 70% of intravenous drug users seeking medical treatment have tested positive for HIV (Kirn, 1989). Intravenous drug users dissolve powdered drugs in water, partially fill a syringe with the solution, withdraw blood from a vein into the syringe and then inject the resulting solution back into the body. Syringes will often be used by different people one after

another, thus transferring any HIV which may be present in one person's blood to other participants (Friedland & Klein, 1987; Schoenbaum *et al.*, 1989).

8.8 The epidemic of HIV infection amongst drug users is forming a bridgehead between the homosexual community, where the initial HIV epidemic in the U.S.A. broke out, and heterosexuals. Many female intravenous drug users support their addiction by prostitution; education campaigns generally have little impact on this sector of the population. Growing prevalence of HIV infection amongst females of child-bearing age is leading to a significant amount of vertical transmission of HIV in New York, from mother to foetus. Of 1,087 cases of perinatally acquired AIDS reported in the U.S.A. up to January 1989, 53% were children born to intravenous drug-using women and 20% were children born to the female sexual partners of male intravenous drug users (Selwyn *et al.*, 1989).

Accidents

8.9 If HIV is present in the blood of an infected person, transmission could, in principle, occur through accidental contact with such blood, for example through needlestick injuries in hospital, splashes during surgical operations or injuries sustained during post mortem examinations. One case was reported in the U.K. of a nurse who seroconverted after sustaining a needlestick injury (*Lancet* editorial, 1984).

8.10 In the U.S.A. McCray *et al.* (1986) followed up, for an average period of 15 months, 938 cases of health care workers who had been exposed to the risk of HIV through parenteral or mucous membrane exposures to blood or other bodily fluids of patients with AIDS. Two workers seroconverted during follow-up, but one was the sexual partner of someone who was HIV positive, so heterosexual transmission could not be ruled out. Only one case seemed unequivocally to arise from parenteral exposure (Stricof & Morse, 1986). A further case, from a hospital in Paris, involved a superficial needlestick injury to the finger of a female nurse with pleural fluid from an infected patient (Oksenhendler *et al.*, 1986).

8.11 A prospective study of 150 health care workers in the U.K. who had been accidentally exposed to HIV revealed no evidence of transmission (McEvoy *et al.*, 1987). The chances of developing HIV infection as a result of a single accidental exposure have been estimated at less than 1%. HIV is much less likely to be transmitted than hepatitis B in similar circumstances. Substantial proportions of hospital workers in Kinshasa, Zaire have been found to be seropositive, but this was thought to be representative of the general population seroprevalence and not to reflect transmission in the working environment (N'Galy *et al.*, 1988, 1989).

8.12 McEvoy *et al.* (1987) record a total of 7 known cases, around the world, of occupationally acquired HIV infection and three cases resulting from similar exposures occurring in a domestic situation. It is clear, therefore, that infection by this route is extremely rare. Nevertheless, it is sensible for health care workers,

and others who might be exposed to infection through occupational accidents, to take precautions in case any patient is infected with HIV (Pitts & Nuttall, 1988; Aoun, 1989).

8.13 A few cases have been reported of transmission of HIV through organ transplants (Prompt *et al.*, 1985; L'Age-Stehr *et al.*, 1985; Kumar *et al.*, 1987). Potential donors are now screened for antibody to HIV, but, as with blood donors, there is still a risk that a donor might have become infected recently and might not yet have seroconverted (Quarto *et al.*, 1989).

Sexual-homosexual

8.14 In spite of significant numbers of infections from blood transfusions, blood products and intravenous drug use, HIV is most commonly transmitted sexually. It is transmitted by both homosexual and heterosexual penetrative intercourse. The majority of cases of AIDS, and of known HIV infection, in the U.S.A. are in homosexual men. In the U.K. some 82% of all reported cases of AIDS are male homosexuals. In Africa the majority of cases of AIDS are thought to have arisen as a result of heterosexual transmission.

8.15 Since, until recently, by far the greatest number of cases in the industrialised countries have been male homosexuals, many of the early studies of people with HIV infection and AIDS considered only homosexual transmission. Such studies have shown that the likelihood of being infected increases with the number of sexual partners and with involvement in the practice of anal-receptive intercourse (Goedert *et al.*, 1984; Kingsley *et al.*, 1987; Winkelstein *et al.*, 1987). No consistent correlation has been shown between infection and the length of sexual relationships or the number of sexual encounters with each partner.

8.16 There may be some small risk of transmission by oral sex (Lyman *et al.*, 1986; Rozenbaum *et al.*, 1988, 1988a; Goldberg *et al.*, 1988). However, transmission between homosexuals is normally the result of anal intercourse. HIV infection spread rapidly in a number of homosexual communities where such practices were common and where there were high rates of partner change. There is much evidence, however, that significant changes of behaviour began to take place in many homosexual communities in the U.S.A. from about 1982 or 1983 onwards. Frequency of partner change was dramatically reduced and most people began to avoid high risk behaviours (Martin, 1987; Kaplan *et al.*, 1988a). Behavioural change was probably greatest in communities where the effects of HIV infection had already become evident and may not have taken place to a significant extent in areas which were initially at lower risk (Fleming *et al.*, 1987).

8.17 Similar changes in behaviour have been reported in the U.K. Carne *et al.* (1987) and Weber *et al.* (1986) reported reductions between 1984 and 1986 in average numbers of partners and a trend towards safer sexual practices in cohorts of homosexuals attending sexually transmitted disease clinics in London. Another study (Evans *et al.*, 1989) reported a decrease in the number of casual partners and in the number of partners from other countries, far fewer people

with large numbers of partners in a recent period and some reduction in high risk behaviours. The greatest changes had taken place during 1985, and there was less clear evidence that the changes were continuing into 1987. Others have been sceptical that there has really been a general change in the lifestyle of homosexual men (Serraino, 1989; Harvey *et al.*, 1989).

8.18 Indirect evidence for major changes in sexual behaviour, or for high risk behaviour having been confined to a minority of homosexual men in the U.K., is provided by the stabilisation and even reduction in the proportion of homosexual men attending clinics who test positive for HIV antibodies (Carne *et al.*, 1987; Loveday *et al.*, 1989; Evans *et al.*, 1989). There has also been a substantial fall in the incidence of other sexually transmitted diseases amongst homosexuals (Johnson, 1988; Johnson & Gill, 1988; Thompson & Robertson, 1989), suggesting a trend towards fewer partners and safer sex practices. Similar evidence of behavioural change amongst male homosexuals has been reported in Amsterdam (van Griensven *et al.*, 1989) and a more general review is given by Coutinho *et al.* (1989).

8.19 Grant *et al.* (1987) estimated the average infectivity of HIV associated with the practice of unprotected receptive anal intercourse as 0·102, with a 95% confidence interval of 0·043 to 0·160. Infectivity is defined as the probability that sexual union with an infected partner will result in transmission of the infective agent. However, infectivity is probably much increased in the presence of genital ulcerative diseases (Quinn *et al.*, 1988; Stamm *et al.*, 1988) as has also been shown in relation to heterosexual transmission (Greenblatt *et al.*, 1988; Simonsen *et al.*, 1988). The recent fall in the incidence of other sexually transmitted diseases among homosexual men in the U.K., possibly as a consequence of changes in sexual behaviour, may in itself further reduce the rate of spread of HIV infection.

8.20 Most of the studies referred to are based on highly select populations of homosexual men attending particular clinics. More general evidence of behavioural change in the homosexual population is provided by the survey which is being carried out by the British Market Research Bureau (BMRB) for the Health Education Authority, in order to monitor the response to the AIDS Information campaigns mounted by the government since 1986 (Department of Health and Social Security, 1987). A survey amongst homosexuals in gay bars took place in a series of 'waves', from March 1986 to February 1988. The figures for the final wave are probably not comparable with the earlier waves, because of changes in the design of the questionnaire used.

8.21 Table 1 shows a comparison of the distributions of numbers of male partners in the last 12 months between the different waves of the survey.

8.22 The number of respondents is too small to draw many conclusions from the fluctuations in the individual percentages, but the trend in the mean number of partners between March 1986 and February 1987 is clear. By November 1986, over 30% claimed to have had less than two male partners in the preceding 12 months, compared with only 20% in March 1986. Answers to other questions in the survey indicated that there had been noticeable changes in reported sexual

Table 1. *Numbers of partners of male homosexuals responding to British Market Research Bureau survey in gay bars*

Number of male partners in last 12 months:	Wave 1* %	Wave 2* %	Wave 3* %	Wave 4* %	Wave 5* %
0	3	4	6	12	7
1	17	18	26	26	16
2	7	9	12	11	9
3–10	47	48	40	37	44
11–20	5	5	4	3	11
21–30	3	3	1	2	5
31–40	1	1	†	1	1
41–50	4	1	2	1	2
51 or more	3	2	1	†	5
Mean number of partners	10·5	8·7	7·1	4·8	10·9
Number of respondents	156	298	284	251	285

† Indicates less than 0·5% but more than zero, i.e. just 1 respondent.
* Wave 1: early March 1986; Wave 2: mid-April 1986; Wave 3: mid-November 1986; Wave 4: early February 1987; Wave 5: February 1988.

practice, with a trend away from high risk sex practices. Since other studies show that these changes were already under way before 1986, it is not altogether clear that the changes that have been observed since 1986 are necessarily the result of the government publicity campaign (Evans *et al.*, 1989), but there seems little doubt that changes have taken place.

8.23 The February 1988 wave of the BMRB survey showed a reversal of most of the changes that had been observed between March 1986 and February 1987. However, somewhat different questions were asked in Wave 5, so too much should not be read into these figures, at least until a further set is available on the new basis.

Sexual-heterosexual

8.24 Although the epidemic of HIV infection in the U.S.A. started amongst homosexual men, heterosexual transmission is now playing an increasingly important role. This is hardly surprising in the context of the world-wide epidemiology of HIV infection, since on a global basis there are probably about as many females infected as males (Mann, 1988) and the spread of HIV infection in most African countries is predominantly as a result of heterosexual transmission (Quinn *et al.*, 1986; Fleming, 1988).

8.25 Cases of AIDS were diagnosed in Central Africa and in Haiti in the late 1970s (Clumeck *et al.*, 1984; Piot *et al.*, 1984; van de Perre *et al.*, 1984; Pape *et al.*, 1983). Similar clinical features were observed to those seen in the early cases of AIDS in the U.S.A., including Kaposi's sarcoma and opportunistic infections. In Haiti the first probable case of AIDS died in July 1978 (Pape *et al.*, 1983) and of the 61 cases of AIDS observed in Haiti between 1979 and 1982, 9 were female. In

Rwanda and Zaire cases of AIDS were more evenly distributed between males and females.

8.26 In 1982 Harris *et al.* carried out a study on 7 female sexual partners of heterosexual male drug users with AIDS (Harris *et al.*, 1983). One partner had AIDS, one an AIDS-related condition and 4 had generalised lymphadenopathy. These observations were strongly suggestive of AIDS being transmitted from heterosexual men to their female sexual partners.

8.27 Redfield *et al.* (1985) followed up the female spouses of 7 patients with AIDS or ARC who had been referred to the Walter Reed Army Medical Center. Four spouses were antibody positive, 3 of these already showing symptoms of ARC, and HIV was isolated from a fifth spouse, although she had not apparently seroconverted. Only one of the 11 children of these couples showed any evidence of HIV, a 14-month child whose parents both had ARC or AIDS. The authors concluded that close household contact between parents and children was not a significant mode of transmission of HIV, but vertical or perinatal transmission seemed to occur and the relationship between spouses was an efficient mechanism for transmission of the virus.

8.28 In another study published later in 1985, the same team at the Walter Reed Army Institute showed that heterosexual transmission seemed to occur in both directions (Redfield *et al.*, 1985a). Fifteen out of 41 patients diagnosed as having AIDS or ARC appeared to have become infected heterosexually. Five were females, 3 of whom had male partners with AIDS and the other 2 male partners who were in one case bisexual and in the other a drug user. Of the 10 males, one had had sexual contact with a female Haitian immigrant and the other 9 had had multiple heterosexual contacts in recent years, including in most cases relations with female prostitutes. No firm conclusions could be reached about the mechanism of transmission, although it seemed clear that anal intercourse was not a necessary condition for the virus to be transmitted.

8.29 A number of commentators were sceptical about the transmission of HIV from females to males (Polk, 1985; Schultz *et al.*, 1986; Wykoff, 1986). Some felt that the index AIDS cases, in Redfield *et al.* (1985a) for example, were suppressing information about homosexual activity or intravenous drug use, which could have caused their infection with HIV, because of fears of possible discharge from military service. Others argued that contact with prostitutes may be no more than a marker for some other risk factor for HIV infection.

8.30 Evidence continued to build up to support male to female heterosexual transmission. Kreiss *et al.* (1985) studied 42 haemophiliacs and their wives between the end of 1982 and early 1984. Twenty-one of the haemophiliacs were HIV positive and, at the end of the study period, 2 of their wives were also HIV positive. Although it could not be proved unequivocally that the husbands were the source of infection for these 2 women, neither had any other identifiable risk factor.

8.31 In another study of household contacts and sexual partners of haemophiliacs in the U.S.A., 3 out of the 14 spouses of sexual partners of haemophiliacs

with AIDS or ARC registered as HIV positive themselves. No sexual partners of HIV positive but clinically well haemophiliacs seemed to have become infected (Jason *et al.*, 1986). No other non-haemophiliac household contacts of infected haemophiliacs were infected.

8.32 In a French national epidemiological survey on the incidence of HIV infection in haemophiliacs, 10 wives or sexual partners of 148 seropositive haemophiliacs were found to be HIV positive (Allain, 1986). In another study of seropositive haemophiliacs in France, 3 female sexual partners seroconverted out of 31 observed (Laurian *et al.*, 1989). No female seroconversions took place in couples who always used condoms. All 3 seroconversions were partners of men showing the presence of HIV antigen in serum when tested (the infection rate was in fact 3 out of 6 partners of men in this category).

8.33 Similar results were obtained in a British study of haemophiliacs (Jones *et al.*, 1985). In a Dutch study, however, no partners of 13 seropositive haemophiliacs were found to seroconvert, in spite of frequent sexual contacts (van der Ende *et al.*, 1988). One of the partners had unexplained lymphadenopathy, which may prove to be symptomatic of HIV infection on subsequent follow-up.

8.34 Low levels of transmission were also found by Kim *et al.* (1988) in another study of wives of haemophiliac men in the U.S.A. Only one out of 14 sexually active wives of HIV positive haemophiliacs seroconverted. In this case the man had been HIV positive for 4 years and had shown positive evidence of HIV antigen for 2 years.

8.35 A rather different picture was reported from Italy, where 15 out of 28 healthy heterosexual partners of HIV positive men or women were found to have seroconverted (13 out of 22 female partners of HIV positive males and 2 out of 6 male partners of HIV positive females) (Luzi *et al.*, 1985). In Edinburgh 5 out of 34 female partners of HIV positive males seroconverted and 1 out of 7 male partners of HIV positive females (France *et al.*, 1988).

8.36 Fischl, Dickinson *et al.* (1987) studied 45 spouses, 109 children and 29 household contacts of 45 adults with AIDS (28 males and 17 females). Four out of 28 female spouses and 9 out of 17 male spouses were HIV positive at enrolment to the study. A further 13 developed antibody during the study, 3 out of 8 (38%) initially seronegative male spouses and 10 out of 24 (42%) initially seronegative female spouses. This suggested that HIV infection could be transmitted heterosexually in either direction with a similar efficiency.

8.37 Some of the scepticism about transmission of HIV from females to males was allayed by reports that the virus had been isolated from cervico-vaginal secretions (Vogt *et al.*, 1986; Wofsy *et al.*, 1986).

8.38 By 1985, Kreiss *et al.* (1986) found that two-thirds of a group of 64 female Nairobi prostitutes of low economic status were HIV positive. The virus was showing all the features of a typical sexually-transmitted disease and was being transmitted from male to female and female to male. Although other factors may be playing a part in the spread of HIV infection in East and Central Africa, a

number of indicators point to heterosexual transmission as the major factor. Cases are roughly equally divided between the sexes and the majority of those infected are young sexually active adults. Female patients with AIDS are generally younger than male patients and are usually unmarried. People with AIDS are likely to have a higher number of heterosexual partners than others and males with AIDS are more frequent clients of female prostitutes than those not infected (Clumeck *et al.*, 1985; van de Perre *et al*, 1985; Melbye, 1986; Carael *et al.*, 1988; Rwandan HIV Seroprevalence Study Group, 1989).

8.39 A large number of studies have sought to throw light on the reasons for the wide differences in the apparent efficiency of heterosexual transmission of HIV. Results presented at International Conferences on AIDS in Paris (1986), Washington (1987) and Stockholm (1988) have been summarised in a number of review papers on heterosexual transmission (Piot & Mann, 1987; Piot, Kreiss *et al.*, 1987; Chamberland & Dondero, 1987; May, 1988; Holmes & Kreiss, 1988; Johnson, 1988; Johnson & Laga, 1988; Kapila & Carne, 1989).

8.40 Attention has focussed on possible risk factors for transmission. Padian *et al.* (1987) studied 97 female sexual partners of 93 HIV infected men and found 22 (23%) to be themselves infected. Factors statistically associated with transmission were the practice of anal intercourse and the total number of sexual contacts with an infected person. No particular association was found with past history of sexually transmitted disease or number of previous sexual partners.

8.41 Peterman *et al.* (1988), on the other hand, reported no clear association of transmission with particular sexual practices or with frequency of sexual contact. They interviewed and tested 80 spouses of people with transmission-associated HIV infection who had had sexual contact with the infected person since the transfusion. Two of the 25 husbands (8%) and 10 of the 55 wives (18%) of the index cases had confirmed HIV antibody. One infected husband has been excluded from these figures because there were other possible risk factors for infection. Eleven wives remained uninfected after more than 200 sexual contacts with their infected spouse. Wives who had become seropositive tended to have had *fewer* sexual contacts than those who had not seroconverted and to be on average somewhat older.

8.42 There are various possible reasons for differences in transmissibility. Infectivity may depend on the quantity of virus particles in body fluids and this may vary according to the duration since infection or the clinical state of the infected person (cf. Section 7). Some have suggested that some people may be genetically more susceptible to infection than others (Eales *et al.*, 1987), but other researchers have been unable to confirm this result (Peterman *et al.*, 1988). A significant factor could be the presence of other sexually transmitted diseases, either because of ulceration and possible damage to the mucous membrane, or because of increased viral activity in infected areas (Greenblatt *et al.*, 1988; Piot & Laga, 1989). Exposure to other viruses and parasites may cause activation of the immune system which could increase susceptibility to infection (Quinn *et al.*, 1987).

8.43 A major study involving 9 participating centres in 6 European countries has been seeking to identify the factors most associated with heterosexual transmission of HIV (European Study Group, 1989). In 155 couples with a male index patient positive for HIV and with a known risk of HIV infection, 42 female partners (27%) seroconverted. Cases where the female partner had some other risk factor for HIV infection were excluded. Infection rates varied from 0% in Amsterdam (0 out of 13) and Berlin (0 out of 3) to 43% in Paris (12 out of 28).

8.44 The transmission ratio was greater for men with AIDS (53%) than for those without symptoms (18%), with an intermediate rate for those with lymphadenopathy or ARC (27%). Low T4 lymphocyte counts were also associated with a higher level of transmission. No significant association was observed with duration of sexual relationship or with frequency of sexual contact. Higher rates of transmission were recorded in couples who practised anal intercourse (52% compared with 16% amongst those who had never practised anal intercourse). The most important factors seemed to be the clinical state of the index case, history of sexually transmitted disease in the partner and the practice of anal intercourse. 67% of couples in which both partners were positive for HIV had at least two of these three risk factors and only 7% had none of them. Differences in transmission ratios between participating centres were largely explicable in terms of the relative frequency of these three risk factors.

8.45 The presence of other sexually transmitted diseases, together with a high incidence of other infectious agents and parasites, could account for the high level of heterosexual transmission in East and Central Africa (Pepin *et al.*, 1989; Latif *et al.*, 1989; Cameron *et al.*, 1989). These factors are likely to be relatively unimportant in many of the couples studied in the U.S.A. and in Europe. Here anal intercourse would appear to be a significant risk factor, but not an essential one. The main reason for wide differences in transmission ratios between the various studies could be variation in infectivity according to the clinical state of the index case (Laga *et al.*, 1989; Johnson *et al.*, 1989).

8.46 The majority of women infected with HIV in the U.S.A. are intravenous drug users and have probably become infected through needle-sharing. The second largest category is of those with heterosexual contact with a person at risk for AIDS. This second category is increasing rapidly in relative importance (Guinan & Hardy, 1987). Over 70% of women with AIDS are of black or Hispanic origin and over 80% are of child-bearing age. The growing prevalence of HIV infection amongst women in their most fertile years is associated with an increasing level of vertical transmission of the virus to newborns (see §§ 8.50 ff.).

8.47 Elsewhere than in Africa, heterosexual transmission has so far mainly been to the heterosexual partners of those with other risk factors for HIV infection: bisexuals, haemophiliacs, transfusion recipients and intravenous drug users. This can be seen as a second phase of the epidemic in industrialised countries. With the prevalence of HIV infection still very low amongst heterosexuals, relatively few cases can be expected to have occurred of heterosexuals without any other risk factor infecting other heterosexuals. This

will be the third phase of the epidemic and can be expected to become increasingly important. Intravenous drug users and partners of intravenous drug users could play a critical role in paving the way to a more general spread of HIV infection amongst heterosexuals (Landesman *et al.*, 1987; Moss, 1987; Delamothe, 1989; Cowan *et al.*, 1989).

8.48 In the absence of the risk factors for heterosexual transmission indicated above (§§ 8.44 and 8.45), transmission by heterosexual contact may be relatively infrequent. There is, therefore, considerable doubt about the likely future spread of AIDS amongst heterosexuals in the U.K. Heterosexuals in general have fewer partners than homosexuals, so that the risk of exposure to the virus may be less. Nevertheless, studies have shown a significant level of partner change amongst some young heterosexuals, both males and females, and little evidence of changes in behaviour in response to information campaigns about HIV infection (Forman & Chilvers, 1989; McGarry, 1989).

8.49 In addition to the survey among men frequenting gay bars, the BMRB has a rolling survey of sexual behaviour for all adult males. To the end of 1987 this showed over 10% of men interviewed claiming to have had 2 or more sexual partners in the previous 12 months, with a mean number of female sexual partners of about 4. Interviews carried out in 1988 showed a reduction in the proportion in this category to 7%, but, within this overall figure, 24% of 18- to 24-year olds, 12% of 16- to 17-year olds and 10% of 25- to 34-year olds claimed to have had 2 or more partners in the previous 12 months. This level of partner change in a subgroup of heterosexual young people, who probably have an enhanced incidence of other sexually transmitted diseases, could be sufficient to sustain a heterosexual epidemic of HIV infection in the U.K. of an appreciable size.

Vertical transmission

8.50 HIV could be transmitted from mother to child by three possible routes: to the foetus *in utero* through the circulation of blood, by the child swallowing infected blood or other bodily fluids during labour and delivery and through the child sucking infected breast milk (Friedland & Klein, 1987). Substantial numbers of children in parts of East and Central Africa have been found to be HIV positive. In one study some 10% of children under 5 were seropositive (Rwandan HIV Seroprevalence Study Group, 1989). A large proportion of seropositive children has been found to have seropositive mothers, indicating vertical transmission as a major factor, although infected transfusions may be responsible for some cases (Mann *et al*, 1986). In the U.S.A. 80% of children with AIDS are known to have a parent who has AIDS or is at risk and presumed to be HIV positive (C.D.C., 1987a; Katz & Wilfert, 1989; Scott *et al.*, 1985; Minkoff *et al.*, 1987).

8.51 Novick *et al.* (1989) have reported an overall HIV seroprevalence rate of 0·66% among newborns in New York State (1,816 out of 276,609) in the year from December 1987 to November 1988. The seroprevalence rate was as high as

1·65% in Manhattan (360 seropositives) and 1·70% in the Bronx (418 seropositives) and was much higher for black mothers and, to a lesser extent, Hispanic mothers, than for white mothers.

8.52 Although babies born to HIV positive mothers may test positive, this is often because of the presence of maternal antibodies in the blood. These antibodies will usually disappear within 12 months and only a proportion will show evidence of continuing infection. In a study involving 3 European centres, 71 children of HIV seropositive mothers were followed up for periods of up to 15 months (Mok *et al.*, 1987). Symptoms of AIDS or ARC developed in 5 during this time and another 4 had substantial symptoms which could have been indicative of HIV infection. A total of 16 (22%) were known to be infected, since HIV culture or antigen tests were positive, but only a small proportion were tested in this way, so this figure is very much a minimum. The authors estimated that 75% would lose maternal antibodies within the first year of age, but cautioned that this did not necessarily mean that they were not infected. The study suggested that the risk of infection being transmitted to the child is higher if the mother has symptoms of AIDS during pregnancy.

8.53 These results have been further confirmed as the study has progressed, with 271 children born to HIV-infected mothers in 8 European centres now under observation (European Collaborative Study, 1988). 10 children had developed AIDS or AIDS-related complex, all by the age of 9 months, and 22 other children had symptoms or signs suggestive of HIV infection. The estimated vertical transmission rate was 24%.

8.54 In a study in Kinshasa, Zaire, over 10% of children of HIV seropositive mothers had died of AIDS or showed symptoms of AIDS within a year (Ryder *et al.*, 1989). It was estimated that the virus was transmitted from mother to child in at least 39% of cases. The proportion of neonatal deaths (not specifically attributed to AIDS) was 5 times higher than amongst children born to seronegative mothers.

8.55 Blanche *et al.* (1989) attempted to follow up 128 children of seropositive mothers who had been born 18 to 24 months earlier. Of these 9 could not be traced and 2 had died suddenly, without a known cause. Of the remaining 117, 27% had evidence of HIV infection and another 8% were seronegative, but had clinical or laboratory abnormalities which could be related to HIV infection. The authors suggest that the rate of transmission from mother to infant is about 30%, or rather lower than earlier estimates of 40 to 50% (Friedland & Klein, 1987).

8.56 Whether or not transmission of HIV can occur by means of breast milk is less clear. Ziegler *et al.* (1985) have reported a case of apparent postnatal transmission from mother to infant. The mother was uninfected before delivery but acquired the infection as a result of a subsequent blood transfusion. Since she breast-fed the child for 6 weeks, this seemed a possible route of transmission. HIV has been isolated from the breast milk of seropositive women (Thiry *et al.*, 1985).

Other modes of transmission

8.57 The possibilities for transmission of HIV, other than by the main routes described in the foregoing paragraphs, have been reviewed by Lifson (1988). HIV has been isolated from saliva, but only infrequently (Ho *et al.*, 1985). Only one case of possible transmission of HIV through a human bite seems to have been reported. There is no evidence for health care workers who have been exposed to the saliva of infected persons having seroconverted. One case of possible HIV transmission by kissing was reported, but could not be confirmed (Lifson, 1988). Some possibility remains of transmission by orogenital contact, but this is more likely to be through semen than through saliva (see §8.16).

8.58 HIV has been isolated from the tears of an infected person and from urine in a small proportion of cases. There is no evidence of transmission by such fluids. More generally there is no evidence of transmission occurring in a normal household environment, other than where there is sexual contact. (Friedland *et al.*, 1986; Jason *et al.*, 1986; Fischl, Dickinson *et al.*, 1987; Friedland & Klein, 1987; Lifson, 1988). It is even less likely that transmission would occur through ordinary social contact in the workplace or at school, through the preparation and serving of food, use of office equipment, telephones, toilets, etc.

8.59 Transmission of the virus could, in theory, take place through the agency of insects. However, there is no evidence that insects can transmit HIV from infected to uninfected blood, even under conditions of artificially high concentration of virus. A significant level of insect-borne transmission would not be consistent with the very clear age dependency of HIV infection, very low prevalence rates having been observed in children aged between 1 and 15 years of age (Mann *et al.*, 1986; Quinn *et al.*, 1986; Friedland & Klein, 1987; Lifson, 1988).

9. PREVALENCE OF HIV

9.1 Monthly reports on the worldwide incidence of AIDS are prepared by the Global Programme on AIDS of the World Health Organisation. To the end of February 1990 some 223,000 cases had been reported from 153 countries (W.H.O., 1990). The extent to which AIDS cases are reported varies considerably, particularly in developing countries, and some of the reports are only infrequently updated, so the W.H.O. statistics are likely to significantly underestimate the true incidence of AIDS. Table 2 shows the cumulative incidence of AIDS cases reported so far in 50 of the countries most seriously affected, expressed in terms of cases per million population.

9.2 Cases of AIDS reported to W.H.O. continue to be at a substantial rate, although the annual number of new cases reported from the U.S.A., which currently represents 55% of the total, has fallen from a peak in 1987. It is suspected, however, that the number of cases reported from the African continent is considerably understated; there is no sign of a slow-down here. Cases of AIDS, even when reported, represent only the tip of the problem. With a long incubation period and a growing incidence of new infections, the numbers

Table 2. *AIDS cases reported to the W.H.O. as at 28 February 1990 and cases per million population*

	Cases	Cases per million		Cases	Cases per million
Bermuda	131	2,264	Canada	3,509	132
Bahamas	435	1,749	Dominica	10	125
French Guyana	150	1,609	Grenada	14	120
Congo	1,250	632	St Lucia	16	118
Guadeloupe	175	515	Spain	4,633	117
United States of America	121,645	491	Denmark	531	104
Burundi	2,355	437	Australia	1,707	103
Barbados	111	426	Honduras	512	101
Uganda	7,375	405	Gambia	66	93
Trinidad & Tobago	509	399	Italy	5,307	92
St Christopher	18	376	Ivory Coast	1,010	88
Martinique	115	348	Guyana	84	81
Zambia	2,709	346	Guinea-Bissau	76	78
Malawi	2,586	319	Cape Verde	28	77
Haiti	2,331	313	Netherlands	1,130	77
Rwanda	1,806	254	Federal Republic of Germany	4,433	73
Kenya	6,004	239	Burkina Faso	555	71
Central African Republic	662	229	Reunion	40	70
Tanzania	5,627	211	Ghana	1,077	68
Switzerland	1,159	181	Luxembourg	24	66
St Vincent	19	173	Panama	155	65
Dominican Republic	1,200	173	Brazil	9,555	64
France	8,883	160	Belgium	596	60
Zimbabwe	1,632	157	Belize	11	60
Zaire	4,636	134	Qatar	23	57
United Kingdom	2,830	50			

Note: Countries with fewer than 10 cases have been omitted, even though the number of cases per million population is high.

Source: W.H.O. Update to 28 February 1990. Figures relate to earlier effective reporting dates, which differ from country to country. The U.K. and U.S.A. figures are as at 31 December 1989 and 31 January 1990 respectively.

infected but not yet diagnosed as AIDS may represent a large multiple of the cumulative reported cases of AIDS (perhaps 30 to 40 times). W.H.O. have estimated that the true figure for cumulative cases of AIDS could be nearer 500,000 and that some 5 to 10 million people worldwide could already be infected with HIV (Sato *et al.*, 1989).

Prevalence in Africa

9.3 A substantial proportion of the global numbers infected with HIV is in East and Central Africa. However, information on the true prevalence of infection there is sparse and is based on a number of small studies. Seroprevalence in the early 1980s in this region ranged from 0·7% among blood donors in the Congo to 18% for blood donors in Kigali, Rwanda (Quinn *et al.*, 1986).

Among selected high risk groups, such as female prostitutes, seroprevalence rates were reported to range from 27% to 80% (Clumeck *et al.*, 1985, 1985a; van de Perre *et al.*, 1985).

9.4 Some studies have provided longitudinal data on particular populations. Seroprevalence among female prostitutes in Nairobi rose from 4% in 1981 to around 60% in 1985 (Quinn *et al.*, 1986; Kreiss *et al.*, 1986; Piot *et al.*, 1987, 1987a). In men attending STD clinics in Nairobi, seroprevalence rose from 1–3% in 1980–81 to 15–18% in 1985–86. Seroprevalence among pregnant women in Nairobi rose from 0% in 1980–81 to 2% in 1985–86 (Quinn *et al.*, 1986; Piot, Kreiss *et al.*, 1987; Piot, Plummer *et al.*, 1987). In Kinshasa, Zaire, seroprevalence amongst pregnant women rose from 0·2% in 1970 to 3% in 1980–81 and 8% in 1985–86 (Quinn *et al.*, 1986; Mann *et al.*, 1986). From testing over 5,000 healthy people in Kinshasa, Zaire in 1984–85, 6% were found to be seropositive. Prevalence ranged from about 1% at ages 1 to 14 to 10% in females aged 15 to 29, 7% in males aged 30 to 39 and 8% in infants under a year old (Quinn *et al.*, 1986).

9.5 In spite of rapid growth in seroprevalence in Zaire in the early 1980s, other studies have shown some stabilisation in more recent years. The prevalence of HIV infection in pregnant women in Kinshasa, Zaire has remained at around 7% since 1985 (N'Galy *et al.*, 1988a). Amongst blood donors seroprevalence has fallen from 9% in 1986 to under 7% in 1988. Among employees in a Kinshasa hospital, seroprevalence rose from 6·4% in 1984 to 8·7% in 1986 (N'Galy *et al.*, 1988). In some rural areas of Zaire seroprevalence appears to be much lower and has been reported at 0·8% throughout a period of 10 years (Nzilambi *et al.*, 1988).

9.6 In Kampala, Uganda the prevalence of HIV infection in pregnant women rose from 10·6% in October 1985 to 24·1% in February 1987, whilst 21% of 214 female blood donors and 15% of 1,370 male blood donors were seropositive in 1986–87 (Carswell, 1987). Much lower prevalence has been reported in some rural areas.

9.7 A nationwide survey of HIV prevalence in Rwanda in December 1986 showed 17·8% seropositive in urban areas (out of 1,870 tested) and 1·3% in rural areas (out of 742). In the urban sample 21·0% of females were HIV positive and 14·6% of males. At ages 26 to 40 seroprevalence reached 30·0% in the urban areas and 2·8% in the rural areas (Rwandan HIV Seroprevalence Study Group, 1989).

9.8 Similar high rates of prevalence have been observed in northern parts of Tanzania, with 16% among 100 pregnant women in 1986 and 32·8% among 573 people tested in 1987 (41·3% in 213 persons aged 25 to 34) (Mhalu *et al.*, 1987; Frösner, 1988a). Although very high rates of prevalence have been reported among prostitutes in Nairobi, general seroprevalence in Kenya has been reported as relatively low. However, in Lusaka, Zambia 18% of 207 blood donors were found to be seropositive for HIV antibodies, 19% of 100 hospital workers and 29% of 144 people attending STD clinics (Melbye *et al.*, 1986), and 16% of 688 adults from 8 different cities in Malawi (Frösner, 1988a). In October

1988 10% of patients on the wards in Zomba General Hospital, Malawi were seropositive (Reeve, 1989). In April 1989 testing at the same hospital showed 19% seropositive (Gompertz & Harrison, 1989).

9.9 It is clear that HIV infection is widespread in East and Central Africa and that it has attained alarming levels of prevalence, particularly in urban areas. Some rural areas are still relatively little affected.

Prevalence in the United States of America

9.10 In the U.S.A. there have been a large number of separate studies of seroprevalence in different populations and subpopulations. These are summarised in the Quarterly Reports from the C.D.C. to the Domestic Policy Council (C.D.C., 1988) and in occasional C.D.C. reviews (C.D.C. 1987b). Seroprevalence levels of between 10% and 70% have been reported amongst male homosexuals tested at STD clinics, although mostly in the range 20% to 50%, 70% amongst males with haemophilia A and 35% amongst males with haemophilia B. Drug users in New York have been 50% to 60% seropositive, although the level has been less than 5% amongst drug users elsewhere in the country (Frösner, 1988a).

9.11 General population seroprevalence is not known, since most testing programmes relate to special groups, such as those entering hospital, being treated at clinics, etc. Blood donors should show fairly low seroprevalence, since those most at risk of HIV infection have been strongly discouraged from donating blood. Among first time donors in 1985 to 1987 an overall seroprevalence of 0·043% was recorded.

9.12 Of some interest in this context, although not quite a sample of the general population, is the screening programme operated by the U.S.A. for civilian applicants for military service and active members of the army. Between October 1985 and October 1987 this involved about 2 million tests. Some 0·15% overall were found to be seropositive in the first few months of testing, with figures of 0·16% for men and 0·06% for women. Male prevalence increased from 0·03% at age 18 to 0·57% at age 27. Female prevalence was highest for the over 30s, where it reached almost 0·3% (Burke *et al.*, 1987). In a study of 172,000 individuals who had been tested more than once, it was estimated that there were 0·77 new seroconversions per 1,000 people per year (McNeil *et al.*, 1989).

9.13 Anonymous testing of blood samples from patients admitted to the emergency department of a hospital in the centre of Baltimore, U.S.A. revealed a seroprevalence level of 5·2% (Kelen *et al.*, 1988). The proportion HIV positive amongst 636 patients admitted to a hospital in Washington was 3·7%. In the Bronx, New York City, 14·1% of 142 sera tested in the emergency department were HIV positive.

9.14 Landesman *et al.* (1987) found 2% of pregnant women giving birth at a New York inner city hospital to be HIV positive. Novick *et al.* (1989) observed similar levels of seroprevalence in areas of New York with high rates of drug use and an overall seroprevalence rate of 1·25% in 125,000 women giving birth in

New York City. In upstate New York the seroprevalence rate was only 0·16% in 147,000 women. Between December 1986 and June 1987 0·21% of all children born in Massachusetts were born to seropositive mothers, with the proportion rising to 0·8% in big cities (Hoff *et al.*, 1988).

9.15 Routine testing of job corps entrants in the U.S.A. in 1987 revealed overall seroprevalence of 0·33%, as did anonymous testing of patients being admitted to a group of 'sentinel' hospitals, although the figure varied a great deal between hospitals, from 0·09% to 0·89% (C.D.C., 1987b). Estimates of HIV prevalence in the U.S.A. made at the Coolfont consultation in 1986 were based on prevalence of 20% to 25% among 2·5 million homosexual men, 5% to 10% among 2·5 to 7·5 million homosexuals and men with occasional past potential exposure to HIV, 25% to 30% among 900,000 regular intravenous drug users, 5% among 200,000 intermittent drug users and 0·021% among 142 million heterosexuals. With various adjustments this led to an estimate of 1 million to 1·5 million people infected. More recent estimates have come up with similar figures, suggesting that this may have been an overestimate in 1986 (Wiley & Samuel, 1989).

Prevalence in the United Kingdom

9.16 In a study of HIV infection in patients attending STD clinics in England and Wales, about 15% of homosexual men tested at two clinics in the south east in 1986 and 1987 were HIV positive, with 6·3% and 3·1% respectively seropositive in the two years in clinics elsewhere (Polakoff *et al.*, 1989). Among heterosexual patients in the south east 3·0% of men (7 out of 230) and 1·3% of women (3 out of 233) were found to be seropositive in 1986 and 1% (10 out of 962) and 0·7% (7 out of 949) respectively in 1987. Elsewhere only 3 men out of 5,312 (0·06%) and 1 women out of 4,778 (0·02%) were found to be HIV positive in 1987. All but one of the seropositive heterosexuals were intravenous drug users or had had sexual contacts in, or were from, an area abroad with a high prevalence of AIDS.

9.17 In a similar study at a London STD clinic, 25·6% of homosexual and bisexual men attending in 1987 were positive for HIV antibodies (Loveday *et al.*, 1989). Prevalence had been at about this level since the beginning of 1986, having risen sharply from the 1982 level of 4% to 21% in 1984 and then levelled off. Corresponding seroprevalence rates among heterosexuals were 1% in 1987 for both men and women.

9.18 In another study of HIV seroprevalence in both high and low risk groups, 34,222 people were tested in England between October 1986 and December 1987 (Public Health Laboratory Service Working Group, 1989). Seroprevalence rates of 15·1% among homosexual men in London (213 out of 1,412) and 4·0% outside London (146 out of 3,607) were consistent with those reported by Polakoff *et al.* (1989) (see §9.16). Among 632 initially negative homosexuals and bisexuals, 14 seroconversions were identified at a retest 30 to 40 weeks later, giving a yearly incidence rate of new infections of 3%.

9.19 The PHLS Working Group found that 5·7% of intravenous drug users tested in London and 1·5% tested outside London were seropositive. Of 3,272 heterosexuals tested with a partner in a risk group, 1·6% (8 out of 515) in London and 0·2% (6 out of 2,757) outside were positive for HIV antibodies. Another 6,390 heterosexuals were tested with a history of multiple sexual partners, but only 0·2% (4 out of 2,396) of men and 0·03% (1 out of 3,994) of women were seropositive. Only 1 man out of 14,065 heterosexuals with no identified risk factor was HIV antibody positive. These results confirm high prevalence amongst homosexuals and drug users, especially in London, but suggest that heterosexual spread was, in 1987, still largely confined to people with a partner at identifiable risk of HIV infection.

9.20 A Working Group chaired by Sir David Cox (Department of Health/ Welsh Office, 1988) estimated that 20,000 to 50,000 people were infected with HIV in England and Wales at the end of 1987. This conclusion was reached using a variety of methods, including epidemiological modelling and back projection. A direct estimate based on numbers in risk categories and estimated seroprevalence gave 13,000 to 31,000 homosexuals infected, with assumed seroprevalence of 15% to 20% among 50,000 London clinic attenders and much lower prevalence among other homosexuals. Some 5% to 15% of 40,000 regular sharers of needles among injecting drug users, together with a lower proportion of another 80,000 drug users, led to an estimate of 3,000 to 10,000 in this category. Some 2,000 to 5,000 heterosexuals were taken as infected, based on prevalences of 0·2% to 0·5% among London genito-urinary medicine (GUM) clinic attenders, 0·1% to 0·2% amongst GUM clinic attenders outside London, and 0·001% to 0·002% among 27·4 million other 'low risk' heterosexuals.

9.21 In a more recent study updating the Cox report, Day *et al.* (1990) estimate that at the end of 1988 there were between 12,500 and 26,500 HIV positive individuals in England and Wales, of which the homosexual community contributed between 8,750 and 17,500. The report concludes that there is now a substantial amount of evidence to support the view that homosexual transmission slowed sharply in 1984/85, but that there remains a significant possibility of future growth in infection, not only among homosexuals, but more particularly among injecting drug users and other heterosexuals.

10. CONCLUSION

10.1 A great deal of scientific effort has already been expended in the study of HIV infection and AIDS. Enormous numbers of papers have been written, so that keeping track of relevant research is a difficult task. Indeed, the pace of developments is such that significant new advances can be expected to be announced whilst any review is being printed. In this review of scientific, medical and epidemiological studies that have come to the attention of the Institute of Actuaries AIDS Working Party, I have attempted to draw out aspects which are of interest from an epidemiological point of view and which might have a bearing

on projections of the possible future spread of HIV infection and numbers of cases of AIDS, in the U.K. and worldwide.

10.2 Thanks are due to many who have brought items to my notice, in particular to other members of the AIDS Working Party. I am especially appreciative of the efforts of Ann Sutcliff, and more recently Sally Grover, at the Institute of Actuaries Library, who has obtained for me copies of all the papers referenced here (and many more besides).

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