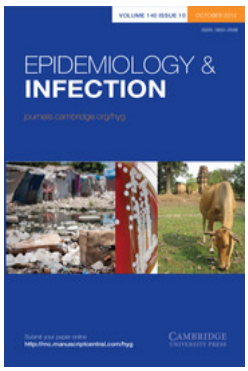

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The UK Register of HIV Seroconverters: methods and analytical issues

UK Register of HIV Seroconverters (UKRHS) Steering Committee*

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SUMMARY

A Register of HIV-infected persons who have had a negative antibody test within 3 years of their first antibody positive test (seroconverters) is being set up in the UK to monitor the distribution of times from HIV seroconversion to AIDS (the incubation period) and to death. It will also provide a national resource for use by those designing studies in this group of individuals. Clinicians caring for HIV-positive persons in Genito-Urinary Medicine, Infectious Disease and other departments throughout the UK were asked to participate by providing information on eligible subjects. Most laboratories undertaking HIV antibody testing were also contacted and asked to provide the name of the attending clinician for all seroconverters identified through the HIV laboratory reporting systems of the PHLS Communicable Disease Surveillance Centre (CDSC) and the Scottish Centre for Infection and Environmental Health (SCIEH) and for any other seroconverters known to them but not identified by CDSC or SCIEH. Data items sought for the Register include: sex, ethnic group, probable route of HIV transmission, annual CD4 counts, details of therapy and prophylaxis prescribed, AIDS-defining events and vital status. Follow up information is collected annually. Wherever possible, all seroconverters known to a clinic have been identified, whether currently alive or dead, either from clinic records or laboratory reporting or both. The objective is to establish and update a complete register of seroconverters on a long-term basis to provide reliable estimates of the incubation period on which future projections of AIDS cases in the UK can be made.

BACKGROUND AND OBJECTIVES

Knowledge of the distribution of intervals from human immunodeficiency virus (HIV) infection to the development of acquired immunodeficiency syndrome (AIDS) and to death, and the factors affecting these intervals is vital for an understanding of the natural history of HIV infection and for making projections of future numbers of AIDS cases. These distributions have changed since the beginning of the epidemic due particularly to the introduction of anti-retroviral treatment and prophylaxis for *Pneumocystis carinii* pneumonia and other opportunistic infections [1, 2]. It is likely that new advances in the management of individuals with HIV infection will influence these distributions. Further, changes in the incubation

* V. Beral, (*Chair*), ICRF Cancer Epidemiology Unit, Oxford; A. Babiker†, MRC HIV Clinical Trials Centre; UCLMS, London; R. P. Brettle, City Hospital, Edinburgh; C. Carne, Addenbrooke's Hospital, Cambridge; J. H. Darbyshire†, MRC HIV Clinical Trials Centre; UCLMS, London; B. G. Evans†, PHLS Communicable Disease Surveillance Centre, London; R. J. C. Gilson, Academic Dept of Sexually Transmitted Diseases, UCLMS, London; D. Goldberg, Scottish Centre for Infection and Environmental Health, Glasgow; D. A. Hawkins, Chelsea & Westminster Hospital, London; D. Jeffries, St Bartholomew's Hospital, London; A. M. Johnson†, MRC UK HIV Epidemiology Co-ordinating Centre, UCLMS, London; M. A. Johnson, Royal Free Hospital, School of Medicine, London; A. J. McMichael, Institute of Molecular Medicine, Oxford; P. P. Mortimer, PHLS Central Public Health Laboratory, London; A. N. Phillips†, Royal Free Hospital School of Medicine, London; K. Porter (*Project Co-ordinator*), MRC HIV Clinical Trials Centre; UCLMS, London; A. Pozniak, King's College Hospital, London; J. Weber, St Mary's Hospital, London and S. Wellsteed UK Department of Health, London.
† Members of the Executive Committee.
Correspondence to: Kholoud Porter, MRC HIV Clinical Trials Centre, University College London Medical School, The Mortimer Market Centre, Mortimer Market, London WC1E 6AU, UK.

period distribution could occur even in the absence of changes in available treatments and treatment uptake, due to the evolving distributions of new viral strains in HIV-infected persons [3, 4]. It is therefore important to monitor whether there are changes in the incubation period distribution and, if so, the extent of those changes and factors associated with them.

A number of studies have provided estimates for these incubation periods in different population groups [5–22]. Most studies have tended to focus on one transmission category, e.g. homosexual men, injecting drug users, or haemophiliacs, are small in size, or are no longer recruiting new subjects.

A Register of HIV-infected individuals in whom the date of seroconversion is known with reasonable precision (seroconverters) is currently being set up in the UK to monitor changes in the distribution of intervals from seroconversion to onset of AIDS, using the 1993 European case definition [23] (referred to as 'the incubation period') and death. Seroconversion is estimated as the mid-point between the last negative and first HIV positive antibody test dates, and is used to approximate the time of infection with HIV. The Register will also provide information on factors associated with the length of these intervals. It is intended to be complete and ongoing to provide constant and regular monitoring of these periods. The Register will be a shared national resource for use by those designing studies to help improve understanding of HIV pathogenesis and of immunological and virological markers of infection and their relation to prognosis.

METHODS

Definition of a seroconverter

For the purposes of the Register, a seroconverter is defined as an HIV-seropositive person aged 16 years or over on whom an HIV antibody test was performed and found to be negative no more than 3 years prior to the first positive antibody test. In the absence of a negative result, persons identified during the acute infection stage, namely when infection has occurred but before full seroconversion, will also be included in the study. Laboratory evidence for this acute infection is required, the details of which were reached by consensus among expert virologists at the request of the Steering Committee (see Appendix). The Register is not actively recruiting haemophiliac patients because they are followed up by the UK Haemophilia Centre Directors' HIV Working Party.

A maximum period of 3 years between the negative and positive tests was chosen, but additional analyses using a narrower period will also be undertaken as appropriate. Too narrow a period would inevitably result in the selection of a group of individuals undergoing HIV testing at very frequent intervals.

Identifying study subjects

Clinicians in the UK have reported AIDS cases to the Public Health Laboratory Service AIDS Centre at the Communicable Disease Surveillance Centre (CDSC) and the Scottish Centre for Infection and Environmental Health (SCIEH) since 1982 on a voluntary and confidential basis. Laboratory reporting to CDSC and SCIEH of newly-identified HIV infection began in the latter part of 1984. AIDS case reporting is estimated to be 87% complete while the HIV laboratory reporting is estimated to cover around 80% of known infections [24, 25]. Clinical and laboratory reporting run independently but the use of a soundex code (a code derived from the patient's surname comprising of a letter followed by three digits) as well as the date of birth allow both the link between an HIV and an AIDS case report on the same individual to be made, and the elimination of possible duplicates on either system.

Clinical centres

Clinicians from Genito-Urinary Medicine, Infectious Disease and other specialities from centres in the UK taking part in the Medical Research Council (MRC) clinical trials in HIV infection were invited to participate by providing information on patients who meet the definition of a seroconverter. Additionally, clinicians from centres not taking part in the MRC trials but whose centre has reported a total of 10 or more AIDS cases to CDSC or to SCIEH were also invited to participate.

Laboratories

Laboratory directors and medical microbiologists were also contacted by letter and telephone and asked to participate by helping to identify eligible subjects. These include National Health Service, Public Health and private laboratories, as well as regional Blood Transfusion Centres.

In October 1986 the PHLS Collaborative Laboratory Study on HIV infection (the 'Denominator Study') was initiated to gather information on all HIV

testing and therefore identify repeat tests on the same individual and hence incident infections. It comprised nine laboratories and expanded to include 18 laboratories by the end of 1989. As participating laboratories record all HIV tests, both negative and positive, the identification of seroconverters at these laboratories was made much simpler. A similar surveillance mechanism was set up in November 1988 in Scotland through which all laboratories performing HIV testing report centrally to SCIEH. Colleagues at SCIEH have also undertaken follow up, through the Blood Transfusion Service, of HIV seropositive donors with previous HIV negative donations.

Detection of duplicate reports

The current CDSC HIV laboratory reporting form, which has been in use since March 1993, contains a specific question asking whether a negative result had previously been obtained. For all reports where this item of information was provided, the reporting laboratory was contacted and asked for the name and address of the clinician looking after the patient, or, if this was not known, the name and address of the clinician requesting the HIV test. The clinician was then asked to register the patient by completing a registration form and also to identify and register all other seroconverters from their centre including those known to be dead, transferred to other centres, or lost to follow-up. Duplicate reports made by the clinic and the laboratory on the same individual were identified by using soundex code and date of birth matching. Prior to March 1993, there was no specific question regarding a previous negative test on the CDSC form. All laboratories who have reported new HIV infections first diagnosed by them since January 1990 were also asked to check for any previous negative results for all individuals with a positive result between January 1990 and March 1993 who were not already known to have had a previous negative result.

Retrospective ascertainment

A number of laboratories and clinical centres, particularly those with large case loads of HIV-infected persons, include information on previous negative results on their patient databases. In order to identify subjects eligible for the Register retrospectively, information is sought, wherever possible, from the local laboratory performing HIV testing. This method is least likely to result in biased estimates of the incubation period distribution as it is independent of the patient's vital status and attendance at a clinic. As this is not always possible, information from the clinic is also used; this may give biased estimates towards survivors if they include only current attenders, but seroconverters with a negative test performed at another laboratory can also be identified. Computerized records from the clinic are used whenever available, but in order to identify eligible subjects who had died or transferred to other centres before the computerization of records had taken place the search is supplemented by case note review where feasible. By close contact with centres and laboratories we aim to identify and minimize potential biases in the incubation period estimate (discussed below), which are due to the method of recruitment of eligible cases, by seeking information on the completeness of the local records, either electronic or manual, in particular the inclusion of patients no longer attending the centre or who had died.

Clinicians are also asked, with informed and written consent from the patient, to take a blood sample for central serum storage. Ethics committee approval was obtained for this from all participating clinical centres.

Information collected

The following information is collected for all seroconverters either by asking the clinician or research nurse to complete a form or by extraction from the clinic database: Soundex code, initials, date of birth, clinic/hospital number, sex, ethnic group, probable route of virus transmission, likely country of infection, presence of a seroconversion illness (with date and main symptoms), dates of last negative and first HIV positive antibody tests and where these were performed, vital status and, if dead, date of death.

The following data are also collected initially and on an annual basis: CD4 cell counts, details of antiretroviral therapy and prophylaxis for opportunistic infections (either as open label therapy or as part of a clinical trial), AIDS-defining events, vital status and, if dead, date and likely cause(s).

Information about the nature and completeness of any existing local databases was sought from the major centres caring for HIV infected individuals. On the basis of this, the study registration and follow up forms were designed to be compatible with the information collected routinely. This was of particular relevance to information on drugs prescribed. At registration, only information on the date of start of

Table 1. *Characteristics of seroconverters reported to the Register: October 1994–February 1996*

		Number of reports (n = 1348)	Proportion of cases (%)
Sex	Male	1203	89
	Female	145	11
Exposure category	Sex between men*	1040	77
	Sex between men and women	134	10
	Injecting drug use	146	11
	Other/undetermined†	28	2
Seroconversion interval	1 calendar month	57	4
	1–12 months	688	51
	13–24 months	382	28
	25–36 months	221	16
Age at first antibody positive test (yrs)	Median (range)	28 (15–64)	

* Includes 22 men who also reported to have injected drugs.
† The Register is not actively recruiting haemophiliacs as they are already followed up by the UK Haemophilia Centre Directors' HIV Working Party.

each drug prescribed is requested. Strict confidentiality is maintained. No names or addresses of seroconverters are requested. The database for the study is held within a secure building with separate coded access and data are completely inaccessible except through the use of passwords known to key individuals only. Data released to other researchers, which would require the approval of the Steering Committee, would contain no information that could lead to the identification of seroconverters.

Follow up information

Follow up data is collected on an annual basis through the appropriate clinical centre. Only information on whether the patient is currently taking the drug or any additional drugs prescribed or any stopped in the interval since last follow up will be sought. Any temporary changes in medication in the intervening period will not be recorded as details are unlikely to be available. It is unlikely that this level of detail would have a substantial impact on the analyses. The AIDS databases both at CDSC and SCIEH will also be used to identify AIDS cases and deaths occurring in patients who have stopped attending their clinic.

The Office of Population Censuses and Surveys (OPCS) in England and Wales and the General Register Office (GRO) in Scotland are the central registries for birth, marriage, and death. It is expected that they will provide information annually on deaths not known to CDSC or SCIEH by matching records of deaths in the UK against those of all patients lost to follow up on the Register based on Soundex code, date of birth and sex. As no names will be disclosed to the Register by OPCS or GRO, once a possible match or a number of probable matches are made they will be verified with the collaboration of the clinician last known to have provided patient care. In this manner the HIV status of persons on the Register will not become disclosed to either OPCS or GRO.

RESULTS

By the end of February 1996, 142 clinical centres and 136 laboratories had been contacted, of which 131 (92%) and 103 (76%), respectively, have agreed to participate, representing 91% of AIDS case reports and 97% of HIV infection reports in the UK to date. A total of 2070 HIV antibody positive persons aged 16 years or more who were not known to be haemophiliac patients and had had a previous negative antibody test were identified from all sources. Full information has been received on 1526 individuals, 806 of whom appear not to be known to either CDSC or SCIEH. The remaining 544 are known to the CDSC HIV laboratory reporting system and to SCIEH and, as clinical information has not yet been received, are not included on the Register.

Of the 1526 seroconverters reported to the Register, 987 (65%) were reported from 13 centres in London, 219 (14%) from 12 centres in Scotland, and 320 (21%) from 52 centres in the rest of the UK. Of these, 1120 were identified through clinic records, 295

Table 2. *Year of estimated seroconversion* for cases reported October 1994–February 1996*

Year	Number of cases
1983	31
1984	49
1985	40
1986	55
1987	58
1988	86
1989	114
1990	155
1991	168
1992	203
1993	214
1994	134
1995	40
1996	1

* Mid-point between the first positive and last negative HIV antibody tests.
NB. not all individuals will contribute information to estimates of the incubation period from this point (see Discussion – Statistical issues and possible biases).

through laboratory records, and 111 through both the clinic and laboratory. The seroconversion interval, i.e. the time difference between a first antibody positive and last antibody negative tests for HIV, is within one calendar month for 57 reports, 1–12 months for 688 reports, 13–24 months for 382 reports, 25–36 months for 221 reports and over 36 months for 153 reports. For 25 reports no date was given for either the positive or negative tests or both.

The characteristics of the 1348 reports with a seroconversion interval of 3 years or less are outlined in Table 1. Most (77%) were infected through sex between men, 10% through sex between men and women, and 11% through injecting drug use. This contrasts with 65%, 19% and 12%, respectively, among reported cases of HIV infection in the UK [26]. Most seroconversions are estimated to have taken place in 1992 and 1993 but information is available on persons believed to have seroconverted since 1983 (Table 2).

DISCUSSION

Statistical issues and possible biases

The incubation period distribution, given by the cumulative probability of developing AIDS within t years of infection will be estimated using Kaplan-Meier estimation. Attempts will also be made to fit various parametric models such as Weibull or Gamma distributions. The effects of variables on the length of survival will be examined using, principally, Cox proportional hazard models.

The aim is to include all seroconverters known to clinics and laboratories on the Register including patients alive at the time the Register is set up and all patients who have died. However, serious bias may arise if the likelihood of a person being included on the Register is dependent on how rapidly that individual develops AIDS and/or dies. For example, in some centres seroconverters who have progressed rapidly and died may be less likely to be registered than those who are currently attending. This problem arises when a clinic/laboratory does not have a complete record of all patients ever seen. In such centres data on, for example, a person who seroconverted in 1987, and is registered in 1995, cannot be used to derive information on the first 8 years of the incubation period since, if the patient had died within 8 years (i.e. before 1995), they may well have not been included on the Register. Such a patient can thus only be entered in the 'risk set' for the analysis in 1995 at 8 years. This is referred to as 'late entry'. If such a patient had attended at a clinic or was identified through a laboratory with complete records of every patient seen/tested since, for example 1990, they can be entered into the risk set at 3 years from seroconversion (1990–1987 = 3 years) since survival or death after this date will not have influenced whether they are included on the Register.

For individuals from centres whose ascertainment is believed to be complete from laboratory and/or clinic records (that is, all patients alive, dead, transferred and lost to follow up are included), follow up through the Register commences from each individual's seroconversion time. However, for centres where ascertainment is judged to be complete only from a given date, h, seroconverters are treated as 'late entry' subjects and each enters the 'risk set' at (h – estimated date of seroconversion). If ascertainment from a centre is not complete from any point in time, follow up for all seroconverters from that centre will commence from the date of entry to the Register. Follow up (i.e. entry into the 'risk set') for subjects already known to be HIV infected when transferring into a centre commences from the date they first attended the clinic with complete records on all patients. If this is uncertain, or if neither clinic have complete records the follow up of such subjects commences from date of entry to the Register.

Table 3. *Number of patients recruited from each of 3 hypothetical clinics*

Clinic	Estimated year of seroconversion											Total number recruited
	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	
A	20*	10	0	20	0	25	0	0	20	0	5	100
B	0	25	0	0	0	25	0*	0	25	0	25	100
C	25	25	0	25	0*	0	0	0	25	0	0	100

* Time *h* from which records are believed to be complete. Patient numbers to the left of these are treated as 'late entry' subjects in the analysis.

Table 4. *Life table of retrospectively identified seroconverters*

Time from seroconversion (yrs)	Numbers of patients in risk set	Number of events	Cumulative event-free survival probability
0	175*	10	0·94
1	165+25†+25‡	10	0·90
2	205	15	0·83
3	190+25‡	6	0·81
4	209+25‡	10	0·78
5	224+25†	12	0·74
6	237	7	0·72
7	230	10	0·69
8	220	14	0·64
9	206	13	0·60

* 100 patients from clinic A, 50 from clinic B, and 25 from clinic C.
† Late entry subjects from clinic B.
‡ Late entry subjects from clinic C.

To give examples of this potential bias, consider the following scenarios (Table 3):

(i) In clinic A, it is possible to identify all HIV infected persons who have ever attended the clinic regardless of whether they have since died, transferred to other centres or are currently alive and attending at this clinic.

(ii) In clinic B, records became computerized for patients attending from January 1990 onwards. Therefore, eligible subjects who had died or transferred to other centres prior to January 1990 were not entered onto the system and cannot, therefore, be identified.

(iii) In clinic C, complete records for attenders are available from January 1988, and so patients who had died or transferred to other centres prior to that date are not included.

For patients in clinic A follow up can be backdated to the date of their individual HIV positive tests and their date of entering the risk set is, therefore, the estimated seroconversion date.

For patients in clinic B follow up can only start from January 1990 since information is incomplete for the period prior to this date and their follow up commences from that point so that they enter the risk set at the number of years after seroconversion they were in 1990. Similarly, patients registered from clinic C enter the risk set at the number of years after seroconversion they were in 1988 and their follow up begins from that point. To illustrate how the problem of 'late entry' is dealt with, let us suppose that 100 eligible seroconverters are identified from each of the three centres A, B and C and their estimated dates of HIV seroconversion are as illustrated in Table 3. The resulting lifetable for analysis would resemble Table 4.

A bias concerning the representativeness of seroconverters on the Register may arise because persons who undergo repeat testing for HIV are not likely to be truly representative of all HIV infected persons. For example, heterosexuals acquiring the virus through sexual contact often have not previously perceived themselves to be at risk of HIV infection

and so tend not to have had previous negative tests for HIV and, therefore, are under-represented among seroconverters.

Future developments

As persons with a previous negative antibody test are likely to remain a small proportion of all HIV-infected individuals, international collaboration is important in order to pool information and increase the degree of confidence in estimates of the incubation period, not only for homosexual and bisexual men but also for heterosexual men and women. This is of crucial importance for making reliable estimates of current and future AIDS case load and recent HIV prevalence [24, 25].

Due to the relatively low incidence of HIV infection, incident cohorts, i.e. cohorts of initially HIV seronegative persons followed up through seroconversion to AIDS and death, require many years of follow up. A number of studies on the incubation period overcome this problem by using information from prevalent cohorts [6, 8, 11, 12, 27, 28], i.e. persons already known to be HIV seropositive when recruited. As subjects in prevalent cohorts are by definition already HIV infected, the unobserved period of their HIV infection has to be accounted for and supplemented with information from other sources. The UK Register of HIV Seroconverters aims to include all seroconverters, to identify all potential biases and to account for them in the analysis. This will ensure that the Register is as close as possible to a cohort of individuals with incident HIV infection.

Response from laboratories and clinical centres in the UK has been encouraging. Much of the effort in identifying eligible subjects is concerned with retrospective identification and ascertainment of the completeness of the records in individual clinical centres. The mechanism for identifying seroconverters prospectively is unlikely to require as much effort.

APPENDIX

Definition of 'acute infection'

(*a*) An individual believed to be at increased risk for HIV infection presenting with an illness compatible with acute primary HIV infection without documentation of a negative HIV antibody test will be enrolled into the study pending the outcome of laboratory investigations to establish evidence of recently acquired infection, as detailed below. When the results of the investigations are available, individuals not meeting these criteria will be removed from the Register.

(*b*) Any other HIV positive individual without a previous negative test in whom the laboratory criteria below have been met will be enrolled.

Laboratory criteria of recent seroconversion (one criterion required)

(*a*) The presence of p24 antigen, confirmed by neutralization, and/or PCR positivity, in the absence of total anti-HIV at that time, but in whom anti-HIV is demonstrated in a specimen collected within 6 months.

(*b*) Weak reactivity in EIA or low titre (< 256) by Serodia-HIV *and* IgM anti-HIV or p24 antigen *and* seroconversion-type Western Blot pattern, with either:

- increasing titres of anti-HIV/EIA reactivity in specimens collected within a 3-month period but tested simultaneously, or
- development of new bands or intensification of weakly reactive bands in two or more sequential sera collected at an interval of no more than 3 months and tested contemporaneously by Western Blot.

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