Viral subtype and heterosexual acquisition of HIV infections diagnosed in Scotland

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Objective: As at December 1998, 87% of the estimated 33 million people living with HIV throughout the world resided in Africa and South East Asia. In Scotland (and the United Kingdom), a major public health concern has been that non-B subtypes of HIV which predominate in the regions above might enter the country and spread heterosexually among the indigenous population. The authors conducted an investigation to determine if, and to what extent, such transmission had occurred.

Methods: Stored blood samples from people who were diagnosed as HIV positive in central Scotland during 1995–7 and who were reported to have acquired their infection heterosexually, were identified. Sequence data were sought from each sample and, where obtained, viral subtype was assigned. For each case, viral subtype was linked to corresponding epidemiological details on heterosexual risk.

Results: Viral sequence was obtained from specimens for 53 of 59 cases. For 43 of the 53 cases, information on region of sexual contact was known. All 19 cases who had a sexual risk in Africa or Asia had a non-B subtype (A, C, or E) while 20 of 24 cases who did not report sexual contact in these regions had a B subtype (p < 0.0001). Of the remaining 10 cases, nine had a subtype B and one a subtype C virus.

Conclusion: There is no evidence that non-B viral strains from developing countries have yet disseminated appreciably among indigenous heterosexual men and women within Scotland. Continuing to collect both demographic and molecular data from indigenous heterosexuals who are newly diagnosed with HIV would improve the chances of detecting rapidly any appreciable dissemination of non-B subtypes among this population if it were to occur. Such information would be helpful in informing HIV prevention strategies.

Keywords: heterosexual transmission; HIV-1 subtypes; DNA sequencing; genotyping; Scotland

Introduction

To December 1998 UNAIDS estimated that throughout the world 33.4 million people were living with HIV. Of these, approximately 770 000 were in Europe and central Asia, 890 000 in North America, 1.4 million in South America, 6.7 million in south and South East Asia and 22.5 million in sub-Saharan Africa. The great majority of all cases are newly diagnosed with HIV abroad (including 124 from Africa and 10 from Asia) and 138 had a high risk partner (including 123 with an IDU partner and 10 a bisexual male partner). For 87, no further information was available and for 80, no high risk partner could be identified and infection probably occurred in the United Kingdom. A major public health concern has been that people travelling between Scotland (and the rest of the United Kingdom) and Africa and Asia could bring into Scotland non-B strains of HIV which might then spread heterosexually among the wider population. While there is ample evidence to indicate that HIV infected IDUs and homosexual/bisexual males in Scotland harbour the subtype B strain, there were no HIV strain data for individuals who probably acquired their infection heterosexually. Accordingly, it was unknown if imported infection from these regions had seeded into the indigenous heterosexual population of Scotland. The investigators set out to link strain and demographic data on heterosexually infected individuals who had been diagnosed in Scotland in recent years.

Methods

Background

Since 1985 HIV testing laboratories throughout Scotland have reported cases of HIV
seropositivity to the Scottish Centre for Infection and Environmental Health (SCIEH). Reporting is near 100% complete and the information held on each case includes sex, date of birth, soundex code of surname, first part of postal code of residence, date of earliest positive specimen, and risk category; these data are collected through the use of a national HIV reporting form. Where heterosexual intercourse is the only risk activity indicated, an active system of surveillance is implemented to gather additional information and verify the probable route of transmission. A letter is written to the patient’s attending physician asking specific questions to determine if the cases or any of their sexual partners belonged to a high risk category and if they or their partners had sexual exposure abroad; up to 25% of cases are recategorised as IDUs or homosexual/bisexual males.

In Scotland, 154 people who were categorised as probably having acquired their HIV infection through heterosexual intercourse had an earliest positive specimen between 1 January 1995 and 31 December 1997. Of these, 55 were diagnosed in Lothian Health Board (includes Edinburgh), 41 in Greater Glasgow, 22 in Tayside (includes Dundee), and 36 in the rest of Scotland.

OBJECTIVES
(1) To identify a single, stored blood sample from each of a selection of patients, diagnosed as HIV positive during 1995–7, who had been recorded on the SCIEH database as having probably acquired their infection through heterosexual intercourse.
(2) To ascertain the HIV subtype in each sample.
(3) For each patient, to link the details of viral subtype with corresponding epidemiological information on heterosexual risk.

SAMPLE SELECTION
Eligible individuals were restricted to those who (a) met the criterion as indicated in objective (1) above, and (b) were undergoing clinical follow up in either Edinburgh or Glasgow because over 60% of heterosexual cases in Scotland were from these two areas; furthermore, immunology laboratories in both cities were able to provide blood specimens which were residual following routine CD4 count analysis.

In Edinburgh, an aliquot of plasma from all CD4 count specimens from each of a selection of patients, diagnosed as HIV positive during 1995–7, who had been recorded on the SCIEH database as having probably acquired their infection through heterosexual intercourse, was performed to differentiate between true A and E subtypes. This further analysis revealed that one was indeed subtype E.

The 53 gag sequences were compared by phylogenetic analysis with homologous sequences from international databases as a reference. Phylogenetic trees were constructed, using reference subtype strains from international databases as comparisons, so that a viral subtype could be assigned to each case.

Results

SAMPLES
From the 55 identified patients from Lothian Health Board, stored plasma specimens were located for 48 and sequence material from the gag region was obtained in 42 of these. Of the 41 identified patients from Greater Glasgow, 11 whole blood samples were obtained and all yielded gag sequence data.

SUBTYPE ASSIGNATION
The 53 gag sequences were compared by phylogenetic analysis with homologous sequences from international databases and assigned to subtype (table 1). Twenty three (43%) of the specimens examined were HIV-1 subtypes other than B; 17 were subtype C and six subtype A. No other gag subtypes were identified. However, since subtype E is a recombinant virus with a subtype A gag gene, further sequencing of gag subtype A viruses in the v3/v4 region of the env gene (data not shown) was performed to differentiate between true A and E subtypes. This further analysis revealed that one was indeed subtype E.

ASSOCIATION OF SUBTYPE WITH CONTACT DATA
(TABLE 2)
Details of viral subtype were linked with corresponding epidemiological information on
heterosexual risk for the 53 cases of whom 18
(seven from Greater Glasgow and 11 from
Lothian) were female. For eight cases, all of
whom had a B subtype, no information was
available. Two cases, one who had a B and the
other a C subtype, reported sexual risk in
many, unspecified, countries. Of the nine cases
who reported sexual contact with an IDU (in
the United Kingdom or elsewhere in Europe),
eight had a B and one an A subtype; this latter
case indicated sexual contact with an IDU in
Austria. Of the remaining 34 cases, 10 (eight
with B and two with C subtype) reported
sexual contact only in the United Kingdom,
four (three with B and one with C subtype)
contact outside the United Kingdom but only
in Europe, 17 (13 with C and four with A sub-
type) contact in sub-Saharan Africa, two (one
with C and one with E subtype) contact in
Asia, and one (B subtype) contact in the
United States.

Both cases who had subtype C viruses which
were reportedly acquired in the United King-
dom had an African connection; one was a
Zambian national who claimed not to have
been sexually active before his arrival in
Scotland and the other had sexual contact with
an African partner in the United Kingdom.
Seventeen cases almost certainly acquired their
HIV in sub-Saharan African countries which
included Zambia, Botswana, and Uganda. The
two isolates from Asia were from India
(subtype C) and Thailand (subtype E), a find-
ing which is consistent with what is known
about the prevalent subtypes in these coun-
tries. Indeed, the only non-B subtype for which
no country of origin was specified was a
subtype C virus. A comparison of this with
other subtype C viruses from around the world
showed it with isolates from India (data not
shown) thus suggesting this to be the likely
region where the infection was acquired.

For 43 cases, information on region of sexual
contact was known. All the 19 cases who
reported sexual risk in Africa or Asia had a
non-B subtype while 20 of 24 cases who did
not report sexual contact in Africa or Asia had
a B subtype. This association was highly
significant (p <0.0001, Fisher’s exact test).

Discussion

A recent survey of 211 HIV infected IDUs and
heterosexual/bisexual males living in the north-
ern part of the United Kingdom and Ireland
demonstrated that all had subtype B
infection.14 To ascertain the extent to which
non-B subtypes had entered Scotland, and on
the understanding that, worldwide, most
non-B infections are spread through hetero-
sexual intercourse, the study was restricted to
those infected people who had reported this
activity as their only risk of infection. While the
53 cases sequenced were not necessarily
representative of HIV infected heterosexuals
throughout Scotland, they comprised 34%
(53/154) and 55% (53/96) of all cases diag-
nosed in Scotland and central Scotland respec-

Just over half of the cases investigated had a
subtype B strain and, where information was
available, heterosexual risk was confined to
the United Kingdom, United States, or Europe.
Thus, in this series of cases, molecular typing
to distinguish B from non-B subtypes was
shown to be highly predictive of the region
(developed or developing world) where HIV
was probably acquired. This is an important
finding because in instances where risk and
demographic information cannot be obtained
from the patient, molecular data can assist in
tracing the likely origins of infection. No infor-
mation was available from eight of the 53 cases
and since they were all subtype B, the chances
of them having been infected outside the
United Kingdom, United States, or Europe are
low.

If, as this study suggests, non-B subtypes
have not disseminated into Scotland’s hetero-
sexual population it is not because people
infected with non-B subtypes have only come
to Scotland recently. Indeed, HIV infected het-
erosexuals in Scotland who acquired their
infection in Africa have been a potential source
of HIV since the mid to late 1980s; between
1985 and 1990, 37 cases were diagnosed in
central Scotland, the area covered by this study.
It is possible that some dissemination has
occurred but, as yet, remains undetected since
HIV infected heterosexuals tend to be tested
for HIV serostatus at a relatively late stage of
their HIV disease.19 A possible explanation for
the lack of dissemination is that there has been
insufficient heterosexual mixing between those
infected in either Africa or Asia and indigenous
people for cultural reasons and/or the transient
nature of the former group’s stay in Scotland.

To date, those who have been most at risk of
acquiring HIV heterosexually in Scotland have
been the sexual partners of IDUs. During the
late 1980s and the 1990s, however, needle/
syringe exchange programmes reduced the
spread of HIV among IDUs and thus the risk of
HIV transmission from them to their
partners.20-22 Few cases of heterosexual trans-
mision in Scotland have occurred among
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prevention strategies.

information would be helpful in informing HIV

appreciable dissemination of non-B subtypes

improve our chances of detecting rapidly any

molecular data from indigenous heterosexuals

in the future.

Scotland (and the rest of the United Kingdom)

might alter the dynamics of HIV transmission

Continuing to collect both demographic and

molecular data from indigenous heterosexuals

who are newly diagnosed with HIV would

improve our chances of detecting rapidly any

appreciable dissemination of non-B subtypes

among this population if it were to occur. Such

information would be helpful in informing HIV

prevention strategies.

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Contributors: DY designed the project, performed the viral

subtyping, and wrote the paper; DG designed the project and

wrote the paper; CMcS and JW provided the samples for testing

subtyping, and wrote the paper; DG designed the project and

performed the epidemiologi-

cal investigations to ascertain risk factor information on cases of heterosexual transmission, and wrote the paper.


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