Diagnosis delays in the UK according to pre- or post-migration acquisition of HIV

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Running head: Diagnosis delays for migrants with HIV

Abstract

Objectives

To evaluate whether infection occurred pre- or post-migration and the associated diagnosis delay in migrants diagnosed with HIV in the UK.

Design

We analysed a cohort of individuals diagnosed with HIV in the UK in 2014-2016 born in Africa or elsewhere in Europe. Inclusion criteria were arrival within 15 years before diagnosis, availability of HIV \textit{pol} sequence and viral subtype shared by at least 10 individuals.

Methods

We examined phylogenies for evidence of infection after entry into the UK and incorporated this information into a Bayesian analysis of timing of infection using biomarkers of CD4+ cell count, avidity assays, proportion of ambiguous nucleotides in viral sequences and last negative test dates where available.
Results

1256 individuals were included. The final model indicated that HIV was acquired post-migration for most men who have sex with men (MSM) born in Europe (posterior expectation 65%, 95% credibility interval 64%-67%) or Africa (65%, 62%-69%), whereas a minority (20%-30%) of men and women with heterosexual transmission acquired HIV post-migration. Estimated diagnosis delays were lower for MSM than for those with heterosexual transmission, and were lower for those with post-migration infection across all subgroups. For MSM acquiring HIV post-migration the estimated mean time to diagnosis was <1 year, but for those who acquired HIV pre-migration the mean time from infection to diagnosis was >5 years for all subgroups.

Conclusions

Acquisition of HIV post-migration is common, particularly among MSM calling for prevention efforts aimed at migrant communities. Delays in diagnosis reinforce the need for targeted testing initiatives.

Key words: evidence synthesis; HIV/AIDS; late diagnosis; molecular epidemiology; phylogenetic

Introduction

Knowledge regarding the timing of HIV acquisition in migrant populations is important for guiding public health interventions and ensuring reliable estimates of undiagnosed infection and incidence. The majority of new HIV diagnoses with heterosexual transmission risk in the UK are among people born outside of the UK[1]. The total number of new diagnoses acquired through heterosexual contact has fallen over recent years, due at least in part to reduced levels of immigration from high prevalence countries[2]. Nevertheless migrants, particularly from sub-Saharan origin, remain a key group for targeted testing to minimise HIV-related morbidity and mortality and to prevent onward transmission of HIV through antiretroviral therapy[3]. Up until 2019 men born outside of the UK constitute a minority of new HIV diagnoses amongst men who have sex with men (MSM), but they have been increasing as a proportion of total diagnoses in recent years following a sharp fall in HIV diagnoses among UK-born men[1, 4].

The analysis of diagnosis delays in HIV presents a substantial analytical challenge because acquisition dates can usually only be indirectly inferred, and such analyses are further complicated by the issue of migration. Public Health England (PHE) make use of a CD4 back-calculation method in combination with recorded year of arrival to determine whether newly diagnosed infections were acquired pre- or post-migration[5], but it should be possible
to develop a detailed understanding through the combined analysis of multiple biomarkers\textsuperscript{[6, 7]}.

The use of phylogenetic analysis alongside modelling of biomarkers can provide additional information regarding whether any given case of HIV is likely to have been acquired within the country of diagnosis or elsewhere\textsuperscript{[8]}. We aimed to generate new insights into the association between migration and HIV acquisition in the UK by combining information from biomarkers with phylogenetic analysis of viral sequences. Our analysis focused on migrants diagnosed with HIV in the UK who were born in either Africa or Europe, representing the largest groups by continent.

**Methods**

We further developed statistical models\textsuperscript{[7]} to analyse the timing of infection in migrants diagnosed with HIV in the UK, and to relate timing of infection to their date of migration to the UK. We analysed people diagnosed in 2014–2016 with at least one ART-naïve viral $pol$ sequence (HXB2 positions 2253-3549) collected by the UK HIV Drug Resistance Database (UK-HDRD)\textsuperscript{[9]}. These data were linked to the HIV & AIDS Reporting System (HARS)\textsuperscript{[10]} held at Public Health England which included demographic information and year of migration to the UK. We considered the time period specified due to the availability of Sedia Limiting Antigen Avidity (LAg-Avidity) assay scores, a marker of recent HIV infection\textsuperscript{[11, 12]} used by PHE, in a substantial proportion of new diagnoses. The biomarkers analysed also included CD4 cell count at diagnosis and the proportion of ambiguous nucleotide counts at first ART naïve viral $pol$ sequence. We only included individuals diagnosed with HIV within 15 years of their migration to the UK, with country of birth within either Africa or Europe. People who likely acquired HIV via injecting drug use or vertical transmission were excluded, as was anyone with unknown transmission route. Analysis was restricted to viral subtypes with at least 10 eligible people.

Phylogenetic analysis was carried out to evaluate whether viral sequences clustered with other UK sequences or whether they showed more similarity to global reference sequences. Recent common ancestry with viral lineages established in the UK before migration of an individual was taken as strong evidence of acquisition of HIV in the UK.

We summarised the proportion of cases likely to have acquired HIV prior to migration or post-migration to the UK, and we also quantified diagnosis delays by subgroups defined by global region of birth (Africa or Europe), sex (male or female) and probable exposure (MSM or heterosexual transmission). The final groups compared were 1) MSM from Europe, 2) MSM from Africa, 3) women from Europe, 4) women from Africa, 5) men from Europe with heterosexual transmission, and 6) men from Africa with heterosexual transmission.

**Phylogenetic analyses**

Phylogenetic analyses were conducted separately for each HIV subtype, using the REGA classification. We made use of the first treatment-naïve partial $pol$ sequence for all individuals within the UK-HDRD (not just those within the defined analysis window,
summarised in Table S1, http://links.lww.com/QAD/C356). In addition, for each UK sequence we used the BLAST software to identify the five most similar sequences from the Los Alamos National Laboratory global database (excluding UK sequences). Matching sequences can overlap between UK individuals, meaning that the final ratio of external reference sequences is much lower than 5:1. A subtype B reference sequence was included for subtypes other than B as an outgroup, with a subtype D reference used as the outgroup for the subtype B analysis (from LANL). For each subtype, we then obtained a phylogenetic tree using FastTree Version 2.1.11\cite{13} specifying a generalized time-reversible model with gamma-distributed substitution rates. 100 bootstrap resamples were generated using Seqboot from the Phylip software suite to obtain bootstrap support for each node. Internal nodes were then dated using least squares dating (LSD software version 0.2)\cite{14}, making use of the specified outgroup sequences. IAS resistance mutations were removed prior to phylogenetic analysis\cite{15}.

We used the dated phylogenetic trees to assess whether HIV sequences from individuals included within our primary analysis cohort were nested within clusters that were already established within the UK at their time of migration. To do this, we start at the tip of the tree relating to each individual in the analysis and trace back to successive nodes in the tree, creating an enlarged subtree each time. For each iteration of the process, we check whether any HIV sequences from UK-born people have been added to the subtree and record the date estimate of the node if the bootstrap support value is ≥0.9. The process is terminated when one or more global LANL sequences is added to the subtree, and the earliest node date recorded (if any) is stored for that individual. In this manner, we generated an estimate of the earliest identifiable most recent common ancestor (MRCA) for a monophyletic HIV cluster within the UK for each patient, with root node of the cluster selected having bootstrap support ≥0.9. It is assumed that the time of MRCA with a UK sequence from a UK-born individual (within a cluster excluding LANL sequences) must represent a transmission event that occurred in the UK. If the MRCA for the cluster pre-dates the arrival of a migrant to the UK, then the viral lineage must have already been present in the UK at their time of arrival and we can be confident that they acquired HIV in the UK; if they are linked to a cluster that cannot be traced back before their arrival then the result is ambiguous as they may have themselves seeded the cluster.

Functions from the treeio\cite{16} and ape\cite{17} packages within R were used to carry out the tree manipulations necessary for this analysis. This approach drew inspiration from the Cluster Picker software\cite{18}. Examples are provided in Appendix S1, http://links.lww.com/QAD/C355, along with an explicit statement of the assumptions required for this approach.

**Biomarker model**

The analysis of individual-level biomarker data and diagnosis delays was developed from the Bayesian models previously described by Stirrup and Dunn\cite{7}. However, instead of fitting a joint model with the population-level incidence of new HIV infections through calendar time we constructed a model for the hazard of HIV infection at the individual level (further details in Appendix S1, http://links.lww.com/QAD/C355). As previously, we treat the time of HIV
acquisition for each individual as a random variable and generate a posterior distribution for acquisition date conditional on the observed biomarker and negative test data for each person.

For the biomarkers of CD4 cell count and nucleotide ambiguity of HIV sequence, the natural history of untreated HIV from infection was calibrated using data from the UK Register of Seroconverters (UKR) cohort\cite{19} as in Stirrup and Dunn\cite{7}. The relationship between Sedia LAg-Avidity scores and time from HIV acquisition was calibrated using data from treatment-naïve patients diagnosed during primary HIV infection published by Serhir et al.\cite{11}.

Bayesian analysis was conducted using the Stan software\cite{20}. Four sample chains of 1000 iterations each were generated, with warm-up of 500 for each chain. Quantities of interest such as the proportion of individuals within each subgroup who acquired HIV post-migration were calculated for each Markov chain Monte Carlo (MCMC) iteration within Stan, allowing the posterior expectation and credibility intervals to be estimated taking into account uncertainty in both model parameters and in the timing of infection of individuals. Average diagnosis delays within each subgroup were estimated in this manner conditional on pre- or post-migration HIV acquisition within each MCMC iteration. Inferences from the analysis are based on summarising the findings for individual patients rather than direct interpretation of model parameters, as such the reported posterior expectations and credibility intervals represent estimates for this specific sample of patients.

**Results**

Between 2014-2016, a total of 5667 people born in Africa or Europe (excluding the UK) were diagnosed with HIV in the UK with probable route of transmission recorded as heterosexual contact or sex between men, and 3917 had a year of arrival recorded within 15 years prior to diagnosis. Of these, a total of 1369 non-UK born people diagnosed in 2014–2016 were identified for whom all necessary data were available (following exclusion of 253 with arrival-to-diagnosis >15 years), and a subset of 1256 had a viral subtype shared by ten or more individuals within the dataset and were included in the analyses (Table 1). Most of the individuals included who were born in Africa were women, whilst most of those born in Europe were MSM.

Strong phylogenetic evidence of HIV acquisition within the UK was found in 117/1256 (9.3%) individuals overall, ranging from 11/429 (2.6%) for women born in Africa to 79/390 (20.3%) for MSM born in Europe (Table 2). The Bayesian biomarker model was fitted including information on definite within-UK infections from the phylogenetic analyses. The final model indicated that 65% (64%-67%) of MSM born in Europe and 65% (62%-69%) of MSM born in Africa acquired HIV post-migration, but that a minority (20%-30%) of men and women born in Europe or Africa with heterosexual transmission acquired HIV post-migration (results reported as posterior expectation, 95% credibility interval). These differences can be observed in plots of the estimated probability of post-migration HIV infection in individual people (Figure 1), with most men and women with heterosexual transmission having an estimated probability <0.05 whilst most MSM had an estimated probability >0.95.
Among individuals with post-migration HIV infection, the mean time from HIV acquisition to diagnosis was estimated to be less than 1 year for MSM born in Europe (0.32 years, 0.26-0.38) or in Africa (0.62 years, 0.4-0.9) but ranged from 1.39 to 2.42 years for those with heterosexual transmission (Table 2). The mean time from arrival in the UK to diagnosis for those individuals with pre-migration HIV acquisition was estimated to be substantially higher for all subgroups than the mean time to diagnosis for those with a post-migration HIV acquisition. The mean times from HIV infection to diagnosis were even greater. For example, for women born in Africa and acquiring HIV in the UK, the mean time to diagnosis was 2.11 (1.8-2.45) years, but for women acquiring HIV pre-migration the mean time from arrival to diagnosis was 5.24 (5.1-5.36) years and the mean time from acquisition to diagnosis was 10.69 (10.29-11.07) years. These substantial differences between the subgroups can also be observed in plots of the estimated times from acquisition to diagnosis in individual people (Figure 2).

**Discussion**

We have developed new phylogenetic and statistical methodology for the investigation of diagnosis delays and location of HIV acquisition in migrant populations. Applying these methods to data from people diagnosed with HIV in the UK in the period 2014-2016, we found that the proportion of individuals who acquired HIV infection post-migration is substantially higher in MSM than in people with heterosexual transmission, and that the intervals from infection to diagnosis were substantially higher for people who acquired their infection pre-migration. Differences between exposure groups were far more significant than differences based on region of origin. Our findings regarding the proportion of heterosexual transmissions occurring before diagnosis in the UK are consistent with those published by PHE[1].

Previous studies in the UK and elsewhere in Europe have also found that among migrants diagnosed with HIV, MSM are more likely to have acquired the infection post-migration. Alvarez-del Arco conducted an analysis of data from HIV clinics in nine European countries (18% from the UK) from July 2013 to July 2015 and reported overall proportions for post-migration infection of 72% among MSM and 58% and 51% in men and women with heterosexual transmission, respectively[21]. Their study implemented a Bayesian analysis of CD4+ cell counts and viral load data that has similarities with our approach (although there was no explicit modelling of infection and diagnosis hazards within the specified likelihood functions). Further analysis of the same dataset by Pantazis et al. also incorporated prior assumptions linked to subject-specific behavioural data. Conclusions were similar, with 71% of MSM and 55% of people with heterosexual transmission thought to have acquired the virus post-migration[22]. The lower percentage of people with heterosexual transmission with post-migration acquisition in our analysis may be at least partially due to our exclusion of individuals arriving in the UK more than 15 years before their HIV diagnosis.

A systematic review conducted to the end of 2014 found the proportion of post-migration acquisitions to be consistently below 50% for people diagnosed with HIV in European countries who were born in Africa or who were of Black African ethnicity[23]. An analysis of
black African adults diagnosed with HIV in the UK found that, based on CD4+ cell counts at diagnosis, the proportion of individuals acquiring the virus post-migration increased from 9.1% in 2002 to 37% in 2011[24]. Our findings are consistent with the latter figure and indicate that post-migration HIV infections remain an important issue among all migrant groups.

We estimated that the average times from HIV acquisition to diagnosis were substantially higher for people with heterosexual transmission than for MSM, whether or not the infection was acquired pre-migration. This is consistent with the findings across nine European countries reported by Pantazis et al.[22]. The exact magnitude of the diagnosis delays will vary according to local engagement of migrant groups with healthcare and testing initiatives. Regular HIV testing for MSM was becoming more common in the UK in the period 2012-2016[2], and it is encouraging that we found an average time to diagnosis of less than 1 year for MSM with post-migration acquisition. It is believed that the success of testing campaigns has played an important role in recent declines in new diagnoses of HIV among MSM in the UK[2] in combination with changes to treatment guidelines that recommend prompt initiation of ART in all people[25] as well as expansion of pre-exposure prophylaxis among this group since 2017[26].

People acquiring HIV post-migration via heterosexual transmission had higher average diagnosis delays, ranging from 1.39 (0.79-2.06) years for women born in Europe to 2.42 (1.97-2.91) years for men born in Africa. People acquiring HIV via heterosexual transmission pre-migration had the highest times from arrival to diagnosis in the UK, with average estimates over 4 years for all subgroups. The estimated average time from acquisition to diagnosis was even higher in these groups, ranging from 8.53 (7.76-9.25) years for women born in Europe to 11.79 (11.28-12.31) years for men born in Africa with heterosexual transmission. The median time from HIV infection to the appearance of AIDS-defining symptoms has been estimated to be around 10 years[27], so this implies that a substantial proportion of people within these groups were only diagnosed following the appearance of symptoms linked to their immune suppression caused by chronic HIV infection.

In a sample of 463 people recruited from social and commercial venues frequented by black African adults in London in 2016, Fakoya et al. found that among those testing positive for HIV 18/38 (47%) were undiagnosed[28]. Our finding of significant diagnosis delays among migrant groups with HIV is further evidence for substantial numbers of undiagnosed cases. The incidence of HIV linked to heterosexual transmission in the UK has been falling more slowly than that for MSM[1], and improved engagement with testing among at-risk heterosexual groups will be required for the elimination of HIV transmission in the UK.

A novel aspect of this study is the integration of information from both phylogenetic analysis and from biomarkers of the timing of infection. Phylogenetic analyses have been used to evaluate the structure of HIV epidemics within countries[8], but we linked our phylogenetic analysis to the timing and location of HIV acquisition in individual patients. Using the methodology developed we only found strong phylogenetic evidence of infection within the UK in a minority of patients, with a higher proportion within MSM, as would be expected.
Ideally, the analyses of viral sequence data and individual biomarker data would be integrated within a single coherent model, but this would require substantial further methodological development.

A limitation of our analysis is that, given that the dataset was based on the UK-HDRD, we only included patients diagnosed within the study period who had a viral sequence available. A fully comprehensive analysis of diagnosis delays and acquisition locations within the populations of interest would include all patients diagnosed in the UK within the specified period. However, monitoring of viral drug resistance in newly diagnosed patients is routine in the UK and so we expect our dataset to be representative [29].

There has been substantial progress in recent years in reducing diagnosis delays and the incidence of HIV among MSM in the UK [2], and our results are consistent with this in demonstrating average diagnosis delays below 1 year in MSM with post-migration HIV acquisition. However, equivalent declines in the time to diagnosis have not been observed among all at-risk migrant communities. Targeted engagement with groups most at risk of undiagnosed HIV infection is needed to accelerate progress towards elimination of HIV transmission within the UK and to minimise the mortality and morbidity associated with late diagnosis of HIV.

Acknowledgments

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Declaration of Competing Interest

FB has received conference support and consultancy fees from Gilead Sciences Ltd and Viiv Healthcare. The remaining authors do not have any competing interests to disclose.

Author contributions

OS conducted statistical and phylogenetic analyses and drafted the first version of the manuscript. AT carried out data linkage and processing. MR-C, EV and DD reviewed and provided contributions towards development of the statistical methodology. FB and VD contributed to the clinical and public health interpretation of the findings. All authors reviewed and approved the final manuscript.
References


Figure 1 Histograms of the estimated probability of post-migration HIV infection for each individual from the final Bayesian model for biomarker data, according to region of birth, sex and recorded mode of transmission. Probability bin widths are set at 0.05.

het., heterosexual transmission; MSM, men who have sex with men.
**Figure 2** Histograms of the expected total time from infection to diagnosis for each individual from the final Bayesian model for biomarker data, according to region of birth, sex and recorded mode of transmission. Bin widths are set at 1 year.

Dx, diagnosis; het., heterosexual transmission; MSM, men who have sex with men.
Table 1 Demographic characteristics and viral subtype of the individuals included in the analyses, according to region of birth and recorded mode of transmission.

<table>
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<td>1369</td>
<td>738</td>
<td>1114</td>
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<td>256</td>
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<td>429</td>
<td>234</td>
<td>390</td>
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<td>Age at Dx (years)</td>
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<td>40.7 (35.2-45.5)</td>
<td>31.3 (27.2-36.7)</td>
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<td>31.4 (25.3-37.4)</td>
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<td>CD4 at Dx (cells/µL)</td>
<td>390 (244-558) [48]</td>
<td>268 (139-439) [382]</td>
<td>214 (76-358) [219]</td>
<td>478 (340-649) [368]</td>
<td>336 (187-528) [74]</td>
<td>190 (60-454) [65]</td>
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<td>-ve HIV test in UK</td>
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<td>89 (20.7)</td>
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<td>8 (11.1)</td>
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<td>8 (2.1)</td>
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Data shown as n, n (%) or median (interquartile range) [n observations].

Dx, diagnosis; MSM, men who have sex with men; het., heterosexual transmission; PHE, Public Health England. *People born in Africa or elsewhere in Europe and within the specified transmission subgroups were diagnosed in the UK in 2014–2016, with recorded year of arrival within 15 years prior to diagnosis (data provided by PHE)
Table 2 Results of phylogenetic analyses and Bayesian modelling of biomarker data, according to region of birth and recorded mode of transmission.

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<th>Region of birth:</th>
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<td>Strong evidence UK infection</td>
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<td>11 (2.6)</td>
<td>13 (5.6)</td>
<td>79 (20.3)</td>
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<td>10 (2.3)</td>
<td>9 (3.8)</td>
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<td>212 (90.6)</td>
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<td>74 (96.1)</td>
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<td>Final model results†</td>
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<tr>
<td>Proportion with post-migration infection</td>
<td>0.65 (0.62-0.69)</td>
<td>0.28 (0.27-0.3)</td>
<td>0.29 (0.27-0.3)</td>
<td>0.65 (0.64-0.67)</td>
<td>0.3 (0.26-0.35)</td>
<td>0.2 (0.16-0.25)</td>
</tr>
<tr>
<td>Mean time to HIV Dx following post-migration acquisition</td>
<td>0.62 (0.4-0.9)</td>
<td>2.11 (1.8-2.45)</td>
<td>2.42 (1.97-2.91)</td>
<td>0.32 (0.26-0.38)</td>
<td>1.39 (0.79-2.06)</td>
<td>1.67 (0.81-2.66)</td>
</tr>
<tr>
<td>Mean time to Dx from arrival in UK for pre-migration cases</td>
<td>2.09 (1.55-2.47)</td>
<td>5.24 (5.1-5.36)</td>
<td>6.16 (5.97-6.33)</td>
<td>1.39 (1.24-1.56)</td>
<td>4.27 (3.92-4.53)</td>
<td>4.26 (3.92-4.5)</td>
</tr>
<tr>
<td>Mean time to Dx from HIV acquisition for pre-migration cases</td>
<td>7.16 (5.75-8.58)</td>
<td>10.69 (10.29-11.07)</td>
<td>11.79 (11.28-12.31)</td>
<td>5.48 (4.97-6.00)</td>
<td>8.53 (7.76-9.25)</td>
<td>9.53 (8.75-10.3)</td>
</tr>
</tbody>
</table>

*Sequence clusters with UK sequences, but most recent common ancestor is dated to after arrival of index patient in the UK. †Displayed as posterior expectation (95% credibility interval), over the posterior distributions of infection times for individuals included in the analysis. Dx, diagnosis; MSM, men who have sex with men; het., heterosexual transmission.