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Predictors of human immunodeficiency virus (HIV) infection in primary care among adults living in developed countries: a systematic review

Benhildah N. Rumbwere Dube1*, Tom P. Marshall1, Ronan P. Ryan1 and Modupe Omonijo2

Abstract

Background: Early diagnosis of human immunodeficiency virus (HIV) is important because antiretroviral therapies are more effective if infected individuals are diagnosed early. Diagnosis of HIV relies on laboratory testing and determining the demographic and clinical characteristics of undiagnosed HIV-infected patients may be useful in identifying patients for testing. This systematic review aims to identify characteristics of HIV-infected adults prior to diagnosis that could be used in a prediction model for early detection of patients for HIV testing in UK primary care.

Methods: The population of interest was adults aged ≥18 years in developed countries. The exposures were demographic, socio-economic or clinical characteristics associated with the outcome, laboratory confirmed HIV/AIDS infection. Observational studies with a comparator group were included in the systematic review. Electronic searches for articles from January 1995 to April 2016 were conducted on online databases of EMBASE, MEDLINE, The Cochrane Library and grey literature. Two reviewers selected studies for inclusion. A checklist was developed for quality assessment, and a data extraction form was created to collate data from selected studies.

Results: Full-text screening of 429 articles identified 17 cohort and case-control studies, from 26,819 retrieved articles. Demographic and socio-economic characteristics associated with HIV infection included age, gender and measures of deprivation. Lifestyle choices identified were drug use, binge-drinking, number of lifetime partners and having a partner with risky behaviour. Eighteen clinical features and comorbid conditions identified in this systematic review are included in the 51 conditions listed in the British HIV Association guidelines. Additional clinical features and comorbid conditions identified but not specified in the guidelines included hyperlipidemia, hypertension, minor trauma and diabetes.

Conclusion: This systematic review consolidates existing scientific evidence on characteristics of HIV-infected individuals that could be used to inform decision making in prognostic model development. Further exploration of availability of some of the demographic and behavioural predictors of HIV, such as ethnicity, number of lifetime partners and partner characteristics, in primary care records will be required to determine whether they can be applied in the prediction model.

Keywords: Acquired immuno-deficiency syndrome, Antiretroviral therapies, Diagnosis, Human immunodeficiency virus, Patient characteristics, HIV predictors, Primary care
Background

Human immunodeficiency virus (HIV) is a retroviral infection that weakens the immune system and is a subsequent causative agent of acquired immuno-deficiency syndrome (AIDS) [1, 2]. The virus is transmitted through the exchange of a variety of bodily fluids mainly sexually, perinatal and blood-borne [2, 3]. HIV/AIDS is one of the highest contributors to morbidity and the sixth leading cause of mortality worldwide [2, 4]. The World Health Organization (WHO) estimated that 1.5 million people died of HIV/AIDS-related diseases and 36.7 million lived with HIV worldwide, in 2015 [5]. In 2015, it was estimated that 594 deaths were associated with HIV/AIDS in England and 101,200 people were estimated to live with HIV in the UK [6].

The life expectancy of HIV-infected individuals has increased over the years and is approaching that for the general population [7, 8]. This is a result of the effectiveness of antiretroviral therapies (ART) that has led to most individuals coping with HIV infection as a chronic condition rather than an illness inevitably leading to death [9]. The use of ARTs has led to a better quality of life for infected individuals and a reduction in morbidity and mortality [4].

In the 1980s/1990s, more focus was placed on HIV prevention strategies and treatment of symptomatic diseases but due to the benefits of ART, the emphasis has now moved to earlier HIV diagnosis [10]. WHO developed a strategy aimed at reducing new HIV infections, AIDS-related mortality and discrimination to zero with one of the HIV strategies being optimisation of ‘HIV prevention, diagnosis, treatment and care outcomes’ [11].

The CD4 count is an indicator of immunosuppression in an individual infected with HIV [9]. Early diagnosis of people with HIV (cluster of differentiation 4 (CD4) > 350/mm³) improves the effectiveness of antiretroviral therapies, and additionally, the treatment and advice provided reduces onward transmission, thereby making late diagnosis of HIV (CD4 < 350/mm³) an important public health concern [12, 13]. Furthermore, early diagnosis of HIV and earlier use of therapies reduce health and social care costs by preventing illness associated with HIV [4, 14]. On the other hand, delayed diagnosis of HIV to late stages (CD4 < 350/mm³) leads to worse prognosis for the patient due to irreversible immunologic damage and associated problems [13, 15].

Public Health England estimated that out of the 101,200 individuals living with HIV in 2015, 6095 were newly diagnosed and 13% were unaware of their HIV status [6]. In that year, 39% of people that were newly diagnosed with HIV in the UK were detected late (CD4 < 350/mm³), which is an intolerably high proportion [6]. Meanwhile, evidence shows that about 33% of patients that are diagnosed with HIV in the UK would have seen a general practitioner (GP) within the previous year [9, 16, 17]. One study found that one in three patients that presented at least one HIV-related symptoms to their GPs was consequently diagnosed with HIV by their GP [18]. Therefore, primary care has a role to play in increasing uptake of HIV diagnostic testing since nearly all the UK population is registered with a GP [19]. HIV testing in general practices can be done by either sending blood samples for laboratory testing or conducting combined HIV antibody and protein 24 (P24) antigen tests followed by laboratory confirmation [9]. However, among those who visit their GP, a challenge is the fact that HIV/AIDS has many signs and symptoms such as rashes, weight loss and respiratory infections and these are not specific to HIV/AIDS.

Current UK guidelines from British HIV Association (BHIVA) recommend HIV testing to individuals from high-risk groups, those with symptoms indicative of HIV or where HIV forms part of the diagnosis [20]. However, approximately three-quarters of patients consult their GPs in the period prior to diagnosis may not present these indicator symptoms and diagnoses [17]. This suggests that these currently recommended predictive factors are of limited use in the identification of possible HIV-infected individuals.

The methods used in routine HIV testing either involve use of screening assays on blood for laboratory testing or rapid tests conducted on samples from a finger-prick or mouth swab at point of care. The commonly used and recommended first-line assays test for HIV antibodies and the HIV p24 antigens simultaneously [9, 20]. These assays can be utilised within a month of HIV infection [9, 20]. The sensitivity of these assay tests ranges from 99.8–100% and the specificity ranges from 99.4–100% [21, 22]. Point-of-care tests (POCTs) are rapid testing devices that diagnose HIV within 15 min. However, such tests have lower specificity in comparison to laboratory tests, thereby giving significantly high proportion of false positives, especially when used in low prevalence settings [9]. It is therefore possible to test for and diagnose HIV using simple blood tests with few false positives and false negatives.

The UK primary care clinicians need to identify patients who should be offered HIV testing. A systematic review is therefore necessary to identify demographic, lifestyle, clinical and laboratory characteristics of patients which might be associated with HIV infection in primary care. The identified characteristics will be investigated to determine if they are documented in electronic primary care records and whether they can be used to predict which primary care patients are likely to have HIV infection.

This systematic review identifies, critically evaluates and interprets available evidence related to the demographic, lifestyle, clinical and laboratory characteristics associated with HIV/AIDS infection in adults in the developed world [23, 24].
Methods
This systematic review conforms to the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (Additional file 1, PRISMA) [25]. The methods were detailed in a published protocol, but a summary is included in this section [26]. The PROSPERO registration number for the protocol is CRD42016042427.

Review question
This systematic review systematically identifies and summarises evidence on characteristics of HIV-infected adults which could be used in a prediction model for early detection of HIV in primary care.

The review question is:

What demographic, lifestyle, clinical and laboratory characteristics are associated with HIV infection in adults aged 18 years and over?

Population, exposure and outcome
Studies selected included human participants ≥18 years. Exposures may be demographic, socio-economic or clinical risk factors or characteristics associated with HIV infection. The comparison group is either people without risk factors or no comparison group. The outcome is laboratory-confirmed HIV/AIDS infection.

Study design
This review considers observational (analytical) studies, comparing groups and produces predictive values or likelihood ratios (case-control and cohort, both retrospective and prospective studies) [27].

Search strategy
Studies are identified via electronic searches of EMBASE (Ovid), MEDLINE (Ovid), The Cochrane Library (Wiley) and the unpublished grey literature (SIGLE, Google Scholar and BASE). Additional searches are conducted on abstracts or conference proceedings using Web of Science Conference Proceedings Citation Index (CPCI), Global Index Medicus, guidelines (NICE, DH) and reference searching [28]. There were no language restrictions, and all studies published from year 1995 to April 2016 were included. The search terms used in Ovid MEDLINE (Additional file 2: Appendix I) are adjusted to suit searches in other databases. References were searched and stored using the Refworks referencing programme.

Inclusion/exclusion criteria
To ensure generalisability to a UK setting, only studies undertaken in the following developed countries are included in this review: Europe (all countries) and North America (USA and Canada), Australia and New Zealand. Studies which include children only are excluded.

Selection procedure
Two reviewers independently selected articles in the first and second screening of articles. The first screening checked titles/abstracts to find out if articles addressed the review question and fulfilled the inclusion and exclusion criteria (Additional file 3: Appendix II). The second screening was the full article review. Differences between the reviewers were resolved through discussions.

Quality assessment and data extraction
Quality assessment was done using a checklist for cohort and case-control studies modified from the Scottish Intercollegiate Guidelines Network (SIGN) [29].

A data extraction form was developed to collate data from selected articles. Tabulation and narrative of the results were produced, and the tabulation contains description of the articles (the author, publication year, the study design, number of participants, population under study and outcome).

Results
Selection procedure
A total of 26,819 hits were returned from the database searches and NICE and DH, 6173 duplicates were removed and 20,646 articles were pre-screened (Fig. 1). The first review resulted in selection of 429 articles using titles/abstracts. A discussion was held to agree on the articles selected. The reviewers independently selected suitable articles using full text and a second discussion was held. The reviewers agreed on 17 articles: 11 cohort and 6 case-control studies.

Quality of studies
All 11 cohort studies were of acceptable standard, but only 2 were of high quality, in terms of participant recruitment, sample size and how they dealt with bias. The other articles were not clear about how they dealt with confounding factors (Table 1). All 6 case-control studies were of acceptable standard, and half of them were of high quality, in terms of participant recruitment, sample size and how they dealt with bias.

Study characteristics
The cohort studies were conducted in the UK (3), Ireland (1), Australia (1) and USA (6). The number of participants ranged from 32 to over 20,000 with most studies focusing on patients aged ≥18 years. The study duration ranged from 1 to 5 years, but some of the studies did not state follow-up intervals (Table 1).

The case-control studies were conducted in the UK (1), Netherlands (1), the USA (2) and Canada (2). In
total, they included 1412 cases and 3423 controls. The study duration ranged from 1 to 12 years with a 6-month follow-up for most of the studies.

**Identified predictors of HIV infection**

The predictors of HIV identified were categorised into demographic and socio-economic, behavioural or lifestyle, clinical features and comorbidities. Statistically significant characteristics or those with highest percentages were included.

**Demography and socio-economic**

The significant demographic characteristics (Table 2) associated with HIV infection were (i) homosexuals and/or bisexuals, mainly men who have sex with men (MSM) (5 studies) 1.8 to 2.7 times risk [30–34], (ii) black ethnicity (1 study); 6.8 times risk [30] and (iii) age ranges (3 studies), mainly between 27 and 40 years with up to 11.5 times the risk [31, 35, 36]. Two studies revealed that gender had no significant association with the risk of HIV infection [30, 31]. Two studies showed conflicting evidence on the increased risk of HIV infection associated with country of birth; one study from the USA showed that being born in the USA was associated with 1.76 times the risk [30], but a study from Australia showed that being born in Australia had a non-significant risk [35].

Socio-economic conditions associated with increased risk of HIV identified were (i) poverty in urban but not in rural areas (1 study) [37], (ii) annual income under $10,000 having 13 times the risk (1 study) [30], (iii) unemployment (1 study) [30], (iv) housing problems (1 study) [30] and (v) not being a high school graduate or having low education attainment (2 studies); 2.2 times the risk [30, 38].

**Behavioural characteristics**

Behavioural characteristics (Table 3) associated with an increased risk of HIV infection can be categorised into personal lifestyle, partner lifestyle and effects of life events.
# Table 1 Data extract and quality assessment summary: cohort and case-control studies

| Study                                                                 | Design                     | Population, setting                                                                 | Outcome: duration and follow-up                                                                 | Study addresses an appropriate and clearly focused question | Participants being studied are selected from the same source populations | Indicate how many people participated | Main potential confounders identified and accounted for | How well was the study done to minimise the risk of bias or confounding? |
|----------------------------------------------------------------------|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------|-----------------------------------------------------------------------|-------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------|
| 1. Joore I.K. et al., (2015) [42]                                    | Case-control study         | 102 cases and 299 controls, Amsterdam, Netherlands                                                                                           | HIV infection: 2002–2012                                                                    | Yes                                                        | Yes                                                                 | Yes                                               | Cannot say                                             | +                                                                                    |
| 2. Damery S. et al. (2013) [17]                                      | Case-control study         | 939 cases and 2576 control, UK                                                                                                               | HIV/AIDS diagnosis: Jan 1989–Sept 2010                                                        | Yes                                                        | Yes                                                                 | Yes                                               | Yes                                                     | ++                                                                                   |
| 3. Szerlip M.A. et al. (2005) [39]                                   | Case-control study (retrospective) | Older patients aged 55 years and over (53 cases and 106 controls), New Orleans, USA                                                          | Diagnosis of HIV infection: 6 months interval up to 12 months                              | Yes                                                        | Yes                                                                 | Yes                                               | Cannot say                                             | +                                                                                    |
| 4. Ellerbrock T.V. (2004) [33]                                       | Case-control study         | 217 cases 395 controls, FL, USA                                                                                                             | HIV diagnosis: 1998–2000                                                                  | Cannot say                                                | Yes                                                                 | Yes                                               | Cannot say                                             | +                                                                                    |
| 5. Burchell, A.N. (2010)                                             | Case-control study         | Gay and bisexual men 123 cases and 240 controls, Ontario, Canada                                                                            | HIV infection: 1998–2006                                                                  | Yes                                                        | Yes                                                                 | Yes                                               | Yes                                                     | ++                                                                                   |
| 6. Burchell, A. N. (2003) [41]                                       | Case-control study         | Adults aged 18 years and over 80 cases (seroconverts) and 106 controls, Ontario, Canada                                                     | Diagnosed HIV infection: June 1998–Dec 2001                                                 | Yes                                                        | Yes                                                                 | Yes                                               | Yes                                                     | ++                                                                                   |
| 7. Hodder, S.L. (2013) [36]                                          | Cohort study (prospective) | N = 2099 (women aged 18–44 with 1 or more personal or partner risk factors), USA                                                          | HIV prevalence and incidence: 2009–2010 with 6-month follow-up to 12 months                 | Yes                                                        | Yes                                                                 | Yes                                               | Yes                                                     | +                                                                                    |
| 8. Moran, J. (2012) [34]                                             | Cohort study               | N = 1404 Ireland                                                                                                                             | HIV infection: 2008–2011                                                                   | Yes                                                        | Cannot say                                                | Yes                                               | No                                                      | +                                                                                    |
| 9. Desai M. (2012) [38]                                              | Cohort study               | N = 328 UK                                                                                                                                  | HIV infection: Sept 2010–Dec 2011                                                           | Yes                                                        | Cannot say                                                | Yes                                               | No                                                      | +                                                                                    |
| 10. Guy R.J. (2011) [33]                                             | Cohort study               | N = 7857 (MSM) Victoria, Australia                                                                                                          | HIV positivity: Apr 2006–Jun 2009                                                          | Yes                                                        | Yes                                                                 | Yes                                               | Cannot say                                             | +                                                                                    |
| 11. Krauskopf K. (2011) [45]                                         | Cohort study               | N = 643 (HIV-infected and at-risk men aged 49 years and older), Bronx, NY, USA                                                            | HIV infection: 2001–2006 6-month follow-up                                                 | Yes                                                        | Yes                                                                 | Yes                                               | Yes                                                     | ++                                                                                   |
| 12. Niyonsenga T (2013) [37]                                         | Cohort study               | N = 20,528 (all cases with HIV/AIDS diagnosis), FL, USA                                                                                      | AIDS/HIV incidence: 1998–2002                                                             | Yes                                                        | Cannot say                                                | Yes                                               | Cannot say                                             | +                                                                                    |
| 13. Ross, J. D. (1997) [31]                                          | Cohort study               | N = 8466 (population aged 16 and over), Lothian and Glasgow region of Scotland                                                             | HIV positive results: Jan 1989–Dec 1993                                                   | Yes                                                        | Yes                                                                 |                                                   |                                          | Yes                                                                       |
| Study | Design     | Population, setting | Outcome: duration and follow-up | Study addresses an appropriate and clearly focused question | Participants being studied are selected from the same source populations | Indicate how many people participated | Main potential confounders identified and accounted for | How well was the study done to minimise the risk of bias or confounding? |
|-------|------------|---------------------|--------------------------------|----------------------------------------------------------|---------------------------------------------------------------------|-----------------------------|-------------------------------------------------|----------------------------------------------------------|
| 14.   | Cohort     | $N = 32$ (HIV-positive patients aged ≥ 60) Atlanta, GA, USA | HIV positivity: Jan 1985–July 1992 | Yes                                                      | No                                                                  | Yes                          | No                                              | +                                                       |
| 15.   | Cohort     | Intravenous drug users (99 HIV+ve patients 124 HIV−ve patients), New York City, USA | HIV infection: recruited 1988 and followed up for 3.5 years and 6-month follow-up | Yes                                                      | Yes                                                                  | Yes                          | Yes                                             | ++                                                      |
| 16.   | Cohort     | $N = 344$ Albuquerque, NM, USA | HIV diagnosis: 19-month period July 1993–Jan 1995 | Yes                                                      | Yes                                                                  | Cannot say                  | +                                               |
| 17.   | Cohort     | $N = 133$ (A&E patients aware and unaware of HIV status), London, UK | HIV infection: 1991–1994 | Yes                                                      | Yes                                                                  | Yes                          | No                                              | +                                                       |

Modified from Scottish Intercollegiate Guidelines Network (SIGN)

Minimise risk of bias or confounding: high quality (++) □ acceptable (+) □ unacceptable—reject 0
| Demographic characteristics identified in selected studies | Ellerbrock 2004 [30] | Guy 2011 [35] | Hodder 2013 [36] | Ross 1997 [31] | Niyonsenga 2013 [37] | Gordon 1995 [32] | Desai 2012 [38] | Hafner 1997 [33] | Moran 2012 [34] |
|----------------------------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Age                                                      | < 30 y                  | 18–26 years              | 21–25 years              | 26–30                  | 1.7 (1.05–2.8)          | 5.83 (122–27.96)       | 1.91 (1.27–2.87)         | 0.3*                    | 11.54 (2.71–49.05)       |
| Sexuality                                                | Homosexual/ bisexual    | 1.79* (0.67–4.79)        | 2.7 (1.5–4.8)            | 37%                    | 57%                    | 61%                    |
|                                                          | Heterosexual            | 1.00                     | 1.0                     | 3%                     | 28%                    |
| Ethnicity                                                | Black race              | 6.77 (4.17–11)           | 1.68* (0.41–6.94)        | 1.76 (1.22–2.53)       | 1.42* (1.00–202)        |                         |
|                                                          | Aboriginal or Torres    |                          |                         |                         |                         |                         |
|                                                          | Strait Islander         |                          |                         |                         |                         |                         |
| Country of birth                                         | Born in USA             | 1.76 (1.22–2.53)         | 1.42* (1.00–202)        |                         |                         |                         |
|                                                          | Born in Australia       |                          |                         |                         |                         |                         |
| Socio-economic factor                                    | Housing problems        | 17%                      |                         |                         |                         |                         |
|                                                          | Poverty index in rural areas | − 0.25*              |                         |                         |                         |                         |
|                                                          | Poverty index in urban areas | 0.58                   |                         |                         |                         |                         |
|                                                          | Annual income < $10,000 | 132 (791–22)             |                         |                         |                         |                         |
|                                                          | Farmworker              | 2.09 (1.47–2.96)         |                         |                         |                         |                         |
|                                                          | Unemployed              | 5.08 (3.18–8.14)         |                         |                         |                         |                         |
|                                                          | Education beyond high school | 0.43* (0.15–1.24)      |                         |                         |                         |                         |
|                                                          | Not a high school graduate | 2.15 (1.48–3.1)         |                         |                         |                         |                         |

NB % do not add up to 100% because they are provided for all risk factors
*Not statistically significant
**Correlation coefficient
Personal lifestyle choices identified were (i) injecting drugs (7 studies); 2 to 21 times the risk [30, 31] [32–36], (ii) smoking crack cocaine (1 study); 22.8 times the risk [30], (iii) being a current smoker (1 study) [38], (iv) binge-drinking (1 study); 12.8 times the risk [34], (v) exchanging money or drugs for sex (1 study); 19 times the risk [30], (vi) male anal sex (1 study); 1.6 times the risk [35] and (vii) being obese (1 study) [30]. Personal sexual behaviours identified were unsafe sex (2 studies); 1.8 times the risk [35, 38] and having multiple sex partners (1 study); 5.5 to 19.8 times the risk [30]. Partner-related behaviours identified were (i) HIV-positive partner (2 studies); 3.24 times the risk [17, 41], (ii) partner’s use of illicit drugs (2 studies); 1.57 and 17 times the risk [30, 36], (iii) partner’s alcohol dependence/binge-drinking (1 study); 1.4 to 1.8 times the risk [39].

One study revealed risk-associated stressful events in men having sex with men to be; (i) the number of stressful events, (ii) events occur in ages under 30 years associated with 7 times the risk, (iii) type of stressful events such as bereavement and death of close friend and financial crisis and relationship breakdown (romantic and other relations); 3 times the risk [40].

**Clinical features**

Evidence from 4 studies (Table 4) revealed that HIV infection was associated with clinical features; (i) flu-like symptoms including fever/chills and cough (3 studies); 4.5 times the risk [33, 39, 41], (ii) rash (1 study); 4.5 times the risk [39], (iii) weight loss (2 studies); 13 to 39 times the risk [17, 41], (iv) diarrhoea (2 studies); 2 to 4.4 times the risk [17, 41] and one study identified abdominal pain, minor trauma and nausea/vomiting as the condition affecting 5–6% of the HIV-positive patients [33].

**Comorbidities associated with HIV**

The clinical indicator conditions (Table 4) were categorised into the following: respiratory, dermatology, neurology, gastroenterology, gynaecology, haematology, ophthalmology, ear, nose and throat (ENT) and other (not classified).

The respiratory conditions identified were pneumonia (2 studies); 8 and 48 times the risk [17, 41] and pneumocystis in 52% of the HIV-infected patients (1 study) [42]. The neurological conditions identified were psoriasis (2 studies); 2.6 to 3 times the risk [17, 41] and herpes zoster (2 studies); 10.9 and 25.4 times the risk [17, 41].

The evidence revealed that HIV infection was significantly associated with peripheral neuropathy (1 study); 15.9 times the risk [41] and neurologic disabilities cranial nerve abnormalities and fine limb movement (1 study); 2.4 times the risk in women and 1.9 times the risk in men [43]. The gastroenterological conditions identified were oral candidiasis (2 studies); 7.1 and 29.4 times the risk [17, 41], hepatitis B (2 studies); 8.3 and 11.5 times the risk [44, 41] and liver diseases (1 study), affecting 22%
Table 4 Clinical features and comorbidities identified in selected studies

| Condition                        | Damery 2013 [17] | Joore 2015 [42] | Hafner 1997 [33] | Marder 1995 [44] | Burchell 2008 [41] | Szerlip 2005 [39] | Krauskopf 2011 [45] | Landau 1997 [43] | Hodder 2013 [36] | Guy 2011 [35] | Ellenbrock 2004 [30] |
|----------------------------------|------------------|-----------------|------------------|------------------|-------------------|------------------|-------------------|------------------|------------------|----------------|---------------------|
|                                  | OR (CI)          | OR (CI)         | %                | OR (CI)          | % & OR            | %                | OR (CI)           | %                | OR (CI)          | %                | OR (CI)              |
| **Clinical features**            |                  |                 |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Weight loss                      | 13.4 (5.15–6.7)  | 396 (6.2–∞)     |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Fever or chills                  | 45* (0.5–54.3)   |                 |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Cough                            |                  | 7%              |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Flu-like symptoms                |                  | 76%             |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Diarrhoea                        |                  | 2* (0.2–17.4)   |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Diarrhoea consultation one only  | 3.7* (0.9–54.8)  |                 |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Diarrhoea consultation two       | 4.4 (2.3–281)    |                 |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Abdominal pain                   |                  | 5%              |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Minor trauma                     |                  | 6%              |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Nausea/vomiting                  |                  | 6%              |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Rash                             |                  |                  |                  |                  |                   |                   | 4.5               |                  |                  |                 |                     |
| Number of HIV indicator conditions |                  |                  |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| One                              | 117 (6–23.6)     |                 |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Two                              | 775 (18.2–700.8) |                 |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| **Comorbidities**                |                  |                 |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Respiratory                      |                  |                 |                  |                  |                   |                   |                   |                  |                  |                 |                     |
| Pneumonia                        | 47.7 (3.5–52)    | 8.3 (2–49.8)    |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Pneumocystis carinii             | 52%              |                 |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Dermatology                      |                  |                 |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Psoriasis                        | 29* (0.1–∞)      |                 |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Psoriasis—one consultation only  | 2.6 (1.6–1.5)    |                 |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Psoriasis—two consultations      | 3 (1.3–2.5)      |                 |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Herpes zoster                    | 25.4 (5.7–14.2)  | 109 (2–108.9)   |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Neurology                        |                  |                 |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Peripheral neuropathy            | 159 (2–∞)        |                 |                  |                  |                   |                  |                   |                  |                  |                 |                     |
| Condition                          | Damery 2013 [17] | Joore 2015 [42] | Hafner 1997 [33] | Marder 1995 [44] | Burchell 2008 [41] | Szerlip 2005 [39] | Krauskopf 2011 [45] | Landau 1997 [43] | Hodder 2013 [36] | Guy 2011 [35] | Ellerbrock 2004 [30] |
|-----------------------------------|-----------------|-----------------|------------------|-----------------|------------------|------------------|------------------|-----------------|-----------------|-----------------|------------------|
|                                   | OR (CI)         | OR (CI)         | %                | % & OR          | OR               | %                | %                | % & OR          | OR              | OR              | OR               |
| Neurologic disability in women    |                 |                 |                  |                 |                  |                  |                  |                 |                 |                 |                  |
| Neurologic disability in men      |                 |                 |                  | 1.9             | (1.1–3.2)        |                  |                  |                 |                  |                 |                  |
| Gastroenterology                  |                 |                 |                  |                 |                  |                  |                  |                 |                 |                 |                  |
| Oral candidiasis                  | 29.4            | 7.1*            | (4.57–21.8)      |                 |                  |                  |                  |                 |                 |                 |                  |
| Hepatitis B                       | 115             | 8.3             | (1.2–∞)          |                 |                  |                  |                  |                 |                 |                 |                  |
| Chronic liver disease             |                 |                 |                  |                 |                  |                  |                  | 22%             |                 |                 | (15%–29%)        |
| Oncology                          |                 |                 |                  |                 |                  |                  |                  |                 |                 |                 |                  |
| Non-Hodgkin's lymphoma            | 12.6            |                 | (2.13–15)        |                 |                  |                  |                  |                 |                 |                 |                  |
| Lymphogranuloma venereum          |                 | 7.1*            | (0.6–∞)          |                 |                  |                  |                  |                 |                 |                 |                  |
| Gynaecology                       |                 |                 |                  |                 |                  |                  |                  |                 |                 |                 |                  |
| Cervical dysplasia                | 29*             |                 | (0.4–232.4)      |                 |                  |                  |                  |                 |                 |                 |                  |
| Condyloma acuminata               | 121             |                 | (1.2–600.9)      |                 |                  |                  |                  |                 |                 |                 |                  |
| Haematology                       |                 |                 |                  |                 |                  |                  |                  |                 |                 |                 |                  |
| Leucocytopenia                     | 115             |                 | (1.2–∞)          |                 |                  |                  |                  |                 |                 |                 |                  |
| Blood dyscrasia                   | 5.7             |                 | (2.44–4)         |                 |                  |                  |                  |                 |                 |                 |                  |
| ENT                               |                 |                 |                  |                 |                  |                  |                  |                 |                 |                 |                  |
| Lymphadenopathy                   | 11.3            | 29.8            | (5.15–5.3)       |                 |                  |                  |                  |                 |                 |                 |                  |
| Parotitis                         | 8.6             |                 | (1.68–11)        |                 |                  |                  |                  |                 |                 |                 |                  |
| Other                             |                 |                 |                  |                 |                  |                  |                  |                 |                 |                 |                  |
| Mononucleosis-like illness        | 62              |                 | (1.6–29)         |                 |                  |                  |                  |                 |                 |                 |                  |
| Pyrexia of unknown origin         | 7.2             |                 | (4.05–3.5)       |                 |                  |                  |                  |                 |                 |                 |                  |
| Hyperlipidemia                    |                 |                 |                  | 25%             | (17%–32%)        |                  |                  |                 |                 |                 |                  |
| Hypertension                      |                 |                 |                  | 10%             | (4%–16%)         |                  |                  |                 |                 |                 |                  |
| Diabetes                          |                 |                 |                  | 10%             | (5%–14%)         |                  |                  |                 |                 |                 |                  |
| Condition                        | Damery 2013 [17] | Joore 2015 [42] | Hafner 1997 [33] | Marder 1995 [44] | Burchell 2008 [41] | Szerlip 2005 [39] | Krauskopf 2011 [45] | Landau 1997 [43] | Hodder 2013 [36] | Guy 2011 [35] | Ellenbrock 2004 [30] |
|---------------------------------|-----------------|-----------------|------------------|------------------|-------------------|-------------------|-------------------|----------------|----------------|-------------|-------------------|
| Sexually Transmitted Infection (STI) |                 |                 |                  |                  |                   |                   |                   |                 |                 |             |                   |
| STI diagnosis ≤ 2 years         | 10.8 (3.38–7.6) |                 |                  |                  |                   |                   |                   |                 |                 |             |                   |
| STI diagnosis ≤ 14 days         |                 |                 |                  |                  |                   |                   |                   |                 |                 |             |                   |
| Number of STIs per patient One  |                 |                 |                  |                  |                   |                   |                   |                 |                 |             |                   |
| Number of STIs per patient ≥ 2 |                 |                 |                  |                  |                   |                   |                   |                 |                 |             |                   |
| Syphilis ≤ 2 years              | 393 (5.7–1703.9)|                 |                  |                  |                   |                   |                   |                 |                 |             |                   |
| Syphilis ≤ 14 days              | 735 (2.52–21.5) |                 |                  |                  |                   |                   |                   |                 |                 |             |                   |
| Seropositive for syphilis*      |                 |                 |                  |                  |                   |                   |                   |                 |                 |             |                   |
| Infectious syphilis diagnosis ≤ 2 years |                 |                 |                  |                  |                   |                   |                   |                 |                 |             |                   |
| Infectious syphilis diagnosis ≤ 14 days |                 |                 |                  |                  |                   |                   |                   |                 |                 |             |                   |
| Chlamydia ≤ 2 years             | 118 (3–67.5)    |                 |                  |                  |                   |                   |                   |                 |                 |             |                   |
| Chlamydia ≤ 14 days             |                 |                 |                  |                  |                   |                   |                   |                 |                 |             |                   |
| Gonorrhoea                      | 159 (2–∞)       |                 |                  |                  |                   |                   |                   |                 |                 |             |                   |
| Genital herpes                  | 29* (0.1–∞)     |                 |                  |                  |                   |                   |                   |                 |                 |             |                   |

*Not statistically significant
∞ Means infinity upper limit
| Category of predictor | Predictor of HIV infection | Likelihood of being recorded in primary care records |
|-----------------------|----------------------------|-----------------------------------------------------|
| Sociodemographic      | Age                        | Present for all patients                            |
|                       | Gender                     | Present for all patients                            |
|                       | Social status              | Inferred from postcode                              |
|                       | Poverty index              | Present as deprivation quintile                     |
|                       | Annual income              | Inferred from prescription payments, benefits       |
|                       | Employment status          | Likely to be poorly recorded                        |
|                       | Sexual orientation         | Require further investigation                       |
|                       | Not a high school graduate | Not present                                         |
|                       | Country of birth           | Not present                                         |
|                       | Ethnicity                  | Present for some patients                           |
| Behavioural           | Smoking status             | Very likely to be present                           |
|                       | Drug use                   | Present for some patients                           |
|                       | Binge-drinking or alcohol misuse | Present for some patients                        |
|                       | Obesity                    | Very likely to be present                           |
|                       | Contact abroad             | Might be present                                    |
|                       | Stressful events           | Present for some patients                           |
|                       | Unsafe sex                 | Likely not present                                  |
|                       | Ever exchanged money or drugs for sex | Likely not present                              |
|                       | Male anal sex              | Likely not present                                  |
|                       | Number of lifetime partners| Likely not present                                  |
|                       | Partner characteristics    | Likely not present                                  |
| Clinical and comorbid conditions | Weight loss               | Likely to be present                                |
|                       | Fever or chills            | Likely to be present                                |
|                       | Cough                      | Likely to be present                                |
|                       | Flu like symptoms          | Likely to be present                                |
|                       | Diarrhoea                  | Likely to be present                                |
|                       | Abdominal pain             | Likely to be present                                |
|                       | Minor trauma               | Likely to be present                                |
|                       | Nausea/vomiting            | Likely to be present                                |
|                       | Rash                       | Likely to be present                                |
|                       | Pneumonia                  | Likely to be present                                |
|                       | Pneumocystis carinii       | Likely to be present                                |
|                       | Psoriasis                  | Likely to be present                                |
|                       | Herpes zoster              | Likely to be present                                |
|                       | Peripheral neuropathy      | Likely to be present                                |
|                       | Neurologic disability      | Likely to be present                                |
|                       | Oral candidiasis           | Likely to be present                                |
|                       | Hepatitis B                | Likely to be present                                 |
|                       | Chronic liver disease      | Likely to be present                                |
|                       | Non-Hodgkin’s lymphoma     | Likely to be present                                |
|                       | Condyloma acuminata        | Likely to be present                                |
|                       | Leucocytopenia             | Likely to be present                                |
|                       | Blood dyscrasia            | Likely to be present                                |
|                       | Lymphadenopathy            | Likely to be present                                |
of the HIV-infected patients [45]. One oncological condition identified was Non-Hodgkin’s lymphoma (1 study); 12.6 times the risk [17].

Only one study identified gynaecological conditions associated with increased risk of HIV diagnosis and condyloma acuminata; 12.1 times the risk [41]. The two haematological conditions identified in the studies were leukocytopenia (1 study); 11.5 times the risk [41] and blood dyscrasia (1 study); 5.7 times the risk [17]. ENT conditions identified were lymphadenopathy (2 studies); 11.3 and 29.8 times the risk [17, 41] and parotitis (1 study); 8.6 times the risk [17].

The other conditions identified were mononucleosis-like illness (1 study); 6.2 times the risk [41], pyrexia of unknown origin (1 study); 7.2 times the risk [17] and one study which had 10–25% of the HIV-infected patients with hyperlipidemia, hypertension and diabetes [45]. The other conditions identified were sexually transmitted infections (5 studies), 2.7 to 37.9 times the risk [17, 30, 35, 44, 41], and the following infections were identified: (i) syphilis (3 studies), 3.9 to 39.3 times the risk [30, 44, 41]; (ii) chlamydia (2 studies), 2.3 to 11.8 times the risk [30, 35]; (iii) gonorrhoea (2 studies), 6.5 to 15.9 times the risk [30, 41] and (iv) genital herpes (1 study), 2.9 times the risk [41].

**Table 5** Predictors identified and availability in electronic primary care records (Continued)

| Category of predictor | Predictor of HIV infection | Likelihood of being recorded in primary care records |
|-----------------------|---------------------------|------------------------------------------------------|
| Parotitis             |                           | Likely to be present                                  |
| Mononucleosis-like illness |                       | Likely to be present                                  |
| Pyrexia of unknown origin |                         | Likely to be present                                  |
| Hyperlipidemia       |                           | Likely to be present                                  |
| Hypertension         |                           | Likely to be present                                  |
| Diabetes             |                           | Likely to be present                                  |
| Sexually transmitted infection |                 | Likely to be present                                  |
| Syphilis             |                           | Likely to be present                                  |
| Chlamydia            |                           | Likely to be present                                  |
| Gonorrhoea           |                           | Likely to be present                                  |
| Genital herpes       |                           | Likely to be present                                  |

**Discussion**

This systematic review identified 10 demographic and socio-economic characteristics, 11 behavioural characteristics, and 27 clinical features and comorbid conditions that are significantly associated with HIV infection.

The purpose of this systematic review was to identify predictors of HIV infection available in electronic patient records that could be incorporated in a prediction model to identify primary care patients with undiagnosed HIV. Candidate predictors identified are either routinely recorded in electronic primary care records or require further investigation to assess if they can be reliably identified and included in a future clinical prediction model (Table 5).

The demographic and socio-economic predictors identified and available in primary care records are age, gender and deprivation quintile as a proxy for some of the socio-economic predictors. Behavioural predictors identified and available in electronic health records are drug use, binge-drinking or alcohol misuse, current smokers and obesity. All the clinical features and comorbid diseases identified are most probably available in electronic health records (Table 5).

Some of the demographic, socio-economic and behavioural predictors identified in literature, such as ethnicity, country of birth, income and education levels, might be available in primary care records and therefore require further investigation on completeness.

**Limitations**

This systematic review focused on studies conducted in developed countries whereas most of the studies on HIV predictors were conducted in developing countries, mostly in Africa. Most of the studies conducted on HIV were case studies, qualitative studies and cross-sectional studies which are not suitable in identifying risk factors.

Some of the studies identified in this systematic review reported percentages rather than odds ratio in their results making the interpretation of risk association difficult.

**Conclusion**

This systematic review revealed existing scientific evidence on predictors of HIV that can be used to inform decision making in prognostic model development [46]. Only 2 demographic and socio-economic characteristics (age and gender) and 4 behavioural characteristics (drugs use, binge-drinking or alcohol misuse, current smokers and obesity) identified in literature are available in electronic health records.
primary-care records. The other 8 demographic and socio-economic and 7 behavioural characteristics require further investigation on completeness or if they are not available at all. Further exploration will determine whether the characteristics can be applied in a model.

Of the 51 clinical conditions in BHIVA guidelines, 18 were identified as significant predictors of HIV infection in this systematic review. The following predictors identified in literature are not included in the guidelines: fever/chills/flu-like symptoms, cough, abdominal pain, minor trauma, nausea/vomiting, rash, hyperlipidaemia, hypertension and diabetes.

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BRD conducted the literature search and wrote the systematic review. MO was the second reviewer for this systematic review. TM and RR are supervising the project. BRD is a PhD student at the University of Birmingham, MO was the second reviewer and TM and RR are supervising the project.

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Not applicable.

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