ORIGINIAL ARTICLE

HIV indicator condition-guided testing to reduce the number of undiagnosed patients and prevent late presentation in a high-prevalence area: a case–control study in primary care

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ABSTRACT

Objectives Recent guidelines advocate accelerated provider-initiated HIV testing by general practitioners (GPs). We aimed to identify the number of patient consultations in six general practices in the South-East of Amsterdam, and the incidence of HIV indicator conditions reported in their medical files prior to diagnosis.

Methods A cross-sectional search in an electronic general practice database. We used a case–control design to identify those conditions most associated with an HIV-positive status.

Results We included 102 HIV cases diagnosed from 2002 to 2012, and matched them with 299 controls. In the year prior to HIV diagnosis, 61.8% of cases visited their GP at least once, compared with 38.8% of controls. In the 5 years prior to HIV diagnosis, 58.8% of HIV cases had exhibited an HIV indicator condition, compared with 7.4% of controls. The most common HIV-related conditions were syphilis and gonorrhoea. The most common HIV-related symptoms were weight loss, lymphadenopathy and peripheral neuropathy. During this period, average HIV prevalence among people aged 15–59 years increased from 0.4% to 0.9%.

Conclusions This study revealed many opportunities for HIV indicator condition-guided testing in primary care. As yet, however, HIV indicator conditions are not exploited as triggers for early HIV testing.

INTRODUCTION

An estimated 25 000 individuals in the Netherlands are living with HIV, a quarter of whom are estimated to be undiagnosed.1 In 2013, 1100 patients with HIV were diagnosed. Of these, 43% presented late for care, with AIDS or with a CD4 count <350 cells/mm3.1 Late diagnosis is associated with higher morbidity and mortality.2 3 In the Netherlands, the HIV epidemic is concentrated among men who have sex with men and individuals from HIV-endemic countries.1

In recent years, ‘Treatment as Prevention’ has become an important strategy in fighting the HIV epidemic.4 The early detection and treatment of HIV infection provide benefits for the health of the individual and that of the public at large.5 6

As the primary point of access to healthcare, general practitioners (GPs) have a pivotal role. They could play an important part in provider-initiated HIV testing for early case-finding.7–10 For many years, national guidelines for GPs have recommended HIV testing strategies that target populations at higher risk of HIV.11 However, this ‘high-risk’ approach has certain intrinsic limitations, which restrict its implementation in primary healthcare.7 There is a need for alternative and additional provider-initiated HIV testing strategies.

METHODS

Data source The ‘HAG-net-AMC’ general practice database contains the electronic patient records of...
approximately 46 000 patients. These individuals are registered in six general practices located in the South-East of Amsterdam, a culturally diverse and socioeconomically deprived area. The database contains information on laboratory results, medical diagnoses, prescriptions and treatments. The standard information recorded in patients’ medical files does not include details of sexual orientation, ethnicity and socioeconomic status.

Study design
A search was performed for patients with HIV infection who were diagnosed between July 2002 and July 2012 using International Classification of Primary Care (ICPC) code B90 (HIV-infection).16 We used a case–control design to evaluate the number of patient consultations and HIV indicator conditions for each patient prior to HIV diagnosis. We matched cases to controls that were considered to be HIV free. Inclusion criteria for cases were: newly diagnosed HIV infection in the study period, age ≥ 18 years and more than 1 year of information available in the medical file prior to HIV diagnosis. Controls (ratio 1:3) were matched for age, sex, practice, year the cases received their diagnosis and years of information in the medical file available prior to diagnosis.

Patient consultations prior to HIV diagnosis
We obtained details from the database of the number of times that each patient had consulted his/her GP. This was supplemented by data on the number of laboratory blood tests for patients 1 year prior to HIV diagnosis plus details of the number of new patients registering with the general practice.

HIV indicator conditions prior to HIV diagnosis
We searched the data on patient consultations prior to HIV diagnosis for preselected HIV indicator conditions based on the ECDC guideline (Table 1).14 We selected those HIV indicator conditions that GPs in the Netherlands diagnose themselves. As many HIV indicator conditions are not ICPC coded, we also searched the consultation records’ open evaluation text fields (where most of the important symptoms and clinical diagnosis details are reported). Any conditions that are unlikely to be diagnosed by a GP (such as visceral leishmaniasis, Guillain–Barré syndrome, Kapo’s sarcoma and pneumocystis carinii pneumonia) were excluded. No neoplasms were included, as these conditions are also diagnosed in secondary or tertiary hospital settings. Pregnancy was excluded, as all pregnant women in the Netherlands are routinely tested for HIV with an opt-out approach.1 A mononucleosis-like illness was considered if at least two of the following symptoms were present in the medical record’s open evaluation text fields: fever, swollen lymph glands and rash, with or without pharyngitis, muscle aches and feeling sick.17 If there were symptoms in the evaluation text fields that might indicate a mononucleosis-like illness, we also searched the other text fields for validating evidence. We used the same strategy for the controls.

Statistical analyses
Exact logistic regression was used to identify preselected HIV indicator conditions associated with the occurrence of HIV. This type of regression was used because the sample size was too small to accommodate all of the selected variables, and some of the cells had no observations at all. We included 26 HIV indicator conditions as variables, as well as the total number of HIV indicator conditions and the total number of sexually transmitted infections (STIs) prior to HIV diagnosis. ORs were calculated with 95% CIs using STATA statistical analysis software (V13.1). The numbers of patient consultations were analysed for significance using $\chi^2$ statistics. $p$ Values ≤ 0.05 (two-tailed) were considered to be significant.

RESULTS
Characteristics of cases and controls
A total of 452 cases were found by searching for B90 (the ICPC code mentioned above). We excluded 350 cases for the following reasons: one case did not have HIV, 291 cases were diagnosed before 1 July 2002, 10 cases involved individuals below the age of 18 and 48 cases had medical files that predated HIV diagnosis by no more than 1 year. Data from 102 HIV-positive cases were matched to 299 controls considered to be free of HIV. The majority of cases (72.5%) were male, with a mean age of 44.5 (SD 9.5). The median period covered by the available medical data was 5.0 years for both groups.

Patient consultations in general practices
The majority of cases (61.8%) visited their GP at least once (median 3), compared with 38.8% of the controls (median 2)
In 39.2% of the HIV cases, one or more laboratory blood tests were performed in the year prior to diagnosis, against 18.7% in the control group. Each year, approximately n=2554 (5.6%) patients registered with these general practices, and visited them for the first time.

**HIV indicator conditions**

In the 5 years prior to HIV diagnosis, more than half of all HIV cases (58.8%) were diagnosed with one or more of the HIV indicator conditions, compared with 7.4% for controls (table 3). The most common HIV-related conditions were syphilis (n=12), chlamydia (n=11), pneumonia (n=8), mononucleosis-like illness (n=8) and herpes zoster (n=7). The most common HIV-related symptoms recorded were weight loss (n=9) and lymphadenopathy (n=7).

Several HIV indicator conditions were not observed in the control group. As a result, the 95% CIs of a number of HIV indicator conditions ranged from OR to infinity (∞) (table 3). The HIV indicator conditions most strongly associated with the occurrence of HIV were weight loss (OR 39.6, 95% CI 6.2 to ∞), syphilis (OR 39.3, 95% CI 5.7 to 1703.9), lymphadenopathy (OR 29.8, 95% CI 4.4 to ∞), gonorrhoea (OR 15.9, 95% CI 2.0 to ∞) and peripheral neuropathy (OR 15.9, 95% CI 2.0 to ∞). The number of HIV indicator conditions prior to HIV diagnosis was associated with the occurrence of HIV: one HIV indicator condition OR 11.7 (95% CI 6.0 to 23.6) and two or more HIV indicator conditions OR 77.5 (95% CI 18.2 to 700.8). Also, the total number of STIs in the 5 years prior to HIV diagnosis was associated with the occurrence of HIV: one STI OR 14.6 (95% CI 5.5 to 45.6) and two or more STIs OR 37.9 (95% CI 5.6 to ∞).

**HIV prevalence rates at six general practices in South-East of Amsterdam**

From 2002 to 2012, average HIV prevalence among people aged 15–59 years increased from 0.4% to 0.9% (figure 1), which is well above the average of 0.2% that represents a high-prevalence area, according to the UK’s NICE guideline.12 13

**DISCUSSION**

In the year prior to their diagnosis, most patients with HIV consulted their GP and more than half of them were diagnosed with an HIV indicator condition in the 5 years preceding the diagnosis, compared with only 7.4% of the controls. The presence of HIV was mostly associated with symptoms of weight loss, lymphadenopathy and peripheral neuropathy and with the clinical diagnoses of syphilis and gonorrhoea. From 2002 to 2012, in the South-East of Amsterdam, average HIV prevalence among people aged 15–59 years increased from 0.4% to 0.9%.

A UK study reported that in the year prior to HIV diagnosis, 76.4% of African patients who were newly diagnosed with HIV had consulted their GP.18 A French study reported that 89% of patients newly diagnosed with HIV had consulted a GP at least once a year.19 In our study, 61.8% of patients in the year prior to HIV diagnosis had consulted their GP, compared with 38.8% of controls. All studies showed that patients frequently visited their GP, indicating that opportunities to diagnose HIV at an earlier point in time had been missed. In our study, the number of consultations prior to HIV diagnosis was higher among cases than among controls. This might be explained by the fact that patients with HIV tend to visit their GP more often, in connection with HIV-related conditions.

The revised national STI guideline for GPs in the Netherlands addresses the importance of offering an HIV test to individuals who display HIV indicator conditions, which is in line with the ECDC guideline.11 14 A large Italian cohort showed the importance of testing for HIV following the diagnosis of HIV indicator conditions, as this significantly decreases the probability of late HIV diagnosis.20 A UK general practice case-control study found that 25.8% of HIV cases had presented with one or more HIV indicator conditions 1 year prior to receiving a diagnosis of HIV.21 In our study, we found that 58.8% of the HIV cases had HIV indicator conditions in the 5 years prior to HIV diagnosis. The large numbers of local residents who originate from countries where HIV is endemic may well account for the higher percentage of HIV indicator conditions found in our study population in the South-Eastern suburbs of Amsterdam.12 22

Mononucleosis-like illness is an important HIV indicator condition because it can indicate acute HIV infection.14 In primary healthcare settings, individuals presenting with a mononucleosis-like illness should be strongly advised to take an HIV test, as this condition meets the criteria for cost-effectiveness.23 24 This illness was observed in our study in 7.8% of HIV cases in the 5 years prior to diagnosis.

A recent ‘landmark’ article concluded that epidemics differ in concentration from one country to another, exhibiting different levels of transmission and different risk groups, and changing over time. Its authors recommended a focused public health approach that prioritises high-transmission geographies and populations at higher risk of HIV, while combining the most cost-effective interventions.23 The UK NICE guideline also builds on prioritising high-transmission geographies, by recommending more ‘routine HIV testing’ in high-prevalence areas, for example, in newly registered patients and during routine laboratory blood tests.12 13 In the UK, however, the concept of ‘routine HIV testing’ in high-prevalence areas is not well implemented.26 27 Our data indicate opportunities for routine testing in this particular area of Amsterdam, which qualifies as a high-prevalence area: in 39.2% of HIV cases, one or more laboratory blood tests were performed.
performed 1 year prior to diagnosis. In addition, each year, approximately 5.6% of patients registered with these general practices and visited them for the first time. Greater insight is needed into the barriers or motivators encountered by GPs in implementing these new provider-initiated HIV testing strategies.

Our data have several limitations due to the cross-sectional nature of the study design and due to limitations in the electronic registration system used by the general practices in question. In the control group, 7.4% of the patients exhibited at least one HIV indicator condition prior to diagnosis. It is possible that some of the controls with HIV indicator conditions were HIV positive as their HIV status was unknown. However, this misclassification would tend to increase rather than decrease the ORs.

Additionally, wide 95% CI were observed for many indicator conditions due to the low number of HIV indicator conditions. HIV indicator conditions in the evaluation lines could be subject to under-reporting by GPs. However, this would be expected to occur in both groups. Finally, potential confounders or effect modifiers (ethnicity, sexual orientation and socioeconomic status) could not be included in the analyses.

This study revealed many opportunities for HIV indicator condition-guided testing in primary care. At this stage, however, HIV indicator conditions are not exploited as triggers for early HIV testing. According to the UK guideline, insight in a country’s high-prevalence areas is a prerequisite for developing ‘routine HIV testing’ strategies. To move from policy to practice, there is an urgent need to identify the barriers and facilitators that affect effective implementation by GPs.

### Table 3  Number of HIV indicator conditions in cases and controls

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Cases N=102</th>
<th>Controls N=299</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
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<tr>
<td>Sexually transmitted infections (STIs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Number of STIs per patient</td>
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<tr>
<td>None</td>
<td>29 (28.4)</td>
<td>6 (2.0)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>One</td>
<td>73 (71.6)</td>
<td>293 (98.0)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Two or more</td>
<td>22 (21.6)</td>
<td>6 (2.0)</td>
<td>14.6</td>
<td>5.5</td>
<td>&lt;0.001</td>
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<td>Syphilis</td>
<td>7 (6.9)</td>
<td>0 (0)</td>
<td>37.9</td>
<td>5.6</td>
<td>&lt;0.001</td>
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<tr>
<td>Gonorrhoea</td>
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<td>0 (0)</td>
<td>15.9</td>
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<td></td>
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<tr>
<td>Condyloma acuminata</td>
<td>4 (3.9)</td>
<td>0 (0)</td>
<td>12.1</td>
<td>1.2</td>
<td>0.032</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>11 (10.8)</td>
<td>3 (1.0)</td>
<td>11.8</td>
<td>3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatitis B</td>
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<td>0 (0)</td>
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<td>1.2</td>
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<td>Lymphogranuloma venereum</td>
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<td>0 (0)</td>
<td>7.1</td>
<td>0.6</td>
<td>0.129</td>
</tr>
<tr>
<td>Genital herpes</td>
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<td>0 (0)</td>
<td>2.9</td>
<td>0.1</td>
<td></td>
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<tr>
<td>Trichomoniasis</td>
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<td>1 (0.3)</td>
<td>2.9</td>
<td>0.0</td>
<td>1.000</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucocytopenia</td>
<td>3 (2.9)</td>
<td>0 (0)</td>
<td>11.5</td>
<td>1.2</td>
<td>0.032</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>7 (6.9)</td>
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<td>10.9</td>
<td>2.0</td>
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<td>Pneumonia</td>
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<td>3 (1.0)</td>
<td>8.3</td>
<td>2.0</td>
<td>49.8</td>
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<tr>
<td>Oral candidiasis</td>
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<td>0 (0)</td>
<td>7.1</td>
<td>0.6</td>
<td>0.129</td>
</tr>
<tr>
<td>Mononucleosis-like illness</td>
<td>8 (7.8)</td>
<td>4 (1.3)</td>
<td>6.2</td>
<td>1.6</td>
<td>29.0</td>
</tr>
<tr>
<td>Psoriasis</td>
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<td>0 (0)</td>
<td>2.9</td>
<td>0.1</td>
<td>0.509</td>
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<tr>
<td>Cervical dysplasia</td>
<td>1 (1.0)</td>
<td>1 (0.3)</td>
<td>2.9</td>
<td>0.4</td>
<td>232.4</td>
</tr>
<tr>
<td>Seborrhoeic dermatitis</td>
<td>1 (1.0)</td>
<td>3 (1.0)</td>
<td>1.0</td>
<td>0.0</td>
<td>12.3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
<td>1.000</td>
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<tr>
<td>Chronic renal impairment</td>
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<tr>
<td>Hepatitis A</td>
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<tr>
<td>Hepatitis C</td>
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<tr>
<td>Mononeuritis</td>
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<td></td>
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<td>Symptoms</td>
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<td>Weight loss</td>
<td>9 (8.8)</td>
<td>0 (0)</td>
<td>39.6</td>
<td>6.2</td>
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<tr>
<td>Lymphadenopathy</td>
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<td>0 (0)</td>
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<td>Peripheral neuropathy</td>
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<td>15.9</td>
<td>2.0</td>
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<tr>
<td>Fever</td>
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<td>2 (0.7)</td>
<td>4.5</td>
<td>0.5</td>
<td>54.3</td>
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<td>Diarrhoea</td>
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<td>3 (1.0)</td>
<td>2.0</td>
<td>0.2</td>
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<td>HIV indicator conditions</td>
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<td>22 (7.4)</td>
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</tr>
</tbody>
</table>

∞ = infinity.

According to the Medical Research (Human Subjects) Act (WMO), Ethics approval None declared.

Competing interests Fonds, Amsterdam, the Netherlands.

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Formal approval for this research project by a medical ethics committee was not obtained. This was an opportunistic study of general practitioners who visited the network. We sought and obtained consent for medical information from at least one of the general practitioners involved in the care of all patients included. The privacy protection of patients and GPs. In addition, we sought and obtained formal approval for this research project by a medical ethics committee was not obtained. This was an opportunistic study of general practitioners who visited the network. We sought and obtained consent for medical information from at least one of the general practitioners involved in the care of all patients included.

Contributors IKJ and DLA wrote the manuscript and performed the statistical analyses. All authors contributed to the design and/or interpretation, provided feedback and approved the final submitted version of the manuscript.

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Provenance and peer review Not commissioned; externally peer reviewed.

Key messages

- In the year prior to diagnosis, the majority of cases in our cohort (61.8%) visited their general practitioner at least once.
- In the 5 years prior to diagnosis, more than half (58.8%) of all HIV cases presented with one or more HIV indicator conditions.
- This study revealed many missed opportunities for HIV indicator condition-guided testing in primary care.

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Correction notice This article has been corrected since it was published Online First. The first author’s first name has been added.

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Contributors IKJ and DLA wrote the manuscript and performed the statistical analyses. All authors contributed to the design and/or interpretation, provided feedback and approved the final submitted version of the manuscript.

REFERENCES


