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Promoting rapid testing for HIV in primary care: a cluster randomised controlled trial (RHIVA2)

Werner Leber PhD*¹, Heather McMullen MSc*¹, Jane Anderson FRCP², Nadine Marlin MSc¹, Andreia C Santos PhD³, Stephen Bremner PhD¹, Kambiz Boomla FRCGP¹, Sally Kerry PhD¹, Danna Millett MSc², Sifiso Mguni MSc², Sarah Creighton FRCP², Jose Figueroa FRCPH⁴, Richard Ashcroft PhD⁵, Graham Hart PhD⁶, Valerie Delpech FPHM⁷, Alison Brown PhD⁷, Graeme Rooney MSc⁷, Maria Sampson MSc⁸, Adrian Martineau PhD¹, Fern Terris-Prestholt PhD³, Chris Griffiths DPhil¹.

Centre for Primary Care and Public Health, Queen Mary University of London¹; Homerton Sexual Health Services, Homerton University Hospital NHS Foundation Trust²; Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine³; NHS City and Hackney⁴; School of Law, Queen Mary University of London⁵; Faculty of Population Health Sciences, University College London⁶, Centre for Infectious Disease Surveillance and Control, Public Health England⁷; Department of Virology, Barts Health NHS Trust⁸.

* These author contributed equally to the manuscript.

Corresponding author:

Dr Werner Leber

NIHR Clinical Lecturer in Primary Care

Centre for Primary Care and Public Health

Queen Mary, University of London

London E1 2AB

w.leber@qmul.ac.uk

00 44 207 882 7084

Summary

BACKGROUND

Many people with human immunodeficiency virus (HIV) are undiagnosed. Early diagnosis saves lives and reduces onward transmission. We tested the hypothesis that an education programme promoting rapid HIV testing in general practice would lead to increased and earlier HIV diagnosis.

METHODS

In a cluster randomised controlled trial in east London, 40 of 45 (89%) general practices were randomised and either trained to offer opt-out rapid HIV testing to newly registering adults, or continued usual care. The primary outcome was CD4 count at diagnosis.

FINDINGS

During the study 44,971 adults registered with 20 intervention practices, and 38,464 with 20 controls. Intervention practices newly diagnosed 32 people with HIV compared with 14 in control; rate of HIV diagnosis was fourfold higher in intervention than control practices: 0.30 per 10,000 patients per year (95% CI, 0.11 to 0.85) *versus* 0.07 (95% CI, 0.02 to 0.20); adjusted ratio of geometric means: 4.51 (95% CI, 1.27 to 16.05; P=0.021). Mean CD4 count at diagnosis was 356 cells/ μ L (SD 254) intervention *versus* 270 (SD 257) control; adjusted difference in square root CD4 count: 3.1 (95% confidence interval [CI], -1.2 to 7.4; P=0.16); in a pre-planned sensitivity analysis excluding patients diagnosed *via* antenatal care, this difference was 6.4 (95% CI, 1.2 to 11.6; P=0.017). All people diagnosed *via* rapid testing were successfully transferred into specialist care. No adverse events have occurred during the trial.

INTERPRETATION

Promoting opt-out rapid testing in general practice led to increased and earlier detection of HIV.

FUNDING

Department of Health, NHS City and Hackney; (ClinicalTrials.gov: ISRCTN63473710).

Introduction

Timely diagnosis of HIV remains a major challenge. Undetected HIV and late diagnosis are associated with ill health, increased risk of death and onward viral transmission, constituting a significant burden to public health budgets worldwide.¹⁻³ Of 107,800 people living with HIV (PLHIV) in the UK, almost one quarter are undiagnosed,⁴ 42% are diagnosed late (after they should have begun antiretroviral treatment, CD4<350), and 24% diagnosed very late (CD4<200).⁴ These figures are mirrored in the World Health Organisation (WHO) European Region and the USA, where an estimated one half of 2.2 million, and one sixth of 1.1 million PLHIV respectively, are undiagnosed.^{1,5,6}

Expanding HIV testing is key to improving HIV outcomes. In 2008, the British HIV Association (BHIVA) recommended universal HIV testing in primary care settings in high prevalence areas (2 per 1000 population), in addition to the routine screening programmes in antenatal settings and STI clinics.⁷ This approach was endorsed by the National Institute for Health and Care Excellence (NICE).^{8,9} Pilot projects have shown the acceptability and feasibility of HIV testing in primary care.¹⁰⁻¹² However, wide-spread adoption of HIV testing in these non-traditional settings is lacking; in particular, there is no evidence on outcomes from robust screening trials. The US Preventative Services Task Force recently noted: ‘no randomised trial or observational study compared clinical outcomes between adults and adolescents screened and not screened for HIV infection,¹³ a conclusion also reached by the UK National Institute for Health and Care Excellence.^{8,9} To our knowledge, there is no randomised trial evidence that HIV screening leads to increased and earlier diagnosis. This represents a key evidence gap in current guidance.^{14,15}

Primary care is ideally placed to offer HIV testing.⁷ General practices provide health checks for newly registering patients and are a referral point to specialist care. HIV testing in general practice is feasible and acceptable.^{10,11,16} and may be preferable for people who would not normally attend traditional HIV testing settings such as sexual health clinics.¹¹

We report on a pragmatic cluster randomised controlled trial (RCT) to test the hypothesis that a multifaceted educational outreach programme promoting rapid HIV testing in general practice leads to increased and early diagnosis of HIV. We used a cluster randomised design because the intervention was directed at practices, rather than individual patients.

PANEL – Research in context – about here

Methods

The study was set in Hackney, a multi-ethnic, socioeconomically deprived inner London borough, which has the ninth highest rate of diagnosed HIV infection (8 per 1000 adult population) in the UK.⁴ There were no exclusion criteria for clusters. At entry, practices offered no systematic screening for HIV but did carry out opportunistic serology testing where clinically indicated. Visiting midwives offered HIV screening for women receiving antenatal care. Consent from participating practices was sought before randomisation. The study ran from April 2010 to August 2012. An independent data monitoring committee (DMC) was established.

Participants

Patients aged 16 years (the age of consent to medical procedures in the UK) and older, who newly registered with study practices and were able to undertake a pre-test discussion in English, or with a suitable translator, were included. Patient information sheets, available in English and eight locally spoken languages, were displayed at reception desks. The ethics committee approved a process of valid implied consent for patient participation.¹⁶

Randomization of general practices and masking

Practices were randomised between April 2010 and August 2011 by an independent clinical trials unit statistician using a minimisation program (Minim, v1.3),¹⁷ maintaining allocation concealment. Minimisation criteria were: practice list size (<5,000 registered patients; 5,000-7000; ≥7,000); practice deprivation (Index of Multiple Deprivation score:<47; ≥47);¹⁸ and male HIV testing rate (male adults tested between April and October 2009/male adults registered x1000: <7; ≥7). The nature of the intervention meant that neither investigators nor clinical teams were masked to allocation.

Procedures

The intervention was multifaceted and comprised:

- a practice-based outreach educational program, with follow up training for a nominated practice HIV lead nurse or health care assistant (HCA);

- integration of rapid HIV testing into the registration health check and management of reactive tests;
- provision to the practices of free rapid HIV tests and payment of £10 (\$16.14) per test completed;
- Quality assurance testing programme.

The educational programme was based on proven theory-based clinician behaviour change strategies from the literature together with our experience of delivering similar effective interventions.¹⁹⁻²¹ Initial training sessions were held at individual practices, lasted 90 minutes, targeted the whole practice team, and included didactic and interactive elements. Session leaders (WL, HM) were trained to ensure intervention fidelity (Supplement A). Rapid HIV test operators completed competency-based training. An HIV lead was nominated in each practice to co-ordinate rapid testing and quality assurance (Supplement B).

Registration health checks are performed by a nurse or HCA, who follow prompts on a template in the patient's electronic health record. We inserted additional prompts to offer rapid HIV testing, linked to bespoke Read codes (<http://www.hscic.gov.uk/>) to record test outcomes: non-reactive, reactive, indeterminate, invalid, and test declined. Read coding enabled remote data collection of testing activity (Supplement C). The INSTI HIV1/HIV2 Rapid Antibody Test (bioLytical Laboratories, Canada) finger prick system was used for rapid testing.

The intervention was adaptable to each individual practice: e.g. staff could additionally offer rapid HIV testing in a range of clinical settings (e.g. sexual health checks) and were encouraged to continue opportunistic HIV testing by serology.

The core components of the testing process included:

- an offer of a rapid HIV test as part of the routine new registration health check to eligible patients including a pre-test discussion for them to make an informed decision regarding the HIV testing;
- a rapid HIV test followed by a post-test discussion for patients with a non-reactive test result;

- an immediate notification of the rapid test operator to the general practitioner (GP) of any patient with a reactive/indeterminate/twice invalid test result with confirmatory serology sampling, and follow up by a GP (Supplement D).

Any venous blood sample detected as reactive for HIV 1 or 2 on an Abbott Architect ci8200 analyser at Homerton Hospital was sent on for confirmatory testing at NHS Bart Health Trust using the Bayer ADVIA Centaur anti-HIV 1 & 2 test, the BioMerieux VIDAS HIV DUO Quick, and the Alere ImmunoComb II HIV 1 & 2 BioSpot.

Patients confirmed HIV1/HIV2 antibody positive (Supplement E) were referred to Homerton Hospital for specialist care. Practices implemented rapid testing immediately after the educational session. Ongoing support from the education team was available to practice staff for queries related to rapid testing *via* telephone or email. Control practices were informed by email about current national guidance on HIV testing. All study practices continued to provide standard care of HIV testing and were supported by a community HIV liaison nurse.

At Homerton Hospital, all patients testing HIV positive at participating practices were allocated a unique study number. Newly diagnosed patients were distinguished from known HIV positive patients already in care or defaulted from specialist care using the Genitourinary Medicine Clinical Activity Dataset.²² The Homerton clinical team (JA, SM) extracted clinical record data onto anonymised confidential clinical case report forms. Accuracy of data extraction for all patients was verified by an independent clinician (AM), blinded to study allocation, before being passed to the study statistician. For more details on patient ascertainment, see Supplement G.

Rapid HIV antibody test result codes were specifically generated for the trial as follows: EMISNQRE117 (reactive), EMISNQNO26 (non-reactive), EMISNQIN61 (indeterminate), and EMISNQIN62 (invalid). The following additional READ codes were used: HIV [serology] screening test (4JR7) and rapid HIV test declined (8I3P). Rapid HIV testing data and serology testing data were remotely extracted from general practice computer systems (EMIS, Egton Medical Information Systems Limited; and Vision, In Practice Systems Limited; [both UK]) by the Clinical Effectiveness Group at Queen Mary, University of London (KP, MS, AC, and JD).

Outcomes

Early and increased diagnosis of HIV are key clinical and public health outcomes.^{4, 7-9} The primary outcome measure was the mean CD4 count at diagnosis of newly diagnosed patients. Women newly diagnosed with HIV by the UK Antenatal HIV Screening Programme were included. For exclusion criteria for the primary outcome and definition of a newly diagnosed patient, see Supplement F. Secondary outcome measures were number of new HIV diagnoses (expressed as rate: patients diagnosed/year/10,000 practice list size), and percentages of patients with CD4<350 and CD4<200.

The original primary outcome for the study was the number of new HIV diagnoses. However, our initial assumptions were based on limited data and the number of new diagnoses early in the study was lower than expected. Thus, early in the trial, and with the approval of the data monitoring committee, we recalculated statistical power with CD4 count as the primary outcome, retaining numbers of new diagnoses as the main secondary outcome. For clarity we report both outcomes.

Statistical analysis

Allowing for clustering, and assuming 20 practices in each arm and analysis of CD4 on the square root scale with a SD of 6 and ICC of 0.05, we expected to identify 72 new HIV diagnoses, with 80% power and 5% significance. This would be sufficient to detect an increase in the mean CD4 count from 300 to 470 cells/ μ L, corresponding to a reduction in the proportion of late presenters from 30% to 10%. Allowance was made for practices to identify variable numbers of patients or none at all.²³

Intervention effect on CD4 count and rate of diagnosis was estimated using a linear regression model adjusted for clustering of practices in Stata (v12) using the cluster option (except for rate of diagnosis where practice summary data was used) and adjusted for minimisation factors. CD4 count was transformed using a square root transformation and rate of diagnosis was log transformed after adding 0.01 to zero counts. Using the intervention effect from the primary analysis and the normal distribution, we estimated the relative reduction in percentage of patients diagnosed with both CD4<350 and CD4<200 cells/ μ L using a novel method developed by Peacock et al, 2012.²⁴

Although we originally planned a secondary, as treated secondary analysis based on excluding all practices who had done less than 50 tests, this was not feasible as there were

only four practices in this category and no patients from these practices had been . This was recorded in the statistics analysis plan.

The UK Antenatal HIV Screening Programme offers all women in antenatal care an HIV test. We carried out a pre-planned sensitivity analysis excluding women diagnosed *via* this programme.

Some patients testing positive had previously been diagnosed but had defaulted from specialist care: ‘re-diagnosis’ in general practice therefore led to re-entry to specialist care. A further sensitivity analysis therefore included those testing positive who had defaulted from care.

Role of the funding source

NHS City & Hackney and the Department of Health co-funded the study.

JF, a clinician employed by NHS City and Hackney, was involved in co-designing the study, data interpretation, and writing of the report, but had no role in data collection or analysis.

The Department of Health had no role in any aspect of the study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication ***Results***

General practices and populations

Forty of 45 (89%) general practices agreed to take part; and five declined (Figure 1). The five practices that declined participation had similar characteristics to those that joined the study. Twenty practices were randomised to intervention and 20 to the control group. Three intervention practices withdrew during the study (one stopped offering registration health checks; one for workload reasons; and one closed), but all provided complete study data and were included in the intervention arm in the analysis (intention to treat). Practice and population characteristics and numbers of newly registering patients were well balanced after randomisation (Tables 1a and 1b).

Intervention practices offered 11,187 rapid tests, of which 4,978 (44.5%) were accepted (Table 2). Of these, 4,964 were not reactive and 14 were reactive, including 11 that were confirmed HIV positive (true reactive) and three confirmed HIV negative (false reactive).

INSERT FIGURE 1 (Flow chart) here

INSERT TABLE 1a and 1b (Practice and patient characteristics) here

INSERT TABLE 2 (HIV tests and diagnoses) here

INSERT TABLE 3 (CD4 counts) here

Overall, intervention practices identified 43 HIV positive patients, of whom 11 had previously been diagnosed, giving a total of 32 new HIV diagnoses, 11 of which were diagnosed by rapid testing. Control practices identified 21 HIV positive patients, of which seven had previously been diagnosed, giving a total of 14 new HIV diagnoses (Figure 1).

The UK Antenatal Screening Programme led to three new HIV diagnoses in intervention practices, and four in controls.

Of the 32 new diagnoses in the intervention group, 19 (59%) were men, 20 (63%) were of black African origin, and six (16%) were men who have sex with men (MSM). Of the 14 patients diagnosed in control practices, eight (57%) were men, and 10 (71%) were of black African origin; no MSM were recorded in the control group, although there were no data on sexual orientation for three men. No adverse event occurred during the study.

Primary outcome: CD4 count at diagnosis

CD4 count data were available in 30 of the 32 newly diagnosed patients from intervention practices, and in all 14 patients from controls. The mean CD4 count in intervention practices was higher compared to control: 356/ μ L (SD 254), and 270/ μ L (SD 257) respectively, but not significantly so; (adjusted difference in square root transformed CD4: 3.1; 95% confidence interval [CI], -1.2 to 7.4; $P=0.16$, Table 3). Two pre-planned sensitivity analyses showed that the effect of the intervention on CD4 count was significantly greater when patients diagnosed *via* the UK antenatal HIV screening program were excluded (6.4; 95% CI, 1.2 to 11.6; $P=0.017$, Table 3), and when patients who had been previously diagnosed with HIV but defaulted from care were included in the analysis (4.1; 95% CI, 0.0 to 8.1; $P=0.049$, Table 3).

Secondary outcomes

Rate of new HIV diagnoses

Rate of HIV diagnosis was fourfold higher in intervention than control practices: with 0.30 (95% CI, 0.11 to 0.85) per 10,000 patients per year in the intervention, and 0.07 (95% CI,

0.02 to 0.20) in the control arm; (adjusted ratio of geometric means: 4.51; 95% CI, 1.27 to 16.05; P=0.021, Table 2). In a sensitivity analysis, the effect of intervention on rates of diagnoses was similar in all population subgroups (Table 2).

Proportions of diagnoses with CD4 counts <350, and <200 cells/ μ L

Using a method developed by Peacock et al (2012),²⁴ we estimated that of patients in the control practices had a CD4 count less than 350 cells/ μ L, compared with of intervention patients; (risk ratio 0.75, 0.53 to 1.07). Corresponding figures for CD4 less than 200 cells/ μ L were 46% versus 28%; (risk ratio 0.60, 0.32 to 1.13).

Discussion

We demonstrate that an educational outreach programme promoting opt-out rapid HIV testing of people newly registering in general practice leads to increased and earlier diagnosis of HIV. These are key goals of HIV-focussed clinical and public health programmes. Effects were more strongly significant in sensitivity analyses excluding women diagnosed through the UK's existing antenatal HIV screening programme. Practices used both rapid (N=11 newly diagnosed patients) and opportunistic serology testing (N=21 patients) to make new diagnoses. A high proportion (62%) of newly diagnosed patients were of Black African origin, reflecting successful integration of testing into a multi-ethnic community, recognised as a hard to reach population.²⁵ To our knowledge this is the first randomised trial to demonstrate improvements in clinical outcomes from HIV screening.

Strengths of our study included a pragmatic 'real world' design that included almost all practices (89%) in the borough, improving generalisability of our findings. Randomisation was robust, maintaining allocation concealment. Analysis was by cluster at the level of general practices. Remote searching of practice computer systems ensured consistent data capture of testing activity and outcomes across practices. Access to test results from the regional laboratory ensured complete capture of all positive tests, minimising detection bias. The Public Health England national surveillance system allowed accurate distinction between patients newly diagnosed in primary care from those who had previously tested positive. Validation of data extraction by an independent clinician, blinded to allocation, of all newly diagnosed patients ensured accuracy and completeness of primary and secondary outcomes.

Our multi-faceted intervention was based on a previously successful screening intervention for tuberculosis in general practice,¹⁹ which used a variety of effective behaviour change techniques. The effectiveness of outreach visits, and clinician education combining mixed didactic and interactive elements, is well established.²⁶ Computer prompts to testing and incentive fees may also have enhanced behaviour change.²⁷ A quality assurance scheme, which included competency-based training for rapid HIV testing, regular electronic monitoring of point-of-care results and bi-monthly assessment of staff using external control serum samples, enhanced patient safety by reducing the chances of false positive rapid test results. All patients diagnosed *via* rapid testing were successfully transferred to secondary care indicating that the links we established between general practice and specialist services were safe and effective. Some patients who had defaulted specialist care re-entered specialist services following a ‘re-diagnosis’ by their GP, suggesting that primary care can play an important role in maintaining the patient care continuum.

A weakness was that three intervention practices discontinued testing. These discontinuations reflect the pragmatic real world study design. We were, nonetheless, able to include complete data from all practices in the analysis. Registration health checks are optional, thus only those that attend (about 50% of all registering patients) can be offered a test. Increasing attendance at checks would increase the impact of our intervention. Whilst it was impossible to blind clinical and research teams to allocation, validation of data extraction by a blinded independent clinician helped ensure validity of study data.

Observational studies suggest that targeted community-based approaches to HIV testing achieved high uptake, and a higher proportion of cases with CD4 count at diagnosis >350.²⁸ In community centres in the USA, nurse-initiated routine universal non-targeted rapid HIV testing achieved similar uptake and yields of new diagnoses to those seen in the current study.²⁹ Nurse-initiated rapid testing with streamlined counselling in primary care is feasible compared to traditional approaches.^{29,30} These observations lend credibility to our findings.

Our findings provide firm evidence that HIV screening in primary care leads to increased and earlier HIV diagnosis. This finding addresses a key gap in the evidence base for HIV testing, lending randomised evidence in support of guideline recommendations.

Our results justify renewed efforts to implement community screening for HIV. This study builds on our previous work showing opt-out screening for tuberculosis using a multi-faceted

educational intervention and valid implied consent is effective in primary care.¹⁹ Screening for multiple infectious agents in at-risk populations seems justifiable.

Our findings provide robust high quality evidence to support HIV screening programmes in primary care to reduce undiagnosed and late diagnosed infection in high prevalence settings.

PANEL - Research in context

Evidence before this study:

We searched PubMed for randomised controlled trials, from year 2000 to 2009, testing the effects of screening for HIV in primary care on rate of HIV diagnosis and stage of diagnosis, according to the following PICO:

Populations: Adults

Interventions: HIV screening and HIV testing interventions

Comparator: Randomized controlled trials with usual care as a comparator

Outcomes: Rate of HIV diagnosis; CD4 count; HIV stage of diagnosis

We found no studies that met these criteria.

A similar search was carried out in 2011 by the US Preventative Services Task Force as part of their evidence review to update the 2005 U.S. Preventive Services Task Force recommendations on HIV screening. They noted: ‘no randomised trial or observational study compared clinical outcomes between adults and adolescents screened and not screened for HIV infection’

Added value:

These findings provide, to our knowledge, the first robust randomised evidence that a screening programme leads to increased and early HIV diagnosis

Implications:

Public Health leads should consider implementing primary care based screening for HIV in high prevalence areas

Contributors

CG had the original idea for the study. WL, HM, CG, JA, SC, DM, SM, JF, GH, RA, KB, SB, SK, AS, FTP, and MS designed the study; WL, HM, DM, SC, JA, and CG contributed to general practice staff training and education; WL, HM and MS undertook the quality assurance of the study; SK and NM did the statistical analysis; and RA provided advice on ethical aspects of the trial, including data management and data protection. AM completed data quality assurance checks. VD, AB and GR validated HIV diagnoses data. WL and CG wrote the first draft of the manuscript with input from ACS, HM, JA, SK, SB, JF, AM, VD, and FTP. All authors have seen and approved the final version of the manuscript for publication.

Conflicts of Interests

Dr. Anderson reports fees and non-financial support from Bristol Myers Squibb, grants and personal fees from Gilead Sciences, personal fees from ViiV, personal fees from MSD, grants from Janssen, personal fees from AbbVie, outside the submitted work. The remaining co-authors declare that they have no conflicts of interest.

Acknowledgments

We thank all participants and general practices. We thank Keith Prescott, Arun Chinnaraj, Martin Sharp, and Jack Dunne (Clinical Effectiveness Group, Queen Mary, University of London, UK) for the extraction of demographic and HIV testing data. We are grateful to Damilola Awosika for her assistance in collating data of newly diagnosed patients. Many thanks to Clare Rutterford for the practice randomization and for undertaking quality checks on the final analysis. Finally, we thank the members of the data monitoring committee, Claudia Estcourt, Karen Smith, and Jill Zelin, for their important contributions.

Funding

Department of Health, NHS City and Hackney; (ClinicalTrials.gov: ISRCTN63473710).

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