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

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Abstract: BACKGROUND
Many people with human immunodeficiency virus (HIV) are undiagnosed. Early diagnosis saves lives and reduces onward transmission.

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/μL (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.

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

FUNDING

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

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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/μL (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.

INTERPRETATION

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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 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. [2,5,6]

Expanding HIV testing is key to improving HIV outcomes, however evidence on outcomes from robust screening trials is lacking. 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,[7] 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.[10,11]

Primary care is ideally placed to offer HIV testing.[12] 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,[13-15] and may be preferable for people who would not normally attend traditional HIV testing settings such as sexual health clinics.[15]

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 with a rate of diagnosed HIV infection of 8/1000 adults. Forty of 45 (89%) general practices in Hackney enrolled by the study team were cluster randomised to the HIV testing

programme or usual care. There were no exclusion criteria for clusters. Consent from participating practices was sought before randomisation.

The study was approved by Camden and Islington Community Research Ethics Committee (09/H0722/67). An independent data monitoring committee (DMC) was established.

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),[16] 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);[17] and male HIV testing rate (male adults tested between April and October 2009/adults registered x1000: <7; ≥7). The nature of the intervention meant that neither investigators nor clinical teams were masked to allocation.

Inclusion criteria for eligible patients

Patients aged 16 years 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 consent for study participation

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]

Intervention

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 of free rapid HIV tests and payment of £10 ($16·14) per test completed;
- Quality assurance testing programme.

Practice-based outreach educational programme for intervention practices

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.[18-20] 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).

Integrating rapid HIV testing into the registration health check, management of reactive tests and confirmatory serology testing

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 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 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).

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

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.

Primary and secondary outcomes

Early and increased diagnosis of HIV are key clinical and public health outcomes.[4,8,9,12]

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.

Patients newly diagnosed with HIV in general practice, data extraction and validation

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.[21] 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.

Study power

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 and, with 80% power and 5% significance. This would be sufficient to detect an increase in the mean CD4 count from 300 to 470 cells/µL, 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.[22]

Analysis

Intervention effect on CD4 count and rate of diagnosis was estimated using a regression model adjusted for clustering 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. We estimated the relative reduction in the percentage of patients diagnosed with both CD4<350 and CD4<200 cells/µL, using the normal distribution.[23]

Sensitivity analyses

The UK Antenatal HIV Screening Programme offers all women in antenatal care an HIV test. We carried out a pre-planned a 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 Hackney and the Department of Health funded the study; they had no role in the analysis.

Results

General practices and populations

Forty of 45 (89%) general practices agreed to take part; and five declined (Figure 1). 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 analysis. Practice and population characteristics and numbers of newly registering patients were well balanced after randomisation (Tables 1a and 1b). The study began in April 2010, and ended in August 2012 when funding expired.

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).

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/μL (SD 254), and 270/μL (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; P0·017, 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/μL

We estimated that 73% of control patients had a CD4 count less than 350 cells/μL, compared with 55% of intervention patients; (risk ratio 0·75, 0·53 to 1·07). Corresponding figures for CD4 less than 200 cells/μL were 46% versus 28%; (risk ratio 0·60, 0·32 to 1·13).

Discussion

Summary

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 and opportunistic serology testing 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.[24] To our knowledge this is the first randomised trial to demonstrate improvements in clinical outcomes from HIV screening.

Strengths and weaknesses

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,[18] 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.[25] Computer prompts to testing and incentive fees may also have enhanced behaviour change.[26] 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.

Comparison with previous research

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.[27] 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.[28] Nurse-initiated rapid testing with streamlined counselling in primary care is feasible compared to traditional approaches.[28,29] These observations lend credibility to our findings.

Clinical and research implications

Our findings provide the strongest evidence yet 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 screening for tuberculosis is effective in primary care.[18] Screening for multiple infectious agents in at-risk populations seems justifiable.

Conclusion

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.

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Figure 1

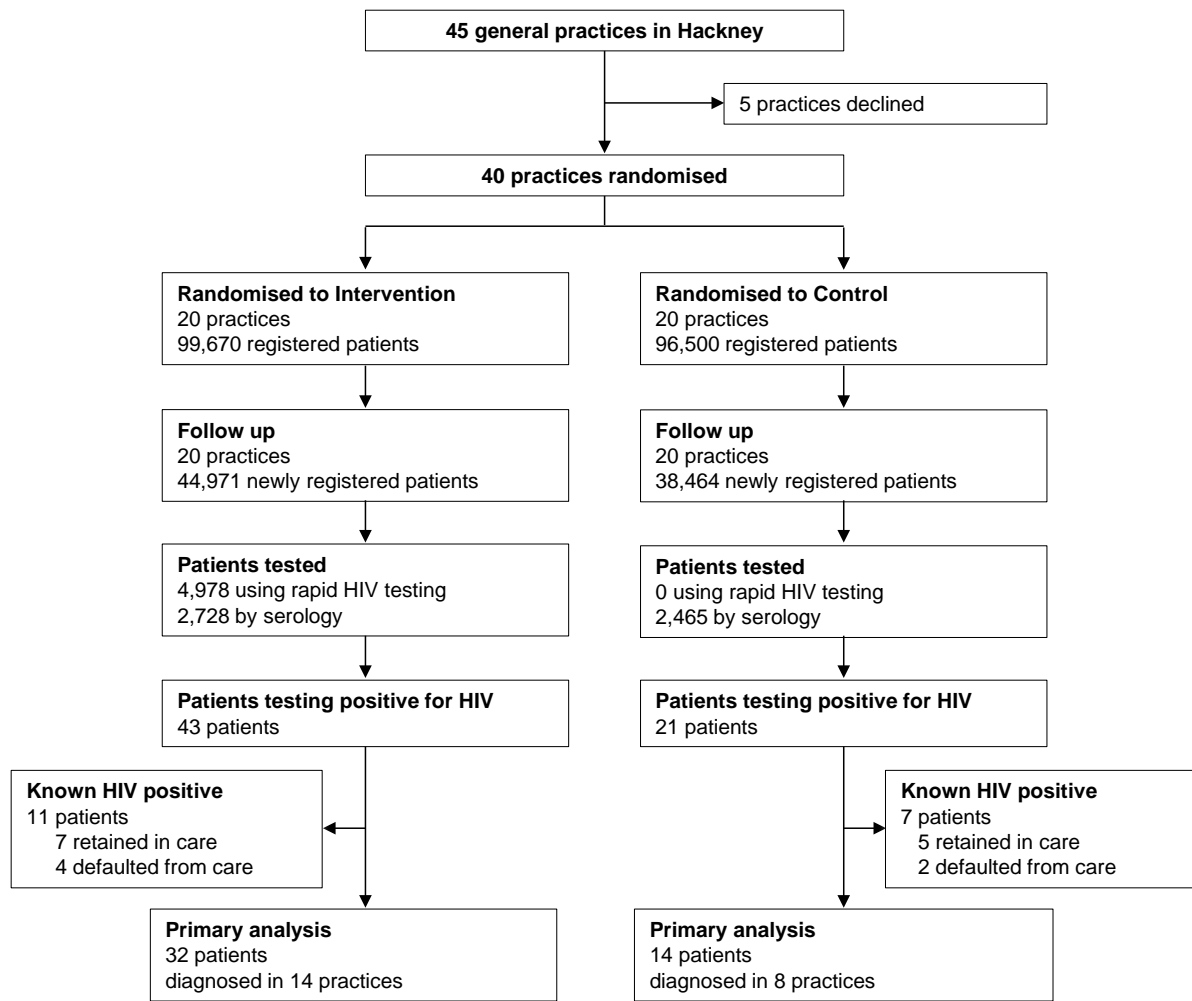Figure 1. Flow of clusters and trial arm specific data.

Table 1a. Baseline characteristics of participating clusters (general practices) according to minimisation factors and registered patients.

Characteristic	Intervention practices (N=20)	Control practices (N=20)
Practice factors at baseline		
List size – no. of practices (%)		
Low (<5000)	8 (40%)	8 (40%)
Medium (5000-7000)	5 (25%)	5 (25%)
High (≥7000)	7 (35%)	7 (35%)
HIV testing rate in males*		
Low (<7)	13 (65%)	13 (65%)
High (≥7)	7 (35%)	7 (35%)
Index of multiple deprivation score		
Low (<47)	11 (55%)	10 (50%)
High (≥47)	9 (45%)	10 (50%)
Patient factors at baseline		
Number of registered patients	99,670	96,500
Age (range)		
16-24 – no. (%)	15,623 (15·7%)	13,198 (13·7%)
25-34 – no. (%)	28,200 (28·3%)	29,292 (30·4%)
35-49 – no. (%)	31,218 (31·3%)	31,990 (33·2%)
>50 – no. (%)	24,629 (24·7%)	22,020 (22·8%)
Male sex – no. (%)	50,224 (50·4%)	48,929 (50·7%)
Ethnicity – no. (%)		
White	40,250 (40·4%)	48,262 (50·0%)
Black	20,467 (20·5%)	17,690 (18·3%)
Asian	8,487 (8·5%)	8,002 (8·3%)
Mixed	3,396 (3·4%)	4,207 (4·4%)
Other	7,134 (7·2%)	3,562 (3·7%)
Unknown	19,934 (20·0%)	14,777 (15·3%)

* The male HIV testing rate is defined as the number of male adults tested between April and October 2009/adults registered x1000.

Table 1b: Characteristics of newly registering patients.

Characteristic	Intervention practices (N=20)	Control practices (N=20)
Total number of new registrants	44,971	38,464
Number of new registrants per practice – median (range)	1,379 (150-7830)	1,802 (280-4039)
Age (range)		
16-24 - no. yr (%)	7,667 (17·0%)	6,207 (16·1%)
25-34 - no. yr (%)	19,491 (43·3%)	18,170 (47·2%)
35-49 - no. yr (%)	10,950 (24·3%)	9,016 (23·4%)
>50 - no. yr (%)	6,863 (15·3%)	5,071 (13·2%)
Male sex - no. (%)	20,219 (45·0%)	17,119 (44·5%)
Ethnicity – no. (%)		
White	23,947 (53·2%)	22,365 (58·1%)
Black	6,400 (14·2%)	5,253 (13·7%)
Asian	3,472 (7·7%)	3,011 (7·8%)
Mixed	1,296 (2·9%)	1,442 (3·7%)
Other	2,066 (4·6%)	1,389 (3·6%)
Unknown	7,790 (17·3%)	5,004 (13·0%)

The percentages may not total 100 due to rounding.

Table 2

Table 2. HIV testing and diagnoses.

Characteristic	Intervention practices (N=20)		Control practices (N=20)		Ratio of rates of diagnosis[b] (95% CI)
	Numbers of patients	Rate of diagnosis per 10,000 registered patients per year[a]	Numbers of patients	Rate of diagnosis per 10,000 registered patients per year[a]	
HIV testing					
Total number of new registrants	44,971		38,464		
Number of patients offered rapid tests	11,187 (24·9%)		NA		
Number of patients accepting rapid tests	4,978 (44·5%)		NA		
Number of patients with NOT reactive rapid tests	4,964 (99·7%)		NA		
Number of patients with reactive tests	14		NA		
Number of patients confirmed HIV positive	11		NA		
Number of patients with serology test performed	2,728		2,465		
HIV diagnoses					
Total number of diagnoses (new and previously diagnosed)	43		21		
New HIV diagnoses	32	0·30 [0·11,0·85]	14	0·07 [0·02,0·20]	4·51 [1·27,16·05]
Rapid testing	11		NA		
Opportunistic testing	18		10		
Antenatal screening program	3		4		
Previously diagnosed with HIV	11		7		
Previously diagnosed patients defaulted from care	4		2		
Previously diagnosed patients retained in care	7		5		
Sensitivity analysis					
All new diagnoses excluding antenatal	29	0·23 [0·07,0·70]	10	0·04 [0·01,0·11]	5·88 [1·71,20·17]
All new diagnoses plus those defaulted from care	36	0·32 [0·11,0·91]	16	0·07 [0·02,0·21]	4·53 [1·25,16·38]

[a] Calculated as geometric mean of rates for each practice
[b] Calculated as ratio of geometric means.

Table 3

Table 3. CD4 count of newly diagnosed patients in intervention and control practices.

Characteristic	Intervention practices (N=20)			Control practices (N=20)			Difference adjusted for minimisation factors[a] (95% CI)
	Number of patients	CD4 count Mean (SD)	Square root of CD4 count Mean (SD)	Number of patients	CD4 count Mean (SD)	Square root of CD4 count Mean (SD)	
New diagnoses	32*	356 (254)	17·7 (6·6)	14	270 (257)	14·7 (7·7)	3·1 [-1·2,7·4]
All new diagnoses excluding antenatal	29*	369 (262)	18·0 (6·7)	10	194 (169)	12·4 (6·7)	6·4 [1·2,11·6]
All new diagnoses plus those defaulted from care	36*	411 (288)	19·0 (7·2)	16	259 (242)	14·5 (7·3)	4·1 [0·0, 8·1]

[a] Calculated from square root of CD4 count
* CD4 count unavailable in 2 patients.

Supplement

Supplement part A: Practice based educational program for intervention practices

The GP educational outreach program comprised two parts: the first (30 minutes), aimed at the whole practice team, introduced the rational for HIV testing, local epidemiology, trial design, and information on the safe implementation of rapid HIV testing; the second (60 minutes) was a competency-based practical training for rapid test operators only.

This competency-based training included successful completion of rapid testing (INSTI HIV1/HIV2 Rapid Antibody Test, bioLytical Laboratories, Canada) on two different HIV-negative volunteers including a pre-test discussion and one human serum control sample containing HIV-1 antibody. Results were recorded on training record sheets. rapid test operators, who had correctly conducted an HIV pre- and post-test discussion, adequately processed the test samples and correctly interpreted the test results, received a certificate of completion of training.

Supplement part B: Practice HIV lead nurse training and quality assurance

At the end of the educational session, each surgery was asked to nominate a surgery HIV lead to co-ordinate rapid HIV testing and to act as a contact point for the study team. The lead nurse received additional training 2-6 weeks later, comprising a follow up visit including instructions on supervising and co-ordinating rapid testing within the surgery, on the importance of follow up of patients with a reactive, indeterminate or twice invalid rapid test result, and on the quality assurance program.

For the quality assurance program, intervention practices were sent, at two monthly intervals, two control serum samples by the local virology laboratory for testing at. They reported results to the QA manager (MS). Practices received feedback; any that returned incorrect results were offered further support in rapid testing. During alternative months, control samples containing HIV1 antibody were sent to the practices for internal control. Participation in internal control was optional.

Supplement part C: Testing activity and outcomes from study practices

We carried out quarterly remote searches of participating practices' computer systems to obtain Read coded data on rapid test outcomes and rapid tests declined. Any reactive/indeterminate/twice invalid test result was checked via email or phone call with the practice HIV lead nurse or health care assistant for its clinical relevance. Serology test activity was collated at the end of the study. Thirty eight practices used EMIS (Egton Medical Information Systems Limited, UK), and two practices used Vision (In Practice Systems Limited, UK) electronic medical record software.

Supplement part D: The rapid testing process

Pre-test discussion

1. When offering the rapid HIV test, GP staff was advised to use the following phrases:

"Is it ok if we do an HIV test? We are offering them to everyone; we'll get the result within the consultation. Things have changed in HIV; it is now a treatable medical condition, people can have a family and children, and there are drugs available free for everyone and like all medical conditions it is better to pick it up in the early stages."

2. To secure confidentiality in the case of an accompanied patient, rapid test operators were advised to state the following:

"For this portion of the health check, I am going to ask your guest to step outside for a moment". And once the patient's guest would have left the consultation room, the rapid test operator was advised to say: "I just wanted to make sure you were comfortable saying 'yes' or 'no' to a rapid HIV test. If you are comfortable having the test and receiving the result in front of your guest, I have no problem inviting them back in".

Post-test discussion

After completion of the testing procedure and according to the test outcome, the nurse or health care assistant was advised to say the following to the patient:

1. Non-reactive result

"We did not find HIV today. If you have had any risk in the last 3 months you need to retest in one and three months' time. Recent risk means sex without condoms, unsterile procedures or infected blood transfusions abroad, or sharing needles."

2. Reactive or indeterminate result

"While we are awaiting the result of your HIV test would you mind taking a seat in the waiting room? A GP or nurse will see you shortly." Or: " I am a bit unsure about the test result so I have asked the GP or nurse to come in and explain it to you."

3. Twice invalid result

"Your rapid test result has been twice invalid. This means that there may be some problem with the test device. To be sure you are not infected, I am going to take some blood from your arm."

Specific points:

1. Non-reactive rapid test result

Any patient with a non-reactive rapid HIV test result but recent risk was advised to have a repeat rapid HIV test three months after their most recent exposure; confirmatory test using venous blood test was offered as an alternative one and three months after their most recent exposure, particularly when the patient was anxious.

2. Reactive/indeterminate or twice invalid result

Practices were advised that any reactive/indeterminate or twice invalid rapid test result be verified by another INSTI trained nurse or a GP within five minutes of completion of the testing procedure and that a GP or senior practice nurse undertake a post-test discussion with the patient. The GP was advised to share the rapid test result with the patient, address any immediate concerns they might have, request a venous blood for confirmatory testing, and arrange a follow up appointment, indicating the method and timing of receiving the test result to the patient.

3. Seroconversion illness

Patients with a non-reactive rapid test result presenting with symptoms suggestive of HIV seroconversion illness were offered immediate venous blood sampling.

Alternatively, the patient was offered immediate referral to the Department of Sexual Health at Homerton Hospital to exclude early HIV infection.

Supplement part E: HIV1/HIV2 confirmatory testing

All serology samples were sent to Homerton Pathology for combined screening of HIV p24 antigen and HIV1/HIV2 antibody using the Abbott Architect ci8200 fourth generation assay. Any reactive serology specimen was sent to the Department of Virology, Barts Health NHS Trust, for confirmatory testing.

Supplement part F: Exclusions and definitions

Exclusion of patients from the primary outcome measure

Patients in whom the GP had not performed HIV testing prior to referral, and patients who were referred by their GP to secondary care at Homerton Hospital either for HIV testing or for further management of a suspected HIV-related illness were excluded from the primary outcome measure.

Definition of a newly diagnosed patient

A newly diagnosed patient was defined as a person who was unaware of their HIV status at the time of testing, but who tested either HIV1 or HIV2 antibody positive following a GP request for HIV confirmatory testing at Homerton Pathology.

Supplement part G: Patient ascertainment

All those testing HIV positive were allocated a unique study number, which was used to send communicate anonymised data to the research team. A confidential register linking study number to personal data was maintained by the clinical team at Homerton Hospital. No personally identifiable information was shared with the research team. Evidence of any prior HIV diagnosis, whether in or defaulted from care, was obtained from Public Health England. For each newly diagnosed patient, study clinicians compiled data on a clinical record form. These data were extracted onto a fully anonymised summary table. Accuracy of data extraction for all patients was checked by an independent clinician blinded to study allocation, before being passed to the study statistician.

Effectiveness of HIV screening in Primary Care:
A cluster RCT and economic analysis

Study Protocol

Version 5.0
Signed by Dr Werner Leber
Chief Investigator
Dated: 04 May 2012

Full title of the protocol:	**Effectiveness of HIV screening in Primary Care: A cluster RCT and economic analysis**
Short title (Acronym):	**Trial of HIV Screening in Primary Care (RHIVA 2)**
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Study Summary
Glossary of Terms and Abbreviations
Tale of Contents

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Study Summary

Full Title	**Effectiveness of HIV screening in Primary Care: a cluster RCT and economic analysis**
Short Title	**Trial of HIV Screening in Primary Care**
Protocol Version	Version 5.0
Date	02 May 2012
Methodology	Cluster randomized controlled trial
Trial Start Date	19 April 2010
Study Duration	2 years and 4 months and 12 days
Study Centres	Queen Mary, University of London; Homerton University Hospital NHS Trust; Royal Free and UCL Medical School; NHS City and Hackney; London School of Hygiene and Tropical Medicine
Primary Objective	To determine whether a targeted intervention with rapid point of care testing in GP surgeries leads to earlier detection of HIV
Numbers of GP Surgeries invited to participate	45
Numbers of GP Surgeries enrolled to date	40
Number of Patients	23,000 patients (estimated)
Main Inclusion Criteria	(1) Individuals aged 16 years or older registering at study practices (2) Individuals able to undertake the pre−test discussion in English or with a suitable translator.
Statistical Methodology and Analysis	A pragmatic, cluster randomised, controlled trial across up to 45 GP surgeries in Hackney

Glossary of Terms and Abbreviations

Advanced HIV infection	An advanced HIV infection is defined as CD4 count lower than 200 cells per cubic millimetre of blood.
AIDS	Acquired immunodeficiency syndrome
BHIVA	British HIV Association
BLT	Barts and The London NHS Trust
CI	Chief Investigator
DMC	Data monitoring committee
GP	General Practitioner
HIV	Human immunodeficiency virus
PCT	Primary Care Trust
Rapid HIV test	HIV test performed on a finger prick blood sample using a rapid point of care test device.
Standard HIV test	HIV test performed on a venous blood sample using fourth generation HIV assays (gold standard).
Usual HIV care	A GP practice offering a HIV test from a venous sample

1   Introduction

1.1   Background

HIV is a serious but treatable chronic disease affecting more than 80.000 patients in the UK, of who about a quarter (28%) are unaware of their infection (HPA, 2008a). Despite enormous public health efforts, HIV continues to spread in the community. In the year 2007 alone, 7700 new cases of HIV were reported in the UK and nearly a third (31%) of those presented with advanced disease. Until recently, standard HIV care focused on testing of high−risk groups and of those presenting with AIDS−related conditions such as tuberculosis. Early detection of HIV is important to reduce unwitting onward transmission of HIV to partners and children, and to prevent late presentation that is associated with adverse outcomes, notably risk of AIDS and death.

1.2   Rapid point of care HIV testing

Rapid point of care (near patient) HIV testing combined with pre− and post−test counselling has been accepted as an important tool for the prevention and early management of HIV. For patients with a negative test result, rapid point of care HIV testing is a great opportunity for sexual health education to prevent future disease. Patients with a positive test are more likely to attend specialist services to receive adequate treatment and psycho−social support for both the individuals affected and their families.

In East London, rapid HIV testing is being offered routinely on an 'opt−out' basis to risk groups in sexual health clinics, charities and community programs. It is now commonly believed that the widening of access to rapid HIV testing in GP surgeries in Hackney would promote both prevention and identification of HIV infection. New expert guidelines recently published by the British HIV Association (BHIVA) recommend universal opt−out HIV testing in Primary Care in areas where two or more people per 1000 are infected with HIV (BHIVA, 2008). Estimates based on unlinked anonymous data indicate that the numbers for Hackney are four times as high (8 per 1000) (HPA, 2008b). In addition, we have recently demonstrated in a pilot study that rapid point of care HIV testing performed during the new patient health check in a single GP surgery in Hackney was welcomed and accepted by patients and achieved an uptake of 45% (Prost et al., 2009).

1.3   Rationale and risk/benefit assessment

For the reasons given above, data from clinical trials evaluating the feasibility of large-scale rapid HIV testing are timely to inform the ongoing implementation of testing guidelines in Primary Care. More specifically, expansion of rapid point of care HIV testing across a large number of surgeries has the potential to: (1) demonstrate an increase in the proportion of cases that are diagnosed early to reduce unwitting onward transmission of the virus, to prevent medical complications and to lower socio−economic costs associated with late (2) to demonstrate an increase in the rate of patients being tested and diagnosed with HIV and (3) normalise and de−stigmatise HIV by strengthening the central role of General Practice in diagnosing and preventing the disease.

2   Study Aims and Objectives

The primary objective is to demonstrate that rapid HIV testing offered in the new patient health check or at first consultation, when combined with an educational package for health care professionals, reduces the proportion of newly diagnosed patients who present with advanced HIV infection from 30% to 10%. An advanced HIV infection is defined as CD4 count lower than 200 cells per cubic millimetre of blood. This is estimated from the mean CD4 count, using the Normal distribution.

The secondary objectives are to demonstrate (1) an increase in proportion of new HIV cases that qualify for the start of antiretroviral therapy, defined as a CD4 count less than 350 cells per cubic millimetre of blood (this will also be estimated from the mean CD4 count) (2) an increase in proportion of patients newly diagnosed in general practice (3) an increase in the rate of standard HIV tests performed opportunistically (4) a reduction in proportion of HIV cases with a high risk of progression to AIDS, defined as a viral load of higher than 200,000 copies per million peripheral mononuclear cells and (5) a reduction in financial and economic costs incurred to the PCT.

3   Investigational Plan

3.1   Overall design

Pragmatic, cluster randomised, controlled trial

3.2   Schema for intervention surgeries

	-2 months	-1 month	0 day	+2 days	+14 days
			Registration with GP	Registration health check	
Randomisation of practices	X				
Education of intervention practices		X			
Patient recruitment			X		
Valid implied consent			X		
HIV pre-test counselling				X	
Rapid HIV test				X	
Blood sample for confirmatory HIV test				X	
GP visit of rapid HIV positives				X	
GP referral to specialist rapid HIV positives				X	
Written informed consent confirmed HIV positives					X

3.3 Overview of study population

The study population will comprise all patients aged 16 years and older registering with a GP surgery in Hackney, who fulfil the eligibility criteria stated in section 4 of this protocol.

3.4 Target accrual

Target accrual is (1) all surgeries in Hackney and (2) 23,000 participants.

4 GP Surgery Selection

All GP surgeries in Hackney will be invited to take part.

5 Subject Selection

5.1 Inclusion criteria

(1) Individuals aged 16 years or older registering at study practices
(2) Individuals able to undertake the pre−test discussion in English or with a suitable translator.

5.2 Exclusion criteria

(1) Age under 16 years
(2) Individuals with limited English abilities, who are unable to understand the info sheet or, who are unable to engage with the pre−test discussion for HIV testing
(3) Known HIV positive patients.

6 Study Procedures and Schedule of Assessments

6.1 Recruitment of GP surgeries

Participating surgeries will be randomised into two groups: (1) An intervention group offering rapid point of care HIV testing during GP registration in addition to providing routine (usual) HIV care and a (2) control group providing usual HIV care only. Usual care means that a practice GP would offer a HIV test from a venous sample upon patient request or if it is clinically indicated.

6.2   Randomisation procedures

Practice will be randomised using a computer generated minimisation, by: 1) practice list size 2) practice deprivation and 3) HIV male testing rate per surgery.

6.3   Formative phase for GP practice staff

6.3.1   Intervention surgeries

The formative phase for intervention surgeries will include the following:

6.3.1.1   Analysis of the educational requirements for GPs nurses and health care assistants.

6.3.1.2   Provision of training in performing the rapid point of care HIV test.

6.3.1.3. Setting up the operating procedure for HIV testing as an integrated part of the new patient health check.

6.3.1.4   Confirmation of referral pathways for newly diagnosed patients into specialist care.

6.3.1.5   Establishing the role of the HIV liaison nurse as the key figure to facilitate communication about newly diagnosed patients between clinicians including GPs and the HIV specialist team, the Virology lab and the researchers.

6.3.1.6   Establishing the role of the HIV point of care test co-ordinator, a member of the RHIVA 2 research team, as the first point of call for all technical problems related to using the test devices.

6.3.2   Control surgeries

Control surgeries will be informed about the most recent specialist recommendations for HIV testing and receive support from the HIV liaison nurse throughout the study period.

6.4   Patient consent procedures

6.4.1   Valid implied consent for registering patients.

6.4.1.1   Valid implied consent for participation in the study will be obtained in identical fashion to our recent tuberculosis screening trial (Griffiths et al., 2007). Briefly, during registration, the practice reception will provide patients with a laminated information sheet available in multiple languages (see Attachments 1 and 2). Spare copies of the information sheet will be obtainable at the surgery for patients to take home. The sheet details information that the practice is taking part in a study, which compares the delivery of routine clinical care in two different ways: either usual care (control) or through an extended new patient health check that includes a rapid HIV screening test for those that would like to be tested (intervention).

6.4.1.2   Most patients will be given a minimum of two days to consider whether they wish to participate in the study. In addition, surgeries will have the additional option of handing out the patient information sheets immediately prior to the testing procedure. Before offering the test, the rapid test operator will check that the patient has read and understood the patient information sheet.

6.4.1.3   During the extended new patient health check in intervention surgeries, a suitably trained health care assistant or nurse will offer the rapid HIV test to eligible patients following a HIV pre-test discussion.

6.4.1.4   Patients are completely free to refuse to enter the study or withdraw from the study at any time and without having to specify a particular reason.

6.4.1.5   Patients will be reminded that 'opportunistic' HIV testing from venous blood will continue to be offered at both intervention and control surgeries either upon patient request or if clinically indicated.

6.4.2   Written informed consent for patients testing HIV positive

6.4.2.1   For newly diagnosed HIV patients, we will, with written informed consent, obtain anonymised basic demographic data (including age, gender, ethnicity and Soundex code), mode of diagnosis, route of acquisition, and CD4 counts and viral parameters (including viral load, clade and genotype of the virus) at the time of diagnosis.

6.4.2.2   The HIV liaison nurse has clinical responsibility for care of patients with HIV and will obtain information on identity and practice registration of new diagnoses from general practice and from Homerton Pathology.

6.4.2.3   The HIV liaison nurse may ask GPs to obtain written informed consent from patients to allow divulgence of the above anonymised variables from their medical records. Copies of written informed consent will be retained by the HIV liaison nurse.

6.4.2.4   For patients registering at Homerton Hospital, written informed consent may additionally be obtained by GCP-trained Homerton clinicians.

6.4.2.5   For the few patients registering with GUM clinics other than Homerton, Dr Sarah Creighton, the NHS City & Hackney community liaison consultant, will arrange for written informed consent to be taken by herself or a GCP-trained member of her team with potential assistance from surgery GPs.

6.5   Registration procedure and pre-test discussion

6.5.1   All patients aged 16 years and above registering who are able to communicate in English or using a suitable translator will be offered a rapid HIV point of care test as part of the new patient health check.

6.5.2   During the course of the new patient health check, the health care assistant or practice nurse will provide a short pre−test discussion and offer a rapid HIV test.

6.6   Giving the test result and the post-test discussion

6.6.1   A Non-Reactive rapid test result

1.   Following a non-reactive result, the patient will be assured that they do not have HIV.

2.   Any patient with recent risk will be advised to have a blood test from the arm one and three months after the most recent exposure. Recent risk will be defined as having had within the three previous months any of the following: medical procedures abroad including blood transfusions and tattoos; unprotected sex or sharing needles.

6.6.2   Two consecutive Invalid reactive tests occurring during the same consultation

1.   Any patient with two consecutive invalid results and a **NEGATIVE** blood test without recent risk will be reassured they do not have HIV.

2.   Any patient with two consecutive invalid results and a **NEGATIVE** blood test result but recent risk will be advised to have repeat serology one and three months after the most recent exposure.

3. Any patient with two consecutive invalid results and a **NEGATIVE** blood test but recent risk and symptoms suggestive of sero-conversion will be offered a repeat serology test within one and three month time following most recent exposure or referral to Homerton to exclude early HIV infection.

6.6.3 An Indeterminate rapid test result

1. If the confirmatory test is **POSITIVE**, the GP will refer the patient to the HIV Liaison Nurse and follow the confirmed HIV positive algorithm.
2. If the confirmatory test is **NEGATIVE**, the GP uses clinical judgement to determine whether the patient is potentially sero-converting. Any patient with recent risk should be offered repeat serology one and three months after most recent exposure. Alternatively, the GP may consider referring the patient to Homerton Hospital to exclude early HIV infection.

The GP may wish to inform the HIV Liaison nurse about an indeterminate test prior to receiving the confirmatory test result.

6.6.4 A Reactive rapid test AND a Positive confirmatory result (concordant result)

A concordant result is one in which the result from the INSTI HIV1&2 Antibody kit is reactive and the subsequent Homerton/BLT Virology results are positive.

If the confirmatory result is **POSITIVE**, Barts Virology will inform the GP and the HIV Liaison nurse via telephone. The HIV Liaison nurse will contact the GP to confirm the result. The GP will invite the patient to re-attend the surgery to learn about the test result. During this consultation, the GP will refer the patient to the HIV Liaison Nurse at Homerton Hospital. At Homerton Hospital, patients will be asked by GCP-trained clinicians for written informed consent for divulgence of anonymised data from their medical records. These anonymised data include CD4 count and viral load at the time of diagnosis; as well as mode of diagnosis, patient ethnicity, age, gender and Soundex code. If a confirmed HIV patient chooses to take up their specialist care at a GUM clinic other than the Homerton Department of Sexual Health, Dr Sarah Creighton from Homerton Hospital will chase up the required patient specific data for the study. For details on how GPs can obtain written informed consent, please see section 6.4.1.

The GP may wish to inform the HIV Liaison nurse about a reactive test prior to receiving the confirmatory test result.

6.6.5 A Reactive rapid test but a Negative confirmatory result (discrepant result)

A discrepant result is one in which the result from the INSTI HIV-1/2 Rapid Antibody test is reactive and the subsequent laboratory result proves negative.

6.6.5.1 The GP has responsibility for patients with discrepant results
If the confirmatory result from Virology is negative, responsibility for patient care lies with the General Practitioner having been notified by Homerton Pathology.

6.6.5.2 Patient follow-up at the GP surgery
If the result is known prior to the patient's follow up appointment, the General Practitioner should inform the patient at the earliest opportunity by telephone and the patient should be informed that it is likely that the INSTI HIV-1/2 Rapid Antibody test was a false reactive result. The patient should be invited to attend the surgery to talk about possible symptoms of

HIV sero-conversion, the use of barrier methods until their final HIV status is confirmed and to discuss the need for a referral to Homerton Hospital for exclusion of an early HIV infection.

If the patient prefers to be retested at the surgery, the GP sends the second confirmatory blood test to Homerton Pathology.

6.6.5.3 Patient follow-up at Homerton Hospital
If the patient is referred to Homerton, a second confirmatory test and an EDTA sample for HIV pro-viral DNA test will be obtained. This will determine whether the patient is sero-converting or truly negative. The HIV Liaison Nurse or a deputy should make a further appointment to see the patient in 10 working days to inform them of the result of the HIV antibody +/- the pro-viral DNA test/s.

The HIV Liaison Nurse sends the second confirmatory blood test to Homerton Pathology.

6.6.5.4 Quality control check
The HIV Liaison Nurse informs the Practice HIV Lead Nurse and the RHIVA 2 team about any discrepant result. The RHIVA 2 team then arranges for a quality control check to be done as soon as possible, using the same batch number as the false reactive test and the internal quality control sera. Once this has been done, the RHIVA 2 team confirms the outcome by e-mail to the Practice GP, the Practice HIV Lead Nurse, and the BLT Virology POCT Lead. The outcome of this test is then recorded appropriately on the INSTI HIV1 & 2 Antibody Internal Quality Control Result Sheet by the person performing the quality control check. If a quality check has been done on the same day as the false reactive is received, the quality check need not be repeated. If a false reactive quality check is done, this can replace the regular quality control check if it is due**.**

6.6.6   Repeat testing following risk exposure

The British Association for Sexual Health and HIV (BASHH, 2010) gives the following advice on repeat testing following risk exposure: Patients attending for HIV testing who identify a specific risk occurring more that 4 weeks previously, should not be made to wait 3 months (12 weeks) before HIV testing. They should be offered a 4th generation laboratory HIV test (available at Homerton Hospital) and advised that a negative result at 4 weeks post exposure is very reassuring/highly likely to exclude HIV infection. An additional HIV test should be offered to all persons at 3 months (12 weeks) to definitively exclude HIV infection. Patients at lower risk may opt to wait until 3 months to avoid the need for HIV testing twice.

Flow diagram for RHIVA intervention GP surgeries

```
┌──────────────────┐     ┌──────────────┐     ┌──────────────┐   Reactive,        ┌──────────────┐
│   Registration:  │     │ New Patient  │     │              │   Indeterminate    │  Immediate GP│
│ Info sheet and   │ ──▶ │ Health Check │ ──▶ │Rapid HIV test│   or 2x Invalid    │ consultation │
│ valid implied    │     │              │     │              │ ─────────────────▶ │              │
│     consent      │     │              │     │              │                    │              │
└──────────────────┘     └──────────────┘     └──────────────┘                    └──────────────┘
         │                      │                    │                                    │
         ▼                      ▼                    ▼                                    ▼
    Decline NPHC           Decline test        Non-Reactive
```

```
┌───────────────────────────────────────┐        ┌───────────────────────────────────────┐
│ Homerton HIV Liaison Nurse calls GP to │        │  Reactive/Indeterminate rapid test     │
│ confirm case and GCP-trained Homerton  │ ◀───── │                  or                     │
│ clinician obtains written informed     │        │  Positive confirmatory HIV 1&2 antibody │
│              consent                   │        │                test                     │
└───────────────────────────────────────┘        └───────────────────────────────────────┘
                    │                                              │
                    ▼                                              ▼
┌───────────────────────────────────────┐        ┌───────────────────────────────────────┐
│ Homerton HIV Research Nurse informs    │        │    Homerton Pathology calls GP         │
│ research team using anonymised data    │        │          to confirm case               │
└───────────────────────────────────────┘        └───────────────────────────────────────┘
```

6.7   Follow-up procedures

Any patient with a reactive, indeterminate or 2x invalid HIV rapid test will be seen by the GP immediately for information; a further test and specialist follow up if indicated (see Flow diagram for RHIVA intervention GP surgeries). The HIV liaison nurse, a member of the clinical management team at the Department of Sexual Health at Homerton Hospital, will liaise with both GP surgeries and Homerton Pathology at least fortnightly to minimise the loss of patients followed up in specialist care. If a patient fails to attend specialist follow up, the HIV research nurse will make appropriate attempts to contact the patient.

6.8   Laboratory assessments

6.8.1   Rapid HIV test

The rapid HIV test will be performed using the INSTI HIV-1/HIV-2 Rapid Antibody Test (bioLytical Laboratories, Canada) according to the manufacturer's instructions. The INSTI test device has CE-marking and detects antibodies to the Human Immunodeficiency Virus Type 1 and Type 2. Briefly, 50 microlitres of blood drawn from a finger prick using a pipette is mixed with a Sample Diluent and poured onto a Sample Membrane. Signals are visualised by applying a Colour Developer onto the membrane and by de-staining the background using a Clarifying Solution. Results are available in 60 seconds. A single dot (control) on the Sample Membrane indicates a negative result; an additional blue test dot suggests HIV infection, and any other staining pattern including the absence of any signal indicates an invalid result. For further information, please see http://www.biolytical.com/ourtechnology.html.

6.8.2 CD4 counts and viral parameters including HIV viral load, clade and genotype of the virus

Laboratory assessments of immunological and viral endpoints specified in section 8.1.2.1 of this protocol will be performed according to approved standard operating procedures.

6.9 Withdrawal

6.9.1 Withdrawal of subjects

Subjects will be withdrawn from the study if they withdraw consent to participate.

6.9.1.1 When and how to withdraw subjects

Subjects will not be asked to specify reasons for withdrawal from the study. Patients who have given consent, but lose capacity to consent during the study will be withdrawn from the study. However, identifiable data or blood already collected would be retained and used in the study. No further data would be collected in relation to the patient.

6.9.1.2 Data collection and follow-up for withdrawn subjects

The HIV research nurse will make appropriate attempts to contact any withdrawn HIV positive subject who fails to attend HIV specialist follow up. Only non-identifiable patient information collected with consent will be used and retained in the study.

6.9.2 Withdrawal of surgeries

Surgeries will be withdrawn from the study if they withdraw consent to participate. A note of the conversation with the practice manager or the lead GP stating the date and reason for withdrawal needs to be made and signed by the CI for filing in the Trial Master File. Any unused INSTI test kits left at the surgery and the GP folder including the records from the Quality Assurance program need to be removed from the surgery premises once the RHIVA 2 team has been notified about the study withdrawal by the surgery.

6.9.2 Data Handling and Record Data collection and follow-up for withdrawn subjects

The HIV research nurse will make appropriate attempts to contact any withdrawn HIV positive subject who fails to attend HIV specialist follow up. Only non-identifiable patient information collected with consent will be used and retained in the study.

7 Data Handling and Record Keeping

7.1 Confidentiality

Subjects' personal data will remain confidential, and will be handled, processed, stored and destroyed according to the terms of the Data Protection Act 1998.

7.2   Study documents

Study documentation will be maintained in a Trial Master File, to be stored at the Centre for Health Sciences, Barts and The London Medical School.

7.3   Case report forms

Case Report Forms will include the following data: anonymised patient study identifier, participants' demographic details (including age, gender, ethnicity and Soundex code), checklist of eligibility criteria, mode of diagnosis; and results from CD4 counts and viral parameters such as viral load, clade and genotype of the virus.

7.4   Record retention and archiving

Trial records will be retained for 20 years. Records will be stored in the Centre for Health Sciences, Barts and The London Medical School while the study is being conducted, after which they will be transferred to the QMUL archive.

7.5   Compliance

The CI and the Principal Investigator will ensure that this study is conducted in accordance with the latest version of the "Declaration of Helsinki" (http://www.wma.net/e/policy/b3.htm). The study will adhere to the principles outlined in the Guidelines for Good Clinical Practice.

7.6   Definition of the end of the study

The end of the study will be defined as the date when the patient recruitment phase has been completed defined as sufficient patient accrual to meet the study power requirements [expected to be 24 months] (see section 8.2.1) and the HIV research nurse has checked that all HIV positive patients have been referred to specialist care.

8   Clinical Governance Issues

8.1   Ethical considerations

The main ethical considerations arising from the design and conduct of this trial are as follows:

8.1.1   Rationale for research

We have thoroughly reviewed existing literature and consulted with a wide range of professional and non-professional stakeholders for the planning and design of this study. HIV continues to spread in the UK despite enormous public efforts to curb the epidemic.

Current specialist consensus states that HIV testing should be expanded into Primary Care, particularly in areas such as Hackney where the disease is highly endemic.

8.1.2   Design of research

Ethical research must employ the most appropriate design in order to answer the research question. When investigating effectiveness of a clinical intervention at the GP practice level, a cluster randomised, controlled trial is the gold standard methodology.

8.1.3   Minimisation of inconvenience, discomfort and risk for participants

During the pre−test discussion, patients may feel uncomfortable talking about past risk exposures and their sex life. They may also find it inappropriate to discuss issues like these in a Primary Care setting.

Patients may feel anxious about HIV testing, but we have shown that most patients welcomed rapid HIV testing if offered as part of the routine GP registration process (Prost et al., 2009).

Patients will be informed that they may experience minor pain during the finger prick HIV test. The rapid HIV test will be carried out at the beginning of a consultation and results will be available immediately to alleviate anxiety.

Patients with 2 consecutive invalid rapid test results will learn that the test cannot be interpreted and that they are not more likely to have HIV. This group of patients will be offered by their GP a standard HIV test from venous blood to confirm their HIV status. Patients with a reactive rapid HIV test will be seen by their GP immediately for further information, a confirmatory HIV test and specialist referral.

Most patients with an HIV diagnosis will feel emotionally distressed and make changes to their lifestyles. However, all patients will be given sufficient time to consider whether they wish to participate in the study and at no time they will be pressurised to undergo an HIV test. They will also be made aware that neither refusal to participate nor a HIV diagnosis will have an effect on the quality of care they receive from their health care provider. All health care professionals including GPs, nurses and health care assistants involved in patient care will be instructed in providing support for patients with a positive diagnosis.

Finally, patients will be made aware of the fact that having an HIV test will not itself affect future life insurance applications, but that an HIV infection would have to be declared on such applications.

8.1.4   Recruitment procedure

The study is designed in a way that allows for broad patient recruitment. Firstly, anyone aged 16 years and older registering with a GP will be invited to participate. Secondly, patient information sheets will be translated into the most commonly locally spoken non-English languages including French, Turkish and Vietnamese. Finally, patients who are unable to undertake the pre-test discussion in English will be invited to use a suitable interpreter.

8.1.5   Confidentiality

We will ensure that participants' personal data remain confidential. Our procedures for handling, processing, storage and destruction of data are compliant with the Data Protection Act 1998.

8.1.6 Data handling and record keeping

Case report forms will be anonymised and held in locked filing cabinets in the Centre for Health Sciences, Barts and The London School of Medicine and Dentistry. Only trial staff will have access to these. Trial staff will enter all non-identifiable patient data from case report forms into an electronic database held on a password protected internal hard drive on stand-alone computer, linked to an ID code, which will be unique for each trial participant. A back-up copy will be held on a password-protected file on the internal hard drive of a stand-alone desk-top computer by Sandy Smith, data manager. Both stand-alone computers will be kept in a locked office in the Centre for Health Sciences, Barts and The London School of Medicine and Dentistry. Only practice GP staff and the HIV liaison nurse will have access to identifiable patient data. The other members of the research team will not have access to patient identifiable information. Representatives of the sponsor, participating NHS Trusts or regulatory authorities will be the only people with potential access to view study data that could be linked to identifiable patient information.

8.2 Audit and inspection

Trial documentation will be made available to auditors and inspectors representing the sponsor and the regulatory authorities. Representatives of the Pragmatic Clinical Trials Unit at QMUL will perform regular audits on document filing, standard operating procedures and consenting on the RHIVA 2 trial.

8.3 Reporting of serious breaches in GCP or trial protocol

Serious breaches in Good Clinical Practice (GCP) and serious breaches of the trial protocol will be reported to the sponsor.

8.4 Quality assurance

Data quality will be audited according to GCP guidelines, and a trail will be maintained of any change or correction to the case report form or the electronic database. The sponsor will have direct access to all trial-related sites, source data and reports in order to ensure that the trial is conducted, and data are generated, recorded and reported in compliance with the protocol and with GCP.
In addition, quality assurance we will be achieved by 1) using a rapid HIV test device (INSTI HIV1&2 Rapid Antibody Kit, bioLytical Laboratories, Canada) that has CE-marking and has been shown to be highly accurate and 2) by setting up a quality assurance scheme with the Department of Virology at Barts and The London NHS trust.

8.5 Data monitoring committee

A data monitoring committee (DMC) will be established for the trial. The chair of the DMC will keep a record of DMC communications and activities. The central responsibilities of this DMC will be to make recommendations to the sponsor and the Trial Steering Committee on further conduct of this trial, based on results of the monitoring procedures described below. Such recommendations could include continuing or terminating the trial, or modifying its protocol. Any such modifications should not violate the concepts behind the original study protocol. If changes in the study conduct are recommended by the DMC, sufficient

information should be provided to allow the sponsor and the CI to decide whether and how to implement them. The implementation of any DMC recommendation is the responsibility of the sponsor and CI who are also free to neglect (in whole or in part) any recommendations of this DMC. The sponsor and the investigators bear the final responsibility for the conduct of the trial. This responsibility cannot be transferred to the DMC.

8.5.1   Monitoring procedures

Six months following the start date of the trial, the trial statistician will perform an interim analysis using the statistical methods specified in the protocol to analyse study outcome measures and provide the DMC with data and analysis for checking. The DMC will review accumulating data in an un-blinded fashion in order to monitor the study conduct. The accumulating data will be available to the DMC as well as to the study statistician and the CI. Interim data and analyses by trial arm (and the deliberations of the DMC) should be available only to those present in the closed session i.e. only members of the DMC as agreed by the DMC. However, the DMC can decide whether to invite the study statistician and/or the CI to take part in the closed session. However, the DMC may in the closed session share confidential information with the study statistician if they consider it necessary (see Section 7, DMC charter). In view of the low recruitment at the beginning of the trial and a change in the primary outcome measure, the study statistician will perform an additional interim analysis 18 months after the start date of the trial. If a significant difference between intervention and control groups for the primary outcome is detected at interim analysis (P-value <0.001), the DMC may recommend that the trial be stopped early.

8.5.2   Declaration of possible conflicts of interest of DMC members

The members of the DMC have no involvements that might raise the question of bias in their reports to the sponsor or investigators in this study. Specifically, they have no financial interest in the outcome of this study, and they will not be authors on publications arising from this study.

8.5.3   Frequency and format of DMC meetings

It is anticipated that the DMC will meet up once before the start or during the early stages of the trial; and that any future communication can be conducted by email and telephone call, rendering any additional physical meeting between members, investigators and representatives of the sponsor unnecessary. The DMC will check the effectiveness analysis six months after beginning of the study.

8.5.4   Communication procedures

The DMC will communicate results of the assessment of the effectiveness analysis by email to the Trial Steering Committee.

8.5.5   Responsibilities, timelines and methodological aspects

Members of the DMC will be jointly responsible for checking the interim effectiveness analysis. It is anticipated that the results of these checks will be available to the Trial Steering Committee within three weeks of submitting data to the DMC.

8.5.6 Documentation of the DMC activities

The DMC will not share the results of the assessment of the interim effectiveness analysis with the CI unless the decision has been made to stop the trial. Any safety issues, recommendations to amend the protocol and suggestions with regard to patient recruitment arising in the interim analysis however will be shared with the CI.

9   Trial Steering Committee

The TSC will monitor and supervise the progress of the trial towards its interim and overall objectives. The TSC will also review at regular intervals relevant information from other sources and consider recommendations to the Data Monitoring Committee. The TSC members will nominate a chairmen and meet at the beginning of the trial and then annually. The CI will organise the TSC meetings, which may be attended by representatives of the investigators. The TSC will also be invited to read and comment on any draft publications that report outcome measures and/ or details of the DMC.

10 Statistics

10.1 Endpoints

10.1.1 Primary endpoint

The primary outcome measure for this trial is:
Mean CD4 count of newly diagnosed HIV patients in general practice after square root transformation. Using the Normal distribution, the percentage of patients who present with advanced HIV infection as measured by CD4 count <200 cells per cubic millimetre of blood will be estimated. A newly diagnosed HIV patient in general practice is defined as a person, who is unaware of their HIV status at the time of testing but who tests either HIV 1 or HIV 2 antibody positive following a GP request for HIV confirmatory testing at Homerton Pathology. All patients including antenatal patients whose tests are requested from general practice will be included. Patients of unknown HIV status in whom the GP has not performed HIV testing prior to referral and who are referred by their GP to secondary care at Homerton Hospital either for HIV testing or for further management of a suspected HIV-related illness are excluded from the primary outcome measure.

10.1.2 Secondary endpoints

10.1.2.1   Clinical outcomes
• Numbers of newly diagnosed patients in general practice
• Proportion of newly diagnosed patients in general practice
• Percentage of patients that qualify for the initiation of anti-retroviral treatment, defined as CD4 count lower than 350 cells per microlitre of blood, as estimated from mean CD4 count.
10.1.2.2   Viral outcomes
• Numbers of HIV cases with a high risk of progression to AIDS, defined as a viral load of higher than 200,000 HIV-1 RNA copies per million peripheral mononuclear cells as a predictor of disease progression

- Clade and genotype of the virus at the time of diagnosis as predictors of disease progression

10.1.2.3   Health service use

- Numbers of standard HIV tests done opportunistically
- Numbers of rapid HIV tests done in new patient health checks and at first patient consultations.

10.1.2.4   Economic outcomes

- Cost−effectiveness of the intervention compared to standard of care.

10.1.3 Study definitions

Early HIV disease in a subject will be defined as that subject having a CD4 count of 200 or more cells per cubic millimetre at the time of diagnosis.

10.2 Statistical considerations

10.2.1 Sample size

The analysis will compare mean CD4 count in the intervention and control groups. To aid interpretation this will be converted into the estimated numbers less than 200 and less than 350 using the normal distribution, based on the square root of the CD4 count.

Data were obtained from the Department of Sexual Health at Homerton Hospital for the period 1st April 2009 to 31st March 2010. The mean CD4 count in 18 cases was 300 cells/ml (SD = 200). On the transformed scale, the mean was 17 and the SD 6. The intra-cluster correlation coefficient (ICC) is assumed to be 0.05, a value typical in GP settings. We assume that 20 practices will be randomised to screening and 20 to control. We also assume that screening practices will identify twice as many cases as control practices. Allowance is also made, following the method of Eldridge and Kerry (2006) for practices to recruit variable numbers of patients and allowing for some practices to fail identifying any cases (Kerry and Martin Bland, 2001; Eldridge et al., 2006). Power is 80% at the 5% significance level.

Allowing for clustering, we would need to identify 48 new cases in screening practices and 23 in control practices in order to be able to detect an increase in the mean CD4 count from 306 to 470, which corresponds to a reduction in the proportion of late presenters from 30% to 10%. This should be feasible if the trial continues until May 2012.

10.2.2 Cluster randomisation

Practice will be randomised using a computer generated minimisation, by: 1) practice list size {≤ 5000; > 5000 - < 7000; ≥ 7000} 2) practice deprivation {IMD Score < 47; ≥ 47} and 3) HIV male testing rate per surgery {< 7; ≥ 7}.

10.2.3 Planned patient recruitment rate

All patients aged 16 years and older registering with a GP surgery during the study period will be invited to participate.

10.3 Statistical analysis

Statistical analysis will be performed with the assistance of a suitably qualified statistician.

10.4 Frequency of analysis

An effectiveness analyses will be conducted 6 months after the start of the recruitment period and on termination of the trial. A plan of statistical analysis will be drawn up and agreed with TSC prior to closure of the dataset. In view of the low recruitment at the beginning of the trial and the change in the primary outcome measure, an additional interim analysis will be conducted 18 months after the start date of the trial.

10.5 Analysis of participants' baseline characteristics

Following data entry and data cleaning, baseline characteristics including age, sex, ethnic group and Soundex code and viral parameters including HIV viral load, clade and genotype of the virus will be descriptively compared between intervention and control groups.

10.6 Analysis of study endpoints

The CD4 count of all patients registered with the practice in the period from randomisation of the practice to the end of the trial will be compared in the intervention and control groups using regression analysis to adjust for stratification factors and clustering. Data will be transformed using a square root transformation prior to analysis. Difference in mean CD4 count and 95% confidence interval will be presented. Proportions of patients less than 200 and less than 350 in each group will be estimated using the normal distribution. A secondary analysis will also adjust for CD4 count per practice in the period from 12 months prior to study start to randomisation of the practice, if there are sufficient cases diagnosed.

The primary analysis will be by intention to treat. A secondary per protocol analysis will be carried out, comprising practices that initiated regular screening for HIV and excluding those that did not.

10.7 Health economic analysis

The costs adding HIV screening onto routine health checks within GP practices in Hackney will be estimated using established costing methods (Kumaranayake et al., 2000; Drummond et al., 2005). The incremental financial and economic costs will be collected from the provider's perspective for the one year of the intervention. The financial costs represent the actual expenditures on goods and services used in the intervention. Economic costs represent the value of all resources used. This includes the costs of donated goods and services. The provider is considered the PCT. Start-up costs, including training, will be collected and treated as a capital cost. Cost data will be collated from project accounts, observations of intervention implementation (not during post-test discussion), interviews with medical staff implementing HIV testing in both intervention and control clinics and a self-complete time allocation questionnaire for these medical staff. Total costs per clinic in each arm of the intervention will be estimated as will the cost per person tested, cost per positive case identified, cost per early case detected.

10.8 Interim analysis

An effectiveness analysis will be conducted six months after the beginning of the recruitment phase. In view of the low the initial low recruitment and the change in the primary outcome measure, an additional effectiveness analysis will be conducted 18 months after the beginning after the start date of the trial. This will be undertaken blind to allocation of practices and will include the following outcomes; CD4 count, percentage of HIV positive patients diagnosed in primary care, number of standard HIV tests performed opportunistically.

11 Study Finances

11.1 Funding source

This Trial is funded by the NHS City and Hackney, the Department of Health and Central and East London Local Research Network (CLRN).

11.2 Subject expenses and payments

Subjects will not receive any payments for participating in the study.

12 Sponsorship and Indemnity

Queen Mary, University of London will sponsor this trial. The Joint Research Office for Queen Mary, University of London will arrange for suitable indemnity for negligent harm arising as a result of participation in this study to be in place.

13 Publication Policy

Any manuscript reporting trial findings will be prepared according to CONSORT guidelines and submitted to peer-reviewed biomedical journals according to ICMJE Uniform Requirements. Authorship will be based on individuals' contribution to study design, conduct, analysis, drafting/revision of manuscript and final approval of the version to be published. Authorship will not necessarily be restricted to individuals named on this protocol; neither is authorship guaranteed to any individual named on this protocol. Contributors who do not meet authorship criteria will be listed in 'Acknowledgements'.

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15 Attachments

Attachment 1:

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NHS City and Hackney Teaching Primary Care Trust
Information about a Research Project:
Can rapid HIV testing improve the diagnosis of HIV infection in general practice?

</div>

Part 1:

Your practice is taking part in a research study and we would like to invite you to take part. Before you decide we would like you to understand why the research is being done and what it would involve for you.

- ***What is the purpose of the study?***
The study compares shorter and slightly longer health checks. The longer health check includes a brief discussion about HIV and an offer of a HIV test that gives an immediate result. We want to find out whether surgeries offering this rapid test detect more people with the infection.

- ***Why have I been invited?***
All those aged 16 years and older joining a GP practice are invited to take part.

- ***Do I have to take part?***
It is up to you to decide whether to join the study. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

- ***What is involved in taking part?***
When you join the surgery you may be offered a health check. Which check your practice offers has been decided by chance. **Your practice is offering the slightly longer one that includes a brief discussion about HIV and an offer of the rapid test.** This involves taking a small amount of blood from a finger prick. You will get your result immediately.

The possible test results are: non-reactive, reactive, and invalid. What do these mean?
1. Non-reactive: Most people will have a non-reactive test result and will be reassured they do not have HIV. If you have had a non-reactive test and have had unprotected sex or have shared needles within the previous three months, you will be advised to repeat the HIV test in three months time to ensure that you have not acquired the infection in that so-called 'window' period. **2. Reactive:** A small minority of people will have this test result and if you do, you will be seen by your GP and given more information. You will have another blood sample taken (approximately one teaspoonful) taken from a vein in the arm near the elbow joint so that the test can be repeated in a laboratory. You will be given full support and time with a GP to discuss what this means, and you will be given an appointment with a specialist. If the laboratory test confirms that you have HIV infection, your GP will ask you to agree (in writing) to give access to selected aspects of your medical records to record research data.
3. Invalid: This means that the test result cannot be interpreted and it does not suggest that you have HIV. A GP will see you immediately to offer you more information and a standard HIV test from venous blood.

- ***What will I have to do?***

We only ask you to read this information sheet before attending the new patient health check, and to decide whether you wish to have a test.

- ***What are the alternatives for diagnosis?***

The standard HIV test using venous blood taken from a vein in your arm is also available at the surgery. The result of this test will be available within one week.

- ***Are there any disadvantages, risks or dangers for me if I take part?***

There may be minor discomfort due to the finger prick test. Having an HIV test will not itself affect future life insurance applications. However, HIV infection would have to be declared on such applications.

- ***Are there any benefits for me if I take part?***

Yes. You will know whether or not you have HIV. The few diagnosed with the infection will receive full support and learn how to protect partners and children.

- ***What if there is a problem?***

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

- ***Will my taking part in the study be kept confidential?***

Yes. We will follow ethical and legal practice and all information about you will be handled in total confidence. The details are included in Part 2.

Part 2:

- ***What if new relevant new information becomes available?***

If the study is stopped early for any reason, we will tell you and give appropriate advice.

- ***What will happen if I don't want to carry on with the study?***

We will need to use data collected up to your withdrawal. Patients needing a blood test because of a rapid, or invalid HIV test, can ask for any stored blood samples that can still be identified as theirs to be destroyed if they wish.

- **What would happen if, once given informed consent, I lose capacity to consent during the study?**

You would be withdrawn from the study. Identifiable data or blood already collected would be retained and used in the study. No further data would be collected in relation to you.

- ***What happens if there is a problem?***

We would not expect you to suffer any harm or injury because of your participation in this study. If you are harmed by taking part in this study, there is no special compensation arrangement. If you are harmed due to someone's negligence, then you may have grounds for legal action, but you may have to pay your legal costs. Regardless of this, if you wish to complain or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms should be available to you.

Please contact Patient Advisory Liaison Service (PALS) if you have any concerns regarding the care you have received, or as an initial point of contact if you have a complaint. Please telephone 020 7377 6335, minicom 020 7943 1350, or email

pals@bartsandthelondon.nhs.uk, you can also visit PALS by asking at any hospital reception.

If you want to find out more about this study, please leave a message on our dedicated phone line (Telephone: 0207 882 7084) saying what language you speak and when is a good time for you to talk. The research team will then arrange for a fluent speaker to call you.

- ***Will my taking part in this research be kept confidential?***
All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the surgery will have your name and address removed so that you cannot be recognised (if it is applicable to your research).

- ***What will happen to any samples I give?***
Finger prick blood applied onto the rapid HIV test device will be disposed of immediately. Venous blood taken from the few patients with a reactive, or invalid rapid test will be sent to established clinical laboratories and disposed of according to standard laboratory procedures.

- ***Will any genetic tests be done on humans?***
No.

- ***What will happen to the results of the study?***
Results of the study will be published in scientific journals and presented at conferences. Patients will be informed about the results by a leaflet distributed in GP surgeries.

- ***Who is organising and funding the research?***
The study is organised by Barts and The London School of Medicine and Dentistry and funded by the City and Hackney Teaching Primary Care Trust.

Attachment 2

NHS CITY AND HACKNEY TEACHING PRIMARY CARE TRUST
Information about a Research Project:
Can rapid HIV testing improve the diagnosis of HIV infection in general practice?

Part 1:

Your practice is taking part in a research study and we would like to invite you to take part too. Before you decide we would like you to understand why the research is being done and what it would involve for you.

- ***What is the purpose of the study?***
The study compares shorter and slightly longer health checks. The longer health check includes a brief discussion about HIV and an offer of a HIV test that gives an immediate result. We want to find out whether surgeries offering this rapid test detect more people with the infection.

- ***Why have I been invited?***
All those aged 16 years and older joining a GP practice are invited to take part.

- *Do I have to take part?*

It is up to you to decide whether to join the study. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

- *What is involved in taking part?*

When you join the surgery you may be offered a health check. Which check your practice offers has been decided by chance. **Your practice is providing the shorter, standard check that will not include the offer of a rapid HIV test.**

- *What will I have to do?*

We only ask you to read the information sheet before attending the new patient health check, and to decide whether you wish to take part.

- *What are the alternatives for diagnosis?*

The standard HIV test using venous blood taken from a vein in your arm is available at the surgery. The result of this test is available within one week.

- *Are there any disadvantages, risks or dangers for me if I take part?*

No.

- *Are there any benefits for me if I take part?*

Yes, you will be offered a routine health check.

- *What if there is a problem?*

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

- *Will my taking part in the study be kept confidential?*

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

Part 2:

- *What if new relevant new information becomes available?*

If the study is stopped early for any reason, we will tell you and give appropriate advice.

- *What will happen if I don't want to carry on with the study?*

We will need to use data collected up to your withdrawal. Patients needing a blood test as part of the study can ask for any stored blood samples that can still be identified as theirs to be destroyed if they wish.

- *What would happen if, once given informed consent, I lose capacity to consent during the study?*

You would be withdrawn from the study. Identifiable data or blood already collected would be retained and used in the study. No further data would be collected in relation to you.

- *What happens if there is a problem?*

We would not expect you to suffer any harm or injury because of your participation in this study. If you are harmed by taking part in this study, there is no special compensation arrangement. If you are harmed due to someone's negligence, then you may have grounds for legal action, but you may have to pay your legal costs. Regardless of this, if you wish to complain or have any concerns about any aspect of the way you have been approached or

treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Please contact Patient Advisory Liaison Service (PALS) if you have any concerns regarding the care you have received, or as an initial point of contact if you have a complaint. Please telephone 020 7377 6335, minicom 020 7943 1350, or email **pals@bartsandthelondon.nhs.uk**, you can also visit PALS by asking at any hospital reception.

If you want to find out more about this study, please leave a message on our dedicated phone line (Telephone: 0207 882 7084) saying what language you speak and when is a good time for you to talk. The research team will then arrange for a fluent speaker to call you.

- ***Will my taking part in this research be kept confidential?***
All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the surgery will have your name and address removed so that you cannot be recognised (if it is applicable to your research).

- ***What will happen to any samples I give?***
Venous blood taken as part of the study will be sent to established clinical laboratories and disposed of according to standard laboratory procedures.

- ***Will any genetic tests be done on humans?***
No.

- ***What will happen to the results of the research study?***
Results of the study will be published in scientific journals and presented at conferences. Patients will be informed about the results by a leaflet in GP surgeries.

- ***Who is organising and funding the research?***
The study is organised by Barts and The London School of Medicine and Dentistry and funded by the City and Hackney Teaching Primary Care Trust.

Attachment 3

Protocol Signature Page

Chief Investigator: Dr Werner Leber

Signed

Principal Investigator: Professor Chris Griffiths

Signed

Co-Investigator: Professor Jane Anderson

Signed

Co-Investigator: Dr Jose Figueroa

Signed

Research Assistant: Ms Heather McMullen

Signed

Consultant Virologist: Dr Ines Ushiro-Lumb

Signed

Laboratory Manager: Ms Maria Sampson

Signed

Consultant Clinical Biochemist: Mr Peter Timms

Signed

Laboratory Service Compliance Director: Mr Cyril Taylor

Signed

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Prost, A., Griffiths, C., Anderson, J., Wight, D., Hart, G., 2009. Feasibility and acceptability of
    offering rapid HIV tests to patients registering with primary care in London (UK): a
    pilot study. Sex Transm Infect.

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	**Page 1**
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	**Page 2**
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	**Page 3**
	2b	Specific objectives or hypotheses	Whether objectives pertain to the cluster level, the individual participant level or both	**Page 3**
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	**Page 3**
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		**Page 6**
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	**Page 3**
	4b	Settings and locations where the data were collected		**Pages 5, 6**
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	**Page 3, 4**
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and	Whether outcome measures pertain to the cluster level, the individual participant level or both	**Page 6**

		when they were assessed		
	6b	Any changes to trial outcomes after the trial commenced, with reasons		**Page 6**
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	**Page 7**
	7b	When applicable, explanation of any interim analyses and stopping guidelines		**Page 6, but results of interim analysis not specified**
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		**Page 4**
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	**Page 4**
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	**Page 4**
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	**Pages 3, 4**
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete	**Page 4**

			enumeration, random sampling)	
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	**Page 4**
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		**Pages 6, 10**
	11b	If relevant, description of the similarity of interventions		**NA**
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	**Page 7**
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		**Page 7**
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	**Please see Figure 1**
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	**Please see Figure 1. For loss or practices, see pages 7 and 8**
Recruitment	14a	Dates defining the periods of recruitment and follow-up		**Page 8**
	14b	Why the trial ended or was stopped		**Page 8**

Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	**Tables 1a and 1b**
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	**Page 7**
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	**Pages 8 and 9. For ICC, see page 7.**
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		**NA**
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		**Page 9**
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		**NA**
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		**Pages 9, 10**
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	**Page 9**
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		**Page 9, 10**
Other information				

Registration	23	Registration number and name of trial registry	**Page 13**
Protocol	24	Where the full trial protocol can be accessed, if available	**The trial protocol has been submitted with the manuscript**
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	**Page 2, 7**

* Note: page numbers optional depending on journal requirements

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised Yes**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	**Yes**
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters Yes**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both Yes**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both Yes**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions Yes**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	**NA**
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group Yes**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group Yes**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome Yes both**
Harms	Important adverse events or side effects	**NA**
Conclusions	General interpretation of the results	**Yes**
Trial registration	Registration number and name of trial register	**Yes**
Funding	Source of funding	**Yes**

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[1] Relevant to Conference Abstracts

REFERENCES

1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

Analysis Plan RHIVA

RHIVA-2

Statistical Analysis Plan

Version 2.0
21/05/2013

Approved by TMG: Chris Griffiths

Signature (Chair): _____Date: ___/___/_____

Approved by Trial statistician; Sally Kerry

Signature: _____ Date: ___/___/_____

Reviewed by DMC statistician: Karen Smith

Signature: _____ *Karen L. Smith* _____ Date:

Trial Statisticians: Sally Kerry, Nadine Marlin.

This document was created based on the Mental Health & Neuroscience Clinical Trials Unit (MH&N CTU) Analysis Strategy template (version 1.5; 13/02/2008) based on an earlier version developed by Rebecca Walwyn and Sally Lee.

1   INTRODUCTION

1.1   Purpose of statistical analysis plan

The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported within the principal paper(s) of the RHIVA-2 trial. Subsequent papers of a more exploratory nature (including those involving baseline data only) will not be bound by this strategy but will be expected to follow the broad principles laid down in it. Any exploratory, post-hoc or unplanned analyses will be clearly identified in the respective study analysis report.

The structure and content of this document provides sufficient detail to meet the requirements identified by the International Conference on Harmonisation (ICH) and the PCTU SOP (PCTU/07).

   The following were reviewed in preparation for writing this document:
   Protocol version 5.0 dated 4th May 2012
   DMC report dated 27th Jan 2012
   CONSORT guidelines for the reporting of randomised trials, including extensions to cluster-randomised trials and trials of non-pharmacological treatments

1.2   Members of the writing committee

Sally Kerry was primarily responsible for (i) writing the Statistical Analysis Strategy with Nadine Marlin responsible for writing the computer code implementing the analysis strategy and implementing the strategy at the point of analysis. A senior statistician within the Pragmatic Clinical Trials Unit (PCTU) will also review and sign off the final analysis strategy. If decisions are required during the course of the analysis they will be discussed with a statistician within the PCTU, independent of the trial.

This document has been developed prior to examination of trial data and will not be implemented prior to final approval.

1.3   Summary

The full analysis plan outlined in this document was developed prior to looking at the final databases, although after preparation of the DMC report for the meeting on the 1st February 2012. The plan covers the analysis required to meet all primary and secondary objectives. In the event of a discrepancy the analyses described in the Statistical Analysis Plan will supersede those outlined in the funding application and the protocol.   `

1.4   Changes from planned analysis in the protocol

   The primary outcome was changed in version 4.0 (3/6/2011) to the average CD4 count in each group, which for presentation purposes will be converted to percentage below 200, and percentage below 350 using the Normal distribution. The original primary outcome was the rate of HIV diagnoses in intervention and control surgeries.

2   <u>STUDY OBJECTIVES AND ENDPOINTS</u>

2.1   Study objectives

To determine whether a targeted intervention with rapid point of care testing in GP surgeries leads to earlier detection of HIV.

2.1.1   <u>Primary objectives</u>

To demonstrate that rapid HIV testing offered in the new patient check or at first consultation, when combined with an education package for healthcare professionals, reduces the proportion of newly diagnosed patients who present with advanced HIV infection An advanced HIV infection is defined as CD4 count lower than 200 cells per cubic millilitre of blood. This is estimated from the mean CD4 count, using a Normal distribution.

2.1.2   <u>Secondary objectives</u>

To demonstrate (1) a reduction in the proportion of new HIV cases that require initiation of HAART, defined as CD4 count less than 350 cells per cubic millilitre of blood (also estimated from the Normal distribution) (2) an increase in the proportion of patients newly diagnosed in general practice (3) an increase in the rate of standard HIV tests performed opportunistically including diagnostic and antenatal testing (4) a reduction in proportion of HIV cases with high risk of progression to AIDS, defined by a viral load of higher than 200,000 copies per million peripheral mononuclear cells and (5) a reduction in financial and economic costs incurred to the PCT

2.1.2   <u>Exploratory objectives</u>

None

2.2   Outcome measures

2.2.1   <u>Primary outcomes</u>

CD4 count of newly diagnosed patients following a GP request for HIV confirmatory testing at Homerton pathology. Square root transformation will be used to normalize data.

2.2.2   <u>Secondary outcomes</u>

Numbers of newly diagnosed patients in general practice
Proportion of newly diagnosed patients in general practice
Percentage of patients that qualify for the initiation of anti-retroviral treatment, defined as CD4 count lower than 350 cells per microlitre of blood, as estimated from mean CD4 count.
Viral load. Log transformation will be used to normalize the data
Number of HIV cases with high risk of progression to AIDS (viral load >200,000).
Numbers of serology tests (i.e. standard HIV tests) done
Numbers of rapid HIV tests done
Numbers of rapid HIV tests declined

2.2.3   <u>Safety outcomes</u>

Not applicable

3   <u>STUDY METHODS</u>

3.1   Overall study design and plan

Target for randomisation: 40 practices
Date of randomization: March 2010
Date of first random allocation: 19/04/2010
Date of last randomisation: 01/06/2011
Trial design: cluster randomised, parallel group
Blinding: practices and researchers are unblinded
Randomised Interventions: intervention Vs usual care
Allocation ratio: 1:1

3.2   Selection of study population

All practices in Hackney were invited to take part.

Patients were eligible for screening if they were 16 years and older, able to undertake pre-test discussion in English or with suitable translator, not known to be HIV positive.
There are two main sources of data; primary care and Homerton University Hospital including the Hospital pathology lab and the Department of Sexual Health (DOSH)

Primary care data
Patient data at was obtained from General Practice records for five different cohorts of patients. For all cohorts practice level summaries were obtained. The first cohorts record the age in categories, gender and ethnicity. The remainder simply record number of patients or number of tests per practice.
Demographic cohorts
1. All adults who were registered patients on 19/April/2010 for demographic characteristics of practices
2. All patients newly registered between 19/April/2010 and 31/August /2012
3. All patients who had at least one INSTI test result (reactive, non-reactive, indeterminate, or invalid) recorded between notification and 31/August 2012.
4. All patients who had at least one INSTI test declined recorded between notification of trial allocation and 31/August 2012.
5. All patients who had at least one serology test result between notification and 31/August/2012

Numbers of patients per practice
6. All patients who had at least one **INSTI** test result recorded between notification and 31/August 2012.
7. All patients who had at least one **REACTIVE INSTI** test result recorded between notification and 31/August 2012.

Number of tests per practice
8. The number of **serology** test results between notification and 31/August/2012

Homerton data
All patients newly diagnosed with HIV by rapid testing, opportunistic testing or antenatal testing from participating practices. This will be individual patient data.

3.3   Method of treatment assignment and randomisation

Practices were allocated to intervention or control using minimization using the following factors
1. HIV testing rate in males April 2009 to October 2009; <7 v >=7 (testing rate is HIV male tests per year / male patients on list)
2. Index of multiple deprivation of practice <47,>=47

3. Practice List Size <5000, 5000-7000, >=7000
Randomisation was carried out using MINIM by Clare Rutterford (Independent PCTU statistician). The first 32 surgeries were allocated at once, the remaining surgeries after practice agreed to take part.

3.4 Treatment masking (Blinding)

Practices agreed to take part prior to allocation.

3.5 Sample size determination

The sample size calculations for the original study protocol were based on detecting a difference in the rates of HIV diagnoses between the control and intervention arms. The minimally important difference was 15 cases per arm per year with an expected control event rate of 21 per year; 80% power and 5% significance.

The event rate was lower than expected and in reviewing the sample size calculations after the January 2011 DMC meeting, it was found the original calculations were not reproducible. Based on the recruitment rate to December 2010 the study could not give adequate power for a sensible minimally important difference. It was decided to base calculations on a measure of early diagnosis rather than numbers of cases.

The analysis will compare mean CD4 count in the intervention and control groups. To aid interpretation this will be converted into the estimated numbers less than 200 and less than 350 using the normal distribution, based on the square root of the CD4 count.

Data were obtained from the Department of Sexual Health (DOSH) at Homerton University Hospital for the period 1st April 2009 to 31st March 2010. The mean CD4 count in 18 cases was 300 cells/ml (SD = 200). On the transformed scale, the mean was 17 and the SD 6. The intra-cluster correlation coefficient (ICC) is assumed to be 0.05, a value typical in GP settings. We assume that 20 practices will be randomised to screening and 20 to control. We also assume that screening practices will identify twice as many cases as control practices. Allowance is also made, following the method of Eldridge and Kerry (2006) for practices to recruit variable numbers of patients and allowing for some practices to fail identifying any cases (Kerry and Martin Bland, 2001; Eldridge et al., 2006). Power is 80% at the 5% significance level.
Allowing for clustering, we would need to identify 48 new cases in screening practices and 23 in control practices in order to be able to detect an increase in the mean CD4 count from 306 to 470, which corresponds to a reduction in the proportion of late presenters from 30% to 10%.

4   DATA COLLECTION

4.1   Baseline

Practice level
List size
HIV testing rate
IMD score
Registrants on 19/04/2010
Proportion patients aged 16-24
Proportion patients aged 25-34
Proportion patients aged 35-49
Proportion patients aged over 50
Proportion of male patients
Proportion of patients who were white
Proportion of patients who were black or black British
Proportion of patients who were Asian or Asian British
Proportion of patients from mixed background

4.2 Follow up

Please list all variables collected during follow up
Data are collected on a number of groups of patients but these are not linked to each other

From EMIS Web:

New registrants in study surgeries between 19th April 2010 and August 2012
Practice level for all practices
    Proportion patients aged 16-24
    Proportion patients aged 25-34
    Proportion patients aged 35-49
    Proportion patients aged over 50
    Proportion of male patients
    Proportion of patients who were white
    Proportion of patients who were black or black British
    Proportion of patients who were Asian or Asian British
    Proportion of patients from mixed background

Patients who have an INSTI test result (reactive, non reactive, invalid, indeterminate)
Practice level for all practices

    Proportion patients aged 16-24
    Proportion patients aged 25-34
    Proportion patients aged 35-49
    Proportion patients aged over 50
    Proportion of male patients
    Proportion of patients who were white
    Proportion of patients who were black or black British
    Proportion of patients who were Asian or Asian British
    Proportion of patients from mixed background

Patients who have had declined an INSTI test
Practice level for all practices

    Proportion patients aged 16-24
    Proportion patients aged 25-34
    Proportion patients aged 35-49
    Proportion patients aged over 50
    Proportion of male patients
    Proportion of patients who were white
    Proportion of patients who were black or black British
    Proportion of patients who were Asian or Asian British
    Proportion of patients from mixed background

Patients who had serology tests
Practice level for all practices

    Proportion patients aged 16-24
    Proportion patients aged 25-34
    Proportion patients aged 35-49
    Proportion patients aged over 50
    Proportion of male patients
    Proportion of patients who were white

Proportion of patients who were black or black British
Proportion of patients who were Asian or Asian British
Proportion of patients from mixed background

Patients who have a INSTI test result (reactive, non reactive, indeterminate, invalid)
Number of patients per practice

Patients who have a REACTIVE INSTI test result
Number of patients per practice

Number of serology test results between notification and 31st August 2012

From Homerton Hospital pathology lab:

HIV patients from Homerton pathology

There will be two sources of data;

The first will contain individual patients records for patients diagnosed in primary care from participating practices

Age
Gender
Ethnicity (White; Black; Asian; Mixed; Other)
Mode of diagnosis (INSTI in new patient; INSTI non-new patient, opportunistic/diagnostic, antenatal)
Route of acquisition (Men who have sex with men; Heterosexual; Mother to child; intravenous drug user; blood products recipient; other; unknown)
CD4 count including date
Viral load including date
Soundex code

The second will contain numbers of patients from participating practices diagnosed during the study period in primary care and via other routes including the DOSH, A&E, inpatient and outpatient clinics and community testing sites.

4.3   Timing of data collection

Baseline practice level data has been collected at the end of the study.
Follow up data from DOSH has been collected twice, namely at the interim analysis in January 2011 and at the end of the study.
Follow up demographic data from EMIS Web for 38 practices and for 2 practices using VISION will be downloaded at the end of the study.
Follow up data of patients who had an INSTI test were collected on the 17th of November 2011 (April 2010 – October 2011), and then once every 1-3 months using data collected prospectively in general practice over the course of the study (November 2011 to August 2012).
Follow up data of patients who declined an INSTI test were collected on the 17th of November 2011 (19 April 2010 – 31 October 2011), and then 1-3 monthly using data collected prospectively in general practice over the course of the study (01 November 2011 to 31 August 2012).
Follow up data of patients who had a serology test result recorded have been collected at the end of the study.

5 GENERAL ISSUES FOR STATISTICAL ANALYSIS

All analyses will be conducted two sided and significance interpreted at the 5% significance level.

5.1 Blinding of the statistical analysis

The statistician analyzing the data is not blind to intervention group.

5.2 Analysis populations

5.2.1 Intent-to-treat population

All practices randomized will be included in the analysis. No practices have withdrawn from data collection. No patients recorded on the practice computer system will be withdrawn.

5.2.2 Available-case population

Not applicable

5.2.3 Per protocol population

There will be no per protocol analysis. In the DMC report dated January 2012 a per protocol analysis excluding all practices who had done less than 50 tests was considered. This was not feasible as there were only 4 practices in this category and no patients from these practices had been referred to DOSH.

5.2.4 Safety population

Not applicable

5.2.5 Other populations

Not applicable

5.3 Database

5.3.1 Description

Excel 2007 was used to transfer the data from EMIS and DOSH to Stata.

5.3.2 Data quality

All reactive, indeterminate and invalid INSTI tests will be followed with the practice up by the research team and any entry errors corrected.

Data from DOSH patients was extracted by one of the HIV consultants (JA) from DOSH hospital records and checked by two GP investigators (CG, WL). Checks are made on accuracy of entered data and completeness and eligibility of patient sample. A randomly selected 20% check was carried out by an independent external monitor (Adrian Martineau).

Once the trial team have completed all data entry and checking, the statistician will merge practice level data with individual patients level data and check any non-matching records. There will be 4 final data files;

1. Patient level data for INSTI tests with minimisation factors
2. Patient level data for HIV serology tests with minimisation factors
3. Practice level data from DOSH with minimisation factors
4. All practice level data

All variables will be tabulated (and cross tabulated where appropriate) and range of values verified. Notes column will be checked on DOSH data to ensure all patients are eligible and known positives

are excluded. Dates will be checked to ensure they are post allocation of the practice and prior to 31st August 2012.

Once any discrepancies have been dealt with the databases will be locked for analysis. This means that the database will be made read-only. If during the analysis unforeseen queries are generated they will be dealt with on a case-by-case basis. Any subsequent changes to the data can be made but will be recorded and reported.

5.4 Analysis software

The analysis will be carried out using Stata version 12.

5.5 Methods for withdrawals, loss to follow-up and missing data

Withdrawals and loss to follow up of patients is not applicable. No practices are lost to follow up. Data may be missing for CD4 counts and viral load but the data is too sparse for multiple imputation methods.

5.6 Method for handling centre effects

Not applicable

5.7 Method for handling minimisation factors

Analysis will be carried out adjusting for minimisation factors

5.8 Method for handling clustering effects

The small number of clusters and units within cluster including a high percentage of singleton clusters suggests using a mixed model approach allowing a random effect for practice. Bell(2008) and Clarke(2007) both describe that the coefficients should be unbiased using this approach whereas the error terms including the confidence intervals will likely be biased. Any potential modeling results will be interpreted with caution.

5.9 Method for selecting other variables that will be adjusted for

None

5.10 Multiple comparisons and multiplicity

Not taken into account. CD4 count is the main outcome measure; there are only three other secondary outcome measures

5.11 Method for handling non-adherence

Not applicable

5.12 Method for handling time-varying interventions

Not applicable

5.13 Method for handling outliers

None

5.14 Derived and computed variables

All derived and computed variables will be documented in the analysis programs.

Ethnicity data from practices will be classified as follows
    White
    Black

Asian
Mixed race
Other

These correspond to the main headings for the data collected from DOSH but EMIS collects data in more detailed form. A classification list is in Appendix 2.

Viral load has a lower limit of 40. Since only a very small proportion of patients are expected to have a viral load <40 it will be replaced by 40 in the analysis. A sensitivity analysis will be performed excluding values below 40.
Square root transformation of CD4 count used in analysis
Log of viral load used in the analysis

6   DESCRIPTIVE ANALYSES

6.1   Participant flow

Practice and Participant throughput will be summarized in a CONSORT diagram.
Template in Appendix 3

6.2   Representativeness of sample

Number of practices who declined to take part will be reported
Practice characteristics for those taking part will be described; age, sex, ethnicity and IMD score.
These will be compared with Hackney as a whole and London as a whole.

6.3   Baseline comparability of randomised groups

6.3.1   Demographics

Age groups, sex and ethnicity will be tabulated by intervention arm (Appendix 4 table 1)

6.3.2   Prior and concurrent medications

Not applicable

6.3.3   Baseline and screening conditions

Not applicable

6.3.4   Baseline medical history

Not applicable

6.3.5   Baseline physical exam

Not applicable

6.3.6   Cluster characteristics if cluster randomized

For all characteristics the proportions will calculated across all practices i.e. equal weight to each patient not each practice. The range between practices will be given.
Practice list size at time of minimisation
IMD score
Male HIV testing rate at minimization

6.3.7   Characteristics of care providers where applicable

Not applicable

6.4 Comparison of losses to follow-up

Not applicable

6.5 Comparison of compliance to treatment and protocol

Comparison of practices who have withdrawn from the intervention with those continuing

Number of practices
Percentage in age groups (weighted by practice size)
Percentage female, range (weighted by practice size)
Percentage White, Black, Asian, Mixed ,range (weighted by practice size)
Number of newly registered patients

6.6 Emergency or accidental unblinding of randomised treatment

Not applicable

7   INTERIM ANALYSES AND SAFETY MONITORING ANALYSES

7.1 Purpose of interim analyses

An effectiveness analysis was carried out 6 months after the start of the trial and in view of the low recruitment rate a further analysis was carried out after 18 months. The purpose of the analysis was to ensure the trial was still in equipoise and to review the sample size calculations.

7.2 Monitoring plan

Data was extracted up to 31st December prior to the DMC meeting.
The interim analysis was carried out prior to DMC meetings in January 2011 and February 2012.

7.3 Stopping rules

The DMC charter states the p-value for consideration of stopping to be <0.001

7.4 Measures taken to minimize bias

Low p-value stated for stopping the trial.

7.5 Adjustment for p-values

Not applicable

7.6 Interim analysis for sample size adjustment

The sample size calculations were revised in May 2011 (Protocol version 4.0). This was based on the numbers of cases diagnosed up to December 2010, using data from the DOSH.

8   ANALYSIS OF PRIMARY OUTCOME

8.1 Definition of outcome measure

The primary outcome is CD4 count obtained from the DOSH. This will be transformed with a square root transformation prior to analysis.

8.2 Descriptive statistics for outcome measure

Mean and SD of the raw data and the transformed data will be given for intervention and control groups, without adjusting for clustering

8.3   Primary analysis

- The primary analysis pertains to the individual rather than the cluster.
- The square root of the CD4 will be compared between intervention and control, allowing for clustering effect of practices in the mixed model and adjusting for minimisation factors.
- Following analysis the relative risk for the percentage with CD4 could below 200 and below 350 will be estimated using the methods of Peacock et al 2012.
- The iccs will be calculated using analysis of variance methods. If the ICC estimates are negative analysis will be carried out ignoring the clustering.

8.4   Assumption checks

The distribution of CD4 count before and after transformation will be assessed by examination of using normal plots, SD and histograms of the data. The square root transformation will be used unless there is strong evidence to the contrary.

8.5   Other analysis supporting the primary (inc. sensitivity analyses)

The following sensitivity analyses will be carried out:
1. Analyses of primary and secondary outcomes, EXCLUDING patients diagnosed through antenatal testing.
2. Analyses of primary and secondary outcomes, EXCLUDING patients with CD4 count <40
3. Analyses of primary and secondary outcomes to include all patients diagnosed with HIV in general practice, whether or not there is a previous record of an HIV diagnosis and WHERE THE PATIENT HAS DEFAULTED CARE (IE >12m).

Rationale for 3: Some patients who test positive for HIV either do not access care, or access care and default or are lost to follow up. For such patients, a further positive test can lead to them re-accessing care, with potential beneficial health outcomes. We want to quantify this aspect of HIV diagnosis and 're-diagnosis', recognizing that a prior diagnosis introduces a delay which will affect CD4 and viral load counts. The primary analysis excludes patients with a prior positive HIV test (data available from the HPA). We therefore will carry out the above sensitivity analysis to include those with a prior positive test but who have defaulted care.

9   ANALYSIS OF SECONDARY OUTCOMES

9.1   Definition of outcome measure

1. Numbers of newly diagnosed patients in general practice
The number of patients diagnosed will be obtained from Homerton records. The rate of diagnosis per 1,000 patients per year will be estimated using the time the practice has been in the study since allocation to intervention arm and the list size at randomization.

2. Proportion of newly diagnosed patients in general practice
This is the number of patients diagnosed in each practice through primary care as a percentage of all patients diagnosed in each practice either through primary or secondary care (Data source: DOSH).

3. Viral load
The log transformation of the viral load will be compared between intervention and control, adjusting for clustering using the cluster option and adjusting for minimisation factors.

9.2   Descriptive statistics for outcome measure

For the intervention and control groups the following data will be presented for the period of the intervention

Number of patients registered on 19/April/2010
Number of newly registered patients
Number of HIV (BROKEN DOWN BY INSTI TESTS AND SEROLOGY TESTS) tests done
Number of HIV (BROKEN DOWN BY INSTI TESTS AND SEROLOGY TESTS) tests done as a percentage of baseline list size and range
Numbers newly diagnosed in general practice and rate of diagnosis per 1,000 patients and range./
Number of practices who have diagnosed at least one case

Mean (SD) CD4 count
Mean (SD) Square root of CD4 count
Intervention effect for CD4 count with 95% confidence interval

Mean (SD) viral load
Mean (SD) Log of viral load
Intervention effect for viral load with 95% confidence interval back transformed

9.3   Secondary analysis

The secondary analysis pertains to the individual rather than the cluster.

1. Numbers of newly diagnosed patients in general practice
The intervention effect will be calculated using a regression model on the log of the rate for each practice, adjusting for clustering. To allow practices who fail to diagnose a patient 0.01 will be added to the number of cases for each practice prior to log transformation. The results will be presented at the rate of diagnosis for all practices in each intervention arm and the adjusted rate ratio between intervention and control arms.

2. Proportion of newly diagnosed patients in general practice
This will be analysed using a mixed effects logistic regression model allowing for clustering and minimization factors

9.4   Assumption checks

The analysis adjusts for minimisation factors. This is the recommended approach and should lead to more precise estimation of the intervention effect. However if the rate ratio of the diagnoses varies between minimisation factors the intervention effect may be underestimated, because the patients in the intervention group practices with the characteristics associated with more cases are down weighted.

The following analysis explores this hypothesis

CD4 count will be analysed without adjustment for minimization factors.

A comparison of the number of cases diagnosed for each minimization factor will be investigated to see if the intervention effect appears constant across all factors. Intervention effect will be measured using the rate ratio.
If the rate ratio is not constant then adjusting for minimization factors may weaken the observed effect of the intervention.
This may be reported as an exploratory analysis

9.5   Other analysis supporting the secondary (inc. sensitivity analyses)

The implementation of the intervention
Within the intervention arm the following will be reported
Mean number per practice (range) of rapid tests offered
Mean number per practice (range) rapid tests done
Mean number per practice (range) SEROLOGY tests done
Mean number per practice (range) ALL (i.e. rapid AND SEROLOGY) tests done

Number of true rapid reactive tests and number of practice contributing to true reactive tests

10 AMENDMENTS FROM THE PROTOCOL

Analysis for the following secondary outcomes will not be performed.
  • Clade and genotype of the virus at the time of diagnosis as predictors of disease progression
This is due to the data not being collected.

11 AMENDMENTS TO VERSION 1.0

This is the first version of the analysis plan

12 REFERENCES

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Clarke P. When can group level clustering be ignored? Multilevel models versus single-level models with sparse data. J Epidemiol Community Health 2008;62:752–758

13 APPENDICES

Appendix 1: List of variables and datasets

Appendix 2: Classification of ethnicity from EMIS practices

Appendix 3: CONSORT Flowchart

Appendix 4: Table templates