SPEAKING OUT
CHANGING LIVES

NATIONAL AIDS TRUST

Report: July 2008

Primary HIV Infection

A policy report from the National AIDS Trust

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Executive Summary

There is convincing evidence that symptoms of primary HIV infection are at present commonly missed both by infected individuals and by healthcare workers. This is a lost opportunity to diagnose HIV before a period, often of many years, during which chronic HIV infection is asymptomatic.

There is also strong evidence to suggest primary HIV infection contributes significantly to onward HIV transmission because the individual is particularly infectious at this stage (one recent study estimated that early infection accounted for approximately 50 percent of onward transmissions *Brenner at al Journal of Infectious Diseases 2007:195*).

More effective diagnosis of primary HIV infection is crucial to current ambitions to reduce the average time between HIV infection and HIV diagnosis, and thus also reduce the proportion of people diagnosed 'late' (CD4 count <200). This will bring considerable health benefits to individuals. It will also bring very significant benefits for HIV prevention, as those diagnosed during primary HIV infection can receive counselling and support in reducing high risk behaviour.

The National AIDS Trust (NAT) believes that HIV testing and prevention strategies must be revised at both national and local level to take into account the urgent need to improve diagnosis of primary HIV infection.

In particular, we recommend:

- The reviews of the national HIV prevention programmes taking place in 2008 should take account of the important role of diagnosing primary HIV infection in HIV prevention.

- The two key national HIV prevention frameworks – that for men who have sex with men, *'Making it Count'*, and that for Africans in England, *'The knowledge, the will and the power'* – should explicitly address primary HIV infection and identify needs and recommendations for action.

- New HIV testing guidelines, currently being prepared by BHIVA, BASHH and BIS[1] should emphasise the importance of diagnosing primary HIV infection, as well as identifying effective approaches to do so, and this should be publicly recognised and supported by the Chief Medical Officers of the United Kingdom.

- Fourth generation assay tests for HIV should be consistently available in all laboratories testing for HIV.

- Clear protocols should be agreed on how to conduct point of care testing to ensure this important testing tool does not inadvertently allow more primary HIV infection to go undiagnosed.

- Messages explaining what primary HIV infection is, and what symptoms might look like, should be communicated to relevant communities (for example, men who have sex with men, African communities, injecting drug users, those in sero-discordant relationships). However, care must be taken to explain that these symptoms are not universal to avoid discouraging people who have put themselves at risk but do not experience these symptoms from testing.

- HIV prevention messages should emphasise that most HIV transmission is from those as yet undiagnosed, and stress the contribution of primary infection to onward transmission. People should be discouraged from making assumptions about their own HIV status, or that of their sexual partner, in the absence of a positive diagnosis. Safer sex remains essential to reduce the risk of HIV transmission, whether being infected or inadvertently infecting someone else.

- Anyone who suspects he or she has symptoms of primary HIV infection should be encouraged to seek clinical advice and care immediately.

- Anyone who has possible symptoms of primary HIV infection should be encouraged to abstain from sex whilst they seek an HIV test and receive the result. Anyone diagnosed HIV positive during the primary HIV infection period should be provided with safer sex advice and support, with information on the particular risks of onward HIV transmission at such an early stage of infection.

- Information on when to test for HIV needs to be revised to remove confusion about a three-month window period. People concerned about possible HIV infection should be encouraged to seek clinical advice without delay, and informed that HIV tests using latest technologies can detect most HIV infection after 12 days.

- Clinicians, nurses and other healthcare workers should be trained to recognise risks and symptoms relating to primary HIV infection, in order to test for HIV when indicated. There is a particular need for better education for GPs and acute medicine clinicians.

- Services that can act as gatekeepers to primary care and acute medical services - specifically NHS Direct, GP out-of-hours services and sexual health helplines - should review their protocols and staff training to ensure that an HIV test is recommended when primary infection is indicated.

1: The three relevant clinician bodies - the British HIV Association (BHIVA), the British Association for Sexual Health and HIV (BASHH) and the British Infection Society (BIS).

National AIDS Trust
July 2008

Discussions

Introduction

There is an increasing consensus that primary HIV infection is an important opportunity to ensure early diagnosis of HIV, given the high proportion of people who are symptomatic during this stage of infection, only then to be asymptomatic for a number of years during the chronic infection period.

There is also strong evidence that the primary HIV infection stage is responsible for a high proportion of onward HIV transmissions, as a result of the very high viral load during this period. Prompt diagnosis of primary HIV infection can affect sexual behaviours and thus reduce further transmission.

Given the potential for diagnosis of primary HIV infection to ensure early treatment and care, and also as a possible prevention strategy, the National AIDS Trust decided to hold an expert seminar to explore these issues further.

We are grateful to all who attended and shared their expertise on the day (see Annex), and especially to our three speakers, Dr Valerie Delpech (Health Protection Agency), Dr Deenan Pillay (University College London) and Dr Martin Fisher (Brighton and Sussex University Hospitals). We would also like to thank Gus Cairns for his advice and input to this seminar report.

Their three presentations form the second half of this report. They are preceded by a summary of the discussions which took place on the day. The key conclusions and recommendations from NAT, arising from the seminar, are found in the Executive Summary. These conclusions and recommendations are the responsibility of NAT alone, and do not necessarily reflect the opinion of every participant at the seminar.

What is primary HIV infection?

Primary HIV infection is the period immediately after an individual has been infected with HIV and before they have produced sufficient antibodies to reduce significantly viral load and stabilise their condition. The development of detectable antibodies in the blood is known as sero-conversion.

Primary HIV infection (sometimes abbreviated to 'PHI') can also be referred to as 'acute infection' and 'recent infection'. These terms are often used interchangeably and generally refer to the first six months of infection, though each can describe specific moments within this six-month period. For the purpose of this report, we have used the term 'primary infection' throughout.

A very high viral load develops about five days after infection. Symptoms, when they occur, develop about 10 days after infection. Symptoms occur in between 70 and 90 percent of people during primary HIV infection. Such illness is sometimes referred to as 'sero-conversion illness'. Symptoms include fever, rash (maculopapular), myalgia, pharyngitis (sore throat), headache/ aseptic meningitis. Such symptoms disappear within two to three weeks. Specifically, the 'triad' of fever, rash and severe pharyngitis all occurring together should always be considered a potential indicator of possible primary HIV infection.

Primary HIV infection and HIV prevention

Studies are now suggesting that between 30 and 50 percent of HIV transmissions are from people who are themselves infected in the previous six months. This is because of the extremely high viral load during this stage of infection. As Deenan Pillay showed in his presentation, this claim is corroborated by data on transmission of HIV drug resistance.

In discussion, some questioned the rate of partner change amongst those sero-converting, and in particular amongst gay men, claiming this was not supported consistently by UK behavioural data. Others argued the other way, that the consistent scientific data on HIV transmission (and the likely contribution of primary infection) cast doubt on the reliability of such self-reporting surveys in relation to sexual behaviour.

The preventive value of diagnosis during the primary infection stage depends on an assumption about the impact of a diagnosis on risk-taking behaviour. Research has shown a variation in condom use amongst those diagnosed as HIV positive, with some not changing their behaviour, some not having sex at all, and some modifying behaviour (increasing condom use and reducing the number of partners). However, it is reasonable to believe that diagnosing people at this stage would reduce onward HIV transmission if safer sex information and ongoing support are provided to individuals immediately following a positive diagnosis.

There have been campaigns in the United States advising gay men not to have sex if experiencing flu-like symptoms.

Some participants said that if we take 30 percent of HIV transmissions as being passed on during primary HIV infection, that still leaves 70 percent passed on during the chronic infection stage.

It is therefore important not to lose sight of the prevention needs of people during chronic infection. This was accepted. But significantly increasing diagnosis during primary infection will reduce numbers of onward transmissions both in primary and chronic infection periods (there will be fewer people undiagnosed with chronic infection) – it remains therefore an essential intervention.

A further preventive advantage of diagnosis during primary HIV infection is the greater ease in identifying recent sexual partners and thus engaging in effective contact tracing.

The challenge of diagnosing primary HIV infection

Martin Fisher in his presentation had shown evidence of many missed opportunities to diagnose primary HIV infection, especially in primary and acute care settings.This is partly because people with sero-conversion symptoms did not present for diagnosis or care, and partly because doctors did not recognise symptoms as being those of HIV infection. The difficulty often stated in diagnosing sero-conversion illness is the fact that symptoms are not specific to sero-conversion but could have a wide range of quite common causes. But Martin Fisher said that the 'triad' of fever, rash and sore throat should always suggest primary HIV infection as a possible diagnosis, and testing should be encouraged independently of questions around risk factors or the individual being from an 'at risk group'.[2] Where primary HIV infection is suspected, it is very important that an appropriate HIV test is used, and referral to a specialist GU clinic or HIV service is recommended.

There was therefore an urgent need, agreed by participants, to improve education of clinicians, and in particular those in primary care and acute care (Accident and Emergency Departments or Acute General Medical teams) since these were the two settings outside Genito-Urinary (GU)/Infectious Disease where someone with such symptoms would usually present. Too often people were advised to 'come back if symptoms persisted' – the symptoms then ended and the opportunity to diagnose was missed.

In addition, it was recognised that some services – specifically NHS Direct, GP out-of-hours services and sexual health helplines – can effectively act as 'gatekeepers' to primary care and acute medical care services. It was suggested that it would be useful to assess what advice was given if someone presented with the 'triad' of fever, rash and serious pharyngitis symptoms (for example through a 'mystery shopper' exercise) and, if necessary make recommendations for changes to their referral protocols and staff training.

An HIV positive diagnosis can be a great shock to people, particularly when they had what they thought were merely 'flu-like' symptoms. It will be very important to provide prompt and effective referral to GU, counselling and support, and advice on how to address difficult issues of disclosure to others.

As important as training for doctors and other healthcare workers, is information for those groups most affected by HIV on what primary HIV infection is, and of possible symptoms. It was said that there had been a traditional reluctance to inform gay men of primary infection in health promotion campaigns because of fears of the 'worried well' besieging GU clinics for HIV tests.

There was consensus amongst participants that gay men, injecting drug users, those from African communities and those in sero-discordant relationships should be informed of what primary HIV infection is and be able to recognise symptoms.

Whilst symptomatic sero-conversion illness was an important opportunity to test for HIV infection, there had to be care not to encourage complacency in the absence of symptoms. People who believe they have put themselves at risk of infection should certainly be encouraged to test, even in the absence of symptoms.

Current national prevention frameworks, and in particular *Making it Count* (men who have sex with men) and *The knowledge, the will and the power* (African men and women), currently make no reference to the need to improve recognition of primary HIV infection amongst affected communities.

HIV testing and primary infection

Whilst it is clear that diagnosing primary HIV infection brings great benefits to both individual and public health, it is not easy to test for HIV sensitively and accurately in the very early stages of infection. This is because the main test for HIV remains a test for the antibodies the body makes in response to HIV infection. This immune response is not immediate and thus someone very recently infected may not be diagnosed by an HIV antibody test. Nevertheless, 90 percent of people have detectable antibodies within four weeks of infection and 99 percent of people within three months.

The fourth generation assay test is increasingly used in laboratory tests for HIV in the UK, and is recommended as the required test for laboratory HIV testing by current guidelines, in draft, from BHIVA, BASHH and BIS. This test combines a test for HIV antibodies with a test for the p24 antigen (the protein which makes up the core of HIV, and which is made in large quantities in early infection). This test can detect HIV as little as 12 days after infection. There is also a test available for RNA,

2: See 'HIV in Primary Care' MedFASH for further useful advice.

HIV's genetic material, but it provides only a marginal time benefit over the fourth generation assay test.

There is increasing interest in point of care testing (POCT), also known as 'rapid testing', particularly as a way to make HIV tests more acceptable and accessible, for example in primary care and community settings. Such use of rapid testing is widely supported, but it should be noted that rapid tests are less sensitive and thus less able to pick up recent infections. It is also important to make a distinction between low-prevalence populations, where there would be a predominance of false-positives, and high-prevalence populations, where POCT will have a much higher positive predictive value.

Consistent protocols for follow-up and/or referral are necessary to ensure rapid test roll-out does not result in an increase in missed diagnoses. Those using rapid tests need always to ask about symptoms of sero-conversion, as well as possible recent exposures to the risk of HIV transmission. There must be clear processes of recall for a second test, or alternative rapid access to a laboratory test.

In the seminar discussions it was felt that too many people, after possible infection, are deterred from getting an HIV test because of the widespread message that one has to wait for a 'three-month window period' before HIV becomes detectable. By the time three months have passed any symptoms of sero-conversion will have disappeared, and very often also immediate concern at the possibility of infection will have subsided. So the incentive for testing and diagnosis may well be lost. It is true that to **exclude with certainty** the possibility of HIV infection, a test after three months is advisable. But, as we have seen, the vast majority of people infected with HIV can be detected by the fourth generation assay test from about twelve days after infection.

The best advice must be to seek clinical advice and testing whenever one is concerned at the possibility of HIV infection, and as soon as possible. Appropriate testing, and advice on the need for any second test, can then be provided as well as Post-Exposure Prophylaxis (PEP) for those who may have been exposed in the previous 72 hours. This will result in much more primary HIV infection being diagnosed.

There was debate as to whether there is a real need to diagnose primary HIV infection, or whether the real aim is rather to ensure HIV infected people are diagnosed earlier (in other words, the message is more simply 'just get tested more often'). There is, for example, a new emphasis on annual testing for gay men. What 'additional benefit' can be identified to encourage gay men to test if they suspect primary HIV infection, rather than, for example, just wait for their annual check-up?

One reason to get tested during primary infection is how much more infectious one is to sexual partners during this period – elevated infectiousness can continue for a number of weeks after the disappearance of any symptoms. Not only can diagnosis result in greater care to avoid risk of transmission, it also allows, as has been stated, much more effective contact tracing of recent sexual partners. Many felt it was wrong to dismiss out of hand the incentive of altruism and responsibility to others.

It is also wrong to see an annual testing strategy and a strategy to promote HIV testing during primary HIV infection as alternatives. Both are important and necessary. It will continue to be the case that some people infected with HIV are unaware they have been at risk, present no symptoms of sero-conversion, or miss such symptoms (or have them missed) – and so need to be diagnosed through the 'regular test' approach. But it will also be the case that some resist regular testing, or forget or get their timings wrong.

Primary HIV infection is a key opportunity for early diagnosis, where motivation to test is for many at its strongest. Messages and services must meet this need, not assume people will turn up in due course for an annual test.

Two further points should be noted. Firstly, for a few HIV infected individuals, even a delay of some months can result in serious and avoidable ill-health. Secondly, the SPARTAC study is currently looking at the possible treatment benefits of a course of anti-retrovirals (ARVs) during primary infection (www.ctu.mrc.ac.uk/studies/spartac.asp). Results will only be available in 2010, but could possibly provide further reasons to diagnose during primary infection.

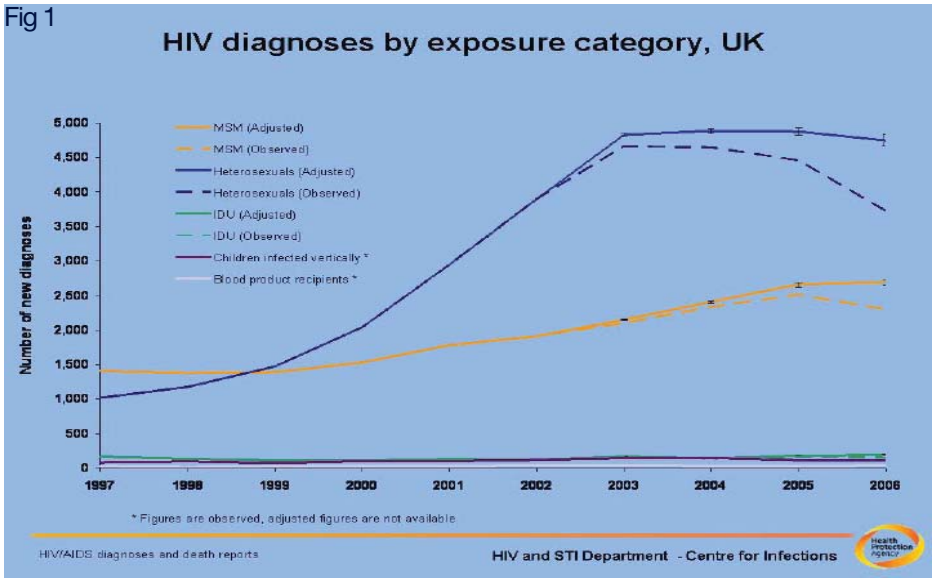
Presentations

Primary HIV infection and surveillance

Dr Valerie Delpech, Health Protection Agency

> **Primary HIV infection is a key opportunity for early diagnosis, where motivation to test is for many at its strongest.**

Fig 1



The identification of acute, or primary, infections using routine surveillance data is challenging. This is largely because HIV has a long incubation and current routine diagnostic tests for HIV do not distinguish longstanding from recent or acute infection. It is therefore difficult to know whether the increase in diagnoses in recent years [fig 1] is due to an increase in incidence or increased offer and uptake of HIV testing.

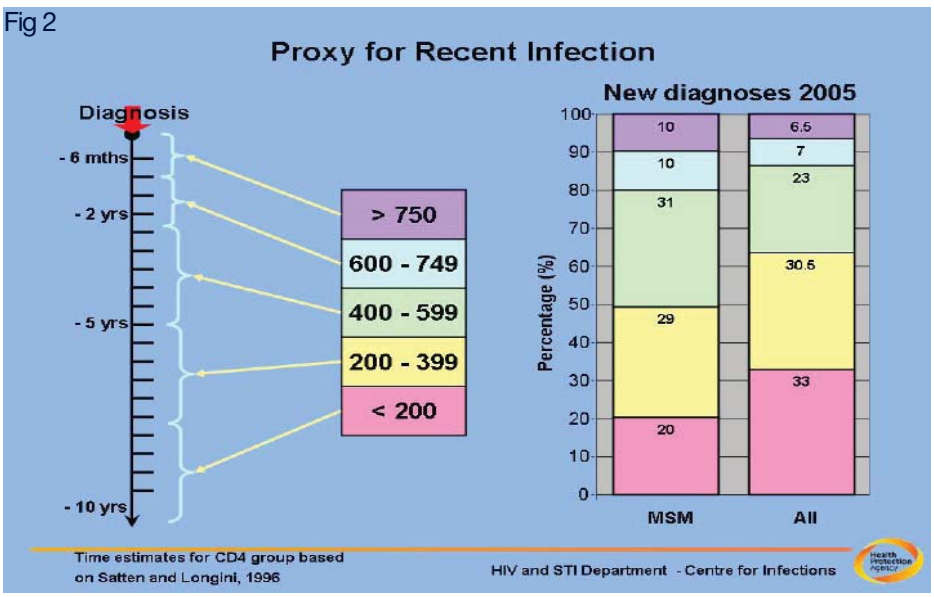
CD4 count at diagnosis does provide a clue to the time of infection [fig 2]. Patients diagnosed with a CD4 count <200 are referred to as 'late presenters' and are likely to have had their HIV infection for five to eight years, or longer.

There is a worldwide goal to reduce such late diagnoses through earlier testing of HIV. At the other end of the spectrum, it is likely that people diagnosed with a higher CD4 count (>500) are likely to have been infected less than a year. A recommended target to reduce individuals in the UK diagnosed late has now been identified.

A larger proportion of MSM (men who have sex with men) infections are likely to have been acquired in the last five years. However, CD4 counts during and soon after sero-conversion can vary greatly in an individual and it is therefore difficult to use these data to identify individuals very recently infected, say in the last six months. Primary HIV infection can be defined in several ways according to clinical symptoms, laboratory markers or the surveillance of acute infection:

Clinical symptoms of a sero-conversion illness - these typically occur within the first six weeks of infection. Unfortunately, because many of the symptoms are non-specific and relatively mild, such as flu-like illness and raised lymph nodes, these symptoms have often been missed in the past and it has been reported that many sero-converters remain asymptomatic. Martin Fisher, however, will explain how patients and clinicians can improve the likelihood of diagnosing a sero-conversion illness in HIV infected individuals and show from the Brighton cohort that sero-conversion illness occurs more frequently than is generally thought.

Fig 2

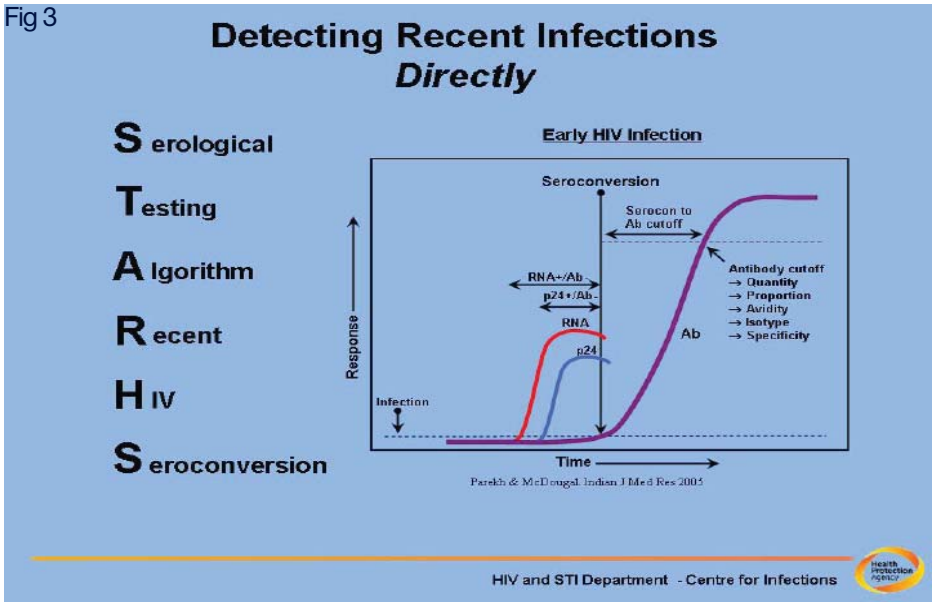


Laboratory markers – Improved diagnostic tests have made it possible to diagnose HIV earlier. In particular, some recent diagnostic tests are able to detect the RNA virus which is present in high concentrations in the blood prior to the detection of the body's antibody response against HIV (detected by traditional diagnostic tests). These tests, known as NAATS tests, are used in parts of the United States to detect acute infections in individuals with negative anti-HIV tests. The merit of using these tests in the UK, however, is likely to be limited given that fourth generation ELISA tests are used in most laboratories across the UK (compared with mostly second and third generation tests used in the US) and these can detect viral antigens and an antibody response to HIV as early as one to two weeks after infection.

New tests which can differentiate early (within six months of infectivity) from long standing infection known as STARHS (Sero-conversion Testing Algorithm for Recent HIV infection) are being rolled out across the UK [fig 3].

It is the intention that these tests will be conducted on all newly diagnosed individuals as part of the routine diagnostic tests conducted. This information can be used to estimate incidence (new cases) of HIV and thereby identify groups of individuals most at risk of acquiring HIV in the UK.

Fig 3



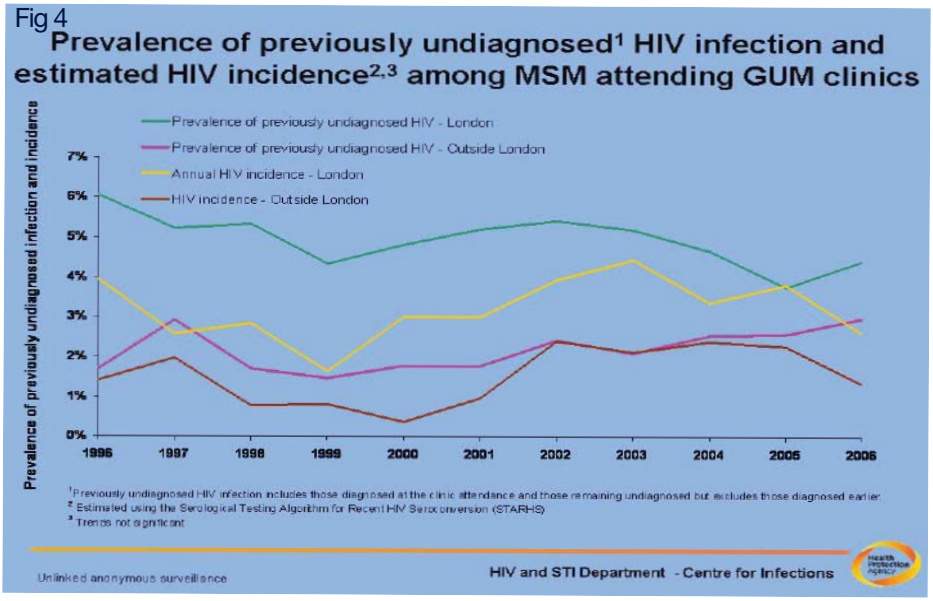
STARHS tests have been conducted on newly diagnosed patients in Brighton and have also been applied to samples retrieved as part of the unlinked anonymous programme conducted in GU clinics for over a decade.

Between 1998 and 2007, based on STARHS results, the annual incidence of HIV among MSM attending GUM clinic varied between 1.3 and 3.4 percent and was higher in London [fig 4].

People with a recent previous negative HIV test result are identified as 'sero-converters' primarily for **surveillance** and research purposes and many are enrolled in 'sero-converters' cohort studies. The inclusion time from negative to positive test result varies for different cohorts and may include individuals with an interval of up to three years. CASCADE is a European collaboration of over 20 sero-converter cohorts worldwide and has been key to studying the natural progression of HIV and the impact of ARVs.

The identification of primary infections using clinical and laboratory information collected through routine surveillance data has been limited to date. Many individuals who are diagnosed with HIV may not have been tested previously and will therefore not have a previous test result. In addition, the test date of those individuals previously tested is often not known or not provided. Between 2000 and 2007, only 2,680 (5 percent) of newly diagnosed individuals in the UK had a negative test date. 45 (1.7 percent) of these were negative within three months of diagnosis and 590 (22 percent) within a year of diagnosis. Furthermore, only 3 percent had been tested because the patient presented with a clinical sero-conversion illness. There are clearly missed opportunities for identifying sero-conversion illnesses among persons

Fig 4

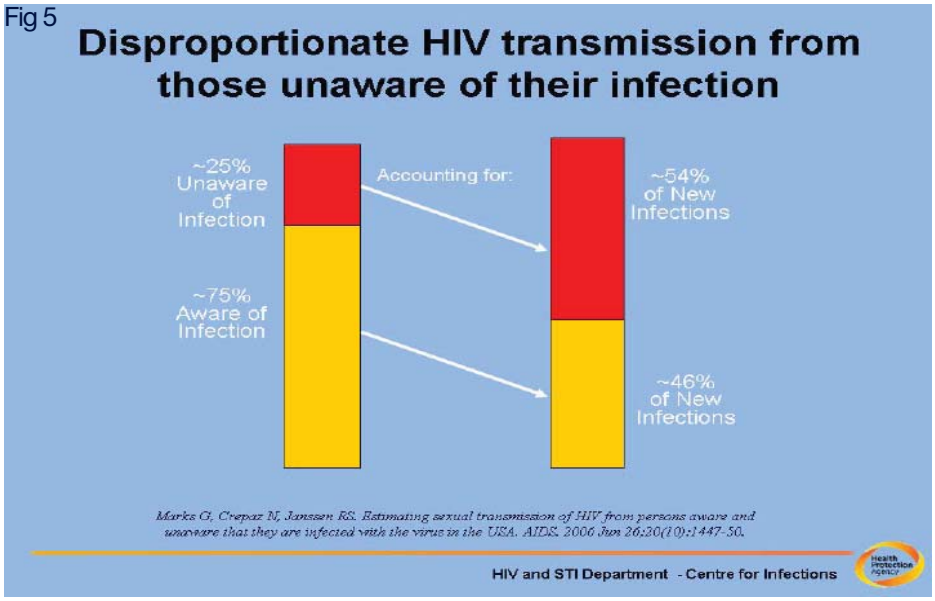


most at risk such as MSM.

Individuals who have been recently infected with HIV are most infectious, and are likely to account for a disproportionate number of onward transmissions of HIV [fig 5]. Overall it is estimated that over half of all new infections are contracted from people who are unaware of their infection.

Encouraging individuals to test earlier, through the recognition of at risk behaviours and symptoms of sero-conversion, will therefore have an important public health benefit as well as individual benefit.

Fig 5

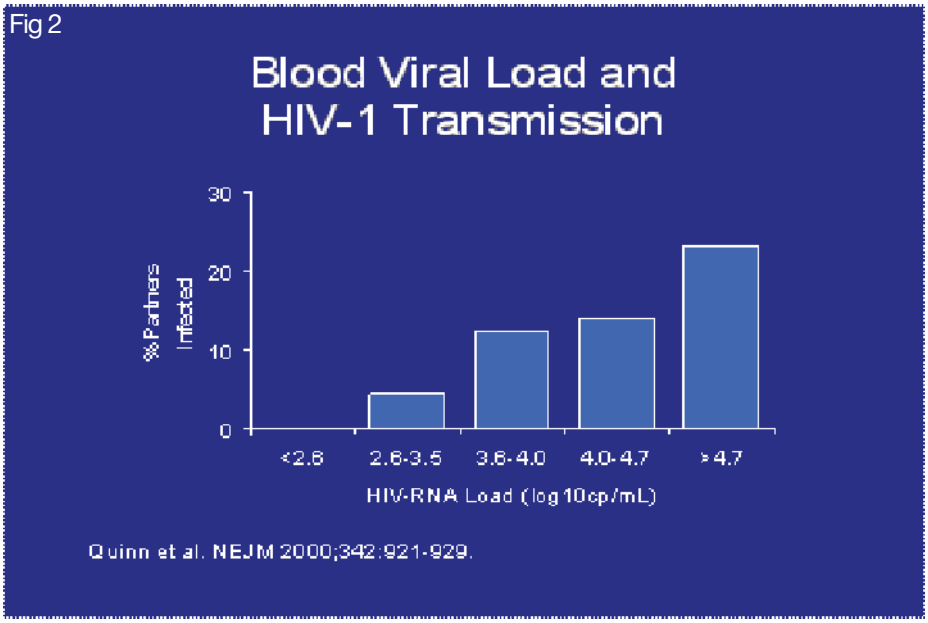


Primary HIV infection and testing

Dr Deenan Pillay, University College London

> **It is worth stating at the outset the most fundamental point, that to diagnose primary HIV infection we must roll out widely and effectively HIV testing.**

Fig 2



There is a demonstrable evidence base on the relationship between primary HIV infection and HIV transmission [fig 1]. It is worth stating at the outset the most fundamental point, that to diagnose primary HIV infection we must roll out widely and effectively HIV testing.

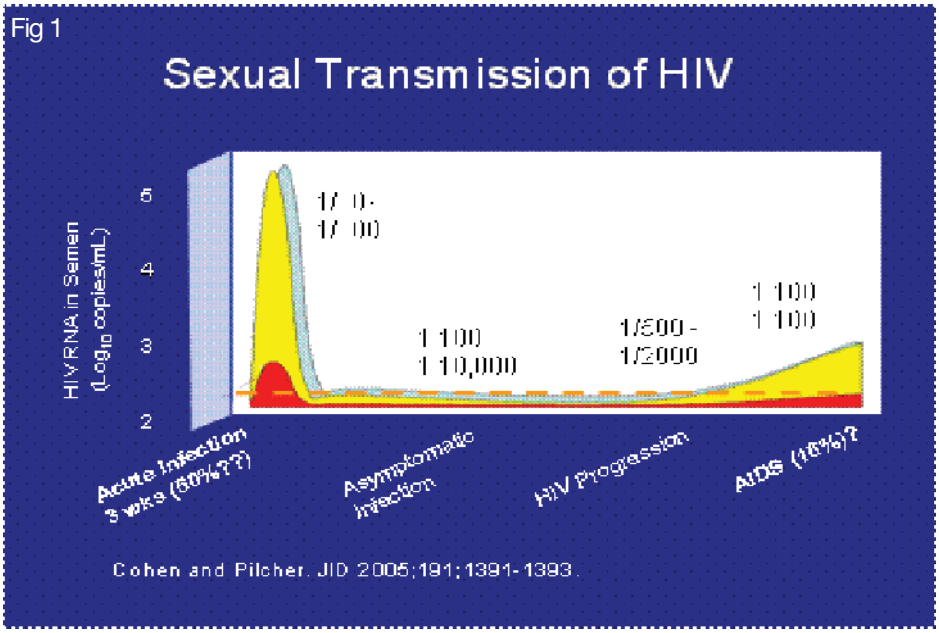
Prior to recent studies on the relationship between primary HIV infection and transmission there had been data on the impact on mother to child transmission of reduction in the amount of virus in the mother, which proves to be the best surrogate for a reduction in risk of transmission to the child.

There has also been data from the Rakai cohort where sero-discordant couples were recruited and followed, looking at the risk of HIV transmission and the relationship to viral load [fig 2]. There are of course limitations to the study – the study is of heterosexual couples in a resource-poor setting and there are issues around behavioural risk factors and the extent to which results can apply to sex amongst MSM. Nevertheless, the Rakai study shows a logarithmic increase in risk of transmission with increase in viral load. Plasma viral load acts as a surrogate for genital tract viral load – that in the genital tract is about half that of plasma but can still be high. Given these findings, it is clear that primary HIV infection must be a major source for transmission.

A correlation was identified between primary HIV infection and presentation with other STIs (of course themselves indicators of unsafe sex) – where the STI adds to the risk of HIV transmission. There has been debate as to whether intervention to treat STIs can reduce HIV transmission, and a recent study of Herpes simplex suggests it did not, so perhaps STIs have only a minor role in increasing HIV transmission risk.

From a cohort studied by Mike Cohen it was estimated that about 50 percent of global infectivity was in the primary infection period. The Rakai cohort study estimated between 30 and 40 percent had been infected by someone in the primary infection period. There was a debate as to whether the data in this instance had been 'over-interpreted'.

Fig 1



Can treatment of individuals have a public health role? It is important to get information on the 'infectivity curve' to influence our expectations of various interventions. This is with the background of recent disappointing results in microbicide and vaccine research.

Martin Fisher's Brighton cohort provides information on the infectivity of the diagnosed cohort in Brighton over time. In 1998 the majority of virus transmissions were from those who had 'ever had treatment'.
By 2003, with better treatment available, the main burden of infection was from those who had never been on treatment. Thus there is evidence that at the population level ARV interventions can reduce infectivity. This trend is probably even more marked were we able to see the data for 2008. With the rise in new diagnoses there is a greater percentage of those infected now on first line treatment which is very effective, with only a low percentage having a detectable viral load.

It is also interesting to explain recent data on transmission of drug resistance – transmission of resistance peaked in 2002 and is now coming down.
A sero-converter sample from UK CHIC was looked at so one could be confident that year of sample was also year of infection. The results validate the claim of a reduction in transmission of direct resistance as modelled from the San Diego group [fig 3]. The wider use of ARVs to reduce viral load to non-infectious levels seems to be the best explanation [*AIDS 2007 21:8 1035-1039]*.

It is also clear from Martin Fisher's Brighton sample that the transmission of resistant virus from the drug-naïve is increasing [fig 4]. As ARV management improves, an increasing proportion of transmitted viruses come from the drug naïve, including drug resistant viruses. There is currently a lack of guidance on how to treat this group.

Resistance testing is providing a lot of important data on HIV transmission. For example, in the case of one study of the Brighton cohort [fig 5] it demonstrated that one third of Brighton sero-converters were linked to each other [*AIDS 2005 19 (1): 85-90*].

As a result of this broad range of evidence on the significant contribution of primary HIV infection to HIV transmission, there has been an increased interest in RNA detection of early infection, using pooling to make the process more cost effective. This is particularly being considered in the US and the developing world, but in these contexts routine screening tests are not as good as in the UK. In the UK where fourth generation assay tests are being recommended which detect both the HIV antibody and the HIV antigen (the antigen earlier than the antibody), earlier diagnosis is already possible. RNA testing only provides a few days' earlier results.

Fig 3

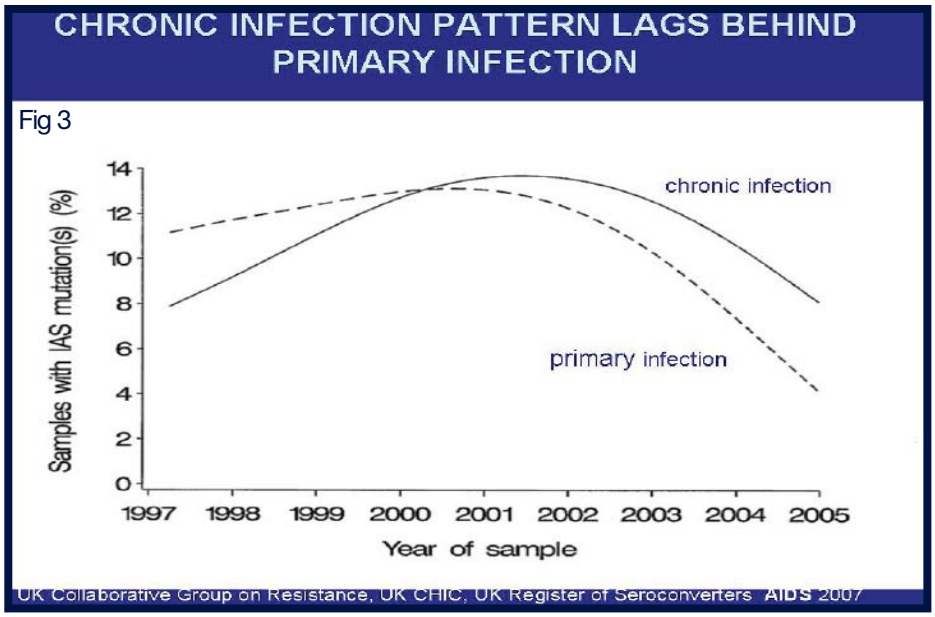
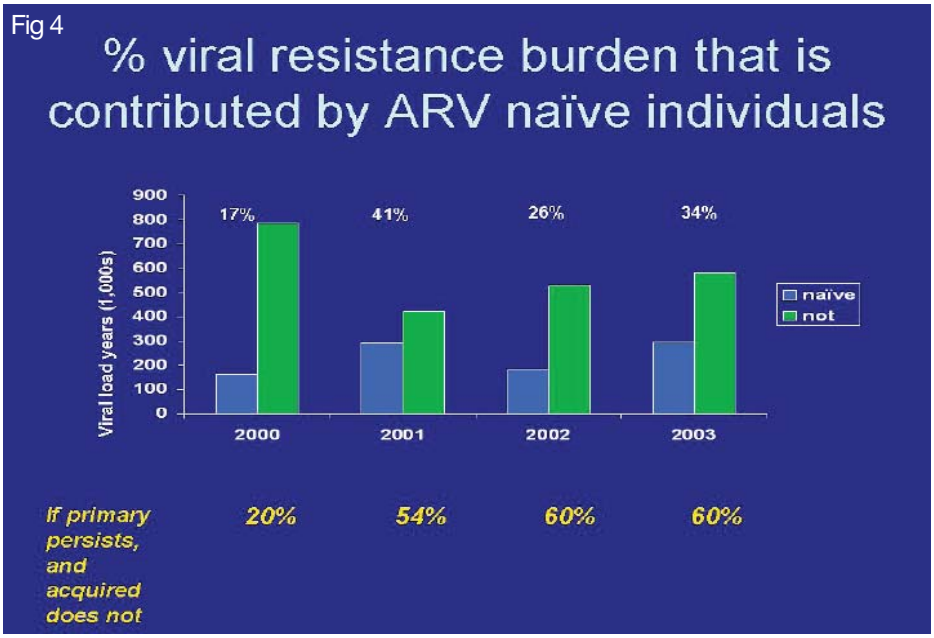


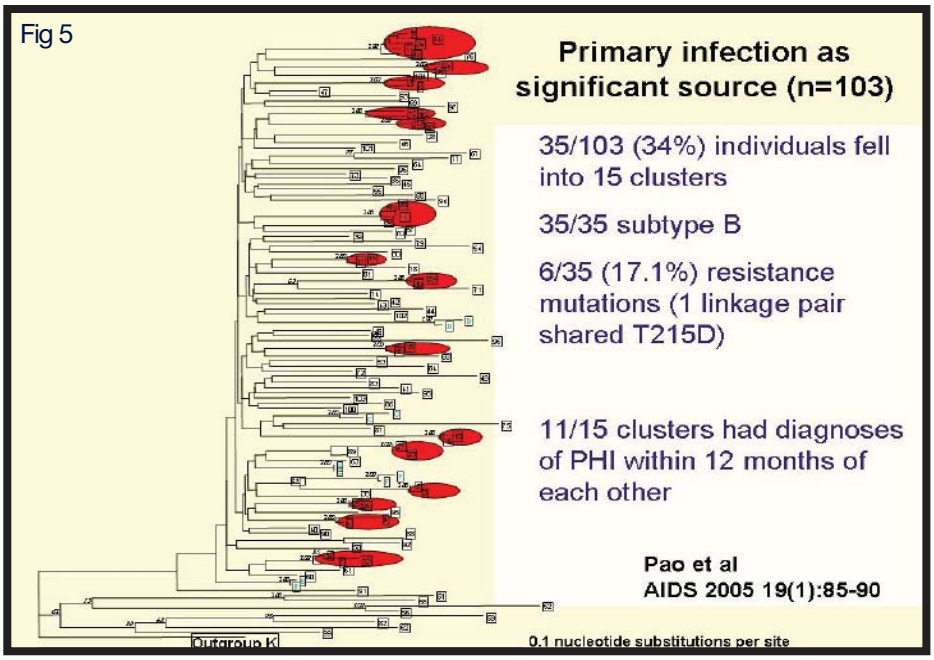
Fig 4



It is, however, also important to point out that point of care ('rapid') testing is less sensitive when it comes to early detection of HIV infection. Such point of care testing is key to much of the strategies around wider roll-out of HIV tests. There must therefore be careful consideration of how we marry wider use of point of care testing with a concern to improve diagnosis of primary HIV infection.

It is particularly important that we push for all laboratories to be using fourth generation assay tests, ensure Commissioners realise that this is the necessary standard of care, and resist any attempts to cut costs and opt for inferior testing.

Fig 5



Primary HIV infection and missed opportunities

Dr Martin Fisher, Brighton and Sussex University Hospitals

Primary HIV infection is a time-limited but vital opportunity to provide testing, diagnosis and care for an individual. Given the high proportion of instances where primary infection involves symptoms of sero-conversion, it is a one-off opportunity to diagnose before a long period of asymptomatic chronic infection which may only end with the individual presenting seriously ill in hospital eight years or so later. Too often people assume they have been tested for HIV as part of a check-up or battery of tests when in fact they have not, which simply adds to the risk of late diagnosis.

There is evidence that diagnosis has an important impact on risk-taking behaviour. For example, a meta-analysis by Marks in the *Journal of AIDS 2005* found that there was a 50 percent reduction in risk taking behaviour amongst those aware of their HIV positive status, with an even greater reduction where the partner is known to be HIV negative [fig 1].

It is also clear that if you diagnose people earlier you are likely to get much better results and more positive diagnoses from contact tracing: *Roberts et al, BHIVA 2006.*

There is also evidence of a significant reduction in infectiousness from ARVs [fig 2]. Whilst there may be concern as to the formulation of the recent Swiss statement which stated that those with an undetectable viral load, without STIs, and well managed are 'not infectious', the fact remains that both clinical and behavioural interventions post-diagnosis have a substantial and important impact in reducing onward transmission of HIV.

Fig 1

Effect of knowing HIV status on sexual behaviour

- Meta-analysis of 11 study analyses
  - 6 HIV+ "aware" versus HIV+ "unaware"
  - 5 pre- and post- HIV seroconversion
  - rates of unprotected anal or vaginal intercourse
- UPI 53% (CI 45-60%) lower in those aware versus unaware of HIV+ status
  - If only considering where partner HIV-, 68% (59-76%)

Marks, JAIDS, 2005

A meta-analysis by Marks in the *Journal of AIDS 2005* found that there was a 50 percent reduction in risk taking behaviour amongst those aware of their HIV positive status.

Fig 2

Impact of ART on HIV Transmission Among HIV Sero-discordant Couples

- Cohort of 1487 serodiscordant couples in Kigali Rwanda
- Historical serocoversion rates 1.6-3%/year
- Similar numbers of men and women were index cases
- ART (mostly d4T/3TC/NVP) given for WHO stage III/IV disease or CD4 <200

Index on ART	#sero-converted	Patient-Years of follow-up	Rate/100 patient-years	95% CI
Yes (n=217)	1	264	0.4	0.01, 2.11
No (n=1270)	49	1991	2.5	1.82, 3.25

- HR: 0.19 (0.05-0.80)
- "the benefit of ART may go beyond the expected effect…with a protective effect on negative partners"

Kaytendore, et al. XVI International AIDS Conference, 2006, MOKC101

To this must be added the fact that, for example, in Brighton those diagnosed during primary infection are twice as likely to be co-infected with an STI compared with those diagnosed during chronic infection. Co-infection with an STI increases between two to five times the likelihood of HIV transmission to a sexual partner [fig 3].

When considering the diagnosis of primary HIV infection the point is often made that the relevant symptoms are non-specific. But in fact, irrespective of knowledge of a patient's sexuality, the 'triad' of fever, rash and pharyngitis (sore throat) all occurring together should always suggest possible primary HIV infection and thus require an HIV test [fig 5].

A study in Brighton was conducted with the aim of assessing what proportion of individuals diagnosed with HIV recalled symptoms relating to sero-conversion, how many accessed healthcare at the time, and how many were diagnosed with primary HIV infection. Of 108 persons 76, or 70 percent, reported recalling symptoms, and 40 (or 53 percent of those with symptoms) sought medical advice. In 21 (52 percent of those who sought medical advice) primary HIV infection was diagnosed and in 19 (48 percent) it was missed. A striking comparison was between healthcare settings – only one of the 13 GU clinic presentations resulted in a failure to diagnose HIV, but 15 of the 20 GP presentations failed to diagnose, and whilst there were four diagnoses in a hospital there were also three missed diagnoses in Accident & Emergency (A&E).

Recurring themes were comments such as 'probably glandular fever', 'it's a viral illness' or 'come back in two weeks if you're not feeling better'.

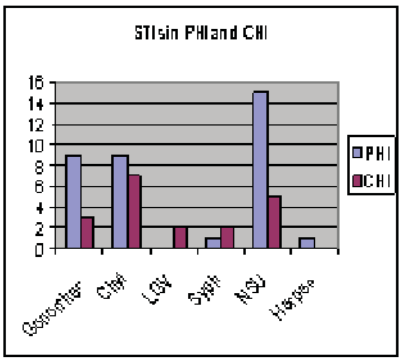
Sexual history was rarely taken and the clinician was often unaware of the person's sexuality. Blood was rarely sampled but there was also often an assumption by the patient, where there had been tests, that HIV had been tested for when this was not in fact the case.

Three US studies have come up with very similar results [fig 4]. It is worth noting that between 70 and 90 percent of people who sero-convert are symptomatic.

Fig 3

STIs and PHI

- STIs facilitate HIV transmission
  - 2-5x
- PHI facilitates HIV transmission
  - ? > 10x
- Brighton Study:
  - STIs more common in new diagnosis of PHI (45%) vs CHI (26%) [p=0.02]



Sudarshi D et al, BHIVA, 2007

Fig 4

"Missed" PHI Studies

	Brighton (Sudarshi, STIs, 2008)	Schacker (1996)	Weintrob (2003)	McGee (CROI, 2008)
Number	108	45	29	110
Symptomatic	70%	89%		94%
Presentation to healthcare	53%	85%	52%	54%
Diagnosis made (of presenting)	52%	25%		24-39%
Diagnosis made (of symptomatic)	19%	22%	17%	14%

10-20% hospitalised !!

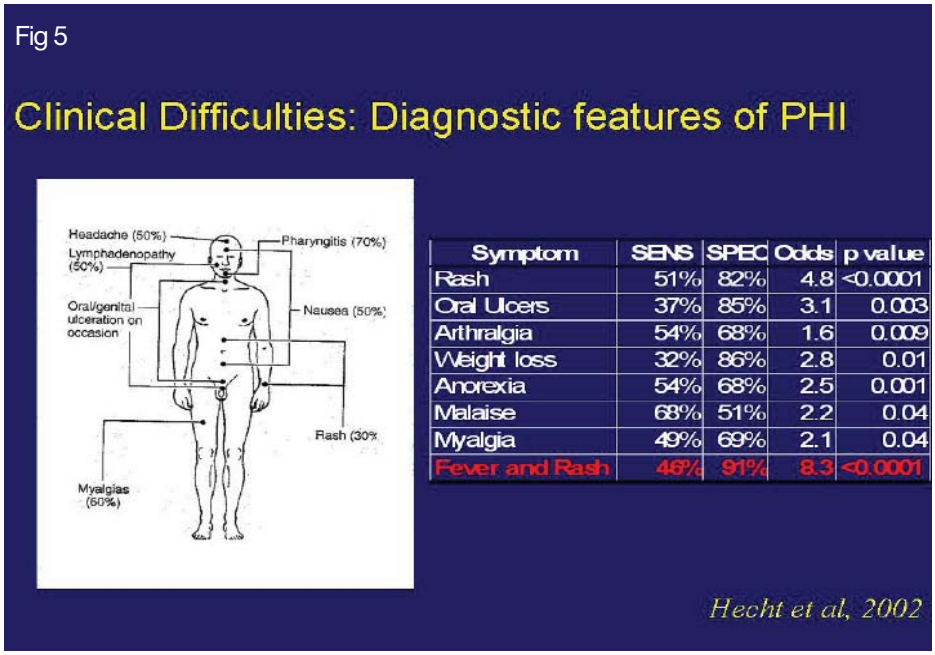
There is currently a big push to roll out point of care testing in community settings. There is, however, a worry that such rapid tests will be used and interpreted incorrectly by gay and bisexual men.

A study took place in Brighton of fasTest between May and September 2007, during which period 105 MSM were tested with 22 of them reporting unprotected anal intercourse in the last six weeks. Nine of those 22 attended as recommended for further testing and were either repeat tested with fasTest or had a fourth generation assay performed in the GU clinic. Of those, one tested HIV positive who had been negative at point of care test. 13 did not re-test, comprising 59 percent of those 'at risk', or 12 percent of the total number who were tested.

Priorities are:

- Educating patients through information on possible symptoms of primary HIV infection and on the differences between testing methods
- Educating, educating, educating clinicians, in particular GPs, A&E and those in acute medicine
- Laboratories all using fourth generation assay tests and ensuring appropriate use of point of care testing.

Fig 5



Symptom	SENS	SPEC	Odds	p value
Rash	51%	82%	4.8	<0.0001
Oral Ulcers	37%	85%	3.1	0.003
Arthralgia	54%	68%	1.6	0.009
Weight loss	32%	86%	2.8	0.01
Anorexia	54%	68%	2.5	0.001
Malaise	68%	51%	2.2	0.04
Myalgia	49%	69%	2.1	0.04
Fever and Rash	46%	91%	8.3	<0.0001

Annex

Primary HIV Infection Seminar Attendees 13 March 2008

Dr Immy Ahmed	British Association for Sexual Health and HIV (BASHH)
Ray Appleby	Kensington and Chelsea PCT
Yusef Azad	NAT
Alison Brown	Health Protection Agency
Carl Burnell	GMFA
Michael Carter	NAM
Enrique Castro Sanchez	Royal College of Nursing
Dr Valerie Delpech	Health Protection Agency
Tom Doyle	Yorkshire MESMAC
Dr Jonathan Elford	City University London
Dr Martin Fisher	Brighton and Sussex University Hospitals
Dr Wiliam Ford -Young	General Practitioner, Broken Cross Surgery
Dr Julie Fox	Imperial College London
Deborah Jack	NAT
Dr Sam Lattimore	Health Protection Agency
Linda Lazarus	Health Protection Agency
Alana Lewis	NAT
Dr Edmund Ong	Newcastle University
Ruth Lowbury	MedFASH
Chris Morley	George House Trust
Joe Murray	NAT
Angelina Namiba	Positively Women
Kay Orton	Department of Health
Dr John Parry	Health Protection Agency
Dr Deenan Pillay	University College London
Lisa Power	THT
Richard Scholey	THT
Dr Pam Sonnenberg	University College London
Hong Tan	London Specialised Commissioning Group
Matthew Williams	The Monument Trust
Heather Wilson	Barnet and Chase Farm Hospitals

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About the National AIDS Trust

The National AIDS Trust is the UK's leading independent policy and campaigning charity on HIV and AIDS. The National AIDS Trust develops policies and campaigns to halt the spread of HIV and improve the quality of life for people affected by HIV, both in the UK and internationally.

All the National AIDS Trust's work is focused on achieving four strategic goals:

- Effective HIV prevention
- Early diagnosis of HIV through ethical, accessible and appropriate testing
- Equitable access to treatment, care and support for people living with HIV
- Eradication of HIV-related stigma and discrimination.

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