ABC of AIDS

P P MORTIMER

THE VIRUS AND THE TESTS

Although it is clear that human immunodeficiency virus (HIV) is the cause of the acquired immune deficiency syndrome (AIDS) and AIDS associated disease, its origin remains obscure. It seems to have infected humans for the first time 15-20 years ago, but earlier unrecognised infections may have occurred. There is firm serological evidence of infection on the east and west coasts of the United States of America from the mid-1970s, but observations of AIDS associated illness suggest that in central Africa HIV infection may have antedated infection in North America. Nowhere is there a good explanation of how the first infections came about. With modern tissue culture techniques several human and simian retroviruses have come to light. Like other RNA viruses, these are potentially labile, and shifts in host range and virulence which might explain how a new, pathogenic, retrovirus could arise in man are therefore conceivable.

Retroviruses are so named because their genomes encode an unusual enzyme, reverse transcriptase, which allows DNA to be transcribed from RNA. Thus HIV can make copies of its own genome, as DNA, in host cells such as the human T4 "helper" lymphocyte. The viral DNA can become integrated in the lymphocyte genome, where it forms the basis for chronic HIV infection. This integration of the HIV genome into host cells is likely to be a formidable obstacle to the development of any antiviral agent that might not just suppress but also eradicate the infection.

HIV and related viruses

HIV particles, many showing typical lentivirus morphology ($\times 100\,000$).

HIV—LAV, HTLV-III, ARV, etc

HTLV-I and HTLV-II are rare causes of leukaemia and lymphoma

HIV-II—LAV-II, HTLV-IV, STLV-III

The AIDS virus was discovered by Barré-Sinoussi, Montagnier, and colleagues at the Institut Pasteur, Paris, in 1983 and given the name lymphadenopathy associated virus (LAV). In 1984 Popovic, Gallo, and coworkers described the development of cell lines permanently and productively infected with another AIDS virus isolate, which, in line with two previously described retroviruses, HTLV-I and HTLV-II, they referred to as HTLV-III. LAV, HTLV-III, and the other viruses since isolated from patients with AIDS and AIDS related disease in America, Europe, and Central Africa are all the same virus, and this is the virus now called HIV.

Within the past year another retrovirus, different from HIV, has been recognised in patients with west African connections. This virus, referred to by the Paris investigators as LAV-II and more recently as HIV-II, is also associated with AIDS and AIDS related disease, though it is structurally more like the simian retrovirus STLV-III than HIV. The simian virus is carried by healthy African green monkeys, but in captive rhesus monkeys it causes an AIDS like disease. A very similar retrovirus of humans has been described by workers at Harvard University as HTLV-IV, but this has not been associated with AIDS related disease. Though apparently new and potentially important, LAV II and HTLV-IV infections are rare outside west Africa.

Transmission of HIV infection

Transmission factors

Virus titre

Trauma

Secondary infection

Epithelial receptors

Intensity of exposure

Phase of infection

HIV, the classic AIDS retrovirus, is transmitted in ways that are typical for all retroviruses—"vertically" from mother to infant and "horizontally," especially through sexual intercourse. Some carriers of HIV probably excrete much more virus than others, though the titre of virus in infected material is difficult to measure. Successful transmission will also depend on other factors, such as trauma, secondary infection, the efficiency of epithelial barriers, and the presence or absence of cells with receptors for HIV. These factors may explain why the virus spreads more rapidly in some circumstances—for example, by homosexual intercourse—than in others. All infections with HIV seem to be chronic and some have been shown to be continually productive of virus. Thus the ultimate risk of spread to those repeatedly exposed is high.

An important determinant of infectivity may be the stage of infection. In most virus infections the highest titres of virus are reached early in infection, before antibody is produced. For HIV this phase is difficult to study because it is usually asymptomatic and the anti-HIV response is absent or weak; nevertheless, it is the time when an individual is most likely to be infectious and to infect contacts. There is also evidence that when, much later, AIDS supervenes the individual again becomes more infectious.

Tests for anti-HIV

Anti-HIV

Appears 3 weeks to 3 months after exposure

Has weak neutralising capacity

The first strip, a Western blot result from a serum specimen collected soon after HIV infection, shows antibody to p24 without other bands being clearly visible. The second strip, a result on a serum sample collected from the same patient three months later, shows antibody to many viral proteins, including p15, p24, p31, gp41, and p55.

Over the past three years anti-HIV tests have transformed our understanding of the epidemiology of HIV. Anti-HIV appears three weeks to three months after exposure to HIV and thereafter is almost invariably detectable in spite of any detrimental effect the virus might have on lymphocyte function and antibody production. Though neutralising antibodies to HIV are measurable, their titres are low and their effect weak in that they do not obviously limit the progress of infection and disease.

For diagnostic purposes HIV can be prepared from cell lines in large amounts, purified, and used as an antigen in serological tests. Several types of anti-HIV test exist, and three that are available commercially are illustrated. Most tests use an enzyme conjugate and give a colour signal due to the reaction between specifically bound enzyme and a substrate; other tests depend on radioisotopes, the binding of a fluorescein conjugate, or the agglutination of HIV-coated gelatin or latex particles.

Since anti-HIV tests became commercially available in 1985 they have been widely used in diagnostic and transfusion laboratories in the developed world. The accuracy—both sensitivity and specificity—of the antibody assays is being improved all the time, and the occurrence of false positive and false negative results is less and less frequent. The proportion of true to false results depends on the population studied, but even in low risk groups such as blood donors is now relatively high.

In addition to methods for detecting "whole" anti-HIV, more discriminating tests recognise the components of the antibody response. The serological response to individual HIV proteins has been closely studied by Western blot and by radioimmunoprecipitation. The immunoglobulin class response in blood and other fluids can also be investigated. The IgM anti-HIV response is of particular interest as it slightly precedes the IgG response early in infection and is therefore the first antibody to be made.

Simpler anti-HIV screening tests are being developed for large scale testing in unfavourable laboratory conditions and when results are needed urgently—for instance, before transplantation procedures. The possibility of using saliva as a specimen to investigate for anti-HIV is also being studied.

Indirect ELISA

Ag—specimen—anti-IgG enzyme

Competitive ELISA

Ag ← Specimen
 Ag ← Anti-HIV enzyme

Sandwich ELISA or agglutination

Ag—specimen—Ag (enzyme attached)

Performance assessment: confirmatory testing—In many countries, including the UK, procedures have been introduced to ensure accurate testing. Stringent checks are made, the most important being that when there is a positive anti-HIV finding the test is repeated and the implicated specimen is tested by other, methodologically independent, anti-HIV tests. Although this may lead to some delay in confirming positive findings, anti-HIV results are as a consequence very precise. The greatest remaining anxiety is that a few infected individuals either do not have anti-HIV when tested or have it in such low concentrations that even sensitive assays fail to detect it. This is particularly likely to occur early in infection, and without follow up these HIV infections can be missed.

Test for HIV antigen and viraemia

Also present in serum are viral antigens, in particular the main HIV core antigen (p24). This is detectable only for as long as it is in excess of antibody to p24, most typically at the outset of infection. Tests for HIV antigen are commercially available and their role in screening as an adjunct to antibody tests is currently under consideration. Viraemia, recognised by isolation of HIV from lymphocytes, is demonstrable even in the presence of high titres of anti-p24 and antibodies to other HIV proteins. However, virus isolation is time consuming, and a more important element in the successful laboratory diagnosis of HIV infection in individuals with little or no antibody is access to follow up specimens. When newly infected individuals are followed up both the titre and range of HIV antibodies usually increases. Those who have been infected for several months or more almost invariably have strong anti-HIV reactions. Therefore persistently weak anti-HIV reactions should be viewed with scepticism.

Testing of patients and blood donors**People who must not give blood**

These are the people who are most likely to have been exposed to the AIDS virus. They must **not** give blood:

- X** Men who have had sex with another man at any time since 1977.
- X** Drug abusers, both men and women, who have injected drugs at any time since 1977.
- X** Haemophiliacs who have received unheated blood products at any time since 1977.
- X** People who have lived in or visited Africa south of the Sahara at any time since 1977 and have had sex with men or women living there.
- X** Sexual partners of people in these groups. This includes single contacts as well as regular relationships.

People who think they may have been exposed to the AIDS virus can get a blood test, in strict confidence, either through their own doctor or at a sexually transmitted diseases (STD) clinic. Clinics can be found in the phone book under 'venereal disease' or 'sexually transmitted diseases'. People whose test is negative should still not give blood.

Tests for anti-HIV, though not those for antigen or HIV culture, are now widely available in UK. They are done regularly in most public health laboratories and are also used in all transfusion centres (though the facilities in transfusion centres emphatically do not exist to provide testing for those at risk. Indeed, the main method by which the blood supply is protected from contamination with HIV is through those individuals at increased risk of HIV infection refraining from giving blood).

Those who want to be tested for anti-HIV should instead consult their general practitioner or attend a genitourinary medicine clinic, where the advisability of HIV testing will be discussed. If a decision to test is made the investigation is readily and freely available.

Future tests for anti-HIV are likely to be quicker and more convenient and to incorporate synthetic antigens and other innovations. New anti-HIV test kits may also detect antibody to related retroviruses such as HIV-II. Further tests for HIV components, antigen or genome, and assays with which people can test themselves are also likely. It is likely that some assay results will be found to imply a poor prognosis or increased infectiousness, and it is important to be aware of the psychological impact of such findings on those who are being tested.

From *AIDS: What you must know before you give Blood*. National Blood Transfusion Service, 1987.

Important precautions

Taking and transporting specimen

Careful venepuncture (clotted blood)

Dispose of syringe and needle safely

Place blood in a leakproof container that has a screw cap with rubber liner. Tighten firmly

Label specimen with patient's number and date of collection

Seal specimen in polythene bag, preferably using heat sealer, with request form attached outside

Send container to laboratory by secure route

Share information only with named staff in confidence

The need to discuss investigations for HIV infection with patients beforehand and to interpret the results to them afterwards is discussed elsewhere in this series. Except in special circumstances, permission to collect a sample for anti-HIV testing should have been sought by the doctor and expressed or implied by the patient. Clotted blood should be obtained by careful venepuncture without spillage or risk of an inoculation accident. The needle and syringe should be disposed of safely and the blood placed in a leakproof container, properly identified, and sent by a secure route to the laboratory.

The patient's identity and the suspected diagnosis should not be exposed, so numbers or codes rather than names may have to be used, even though the risk of misidentification is increased. In this delicate area information should be shared over the telephone only between individuals who know each other and written reports should be sent to named members of staff in confidence. All positive results should be checked again on a freshly drawn specimen. The consequences of failures and breaches of these procedures may be very serious for patients and prove costly to doctors. Because of the implications of positive laboratory findings for the patient's health, for his family and contacts, and for his social and professional life a high level of competence and sensitivity is to be expected from all who are concerned in instigating investigations for HIV infection.

Laboratory tests for HIV have increased understanding of AIDS and greatly facilitated diagnosis, management and control measures. However, to derive most benefit and do least harm with them they must be used wisely.

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The Western blot illustration was provided by J P Clewley, the electron micrograph by J E Richmond. "People who must not give blood" is taken from a Department of Health pamphlet, and the scanning electron micrograph by Dr David Hockley.

Lesson of the Week

Obstructive sleep apnoea and tonsillar lymphoma

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Obstructive sleep apnoea has been associated with several disorders. In particular, narrowing of the upper airway by fat in obese subjects, by structural abnormalities of the jaws in children, and by enlargement of the tongue and larynx in acromegaly are well recognised causes.¹ Adenotonsillar enlargement may be a problem in children and has been related occasionally to sleep apnoea in adults.² Current treatment of obstructive sleep apnoea may include

Patients with symptoms of possible sleep apnoea need careful, expert examination of the oropharynx

weight loss, drug treatment, nasal positive airway pressure, or surgery. We describe a case illustrating the importance of careful examination of the upper airway in these patients.

Case report

A 66 year old man was admitted to hospital after a road traffic accident in which he fractured his left wrist. He reported that the accident had been caused by his falling asleep at the wheel. He gave a history of tiredness during the day with pronounced daytime somnolence for six to 12 months.

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