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Tests for infection with HIV: slandered goods

Some of the early tests for infection with human immunodeficiency virus (HIV) gave inaccurate results, especially when applied to samples of serum collected in Africa. Important improvements have since taken place, but the harm done to the reputation of HIV tests lingers on.[1,2] The problem for those now doing the tests is to promote a better understanding of them and to show that the current assays, properly used, are sensitive and specific. They also have to devise measures that will eliminate the few technical mistakes, clerical errors, misinterpretations of results, and breaches of confidentiality that persist.

The course of HIV infection is characterised by a variable period before viraemia develops and an antibody response is made. The length of that interval is probably determined by the route of exposure, the dose and nature of the inoculum, and the age and natural defences of the host. After iatrogenic exposure to tissues infected with HIV, in particular blood and blood products, the interval has varied from about one month to one year, though antibodies usually develop within three months of exposure.[3,4] The same interval probably applies in sexual exposure to HIV, but this has not been definitely determined, and in a few cases the interval may be more than a year.[5]

During the time between exposure to HIV and antibody response a gross antigenaemia develops,[6] and probably the host is briefly highly infectious. Antibody is usually first detectable to viral envelope proteins, but antibody to core proteins is measurable as soon as antigenaemia wanes.[4] IgM class antibodies are prominent in the initial antibody response,[7] but then the response broadens in immunoglobulin class and range and increases in titre. Much later, antibody to the main core protein (p24) may become undetectable if that antigen is in excess[8]; and as immunosuppression increases HIV may be isolated from blood in tissue culture in an increasing proportion of cases.[9] The results of these investigations may relate to infectivity, have prognostic implications, and help in monitoring antiviral treatment, but they offer no additional diagnostic information. Once seroconversion has occurred simple antibody assays will detect HIV infection whatever the immunological competence of the subject.

Except at the outset of infection, therefore, infection with HIV is easily diagnosed with tests for antibody, whether based on enzyme or radioimmunoassay,[10] on latex or gelatin particles coated with antigen, or on viral proteins separated by electrophoresis and blotted on to strips of nitrocellulose paper (Western blots). The test antigens may be prepared from native virus proteins, from polypeptide replicas of the antigenic domains of these proteins, or by recombinant DNA technology and may be presented in various formats, each of which may have differing specificity and sensitivity.[10-12] Because of cross reactions between HIV antigens and other retroviral antibodies no assay is entirely specific, though some, especially those using native antigens and an anti-human immunoglobulin reagent in their final stage, tend to be less specific than others. Sensitivity, too, depends on several factors, including reactivity in the twilight interval that precedes the full antibody response to HIV infection, the breadth of antigenic representation in the assay, and the inherent responsiveness of the assay format.

In reasonably skilled hands many of the current commercial assays can achieve high specificity and sensitivity,[12] and the greatest benefits in screening blood donors and others are now likely to come not from attempting to identify a single best screening assay (a choice that will depend on local circumstances) but from providing accurate and prompt confirmatory testing, making adequate controls available, and doing regular performance assessment. In Britain screening blood donors has been facilitated by ready access to confirmatory testing centres and by the distribution of control sera that are weakly reactive to HIV and other small panels of samples of serum of varying reactivity. These provisions together with alternative testing sites and a rigorous self exclusion policy for donors at risk have, so far as can be judged, virtually eliminated the risk of HIV infection from blood given by Britain's voluntary donors.[13] Blood supplies have not been disrupted, and few donors have been deferred.

In the United States the problem of deferred blood donors with indeterminate reactions in Western blot assays has been greater, affecting about one in 3000 blood donors.[14] This experience has emphasised the need to agree on standard criteria for laboratory diagnoses of HIV infection, particularly when subjective assays such as Western blot and immunofluorescence are used. The confirmation of HIV in people with associated disease and known risk factors is usually straightforward and borne out by follow up investigations, but the status of blood donors with reactive

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screening tests that do not alter on follow up is problematical. It is best decided by agreed (albeit arbitrary) criteria that define the minimum test signals consistent with HIV infection. Those recommended by the manufacturer of the Western blot strips licensed by the Food and Drug Administration are reactions with viral protein bands p24, p31, and either gp41 or gp160.[14] It may, however, be six months before a recently infected person develops all these antibodies and thus, when there is a lesser reaction on Western blot, a donor can be fully reassured only after many months' follow up without increase in reactivity. Whatever is decided, it is doubtful whether blood that continues to be reactive in the local anti-HIV screening assay can justifiably be transfused.

Recent controversy over screening for infection with HIV in other contexts has tended to concentrate on these false positive reactions. Opponents of large scale testing programmes—for example, of antenatal patients or hospital inpatients—have invoked assay non-specificity as a reason not to attempt surveillance in populations with low prevalence of HIV infection.[12 14-16] There may be good reasons to hesitate before embarking on such initiatives, but the success of the British screening programme for blood donors shows that false positivity need not be one of them. Even on a single specimen a high degree of specificity can be achieved by applying several assays of different methods,[17] and this approach, which has worked well in confirmatory testing in the transfusion service, would be easy to apply in seroepidemiological studies. When the prevalence of HIV infection is low so few truly infected individuals would have an uncorroborated reaction by a single assay method that such reactions could be ignored.

A more proper concern, but one which has attracted less attention, is false negative results. These may arise because antibody has not yet appeared, because the antibody that is present is not detected, or because there has been a technical or clerical error. Errors may easily happen through fatigue or, when prevalence is very low, through boredom, and no system can be devised that will protect against all the ways that they can arise. If, however, laboratories were to test twice specimens from patients known to have suggestive illness or increased risk and doctors were never to accept unquestioningly an unexpected negative result some errors would be avoided.

Only by such attention to detail can the fullest advantage be gained from assays for antibodies to HIV. Properly used, these are excellent tests, and they will gradually win the good reputation they deserve. Moreover, the lessons learnt in developing, evaluating, and applying them will eventually raise standards in many other areas of diagnostic serology.

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100 years of contact lenses

Leonardo da Vinci described the optics of contact lenses over 500 years ago. Centuries later German glass blowing technology finally achieved the necessary precision, and Fick, a Zürich ophthalmologist, fitted his first patient 100 years ago. A recent conference in London celebrated the centenary and reviewed the possibilities and problems of modern lenses.

The early lenses were scleral. These large lenses compress the limbal blood vessels and obstruct the exchange of tears, reducing the oxygen diffusion essential for normal corneal metabolism. They are used occasionally to fit eyes whose irregular contours preclude corneal lenses.

Rigid small diameter corneal lenses were developed in the 1940s. The exchange of tears and hence oxygen transmission is encouraged by the considerable lens movement that occurs with every blink. More recently gas permeable materials have been introduced. These allow oxygen to diffuse directly through to the cornea, and some of the latest are sufficiently permeable to allow extended wear.

Soft contact lenses originated in Czechoslovakia in the 1950s. They extend just on to the limbal conjunctiva and are immobile. Corneal oxygenation relies on their gas permeability, not on exchange of tear fluid. Worn either daily or continuously for up to three months, patients like soft lenses because they are comfortable. In contrast, rigid lenses are uncomfortable on the first use and tolerance builds up only over weeks. Soft lenses are optically inferior to rigid lenses: corrected visual acuity may not be so good, and astigmatism is not so readily corrected.

Most patients are fitted with lenses for cosmetic or social reasons. A minority wear them, often on the recommendation of an ophthalmologist, as the best means to correct their eyesight. These patients include high myopes and those with aphakia and keratoconus. Therapeutic soft lenses are used occasionally to treat conditions such as bullous keratopathy or recurrent corneal erosions.

Contact lenses are generally considered safe; but there are few data on their use in the community, and the incidence of complications can only be estimated. Hospital based studies show more complications with soft contact lenses, especially when worn continuously, than with rigid types. One study of elderly patients with aphakia showed that serious complications occurred 10 times more often with soft lenses worn continuously than with hard lenses removed daily.[1] In two years of follow up the most serious complication, suppurative