EARLY AND COMPLETE DETECTION OF HIV EXPOSURE

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ABSTRACT. Currently, HIV diagnosis relies on serology. Yet in groups at high risk for HIV serology is not sufficient because of the window period between infection and seroconversion. There is a growing body of reports on HIV-infected yet seronegative individuals. Some tests have been developed to identify exposure to HIV by its effect on the cells of the immune system that would differentiate following exposure to the foreign antigens. Detection, in vitro, of HIV-specific B and T cells in seronegative, at risk individuals has been reported. In only some of these individuals was an HIV infection confirmed by other methods. These new assays to detect HIV immunity enable us to identify two new groups among seronegative, at risk individuals: namely those with immunity to HIV and a detectable HIV infection (silent carriers), and those with immunity and no proof of infection. Both groups have been exposed to HIV yet are not being detected by serology. Both might hold information on other forms of HIV immunity, possibly a protective one. Thus there could be an important role for other immunological assays in early detection of HIV exposure.

Keywords: AIDS; HIV; serology; diagnosis

Diagnosing an infection, or diagnosis at large, is based on certain assumptions. The validity of one depends on the other. Currently, HIV diagnosis is based on two major assumptions or dogmas: a) HIV infection is not transient, but rather chronic and is never cleared. Whoever becomes exposed to or infected with HIV remains an HIV carrier forever. b) HIV is a good immunogen, and all those exposed to it develop a panel of HIV-specific antibodies that are detectable in their serum. Based on these two assumptions, HIV testing, globally, relies on serology. Yet it has some major limitations. The blood banks spend time and money to exclude all individuals at risk for HIV regardless of their HIV serology. The need for that became apparent when blood from seronegative donors transmitted HIV to some recipients (1–5). Most of the donors who were tracked down eventually seroconverted weeks or months later. The period between exposure to HIV (and infection) and seroconversion is the “window period”. Because of this window period (50% seroconvert within 3 months of infection and 95% within 6 months)(6) there is a true need to eliminate individuals at high risk for HIV infection from the donor pools. This need for an additional parameter of HIV screening in the blood banks should set off the alarm for those involved in epidemiological studies based on HIV serology which often deal with populations at risk for HIV.

SILENT HIV INFECTIONS

A close look at the reports from different parts of the world reveals that there is more to the story of HIV infection than meets the eye (i.e., serology). There is a growing body of information about individuals who have HIV sequences in their cells, concomitant with a negative serology (7–13). Prospective studies have shown that some of them remain in that “seronegative yet infected” state for months and even years (7,11–13).

Immunology can offer two main avenues to explain this phenomenon: a) The immune system has not yet reacted against the virus. This can happen if: the virus entered and settled into the body in such a way that it totally avoided the immune system; or if the immune system did not have the ability to respond against the virus even though it “saw” it. (Low levels of expressed antigens or a “hole” in the T/B cell repertoire). b) The immune system “saw” the virus and reacted to it, but not by producing antibodies (at least not at detectable levels), i.e., it is the reliance on serology that masks the infection.
Immunity to HIV without Seroconversion

There have been some recent attempts to address this issue of possible immunity to HIV without seroconversion. In these studies two directions were taken: the first looked for anti-HIV responses other than antibodies, i.e., HIV-specific T cells; and the second looked for B cells that had differentiated to mature HIV-specific cells, but were not secreting antibodies. The logic behind both directions of research is that the immune system has a variety of mechanisms (perhaps even more efficient ones) to fight a viral infection other than a massive antibody response. In such a case, the HIV-specific B cells, even if they proliferate and mature post-exposure to HIV, will be suppressed and thus will not secrete antibodies (seronegative). On the other hand some subsets of HIV-specific T cells could be fully activated but not detected because they are not searched for.

Shearer and Clerici (14) have reported a method where HIV-specific peptides, predicted by Berzofsky et al. (15) to fit T cell epitopes, can cause the proliferation of T cells from HIV-seropositive individuals but not from low risk seronegatives. Using this system to look for HIV immunity in workers exposed to contaminated body fluids, they found that four of six had T cells that proliferated in response to at least two different HIV-specific peptides (16). They all remained seronegative months later. (This rate of detectable immunity post-exposure is in marked contrast to the reported seroconversion rate for needle sticks which stands at 1/2,000.) Shearer's group also reported such T cell immunity in a high risk individual over a year prior to seroconversion (17).

An in vitro polyclonal B cell activation test (P-BAT) was developed in an attempt to detect HIV-specific B cells that differentiated and matured following exposure to HIV but might be kept under some suppression or down-regulation. Its design was based on reports that some mitogens can activate B cells even out of a state of tolerance. After a few days in culture the supernatant fluids were tested for the presence of HIV-specific antibodies. A P-BAT study was done on a downtown hospital population in Atlanta, GA, USA, where 25% of those tested for HIV were found to be seropositive. It revealed that 30 of 165 seronegatives were P-BAT positive, i.e., they had detectable HIV-specific antibodies in vitro (18). Similar studies were carried out in Israel (19) and in Spain (20). The population studied comprised the wives and children of HIV-seropositive carriers. In both these groups individuals were identified who showed in vitro HIV-specific immunity, with no seroconversion.

Immunity vs. Infection

HIV-specific immunity is a telltale sign of an exposure to HIV. It does not provide us with information on the current state of the infection. For that one must look for HIV itself, using methods such as polymerase chain reaction (PCR), in situ hybridization, virus isolation, and antigen detection. In animal models of AIDS, seronegative yet infected monkeys and cats have been reported (21,22) which remain healthy although the virus can be isolated (though not easily) from their blood and they can transmit the infection to others (23,24). Shearer's group reported a full correlation between serology and PCR, thus those that were seronegative but demonstrated specific T cells were PCR negative (16). On the other hand using the P-BAT, some seronegative, yet PCR-positive, individuals were identified (18,19).

A negative result of PCR or virus isolation could mean that either there is no virus or the virus, although present, is not detectable by the method used. The reason for the latter can be that the virus levels are below the detection level. The wrong tools were used to search for the virus [i.e., the virus is defective or mutated (21)], or the wrong place was searched (it could be sequestered in a tissue other than blood). Regardless of what the reason is, the presence of an HIV-specific immunity with no detectable virus probably means that there was an exposure to the virus but it did not lead to an active infection.

SEROLOGY — A LIMITED VIEW OF HIV EXPOSURE

These data indicate that serology does not tell the whole story about exposure to, and infection with, HIV. Serology as the golden standard of HIV diagnosis has offered us a study of HIV immunity via a biased population: the seropositives. There are probably many exposures to HIV that do not lead to the path of seropositivity, disease and death. This means that to date we do not know the full extent of exposure to HIV in any population. Looking for specific immunity, formed within the immune system following an exposure to a pathogen, offers an amplification of a signal for the detection of that exposure. No one really needs a higher incidence of reported HIV infection or exposure in the general population than already known, but an ostrich attitude will not provide a solution at any time. In this case, following and understanding hidden HIV exposures could offer new hope for the emergence of possible novel solutions to the epidemic.

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REFERENCES

1. Ward JW, Holmberg SD, Allen JF, et al. Transmission of human immunodeficiency virus (HIV) by blood transfu-