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Six Reasons to Re-Test HIV Positive Subjects through Enhanced Protocols under a Yearly Basis, and to Communicate the Results to the Scientific Community

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Editorial

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Editorial

Almost 40 years after being described by Luc Montagnier, the Human Immunodeficiency Virus (HIV)presents innumerable intriguing issues [1]. We consider it is convenient to re-test HIV positive subjects with enhanced protocols and that investigators of the international community join their efforts for reaching better results on the health conditions and quality of life of these subjects. To gather adequate information, it urges to implement a complete and detailed Global Diagnostic and Treatment Database (GDTDB) in which researchers on this topic would be able to register and query information on the evolution of HIV positivesubjects. Anonymized data about gender, age, full diagnostic information available, including Immunoassays, Western Blot strips, microscopy imaging, prescribed medications - with their doses-among others, should be registered. In addition, subjects' rights to be periodically informed about their evolution must be fulfilled. Here, we present six relevant problems that can be addressed through this initiative:

The Need for a Better Understanding of the Effectiveness of Natural Antibodies against the Infection

HIV is a rare kind of virus in which the presence of the own antibodies in the human blood does not warrant immunity for the affected subjects, but infection. Neutralizing antibodies (NAbs) typically play a key role in controlling viral infections and contribute to the protective effect of many successful vaccines. In the case of HIV-1 infection, there is compelling data in experimental animal models that NAbs can prevent HIV-1 acquisition, although there is no similar data in humans and their role in controlling established infection in humans is also limited [2]. We cannot discard the possibility that high levels of antibodies in the blood, associated to changes in structure and function of the virions due to their successive replicationsmighteventuallylead to the complete eradication of the virusand its reservoirs from the organism. It is necessary to bear in mind that the conformation of fully functional virions heavily depends on complex assembly processesthat may degenerate along with each new replication [3].

The inadequacy of the existent testing protocols and algorithms

Currently, the Centers for Disease Control and Prevention of U.S.A. (CDC) recommends up to three stages in the diagnostic process [4]:

a. The screening phase, using immunoassays, to detect the presence of P24 antigens and/or antibodies. P24 is an HIV viral protein, and is part of the GAG, the genomic region encoding the capsid proteins (group specific antigens). The precursor is the p55 myristoylated protein, which is processed to p17

(MAtrix), p24 (CApsid), p7 (NucleoCapsid), and p6 proteins, by the viral protease [5]. If the first stage result is not reactive, the presence of the virus in the subject at that moment is discarded. If this result is reactive, the algorithm indicates:

b. Immunoassays for discriminating the presence of HIV-1 and/or HIV-2, and, after this second stage beingreactive, the algorithm indicates:
c. Nucleic Acid Tests (NATs) tests [4].

CDC claims that **NATs** look for the actual virus in the blood, but this is not true, as NATs kits look only for the presence of proteins nucleic acid precursors, usually p24. So, in fact, solely the presence of p24 protein is tested across the whole algorithm [6]. Under the recommended current protocols, the presence of all the other nine proteins of the virus is never really tested. Moreover, as diagnostic algorithms of the Centers of Disease Control and Prevention (CDC, U.S.A.) have been changing constantly since 1982, the vast majority of subjects diagnosed as HIV positive today, has been tested and confirmed with techniques that are not in use by now. Again, it would be very important to know how these subjects test actually, and compare the updated data with the previous one. Furthermore, as we cannot infer that the existence of only one viral protein, from a total of 10, assures the existence of complete and competentvirions, it urges to determine how the presence of p24 antigens and antibodies correlates with the presence of fully structural and functional virions. So, microscopy images, among complementary functional information would be very useful, and whenever possible, should be added to the GDTDB.

The Lack of Adequate Confirmatory Tests

Because of the previously mentioned reasons, it is mandatory to claim for very precise confirmatory tests after the screening stage of the diagnostic process. However, no gold standard for confirming the presence of an HIV infection is currently available. Not even for the research community. Diagnostic confirmation tests had been conducted through Western Blot diagnosing techniques for more than thirty years, but ceased to be part of the recommended protocols of the CDC in 2014 [7]. As we have shown, instead of WB techniques, CDC recommends the employ of NATs, and, as a matter of fact, CDC does not consider this tests as being "confirmatory". As an illustration of this controversy, the Geenius™ HIV 1/2 Confirmatory Assay, which is intended as an aid in the diagnosis of infection with HIV-1 and or HIV-2., clearly warns that *"HIV and AIDS related conditions are clinical syndromes and their diagnosis can only be established clinically* [8]. Thus, we strongly suggest that WB techniques should be used again for each annual subject re-testing, as is the only resource that brings information about the complete protein profile evolution in time of an eventual infection.

There are no standards to measure the Viral Load

Once a subject has been diagnosed as HIV positive, NATs, or Polymerase Chain Reactions (PCR), are used to measure his or her viral load. Being known as if it were a univocal testing technique, PCR techniques are far from being unique, and strongly depend on the primers that are used to detect certain short segments of nucleic acid that are supposed to originate certain full viral proteins [9].

The dangers of Rapid Diagnostic Tests (RDT)

Recently released HIV rapid diagnostic tests (RDT) have enabled widespread implementation of HIV programs in resource-limited settings. If the tests used in the diagnostic algorithm are susceptible to the same cause for false positivity, a false-positive diagnosis may result in devastating consequences. In resource-limited settings, the lack of routine confirmatory testing, compounded by incorrect interpretation of weak positive test lines and use of tie-breaker algorithms, can leave a false-positive diagnosis undetected [10].

The need for updating Informed Consents

CDC states that: Separate written consent for HIV testing is not recommended. General informed consent for medical care that notifies the patient that an HIV test will be performed unless the patient declines (opt-out screening) should be considered sufficient to encompass informed consent for HIV testing.

Prevention counseling-defined as an interactive process of assessing risk of infection, recognizing specific behaviors that increase this risk, and developing a plan to reduce risk-should not be required with HIV diagnostic testing or as part of HIV screening programs in health-care settings [11].

We cannot agree with these statements. We consider that HIV positive subjects have to be fully and frequently informed about their condition and evolution. A yearly based re-testing session is a good opportunity to update their informed consent, and to communicate them

eventual changes in testing protocols, advances in clinical and scientific research related to their condition and reports on drug toxicity and adverse reactions. With the advent of antiretroviral therapy (ART), individuals with HIV are now experiencing the effects of long-term-and, in some cases, lifelong-exposure to HIV treatment. Individuals with HIV are at increased risk of end stage organ disease relative to their peers and may experience accelerated age-associated comorbidities. In particular, long-term HIV infection and its treatment have been implicated in renal disease, abnormalities in bone mineral density (BMD), and osteoporosis [12].

Conclusions

We strongly recommend that all HIV positive subjects should be re-tested in a yearly basis, having their anonymousinformation registered in a public accessible database. All the diagnostic procedures should be standardized and registered, using the same reactive, assays, primers and protocols to univocally detect the existence of various viral proteins or their precursors. Western Blottechniquesshould be used consistently for each re-testing session to gain information about the yearly protein profile evolution of the infection. Microscopy evidence should be added to each annual record whenever possible. Patients should be informed permanently about their conditions and evolution in each re-testing session.

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