Serodeconversion of HIV Antibody-Positive AIDS Patients Following Treatment with V-1 Immunitor

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It is extremely rare when HIV seropositive adult patients experience spontaneous loss of antibodies, that is, seroreversion. The disappearance of HIV antibodies was occasionally attributed to iatrogenic intervention—serodeconversion. Such interventions include: HAART; oral interferon; Chinese herbal remedies; and therapeutic AIDS vaccines derived from pooled blood. Oral therapeutic, alloimmune AIDS vaccine, V-1 Immunitor (V1), was administered to 60000 HIV-positive Thai patients. The administration of V1 resulted in serodeconversion among 23 individuals. The patient group consisted of 9 females (39%) and 14 males (61%) including two 2-year-old boys. The age range was 2–58 years with mean/median 29/29.3 years. Patients were tested seropositive for HIV at least once before being enrolled on V1. The duration of treatment until discovery of seronegative status ranged between 2 weeks and 15 months with average/median 7.2/8 months. Time to seronegativity was correlated with baseline disease stage ($R = 0.62; P = .002$). The seronegative status was positively associated with V1-induced undetectable or low viral load ($R = 0.65; P = .0008$). The odds ratio analysis comparing the outcome of our study with published surveys of diagnostic accuracy of laboratory tests suggested that the probability of HIV antibody testing error was remote ($P < .000001$). The possible causes responsible for this unusual phenomenon are discussed.

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1. Introduction

The HIV seropositivity revealed by an antibody test is indicative of virus infection. Due to a small proportion of false-positive, false-negative, and ambiguous (indeterminate) findings occurring in a general population, this test is not perfect but remains, however, the first-line laboratory procedure for diagnostic purposes. It is currently accepted that antibody tests are nearly 100% sensitive and about 99% specific [1, 2]. The frequency of false-positive HIV serology in a low-prevalence population, for example, military recruits from rural United States, is 1/135 000 [1], while for blood donors in Minnesota is 6/million [2]. A survey of 5 million blood donors’ samples found that the prevalence of false positives was 1/251 000 [1]. To reduce the chances of technical or clerical error, the antibody tests are confirmed by additional tests like ELISA, western blot, and PCR analysis. When tests are combined, for example, ELISA and western blot, the false-positive rate has been reported to be as low as 1/100 000 [3]. Others have indicated that even when tests are combined, about 3% of the investigated sera were false-positive, false-negative, or noninterpretable [4].

It is extremely unusual when symptomatic or asymptomatic individuals with culture- or PCR-confirmed HIV infection do not produce virus-directed antibodies and remain persistently negative beyond the expected window period. A few such cases have been reported in the literature, and most of which were due to agammaglobulinemia of unknown immune dysfunction [5–11]. These exceptions only reinforce the general notion that once a person is diagnosed with HIV, he or she remains antibody-positive for the rest of his or her life.

Newborn babies usually lose HIV antibodies acquired from their HIV-positive mothers. The average time to seroreversion after birth is usually 12–16—maximum 18 months [12]. However, with the exception of very few instances,
these infants are not HIV-infected [13]. An adult with confirmed HIV infection seldom changes seropositive status. Occasionally, this has been observed among individuals who were at the terminal stage of disease [14, 15]. Cases of spontaneous seroreversion among patients from other categories are exceedingly rare [16–18].

In addition to cases of spontaneous loss of antibodies, there are several reports attributing this phenomenon to iatrogenic intervention, referred to as serodeconversion. The earliest known report is related to administration of low-dose oral interferon, whereby 18 out of 204 treated patients became HIV-negative [19]. A clinical study of Chinese herbal preparations revealed serodeconversion in eight AIDS patients [20]. Two recent reports have shown for the first time that patients with acute or early HIV infection may lose HIV antibodies as a result of highly active antiretroviral therapy [21, 22], supporting the notion that serodeconversion seldom occurs in patients on antiviral therapy [1]. Finally, both therapeutic AIDS vaccines produced from the blood of HIV patients, that is, Nigerian Abalaka’s vaccine and Cameroonian Anomah Ngu’s vaccine, were reported to produce seroreversion in several dozen AIDS patients [23, 24].

V-1 Immunitor (V1)—the first commercial therapeutic AIDS vaccine—has been registered by the Thai FDA as a food supplement and experimental drug [25]. The vaccine comprises heat-inactivated HIV antigens derived from pooled blood of HIV-infected donors. Extensive preclinical studies have shown that V1 is safe [25]. In a longitudinal survey in 400 patients, about 85% reported improvement, 6% reported no difference, and 9% reported minor adverse reactions, which did not last more than one week [26]. Our earlier open-label and subsequent placebo-controlled clinical studies have shown that V1 administration increases absolute CD4 and CD8 cell counts in both HIV-positive and HIV-negative subjects [27–29]. Viral load measurements have shown statistically significant trend toward decrease [27]. Other clinical benefits included the reversal of AIDS-associated wasting and normalization of elevated liver enzymes in HIV-positive patients coinfected with hepatitis viruses [26]. Patients on V1 rarely develop new fungal or bacterial infections, suggesting that V1 restores the mucosal immune response to opportunistic infections [26]. Finally, in a survival study, the end-stage AIDS patients had 15.8 times longer life expectancy than those who declined V1 treatment [30]. This single clinical endpoint is clearly more important than surrogate endpoints such as viral load and T-cell counts. In this study, we analyze yet another phenomenon associated with V1 therapy, that is, an observation that some AIDS patients who received V1 became HIV-antibody-negative.

2. Materials and Methods

2.1. Patients. Sixty thousand patients from Thailand with documented history of HIV infection have received or are currently receiving V1. In this retrospective survey, every patient who became aware of HIV-antibody-negative status following treatment with V1 was considered for the analysis. Patients who did not have reliable antibody test, traceable to the original issuing lab, were not included and only those with confirmed serodeconversion as compared to baseline status were included in this survey. The physical examination and patients’ interviews were performed at Rajavithi General Hospital in Bangkok. Patients self-administered either one or two V1 tablets per day. The dose for children was twice smaller. With the exception of one patient (no. 22), none of them received conventional antiretroviral therapy or participated in any AIDS vaccine trials conducted in Thailand during treatment period. Patient no. 22, a two-year-old boy from Tanzania, was on AZT monotherapy for a few months shortly after the birth but due to drug intolerance and lack of clinical improvement he discontinued treatment before starting on V1.

2.2. Vaccine. V-1 Immunitor (V1) is derived from specially processed heat and chemically inactivated, pooled blood of HIV-infected Thai donors. The vaccine is formulated into an oral tablet according to a proprietary process developed by us [25]. As pooled blood from unrelated donors was used for vaccine manufacturing, V1 can be regarded as an allovaccine since in addition to viral proteins it also contains alloantigens from the blood. The vaccine is manufactured in Thailand by Immunitor (Thailand) Co., Ltd., and is approved by Thai Food and Drug Administration (FDA) as a dietary supplement and investigational drug. V-1 Immunitor is provided as 850 mg coated tablet—ten of which are sealed in a “blister” package (Figure 1).

2.3. HIV Tests. Most of patients’ sera were examined by rapid tests for HIV antibodies (Bioline HIV1/2, Immunochemical Lab, Thailand and Determine HIV1/2 Abbott/Dainabot, Japan). Another approved antibody test used in Thailand as a second-line test is ELISA or enzyme immunoassay (EIA). These tests are also commercially available: Uniform II Ag/Ab kit (Organon Technika, The Netherlands) or HIV1/2 (Abbott Laboratories, USA). Occasionally, latex particle agglutination test (GPA, Serodia-HIV 1/2, Fujirebio Inc., Japan) was utilized as an alternative to ELISA. The choice of second-line tests depended on their availability at the testing lab and patients’ ability to pay for them. In some cases, commercial western blot assay was conducted in addition to antibody tests (HIV Blot 2.2, Genelabs
Diagnostics, Singapore). As tests were performed in different labs, the QA/QC standards may vary but these variables were beyond our control due to retrospective nature of this study.

2.4. Viral Load Measurement. Plasma viral concentrations were measured at various independent hospitals and commercial labs at patients’ own choice. As PCR tests are expensive, very few patients were able to afford such tests. Depending on the individual lab, the commercial viral load kits were used without any specific preference. These qualitative PCR kits were either RNA PCR kit (Roche Diagnostic Systems, Inc., Branchburg, NJ, USA) or branched DNA kit (Bayer, Tarrytown, NJ, USA). The sensitivities of these tests were 400 and 50 viral copies per mL, respectively. In addition, qualitative tests for HIV-1 were performed by in-house developed PCR method according to our own published protocol [31]. The lowest detection threshold of this test was estimated to be not less than 100 HIV copies per mL.

2.5. Statistical Analysis. Data were analyzed with StatMost software version 2.5 (DataMost Corporation, Salt Lake City, Utah, USA) and SISA—free online program—with courtesy of Daan Uitenbroek. The main parametric pairwise test was Student’s t-test. The odds ratio (OR) was estimated at 95% Wald confidence interval (CI). For assessment of correlation between seronegative status and viral load, we have used nonparametric Spearman’s rank-order test. The significance level for all tests was set at $P \leq .05$.

3. Results

The patient group consisted of 9 females (39%) and 14 males (61%) including 2 two-year-old boys. Ages ranged within 2–58 years with a mean age of 29 years (median age = 29.5 years). The duration of V1 treatment until a patient sought to check the antibody status ranged between 2 weeks and 15 months with an average of 7.2 months (median range = 8 months). All patients were tested for HIV seropositivity prior to administration of V1. While most of them were tested only once before treatment initiation, on average, there were two positive tests per patient. Once patients knew the qualitative tests for HIV-1 were performed by in-house developed PCR method according to our own published protocol [31]. The lowest detection threshold of this test was estimated to be not less than 100 HIV copies per mL.

Due to the retrospective nature of this study, the data, especially concerning viral load, are incomplete. Nevertheless, it is clear that obtained results are highly unusual. Why would previously HIV-antibody-positive patients become seronegative after treatment with V1?

The possibility that all these patients were false-positive at the baseline is unlikely since they were symptomatic and sought V1 treatment because they were suffering from AIDS-related symptoms. These symptoms, that is, low CD4 counts; weight loss; a whole range of opportunistic infections; such as oral thrush, TB, skin lesions, persistent diarrhea, and in one case even Kaposi’s sarcoma, were severe enough to score them as belonging to advanced disease stage [33].
Table 1: Summary of lab tests on serodeconverted HIV-positive patients treated with V1.

<table>
<thead>
<tr>
<th>No.</th>
<th>Gender</th>
<th>Age</th>
<th>No. of Months since known as being infected as per patient’s recollection</th>
<th>Months on V1</th>
<th>HIV positive times</th>
<th>HIV negative times</th>
<th>HIV PCR copies before</th>
<th>HIV PCR copies after</th>
<th>Qualitative PCR positive</th>
<th>Qualitative PCR negative</th>
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aTests were done at baseline before treatment initiation.
bTests were performed after treatment initiation.
cTests were done after treatment initiation, not at baseline.
dDue to high cost, some patients had qualitative PCR tests, that is, positive or negative, rather than quantitative ones—all of such tests were carried out after treatment initiation.

One may argue that clinical symptoms were not HIV-related and all these patients were initially false-positive due to random incidence of such cases in general population. This scenario, however, remains highly unlikely since, according to the “normal” incidence of false positives in healthy individuals, one would expect no more than 1/4 (0.25%) to 1/2 (0.5%) false-positive persons among 60000 V1-treated individuals [1]. On the contrary, in placebo-controlled, randomized phase II clinical trial of V1 published in 2004, we have shown that one out of 29 V1-treated patients became HIV-negative, suggesting much higher conversion rate [29]. The cases of true, confirmed seroreversion, that is, a seroreactive or positive sample with subsequently one or more nonreactive samples from the same person, are extremely rare [10–18]. In fact, most, if not all, cases of apparent seroreversion seem to be errors of attribution or lab
testing [1–4]. A survey on 2,580,974 army recruits identified 4911 seropositive individuals by two independent samples, among whom only six were potential seroreverters [32]. Further review of these cases revealed that five actually were HIV-seroreactive patients who had samples from nonreactive individuals mistakenly attributed to them, while the sixth had a testing error. Mistakes in the testing process were identified in other 26 cases indicating the cumulative error rate of 12.4 per 1 million individuals. In this paper, we included only those patients who had confirmed tests traceable to the original testing lab and excluded anyone who had indeterminate results or whose records could not be traced. The odds ratio analysis comparing our data with published reports of false-positive or false-negative cases in large surveys rules out that what we have observed is a random event due to testing error (see Table 2).

Even the two infants in our study who were born to HIV-positive mothers are unlikely to be false-positive since they were both symptomatic and tested repeatedly positive past the age of 18 months, a timepoint by which the newborns lose maternal antibodies [12, 13]. Table 1, however, shows only one positive baseline test for each of the boys since other tests could not be traced to original issuing labs.

Another aspect worthy of note is that patient no. 17 tested negative after 2 weeks on V1, whereas patients nos. 6 and 7 became seronegative after 1 month. As on average, it took 7–8 months and as long as 15 months to attain seronegative status; the two-week period appears to be very short. Nevertheless, considering that half life of anti-p24 IgG immunoglobulin is 11–19 days, it is possible that HIV antibodies were still present but their levels have decreased below detection limit of standard assays [34]. This possibility is not entirely implausible. The antibody tests of some of the patients were fluctuating from positive to negative and back to positive during the therapy suggesting that the levels of anti-HIV antibodies were at the borderline of detection threshold. Furthermore, despite being seronegative, four patients—nos. 3, 9, 10, and 11—were still showing the presence of the virus as detected by PCR analysis. Latter situation is reminiscent of extensively studied high-risk seronegative (HRSN) individuals who have remained HIV-negative despite repeated exposure to the virus. It has been shown recently that HRSNs often carry extraordinary low levels of HIV-1 DNA [35]. However, as opposed to our patients, these individuals are free of disease symptoms and are commonly known as long-term survivors.

It is not unusual to see the decline in antibodies in very late stage of HIV disease which may be explained, in part, by higher viral burden and reduced availability of circulating antibodies due to antibody-antigen complex formation. In our situation, as there is a documented decrease in viral burden, we would expect to see a surplus of antibodies rather than their reduction. Furthermore, time to reach seronegative status was not random. It was correlated with baseline disease stage, meaning that those who are better off initially were likely to require less time to convert than those with advanced disease (R = 0.62; P = .002). Incidentally, all three patients—nos. 17, 6, and 7—who converted to seronegative status under one-month time were all in earlier disease stage.

The therapeutic vaccination was first introduced into clinical practice by the French researcher Daniel Zagury as a treatment option for AIDS more than 20 years ago [36]. Due to inherent problems associated with HAART, this concept has become increasingly popular nowadays. However, nearly 30 therapeutic vaccine candidates were tested in over 60 clinical trials, but they have not produced any evidence of clinical benefit, let alone serodeconversion [37]. The only exception are pooled blood-derived AIDS vaccines, developed by Drs. Abalaka and Ngu, THIVAC and VANHIVAX, respectively, which produced favorable clinical outcomes and have caused serodeconversion in some of their patients [23, 24]. Their results provide further support to a possibility that what we have observed with V1 is not due to testing or clerical error.

From the immunological point of view, this phenomenon seems to be related to an observation first made by Stott, who reported that macaques vaccinated with a preparation of whole killed human cells infected with SIV were fully protected against subsequent challenge [38]. Curiously, animals immunized with a control preparation consisting of killed human cells without SIV were also protected. This observation appears to relate to the fact that during the budding process through the cell membrane, SIV as well as HIV acquires several hundred host cell molecules [39]. Thus, the immunization with host’s proteins was equal to or more effective than immunization with viral antigens.

While the interpretation of Stott study has been contested, several studies appear to be in agreement with this seemingly unusual finding. For example, Lopalco et al. reported that the enigmatic phenomenon of exposure to HIV without seroconversion was associated with auticell auto-anti-bodies but not with HIV-neutralizing antibodies directed against viral antigens [40]. Sera from polytransfused, HIV-negative individuals who often develop immune responses against themselves, including anti-HLA antibodies, were shown to neutralize HIV-1 [41].

The concept that AIDS is an autoimmune disease and thus alloimmunization or in other words, immunization with autologous cellular antigens with or without HIV antigens, as a basis for immune-based therapy of HIV has been advocated at length by us and others [42, 43]. Several therapeutic approaches based on this concept have been proposed. Daniel Zagury, who pioneered therapeutic HIV immunization, made his original vaccine from formaldehyde-treated leukocytes derived from the blood of seropositive patients [36]. His vaccine has shown dramatic clinical improvements, but unfortunately his work has not been followed. The autologous T-cell vaccination developed by Abulafia-Lapid et al. has shown encouraging results with over 50% (median of 70%) increase in CD4 cell counts. Their vaccine consists of in vitro propagated, glutaraldehyde-inactivated, autologous T cells which are injected back to HIV-positive donors [44]. Remune is another vaccine in this category; however, due to the purification process of virus particles from the supernatant of cell culture, it may not possess sufficient quantity of alloantigens, which may explain persistent incertitude in clinical effect [45]. Oral feeding of alloantigens, as in case of V1, is an approach that makes sense since it induces immune
tolerance—a strategy that has been shown effective in therapy of chronic hepatitis B and C—diseases that are caused by autoimmune reaction against virus-carrying liver cells rather than direct cytopathic effect of hepatitis viruses [46–48]. Israeli et al. have shown that oral feeding of hepatitis B antigens in combination with allogeneic liver cells to patients with chronic hepatitis leads to a dose-dependent reduction of anti-HBV antibody titers—an observation that supports, albeit indirectly, our findings [46]. In fact, we have shown earlier that oral administration of V1 to normal healthy volunteers does not induce systemic anti-HIV antibodies [28].

These investigations relate to the often ignored notion of autoimmune nature of AIDS as a disease [42, 43]. If this concept is correct, then the prevailing AIDS vaccine strategy aimed at activating the immune response against HIV instead of inducing immune tolerance is flawed. Results of recent trial of therapeutic AIDS vaccine in which HIV-directed immune activation was associated with increase in viral load further support this notion [49]. The observed phenomenon of loss of antibodies against HIV and clinical improvement can be readily explained by tolerance induction. Due to paucity of guiding precedents relating to serodeconversion [50–52], the present findings need to be interpreted cautiously and additional case studies have to be acquired and analyzed to rule out any possible error.

Acknowledgment

This paper is dedicated to the memory of Ms. Sureeporn Limpasupalerk, the Senior Medical Technologist of Lerdsin Hospital who ended her life on October 17, 2002, after being unjustly accused by her superiors of making error in an HIV antibody test of a patient who became seronegative after treatment with V1. The authors did not know her personally and have learned about her fate from the media reports [53]. They express their admiration for her courage to stand behind her results, and convey their sincere condolences to her family and coworkers.

References


