

Nucleic Acid Testing for Diagnosis of HIV in Cases of Negative or Uncertain Antibody-Based Testing Results in China and Abroad Diagnosis in Cases of HIV Antibody Negative or Uncertain

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ABSTRACT

Objective: To summarize the negative or uncertain HIV/AIDS cases reported in domestic and foreign literature from 1994 to 2017 and provide evidence for the diagnosis of HIV/AIDS cases. Methods By reviewing the literature, we collected antibody-negative or uncertain HIV/AIDS cases reported at home and abroad.

Results: We summarize 34 cases with seronegative or uncertain HIV antibody testing results using ELISA or WB methods, which were reported internationally between 1994 and 2017.

Conclusion: These cases demonstrate the crucial need for HIV nucleic acid qualitative or quantitative detection for diagnosis of HIV infection when antibody-based methods yield negative or uncertain results.

Abbreviations: HIV: Human Immunodeficiency Virus; AIDS: Acquired Immune Deficiency Syndrome; ELISA: Enzyme-Linked Immunosorbent Assays; WB: Western Blot; CD4: Cluster of Differentiation 4; VL: Viral Load

Introduction

Normally, HIV infections can be diagnosed with rapid tests or enzyme-linked immunosorbent assays (ELISA), and confirmed by Western blot (WB) methods. However, in rare situations where patients are not producing antibodies in sufficient quantities, these test methods yield negative or inconclusive results. These situations include acute infection, during which the well-known “window period” occurs when viral infection is newly present, but the host has not yet had enough time to generate antibodies to viral antigens Another low-antibody situation occurs when patients are in the advanced stages of AIDS and are so immunocompromised (as evidenced by their extremely low CD4 cell counts) that they fail to make enough antibodies to be detected by conventional

antibody-based methods. In these extreme situations, laboratory results are not consistent with clinical manifestations, which can lead to misdiagnosis or misjudgment of prognosis [1]. In this article, we summarize previous domestic and international reports of HIV diagnosis in patients with negative or uncertain results on antibody-based HIV testing due to insufficient antibody levels [2-3].

Methods

We had a reference to the literature published in the journal AIDS in 2010 by Spivak et al. [4] which identified 25 cases of HIV infection worldwide between 1994 and 2009. Using the same method, We performed a comprehensive literature search in both Chinese, using the scientific and technological literature service system of

the Chinese Center for Disease Control and Prevention (China CDC; <http://literature.chinacdc.cn/>), and in English, using the online search engine of the United States National Library of Medicine (US NLM; <https://www.ncbi.nlm.nih.gov/pubmed/>) between 1994

and 2017. Search terms used were “HIV seronegative” and “HIV uncertain.” Articles were screened to ensure that they reported on one or more HIV cases with negative or uncertain HIV antibody-based testing results at the time of diagnosis of HIV infection.

Results

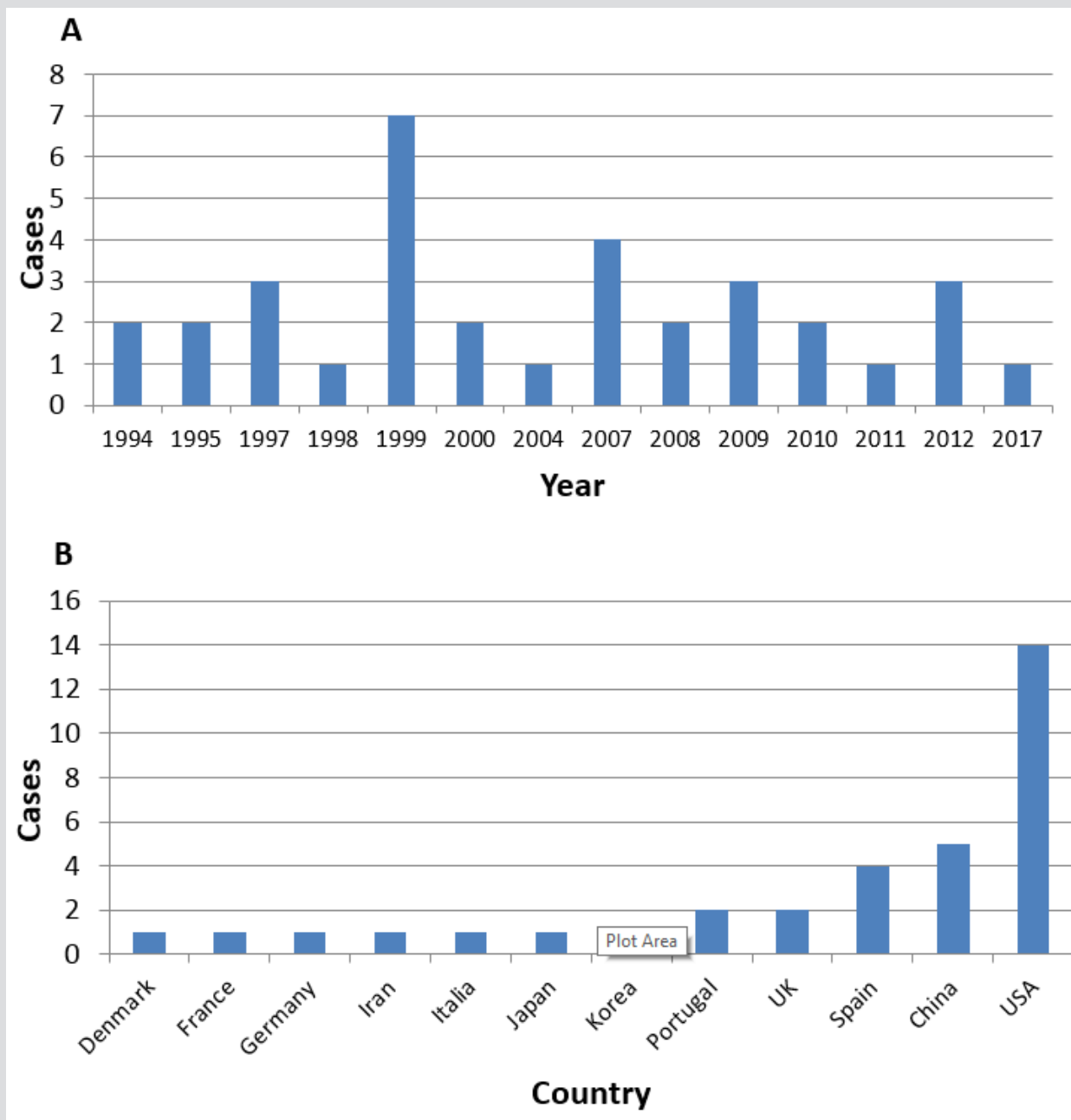


Figure 1: Year [A] and country [B] of HIV cases that were either HIV-seronegative or uncertain upon initial antibody testing worldwide, 1994-2017.

Included Studies

Between 1994 and 2017, a total of 28 publications, documenting 34 individual cases, met the study eligibility criteria were included in the analysis. 5 cases were found and reported in China. In

addition to the 25 cases summarized by Spivak et al., another 4 cases were reviewed and collated, they were N0.27,32-34 cases in Table 1. Demographic and clinical characteristics of all 34 cases are tabulated in Table 1, and the numbers of cases by year, and by country are plotted in Figure 1.

Table 1: Demographics and clinical features of HIV cases that were either HIV-seronegative or uncertain upon initial antibody testing worldwide, 1994–2017.

Case No.	Year Reported	Sex	Age	Country	Viral Load (copies/mL)	CD4 Count (cells/ μ L)	HIV-Related typical Complications & Opportunistic Infections	References
Cases Reported in China								
1	2007	Male	37 yr	China	153,000	5	pneumocystis carinii pneumonia	Hei Fa Xin [4]
2	2008	Male	16 mo	China	150,000	-	oral candidiasis	Zhang Yun Zhi [5]
3	2010	Female	33 yr	China	>1,000,000	7	persistent diarrhea	Li Yan [6]
4	2012	Male	69 yr	China	72,000	8	tuberculosis	Qin Ying Mei [7]
5	2017	Male	46 yr	China	42,969	6	Kaposi sarcoma	Zhang Hong [8]
Cases Reported Elsewhere								
6	1994	Male	26 yr	Spain	-	208	tuberculosis	Soriano [15]
7	1994	Male	24 yr	Japan	-	230	pneumocystis pneumonia	Oka [16]
8	1995	Female	24 yr	USA	105,000	27	acute interstitial pneumonitis	Wegner [17]
9	1995	Male	19 yr	Denmark	-	87	cerebral abscesses	Martin-Rico [18]
10	1997	Male	36 yr	USA	-	129	pneumocystis pneumonia	Reimer [19]
11	1997	Female	38 yr	France	>1,000,000	0	bacillary angiomatosis	Montagnier [20]
12	1997	Male	31 yr	USA	-	230	pneumocystis pneumonia	Michael [21]
13	1998	Female	4 mo	USA	577,697	10	pneumocystis pneumonia	Quinonez [22]
14	1999	Male	30s	USA	337,000	94	pneumocystis pneumonia	Sullivan [23]
15	1999	Male	30s	USA	>1,000,000	15	pneumocystis pneumonia	Sullivan [23]
16	1999	Male	20s	USA	773,000	11	pneumocystis pneumonia	Sullivan [23]
17	1999	Female	10s	USA	480,000	8	pneumocystis pneumonia	Sullivan [23]
18	1999	Female	20s	USA	254,000	2	pneumocystis pneumonia	Sullivan [23]
19	1999	Female	29 yr	UK	570,000	100	pneumocystis pneumonia	Rice [24]
20	1999	-	-	USA	38,000	2	-	Ellenberger [25]
21	2000	Female	29 yr	UK	-	229	herpes	Candotti [26]
22	2000	Female	2 mo	Italy	>1,000,000	170	neurologic symptoms	De Rossi [27]
23	2004	Female	29 yr	Portugal	-	102	typhoid fever	Cardoso [28]
24	2007	Male	47 yr	Germany	242,287	2	esophageal ulcer	Monkemuller [29]
25	2007	Male	37 yr	Korea	>1,000,000	89	diarrhea	Chin [30]
26	2007	Female	46 yr	USA	>750,000	38	weight loss	Novitsky [31]
27	2008	Male	28 yr	Spain	122,000	4	Kaposi sarcoma	Ortiz de Lejarazu [32]
28	2009	Male	26 yr	USA	320,000	108	pneumocystis pneumonia	Dalmau [33]
29	2009	Female	15 yr	USA	20,000	0	cryptococcus	Dalmau [33]
30	2009	Male	29 yr	Portugal	>8,000,000	52	candidiasis	Bartolo [34]
31	2010	Male	59 yr	USA	>100,000	90	pneumocystis pneumonia	Spivak [35]
32	2011	Male	43 yr	Iran	-	<300	orbital lymphoma	Eftekhari [36]
33	2012	Male	55 yr	Spain	-	166	bullous pemphigoid	Ollé-Goig [37]
34	2012	Female	30 yr	Spain	-	28	diarrhea	Ollé-Goig [37]

Cases Reported in China

In China, Hei Faxin et al. [5] (Beijing) first reported a case of insufficient HIV antibodies affecting diagnosis in 2007. This case involved a 37-year old male patient who had a positive ELISA result, but an indeterminate WB result—only the gp160 band was observed. This was insufficient evidence for an HIV diagnosis based on the HIV testing algorithm at that time. However, the patient reported male-male sexual contact, and presented with symptoms that were consistent with the typical manifestation of AIDS, including *Pneumocystis carinii* pneumonia and mucosal fungal infections. Therefore, to further explore a diagnosis of HIV infection, a second blood sample was obtained and tested for HIV antibodies, HIV viral load (VL), and CD4 count. Antibody results remained unchanged. However, VL was 153,000 copies/mL, and CD4 count was only 5 cells/ μ L, and thus, the patient was diagnosed with HIV infection and AIDS. Another case was reported by Zhang Yunzhi et al. [6] (Shanghai) in 2008 involving a 16-month-old child born to a mother with HIV infection.

The infant was tested several times for HIV infection using rapid antibody test kits and results were consistently negative despite the child having multiple AIDS-related symptoms. Eventually, the child was diagnosed with HIV infection by quantitative nucleic acid testing. In 2010, Li Yan et al. [7] (Guangdong) reported on the case of a 33-year-old female patient who had tested a positive result by HIV ELISA, but indeterminate by HIV WB—only the p24 band was detected. Her husband was diagnosed with AIDS in June 2005, she accepted an HIV antibody test. Based on obvious family transmission that her husband was HIV positive before her antibody test and clinical manifestations of AIDS complications such as fungi, monilial infection, and pneumonia, VL and CD4 testing was ordered. VL result was >1,000,000 copies/mL and CD4 cell count result was 7 cells/ μ L, and hence, the patient was diagnosed with HIV infection.

In 2012, Qin Yingmei et al. [8] (Guangxi) reported on a 69-year-old male patient, who had been diagnosed with HIV infection in 2011, and had progressed to AIDS as evidenced by his having a variety of opportunistic infections including tuberculosis, shingles, and others. He also exhibited a serious loss of HIV antibodies. During follow-up WB testing, the typical bands indicating HIV infection decreased in number and intensity, and finally only the gp160 band remained, indicating that the level of antibodies has decreased over the course of AIDS progression. Most recently in 2017, Zhang Hong et al. [9] (Beijing) reported on the case of a 46-year-old male patient with a positive HIV ELISA result and Kaposi's sarcoma, yet had a negative HIV WB result. The patient was then tested for HIV VL and CD4 count. His VL was 42,969 copies/mL, his CD4 count was 6 cells/ μ L, and therefore he was diagnosed with HIV infection.

Cases Reported Elsewhere

Outside of China, a review was published in the journal AIDS in 2010 by Spivak et al. [10] which identified 25 cases of HIV infection

worldwide between 1994 and 2009, where HIV antibody-based testing methods yielded negative or uncertain results. All of these patients had two or more negative results on HIV ELISA testing yet had positive results on antigen or nucleic acid testing. Another 4 cases were reviewed, they were NO.27,32-34 cases in Table 1. NO.27 case reported in 2008, but not included in Spivak et al. [10] review, was found in a paper published by Ortiz de Lejarazu et al. [11] In this case, a 28-year-old male presented with Kaposi's sarcoma and *Pneumocystis carinii* pneumonia. Both HIV rapid testing and HIV ELISA testing results were negative, but his VL was 122,000 copies/mL and CD4 count was only 4 cells/ μ L. Between 2010 and 2017, we were only able to find 3 additional cases of HIV patients with false negative antibody tests, one from Iran and two from Spain, they were NO.32-34 cases in Table 1.

Discussion

In summary, "uncertain" or even "negative" results of HIV antibody-based testing methods should be questioned when HIV disease-related symptoms or opportunistic infections are present and/or when the patient is identified as being at high risk of HIV infection. Although it is rare that individuals would be tested in the "window period" of acute, early infection or after progressing into advanced AIDS disease, when quantities of circulating antibodies are very low, the likelihood of false-negative/uncertain results should not be ignored. For diagnosis verification, HIV nucleic acid testing is the most convincing indicator. Viral replication will continue even as quantity and diversity of antibody levels decline and HIV nucleic acid testing can be used as an effective, reliable method to verify HIV diagnosis.

Due to technical and financial constraints, HIV nucleic acid testing currently is underused as a diagnostic tool for HIV infection in China and elsewhere. However, to prevent misdiagnosis and treatment delay, we recommend it be used to help diagnose patients suspected of being in the very early stages of HIV infection and those who present with HIV disease-related symptoms and opportunistic infections common in the advanced stages of AIDS in China [12]. This recommendation has been documented by the Third Edition of AIDS Diagnosis and Treatment Guidelines (2015) of China [13]. HIV nucleic acid testing was also included as a confirmation strategy and part of the algorithm for the HIV confirmation process in the National Guideline for Detection of HIV/AIDS revised by the China CDC in 2015 of China [14].

Conclusion

We summarize 34 cases with seronegative or uncertain HIV antibody testing results using ELISA or WB methods, which were reported internationally between 1994 and 2017. Five of these cases were reported by China. Although all cases were antibody-negative or uncertain, nucleic acid testing results were positive, CD4 cell counts were low, and typical HIV-related complications and opportunistic infections were present in all cases. These cases

demonstrate the crucial need for HIV nucleic acid qualitative or quantitative detection for diagnosis of HIV infection when antibody-based methods yield negative or uncertain results.

Conflict of Interest

None.

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