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## The importance of transmission time in HIV infections and an epidemiological prospective follow-up study for 1 year in the Marmara Region of Turkey

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### ABSTRACT

It is important to detect recent and new HIV/1 infections and to take preventative measures in order to prevent rapid disease progression in AIDS and to decrease the incidence of infection. We aimed to detect long standing or recent HIV infections by determining transmission times for the cases in which first-time HIV/1 seropositivity were detected. The serum samples of 323 cases which were found to be seropositive by ELISA and Western-blotting were included in this study. The discrimination between long-term and recent HIV/1 infection was made by determining transmission-time with the Aware BED-EIA, HIV-1 incidence test (IgG capture HIV-EIA) tests. Ninety-six healthy blood donors who did not have a positive anti-HIV test and a chronic infectious disease for at least 1 year were included in this study as a negative healthy control group. In the discrimination of long-term and recent HIV/1 infections, only *in vitro* ODn values were used. The cases with normalized optical density (OD) ( $OD_{\text{specimen}}/OD_{\text{calibrator}} < 0.8$  by commercial kit) were accepted as recent HIV infection (155 days history or seroconversion less than 6 months). The cases with ODn >1.2 were accepted as long-term HIV/1 infections (more than 155 days history or more than 6 months). The cases with ODn between 0.8 and 1.2 were accepted as "additional tests needed" cases. We detected recent HIV/1 infections (<6 months) in 60 (18.5%) out of 323 cases and long-term HIV/1 infections (>6 months) in 263 (81.5%) out of 323 cases. The most frequently encountered transmission route in long-term and recent HIV/1 infections was heterosexual sexual intercourse as 54 (50%) and 257 (97%), respectively. 63.3% of newly infected patients were married females and 65.3% of recently infected patients were males.

In conclusion, the detection of the high ratio of long-term HIV/1 infection cases (81.5%) compared to recent infections (18.5%) suggested to us, that the long standing cases may have some activities related with transmission of HIV/1 in the past. The detection of higher HIV/1-infections in individuals which had heterosexual sex and also in married males suggested that this situation poses a very great threat for the health of society.

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## 1. Introduction

Since HIV/AIDS was first identified in 1981, it has become one of the most studied infectious diseases, as it has an increasing occurrence in developing or underdeveloped countries even as it decreases in developed countries, having related social problems and failures in complete treatment and vaccine studies. Despite the large number of treatment studies, and public education and prevention awareness, increases in the number of new cases and outcomes continue to be reported [1]. To prevent increase in HIV prevalence and to achieve a decrease in the number of future cases, and to break the chain of transmission by understanding modes of transmission in risk groups who have a tendency to transmission, preventative measures must be taken. By determining the transmission time, it may be possible to follow-up HIV positive cases and people who may have been a contact with the cases who were diagnosed as long-term infection. The determination of transmission time may also be useful to identify immediate treatment for newly infected cases, and, most importantly, new transmissions may be prevented by this method. We suggest that both of the incidence and prevalence of AIDS may be reduced in society by this method, and the spread of the AIDS may be prevented by the determination of the possible transmission sources. In this study, for the first time in Turkey, (Marmara Region, especially in Istanbul), we aimed to detect new and long term AIDS infections by determining *in vitro* transmission times in cases at three centers that were diagnosed as HIV positive for the first time, and to evaluate epidemiologic and demographic data of these cases over a one-year period.

## 2. Material and methods

### 2.1. Study area

This study was planned prospectively, cross-sectional and case-control based between December 2009 and January 2011. All of the confirmed HIV/1 seropositive cases were included in this study as non-randomized. The study area (Istanbul and surrounding cities) is the most social-economical and social-cultured developed area of Turkey. Serology and ELISA Laboratory of Microbiology Department of Cerrahpasa Medical Faculty, Haseki Education and Training Hospital and Turkey Ministry of Health, Istanbul Leprosy Research Center were the participants of this multicentered study.

### 2.2. Study and control groups

The two serum samples of all HIV-suspected cases were tested by anti-HIV ELISA test and confirmed by Western-blotting in three study centers. All seropositive confirmed HIV/1 cases were included in the study. Three hundred and twenty-three HIV/1 seropositive cases confirmed by Western-blotting were included in this study.

Ninety-six (30%) and 237 (70%) of this 323 cases were female and male, respectively, and the ages of the cases were between 14 and 71 (mean of the ages; 42.2). Control group

individuals were selected from the healthy individuals or healthy blood donors who do not have a travel history to outside of Turkey, a risky sexual intercourse and do not have blood and blood products transfusion for the last 2 years. The anti-HIV 1/2 test was always seronegative for control group individuals. Control group individuals were matched with the study group for age, gender and geographical region. Control group individuals were 30 (31.1%) female, 66 (68.7%) male and the ages were between 15 and 70 (mean; 41.2) and they were from Istanbul or surrounding cities. The serum samples (10 ml) of study and control group individuals were stored at  $-80$  until the study.

### 2.3. Study methods

#### 2.3.1. ELISA and Western-blotting

A commercial ELISA kit (Abbot Murex HIV Ag/AB Combination, England) was used as routine screening test in three study centers. A Western blot kit (INNO-LIA blot 1-2, Diagnostics Innogenetics, Belgium) was used in ELISA Laboratory of Microbiology Department of Cerrahpasa Medical Faculty. A different Western blot kit (HIV BLOT 2.2, MP Diagnostics, Germany) was used in Haseki Education and Training Hospital and Turkey Ministry of Health, Istanbul Leprosy Research Center. Methods and evaluations were performed as described by the manufacturers.

#### 2.3.2. ELISA for research

A commercial Aware BED-EIA IgG-capture (Calypte Biomedical Corporation, Rockville, MD, USA) kit was used. All Western blot-positive samples, including those previously testing positive, were also tested by BED-EIA using gp41 immunodominant regions from subtypes B, E and D. The assay detects increasing levels of HIV-1-specific IgG as a proportion of overall IgG. The BED-EIA was performed according to the manufacturer's instructions by technicians trained in the use of the assay. Specimens with initial ODn  $\leq 1.2$  were tested in triplicate to confirm their ODn values. Specimens that registered less than 0.8 normalized optical density were accepted as positive. Positive specimens were considered 'recent infections' and negatives (ODn  $\geq 0.8$ ) were considered 'longer term infections'. In the evaluation of HIV infections as recent or longer term, and a modified evaluation method was used by using only *in vitro* ODn values.

## 3. Results

Sixty (18.6%) of the 323 confirmed seropositive HIV/1 infections were detected as recent HIV/1 with ODn  $\leq 0.8$  by using only *in vitro* ODn values. The minimum ODn value was detected as 0.14 in this group. The ODn values of 34 (10.53%) specimens were between 0.8 and 1.2. Specimens with ODn  $< 1.2$  were tested again in triplicate to confirm the values. In confirmatory testing, specimens with ODn values  $< 0.8$  were considered as possible recent seroconversion. If the ODn value of the specimen was  $> 0.8$ , the specimen was considered a long-term seroconversion. 229 (70.9%) of 323 specimens with ODn  $> 1.2$  were consid-

ered as long-term HIV/1 infections. 77 (29.3%) of the 229 long-term HIV/1 infection have ODn >3 (Table 1).

Forty-one of the sixty recent HIV/1 cases were male and the highest recent HIV/1 cases were seen in 31–50 years group. The highest HIV/1 case ratio was seen in secondary school educational group as 47 (78.3). The most encountered transmission was by heterosexual sex as 54 (90%) and married couples showed the highest recent HIV/1 case ratio as 38 (63.3%).

One hundred and eighty-six (70.7%) of the two hundred and sixty three long-term HIV/1 cases were male and the highest ratio was seen in 14–30 years old age group. Secondary school educational group (89.4%) and married couples (68.4%) showed the highest long-term HIV/1 case ratio. The probable transmission way for long-term HIV/1 cases was detected as heterosexual sex (97.7%) (Table 2).

**Table 1**

Normalized Optical Density (ODn) Values for recent and long-term HIV/1 cases by BED-EIA.

ODn values	Recent HIV (+) cases (n = 60)	Long-term HIV (+) cases (n = 263)
≤0.8 ODn (recent infection)	60	–
0.14–0.35	23 (38.3)	–
0.36–0.10	14 (23.3)	–
0.60–0.80	23 (38.3)	–
≥1.2 ODn (long-term infection)	–	229
1.2–2.0	–	101 (38.4)
2.1–3.0	–	51 (19.4)
>3	–	77 (29.3)
>0.8 to <1.2 ODn	–	34 (10.53)
Total (323)	60 (18.6)	263 (81.4)

**Table 2**

Demographical properties of recent and long-term HIV/1 (+) cases.

HIV (+) (n = 323)		
Demographical properties	Recent HIV/1 cases (+) (n = 60) %	Long-term HIV (+) cases (n = 263) %
<i>Gender</i>		
Female	19 (31.7)	77 (29.3)
Male	41 (68.3)	186 (70.7)
<i>Age</i>		
14–30	18 (30)	124 (47.2)
31–50	39 (65)	118 (44.8)
51–71	3 (5)	21 (8)
<i>Education</i>		
Secondary school	47 (78.3)	235 (89.4)
University	13 (21.7)	28 (10.6)
<i>Probable Transmission way</i>		
Heterosexual sex	54 (90)	257 (97.7)
Homosexual sex	3 (5)	2 (0.8)
Blood transfusion	0	3 (1.1)
Unknown causes	2 (3.3)	1 (0.4)
	1 (1.7)	0
<i>Marital status</i>		
Married	38 (63.3)	180 (68.4)
Bachelor	22 (36.7)	83 (31.6)

#### 4. Discussion

HIV/AIDS is a worldwide epidemic infectious disease which causes high mortality and morbidity. In addition to all of the above factors, regular reporting of HIV/AIDS infections due to surveillance by the joint United Nations Programme on HIV/AIDS (UNAIDS) and WHO in developed countries and effective and continuous fight of official and public institutions and organizations against to HIV/AIDS were played a big role in decreasing of the disease incidence [2,3]. There is a need for new laboratory methods which detect the timing of the infection to make surveillance for HIV-infected patients. The importance of using new commercial HIV diagnostic test kits which are easy to perform and having high sensitivity and specificity and also different from other screening and diagnostic HIV 1-2 tests but similar to the TORCH (Toxo, Rubella, CMV, HSV) panel which differs long-term and recent infections by detecting time of the disease was emphasized by many researchers in this field [4,5].

In order to determine the avidity index (AI) to differentiate recent and long-term HIV infections, Suligoi and others [5] reported that AI of recently infected cases (82%) which have a 6 months seroconversion was less than 0.90. They also suggested that to determine the time of disease may be helpful to make surveillance easier, to take protective measures and to apply optimal treatment and vaccination. Parekh and others [4] first time, devised a simple enzyme immunoassay (EIA) that detects increasing levels of anti-HIV IgG after seroconversion and can be used for detecting recent HIV-1 infection. The IgG-capture BED enzyme immunoassay (also known as the BED-EIA) developed by the CDC, indirectly measures the proportion of HIV-IgG to total IgG.

Total case number for HIV/AIDS were 4525 from 1985 until the present time by official announcement, but it was assumed the real case numbers were much more than these case numbers because of the numerous reasons related with the nature of HIV/AIDS [1]. The most important basic problem seems to be insufficient feedback from the first-line medical facilities in Turkey. We assumed that the annual incidence and prevalence of HIV/AIDS in Turkey was probably far from the actual real numbers. New strategies should be planned in order to take preventative measures by detecting annual recent and long-term HIV infected patients. A total of 323 HIV/1 infections with have positive anti-HIV tests and confirmed by Western-blotting test were prospectively included in this study and we tried to detect recent and long-term HIV/AIDS infection cases as the first time in Turkey by determining the transmission times using only *in vitro* ODn values in 2010. However, the working procedure and the consideration principles of our commercial BED-EIA kit were not in concordance with the commercial kit used in the study of Suligoi and others [5] to detect recent HIV/1 infected cases. Recent HIV/1 infections were found as 60 (18.5%) in our study. ODn values of the recent infections were below 0.8 ODn and the infections had 155 days seroconversion. Long-term HIV/1 infections were found as 229 (70.9). ODn values of the long-term HIV/1 infections were higher than 1.2 and

long-term infections had seroconversion more than 155 days. Thirty-four HIV/1 infections had intermediate ODn values and additional assays showed them as long-term HIV/1 infections. Finally these intermediate infections were added to the former long-term HIV/1 cases and the total number of the long-term HIV/1 cases were reached to 263 (81.2%). BED-EIA measures the proportion of HIV-1-specific IgG in a given specimen with respect to total IgG. Early seroconverters have a lower proportion of HIV-specific IgG in their serum/plasma than those with long-term infection. Recent HIV/1 infection ratio (18.5%), may be speculative for some reasons. We collected our HIV/1 positive sera samples from the three HIV confirmation centers in Marmara Region, especially in Istanbul. Some of the HIV cases may not have been sent to these centers in order to confirm HIV cases by WB test. These medical facilities may have preferred to confirm HIV infections by using their own WB test kits. Truong et al. [6] reported that application of BED-EIA to identify persons with known long-term infections, for example, in populations with high frequencies of HIV testing and low levels of undiagnosed infections, can generate acceptable HIV-1 incidence estimates. In populations with many late-diagnosed infections, the assay may be more prone to misclassification errors. They also stated that BED-EIA was misclassifying persons with long-term infections as recent not only in the early period after seroconversion but also in a subpopulation of persons who never evolved higher levels of HIV-specific antibody even after many years of infection. This latter phenomenon of longterm misclassification would result in an overestimation of HIV-1 incidence especially in high prevalence populations that include many persons with undiagnosed HIV infections. One hundred and forty-eight (22.4%) of 658 HIV/1 seropositive infections were found as recent HIV/1 infections by BED-EIA kit in their study.

Our recent HIV/1 infection ratio was detected as 18.5%. This ratio can be considered higher than expected by taking into account of people's unconsciousness and educational level related with sexually transmitted diseases and their irresponsibility to apply a medical center to make screening and diagnostic HIV tests. Besides that any subpopulation of persons who never evolved higher levels of HIV-specific antibody should also be considered as stated above literature. In 2008, Hall and others [7] reported that an estimated 39,400 persons were diagnosed with HIV in the 22 states and of 6864 diagnostic specimens tested using the BED assay, 2133 (31%) were classified as recent infections. Their study provided the first direct estimates of HIV incidence in the United States using laboratory technologies previously implemented only in clinic-based settings. Niccolai and others [8] reported also that the 297 participants who were confirmed HIV positive drug users, were tested with BED-EIA and of these, 58 (19.5%) were classified as recent infections. They concluded that the BED EIA may over-estimate incidence even after correction for low specificity. In two studies from China in 2009 and 2010, Wei and others [9] reported that 17 (10%) of the 168 HIV/1 seropositive infections and Wang and others [10] reported that 954 (13.5%) of the 7252 HIV/1 seropositive infections as recent HIV/1 by BED EIA at Guangxi and

Dehung prefecture in Yunnan province, respectively. Wei and others concluded a decline in parenteral drug users in Dehong prefecture and Wang et al., concluded that the proportion of recent HIV infections among newly reported HIV/AIDS cases in Dehong prefecture in Yunnan province was fluctuating slightly.

A significant result from our study was long-term HIV/1 infections (81.5%) were higher than recent HIV/1 infections. One reason may be the status of old HIV/1 infected persons. The other point was long-term HIV/1 infected individuals pose a great threat to society with unprotected sexual intercourse and contaminating some materials by their HIV contaminated blood. They may have played an active role in infectious chain of HIV/AIDS.

In the present study, 41 (68.3%) and 19 (31.7%) of the recent HIV/1 infections were detected as male and female, respectively. The similar gender ratio was also detected for long-term HIV/1 infections. The ratio of recent HIV/1 infections in 31–50 age group was detected as the highest (65%). Mermin and others [11] reported from Uganda that HIV/1 infected cases were detected higher in females (62.2%) by BED-EIA method in 2008 and the most encountered HIV/1 infections were in 35–39 years group. Hall and others [7] reported that recent HIV/1 infections were higher in males (71%) and the highest HIV/1 ratio was detected in 13–29 age group as (41) in 2008. Niccolai and others [8] reported the highest recent HIV/1 infections in males as 69% and they detected the highest ratio was in older than 26 age group (62%). de Castro et al., [12] reported that the male/female ratio (30/31) was similar in 61 recent HIV/1 infections and the highest recent HIV/1 ratio was in 25–40 age group in the same year. Wang and others [10] reported the highest recent HIV/1 infections were detected in 11–19 age female group by BED-EIA method in 2010. In 2011, Kao et al. [13] detected 299 recent HIV/1 infections from 683 HIV/1 seropositive infections by BED-EIA method in Taiwan and 288 (96.3) and 11 (3.7%) of this recent infections were males and females, respectively. Truong and others [14] detected 21 recent HIV/1 infections from 317 HIV/1 seropositive infections and detected a similar gender ratio between male and females (10/11) in Zimbabwe. The highest recent HIV/1 ratio was found in 25–44 age group as 66.7%. Our results were in concordance with the other three studies in the literature. We had detected the highest recent HIV/1 infection ratio in males and the middle-age group had the highest HIV/1 infection ratio than other age groups. Our finding was also in concordance with the other studies in the literature.

In this study, the highest recent HIV/1 infections (73.3%) were detected in the secondary school of educational groups and the same ratio was also similar for the long-term HIV/1 infections. In 2008, Mermin and others [11] detected highest recent HIV/1 infection ratios (80%) in primary or less educated group between 172 recent HIV/1 infections in Uganda. Niccolai and others [8] detected highest recent HIV/1 infections (58) in high school group addicted to intravenous drugs in 2010. Results of this study related with education were in concordance with the results of Niccolai et al.'s but differed the results reported by Mermin and others. Because of we didn't have primary school group.

Results of this study related with marital status were reported as 63% of the 60 recent HIV/1 infection cases were married. Mermin et al. [11] reported that 65% of the 172 recent HIV/1 infection cases were married in 2008 from Uganda. Findings of this study were similar to that reported by Mermin and others. This was a very worrying result. Because of HIV infections can be easily transmitted between married couples by unprotected sexual intercourse and may result horizontal epidemics.

The most encountered transmission way of HIV/1 infections were heterosexual sex and the similar result was valid for the long-term HIV/1 infections. Our results related with the transmission way of HIV/1 infections were in concordance with the results of Mermin and others [11] and Murillo and others [15]. However, Hull and others [7] and Kao and others [13] reported that, the most encountered transmission way of HIV/1 infections was homosexual sex. de Castro and others [12] reported that transmission way of 15 and 16 of the 61 recent HIV/1 infections were heterosexual and homosexual sex in 2010, respectively. It was emphasized that the most encountered transmission ways of HIV/1 infections were varied according to the sexual life related with social-economical and social-cultural level and educational level of the countries in studies using BED-CEIA method to detect recent HIV/1 infections. However, while the most encountered transmission way of HIV seropositive infected individuals was homosexual sex in 1980s, this was changed as heterosexual sex from 2000 until present time [6,16–18]. Results of this study were in concordance with the official HIV/AIDS surveillance reports which were accepted internationally.

In conclusion, our recently infected HIV/1 case ratio results were significantly important for public health beside the declaration problems of official HIV/AIDS cases and restrictive factors of BED-EAI test kit to detect recent HIV/1 infections. In addition, the detection of the highest primary diagnosed long-term HIV/1 infections is a very worrying state for the infection chain in society. We suggest that new preventive measures should be taken immediately against married, middle-aged males because the highest recent HIV/1 infection ratios were detected in this group.

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