CD4 validation for the World Health Organization classification and clinical staging of HIV/AIDS in a developing country

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Summary

Objectives: To validate the World Health Organization (WHO) clinical staging and classification of HIV/AIDS using CD4+ T-lymphocyte counts in the setting of a developing country.

Methods: This was a retrospective chart review of HIV-infected adults at the national HIV referral clinic in the Kingdom of Saudi Arabia. Four hundred HIV-infected individuals were reviewed. All individuals under the age of 15 years and those who had received antiretroviral therapy were excluded. WHO clinical stage at presentation was determined by a single reviewer. The first CD4+ T-lymphocyte count within 6 months of diagnosis of HIV infection was then abstracted by a different reviewer. The main outcome measure was the comparison of the WHO clinical stages of HIV/AIDS at the time of diagnosis and the CD4+ T-lymphocyte counts.

Results: Data were available for 191 individuals, of whom 123 were men and 68 were women. The mean CD4+ T-lymphocyte count was 281/mm³ in the men and 425/mm³ in the women. The distribution of individuals at the WHO clinical stages was 110 at stage I, 10 at stage II, 36 at stage III, and 35 at stage IV. Mean CD4+ T-lymphocyte counts were 457, 337, 188, and 86/mm³ at the respective stages. The difference between the mean CD4+ T-lymphocyte count in patients at stage IV and at each of the other stages was significant; \( p < 0.0001 \). The correlation between the stages and the mean CD4+ T-lymphocyte counts was \( -0.65 \).

Conclusion: The WHO clinical staging and classification of HIV/AIDS correlates well with CD4+ T-lymphocyte counts.

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Introduction

Since the early days of HIV infection and AIDS, it has been recognized that the disease progresses in several stages due to the progression of immunosuppression. The level of immunosuppression is linked directly to the CD4+ T-lymphocyte
Several organizations have classified and staged HIV/AIDS infection. Classification and staging was first introduced for the purpose of surveillance. The World Health Organization (WHO) adopted a clinical staging system for HIV/AIDS in 1990, emphasizing the use of clinical parameters to guide clinical decision-making for the management of HIV-infected individuals. This system was designed mainly for use in developing countries and resource-limited settings, where there is no access to laboratory services and where it is not possible to assess the disease using CD4+ T-lymphocyte counts.

The WHO clinical staging system has been widely used in developing countries, especially in Africa. It has even been used at the first level of referral in the local healthcare systems. Other clinical disease classification systems, specifically the one for North America from the Centers for Disease Control and Prevention (CDC), are based on immunological, clinical, and virological parameters that require laboratory confirmation. Due to the importance of clinical classification and staging of HIV/AIDS infections, the WHO has repeatedly revised the staging system. For developing countries, in particular the African regions, the Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance was released in 2005. In that report the clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance was released in 2005.

Methods

Design and setting

The HIV/AIDS service at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, is the national HIV referral center. It has accumulated rich data on the clinical presentation of patients and their CD4+ T-lymphocyte counts. The setting, being in a developing country, is the first that we are aware of to validate the WHO clinical staging using CD4+ T-lymphocyte counts.

Charts of all adult individuals aged 15 years and older, confirmed to be HIV positive, were reviewed. All individuals who had acquired the disease vertically were excluded. Those who had been diagnosed and had been receiving antiretroviral therapy before referral to our institution were also excluded.

Basic demographic data were collected from charts. Each individual chart was screened for documentation of any of the clinical events listed in the WHO document at the time of first presentation to our clinic. A single reviewer abstracted these events (J.E.). The clinical stage was determined for that particular individual. Individuals who had multiple signs and symptoms were included into the most advanced stage that they were in at the time of presentation.

The first measure of the CD4+ T-lymphocyte count within three months prior to or after presentation to our institution was then abstracted from the records by a different reviewer (B.A.) on a different occasion to eliminate the chance of bias. Subsequently, all HIV-infected individuals were grouped based on their WHO clinical stage: stage I, II, III, or IV. Individuals at the same stage were grouped together and their CD4+ T-lymphocyte counts were used for the analysis and correlation testing.

Participants

Four hundred HIV-infected individuals were registered at the HIV clinic. One hundred and ninety-one HIV-infected patients met the inclusion criteria. HIV diagnosis was confirmed using AxSYM1 HIV 1/2 gO MEIA (Abbott Laboratories, Abbott Park, IL, USA). Positive sera were confirmed using Western Blot or CHIRON2 HIV-1/HIV-2 SIA (Chiron Corp., Emeryville, CA, USA). CD4+ T-lymphocyte counts were measured by standard flow cytometry using FACScalibur3 (Becton Dickinson, San Jose, CA, USA).

Statistical analysis

Statistical analysis was performed using Statistical Software package version 5.0 (StatSoft, Tulsa, OK, USA). The Student’s t-test was used to calculate continuous variables, and the Chi-square or Fisher’s exact test was used for proportions. All reported p values are two-tailed and a value of <0.05 was considered significant.

Results

Data were available for 191 individuals, of whom 123 were men and 68 were women. Men had more advanced disease in this cohort. The mean CD4+ T-lymphocyte count was 281/mm³ in men and 425/mm³ in women (p < 0.001). At all stages, men had lower mean CD4+ T-lymphocyte counts compared to women. The mean age for men was 33 years and for women 35 years.

The stage distribution of participants was 110 at stage I, 10 at stage II, 36 at stage III, and 35 at stage IV. The mean CD4+ T-lymphocyte counts were 457, 337, 188, and 86/mm³ at the respective stages. Figure 1 depicts the CD4+ T-lymphocyte counts for the analysis.

The difference in CD4+ T-lymphocyte counts between the various World Health Organization stages of HIV/AIDS was significant (Table 1). Only between stages I and II was the difference not statistically significant.

Correlation testing revealed Spearman r = –0.65 (Figure 2). There were 16 out of 110 patients at stage I (15%) with a CD4+ T-lymphocyte count of less than 200/mm³; five of them had a CD4+ T-lymphocyte count of less than 50/mm³.

Table 1  p-Values in the comparison of mean CD4+ T-lymphocyte counts between the various World Health Organization stages of HIV/AIDS

<table>
<thead>
<tr>
<th>Stage (mean CD4+ T-lymphocyte count)</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV (86/mm³)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>III (188/mm³)</td>
<td>&lt;0.0001</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>II (337/mm³)</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (457/mm³)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
than 100/mm³ and 11 had a CD4+ T-lymphocyte count between 100 and 197/mm³. On the other hand, of the five out of 35 patients at stage IV (14%) with a CD4+ T-lymphocyte count of more than 200/mm³, only one had a CD4+ T-lymphocyte count of more than 350/mm³. Other stages and groupings of CD4+ T-lymphocyte counts are summarized in Table 2.

Discussion

In our study we have shown that HIV clinical staging and classification based on the recent WHO document does correlate well with CD4+ T-lymphocyte counts, and thereby with the level of immunosuppression. To our knowledge this has not been previously reported. Teck et al. have reported the CD4+ T-lymphocyte count of patients at stages III and IV in relation to active or previous tuberculosis. They found that nine out of 10 HIV-infected patients in Malawi presenting at WHO stages III and IV with active or previous tuberculosis, had a CD4+ T-lymphocyte count of less than 350/mm³. Similar to our study, around 10—15% of patients at stages III and IV had CD4+ T-lymphocyte counts above 350/mm³. Teck et al. only looked at stages III and IV, whereas we looked at all stages. Also, we have shown using Spearman \( r \) correlation testing

![Box-and-whisker plot showing the median values and range of CD4+ T-lymphocyte counts at the different World Health Organization stages of HIV/AIDS.](image1)

![The correlation between the various World Health Organization stages of HIV/AIDS and CD4+ T-lymphocyte counts.](image2)

### Table 2

| CD4+ T-lymphocyte counts in relation to World Health Organization stages of HIV/AIDS |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| CD4 < 200/mm³ \( n \) (\%)      | CD4 200–350/mm³ \( n \) (\%) | CD4 > 350/mm³ \( n \) (\%) |
| Stage I \( n = 110 \)          | 16 (15)         | 29 (26)         | 65 (59)         |
| Stage II \( n = 10 \)          | 3 (30)          | 3 (30)          | 4 (40)          |
| Stage III \( n = 36 \)         | 20 (56)         | 10 (28)         | 6 (16)          |
| Stage IV \( n = 35 \)          | 30 (86)         | 4 (11)          | 1 (3)           |
that there is a good negative correlation between WHO stage and CD4+ T-lymphocyte count at presentation. Kassa et al. looked at CD4+ T-lymphocyte counts among patients at the various WHO stages of 1993. In general, there was a good correlation, but CD4+ T-lymphocyte counts were lower than in our patients.

The difference in CD4+ T-lymphocyte counts between all the WHO stages was significant except between stages I and II. The staging tool was so sensitive that it had separated the mean CD4+ T-lymphocyte counts between stages III and IV. Therefore, it may be simpler to combine stages I and II. It is reassuring to note that only 3% of patients at stage IV would not need antiretroviral therapy if only CD4+ T-lymphocyte count was used. In fact, it appears from our patients that the WHO staging of HIV/AIDS would result in a slight undertreating of patients rather than an over-treating. This is especially suitable in resource-limited countries where the availability of antiretroviral therapy is poor.

Another finding was the gender difference in CD4+ T-lymphocyte counts at all stages. The mean CD4+ T-lymphocyte count in women was significantly higher than in men at the same stage of the disease. We believe this is a pattern in our HIV population related to the source of infection and screening of partners.

Ideally this study should have been undertaken in a prospective manner, but this is not feasible in Saudi Arabia where the number of new HIV infections per year is very low; it would take several years to recruit a reasonable number of individuals presenting at each of the different stages of the disease into the study. Again for accurate clinical staging, healthcare providers should have interviewed and examined the individual with HIV infection, focusing on the symptoms, signs, history, and laboratory findings specified in the WHO document. This could be one of the reasons why we had more patients at stage I as compared to stage II, as most of the clinical signs at this latter stage are subtle, e.g., fungal infection of nails, angular chelitis, previous history of herpes zoster, and recurrent upper respiratory infections, etc.

In spite of the above-mentioned limitations, this study does prove that the WHO clinical staging of HIV/AIDS infection correlates well with the level of immunosuppression and CD4+ T-lymphocyte counts, and will serve as a valuable tool to manage individuals with HIV infection in developing countries with limited resources, where the measurement of CD4+ T-lymphocyte counts is not feasible.

**Ethical approval:** The study protocol was approved by the Research ethics committee of the Research Center at the King Faisal Hospital. An informed consent was not required as no personal identification or information is revealed in this study.

**Conflict of interest:** No conflict of interest to declare.

**References**


