Application of the World Health Organization system for HIV infection in a cohort of homosexual men in developing a prognostically meaningful staging system

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Objective: Validation of a modified version of the recently proposed World Health Organization (WHO) staging system for HIV infection and disease in a cohort of homosexual men.

Methods: Five hundred and thirty HIV-positive men followed for a median of 51 months (range, 1–98 months) were eligible for analysis. Subjects were classified into stages at their first seropositive visit and at all subsequent visits.

Results: As of 1 April 1991, 136 subjects (26%) had progressed to stage IV of the modified WHO system on the basis of their CD4 lymphocyte counts, and 78 subjects (15%) had died. Kaplan–Meier estimates for progression to stage IV from stages I, II and III were 52.8 ±7.5% over 6.6 years, 58.1 ±7.1% over 5.9 years and 66.5 ±9.7% over 5.7 years (log-rank $P = 0.0001$). Estimated median times to stage IV were 6.4, 5.3 and 3.8 years from stages I, II and III, respectively. Estimated median times to death were 10.9, 8.2, 6.3 and 1.7 years from stages I to IV, respectively. Results remained unchanged when CD4 lymphocyte count was replaced with lymphocyte count in the laboratory axis of the staging system.

Conclusions: The proposed staging scheme, based on the WHO system, provides a prognostically meaningful classification for HIV infection in a cohort of homosexual men. Furthermore, the use of absolute lymphocyte count as a valid alternative for CD4 lymphocyte count has implications for the applicability of this system in many parts of the world where diagnostic resources are limited.

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Introduction

A decade has now elapsed since the initial description of AIDS and much more information is now available about the natural history of infection with HIV-1. It is now known that the median incubation period between infection with HIV and diagnosis of AIDS is approximately 10 years [1]. Moreover, observations from a number of prospective studies have provided insight into the characteristic changes in laboratory parameters (most notably CD4 lymphocyte count and appearance of symptoms) that are markers of progression of HIV disease [2].

Since the beginning of the epidemic, a number of classifications have been proposed to stage HIV-infected individuals throughout the course of their disease [3,4]. Staging systems play a critical role because they facilitate communication between practitioners and researchers, assist clinicians in selecting appropriate therapeutic interventions, allow appropriate prognostic stratification for clinical studies, and identify intermediate measures of disease progression that can be used to expedite the assessment of potentially promising therapies. Ideally, a staging system should be universally applicable, be clearly linked to the physiopathology of the disease, convey clinically relevant

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prognostic information, be responsive to therapeutic intervention, and be easy to remember and apply. Until recently, no proposed classification has proved to be prognostically meaningful and widely applicable at the same time.

In 1989, following a number of consultations organized by the World Health Organization (WHO), a staging classification of HIV disease was proposed that attempted to better fulfil the criteria listed above [5]. In summary, as seen in Table 1, this classification relies on two axes: subjects are characterized into one of four clinical groups and into one of three laboratory strata, yielding 12 cells (1A, 2A, etc.). It is critical to stress that, in the WHO proposed system, the laboratory axis can be based on absolute lymphocyte count in the absence of CD4 lymphocyte count determinations.

Table 1. Modified World Health Organization staging system for HIV infection and disease.

	Laboratory			Clinical group			
	CD4 count*	or	Lymphocyte count*	1	2	3	4
A	>500		>2000	I	I	II	IV
B	200–500		1000–2000	II	II	III	IV
C	<200		<1000	III	III	IV	IV

* $\times 10^6$/l. Group 1 (asymptomatic or persistent generalized lymphadenopathy): normal activity. Group 2 (early-stage disease): weight loss <10% of body weight, minor mucocutaneous manifestations, herpes zoster within 5 years, recurrent upper respiratory infections; symptomatic but normal activity. Group 3 (intermediate-stage disease): weight loss >10% of body weight, unexplained chronic diarrhea >1 month, unexplained prolonged fever >1 month, oral candidiasis, oral hairy leukoplakia, pulmonary tuberculosis within 1 year, severe bacterial infections and/or bedridden <50% of day during previous month. Group 4 (late-stage disease): definite or presumptive diagnosis of any AIDS-defining illness, according to 1987 Centers for Disease Control surveillance definition and/or bedridden >50% of day during previous month.

We have previously shown that clinical symptoms and laboratory parameters provide independent information regarding disease progression [6]. Thus, a staging system which simply uses clinical groups or laboratory strata alone would ignore important information, We divided the 12 cells into four stages, denoted I to IV, (see Table 1); this division was carried out *a priori* on an empirical basis. In creating these stages, we attempted to capitalize on independent information captured by clinical and laboratory information.

In this report, we evaluate this four-category staging system for HIV infection within a cohort of homosexual men. We found this novel staging system to be prognostically valuable and potentially applicable, even in areas with limited diagnostic resources.

Methods

Subjects

The Vancouver Lymphadenopathy–AIDS Study (Vancouver, British Columbia, Canada) has been described previously [6]. In brief, 1000 homosexual men already enrolled in eight family practitioner practices in downtown Vancouver were invited to participate in the study.

Initially, 729 men were recruited between 1982 and 1984 from six practices, with an additional 271 enrolled between October 1986 and December 1987 from these and two additional practices. Study participants were followed with semi-annual visits through 1986 and with annual visits thereafter. Each visit consisted of a self-administered questionnaire, complete physical examination by the general practitioner, and laboratory studies, including HIV serology, CD4 and absolute lymphocyte counts. For each participant, AIDS-defining conditions or death were reported immediately to the study centre. Furthermore, a record linkage was performed between the cohort and the appropriate provincial and federal registries in 1989 and again in 1991 to establish the completeness of the database with regard to AIDS and mortality diagnoses.

Subjects were 'seroprevalent' if they were HIV-positive at enrollment and 'seroincident' if they seroconverted during the study. Subjects were classified according to the proposed staging system at their first seropositive visit, designated the index visit. This was the enrollment visit for the seroprevalent group and the visit following seroconversion for the seroincident group. One author (T.N. Le) assigned a clinical group to each study participant at their index visit and at all successive visits, based on records completed by the family physician. This author was blind to study participant outcomes and laboratory profiles. Performance score was not used in clinical staging, as this information was not collected in early stages of the study. Clinical group and laboratory results were then combined to assign a stage, as defined in Table 1.

Statistical methods

We used survival analysis techniques, as described previously [7]. Data were right-censored as of 31 April 1991 and all rates quoted are Kaplan–Meier estimates. First, we studied time to development of stage IV disease (and time to death) for those who were stages I, II, and III at the index visit. Since these curves were independent, the log-rank test was used for comparison. We also studied time to death in those who were in stage IV; however, as only a small number of individuals were in stage IV at index visit, this included all subjects who ever entered stage IV. For the latter analysis, date of stage IV diagnosis was taken to be time zero for survival analysis. Thus, subjects used to estimate stage IV survival were also used to de-

rive the other estimates, and stage IV survival was not included in the log-rank test. To estimate median time to events, Weibull models were fitted to relevant data using maximum likelihood techniques. All analyses were conducted using staging based on CD4 and absolute lymphocyte counts separately. We also included an analysis in which a different stratification for absolute lymphocyte count was derived and tested.

The seroprevalent group included subjects who entered the study at later stages of classification. In order to avoid any bias associated with the lead time spent in a given stage prior to enrollment for seroprevalent subjects, we conducted a secondary analysis restricted to seroincident subjects. We included seroincident subjects whose last negative and first positive visits were within a 1-year interval. Because of the smaller sample size, progression and survival from each stage was based on all subjects who ever entered that stage. For that reason, these curves are not independent observations, and the log-rank test was not applied.

Results

There were 550 HIV-infected individuals in the cohort at the time of our analysis. Of these, 409 (74%) were seroprevalent and 141 (26%) seroincident. Five hundred and thirty subjects were classified satisfactorily at index visit using clinical and laboratory data; 20 subjects could not be classified because of missing information (11 were missing clinical information and nine laboratory data).

Table 2 shows the distribution of the 530 subjects at index visit into the 12 cells of the proposed staging system. At this visit, 50% of subjects were asymptomatic, 29% had mild symptoms, 21% moderate symptoms and none severe symptoms. Seventy-six per cent had a CD4 lymphocyte count $>500 \times 10^6$/l, 22% 200–500 $\times 10^6$/l, and 2% $<200 \times 10^6$/l. A similar distribution was found for absolute lymphocyte count. Sixty per cent of subjects had an absolute lymphocyte count $>2000 \times 10^6$/l, 37% 1000–2000 $\times 10^6$/l, and 3% $<1000 \times 10^6$/l. Using CD4 lymphocyte counts at index visit, there were 336 (63%) subjects in stage I, 146 (28%) in stage II, 44 (8%) in stage III and four (1%) in stage IV of the staging system. Using absolute lymphocyte count, 266 (50%) subjects were in stage I, 199 (38%) in stage II, 59 (11%) in stage III and six (1%) in stage IV of the staging system.

Progression to stage IV

As of 1 April 1991, 136 (26%) subjects had progressed to stage IV of the proposed system using CD4 counts. Progression to stage IV was documented in 66 out of 317 subjects in stage I, 49 out of 137 subjects in stage II and 21 out of 40 subjects in stage III. As seen in Table 3, product–limit estimates for progression to stage IV (and time interval) from stages I, II and III were 52.8 ±7.5% at 6.6 years, 58.1 ±7.1% at 5.9 years, and 66.5 ±9.7% at 5.7 years, respectively (log-rank $P = 0.0001$). The estimated median times to stage IV were 6.4, 5.3 and 3.8 years from stages I, II and III, respectively. Figure 1a shows the Kaplan–Meier progression curves from stages I, II, and III to stage IV.

Table 2. Distribution (with % in parentheses) of 530 seropositive homosexual men at index visit according to the World Health Organization staging system for HIV infection and disease.

	Clinical group				
	1	2	3	4	Total
CD4 count					
>500	214 (40)	122 (23)	68 (13)	0	404 (76)
200–500	47 (9)	31 (6)	37 (7)	0	115 (22)
<200	6 (1)	1 (<1)	4 (1)	0	11 (2)
Total	267 (50)	154 (29)	109 (21)	0	530 (100)
Lymphocyte count					
>2000	170 (32)	96 (18)	53 (10)	0	319 (60)
1000–2000	92 (17)	54 (10)	50 (9)	0	196 (37)
<1000	5 (1)	4 (1)	6 (1)	0	15 (3)
Total	267 (50)	154 (29)	109 (21)	0	530 (100)

Table 3. Kaplan–Meier estimates for progression to stage IV from stages I, II, and III.

Stages	No. events/ total	% progression (± s.e.) at n years	Estimated* median (years)
Based on CD4 count			
Stage I	66/317	52.8 (7.5) at 6.6 years	6.4†
Stage II	49/137	58.1 (7.1) at 5.9 years	5.3
Stage III	21/40	66.5 (9.7) at 5.7 years	3.8
Based on lymphocyte count			
Stage I	55/249	51.3 (7.7) at 6.3 years	6.3†
Stage II	60/187	60.4 (7.2) at 6.6 years	5.8
Stage III	22/57	58.5 (10.4) at 5.8 years	5.7

*Based on Kaplan–Meier estimate. †Based on Weibull model.

Using absolute lymphocyte count for staging, progression to stage IV was documented in 55 out of 249 subjects in stage I, 60 out of 187 subjects in stage II, and 22 out of 57 subjects in stage III. As seen in Table 3, product–limit estimates for progression to stage IV (and time interval) from stages I, II and III were 51.3 ±7.7% at 6.3 years, 60.4 ±7.2% at 6.6 years, and 58.5 ±10.4% at 5.8 years, respectively (log-rank $P = 0.02$). Estimated median times to stage IV were 6.3, 5.8, and 5.7 years from stages I, II and III, respectively. Kaplan–Meier progression curves from stages I, II, and III to stage IV using the staging with absolute lymphocyte count are shown in Fig 1b.

Survival

A total of 78 (15%) subjects had died by 1 April 1991. Using the staging system with CD4 counts, deaths were

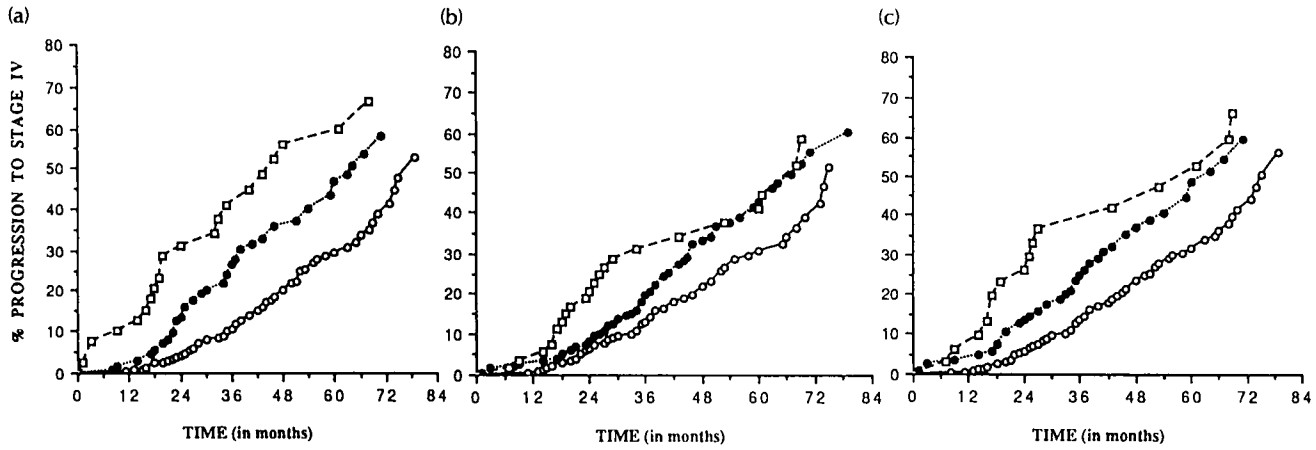

Fig. 1. Cumulative progression to modified World Health Organization system stage IV from stage I (○), stage II (●), and stage III (□) shown for the staging system using (a) CD4 lymphocyte count stratification, (b) absolute lymphocyte stratification, and (c) the alternative lymphocyte stratification discussed in the text.

distributed according to stage at the index visit: 34 out of 336 subjects in stage I, 27 out of 146 subjects in stage II, 15 out of 43 subjects in stage III, and two out of four subjects in stage IV. As seen Table 4, the product–limit estimates for survival (and duration) from stages I, II and III at index visit were 76.8 ± 7.7% at 7.6 years, 70.9 ± 5.7% at 6.7 years, and 53.5 ± 9.9% at 6.6 years, respectively (log-rank $P = 0.0001$). Using all 139 subjects who ever entered stage IV, survival after stage IV diagnosis was 42.5 ± 5.0% at 2 years and 12.3 ± 6.3% at 4 years. Estimated median times to death were 10.9, 8.2, 6.3 and 1.7 years from stages I to IV, respectively. Figure 2a shows the Kaplan–Meier survival curves from stages I, II, III and IV.

Using absolute lymphocyte counts, deaths were distributed according to stage at index visit: 29 out of 266 subjects in stage I, 33 out of 199 subjects in stage II, 14 out of 58 subjects in stage III, and two out of four subjects in stage IV. As can be seen in Table 4, the product–limit estimates for survival (and duration) from stages I, II, and III at the index visit were 72.9 ± 10.1% at 7.6 years, 74.5 ± 4.5% at 6.7 years, and 65.5 ± 8.9% at 6.6 years, respectively (log-rank $P = 0.012$). Using all 142 subjects who ever entered stage IV, survival after stage IV diagnosis was 43.6 ± 4.9% at 2 years and 16.2 ± 8.4% at 4 years. Estimated median times to death were 10.6, 9.0, 8.1, and 1.7 years from stages I to IV, respectively. Kaplan–Meier survival

Table 4. Kaplan–Meier estimates for survival from stages I, II, III and IV.

Stages	No. events/ total	% surviving (± s.e.) at n years	Estimated* median (years)
Based on CD4 count			
Stage I	34/336	76.8 (7.7) at 7.6 years	10.9
Stage II	27/146	70.9 (5.7) at 6.7 years	8.2
Stage III	15/43	53.5 (9.9) at 6.6 years	6.3
Stage IV	78/139	0.0 at 4.3 years	1.7
Based on lymphocyte count			
Stage I	29/266	72.9 (10.1) at 7.6 years	10.6
Stage II	33/199	74.5 (4.5) at 6.7 years	9.0
Stage III	14/58	65.5 (8.9) at 6.6 years	8.1
Stage IV	78/142	8.1 (6.5) at 4.3 years	1.7

*Based on Weibull model.

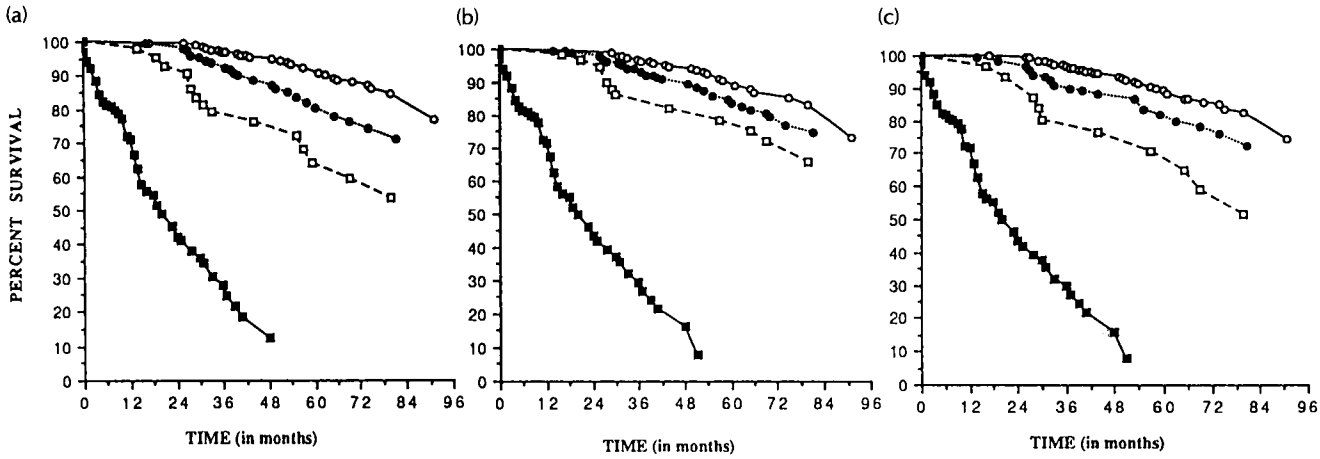

Fig. 2. Survival curves from modified World Health Organization system stage I (○), stage II (●), stage III (□) and stage IV (■) shown for the staging system using (a) CD4 lymphocyte count stratification, (b) absolute lymphocyte stratification, and (c) the alternative lymphocyte stratification discussed in the text.

curves from stages I, II, III and IV are shown in Fig. 2b.

Table 5. Kaplan–Meier estimates for progression to stage IV from stages I, II and III and survival from stages I, II, III, and IV restricted to 123 seroincident subjects using the CD4-based staging classification.

(a)

Stage	No. progressions/ total	% progressing (± s.e.) at n years	Estimated* median (years)
I	27/123	26.3 (4.5) at 6.6 years	9.0
II	17/72	33.8 (7.6) at 6.0 years	7.6
III	11/29	74.8 (19.0) at 5.3 years	4.0

(b)

Stage	No. deaths/ total	% surviving (± s.e.) at n years	Estimated* median (years)
I	14/123	85.5 (3.8) at 6.9 years	11.3
II	10/72	79.9 (5.9) at 5.6 years	9.7
III	6/29	66.8 (11.8) at 3.7 years	4.4
IV	14/27	37.8 (11.5) at 3.5 years	2.6

*Based on Weibull model.

We performed a regression on all 530 paired lymphocyte counts and CD4 cell counts derived from index visits. The slope of the derived regression line expressing the absolute lymphocyte count as a function of CD4 count was 1.65 ($r^2 = 0.56$). This suggested that a range of 300 CD4 cells (i.e., 200–500 $\times 10^6$/l) might better correspond to a range of 500 lymphocytes, rather than the suggested range of 1000 (1000–2000 $\times 10^6$/l). We therefore selected an alternative stratification for the lymphocyte count of <1000, 1000–1500, and $>1500 \times 10^6$/l, and repeated the analysis. Curves for progression from stages I, II and III to stage IV under this alternative lymphocyte stratification are shown in Fig. 1c. Product–limit estimates for progression to stage IV (and time interval) from stages I, II and III were 55.8 ± 7.5% at 6.7 years, 59.4 ± 7.7% at 5.9 years, and 66.2 ± 10.9% at 5.8 years, respectively (log-rank $P = 0.001$). Estimated median times to stage IV were 6.3, 5.3, and 5.1 years from stages I, II and III, respectively. Survival curves from stages I, II, III and IV using the alternative lymphocyte stratification are shown in Fig. 2c. Product–limit estimates for survival (and duration) from stages I, II, and III at index visit were 74.2 ± 8.2% at 7.6 years, 72.4 ± 6.0% at 6.7 years, and 51.5 ± 11.7% at 6.6 years, respectively (log-rank $P = 0.0001$). Survival from stage IV is similar to the standard lymphocyte system (Table 4) since stage IV is unchanged by the alternative stratification. Estimated median times to death were 9.7, 9.0, 6.6, and 1.7 years from stages I to IV, respectively.

There were 123 seroincident subjects eligible for restricted analysis. Of these, there were 27 progressions to stage IV and 14 deaths. Table 5 presents summary data for the seroincident analysis using CD4 cell count stratification. A pattern of results very similar to the overall analysis was found; for example, the estimated median survival times from stages I, II, III and IV were 11.3, 9.7, 4.4 and 2.6 years, respectively.

Discussion

Previous classifications of HIV disease have been found to have significant limitations. The earliest such classification was the so-called Centers for Disease Control (CDC)/WHO classification of HIV disease [4]. In the absence of an alternative, clinicians widely adopted this nomenclature; however, it soon became apparent that the groups within this classification could not be equated with stages since they had little prognostic value. For example, groups I to III in this system consist of acute infection, asymptomatic infection, and persistent generalized lymphadenopathy, respectively. There is now considerable evidence to suggest that there is no difference between these groups in terms of prognosis [6,8,9] and that all useful distinctions in the present CDC/WHO system are compressed into the various subcategories of group IV.

The acronym ARC (AIDS-related complex) was coined to enhance the clinical value of the CDC/WHO classification by describing patients who did not have AIDS, but who were symptomatic and thought to be at high risk of disease progression. Since this approach was not inclusive and failed to recognize that a large number of HIV-infected individuals had mild to moderate symptoms relating to their HIV disease but not yet fulfilling the definition of ARC, it did not provide a definitive staging classification. Furthermore, this approach again discriminated between asymptomatic individuals and those with persistent generalized lymphadenopathy, groups which now appear to have similar prognoses. Moreover, numerous definitions of ARC were in use, which created a considerable degree of confusion.

Some of these issues were addressed successfully by the Walter Reed staging classification proposed by Redfield *et al.* [3] in 1986. This was based on the combination of four clinical and laboratory criteria: the presence or absence of lymphadenopathy, CD4 cell count dichotomized as $>$ or $<400 \times 10^6$/l, the presence or absence of oral thrush, and the presence or absence of cutaneous anergy as measured by delayed hypersensitivity testing. Limitations of the Walter Reed staging classification include its use of lymphadenopathy as a criterion; its failure to include all HIV-infected individuals; and its dichotomization of the CD4 cell count, which results in a significant loss of information. A major limitation of this system relates to its reliance on delayed hypersensitivity testing, an invasive procedure requiring a follow-up visit.

Thus, this staging cannot be performed within a single encounter, making it time-consuming and compliance-dependent, particularly in the outpatient setting.

More recently, Royce *et al.* [10] proposed a simplified staging system based on CD4 cell count and the presence or absence of oral disease. Although this approach was of value in their cohort, it has not been validated independently. Furthermore, the mandatory use of CD4 cell counts once again restricts its use to areas where this measurement is readily available.

The proposed WHO staging system, particularly as modified here, appears to have successfully resolved many of the above problems. This system is all-inclusive, it combines clinical and laboratory parameters, and is far more widely applicable since it does not rely exclusively on CD4 cell counts. Our data suggest that use of the absolute lymphocyte count provides a valid alternative when CD4 cell counts are not available. The latter feature has obvious implications for use of this system in the developing world. Furthermore, this proposed staging classification has been successfully tested in a preliminary cross-sectional study that included data from all areas of the world [11]. Our results further confirm the validity of the proposed staging classification within the context of a cohort of homosexual men in North America. An additional secondary finding within our study concerns possible improvements in the staging system involving lymphocytes when an alternative stratification was used. This must be interpreted cautiously and may reflect local laboratory methods; we therefore do not claim to have found the optimal stratification for lymphocytes, but merely suggest that further improvement might be possible.

It is noteworthy that the proposed system is compatible with other classifications in use. For example, CD4 cell count stratification < 200, 200–500, and $> 500 \times 10^6/l$ is compatible with the criteria that have been widely used in major clinical trials of HIV therapies [12,13] and in published guidelines.

In summary, the proposed modified WHO staging system appears to provide a meaningful classification for HIV infection in a cohort of homosexual men. The inclusion of two independent axes reflecting clinical and laboratory profiles of HIV-infected individuals appears to be a sensible approach, which is compatible with other definitions and common stratifications, and which ensures classification of all HIV-infected individuals. Furthermore, the use of the absolute lymphocyte count as a valid alternative to CD4 lymphocyte count makes this staging classification a potentially useful tool in the many parts of the world where diagnostic facilities are limited, and CD4 counts are not accessible.

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