The Added Value of a CD4 Count to Identify Patients Eligible for Highly Active Antiretroviral Therapy Among HIV-Positive Adults in Cambodia

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Summary: In a retrospective study of 648 persons with HIV infection in Cambodia, we determined the sensitivity, specificity, and accuracy of the 2003 World Health Organization (WHO) criteria to start antiretroviral treatment based on clinical criteria alone or based on a combination of clinical symptoms and the total lymphocyte count. As a reference test, we used the 2003 WHO criteria, including the CD4 count. The 2003 WHO clinical criteria had a sensitivity of 96%, a specificity of 57%, and an accuracy of 89% to identify patients who need highly active antiretroviral therapy (HAART). In our clinic, with a predominance of patients with advanced disease, the 2003 WHO clinical criteria alone was a good predictor of those needing HAART. A total lymphocyte count as an extra criterion did not improve the accuracy.

Nine percent of patients were wrongly identified to be in need of HAART. Among them, almost 50% had a CD4 count of more than 500 cells/μL, and 73% had weight loss of more than 10% as a stage-defining condition. Our data suggest that, in settings with limited access to CD4 count testing, it might be useful to target this test to patients in WHO stage 3 whose staging is based on weight loss alone, to avoid unnecessary treatment.

KeyWords: clinical criteria, HAART, total lymphocyte count, WHO, CD4 count

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The CD4 lymphocyte count (CD4 count) is an important predictor of progression to AIDS. In the developed world, this parameter is used to identify patients who need prophylaxis for opportunistic infections and highly active antiretroviral therapy (HAART). In countries with limited resources, despite the increased access to HAART, CD4 count testing is often not available. CD4 count testing methods, whether flow cytometry based or manual, are still relatively complex and costly, need regular maintenance, and require trained staff. Moreover, quality assessment and assurance are generally not available in district hospitals.[1,2] Studies have shown an association between total lymphocyte counts (TLCs) and absolute CD4 counts.[3] Total lymphocyte count correlates with disease stage and predicts survival.[4,5] As TLC testing is more readily available, it has been suggested to use the TLC to decide when to start HAART.[6,7] Once a patient's TLC is less than 1200 cells/μL, the likelihood that the CD4 count will be less than 200 cells/μL is more than 90%. However, there is no TLC cutoff value that has both a high specificity and sensitivity for detecting patients with a CD4 count of less than 200 cells/μL.[5,8–10] Clinical algorithms that combine clinical manifestations and basic laboratory test results seem to increase the sensitivity to identify patients with low CD4 counts.[7,10] The World Health Organization (WHO) has published guidelines for initiating HAART in resource-poor settings, in situations where CD4 count testing is not available.[11] In our cohort of HIV-positive patients, we studied the sensitivity, specificity, and accuracy of the 2003 WHO guidelines for detecting patients in need of HAART by using clinical criteria, with or without TLC. As a reference test, we used the 2003 WHO criteria, including a CD4 count.

METHODS

Study Setting and Population

The study was conducted at the Sihanouk Hospital Center of HOPE (SHCH), a nongovernment organization hospital in Phnom Penh that provides free HIV care. Data on HIV-positive patients, including clinical diagnoses, WHO stage, weight, and laboratory data such as CD4 count and complete blood count, were entered in a Microsoft Access database in May 2003. At the end of 2004, a total of 1298 patients living with HIV/AIDS were registered in the database, of which 1073 were still in active follow-up in the SHCH and 225 were dead or lost to follow-up. Only 276 of the active patients were receiving HAART.

Laboratory Measurements

CD4 count was initially measured with a FACSCount (Becton Dickinson, Franklin Lakes, NJ) at Institut Pasteur du

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Cambodge. In June 2003, the SHCH introduced a simplified volumetric flow cytometric method to count the CD4 lymphocytes, CyFlow SL Green 2P (Partec, GmbH, Münster, Germany), using a whole-blood "lyse-no-wash" procedure. This technique was evaluated in the field and proved to be a valid method of CD4 enumeration when compared with the FACSCount.[12,13] In June 2004, we switched again to the FACSCount because of maintenance problems with the CyFlow. Hematologic parameters were determined by Sysmex KX-21 (Sysmex Corp., Kobe, Japan) automated hematology analyzer. Internal and external quality control systems were in place in both laboratories.

Statistical Methods

In this retrospective analysis of cohort data from HIV-positive patients in follow-up at the SHCH, we included data from all adult (>18 years old) patients ever registered in the database until the end of 2004 who had a paired CD4 count and TLC on the same blood sample, before the start of HAART. For each patient, the first available CD4-TLC pair was used for the analysis. Data analysis was done using SAS version 9.1 (SAS Institute Inc., NC, USA). When a CD4 count is available, the 2003 WHO guidelines consider that a patient is eligible for HAART when he is in stage 4 regardless of the CD4 count, or when he is in stage 3 and his CD4 count is less than 350 cells/μL, or when he is in stage 1 or 2 and the CD4 count is less than 200 cells/μL. When using the 2003 WHO clinical criteria, without CD4 count or TLC, all patients with a WHO stage 3 or 4 are eligible for HAART. When a TLC is available, also the patients who are in stage 2 and have a TLC of less than 1200 cells/μL are eligible. Sensitivity and specificity were calculated by computing a 2 × 2 table, comparing the 2003 WHO clinical criteria alone (±TLC) with the combined 2003 WHO clinical and immunologic criteria (reference test). Accuracy was measured by the sum of the true positives and negatives divided by the sum of all categories. The Wilson score method without continuity correction was used to calculate 95% confidence intervals (CIs) for sensitivity, specificity, and accuracy.[14] The study protocol was approved by the institutional review board of the SHCH and of the Institute of Tropical Medicine, Antwerp.

TABLE 1. Sensitivity and Specificity Using WHO 2003 Clinical Criteria Only to Start HAART With and Without Taking Into Account Weight Loss of More Than 10%*

	In Need of HAART (n = 528)			Not in Need of HAART (n = 120)		
	n	Sensitivity, %	FN	n	Specificity, %	FP
Stage 3 or 4	508	96.2	20	68	56.7	52
Stage 3 or 4 but excluding weight loss	468	88.6	60	90	75.0	30

*Reference test = WHO 2003 clinical and immunologic criteria.

FN indicates false negatives (incorrectly identified as patients who do not need HAART); FP, false positives (incorrectly identified as patients who do need HAART).

RESULTS

Of the 1298 patients registered in the database between June 1, 2003, and December 1, 2004, 648 (50%, 315 men and 333 women) had a CD4-TLC pair registered before the start of HAART. The mean age (±SD) in years of the patients was 34.2 (±7.9). The median CD4 count was 67 cells/μL (interquartile range, 14–228 cells/μL). Two hundred fifty-seven (39.7%) were in WHO stage 3, and 303 (46.8%) were in stage 4. Two hundred ninety-six (46%) had a CD4 count of less than 50 cells/μL, and 168 (26%) had a CD4 count between 50 and 200 cells/μL. The sensitivity of the 2003 WHO clinical criteria was 96% (95% CI, 94%–97%), the specificity was 57% (95% CI, 48%–65%), and the accuracy was 89% (95% CI, 86%–91%). Adding the TLC as a parameter resulted in a sensitivity of 97% (95% CI, 95%–98%), a specificity of 57% (95% CI, 48%–65%), and an accuracy of 90% (95% CI, 87%–92%). Using the WHO 2003 clinical criteria, 560 (86%) patients would be eligible for HAART. Of these, 508 qualify for HAART when considering also the CD4 count, giving a positive predictive value of 91%. Fifty-two (9%) would start therapy prematurely, 27 (52%) with a CD4 count between 350 and 500 cells/μL, and 25 (48%) with a CD4 count of more than 500 cells/μL, and all had at least 1 WHO stage 3 condition. Thirty-eight (73%) had weight loss of more than 10%, and for 22 (55%) of them, this was the only WHO stage 3–defining condition. Excluding weight loss from the WHO clinical criteria resulted in a marked increase in specificity, from 57% to 75%, and a moderate decrease in sensitivity, from 96% to 89%. Strategies excluding weight loss did not decrease the total number of patients who were misclassified (Table 1).

DISCUSSION

The CD4 count is a critical parameter in monitoring HIV disease. However, the high costs involved and the technical difficulties represent limitations for CD4 enumeration in developing countries.[15] Access to HAART is expanding in Cambodia. At the end of 2004, more than 5000 patients were receiving HAART.[16] There are no published data on the utility of combining TLC and clinical signs as an inexpensive surrogate marker of CD4 count in Cambodia, but most studies show that clinical criteria are not sensitive enough.[10,17]

Starting treatment too late will result in increased mortality. Starting treatment too early increases the cost of a program, exposes patients unnecessarily to the risk of developing adverse effects and toxicities, and increases the risk of noncompliance because of paucity of symptoms.

In our setting, because of a high percentage of patients with advanced disease (86% in WHO stage 3 or 4), the 2003 WHO clinical criteria were very sensitive, and TLC did not add a lot to identify patients in need of HAART. However, when using these clinical criteria, 9% of patients were wrongly identified to be in need of HAART. Almost 50% of them had a CD4 count of more than 500 cells/μL. Weight loss of more than 10% was a frequent (73%) stage-defining condition among them. A history of weight loss may not be reliable in a resource-poor setting, and some clinicians prefer to use the body mass

index.[18] Although they resulted in a marked increase in specificity, strategies excluding weight loss of more than 10% as a criterion for stage 3 did not decrease the total number of misclassifications. In a cohort in Malawi, Zachariah et al[19] found an equally high number of false positives (9%) when using WHO stages 3 and 4 as an indication for HAART. Their conclusion was that CD4 counts should be targeted to patients who have a body mass index of more than 22 kg/m^2 to avoid premature antiretroviral treatment.

We have to do everything possible to make CD4 counts available and to attract patients in an early stage of disease in our programs. However, lack of CD4 counts should not be a limiting factor in the access to treatment. In cohorts of patients with advanced disease, the 2003 WHO clinical criteria are very sensitive. Our data suggest that, in case we have limited access to CD4 counts, it might be useful to target this test to patients in WHO stage 3 whose staging is based on weight loss alone to avoid unnecessary treatment.

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