869

Use of Total Lymphocyte Counts and Hemoglobin Concentration for Monitoring Progression to AIDS

Johns Hopkins University
Bloomberg School of Public Health
615 N. Wolfe Street, Room E7004
Baltimore, MD, US 21210
Phone: 410-955-4320
Fax: 410-614-7125
E-mail: blau@jhsph.edu

Bryan Lau[1], Stephen J. Gange[1], John Phair[2], Sharon A. Riddler[3], Roger Detels[4], Joseph B. Margolick[1], and the Multicenter AIDS Cohort Study

Johns Hopkins School of Public Health., Baltimore, MD, USA[1]; Northwestern Medical School, Chicago, IL, USA[2]; University Pittsburgh, Pittsburgh, PA, USA[3]; and University of California LA, Los Angeles, CA, USA[4]

Background: Prognostic markers for HIV disease besides CD4+ lymphocyte counts and plasma viral load are needed for resource-limited regions. Total lymphocyte counts (TLC) and plasma hemoglobin levels have been shown to decline rapidly prior to AIDS, but the prognostic value of these markers and their declines for predicting AIDS has not been well examined in a prospective, natural history setting.

Methods: Data were examined among 297 seroconverters in the Multicenter AIDS Cohort Study (MACS), a prospective cohort study with semi-annual visits since 1983. Using data prior to 1996, we identified the first time TLC declined by more than 33% per year and, separately, the first time hemoglobin declined by more than 11.6% per year, values previously identified as maximizing sensitivity and specificity for predicting AIDS. The prognostic value of these markers and their declines was evaluated by Cox regression models with time-varying covariates to examine the relative hazard (RH) for progressing to AIDS.

Results: A TLC ≤1200 cells/mm3, the WHO recommendation for initiation of therapy when CD4 counts are not available, predicted progression to AIDS (RH=6.14; 95% CI: [4.33, 8.71]). A rapid decline in either TLC or hemoglobin was also significantly associated with progression to AIDS (RH=4.70 [3.23, 6.86] and 5.55 [3.69, 8.36], respectively). When present along with TLC ≤1200 cells/mm3, a rapid decline in either TLC or hemoglobin was strongly associated with progression to AIDS (RH=11.30 [7.39, 17.31] and 21.19 [12.43, 36.12], respectively). A faster time to AIDS was seen among those with more rapid marker declines. The relationship of TLC and hemoglobin with the incidence of AIDS remained significant after adjusting for HIV RNA concentration albeit with an attenuated relative hazard. After adjusting for CD4+ count, TLC decline was no longer associated with developing AIDS, but hemoglobin decline remained a significant predictor.

Conclusions: In the MACS, a rapid decline in either total lymphocyte count or hemoglobin concentration indicated an increased likelihood of progression of HIV infection to AIDS. These results support the utility of these markers for monitoring HIV infected people in resource-limited regions.

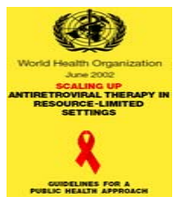
Introduction

- Increasing commitment to provide antiretroviral therapy (ART) for the developing world
- Important question: How to prioritize/stage patients in resource-constrained settings, balancing cost of drugs, laboratory and clinical monitoring, and management of side-effects. [Rabkin *et al* Lancet 2002]
  - Too early: wasted resources, unnecessary toxic effects, drug resistance.
  - Too late: morbidity and mortality.
- Are there alternative markers for guiding treatment initiation decisions?

Evaluation of WHO Guidelines

- Basis for WHO guidelines are largely from cross-sectional studies evaluating correlation of TLC and CD4 counts [Schreibman *et al.* CID 2004]
- Marker levels alone may be inadequate for monitoring since individuals infected in developing countries may be affected by a variety of endemic factors (disease, malnutrition)
- Using new insights into HIV disease pathogenesis, we have demonstrated the occurrence of rapid declines in TLC and hemoglobin markers prior to clinical disease [Lau *et al.* AIDS 2003]
- These data raise the question of whether the WHO guidelines can be enhanced with knowledge of rapid marker declines as predictors of clinical disease

WHO Guidelines - Total Lymphocyte Count (TLC)



CD4 cost: US $30.00
TLC cost: US $ 0.80

[Kumarasamy JAIDS 2002]

Recommendations for Initiating Antiretroviral Therapy in Adults and Adolescents with Documented HIV Infection

- If CD4 testing is available:
  - WHO stage IV irrespective of CD4 cell count
  - WHO stage I, II or III[a] with CD4 cell counts less than 200/mm3[b]
- If CD4 testing is not available:
  - WHO stage IV irrespective of TLC
  - WHO stage II or III[c] with TLC less than 1200/mm3[c]

a. Treatment is also recommended for patients with advanced WHO Stage III disease including recurrent or persistent oral thrush and recurrent invasive bacterial infections irrespective of CD4 cell or total lymphocyte count.
b. The precise CD4 level above 200/mm3 at which to start ARV treatment has not been established but the presence of symptoms and the rate of CD4 cell decline (if measurement available) should be factored into the decision making. A CD4 level of 200/mm3 corresponds to a CD4 percentage of approximately 15%.
c. A total lymphocyte count of below 1200/mm3 can be substituted for the CD4 count when the latter is unavailable and HIV-related symptoms exist. It is less useful in the asymptomatic patient. Thus, in the absence of CD4 cell testing, asymptomatic HIV infected patients (WHO Stage I) should not be treated because there is currently no other reliable marker available in severely resource constrained settings.

Research Questions

- To determine if TLC<1200 is predictive of clinical AIDS
- To determine if rapid declines in TLC and hemoglobin markers can supplement the WHO guidelines by evaluating:
  - The predictive value of these declines
  - The timing of these declines relative to low CD4 counts and clinical disease

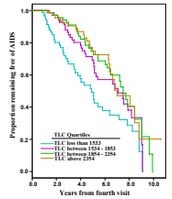
Methods

- Data from 297 seroconverters from the MACS fulfilling the following selection criteria
  - At least 4 visits free of AIDS
  - For those individuals progressing to AIDS at least two visits within 1.5 years of AIDS
- For each individual, we estimated the first time of a rapid decline in TLC and hemoglobin defined by:
  - A TLC decline of 33% per year or greater
  - A hemoglobin decline of 11.6% per year or greater
- Utilizing time-varying Cox proportional hazards regression the prognostic value of these markers and rapid declines were assessed

The Multicenter AIDS Cohort Study is funded by the National Institute of Allergy and Infectious Diseases, with additional supplemental funding from the National Cancer Institute and the National Heart, Lung, and Blood Institute.

Website located at http://www.statepi.jhsph.edu/macs/macs.html.

TLC Association with AIDS



Time-varying TLC < 1200 is Associated with AIDS

Unadjusted Relative Hazard = 6.14

95% Confidence Interval (4.33, 8.71)

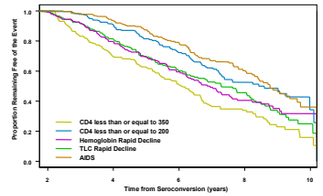
TLC Level and Rapid Decline are Associated with Disease Progression

	TLC Decline		TLC Level	
	Relative Hazard	95% CI (P- value)	Relative Hazard	95% CI (P- value)
Unadjusted	4.70	3.23 - 6.86 (<0.0001)	1.18	1.14 - 1.22 (<0.0001)
Multivariate				
Decline & Marker Level	2.53	1.67 – 3.85 (<0.0001)	1.13	1.09 - 1.17 (<0.0001)
Adjusted for HIV RNA	1.84	1.18 – 2.86 (0.0067)	1.09	1.06 - 1.13 (<0.0001)
Adjusted for HIV RNA & CD4+ Count	1.41	0.91 – 2.18 (0.12)	1.00	0.96 - 1.04 (0.98)

Hemoglobin Level and Rapid Decline are Associated with Disease Progression

	Hemoglobin Decline		Hemoglobin Level	
	Relative Hazard	95% CI (P- value)	Relative Hazard	95% CI (P- value)
Unadjusted	5.55	3.69 - 8.36 (<0.0001)	1.78	1.61 - 1.96 (<0.0001)
Multivariate				
Decline & Marker Level	2.75	1.75 - 4.33 (<0.0001)	1.56	1.39 - 1.75 (<0.0001)
Adjusted for HIV RNA	2.34	1.48 - 3.70 (0.0003)	1.32	1.17 - 1.49 (<0.0001)
Adjusted for HIV RNA & CD4+ Count	1.72	1.08 - 2.75 (0.023)	1.12	0.98 - 1.27 (0.091)

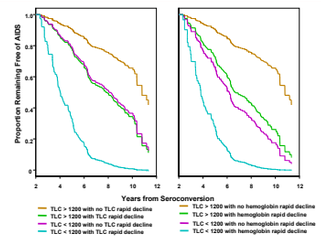
Timing of Events



Marker Declines Supplement the TLC<1200 Criteria

Rapid Decline	TLC ≤1200 cells/mm3	Total Lymphocyte Count: Relative Hazard (95% CI)	Total Lymphocyte Count: Adjusted for HIV RNA and CD4+ count	Hemoglobin: Relative Hazard	Hemoglobin: Adjusted for HIV RNA and CD4+ count
–	–	REF	REF	REF	REF
+	–	2.53 (1.56, 4.10)	1.24 (0.76, 2.03)	5.28 (3.11, 8.97)	2.49 (1.45, 4.31)
–	+	2.39 (0.94, 6.09)	0.83 (0.32, 2.16)	6.85 (3.39, 13.83)	1.97 (0.94, 4.11)
+	+	11.30 (7.39, 17.31)	1.52 (0.93, 2.49)	21.19 (12.43, 36.12)	2.70 (1.46, 4.97)

Extended Kaplan Meier



Conclusions

- TLC ≤1200 cells/mm^3 is prognostic for disease progression
- TLC and Hb demonstrate rapid declines which occur on average prior to clinical disease and between the time that CD4$^+$ cell counts fall from 350 to 200 cells/mm^3
- The risk of AIDS is greatest among those with declines and TLC ≤1200 cells/mm^3.
- Our data support supplementing the WHO guidelines so that individuals are monitored for marker declines in addition to low TLC levels.