Monitoring HIV Treatment in Resource-Limited Settings: Reassuring News on the Usefulness of CD4\(^+\) Cell Counts

Mary Glenn Fowler\(^1\) and Maxensia Owor\(^2\)

\(^1\)Johns Hopkins Medical Institutes, Baltimore, Maryland; \(^2\)Makere University–Johns Hopkins University Research Collaboration, Kampala, Uganda

(See the major article by Brown et al., on pages 1292–300.)

The article by Brown et al. [1] in the current issue of the Journal is a careful assessment of the relative usefulness of virologic and immunologic markers, as well as other markers gathered in the third trimester of pregnancy, in predicting mortality among HIV-infected women in Nairobi, Kenya, during 1–2 years of follow-up after delivery. The findings indicated that the absolute CD4 cell count, as well as the CD4 cell percentage (CD4\%), were the best predictors of mortality and that the measurement of maternal viral load did not improve prediction of maternal death.

With the rapid expansion of antiretroviral therapy (ART) in resource-limited settings, such as East Africa, one of the key clinical challenges has been to find cost-effective methods that are deliverable at the point of care to monitor patients’ responses to treatment and HIV disease progression. The study by Brown et al. [1] contributes to our knowledge by addressing the relative value of the CD4\%, absolute CD4 cell count, and viral load, as well as other possible markers, including total lymphocyte count (TLC), hemoglobin, and body mass index (BMI), in predicting death at 1 and 2 years after delivery among HIV-1–infected women. The data were collected from a prospective cohort of HIV-1–infected pregnant women who were followed at a teaching hospital in Nairobi during 2 distinct periods: 216 women were monitored for 1 year after delivery between 1999 and 2002 and 319 women were monitored for up to 2 years after delivery between 2002 and 2005 (at a time when ART became much more widely available because of international donor funds). These combined data represented 10,150 person-months of follow-up, providing robustness and strength to the analyses and allowing a look not only at the predictive value of individual markers but also at combining multiple markers.

There were a number of interesting findings from these analyses. First, the absolute CD4 cell count was a useful marker during pregnancy and was similar to the CD4\%, despite the effect of hemodilution on the CD4 cell count during late pregnancy. The results also reinforce the prognostic value of a CD4 cell count of <200 cells/\(\mu\)L, which, in the present study, predicted a 19-fold increased risk of death within the first year after delivery (sensitivity, \(\sim\)70%; specificity, 91%). Of note, the addition of the viral load to a hazard model that included the CD4 cell count or CD4\% did not improve the prediction of mortality. Other inexpensive biomarkers, such as TLC, hemoglobin, and BMI, were not highly predictive of death during the first 24 months after delivery.

These findings demonstrate the usefulness of the CD4 cell count and CD4\% to identify those pregnant women who were at the highest risk for death within 24 months after delivery, and they support current World Health Organization (WHO) guidelines on CD4 cell count and CD4\% cutoffs for the initiation of ART among adults. In addition, the results are consistent with recent pediatric findings demonstrating the usefulness of the CD4 cell count in predicting death among older HIV–infected children in both resource-limited and resource-rich settings. In a 10-country meta-analysis of HIV-infected children >12 months of age (median age, 4 years), Gibb et al. [2] assessed the predictive usefulness of a variety of laboratory and growth markers on the risk of death during the course of 1 year. On the basis of the meta-analysis, both the CD4 cell count and the CD4\% were the strongest predictors of death during the course of 1 year; similar to the findings of the analyses done by Brown et al. [1], BMI and TLC were not very helpful as predictors of death after adjustment for the CD4 cell count [2]. Similarly, Musoke et al. [3] found that the TLC was not a useful surrogate marker for the risk of death among Ugandan children. In contrast, CD4 lymphocyte measurements...
have been consistently predictive of pediatric disease progression and associated mortality. In the Pediatric AIDS Clinical Trials Group 152 trial, Palumbo et al. [4] reported that more than one-half of HIV-infected, treatment-naive children who were >6 years of age and had a baseline CD4 cell count of <200 cells/µL experienced progression to AIDS or death within 2 years of follow-up.

Findings for nonpregnant women and for men also demonstrate the usefulness of the CD4 cell count, either alone or in combination with the viral load. Mellors et al. [5] in the United States, as well as Egger et al. [6] in Europe, showed that both the CD4 cell count and the viral load were helpful markers predicting long-term disease progression and associated mortality. Mellors et al. [7] found that combining the viral load and immunologic markers increased predictiveness. However, in international resource-limited settings, the CD4 cell count alone appears to do as well, without the addition of viral load, on the basis of both the study by Brown et al. [1] and a recent prospective study from Uganda among nonpregnant HIV-infected adults who were initiating ART [8].

The Uganda study by Coutinho et al. [8] was a randomized trial of monitoring strategies that compared the use of clinical findings alone (WHO stage 3 or 4), clinical findings plus the CD4 cell count, or clinical findings plus the CD4 cell count plus the viral load determined every 3 months with outcomes of AIDS events and mortality. The Uganda monitoring trial demonstrated that the combined use of the CD4 cell count and clinical findings was significantly better for monitoring the progression of HIV disease than was clinical status alone but that the addition of viral load measurements did not add any benefit over the use of the CD4 cell count plus clinical staging in predicting the risk of death. The differences in the benefit of viral load monitoring seen in the United States, compared with that seen in resource-limited settings, could, in part, be associated with high rates of background infectious diseases in settings such as Kenya and Uganda, with related inflammatory responses leading to increases in viral load that are independent of HIV disease progression.

Thus, although the 2008 US Department of Health and Human Services Adult and Adolescent HIV Treatment Guidelines [9] recommend the combined use of the CD4 cell count and the viral load to monitor patients receiving ART, the WHO currently recommends only the use of the CD4 cell count for both treatment initiation and monitoring of disease progression—without routine use of viral load monitoring [10]. These WHO recommendations are further corroborated by Brown et al. [1] among postpartum women, as well as by other studies performed in resource-limited settings and indicating that viral load monitoring does not add much to predicting disease progression or death, compared with the CD4 cell count alone.

The results of the detailed analyses of prognostic markers reported by Brown et al. [1] among pregnant and postpartum women in Nairobi are reassuring; they strongly support the current WHO recommendations for primary use of the CD4 cell count as a basis for both initiation and monitoring of ART in resource-limited settings, without requiring more expensive viral load monitoring. The data are likewise important in confirming the prognostic usefulness of CD4 cell counts among pregnant and postpartum women, because many HIV-infected women are first identified during pregnancy. Furthermore, the findings reinforce the view that simpler and less expensive markers, such as TLC and BMI, are not particularly sensitive for longer-term follow-up care and treatment of HIV-infected adults, and that the goal should be wider access to, and availability of laboratory monitoring of the CD4 cell count.

However, even given the predictive usefulness of the CD4 cell count as a reliable and valid marker for disease progression, logistic challenges to employing CD4 monitoring remain in many resource-limited settings. These challenges are related to a variety of factors, including a lack of local laboratory capacity to perform CD4 cell counts in many nonurban settings, coupled with delays in getting results back from referral laboratories, CD4 cell count equipment breakdown, or temporary stockouts of reagents, each of which has a negative influence on patient follow-up. International funding to speed the development of innovative and inexpensive point-of-care CD4 cell count and virologic monitoring technologies will be critical to optimize patient care and treatment, because HIV treatment efforts continue to roll out into rural areas in Africa and other resource-limited settings.

In conclusion, the article by Brown et al. [1] in this issue of the Journal is encouraging because it indicates that CD4 cell counts can be used to make decisions about treatment, as well as to monitor HIV disease progression in resource-limited settings where virologic monitoring is not widely available. Continued technologic and operational research efforts need to focus on the development of simple inexpensive virologic and immunologic monitoring assays that can be delivered at point-of-care primary care settings, to improve long-term treatment outcomes for the ~40 million individuals affected by the global HIV pandemic.

References


9. Department of Health and Human Services Panel on Guidelines for the Use of Antiretroviral Agents for HIV-1-Infected Adults and Adolescents. 3 November 2008:1–139.