

Use of Risk Equations for Predicting Disease Progression in HIV Infection

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(See the article by Srasuebkul et al. on pages XXX–XXX)

[Q1]In this issue of *Clinical Infectious Diseases*, Srasuebkul et al. [1] propose models for identifying HIV-1–infected patients at short-term risk of AIDS or death in Asia and resource-limited settings. The models are based on clinical criteria (including body mass index, development of anemia, and age), CD4 cell count criteria (CD4 cell count was incorporated in the risk strata), and CD4 cell count and HIV load criteria (HIV load was incorporated in the risk strata). Three models were developed to enable clinicians to choose the most appropriate model on the basis of the availability of laboratory results, such as CD4 cell count and HIV load, within resource-limited settings.

The Centers for Disease Control and Prevention has proposed various classification systems for HIV-infected patients [2–4], but these have always been intended for use in surveillance rather than to provide prognostic information. Staging systems for HIV infection have previously

been proposed. The systems developed in the **[Q2]**pre-combination antiretroviral therapy (ART) era were based on clinical criteria and CD4 cell count [5–7] but were often criticized because they could not be widely implemented in developing countries. Staging systems, primarily the World Health Organization staging system or a modified version of it, were therefore developed and applied to patients in developing countries [8–11]. **[Q3]**The World Health Organization staging system was based on a combination of clinical and biological parameters, with a clinical and laboratory axis, and on the availability of CD4 cell count measurement or total lymphocyte count measurement in regions where resources were not available for CD4 cell count determinations. Since the introduction of combination ART and the improvement in prognosis, various new prognostic staging systems have been proposed on the basis of information available on the date of initiation of combination ART [12, 13]; **[Q4]**short-term prognostic staging systems have been based on information available during follow-up [14, 15]. The staging system proposed by Srasuebkul et al. [1] is, therefore, one of the first post-combination ART prognostic staging systems that have been developed and applied among patients from resource-limited settings.

There is an important distinction be-

tween models that predict the short-term risk of disease progression and those that predict the long-term risk of disease progression. In general, previous models have generally concentrated on predicting long-term clinical progression on the basis of information known on the date of combination ART initiation [16, 17]. These scores identify groups of patients with elevated risk of disease progression at the time of combination ART initiation on the basis of information known at the date of combination ART initiation, such as CD4 cell count, viral load, age, or HIV exposure category. Patients who initiate combination ART experience rapid changes in CD4 cell count and HIV load that, in turn, affect the risk of disease progression [18, 19]; therefore, it may be more clinically relevant to determine the risk of disease progression when the patient returns to the clinic at some time after initiation of combination ART, depending on the initial response to combination ART. For example, a clinician may want to assess the risk of disease progression before the next scheduled patient visit for a patient who started combination ART 3 years before that visit.

It is important to note that prognostic models that predict the short-term risk of disease progression depend on the frequency of measurement of variables that contribute to the prognostic score. If CD4 cell counts and viral loads are measured a

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mean of [Q5] every 3 months in an observational study, it is reasonable to use that prognostic model to predict the risk of disease progression over the subsequent 3 months. It is possible, of course, to predict disease progression over a longer period of time. If patients are seen less frequently—for example, every 6 or 12 months—then the prognostic model is built on a series of measurements made at 6- or 12-month intervals; therefore, it would not be the best methodology for predicting disease progression in the subsequent 3 months. Although the article by Srasuebku et al. [1] reports prognostic markers for short-term clinical disease progression, it would be useful to know how the mean frequencies [Q6] of the clinical and laboratory assessments are measured, to help decide over which short-term period the predictions are most likely to apply.

Scoring systems and prognostic staging systems are a simplification of the information on which they are based. There is inevitably a trade-off between the best fitting model in statistical terms and a model that will be readily accepted by clinicians. A model that offers the best fit to the data may be cumbersome and poorly understood by nonmathematicians; for example, a square-root-transformed CD4 cell count may provide the best statistical fit of the model but is not easily accessible for the clinician or patient. The arrival of Internet-based computational tools has somewhat eased this problem, and on-line risk calculators are now readily available for a wide variety of diseases, including HIV infection (e.g., that available from the Copenhagen HIV Programme [20] [Q7]). These calculators enable a risk score to be determined using quite complex equations without the need for the clinician or the patient to perform the calculations, although the issue of understanding the risk equation remains. The alternative to the best-fitting model is to use arbitrary cutoff values for included variables; these cutoffs are usually based on previous research and commonly accepted limits. For

example, Srasuebku et al. [1] defined a low body mass index (calculated as the weight in kilograms divided by the square of the height in meters) as <18 and severe anemia as a hemoglobin level <80 g/L; other studies have used similar cutoffs [14–15, 21]. This approach provides a prognostic scoring system that is easy to use. The main disadvantage of using arbitrary cutoffs is that the risk of disease progression is usually a continuous process; the risk of disease progression for a patient with a body mass index of 17.9 is unlikely to be statistically significantly different from the risk for a patient with a body mass index of 18.1, although the prognostic staging system proposed by Srasuebku et al. [1] would classify the former as being at very high risk and the latter as being at low risk of disease progression. Clearly, clinical judgement is needed, in addition to information from repeated laboratory tests and follow-up visits.

As noted in the article by Srasuebku et al. [1], a prognostic model should be validated in other patient populations to assess its accuracy, because the prognostic model will inevitably fit well with the dataset from which it was derived. The validity of this prognostic model can be tested by assessment of the discrimination, calibration, and accuracy of prediction, as well as by the assessment of the overall model fit [22–24]. [Q8] In brief, the discrimination of the model can be assessed by considering the proportion of patients needed for the predictions and outcomes to be consistent. Calibration can be assessed by comparing the predicted survival curves from the prognostic model—stratified by the identified prognostic variables—with use of the Kaplan-Meier estimation. The accuracy of predictions is assessed by separating patients into groups on the basis of low, medium, or high risk of disease progression. Finally, the overall fit of this model can be compared with the fit of this model in a different dataset by comparing the deviance of the different models. In addition, the sensitivity and specificity of the proposed 3 models could

be examined in the context of other patient groups to determine how much accuracy is gained or lost by using a simpler model.

Therefore, in the study by Srasuebku et al. [1], the accuracy of the models was assessed by grouping patients with low, medium, and high risk of disease progression. Additional useful information would be which of the 3 proposed models predicts best in an ideal setting where resources are not limited and whether, on the basis of these models, the authors think that the extra prognostic information provided by CD4 cell counts and/or viral loads warrants their routine measurement. It is worth noting that regular viral load monitoring is performed to ensure virological response to combination ART and is a useful predictor of disease progression in some settings. Finally, the models could have been internally validated against one another; for example, how many of the patients classified as being at high risk with use of the simplest model would also be classified as being at high risk with use of the other predictive models.

In summary, staging systems can play an important role in HIV infection. These systems aid communication between researchers, physicians, and patients and summarize the risk of disease progression in an understandable format, taking into account many different prognostic factors. Patients who enter a clinical trial can be stratified according to risk of disease progression, or the end point of the clinical trial could incorporate moving to a stage with a worse prognosis. The systems, when possible, should be derived for large patient populations that are representative of the population being studied, should be easily applicable to all patients, should be linked to the pathophysiology of the disease being investigated, should be easy to remember, should be easy to apply to all patients receiving follow-up, and should have a meaningful end point. As described above, validation of the prognostic staging system proposed by Srasuebku et al. [1]

is required in different patient populations before it can be introduced in routine clinical practice.

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