The natural history of HIV infection in Africa

Knowledge of the natural history of HIV infection in developing countries is scarce and incomplete,[1] but there are data to suggest that progression to AIDS and/or death may be faster in developing countries. Several studies have demonstrated that co-infections with other pathogens increase short-term viral replication, but none have demonstrated an impact on progression to death. Many other factors may also result in shorter survival of HIV-infected patients in resource-poor settings, including poverty, limited access to health care services, under-resourced medical services, poor nutritional status and the quality of water supply. There may also be considerable regional variation in the prevalence of localised tropical diseases and the spectrum of major HIV-related conditions, which in turn are influenced by the proportion of individuals surviving with advanced immune suppression. In summary, our present knowledge of the morbidity and mortality of HIV-infected individuals prior to antiretroviral therapy (ART) access is based on a limited number of cohort studies, each of which is subject to selection biases. Additionally, comparisons of data between cohorts are further distorted by the use of variable diagnostic criteria for opportunistic diseases in different studies.

In this issue of *SAMJ* Losina *et al*.[2] contribute significantly to the existing body of knowledge by describing the natural history of an HIV-infected urban cohort in West Africa before access to either ART or co-trimoxazole prophylaxis. The study is of a well-characterised cohort of 270 patients followed for a median of 9.5 months entered into the placebo arm of a co-trimoxazole study performed between 1996 and 1998.[3] Patients with symptomatic HIV infection (WHO stages 2 and 3) but not AIDS were selected without knowledge of their CD4 cell counts. Data quality was ensured by use of standardised interviews and physical examinations at enrolment and then monthly until the end of study or death. A team of community social workers ensured active follow-up of participants and all adverse events were reviewed and classified by an independent panel. Such high-quality natural history data describing progression of untreated AIDS in Africa cannot be reproduced, as it would no longer be ethically justified to follow such a cohort without giving access to co-trimoxazole prophylaxis or antiretroviral therapy.

This study is important in describing the spectrum of opportunistic disease in West Africa and defining the baseline morbidity and mortality of HIV infection together with the impact of opportunistic disease on both acute and chronic mortality. Such data are important for determining the effectiveness and cost effectiveness of subsequently instituted therapies. The incidence rate of severe opportunistic diseases in West Africa varied substantially across CD4 cell count strata with the spectrum being widest in those with CD4 cell counts < 50/µl. As is the case in South Africa, tuberculosis and bacterial infections predominated. Malaria and isosporiasis occurred across the spectrum of CD4 cell counts, and the prevalence of these infections in early HIV infection and their susceptibility to co-trimoxazole may in part explain the reported increased effectiveness of co-trimoxazole prophylaxis at higher CD4 cell counts in West Africa relative to South Africa.[3,4]

None of the patients entered the study with a diagnosis of AIDS and the median cohort CD4 cell count was relatively well preserved (261/µl). Despite this, 17% of patients died during the study period resulting in an estimated crude death rate of 20/100 patient-years. Eighteen per cent of these deaths were within 30 days of an opportunistic disease; however the majority of deaths (82%) were not associated with an acute opportunistic disease and constituted chronic mortality, which was the primary focus of the study. Chronic mortality was increased in those with low CD4 cell counts and those with a prior history of opportunistic disease. While these results are not surprising to those caring for HIV-infected patients, they do reinforce the importance of clinical stage as well as CD4 cell count in assessing the prognosis of people living with HIV infection. These findings also highlight the need for wider access to CD4 cell counts in order that patients can begin ART at an optimal threshold prior to the onset of symptomatic HIV infection.

The authors suggest that there is a danger that the emphasis on access to prophylaxis may be lessened due to the increased focus on access to ART and that as opportunistic diseases are associated with increased chronic mortality, prophylaxis against opportunistic diseases is important in order to reduce mortality. However, the demonstration of an association between opportunistic disease and chronic mortality does not necessarily prove causation, and benefits of opportunistic disease prophylaxis would be better demonstrated in controlled trials of specific interventions.

Of particular concern is the 11% annual mortality occurring in individuals without a history of prior opportunistic disease and a 6% annual mortality in patients with CD4 cell counts preserved above 200 cells/µl. This early HIV-associated mortality is consistent with cohort data from Cape Town where mortality of patients attending an HIV clinic with WHO stage 1 and 2 disease was 12% per annum[5] and approximately 50% of mortality in HIV-infected individuals occurred before an AIDS diagnosis.[6] These data would add weight to the argument that in order to minimise mortality, ART should be initiated at an

earlier threshold than that currently recommended in the South African antiretroviral rollout programme.[7]

Linda-Gail Bekker

Desmond Tutu HIV Centre
Institute of Infectious Disease and Molecular Medicine, and
Department of Medicine
University of Cape Town

Robin Wood

Desmond Tutu HIV Centre
Institute of Infectious Disease and Molecular Medicine
University of Cape Town

Corresponding author: *L-G Bekker (Linda-Gail.Bekker@hiv-research.org.za)*

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