Commentary: Sifting through the maze of viral and host diversity and HIV/AIDS clinical progression

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Costello and colleagues describe survival in a cohort of HIV-1 subtype E (circulating recombinant form 01_AE) infected patients in northern Thailand. In Thailand, subtype B (Thai B) is endemic primarily among injecting drug users, whereas subtype E began among female prostitutes and spread through their male clientele to heterosexual couples. Subtype E viruses are now also spreading among the injecting drug user networks. This study is of interest because of the geographical setting, the patient population, and the viral subtype. We have accumulated considerable knowledge regarding host and viral factors that influence infection, pathogenesis, and disease progression. Additionally, environmental and socioeconomic factors including nutrition, ability to access care, and other endemic co-morbidities will influence disease progression. The association of different rates of disease progression in populations infected with different subtypes is not in itself a new finding. In Africa, infection with subtype A was associated with a slower disease progression compared with non-A subtypes, particularly subtype D. Nevertheless, most of our knowledge still comes from subtype B infected patients living in the developed world. This study adds to a nascent body of knowledge regarding diverse subtypes of HIV in diverse populations.

Time to death appears to be shorter in the cohort reported by Costello et al. than in cohorts from industrialized countries. The median survival time was about 8 years post-seroconversion, compared with 11 years in a European study prior to the widespread use of antiretroviral therapy. In a previous survival study of subtype E infected Thai female sex workers, the rate of CD4 decline was similar and disease progression was similar or slightly more rapid compared with cohorts from high income settings. Survival times are influenced by baseline surrogate marker values; for example, 70% of patients with viral loads above 30 000 copies/ml died within 6 years of seroconversion in the US-based MACS cohort compared with a median survival time of 3.6 years in patients with viral loads between 10 000 and 100 000 in the present study.

Unfortunately, an appropriate control group—another Thai population with predominantly non-E subtype, or a non-Thai cohort with a predominantly subtype E infection—to confirm the central finding of Costello’s study and to help elucidate whether viral or host characteristics are associated with the apparent more rapid time to death, is lacking. Costello and colleagues note the difficulty of addressing this question directly, citing the different modes of transmission. However, given that subtype E is now spreading among injecting drug users—up to 80% of seroconvertors as reported in some studies—comparisons of survival should be feasible at least within this population. We need a systematic approach to the study of HIV diversity in the context of host diversity and the impact on pathogenicity, disease progression, and survival.

Assuming the more rapid progression is real, and not primarily due to sociocultural and economic factors, what hypotheses might be generated to explain this finding? We know of viral characteristics that influence disease progression. The more rapid progression associated with CXCR4-dependent viruses compared with CCR5-dependent viruses, for example, is well-known in the subtype B world. In addition, high viral load levels are predictive of more rapid progression. Interestingly, in a study carried out among injecting drug users in Bangkok, individuals infected with subtype E had higher viral loads compared with those infected with subtype B, although CD4...
cell counts were not different and the viral load difference dissipated after 12 months. Less is known about the predominance CCR5 or CXCR4 viruses, and the transition from one form to another, in non-B subtypes, although early studies predict no difference between subtype E and subtype B infected populations.

In addition to the novelty regarding the viral subtype, this paper adds confirmatory information regarding the use of alternative or non-traditional markers for predicting survival. Although these markers do a fair job of predicting death, they will not be so useful in monitoring treatment response and assessing the appropriate time to change treatments. Anti-retroviral treatment roll-out programmes need to include funds to monitor treatment response, and research and development in the area of low-cost and point-of-care laboratory tests is important to reduce costs in the future.

Finally, as the authors noted, there was very little use of antiretroviral therapy in this cohort and little information on prophylaxis for opportunistic infections. In the era of rapidly improving access to potent antiretroviral treatment worldwide, the questions we are asking must change: rather than describing high rates of disease progression and low survival rates in the absence of treatment, we should examine responses to treatments, toxicities associated with treatments, quality of life, and long-term prognosis in the large number of HIV-1 infected patients now starting antiretroviral therapy around the world.

References