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Differential distribution and evolution of HIV-1 RNA variants in the gastrointestinal tract of antiretroviral naïve african AIDS patients with diarrhea and (or) weight loss

Phetole Walter Mahasha
University of Limpopo, South Africa

Background: Due to its continuous exposure to food antigens and microbes, the gastrointestinal tract (GIT) is in a constant state of low level immune activation and contains an abundance of activated CCR5+CD4+ T lymphocytes, the primary target HIV-1. As a result, the GIT is a site of intense viral replication and severe CD4+ T cell depletion, a process that begins during primary HIV-1 infection and continues at a reduced rate during chronic infection in association with increased production of pro-inflammatory cytokines, a breakdown in the epithelial barrier, microbial translocation, systemic immune activation and the continued recruitment and infection of new target cells. AntiRetroviral Therapy (ART) is only partially effective in reversing these pathogenic changes. Despite the importance of the GIT in HIV-1 pathogenesis, and as a reservoir of persistent virus during ART, little is known about the diversity of HIV-1 in the GIT, or how different tissues in the GIT respond to ART.

Objectives: Primary objectives of this thesis were to: 1) characterize the diversity of HIV-1 RNA variants in different parts of the GIT 2) determine whether there is compartmentalized evolution of HIV-1 RNA variants in the GIT and whether these variants are likely to have different biological properties.

Methods: A prospective study of the duodenum, jejunum, ileum and colon of African AIDS patients with chronic diarrhea and/or weight loss, sampled before and during 6 months of ART. RNA extracted from gut biopsies was reverse transcribed and PCR amplified. *Env* and *gag* PCR fragments were cloned, sequenced and subjected to extensive phylogenetic analysis; *pol* PCR fragments were analyzed for drug resistance. Results: Viral diversity varied in different regions of the GIT with *env* HIV-1 RNA variants being significantly more diverse than *gag* variants. *Gag* HIV-1 RNA variants were widely dispersed among all tissue compartments. Some *env* variants formed tight monophyletic clusters of closely related viral quasispecies, especially in the colon, a finding that is suggestive of compartmentalized viral replication and adaptive evolution.

Conclusions: These results advance our understanding of the GIT as a host-pathogen interface by providing new insights into the diversity, evolution and dissemination of HIV-1 variants in the GIT. Strategies aimed at decreasing immune activation, especially in the small intestine, may be highly beneficial in enhancing the therapeutic efficacy of ART.

Biography

Phetole Walter Mahasha, has completed his PhD at the age of 38 years from the University of Pretoria, South Africa and Postdoctoral studies from the University of Virginia, School of Medicine, Division for infectious Diseases and International Health and the Center for Public Health Genomics and the University of Venda, AIDS Virus Research Programme and the NICD in South Africa. He is a Senior Lecturer, in the Department of Pre-Clinical Sciences (Medical Biochemistry) at the University of Limpopo. He has published more than 5 papers in reputed journals and has been serving as an editorial board member of repute.

thakgalo03@gmail.com

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