PROSPECTIVE ANALYSIS OF VIROLOGICAL AND IMMUNOLOGICAL CHARACTERISTICS OF RECENTLY HIV-INFECTED MEN AND WOMEN IN SÃO PAULO AND SANTOS CITIES

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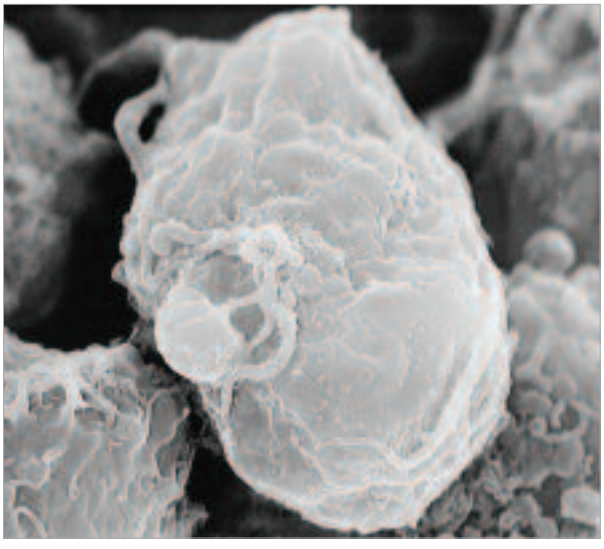

Scranning eletron micrograph of human imunodeficiency virus (HIV), grown in cultured lymphocytes. Virions are seen as small spheres on the surface of the cells

The objective of this project is to develop a well-characterized cohort of recently HIV-infected men and women and to carry out three prospective scientific studies in this group.

We are conducting molecular virology and clinical research investigating primary HIV resistant virus in the cohort and two hypotheses will be investigated:

Given the widespread availability of antiretroviral therapy in Brazil, we hypothesize that the prevalence of primary acquired drug-resistant HIV will increase over four years among newly infected persons We are ascertaining the clinical consequences of primary HIV infection with drug-resistant vs. wild-type HIV. We hypothesize that the rate of CD4+ T cell depletion will be slower in patients infected with drug-resistant HIV vs. drug-susceptible HIV, in part because the drug-resistant variant has reduced replicative capacity. However, the overall rate of disease progression will eventually prove to be greater in those with drug-resistant HIV due to reduced efficacy of antiretroviral therapy.

We are conducting immunological research aimed at understanding the breadth and cross-clade HIV-specific-cytotoxic T lymphocyte (CTL) responses directed against different HIV-1 gene-derived products. We will use state-of-the-art immunological technologies for clade-specific epitope mapping and investigate the role of the immune response in determining the virologic set point. We hypothesize that individuals with broader and stronger CTL response will have lower viral load set points, and we will investigate certain HLA alleles and their association with slower progression to immunodeficiency.

We are investigating and characterizing the unique epidemiology and natural history of the heterogeneous HIV epidemic that exists in Brazil, including assessments of: (i) the genetic diversity of HIV (the epidemic in Brazil is multiclade) and the potential for increased prevalence of recombinant viruses; (ii) the effects of widespread use of antiretroviral therapy and associations with risk in a developing country setting.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

By using the data from the cohort of recently HIV-1-infected subjects in São Paulo, and assessing the relationship between demographics, CD4+ and CD8+ T cell counts, HIV-1 RNA levels and presence of symptoms during acute HIV-1 infection on and over time prior to the initiation of anti-retroviral therapy, we have demonstrated an association between increased age and time to progression to immunodeficiency. Our results have strongly suggested that the presence of symptoms during acute HIV-1 infection does not predict progression to immunodeficiency. However, those patients with acute syndrome maintained higher CD8+ T cell counts and higher viral loads during their follow-up.

The full length HIV genomes generated from recently infected individuals, seeking attention at HIV counseling and testing sites in the city of São Paulo, showed that 83,3% were pure subtypes and 16,7% were recombinants.

Samples from individuals with primary resistance mutations were evaluated from 0 to 80 weeks of follow-up. We verified that mutations includes *tam* (20%), *M184V* (5%), *nnrti* (50%) and *pi* (35%). Only one individual lost mutation *M184V* after 12 weeks of follow-up. Strikingly, although viral load of recently infected individuals stabilized at a lower viral load level, as compared to average viral load observed among individuals infected with wild type strains, the CD4 decrease was more intense among individuals infected with wild type viruses.

HIV-1 is often acquired in the presence of pre-existing co-infections, such as Herpes Simplex Virus 2 (HSV-2). We examined the impact of HSV-2 status at the time of HIV-1 acquisition for its impact on subsequent clinical course, and total CD4+ T cell phenotypes. Among recently HIV-1 infected and sero-positive for HSV-2, there was no difference in initial CD8+ T cell count, or differences between the groups for age, gender, or race based on HSV-2 status. Persons with HIV-1/HSV-2 co-infection sustained higher CD4+ T cell counts over time than those with HIV-1 infection alone. We have also verified also that HSV-2 acquisition after HIV-1 acquisition had no impact on CD4+ count or viral load. We did not detect differences in CD4+ T cell activation or differentiation state by HSV-2+ status. We observed no effect of HSV-2 status on viral load. However, we did observe that treatment naïve, recently HIV-1 infected adults co-infected with HSV-2+ at the time of HIV-1 acquisition had higher CD4+ T cell counts over time. If verified in other cohorts, this result poses a striking paradox, and its public health implications are not immediately clear.

MAIN PUBLICATIONS

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