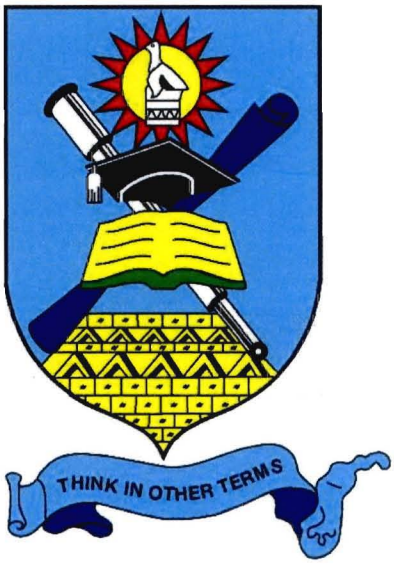

MODELLING THE PATHOGENESIS OF MYCOBACTERIUM TUBERCULOSIS INFECTION AND ITS TREATMENT

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Abstract

Tuberculosis (TB) is one of the most pervasive diseases today, with over one-third of the world population infected with *Mycobacterium tuberculosis* (Mtb). Understanding the dynamics of immune response mechanisms in Mtb infection, its treatment and its dynamics in co-infection with human immunodeficiency virus (HIV), is of major importance in the control of TB epidemic. The thesis first gives a review of the biology of Mtb pathology, its treatment, occurrence of multidrug resistant TB (MDRTB). The priming of Mtb specific immune response and the pathogenesis of Mtb and its treatment in the face of HIV co-infection are also discussed. Systems of ordinary differential equations (ODEs) are used to develop mathematical models to address a number of questions that lie behind the control of TB which are as follows: (a) Why do individuals infected with Mtb experience different disease manifestations? (b) What are the forces that lie behind infection relapse during administration of the first line regimen drugs? (c) What causes the development of MDRTB strains? (d) What are the critical immune mechanisms in the control of Mtb infection? (e) What could be the possible forces that support or undermine their performance and development? (f) Why is HIV replication and Mtb pathology enhanced in Mtb/HIV co-infection? (g) What could be the best way to treat TB during Mtb/HIV co-infection? Concepts of dynamical systems complemented with numerical simulations were employed to analyse the mathematical models that are developed. Disease progression scenarios are predicted, critical immune response mechanisms are identified, treatment options for TB during its co-infection with HIV are explored. Analysis of Mtb models show that occurrence of active disease is much attributed to the Mtb pathogen's ability to persist outside the intracellular environment. High levels of cytotoxic T lymphocytes (CTLs) result in latent TB and low levels of CTLs result in active TB. Levels of CTLs are affected by the expression of dendritic cells (DCs) in the draining lymph node (DLN), whereas the expression of DCs is linked to factors that affect their recruitment, maturation and migration from lungs to the DLN. The Mtb/HIV co-infection study suggests that the expression of HIV and Mtb specific CTLs in the lungs is inversely proportional to the density of the HIV and Mtb pathogens. Modelling TB treatment with first line drugs demonstrates that, if treatment prescriptions are properly followed, cure is normally successful within 6 months. Poor adherence to treatment schemes is a recipe for MDRTB strains. Simultaneous administration of TB and HIV drugs in Mtb/HIV co-infection shows that administration of both drugs benefit the treatment of TB and affects the treatment of HIV. It suggests that effective highly active anti-retroviral therapy (HAART) drugs that reduce replication of HIV in CD4+ T cells might result in preferential replication of HIV in macrophages and such macrophages might be HIV reservoirs that fuel infection rebound in HIV patients during HAART.