Abstract
Untreated infection with human immunodeficiency virus (HIV) in humans infected with hepatitis B virus (HBV) or hepatitis C virus (HCV), frequently leads to cancer of the liver known as hepatocellular carcinoma. Little is known about the extent of HIV and HBV or HCV co-infection and the clinical outcomes of co-infection in Africa. Consequently, the morbidity and mortality due to advanced liver disease induced in the African population as a result of co-infection with these viruses is uncertain. This article examines HIV and HBV/HCV co-infection and the effect on the immune response in the liver.

Introduction
The Liver, HIV and Hepatitis
Hepatocellular carcinoma follows the death (apoptosis) of liver cells (hepatocytes). Damage to the liver and subsequent hepatocytic apoptosis can be induced by alcoholism, diabetes and nonalcoholic fatty liver disease, protein deficiencies caused by malnutrition, and schistosomiasis especially in parts of the world where this parasite is endemic. However, hepatocellular carcinoma is most commonly caused by viral hepatitis by infection with hepatitis B (HBV) or hepatitis C (HCV) virus.(1)

According to WHO, hepatocellular carcinoma is globally the fifth most frequent cause of cancer mortality, responsible for an estimated half a million deaths every year. Hepatitis B infection is the leading cause of hepatocellular carcinoma in the world with an estimated 350 million humans chronically infected worldwide. WHO statistics are that 80% of chronic HBV infections progress to liver disease and hepatocellular carcinoma, which develops 25 times faster in HBV infected humans. HCV infection is less prevalent, with 170 chronically infected individuals globally. According to a WHO estimate, 40 to 60% of liver disease worldwide is due to HCV infection and the largest cohort of HBV and HCV infected humans is in sub-Saharan Africa.(1,2)

An editorial published in the New England Journal of Medicine in 2004 estimates that hepatocellular carcinoma occurs 4 to 6 times faster in HIV/HBV co-infected humans than in humans infected with HBV alone, and hepatocellular carcinoma is projected to become a significant clinical problem in the HIV infected population.(3) WHO reports that of the 42 million humans infected with HIV globally, approximately 2 to 4 million have chronic HBV co-infection and 4 to 5 million are co-infected with HCV.

Although HIV co-infection is recognized to accelerate the course of HBV and HCV induced liver damage, the mechanisms surrounding development of liver disease and hepatocellular carcinoma in HIV and HBC or HCV co-infection is unclear. Hypotheses developed to account for the accelerated course of hepatocellular carcinoma in co-infected humans include that in chronic HBV or HCV infection where replication of the hepatitis virus is repressed, HIV infection may result in reactivation of hepatitis viral replication, and that immunosuppresion and low CD4+ T cell counts may also diminish the body's capacity to fight hepatitis infection.(2-4)

The Liver as an Immune Organ
The liver produces substances that break down proteins, carbohydrates and fats, convert glucose to glycogen, synthesize urea from ammonia, generate amino acids, storage of vitamins and minerals (vitamins A, D, K and B12) and produce cholesterol and bile. The liver also acts as a filter for harmful substances including alcohol, bacteria and viruses. Approximately 20 to 40% of the cells in the liver are non-hepatocytes. Lymphocytes (CD4+ and CD8+ T cells, natural killer cells and B cells) make up approximately 25% of the non-hepatocyte cell population. CD4+ and CD8+ T cells in particular are important in the regulation of the immune response of the liver to infectious agents such as hepatitis B and C viruses.

T Cells and the Immune response to Hepatitis
CD4+ and CD8+ T cells are primed to respond upon detection of viral infection and these cells are at the core of the immune response to both HIV and HBV or HCV infection. CD4+ T cells produce cytokines like interferon gamma that can impair replication of viruses. CD8+ T cells also produce interferon gamma, but have the additional function of being able to directly kill cells that are infected with virus. While the exact role of CD4+ T cells in regulation of chronic hepatitis infection is unknown, studies sug-
gest that CD4+ T cell interferon gamma production is important controlling the replication of virus. CD8+ T cells induce the death of virally infected cells.(7,8)

In HIV infection, CD4+ T cells are infected and killed by the virus, leading to the depletion of the CD4+ T cells in the body, and the immunosuppression that is characteristic of HIV infection. CD8+ T cells are generated in the early stages of HIV infection and help control the initial viremia that occurs. However, CD8+ T cells are dependent on CD4+ T cells to maintain their numbers and function, so as CD4+ T cells are depleted by HIV, CD8+ T cell function wanes and viral replication proceeds unabated.(5)

**T Cells, HIV, Hepatitis and HCC**

In HIV and HBV/HCV co-infected individuals, the numbers of CD4+ T cells are diminished in comparison to those in HBV or HCV mono-infected humans. The diminished numbers of CD4+ T cells enable viral replication to recover and result in the increased replication of the hepatitis viruses with subsequent increases in liver fibrosis. Paradoxically, CD4+ and CD+ T cells play a role in both the promotion of liver disease and the clearance of hepatitis virus. HIV antiretroviral therapy is known to inhibit replication of the hepatitis virus and hence increases CD4+ and CD8+ T cell counts in HIV and HBV/HCV co-infected individuals. These humans experience flares of hepatitis and increased liver damage, perhaps due to CD8+ T cell induced death of hepatocytes infected with hepatitis virus.(8) Alternatively, HIV infection may alter the profile of cytokines secreted by CD4+ and CD8+ T cells that recognize hepatitis infected cells either leading to the production of factors that enhance liver fibrinogenesis or to the inhibition of anti-fibrogenetic factors.(4,9) These conclusions are contradictory: the immune response to co-infection with HIV and HBV/HCV and the resulting impact on the liver has yet to be elucidated.

**Conclusions**

Attention must be paid to the effect of HIV and hepatitis co-infection to mitigate the potential morbidity and mortality due to advanced liver disease and hepatocellular carcinoma on a population already ravaged by HIV.

**References**