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REVIEW

Chronic viral hepatitis may diminish the gains of HIV antiretroviral therapy in sub-Saharan Africa

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Summary There is a heavy burden of HIV—hepatitis B virus (HBV) and HIV—hepatitis C virus (HCV) co-infection in many regions of the developing world. An often unmentioned illness, issues of poverty, socio-economic status, nutrition, access to medical care, and mistrust of Western-style medicine conspire to reduce the opportunity to receive clinical work-up and treatment for chronic viral hepatitis. We discuss key issues specific to the treatment of viral hepatitis and obstacles to success with this endeavor in the context of HIV co-infection in Africa. We predict that provision of viral hepatitis antiviral therapy will become a more pressing issue as more HIV-infected patients receive lifesaving combination antiretroviral therapy only to succumb thereafter from viral hepatitis-induced liver disease. Given the lessons learned from combination antiretroviral rollout in sub-Saharan Africa, establishing expertise and infrastructure for viral hepatitis care and antiviral therapy is relevant. Failure to act now may diminish the milestones and the gains made with antiretroviral therapy in the developing world.

Introduction

There is a heavy burden of HIV co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) in many regions of the developing world.[1] Overlapping risk factors for exposure to these viruses include sex, use of contaminated blood products and needles for medical purposes, injection drug use in some settings, and tattooing and other cultural skin markings including traditional surgeries. Issues related to poverty, socio-economic status, nutrition, access to medical care, and mistrust of Western-style medicine conspire to reduce the opportunity to receive clinical work-up and treatment for

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chronic viral hepatitis.[2] Some experts and decision makers from the developed world have a nihilistic attitude toward considering viral hepatitis treatment in those with HIV in the developing world. This is reminiscent of the recent past when consideration of broad use of highly active antiretroviral therapy (HAART) in developing regions was thought to be naïve, unrealistic, unworkable, and unattainable.[3] Although there are considerable obstacles to providing viral hepatitis antiviral therapy in the presence of competing priorities, there will be no hope of ever confronting the consequences of chronic liver infections without dialogue, contemplation, preparation, and the acquisition of experience through pilot programs. Although liver-related death is not currently a common cause for mortality in those with HIV in developing regions of the world, this issue may become a more pressing one. As we have witnessed in the developed world after the introduction of HAART, we may again observe patients spared a death from HIV/AIDS only to succumb from the complications of advanced, untreated viral hepatitis liver disease.[4–6] In this manuscript we focus on key issues specific to the treatment of viral hepatitis and obstacles to success in the context of HIV co-infection in developing regions of Africa.

Burden of disease

The prevalence of chronic viral hepatitis in many regions of the developing world is uncertain, but estimated to be approximately 10% for HBV[7,8] and to range between 3% and 20% for HCV.[9–12] The incidence and prevalence of viral hepatitis is heterogeneous and dependant on local practices either contributing to or diminishing exposure risk.[13–15] Routine screening seems justified as a first step to determining the relative importance of viral hepatitis in HIV in developing regions of the world.

Reuse of needles for vaccination and other medical procedures contributes to the current incidence and prevalence of HBV and HCV infection in many developing regions.[16] This is best documented in Egypt, where the overall HCV prevalence rate approaches 20% as a consequence of prior schistosomiasis treatment programs.[10–12] China, another developing setting, has suffered a series of important public health catastrophes related to unscreened blood and reuse of needles.[17]

In developed regions of the world the blood product supply is screened sufficiently to diminish HIV and HCV infection risk to well below 1 per million units.[18] In contrast, there are continuing concerns about blood supply safety in developing regions. The demand for blood is high in sub-Saharan Africa, where malaria, pregnancy-related complications, and trauma necessitate blood product use. Therefore, the contribution of blood product use to the overall prevalence of HBV and HCV is not trivial. Guidelines that restrict the unwarranted use of blood products have been implemented in many developing regions. Explicit criteria that qualitatively exclude those at exposure risk to HIV, viral hepatitis, and syphilis infection are applied. Many testing algorithms for simultaneous HIV, HBV, and HCV screening use double ELISA tests with microparticle and microplate technology. Nevertheless, window periods during seroconversion remain an issue of concern given the relatively high incidence of HIV and limitations of these assays.[19] Use of more sensitive blood screening equipment is limited by financial resources and technical support.[14]

Developing regions highly endemic for HBV often lack widely implemented HBV vaccination programs. Consequently, these populations are more vulnerable to HBV infection during childbirth, in early infancy, or at the onset of sexual activity.[20,21] HIV co-infection may further increase the risk of vertical transmission as HBV viral load is greater and hepatitis B e antigen seroconversion is delayed.[22,23] Both of these factors are important predictors for perinatal HBV infection risk. HBV screening during pregnancy and postpartum immunoglobulin and HBV vaccination in neonates born to HBV-infected mothers is far from being universally implemented.[24] Childhood HBV vaccination programs have achieved remarkable success in reducing incidence rates of chronic HBV infection in under-resourced settings.[25,26] Broad application of this simple and relatively inexpensive intervention could reduce HBV and HIV–HBV co-infection rates.

Regional traditional healing practices and cultural activities (e.g., cosmetic tattooing, scarification) may influence the incidence of exposure to HIV, HBV, and HCV.[2] Practices involving blood-to-blood exposure carry with them obvious risk. Rather than ostracizing traditional healers, we believe that these individuals may contribute to reducing the incidence of HIV, HBV, and HCV if engaged and educated as to safe and preventative practices, which they could, in turn, introduce into their practices.

Injection drug use, the primary mode of HCV exposure in the developed world, plays little role in the burden of HBV or HCV infection in most developing regions of Africa. The socio-cultural and economic environment protects against the purchase and use of injection drugs and the equipment needed for their administration. It is plausible that HCV co-infection rates may actually increase due to economic development and urbanization, as increased financial resources will enable individuals to purchase injection drugs and the required material to inject them. There are developing regions of the world where drug supply, the required injection material, and the financial resources, although meager, are available despite a very low mean monthly income.[27,28] Examples include Eastern India, Burma, Cambodia, and parts of Thailand. In these regions, injection drug use contributes to the burden of viral hepatitis infection.

zHistorically, there has been a substantial burden of liver cirrhosis and hepatocellular carcinoma, which is primarily a consequence of highly prevalent chronic viral hepatitis infection[29,30] and aflatoxin hepatotoxicity.[31] Obtaining accurate regional HBV and HCV seroprevalence data in HIV is relevant given that liver fibrosis rates are accelerated, liver-related morbidity and mortality increased, and risk of antiretroviral-related liver complications are greater in those with HIV–viral hepatitis co-infection.[32–34] During the pre-HAART era, viral hepatitis co-infection was of little concern in the developed world. However, following broad introduction of antiretroviral therapy, liver-related disease became and remains a primary cause of death in HIV-infected patients.[4,6] Although these data come from the developed world, there is little reason to believe that viral hepatitis behaves differently in developing regions of the world. As such, the same scenario may unfold here.

Antiretroviral-related liver toxicity

Although antiretroviral therapy is increasingly available in many regions of Africa, the supply of drug, the proportion of patients on treatment, and the presence of expertise to deliver this therapy falls considerably short of the need.[35–37] That supply of medication will hopefully increase considerably once a newly approved pharmaceutical factory in Kampala, Uganda begins production of generic antiretrovirals.[36] Triomune, a combination tablet containing lamivudine, stavudine, and nevirapine, is a staple of antiretroviral therapy in Africa and is one product that will be produced at this plant. Production of HBV and HCV antivirals may follow.

The benefits of antiretroviral therapy are clear. However, the side effects are not inconsequential. Although the true risk of antiretroviral-related liver toxicity is often overstated, it can result in interruption of therapy and clinically apparent signs and symptoms of liver injury.[38,39] Knowledge of chronic viral hepatitis at the individual patient level is relevant as co-infection does increase the likelihood of antiretroviral-related liver toxicity. For this reason alone, screening for HBV and HCV can be justified. Liver toxicity, a term that is nebulous in meaning, is usually manifested as asymptomatic, self-resolving liver enzyme spikes occurring early after the initiation of therapy. This occurs in approximately 5% of treatment-naïve patients.[40] Only rarely (1–2%) is clinically relevant liver toxicity observed. Irrespective of concurrent viral hepatitis, careful observation of liver function and enzymes is essential. Given limited laboratory resources this may not be possible in all locations delivering HIV treatment in developing regions.

A nevirapine reaction consisting of rash and/or liver toxicity occurring within the first 16 weeks of therapy is well described.[38,39] This issue is of great relevance in the developing world given the heavy use of nevirapine in the first-line treatment of HIV.[41] Nevirapine is also recommended for use during pregnancy to prevent maternal–fetal transmission of HIV infection. The occurrence of this early nevirapine reaction is not more frequent in viral hepatitis co-infection. It is noteworthy that after the initial 16 weeks of nevirapine therapy the occurrence of liver complications is similar to efavirenz but increased in those with HBV and HCV.[42]

The incidence of transient liver enzyme increase occurring with low-dose ritonavir-boosted regimens (100–200 mg daily or twice daily) is below 5% in treatment-naïve individuals, between 5% and 10% in treatment-experienced patients, and similar to that of other protease inhibitor-based HAART regimens.[43–51] Fatty liver infiltrate with inflammation and lactic acidosis are rare but life threatening liver complications of HIV nucleoside treatment.[52–55] This is particularly concerning with the use of stavudine and didanosine.[52,55] Ribavirin therapy for HCV indirectly exacerbates this mitochondrial-induced toxicity.[56] The use of stavudine is declining in the developed world. In contrast, over 95% of regimens initiated in sub-Saharan Africa contain stavudine. For multiple reasons, increasing access to nucleosides characterized by reduced metabolic toxicity for first-line HAART should be a priority.

Viral hepatitis therapy

In the case of HIV–HBV co-infection, both viruses can be treated simultaneously with tenofovir and/or lamivudine. HBV monotherapy with these medications is not recommended in HIV–HBV co-infection, as HIV resistance will be fostered. Oral nucleosides such as telbivudine, which lack HIV antiviral activity are options for circumstances in which HBV infection alone requires therapy. Unfortunately, this nucleoside is not available for the same reasons HIV therapy was so long in arriving in Africa: cost, complexity, and lack of registration.

Successful treatment of HBV in HIV is dependant on implementation of pre-HAART screening programs for hepatitis B surface antigen. Knowledge of HBV co-infection will result in the selection of appropriate antiretrovirals with dual antiviral activity, help narrow the differential diagnosis in treatment recipients developing liver complications while on HAART, allow for the anticipation of HBV flares when HAART is interrupted, and increase long-term surveillance for end-stage liver disease and hepatocellular carcinoma. Screening for both HIV and HBV will prevent utilization of lamivudine, tenofovir, or entecavir monotherapy for HBV treatment, which could result in the evolution of HIV resistance.[57]

Delivering HCV treatment in the developing world presents many more challenges. Interferon requires refrigeration that is not universally available. This issue can be resolved by once weekly directly observed or self-administered injections provided by the treatment clinic or outreach program. These options are available in many regions of Africa and are already in use for HIV therapy, tuberculosis treatment, and immunization programs. The decision to treat HCV (and HBV) is based, at least in part, on liver fibrosis scores determined by biopsy. In those with little or no scarring after many years of infection, the likelihood of future liver dysfunction is minimal. The cost and shear number of patients in the developing world preclude this as a reasonable option at the present time. Assuming that the cost issue can be addressed, FibroTest and other non-invasive measures of liver fibrosis may help to overcome this hurdle.[58–60] The need for frequent laboratory checks for safety monitoring and for several expensive HCV RNA studies prior to and during HCV therapy is a significant challenge. Advanced technology for this purpose is available in some specialized HIV clinics in Africa, but the cost and a need for expertise in maintaining these instruments represent major obstacles. This further underscores the need to develop PCR technology that can be used at the primary care level.[61] Although there is no reason to believe that the side effect profile of HCV therapy would differ in developing region populations, the consequences of these side effects may have greater implications. For those on a subsistence income, any loss of productivity due to medication side effects is unacceptable. There are few, if any, social support systems such as medical leave and disability insurance that patients from developed regions can benefit from.

Conclusion: justification for treatment

At first glance successful implementation of screening, work-up, and treatment of viral hepatitis in the context of HIV co-infection may appear unattainable. Current financial conditions preclude treatment in economically underdeveloped regions of the world. This, of course, was the same argument forwarded by some to dissuade use of HIV antiretroviral therapy in these same regions. However, socio-economic

status, donor funding, laboratory capacity, professional expertise, and pharmaceutical pricing can change rapidly.

In resource-limited regions, currently available therapy for HBV and HCV is cost-prohibitive. This issue can be addressed in several ways. Economic development will enable some citizens to have greater purchasing power and allow governments to fund additional health services. As a first priority, broad HBV vaccine programs should be implemented as well as HBV screening in those with diagnosed HIV infection. In time, viral hepatitis therapy will be enabled much in the same way that HIV treatment was by reduced costs for patented HBV and HCV medications and the allowance of generic production of these medications. This is already an option for nucleoside/nucleotide HBV therapy. Interferon and ribavirin are produced generically in India, but similar facilities do not currently exist in Africa. With the development of the Cipla factory in Kampala, this may change. It is noteworthy that Cipla, the Indian generics company that will own this new Ugandan factory, produces ribavirin (Ribacip 200). HCV small molecule development (i.e., HCV protease and polymerase inhibitors) may produce a next generation of more affordable, better tolerated, and easier to distribute therapies. However, the many recent setbacks in HCV drug development suggest that this option may remain years away.

The cost of not acting on viral hepatitis also needs to be considered. Hepatocellular carcinoma accounts for a significant proportion of all case mortality in Africa.[29,30] HBV antiviral therapy has been demonstrated to reduce the rate of liver failure and liver carcinoma in HBV mono-infected individuals.[62] Although this has not been clearly demonstrated to be the same in those with HIV, we and others speculate that antiviral therapy will accomplish the same positive outcome.[63]

In the developed world during the pre-HAART era, increasing access to HCV antiviral therapy made little sense given the high morbidity and mortality associated with HIV infection. Following the introduction of HAART, mortality as a consequence of HIV rapidly diminished. In contrast, the proportion of all deaths in HIV-infected patients attributable to liver-related disease increased and remains a chief cause of mortality in those living with HIV in the developed world.[4–6] This same scenario my play out again as HAART becomes more widely available in developing regions of the world. Therefore, establishing expertise and infrastructure for viral hepatitis care and antiviral therapy is relevant. Failure to act now is likely to result in avoidable morbidity and mortality later.

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