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HIV–HBV Coinfection — A Global Challenge

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Human immunodeficiency virus type 1 (HIV-1) and hepatitis B virus (HBV) exact a high toll worldwide. Both can lead to chronic disease, cancer, and death, and neither can be eradicated with the use of current therapies. Antiviral drug resistance often develops after patients have received treatment for some time and is usually followed by the loss of clinical benefit. Coinfection with the two viruses exacerbates the negative effects.

Worldwide, HBV is the leading cause of chronic liver disease and a leading cause of death, accounting for up to half of all cases of cirrhosis and hepatocellular carcinoma.[1] An estimated 400 million people are infected with HBV,[1] with the majority of cases occurring in regions of Asia and Africa where the virus is endemic. There, up to 70% of adults show serologic evidence of current or prior infection, and 8 to 15% have chronic HBV infection.[1]

These staggering infection rates largely reflect a failure of maternal and child health programs. The majority of HBV infections in settings where the virus is highly endemic occur through perinatal transmission (predominant in East and Southeast Asia) or in young children, transmitted through close household contact or through medical or traditional scarification procedures (predominant in Africa).[1] Perinatal HBV infection is associated with a 90% risk of chronic hepatitis B, as compared with a risk of less than 5% among adults with intact immunity.[1] The risk of perinatal transmission is lower in Africa than in Asia, a disparity that could be due to a lower prevalence of hepatitis Be antigen (HBeAg) and other differences in the pathogenic characteristics of circulating HBV genotypes.[1]

According to the Joint United Nations Program on HIV/AIDS (UNAIDS), about 33 million people are infected with HIV worldwide, and the majority of them live in Asia and Africa. Approximately 10% of the HIV-infected population has concurrent chronic hepatitis B,[2] with coinfection more common in areas of high prevalence for both viruses. In countries where the viruses are highly endemic, the rate can be as high as 25%.[2]

In areas where HBV is less endemic (North America, Europe, and Australia), HBV and HIV are most often acquired during adolescence or adulthood through sexual transmission or injection-drug use. The prevalence of HIV–HBV coinfection in these regions is generally less than 10% of the HIV-infected population.[2] However, up to half of injection-drug users infected with HIV are coinfected with HBV. Worldwide, there may be 3 to 6 million HIV-infected people living with chronic HBV (see maps).

HIV–HBV coinfection increases the morbidity and mortality beyond those caused by either infection alone. People coinfected with HIV have higher levels of hepatitis B viremia, have progression to chronic hepatitis B that is approximately five times as fast as that among people infected with only HBV, and have a higher risk of cirrhosis and hepatocellular carcinoma.[1] HIV immunosuppression can even cause the loss of hepatitis B surface antibodies and reactivation to chronic hepatitis B.[1] As compared with healthy, uninfected persons, those infected with HIV — particularly the most immunocompromised — mount poorer antibody responses to HBV vaccination. Managing hepatitis B in HIV-coinfected patients is further complicated by the dual activity of several nucleoside analogues, the emergence of resistant HIV or HBV strains, the limitations of and decreased response to interferons, and the more rapid development of lamivudine- resistant HBV.[2]

Very few studies have addressed coinfection with HBV among HIV-infected pregnant women. Studies in Africa indicate that they are three times as likely as HIV-negative pregnant women to test positive for HBV DNA and twice as likely to test positive for HBeAg. Both higher HBV DNA levels and HBeAg expression are associated with an increased risk of an HIV-infected pregnant woman’s transmitting HBV to her child.[1]

Vaccination of infants against hepatitis B is highly protective, reducing the risk of infection by more than 70% (the addition of hepatitis B immune globulin reduces the remaining risk by half. However, many countries with a high prevalence of HBV lack universal or timely vaccination coverage, and hepatitis B immune globulin is often unavailable or prohibitively expensive. In 2006, for example, the coverage rate for the vaccine dose at birth was only 36% in countries where the prevalence of chronic HBV infection exceeded 8%.

Even with appropriate vaccination, 5 to 15% of infants born to mothers who test positive for hepatitis B surface antigen (HBsAg) become infected. The proportion is much higher among infants whose mothers have high serum HBV DNA levels; transmission rates of 39% or higher have been noted.[3] High HBV DNA levels are often seen in women with concurrent HIV infection, particularly in Southeast Asia, where HBV is highly endemic and perinatal transmission of HBV is already common.

Additional approaches are needed to protect children of infected mothers. For example, the use of antiviral therapy in pregnant women with high HBV loads has been examined in a few small studies and has shown promise in decreasing perinatal transmission[3]; this strategy appears to be cost-effective and should be explored further.[4] Women coinfected with HIV would be good candidates for this preventive approach.

Even in areas with historically low rates of HBV, challenges exist. In the United States, the number of HBV-infected pregnant women is probably underestimated, with current methods

relying on the expectation that certain ethnic groups are at high risk. In Europe, there is no consistent policy of testing women for HBV infection during pregnancy; some countries rely on assessment of “risk factors” alone. Immigration patterns in Europe and North America suggest that HBV prevalence will vary by region.

There are a number of unanswered questions about disease pathogenesis in coinfected persons and the management of HIV–HBV coinfection, especially in pregnant women. Pregnancy itself can trigger elevations of liver enzymes. The administration, during pregnancy, of antiretroviral prophylaxis containing one agent with anti-HBV activity may be associated with later development of HBV resistance. For pregnant women who, to prevent perinatal HIV transmission, take antiretroviral prophylaxis containing one or two agents with anti-HBV activity, the safety of stopping treatment after delivery is unknown. The administration of antiretrovirals without HBV activity in coinfected pregnant women may leave their infants unprotected against HBV. Finally, infection of the infant with HIV threatens the benefits of HBV immunization for perinatal prevention.

What will it take to address this crisis? First, we must acknowledge that HBV–HIV coinfection represents a major global public health threat. Because each virus affects the other’s natural history and response to therapy, HIV–HBV coinfection requires dedicated research. A willingness to rapidly implement new scientific evidence is critical. Preventing transmission of both viruses to the next generation should be a priority for health policymakers.

Ideally, all pregnant women should receive early prenatal care with voluntary HIV and HBV testing to permit timely interventions aimed at preventing perinatal transmission.[5] Use of antiretroviral agents with dual antiviral activity is a promising preventive approach — one limited, however, by a paucity of data on important agents (e.g., tenofovir) regarding safety during pregnancy, for both the fetus and the mother. As regimens including tenofovir become first-line therapy for many HIV-infected people (and are used as preexposure prophylaxis for the uninfected), determining the safety of these medications during pregnancy becomes a critical research need. Evaluating the HBV viral load in HIV-infected pregnant women should be an essential step of prenatal evaluation, so that the mother’s health can be managed appropriately.

Continued improvements in the coverage and timeliness of HBV vaccination and the education of clinicians about its importance should be priorities everywhere. Making such improvements will require substantial advocacy and political and financial commitment. Now is the time to provide the best care we can for coinfected people and to protect a future generation of children from the largely hidden epidemic of HBV-related liver disease, which is being further fueled by the HIV epidemic.

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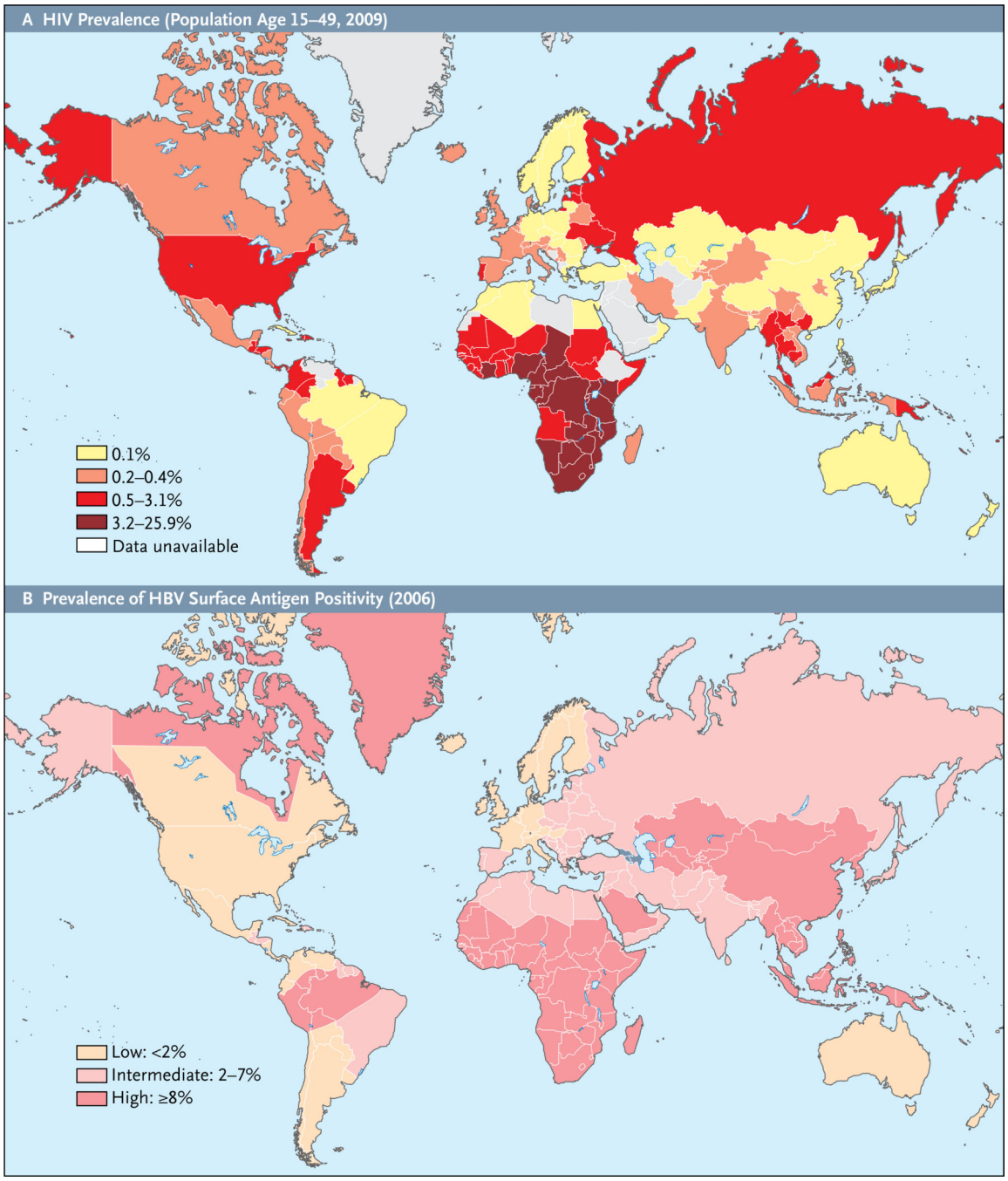

Figure. Prevalence of HIV-1 and HBV Infection, According to Country

Data on HIV are from the United Nations Children's Fund, the World Health Organization, and (in the case of province-level data for China) the China Centers for Disease Control; data on hepatitis B virus (HBV) are from the U.S. Centers for Disease Control and Prevention.