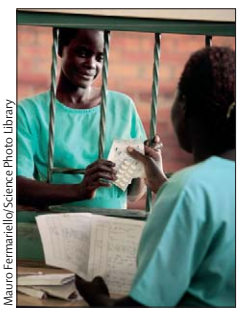
HIV and hepatitis B co-infection in Africa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The Review by Christopher Hoffmann and Chloe Thio[1] brings to the fore the issue of HIV and hepatitis B virus (HBV) co-infection in resource-poor settings. We support their call for further research in this field.

The management of HIV/HBV co-infection in high-income settings involves individualised therapy usually from an expert provider with the support of an array of diagnostic tests. The primary goal of this treatment is to reduce the risk of cirrhosis and hepatocellular carcinoma. However, the public-health approach to antiretroviral therapy (ART) aims to maximise survival at the population level.[2] ART programmes in Africa and other resource-poor settings involve standardised treatment protocols and simplified monitoring to achieve best possible use of available resources. The treatment of hepatitis B is already entwined with the roll-out of ART since lamivudine, a key drug in most first-line HIV treatment combinations, is also active against HBV.

Within a public-health approach, recommendations for management need to be shown as cost effective, using the best evidence available. It is still unclear whether routine testing for hepatitis B surface antigen (HBsAg) in patients starting ART will prove cost effective. In a richer African country with good laboratory infrastructure, such as South Africa, a cost of US$5 per test might be feasible and affordable even with 500 000 new HIV infections every year. However, there is some uncertainty as to whether HBsAg is a sufficient marker, since occult HBV infection (where patients are HBsAg negative but have detectable HBV DNA) could be common in immunosuppressed populations of Africa and Asia.[3] If ongoing work finds occult HBV to be important, it might be better for ART programmes in areas of high HBV prevalence to treat all patients similarly, therefore saving the costs of testing.

A test for HBV can clearly be justified when it is likely to change patient management—eg, prescribing tenofovir, another drug with dual activity against HIV and HBV, and lamivudine (or emtricitabine) in combination for HBV/HIV co-infected patients.[4] WHO has recently recommended tenofovir in the first-line treatment of HIV in place of stavudine because of better tolerability, ease of once-daily dosing, and reduced long-term toxicity.[2] However, the incorporation of tenofovir into ART programmes is still limited by affordability and, in its absence, the benefit of testing for HBV is less clear.

Patients with chronic hepatitis B should perhaps have more intense monitoring, but abnormalities in liver function tests are common both before and after commencing antiretroviral therapy. Monitoring approaches based on clinical assessment may be as effective as ones that include laboratory tests (eg, liver function tests), and ongoing studies might provide evidence to guide such recommendations.[5]

Individuals who might benefit from testing for HBV are those who are switching to second-line treatment. A proportion of HBV/HIV co-infected patients will get a flare of hepatitis if they stop taking HBV-active agents.[6] In ART programmes with fixed treatment regimens, often the second-line treatment will not contain an HBV-active agent. In the government programme in South Africa, for example, patients switch from stavudine, lamivudine, and efavirenz or nevirapine to zidovudine, didanosine, and lopinavir-ritonavir. If such flares are a common finding, it could be that continuation of lamivudine is routinely recommended for all patients, or those that are HBsAg positive where tests are available.

A disadvantage of using lamivudine as the sole HBV-active agent is that it leads to the rapid development of viral resistance. From a public-health perspective it will be important to know whether this could lead to an epidemic of resistant virus, which could also undermine vaccination efforts.[7] The incidence of HBV resistance reaches more than 90% after 4 years of lamivudine therapy in co-infected individuals.[8] Resistance is most commonly characterised by mutations in the reverse transcriptase domain of HBV polymerase—the most important mutations being rtL180M and rtM204V/I. The emergence of a triple polymerase mutation (rtL173V, rtL180M, rtM204V) has more recently been documented in HIV/HBV co-infected individuals on lamivudine therapy,[8–10] and is recognised as a "vaccine-escape" mutant because of the altered structure of HBsAg and reduced binding to anti-HBs. These mutants can also escape detection by standard HBsAg tests.[11] The resistance patterns emerging in areas of high prevalence and poor resources are not well characterised and should be monitored in the future. If resistance becomes an important issue it will support the case for tenofovir to be made more widely available.

Finally, an ethical issue arises from the provision of HBV-active treatment within ART programmes. In

many parts of the world, patients with HIV now have better access to HBV treatment than their HIV-negative neighbours. Although a strategy to treat HBV/HIV co-infection is important for public health and the higher viral replication seen in HIV patients increases the likelihood of progression to hepatic fibrosis, consideration should be given to making HBV treatment accessible for those without HIV infection.

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We declare that we have no conflict of interest.

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Antibiotic resistance and antibiotic development

Kevin Outterson and colleagues[1] should be congratulated for raising awareness of the converging problems of rising antibiotic resistance and declining antibiotic development.[1] However, their conclusions are problematic for patients with life-threatening infections and for the health-care providers searching for drugs to save such patients.

The authors favour antibiotic preservation efforts in lieu of creating incentives for antibiotic development. Conservation is important to prolong the useful lives of current antibiotics, but it cannot mitigate the need to continually develop new antibiotics to treat drug-resistant infections. Unfortunately, very few novel antibiotics are being developed that can treat infections resistant to current antibiotics.[2–4] At the same time, life-threatening infections caused by multidrug-resistant, and increasingly pan-resistant, organisms are sky-rocketing in incidence.[5–8] Outterson and colleagues[1] write that they "characterise the glass as half full rather than half empty". For those of us in the front-line who are watching patients die from drug-resistant infections while running out of antibiotics to throw at them, the glass is neither half-full nor half-empty: it is moving ever closer to being empty.

Outterson and colleagues' cost calculations for patent extensions are based on a 2-year extension for all top-selling drugs at the same time.[1] However, previous proposals have been for a 6-month to 2-year extension, with length determined based on cost-benefit considerations.[8] Furthermore, only antibiotics that treat serious or life-threatening infections caused by organisms resistant to current agents would be eligible for the programme. In view of the difficulty in developing new priority antibiotics, no more than a handful of drugs will be eligible for a patent extension at any one time. Of greatest importance, however, is that the authors do not account for the money priority antibiotics can save society by reducing the enormous costs of multidrug-resistant infections. Our analysis suggested that, by mitigating such costs, wildcard patent extension may well be cost effective.[9]

Another problematic assumption is that prolonging patents will encourage pharmaceutical companies to heavily market their drugs, thereby hurting antibiotic conservation efforts. Companies market their drugs aggressively from the time they receive approval from the US Food and Drug Administration. There is no evidence that the longer the patent protection a company has, the more judicious is their initial marketing: they want an economic return and brand identification as soon as possible. Indeed, Outterson and colleagues' own examples of exuberant pharmaceutical marketing were for drugs that were nowhere near the end of their patents.