Challenges and Priorities in the Management of HIV/HBV and HIV/HCV Coinfection in Resource-Limited Settings

Philippa Easterbrook, M.D., M.P.H., DTM&H [1] Anita Sands, B.Sc. (Hons), M.P.H. [2]
Hande Harmanci, M.D., Dr. P.H. [3]

[1] Department of HIV/AIDS, World Health Organisation, Geneva, Switzerland
[2] Department of Essential Medicines and Health Products
[3] Global Hepatitis Programme, World Health Organisation, Geneva, Switzerland

Address for correspondence and reprint requests Philippa Easterbrook, Treatment and Care, Department of HIV/AIDS, World Health Organization, Building D, 1st Floor, Avenue Appia, 20, Geneve 27, Switzerland, CH-1211 (e-mail: easterbrookp@who.int).

Semin Liver Dis 2012;32:147–157.

Abstract

Liver disease due to chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection is now emerging as an increasing cause of morbidity and mortality in human immunodeficiency virus- (HIV-) infected persons in resource-limited settings (RLS). Existing management guidelines have generally focused on care in tertiary level facilities in developed countries. Less than half of low-income countries have guidance, and in those that do, there are important omissions or disparities in recommendations. There are multiple challenges to delivery of effective hepatitis care in RLS, but the most important remains the limited access to antiviral drugs and diagnostic tests. In 2010, the World Health Assembly adopted a resolution calling for a comprehensive approach for the prevention, control, and management of viral hepatitis. We describe activities at the World Health Organization (WHO) in three key areas: the establishment of a global hepatitis Program and interim strategy; steps toward the development of global guidance on management of coinfection for RLS; and the WHO prequalification program of HBV and HCV diagnostic assays. We highlight key research gaps and the importance of applying the lessons learned from the public health scale-up of ART to hepatitis care.

Keywords

- HIV-hepatitis B coinfection
- HIV-hepatitis C coinfection
- resource-limited settings

The Burden of HIV and HBV and HCV Coinfection in Resource-Limited Settings

Worldwide, ~500 million persons are chronically infected with either hepatitis B (HBV; 350–400 million) or hepatitis C virus (HCV; 150–180 million). Together they account for ~1 million deaths each year, most commonly from liver-related disease (accounting for an estimated 57% of cirrhosis and 78% of hepatocellular carcinoma [HCC] cases).[1–5] There is still a paucity of comparable data on the prevalence of human immunodeficiency virus- (HIV-) HBV and HCV coinfection and its contribution to morbidity and mortality. Current estimates are that between 5% and 25% of the ~33 million HIV-infected persons worldwide also have chronic hepatitis B (2–4 million; 5–20% of HIV-infected), and/or hepatitis C (another 4–5 million; 5–15%).[6–8] The burden of coinfection is greatest in developing countries, particularly in South East Asia and sub-Saharan Africa (SSA) for hepatitis B, where more than 3 million HIV/HBV coinfected persons live.[8] The data on HIV/HCV coinfection prevalence in Africa is particularly scarce. Although preliminary data suggest overall low-rate prevalence, there is wide regional variation, with higher reported rates in West (1–24%) and Central (3–12%) Africa compared with those in East (0–9%) and South Africa (0–3%).[8] However, many of the studies on which these estimates are based were limited by small sample sizes or nonrepresentative study populations, and used HCV-antibody assays with high false-positive rates, so the true prevalence of coinfection remains uncertain.

Although there is no consistent evidence for a significant effect of HBV and HCV on HIV progression,[9–12] HIV coinfection

Issue Theme HIV and Liver Disease; Guest Editor, Vincent Soriano, M.D., Ph.D.

DOI http://dx.doi.org/10.1055/s-0032-1316476.
ISSN 0272-8087.

has been shown to have a profound impact on almost every aspect of the natural history of HBV and HCV infection based on data from Western cohorts.[7,13,14] The consequences include higher rates of chronicity, less spontaneous clearance, higher rates of occult HBV (i.e., HBV-DNA positivity in the absence of HBV surface antigen of [HBsAg]), accelerated fibrosis progression with increased risk of cirrhosis and HCC, higher liver-related mortality, and decreased treatment response.[13–22] Other challenges with coinfection include cross-resistance between HIV and HBV drugs,[23,24] worsening of hepatitis due to antiretroviral therapy- (ART-) related immune reconstitution hepatitis,[25,26] increased rates of hepatoxicity,[27,28] and HCV/HIV drug interactions. In Western cohorts, liver disease has emerged as a leading cause of death in HIV/HBV coinfected persons.[29,30] Although there is little data from RLS, particularly Africa, documenting the course of HIV/HBV coinfection, there is no evidence to suggest a difference in natural history or in HCV treatment response from that observed in the developed world.[31] As HIV-infected persons live longer with increasing access to and uptake of ART in RLS, HBV- and HCV-associated liver disease in coinfected patients will become a significant management problem in these settings also.

Global Policy Survey

The considerable burden and seriousness of viral hepatitis as a global public health problem is now widely recognized. In a 2009 survey undertaken by the World Hepatitis Alliance in collaboration with the World Health Organization (WHO) to examine the current hepatitis prevention and control policies and programs across 193 WHO member states, 80% of 135 responding countries regarded HBV or HCV infection as an urgent public health issue.[32] In Africa, the figure was almost 100%. The survey identified widely varying situations in the 135 countries that responded. ►**Table 1** summarizes the findings on national strategies, vaccination policies, surveillance, testing, and education/awareness programs by region. According to self-reports of member states, national strategies have been implemented in almost three quarters of countries, but only half of the low-income African countries reported having national goals for prevention. Although most regions reported having hepatitis B vaccination policies in place, in low-income countries there was poor coverage for health care providers (only 3 of 19 countries), and only one country covered high-risk groups, such as injection drug users, men who have sex with men, and prisoners. The survey also found that government-funded public awareness initiatives—a critical tool to promote uptake of testing, lifestyle modification, and prevention of transmission—were rare. Although 82% of countries reported having hepatitis B or C surveillance measures in place (Africa: 59%; South East Asia: 57%), the components varied widely from country to country: one third of countries had no prevalence data available even for monoinfection. Access to testing and treatment was also very variable, and in some regions extremely limited. Overall, more than half of the world's population live in countries with no provision for free testing, and only 4% of low-income countries reported ready access to testing. Africa and South East Asia reported below worldwide levels in all four domains (testing availability to more than 50% of the population, anonymous testing, testing free to all, and testing free to some). The majority of participating countries highlighted the value of technical expertise provided by WHO to assist them in implementing or improving their national control programs.

World Health Assembly Resolution 63.18

In 2010, the 63rd World Health Assembly adopted resolution WHA63.18 calling for a comprehensive approach to "support or enable an integrated and cost-effective approach to the prevention, control and management of viral hepatitis, considering the linkages with associated co-infections such as HIV."[33] In this resolution, the WHO was tasked to work closely with the member states of the organization as well as other key parties, including civil society, patient groups, and the private sector to "develop the necessary guidelines, strategies, and tools for the surveillance, prevention and control of viral hepatitis; provide the necessary support to the development of scientific research related to the prevention, diagnosis and treatment of viral hepatitis; improve the assessment of global and regional economic impact and the estimates of the burden of viral hepatitis; mobilize support for the strengthening of surveillance systems, prevention and control programs, diagnostic and laboratory capacity, and management of viral hepatitis to developing countries in an equitable, efficient, and suitable manner; and strengthen the WHO Safe Injection Global Network."[33]

The WHO Global Hepatitis Framework

To achieve the objectives outlined in the World Health Assembly Resolution, WHO has now established the Global Hepatitis Program (GHP) at its headquarters with a distinct team and focal points in the regional offices (http://who.int/topics/hepatitis July 2012). A global interim strategy has been developed by the GHP to provide a vision for the global prevention and control of viral hepatitis; provide an overview of the global burden, current efforts, and remaining challenges in the global response to viral hepatitis, and outline four strategic areas of action with suggested approaches for members states to adopt or adapt. The framework for delivery of this program has been developed based on a 4-axis approach (H. Harmanci, personal communication).

Strategic Axis 1: Raising Awareness, Promoting Partnerships, and Mobilizing Resources

Activities focus on increasing awareness among policy makers, health professionals, and the public about viral hepatitis, and strengthening preventive and control measures while tackling discrimination against those infected. On July 28, 2011, WHO launched World Hepatitis Day with a wide range of campaign materials in multiple languages using the theme, "This is Hepatitis...Know it. Confront it. Hepatitis affects everyone, everywhere."

Table 1 Overview of Global Results for National Government Programs and Policies for Viral Hepatitis[32]

Region (Number of Countries that Responded to the Survey)	Policy				Public Awareness & Education		Surveillance	Testing	TREATMENT & CARE		CIVIL SOCIETY
	Presence of National Strategy % of Region (Total Countries)	Presence of National Goals for Prevention and Control % of Region (Total Countries)	Presence of a HBV Vaccination Policy % of Region (Total Countries)	Prevention in Health Care Settings % of Region (Total Countries)	Presence of Government-Funded Public Awareness Campaigns % of Region (Total Countries)	Presence of Government Action to Reduce Stigma and Discrimination % of Region (Total Countries)	Presence of Disease Surveillance for HBV and/or HCV % of Region (Total Countries)	Availability of Testing for HBV and/or HCV % of region (Total Countries)	Presence of patient pathway for screening, diagnosis, referral and treatment % of region (Total Countries)	Presence of total or partial government funding of treatment for HBV and/or HCV % of region (Total Countries)	Work with non-state sector in program development and implementation % of region (Total Countries)
Africa (30)	60% (18)	60% (18)	93% (28)	66% (19)	25% (7)	3% (1)	59% (17)	*20% (6) †40% (12) ‡10% (3) §27% (8)	37% (11)	43% (13)	76% (22)
South East Asia (8)	71% (5)	86% (6)	100% (7)	86% (6)	43% (3)	29% (2)	57% (4)	*29% (2) †29% (2) ‡29% (2) §14% (1)	57% (4)	57% (4)	71% (5)
Eastern Mediterranean (12)	83% (10)	67% (8)	92% (11)	92% (11)	36% (4)	50% (5)	100% (12)	*83% (10) †42% (5) ‡33% (4) §42% (5)	58% (7)	75% (18)	92% (11)
Europe (44)	66% (29)	70% (31)	98% (43)	84% (37)	45% (20)	36% (16)	98% (43)	*86% (38) †55% (24) ‡27% (12) §55% (24)	68% (30)	75% (9)	63% (27)
Americas (20)	80% (16)	74% (14)	100% (20)	85% (17)	35% (7)	25% (5)	90% (18)	*68% (13) †47% (9) ‡47% (9) §26% (5)	63% (12)	95% (33)	61% (11)

(*Continued*)

Table 1 (*Continued*)

Region (Number of Countries that Responded to the Survey)	Policy				Public Awareness & Education		Surveillance	Testing	TREATMENT & CARE		CIVIL SOCIETY
	Presence of National Strategy % of Region (Total Countries)	Presence of National Goals for Prevention and Control % of Region (Total Countries)	Presence of a HBV Vaccination Policy % of Region (Total Countries)	Prevention in Health Care Settings % of Region (Total Countries)	Presence of Government-Funded Public Awareness Campaigns % of Region (Total Countries)	Presence of Government Action to Reduce Stigma and Discrimination % of Region (Total Countries)	Presence of Disease Surveillance for HBV and/or HCV % of Region (Total Countries)	Availability of Testing for HBV and/or HCV % of region (Total Countries)	Presence of patient pathway for screening, diagnosis, referral and treatment % of region (Total Countries)	Presence of total or partial government funding of treatment for HBV and/or HCV % of region (Total Countries)	Work with non-state sector in program development and implementation % of region (Total Countries)
Western Pacific (21)	76% (16)	81% (17)	100% (21)	90% (18)	62% (13)	62% (13)	71% (15)	*62% (13) †52% (11) ‡48% (10) §24% (5)	70% (14)	71% (15)	86% (18)
World (135)	70% (94)	71% (94)	97% (130)	82% (108)	41% (54)	32% (42)	82% (109)	*62% (82) †47% (63) ‡30% (40) §36% (48)	59% (78)	69% (92)	72% (94)

*Testing for hepatitis B and/or C accessible to >50%.
†Testing for hepatitis B and/or C is anonymous/confidential.
‡Testing for hepatitis B and/or C is free to all.
§Testing for hepatitis B and/or C is free to some.
Adapted from the *World Hepatitis Alliance Report on Viral Hepatitis: Global Policy.*[32]

Strategic Axis 2: Evidence-Based Policy and Data for Action

Core activities are the updating of global prevalence and burden estimates for viral hepatitis, and the development of guidelines and standards for disease surveillance to assist countries in prioritizing resources and tailoring different interventions, ranging from immunization, screening the blood supply, and ensuring safe health care environments and practices to antiviral therapy.

Strategic Axis 3: Prevention of Transmission

WHO is reexamining immunization policies such as schedules and dosages; the protection of high-risk groups including newborns and health care workers, especially against hepatitis B; the expanded roles for existing hepatitis A vaccines and new hepatitis E vaccines; as well as innovative approaches for the future. Safer sex and the safe and rational use of injections remain key messages in the prevention of viral hepatitis. Successful prevention efforts are being adapted to the changing epidemiology and new economic constraints.

Strategic Axis 4: Screening, Care, and Treatment

Guidelines for screening and treatment of patients with chronic hepatitis B and C, especially for those who are HIV-infected and in resource-constrained settings, are also a high priority.

Developing Guidelines for Management of HIV/HBV and HIV/HCV Coinfection in RLS

At present, most guidelines on the treatment of chronic HBV and HCV infection with HIV coinfection have been developed by professional hepatology societies and are focused on tertiary care settings in high- or middle-income countries.[34–37] These management guidelines specify diagnostic methods such as liver biopsy and HBV or HCV viral load and genotype to determine eligibility for treatment, as well as monitor treatment response, and recommend a range of antiviral drugs and treatment protocols. However, despite the benefits of treatment, in most RLS, access to hepatitis care remains extremely limited, particularly across sub-Saharan Africa and many parts of Asia.[38–40] Many of the reasons for the reluctance to make hepatitis- and particularly HCV-drugs more widely available are the same as those confronted by the HIV-treatment advocacy community a decade ago.[39,40] These include lack of availability of key diagnostics and antiviral drugs, the high cost, perceived complexity and significant rate of toxicities associated with the drug regimens, concerns that treatment success rates will be poor (especially in HIV-coinfected patients), shortage of basic health care staff as well as specialists, and lack of political commitment. These challenges have been further compounded by the current lack of global guidance directed at RLS. There is therefore an urgent need for such guidance to improve the identification of both HBV/HCV and HIV coinfection, and so optimize therapy of both diseases.

The HIV department at WHO is currently developing guidance on the diagnosis and management of HBV and HCV infection in HIV-infected persons for RLS, which will cover key topics along the continuum of HIV-hepatitis care. This includes screening (who, when, and how to screen), with the goal of making HBsAg assays more widely available and providing HBsAg (and in future HCV) testing for all HIV-infected persons; diagnostic evaluation to assess stage and chronicity of liver disease and eligibility for treatment, although with a guiding principle that lack of facilities for further diagnostic evaluation should not be a barrier to testing; criteria for both ART initiation and HBV and HCV specific treatment if not ART eligible; appropriate monitoring; and general care and prevention strategies, such as patient education, follow-up vaccination of susceptible contacts, and advice on alcohol reduction.

Survey of Recommendations in National Guidelines from RLS

The development of these guidelines has been informed by other sources. The first of these is a survey of current national guidance on HIV/HBV and HIV/HCV coinfection from low- and middle-income settings to identify areas of concordance/discordance and gaps (relative to international guidelines) in recommendations.[41] Fifty-one of 93 (54.8%) countries surveyed had no guidelines available, but 37 and 32 countries, respectively, provided some guidance on management of HIV/HBV and HIV/HCV coinfection. ►**Tables 2a** and **2b** summarize coverage of these guidelines by region of six key areas of HIV/HBV and HIV/HCV management: screening, diagnosis, staging of liver disease, ART initiation, HBV/HCV treatment, and general care/prevention. The majority lacked comprehensive guidance: Only 30% and 9% covered four or more of the six key areas for HIV/ HBV and HIV/HCV management, respectively. Major gaps were in recommendations for screening and diagnostic assays, diagnostic approach to staging of liver disease (included in only 14% of HIV/HBV and 13% of HIV/HCV guidelines), and criteria for initiation of ART in the absence of indication for hepatitis treatment (8% and 25%), and lack of recommendations on general care and prevention approaches other than hepatitis B vaccination. There were also substantial variations in recommendations in optimal timing of screening, additional recommended tests, and criteria for HBV treatment (11 different criteria across eight guidelines), and timing of ART in HIV/HCV coinfection (evenly split between those recommending early ART and those advocating deferral). The findings of this survey highlight several areas for particular attention when developing guidance focused on RLS. These are the need for much greater clarity on screening strategies, including when to test and the need for retesting; the minimal package of additional diagnostic tests recommended for staging of liver disease to determine the timing of ART and/or HBV/HCV specific treatment; and the need to include general principles of care and prevention, such as vaccination and alcohol reduction.

Table 2a HIV/HBV Coinfection: Number and Percentage of National Guidelines Making a Recommendation on Six Key Areas of Management[42]

Recommendation relating to:	Screening Strategy*	Diagnostic Approach*	Staging of Liver Disease†	Initiation Criteria for ART*	HBV Treatment		General Care and Prevention Strategies*
					Initiation Criteria*	Treatment Regimens*	
Overall ($n = 37$)†	29 (78%)	11 (30%)	5 (14%)	3 (8%)	8 (22%)	25 (68%)	13 (35%)
Sub-Saharan Africa ($n = 17$)	13 (76%)	6 (35%)	2 (12%)	1 (6%)	5 (29%)	16 (94%)	5 (29%)
Latin America & the Caribbean ($n = 8$)	7 (88%)	1 (13%)	1 (13%)	0 (0%)	0 (0%)	2 (25%)	4 (24%)
Middle East and North Africa ($n = 3$)	3 (100%)	2 (67%)	1 (33%)	0 (0%)	2 (67%)	3 (100%)	2 (67%)
South East Asia & Western Pacific ($n = 9$)	6 (67%)	2 (22%)	1 (11%)	2 (22%)	1 (11%)	4 (44%)	2 (22%)

ART, antiretroviral therapy; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

*Percentages based on row total.

†Included countries: Afghanistan, Bolivia, Burundi, Cambodia, China, Comoros, Democratic Republic of Congo, Djibouti, Dominican Republic, El Salvador, Ethiopia, Ghana, Guatemala, Guinea, Guyana, Haiti, India, Kenya, Lesotho, Liberia, Myanmar, Namibia, Nepal, Nicaragua, Nigeria, Pakistan, Papua New Guinea, Paraguay, Philippines, Sierra Leone, South Africa, Swaziland, Tanzania, Thailand, Uganda, Vietnam, Zambia.

Table 2b HIV/HCV Coinfection: Number and Percentage of National Guidelines Making a Recommendation on Six Key Areas of Management[42]

Recommendation relating to:	Screening Strategy*	Diagnostic Approach*	Staging of Liver Disease*	Initiation Criteria for ART*	HCV Treatment		General Care and Prevention Strategies*
					Initiation Criteria*	Treatment Regimens*	
Overall ($n = 32$)†	21 (66%)	2 (6%)	4 (13%)	8 (25%)	4 (13%)	7 (22%)	11 (34%)
Sub-Saharan Africa ($n = 13$)	7 (54%)	0 (0%)	1 (8%)	1 (8%)	1 (8%)	3 (23%)	5 (38%)
Latin America & the Caribbean ($n = 8$)	7 (88%)	0 (0%)	1 (13%)	1 (13%)	0 (0%)	0 (0%)	2 (25%)
Middle East and North Africa ($n = 3$)	2 (67%)	1 (33%)	1 (33%)	1 (33%)	1 (33%)	1 (33%)	1 (33%)
South-East Asia and Western Pacific ($n = 8$)	5 (63%)	1 (13%)	1 (13%)	5 (63%)	2 (25%)	3 (38%)	3 (38%)

HCV, hepatitis C virus; HIV, human immunodeficiency virus.

*Percentages based on row total.

†Included countries: Afghanistan, Bolivia, Burundi, Cambodia, China, Comoros, Democratic Republic of Congo, Djibouti, Dominican Republic, El Salvador, Ethiopia, Guatemala, Guinea, Guyana, Haiti, India, Kenya, Lesotho, Myanmar, Nepal, Nicaragua, Nigeria, Pakistan, Paraguay, Philippines, Sierra Leone, Swaziland, Tanzania, Thailand, Uganda, Vietnam, Zambia.

Other Challenges in RLS

In addition to an appreciation of the generic challenges of providing hepatitis care in RLS,[38–40] there are several important features in the epidemiology and natural history of HIV/HBV and HIV/HCV coinfection, and in access to diagnostics, specific to RLS and particularly SSA, that are relevant to the development of appropriate guidance.

Different Modes of Transmission for HIV and HBV/HCV and Lower Prevalence of Coinfection in High HIV-Prevalence Risk Groups

In RLS, with generalized HIV epidemics, particularly in SSA, there are some key differences in the principal modes of transmission for HIV as compared with HBV or HCV.[8] Although HIV is mainly spread through sexual transmission, HBV is largely acquired early in life through vertical or early horizontal transmission, usually from family members or other infected children.[14,42–47] Other important modes of HBV transmission in RLS include blood transfusion because of the lack of comprehensive screening of blood products, nosocomial transmission, and occupational exposure among health care workers.[44,48–51] With HCV, the most significant risk factors for transmission in these settings include a history of injection therapy or blood transfusion, although many patients have no identifiable risk factors.[8] Rates of vertical HCV transmission appear to be low,[52] whereas the contribution of nosocomial transmission remains unclear.

As a result, of these key differences in routes of transmission, HCV- and to a lesser extent HBV-coinfection rates tend to be low in high HIV-prevalence groups, such as sex workers.[8] In contrast in high resource settings with concentrated epidemics and lower overall HIV prevalence, where the predominant modes of transmission for both HIV and HBV are injection drug use and sexual contact, coinfection is more common in high-risk groups.

Late Diagnosis and Presentation with Advanced Liver Disease

As a result of the lack of access to routine testing, the majority of HIV-hepatitis B and C coinfected patients in RLS remain undiagnosed until symptomatic, and present only when they already have significant liver disease.

Limited Data on Natural History of Coinfection and Factors Potentially Associated with Increased Rate of Progression

There is still limited data from Africa documenting the outcome and progression of HIV/HBV or HIV/HCV coinfection. There are several regional factors that may impact the rate of disease progression: (1) Early age at HBV infection, usually under the age of 5 years (and many years before HIV infection). This results in a much higher likelihood of developing chronic infection, liver cancer, and cirrhosis in these settings, compared with developed countries where transmission occurs much later.[8,53] (2) Regional distribution of HBV and HCV genotypes: For example, HCV genotype 1 is the predominant (with a rising prevalence) HCV genotype in Africa and associated with higher HCV viral load, and increased progression of liver disease in HIV coinfected patients.[54] Similarly, in South East Asia, the predominant HBV genotype is A1, which is associated with HBsAg seroconversion and an increased risk of HCC at a younger age. (3) Exposure to aflatoxin and risk of HCC: HCC is likely to emerge as a major problem as a result of both known frequent contamination of staple foods with aflatoxin—a major promoter of HCC especially in east Africa, and longer life span in HIV/HBV-coinfected patients through increasing access to ART.

Broader Differential Diagnosis of Liver Disease

There are several other important causes of liver disease to consider in patients presenting with liver disease, particularly in SSA, that are much less commonly observed in the developed world, which presents an additional diagnostic challenge. These include TB treatment, exposure to aflatoxin, schistosomiasis, endemic helminth infections, hepatitis E and delta virus infection, Bantu siderosis, and use of herbal medicines.[7,39]

Less Sensitive and Specific Diagnostic Screening Assays Available and Less Quality Assurance/Quality Control

Although most countries screen blood using HBsAg, the assays employed vary widely in their quality.[55] In a study from Ghana using the cheaper particle agglutination or dipstick test, 29% of HBV-DNA viremic patients were not detected, compared with only 3% missed using an enzyme immunoassay.[56] Similarly, there have been high rates of false-positives and false-negatives, particularly using early generation HCV assays in surveys in SSA.[57]

Challenges in Treatment Prioritization: Limited Access to Tests to Allow Reliable Staging of Liver Disease

In settings with limited resources and access to antiviral medications, greater emphasis is placed on treating patients with the most advanced disease and either compensated or decompensated cirrhosis, for whom treatment can be lifesaving, albeit less effective. Ideally, those without cirrhosis should be further evaluated to identify those with evidence of progressive disease who require treatment. However, this is problematic, given that diagnostic assays, such as liver biopsy and HBV-DNA to determine eligibility for treatment and monitoring are not readily available in these settings. Given the paucity of findings before end-stage liver disease and onset of hepatic decompensation, the lack of access to or affordability of these discriminating investigations represents a major challenge for hepatitis B and C treatment programs in RLS. Although use of noninvasive methods to assess liver fibrosis, such as aspartate aminotransferase / alanine aminotransferase (AST/ALT) ratio, AST/platelet ratio (APRI), and Fibroscans[58–61] have emerged as more practical, low cost, and portable (in the case of FibroScan®) tools for selecting persons for treatment in RLS, there remain significant challenges with their use. First, although the biomarker tests generally perform well in distinguishing mild liver disease from advanced fibrosis and cirrhosis, their usefulness is constrained by their limited discriminating performance at intermediate stages of fibrosis when management decisions often need to be made. Second, the lower ALT levels and

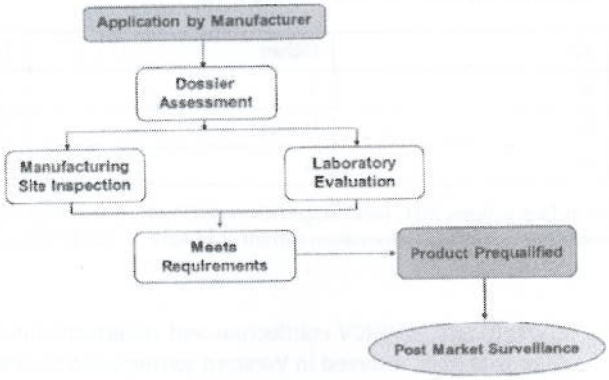

Figure 1 The World Health Organization's Prequalification of Diagnostics procedure.[66]

platelet counts in coinfected patients mean that these measures may be poor surrogates in the evaluation of fibrosis.[62] Third, the use of the FibroScan® requires regular maintenance of equipment, and there may be unreliable readings with inexperienced operators.

There are also some ethical concerns in RLS regarding inequity in access to treatment because HBV and HCV patients coinfected with HIV are likely to have preferential access to drug therapy for their HBV and potentially also HCV.

Lamivudine Resistance

All national and professional society guidelines, including the 2010 WHO adult ART guidelines recommend that tenofovir with either lamivudine or emtricitabine should be included in the ART regimen of HIV/HBV coinfected persons initiating ART.[63] However, this is currently not widely implemented, as HBV testing is not routinely performed before ART is started in most RLS. Most coinfected patients are therefore blindly put on the standard ART regimens for RLS, comprising two nucleoside reverse transcriptase inhibitors (NRTI; one of which is lamivudine) and a non-NRTI, such as nevirapine or efavirenz. The main consequence to this use of lamivudine as the only drug active against HBV is the emergence of lamivudine-resistant HBV. Up to 90% of patients are reported to have resistance after 4 years of treatment, resulting in an increased risk of progressive liver disease, and development of HCC.[25,26] Therefore, the priority in RLS is to identify HBV infection both prior to ART initiation and switching (to ensure lamivudine is continued)[64] to optimize therapy of both diseases.

Higher Incidence of HBV and HCV Immune Reconstitution Syndrome

HBV- or HCV-related immune reconstitution inflammatory syndrome (IRIS) within the first 3 months after ART initiation is a well-recognized phenomenon and characterized by HBV reactivation and worsening of hepatitis.[27,28,67] It is anticipated that ART-related hepatitis B and C IRIS will be a greater problem in RLS because of a higher prevalence of undiagnosed or diagnosed, but untreated HIV/HBV or HIV/HCV coinfection, and initiation of ART in patients with advanced HIV disease and underlying liver disease.

Differentiating between IRIS, ART, and other drug-related outcomes (e.g., TB or nevirapine hepatotoxicity, lamivudine resistance, and liver flares due to underlying HBV or HCV) as the underlying cause of a rise in liver enzymes, is another significant challenge in RLS. This is because of a high prevalence of unrecognized HIV/HBV infection and underling liver disease, more limited use of tenofovir, initiation of ART at an advanced stage of disease, and limited access to diagnostics.

WHO Prequalification Program for Hepatitis B and C Diagnostics

A further important contribution of WHO to hepatitis care in RLS is the prequalification program for hepatitis B and C diagnostics (►**Fig. 1**).[65,66] The main purpose of the WHO Prequalification of Diagnostics program is to promote and facilitate access to safe and appropriate in vitro diagnostics (IVDs) of good quality, and to build the capacity of national authorities to more effectively monitor quality of IVDs post-entry to their market. In general, the production of IVDs has recently shifted to countries with less-stringent regulatory control. Only a third of countries have some type of regulatory system in place for IVDs; and even where regulations for IVDs exist, often they are not enforced. Poor-quality IVDs are able to enter markets in many countries without any stringent assessment of their performance and suitability for field use. In many circumstances, WHO is the only agency that evaluates the quality and performance of IVDs for priority diseases in low- and middle-income countries.

Therefore, WHO specifically targets prequalification of the type of IVDs more commonly used in resource-limited settings such as rapid diagnostic tests (RDTs) and enzyme immunoassays without automated test procedures, which are generally not used in high-income countries where sophisticated centralized laboratory infrastructure exist. The key steps in the prequalification review process include a review of the product dossier compiled by the manufacturer, an inspection of the manufacturing site to ensure that information submitted within the dossier is correct, and a laboratory evaluation to determine the performance (sensitivity, specificity, invalid rate, etc.) and certain operational characteristics such as shelf life, time to produce a result, endpoint stability, requirements for preparation of specific reagents, and any equipment requirements.[65,66] A list of WHO prequalified products can be used by procurement officers and program managers to simplify procurement and develop tender specifications. Transparent procurement leads in turn to a more streamlined supply chain management at country level, and allows manufacturers to time their production cycles more accurately to reflect needs.

The current WHO prequalification pipeline for hepatitis diagnostic assays is healthy with over 34 applications received for HCV and HBsAg IVDs (►**Table 3**). To date, 16 HCV IVDs and 12 HBsAg IVDs have been considered as eligible to proceed for WHO prequalification according to standardized

Table 3 Applications Received for World Health Organization Prequalification of Hepatitis B and C Diagnostics[66]

	RDT	EIA	Other	Total
HCV	10	8	1	19
HBsAg	8	6	0	14
HIV/HCV	1	0	0	1

HCV, hepatitis C virus; HIV, human immunodeficiency virus; HBsAg, HBV surface antigen; RDT, rapid diagnostic test; EIA, enzyme immunoassay. Adapted from World Health Organization's website on diagnostics and laboratory technology (information current as of April 12, 2012) http://www.who.int/diagnostics_laboratory/pg-status/en/index.html.

procedures. The first round of laboratory evaluation for five HCV IVDs and five HBsAg IVDs is due to commence in the third quarter of 2012, with final results expected in early 2013 once inspections have been completed and dossiers found to meet the acceptance criteria. The IVDs to be assessed and prequalified may be suitable for use in blood, blood product, and transplantation screening; in serosurveillance studies; and for diagnostic purposes. More specifically, RDTs with a high degree of ease of use that can be used with capillary (fingerstick) whole blood with reduced requirement for cold chain storage will be prioritized given their unique applicability in resource-limited settings where infrastructure and human resources are lacking, thereby alleviating reliance on phlebotomists and laboratory technicians.[68]

Next Steps

Research Gaps

A major priority is to address key research gaps that will in turn inform the development of global guidance on management of HIV/HBV and HIV/HCV coinfection in RLS.[7,39] The most critical need is for a comprehensive and accurate assessment of the global epidemiology and burden of coinfection, as the current lack of such data are impeding more focused prevention and control initiatives at both international and national levels. The process will involve collating data from multiple sources such as national surveillance programs, periodic demographic surveys, epidemiologic studies in HIV programs, as well as death registries (where available) for information on liver-related deaths. New prevalence studies also need to move beyond the current focus on HBsAg prevalence to include markers of active HBV infection, such as HBsAg and HBV DNA, where possible. Other unanswered questions particularly relevant to coinfection in RLS include establishing the risk of HBV reactivation in anti-HBc-positive coinfected individuals; and the burden and clinical consequences of occult hepatitis B (HBV-DNA in the absence of HBsAg), given that routine HBV-DNA testing of all anti-HBc positive patients would not be feasible in RLS. Such prevalence surveys of HBsAg and HBV-DNA can be further facilitated by the use of new technologies such as dried blood spots.[68] Finally, the wide regional variations in prevalence of HIV/HCV infection observed across Africa presents an opportunity to gain insights into the major sources and risk factors for HCV transmission, and especially the reasons for the high rates of horizontal transmission.

Large prospective cohort studies across Africa also need to be established to document whether the natural history of HIV/HBV and HIV/HCV coinfection and treatment outcomes differ from that observed in Western settings, and to examine the impact of such factors as HBV or HCV genotype or occult HBV infection on liver disease progression risk of HCC and mortality. Such studies will also provide the framework for addressing other key questions, such as the impact of maternal lamivudine and tenofovir therapy on HBV perinatal transmission rates in HIV/HBV coinfection data in children born to infected mothers; validation studies to assess the performance of selected inexpensive noninvasive biomarker profiles in the assessment of fibrosis to identify coinfected patients at high risk of disease progression; the cost-effectiveness of different strategies for screening, diagnostic work-up, and timing of ART initiation; whether all anti-HBc-positive patients require effective anti-HBV therapy as part of ART; and finally optimal HBV vaccination strategies in HIV-positive patients.

Learning the Lessons from Scale Up of ART

The WHO public health approach to the scale-up of ART in resource-poor settings provides an excellent model for a comparable approach to the future delivery of hepatitis care in such settings.[40] Key elements that were integral to the standardization and simplification of HIV care include specifying a limited selection of once or twice daily regimens for first- and second-line therapy; recommending a limited set of desirable but nonessential laboratory tests[63]; development of fixed drug combinations; and simplifying care models through service integration, task shifting, and decentralization to overcome human resource shortages; patient and community engagement; and financial and political commitment. These elements have been summarized in a recent review.[40] There is also now the opportunity to "piggy-back" or integrate many components of HBV and HCV management into existing HIV programs.[39] For example, the same diagnostic instrumentation can be used for HBsAg as for HIV enzyme-linked immunosorbent assay; for HIV-RNA, HBV-DNA, and HCV-RNA; and HIV and HBV drug resistance.[39] However, it is clear that additional financial resources will be required to provide better access not only treatment to and selected diagnostics, but also to vaccination, educational tools, and safer medical equipment, for prevention of onward transmission.

Acknowledgments

The authors would like to thank Rachel Heenan for her work on the survey of national guidelines, and Jonathan Edwin for additional assistance.

Abbreviations

ART	antiretroviral therapy
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IRIS	immune reconstitution inflammatory syndrome
IVDs	in vitro diagnostics
NRTI	nucleoside reverse transcriptase inhibitor
RDTs	rapid diagnostic tests
SSA	sub-Saharan Africa
WHO	World Health Organization

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