Wilton Park: HIV Co-infection with Viral Hepatitis in Asia – Implications for Global Screening and Treatment

Pre-Read Materials
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General Background
Co-infection: new battlegrounds in HIV/AIDS

From June 30 to July 3 many of the world’s leading HIV/AIDS researchers, practitioners, and allied professionals will converge on Kuala Lumpur, Malaysia, for the seventh International AIDS Society Conference on Pathogenesis, Treatment, and Prevention. The content of this issue has been specially selected to reflect some of the key issues in HIV/AIDS with Articles on monitoring and treatment and Reviews on the search for a cure and the biology and effects of HIV superinfection. One of the key themes of the conference is co-infection. HIV/AIDS not only enables opportunistic pathogens that otherwise rarely infect human beings to cause illness, it can also substantially worsen the manifestations of other pathogens—tuberculosis, for example, is more likely to cause active diseases in people infected with HIV, and infections with hepatitis B and hepatitis C viruses more rapidly lead to liver damage.

Since the AIDS epidemic emerged, it has contributed to a global resurgence in tuberculosis. Of the estimated 34 million people infected with HIV in the world today, more than a third are also infected with *Mycobacterium tuberculosis.* In Africa, four-fifths of people with active tuberculosis are also infected with HIV. Worldwide, tuberculosis accounts for 25% of AIDS deaths; in Asia, this proportion is 40%. So it is no wonder that co-infection with tuberculosis and HIV/AIDS has received so much attention from the global health community. Great effort and resources have been invested in the improvement of diagnostic and treatment approaches for tuberculosis, and in recognition of the close association between the two diseases, the developments have simultaneously benefited many living with HIV. However, not all co-infections have, so far, received sufficient attention, and these diseases exact a substantial and growing toll on people with HIV/AIDS.

In this issue, Mark Sulkowski and colleagues report a phase 2 trial of boceprevir used for the treatment of hepatitis C in patients with HIV. In high-income countries, the co-infection rates for hepatitis C mirror those for tuberculosis—the virus infects a quarter of people with HIV in the USA, for example. But despite this burden, trials of the therapy in people also living with HIV have been a long time coming. Boceprevir was approved for treatment of hepatitis C monoinfection in 2011, but owing to concerns about potential interactions of this drug with common antiretroviral regimens it has not been used in patients with HIV. The results of the phase 2 study seem promising: with 63% of patients given boceprevir with pegylated interferon alfa and ribavirin achieving sustained virological response at 48 weeks, compared with 29% of those receiving interferon–ribavirin alone. However, work is still needed to confirm safety, and new direct-acting antivirals are already in development, so whether boceprevir will have a role in the treatment of hepatitis C in patients with HIV remains uncertain.

In their Personal View article, Angela Loyse and coauthors review the treatment of cryptococcal meningitis. This disease contributes to up to 20% of AIDS-related deaths in sub-Saharan Africa. Although appropriate management of HIV infection is one of the most effective routes to preventing this opportunistic infection, access to antiretrovirals in the regions where cryptococcal meningitis is most prevalent is inadequate. And as Loyse and coauthors highlight, so is access to amphotericin B, fluconazole, and flucytosine, the treatments for cryptococcal meningitis. The Personal View concludes with ten recommendations for tackling the burden of this infection in resource-limited settings, focusing on improving cost and access to available drugs and the development of new drugs.

The neglect of some coinfections with HIV/AIDS is something of a paradox. Manifestations of unusual infections such as pneumocystis pneumonia and Kaposi’s sarcoma were, after all, the first signs of the emerging pandemic to be recognised. Although effective management of HIV infection will help to diminish the burdens of other pathogens among infected populations, it is imperative that people living with HIV/AIDS have access to effective treatments for co-infecting pathogens. As Loyse and colleagues point out, access to antifungals, including new drugs, needs to be improved in low-income and middle-income countries. And as highlighted by the trial of boceprevir, HIV should be thought about early in the development of drugs for important co-infections. Patients with HIV must be considered in trial designs and, where possible, included in drug trials to avoid future lags in treatment availability for common co-infections. ■ The Lancet Infectious Diseases
Further reading


4.5 **Prevention and management of coinfections and co-morbidities**

An essential part of HIV treatment and care is the management of opportunistic infections such as TB and viral hepatitis. Addressing HIV effectively also requires addressing other co-morbidities such as other sexually transmitted bloodborne infections and mental health disorders. To synergize prevention and control efforts, it is appropriate to seek opportunities to combine the delivery of HIV testing, treatment and prevention services with those for these coinfections and co-morbidities.
4.5.2 Viral hepatitis

Background and rationale
Viral hepatitis B and C disproportionally affect key populations, as a result of sexual transmission and the sharing of needles, syringes and ancillary injecting equipment. It is estimated that, globally, 240 million people are chronically infected with HBV and 150–170 million with HCV. People who inject drugs account for approximately 1.1 million of those with HBV and 10 million of those with HCV (145).

 Worldwide, of the 35 million people living with HIV, chronic HBV infection affects an estimated 5–20% and HCV affects 5–15%. The burden of coinfection is greatest in low and middle income countries, particularly in South-East Asia, and, for HBV, particularly in sub-Saharan Africa. Among those living with HIV who are coinfect ed with HBV or HCV, liver disease progresses more rapidly and mortality is greater than among those with HBV or HCV who are not living with HIV.

HCV seroprevalence rates in prisons are even higher than HIV rates, and in many countries a history of HCV infection is associated with a history of incarceration (146, 147, 148, 149, 150).

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A comprehensive approach to addressing viral hepatitis among key populations includes prevention, screening, HBV vaccination, and treatment and care for people coinfected with HIV and HBV and/or HCV (4).

**Hepatitis B and C prevention**

The major modes of viral hepatitis transmission include unsterile medical injections or other procedures, transfusions of contaminated blood, unprotected sexual intercourse and unsafe injecting (39, 61, 149, 151, 152, 153). HCV is rarely transmitted through heterosexual sex. Over the past decade, however, several outbreaks of presumed sexually transmitted HCV infection have been reported among HIV-positive men who have sex with men. Similar HCV transmission among HIV-negative men who have sex with men and comparable drug-related behaviour has also been reported (154).

Because modes of transmission for viral hepatitis overlap those for HIV, many interventions that prevent HIV also prevent HBV and HCV. Examples include correct and consistent condom use, needle and syringe programmes and OST and sterile tattooing practices.

**Hepatitis B vaccine**

HBV vaccine is safe, effective and fairly inexpensive. Most countries have both targeted and population-wide HBV vaccination programmes, including infant, catch-up and risk-group vaccination. Risk groups include people who inject drugs, men who have sex with men, sexual partners of people living with HIV, prisoners, and others such as recipients of blood products and health-care workers. By 2012, 181 countries had incorporated HBV vaccination into their national schedule as an integral part of national infant immunization (155). An estimated 79% of the 2012 birth cohort globally received three doses of the HBV vaccine (156). The implication of national HBV vaccination programmes is that HBV vaccination of high-risk groups will become less crucial over time as, increasingly, people are immunized in infancy and thus protected (39).

There is currently no vaccine for HCV. Hence, there is an even greater need to intensify current efforts to prevent HCV transmission among key populations (39).

**Hepatitis B and C treatment**

It is important to manage HIV coinfection with HBV and/or HCV appropriately. Coinfection with HIV and HCV accelerates HCV-related progression of liver fibrosis and leads to a higher rate of end-stage liver disease and mortality (121, 151, 157).

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Key populations should have the same access to hepatitis B and C prevention, screening and treatment services as other populations at risk of or living with HIV.
Recommendations and guidance

ALL KEY POPULATIONS

Hepatitis B

• Catch-up hepatitis B immunization strategies should be instituted in settings where infant immunization has not reached full coverage (3, 10, 32).

• People from key populations with HIV and HBV coinfection who have severe chronic liver disease should be offered ART with a tenofovir (TDF) and lamivudine (3TC) (or emtricitabine (FTC))-based regimen irrespective of CD4 count or WHO clinical stage (strong recommendation, low quality of evidence) (4).1

Hepatitis C

• HCV serology testing should be offered to individuals from populations with high HCV prevalence or who have a personal history of HCV risk exposure/behaviour (strong recommendation, moderate quality of evidence) (158).

• An alcohol intake assessment is recommended for all persons with HCV infection, followed by the offer of a behavioural alcohol reduction intervention for persons with moderate-to-high alcohol intake (strong recommendation, moderate quality of evidence) (158).

• Assessment for antiviral treatment of all adults and children with chronic HCV infection is recommended, including for people who inject drugs (strong recommendation, moderate quality of evidence) (158).

• In addition, a number of recommendations on diagnosis and antiviral treatment regimens for HCV are available (158).

Additional remarks

• WHO is developing clinical guidance on hepatitis B treatment and screening strategies for hepatitis B and C. This guidance should be available in early 2015.

• WHO HCV guidelines provide detailed guidance on treatment and care (158).

• There are challenges in diagnosing and treating active HCV infection in certain populations such as people who inject drugs, particularly in settings with limited access to HCV antibody and RNA assays, diagnostic tools for staging of liver disease and HCV therapy. People receiving ART and HCV drugs require close monitoring for possible drug interactions (158, 159).

1 There is insufficient evidence or favourable risk-benefit profile to support initiating ART in everyone coinfected with HIV and HBV with a CD4 count >500 cells/mm³ or regardless of CD4 cell count or WHO clinical stage. Initiating ART regardless of CD4 count is, therefore, recommended only for people with evidence of severe chronic liver disease, who are those at greatest risk of progression and mortality from liver disease. For people without evidence of severe chronic liver disease, ART initiation should follow the same principles and recommendations as for other adults.
Related recommendations and contextual issues for specific key population groups

PEOPLE IN PRISONS AND OTHER CLOSED SETTINGS

• It is important that prisons offer hepatitis B vaccination (50, 60).
• It is important to offer voluntary HCV/HBV testing, treatment and care for people living with HIV soon after entry to prison, with assessment for and provision of treatment in accord with current WHO recommendations. Harm reduction measures should also be offered to prisoners.

PEOPLE WHO INJECT DRUGS

In addition to the comprehensive harm reduction package of nine interventions for people who inject drugs (8), which include most importantly NSP and OST, specific recommendations include:

• offering the rapid hepatitis B vaccination regimen to people who inject drugs (39);
• needle and syringe programmes should also offer low dead-space syringes (39);
• offering peer interventions to reduce transmission of viral hepatitis among people who inject drugs (39).

It is important also to consider the following:

• A higher-dose HBV vaccine should be used with the rapid regimen.¹
• When the rapid vaccine regimen is not available, the standard regimen should be offered.
• For both the standard and rapid regimens, delivery of the first dose is the priority.
• To reduce transmission of viral hepatitis, needle and syringe programmes should offer all types of syringes and other equipment used for the preparation of injecting drugs, including cookers, sterile water, alcohol swabs, filters and tourniquets, as appropriate to local needs.

Implementation considerations

Lost opportunities. Opportunities to vaccinate people who inject drugs often may be lost because of their poor access or reluctance to be vaccinated (160). Providing incentives to people who inject drugs and offering convenient access may increase uptake and completion of the HBV vaccination schedule (87, 152). Even partial immunization confers some immunoprotection, however (89). The decision whether to offer incentives depends on local acceptability and resources (161).

¹ The standard vaccination schedule for infants and unvaccinated adults is 0, 1, and 6 months, while the rapid schedule is 1, 7 and 21 days (39).
Immunosuppression. Individuals with inadequately treated HIV or with chronic HCV may have suppressed immune response. Therefore, they may benefit more from the standard HBV vaccine regimen than the rapid regimen (39).

Further reading

Pipeline Report

drugs, diagnostics, vaccines, preventive technologies, research toward a cure, and immune-based and gene therapies in development
Introduction and Executive Summary

By Polly Clayden and Mark Harrington

INTRODUCTION

Last year we wrote:

[Getting] the best drugs to the most people as quickly as possible… requires that the compounds and combination products be:

• Discovered and developed in a high-quality research program;
• Approved by a national or multinational regulatory authority;
• Recommended by national or multinational guidelines groups;
• Available in formulations suitable for use in the proposed population;
• Affordable to public-sector programs and through private insurance; and
• Accessible to patients through local health systems.¹

One year later, the research, regulatory, and access landscape for people with HIV, hepatitis C virus (HCV), or tuberculosis (TB) remains one of stark contrasts among the three diseases, and between people with access to affordable health care—whether they live in rich or developing countries—and those without. The research pipelines described in this year’s report show substantial progress in new treatments and preventive interventions against HIV. Revolutionary changes are afoot in the treatment of HCV, which allow—for the first time—the prospect of universal cure and disease eradication—if only cost and access barriers can be overcome. But, in the case of TB, few new diagnostics, even fewer new drugs, poor access, and declining political will create a pipeline woefully underpopulated, slow-moving, and resource-deprived.

Here we highlight the first of the essential requirements outlined above, the requirement that new interventions be “discovered and developed in a high-quality research program.”

A quick scan of worldwide trials data maintained by the U.S. National Institutes of Health (NIH) at clinicaltrials.gov reveals many disparities between research
and development programs for treatments of HIV, HCV, and TB. Newly approved drugs for the three diseases—dolutegravir (for HIV), sofosbuvir (for HCV), and delamanid (for TB)—have respectively 61, 67, and 6 clinical trials registered to investigate their use.

The 61 studies of dolutegravir cover: treatment-naive and -experienced patients (including those with resistance to other integrase inhibitors); comparisons, use, and interactions with the most commonly used antiretrovirals (and a couple of investigative ones); interactions with potential concomitant medicines that include studies with methadone, rifampin, and oral contraceptives; an investigation into how the drug performs in women; use in people with hepatic and renal impairment; pregnancy pharmacokinetics; a pediatric investigation program down to four weeks of age conducted by the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) network; and pharmacokinetics of the pediatric granule formulation. This list is not exhaustive. Despite the limitations of the registrational studies, with the usual underrepresentation of women, people with coinfections, etc., by the time all the studies are completed as well as several in the planning stage that are not yet registered, we will have a pretty good idea how the drug will perform across a diverse population (Polly Clayden looks at some of these that will help with our understanding of how the drug will perform in low- and middle-income settings in her chapter on antiretroviral dose optimization).

Registered sofosbuvir trials are also abundant and include patients with varying treatment experience, liver disease stage, and genotypes. But a closer look reveals limited investigations into regimens with other sponsors’ drugs, nothing in pregnant women or children, few in HIV coinfection (and nothing in other comorbidities), and just one (not yet recruiting) in people who inject drugs. As yet there are very few trials registered by independent investigators (and notably these are usually HIV networks or centers). Tracy Swan details the shortcomings of HCV trial enrollment in her chapter.

The tally for delamanid trials is a paltry 10 percent of those for the other two recently approved agents. It is at least encouraging that two of these trials will provide information for use in children with multidrug-resistant TB (MDR-TB). However, approval of delamanid by the European Medicines Agency (EMA) was delayed due to confusingly presented results from the phase II program, which included a two-month study, a six-month study, and an open-label study. The sponsor claimed a mortality benefit for those treated for six rather than two
months, but neglected to mention that those not surviving or lost to follow-up between the two- and six-month endpoints were excluded from this survival analysis—producing a biased readout.\(^2\) The sponsor’s inexperience and the lack of validated treatment options in multidrug-resistant (MDR) TB cannot excuse the poor design and presentation of this phase II program. A phase III study, now fully enrolled, may shed more light on delamanid’s use.

The other recently approved drug to treat MDR-TB, Janssen’s bedaquiline, had stronger evidence of efficacy at two and six months, but in the “placebo-controlled C208 trial, however, an imbalance of all-cause mortality has been observed with more deaths reported in the bedaquiline group (10/79 versus 2/81 in the placebo group in C208 Stage 2). Causes of death were varied and all but one occurred after the treatment period with bedaquiline.”\(^3\) The U.S. Food and Drug Administration (FDA) carried out a thorough review of each death in the phase II program and could not rule out an association with bedaquiline,\(^4\) resulting in a black box warning on the label and a requirement that Janssen open a U.S. patient registry to monitor safety post-marketing.\(^5\) The excess mortality seen in phase II should have induced Janssen to accelerate its confirmatory phase III study, which has not yet even begun. Rather than mounting its own phase III study, Janssen is trying to piggyback onto an ongoing USAID/British Medical Research Council (BMRC) study of a modified so-called Bangladesh regimen compared with standard of care (SOC). Janssen does not want to compare SOC with or without bedaquiline—which would be the clearest and simplest confirmatory study—but rather wants to compare a bedaquiline-containing modified Bangladesh regimen to one without. This way lies madness. The low standards for TB clinical trials leading to these accelerated (FDA) and conditional (EMA) approvals must be improved in future licensing efforts.

Throughout this report, the authors will be pointing out the need for better-quality research in order to more clearly define how to use new interventions. We will be writing in more detail on the challenges of improving research quality over the coming year.
EXECUTIVE SUMMARY

HIV

The 2014 adult antiretroviral pipeline is robust. As Tim Horn and Simon Collins note, antiretrovirals in late-stage development include a handful of new fixed-dose combinations (FDCs) and coformulations including dolutegravir/abacavir/lamivudine (DTG/ABC/3TC), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (EVG/COBI/FTC/TAF), darunavir (DRV)/cobicistat/FTC/TAF, TAF/3TC, cenicriviroc/3TC, dolutegravir/rilpivirine, and a once-daily regimen of raltegravir (RAL). Five compounds are in phase II including doravirine, BMS-663068, and the long-acting injectables S/GSK1265744 LAP, rilpivirine-LA, and PRO 140. As noted in previous pipelines, another six compounds, some of which hold serious potential for people living with HIV that is cross-class resistant to current antiretrovirals, continue to languish in earlier phases with no relevant development advances since 2013.

The past year saw FDA and EMA registration of the new, low-molecular weight, once-daily integrase inhibitor DTG (Tivicay, ViiV Healthcare), one of the most remarkable new antiretroviral drugs in memory. The sponsor’s development program is one of the most comprehensive ever. DTG as an anchor drug proved robustly noninferior, possibly superior, to regimens containing efavirenz (EFV), atazanavir/ritonavir (ATV/r), DRV/r, or RAL. This led the U.S. Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents to recommend use of DTG as a preferred first-line antiretroviral with a background of either tenofovir disoproxil fumarate (TDF)/FTC or—in those without HLA-B*5701—ABC/3TC. However, if ABC/3TC is used with efavirenz or with ATV/r it is recommended only when baseline viral load is below 100,000 copies/mL.

The sponsor’s new drug application package included adolescents 12 years or older, enabling DTG’s approval for that population alongside adults, and a pediatric development program, including a granule formulation for infants and young children, is well under way. Although the drug is unjustifiably expensive in the United States at $16,926/year at 50 mg/day, $33,852/year for those with prior integrase inhibitor resistant or when taken with EFV, fosamprenavir/ritonavir, or tipranavir/ritonavir, the sponsor has entered into a broad licensing agreement with the Medicines Patent Pool (MPP), allowing generic drug manufacturers to make lower-cost DTG in countries where over 90 percent of adults and children with HIV live. Thus, though the price in rich countries
remains an issue, the sponsor has set a new standard for phase III development in adults, rapid pediatric advancement, and global licensing to allow low-cost generics access. Since FDA approval, the drug has been registered in nine other countries: Canada, Chile, Switzerland, Australia, Japan, Brazil, Uruguay, Argentina, Israel, as well as in the European Union.

Activists, researchers, and providers are interested in the potential of a once-daily combination pill containing DTG, generic 3TC, and TDF, which will become generic in the coming years. This FDC could provide potency, durability, low cost, and increased tolerability if licensing and intellectual property considerations don’t get in the way—and could warrant use of integrase inhibitor–based first-line therapy globally, especially if data continue to support a low risk of resistance. This would displace EFV-based regimens and their neurotoxicity, and allow protease inhibitor–based therapies to remain in second-line recommended regimens. When TAF is approved, an even-lower-molecular-weight DTG/3TC/TAF pill would be possible.

Polly Clayden reports encouraging progress on treatment optimization,10 noting that ENCORE1 showed 400 mg/day of EFV to be noninferior to the currently recommended 600 mg dose; potentially, this could mean a lower cost first line with slightly fewer adverse effects. Further research is needed to bring us closer to the optimal safe, effective, tolerable, durable, universal, and affordable ideal antiretroviral regimen for all.

To recommend DTG-based regimens as preferred global first line we need a bit more information. DTG has been studied in several treatment scenarios and regimens, but so far not in key populations who would be treated with DTG in low- and middle-income countries, such as pregnant women and people with TB coinfection. The registrational trials for DTG were about 80% men, had few non-white participants, and hardly anyone coinfected with other diseases (a few hepatitis B and none with TB or malaria). People with baseline NRTI resistance were excluded.

Clayden describes several planned investigator- and sponsor-led trials that should generate data to fill in some of the gaps. This research needs to be prioritized, funded, and conducted in a timely and coordinated fashion so that the time lag between recommendations and adoption in treatment programs does not take over half a decade between rich and poor countries.
Besides the 12-and-up approval of DTG noted above, Clayden shows how two additional new pediatric formulations have recently been approved, for the youngest age group with the least options: RAL for infants over four weeks of age and ATV for those at least three months old. Global pediatric HIV treatment remains far from ideal, however, with recently updated World Health Organization (WHO) recommendations “not very simple and somewhat aspirational,” with several missing suitable, child adapted formulations of currently approved antiretrovirals including AZT/3TC/lpionavir (LPV)/r, ABC/3TC/LPV/r, ABC/3TC/EFV, DRV/r, ritonavir granules. As with adults, DTG (in kids below 12), cobicistat, and TAF might offer improvement on current options. The UNITAID, Drugs for Neglected Diseases Initiative (DNDi), and the Medicines Patent Pool–cosponsored Paediatric HIV Treatment Initiative provide one granule of hope that these needed new pediatric drugs and formulations will be developed and brought to market more quickly without intellectual property barriers.11

Tim Horn and Richard Jefferys present a synoptic overview of recent developments in HIV preventive technologies, including antiretroviral therapy (ART) and vaccine development.12 Significant research, growing indications of effectiveness, considerable excitement and controversy accompany the newer field of preventive ART, with at least 10 agents being studied as oral or parenteral preexposure prophylaxis (PrEP), vaginal microbicides, tablets, or gels as single drugs (dapivirine, GSK1265744, ibalizumab, maraviroc, rilpivirine-LA, TDF) or in combination (TDF/FTC, already FDA-approved for this use; maraviroc/TDF, maraviroc/dapivirine).

Despite FDA approval of TDF/FTC in mid-2012, uptake has been slow, with fewer than 10,000 people in the U.S. being prescribed PrEP13 while, over the same period, over 100,000 Americans became infected with HIV. In mid-May 2014, the CDC issued the first comprehensive U.S. PrEP guidelines, which suggest that PrEP may be appropriate for as many as 500,000 Americans.14 Complementing this, and helping to provide guidance on who would benefit most from PrEP, Susan Buchbinder of the University of California, San Francisco, and colleagues, published an analysis of the iPrEx PrEP study in gay men and transgender women that assessed which baseline characteristics were most associated with HIV acquisition and with PrEP efficacy. Using these data they determined the population attributable fraction (PAF) of new infections and the number needed to treat based on baseline risk factors. A history of receptive anal intercourse without a condom in the three months before enrollment had
Introduction and Executive Summary

the highest PAF (64% of new infections). Individuals most likely to benefit from PrEP in iPrEx included these, as well as those with a history of recent sexually transmitted infection (STI), syphilis, or cocaine use. Much work remains to be done to scale up use of effective preventive approaches including PrEP.

Horn and Jefferys note that an effective preventive HIV vaccine “remains frustratingly elusive” and show how ill-prepared the HIV vaccine field was to respond to success, citing the RV144 trial in Thailand and the underwhelming advancement of its findings, largely due to the need to produce a new envelope protein boost to replace the discontinued AIDSVAX.

They suggest that the greatest hope might lie in pursuing development of antigens based on the accumulating number of broadly neutralizing antibodies (bNAbs) that have been discovered, and recent advances in understanding both how these bNAbs are generated by the human immune system and how they interact with the HIV envelope to accomplish neutralization. They write: “A vaccine capable of inducing bNAbs remains the holy grail for the HIV vaccine field, and these developments suggest that it is possible.”

Thirty-eight preventive vaccination approaches are in clinical trials, and Horn and Jefferys say there are reasons to be optimistic about long-term prospects, but a licensed product is not on the immediate horizon.

Jefferys provides a clear, concise overview of the growing activity in research toward an HIV-1 cure and sometimes-related immune-based therapies. Research toward the goal of curing HIV infection has rapidly assumed a central role within the overall scientific portfolio, but funding has not swelled at the same pace, although there have been signs of change over the past year. The number of clinical trials under way has increased substantially since 2013, as has the diversity of approaches being evaluated.

Efforts are under way to replicate the apparent cures seen in Timothy Ray Brown after his CCR5-Δ32 heterozygous stem cell transplant, and in the so-called Mississippi baby, now a child. One early transplant recipient has died, while two others rebounded virologically 12 and 32 weeks after stopping ART; both had received wild-type rather than CCR5-Δ32-mutated transplants. IMPAACT network study P1115, funded by the NIH, will attempt to treat immediately “babies infected with HIV because their mothers failed to receive appropriate prevention of mother-to-child transmission (PMTCT). While the possibility of sparing these newborns a lifelong burden of ART needs to be pursued,” notes
Jefferys, “the goal of ensuring that no HIV-positive mother lacks access to PMTCT remains paramount.”

Jefferys notes updates on Sangamo BioSciences’ SB-728-T autologous ex vivo disrupted CCR5 CD4 cell reinfusion therapy studies of cyclophosphamide to deplete CD4 cells, allowing greater growth space for reinfused gene-modified cells, latency-reversing agents, therapies targeting PD-1, exciting basic science research on broadly neutralizing HIV antibodies, therapeutic HIV vaccines, and immune-based therapies including the ill-starred interleukin-7 (IL-7), gut-targeted approaches to reduce immune activation, and a panoply of anti-inflammatories.

“The development of widely accessible interventions capable of curing the majority of HIV-positive people remains a stern challenge with no solution imminent,” he writes. And he stresses the continued need for advocacy to ensure that this work continues, funding support grows, and the understanding of the science among the HIV/AIDS community and broader public is enhanced.

The immune-based therapy field, he concludes, in contrast, remains fallow, with meager commercial interest. A broader dialogue among activists, scientists, funders, pharmaceutical companies, and other interested parties might be needed in order to assess whether the problems in this area can be solved—notably, the incomplete immune reconstitution and extra morbidity seen among immunologic nonresponders and excess morbidity associated with residual immune activation.

**Hepatitis C Virus (HCV)**

Tracy Swan brilliantly summarizes the exploding universe of new HCV treatment and cure regimens, a boon for the 185 million people who have been infected with hepatitis C. In April 2014, the WHO issued its Guidelines for the Screening, Care and Treatment of Persons with Hepatitis C Infection. While the Guidelines support the use of these new regimens in low- and middle-income countries (LMICs), drug pricing has once again become the major barrier to access and the hope of global eradication of HCV.

A hefty pipeline will increase HCV treatment options, especially for people with genotype 1, by mid-to-late 2014. Cure rates
above 95 percent—after only 12 weeks of treatment—have become commonplace in HCV clinical trials. DAAs [direct-acting antivirals] have been miraculous for people with cirrhosis, HIV/HCV coinfection, and before and after liver transplantation.

But the outrage about sky-high DAA prices is quickly overtaking excitement about these wonder drugs. Advocates and clinicians are forced to fight for access to outrageously expensive drugs for people who cannot wait for affordable options—or watch people die from a curable infection.

Gilead’s nucleotide polymerase inhibitor, sofosbuvir—the backbone of most DAA regimens—is US$1,000 per tablet. Such a price limits access to this lifesaving drug, even in high-income countries...

Global eradication of HCV is possible, if pharmaceutical companies will allow generic DAA production in LMICs....DAAs can be produced inexpensively, according to an analysis from the University of Liverpool (using molecular weight, chemical structure, complexity, dose, and cost of comparable HIV antiretroviral agents). The actual production cost for 12 weeks of a single DAA ranges from US$10 to US$270, assuming an annual volume of 1–5 million treatment courses.22,23

Clearing the way through a daunting forest of data, Swan identifies the key elements of an ideal HCV curative regimen—affordable, safe, highly effective against all HCV genotypes, tolerable, simple to administer and undergo, with limited drug-drug interactions—and matches these characteristics with nine of the most advanced regimens studied to date.24 Swan points out the lack of data on these regimens in people who use and inject drugs and in children; in addition, sponsors have failed to provide disaggregated data by gender in many studies.

Swan observes that HCV research has been undermined by commercial competition. Gilead has refused to continue promising clinical collaborations with Janssen and BMS, which has delayed or complicated access to promising DAA combinations. In phase II trials, simeprevir/sofosbuvir cured more than 90% of participants after 12 weeks of treatment—even prior null responders
with compensated cirrhosis. Although sofosbuvir (Sovaldi) and simeprevir (Olysio) are licensed, this combination remains off-label; Janssen is supporting phase III trials. In a phase II trial, the combination of daclatasvir and sofosbuvir cured 100% of people with HCV genotype 1 (regardless of treatment experience), 92% of people with genotype 2, and 89% of people with genotype 3. BMS is supporting phase III trials of this combination in pre- and post-transplantation, HIV/HCV coinfection, and genotype 3. Approval of daclatasvir in the United States and the European Union is expected later this year. Gilead is developing its own daclatasvir analogues, ledipasvir and GS-5816, which will be co-formulated with sofosbuvir in FDCs, whose price one can only shudder to imagine.

The DAA era has been good news for people coinfected with HIV. They have experienced SVR rates similar to the monoinfected when an HCV protease inhibitor was added to pegylated interferon and ribavirin. Now, several interferon-free regimens have demonstrated proof of concept in HIV/HCV coinfection, with SVR rates equivalent to those in HCV monoinfection. Drug interactions between HCV and HIV regimens remain a concern, since they may limit antiretroviral treatment options during HCV treatment.

Swan criticizes the underenrollment of African Americans in U.S.-based HCV trials (below 20% in all but one industry-sponsored study), as well as people of other races and ethnicities. Gender differences are not broken out by race/ethnicity in many studies, limiting our understanding of possible differences in safety, toxicity, or efficacy.

Research and treatment access for people who inject drugs—who make up 80 percent of new HCV infections in developed countries and 10–15 million of the world’s 185 million people with HCV—remain abysmal.

Pregnant and nursing women are excluded from HCV clinical trials because ribavirin is highly teratogenic. At least 60,000 new infant infections occur each year; the advent of ribavirin-free regimens facilitates much-needed research to interrupt vertical HCV transmission. A search on clinicaltrials.gov reveals just nine open intervention studies for children with HCV, most of them with standard therapy with or without already-approved and quite toxic HCV protease inhibitors.

As Swan says, “[t]he hard work—transforming the HCV treatment cascade from scarcely a dribble into a waterfall—is just beginning.” Now that HCV treatment
has become simple, safe, and highly effective, governments “must not continue
to ignore HCV; it is time for national plans to address the epidemic. People
with HCV and their allies, people who inject drugs, epidemiologists, medical
providers, researchers,” policy makers, donors, and industry need to work
together.

Activists have launched an ambitious global campaign to achieve universal
access to HCV prevention, diagnostics, care, and treatment, which Karyn
Kaplan and Tracy Swan summarize in their global brief.26 They have
collaborated with allies around the world on the “Missing” campaign—
targeting WHO Director-General Margaret Chan and highlighting the WHO’s
tardy and underresourced response to HCV; the first HCV World Community
Advisory Board meeting in Bangkok, Thailand; and the first-ever demonstration
at the European Association for the Study of the Liver meeting, protesting the
price of sofosbuvir, a DAA that costs less than US$136 to manufacture for a
12-week treatment course, yet costs US$1,000 a pill.

These are the opening moves in a long and hard-fought struggle for global,
affordable HCV DAAs, with the potential to save hundreds of millions of lives.

Tuberculosis (TB)

TB Diagnostics

Tuberculosis research and development (R&D) continues to present a
disappointing landscape compared with the healthy diversity of HIV R&D and
the explosive advances in HCV treatment. Where HIV research combines
substantial long-term public-sector investment with diverse pharmaceutical
involvement, and HCV research is primarily driven by profit-seeking drug
companies with a dearth of public-sector investment, TB research suffers from
scant and falling public-sector investment and industry fleeing for the exits.
The view is not pretty.

TB diagnostics research has not advanced much in the past year, with the
exception of a vigorous ongoing series of implementation science studies
connected with the rollout of the GeneXpert MTB/RIF DNA polymerase chain
reaction (PCR) system for detection of Mycobacterium tuberculosis and rifampin
resistance, and—to a lesser extent—advances in our understanding of the
usefulness of the Alere Determine LAM urine dipstick for diagnosis of TB in
Global policy report on the prevention and control of viral hepatitis

IN WHO MEMBER STATES
Executive summary

Viral hepatitis is a group of infectious diseases that affects hundreds of millions of people worldwide, causing serious illness and death from acute hepatitis infection, liver cancer and liver cirrhosis. Although there are effective tools and strategies for the prevention and treatment of hepatitis, low awareness of hepatitis has limited their impact. Given the variation in how the five main types of hepatitis (A, B, C, D and E) manifest across and within countries, global prevention and control efforts need to be transformed into national and sub-national prevention and control strategies.

In 2010, the World Health Assembly adopted resolution WHA 63.18 in recognition of viral hepatitis as a global public health problem. The World Health Organization (WHO) followed up on the resolution by crafting a strategy that addresses four axes: awareness-raising, partnerships and resource mobilization; evidence-based policy and data for action; prevention of transmission; and screening, care and treatment.

The periodic evaluation of implementation of the WHO strategy requires an initial baseline survey of all Member States. In mid-2012, WHO, in collaboration with the World Hepatitis Alliance, conducted such a survey, asking Member States to provide information relating to the aforementioned four axes of the WHO strategy. In particular, Member States were asked whether key prevention and control activities are being conducted. This report presents the results. The first chapter provides an introduction to viral hepatitis and to the global response to this group of diseases. The second chapter provides a global overview of the survey findings. Chapters three through eight present findings from the six WHO regions, including summaries of data from all responding countries. Additional survey data, study methodology information and the survey instrument can be found in Annexes A–E.

One hundred and twenty-six Member States submitted the survey for a response rate of 64.9%. The regional response rate varied from 26.1% for the African Region to 100% for the South-East Asia Region. Across income groups, the response rate ranged from 47.4% for low-income countries to 80.0% for high-income countries.

Implementing a national response to comprehensively address viral hepatitis is a challenge for many governments. Because of the high burden of hepatitis-related diseases and the different routes of transmission and health outcomes, they need to simultaneously implement a variety of prevention and care interventions. Additionally, government officials should focus on monitoring hepatitis outbreaks and disease trends while collaborating with civil society to raise awareness about hepatitis. The results of the survey indicate that some Member States are addressing some aspects of this response but that much more needs to be done.

An important step that can help Member States to identify priorities and marshal resources is to develop a written national strategy or plan that focuses exclusively or primarily on viral hepatitis. This plan could either stand alone or function as part of a broader health-planning document. Only 37.3% of responding Member States reported the existence of such a plan. Even fewer (28.6%) had a governmental unit dedicated to addressing hepatitis prevention and control. Furthermore, the number of government staff working full-time on hepatitis-related activities is small; more than half of the countries reported having no more than two employees.

Almost three fourths of responding Member States reported that they had a viral hepatitis prevention and control programme that included activities targeting specific populations. The populations most commonly targeted were health-care workers, including health-care waste handlers (86.0% of responding Member States within this subset), and people who inject drugs (54.8% of responding Member States within this subset).

National governments can play an important role in making their citizens aware of the importance of viral hepatitis, how to avoid getting infected and how to seek care. World Hepatitis Day (28 July), which was established in 2010 as part of the World Health Assembly resolution 63.18, is an important means of raising awareness about hepatitis. Two years after the passage of the resolution, almost 40% of responding Member States reported that they had engaged in activities to mark World Hepatitis Day. However, it is important for the remaining Member States, particularly where the burden of viral hepatitis is high, to organize World Hepatitis Day activities. Civil society organizations can play a significant role in further publicizing health messages for World Hepatitis Day and throughout the year. However, less than half of responding Member States reported that they collaborated with civil society groups within their countries to develop and implement the governmental viral hepatitis prevention and control programme.

Obtaining reliable data is important for planning and monitoring the implementation of hepatitis control activities. Most Member States (82.5%) reported having a national surveillance programme that regularly collected data and reported results regarding hepatitis incidence. In only approximately half of these Member States did the surveillance system include a method for monitoring chronic hepatitis B and C, which are responsible for most hepatitis-related morbidity and deaths. To properly assess the scope of chronic hepatitis requires conducting regular prevalence serosurveys in both the general and most-at-risk populations; however, only about two thirds of Member States reported conducting such surveys.

There have been significant advances in the prevention of viral hepatitis. The most important is the wide-scale implementation of universal childhood vaccination for hepatitis B. As of 2011, 180 countries included hepatitis B vaccination in their routine vaccine schedules and the coverage is approaching 80%. The survey results provide additional data concerning national hepatitis B vaccination policies. Slightly more than three fourths of Member States reported having a specific policy for the prevention of mother-to-child transmission which includes vaccination. This is important as infection transmitted from mothers...
to their children is the principal route of transmission in many countries, particularly in Asia. Health-care workers are another group requiring special attention for vaccination in view of their high risk of infection through needle-stick injuries. Almost two thirds of Member States reported having a vaccination policy for health-care workers.

In many countries, transmission of hepatitis to patients through unsafe injection practices in health-care settings is still a problem. The majority of the responding Member States reported addressing this through a national policy on injection safety and recommending the use of single-use syringes.

With the development of reliable tests to identify hepatitis infections, transmission of hepatitis through transfusions is preventable; 94.4% and 91.3% of Member States reported screening all donated blood units for hepatitis B and C, respectively. The survey was not able to assess other recommended practices, such as the promotion of blood donations from voluntary non-remunerated blood donors or the utilization of quality control measures for laboratory testing.

Hepatitis treatment is undergoing a revolution. New medications are being developed and introduced, which will improve control and provide higher cure rates for hepatitis B and C. It is important for countries to be prepared for the anticipated scale up of treatment by training health-care providers, establishing national treatment guidelines, and including hepatitis medications in their essential medicines lists. The survey results indicate that much progress must be made in these key areas. Only half of reporting Member States indicated that they have clinical guidelines for the treatment of hepatitis, and less than half reported including key medications for the treatment of hepatitis B such as tenofovir or entecavir in their essential medicines list. Only 54.8% reported including pegylated interferon, which is the current mainstay of hepatitis C treatment. Encouragingly, approximately 60% of Member States reported having publicly funded treatment programmes. The survey was not able to assess the geographical coverage of these treatment services or their success in reaching most-at-risk populations.

One of WHO’s core functions is to help Member States in their efforts to improve the health of their populations. In the survey, Member States were asked to indicate areas in which they might want assistance from WHO for the prevention and control of viral hepatitis. Respondents most commonly selected the following: developing a national plan for viral hepatitis prevention and control (58.1%), estimating the national burden of viral hepatitis (54.8%) and developing education/training programmes for health professionals (54.0%). In order to provide this assistance, it will be important to identify adequate resources and coordinate activities at WHO Headquarters and the regional levels.

The survey has limitations that constrain the ability to interpret the results, including a low response rate from the African Region. In addition, it was not possible to collect information concerning the quality of the programmes or their geographical scope. Nevertheless, the survey does document notable achievements, particularly in the area of prevention of hepatitis transmission. National governments still need to do much more to comprehensively address this global killer. Furthermore, in view of limited resources, it will be vital for all relevant organizations at the international, national and local levels to work together to maximize the impact of hepatitis control activities.
Chapter 2: Global findings

One hundred and twenty-six Member States submitted the World Health Organization/World Hepatitis Alliance survey ("WHO/Alliance survey") (Figure 1), a response rate of 64.9%. Respondents and non-respondents are listed by WHO region in Box 1.

Box 1. Responses to the 2012 Global Hepatitis Survey from each WHO region

WHO African Region

Member States that submitted surveys:
Cameroon, Chad, Comoros, Côte d’Ivoire, Mali, Mauritania, Nigeria, Rwanda, Sierra Leone, South Africa, United Republic of Tanzania and Zimbabwe

Member States that did not submit surveys:

WHO Region of the Americas

Member States that submitted surveys:
Antigua and Barbuda, Argentina, Bahamas, Barbados, Brazil, Canada, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Lucia, Suriname, United States of America and Uruguay

Member States that did not submit surveys:
Belize, Bolivia (Plurinational State of), Chile, Dominica, Haiti, Saint Vincent and the Grenadines, Trinidad and Tobago, and Venezuela (Bolivarian Republic of)

WHO Eastern Mediterranean Region

Member States that submitted surveys:
Afghanistan, Bahrain, Djibouti, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Kuwait, Lebanon, Oman, Pakistan, Qatar, Somalia, South Sudan, Sudan, Syrian Arab Republic and Yemen

Member States that did not submit surveys:
Libya, Morocco, Saudi Arabia, Tunisia and United Arab Emirates

WHO European Region

Member States that submitted surveys:
Albania, Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Hungary, Iceland, Israel, Italy, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, Poland, Republic of Moldova, Russian Federation, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Ukraine, United Kingdom of Great Britain and Northern Ireland, and Uzbekistan

Member States that did not submit surveys:
Bosnia and Herzegovina, Greece, Iceland, Kazakhstan, Monaco, Norway, Portugal, Romania and Turkmenistan

WHO South-East Asia Region

Member States that submitted surveys:
Bangladesh, Bhutan, Democratic People’s Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand and Timor-Leste

Member States that did not submit surveys:
no country

WHO Western Pacific Region

Member States that submitted surveys:
Australia, Brunei Darussalam, Cambodia, China, Japan, Kiribati, Lao People’s Democratic Republic, Malaysia, Mongolia, New Zealand, Papua New Guinea, Singapore, Solomon Islands, Tonga and Viet Nam

Member States that did not submit surveys:
Cook Islands, Fiji, Marshall Islands, Micronesia (Federated States of), Nauru, Niue, Palau, Philippines, Republic of Korea, Samoa, Tuvalu and Vanuatu

Table 1. Responses received by WHO region and income group*

<table>
<thead>
<tr>
<th>Region</th>
<th>High income (N=50)</th>
<th>Upper–middle income (N=53)</th>
<th>Lower–middle income (N=50)</th>
<th>Low income (N=38)</th>
<th>Other (N=3)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa (N=46)</td>
<td>0 (0%)</td>
<td>1 (12.5%)</td>
<td>3 (27.3%)</td>
<td>8 (26.9%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Americas (N=35)</td>
<td>5 (83.3%)</td>
<td>16 (80.0%)</td>
<td>6 (85.7%)</td>
<td>0 (0%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Eastern Mediterranean (N=22)</td>
<td>4 (66.7%)</td>
<td>3 (60.0%)</td>
<td>8 (88.9%)</td>
<td>2 (100%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Europe (N=53)</td>
<td>26 (83.9%)</td>
<td>10 (71.4%)</td>
<td>5 (100%)</td>
<td>3 (100%)</td>
<td>n/a</td>
</tr>
<tr>
<td>South-East Asia (N=11)</td>
<td>n/a</td>
<td>2 (100%)</td>
<td>5 (100%)</td>
<td>4 (100%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Western Pacific (N=27)</td>
<td>5 (83.3%)</td>
<td>2 (50.0%)</td>
<td>7 (53.8%)</td>
<td>1 (25.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total: Income group</td>
<td>40 (80.0%)</td>
<td>34 (64.2%)</td>
<td>34 (68.0%)</td>
<td>18 (47.4%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* Source for income group classifications: World Bank 2012 data (http://data.worldbank.org/about/country-classifications/country-and-lending-groups)

* Income group classifications were not available for three Western Pacific countries that did not submit surveys: Cook Islands, Nauru and Niue.

n/a = not available
Figure 1. Map of global responses

Figure 2. Responses to the question, “Is there a written national strategy or plan that focuses exclusively or primarily on the prevention and control of viral hepatitis?”
National coordination
Forty-seven responding Member States (37.3%) reported the existence of a written national strategy or plan that focuses exclusively or primarily on the prevention and control of viral hepatitis (Figure 2).

Eighteen of the 47 Member States with a strategy or plan reported that it focuses exclusively on viral hepatitis, and 20 reported that it addresses other diseases as well. Five countries reported that the strategy or plan addresses only hepatitis B and one reported that it addresses only hepatitis C. Three countries reported that the strategy or plan addresses both hepatitis B and hepatitis C.

The 47 Member States that reported the existence of a strategy or plan were asked about its specific components. Forty-six reported the inclusion of a component for vaccination, Forty-three reported the inclusion of a component for prevention of transmission in health-care settings, and the same number for general prevention and surveillance. Thirty-seven reported the inclusion of a component for treatment and care. Thirty-six reported the inclusion of a component for the prevention of transmission via injecting drug use.

Thirty-six responding Member States (28.6%) reported that they had a governmental unit or department responsible solely for viral hepatitis-related activities. Member States that did so were asked to indicate the number of staff members in the unit or department. Responses (N=30) ranged from 0.1 (New Zealand) to 250 (Brazil) (median, 5).

Member States were asked to report the number of people working full-time on hepatitis-related activities in all government agencies or bodies. Among the 47 Member States that provided data for this question, the number ranged from 0 to 213 (median, 2), with Armenia reporting the highest number.

Ninety-three responding Member States (73.8%) reported that they had a viral hepatitis prevention and control programme that included activities targeting specific populations. The populations most commonly targeted were health-care workers, including health-care waste handlers (86.0% of responding Member States within this subset) and people who inject drugs (54.8% of responding Member States within this subset). Forty-four responding Member States (47.3%) reported the inclusion of activities targeting people living with HIV and 36 responding Member States (38.7%) reported the inclusion of activities targeting prisoners. Groups identified less frequently included migrants, indigenous populations, low-income populations, those who are uninsured and those who are homeless.

Awareness-raising and partnerships
Forty-eight responding Member States (38.1%) reported that they had held events for World Hepatitis Day 2012 (28 July). Since January 2011, 36 responding Member States (28.6%) had funded some type of viral hepatitis public awareness campaign other than World Hepatitis Day (Annex A).

Sixty responding Member States (47.6%) reported that they collaborated with civil society groups within their countries to develop and implement the governmental viral hepatitis prevention and control programme.

Evidence-based policy and data for action
One hundred and four responding Member States (82.5%) reported that they have routine surveillance for viral hepatitis; details are given in Table 2.

Table 2. Types of surveillance in Member States reporting the existence of routine surveillance for viral hepatitis (N=104)

<table>
<thead>
<tr>
<th>Type of surveillance</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Do not know (%)</th>
<th>No response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hepatitis infection for the following forms of hepatitis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hepatitis A</td>
<td>86.5</td>
<td>5.8</td>
<td>0</td>
<td>7.7</td>
</tr>
<tr>
<td>hepatitis B</td>
<td>96.2</td>
<td>2.9</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>hepatitis C</td>
<td>85.6</td>
<td>9.6</td>
<td>0</td>
<td>4.8</td>
</tr>
<tr>
<td>hepatitis D</td>
<td>38.5</td>
<td>41.3</td>
<td>1.0</td>
<td>19.2</td>
</tr>
<tr>
<td>hepatitis E</td>
<td>45.2</td>
<td>35.6</td>
<td>1.0</td>
<td>18.3</td>
</tr>
<tr>
<td>Chronic hepatitis infection for the following forms of hepatitis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hepatitis B</td>
<td>52.9</td>
<td>43.3</td>
<td>0</td>
<td>3.8</td>
</tr>
<tr>
<td>hepatitis C</td>
<td>49.0</td>
<td>46.2</td>
<td>0</td>
<td>4.8</td>
</tr>
<tr>
<td>hepatitis D</td>
<td>23.1</td>
<td>64.4</td>
<td>0</td>
<td>12.5</td>
</tr>
</tbody>
</table>

One hundred and seven responding Member States (84.9%) indicated that their countries have standard case definitions for hepatitis infection and 100 (79.4%) indicated that their countries have a central registry for the reporting of deaths, including hepatitis deaths.

Fifty-seven Member States reported on the proportion of hepatitis cases and deaths registered as “undifferentiated” or “unclassified” hepatitis. The reported proportion ranged from 0% to 100% (median, 1%). Additional survey findings on surveillance are presented in Table 3.

Member States were asked how often hepatitis disease reports were published. Of the responding Member States, 40.5% reported that they publish hepatitis disease reports annually; 4These figures represent data from 55 of the 57 Member States. Data from the Russian Federation and Mali are not included here because those Member States reported the information in a different way. See the Russian Federation and Mali country findings elsewhere in the report for information about undifferentiated/unclassified hepatitis in those Member States.
Figure 3. Responses to the question, “Has your government established the goal of eliminating hepatitis B?” (N=12)

- **Yes** (23.8%)
- **No** (67.5%)
- **Do not know** (4.8%)
- **No response** (4.0%)

Four Member States that answered “yes” to this question (Australia, Latvia, Republic of Moldova and Sweden) added comments indicating that their goals relate to reducing rather than eliminating hepatitis B.

A total of 30 (21.4%, monthly; and 12.7%, weekly) Member States experience a hepatitis disease report. Among the 101 Member States that provided information, responses ranged from 0% to 100% (median, 58.0%).

Thirty-two (25.4%) Member States reported the existence of a national public health research agenda for viral hepatitis. Among this subset, 43.9% indicated that the most recent viral hepatitis serosurvey was carried out in either 2011 or 2012.

Forty-one (32.5%) Member States reported that viral hepatitis serosurveys are conducted regularly. Among this subset, 43.9% reported that the most recent viral hepatitis serosurvey was carried out in either 2011 or 2012.

Prevention of transmission

Fifty-one (40.5%) Member States reported that they have a national hepatitis A vaccination policy.

Thirty (23.8%) Member States reported that they have established the goal of eliminating or reducing hepatitis B (Figure 3).

Member States were asked to report, for a given recent year, the percentage of newborn infants who had received the first dose of hepatitis B vaccine within 24 hours of birth. Among the 86 Member States that provided this information, responses ranged from 0% to 100% (median, 54.8%).

Eighty-eight (69.8%) Member States reported the existence of a specific national strategy and/or policy/guidelines for preventing hepatitis B and hepatitis C infection in health-care settings.

Eighty (63.5%) Member States reported that healthcare workers are vaccinated against hepatitis B prior to starting work that might put them at risk of exposure to blood.

One hundred and eleven (86.5%) Member States reported the existence of a national policy on injection safety in health-care settings. These Member States were asked which types of syringes the policy recommends for therapeutic injections. Single-use syringes are recommended in 77.1% of policies, and auto-disable syringes in 30.3% (Figure 4).

One hundred and thirteen (87.3%) Member States reported that single-use or auto-disable syringes, needles and cannulas are always available in all health-care facilities.

Member States were asked for official estimates of the number and percentage of unnecessary injections administered annually in health-care settings (e.g. injections that are given when an equivalent oral medication is available). One hundred and thirteen Member States reported that the figures are not known and six did not reply. Among the seven responding Member States providing this information, responses ranged from 0% to 68.0% (median, 14.0%), with Denmark and Tonga reporting 0% and Mongolia reporting 68.0%.

Additional findings relating to the prevention of hepatitis transmission are presented in Table 4.

Screening, care and treatment

Member States were asked how health professionals in their countries obtain the skills and competencies required to effectively care for people with viral hepatitis. Responding Member States most frequently indicated that these are acquired in schools for health professionals (pre-service education, postgraduate education and continuing professional development).
Table 4. Hepatitis prevention: policies, practices and guidelines (N=126)

<table>
<thead>
<tr>
<th>Policy Description</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Do not know (%)</th>
<th>No response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is a national infection control policy for blood banks</td>
<td>88.9</td>
<td>5.6</td>
<td>4.0</td>
<td>1.6</td>
</tr>
<tr>
<td>All donated blood units (including family donations) and blood products nationwide are screened for hepatitis B</td>
<td>94.4</td>
<td>3.2</td>
<td>0</td>
<td>2.4</td>
</tr>
<tr>
<td>All donated blood units (including family donations) and blood products nationwide are screened for hepatitis C</td>
<td>91.3</td>
<td>3.2</td>
<td>4.0</td>
<td>1.6</td>
</tr>
<tr>
<td>There is a national policy relating to the prevention of viral hepatitis among people who inject drugs</td>
<td>34.1</td>
<td>51.6</td>
<td>11.1</td>
<td>3.2</td>
</tr>
<tr>
<td>The government has guidelines that address how hepatitis A and hepatitis E can be prevented through food and water safety</td>
<td>50.0</td>
<td>39.7</td>
<td>7.9</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Figure 4. Proportion of responding Member States with national policies on injection safety in health-care settings which recommend single-use syringes and auto-disable syringes for therapeutic injections (N=109)

*Respondents could select both “single-use syringes” and “auto-disable syringes”.

77.0%). Additionally, on-the-job training was identified in 73.0% of responses and postgraduate training in 61.6%.

Sixty-four responding Member States (50.8%) reported the existence of national clinical guidelines for the management of viral hepatitis (Figure 5). Thirty-five of these 64 Member States indicated that the guidelines include recommendations for cases with HIV coinfection. Forty-four of 74 responding Member States indicated that there are national clinical guidelines for the management of HIV, which include recommendations for coinfection with viral hepatitis.

Fifty-nine responding Member States (46.8%) indicated that they have a national policy relating to screening and referral to care for hepatitis B. Forty-eight (38.1%) reported that they have such a policy for hepatitis C.

Regarding hepatitis B testing, 116 responding Member States (92.1%) indicated that people register by name for testing. One hundred and one members of that subset (87.1%) indicated that the names are kept confidential. Fifty-two responding Member States (41.3%) reported that the hepatitis B test is free of charge for all individuals. Among the 70 other Member States that answered the question, 43 (61.4%) reported that the hepatitis B test is free of charge for members of specific groups. Groups identified included blood donors, health-care workers, pregnant women, people living with HIV, patients on haemodialysis, prisoners and people who inject drugs. Sixty-one responding Member States (48.4%) reported that the hepatitis B test is compulsory for members of specific groups. Groups identified included blood donors, health-care workers, pregnant women, people living with HIV, patients on haemodialysis and prisoners.

Regarding hepatitis C testing, 109 responding Member States (86.5%) indicated that people register by name for testing. Ninety-five members of that subset (87.2%) indicated that the names are kept confidential. Forty-eight responding Member States (38.1%) reported that the hepatitis C test is free of charge for all individuals. Among the 69 other Member States that answered the question, 39 (56.5%) reported that the hepatitis C test is free of charge for members of specific groups. Groups identified included blood donors, health-care workers, pregnant women, people living with HIV, patients on haemodialysis, prisoners and people who inject drugs. Fifty-seven responding
Member States (45.2%) reported that the hepatitis C test is compulsory for members of specific groups. Groups identified included blood donors, health-care workers, pregnant women, people living with HIV, patients on haemodialysis and prisoners.

Seventy-nine responding Member States (62.7%) reported that publicly funded treatment is available for hepatitis B. Seventy-five responding Member States (59.5%) reported that publicly funded treatment is available for hepatitis C. Fourteen responding Member States reported the amount spent on publicly funded treatment for hepatitis B and hepatitis C. Details can be found in the summaries of country findings later in this report (see Argentina, Armenia, Bahrain, Croatia, Egypt, Lithuania, Myanmar, New Zealand, Pakistan, Poland, San Marino, Spain, Syrian Arab Republic and Turkey).

One hundred and three responding Member States (81.7%) reported that at least one available drug for treating for hepatitis B is on the national essential medicines list or is subsidized by the government (Table 5). The drugs most commonly reported were lamivudine, interferon alpha and pegylated interferon.

Eighty-three responding Member States (65.9%) reported that at least one available drug for treating for hepatitis C is on the national essential medicines list or is subsidized by the government. The drugs most commonly reported were ribavirin, pegylated interferon and interferon alpha.

**World Health Organization assistance**

Member States were asked to indicate areas in which they might want assistance from WHO for the prevention and control of viral hepatitis. Respondents most commonly selected the following: developing the national plan for viral hepatitis prevention and control (58.1%), estimating the national burden of viral hepatitis (54.8%) and developing education/training programmes for health professionals (54.0%) (Tables 6 and 7). Responses from individual Member States appear in Annex C.

### Table 5. Drugs for treating hepatitis B and C on national essential medicines lists or subsidized by governments

<table>
<thead>
<tr>
<th>Drugs for treating hepatitis B</th>
<th>% of Member States reporting its inclusion (N=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>66.7</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>54.0</td>
</tr>
<tr>
<td>Pegylated interferon</td>
<td>50.8</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>48.4</td>
</tr>
<tr>
<td>Entecavir</td>
<td>34.9</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>34.1</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>23.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs for treating hepatitis C</th>
<th>% of Member States reporting its inclusion (N=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin</td>
<td>57.9</td>
</tr>
<tr>
<td>Pegylated interferon</td>
<td>54.8</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>45.2</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>19.8</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>18.3</td>
</tr>
</tbody>
</table>

### Table 6. Viral hepatitis control and prevention: areas in which Member States indicated interest in receiving WHO assistance (N=126)

<table>
<thead>
<tr>
<th>Awareness-raising, partnerships and resource mobilization (first WHO strategic axis)</th>
<th>% of Member States reporting its interest (N=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing the national plan for viral hepatitis prevention and control</td>
<td>58.7%</td>
</tr>
<tr>
<td>Integrating viral hepatitis programmes into other health services</td>
<td>48.4%</td>
</tr>
<tr>
<td>Awareness-raising</td>
<td>50.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evidence-based policy and data for action (second WHO strategic axis)</th>
<th>% of Member States reporting its interest (N=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis surveillance</td>
<td>52.4%</td>
</tr>
<tr>
<td>Estimating the national burden of viral hepatitis</td>
<td>54.8%</td>
</tr>
<tr>
<td>Developing tools to assess the effectiveness of interventions</td>
<td>43.7%</td>
</tr>
<tr>
<td>Assessing the economic impact of viral hepatitis</td>
<td>49.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevention of transmission (third WHO strategic axis)</th>
<th>% of Member States reporting its interest (N=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing coverage of the birth dose of the hepatitis B vaccine</td>
<td>31.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screening, care and treatment (fourth WHO strategic axis)</th>
<th>% of Member States reporting its interest (N=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing access to treatment</td>
<td>46.0%</td>
</tr>
<tr>
<td>Improving laboratory quality</td>
<td>49.2%</td>
</tr>
<tr>
<td>Developing education/training programmes for health professionals</td>
<td>54.0%</td>
</tr>
</tbody>
</table>

* N = 113 (This response option was not included in the survey completed by Belarus, Colombia and countries in the South-East Asia Region.)
Table 7. Viral hepatitis control and prevention: areas in which Member States indicated interest in receiving WHO assistance by income group (N=126)

<table>
<thead>
<tr>
<th>Area</th>
<th>High income (N=50)</th>
<th>Upper-middle income (N=53)</th>
<th>Lower-middle income (N=50)</th>
<th>Low income (N=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Awareness-raising, partnerships and resource mobilization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developing the national plan for viral hepatitis prevention and control</td>
<td>27.5%</td>
<td>58.8%</td>
<td>73.5%</td>
<td>100%</td>
</tr>
<tr>
<td>Integrating viral hepatitis programmes into other health services</td>
<td>20.0%</td>
<td>58.8%</td>
<td>64.7%</td>
<td>61.1%</td>
</tr>
<tr>
<td>Awareness-raising</td>
<td>17.5%</td>
<td>50.0%</td>
<td>73.5%</td>
<td>83.3%</td>
</tr>
<tr>
<td><strong>Evidence-based policy and data for action</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral hepatitis surveillance</td>
<td>12.5%</td>
<td>55.9%</td>
<td>79.4%</td>
<td>83.3%</td>
</tr>
<tr>
<td>Estimating the national burden of viral hepatitis</td>
<td>25.0%</td>
<td>61.8%</td>
<td>67.6%</td>
<td>83.3%</td>
</tr>
<tr>
<td>Developing tools to assess the effectiveness of interventions</td>
<td>20.0%</td>
<td>52.9%</td>
<td>58.8%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Assessing the economic impact of viral hepatitis</td>
<td>25.0%</td>
<td>55.9%</td>
<td>70.6%</td>
<td>50.0%</td>
</tr>
<tr>
<td><strong>Prevention of transmission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increasing coverage of the birth dose of the hepatitis B vaccine</td>
<td>5.0%</td>
<td>29.4%</td>
<td>47.1%</td>
<td>66.7%</td>
</tr>
<tr>
<td><strong>Screening, care and treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increasing access to treatment</td>
<td>10.0%</td>
<td>41.2%</td>
<td>76.5%</td>
<td>77.8%</td>
</tr>
<tr>
<td>Increasing access to diagnostics</td>
<td>10.0%</td>
<td>44.1%</td>
<td>76.5%</td>
<td>94.4%</td>
</tr>
<tr>
<td>Improving laboratory quality</td>
<td>5.0%</td>
<td>43.3%*</td>
<td>75.9%*</td>
<td>92.9%*</td>
</tr>
<tr>
<td>Developing education/training programmes for health professionals</td>
<td>22.5%</td>
<td>55.9%</td>
<td>76.5%</td>
<td>83.3%</td>
</tr>
</tbody>
</table>

aN = 30 (This response option was not included in the survey completed by Belarus, Colombia, Maldives and Thailand.)

bN = 29 (This response option was not included in the survey completed by Bhutan, India, Indonesia, Sri Lanka and Timor-Leste.)

cN = 14 (This response option was not included in the survey completed by Bangladesh, Democratic People’s Republic of Korea, Myanmar and Nepal.)
Global HIV/Hepatitis Co-Infection
Hepatitis B virus coinfection in human immunodeficiency virus-infected patients: A review

Hsin-Yun Sun, Wang-Huei Sheng, Mao-Song Tsai, Kuan-Yeh Lee, Sui-Yuan Chang, Chien-Ching Hung

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Abstract

Hepatitis B virus (HBV) infection is a leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma worldwide. Due to the shared modes of transmission, coinfection with HBV and human immunodeficiency virus (HIV) is not uncommon. It is estimated that 10% of HIV-infected patients worldwide are coinfected with HBV. In areas where an HBV vaccination program is implemented, the HBV seroprevalence has declined significantly. In HIV/HBV-coinfected patients, HBV coinfection accelerates immunologic and clinical progression of HIV infection and increases the risk of hepatotoxicity when combination antiretroviral therapy (cART) is initiated, while HIV infection increases the risk of hepatitis events, cirrhosis, and end-stage liver disease related to chronic HBV infection. With the advances in antiviral therapy, concurrent, successful long-term suppression of HIV and HBV replication can be achieved in the cART era. To reduce the disease burden of HBV infection among HIV-infected patients, adoption of safe sex practices, avoidance of sharing needles and diluent, HBV vaccination and use of cART containing tenofovir disoproxil fumarate plus emtricitabine or lamivudine are the most effective approaches. However, due to HIV-related immunosuppression, using increased doses of HBV vaccine and novel approaches to HBV vaccination are needed to improve the immunogenicity of HBV vaccine among HIV-infected patients.

Key words: Viral hepatitis; Seroepidemiology; Sexually transmitted diseases; Nucleoside reverse-transcriptase inhibitor; Vaccination

Core tip: We provide an updated review of hepatitis B virus (HBV) coinfection among human immunodeficiency virus (HIV)-infected patients, focusing on the epidemiology, management and prevention of HBV infection. The mutually detrimental interactions between HBV and HIV are discussed. Three updated treatment guidelines for the management of patients with HIV/HBV coinfection are summarized. We also review the published data on the effectiveness or efficacy of HBV vaccination studies, with emphasis on the different approaches to improvement of the serologic responses to HBV vaccination.
conventional HBV vaccine among HIV-infected patients.


INTRODUCTION

Hepatitis B virus (HBV) infection is a leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) worldwide[1]. Due to the shared modes of transmission, coinfection with HBV and human immunodeficiency virus (HIV) is not uncommon. It is estimated by the Joint United Nations Program on HIV/AIDS that 10% of 33 million HBV-infected patients has concurrent chronic HBV infection[2]. The prevalence or incidence of HBV infection among HIV-infected patients may vary widely with risks for HIV and HBV transmission, implementation of HBV vaccination programs, and the geographic regions with different levels of endemicity of HBV infection in the general population[2]. HBV and HIV have a mutually detrimental impact in that HIV infection accelerates HBV-related liver damage, leading to earlier cirrhosis and end-stage liver disease[3-4], and the presence of HBV infection complicates the management of HIV infection, impairs CD4 recovery, accelerates immunologic progression, and increases the morbidity and mortality of HIV-infected patients[4-8]. In this article we review the epidemiology, interactions between HIV and HBV, and management and prevention of HBV infection in HBV-infected patients in the era of combination antiretroviral therapy (cART) that often contains 1 or 2 nucleos(t)ide reverse-transcriptase inhibitors (NRTIs) that are active against HBV as well as HIV.

EPIDEMIOLGY OF HEPATITIS B VIRUS COINFECTION IN HIV-INFECTED PATIENTS

Epidemiology of hepatitis B virus in HIV-infected populations

According to the World Health Organization[9], the world can be divided into 3 areas based on the levels of endemicity of HBV infection that are defined by the prevalence of chronic HBV infection: low endemicity, < 2%; intermediate endemicity, 2%-8%; and high endemicity, > 8%. In areas of high endemicity of chronic HBV infection, the transmission of HBV mainly occurs through perinatal transmission (predominantly in East and Southeast Asia) or in young children through close household contact or through medical or traditional scarification procedures (predominantly in Africa)[2,9]. Given the shared transmission routes of HIV and HBV, coinfection with HBV and HIV is common. Approximately 10% of the HIV-infected population in Asia and Africa has concurrent chronic HBV infection with coinfection more common in areas of high prevalence for both viruses[2,10]. The rate can be as high as 25% in countries where the viruses are highly endemic[10]. 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[10]. In Western Europe and the United States, the overall prevalence of chronic HBV infection among HIV-infected persons is estimated to be 6%-14%[11-13], including 4%-6% of HIV-infected heterosexuals[11,12], 9%-17% of HIV-infected men who have sex with men (MSM)[11,12], and 7%-10% of injecting drug users[11,13]. Previous studies have shown that seropositivity for syphilis and HIV infection, the number of lifetime sexual partners, and receptive anal intercourse are associated with increased risk of HBV infection in MSM[14-16].

Seroprevalence of hepatitis B virus before and after implementation of vaccination

In a recent review of global epidemiology of HBV infection[17], the prevalence of HBV infection has been shown to be decreasing, particularly evident in central sub-Saharan Africa, tropical and central Latin America, southeast Asia and central Europe. Expanded programs of immunization against HBV have been proposed to significantly contribute to such an observation[17]. In areas that implemented universal neonatal HBV vaccination program such as Taiwan and Alaska, the incidence of acute HBV infection[18,19], prevalence of chronic HBV infection[19,20], and incidence of HCC in children have significantly declined[19,20], so has mortality due to chronic liver disease as well as HCC in persons aged 5-29 years[22]. Recent studies that evaluated the long-term impact of universal neonatal HBV vaccination on HBV seroprevalence among HIV-infected populations and persons at high risk for HIV transmission in Taiwan also demonstrated decreasing trends in chronic HBV infection in those persons born after implementation of neonatal HBV vaccination and catch-up vaccination programs (Figure 1)[23,24]. The prevalence of hepatitis B surface antigen (HBsAg) positivity in HIV-infected patients born after July 1984, when the nationwide HBV vaccination program in Taiwan was initially implemented to vaccinate newborns of HBsAg-positive mothers, has declined to 3.3% vs 20.3% in those born before July 1984 (P < 0.05)[20]. Furthermore, the prevalence of HBsAg positivity was similar between HIV-infected MSM and HIV-uninfected MSM (3.7% vs 2.4%) who were born in the era of universal HBV vaccination (in or after 1986), despite the fact that HIV-infected MSM were more likely to have syphilis (21.2% vs 2.8%) and had a higher prevalence of core antibody (anti-HBc) (26.3% vs 19.6%), while HIV-infected MSM born in 1984-1985 had a significantly higher prevalence of HBsAg positivity than HIV-
in Vietnam and Laos a recombinant of genotypes A, C, and G, and was found graphic and ethnic distribution. Genotype I is known as genotypes, I and J, have yet to establish characteristic geo-
America. Unlike other genotypes, the 2 newly identified many, and the United States; and genotype H in Central and South America; genotype G in France, Ger-
ern Europe, and West Africa; genotypes B and C in Asia; and genotype D in Africa, eastern Europe, the Mediter-
region, and India. Other HBV genotypes are less prevalent, with genotype E in West Africa, genotype F in Central and South America; genotype G in France, Ger-
ymany, and the United States; and genotype H in Central America. Unlike other genotypes, the 2 newly identified genotypes, I and J, have yet to establish characteristic geo-
graphic and ethnic distribution. Genotype I is known as a recombinant of genotypes A, C, and G, and was found in Vietnam and Laos[27]. Genotype J was first identified in Ryukyu Island, Japan[28].

Figure 1 Seroprevalence of hepatitis B virus infection in human immu-
nodeficiency virus-infected patients according to birth year in Taiwan. The seroprevalence declined significantly from 20.3% in those who were born before in 1984 (n = 3034) when the neonatal hepatitis B virus (HBV) vaccina-
tion was provided to newborns whose mothers tested positive for HBV surface antigen (HBsAg) to 3.7% in those who were born after 1986 (n = 507) when universal neonatal vaccination and catch-up vaccination were implemented[23,24].

infected MSM born in or after 1986 (7.8% vs 3.7%)[24]. Additionally, syphilis and positive anti-HCV were significantly associated with HBsAg positivity in HIV-infected patients born in the era of universal HBV vaccination.

Genotype distribution of HBV and its impact
Based on the extent of genetic diversity in HBV se-
quencies, HBV can be divided into 10 genotypes (A to J) and several subtypes[25,28]. Genotypes A to D are more prevalent, with genotype A in sub-Saharan Africa, North-
eral Europe, and West Africa; genotypes B and C in Asia; and genotype D in Africa, eastern Europe, the Mediter-
anean region, and India. Other HBV genotypes are less prevalent with genotype E in West Africa; genotype F in Central and South America; genotype G in France, Ger-
many, and the United States; and genotype H in Central America. Unlike other genotypes, the 2 newly identified genotypes, I and J, have yet to establish characteristic geo-
graphic and ethnic distribution. Genotype I is known as a recombinant of genotypes A, C, and G, and was found in Vietnam and Laos[27]. Genotype J was first identified in Ryukyu Island, Japan[28].

Many retrospective and prospective studies have been conducted to determine the impact of HBV genotypes on disease outcomes among the general population. Al-
though some controversial results were observed likely due to the transmission route and age when HBV infec-
tion occurs, which are closely correlated with seropreva-
ience of HBV in the geographic areas studied, several studies suggested that patients infected with genotypes C and D had lower rates of seroconversion than patients infected with genotypes A and B, which is likely cor-
related with the relatively delayed onset of spontaneous HBV envelope antigen (HBsAg) seroconversion and HBsAg seroclearance[29,31]; infection with genotype C was associated with an increased risk of HCC than with genotype B in retrospective, prospective, and case-control studies[32-34]; and patients infected with genotype C tended to have higher HBV viral load and higher frequency of basal core promoter A1762T/G1764A mutation than those with genotype B[34,35,36]. In addition, although HBV genotyping before antiviral therapy is not recommended by current guidelines[38], the impact of HBV genotypes on clinical responses to interferon (IFN) have been de-
scribed. First, in HBsAg-positive patients receiving stan-
dard IFN-α, the sustained virologic response rate was higher in patients infected with genotypes A and B than those with genotypes C and D[39,40]. Even among HBsAg-
negative patients treated with IFN-α, HBsAg clearance was significantly higher in patients with genotype A (20%) than those with genotypes B (6%), C (9%), and D (6%)[41]. While Chien et al[42] first reported that the sustained re-
response rate to lamivudine (LAM) was much higher in patients with genotype B than those with genotype C, subsequent studies demonstrated similar therapeutic re-
sponses or risk of emergence of LAM resistance among patients infected with different HBV genotypes[44-46]. No statistically significant difference was observed in response to adefovir dipivoxil (ADV)[47] and telbivudine (LtD)[48], either.

In HIV/HBV-coinfected patients, HBV genotype A is the most prevalent in Western countries[49], although the distribution of HBV genotypes might also vary according to the risk factors, geographic origin, and coinfection with other hepatitis viruses[50,51]. The impact of HBV genotypes on the course of HBV infection observed included more advanced fibrosis in patients infected with non-A genotypes[52], especially with genotype G[53], although a recent study with more than 5 years of follow-up demonstrated that infection with HBV geno-

type G was not significantly associated with severe liver disease and had no impact on fibrosis progression[53]. In another study in HIV/HBV-coinfected patients receiv-
ing long-term LAM-containing ART by Sheng et al[54], patients coinfected with genotype B were more likely to experience acute exacerbations of hepatitis, HBsAg se-
roconversion, LAM resistance, and liver disease-related death than those coinfected with genotype C.

INTERACTIONS BETWEEN HBV AND HIV IN THE ERA OF COMBINATION ANTIRETROVIRAL THERAPY

Impact of HBV coinfection on HIV infection
It is suggested that a persistent state of immune activa-
tion in patients with chronic HBV infection could up-
regulate HIV replication[55], and an in vitro study showed that HBV X protein could induce ongoing HIV replication and long-term repeated transcription of HIV by syn-
ergizing with kappa B-like enhancer and T-cell activation signals[56,57]. Early prospective cohort studies of HIV/ HBV-coinfected patients revealed a 3.6 to 6.8-fold relative risk of progression to AIDS compared to those without coinfection[58,59]. However, other reports failed to confirm
these results\(^{[34-36]}\). To minimize the influence of duration of HIV infection, a prospective observational cohort of adult patients with primary HIV infection (seroconversion window \(≤ 6\) mo)\(^{[7]}\) has shown that HBV coinfection (adjusted hazards ratio, 3.46; 95%CI: 1.16-10.32) was an independent predictor of immunologic progression that was defined as the occurrence of a CD4 cell count \(< 350\) cells/\(\mu\)L 3 mo or more after diagnosis of primary HIV infection\(^{[7]}\). Chun et al\(^{[8]}\) examined the interactions of HBV and HIV using the composite endpoint of AIDS-defining illnesses and death among HIV-infected individuals who had a seroconversion window of \(≤ 3\) years in a large cohort, which revealed that the hazards ratio for an AIDS or death event was almost double (adjusted hazards ratio, 1.80; 95%CI: 1.20-2.69) for those with HBV coinfection. The adverse impact of HBV on HIV was also recently demonstrated by the Swiss HIV Cohort Study\(^{[9]}\), in which patients who tested positive for HBsAg had significantly impaired CD4 recovery during the first 3 years of cART despite similar virologic effectiveness of antiretroviral therapy compared to patients without HBV infection \([504\text{ cells/\(\mu\)L (95%CI: 496-511) vs 449 cells/\(\mu\)L (95%CI: 428-469)]\).

**Impact of HIV infection on HBV infection**

Compared to HIV-uninfected subjects, patients with HIV infection have a higher risk of chronicity after acute HBV infection\(^{[4]}\). A higher proportion of chronic HBs antigenemia has been found in HIV-infected patients because HIV destroys CD4 cells which compromises host immunity against HBV\(^{[5]}\). A previous study on pregnant women with chronic HBV infection in Zambia showed that those with HIV coinfection had a 3-fold higher HBeAg-positive rate than HIV-uninfected pregnant women (25% vs 8.5%, \(P < 0.05\))\(^{[51]}\). Another similar study showed that HBV DNA was detected in 26.7% of pregnant women with HIV/HBV coinfection vs 9.4% of those with HBV infection alone \((P = 0.06)\)\(^{[52]}\). Clinical observational studies have demonstrated that HIV/HBV-coinfected patients may have faster progression of hepatic fibrosis and a higher risk of cirrhosis, end-stage liver disease, and HCC than HBV-monoinfected patients\(^{[4,6,53]}\). Similarly, compared with HIV-monoinfected patients, those with HIV/HBV coinfection, especially HBV genotype B, had a higher risk of acute hepatitis, hepatic decompensation, and liver-related mortality\(^{[4,34,64]}\). Superinfection or coinfection with hepatitis D virus may further exacerbate the complications in patients with HIV/HBV coinfection, which has recently been observed to increase in incidence in an area which was used to be hyperendemic for HBV infection in the general population\(^{[7,54]}\).

### MANAGEMENT OF HBV COINFECTION IN HIV-INFECTED PATIENTS

#### Interferon and nucleos(t)ide reverse-transcriptase inhibitors

The goal of antiviral therapy for HBV is to suppress HBV DNA replication, reduce necroinflammatory activity, and prevent progression to cirrhosis and HCC. At present, seven therapeutic agents, including IFN, pegylated-interferon (peg-IFN), LAM, emtricitabine (FTC), ADV, entecavir (ETV), LdT and tenofovir disoproxil fumarate (TDF) are approved by the US Food and Drug Administration (FDA) for the treatment of chronic HBV infection\(^{[69]}\). The characteristics of anti-HBV therapeutic agents are shown in Table 1\(^{[70-81]}\). LAM, FTC and TDF have both anti-HBV and anti-HIV activities. According to current treatment guidelines for HIV-infected adult patients, when patients meet the criteria to start cART, 2 agents active against HBV should be included and the most commonly chosen agent is TDF in combination with either FTC or LAM\(^{[82-84]}\). If TDF is not available or not well tolerated, either ADV or ETV in combination with either FTC or LAM are recommended (Table 2)\(^{[85-88]}\). CART regimens containing LAM as the only agent with anti-HBV activity should be avoided due to the high risk of emergence of HBV with LAM resistance during therapy\(^{[85-89]}\).

**IFN**

Peg-IFN is superior to conventional IFN in the treatment of chronic HBV infection because of its long-acting characteristics and weekly administration\(^{[54]}\). The response rate of HBeAg seroconversion and suppression of HBV replication to peg-IFN with or without LAM among HBV-monoinfected patients ranges from 24% to 32%\(^{[90,91]}\), compared with 0% to 20% among HBV/HIV-coinfected patients\(^{[71]}\). Nevertheless, IFN should be avoided in patients with low CD4 counts due to significant lymphocytopenia related to IFN\(^{[92]}\). As IFN has potential anti-HIV effects\(^{[93]}\) without resulting in emergence of IFN-resistant HIV\(^{[91]}\), IFN can be used in those who may need anti-HBV therapy but not anti-HIV therapy (e.g., CD4 count \(\geq 500\) cells/\(\mu\)L). However, IFN is contraindicated in patients with decompensated liver disease because of concerns about hepatic failure and deaths during IFN treatment\(^{[90]}\).

**Lamivudine and emtricitabine**

LAM has activity against both HIV and HBV at the daily dose of 300 mg and 100 mg, respectively. This agent is well tolerated with few adverse effects\(^{[96]}\). The rates of HBeAg seroconversion and HBV viral suppression (HBV DNA < 400 copies/mL) among HBV/HIV-coinfected patients receiving LAM 300 mg daily for 1 year ranged from 22% to 35% and 40% to 84%, respectively\(^{[98,99]}\). However, the genetic barrier to LAM resistance is low and LAM resistance rates may be as high as 50% after 2 years and 90% after 4 years of LAM therapy in HIV/HBV-coinfected patients\(^{[96-99]}\).

FTC is a cytosine analogue that is structurally similar to LAM, and the daily dose for both HIV and HBV is 200 mg. The resistance profile and efficacy of FTC against HIV and HBV are also similar to LAM\(^{[90,96]}\). After 2 years of treatment with FTC, 53% of HBV-monoinfected...
fected patients had undetectable serum HBV DNA (<4700 copies/mL), 33% seroconverted to anti-HBe, and 85% had normal alanine aminotransferase (ALT) levels. The rate of mutations in the YMDD motif was 18% at 2 years of FTC treatment\(^1\). In a small cohort of 16 HBV/HIV-coinfected patients treated with TDF and FTC for 48 wk, 94% patients had undetectable serum HBV DNA and 14% of them seroconverted to anti-HBe\(^1\).

LAM may promote the selection of resistant mutations in the HBV DNA polymerase gene at the YMDD motif, rtM204V/I, which predisposes to FTC and LdT cross-resistance\(^{101}\). Furthermore, the common LAM-resistant mutations, rtL180M and rtM204V, are 2 of the 3 major mutations required for the development of ETV resistance. In addition, the rtA181T/V mutation confers cross-resistance to ADV\(^{102}\). Therefore, the combination of LAM with other anti-HBV agents without cross-resistance as part of antiretroviral therapy is the most effective approach to prevent against emergence of LAM-resistant HBV strains among HIV/HBV-coinfected patients.

### Table 1. Characteristics of antiviral drugs for chronic hepatitis B in human immunodeficiency virus-infected patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Interferon alfa-2b(^1)</th>
<th>Pegylated interferon alfa-2a(^1)</th>
<th>Lamivudine</th>
<th>Etricitabine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir disoproxil fumarate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiviral effect</td>
<td>Immune modulation</td>
<td>Immune modulation</td>
<td>Interference of HBV DNA synthesis</td>
<td>Interference of HBV DNA synthesis</td>
<td>Interference of HBV DNA synthesis</td>
<td>Interference of HBV DNA synthesis</td>
<td>Interference of HBV DNA synthesis</td>
<td></td>
</tr>
<tr>
<td>HIV-1 activity</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No, at low dose(^2)</td>
<td>Yes</td>
<td>No(^2)</td>
<td>Yes</td>
</tr>
<tr>
<td>Dosage and administration</td>
<td>10 million IU SC or IM 3 times a week</td>
<td>180 mg SC once a week</td>
<td>300 mg/d oral</td>
<td>200 mg/d oral</td>
<td>10 mg/d oral</td>
<td>0.5 mg/d oral</td>
<td>600 mg/d oral</td>
<td>300 mg/d oral</td>
</tr>
<tr>
<td>Defined treatment duration</td>
<td>48 wk</td>
<td>48 wk</td>
<td>Indefinite</td>
<td>Indefinite</td>
<td>Indefinite</td>
<td>Indefinite</td>
<td>Indefinite</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Undetectable HBV DNA</td>
<td>-</td>
<td>-</td>
<td>40%-84% at 1 yr</td>
<td>53% at 2 yr</td>
<td>8.6% and 5.7% at 36 wk and 48, respectively(^a)</td>
<td>38% by the end of study (mean follow-up, 74 wk)(^b)</td>
<td>-</td>
<td>Up to 91% at 5 yr</td>
</tr>
<tr>
<td>HBV seroconversion</td>
<td>0%-20%</td>
<td>0%-20%</td>
<td>22%-35% at 1 yr</td>
<td>14% at 48 wk</td>
<td>9% at 144 wk</td>
<td>-</td>
<td>-</td>
<td>50% of TDF use; 57% of TDF plus FTC use at 5 yr</td>
</tr>
<tr>
<td>Tolerability</td>
<td>Poor</td>
<td>Poor</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Major adverse events</td>
<td>Leukopenia, depression</td>
<td>Leukopenia, depression</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Viral resistance barrier</td>
<td>No</td>
<td>No</td>
<td>Low (50% at 2 yr and 90% at 4 yr)</td>
<td>Intermediate (18% at 2 yr)</td>
<td>Good Nephrotoxicity (3%)</td>
<td>Excellent</td>
<td>Good</td>
<td>Good Nephrotoxicity (1%-3%)</td>
</tr>
<tr>
<td>HBV resistance mutations</td>
<td>No</td>
<td>No</td>
<td>M204I/V</td>
<td>M204I/V(^1)</td>
<td>M204I/V(^2)</td>
<td>M204I/V(^2)</td>
<td>M204I(^3)</td>
<td>A194T(^3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L180M</td>
<td>L180M</td>
<td>L180M</td>
<td>L180M</td>
<td>L180M</td>
<td>A181T/V</td>
<td>A181T/V</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A181T/V</td>
<td>A181T/V</td>
<td>A181T/V</td>
<td>A181T/V</td>
<td>A181T/V</td>
<td>A181T/V</td>
<td>N236T</td>
</tr>
<tr>
<td>Cross-resistance to LAM</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Interaction with other antiretrovirals</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Zidovudine; stavudine(^c)</td>
<td>Didanosine; aztalanavir(^d)</td>
</tr>
</tbody>
</table>

\(^1\)HBeAg positive subjects with CD4 cell counts of > 350 cells/μL and aminotransferase levels elevated to at least twice the upper limit of normal would probably achieve the greatest benefit from IFN-alfa therapy\(^{70,71}\). While ADV (20 mg/d) does have minimal HIV-1 activity, the development of HIV-1 resistance mutations has not been demonstrated at low dose adefovir (10 mg/d)\(^78\). TDF mutations have not been clearly associated with decreased anti-HBV efficacy\(^70\). Presence of several mutations is necessary to decrease efficacy for ETV at a dose of 1 mg/d; 3 mg/d for LAM-resistant HBV infection; 1 LdT is a thymidine analogue that might interact with zidovudine or stavudine\(^79\). TDF can interact with didanosine by increasing the concentration of didanosine and impairing immunologic response\(^70\). It also decreases the concentration of atazanavir sulfate\(^80\). LdT showed a potent anti-HBV activity in HIV-1-positive, hepatitis B e antigen-positive patients with high HBV viremia in a case report. However, a transient reduction in HIV-1 RNA between 2 and 3 log10 copies/mL after 24 wk of telbivudine therapy was found in 2 of 3 patients although no genotypic resistance mutations to anti-HIV-1 were found\(^81\). In another study, no significant decline in HIV-1 RNA load or in the selection of genotypic or phenotypic resistance in HIV-1 RT was observed in 2 patients who received LdT treatment\(^82\). In vitro virologic analyses demonstrated that LdT had no activity against wild-type HIV and drug-resistant variants; In a prospective randomized, double-blind, placebo-controlled trial of 10 mg/d ADV vs 300 mg/d of TDF in subjects with HBV and HIV coinfection on stable ART, with serum HBV DNA > 10000 copies/mL, and plasma HIV-1 RNA < 10000 copies/mL, the mean time-weighted average change in serum HBV DNA from baseline to week 48 was -4.44log10 copies/mL for TDF and -3.21log10 copies/mL for ADV\(^83\). In a small cohort of 13 patients with positive HBeAg and detectable HBV DNA who had received > 6 mo of TDF/FTC therapy, add-on ETV to TDF/FTC-experienced patients achieved undetectable HBV DNA load in 38% and normal ALT levels in 8 (62%)\(^84\). ADV: Adefovir dipivoxil; ETV: Entecavir; FTC: Etricitabine; HBV: Hepatitis B virus; HBeAg: HBV envelope antigen; IM: Intramuscularly; LAM: Lamivudine; LdT: Telbivudine; SC: Subcutaneously; TDF: Tenofovir disoproxil fumarate.
Table 2  Comparisons regarding the use of anti-hepatitis B virus agents in human immunodeficiency virus-infected patients among the different guidelines

<table>
<thead>
<tr>
<th>Agents for HBV treatment only</th>
<th>Agents for HBV/HIV treatment</th>
<th>Timing of cART initiation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHHS 2013[82] ADV, ETV, or LdT</td>
<td>TDF can safely be used: TDF/LAM-containing cART or TDF/FTC-containing cART</td>
<td>HBV: NA</td>
<td>CART may attenuate liver disease progression by preserving or restoring immune function and reducing HIV-related immune activation and inflammation</td>
</tr>
<tr>
<td>EACS 2013[83] ADV and LdT</td>
<td>LAM-naive cART including TDF/ LAM or FTC LAM-experienced Add or substitute 1 NRTI with TDF as part of cART HBV treatment indicated Early ART including TDF/FTC or LAM PEF-IFN (if genotype A, high ALT, low HBV DNA)</td>
<td>HBV: HBV DNA &gt; 2000 IU/mL; significant liver fibrosis (F2-F4) even when HBV-DNA is below 2000 IU/mL and liver enzymes are not elevated</td>
<td>The optimal treatment duration for nucleos(t)ide analogues with anti-HBV activity has not yet been determined and experts recommend life-long therapy if anti-HBV nucleos(t)ides are given as part of ART</td>
</tr>
<tr>
<td>BHIVA 2013[84] NA</td>
<td>CD4 count &gt; 500 cells/μL: TDF/FTC-cART Unwilling or unable to receive TDF/FTC: ADV or 48 wk of PEG-IFN or cART CD4 count &lt; 500 cells/μL: Wild-type HBV: TDF/ FTC-cART or TDF/LAM-cART LAM/FTC-resistant HBV or HIV: TDF as the sole anti-HBV active agent TDF is contraindicated: ETV plus cART</td>
<td>HBV: HBV DNA &gt; 2000 IU/mL; more than minimal fibrosis on liver biopsy (Metavir &gt; F2 or Ishak &gt; S2) or indicative of &gt; F2 by TE (FibroScan &gt; 9.0 kPa) regardless of HBV DNA</td>
<td>At least 2 baseline HBV DNA measurements 3 to 6 mo apart to guide initiation of therapy</td>
</tr>
</tbody>
</table>

ADV: Adefovir dipivoxil; ALT: Alanine aminotransferase; cART: Combination antiretroviral therapy; ETV: Entecavir; FTC: Emtricitabine; HBV: Hepatitis B virus; LAM: Lamivudine; LdT: Telbivudine; NA: Not available; Peg-IFN: Pegylated interferon; TDF: Tenofovir disoproxil fumarate; TE: Transient elastography.

Adefovir dipivoxil

ADV had sustained antiviral activity against LAM-resistant HBV strains in 29 HIV/HBV-coinfected patients throughout 144 wk of treatment, with 25% achieving undetectable HBV DNA and 9% HBeAg seroconversion[103]. In a prospective randomized controlled study of 52 HBV/HIV-coinfected patients, the anti-HBV activity of ADV was comparable to TDF (average change in serum HBV DNA from baseline to week 48, -4.44 log copies/mL for TDF and -5.21 log copies/mL for ADV)[78]. The incidence of HBV resistant to ADV is less frequent than that to LAM[104,105]. Mutations at rtN236T and rtA181V, which confer resistance to ADV, occurred in 29% of the patients receiving 5 years of ADV treatment[105]. These mutations are potentially cross-resistant to TDF, and rtA181V is partially cross-resistant to LAM[102]. The rate of ADV resistance is markedly reduced when ADV is added to LAM rather than used as sequential monotherapy in patients with LAM-resistant HBV infection[106,107]. In addition, no genotypic resistance
of HIV to ADV was found after 3 years of therapy\[108\].

**Tenofovir disoproxil fumarate**

TDF is a potent agent and effective against LAM-resistant HBV\[108\] and ADV-resistant HBV\[109\]. In a study that included 110 HIV/HBV-coinfected patients with 57% being HBeAg-positive at baseline, TDF-containing cART led to high rates of HBeAg seroconversion after 5 years of treatment: 21% in the LAM group, 50% in the TDF group and in 57% in the TDF plus FTC group\[114\]. During a median observation period of 83 mo, 91% achieved suppression of HBV replication\[110\]. In a meta-analysis of available data from 23 studies that included 550 HBV/HIV-coinfected patients treated with TDF\[111\], the overall proportion achieving suppression of HBV replication was 57.4%, 79.0% and 85.6% at 1, 2 and 3 years, respectively, and prior or concomitant 3TC or FTC did not impact the virologic response of HBV infection to TDF; furthermore, virologic rebound on TDF treatment was rare. Those findings of dual anti-HBV and anti-HIV activity and a high genetic barrier to resistance have made TDF an attractive option for the treatment of both viruses in patients with HIV/HBV coinfection. However, TDF may cause renal impairment (1%-3%), which includes Fanconi’s syndrome, tubular dysfunction, increases in serum creatinine, and, in rare cases, acute renal failure. Therefore, regular monitoring of renal function in patients receiving TDF-containing regimens is advised\[112\].

**Entecavir**

ETV is a guanosine analogue that is highly active against wild-type HBV at a daily dose of 0.5 mg and LAM-resistant HBV at 1 mg. It has been demonstrated that ETV reduced HBV DNA by 4.20 log10 copies/mL in HIV/HBV-coinfected patients with HBV resistant to LAM at 48 wk of therapy\[113\]. ETV has been found to be associated with a 1-log10 reduction of plasma HIV RNA load and mutation in HIV polymerase (rtM184V) that confers resistance to both LAM and FTC\[114\]. ETV resistance is the result of 3 major mutations, rtL180M, rtM204V and either rtT184G/S, rtS202I or rtM250V. The first 2 mutations also confer resistance to LAM\[113\]. Therefore, ETV is not recommended as monotherapy in HIV/HBV-coinfected patients.

**Telbivudine**

Data on the antiviral effect of LdT against HBV in HIV/HBV-coinfected patients are sparse. In HIV-monoinfected patients, LdT decreased HBV DNA levels by 6.45 log10 copies/mL in HBeAg-positive and by 5.23 log10 copies/mL in HBeAg-negative patients\[88,116,117\]. LdT has greater anti-HBV efficacy than LAM or ADV, and selects for resistance mutations at an intermediate rate. Resistant mutations were selected in 11% of HBeAg-negative and 25% of HBeAg-positive patients after 2 years of treatment with LdT\[104\]. In an in vitro and human study, LdT was not shown to exert antiviral activity against HIV-1\[17\], while a transient reduction in HIV-1 RNA between 2 and 3 log10 copies/mL after 24 wk of telbivudine therapy was seen in 2 of 3 patients without showing genotypic resistance mutations to antiretrovirals\[80\].

**Impact on progression to end-stage liver diseases or regression of cirrhosis and reduced risk of recurrent HCC**

Serum HBV DNA level is a marker of viral replication and efficacy of antiviral treatment in individuals with chronic HBV infection. Maintaining suppression of HBV replication using anti-HBV therapy may reduce the progression of liver fibrosis, reverse advanced fibrosis, reduce the development of cirrhosis, and prevent hepatic decompensation and HCC in patients with advanced fibrosis or cirrhosis. In a prospective cohort study of 3653 HBSAg-positive participants (aged 30-65 years) in Taiwan\[118\], the incidence of HCC increased with increasing serum HBV DNA levels at study entry in a dose-response relationship, from 108 per 100000 person-years for patients with an HBV DNA level of < 300 copies/mL to 1152 per 100000 person-years for those with an HBV DNA level of 1 million copies/mL or greater; the corresponding cumulative incidence rates of HCC were 1.3% and 14.9%, respectively. A high serum HBV DNA level (⩾ 10000 copies/mL) is a significant risk predictor of HCC independent of HBeAg, serum alanine aminotransferase level, and cirrhosis of the liver\[119\].

In a systemic review of 21 studies conducted among 3881 anti-HBV NRTI-treated (for at least 24 mo or more) and 534 untreated patients, HCC developed less frequently in anti-HBV treatment than in those with virologic breakthrough or no response (2.3% vs 7.5%, P < 0.001)\[119\]. In a recent report conducted in an HIV-uninfected population, long-term ETV treatment reduced the incidence of HCC in HBV-infected patients and the treatment effect was greater in patients at higher risk of HCC\[120\]. These findings provide supportive evidence to the well-known association between the biologic gradients of HBV DNA levels and risk of HCC\[118\].

**Management of lamivudine resistance**

If LAM-resistant HBV is present, LAM can be continued for the management of HIV as LAM-resistant HIV has reduced viral fitness in vitro and slower progression in vivo. TDF, ADV and ETV are active against LAM-resistant HBV\[88,103,108,109,113,121\]. A previous study comparing the efficacy of TDF and LAM combination therapy vs TDF after LAM failure for the treatment of HBV in HIV/HBV-coinfected patients revealed no statistically significant difference in terms of HBeAg loss or HBV suppression\[122\]. ETV is less preferred because LAM resistance predisposes to ETV resistance\[115\]. However, a small cohort of 13 patients with positive HBeAg and detect-
able HBV DNA who had received > 6 mo of TDF/FTC therapy, add-on ETV to TDF/FTC-experienced patients achieved undetectable HBV DNA load in 4 (30%) and normal ALT levels in 8 (62%)\(^\text{[76]}\).

During anti-HBV treatment, monitoring of liver functions (alanine aminotransferase, aspartate aminotransferase, and total bilirubin) is advised every 3 to 6 mo and serum HBV DNA levels every 6 to 12 mo\(^\text{[83]}\). The presence of detectable serum HBV DNA with the use of sensitive assays after 24 wk of therapy suggests a suboptimal response or treatment failure, and add-on therapy with agents without cross-resistance should be considered at this stage\(^\text{[102]}\).

**Management of end-stage liver disease**

The advances in therapy for HIV infection have prolonged the life expectancy of HIV-infected patients receiving cART\(^\text{[123]}\), which has led to a greater need for treating HBV-related chronic complications. The 2 major adverse outcomes in patients with chronic HBV infection are cirrhosis and HCC, both of which can lead to liver-related death\(^\text{[124]}\). A low CD4 cell count in HIV/HBV-coinfected patients has been associated with increased risk of cirrhosis and HCC\(^\text{[10,125,126]}\). Overall, less treatable cases and lower survival rates have been described in HIV-infected patients following the diagnosis of HCC\(^\text{[46]}\). New treatment strategies are available for advanced HCC, but data are limited for HIV/HBV-coinfected patients. Case reports suggest some benefit from sorafenib treatment in HIV/HBV-infected patients with newly diagnosed HCC\(^\text{[127-130]}\). For most patients with end-stage liver disease, orthotopic liver transplantation remains the only therapeutic option. Accumulated experience in North America and Europe indicated that the patient and graft survival rates in selected HIV-infected recipients of liver transplants were almost similar to those of HIV-uninfected recipients\(^\text{[131,132]}\). Therefore, HIV infection by itself is not a contraindication to liver transplantation. Together with screening of patients at risk and an early diagnosis, aggressive treatment of HCC, including treatment of relapses and maintenance of HIV and HBV suppression, are the best management strategies for HCC in people living with HIV. All patients should receive anti-HBV NRTIs, and hepatitis B immune globulin indefinitely post-transplantation with a decrease in dose frequency after 12 mo\(^\text{[131]}\). It is recommended that patients with liver disease should start referral and workup for liver transplantation if they become symptomatic with liver disease\(^\text{[133]}\), which includes the development of hepatic encephalopathy, ascites, variceal bleeding, or liver dysfunction with albumin < 3 g/dL and prolongation of prothrombin time by > 5 s\(^\text{[133]}\).

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**PREVENTION OF HBV INFECTION AMONG HIV-INFECTED PATIENTS**

Although the modes of transmission of HBV are the same as those for HIV, HBV is transmitted more efficiently than HIV\(^\text{[134,135]}\). Other than adoption of safe sex practices and avoidance of sharing needles and diluent, HBV vaccination remains the most effective approach to prevent against HBV infection and its chronic consequences. According to the HIV treatment guidelines by the US Department of Health and Human Services\(^\text{[82]}\), pre-vaccination screening should include HBsAg, anti-HBsAg antibody (anti-HBs), and anti-HBc. Serological markers may be time-dependent variables in HIV-infected patients, which are associated with host immunity and viral activities; and, therefore, periodic measurements are recommended\(^\text{[11]}\). The presence of anti-HBs at levels of > 10 international units/L (IU/L) is consistent with seroprotection and at levels of > 100 IU/L is associated with long-term protection\(^\text{[116,117]}\). Anti-HBs antibody titers decrease over time and can fall below protective concentrations.

HBV vaccine series should be administered on the standard schedule (3 × 20-μg doses, administered intramuscularly at 0, 1, and 6 mo) if HBsAg, anti-HBs antibody, and anti-HBc antibody are all negative. Approximately 90% to 95% of healthy adults have protective anti-HBs titers after standard doses of HBV vaccines\(^\text{[138,139]}\). However, only 17.5% to 71% of HIV-infected patients could retain protective anti-HBs\(^\text{[137,139-148]}\) (Table 3). In HIV-infected patients, variable immune responses to HBV vaccine have been shown to be associated with dysfunction of CD4 T cells, specific B-cell defects, and hyper-immune activation status and genes within the human leukocyte antigen complex\(^\text{[149-151]}\).

In HIV-infected patients, those with CD4 cell counts ≥ 350 cells/μL had a higher seroconversion rate (anti-HBs ≥ 10 IU/L) than those with CD4 cell counts < 350 cells/μL (39.3% vs 26.5%)\(^\text{[144]}\). Failure of anti-HBs seroconversion and lower anti-HBs titers after HBV vaccination in HIV-infected patients have been shown to be associated with detectable plasma HIV RNA, lower CD4 cell counts\(^\text{[142,147,152,153]}\), age, HCV coinfection, occult HBV infection, alcohol abuse, and the general health status of the host\(^\text{[144,148,154,155]}\). A favorable response to cART may improve serological response\(^\text{[137,138]}\) (Table 3).

Based on these data, early vaccination is recommended in HIV-infected patients before CD4 cell counts decline. These also strengthen the arguments for universal HBV vaccination of individuals at risk for HIV infection before they become HIV-infected and their immunosuppression worsens. Post-vaccination testing is recommended 1 to 2 mo after administration of the final dose of the primary vaccine series to determine the response to the vaccine. The height of the antibody titers is associated with the durability of effective antibody\(^\text{[144]}\).

To improve the response rate and long-term persistence of antibodies, numerous studies have tried to use a variety of strategies such as increased doses, intradermal vaccination, and co-administration of immunomodulators. A fundamental strategy is to ensure that patients have optimal adherence to the vaccination schedule. A study conducted in a clinic specializing in the care of
HIV-infected adults revealed that 7.5% had evidence or documentation of prior HBV vaccination at screening, and only 49% of those eligible for vaccination completed the standard vaccination schedule. Other studies have also reported completion rates ranging from 29% to 62%.

### Dosing, vaccination schedules, and administration

For patients undergoing hemodialysis and for adults with general immune suppression, higher vaccine doses given on a standard schedule (3 × 40-μg doses administered intramuscularly at 0, 1, 6 mo) are recommended. However, appropriate vaccine dosage has not been well defined in HIV-infected patients. In a double-blinded, randomized, controlled trial in 210 HIV-infected adults, 94 in the standard-dose group (3 × 20-μg doses at 0, 1, 6 mo) and 98 in the double-dose group (3 × 40-μg doses at 0, 1, 6 mo) completed the study. There was no overall benefit in the double-dose group (seroconversion rate 47% vs 34%, P = 0.07), but a statistically significant higher seroconversion rate was observed between the 2 different vaccine doses.

For travelers or subjects exposed to HBV, an accelerated vaccination schedule of 3 doses at 0, 1, and 2 mo, followed by a booster at 12 mo, can be given to achieve rapid protection. A randomized study was designed to evaluate the protective efficacy of an accelerated vaccination schedule (n = 407; 3 × 10-μg doses administered intramuscularly at 0, 1, 2, and 6 mo, followed by a booster at 12 mo) compared with standard-dose strategy in patients with an HIV viral load < 10000 copies/mL (58.3% vs 37.3%, P = 0.01). In a small double-blinded, randomized controlled trial comparing a 40-μg dose to a 10-μg dose in 3 administrations, the increased dose of HBV vaccine did not increase the response rate in HIV-infected subjects (60.0% vs 61.5%, P = 0.89). Stratified by CD4 cell count or viral load, CD4 cell count ≥ 200 cells/μL was the only significant factor associated with the response rate and no difference was observed between the 2 different vaccine doses.

### Table 3  Hepatitis B vaccine in adults with human immunodeficiency virus: Standard and alternative strategies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>Study design</th>
<th>n</th>
<th>Dose (μg)</th>
<th>Schedules/administration</th>
<th>Age, median, yr</th>
<th>CART</th>
<th>HIV-1 VL, RNA copies/ml &lt; 10000</th>
<th>CD4, medium, cells/μL</th>
<th>Response rate</th>
<th>Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard-dose vaccination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey et al[141]</td>
<td>2000</td>
<td>Prospective</td>
<td>20</td>
<td>3 × 20</td>
<td>0, 1, 2 mo, IM</td>
<td>30.5</td>
<td>85%</td>
<td>NA</td>
<td>470</td>
<td>55%</td>
<td>CD4 &gt; 500 cells/μL</td>
</tr>
<tr>
<td>Tedaldi et al</td>
<td>2004</td>
<td>Retrospective</td>
<td>98</td>
<td>52.5% ≥ 3 × 20</td>
<td>NA</td>
<td>41</td>
<td>70.7%</td>
<td>&gt; 75%</td>
<td>406</td>
<td>37.2%</td>
<td>Higher CD4: HIV-1 VL &lt; level of detection</td>
</tr>
<tr>
<td>Overton et al[142]</td>
<td>2005</td>
<td>Prospective</td>
<td>194</td>
<td>3 × 10 (97%-99%)</td>
<td>0.1 to 3, 6-9 mo, IM</td>
<td>34.1</td>
<td>82.0%</td>
<td>≥ 36.1% (&lt; 400)</td>
<td>290</td>
<td>17.5%</td>
<td>HIV-1 VL &lt; level of detection</td>
</tr>
<tr>
<td>Ungulkriwit et al</td>
<td>2005</td>
<td>Prospective</td>
<td>65</td>
<td>3 × 20</td>
<td>0, 1, 6 mo, IM</td>
<td>39</td>
<td>88%</td>
<td>≥ 75%</td>
<td>345</td>
<td>46%</td>
<td>Higher CD4; young age</td>
</tr>
<tr>
<td>Tedaldi et al</td>
<td>2007</td>
<td>Retrospective</td>
<td>65</td>
<td>3 × 20</td>
<td>0, 1, 6 mo, IM</td>
<td>35</td>
<td>100%</td>
<td>100% (&lt; 50)</td>
<td>324</td>
<td>71.4%</td>
<td>Higher CD4: use of efavirenz</td>
</tr>
<tr>
<td>Kim et al[137]</td>
<td>2008</td>
<td>Prospective</td>
<td>28</td>
<td>3 × 20</td>
<td>0, 1, 6 mo, IM</td>
<td>39</td>
<td>31%</td>
<td>≥ 24% (&lt; 400)</td>
<td>325</td>
<td>44%</td>
<td>Nadir CD4 &gt; 200 cells/μL; young age (&lt; 40 yr); HIV-1 VL &lt; level of detection</td>
</tr>
<tr>
<td>Iruungu et al[140]</td>
<td>2013</td>
<td>Prospective</td>
<td>293</td>
<td>3 × 20</td>
<td>0, 1 to 3, 6 mo, IM</td>
<td>31</td>
<td>0%</td>
<td>HIV-1 uninfected</td>
<td>85.7%</td>
<td>64.2%</td>
<td>CD4 &gt; 500 cells/μL; female</td>
</tr>
<tr>
<td>Fonseca et al[141]</td>
<td>2005</td>
<td>RCT</td>
<td>94</td>
<td>3 × 20</td>
<td>0, 1, 6 mo, IM</td>
<td>37</td>
<td>85.1%</td>
<td>80.9%</td>
<td>≥ 350, 59.6%</td>
<td>34%</td>
<td>CD4 &gt; 350 cells/μL; HIV-1 VL &lt; 10000 copies/mL</td>
</tr>
<tr>
<td>Cornejo-Juárez et al</td>
<td>2006</td>
<td>RCT</td>
<td>98</td>
<td>3 × 40</td>
<td>0, 1, 6 mo, IM</td>
<td>37</td>
<td>87.8%</td>
<td>75.5%</td>
<td>≥ 350, 57.1%</td>
<td>47% (P = 0.07)</td>
<td>CD4 &gt; 200 cells/μL</td>
</tr>
<tr>
<td>Potsch et al[142]</td>
<td>2006</td>
<td>RCT</td>
<td>40</td>
<td>3 × 40</td>
<td>0, 1, 6 mo, IM</td>
<td>34.1</td>
<td>72.5%</td>
<td>&lt; 2000, 56.6%</td>
<td>≥ 350, 47.5%</td>
<td>60% (P = 0.89)</td>
<td>CD4 &gt; 200 cells/μL</td>
</tr>
<tr>
<td>Launay et al[143]</td>
<td>2011</td>
<td>RCT</td>
<td>47</td>
<td>3 × 40</td>
<td>0, 1, 2, 6 mo, IM</td>
<td>36</td>
<td>79%</td>
<td>&lt; 80%</td>
<td>402</td>
<td>89%</td>
<td>HIV-1 VL &lt; 80 copies/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>145</td>
<td>3 × 20</td>
<td>0, 1, 6 mo, IM</td>
<td>43</td>
<td>86%</td>
<td>&lt; 50%</td>
<td>516</td>
<td>65% (95%CI: 56-72)</td>
<td>Young age; four-dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>148</td>
<td>4 × 4</td>
<td>0, 1, 2, 6 mo, ID</td>
<td>42</td>
<td>80%</td>
<td>≥ 80%</td>
<td>509</td>
<td>82% (95%CI: 77-78)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>144</td>
<td>4 × 4</td>
<td>0, 1, 2, 6 mo, ID</td>
<td>43</td>
<td>86%</td>
<td>&lt; 50%</td>
<td>482</td>
<td>77% (95%CI: 56-72)</td>
<td></td>
</tr>
</tbody>
</table>

ID: Intradermal injections; IM: Intramuscular injections; RCT: Randomized clinical trial; VL: Viral load; cART: Combination antiretroviral therapy.
casionally at 0, 1 and 3 wk) in comparison to a standard schedule \((n = 434; 3 \times 10^{-\mu g} \text{ doses at 0, 4 and 24 wk})\) in HIV-infected individuals\(^{[164]}\). The study showed that compliance to the accelerated schedule was better than that to the standard schedule \((91.8\% \text{ vs } 82.7\%)\), but the overall response rate was higher in the standard schedule arm \((50\% \text{ vs } 38.7\% \text{ difference, } 11.3\% \text{ (95\%CI: 4.3-18.3)})\). Noninferiority was demonstrated only in patients with CD4 cell counts > 500 cells/\(\mu L\).

Potshc and colleagues reported a higher response rate \((89\%)\) using a modified HBV vaccination schedule that administered \(4 \times 40-\mu g\) doses intramuscularly at 0, 4, and 24 wk, with \(79\%\) achieving antibody titers above \(100\text{ IU/L}\)^{[145]}. A subsequent study confirmed these results with response rates of \(83\% \text{ and } 91\%\) following vaccination with 3 and 4 double doses, respectively\(^{[166]}\).

An alternative vaccine delivery method, the intradermal route, driven by the fact that the dermis and epidermis of human skin are rich in antigen-presenting cells, could permit vaccine dose sparing, as \(20\%\) of the antigen dose has elicited good vaccine responses. It has shown improved immunogenicity in patients with chronic kidney disease\(^{[166]}\). However, there are significant operational challenges, such as reformulation, changing from a single- to a multiple-dose presentation, development of intradermal delivery devices and training health workers.

An open-label, multicenter, 1:1:1 parallel-group, randomized trial compared the standard HBV vaccination schedule \((3 \times 20-\mu g \text{ doses administered intramuscularly at 0, 4, and 24 wk; } n = 145\), 4 double doses \((4 \times 40-\mu g \text{ doses administered intramuscularly at 0, 4, and 24 wk; } n = 148\), and 4 intradermal low-doses \((4 \times 4-\mu g \text{ doses administered intradermally at 0, 4, 8 and 24 wk; } n = 144\) in HIV-infected adults with CD4 cell counts \(\geq 200\) cells/\(\mu L\)^{[144]}. At week 28, both the 4 intramuscular double-dose group \((82\%)\) and the 4 intradermal low-dose group \((77\%)\) showed statistically significant higher response rates than the standard regimen. The four-dose schedule allowed for the possibility of overcoming age, a negative predictor for response in the standard schedule. However, data on long-term persistence of immunity are yet to be seen, and patients with CD4 cell counts of < 200 cells/\(\mu L\) were not evaluated.

**Vaccine safety**

HBV vaccination appeared to be safe in HIV-infected patients compared with HIV-uninfected persons and has no effect on HIV viral load, progression to AIDS or depletion of CD4 cell counts\(^{[166,144,145-147]}\). In the study by Launay et al\(^{[146]}\), 1 serious hepatic cytolysis event possibly related to the vaccine was reported in the 4 intramuscular double-dose group. A higher incidence of injection site adverse events was reported in the 4 intramuscular double-dose group compared with the standard group, but these adverse events were generally mild.

The use of newer adjuvants may also augment hepatitis B vaccine efficacy. Standard hepatitis B vaccines contain aluminum adjuvants. Two new adjuvants in addition to a commercial HBV vaccine have been evaluated in randomized trials in HIV-infected patients\(^{[167-170]}\). The granulocyte macrophage colony-stimulating factor (GM-CSF), a cytokine produced primarily by activated T and B lymphocytes that increases neutrophil count, improves APC function, and is involved in the development and perpetuation of cellular immune responses, has been studied as an adjuvant in HIV-infected individuals\(^{[167,169]}\). GM-CSF is safe with expected side effects in HIV-infected subjects when administered as an adjuvant. While 1 study showed promise for the role of adjuvant to augment immune response\(^{[169]}\), no additive benefits were noted in the 2 other trials\(^{[167,168]}\). CPG 7909, is an oligodeoxynucleotide containing immunostimulatory CpG motifs, which activates human B and plasmacytoid dendritic cells via Toll-like receptor 9. A randomized, double-blind controlled trial was conducted in HIV-infected adults on effective antiretroviral therapy who underwent HBV vaccination \((3 \times 40-\mu g \text{ administered intramuscularly at 0, 1, and 2 mo with/without } 1 \text{ mg CPG } 7909)^{[170]}\). The study showed that significantly more CPG 7909 recipients than control subjects maintained seroprotective titers for up to 60 mo in vaccine-naïve participants and in those who had previously experienced vaccine failure\(^{[170]}\). While more studies are warranted to determine optimal vaccination strategies in patients with advanced immunosuppression, the vaccination series should be initiated at first visit regardless of CD4 cell count.

**TREATMENT WITH COMBINATION ANTIRETROVIRAL THERAPY FOR THE PREVENTION OF HBV INFECTION**

Some health-care practitioners may weigh the risk of vaccination delay and the likelihood of HBV infection in patients when making decisions to postpone vaccination until cART is started and virologic suppression is achieved to improve serologic response to vaccination. A cohort study in Japan examined the prophylactic effect against HBV in HIV-infected patients who had not received HBV vaccination and were negative for HBsAg, anti-HBs, and anti-HBc at baseline\(^{[170]}\). The incidence rate of HBV infection was lower during LAM- or TDF-containing cART \((0.669 \text{ incident infections in } 100 \text{ person-years})\) than during no antiretroviral therapy \((6.726 \text{ incident infections in } 100 \text{ person-years})\) and other antiretroviral therapy \((5.263 \text{ incident infections in } 100 \text{ person-years})\) \((P < 0.001)\). A similar trend was also noted in Taiwan\(^{[170]}\).

**CONCLUSION**

In this review, we have found in the published data that the prevalence or incidence of HBV infection among HIV-infected patients is likely to decrease in areas where HBV vaccination programs are implemented and the coverage of cART containing TDF plus LAM or FTC is
high. The challenges in the prevention of HBV transmission are to ensure that HIV-monoinfected patients have optimal adherence to protected sex and an HBV vaccination schedule, and to identify novel approaches or novel adjuvants to improve vaccination effectiveness. While the experience with management of HBV/HIV-coinfected patients using cART containing TDF plus LAM or FTC is accumulating in clinical practice, early diagnosis of patients using cART containing TDF plus LAM or FTC is warranted to ensure long-term success in the prevention of HBV-related chronic complications. With the progress made in liver transplantation over the past decades, early referral for workup for liver transplantation is advised when HIV/HBV-coinfected patients become symptomatic with liver disease.

REFERENCES

25. McMahon BJ. The influence of hepatitis B virus genotype

Sun HY et al. HBV and HIV coinfection
2. BACKGROUND

2.1 Epidemiology of hepatitis C

According to recent estimates, more than 185 million people around the world have been infected with HCV, of whom 350,000 die each year. Most people infected with the virus are unaware of their infection and, for many who have been diagnosed, treatment remains unavailable. Treatment is successful in the majority of persons treated, and treatment success rates among persons treated in low- and middle-income countries are similar to those in high-income countries. One third of those who become chronically infected are predicted to develop liver cirrhosis or hepatocellular carcinoma.

The prevalence of hepatitis C infection varies substantially around the world (Table 2.1). When countries are grouped into Global Burden of Disease regions, the estimated prevalence of HCV infection is highest in Central and East Asia and in the North Africa/Middle East regions. In view of the larger populations in Asia, the South Asia and East Asia regions have by far the largest number of persons living with HCV infection.

TABLE 2.1 Global seroprevalence of HCV by region

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence (%)</th>
<th>Estimated number of people infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia Pacific</td>
<td>1.4</td>
<td>&gt;2.4 million</td>
</tr>
<tr>
<td>Central Asia</td>
<td>3.8</td>
<td>&gt;2.9 million</td>
</tr>
<tr>
<td>East Asia</td>
<td>3.7</td>
<td>&gt;50 million</td>
</tr>
<tr>
<td>South Asia</td>
<td>3.4</td>
<td>&gt;50 million</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>2.0</td>
<td>&gt;11 million</td>
</tr>
<tr>
<td>Australasia</td>
<td>2.7</td>
<td>&gt;0.6 million</td>
</tr>
<tr>
<td>Caribbean</td>
<td>2.1</td>
<td>&gt;0.7 million</td>
</tr>
<tr>
<td>Central Europe</td>
<td>2.4</td>
<td>&gt;2.9 million</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>2.9</td>
<td>&gt;6.2 million</td>
</tr>
<tr>
<td>Western Europe</td>
<td>2.4</td>
<td>&gt;10 million</td>
</tr>
</tbody>
</table>
Certain groups are at higher risk of HCV infection, and estimates of the prevalence of HCV in these groups are shown in Table 2.2. The relative importance of risk factors for HCV infection varies substantially, depending on the geographical region and population studied. Greater access to HCV testing and better surveillance are important steps to both increase the number of persons diagnosed with HCV and to improve understanding of the distribution of HCV infection in the general population and groups at increased risk.

### 2.1.1 Routes of transmission

**TABLE 2.2 Populations at increased risk of HCV infection**

<table>
<thead>
<tr>
<th>Population</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons who inject drugs(^6)</td>
<td>PWID have the highest risk of infection: Globally, the prevalence of HCV is 67% among PWID.</td>
</tr>
<tr>
<td>Recipients of infected blood products or invasive procedures in health-care facilities with inadequate infection control practices(^7)-(^{16})</td>
<td>Risk of HCV infection varies depending upon the frequency of medical procedures (i.e. number of injections/person/year) and level of infection-control practices. High frequency of injections and low level of infection control can result in high prevalence of HCV in the general population (e.g. prevalence of chronic HCV infection confirmed by nucleic acid testing was 9.8% in Egypt in 2008)</td>
</tr>
<tr>
<td>Children born to mothers infected with HCV(^{17},\ ^{18})</td>
<td>HCV transmission risk is estimated as 4–8% among mothers without HIV infection. Transmission risk is estimated as 17–25% among mothers with HIV infection</td>
</tr>
<tr>
<td>Category</td>
<td>Comment</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>People with sexual partners who are HCV-infected</td>
<td>There is low or no risk of sexual transmission of HCV among HIV-uninfected heterosexual couples and HIV-uninfected men who have sex with men (MSM). The risk of sexual transmission is strongly linked to pre-existing HIV infection.</td>
</tr>
<tr>
<td>People with HIV infection</td>
<td>Persons with HIV infection, in particular MSM, are at increased risk of HCV infection through unprotected sex.</td>
</tr>
<tr>
<td>People who have used intranasal drugs</td>
<td>Non-injecting drug use (e.g. through sharing of inhalation equipment for cocaine) is associated with a higher risk of HCV infection.</td>
</tr>
<tr>
<td>People who have had tattoos or piercings</td>
<td>Tattoo recipients have higher prevalence of HCV compared with persons without tattoos (odds ratio = 2.24, 95%CI 2.01,2.50)</td>
</tr>
</tbody>
</table>

Health-care associated transmission

Hepatitis C virus infection is strongly associated with health inequity; in low- and middle-income countries, infection with HCV is most commonly associated with unsafe injection practices and procedures such as renal dialysis and unscreened blood transfusions. Between 8 and 12 billion injections are administered yearly around the world and 50% of these are considered to be unsafe (mainly in sub-Saharan Africa and Asia). In low- and middle-income countries, infection with HCV is frequently associated with unsafe injection practices and unscreened (or inadequately screened) blood transfusions. According to the latest WHO report on blood safety (2011), 39 countries do not routinely screen blood transfusions for bloodborne viruses. The most well documented example of health-care associated transmission is the generalized epidemic of HCV infection resulting from unsafe injection practices in Egypt, where HCV prevalence is 25% in some regions. Persons who received untested blood products prior to the introduction of screening of blood for HCV in high-income countries are also at risk. Universal access to safe blood transfusion requires the implementation of key strategies to ensure access to a safe and sufficient blood supply, including the implementation of 100% voluntary blood donation and 100% quality-assured testing of donated blood. WHO has developed guidelines on best practices in phlebotomy and best practices for injections and related procedures.

People who inject drugs

In middle- and high-income countries, most HCV infections occur among people who use unsterile equipment to inject drugs and contaminated drug solutions. Of the estimated 16 million people in 148 countries who actively inject drugs, 10 million are infected with HCV. PWID infected with HCV are at increased risk of all-cause mortality, reflecting the role of injecting drug use, low socioeconomic status, poor access to health care and environmental factors.
Mother-to-child transmission
The risk of transmission of HCV from a mother to her child occurs in 4–8% of births to women with HCV infection and in 17–25% of births to women with HIV and HCV coinfection (Table 2.2).17,18

Sexual transmission
Sexual transmission of HCV occurs infrequently in heterosexual couples.39 It is more common in HIV-positive persons, particularly in men who have sex with men (MSM).30 In several recent outbreaks of HCV infection among MSM in Europe, Australia and the US, transmission has been linked to sexual exposure as well as potentially to underreported use of non-injecting recreational drugs.41,42 HIV-infected heterosexual partners of HCV-infected people are also more likely to acquire HCV; this may be due to sexual transmission or other exposure to blood or due to unreported injection or non-injection drug use, such as sharing of straws for inhaling cocaine.41

Other
Other routes of transmission of HCV include intranasal drug use and other modes of bloodborne transmission, such as acquisition by health-care workers, cosmetic procedures (such as tattooing and body piercing), scarification and circumcision procedures.33,43

2.1.2 Coinfections
HIV and HCV coinfection
HIV and HCV have common routes of transmission, and it is estimated that, globally, 4–5 million persons are coinfected with these two viruses.44 With the widespread use of antiretroviral therapy (ART), which reduces the risk of HIV-associated opportunistic infections, HCV-related liver disease has started to overtake AIDS-defining illnesses as a leading cause of death in some high-income countries.45

HBV and HCV coinfection
Hepatitis B virus (HBV) and HCV coinfection is commonly found in HBV-endemic countries in Asia, sub-Saharan Africa and South America. Up to 25% of HCV-infected persons may be coinfected with HBV in some areas.46-51 HBV and HCV coinfection is discussed further in Chapter 9.

Tuberculosis and HCV coinfection
Groups at increased risk of infection with HCV are also at risk of infection with tuberculosis (TB). TB is endemic in many countries where blood products are not screened routinely. TB is the most common AIDS-defining illness and the leading cause of HIV-associated mortality. PWID are more at risk of developing TB, regardless of their HIV status. Among PWID who develop TB, two out of three will have HCV antibodies. People who live with HIV and inject drugs have a two- to sixfold increased risk of developing TB compared with non-injectors. Prisoners, who have a high risk of acquiring HCV, are also at increased risk of coinfection.
with TB; incarceration is associated with a 23 times higher risk of TB than in the general population.\textsuperscript{52,53} Appropriate care for persons being considered for hepatitis C treatment would include screening for active TB, as the co-management of such persons needs sound clinical judgement and the provision of treatment that takes into consideration the side-effects and interactions of the drugs used to treat HIV, TB and viral hepatitis.

### 2.2 Hepatitis C virus

The hepatitis C virus is a small, positive-stranded RNA-enveloped virus that is approximately 9.6 kb in length. The genetic sequence was first characterized in 1989,\textsuperscript{54} placing the virus in the Hepacivirus genus within the Flaviviridae family.\textsuperscript{55,56} It has a highly variable genome and multiple genotypes and subgenotypes.\textsuperscript{57} The distribution of HCV genotypes and subgenotypes varies substantially in different parts of the world (Figure 2.1). Some genotypes are easier to treat and, thus, the duration of and recommended medicines for therapy vary by genotype. For this reason, determining a patient’s genotype is important to appropriately tailor therapy. It is possible that this advice may change when antiviral agents that are active against all genotypes (referred to as pangenotypic) are licensed.

*FIGURE 2.1 Global distribution of genotypes of HCV*

2.3 Natural history of HCV infection

Hepatitis C virus causes both acute and chronic infection. Acute HCV infection is defined as the presence of HCV within six months of exposure to and infection with HCV. It is usually clinically silent, and is only very rarely associated with life-threatening disease. Spontaneous clearance of acute HCV infection occurs within six months of infection in 15–45% of infected individuals in the absence of treatment. Almost all the remaining 55–85% of persons will harbour HCV for the rest of their lives (if not treated) and are considered to have chronic HCV infection. Anti-HCV antibodies develop as part of acute infection and persist throughout life. In persons who have anti-HCV antibodies, a nucleic acid test (NAT) for HCV RNA, which detects the presence of virus, is needed to confirm the diagnosis of chronic HCV infection.58,59

Left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and hepatocellular carcinoma (HCC; Figure 2.2). Of those with chronic HCV infection, the risk of cirrhosis of the liver is 15–30% within 20 years.60,61,62 The risk of HCC in persons with cirrhosis is approximately 2–4% per year.63

FIGURE 2.2 Natural history of HCV infection

The risk of cirrhosis and HCC varies depending upon certain patient characteristics or behaviours. For example, men, persons who consume excess alcohol, persons with hepatitis B or HIV coinfection and immunosuppressed individuals are all at higher risk of developing cirrhosis or HCC.64 Disease associated with HCV is not confined to the liver. Extrahepatic manifestations of HCV include cryoglobulinaemia, glomerulonephritis, thyroiditis and Sjögren syndrome, insulin resistance, type-2 diabetes mellitus, and skin disorders such as porphyria cutanea tarda and lichen planus. Persons with chronic HCV infection are more likely to develop cognitive dysfunction, fatigue and depression.65 These outcomes may
be associated with replication of the virus in the brain; however, the causal link between these manifestations and chronic HCV infection is not certain.66

Natural history of HIV/HCV coinfection
Coinfection with HIV adversely affects the course of HCV infection, and coinfected persons have a significantly accelerated progression of liver disease to cirrhosis, decompensated liver cirrhosis and HCC than HCV-monoinfected persons, particularly those with advanced immunodeficiency (CD4 count <200 cells/mm³).67-70 In high-income countries, death due to HCV-associated liver disease has become a leading cause of death in people living with HIV in the era of combination ART,45,71,72 accounting for around 47% of deaths in one series from the United States.

It remains unclear whether HCV infection accelerates HIV disease progression, as determined by AIDS-related events or death.73 Two large European cohorts have shown that after ART initiation, CD4 recovery was impaired in HIV/HCV-coinfected persons when compared to those infected with HIV alone. HIV/HCV-coinfected persons also demonstrated more rapid HIV disease progression compared to those who were HIV-infected alone, and had an impaired recovery of CD4 cells. However, other studies have shown no such differences in response.73-77 Assessment of the impact of HCV infection on HIV disease progression may be confounded by the negative health consequences of injecting drug use, which is strongly linked to HCV infection.78,79 In persons with HIV infection, HCC tends to occur at a younger age and within a shorter time period.80

2.4 Prevention of HCV infection
In the absence of a vaccine for hepatitis C, prevention of HCV infection depends upon reducing the risk of exposure to the virus. This is challenging because of the various routes of transmission and the different populations that are affected. Globally, most HCV infections occur in health-care settings as a result of inadequate infection control procedures, for example, the reuse of injection equipment. HCV infections in health-care settings also occur through the transfusion of blood that has not been screened for HCV antibodies. WHO has published guidelines with recommendations to prevent health-care associated HCV infection (Table 2.3).

PWID are at great risk of HCV infection through the use of contaminated injection equipment as well as non-injection drug use. WHO, United Nations Office on Drugs and Crime (UNODC), and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have developed a set of nine core interventions for the prevention, care and treatment of HIV infection among PWID (Table 2.4). These interventions are also relevant for the prevention and management of viral hepatitis in this population. In addition, WHO has developed guidelines with recommendations for preventing transmission of viral hepatitis among PWID (Table 2.5).
### TABLE 2.3  WHO guidance on prevention of HCV infection in health-care settings

**Focus of guidance documents:**

- Hand hygiene: including surgical hand preparation, hand washing and use of gloves
- Safe handling and disposal of sharps and waste
- Safe cleaning of equipment
- Testing of donated blood
- Improved access to safe blood
- Training of health personnel

**References**


### TABLE 2.4  WHO/UNODC/UNAIDS comprehensive package of interventions for HIV prevention treatment and care in PWID

**Interventions**

1. Needle and syringe programmes including other drug-using paraphernalia
2. Opioid substitution therapy and other drug dependence treatment
3. HIV testing and counselling
4. Antiretroviral therapy
5. Prevention and treatment of sexually transmitted infections
6. Condom programmes for people who inject drugs and their sexual partners
7. Targeted information, education and communication for people who inject drugs and their sexual partners
8. Vaccination, diagnosis and treatment of viral hepatitis
9. Prevention, diagnosis and treatment of tuberculosis

**References**

Focus of guidance documents:

- Promotion of correct and consistent condom use
- Routine screening of sex workers in high-prevalence settings
- Integrated action to eliminate discrimination and gender violence and to increase access to medical and social services for vulnerable persons

References


The risk of sexual transmission of HCV varies depending on the type of exposure. The risk is lowest among heterosexual couples and highest among MSM with HIV coinfection. Existing guidelines for prevention of HCV infection through sexual exposure are listed in Table 2.6.

### TABLE 2.5 WHO recommendations for prevention of HCV infection among people who inject drugs, in addition to interventions described in Table 2.4

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer people who inject drugs the rapid hepatitis B vaccination regimen.</td>
</tr>
<tr>
<td>Offer people who inject drugs incentives to increase uptake and completion of the hepatitis B vaccination schedule.</td>
</tr>
<tr>
<td>Implement sterile needle and syringe programmes that also provide low dead-space syringes for distribution to people who inject drugs.</td>
</tr>
<tr>
<td>Offer peer interventions to people who inject drugs to reduce the incidence of viral hepatitis.</td>
</tr>
<tr>
<td>Offer opioid substitution therapy to treat opioid dependence; reduce HCV risk behaviour and transmission through injecting drug use; and increase adherence to HCV treatment.</td>
</tr>
<tr>
<td>Integrate treatment of opioid dependence with medical services for hepatitis.</td>
</tr>
</tbody>
</table>

References


### TABLE 2.6 WHO guidance on prevention of sexual transmission of HCV infection

<table>
<thead>
<tr>
<th>Focus of guidance documents:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promotion of correct and consistent condom use</td>
</tr>
<tr>
<td>Routine screening of sex workers in high-prevalence settings</td>
</tr>
<tr>
<td>Integrated action to eliminate discrimination and gender violence and to increase access to medical and social services for vulnerable persons</td>
</tr>
</tbody>
</table>

References


Prevention of mother-to-child transmission of HCV is difficult as there are no proven interventions to reduce this risk. Neither mode of delivery nor breastfeeding are reliably linked with transmission. The development of effective drugs against HCV that can be given safely during pregnancy might be a future option.

2.5 Screening for HCV infection

Screening for HCV infection is done using HCV serological testing. If positive, a NAT for HCV RNA assay is needed to confirm chronic HCV infection. Several screening assays have been evaluated by WHO, and sensitivity, specificity, and positive and negative predictive value results are available. It is important to consider the possibility of infection with other bloodborne viruses in persons with HCV, and to offer screening for HBV and HIV in addition to HCV. Screening for other infections, for example TB, is also indicated in some groups at risk, such as people living with HIV, prisoners and PWID.

2.6 Care of patients with HCV infection

The spectrum of disease in persons infected with HCV extends from mild fibrosis to cirrhosis and HCC. Compensated cirrhosis may progress over time to decompensated cirrhosis associated with ascites, oesophageal and gastric varices, and eventually to liver failure, renal failure and sepsis, all of which are life-threatening. HCC may also occur at a rate of 2–4% per year in persons with cirrhosis. The diagnosis of decompensated liver disease is based on both clinical examination and laboratory monitoring, and therefore a careful medical examination of patients must be made prior to commencing therapy. The stage of disease may be assessed by liver biopsy or by using a variety of non-invasive methods. These are discussed further in Chapter 6.2.

Staging of HCV infection is important as it results in the identification of patients with advanced disease, a group that requires enhanced monitoring and prioritization for treatment before the onset of decompensated cirrhosis. In many high-income countries, all persons with chronic HCV infection who do not have a contraindication for therapy are considered to be suitable for treatment (although many persons with mild-to-moderate disease may elect to wait for newer, less toxic and more efficacious medicines). In low- and middle-income countries, where access to treatment is limited, the stage of fibrosis may be used to prioritize treatment for patients with more advanced disease (e.g. patients with cirrhosis or those with ≥F2 fibrosis).

Patients infected with HCV often have other co-morbidities such as HBV, HIV, TB and substance use. Related WHO guidance is available for persons who inject
drugs and for those infected with HIV (see section 2.4). Excessive alcohol use is common in some populations infected with HCV and can accelerate disease. WHO guidance on alcohol reduction is discussed in detail in Chapter 6.1.

2.7 Treatment of patients with HCV infection

HCV is a now a curable disease, and advances in HCV therapy have resulted in steadily higher cure rates. Identification and treatment of chronic HCV infection has a prevention benefit, as persons who are cured of HCV cannot transmit the virus to others. HCV cure is also beneficial for the patient’s health, as it reduces the risk of development of HCC among persons at all stages of fibrosis by >75%. At the time of writing (December 2013), six drugs are licensed for the treatment of HCV – standard interferon (IFN) or pegylated interferon alpha (PEG-IFN), ribavirin (RBV), the protease inhibitors (PIs) boceprevir, simeprevir and telaprevir, and the nucleotide analog polymerase inhibitor sofosbuvir. The limitations of treatment include high cost, the need for sophisticated laboratory tests and trained clinicians, as well as the limited efficacy and high toxicity of some of the medicines. It is anticipated that the number of medicines for the treatment of HCV will expand rapidly over the coming years, and WHO plans to periodically update these guidelines to include newly licensed drugs.

Before treatment for HCV can be commenced, it is necessary to genotype the virus as different genotypes require different types and durations of treatment, and the protease inhibitors boceprevir, simeprevir and telaprevir are licensed only for genotype 1 infection. Current therapy for genotype 1 infection is a combination of PEG-IFN, RBV and a PI or nucleotide polymerase inhibitor, which results in high rates of sustained virological response (SVR; a negative HCV RNA test three or six months after the end of treatment). Dual therapy with PEG-IFN and RBV or sofosbuvir with RBV is used for genotypes 2 and 3 infections. Patients with genotype 4 infection treated with treated with sofosbuvir, PEG-IFN and RBV have similar response rates when compared with genotype 1-infected individuals. Small studies of genotypes 5- and 6-infected patients have shown similar SVR rates to genotypes 2- and 3-infected ones. Larger studies in these groups are required to confirm these results and to identify predictors of response or non-response to treatment.

Treatment with some HCV medicines may result in marked side-effects and therefore careful patient assessment and close monitoring is required.

2.8 Cost–effectiveness of treatment

Among the major hurdles in setting up a treatment service for patients with HCV are the high cost of medications, need for regular monitoring, setting up, running
and maintaining appropriate facilities, and assuring adequate numbers and training of staff. The benefits of instituting treatment programmes include the benefit to individual patients as well as the potential reduction of transmission of infection from treated persons who are no longer infected with HCV.

In high-income settings, HCV treatment with PEG-IFN/RBV and with PEG-IFN/RBV and telaprevir or boceprevir has been evaluated as being cost–effective.95,96 PEG-IFN and RBV treatment in current PWID has also been shown to be cost–effective in high-income settings, despite the potential risk of reinfection, and may be even more cost–effective than treating those with lower risks of transmission to others.97,98 HCV case-finding and treatment in specialist drug dependency services has also been shown to be cost–effective. The higher the treatment rates, the more cost–effective HCV case-finding becomes, as more of those identified will be treated, and a greater population impact would be seen.97

In low- and middle-income countries, data on cost–effectiveness are limited but have been evaluated in some settings, for example, in Egypt and Viet Nam.99,100 Where the availability of medication is restricted, treatment of persons with more advanced disease may be the most cost–effective strategy.100
Quantum Leaps, Microeconomics, and the Treatment of Patients With Hepatitis C and HIV Coinfection

Michael S. Saag, MD

Until very recently, patients with hepatitis C virus (HCV) infection were treated with pegylated-interferon administered weekly by subcutaneous injection plus ribavirin given orally twice daily. Over the last decade, however, by virtue of development of directly acting agents, therapy for hepatitis C infection has advanced by several orders of magnitude, creating a transformative and unprecedented revolution.

Telaprevir and boceprevir were the first directly acting agents released. In previous studies among patients with HCV genotype 1 only (ie, without human immunodeficiency virus [HIV] coinfection), treatment with pegylated-interferon-ribavirin plus either boceprevir or telaprevir achieved sustained virologic response rates at 24 weeks after cessation of therapy (SVR 24 or “cure”) of 60% to 75% with 24 to 48 weeks of treatment.1-3 For those monoinfected with genotype 2 or 3, SVR-48 rates of approximately 80% were reported with 48 to 72 weeks of treatment with pegylated-interferon plus ribavirin alone.4,5 Patients who are coinfected with HIV and HCV have similar outcomes as those with HCV monoinfection but require a longer duration of therapy with those treatments (48 weeks). Coinfected patients with genotype 1 infection treated with pegylated-interferon-ribavirin plus either telaprevir or boceprevir for 48 weeks have achieved SVR-12 and SVR-24 rates of 74% with telaprevir and 67% with boceprevir.6-8 However, telaprevir and boceprevir did not achieve the real promise of the directly acting agents, which is their use as components of an all-oral, interferon-free regimen.

In this issue of JAMA, Sulikowski and colleagues9 report the results of the PHOTON-1 study, which demonstrates the efficacy of the all-oral regimen of the directly acting agent sofosbuvir plus ribavirin in patients who are coinfected with HIV. SVR-12 rates among coinfected treatment-naive patients were 76% for 114 patients with HCV genotype 1 after 24 weeks of sofosbuvir plus ribavirin therapy, 88% for 26 patients with genotype 2, and 67% for 42 patients with genotype 3 after both latter groups received 12 weeks of therapy. Of note, among the 17 other patients with HCV genotype 3 who had received previous treatment with pegylated-interferon and ribavirin, 24 weeks of treatment resulted in an SVR-12 rate of 94%, indicating that genotype 3 patients likely need a longer course of therapy, as recommended in current guidelines.10

The PHOTON-1 trial demonstrates that the all-oral combination of sofosbuvir plus ribavirin yielded results comparable with those of standard pegylated-interferon-ribavirin-based regimens for each of the genotypic groups, thereby demonstrating that an all-oral combination could achieve similar outcomes as those derived from an injectable therapy. Yet, the benefits of using an all oral regimen as that used in the PHOTON-1 study go beyond the simple comparability of the overall efficacy results, especially for patients coinfected with HIV and HCV. In this trial, the authors demonstrated that 24 weeks of sofosbuvir-ribavirin was required to achieve similar efficacy outcomes as 48 weeks of pegylated-interferon-ribavirin plus either telaprevir or boceprevir. Similarly, both telaprevir and boceprevir must be given at least twice daily compared with the once daily dosing of sofosbuvir and twice daily dosing of ribavirin. The most important difference, however, was related to the relative lack of drug-drug interactions with sofosbuvir-ribavirin compared with either boceprevir or telaprevir, both of which interact extensively with the cytochrome P450 3A4 (CYP3A4) isoenzyme system, thereby generating substantial drug-drug interactions with many of the standard antiretroviral agents. Moreover, because the relatively high toxic effects and length of therapy of interferon-based regimens, elaborate stopping rules were created to indicate when further therapy with the current regimen had become futile. With the newer directly acting agent treatments, the efficacy of the regimens are generally better, the daily process of taking the drug is simpler, the duration of treatment is shorter, and the toxic effects of the regimens are substantially less, thus eliminating the need for these stopping rules that are challenging to incorporate into clinical practice. However, the PHOTON-1 study, like other reports on directly acting agent treatments, was a relatively short-term study and longer-term data on durability of response and long-term adverse effects are needed.

Although the PHOTON-1 study represents a quantum leap forward in the treatment of patients coinfected with HIV and HCV, it is just the beginning. The pending release of other nucleotide (NS5b), nonnucleotide (NS5b), protease (NS3-4A), and NS5A inhibitors are showing evidence of even better efficacy (up to 95%-98% SVR-12 rates with 12 weeks of therapy) when used in combination with each other, often without the need for ribavirin.11 Work is now under way to create regimens that require even shorter duration of therapy (eg, ≤6 weeks). Many of these new agents are also not metabolized by the CYP3A4 enzyme systems, permitting use in more coinfected patients who are receiving antiretroviral therapy. Therefore, in the next 18 months, it is expected that all oral, non-ribavirin-based treatments will be available that eradicate HCV in more than 95% of all patients who are either monoinfected or coinfected. The primary considerations of which regimen...
and affordable for everyone with chronic HCV. Hopefully, it will be possible to accurately identify those patients who will have their cure within 12 weeks, but rather the “cost per cure.”

The difficulty is that it is not possible to accurately identify those patients who will have progressive liver disease, so treatment needs to be affordable for everyone with chronic HCV. Hopefully, competition among the new products coming to market in the next 18 months will result in substantially lower pricing for the drugs. Indeed, the release of the new products will be, perhaps for the first time, a genuine test of whether there is a free market, microeconomic system in the pharmaceutical industry.

In physics, quantum mechanics are used to describe the transition of an electron from one state to another within an atom. The electron appears to jump from one energy level to the next in a process defined as a *quantum leap*. When this leap happens, the electron transition causes the emission of electromagnetic radiation in the form of a photon. Accordingly, it seems that the name *photon* may be an appropriate metaphor for the effect these transformative, novel therapeutics are having on the HCV treatment landscape. The quantum leaps in efficacy, safety, and tolerability of the new regimens for HCV treatment are substantial. Based on the pipeline of new drugs anticipated for release over the next 18 months, it is likely that many more quantum leaps and emissions of several more photons are yet to come. However, despite the progress, the question remains, can the health care system and society afford them?

### References

HIV/Viral Hepatitis Co-Infection in Asia
Report from a Viral Hepatitis Policy Forum on implementing the WHO framework for global action on viral hepatitis in North Asia

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Background & Aims: The World Health Organisation (WHO) Prevention & Control of Viral Hepatitis Infection: Framework for Global Action offers a global vision for the prevention and control of viral hepatitis. In October 2012, the Coalition to Eradicate Viral Hepatitis in Asia Pacific (CEVHAP) organised the North Asia Workshop on Viral Hepatitis in Taipei to discuss how to implement the WHO Framework in the North Asia region. This paper presents outcomes from this workshop.

Methods: Twenty-eight representatives from local liver associations, patient organisations, and centres of excellence in Hong Kong, Japan, Korea, and Taiwan participated in the workshop.

Findings: Priority areas for action were described along the four axes of the WHO Framework: (1) awareness, advocacy and resources; (2) evidence and data; (3) prevention of transmission; and (4) screening and treatment. Priorities included: axis 1: greater public and professional awareness, particularly among primary care physicians and local advocacy networks. Axis 2: better economic data and identifying barriers to screening and treatment uptake. Axis 3: monitoring of vaccination outcomes and targeted harm reduction strategies. Axis 4: strengthening links between hospitals and primary care providers, and secure funding of screening and treatment, including for hepatocellular carcinoma.

Conclusions: The WHO Framework provides an opportunity to develop comprehensive and cohesive policies in North Asia and the broader region. A partnership between clinical specialists, primary care physicians, policy makers, and people with or at risk of viral hepatitis is essential in shaping future policies.

Introduction

In 2012, the World Health Organisation (WHO) launched the Prevention & Control of Viral Hepatitis Infection: Framework for Global Action. This strategy offers a global vision for the prevention and control of viral hepatitis [1]. The Framework was welcomed by hepatitis experts and advocacy groups who have been struggling for the attention of policymakers about this ‘silent epidemic’ for many years [2,3].

Asia is home to 75% of all chronic hepatitis B cases [4] and China alone has more cases of hepatitis C infection than all of Europe or the Americas [5]. The majority of people infected with either hepatitis B virus or hepatitis C virus do not know that they are infected, and are not aware of the precautions they need to take to avoid infecting others or to enable them to reduce the impact of the infection [6]. Uptake of screening, when available, is low, and treatment rates are 4–10% in Asia compared to rates of 20% in the United States [7].

Against this background, the Coalition to Eradicate Viral Hepatitis in Asia Pacific (CEVHAP) was established in 2010 to contribute towards an Asia Pacific region free from the significant health, social and economic burden of viral hepatitis (www.cevhap.com). CEVHAP is uniquely positioned to support and facilitate the implementation of the WHO framework in different countries across the region through its network of members who are experts in their respective fields in the Asia Pacific region and globally.

In October 2012, CEVHAP organised the North Asia Workshop on Viral Hepatitis in Taipei, with participants from Hong Kong, Japan, Korea, and Taiwan. These four jurisdictions were chosen because, to varying degrees, they have some initiatives in place...
in the area of viral hepatitis and have broadly similar health infrastructures. These localities are also in a privileged position compared to other countries in the Asia Pacific region, in that they have the resources to build on existing successes and lead the drive for further policy change across the region. Summary epidemiological data on hepatitis B and hepatitis C in these four jurisdictions is presented in Table 1.

The aim of the workshop was to ensure that participants understood the WHO framework; to support participants in building or strengthening advocacy networks, and to identify local priorities for implementing the framework within their respective jurisdictions.

This paper summarises the outcomes of this workshop and identifies steps to be taken to translate the WHO Framework into sustainable national policies on viral hepatitis in North Asia.

Materials and methods

The 28 workshop participants were identified within the existing CEVHAP network of local liver associations, patient organisations, and centres of excellence in Hong Kong, Japan, Korea, and Taiwan. The agenda for the one and a half day workshop was developed in close consultation with a small group of CEVHAP experts. To assist participants in their preparation, a briefing paper describing the scope of viral hepatitis, focusing on hepatitis C and hepatitis C virus, within the four jurisdictions was distributed prior to the meeting (CEVHAP, data on file).

Results

This paper uses the four axes of the WHO framework to describe the workshop results. The priority areas for action in the four participating jurisdictions are presented in Table 2 and are discussed in more detail in the section below.

Axis 1: Raising awareness, promoting partnerships, and securing resources

In North Asia, the general public, people at risk of infection, the medical community and policymakers generally have a poor understanding of viral hepatitis, its natural history and
manifestations. Awareness among primary care physicians is particularly low and targeted educational efforts are needed to encourage these providers to test their patients for viral hepatitis and refer them towards appropriate care pathways. Investment in developing better relationships between primary care and hepatitis specialist services may help engage primary care physicians.

Local advocacy networks that bridge civil society, liver specialists, primary care physicians and other community care providers are still lacking in Taiwan, Hong Kong, and Korea particularly. This lack of a strong advocacy base makes it more difficult to engage the media in the first place or to overcome media fatigue about viral hepatitis. The media plays a vital role in raising awareness of viral hepatitis, particularly among the general public and those at risk of infection. The awareness campaigns run in the United States and Korea provide interesting examples of media engagement on viral hepatitis (Case studies 1 and 2).

A key to the success of awareness campaigns on viral hepatitis is to find the issues that resonate best with media, the public, and policymakers. The fact that viral hepatitis is one of the main causes of liver cancer is indeed compelling and one with potential to grab the attention of these key stakeholders. For example, a recent study by the International Agency for Research on Cancer showed that one in six cancers was caused by infection and concluded that prevention of viral hepatitis and other infections could have a substantial effect on reducing the future burden of cancer [8]. These data may be very powerful in convincing policymakers of the need to mobilise resources towards the prevention and management of viral hepatitis.

Fig. 1. The four strategic axes for policy development recommended in the WHO Prevention & Control of Viral Hepatitis Infection: Framework for Global Action.

Table 2. Priorities for action in Hong Kong, Japan, Korea, and Taiwan according to the four strategic axes of the WHO Global Framework.

<table>
<thead>
<tr>
<th>Priorities for action</th>
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</thead>
<tbody>
<tr>
<td><strong>1. Raising awareness, promoting partnerships and mobilizing resources</strong></td>
</tr>
<tr>
<td>Greater public awareness</td>
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<tr>
<td>Greater awareness of primary care physicians</td>
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<tr>
<td>Building patient advocacy</td>
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<tr>
<td>Strengthening hospital-primary care networks</td>
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<tr>
<td><strong>2. Evidence-based policy and data for action</strong></td>
</tr>
<tr>
<td>Economic data on the burden of viral hepatitis</td>
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<tr>
<td>Better data on barriers to screening and treatment</td>
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<tr>
<td>Centralised surveillance</td>
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<tr>
<td>Accurate estimates of the number of chronic hepatitis cases</td>
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<tr>
<td><strong>3. Prevention of transmission</strong></td>
</tr>
<tr>
<td>Better monitoring of vaccine effectiveness</td>
</tr>
<tr>
<td>Universal vaccination of children and improved access to vaccination by people at greater risk</td>
</tr>
<tr>
<td>Targeted harm reduction strategies</td>
</tr>
<tr>
<td>Better data on vaccine failure</td>
</tr>
<tr>
<td><strong>4. Screening, care and treatment</strong></td>
</tr>
<tr>
<td>Improved availability and funding of screening [public funds and/or employer-based]</td>
</tr>
<tr>
<td>Linking screening to effective monitoring and treatment</td>
</tr>
<tr>
<td>Funding screening for hepatocellular carcinoma</td>
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<tr>
<td>Improved access to treatment of chronic hepatitis and hepatocellular carcinoma</td>
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Case Study 1: How to engage the public on hepatitis: the ‘KNOw More Hepatitis’ in the United States

In 2011, the United States Centers for Disease Control and Prevention (CDC) launched an education campaign, ‘KNOw More Hepatitis’ [9]. Insights from focus groups consisting of people with high prevalence rates of infection (for example, ‘baby-boomers’ for hepatitis C) helped guide the development of targeted messages for each risk population [10]. The campaign made creative use of social and other media:

• It used powerful, evidence-based messages to engage the media. One example was “Hepatitis now kills more Americans than HIV”, which was the key conclusion of a recently published article in the *Annals of Internal Medicine* [11].

• An online hepatitis risk assessment tool was featured on the CDC website, which allowed individuals to conduct a quick, confidential assessment of their risk for hepatitis A, hepatitis B or hepatitis C in the privacy of their own homes.

• The campaign has an active Facebook page, 11,000 followers on Twitter, and public service advertisements on YouTube. 400 tweets translated into over 3.3 million media impressions, demonstrating the power of social media to engage target audiences on viral hepatitis.

• Six national airports donated space worth up to $4 million for Dioramas which featured rotating posters on viral hepatitis (Fig. 2).

Case Study 2: Conveying the ‘right level of fear’? The Korean experience

In March 2011, the Korean Association for the Study of the Liver (KASL) launched an awareness campaign on viral hepatitis. A 30-minute television advertisement showed patients with end-stage liver disease. The message was: “If you don’t manage your disease, this is what is going to happen.” The goal was to shock the public into action.

The impact of the advertisement was significant; the day after it featured, KASL was ranked top of Google searches. But the increased attention also had unintended adverse consequences: people infected with viral hepatitis reported the loss of relationships or employment as a result of the advertisement. KASL immediately launched a lower-intensity campaign that focused on the importance of seeking proper care for chronic hepatitis infection.

The lesson learned by KASL was that it is important to convey the ‘right’ level of fear about viral hepatitis in order to raise awareness of the urgency of the situation in terms of the risks of advanced liver disease. However, too much fear may create panic and inertia, if the perceived message is that nothing that can be done to improve the outcomes of people with the viral hepatitis or that policy makers, physicians, and the public are powerless to effect change.

Axis 2: Evidence-based policy and data for action

One key condition for successful advocacy and a sustained public health response is reliable data. With viral hepatitis, the fact that so many people remain undiagnosed makes it difficult to convey to policy makers the full scale of the problem [12]. Better surveillance is needed to capture chronic as well as acute cases of viral hepatitis. More reliable prevalence estimates in high risk populations, such as people who are poor, those who inject drugs, prisoners, and sex workers, are needed as these groups are usually poorly represented in existing surveillance studies.

Reliable economic data are critical to demonstrate to national governments the need for them to invest in viral hepatitis prevention and control. Sometimes showing policy makers the cost of ‘doing nothing’ can exemplify the most compelling case for investment [13].

One area where more research is greatly needed is to find the barriers to uptake of screening and treatment among individuals at risk. These data are critical to shift the behaviours of individuals towards more active disease management.

Finally, insights from patients, such as those gathered in a survey of the Japan Hepatitis Council (Case study 3) may help channel efforts towards areas that will make the greatest difference to individuals living with viral hepatitis.
Case Study 3: The combined power of advocacy and data: The Japan Hepatitis Council

Japan has a powerful patient advocacy base consisting of over 80 local, regional and national associations acting under the umbrella of the Japan Hepatitis Council. Pressure from these groups over the government’s failure to implement blood and mass vaccination safety measures was instrumental in the creation of the Basic Act of Hepatitis Measures in 2010. As part of this Act, each prefecture is required to have a hepatitis patient representative on its local council.

A recent survey of members of the Japan Hepatitis Council helped identify some of the main challenges for policy development in Japan [14]:

- **High mortality from hepatocellular carcinoma (HCC):** Japan has one of the highest rates of HCC in the world and counts 30,000 deaths due to HCC every year.
- **Low uptake of screening:** A national screening programme against hepatitis B and C has existed since 2002, targeting individuals aged 40-70 years. However, uptake rates remain low (7-27%) and screening is poorly integrated into general practice [15, 16].
- **Poor linkage to treatment:** 48% of those who test positive for hepatitis B (and 65% of those testing positive for HCV) fail to seek medical care [12] and only half of those with hepatitis C who do seek care complete their course of treatment [14].
- **High costs of care:** Government funding for antiviral treatment of hepatitis B and hepatitis C has gradually increased since 2008, however patients are still left with a significant co-payment and many patients report crippling personal economic costs.
- **Stigma and discrimination:** Thirty percent of respondents report having experienced discrimination due to viral hepatitis, especially in medical institutions. Several respondents felt that their hepatitis status hindered their marriage prospects and employment options. Many admitted that they hid their condition from others as a result.

**Axis 3: Prevention of transmission**

Vaccination against hepatitis B has had a marked impact on reducing the incidence of hepatitis B infection (Case study 4). However, gaps in the region remain. Japan only offers vaccination to infants born to hepatitis B-infected mothers, whereas in Taiwan this is one group in whom vaccination efforts have been less successful. In all countries, careful evaluation of the impact of vaccination and of the benefits of extending vaccination to high risk groups is needed.

Injecting drug use is now the predominant route of transmission for hepatitis C in north Asia [17] and this is a critical target group for prevention strategies. Co-infection of hepatitis B and hepatitis C and/or HIV is a key concern in people who inject drugs, as it is associated with more rapid progression to liver disease and death [18,19]. Targeted education and pre-

**Case Study 4: Taiwan: a vaccination success story**

Taiwan launched one of the first universal vaccination programmes against hepatitis B in 1984 and the programme is heralded around the world as a true success story [24, 25]. Today, systematic vaccination is offered to all newborns, health workers and schoolchildren who missed the neonatal vaccination (catch-up vaccination). The impact of the programme on seroprevalence levels has been considerable (Fig. 3) and horizontal transmission amongst children decreased [26]. The HCC incidence among children has been significantly reduced, making the hepatitis B vaccine the first effective vaccine for the prevention of cancer [27]. The programme has also provided important insights into the natural history of hepatitis B, for example about the duration of conferred immunogenicity and the potential need for booster vaccinations [28].

Complacency must be avoided, however, as thousands of deaths due to viral hepatitis still occur every year in Taiwan. Prevalence rates have not decreased in adults [29] and the impact of vaccination is much lower in rural areas than in urban centres [28, 30]. Also, the success of vaccination cannot be taken for granted: diligent, continuous monitoring of the quality of available vaccines and of the outcomes of vaccination programmes is needed for the public health impact of the vaccination programme against hepatitis B virus to continue in Taiwan [31, 32].

**Fig. 3. Incidence of HCC by age in cohorts born before and after infant vaccination program against hepatitis B virus in Taiwan (started in 1984)** [27].
Special Report

**Axis 4: Screening, care, and treatment**

Greater availability, awareness and uptake of screening for both hepatitis B and hepatitis C were highlighted as the most pressing needs by participants from all countries in the CEVHAP workshop. Countries differ in what screening programmes have been implemented and to what extent screening is covered by public funds. Barriers to screening are likely to be specific to each local context, not to mention each individual (Table 3). It is critical that the confidentiality of screening results is ensured; in many countries, the results of screening may be sent to a person’s employer, causing discrimination and often loss of employment for the person concerned.

Another significant issue is the need to ensure greater linkage from screening to treatment, given a large proportion of individuals who test positive at screening are known not to seek treatment. Comprehensive care models are urgently needed to make sure that individuals who are infected receive appropriate information, counselling, and care throughout all phases of their condition [33]. In many countries, better collaboration between primary care physicians and liver specialists is needed to ensure that individuals who test positive are referred to appropriate care.

A commonly cited barrier to treatment was lack of public funding. Overall, government funding for antiviral therapies for both hepatitis B and hepatitis C has improved considerably over the past decade in all four jurisdictions (see Case study 5). However, out-of-pocket costs are often still high for many patients, be it for diagnosis, monitoring tests [21,34], or antiviral therapies. Funding of antiviral therapies in some countries is often limited to a given number of years, which may impact on compliance with long-term treatment regimens.

It is also important to recognise that lack of funding may sometimes be used as an excuse for not offering available treatments to patients. In truth, physicians are often unaware of existing treatment options, or they remain unconvinced of their benefit despite their inclusion in clinical guidelines and thus adopt a ‘watch and wait’ approach to treatment.

<table>
<thead>
<tr>
<th>Source of barrier</th>
<th>Barriers</th>
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<tbody>
<tr>
<td>Individuals</td>
<td>Unaware that one is at risk of viral hepatitis</td>
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<tr>
<td></td>
<td>Unaware that the disease can have serious long-term effects</td>
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<tr>
<td></td>
<td>Unaware that effective treatments exist</td>
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<td></td>
<td>Cultural beliefs</td>
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<td></td>
<td>Stigma associated with viral hepatitis</td>
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<tr>
<td></td>
<td>Costs associated with testing [lack of funding]</td>
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<tr>
<td>Health care providers</td>
<td>Social stigma</td>
</tr>
<tr>
<td></td>
<td>Poor understanding of the availability and effectiveness of treatment</td>
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<td></td>
<td>‘wait and see’ attitude to viral hepatitis</td>
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<tr>
<td></td>
<td>Cost barriers to access treatment</td>
</tr>
<tr>
<td></td>
<td>Lack of awareness about the need for monitoring [hepatitis B]</td>
</tr>
<tr>
<td>Healthcare system</td>
<td>Lack of continuity/no linkage from screening to care</td>
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<tr>
<td></td>
<td>Cost of therapy/lack of government reimbursement</td>
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</tbody>
</table>

Adapted from [38].

**Discussion**

Medical science and public policy have reached a critical, and exciting, juncture for viral hepatitis: 179 countries worldwide have implemented vaccination programmes against hepatitis B. Up to 95% of cases of hepatitis B infection are now treatable and up to 60% of those of hepatitis C infection are curable [27,35,36]. Cirrhosis can be reversed [37] and treatment of liver cancer, once thought to be impossible, is now possible. Yet three-quarters of those infected with hepatitis B virus and 65% of those infected with hepatitis C virus do not know they are infected [3]. Screening uptake is low, as is uptake and adherence to treatment, with the result that outcomes for individuals infected with viral hepatitis remain suboptimal.

The CEVHAP North Asia Workshop on Viral Hepatitis highlighted the key challenges facing Hong Kong, Japan, Korea, and Taiwan in their fight against viral hepatitis. These challenges are similar to those in other regions [2,3]. The WHO Framework provides a blueprint for action, but the onus is on governments to reduce the burden posed by hepatitis locally, within the constraints and possibilities of their local epidemiology, resources, health care infrastructure, and advocacy base.
The research community has an important role to play in guiding policy development on viral hepatitis. Liver specialists, in partnership with voluntary sector organisations, may help ensure that key facts about viral hepatitis – for example, that hepatitis B is treatable and hepatitis C is curable – are communicated to the media, the public and policymakers in a way that is accessible and compelling. Social research and observational studies may help create a better understanding of the health seeking behaviours of people at risk of viral hepatitis and identify existing barriers to screening, diagnosis, and proper treatment.

The WHO Framework provides a unique opportunity to countries around the world to take stock of how they have addressed the challenges posed by viral hepatitis in the past and create comprehensive, cohesive policies that may have a lasting impact. This will require a collaborative effort from primary care physicians, specialists, governments, individuals at risk and people living with viral hepatitis. Working in partnership with other more high-profile disease areas, for example non-communicable diseases, may present opportunities to raise the profile of viral hepatitis. Indeed, lessons may be learned from other disease areas – such as breast cancer, cardiovascular disease and HIV/AIDS – which have raised awareness, secured funding and developed comprehensive policies that have changed the lives of people living with the condition. The WHO Framework provides the steer to do the same for the millions of people worldwide infected with viral hepatitis.

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Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Addendum

Participants of the Coalition to Eradicate Viral Hepatitis in Asia Pacific [CEVHAP] North Asia Workshop on Viral Hepatitis included: from Taiwan: Ding-Shinn Chen, Pei-Jer Chen, Sheng-Nan Lu, Pei-Ming Yang; from Hong Kong: Joseph Sung, Ching-Lung Lai, James Y.Y. Fung; from Korea: Si Hyun Bae, June Sung Lee, Hong Soo Kim, Sang-Hoon Ahn, Goo Hyeon Yoon; from Japan: Junko Tanaka, Takaji Wakita, Hideki Aizaki, Atsuko Yonezawa, Yukio Lino, Yoichi Abe; from the United States: John Ward, Lily Lou; from the UK: Charles Gore; from Malaysia: Rossmawati Mohamed; from Australia: Stephen Locarnini and Jack Wallace. The workshop was facilitated by Suzanne Wait (UK) and Jennifer Johnston (Australia).

References

[7] IMS Health Taiwan. Taiwan hepatitis B disease awareness and attitude in general population. IMS Health Taiwan; 2005.
Global policy report on the prevention and control of viral hepatitis

IN WHO MEMBER STATES
Chapter 7: WHO South-East Asia Region

Eleven Member States make up the World Health Organization (WHO) South-East Asia Region, which has a total population of 1.83 billion.\(^1\) India, with a population of 1.24 billion, accounts for approximately two thirds of the Region's population.\(^1\) The South-East Asia Region hosts one fourth of the world's population and carries about 30% of the world's total disease burden.\(^2\) In 2009, life expectancy at birth for the South-East Asia Region was 65 years.\(^3\)

The greatest contributors to morbidity and mortality are noncommunicable diseases: cardiovascular diseases and cancer account for about 30% and 9% of deaths, respectively.\(^4\) Age-standardized mortality rates (2008) indicate that communicable diseases account for about 30% of deaths.\(^5\) The South-East Asia Region has high child mortality, with three fourths of these deaths resulting from diarrhoeal diseases, pneumonia and neonatal conditions.\(^6\) The Region is home to more than two thirds of the world's malnourished children.\(^6\) Unsafe water and inadequate sanitation and hygiene pose major health risks to both children and adults; the Region has the highest incidence of diarrhoeal disease in the world.\(^7\)

Responses to the WHO/Alliance survey were received from all 11 Member States in the South-East Asia Region (100%).

**Box 1.** Responses to the 2012 Global Hepatitis Survey: WHO South-East Asia Region

<table>
<thead>
<tr>
<th>Member States that submitted surveys:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
</tr>
<tr>
<td>Bhutan</td>
</tr>
<tr>
<td>Democratic People’s Republic of Korea</td>
</tr>
<tr>
<td>Indonesia</td>
</tr>
<tr>
<td>Maldives</td>
</tr>
<tr>
<td>Myanmar</td>
</tr>
<tr>
<td>Nepal</td>
</tr>
<tr>
<td>Sri Lanka</td>
</tr>
<tr>
<td>Thailand</td>
</tr>
<tr>
<td>Timor-Leste</td>
</tr>
</tbody>
</table>

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**Viral hepatitis in the WHO South-East Asia Region**

The endemicity of hepatitis A in the Region ranges from low (<50% exposed by the age of 30 years) in the eastern areas to high (>90% exposed by the age of 10 years) in the southern areas.\(^8\)

Approximately 14 million cases of hepatitis E infection occur annually in the Region, which accounts for more than half the global burden. Indeed, the prevalence of hepatitis E is estimated to be above 25% in those >50 years of age.\(^9\)

The seroprevalence of hepatitis B in the young age groups of 0–14 years is 1.2%–1.4%. However, in adults, the seroprevalence is higher, at above 5%.\(^10\)

There are up to 50 million people with chronic hepatitis C infection in the South Asia.\(^11\) Because of the asymptomatic nature of chronic hepatitis B and hepatitis C, most people infected with these are not aware of their status until they have symptoms of cirrhosis or liver cancer many years later.\(^11\)
National coordination

Four responding Member States (36.4%) reported the existence of a written national strategy or plan that focuses exclusively or primarily on the prevention and control of viral hepatitis (Figure 1). Three of the four Member States with a strategy or plan (Democratic People’s Republic of Korea, India and Indonesia) reported that it focuses exclusively on viral hepatitis, and one (Myanmar) reported that it addresses other diseases as well.

Figure 1. Responses to the question, “Is there a written national strategy or plan that focuses exclusively or primarily on the prevention and control of viral hepatitis?”

The four Member States that reported the existence of a strategy or plan were asked about its specific components. All four reported the inclusion of components for raising awareness, surveillance, vaccination, general prevention, prevention of transmission in health-care settings, and treatment and care. Three reported the inclusion of a component for the prevention of transmission via injecting drug use.

Three responding Member States (27.3%) reported that they have a governmental unit or department responsible solely for viral hepatitis-related activities. Member States that did so were asked to indicate the number of staff members in the unit or department. Responses ranged from 4 to 20 (median, 4), with Myanmar reporting the largest number.

Member States were asked to report the number of people working full-time on hepatitis-related activities in all government agencies or bodies. Among the three Member States that provided data for this question, the number ranged from 0 to 49 (median, 30.5), with Myanmar reporting the largest number.

Nine responding Member States (81.8%) reported that they have a viral hepatitis prevention and control programme that includes activities targeting specific populations. The populations most commonly targeted were health-care workers, including health-care waste handlers (77.8% of responding Member States within this subset) and people who inject drugs (44.4% of responding Member States within this subset). The following populations were each targeted by one third of responding Member States within this subset: migrants, prisoners and people living with HIV. Groups identified less frequently included indigenous populations, low-income populations, those who are uninsured and those who are homeless.

Awareness-raising and partnerships

One responding Member State (9.1%) reported that it had held events for World Hepatitis Day 2012 (28 July). Since January 2011, three responding Member States (27.3%) had funded some type of viral hepatitis public awareness campaign other than World Hepatitis Day (Table 1).

Four responding Member States (36.4%) reported that they collaborated with civil society groups within their countries to develop and implement the governmental viral hepatitis prevention and control programme. For example, Bangladesh reported collaborating with the Liver Foundation of Bangladesh, and Myanmar reported collaborating with health-care provider associations and with the Myanmar Red Cross Association. (Further examples can be found in the summaries of country findings later in this chapter.)

Table 1. Topics of public awareness campaigns on viral hepatitis held in Member States since January 2011 (N=3)

<table>
<thead>
<tr>
<th>Topic</th>
<th>Democratic People’s Republic of Korea</th>
<th>Indonesia</th>
<th>Myanmar</th>
</tr>
</thead>
<tbody>
<tr>
<td>General information about hepatitis and its transmission</td>
<td>X</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Vaccination for hepatitis A and hepatitis B</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Importance of knowing one’s hepatitis B and hepatitis C status</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Safe water and good sanitation</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safer sex practices</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Harm reduction for people who inject drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safe workplace practices</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
Evidence-based policy and data for action
Six responding Member States (54.5%) reported that they have routine surveillance for viral hepatitis; details appear in Table 2.

Seven responding Member States (63.6%) indicated that their countries have standard case definitions for hepatitis infection and seven (63.6%) indicated that their countries have a central registry for the reporting of deaths, including hepatitis deaths.

Two Member States reported on the proportion of hepatitis cases and deaths registered as “undifferentiated” or “unclassified” hepatitis. One reported this to be 25.1% and the other less than 5.0%. Additional survey findings about surveillance are presented in Table 3.

Table 2. Types of surveillance in Member States that reported the existence of routine surveillance for viral hepatitis (N=6)

<table>
<thead>
<tr>
<th></th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Do not know (%)</th>
<th>No response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is a national surveillance system for acute hepatitis infection for the following forms of hepatitis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hepatitis A</td>
<td>83.3</td>
<td>0</td>
<td>0</td>
<td>16.7</td>
</tr>
<tr>
<td>hepatitis B</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>hepatitis C</td>
<td>83.3</td>
<td>0</td>
<td>0</td>
<td>16.7</td>
</tr>
<tr>
<td>hepatitis D</td>
<td>33.3</td>
<td>33.3</td>
<td>0</td>
<td>33.3</td>
</tr>
<tr>
<td>hepatitis E</td>
<td>33.3</td>
<td>33.3</td>
<td>0</td>
<td>33.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Do not know (%)</th>
<th>No response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is a national surveillance system for chronic hepatitis infection for the following forms of hepatitis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hepatitis B</td>
<td>33.3</td>
<td>66.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>hepatitis C</td>
<td>33.3</td>
<td>66.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>hepatitis D</td>
<td>0</td>
<td>83.3</td>
<td>0</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Member States were asked how often hepatitis disease reports are published. Of the responding Member States, 45.5% said that reports are not published. Among the six Member States with published reports, one said reports are published weekly, one weekly and annually, two monthly and annually, and one annually. The sixth said reports are published in journal articles.

Three responding Member States (27.3%, Democratic People’s Republic of Korea, Indonesia and Myanmar) reported the existence of a national public health research agenda for viral hepatitis.

Two responding Member States (18.2%, the Democratic People’s Republic of Korea and Myanmar) reported that viral hepatitis serosurveys are conducted regularly. Myanmar indicated that serosurveys take place at least once per year. The Democratic People’s Republic of Korea said that its serosurveys target children under the age of 17 years, while Myanmar said that its serosurveys target children over the age of 5 years and the general population. The most recent serosurvey in the Democratic People’s Republic of Korea was conducted in 2009, and the most recent one in Myanmar was conducted in 2010.

Prevention of transmission
No responding Member State reported that they have a national policy on hepatitis A vaccination.

Two responding Member States (18.2%) reported that they have established the goal of eliminating hepatitis B (Figure 2). Member States with this goal were asked to specify the timeframe in which they seek to eliminate hepatitis B. The Democratic People’s Republic of Korea said by 2016, and Sri Lanka said by 2015.

Member States were asked to report, for a given recent year, the percentage of newborn infants who had received the first dose of hepatitis B vaccine within 24 hours of birth. Among the seven governments providing this information, responses ranged from 0% to 99.9% (median, 75.4%). Governments were

Figure 2. Responses to the question, “Has your government established the goal of eliminating hepatitis B?” (N=11)
also asked to report, for a given recent year, the percentage of one-year-olds (ages 12–23 months) who had received three doses of hepatitis B vaccine. Among the eight governments providing this information, responses ranged from 38.0% to 99.0% (median, 93.9%).

Seven responding governments (63.6%) reported the existence of a national policy that specifically targets mother-to-child transmission of hepatitis B; details are presented in Table 4. Five governments with such a policy indicated that one component of the policy calls for screening of all pregnant women for hepatitis B. Seven governments with such a policy indicated that one component of the policy calls for administering the second and third doses of hepatitis B vaccine to all infants within 12 months of birth.

Table 4. Activities called for in national policy targeting mother-to-child transmission of hepatitis B (N=7)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Bhutan</th>
<th>Democratic People's Republic of Korea</th>
<th>India</th>
<th>Maldives</th>
<th>Myanmar</th>
<th>Nepal</th>
<th>Thailand</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pregnant women are screened for hepatitis B</td>
<td>X X</td>
<td>X</td>
<td>X</td>
<td>X X</td>
<td>X X</td>
<td>X</td>
<td>X X</td>
<td>5</td>
</tr>
<tr>
<td>All pregnant women found to have hepatitis B are counselled</td>
<td>X X</td>
<td>X</td>
<td>X</td>
<td>X X</td>
<td>X X</td>
<td>X</td>
<td>X X</td>
<td>6</td>
</tr>
<tr>
<td>Health-care providers follow up with all pregnant women who have hepatitis B and counsel them on the need for discouraging infanticide at health-care facilities</td>
<td>X X</td>
<td>X</td>
<td>X</td>
<td>X X</td>
<td>X X</td>
<td>X</td>
<td>X X</td>
<td>4</td>
</tr>
<tr>
<td>Upon delivery, all infants born to mothers with hepatitis B receive hepatitis B immunoglobulin</td>
<td>X X</td>
<td>X</td>
<td>X</td>
<td>X X</td>
<td>X X</td>
<td>X</td>
<td>X X</td>
<td>3</td>
</tr>
<tr>
<td>All infants receive the first dose of hepatitis B vaccine within 24 hours of birth</td>
<td>X X</td>
<td>X</td>
<td>X</td>
<td>X X</td>
<td>X X</td>
<td>X</td>
<td>X X</td>
<td>6</td>
</tr>
</tbody>
</table>

Five responding Member States (45.5%) reported the existence of a specific national strategy and/or policy for preventing hepatitis B and hepatitis C infection in health-care settings.

Five responding Member States (45.5%) reported that health-care workers are vaccinated against hepatitis B prior to starting work that might put them at risk of exposure to blood.

Ten responding Member States (90.9%) reported that single-use or auto-disable syringes, needles and cannulas are always available in all health-care facilities.

Member States were asked for official estimates of the number and percentage of unnecessary injections administered annually in health-care settings (e.g. injections that are given when an equivalent oral medication is available). Ten Member States reported that the figures are not known and one did not reply.

Additional findings relating to the prevention of hepatitis transmission are presented in Table 5.

Screening, care and treatment

Member States were asked how health professionals in their countries obtain the skills and competencies required to effectively care for people with viral hepatitis. Eight Member States indicated that these are obtained in schools for health professionals (pre-service education) and on-the-job training.

Four responding Member States (36.4%) reported the existence of national clinical guidelines for the management of viral hepatitis (Figure 4). Two of these four responding Member States (50.0%) indicated that the guidelines include recommendations for cases with HIV coinfection.
**Table 5.** Hepatitis prevention: policies, practices and guidelines [N=11]

<table>
<thead>
<tr>
<th>Policy/Practice</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Do not know (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is a national infection control policy for blood banks</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All donated blood units (including family donations) and blood products nationwide are screened for hepatitis B</td>
<td>90.9</td>
<td>9.1</td>
<td>0</td>
</tr>
<tr>
<td>All donated blood units (including family donations) and blood products nationwide are screened for hepatitis C</td>
<td>81.8</td>
<td>9.1</td>
<td>9.1</td>
</tr>
<tr>
<td>There is a national policy relating to the prevention of viral hepatitis among people who inject drugs</td>
<td>18.2</td>
<td>63.6</td>
<td>18.2</td>
</tr>
<tr>
<td>The government has guidelines that address how hepatitis A and hepatitis E can be prevented through food and water safety</td>
<td>45.5</td>
<td>54.5</td>
<td>0</td>
</tr>
</tbody>
</table>

Three responding Member States (27.3%) indicated that they have a national policy relating to screening and referral to care for hepatitis B. Two (18.2%) reported having such a policy for hepatitis C.

Regarding hepatitis B testing, ten responding Member States (90.9%) indicated that people register by name for testing. Eight of the ten members of that subset (80.0%) indicated that the names are kept confidential. Five responding Member States (45.5%) reported that the hepatitis B test is free of charge for all individuals. Among the six other Member States, Myanmar and Thailand reported that the hepatitis B test is free of charge for members of specific groups. Groups identified include blood donors and pregnant women. Six responding Member States (54.5%) reported that the hepatitis B test is compulsory for members of specific groups. Groups identified include blood donors and people living with HIV.

Regarding hepatitis C testing, ten responding Member States (90.9%) indicated that people register by name for testing. Eight of the ten members of that subset (80.0%) indicated that the names are kept confidential. Five responding Member States (45.5%) reported that the hepatitis C test is free of charge for all individuals. Among the six other Member States, Myanmar and Thailand reported that the hepatitis C test is free of charge for members of specific groups. Groups identified include blood donors and pregnant women. Six responding Member States (54.5%) reported that the hepatitis C test is compulsory for members of specific groups. Groups identified include blood donors and people living with HIV.

Six responding Member States (54.5%) reported that publicly funded treatment is available for hepatitis B and six (54.5%) that publicly funded treatment is available for hepatitis C. Information was not provided by any Member State regarding the amount spent on publicly funded treatment for hepatitis B and hepatitis C.

Nine responding Member States (81.8%) reported that at least one available drug for treating hepatitis B is on the national essential medicines list (Table 6). The drugs most commonly reported were lamivudine, interferon alpha, tenofovir and pegylated interferon.

Seven responding Member States (63.6%) reported that at least one available drug for treating hepatitis C is on the national essential medicines list. The drugs most commonly reported were interferon alpha, pegylated interferon and ribavirin.

**World Health Organization assistance**

Member States were asked to indicate areas in which they might want assistance from WHO for the prevention and control of viral hepatitis. Respondents most commonly selected the following: developing the national plan for viral hepatitis prevention and control (81.8%), estimating the national burden of viral hepatitis (81.8%) and conducting viral hepatitis surveillance (81.8%) (Table 7). Responses from individual Member States appear in Annex C.
Table 6. Proportion of Member States reporting drugs for treating hepatitis B and C on national essential medicines lists or subsidized by governments

<table>
<thead>
<tr>
<th>Drugs for treating hepatitis B</th>
<th>% of Member States reporting its inclusion (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>63.6</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>45.5</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>45.5</td>
</tr>
<tr>
<td>Pegylated interferon</td>
<td>36.4</td>
</tr>
<tr>
<td>Entecavir</td>
<td>36.4</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>36.4</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>27.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs for treating hepatitis C</th>
<th>% of Member States reporting its inclusion (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin</td>
<td>54.5</td>
</tr>
<tr>
<td>Pegylated interferon</td>
<td>45.5</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>45.5</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>27.3</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Table 7. Viral hepatitis control and prevention: areas in which Member States indicated interest in receiving WHO assistance (N=11)

<table>
<thead>
<tr>
<th>Awareness-raising, partnerships and resource mobilization (first WHO strategic axis)</th>
<th>% of Member States reporting its inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing the national plan for viral hepatitis prevention and control</td>
<td>81.8%</td>
</tr>
<tr>
<td>Integrating viral hepatitis programmes into other health services</td>
<td>63.6%</td>
</tr>
<tr>
<td>Awareness-raising</td>
<td>72.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evidence-based policy and data for action (second WHO strategic axis)</th>
<th>% of Member States reporting its inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis surveillance</td>
<td>81.8%</td>
</tr>
<tr>
<td>Estimating the national burden of viral hepatitis</td>
<td>81.8%</td>
</tr>
<tr>
<td>Developing tools to assess the effectiveness of interventions</td>
<td>63.6%</td>
</tr>
<tr>
<td>Assessing the economic impact of viral hepatitis</td>
<td>54.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevention of transmission (third WHO strategic axis)</th>
<th>% of Member States reporting its inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing coverage of the birth dose of the hepatitis B vaccine</td>
<td>54.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screening, care and treatment (fourth WHO strategic axis)</th>
<th>% of Member States reporting its inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing access to treatment</td>
<td>54.5%</td>
</tr>
<tr>
<td>Increasing access to diagnostics</td>
<td>63.6%</td>
</tr>
<tr>
<td>Improving laboratory quality</td>
<td>0%*</td>
</tr>
<tr>
<td>Developing education/training programmes for health professionals</td>
<td>63.6%</td>
</tr>
</tbody>
</table>

*N=26 (This response option was not included in the survey completed by Member States of the South-East Asia Region.)
Twenty-seven Member States make up the Western Pacific Region, which has a total population of 1.8 billion. The population of China accounts for approximately three fourths of this total.\(^7\)

The Western Pacific Region encompasses countries at different levels of socioeconomic development, and includes six high-income countries.\(^2\) It also includes geographically isolated Pacific Island Countries with poor infrastructure.\(^3\) Health indicators for the Region vary widely. Across countries, the median life expectancy at birth is 70 years. However, it is 8–11 years lower in five countries of the Region, while Japan's life expectancy of 83 years is the highest in the world.\(^4\) Similarly, the median under-five mortality rate across countries is 19 per 1000 population (Papua New Guinea) and the lowest is 3 per 1000 (Japan and Singapore).\(^4\)

Noncommunicable diseases caused 80% of deaths in the Western Pacific Region in 2008,\(^4\) with cardiovascular diseases accounting for almost half of the deaths from noncommunicable diseases.\(^5\) Among WHO regions, the Western Pacific Region has the highest prevalence of daily tobacco smoking among men (46%); it also has the highest rates of lung cancer among both sexes (combined).\(^6\) Alcohol is another major risk factor, particularly in low- and middle-income countries in the Region.\(^4\) Liver cancer rates in the Region are far higher than in other regions.\(^7\)

Responses to the WHO/Alliance survey were received from 15 of the 27 Member States in the Region (55.6%).

### Box 1. Responses to the 2012 Global Hepatitis Survey: WHO Western Pacific Region

<table>
<thead>
<tr>
<th>Member States that submitted surveys:</th>
<th>Member States that did not submit surveys:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Lao People’s Democratic Republic</td>
</tr>
<tr>
<td>Brunei Darussalam</td>
<td>Cambodia</td>
</tr>
<tr>
<td>Cambodia</td>
<td>China</td>
</tr>
<tr>
<td>China</td>
<td>Japan</td>
</tr>
<tr>
<td>Japan</td>
<td>Kiribati</td>
</tr>
<tr>
<td>Kiribati</td>
<td>New Zealand</td>
</tr>
<tr>
<td>Cook Islands</td>
<td>Nauru</td>
</tr>
<tr>
<td>Fiji</td>
<td>Niue</td>
</tr>
<tr>
<td>Marshall Islands</td>
<td>Palau</td>
</tr>
<tr>
<td>Micronesia (Federated States of)</td>
<td>Philippines</td>
</tr>
</tbody>
</table>

Viral hepatitis in the WHO Western Pacific Region

Very low prevalence rates (<50% of population exposed by the age of 30 years) for hepatitis A have been consistently reported from high-income Asia-Pacific countries and Australasia (Australia and New Zealand). Very little information is available from island nations in the Region, though they appear, on average, to have an intermediate prevalence rate.\(^8\)

Similarly, for hepatitis E, studies are scarce; however, prevalence estimates above 5% are not reported in the Region.\(^9\)

In this Region, with the exception of Australia, Japan and New Zealand where the chronic hepatitis B infection rate varies from 2% to 4%, countries have an estimated rate of 5%–7% or more.\(^4\)

The Region accounts for 48% of global liver cancer cases among men and 62% among women. Moreover, liver cancer is the third most common cause of cancer mortality among men in the Region.\(^4\)

For hepatitis C infection, prevalence estimates are 2.6% for the Region.\(^8\) Although strategies have been implemented to reduce the risk factors for hepatitis C infection, unsafe blood transfusion, unsafe injections and injecting drug use are the major routes of transmission in the Region.

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National coordination

Ten responding Member States (66.7%) reported the existence of a written national strategy or plan that focuses exclusively or primarily on the prevention and control of viral hepatitis (Figure 1). One of the ten Member States with a strategy or plan (Mongolia) reported that it focuses exclusively on viral hepatitis, and five (Brunei Darussalam, Cambodia, Lao People’s Democratic Republic, Malaysia and Tonga) reported that it addresses other diseases as well. Two countries (China and Kiribati) reported that the strategy or plan addresses only hepatitis B, and two (Australia and Japan) reported that it addresses hepatitis B and hepatitis C.

Figure 1. Responses to the question, “Is there a written national strategy or plan that focuses exclusively or primarily on the prevention and control of viral hepatitis?”

Yes  No  No response  No data

The ten Member States that reported the existence of a strategy or plan were asked about its specific components. All ten reported the inclusion of components for raising awareness, vaccination and general prevention. Nine reported the inclusion of a component for prevention of transmission in health-care settings, eight reported the inclusion of a component for surveillance and seven reported the inclusion of a component for treatment and care. Five reported the inclusion of components for coinfection with HIV and the prevention of transmission via injecting drug use.

Five responding Member States (33.3%) reported that they have a governmental unit or department responsible solely for viral hepatitis-related activities. Member States that did so were asked to indicate the number of staff members in the unit or department. Responses (N=5) ranged from 0.1 (New Zealand) to 80 (Cambodia) (median, 7).

Member States were asked to report the number of people working full-time on hepatitis-related activities in all government agencies or bodies. Among the six Member States that provided data for this question, the number ranged from 0 to 84 (median, 0.5), with Mongolia reporting the largest number.

Thirteen responding Member States (86.7%) reported that they have a viral hepatitis prevention and control programme that includes activities targeting specific populations. The populations most commonly targeted are health-care workers, including health-care waste handlers (69.2% of responding Member States within this subset) and people who inject drugs (46.2% of responding Member States within this subset). Groups identified less frequently included indigenous populations, low-income populations, prisoners, migrants, people living with HIV, those who are uninsured and those who are homeless.

Awareness-raising and partnerships

Six responding Member States (40.0%) reported that they had held events for World Hepatitis Day 2012 (28 July). Since January 2011, nine responding Member States (60.0%) had funded some type of viral hepatitis public awareness campaign other than World Hepatitis Day (Table 1).

Eight responding Member States (53.3%) reported that they collaborated with civil society groups within their countries to develop and implement the governmental viral hepatitis prevention and control programme. For example, China reported collaborating with the Wu Jieping Medical Foundation and Chinese Foundation for Hepatitis Prevention and Control, while Malaysia reported collaborating with the Malaysian Liver Foundation. (Further examples can be found in the summaries of country findings later in this chapter.)

Evidence-based policy and data for action

Twelve responding Member States (80.0%) reported that they have routine surveillance for viral hepatitis; details appear in Table 2.

Twelve responding Member States (80.0%) indicated that their countries have standard case definitions for hepatitis infection and 12 (80.0%) indicated that their countries have a central registry for the reporting of deaths, including hepatitis deaths.

Seven Member States reported on the proportion of hepatitis cases and deaths registered as “undifferentiated” or “unclassified” hepatitis. The reported proportions ranged from 0% to 30.0% (median, 1.0%). Additional survey findings about surveillance are presented in Table 3.

Member States were asked how often hepatitis disease reports are published. Of the responding Member States, 33.3% reported that they publish hepatitis disease reports annually; 13.3%, monthly; and 13.3%, weekly. No hepatitis disease report is published by 33.3% of responding Member States.
Table 2. Types of surveillance in Member States that reported the existence of routine surveillance for viral hepatitis (N=12)

<table>
<thead>
<tr>
<th>Surveillance</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Do not know (%)</th>
<th>No response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is a national surveillance system for acute hepatitis A infection for the following forms of hepatitis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hepatitis A</td>
<td>75.0</td>
<td>8.3</td>
<td>0</td>
<td>16.7</td>
</tr>
<tr>
<td>hepatitis B</td>
<td>91.7</td>
<td>8.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>hepatitis C</td>
<td>75.0</td>
<td>16.7</td>
<td>0</td>
<td>8.3</td>
</tr>
<tr>
<td>hepatitis D</td>
<td>25.0</td>
<td>41.7</td>
<td>0</td>
<td>33.3</td>
</tr>
<tr>
<td>hepatitis E</td>
<td>50.0</td>
<td>25.0</td>
<td>0</td>
<td>25.0</td>
</tr>
<tr>
<td>There is a national surveillance system for chronic hepatitis infection for the following forms of hepatitis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hepatitis B</td>
<td>58.3</td>
<td>33.2</td>
<td>0</td>
<td>8.3</td>
</tr>
<tr>
<td>hepatitis C</td>
<td>41.7</td>
<td>50.0</td>
<td>0</td>
<td>8.3</td>
</tr>
<tr>
<td>hepatitis D</td>
<td>25.0</td>
<td>58.3</td>
<td>0</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Table 3. Data registration and surveillance (N=15)

<table>
<thead>
<tr>
<th>Description</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Do not know (%)</th>
<th>No response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver cancer cases are registered nationally</td>
<td>73.3</td>
<td>20.0</td>
<td>6.7</td>
<td>0</td>
</tr>
<tr>
<td>Cases with HIV/hepatitis coinfection are registered nationally</td>
<td>26.7</td>
<td>66.7</td>
<td>6.7</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis outbreaks are reported</td>
<td>93.3</td>
<td>0</td>
<td>6.7</td>
<td>0</td>
</tr>
<tr>
<td>If YES – Hepatitis outbreaks are further investigated (N=115)</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Five responding Member States (33.3%, Australia, Cambodia, China, Japan, Lao People’s Democratic Republic) reported the existence of a national public health research agenda for viral hepatitis.

Six responding Member States (40.0%) reported that viral hepatitis serosurveys are conducted regularly. Among this subset of responding Member States, two (Australia and Lao People’s Democratic Republic) indicated that serosurveys take place every five years. Two Member States in the same subset (Lao People’s Democratic Republic and Singapore) reported that the most recent viral hepatitis serosurvey was carried out in 2012.

Prevention of transmission

Five responding Member States (33.3%) reported that they have a national policy on hepatitis A vaccination.

Nine responding Member States (60.0%) reported that they have established the goal of eliminating or reducing hepatitis B. Of the six Member States that answered this question, three (Brunei Darussalam, China and Mongolia) said 2012 and three (Cambodia, Lao People’s Democratic Republic and Papua New Guinea) said 2017.

Member States were asked to report, for a given recent year, the percentage of newborn infants who had received the first dose of hepatitis B vaccine within 24 hours of birth. Among the 13 Member States that provided this information, responses ranged from 0% to 98.0% (median, 55.0%). Member States were also asked to report, for a given recent year, the percentage of one-year-olds (ages 12–23 months) who had received three doses of hepatitis B vaccine. Among the 15 Member States that provided this information, responses ranged from 0% to 98.8% (median, 93.0%).

Fifteen responding Member States (100%) reported the existence of a national policy that specifically targets mother-to-child transmission of hepatitis B; details are presented in Table 4. One third of Member States with such a policy (33.3%) indicated that one component of the policy calls for screening of all pregnant women for hepatitis B.
One Member State that answered “yes” to this question (Australia) added a comment indicating that the goal relates to reducing rather than eliminating hepatitis B.

Fourteen responding Member States (91.3%) reported the existence of a specific national strategy and/or policy/guidelines for preventing hepatitis B and hepatitis C infection in health-care settings.

Eleven responding Member States (73.3%) reported that health-care workers are vaccinated against hepatitis B prior to starting work that might put them at risk of exposure to blood.

Twelve responding Member States (80.0%) reported the existence of a national policy on injection safety in health-care settings. These Member States were asked which types of syringes the policy recommends for therapeutic injections. Single-use syringes are recommended in 100% of policies, and auto-disable syringes in 16.7% (Figure 3).

Twelve responding Member States (80.0%) reported that single-use or auto-disable syringes, needles and cannulas are always available in all health-care facilities.

Member States were asked for official estimates of the number and percentage of unnecessary injections administered annually in health-care settings (e.g. injections that are given when an equivalent oral medication is available). Twelve Member States reported that the figures are not known and one (Tonga) reported that no unnecessary injection is administered annually in health-care settings. Cambodia reported that 50.0% of the total injections that are administered annually in health-care settings are unnecessary and Mongolia reported that 68.0% are unnecessary.

Additional findings relating to the prevention of hepatitis transmission are presented in Table 5.

Screening, care and treatment

Member States were asked how health professionals in their countries obtain the skills and competencies required to effectively care for people with viral hepatitis. Responding Member States most frequently indicated that these are obtained in schools for health professionals (pre-service education, 80.0%). Additionally, on-the-job training was identified in 66.7% of responses, and postgraduate training in 53.3%.

Nine responding Member States (60.0%) reported the existence of national clinical guidelines for the management of viral hepatitis (Figure 4). Two of these nine Member States indicated that the guidelines include recommendations for cases with HIV coinfection. Five of 11 responding Member States (45.5%) indicated that there are national clinical guidelines for the management of HIV, which include recommendations for coinfection with viral hepatitis.
Ten responding Member States (66.7%) indicated that they have a national policy relating to screening and referral to care for hepatitis B. Five (33.3%) reported having such a policy for hepatitis C.

Regarding hepatitis B testing, 13 responding Member States (86.7%) indicated that people register by name for testing. Twelve members of that subset (92.3%) indicated that the names are kept confidential. Seven responding Member States (46.7%) reported that the hepatitis B test is free of charge for all individuals. Among the eight other Member States, three (37.5%) reported that the hepatitis B test is free of charge for members of specific groups. Groups identified included blood donors and health-care workers. Seven responding Member States (46.7%) reported that the hepatitis B test is compulsory for members of specific groups. Groups identified included blood donors, pregnant women and imprisoned people who inject drugs.

Regarding hepatitis C testing, 10 responding Member States (66.7%) indicated that people register by name for testing. All members of that subset (100%) indicated that the names are kept confidential. Four responding Member States (26.7%) reported that the hepatitis C test is free of charge for all individuals. Among the eight other Member States that answered the question, three (37.5%) reported that the hepatitis C test is free of charge for members of specific groups. Groups identified included blood donors and health-care workers. Seven responding Member States (46.7%) reported that the hepatitis C test is compulsory for members of specific groups. Groups identified included blood donors, pregnant women and imprisoned people who inject drugs.

Eight responding Member States (53.3%) reported that publicly funded treatment is available for hepatitis B and seven (46.7%) that publicly funded treatment is available for hepatitis C. One responding Member State reported the amount spent on publicly funded treatment for hepatitis B and hepatitis C. Details can be found in the summaries of country findings later in this chapter (see New Zealand).
Eleven responding Member States (73.3%) reported that at least one available drug for treating hepatitis B is on the national essential medicines list or subsidized by the government (Table 6). The drugs most commonly reported were lamivudine and interferon alpha.

Eight responding governments (53.3%) reported that at least one available drug for treating hepatitis C is on the national essential medicines list or subsidized by the government. The drugs most commonly reported were ribavirin, interferon alpha and pegylated interferon.

World Health Organization assistance

Member States were asked to indicate areas in which they might want assistance from WHO for the prevention and control of viral hepatitis. Respondents most commonly selected the following: increasing access to treatment (46.7%), increasing access to diagnostics (46.7%), improving laboratory capacity (46.7%) and developing education/training programmes for health professionals (46.7%) (Table 7). Responses from individual Member States appear in Annex C.

<table>
<thead>
<tr>
<th>Drugs for treating hepatitis B</th>
<th>% of Member States reporting its inclusion (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>60.0</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>53.3</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>40.0</td>
</tr>
<tr>
<td>Pegylated interferon</td>
<td>40.0</td>
</tr>
<tr>
<td>Entecavir</td>
<td>40.0</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>33.3</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>20.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs for treating hepatitis C</th>
<th>% of Member States reporting its inclusion (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin</td>
<td>46.7</td>
</tr>
<tr>
<td>Pegylated interferon</td>
<td>40.0</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>40.0</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>6.7</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>0.0</td>
</tr>
</tbody>
</table>

| Table 6. Proportion of Member States reporting drugs for treating hepatitis B and C on national essential medicines lists or subsidized by governments |

| Table 7. Viral hepatitis control and prevention: areas in which Member States indicated interest in receiving WHO assistance (N=15) |
| Awareness-raising, partnerships and resource mobilization (first WHO strategic axis) |
| Developing the national plan for viral hepatitis prevention and control                  | 40.0% |
| Integrating viral hepatitis programmes into other health services                       | 40.0% |
| Awareness-raising                                                                       | 33.3% |

| Evidence-based policy and data for action (second WHO strategic axis) |
| Viral hepatitis surveillance                                                             | 33.3% |
| Estimating the national burden of viral hepatitis                                       | 26.7% |
| Developing tools to assess the effectiveness of interventions                          | 13.3% |
| Assessing the economic impact of viral hepatitis                                        | 20.0% |

| Prevention of transmission (third WHO strategic axis) |
| Increasing coverage of the birth dose of the hepatitis B vaccine                          | 40.0% |

| Screening, care and treatment (fourth WHO strategic axis) |
| Increasing access to treatment                                                                        | 46.7% |
| Increasing access to diagnostics                                                                      | 46.7% |
| Improving laboratory quality                                                                         | 46.7% |
| Developing education/training programmes for health professionals                                   | 46.7% |
Hepatitis C and HIV: Addressing the Dual Epidemic

INTRODUCTION

An estimated 150–180 million people are infected with the hepatitis C virus (HCV) globally.1 If left untreated, HCV can cause chronic and debilitating liver diseases—including fibrosis, cirrhosis, and cancer—that can result in death.

HCV has been described as a “dual epidemic” with HIV because it is highly prevalent in HIV-endemic areas and it disproportionately affects vulnerable populations that also have a high risk of developing HIV infection—especially in Asia and Eastern Europe.2 HIV/HCV co-infection has emerged as an urgent public health issue that is jeopardizing the progress made in addressing the HIV epidemic.

However, HCV treatment can reduce the chances of transmitting the infection to another person and reverse the course of liver disease. Most people with HCV in Asia can be cured after receiving between 24 and 48 weeks of treatment with currently available medicines.3,4 Unfortunately, creating access to HCV medicines in resource-limited settings is an uphill battle. A standard course of treatment in the Asia-Pacific region ranges between US$18,000 and US$33,0005—an unimaginable cost for most of those who are co-infected with HIV that is rarely covered by national health programs or private insurance.

If the HCV epidemic remains unchecked, the number of patients with end-stage liver disease who will eventually require complex and even more expensive medical care will only grow.6 Although people living with HIV (PLHIV) are living longer lives due to greater access to antiretroviral therapy, liver disease caused by HCV is becoming a leading cause of death among them.7,8

Equitable access to both HIV and HCV treatment is essential in order to secure the long-term health of PLHIV and millions of others.

WHAT IS HEPATITIS C?

Becoming infected with hepatitis C

HCV is transmitted by exposure to infected blood through injection drug use, sex, contaminated blood products or medical equipment, or from a pregnant woman to her infant. In Thailand, which is estimated to have an HCV prevalence rate of 2.8%, injection drug use is the leading risk factor, followed by unsafe tattooing and blood transfusions. Vietnam’s HCV prevalence falls between 2 and 2.9%, with unsafe blood transfusions as the leading risk factor.9
Living with hepatitis C

The human immune system can clear the virus by itself in one out of every four people with HCV infection, also known as spontaneous clearance. Those who do not get rid of the virus within six months have what is called chronic HCV infection. Out of 100 people who have chronic infection, about 30 may never develop liver problems, but they can still transmit their infection to others. The other 70 people may develop some liver damage, but they may have no symptoms or only mild ones. After about 20 years, 10 to 15 of these people will develop cirrhosis (scarring of the liver), and five to seven people will develop liver failure or liver cancer. Because most people with HCV have no noticeable symptoms, it is a “silent” infection that can be unknowingly transmitted to others and that may not be detected until it has already caused significant damage to the liver.

There is no vaccine against HCV, making prevention, testing, and treatment initiatives critically important.

Curing hepatitis C

HCV can be cured through treatment. The treatment currently available in resource-limited settings is a combination of a weekly injection of pegylated interferon alfa and twice-daily oral ribavirin. The treatment duration required and the rate infections are cured vary by the genetic type (or genotype) of HCV with which the individual is infected. Those with genotype 2 or 3 may only need 24 weeks of treatment and are more likely to achieve a cure. Those with other genotypes may require up to 48 weeks, and have lower rates of being cured. Some newer medicines have recently been approved that may be able to cure HCV in as little as 12 weeks.

THE GLOBAL IMPACT OF THE DUAL EPIDEMIC

The global prevalence of HCV is continuing to increase, rising from 2.3% in 1990 to 2.8% in 2005. Central and East Asia have high HCV prevalence (≥3.5%), while South and Southeast Asia have moderate prevalence (1.5–3.5%). These figures likely underestimate the true burden of HCV due to limited population-based testing and surveillance.

Epidemiologic data suggest that 4–5 million (5–15%) of PLHIV are also infected with HCV, with Southeast Asia and Africa bearing a greater burden of co-infection than other regions. Co-infection rates are higher among people who inject drugs (PWID), and data indicate that 75–99% of PWID who are HIV-positive are also co-infected with HCV. HIV co-infection negatively affects HCV at every stage of disease, and co-infected individuals have significantly lower survival rates than those infected with HIV alone, regardless of whether they are on HIV treatment. It is clear that antiretroviral therapy alone is not sufficient to prevent HCV-related medical complications and liver disease in PLHIV.

PLHIV are less likely to spontaneously clear HCV following infection. They also have higher HCV viral loads and experience more rapid progression of HCV-related liver disease than those without HIV infection. Co-infected individuals are twice as likely to develop cirrhosis and six times as likely to develop end-stage liver disease as those with HCV alone.
Studies have shown that Asians with HCV have higher cure rates than people in other regions of the world. This is both because the genotypes of HCV that are circulating in Asia (genotypes 2 and 3) are easier to treat, and because many Asian populations frequently carry a variant of a gene (IL-28B) that makes them three times more likely to respond to treatment and be cured than those without this gene variant.

A meta-analysis of HCV treatment research showed that 86% of Asian patients studied had the favorable IL-28B genotype. Of this group, 86% were cured of their infection after treatment as opposed to a cure rate of 75% for their counterparts without the IL-28B gene. National health programs in Asia can consequently achieve long-term benefits by treating and curing people with HCV to prevent the development of serious liver disease that would require costly medical care, and simultaneously eliminate their risk of transmitting the infection to others.

**The socio-economic impact of hepatitis C**

The HCV epidemic stresses healthcare systems and is a significant economic burden to society. Data from a 2009 United States National Health and Wellness Survey reported that in a six-month period, those infected with HCV visited an emergency room or physician significantly more often than their uninfected counterparts, and HCV was associated with higher levels of absenteeism and poor work performance.

Treating and curing individuals not only avoids this burden on healthcare systems, but also has long-term economic benefits. A cost-effectiveness analysis in Thailand found a projected lifetime savings of 556,862 Baht (US$16,784) associated with treating a Thai patient infected with HCV genotypes 2 and 3—a significant savings when compared to Thailand’s annual per capita health spending of 6,320 Baht (US$202). HCV treatment has the potential to help governments save on long-term health spending.
Treatment is a powerful tool for prevention

As with HIV, HCV treatment is a potent tool for preventing new infections because it reduces the amount of HCV circulating in the community. A modeling study in Vietnam showed that treating HCV-infected PWID could decrease HCV transmission and prevalence in the broader community by 25–85%. Providing treatment to even 25% of people who need it could result in a 21% reduction in HCV prevalence, and 50% treatment coverage could lead to a 37% reduction.

Hepatitis C treatment strengthens HIV control

Tremendous strides have been made in the HIV epidemic. HIV treatment scale-up has changed the trajectory of the epidemic, and a diagnosis that was formerly considered a death sentence has evolved into a manageable chronic disease. Creating that access to affordable HIV treatment required aggressive advocacy, and adopting a similar approach for HCV treatment could have a similar impact.

Despite compelling evidence that HCV treatment is a sound investment with valuable social and economic returns, the vast majority of those with HCV cannot access treatment. It is imperative that we work to change this reality. The remarkable achievements of the global HIV treatment access campaign have shown us that this is possible.

LOOKING FORWARD

The cost of continuing to ignore this public health issue is substantially greater than the cost of addressing it now. Advocacy priorities should include:

- **Providing** and scaling up routine HCV testing and screening to assess treatment need and eligibility among PLHIV.
- **Establishing** national surveillance systems to better understand the burden of HCV among PLHIV.
- **Including** pegylated interferon alfa and ribavirin in national essential medicines lists, as recommended in the World Health Organization's Model List of Essential Medicines.
- **Facilitating** price reductions for pegylated interferon alfa through collaborative negotiations between national governments, civil society, and pharmaceutical companies.
- **Providing** HCV treatment as part of national health and HIV programs, to both reduce the long-term costs of HCV and prevent new infections.

For further information, please contact Giten Khwairakpam, project manager for community and policy at TREAT Asia/amfAR, at giten.khwairakpam@treatasia.org or +66 2 663 7561 (Thailand).