CLINTON HEALTH ACCESS INITIATIVE

HCV Market Intelligence Report 2021 and Preliminary HBV Market Insights

Photography by: Soksamphoas Im, Christine McNab, Melinda Stanley

Disclaimer: The data sources primarily used for analysis in the report include the India Import Export data, CHAI country teams, Ministry of Health counterparts, stakeholder (WHO, MPP, and NGO and civil society partners, such as FIND, TAG, World Hepatitis Alliance, etc.) conversations, and regulatory information provided by drug suppliers. CHAI has taken precautions to verify the information shared on the report. However, the analysis in the report is not exhaustive, and the responsibility for the interpretation and use of the material lies with the reader. The mention of specific companies or supplier products does not imply that CHAI is endorsing or recommending them.

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Acronyms

Ab	Antibody
Ag	Antigen
ALT	Alanine transaminase
API	Active pharmaceutical ingredient
APRI	Aspartate aminotransferase to platelet ratio index
AST	Aspartate transaminase
BMS	Bristol Myers Squibb
CHAI	Clinton Health Access Initiative
CBC	Complete blood count
CE	Conformitè Europëenne
CO	Country office
COVID-19	Coronavirus disease 2019
CMV	Cytomegalovirus
CPT	Carriage paid to incoterm
CRP	Collaborative Registration Procedure
CT	Chlamydia trachomatis
CY	Calendar year
DAA	Direct-acting antivirals
DAP	Delivery at place incoterm
DBS	Dried blood spot
DCV	Daclatasvir
DNA	Deoxyribonucleic acid
EID	Early infant diagnosis (HIV)
ELISA	Enzyme-linked immunoassay
EMA	European Medicines Agency
EMLc	Essential medicines list for children
EML	Essential medicines list
ERP	Expert Review Panel
EXW	Ex works incoterm
FBC	Full blood count
FDC	Fixed-dose combination
FDF	Finished dosage form
FIB-4	Fibrosis index based on 4 factors
FIND	Foundation for Innovative New Diagnostics
FOB	Freight on board incoterm
FPP	Finished pharmaceutical product
FS	Fingerstick
GAI	Global Access Initiative (Hologic pricing)
GAP	Global Access Program (Roche pricing)
GAP-f	Global Accelerator for Pediatric Formulations
GFATM	The Global Fund to Fight AIDS, Tuberculosis and Malaria
GHSS	Global health sector strategy
G/P	Glecaprevir/pibrentasvir (fixed-dose combination)
HBDC	High-burden developing countries (Cepheid pricing)
HBV	Hepatitis B virus
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HCVST	Hepatitis C virus self-testing
HCV cAg	Hepatitis C core Antigen
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
INR	Indian rupee
KPI	Key performance indicator
KSM	Key starting materials
LDV	Ledipasvir
LMICs	Low- and middle-income countries
LTFU	Loss to follow up
MoH	Ministry of health
MPP	Medicines Patent Pool
MSF	Médecins Sans Frontières
MTB	Mycobacterium tuberculosis
NAT	Nucleic acid test
NG	Neisseria gonorrhoea
PAHO	Pan American Health Organization
POC	Point-of-care
PCR	Polymerase chain reaction
PLHIV	People living with HIV
PPM	Pooled procurement mechanism
PPP	Public private partnership
QA	Quality assured
RBV	Ribavirin
RDT	Rapid diagnostic test
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDGs	Sustainable Development Goals
SOF	Sofosbuvir
SOF/DCV FDC	Sofosbuvir/daclatasvir fixed-dose combination
SOF+DCV	Sofosbuvir and daclatasvir used in combination
SOF/LDV FDC	Sofosbuvir/ledipasvir fixed-dose combination
SOF/VEL FDC	Sofosbuvir/velpatasvir fixed-dose combination
SOF/VEL/VOX FDC	Sofosbuvir/velpatasvir/voxilaprevir fixed-dose combination
SRA	Stringent regulatory authority
SVR12	Sustained virologic response at week 12
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TE	Transient Elastography
US FDA	United States Food and Drug Administration
USD	US dollars
VL	Viral load
WHO	World Health Organization
WHO PQ	World Health Organization Prequalification
WHO PQ'd	World Health Organization Prequalified

The state of HCV

Patients treated globally

↑8.4M

from 1M in 2016 to 9.4M in 2019

Treatment coverage worldwide

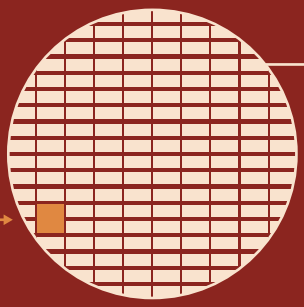
↑650%

from 2% in 2016 to 13% in 2019

Overview of DAA market in LMICs

16M

Market size of DAAs supplied by Indian generics in 2020



$1-1.5B

Untapped market size

based on current market price and untreated HCV cases across LMICs (USD)

↓75%

Decrease in treatment price since 2016

↑223%

Increase in volume since 2016

Lowest price of full treatment course

$60

WHO prequalified product (USD)

$28

Locally approved product (USD)

Pricing breakdown of HCV care commodities in Rwanda

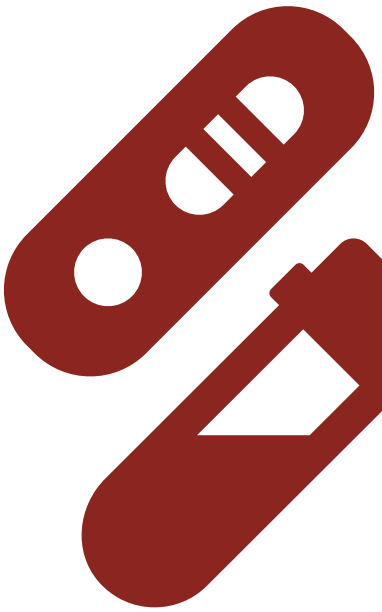
$0.70 Rapid diagnostic test + **$9.36** Viral load test + **$60** Treatment* + **$9.36** SVR12 test = **$79.42** total per patient (USD)

**$60/patient course for 12 weeks of WHO PQ'd SOF and DCV*

All prices in USD

Executive summary

The increasing availability of cost-effective, quality-assured diagnostics has lowered barriers to effective hepatitis C virus (HCV) diagnosis in LMICs



- Low, benchmark prices have been achieved by Georgia for Conformitè Europëenne (CE) marked HCV rapid diagnostic tests (RDTs) at US$0.12 and Egypt for World Health Organization (WHO) prequalified (PQ'd) RDTs at US$0.58, as well as Rwanda for HCV viral load (VL) at US$9.30.
- Many suppliers of viral load tests have access pricing available to select low- and middle-income countries (LMICs) and offer commodities at standardized price points.
- Dried specimens, like dried blood spot (DBS) samples, do not require cold chain thus offering decentralized sample collection and may be cost competitive with plasma samples as determined by cost analysis. However, the number of suppliers that have included DBS for HCV VL is limited at present.
- Blood tests for aspartate transaminase/alanine transaminase (AST/ALT) and platelets used in liver staging are commonly available in LMICs. Utilizing these for noninvasive assessment of fibrosis by aspartate aminotransferase to platelet ratio index (APRI) or fibrosis index based on 4 factors (FIB-4) scores are effective options when transient elastography is not accessible.

Increase in direct acting antivirals (DAAs) uptake has been driven by significant price reductions over the last few years. However, access to treatment has been uneven across LMICs.

- The overall Indian generic DAA market across LMICs expanded to approximately US$16 million in 2020. Generic daclatasvir (DCV) sales reached a milestone of 3 million packs by end of 2020.
- Expected WHO guideline revisions are likely to grow the market by recommending pangenotypic DAAs for HCV treatment for adolescents and children.
- Most WHO-recommended DAA regimens now have at least one WHO PQ'd product available.
- DAA price decreases have slowed; the next major drop in treatment cost is likely to be driven by supply chain optimization and centralized procurement by countries.

As countries continue to adapt to the COVID-19 situation, the hepatitis community needs to sustain efforts to make HCV diagnostics and treatment more accessible. Strategies to build programs with affordable testing and treatment commodities include:

Leveraging volume and forecast-based pricing

Countries can leverage volume-based pricing to procure drugs at a lower cost and maximize the value of their budgets by optimizing order quantity through procurement planning exercises. By forecasting demand to bundle order sizes and pooling volumes through a centralized buying process, countries can place higher volume orders instead of multiple orders of lower volumes.

Accessing international procurement mechanism-negotiated terms and pricing

Countries can consider accessing The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), United Nations Development Programme (UNDP), and Pan American Health Organization (PAHO) negotiated terms and pricing for product procurement. Governments can also use these prices as benchmarks for local tenders or for negotiating price deals with suppliers.

Ensuring price transparency and reducing price mark-ups

Procurement agents should achieve comprehensive cost component visibility, allowing programs to accurately assess their budgets and maximize value by optimizing contract terms. Countries observing high internal price mark-ups can then optimize price for patients by identifying components of in-country mark-ups and devising strategies to limit these contributing factors by imposing limits on fee charges and facilitating a competitive tendering for distribution and logistics partners.

Facilitating expedited in-country supplier registration

Countries can expedite the registration of generic diagnostic commodities and DAAs by using the WHO's Collaborative Registration Procedure (CRP). It enables national medicines regulatory authorities to use WHO PQ evaluations and inspections to shorten the time for registration of products by reducing duplication of work. The time frame for registration of products via the CRP is ninety days once filed in the country.

Integrating testing across diseases

While testing is often siloed by disease for programmatic reasons beyond the technical capability of the platforms, the broad test menus of VL diagnostics platforms are highly amenable to integrated testing across diseases. Integrated testing for HCV on existing platforms, for example point-of-care (POC) platforms originating in tuberculosis (TB) programs or high-throughput or central laboratory-based instruments used for HIV testing, are often critical entry points for early-stage public hepatitis programs.[1] A recent pilot study (publication in development) of integrated testing for HIV and HCV VL on central laboratory-based platforms in Myanmar, supported by CHAI in partnership with The Foundation For Innovative New Diagnostics (FIND), indicated that integrated testing was operationally feasible without adversely impacting HIV diagnostic testing and was also acceptable to laboratory staff. This study illustrated how integration may be an important strategy to expand testing capacity.

Public-Private Partnership (PPP)

While not a path to universal access, a PPP could be considered as a means to increase public access to care by leveraging private entities where public investment is limited. For example, Myanmar initiated a PPP in three healthcare facilities in Yangon and Mandalay allowing patients who can afford the subsidized price to skip the waiting list of the limited number of free treatment courses. The Indian states of Punjab and Haryana also offer examples of the successful use of a PPP to provide HCV and hepatitis B virus (HBV viral load) at a cost per test of 875INR (approximately US$12), which is competitive with procurement price of many public programs. However countries should note the limitation of PPPs in providing free, universal access to care to underprivileged populations. While PPPs help programs to pool limited demand and access volume based pricing for DAAs without significant investment in the short run, it doesn't substitute the need for sustainable investment towards universal access.

1 Japaridze, M. et al. (2020), Novel approach to near POC testing for HCV RNA; integration of HCV RNA testing into existing near POC machines used in National TB program, Georgia. International Journal of Infectious Diseases, 101: 1260. https://10.1016/j.ijid.2020.09.1351

Viral Hepatitis TWG meeting held virtually in Jakarta Indonesia.

Photo by Soksamphoas Im

Introduction

In May 2020, CHAI published its first edition of the HCV Market Report. This second edition documents the changes in the HCV diagnostic and drug landscape in 2020, along with preliminary insights into the HBV market.[2] During Q2-Q4 2020, the COVID-19 pandemic disrupted viral hepatitis programs across low- and middle-income countries (LMICs). Though the future remains uncertain due to surges in case numbers, development of variants, and the inequitable distribution of vaccines, programs have adapted and found ways to strengthen their hepatitis services. Country programs, funders, and manufacturers have been able to continue through the pandemic, albeit with periodic setbacks.

The purpose of this report is to examine market trends and current challenges for hepatitis commodities and serve as a resource for a variety of stakeholders in the global hepatitis community. Ministries of finance, ministries of health, and viral hepatitis programs across LMICs may find this report useful for identifying opportunities to achieve price and volume optimization for drugs and diagnostics based on market trends. Partners such as civil society organizations can use the information as an advocacy tool to improve current market inefficiencies, while donors can leverage this report to identify potential opportunities for high value-for-money investments. On the supply side, manufacturers and distributors can utilize this report to inform their product portfolio and market development strategies.

New topics covered in the report include:

- Impact of COVID-19
- Products and pricing of diagnostics for liver staging
- Dried samples for HCV viral load testing
- Emerging market for retreatment and pediatrics, including addressable pediatric market-sizing estimates
- Preliminary information on the HBV Market

COVID-19 impact and potential opportunities

Disruptions in demand and supply of direct-acting antivirals (DAAs) have been significant but temporary. Both suppliers and HCV programs were able to adapt and ensure that the gained momentum in response to hepatitis C was not lost in 2020. The hepatitis community, as with other areas of global health, needs to continue adapting to the unpredictability of the COVID-19 situation due to recurring surges in case numbers and the inequitable distribution of vaccines across LMICs.

The global response to limit the spread of COVID-19 diverted attention and resources from existing local health priorities, particularly in LMICs. Case-finding activities and care-seeking for many diseases, including HCV, decreased across most LMICs due to nation-wide lockdowns and movement restrictions. In the Indian state of Punjab, for example, there was a decline in the number of patients tested and started on HCV treatment in the second quarter of 2020 when a nationwide lockdown was instituted to manage the spread of COVID-19. HCV testing and treatment numbers declined by approximately half in this period and subsequently increased over the next two quarters as the program piloted alternate ways of service delivery.

The response to the pandemic has created opportunities to strengthen hepatitis services. In several countries (e.g. Myanmar, India, Nigeria), physicians have trialed multi-month treatment

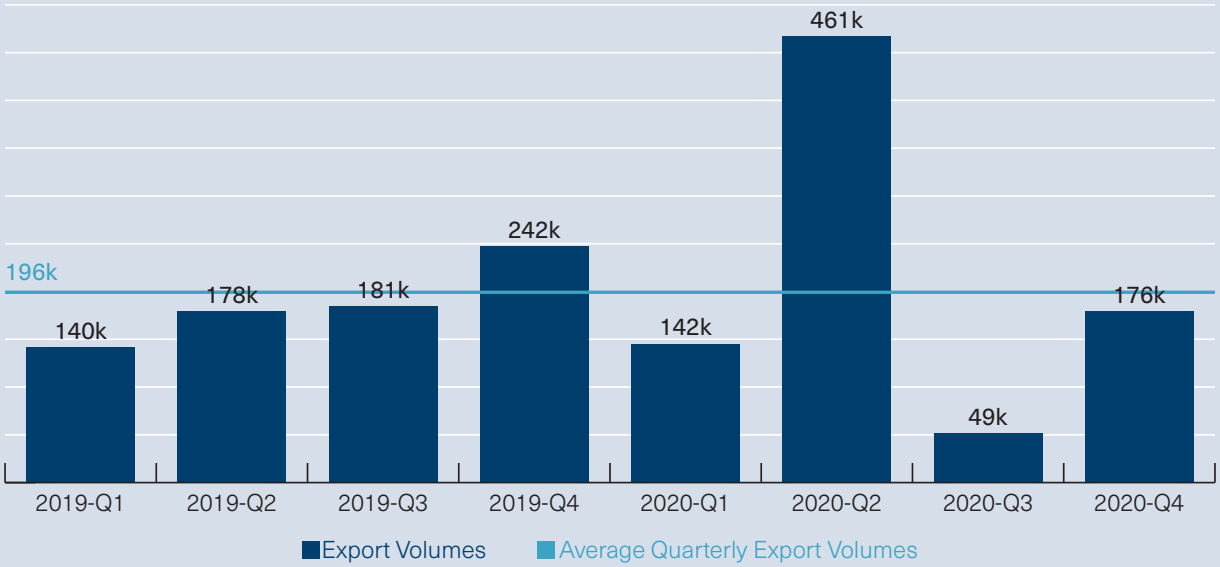
2 Note: The report focuses on LMICs with a high HCV burden (Appendix 1), and WHO PQ'd/ ERP reviewed products as they meet quality assurance standards and have been declared bioequivalent to the innovator products. While CHAI supports the use of products approved by stringent regulatory authorities (USFDA, EMA) or WHO PQ, pricing information in the report also accounts for locally approved products (which have not been assessed against global quality standards but meet local quality standards), as these products are used in several LMICs.

dispensation, reducing the number of facility visits required by patients. Online meetings, remote installation of equipment, and virtual trainings have been adopted by some countries in response to domestic travel restrictions with some of these innovative methods expected to be mainstreamed going forward. The strengthening of the laboratory network as well as telemedicine infrastructure can improve and further simplify hepatitis care, expanding access to hepatitis testing and treatment.[3] In addition, a large number of both automated and manual (open) platforms have been activated for COVID-19 testing and some governments have acquired additional polyvalent platforms for COVID-19 testing able to be used for multiple diseases including HCV.

Diagnostic and DAA manufacturers adapted to ensure that the impact of COVID-19 on the supply chain was temporary. From Q1 2020, lockdowns in various countries and supply chain challenges impacted active pharmaceutical ingredients (APIs) and key starting materials (KSM) imports from China.[4] Prices of KSM subsequently increased during this period leading to a higher cost of production for finished dosage manufacturers. Indian generic manufacturers also reported a 50 percent increase in lead-time for materials from China. From Q2 to the end of Q3, limited freight availability and frequent changes to the lockdown protocols continued to affect the movement of domestic goods across different states. High prices and long lead times of KSM supplies from China for some drugs remains a challenge, but suppliers are mitigating it by exploring alternate procurement options.

The demand and supply side impacts of COVID-19 are reflected in the Indian export data for DAAs. From Q1 2019 through Q2 2020 there was growth in export volumes averaging 224,000 packs quarterly, until a significant drop in Q3 2020 to less than 50,000 packs (Exhibit 1). Decrease in patients receiving HCV treatment and subsequent decline in DAA procurement aligns with the emergence of COVID-19, lockdowns and supply chain disruptions. The increase in procurement volumes in the last quarter of 2020 suggests a rebound in the supply and number of patients receiving hepatitis services.

Exhibit 1: Number of DAA packs exported from Indian generic manufacturers to LMICs: 2019-2020



Source: India Export Data; CHAI Analysis

3 Laury, J., Hiebert, L. and Ward, J.W. (2021), Impact of COVID-19 Response on Hepatitis Prevention Care and Treatment: Results From Global Survey of Providers and Program Managers. Clinical Liver Disease, 17: 41-46. https://doi.org/10.1002/cld.1088.

4 Source: Supplier Interviews

WHO-recommended HCV testing and treatment guidance updates

HCV self-testing (HCVST) is recommended as an additional approach to HCV testing services. Expected treatment guideline revisions are likely to expand eligibility for HCV treatment and grow the DAA market.

HCVST offers an opportunity to reach populations who would not otherwise access testing services and may prefer self-care options. Profession-use testing remains the backbone of screening programs, and self-testing should supplement existing services. Programs with HCVST must provide linkages for persons with reactive HCVST results to a trained provider to confirm chronic viremic infection and perform treatment assessment. HCVST programs should be adapted to national and local context, and community involvement is key to success. The guidelines build on evidence and experience from self-testing with HIV, which was first recommended by WHO in 2016 and has been shown effective at increasing access and uptake of HIV testing.

Upcoming WHO revisions to treatment guidelines are expected in 2021-2022. New recommendations on the treatment of children and adolescent populations are likely to reflect recent stringent regulatory authority (SRA) approvals of pediatric DAA dosages and further research findings and are expected to recommend the use of all currently recommended pangenotypic DAA regimens among lower age bands, including children and adolescents.

Refer to Appendix 2 for a summary of WHO-recommended HCV testing and treatment guidelines.

Photo by Christine McNab

HCV landscapes and trends

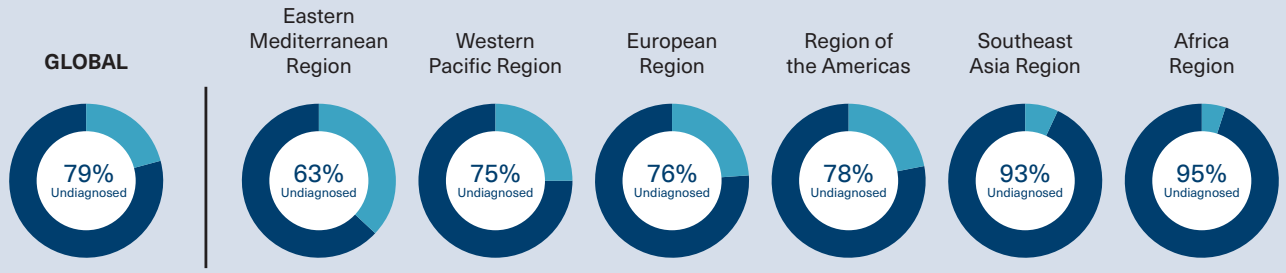
HCV diagnostics

There is significant room for growth in the HCV diagnostics market, as 1.5 million (1.3 million – 1.8 million) people were newly infected with chronic hepatitis C infection in 2019. Globally, only 21 percent of people living with HCV (15.2 million) knew their status in 2019.[5]

While the number of people who know their HCV status continues to increase, most HCV positive individuals remain undiagnosed. For example, in Africa 95 percent of people do not know they are HCV positive.[6] The large percentage of undiagnosed cases demonstrates an untapped diagnostics market which may be available by reducing the barriers to access through increased awareness, as well as donor and domestic funding for testing and treatment.

The absence of a public database on global diagnostics volumes and prices that is routinely updated continues to present a significant challenge to pricing and volume transparency, as well as to predicting diagnostic market trends.

Exhibit 2: Percent of HCV positive individuals undiagnosed at the end of 2019



Source: WHO 2021 global progress report on access to hepatitis C treatment and diagnostic, at: https://www.who.int/publications/i/item/9789240019003

5 WHO 2021 global progress report on access to hepatitis C treatment and diagnostic, at: https://www.who.int/publications/i/item/9789240019003
6 Ibid

Supplier landscape

Quality-assured HCV antibody screening tests

The selection of HCV antibody tests which have WHO prequalification (PQ) remains unchanged since 2019. These include four rapid tests (RDTs) and six lab-based tests.

The WHO prequalification process serves as a valuable tool to donors, governments, and private payers in the identification of QA tests. As of May 2021, ten HCV antibody tests have received WHO PQ, including four RDTs and six lab-based tests as shown in Exhibit 3. No new HCV antibody tests have received WHO PQ since the first edition of this HCV Market Intelligence report was published in May 2020. Note that while Exhibit 3 contains only WHO PQ's tests, additional high-quality tests not listed may have approval from a SRA. Other products without approval from a SRA are also available, however the quality of these tests are not known. While guidance for HCVST was released in July 2021 by WHO,[7] currently no HCV product has approval for self-testing.

Quality-assured HCV antibody RDTs have significant programmatic benefits over lab-based assays for streamlined screening, including enabling decentralization of screening, mitigating challenges of sample collection and transportation, and supporting faster turnaround in results. These tests have been successfully implemented in test and treat approaches by programs including the Rwanda national program, the HEAD-Start project in countries such as India and Malaysia, and the Médecins Sans Frontières (MSF) decentralized care model in Cambodia.[8] The RDT market share, compared to lab-based immunoassays, may increase in the next three to five years as programs continue to recognize the value of using RDTs for screening at the point of need.

Liver staging and monitoring

Common blood tests that are routinely available in LMICs provide a means of assessing hepatic fibrosis where transient elastography (TE) is not available.

Exhibit 3: WHO prequalified rapid tests (RDTs) and lab-based HCV immunoassays antibody tests

Rapid HCV antibody tests

Product name	Manufacturer	Sample type
Rapid Anti-HCV	Intec Products	Whole blood, plasma, serum
Bioline HCV*	Abbott Diagnostics Korea	Whole blood, plasma, serum
OraQuick HCV Rapid Antibody	OraSure Technologies	Whole blood
Standard Q HCV Ab	SD Biosensor	Whole blood, plasma, serum

Lab-based HCV immunoassays

Product name	Manufacturer	Sample type
ARCHITECT HCV Ag**	Abbott	Plasma, serum
INNOTEST HCV Ab IV	Fujirebio Europe	Plasma, serum
INNO-LIA HCV Score	Fujirebio Europe	Plasma, serum
Murex Anti-HCV	DiaSorin South Africa	Plasma, serum
Bioelisa HCV 4.0	Biokit South Africa	Plasma, serum
MONOLISA HCV Ag-Ab ULTRA V2	Bio-Rad	Plasma, serum

**The prequalification for Bioline HCV RDT, previously listed as SD BIOLINE HCV, was amended in March 2020 to account for the transition of manufacturer from Standard Diagnostics (SD) to Abbott Diagnostics Korea; the product however remains the same. All PQ'd RDTs include whole blood as a valid sample type, however the PQ lab-based tests do not include whole blood rather using only plasma or serum.*

***ARCHITECT HCV Ag is an antigen, not antibody, test.*

Source: WHO PQ HCV diagnostic list

7 WHO recommendations and guidance on hepatitis C virus self-testing, at: https://www.who.int/publications/i/item/9789240031128

8 Decentralised hepatitis C testing and treatment in rural Cambodia: evaluation of a simplified service model integrated in an existing public health system, The Lancet Gastroenterology and Hepatology, volume 6, issue 5, P371-380, MAY 01, 2021. https://doi.org/10.1016/S2468-1253(21)00012-1

WHO guidelines (Appendix 2) recommend assessment of hepatic fibrosis to determine the appropriate duration of DAA treatment. WHO does not provide PQ for any liver staging product at this time. In settings where HCV diagnosis and management is increasingly decentralized, including access to VL, accessing liver staging may present a delay in the care pathway.

Transient elastography (TE), often performed using Echosens' FibroScan, is a non-invasive ultrasound diagnostic for assessing fibrosis and recommended by WHO where it is available. As TE is often unavailable in LMICs, liver health is frequently assessed using common blood chemistry tests for alanine transaminase (ALT), aspartate transaminase (AST), and platelet count. The results of these tests are used to calculate APRI or Fibrosis-4 (FIB-4) scores which indicate the level of fibrosis.

These blood tests are also utilized to assess a variety of non-hepatitis conditions and are commonly available in LMIC labs from a variety of suppliers. Other blood work (e.g. albumin, bilirubin, etc.) is sometimes included or performed based on clinical judgment. Given the lack of PQ evaluation of these blood tests, the quality of these products is not known.

Monitoring tests are not required during treatment to evaluate response to DAAs, but sustained virologic response (SVR12) should be evaluated by a viral load test 12 weeks after treatment completion. Patients with cirrhosis should be screened for hepatocellular carcinoma with ultrasound every six months.

Quality-assured HCV viral load tests

Diagnostic platforms commonly used for hepatitis viral load have a large global footprint in part due to their use in HIV and TB programs.

The viral load platforms commonly used for HCV have broad test menus, enabling testing for multiple diseases using the same platforms. A representative (non-exhaustive) list of the assays available for common HCV VL platforms is presented in Exhibit 4. All of the HCV tests in Exhibit 4 have approval by a SRA. In addition, the Abbott Alinity m, Abbott *m*2000, Roche cobas 6800/8800 Systems, and Cepheid GeneXpert all have HCV VL tests with WHO PQ. The ability to test across diseases using these platforms enables the opportunity for integration of HCV testing with other diseases.

Since the publication of the last market report, three additional HCV virology products have received WHO PQ. The Abbott RealTi*me* HCV (*m*2000) became the first viral load assay with PQ that can use dried blood spot (DBS) samples. The Genedrive HCV ID Kit was approved for use on the Genedrive instrument, which can be placed in decentralized settings. Lastly, The Roche cobas HCV viral load test (cobas 6800/8800 Systems) was listed in March 2021.

Exhibit 4: Cross-disease test menus of platforms commonly used for HCV viral load (non-exhaustive list)

Viral load platforms commonly found in central laboratories (non-exhaustive)

	Roche			Hologic	Qiagen	Cepheid	Abbott	
Platform	**COBAS AmpliPrep/ COBAS TaqMan**	**cobas 4800 System**	**cobas 6800/ 8800 Systems**	**Panther**	**QIAsymphony SP/AS**	**GeneXpert***	**Alinity m**	***m*2000**
HCV	X	X	X	X	X	X	X	X
HBV	X	X	X	X	X	X	X	X
HIV-1	X	X	X	X	X	X	X	X
HPV		X	X	X		X	X	X
SARS-CoV-2			X	X		X	X	X
MTB			X			X		X
CT/NG, CT, NG		X	X	X		X	X	X

**GeneXpert may be operated as a near point of care platform, though is frequently used in centralized labs.*

Source: Publicly available information

Decentralized viral load testing

New point-of-care products (POC) for decentralized VL testing may increase access to testing at lower levels of health facilities.

Moving diagnostics closer to the individual through decentralized testing may be an effective strategy to increase access. Due to infrastructure requirements, most of the platforms in Exhibit 4 are considered centralized, laboratory-based platforms with the exception of the Cepheid GeneXpert which can be used at POC. POC platforms can be decentralized to lower levels of health facilities given their smaller footprint, relative ease-of-use, and ability to run single tests.

Cepheid offers two HCV VL tests: Xpert HCV Viral Load and Xpert HCV VL Fingerstick (FS). Both tests are available in LMICs, compatible with the same GeneXpert platforms, and perform quantitative analysis based on plasma/serum and whole blood samples respectively. Genedrive also provides POC access for HCV VL testing. While Genedrive's test menu is limited as yet, the recent PQ for the HCV VL test increases competition in the POC testing space.

Pricing and cost considerations of screening and liver staging

Costs of HCV antibody RDT in public programs by country

Georgia has secured the lowest global price for HCV RDTs (CE marked) at US$0.12 per test and Egypt has the lowest price for WHO PQ'd RDTs at US$0.58.[9]

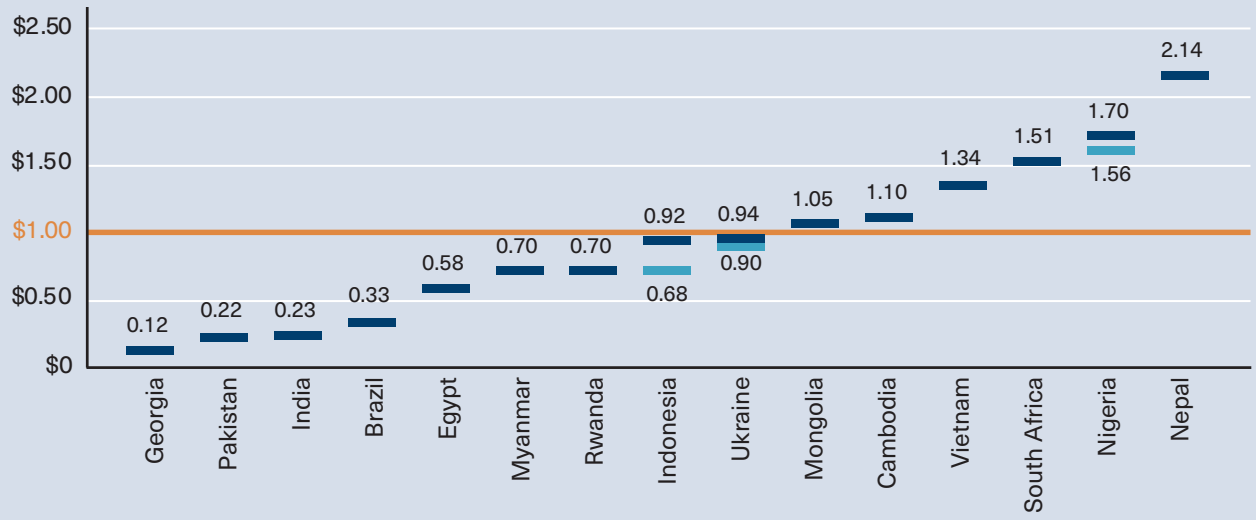
There are no significant pricing changes to screening tests since the previous market report.

Exhibit 5 presents the prices paid to public programs for antibody RDTs from a representative sample of high-burden countries. The prices reported are generally consistent with the previous market report, except for Georgia, which reported a significant reduction in price from US$0.50 last year to US$0.12 this year.

While the lower prices some countries have achieved may serve as benchmarks for other programs to target, due to the lack of a centralized global reporting structure and database for viral hepatitis diagnostics, the quality assurance of many of the products represented in Exhibit 5 are unknown. It is important to

9 A CE mark indicates that a medical device or in vitro diagnostic complies with the applicable European Union regulations and is a legal requirement to place a device or in vitro diagnostic on the market in the European Union.

Exhibit 5: HCV antibody RDT price per test paid by public programs. Data collected in 2020-2021



Note: The horizontal line is a visual aid to compare prices to $1; all prices in USD.

Source: CHAI supported country teams, individual contacts and partner organizations including Global Fund, FIND and Treatment Action Group. Where more than one price was reported for a country, the upper and lower costs are shown. Public information, Treatment Action Group/Médecins du Monde. mapCrowd database [Internet]. New York (NY): mapCrowd; 2021 [cited 2020-2021]. https://mapcrowd.org/

note that while these data represent the costs in public programs, there may also be significant HCV testing and treatment in the private sector. When parallel procurement channels are present within a country, different prices may exist. In these instances, the upper and lower costs per test are presented in the graph.

Different modes of testing should be considered in terms of the programmatic and the cost impacts to establish the most effective and feasible screening strategy. A cost comparison of testing types may therefore be valuable to assess the overall cost and benefit to a program. Exhibit 6 illustrates the outputs of a costing exercise to compare the costs associated with HCV antibody screening by RDT versus a lab-based ELISA. This high-level assessment considers the variable costs in terms of the consumables required to collect the sample and to perform the test.

Exhibit 6: Example costs of screening by RDT versus ELISA

Variable costs per test:	HCV RDT	HCV ELISA
Test or reagent	US$0.24	US$0.13
Sample collection consumables	US$0.07	US$0.46
Total variable costs per test	**US$0.31**	**US$0.58**

Source: CHAI analysis based on publicly available information

In this example, the net cost per test of an ELISA (US$0.58) was found to be nearly twice that of an RDT (US$0.31). While the exercise is instructive for the process of comparing the costs of testing modalities, this specific output indicating that the RDT is more cost effective is not universally applicable as cost components will be highly context dependent. The process is nonetheless informative of a generally applicable method for assessing the various screening options based on cost.

Costs of liver staging

APRI and FIB-4 may be an affordable and more accessible form of liver staging in many settings.

The inclusion of the costs associated with staging and monitoring is new to this edition of the market report, expanding on the content of the previous publication. While access to global pricing of staging and monitoring tests is limited at present, this information will continue to be developed in subsequent editions of the report.

TE is valuable in assessing liver fibrosis, however there are often significant upfront costs (e.g. approximately US$70k - 300k per FibroScan instrument) which may be prohibitive and limit their use in LMIC programs.[10] While there are no reagent consumables required to use TE, there may be high out-of-pocket fees charged to the patient as the health facility endeavors to recoup the initial capital expenditure as experienced in the Morocco context.[11]

Although TE may not be widely available in LMICs, blood chemistry and hematology tests used to assess liver function are commonplace as they are also used to assess a variety of non-hepatitis related conditions and these tests do not typically represent a significant cost burden. As an illustration, Exhibit 7 presents example prices for ALT/AST and platelet, sometimes included in complete/full blood count, for three representative countries.

Exhibit 7: Example costs for standard liver function tests

	ALT/AST cost	Platelet cost
Cambodia	US$2.34	US$2.55
India*	US$0.88	US$2.17
Nigeria	US$3.90	US$2.08

*https://cghs.gov.in/showfile.php?lid=4334

Sources: CHAI country teams and publicly available information. Data collected in 2020-2021.

10 Diagnosis and Monitoring of Hepatitis C (HCV) in Morocco, Current Status and Strategies for Universal Access. May 2018.
11 Ibid

HCV viral load cost considerations

Costs of viral load in public programs by country

Rwanda serves as a valuable benchmark for HCV VL having achieved the lowest price at US$9.30.

The cost of HCV viral load testing has remained relatively stable since the last edition of the market report.

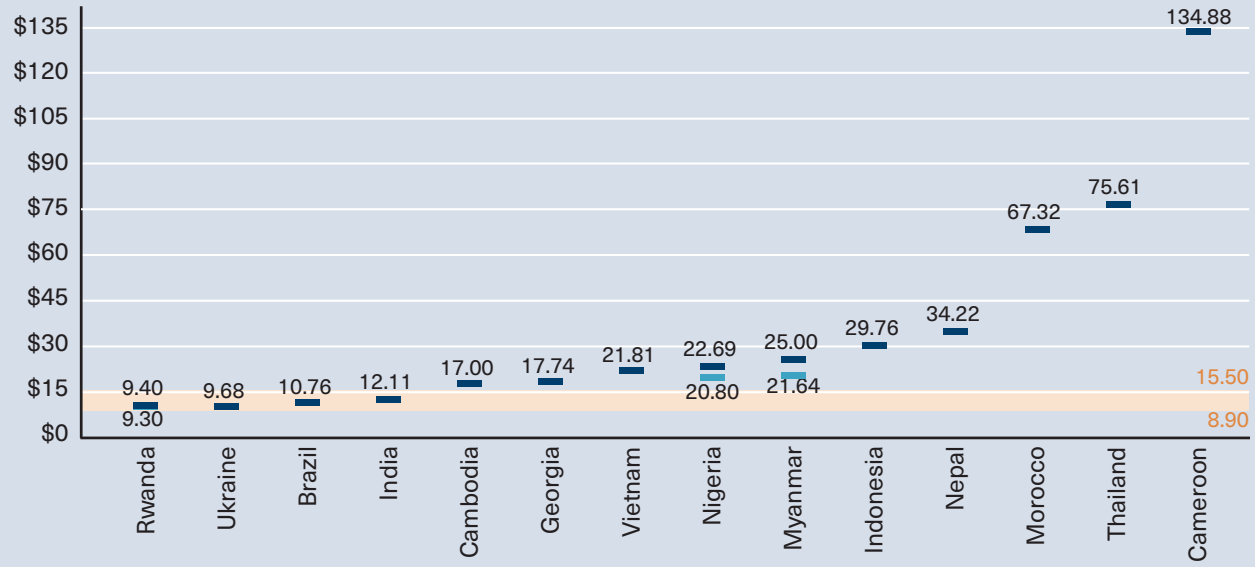
Exhibit 8 presents the prices for VL paid by public programs from a representative sample of high-burden countries. There have not been any significant changes in the reported prices since the previous report. However, the prices reported in 2021 were slightly greater than last year for Thailand and Morocco while somewhat lower for Nigeria, Georgia, and India. It should be noted that due to the lack of a centralized global reporting structure and database for viral hepatitis diagnostics, the quality assurances of many of the products represented by the data are unknown. When multiple prices are reported for a country, the upper and lower values are presented in the graph.

Viral load global pricing agreements

Leveraging suppliers' global pricing agreements can provide benefits to programs, but understanding the specific inclusions is important to ensure the benefits are maximized during implementation with full transparency on the final cost to the program.

As shown in Exhibit 9, Abbott, Cepheid, Roche, and Hologic have global pricing available for HCV VL tests. The existence of this specific global pricing does not however prevent procurers from negotiating potentially more advantageous terms outside of this global pricing. The characteristics of this pricing, including the specific incoterms,[12] are described in detail in Exhibit 9. While the details are unique, all global pricing combines the base price of the test with additional cost components. Some pricing may also include key performance indicators (KPIs) that the supplier agrees to meet, such as the maximum permissible instrument downtime.

Exhibit 8: HCV viral load price per test paid by public programs. Data collected in 2020-2021



Note: The horizontal band represents the highest and lowest prices (Abbott low test volume and Roche respectively) available under the global pricing agreements in Exhibit 9; all prices in USD.

Source: CHAI supported country teams, individual contacts and partner organizations including Global Fund, FIND and Treatment Action Group. Where more than one price is reported for a country, the upper and lower costs are presented. Public information, Treatment Action Group/Médecins du Monde. mapCrowd database [Internet]. New York (NY): mapCrowd; 2021 [cited 2020-2021]. https://mapcrowd.org/

12 Incoterm (International Commercial Term) are three letter terms which describe contractual obligations such as shipping, unloading or other tasks or risks associated with sale and delivery or a product.

Exhibit 9: Viral load global pricing

	Suppliers	Hologic	Roche[a]	Cepheid[a]		Abbott[a,b]
	Platforms	**Panther**	**cobas 4800 System, cobas 6800/8800 Systems and COBAS AmpliPrep / COBAS TaqMan System**	**GeneXpert (all systems)**	**GeneXpert (all systems) with GX XVI placement[b]**	***m*2000**
	Corresponding assays	**HBV, HCV, HIV (VL and EID), HPV**	**HBV, HCV, HIV (VL and EID), HPV, MTB/RIF/INH, SARS-CoV-2**	**HBV, HCV (VL and VL FS), HIV (VL and EID), HPV**	**HBV, HCV (VL and VL FS), HIV (VL and EID), HPV, SARS-CoV-2**	**HBV, HCV, HIV**
Access pricing	*Volume commitment*	30,000 tests/yr (avg per instrument)[c]	None	None	10,000 tests/yr for each GX XVI placed[d]	Volume-based pricing 50,000 to >1,000,000 tests/yr (avg per instrument)
	Price per test (USD)	$11.28 (ceiling)[e]	~$8.90[f]	~$14.90	$14.90 (ceiling)[g]	Price ranges based on volume:[h] Plasma: ~$9.60 to ~$15.55 DBS: ~$11.10 to ~$17.05
	Incoterm	DAP	CPT	EXW	EXW, CIP, or CPT[i]	FCA
	Instrument purchased or placed	Placed	cobas 4800 System, cobas 6800/8800 Systems are typically placed	Purchased	Placed GX XVI 10-color instrument model(s)	Purchased or placed depending on the contract (if placed, price per test may vary depending on volumes)
	Price per instrument, if purchased (USD)	Included in price per test	cobas 4800 System: ~$100,000 cobas 6800 System: ~$300,000 cobas 8800 System: ~$600,000 *(COBAS AmpliPrep / COBAS TaqMan System is being phased out by Roche and new systems are no longer available for purchase)*	6-color instruments: GX IV module w/desktop: ~$17,000 GX IV module w/laptop: ~$17,500 GX XVI module w/desktop: ~$63,850 GX XVI module w/laptop: ~$64,350 10-color instruments: GX IV module w/desktop: ~$19,000 GX IV module w/laptop: ~$19,500 GX XVI module w/desktop: ~$71,850 GX XVI module w/laptop: ~$72,350	Included in price per tests for GX XVI model(s)	~$160,000
Agreement specifications	*Time commitment*	None	None	None	3 years	None
	Eligible countries	See list here	See list here and information here	See list here	See list here	See Appendix 3
Laboratory	*Reagents and proprietary consumables*	X	X	X	X	X
	Invalid results due to instrument errors	X				
	Service and maintenance (S&M)	X			X[j]	
	Service and maintenance fee per instrument (if not included in price)	N/A		• 2-year warranty included in instrument price • Warranty extensions for GX4: 1 yr: $2,898, 3 yr: $7,902; 3 yr (if purchased at same time as instrument): $6,840	N/A	$18,000/year (payable in advance) or $1,500/month
Supply chain	*Distributor and local agent fees*	X		X[k]	X[k]	
	Packaging	X	X	X	X	X
	Loading from warehouse	X	X		Optional	X
	Pre-carriage	X	X		Optional	X
	Export customs clearance	X	X		Optional	X
	Handling at departure	X	X		Optional	
	Main transportation	X	X		Optional	
	Transportation insurance	X				
	Handling at arrival	X				
	Post-carriage	X				

Exhibit 9: Viral load global pricing (footnotes)

[a] *All prices for Roche, Cepheid, and Abbott are indicative; small variations are possible based on the individual components in any given order*

[b] *This global pricing was recently communicated with CHAI. There has been no procurement at these prices as of publication.*

[c] *If the 30,000 test/instrument annual average cannot be met, Hologic has a separate pricing model that may be applicable for certain eligible countries*

[d] *Each GX XVI placement requires an annual purchase of 10,000 tests (of any corresponding assay listed except SARS-CoV-2) spread across all GeneXpert systems in the participating country.*

[e] *This is a ceiling price associated with the volume commitment outlined above; lower prices may be accessed on a country-by-country basis, depending on number of placements, total testing volume, AccessCare, and other conditions.*

[f] *All inclusive prices are determined per country to provide a more accurate assessment based on country context and needs. Different prices may apply for special projects/grants. Please contact Roche directly.*

[g] *This is a ceiling price associated with the volume commitment outlined above; lower prices may be accessed on a country-by-country basis, depending on number of placements, total testing volume, cost of access care, and other conditions.*

[h] *Abbott: m2000 platform HCV, HBV and HIV assays:*

Volume commitment	50,000 - 100,000 tests/yr (average per instrument)	100,000 - 250,000 tests/yr (average per instrument)	250,000 - 500,000 tests/yr (average per instrument)	500,000 - 750,000 tests/yr (average per instrument)	750,000 - 1,000,000 tests/yr (average per instrument)	>1,000,000 tests/ year (average per instrument)
Price per test	Plasma: ~US$15.55 DBS: ~US$17.05	Plasma: ~US$14.39 DBS: ~US$15.89	Plasma: ~US$12.23 DBS: ~US$13.73	Plasma: ~US$11.01 DBS: ~US$12.51	Plasma: ~US$10.13 DBS: ~US$11.63	Plasma: ~US$9.60 DBS: ~US$11.10

[i] *Specific incoterm to be decided based on negotiation.*

[j] *S&M would be included for all GX XVI platforms placed in the price per test*

[k] *Cepheid's pricing for all GX assays indicated above include distributor margin when tests are prepaid (payment made in full before goods are shipped), in all countries except Myanmar*

Source: CHAI communication with suppliers

Awareness of the particular characteristics of the global pricing shown in Exhibit 9 is essential to assure that the full benefits are obtained. It is therefore important to note that none of the global pricing includes every cost component and other charges may therefore be added to the prices in Exhibit 9.

Suppliers may offer different terms associated with their viral load pricing to be more inclusive of other cost components, which can potentially save compared to purchasing these additional components separately. These may include instrument placement, service and maintenance, and incoterms where the buyer assumes less risk. Often to be eligible for pricing which is more inclusive of other costs, the buyer must meet annual test volume requirements which may be applicable across disease assays. As nascent hepatitis programs scale-up, the HCV test volumes may initially be too low on their own to achieve test volume thresholds. However, by pooling HCV VL procurement with other disease programs, cross-disease test volume minimums may be more readily achievable.

Programs could consider agreements or negotiations which include instrument installation at no additional cost, which may depend on a certain volume commitment. Providing instrument installation at no additional costs can be a significant driver of demand, as it mitigates large capital expenditures for programs and enables flexibility in upgrades as user needs evolve.

Dried samples have the potential to increase access to viral load testing

To address the unmet HCV testing need, the expansion of viral load services will be needed in regions where liquid plasma separation and cold-chain transport and storage are challenging. As shown in Exhibit 10, dried samples do not require cold chain for short-term (on the scale of months) storage and transportation, enabling access to testing where gaps exist in plasma sample networks.

The use of dried samples can facilitate decentralized access by enabling samples to be collected at lower levels of the health system, where cold chain may not be available, while leveraging centralized diagnostics for testing. Dried samples may be collected from a simple fingerstick as a dried blood spot (DBS) on filter paper. WHO PQ for dried samples of HCV VL is currently limited to DBS using Abbott HCV RealTi*me* (*m*2000). While the use of dried samples is well established in the HIV space, the use of DBS for HCV VL is restricted by the limited inclusion of dried samples as valid sample types by suppliers. For example, dried plasma samples, from whole blood samples with the Roche cobas Plasma Separation Card, have approval for HIV viral testing though not for HCV.

Exhibit 10: Cost and programmatic advantages of dried samples over liquid plasma

Attribute	Whole blood / plasma	Dried sample
Health care worker skill requirement for collection	Qualified phlebotomist for venipuncture	Minimal training; sample may be obtained by fingerstick
Stability at 20°C	Six hours (whole blood), 24 hours (plasma)	Multiple weeks or months
Associated costs	Potentially lower cost for collection materials than dried samples in some markets due to economies of scale. Higher cost for cold chain transportation and storage.	Potentially higher cost for collection materials (in some markets). Lower cost of transportation and storage.

Source: FIND and CHAI, Dried Blood Spot Sampling for HCV Viral Load. First Market Potential Report.

Demand and challenges for uptake of dried samples for viral load

Increased access to HCV services is a key driver of demand for dried samples. The 2018 Unitaid-funded FIND/CHAI DBS Market Potential Report is an important publication describing the need for DBS to increase access to testing. It also describes the total market 'need' for HCV diagnostics to achieve WHO targets compared to the 'demand' based on country characteristics and trends. The potential need for HCV DBS was projected to be nine million (32 percent) out of the 28 million total tests for the 2018-2021 period. However, potential demand over the same period, based on historical procurement trends, was expected to be lower than the need at only two million DBS and 13 million plasma tests. (Updated data is not currently available.)

Costing analysis of DBS versus plasma samples for viral load

DBS may offer cost savings over plasma as determined through a comparative cost analysis.

There is limited costing data on the use of dried samples for HCV, however analyses comparing plasma and dried samples for HIV viral load have relevance. While the cost comparison by Nichols et al.[13] presented in Exhibit 11 represents the specific context of the Zambia HIV study, the data demonstrate the higher cost of transporting plasma due to cold chain requirements. Despite the additional reagents required to extract the dried sample prior to analysis, the final cost of per plasma sample (US$4.69) in this study is still greater than that of DBS (US$3.78).

Exhibit 11: Cost comparison of plasma with DBS in Zambia study

Sample type	Collection	Trans-portation	Dried sample extraction	Total
Plasma	US$1.18	US$3.51	-	**US$4.69**
DBS	US$1.39	US$2.07	US$0.32	**US$3.78**

Source: Nichols et al. 2020

In the Nichols study, dried samples were transported by sample courier similar to plasma, however the nature of dried samples could enable transportation by less expensive means thereby further reducing the cost of using dried samples compared to plasma. The case for the use of dried samples is not universal however. Where strong plasma sample transport networks are present, economies of scale and a competitive market for plasma sample commodities may reduce the cost differential for the transportation of plasma over dried samples. In this instance, the true driver for the uptake of dried samples may rather be the ability to extend access to testing to individuals outside of traditional sample transport networks.

Complexity of diagnostic cost components, importance of price transparency, and cost comparison of potential testing pathways

Multiple cost components add to the final cost paid by the program for testing and different possible testing pathways will have different costs.

The pricing structure of testing commodities is complex. The price on an invoice, which reflects the true cost to the program, frequently includes a range of cost components in addition to the base, ex works (EXW) price. For example, additional cost components may include the following:

- Ancillary consumables; proprietary (e.g. supplier's test reagents) and non-proprietary (e.g. pipette tips and plastic tubes)
- Instrument rental
- Service and maintenance
- Supply chain costs
- Country specific tariffs, taxes and associated fees

Due to this complexity, it is essential that programs and procurement agents have visibility across the cost components which lead to the final cost of testing.

Exhibits 12 and 13 present the outputs of real-world, cost visibility exercises for HCV VL tests procured under Roche's Global Access Program (GAP) and Cepheid's High-Burden Developing Country (HBDC) program respectively in two anonymous countries. While these specific examples do not represent universal costs experienced in all countries, the addition of similar cost components is broadly generalizable to other suppliers/countries and may therefore serve as valuable illustrations for achieving pricing visibility.

13 "Cost and Impact of Dried Blood Spot Versus Plasma Separation Card for Scale-up of Viral Load Testing in Resource-limited Settings." Nichols et al., Clinical Infectious Diseases, issue 70, pg 1014, March 15, 2020.

Without price visibility outputs similar to Exhibits 12 and 13, a program or procurement agent may be challenged to effectively:

- Negotiate contract terms
- Compare costs and services from different suppliers
- Identify opportunities for cost reductions
- Assess total budget impacts

Exhibit 12: Example Roche HCV VL cost components from anonymous country

Price component	Cost %	Incremental price	Total price
Test (FOB)			**US$8.90**
Logistics/ clearing fees/ handling	15%	US$1.34	**US$10.24**
Distributor fees	5%	US$0.51	**US$10.75**
Flat distributor service charge		US$1.00	**US$11.75**
Cost to facility			**US$11.75**

Source: CHAI country teams

Exhibit 13: Example Cepheid HCV VL cost components from anonymous country

Price component	Cost %	Incremental price	Total price
Test (EXW)			**US$14.90**
Shipping and insurance	8%	US$1.19	**US$16.09**
Logistics/ clearing fees/ handling	20%	US$3.22	**US$19.31**
Cost to facility			**US$19.31**

Source: CHAI country teams

While there is no one-size-fits-all approach to achieving cost visibility, open communication with the supplier, distributor, and government import agencies can lead to the development of a complete picture of each cost component. (Appendix 4 provides additional guidance to achieve pricing transparency).

Pursuing a comprehensive approach to understanding the net individual costs of differing testing strategies provides a fuller understanding of costs to enable the optimization of diagnostics cascades. While the comparison of the two alternate modes of screening (as previously shown in Exhibit 6) is valuable, to achieve the most cost effective and efficient testing pathway a more comprehensive, holistic pricing framework of potential modes of testing and their associated costs provides greater utility to programs. Key considerations in such an overarching framework may include cost elements such as:

- Sample collection, transportation and storage
- Testing reagents and ancillary consumables (e.g. pipette tips, gloves, etc.)
- Lab operations including human resources
- Diagnostic platforms (annualized using a depreciation schedule)
- Equipment service and maintenance
- Data connectivity and management including results return

To assist in determining the most cost-effective testing pathway based on multiple factors, FIND has developed a comprehensive online decision tool called the Hep C Testing Calculator. This tool permits the user to input costs along the diagnostics cascade, as well as country specific epidemiological parameters. It is expected that FIND's Testing Calculator will continue to be refined and expanded, and that other holistic costing tools may evolve to aid in the development of efficiently structured testing and treatment networks. In addition to optimizing country programs, insights afforded by this type of analysis can inform diagnostic manufacturers' strategies for designing complementary product offerings that address a program's complete testing needs.

Photo by Christine McNab

HCV treatment

Treatment costs continue to decline as the overall Indian generic DAA market across LMICs expanded to ~ US$16 million in 2020. Generic daclatasvir sales reached a milestone of three million packs by end of 2020.

Supplier landscape

Licensing

With Bristol Myers Squibb's (BMS) decision in 2020 to withdraw its daclatasvir patent, an additional 26 countries originally excluded from the initial licensing agreement between BMS and Medicines Patent Pool (MPP) are now expected to access generic daclatasvir.

Originators of the key HCV drugs (DAAs) - Gilead, BMS, and AbbVie - each have licensing agreements that continue to allow generics to manufacture and sell these drugs in a large number of LMICs.

For sofosbuvir (SOF), ledipasvir (LDV), velpatasvir (VEL), and voxilaprevir (VOX), Gilead continues its sublicensing agreements with 11 Indian manufacturers to produce and/or sell generic versions in 105 countries.[14] An additional three non-Indian generics (two in Egypt and one in Pakistan) have sublicensing agreements to manufacture and sell in their local markets. Learn more about eligible countries covered under the licensing agreements here.

For daclatasvir, BMS announced in early 2020 that the marketing authorizations and resulting patent protection for its originator product would be withdrawn or allowed to lapse in countries where the product is no longer routinely prescribed or where there are other therapeutic options available. As a result, an additional 28 countries are expected to have access to generic daclatasvir (see details). BMS' initial license with Medicines Patent Pool (MPP) included 112 countries and seven manufacturers sub-licensed to manufacture the generic version.[15]

For glecaprevir/pibrentasvir (G/P), another pangenotypic regimen, the licensing agreement signed between AbbVie (originator) and MPP excludes India, a major market (list of countries can be found here).[16] As of early 2021, one generic manufacturer has signed a sublicense agreement with MPP, but the product is still under development, and it is expected to enter the market by 2023.

14 Gilead Licensing Agreement
15 BMS-MPP Licensing Agreement
16 Abbvie-MPP Licensing Agreement

Quality-assured generics

Most DAA regimens now have at least one WHO prequalified product available.

SOF and DCV, the most widely used, best priced, pangenotypic DAA regimen for HCV treatment, are vailable as WHO PQ'd products from a number of generic suppliers. SOF and DCV have five and four generic manufacturers with WHO PQ, respectively. In 2020, Viatris (formerly known as Mylan) became the first generic to recieve WHO PQ for SOF/DCV fixed-dose combination (FDC), SOF/LDV FDC, and SOF/VEL FDC. In addition, Laurus Labs achieved WHO PQ for daclatasvir (30mg and 60mg) in 2020. Exhibit 14 displays the landscape for QA generic suppliers.

Exhibit 14: Generic supplier quality status (as of July 2021)

DAAs	WHO PQ'd
SOF (400 mg)	Cipla, Hetero, Strides, Viatris, European Egyptian Pharmaceutical Limited (Pharco)*
DCV (30 mg and 60 mg)	Cipla, Hetero, Viatris, **Laurus Labs**
SOF/DCV FDC (400mg/60mg)	**Viatris**
SOF/LDV FDC (400mg/90mg)	**Viatris**
SOF/VEL FDC (400mg/100mg)	**Viatris**
SOF/VEL/VOX FDC	None
G/P (300/120mg)	None

Note: Pharco's SOF was removed from the Global Fund's List of quality-assured products in early 2020 due to non-compliance with GMP and regulatory requirements identified during WHO's on-site inspection in May 2019. A follow-up on-site inspection on the implementation of Pharco's corrective and preventative actions by WHO is expected to take place in 2021. Supplier names in bold recieved WHO PQ in 2020.

Source: The Global Fund List of Antihepatitis Pharmaceutical Products, July 2021, Version 22; The WHO List of Finished Pharmaceutical Products (FPPs) that have received WHO PQ as of July 2021

In-country supplier registrations (as of Q4 2020)

Countries with a larger number of DAA suppliers registered are accessing more product options at lower prices.

An expedited and streamlined drug registration process leads to a more extensive supplier network which increases competition and allows for more successful tender processes to ensure supply security within the country. India has ten or more suppliers registered for both SOF and DCV, and the national tender was able to secure a price of US$39 per patient course for a 12-week treatment with SOF and DCVin 2019. Generally, registering multiple suppliers leads to lower in-country prices as observed in India. In some countries, however, structural barriers or elongated supply chains continue to keep costs high.

In the last year, four additional countries had at least one WHO PQ'd generic DAA registered product. In total, 23 of the 30 high hepatitis burden LMICs have at least one WHO PQ'd generic DAA registered. Seventeen of these countries have more than one WHO PQ'd Indian generic registered for sofosbuvir. Similarly, for sofosbuvir and velpatasvir, the number of countries with access to WHO PQ'd generics has increased to 16. The six countries with no generic DAAs registered are Brazil, Colombia, Georgia, Nepal, Sierra Leone, and South Africa. Brazil, China and Colombia are procuring innovator products, while Georgia is using donations from originators for its HCV program. South Africa is able to import generics under a special waiver as no SOF+DCV manufacturer, neither originators nor generics, are currently registered in the country. (Please refer to Appendix 5 for in-country supplier registration status of essential drugs)

Photo by Christine McNab

Volume trends

Methodology

Visibility into volume trends has been limited due to the lack of publicly available procurement data across LMICs. We focus primarily on India's generic export market, Medicines Patent Pool's (MPP) report on daclatasvir sales by sublicencees,[17] and public sector program data, for which the most robust data is available, which encompasses the majority of sales to LMICs. Where possible, we also add insight into the generic-inaccessible market based on publicly available data. This methodology is limited as it doesn't account for the use or export of DAAs manufactured outside India, such as Egypt, Uzbekistan, and Vietnam. It also does not include sales or donations by originators. These limitations may lead to underestimating the volume of drugs procured across LMICs shown in Exhibit 15. An overview of the CHAI analyses and methodologies used in this section is provided in Appendix 6.

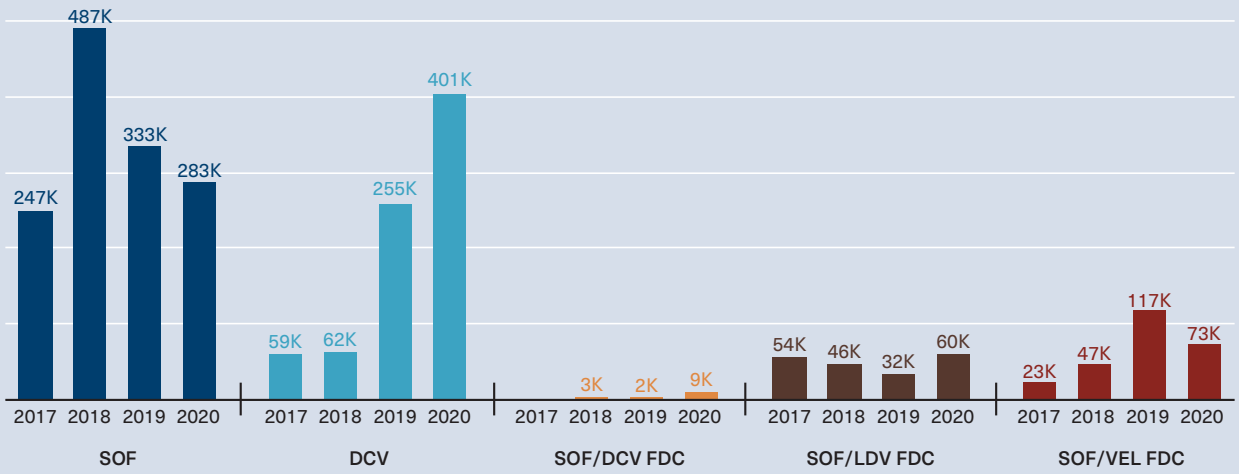
DAA procurement trends

Continued scale-up across LMICs is required to meet the substantial remaining need for HCV treatment.

Despite a decline in sofosbuvir procurement, DAA volumes exported by Indian generics increased by approximately 12 percent (87,000 bottles) in 2020. This increase was primarily driven by high demand for daclatasvir, which previously was procured at a rate of approximately 1:3 as compared to sofosbuvir, despite the two drugs being used in equal combination. This previous mismatch in exported volumes of sofosbuvir and daclatasvir may be due to the use of locally manufactured daclatasvir, as well as variability in procurement timelines for the two products.

In 2020, 50 percent of DCV exports from India were concentrated to two countries, Pakistan and Ukraine, with both these countries procuring significantly higher volumes than in previous years and at higher rates compared to sofosbuvir (Appendix 8). Conversely, sofosbuvir procurement has declined since 2018. DAA procurement by countries has been inconsistent, making demand forecasting a challenge. Transparency into the countries' procurement plans can help suppliers plan production capacity, leading to lower lead times and prices.

Exhibit 15: 2017-2020 India generic DAA packs exported to LMICs



Note: Only orders >50 bottles in the India Import Export data included in analysis; Each bottle has 28 pills.

Source: India Import Export Data; CHAI Analysis.

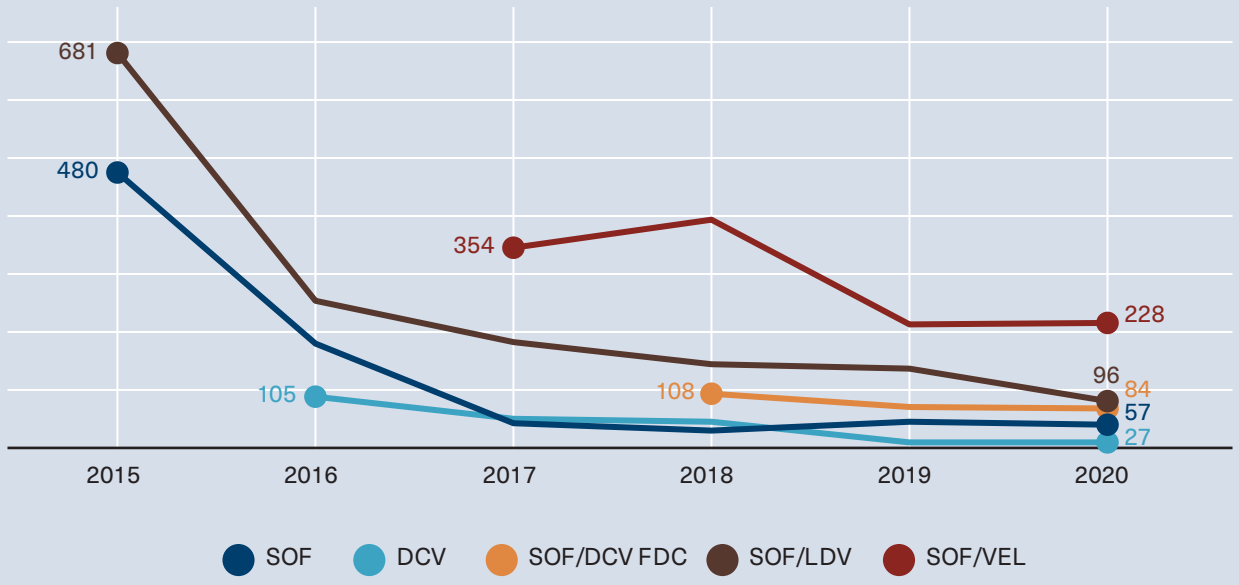
17 Implementation of Daclatasvir Licenses, MPP Development Report 2021, at: https://medicinespatentpool.org/uploads/2021/06/MPP_DAC_licence_implementation_update_June_2021.pdf

Sofosbuvir paired with daclatasvir remains the most widely used and lowest cost HCV regimen, constituting over 70 percent of overall DAA procurement. More than one million treatment courses (three million packs) of generic daclatasvir have been procured as of December 2020.[18] Sofosbuvir and velpatasvir fixed-dose combination is mostly being used as second line treatment across LMICs. Countries such as Pakistan, India, and Rwanda have chosen to use sofosbuvir and velpatasvir, in combination with ribavirin, to retreat patients who failed HCV treatment.

A small number of countries drove the increase in DAA procurement in the years 2015 to 2018. In 2018, the HCV programs' scale-up in Egypt, India, and Pakistan contributed to more than 85 percent of generic DAA procurement. In 2020, procurement from these countries decreased, reflecting a need for programs that prioritized patients who were previously diagnosed and awaiting care for HCV treatment to focus on active case finding. Other countries, including Rwanda, Vietnam, Uzbekistan, and Ukraine, have scaled-up procurement of DAAs in the last two years. Continued scale-up of HCV programs in LMICs is required to sustain the DAA market and achieve WHO elimination goals by 2030. Stagnating volumes can threaten supply security, as existing suppliers may exit the market due to low volumes and/or new suppliers are discouraged from entering the market. Though 13 percent of chronic HCV infections are estimated to have been treated worldwide, more than 50 million patients remain untreated.[19] This demonstrates a significant opportunity to build on the current momentum in HCV treatment and scale programs more rapidly.

Based on these volumes, there remains a significant, untapped market for suppliers with a total market size of over US$1–1.5 billion across LMICs.[20] While a single manufacturer currently has more than 90 percent market share of Indian generic DAA supply, the potential market provides an opportunity for manufacturers to increase their DAA portfolio. By obtaining WHO prequalification, offering competitive pricing, and expediting in-country registrations, manufacturers can aim to expand their market share. Countries and donors can ensure market competitiveness by providing visibility into their HCV scale-up strategies and procurement plans to inform manufacturers' market development strategies and supply plans.

Exhibit 16: Weighted average FOB price for 12 weeks of treatment with DAAs in LMICs



Note: Pricing reflects 'Freight on Board' price, which does not include shipping, customs and distributor-associated costs. Usually there are in-country costs added to the FOB price which result in a higher final price to the buyer; The price is weighted average of volumes of all orders >50 bottles and their respective prices per bottle; Only orders above 50 bottles considered; Each bottle has 28 pills; Prices are for both WHO PQ'd/ ERP reviewed and locally approved products; all prices in USD.

Source: India Export Data, CHAI Analysis

18 Implementation of Daclatasvir Licenses, MPP Development Report 2021, at: https://medicinespatentpool.org/uploads/2021/06/MPP_DAC_licence_implementation_update_June_2021.pdf
19 WHO 2021 global progress report on access to hepatitis C treatment and diagnostic, at: https://www.who.int/publications/i/item/9789240019003
20 Estimated based on current DAA prices and untreated HCV cases across LMICs

Pricing trends

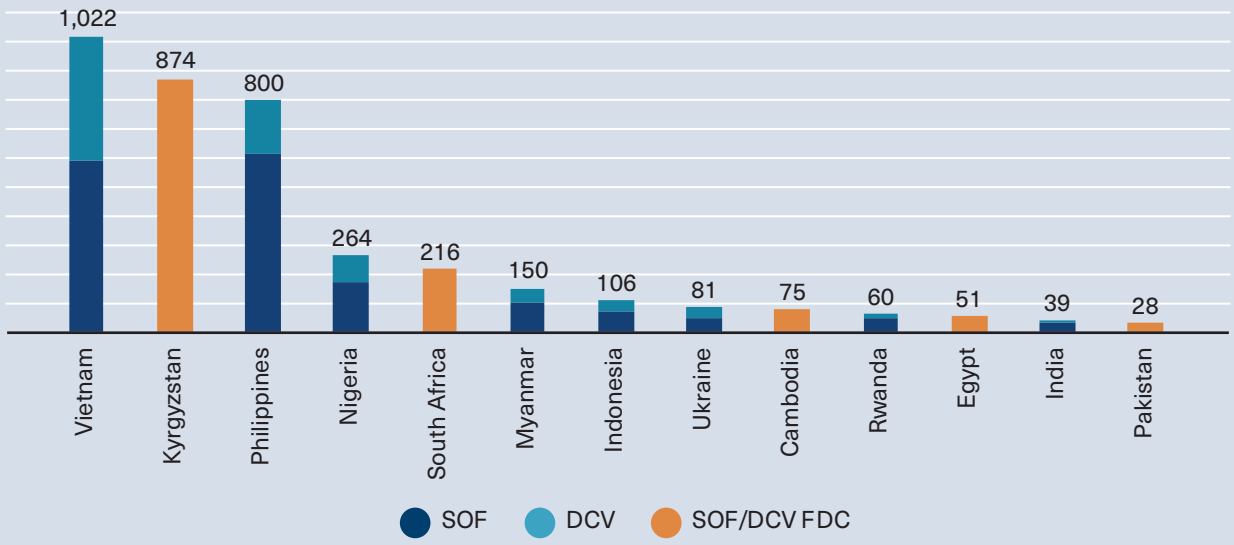
DAA price decreases have slowed; further decreases in treatment cost can be expected to be driven by supply chain optimization and centralized procurement by countries where the in-country mark-ups are still high.

Though there has been a general downward trend in prices since 2015, the average price of most generic DAAs fell only marginally in 2020 (Exhibit 16). The prices for SOF, DCV, SOF/DCV FDC, and SOF/VEL FDC remained relatively unchanged from 2019 to 2020. Nonetheless, there is now more than an 80 percent reduction in the average freight-on-board price of SOF+DCV from originators' access price of US$750 at the time of their introduction in 2014.

While DAA prices have fallen significantly due to expansion of the competitive landscape of generic DAAs and increase in demand, there is significant variability in prices accessed across LMICs. Exhibit 17 displays in-country prices for a 12-week treatment course of SOF+DCV. Rwanda continued to procure WHO PQ'd SOF+DCV at US$60 for a 12-week treatment course, setting a price benchmark for WHO PQ'd DAA regimens. Countries such as India and Pakistan are procuring locally manufactured, non-PQ'd regimens at an even lower price of US$39 and US$28 respectively, for a 12-week treatment course. Conversely, prices are as high as US$1,073 and US$874 for a 12-week treatment course of SOF+DCV in Vietnam and Kyrgyzstan, respectively.

In 2020-2021, Indonesia renegotiated SOF and DCV prices to secure more than 85 percent reduction in price for a 12-week treatment course. A 12-week treatment course of SOF and DCV in Indonesia is currently priced at US$106 as compared to the previous price of US$750. These changes in prices of SOF and DCV over the past year will allow the program to increase their DAA purchase seven-fold if the program is able to utilize these price reductions for additional procurements.

Exhibit 17: In-country prices of SOF, DCV, and SOF/DCV FDC



Note: SOF and DCV refer to singles; The prices mentioned are public sector prices paid by the government in each country, if available, or the lowest identified private sector price if a public sector price is not available; Prices shown can be for originator or generic product; Amongst generic products, prices can be for WHO PQ'd/ ERP reviewed or locally quality assured products; Price as of 2019 for Pakistan; Price as of 2018 for Kyrgyzstan; all prices in USD.

Source: CHAI analysis for Nigeria, Indonesia, Vietnam, Rwanda, Cambodia, Myanmar; World Hepatitis Alliance and members for Egypt, Philippines; International Treatment Preparedness Coalition in Eastern Europe and Central Asia (ITPCru) and 100% life for Ukraine; Partnership Network for Kyrgyzstan; South African National Department of Health's Affordable Medicines Unit; Aga Khan University for Pakistan

For SOF/VEL FDC, the lowest price for a 12-week course from a WHO PQ'd manufacturer is US$222. India and Pakistan are procuring locally manufactured products at a low price of US$105 and US$118 respectively, per treatment course, while countries such as Brazil and Colombia are still procuring from originators and paying high prices of US$1,470 and US$4,500, respectively, for a 12-week course of treatment using SOF/VEL FDC. Refer to Appendix 9 for in-country prices of SOF/VEL FDC.

International procurement mechanism negotiated terms and pricing

International and regional organizations such as The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the United Nations Development Programme (UNDP), and the Pan American Health Organization (PAHO) Strategic Fund have implemented central mechanisms to pool procurement orders and negotiate lower prices with suppliers (Exhibit 18). Member states can purchase DAAs through these organizations.

Volume-based pricing

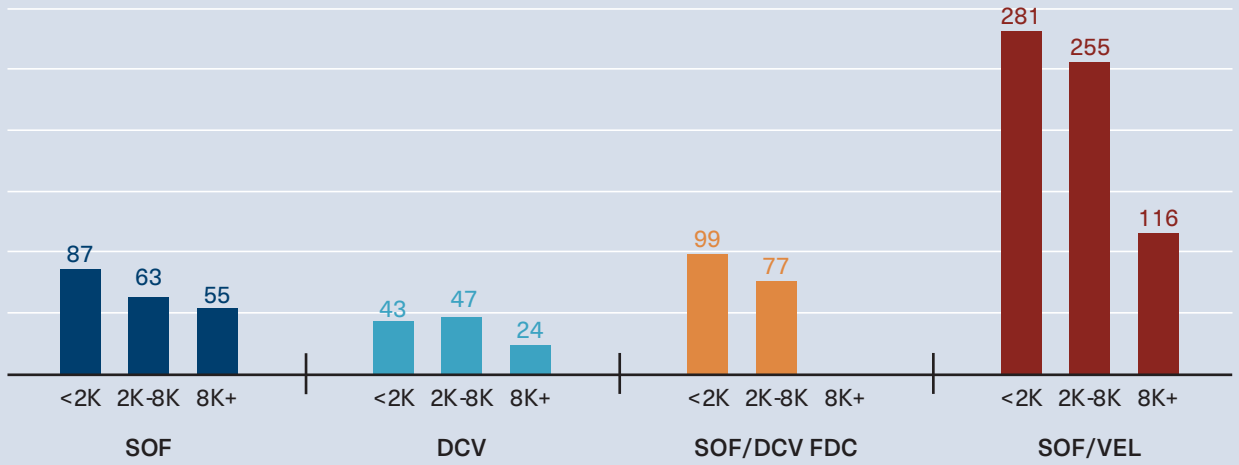
Large orders allow drug suppliers to more efficiently manufacture product, which in turn can lead to lower prices for buyers. As shown in Exhibit 19, programs with scaled-up HCV treatment and planned procurement to pool volumes have obtained lower prices for treatment. In 2020, large orders continued to increase in number and volumes, increasing the average order size by 23 percent. On average, the unit freight on board incoterm (FOB) price for orders above

Exhibit 18: Negotiated prices by international and regional organizations for 12 weeks of treatment

Mechanism	Eligible countries	Products available	2020 select example procurements
GFATM	Click here to view list	SOF+DCV (US$89) SOF/DCV FDC (US$75) SOF/LDV FDC (US$79)	~1.6K SOF+DCV for Vietnam
UNDP	105 member states	SOF/DCV (US$79) SOF/LDV (US$90) SOF/VEL (US$270)	~2.2K SOF/VEL FDC for Tajikistan ~750 SOF/VEL FDC + ~3.7K SOF+DCV for Turkmenistan
PAHO	34 member states in Latin American & Caribbean	SOF/DCV (US$102) SOF/VEL (US$4050) SOF/LDV (US$4050)	

Note: DAAs offered through these organizations are from WHO PQ/ERP reviewed suppliers.
Learn more about The Global Fund Pooled Procurement Mechanism here, the PAHO Strategic Fund here.

Exhibit 19: Average weighted FOB price per 12 weeks treatment in 2020



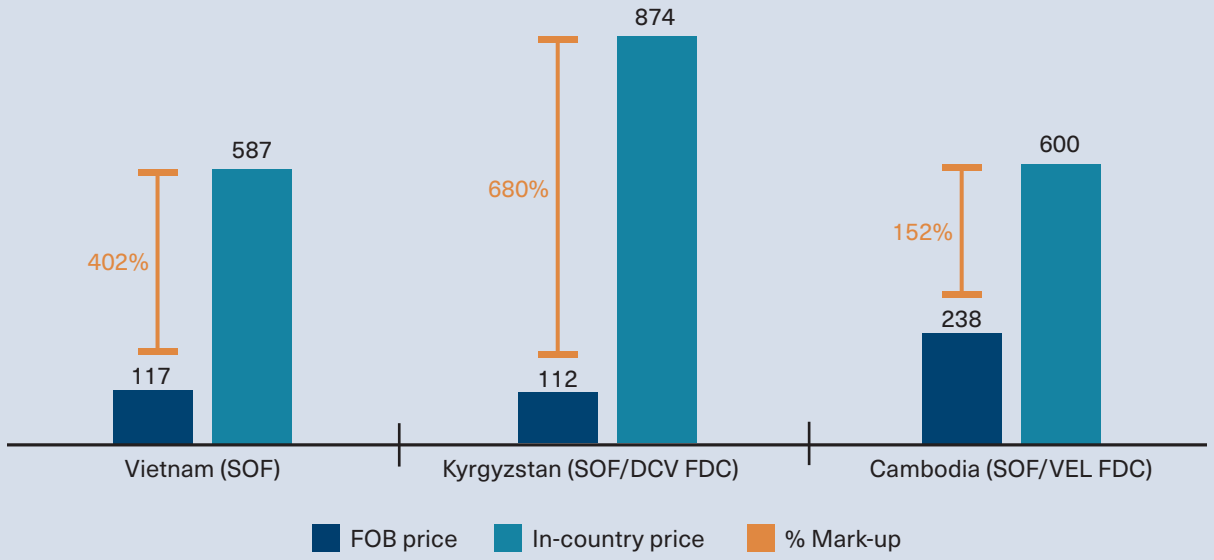
Note: All prices in USD.
Source: India Export Data, CHAI Analysis.

8,000 packs is 35 to 60 percent lower when compared to orders below 2,000 packs. Indonesia and Myanmar have achieved more than a 50 percent reduction in FOB prices for sofosbuvir and daclatasvir for order volumes above 2,000 units. Similarly, Nigeria accessed daclatasvir at a 25 percent lower cost by increasing the order quantity.

Price mark-ups

Despite a decline in freight-on-board prices of DAAs, in-country prices continue to be high due to structural barriers leading to high mark-ups. In-country mark-ups typically include shipping and insurance, import duties and in-country taxes, storage, facility maintenance, and transportation costs, pharmacy charges, distributor margins, and other logistical costs. In countries lacking a centralized procurement and distribution system managed or contracted by the government, mark-ups are as high as three to six times the FOB cost (Exhibit 20 shows indicative price mark-ups on DAAs in select countries).

Exhibit 20: In-country price mark-ups for DAAs (indicative)



Note: All prices in USD.
Source: CHAI Analysis.

Retreatment market trends

Countries that have scaled-up their HCV programs such as Egypt, India, Rwanda, and Pakistan, are now looking at retreating patients who did not achieve SVR 12 (were not cured). With a greater than 95 percent cure rate in a programmatic setting for patients on DAAs, the retreatment market is small, though as countries scale-up HCV treatment the number of patients needing retreatment is expected to increase.[21] The current WHO guidelines recommend second-line therapy of SOF/VEL/VOX or extending the initial DAA therapy to 16 or 24 weeks, while reinforcing adherence as an alternative option. However, SOF/VEL/VOX is currently only available from the originator Gilead, as generics are not incentivized to enter the small, fragmented market, and are priced out of reach for most LMICs. A 24-week course of ribavirin (RBV) with either SOF/LDV, SOF/DCV, or SOF/VEL are the most commonly used second line therapy regimens across LMICs.[22]

Ribavirin is an older, off-patent antiviral used sparingly for HCV as well as viral hemorrhagic fevers. Currently, there are no WHO PQ'd or ERP-approved suppliers for RBV. Though there are eight generics with US FDA approval, five have discontinued marketing in the US and have limited production of the product (Exhibit 21). Only Aurobindo and Teva are supplying in LMICs.

India, one of the high-burden countries, that has scaled-up HCV programs and is also retreating patients, is procuring locally approved RBV at a US$86 per 24-weeks treatment course.[23] In 2020, a minimal amount of RBV was exported from Indian generics at an average weighted FOB price of US$170 per 24-weeks treatment course.

SOF/DCV or SOF/VEL administered for 24 weeks with the addition of ribavirin seems to be the most accessible retreatment regimen for LMICs at the present time. In 2021, the Rwandan government will be initiating a retreatment program using SOF/VEL FDC + RBV for 24 weeks for patients who failed an initial SOF+DCV regimen. This retreatment program will be closely monitored and documented to assess cure rates as well as side effects and adverse events. Results of this assessment will be published to be included for review in future WHO guideline processes regarding retreatment options.

The small retreatment market and limited quality-approved generic suppliers pose a supply risk for the HCV retreatment market. Better quantification

Exhibit 21: US FDA approved ribavirin (as of Dec 2020)

Drug	Manufacturer	Dosage forms	Marketing status*
Ribavirin	Zydus Pharms USA	Tablet and Capsule	Prescription
Ribavirin	Sandoz	Tablet	Prescription
Ribavirin	Aurobindo Pharma	Tablet and Capsule	Prescription
Ribavirin	Chartwell	Capsule	Discontinued
Ribavirin	Teva	Capsule	Discontinued
Ribavirin	Heritage Pharma	Tablet	Discontinued
Ribavirin	Chartwell Rx	Tablet	Discontinued
Ribavirin	Beximco Pharms USA	Tablet	Discontinued

**Marketing status indicates how a drug product is sold in USA. Products listed as "discontinued" are approved products that have never been marketed, have been discontinued from marketing, are for military use, are for export only, or have had their approvals withdrawn for reasons other than safety or efficacy after being discontinued from marketing. A prescription drug requires a doctor's authorization to purchase.*

Source: US FDA List of approved drugs as of Dec 2020

21 Boeke CE, Adesigbin C, Agwuocha C, et al. Initial success from a public health approach to hepatitis C testing, treatment and cure in seven countries: the road to elimination BMJ Global Health 2020;5:e003767.

22 Boeke CE, Hiebert L, Waked I et al. Retreatment of Chronic Hepatitis C Infection: Real-World Regimens and Outcomes from National Treatment Programs in Three Low- and Middle-Income Countries. Clinical Infectious Diseases 2021; ciab461, https://doi.org/10.1093/cid/ciab461

23 Price from Procurement Cell of Government of Maharashtra (state in India). https://www.vaccinehaffkine.com/images/procurement_cell/Order-NO-3162--Supply-of-Cap-Ribavirin-200mg.pdf

of patients needing retreatment, transparency into procurement plans, and pooling of demand across countries could help suppliers plan production capacity, leading to lower lead times and prices.

Pediatric HCV treatment

Current WHO guidelines recommend deferring HCV treatment of children under the age of 12 and recommend only non-pangenotypic treatment regimens for adolescents aged 12 to 17. There is therefore no guidance as yet on appropriate dosing for children and no available generic pediatric formulations of pangenotypic DAA regimens. A 2020 Lancet publication of a modeling exercise from the Center for Disease Analysis Foundation estimated that there are 3.26 million children living with chronic HCV infection globally, with 20 countries accounting for 80 percent of all cases in patients 0-18 years of age.[24] Countries with the highest number of children with chronic HCV include Pakistan, China, India, Nigeria, and Egypt.

Elimination of HCV cannot succeed unless it includes the treatment of children. Countries with a high burden of HCV infection and robust adult treatment programs are beginning to develop case-finding strategies and treatment programs for children. Revised WHO treatment guidelines are planned for 2021-2022, which will include new recommendations on the treatment of children and adolescents.

Gilead and AbbVie received US FDA approval in Q2 2021 for the use of SOF/VEL and G/P respectively among children down to the age of three years. The Global Accelerator for Pediatric Formulations (GAP-f), a WHO network co-chaired by CHAI, reached consensus on the importance of aligning treatment regimens for adults and children, given the opportunities for lower pricing, streamlined procurement, and simplified service delivery. In the absence of a clinical trial for DCV in patients less than 18 years, WHO commissioned a pharmacokinetic modeling exercise of DCV 30mg for HCV treatment of younger children, which demonstrated that the 30mg dose will provide appropriate drug exposure (i.e., similar to that found to be safe and effective in adults) for children with a weight as low as 14kg.[25] While WHO PQ'd DCV 30mg is available from multiple generics, given the need for the 30mg DCV for HIV-HCV co-infected individuals on efavirenz-containing ART regimens, SOF 200mg is not yet available as a generic product to pair with it. Consequently, SOF 200mg is expected to soon be included on the list of products eligible for WHO PQ (known as the "expression of interest" or "EOI" list).


Photo by Melinda Stanley

24 Schmelzer J, Dugan E, Blach S, et al. Global prevalence of hepatitis C virus in children in 2018: a modelling study. The lancet. Gastroenterology & Hepatology. 2020 Apr;5(4):374-392. DOI: 10.1016/s2468-1253(19)30385-1.

25 Cressey et al., Adequate daclatasvir exposures in children 14-35 Kg with available adult formulations (abstract). In: Conference on Retroviruses and Opportunistic Infections; June 3-November 3, 2021; Virtual; Abstract nr 444.

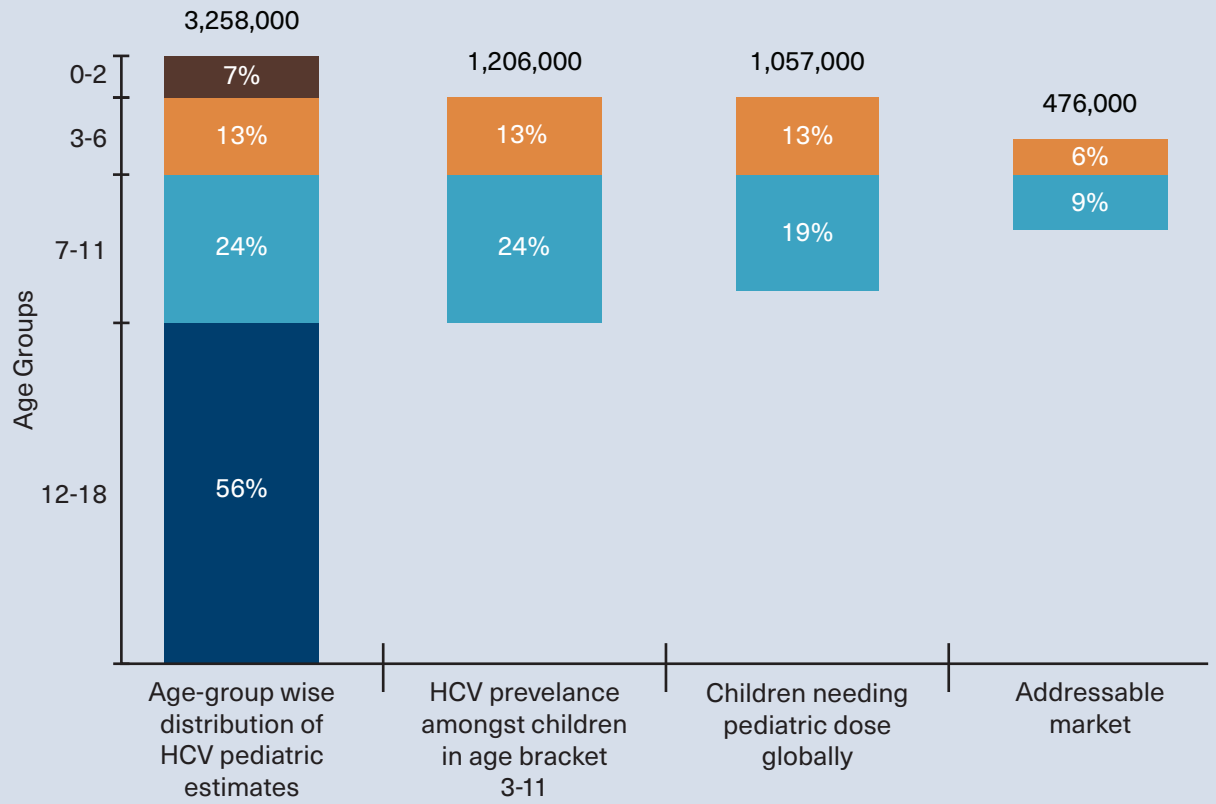
Dossiers for pediatric regimens of SOF singles, DCV singles, SOF/DCV FDC, SOF/VEL FDC, and G/P have been submitted to the WHO Expert Committee for review requesting inclusion on the core list of the essential medicines list for children (EMLc). A decision by the Essential Medicines List (EML) Expert Committee is expected by Q3 2021. WHO's revised HCV guidelines are expected to be published in 2021-2022 to include recommendations around HCV treatment of children.

Addressable Pediatric Market Sizing

Countries with robust adult HCV programs, which include Rwanda, India, Pakistan, Egypt, Ukraine, Mongolia, and Georgia, could be focal countries for the expansion of pediatric HCV treatment in the next three to five years. Among these seven countries, there is an estimated addressable market of approximately 500,000 children requiring pediatric formulations (Exhibit 22). An overview of the CHAI analyses and methodologies used in this section is provided in Appendix 10.

The HCV community must focus efforts to overcome market challenges and ensure that children receive the HCV treatment they need. Suppliers generally operate on models of large volumes planned quarterly and are often unable or unwilling to adequately respond to small, uncoordinated orders that would characterize the pediatric market. Suppliers also often lack visibility around volumes to aggregate demand and plan capacity for ensuring supply at accessible prices. To help create a sustainable pediatrics market, it will be essential for countries to plan and pool their pediatric treatment volumes, engage with suppliers, provide visibility into procurement planning, and focus on case finding strategies.

Exhibit 22: Addressable market estimate for pediatric DAA formulations



Key assumptions:

1. Excluded age group 0-2 and 12-18

2. 100% children within the age-group 3-6, and 80% within the age-group 7-11 have weight lower than 35 kg

3. 'Addressable market' defined as children requiring pediatric dosage across seven countries with robust adult programs – Rwanda, Egypt, India, Mongolia, Pakistan, Georgia, Ukraine

Source: CHAI Analysis

Looking forward

India, Egypt, Pakistan, Rwanda, Georgia, Mongolia, and Ukraine are examples of countries that have committed to scaling up their HCV programs and have made significant progress towards HCV elimination. Some of these countries have taken a multi-pronged approach to scaling-up HCV programs. To illustrate, countries such as India and Indonesia started with an HCV program in a few of their states and provinces before expanding viral hepatitis program to other states. Other countries such as Rwanda, Nigeria, and Cambodia started with prioritizing HCV testing and treatment for people living with HIV. Results from their HIV/HCV co-infection programs informed the development of the countries' national strategic plans.

Rwanda, which started with HCV screening of people living with HIV (PLHIV), intensified its case finding activity amongst its general population, screening over four million, in the last three years. Rwanda is now on track to achieve HCV elimination within the next year. Other countries that prioritized patients who were previously diagnosed and awaiting care for HCV treatment will need to focus on active case finding. Similarly, other sub-Saharan African countries such as Ethiopia, Kenya, and Zimbabwe have recently updated or are developing national strategic plans on viral hepatitis leveraging HIV infrastructure to integrate care.

While some countries that have successfully scaled-up their programs have lowered HCV diagnostic and treatment barriers, many LMICs continue to pay high prices for diagnostic and drug commodities. Limited program funding, decentralized, and uncoordinated activities including procurement across disease areas result in disparate and high in-country prices. Gains in the accessibility of HCV commodities are slowing with plateauing prices and stagnating volumes. There exists, however, a significant untapped market.

Some of these barriers around availability and affordability can be overcome with strong political will from country leadership, dedicated funding, and a public commitment towards HCV elimination within a reasonable timeframe. Expedited in-country registration of WHO PQ'd diagnostics and treatment products can facilitate competition in the market and rapid entry for suppliers to new markets. A lower than US$100 per patient price for treatment and diagnostics can be achieved by optimizing procurement volumes and leveraging international procurement mechanisms to access volume-based pricing. Countries and partners can work together to ensure low in-country prices by reducing price mark-ups on commodities through supply chain cost optimization.

COVID-19 disrupted hepatitis services across LMICs, and programs adapted by introducing innovative approaches to service delivery. Programs that are beginning to implement HCV treatment programs should consider the opportunities of rapid scale-up to secure affordable pricing of diagnostics and drugs and decrease the need for ongoing costs by eliminating the disease faster in their countries. Increased donor and domestic financing for HCV elimination could significantly aid such a mission in these countries.

Photo by Christine McNab

Preliminary information on the HBV market

Introduction

Chronic HBV infection remains a major cause of liver disease globally, with an estimated 296 million people living with chronic HBV as of 2019.[26] The prevalence of chronic HBV infection varies geographically, from greater than six percent in African and Western Pacific regions, to 1.5 to 3.5 percent in Mediterranean, Southeast Asian, and European regions. In 2019, HBV resulted in an estimated 820,000 deaths, mostly from cirrhosis and liver cancer. Chronic HBV infection is completely preventable by vaccines. However, there is no cure for this infection; treatment can only suppress the replication of the virus. Similar to antiretrovirals for HIV management, people who start hepatitis B treatment must continue it for life.

Fortunately, the availability of a highly effective HBV vaccination has helped meet the global target of the Sustainable Development Goals (SDGs) and the global health sector strategy to reduce hepatitis B surface antigen prevalence to less than one percent among children younger than five years by 2020.[26] However, uptake of HBV birth dose vaccine, testing, and treatment is lagging despite high morbidity and mortality. Global coverage for timely HBV birth dose vaccine was 43 percent in 2019; only 10 percent (approximately 30.4 million) of people with HBV knew their status in 2019, and only 22 percent (approximately 6.6 million) of the people diagnosed were on treatment worldwide.

Few LMICs have public programs for HBV testing and treatment. Many factors contribute to this significant gap in access, including limited awareness and lack of funding for a public program. In addition, a complex diagnostic algorithm that makes it difficult to implement a public health approach to treatment, relatively high drug costs, long-term and/or life-long therapy that does not result in cure contribute to limited public health programs. Some countries have started to expand HBV testing and treatment by building on the foundation of their HCV program. India has now expanded its HCV infrastructure to screen and treat patients for HBV. Similarly, Rwanda has scaled-up its viral HCV program to include HBV testing as well.

26 WHO 2021 global progress report on access to hepatitis C treatment and diagnostic, at: https://www.who.int/publications/i/item/9789240019003

WHO-recommended HBV testing and treatment guidelines

The testing and treatment algorithm for HBV remains fairly complex. However, new WHO HBV prevention of mother-to-child transmission (PMTCT) guidelines and the expansion of HBV birth dose vaccine provide opportunities for building upon the backbone of HIV and syphilis PMTCT programs to scale up testing and treatment among pregnant women to eliminate vertical transmission.

WHO guidance on testing and treatment of HBV are referenced across several guidelines that address prevention, care and treatment for the general population, screening and diagnosis for the general population, and prevention of vertical or mother to child transmission of HBV, focusing on specific interventions among mothers and infants.[27,28,29]

The guidelines highlight key steps for HBV prevention, testing and treatment, including:

- **Serological testing**: The guidelines recommend the use of a single quality-assured serological diagnostic tool (i.e. laboratory-based immunoassay or RDT) to detect hepatitis B surface antigen (HBsAg). RDTs used should meet minimum performance standards and be delivered at the point-of-care to improve access and linkage to care and treatment.

- **Assessment for long-term treatment or maternal prophylaxis (in the case of pregnant women)**: Following a positive HBsAg serological test, the use of quantitative VL for HBV is recommended, along with other factors (presence of cirrhosis, age, and ALT levels), to guide who to treat or not to treat. In settings where antenatal HBV VL testing is not available, the use of hepatitis B e antigen (HBeAg) testing can be used for pregnant women to determine eligibility for tenofovir prophylaxis to prevent vertical transmission.

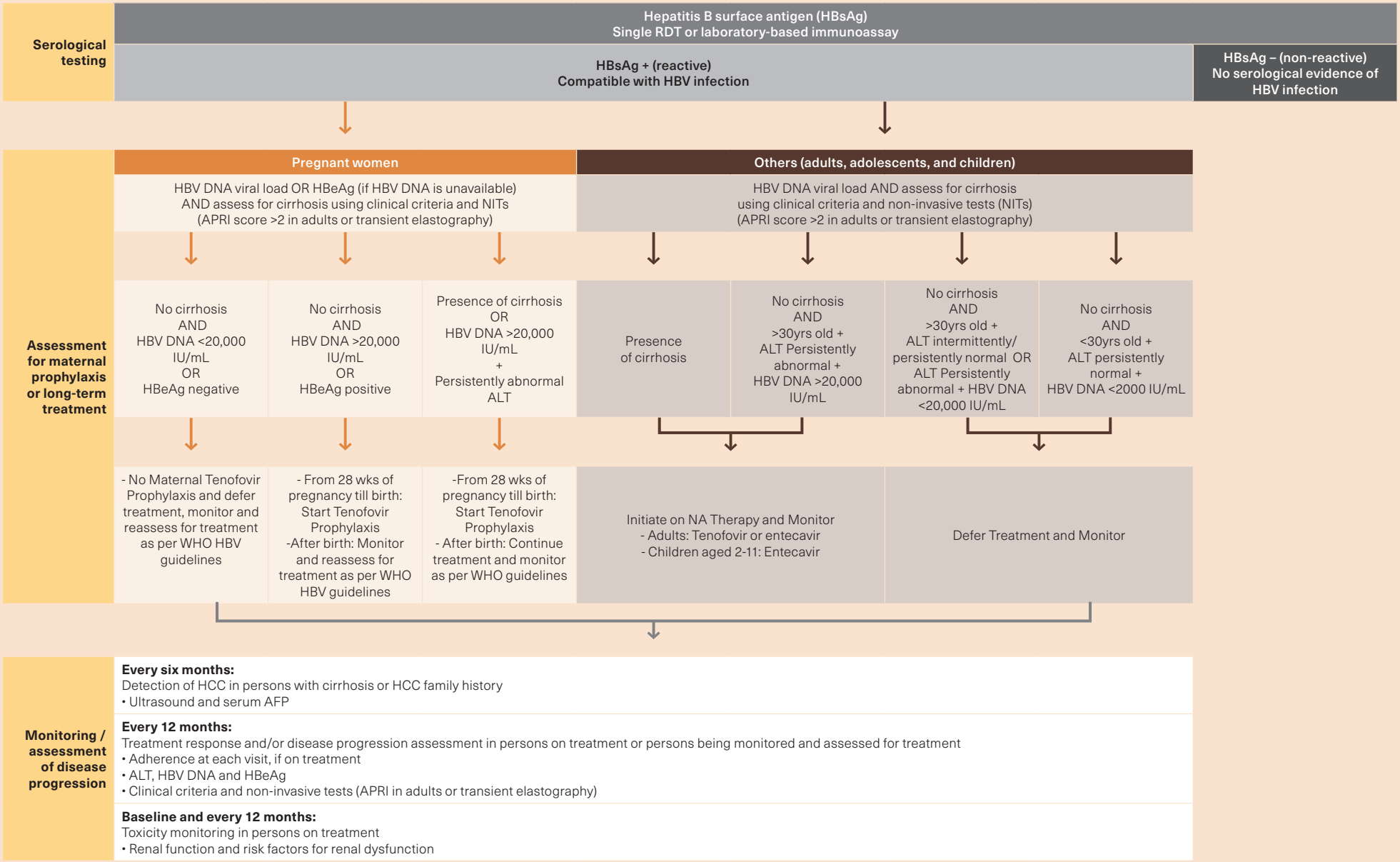
- **Treatment and maternal prophylaxis:** In all adults, adolescents, and children aged 12 years or older for whom antiviral therapy is indicated (based on the assessments noted above), tenofovir or entecavir is recommended. Only entecavir is recommended for children aged two to 11 years. Pregnant women should be started on long-term treatment based on the adult guidelines using ALT, HBV deoxyribonucleic acid (DNA), and cirrhosis status (Exhibit 23: cirrhosis, HBV DNA >20,000 IU/mL or persistently abnormal ALT). In addition, they should be considered for tenofovir prophylaxis from 28 weeks of pregnancy if HBV DNA is > 20,000 IU/mL or HBeAg is positive.

- **Monitoring / assessment of disease progression:** For patients on treatment and persons being monitored and assessed for treatment, the guidelines recommend that the ALT levels (and AST for APRI), HBsAg, HBeAg, and HBV DNA levels (where HBV DNA testing is available) be monitored annually. Additionally, for individuals without a cirrhosis baseline, assessment for the presence of cirrhosis (through non-invasive tests like APRI score or TE) is recommended, along with monitoring adherence on treatment.

- **Infant vaccination:** WHO recommends that all infants receive the hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, followed by two or three doses of hepatitis B vaccine at least four weeks apart to complete the series.

27 WHO Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection; 2015
28 WHO Guidelines on Hepatitis B and C testing; 2017
29 WHO Prevention of Mother-to-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis in Pregnancy; 2020

Exhibit 23: HBV testing and treatment algorithm



Source: 1. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015; 2. Guidelines on Hepatitis B and C testing. Geneva: World Health Organization; 2017; 3. Prevention of Mother-to-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis in Pregnancy. Geneva: World Health Organization; 2020

HBV diagnostic market trends

Supplier landscape

There are a range of quality-assured HBsAg and viral load tests available, however, the LMICs market for HBeAg tests is less developed. The absence of a public database on global diagnostics volumes or prices presents challenges to transparency and accurately predicting market trends.

The use of quality-assured diagnostics for the detection of the HBsAg is critical, as this diagnostic is the entry point for the cascading of care. There are a number of high-quality HBsAg diagnostics, five of which have WHO PQ presented in Exhibit 24: three RDTs and two lab-based ELISAs. At present, these five HBsAg tests are the only HBV diagnostics which have been PQ'd. Similar to the HCV antibody WHO PQ'd diagnostics, the HBsAg lab-based tests require plasma or serum while the RDTs can also use whole blood.

As shown in Exhibit 23, the use of hepatitis B e antigen (HBeAg) testing is recommended for pregnant women when HBV viral load is unavailable. While both RDT and lab-based HBeAg tests are commercially available, there is currently no WHO PQ process for HBeAg. A list of current HBeAg tests which have received US FDA approval are listed in Exhibit 25.

The landscape for HBV viral load tests is similar to that of HCV. The test menus of all of the platforms commonly used for HCV VL shown in Exhibit 4 include both hepatitis B and C tests.

Exhibit 24: WHO prequalified rapid (RDT) and lab-based HBsAg tests

Rapid HBsAg tests

Product name	Manufacturer	Sample type
Determine HBsAg 2	Abbott Diagnostics	Whole blood, plasma, serum
VIKIA HBs Ag	BioMerieux SA	Whole blood, plasma, serum
Bioline HBsAg WB	Abbott Diagnostics Korea Inc	Whole blood, plasma, serum

Lab-based HBsAg tests

Product name	Manufacturer	Sample type
DS-EIA-HBsAg-0.01	RPD Diagnostics Systems	Plasma, serum
Murex HBsAg Version 3	DiaSorin S.p.A. UK Branch	Plasma, serum

Source: WHO PQ HBsAg diagnostic list

Exhibit 25: US FDA approved HBeAg tests (lab-based)

Supplier	HBeAg test
Siemens Healthcare Diagnostics	ADVIA Centaur
	Atellica
Ortho-Clinical Diagnostics	VITROS
Roche Diagnostics Operations	Elecsys
DiaSorin	Liason XL

Source: US FDA

Global pricing for HBsAg and HBV VL

Global pricing for HBsAg RDTs is similar to that of HCV antibody RDTs. Supplier's VL global pricing include both hepatitis B and C.

The global prices for HBsAg RDTs are generally comparable with other RDTs; such as HCV antibody RDTs. Exhibit 26 presents prices for HBsAg RDTs procured through public programs with India achieving the lowest price at US$0.09 and Cambodia paying US$0.60 for a PQ'd test. When multiple prices are available for a country, the upper and lower costs are presented in the graph.

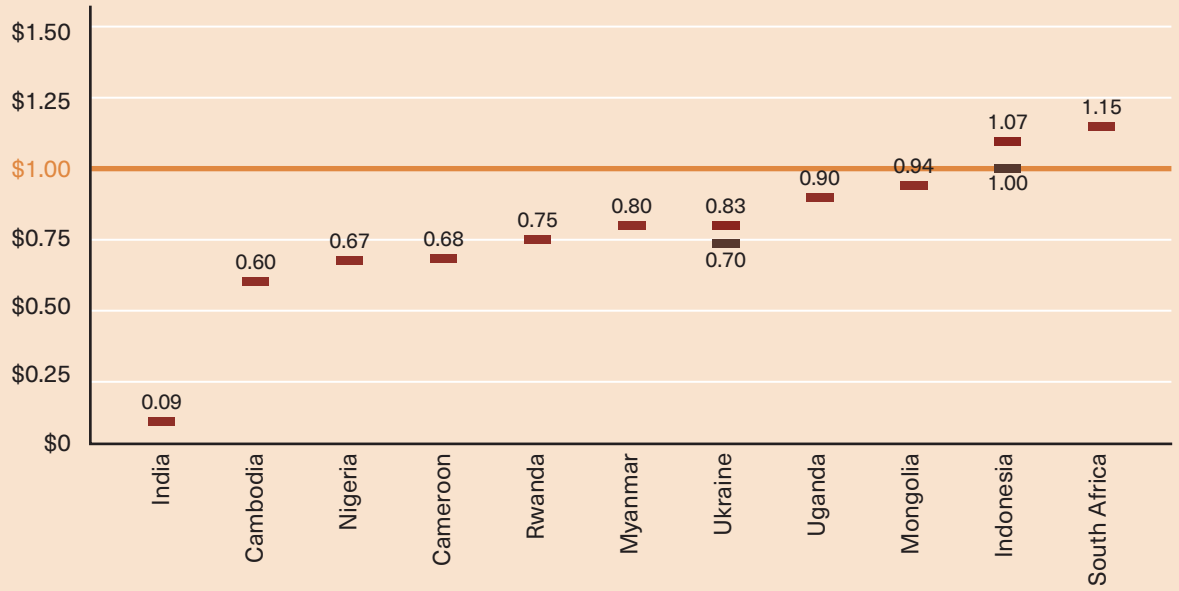
In addition to HBV antigen and viral load tests, the other ancillary blood tests which support the clinical care of individuals living with HBV are not HBV-specific and are described previously in the section on Liver Staging and Monitoring. Most viral load global pricing includes both HCV and HBV such that Exhibit 9 may be referenced for both hepatitis B and C.

Global market for HBeAg

Visibility of global HBeAg pricing and product availability in LMICs is limited at this time.

As data is limited, it is not possible to present HBeAg test prices for a broad range of representative countries. While a single datum only, SD BIOLINE HBeAg RDTs (Abbott) were recently procured for the public program in Cambodia at US$1.50 per test. A study by Boucheron et al.[30] determined prices for RDT and lab-based HBeAg tests in LMICs to fall within the range of US$0.50-15.00, consistent with this price point for Cambodia.

Exhibit 26: HBsAg RDT prices per test paid by public programs



Note: The horizontal line is a visual aid to compare prices to $1; all prices in USD.

Source: CHAI supported country teams, individual contacts, public information and partner organizations including Global Fund, FIND and Treatment Action Group collected in 2020-2021. Where more than one price is reported for a country, the upper and lower costs are presented. Public information.

30 Accuracy of HBeAg to identify pregnant women at risk of transmitting hepatitis B virus to their neonates: a systematic review and meta-analysis, The Lancet Infection, Aug 14 2020, pg 1-11, https://doi.org/10.1016/S1473-3099(20)30593-4

HBV treatment market trends

Supplier landscape

The recommended HBV treatment regimen of TDF has been a mainstay for HIV treatment and has a broad supplier base of quality-approved generics.

WHO recommends the use of tenofovir disoproxil fumarate (TDF) or entecavir for the treatment of hepatitis B infection, both of which are off-patent globally. TDF is widely used for the treatment of HIV, and there is a broad supplier base with six generic suppliers with WHO PQ. Currently, only one generic (Hetero) has achieved WHO PQ for entecavir, while an additional eleven are FDA approved and three have EMA approvals (refer to Appendix 11 for list).

Volume and pricing trends

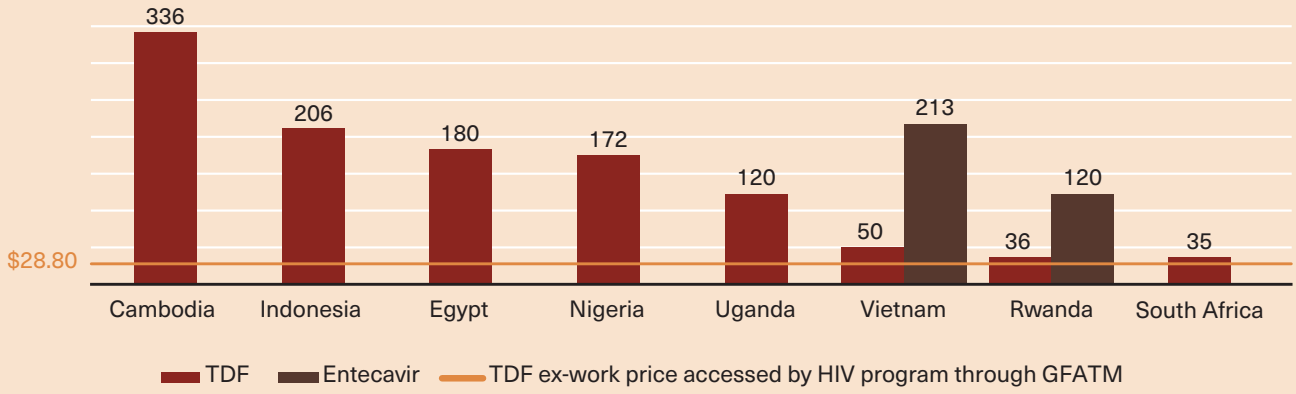
Though TDF is commonly used as both an HBV and HIV treatment, the price paid by HBV programs and patients is often not at parity with the price accessed by HIV programs across LMICs.

TDF, a backbone of first-line HIV treatment, has the same dosage approved for HBV treatment (300 mg/day). In 2020, 1.3 million packs of TDF singles were exported by Indian generics to LMICs, the majority of this demand being for HIV. PLHIV on tenofovir-containing ART who are co-infected with HBV can be considered the largest de facto cohort of people with HBV receiving treatment in LMICs.

The median price of WHO PQ generic tenofovir on the international market fell from US$208 per year to US$32 per year in 2016. The current price of TDF negotiated by GFATM is US$28.80 per year. However, several countries report procuring TDF at significantly higher prices for HBV mono-infection. Besides, there is significant variability in prices accessed by LMICs. Countries such as Cambodia and Indonesia are paying more than US$200 for a one-year TDF course (Exhibit 27). The drivers of price variation of TDF between HBV and HIV programs needs to be better understood, though differences in factors like financing availability, procurement channels, and roll-out of services could be contributing to this price variation.

The other recommended HBV treatment, entecavir, is costlier than TDF. The price of TDF has been driven down over the past two decades due to its wide use in HIV treatment, while the market for entecavir has been much smaller and there has been significantly less investment in the product. The current price negotiated by GFATM for a one-year course of WHO PQ'd entecavir is approximately US$96, over three times the price of TDF.

Exhibit 27: Price per one year HBV treatment course in 2020



Note: all prices in USD.

Source: CHAI analysis for Nigeria, Indonesia, Vietnam, Rwanda, Cambodia; World Hepatitis Alliance and members for Egypt; South African National Department of Health's Affordable Medicines Unit; The National Organization for People Living with Hepatitis B


Photo by Melinda Stanley

HBV birth dose vaccine market trends

Price of HBV birth dose vaccine is relatively cheap as compared to other vaccines.

Two generic suppliers, Serum Institute of India and LG Life Sciences Ltd., have received WHO PQ for HBV birth dose vaccine.[31] UNICEF supply division currently offers HBV birth dose vaccines to LMICs at US$0.25 per child.[32]

HBV markets – on the horizon

The 2020 WHO HBV PMTCT guidelines offer a significant opportunity to advance integrated maternal and child health towards elimination of vertical transmission of communicable diseases. Countries working towards the dual elimination of perinatal HIV and syphilis infection are including elimination of mother-to-child HBV transmission within their programs as part of a triple elimination agenda. Integrating screening and viral load testing for HBV within antenatal care settings will not only support the expansion of HBV programs, but also promote the development of patient management systems that can effectively monitor patients on treatment and those at risk for discontinuing treatment.

While current prevention, testing, and treatment tools already provide effective interventions to reach HBV elimination, innovations in the commodities landscape may accelerate progress. New presentations of the HBV birth dose vaccine and control temperature chain could increase coverage and access to the vaccine at a community level. An integrated rapid diagnostic test for HIV, syphilis, and HBV could help improve screening coverage in antenatal care settings by incorporating all three diseases in the triple elimination initiative. This could build off the existing dual HIV/syphilis RDT which is recommended by WHO in antenatal care and cost-saving compared to standard testing, however no multiplex product including HBV is commercially available with WHO PQ.[33] Point-of-care testing for HBV has the potential to broaden testing in low-resource settings; however, more tests need to be ratified for clinical use by international regulatory bodies to enable uptake of point-of-care testing in HBV programs. Further evidence on the introduction and scale-up of innovations for the prevention, testing and treatment of HBV can help further broaden and shape the HBV market.

31 https://extranet.who.int/pqweb/vaccines/prequalified-vaccines
32 https://supply.unicef.org/s359323.html
33 Dual HIV/syphilis rapid diagnostic tests can be used as the first test in antenatal care: policy brief https://apps.who.int/iris/handle/10665/329965?locale-attribute=ar&

Glossary

Expert Review Panel (ERP)	ERP is a risk based review by WHO PQ Team. It provides advice to allow for interim procurement, time limited for a maximum of one year, during which time the product should progress towards prequalification by WHO or approval by a Stringent Regulatory Authority (SRA).
Finished Dosage Form (FDF)	A final drug product, for example, tablet, capsule, solution, etc.
Freight on Board (FOB)	Export price which does not include shipping, customs and distributor associated costs. Usually there are in-country costs added to the FOB price which result in a higher final price to the buyer.
Global Accelerator for Pediatric Formulations (GAP-f)	GAP-f is a WHO Network hosted within the Research for Health Department in the Science Division and was created to respond to the pediatric treatment gap. GAP-f was conceived to build on and formalize the model developed within the HIV community to provide a sustainable mechanism that ensures that safer, more effective, and more durable pediatric formulations are developed and made available to children against an accelerated timeline.
Medicines Patent Pool (MPP)	The Medicines Patent Pool (MPP) is a United Nations-backed public health organization that negotiates with patent holders for licenses on lifesaving medicines for LMICs. These licenses permit multiple suppliers to produce and distribute generic versions of patented medicines in developing countries. Competition between quality-assured generic pharmaceutical companies helps bring prices down and accelerates access to new treatments in developing countries.
Stringent Regulatory Authorities (SRA)	The national drug regulatory authorities which are members or observers or associates of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) are considered as Stringent Regulatory Authority as per the GFATM Quality Assurance Policy for Pharmaceutical Products. Members include European Union member States, Japan, and the United States
WHO Prequalification Program	WHO Prequalification Program aims to ensure that diagnostics, medicines, vaccines and immunization-related equipment and devices for high burden diseases meet global standards of quality, safety and efficacy. This information is used by UN and other procurement agencies to make purchasing decisions.

Appendix

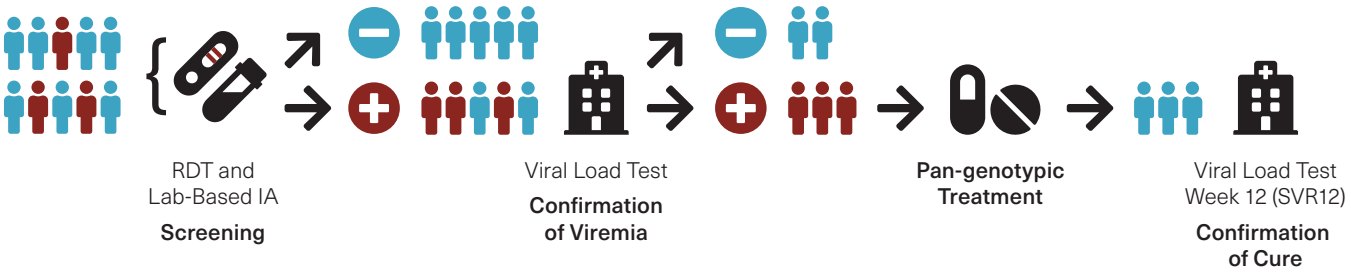
Appendix 1: List of high hepatitis burden low- and middle-income countries

Brazil	Cameroon	Colombia	Ethiopia	India
Kyrgyzstan	Mongolia	Myanmar	Nigeria	Peru
Rwanda	South Africa	Thailand	Ukraine	Vietnam
Cambodia	China	Egypt	Georgia	Indonesia
Malaysia	Morocco	Nepal	Pakistan	Philippines
Sierra Leone	Tanzania	Uganda	Uzbekistan	Zimbabwe

Source: https://www.who.int/hepatitis/news-events/eliminate_hepatitis_map_2017.pdf?ua=1

Appendix 2: Summary of WHO recommended HCV guidelines

At the time of publication, the current WHO testing and treatment algorithm is contained within the 2018 Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection.[34].



Diagnostics algorithm

The WHO recommends a simplified, two-step algorithm to diagnose HCV. First, a blood test to screen for HCV antibodies, using either a RDT or lab-based immunoassay (IA) is performed. A positive antibody result indicates that the individual has been exposed to the pathogen. While someone may have antibodies against the pathogen due to exposure, their immune system may have successfully cleared the virus from their body. A subsequent RNA nucleic acid VL test is therefore performed for individuals who screen positive for HCV antibodies to confirm active viremia prior to initiating treatment. If screening is done with lab-based testing, the same sample may be used for reflex HCV RNA testing, as encouraged by US Center for Disease Control[35] and the European Association for the Study of the Liver[36] to improve linkage to viremic testing and subsequent care. All those who test positive for VL should be referred for treatment regardless of disease stage, though the duration of treatment may differ depending on the presence of cirrhosis.

When RNA testing is not available, detection of HCV core antigen (HCV cAg), currently available by the lab-based Abbott ARCHITECT platform, may serve as confirmation of viremia. Twelve weeks after completing a full treatment course, a VL test is recommended to provide a confirmation of HCV cure. Due to the sensitivity required for SVR12 however, HCV cAg testing is not recommended for confirmation of cure. The need to maintain VL testing for SVR12 is therefore essential and cannot be replaced solely through the use of quantification of cAg in the diagnostics cascade. In targeting elimination as set by the WHO, testing needs to be cost-effective and streamlined. Screening using rapid antibody tests and confirmation of viremia and cure by VL is therefore the method most often employed in elimination programs.

Previous diagnostic guidelines recommended the use of viral load monitoring at week four and required the determination of the viral genotype to enable appropriate treatment. The current diagnostics cascade, recommended by WHO in 2018, is simplified from the previous guidance. Assessing viral load at week four has been eliminated due to the lack of evidence correlating viral load at week four with those who achieve cure. In addition, when pangenotypic DAAs are utilized in treatment, genotyping is not required, thereby significantly reducing the cost and complexity of testing.

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34 Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection, World Health Organization (WHO); July 2018.
35 CDC Recommendations for Hepatitis C Screening Among Adults — United States, 2020. https://www.cdc.gov/mmwr/volumes/69/rr/rr6902a1.htm
36 EASL recommendations on treatment of hepatitis C: Final update of the series. Journal of Hepatology. Nov 2020; 73(5):1170-1218. https://doi.org/10.1016/j.jhep.2020.08.018

Treatment algorithm

Pangenotypic treatment regimens are now recommended for all adults. These regimens include sofosbuvir + daclatasvir for 12 or 24 weeks depending on cirrhosis diagnosis, sofosbuvir + velpatasvir for 12 weeks, or glecaprevir + pibrentasvir for eight or 12 weeks.

Children (<12 years)	Defer treatment	
Adolescents* (12-17 years)	Sofosbuvir/ledipasvir – 12 weeks in genotypes 1, 4, 5 and 6 Sofosbuvir/ribavirin – 12 weeks in genotype 2 Sofosbuvir/ribavirin – 24 weeks in genotype 3	
Adults (18 years or above)	Without cirrhosis (no genotyping required)	Sofosbuvir/daclatasvir – 12 weeks Sofosbuvir/velpatasvir – 12 weeks Glecaprevir/pibrentasvir – 8 weeks**
	With compensated cirrhosis (no genotyping required)	Sofosbuvir/daclatasvir – 24 weeks Sofosbuvir/daclatasvir – 12 weeks*** Sofosbuvir/velpatasvir – 12 weeks Glecaprevir/pibrentasvir – 12 weeks**

**Treatment in adolescents at this time still requires genotyping to identify the appropriate regimen*

***16 weeks for patients who were previously treated on interferon and/or ribavirin*

****May be considered in countries where genotype distribution is known and genotype 3 prevalence is <5%*

Appendix 3: Countries eligible for Abbott viral load global pricing

EMEA			
Algeria	Egypt, Arab Republic	Mali	Sudan
Angola	Eritrea	Mauritania	Syrian Arab Republic
Benin	Eswatini	Mauritius	Tajikistan
Burkina Faso	Ethiopia	Moldova	Tanzania
Burundi	Gambia, The	Morocco	Togo
Cabo Verde	Ghana	Mozambique	Tunisia
Cameroon	Guinea	Niger	Uganda
Central Africa Republic	Guinea-Bissau	Nigeria	Ukraine
Chad	Kenya	Rwanda	Uzbekistan
Comoros	Kyrgyz Republic	São Tomé and Príncipe	West Bank and Gaza
Congo, Dem. Republic	Lesotho	Senegal	Yemen, Republic
Congo, Republic	Liberia	Sierra Leone	Zambia
Côte d'Ivoire	Madagascar	Somalia	Zimbabwe
Djibouti	Malawi	South Sudan	
APAC			
Cambodia	India	Myanmar	Vietnam
China	Indonesia	Pakistan	
LAC			
Bolivia	Haiti	Nicaragua	
El Salvador	Honduras		

Source: CHAI communication with Abbott

Appendix 4: Pricing visibility guidance for HCV and HBV viral load tests

The following questions and considerations may be valuable for developing an understanding of the cost components which make up the final price to programs:

- Do the itemized costs which appear on the invoice match the expected prices based on the procurement agreement?
- Is the program accessing the global pricing for viral load tests through the procurement contract?
- If the specific inclusions for each cost component on the invoice is not known, it is recommended to inquire with the distributor or supplier to gain clarity of which incoterms are included .
- It is valuable to understand which cost components are flexible. For example, are local taxes or import tariffs avoidable based on the compassionate use of the products?
- Are the distributor mark-ups/margins reasonable? To understand what mark-up is reasonable, it may be helpful to benchmark off other programs such as HIV or TB.

Appendix 5: Generic supplier in-country registrations in viral hepatitis high burden countries (non-exhaustive list as of Q4 2020)

Product	Sofosbuvir tablets	Daclatasvir tablets		Sofosbuvir + Daclatasvir FDC	Sofosbuvir+ Ledipasvir	Sofosbuvir + Velpatasvir
Country	**400 mg**	**30 mg**	**60 mg**	**400mg + 60mg**	**400 mg + 90 mg**	**400 mg + 100 mg**
Brazil	No generic registered					
Cambodia	Viatris, Hetero, Strides, Natco, Getz, Swiss Garnier, Global Pharmaceuticals, Genome Pharmaceuticals, Dyson Research Lab, Hilton Pharma, Faas Pharma, Genix, Incepta, Searle Company Limited, Beximco Pharmaceuticals	Natco, Getz, PharmEvo	Viatris, Hetero, Natco, Geniz, Cambodia Pharmaceutical Enterprise, Searle Company Limited, Getz, Incepta, Hilton Pharma		Viatris, Hetero, Strides, Natco, Genix, Searle Company Limited, Getz, Incepta, Swiss Garnier Life Sciences	Viatris, Hetero, Getz, Searle Company Limited, Geniz, Beacon Pharmaceuticals, Genome Pharmaceuticals
Cameroon	Viatris, Strides	Viatris	Viatris		Viatris	Viatris
China	Kawin's Techonology					
Colombia	No generic registered					
Egypt	Viatris, EVA, Global Napi, Zeta Pharm, Dawood Pharm, Biomed, Pharco, Sabaa, Debeky, EPCI, AUG, Magic pahrm, Mash primere, Aseya Mary, Royal link, Pharmed, Andalus, E.E.PI, Innovative, Marcyrl, Future, Epico		Aug, E.E.PI, Marcyrl, EVA, Global Napi, Sabaa, Mash Primere, Multicare		Viatris	Viatris, Pharmed, EVA
Ethiopia	Viatris, Hetero, Strides	Viatris	Viatris	Viatris	Viatris, Strides	Viatris
Georgia	No generic registered					
India	All Licensee	All Licensee	All Licensee	All Licensee	All Licensee	All Licensee
Indonesia	Viatris, Hetero, Strides, Natco, Aurobindo	Viatris, Hetero	Viatris, Hetero, Natco		Hetero	Viatris
Kyrgyzstan	Viatris, Hetero, Strides, Natco, Wilshire Lab, Global Napi Pharma, Amoun Pharma, Shrook Pharma	Natco	Hetero, Global Napi, NovaMed		Viatris, Strides, Natco, Shrook Pharma, Wilshire Lab	Hetero, Natco, NovaMed
Malaysia	Strides	Hetero	Hetero		Strides	Viatris
Mongolia	Viatris, Hetero, Strides	Viatris	Viatris		Viatris, Hetero, Strides	Strides
Morocco					Viatris	Viatris

Product	Sofosbuvir tablets	Daclatasvir tablets		Sofosbuvir + Daclatasvir FDC	Sofosbuvir+ Ledipasvir	Sofosbuvir + Velpatasvir
Country	**400 mg**	**30 mg**	**60 mg**	**400mg + 60mg**	**400 mg + 90 mg**	**400 mg + 100 mg**
Myanmar	Viatris, Hetero, Strides, Natco, Unipharm, Genix, Top Prime, Zifam, Getz, Incepta, Zydus, Sun Pharma, Noa Hemis Pharmaceutical, Searle Company Limited, Mega Life Sciences, Global Pharma Healthcare, CCL Pharmaceutical	Hetero, Zydus	Hetero, Natco, Getz, Genix, Unipharm, Zydus	Viatris	Viatris, Hetero, Strides, Natco, Genix, Winvir, Mega Life Sciences, Noa Hemis Pharmaceuticals	Viatris, Hetero, Natco, Genix, Getz, Pharmevo, Incepta
Nepal	No generic registered					
Nigeria	Viatris, Hetero, Natco	Hetero	Viatris, Hetero, Natco	Viatris	Viatris, Natco	Viatris, Hetero
Pakistan	Viatris, Strides	Viatris	Viatris		Viatris, Strides	Viatris
Peru	Hetero					
Philippines	Viatris, Hetero	Viatris			Viatris	
Rwanda	Viatris, Hetero	Hetero	Viatris, Hetero		Hetero	Viatris
Sierra Leone	No generic registered					
South Africa	No generic registered					
Tanzania	Hetero, Strides	Hetero	Hetero		Hetero	Viatris
Thailand	Viatris, Hetero				Viatris	Viatris
Uganda	Viatris, Hetero	Viatris, Hetero	Hetero	Viatris	Viatris, Hetero	
Ukraine	Viatris, Hetero, Strides		Viatris, Hetero		Viatris, Hetero, Strides	Viatris
Uzbekistan	Viatris, Hetero, Strides, Jurabek, NovaMed, Davis Pharma, Wilshire Lab, Sign Pharma, Incepta, Genix, Rotapharm, Aurobindo, English Pharmaceutical, China-Uzbekistan Medicine Technical Park	Viatris	Viatris, Hetero, Sign Pharma , IS Group Pharma, Davis Pharma, Incepta, Rotapharm, Genix		Viatris, Hetero, Strides, Belek Group, Wilshire Lab, Sign Pharma, Shrooq Pharma, Incepta, Genix, English Pharmaceutical Industries	Viatris, Hetero, Strides, Natco, Incepta, Genix, Sign Pharma, Scilife Pharma, Davis Pharma, Hilton Pharma, IS Group Pharma
Vietnam	Viatris, Natco, Hetero, Strides, Astra, Cipla, Ampharco, Hera, BV Pharma, Pymepharco, Minh Hai, Phong Phu	Viatris, Natco, Hera	Viatris, BRV Healthcare, Medisun, Natco		Viatris, Hetero, Natco, Hera, BV Pharma, Ampharco, Pymepharco, Minh Hai, BRV Healthcare	Viatris,
Zimbabwe	Viatris, Hetero	Viatris	Viatris		Hetero	

Note: Viatris has interim approval by Rwanda FDA for supply but isn't registered yet.

Source: Hetero, Viatris, Strides, CHAI, Coalition PLUS, World Hepatitis Alliance and its members. MPP access to medicine tracker.

Appendix 6: India export data analysis methodology

The India Import Export Data provides details on the volumes and prices of drugs exported from India to the rest of the world. As shown below, the data has relevant details on date of export, importer name, the product exported and the country to which it was exported, size of the export order, and the freight on board price. FOB prices are the prices at which the supplier exports the drug from the country. These prices do not include shipping, customs, storage and distributor-associated costs. Usually there are in-country costs added to the FOB price, resulting in a higher final price to the buyer.

Date	Importer	Products	Destination	Quantity	Unit	Unit rate
05/05/20	M/S. Alliance For Public Health	Daclatasvir 60mg	Ukraine	12,000	PAC	US$6.76
25/06/20	State Enterprise Ukrvakcyna Of The,	Sofosbuvir/Ledipasvir	Ukraine	10,500	PAC	US$29.93
25/06/20	State Enterprise Ukrvakcyna Of The,	Sofosbuvir/Ledipasvir	Ukraine	10,500	PAC	US$29.93
25/06/20	State Enterprise Ukrvakcyna Of The,	Sofosbuvir/Ledipasvir	Ukraine	12,023	PAC	US$29.93
25/06/20	State Enterprise Ukrvakcyna Of The,	Sofosbuvir/Ledipasvir	Ukraine	12,023	PAC	US$29.93
25/06/20	State Enterprise Ukrvakcyna Of The,	Sofosbuvir/Ledipasvir	Ukraine	138	PAC	US$29.72
25/06/20	State Enterprise Ukrvakcyna Of The,	Sofosbuvir/Ledipasvir	Ukraine	138	PAC	US$29.72
25/06/20	State Enterprise Ukrvakcyna Of The,	Sofosbuvir	Ukraine	18,517	PAC	US$18.18
25/06/20	State Enterprise Ukrvakcyna Of The,	Sofosbuvir	Ukraine	18,517	PAC	US$18.18
25/06/20	State Enterprise Ukrvakcyna Of The,	Daclatasvir 60mg	Ukraine	18,574	PAC	US$11.75
25/06/20	State Enterprise Ukrvakcyna Of The,	Daclatasvir 60mg	Ukraine	29,059	PAC	US$11.75
25/06/20	State Enterprise Ukrvakcyna Of The,	Sofosbuvir/Velpatasvir	Ukraine	3,604	PAC	US$89.78
25/06/20	State Enterprise Ukrvakcyna Of The,	Sofosbuvir/Velpatasvir	Ukraine	3,604	PAC	US$89.78
25/06/20	State Enterprise Ukrvakcyna Of The,	Sofosbuvir	Ukraine	95	PAC	US$18.02
25/06/20	State Enterprise Ukrvakcyna Of The,	Sofosbuvir	Ukraine	95	PAC	US$18.02
25/06/20	State Enterprise Ukrvakcyna Of The,	Daclatasvir 60mg	Ukraine	18,574	PAC	US$11.72
25/06/20	State Enterprise Ukrvakcyna Of The,	Daclatasvir 60mg	Ukraine	29,059	PAC	US$11.72

Summary of above data:

	SOF	DCV	SOF/LDV	SOF/VEL
No. of packs (28 tab)	37,224	1,07,266	45,322	7,208
# of patient courses	8,863		15,107	2403

Assumptions:

1. SOF and DCV are used in combination. Hence, 37,224 despite higher DCV volumes would be 37,224 packs of SOF/DCV treatment regimen
2. 40% cirrhotic cases. SOF and DCV course is 24 weeks for cirrhotic and 12 weeks for non-cirrhotic patients; SOF/LDV and SOF/VEL course is 12 weeks

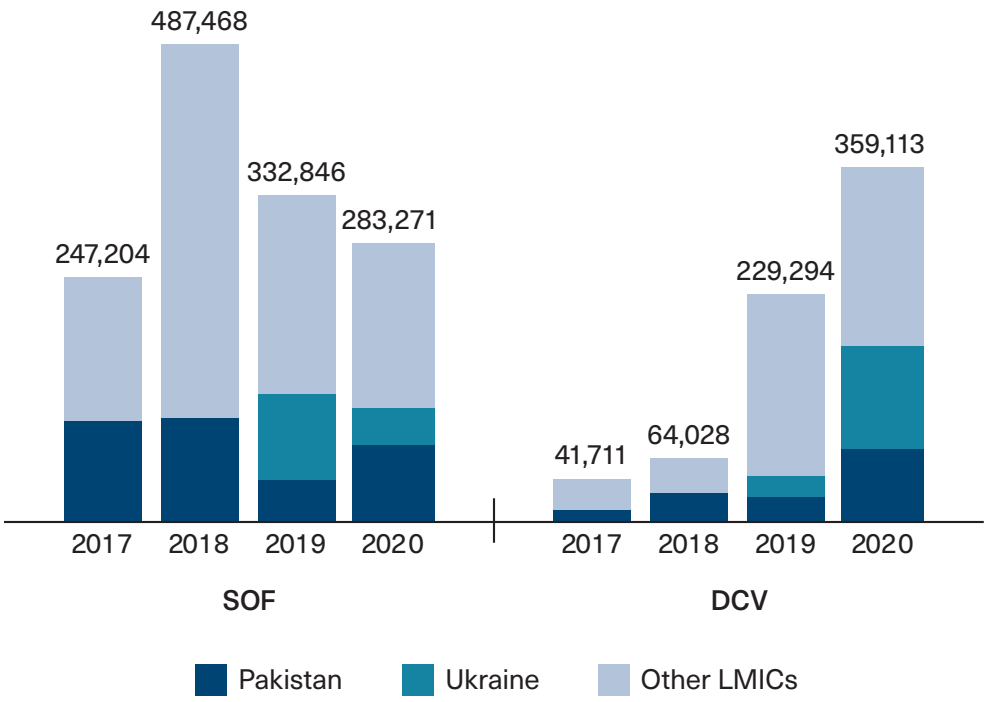
Appendix 7: Volumes (packs) and pricing (USD) of DAAs exported from India to LMICs (2017 - 2020)

		2020		2019		2018		2017	
		Volumes	FOB	Volumes	FOB	Volumes	FOB	Volumes	FOB
Afghanistan	SOF								
	DCV							11,000	$21
Bangladesh	SOF	300	$18	300	$18				
	DCV	570	$14	450	$11				
Benin	SOF/LDV			50	$59				
Bolivia	SOF	400	$21						
	DCV	800	$15	120	$15				
Brazil	SOF							60	$247
Burkina Faso	SOF/VEL	3,593	$154						
Burundi	SOF/VEL	360	$99	770	$102	240	$101		
	SOF			300	$100				
Cambodia	SOF/VEL	420	$79	2,525	$85	700	$103		
	SOF/DCV FDC	6,000	$26	90	$40				
	SOF	1,520	$20	1,289	$28	2,542	$45	2,094	$40
	DCV	8,640	$23	2,550	$24	3,000	$30	1,550	$31
Cameroon	SOF/VEL	384	$106			1,642	$141		
	SOF					250	$84	2,550	$86
China	SOF					129	$415	800	$352
Côte d'Ivoire	SOF/VEL					30,000	$134		
Republic of the Congo	SOF/VEL			144	$149				
East Timor	SOF/VEL	240	$83	480	$86				
	SOF	60	$15	120	$18				
	DCV	90	$10	180	$11				
Egypt	SOF			1,19,020	$13	2,96,079	$12	1,00,734	$15
Ethiopia	SOF/VEL	270	$92						
	SOF/LDV	70	$39						
	SOF/DCV FDC	73	$41						
Ghana	DCV	60	$16						
Indonesia	SOF	18,747	$66	6,300	$85	9,700	$72	6,000	$17
	DCV	19,306	$10	298	$30	12,600	$30		
Kenya	SOF/VEL	4,320	$79						
	SOF/LDV			3,600	$58	50	$34	100	$188

		2020		2019		2018		2017	
		Volumes	FOB	Volumes	FOB	Volumes	FOB	Volumes	FOB
Kyrgyzstan	SOF/VEL	3,226	$108	1,870	$77				
	SOF/LDV	740	$43	1,755	$50	1,002	$74		
	SOF/DCV FDC	300	$37						
	SOF	1,190	$22	3,329	$37	2,251	$51	790	$50
	DCV	6,060	$14			6,498	$28	300	$25
Laos	SOF/VEL	2,000	$66	1,350	$71				
	SOF/LDV	548	$35						
	SOF/DCV FDC	1,050	$35	300	$36				
	SOF					150	$40		
Malaysia	SOF	3,319	$27	3,960	$27				
	DCV			11,220	$10	1,811	$16		
Mali	SOF/VEL	100	$118						
Moldova	SOF/VEL	360	$68	400	$85				
Mongolia	SOF/LDV	8,700	$42	2,294	$55	32,570	$52	23,189	$46
	SOF	200	$39	300	$41			300	$49
	DCV	200	$19	300	$17			500	$20
Morocco	SOF/VEL			4,043	$29				
Myanmar	SOF/VEL			52,161	$80	5,436	$164	3,300	$117
	SOF/LDV	2,917	$27					5,108	$81
	SOF/DCV FDC			1,726	$27	3,000	$36		
	SOF	8,520	$12	28,418	$18	44,061	$28	12,545	$45
	DCV	19,292	$11	3,755	$23	9,806	$25	4,519	$27
Nepal	SOF/VEL	600	$73	800	$84				
	SOF/LDV							576	$120
	DCV					200	$32		
Nigeria	SOF/VEL	3,000	$80	75	$113	300	$139		
	SOF	3,700	$30	1,000	$18			5,040	$49
	DCV	3,000	$10	1,000	$12	400	$27		
Pakistan	SOF/VEL	17,228	$39	25,581	$42				
	SOF	76,902	$11	43,080	$22	1,04,504	$11	1,00,002	$16
	DCV	1,14,330	$3	51,260	$3	25,067	$9	27,000	$12
Philippines	SOF/VEL			1,000	$90				
	SOF			3,442	$40	13,765	$40		
	DCV			4,135	$15				
Rwanda	SOF	79,308	$16	2,996	$16				
	DCV	60,597	$7	1,17,898	$7				

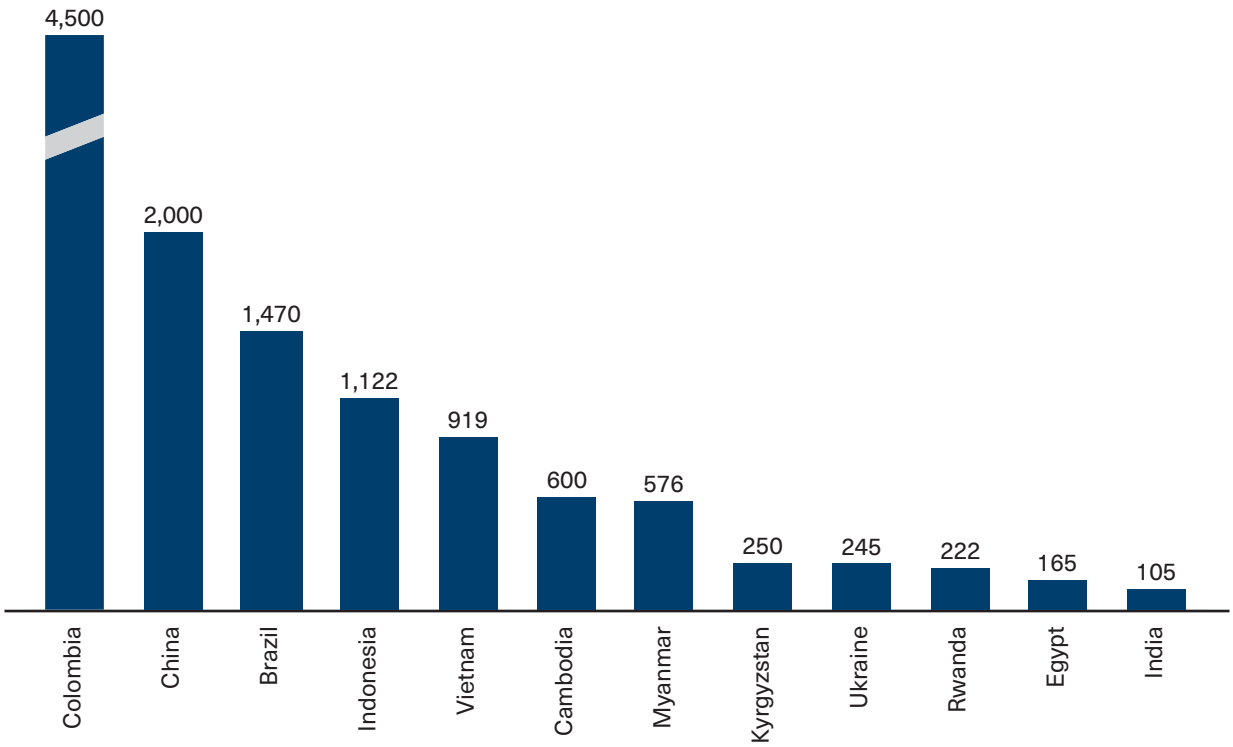
		2020		2019		2018		2017	
		Volumes	FOB	Volumes	FOB	Volumes	FOB	Volumes	FOB
South Africa	SOF/VEL			50	$229				
	SOF/LDV							150	$138
	SOF/DCV FDC	4,290	$27						
	SOF			100	$134	50	$88		
Sri Lanka	SOF							100	$101
Syrian Arab Republic	DCV					100	$25		
Tajikistan	SOF/VEL	8,923	$74	848	$71				
	SOF/LDV	489	$55	864	$52	1,584	$49	621	$59
	SOF					50	$30		
	DCV	300	$17						
Tanzania	SOF/LDV	600	$59						
	DCV	5,320	$12						
Thailand	SOF/VEL			14,811	$197				
	SOF/LDV	599	$59	4,060	$61	23,966	$56		
	SOF			824	$75	29,644	$76	13,395	$77
Tunisia	SOF	180	$44	240	$41				
Ukraine	SOF/VEL	7,208	$90	7,475	$90				
	SOF/LDV	45,322	$30	9,648	$30				
	SOF	37,224	$18	84,698	$20				
	DCV	1,07,266	$12	21,234	$10				
Uzbekistan	SOF/VEL	520	$71	9,657	$93				
	SOF/LDV	550	$40	5,101	$54	7,162	$49	12,722	$56
	SOF/DCV FDC	450	$34						
	SOF	2,550	$27	35,846	$23	1,558	$34	9,007	$19
	DCV	2,850	$9	50,145	$13	3,236	$40	5,737	$46
Vietnam	SOF/VEL	19,779	$87	7,891	$90	8,800	$115	19,245	$117
	SOF/LDV			8,720	$65	4,012	$59	12,033	$89
	SOF/DCV FDC	1,345	$30						
	SOF	52,200	$20	2,168	$75	12,558	$43	8,042	$58
	DCV	52,268	$13	2,162	$36	1,188	$36	8,500	$36

Appendix 8: 2017-2020: Indian generic manufacturers export of SOF and DCV to Pakistan, Ukraine, and rest of LMICs



Source: India Export Data, CHAI Analysis

Appendix 9: In-country prices of SOF/VEL FDC



Note: The prices mentioned are public sector prices paid by govt. in country if available, or lowest identified private sector prices if public sector price not available; Prices shown can be for originator or generic product; Amongst generic products, prices can be for WHO PQ'd/ ERP reviewed or locally quality assured products; Price as of 2019 for Pakistan; Price as of 2018 for Kyrgyzstan; all prices in USD

Source: CHAI analysis for Indonesia, Vietnam, Rwanda, Cambodia, Myanmar, China; Coalition PLUS for Brazil and Colombia; World Hepatitis Alliance and members for Egypt; Aga Khan University for Pakistan; ITPCRU and 100% Life for Ukraine and Partnership Network for Kyrgyzstan

Appendix 10: Addressable pediatrics HCV market sizing methodology

1. Referenced 2020 Lancet paper on HCV prevalence estimates country by country for the baseline HCV pediatric numbers
2. Excluded age group (0-2) and (12-18) as children below three are likely to be excluded and children above 12 would be recommended adult dosage
3. Estimated children requiring pediatric dosage globally by apply weight-age assumption: 100% within the age-group (3-6), and 80% within the age-group (7-11) based on age-weight estimates
4. Defined *'addressable market'* as children requiring pediatric dosage across seven countries with robust adult programs – Rwanda, Egypt, India, Mongolia, Pakistan, Georgia, Ukraine –rapid uptake of use of pediatric regimens is expected in these countries. Subsequently estimated children requiring pediatric dosage for the above mentioned seven countries
5. Ran a sensitivity analysis on weight-age assumption to estimate effect on addressable market estimates addressable HCV pediatric volume estimates ranged between +/- 20% on varying weight-age assumption between 50% to 100%

Appendix 11: US FDA and EMA approved entecavir list (as of Dec 2020)

Drug	Manufacturer	Approval agency
Entecavir	Hetero	US FDA
Entecavir	Accord	US FDA
Entecavir	Aurobindo	US FDA
Entecavir	Amneal Pharms	US FDA
Entecavir	Casi Pharms INC	US FDA
Entecavir	Zydus Pharms	US FDA
Entecavir	Cipla	US FDA
Entecavir	Breckenridge	US FDA
Entecavir	Prinston INC	US FDA
Entecavir	Pharmadax INC	US FDA
Entecavir	Brightgene	US FDA
Entecavir	Baraclude	EMA
Entecavir	Mylan	EMA
Entecavir	Accord	EMA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