



Viral hepatitis in sub-Saharan Africa 2

Hepatitis C in sub-Saharan Africa: the current status and recommendations for achieving elimination by 2030

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This is the second in a **Series** of two papers on viral hepatitis in sub-Saharan Africa

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In 2016, WHO adopted a strategy for the elimination of viral hepatitis by 2030. Africa, and more specifically, sub-Saharan Africa, carries a substantial portion of the global burden of viral hepatitis, especially chronic hepatitis B and hepatitis C virus infections. The task that lies ahead for sub-Saharan Africa to achieve elimination is substantial, but not insurmountable. Major developments in the management of hepatitis C have put elimination within reach, but several difficulties will need to be navigated on the path to elimination. Many of the challenges faced are unique to sub-Saharan Africa and the development of strategies is complicated by a scarcity of good data from countries and regions within sub-Saharan Africa. However, this hindrance should not act as a barrier to delay interventions in screening, detection, and linkage to care. Moreover, by sharing experiences from across sub-Saharan Africa, countries can create supranational synergies to develop their programmes and work together in a more cohesive manner to tackle the burden of hepatitis C in sub-Saharan Africa. In this Series paper, several issues related to hepatitis C in sub-Saharan Africa are addressed, including prevalence, risk factors, and fibrosis assessment, and recommendations are given by experts from across the region. Simplified diagnostic algorithms and treatment regimens for both HIV co-infected and hepatitis C mono-infected patients are suggested. The recommendations are consensus based and provided to guide the development of programmes in sub-Saharan Africa. Political will and appropriate funding will be required to provide impetus to implement these recommendations.

Introduction

Globally, hepatitis C virus (HCV) is a leading cause of chronic liver disease, and persistent HCV infection is associated with cirrhosis, hepatocellular carcinoma, liver failure, and death.¹ The net effect is that HCV-related and liver-related mortality is rising and, collectively, viral hepatitis now accounts for a greater proportion of global infectious disease mortality than does HIV.² The global HCV seroprevalence is between 2% and 3%, with an estimated 71·1 million patients with active viraemia.³ In sub-Saharan Africa, the number of estimated deaths due to cirrhosis almost doubled from 53 000 in 1980, to 103 000 in 2010. In the southern region of Africa, the prevalence of cirrhosis-associated mortality is about half that of the central, eastern, and western regions of Africa. These patterns are consistent with the regional prevalence of hepatitis B, hepatitis C, and hepatitis D disease.⁴ Cirrhosis-associated mortality in the Central African Republic, Gabon, Malawi, Uganda, and Côte d'Ivoire was ranked in the top 10th global percentile in 2010.⁵ In sub-Saharan Africa, HCV is the second leading cause of end-stage liver disease and hepatocellular carcinoma-related mortality.⁵

For two decades, the combination of subcutaneous interferon alfa and ribavirin was the standard of care for HCV infection. Treatment lasted 6–12 months and had numerous adverse effects with suboptimal efficacy.⁶ The paucity of infrastructure to manage interferon and ribavirin for treatment of HCV infection in sub-Saharan

Africa, together with poor health-care systems prevailing in the region, effectively made treatment unattainable for most of the population. The advent of direct-acting antivirals, with few side-effects, short course of treatment, and a sustained virological response (SVR) rate above 90%, has made treatment of HCV infection simpler and provided the potential to achieve elimination. However, the path to achieving elimination is challenging and complex, and access to affordable treatment is only one aspect of the problem. To move towards the potential elimination of HCV, a clearer understanding of the burden of HCV in sub-Saharan Africa is needed.

HCV prevalence in sub-Saharan Africa

Sub-Saharan Africa has a substantial HCV disease burden, but a detailed epidemiology and understanding of the disease burden is absent. A severe limitation in this respect is the scarcity of reliable prevalence data, and population-based studies and an estimate of the diagnosed and treated proportion of the population are needed.⁷ A recent meta-analysis suggested an overall HCV seroprevalence of 2·98% in sub-Saharan Africa.⁸ Substantial regional and national variation exists in the reported seroprevalence and the most likely mode of HCV infection. The variation in prevalence data might be related to the sensitivity and specificity of serological tests used in various studies, the inhomogeneous populations screened (eg, blood donors vs injecting drug users), and the HIV seroprevalence within the countries

and regions screened.^{7,9} Accurate estimates of the number of individuals who are viraemic are difficult to ascertain. A previous linear mixed model¹⁰ was developed to estimate the burden of HCV and forecast appropriate interventions by examining at-risk cohorts and weighting with known populations. Incremental prevalence estimates in southern Africa (0.72%), eastern Africa (3.00%), western Africa (4.14%), and central Africa (7.82%) were calculated.¹⁰ Based on seroprevalence, blood donors had the lowest documented prevalence at 1.78%, followed by pregnant women (2.51%), people living with HIV (3.57%), and the general population (5.41%). In high-risk populations (such as people who inject drugs [PWID] or those who have received blood or blood products), western Africa had the highest seroprevalence at 15.69%, whereas the highest seroprevalence in the general population was observed in central and southern Africa, with adult seroprevalence estimates of 16.26% and 6.40%, respectively. In 2017, estimated viraemic prevalence rates were published using country-level disease-burden modelling in conjunction with country experts.³ Globally, the 71.1 million patients with active viraemia represent a global viraemic prevalence of 1%. In sub-Saharan Africa, approximately 10.15 million individuals are viraemic.³

Table 1 juxtaposes the estimated viraemic data with a previous meta-analysis^{3,11} of HCV antibody seroprevalence divided into four regions: western Africa, middle Africa, eastern Africa, and southern Africa. Looking specifically at the Horn of Africa, a meta-analysis¹² found the seroprevalence in the general population in Somalia, Sudan, and Djibouti to be 0.9%, 1.0%, and 0.3%, respectively (the Djibouti data were from a cohort of blood donors¹²). Thus, seroprevalence data for the general population in sub-Saharan Africa are inhomogeneous and variable with high, medium, and low HCV prevalence reported. However, data are scarce for high-risk groups, and data collection is complicated by inherent cultural biases and statutes against PWID and men who have sex with men (MSM). Globally, approximately 8% of PWID reside in sub-Saharan Africa.¹³ Five sub-Saharan African countries have published HCV seroprevalence data in PWID:^{14,15} Kenya (51.4%), Tanzania (22.2%), Ghana (40.1%), Mauritius (97.3%), and Senegal (39.9%). In an unpublished study from Dar es Salaam, Tanzania (Nyandindi C and Rwegasha J, Muhimbili University of Health and Allied Sciences, personal communication), anti-HCV antibodies were detected in 51.1% of PWID, whereas ranges of 24–77% have been informally reported for Pretoria, South Africa. Few accurate assessments of seroprevalence in MSM in sub-Saharan Africa exist. A study¹⁶ reviewing risk in high-risk groups in Sudan found the range of HCV seroprevalence to be from 0.1% to 1% in MSM. A seroprevalence survey in HIV-positive MSM in Cape Town found a 6% HCV seroprevalence.¹⁷

	Estimated seroprevalence (95% PI) ¹¹	Viraemic prevalence (95% UI) ³
Western Africa		
Burkina Faso	6.1% (1.3–14.2)	1.3% (1.0–1.4)
Benin	3.8% (0.7–9.2)	..
The Gambia	2.4% (0.0–9.7)	0.8% (0.5–1.3)
Ghana	3.2% (0.5–8.1)	1.4% (1.1–3.4)
Guinea	1.5% (0.5–9.5)	..
Côte d'Ivoire	2.2% (0.3–6.1)	..
Mali	1.9% (0.3–10.6)	..
Nigeria	3.1% (0.1–10.0)	1.4% (1.0–1.4)
Senegal	1.0% (0.0–4.6)	..
Middle Africa		
Angola	3.9% (0.6–10.1)	..
Burundi	3.1% (0.2–9.1)	1.0% (0.8–4.0)
Cameroon	4.9% (0.9–11.9)	0.7% (0.5–0.8)
Democratic Republic of the Congo	2.1% (0.4–12.0)	..
Gabon	4.9% (1.0–11.5)	7.0% (5.1–7.3)
Congo (Brazzaville)	2.9% (0.0–11.7)	..
Rwanda	3.1% (0.3–12.0)	..
Eastern Africa		
Ethiopia	2.7% (0.1–9.2)	0.6% (0.4–0.7)
Kenya	2.8% (0.4–7.3)	0.2% (0.1–0.3)
Madagascar	1.7% (0.0–7.7)	0.2% (0.2–0.3)
Malawi	2.0% (0.0–7.0)	..
Mozambique	1.3% (0.1–6.9)	..
Somalia	2.6% (0.1–8.5)	..
Tanzania	2.7% (0.2–7.8)	..
Uganda	2.7% (0.4–7.0)	..
Southern Africa		
Namibia	1.6% (0.0–7.3)	..
South Africa	1.1% (0.0–5.8)	0.7% (0.4–0.9)
Zambia	1.1% (0.0–3.7)	..
Zimbabwe	1.6% (0.0–5.9)	..

Data estimated HCV seroprevalence and 95% prediction interval (PI) as predicted by a model for median age of the adult population (15–59 years) in each country.¹¹ Viraemic prevalence and 95% uncertainty interval (UI) compiled from Polaris Observatory HCV collaborators.³

Table 1: Seroprevalence and viraemic prevalence by region and country in sub-Saharan Africa

Recommendations to establish HCV prevalence

Although detailed and reliable HCV seroepidemiological data are scarce in many parts of sub-Saharan Africa, available estimates are indicative of a substantial burden. To establish the true burden, systematic population-based seroprevalence studies should be included when constructing models of national programmes for control of HCV in the region. Notably, the scarcity of seroprevalence data should not act as a barrier to the expansion of screening for HCV in people at risk and in the general population, or to the improvement of HCV detection, linkage to care, and effective treatment of HCV infection.

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For the United Nations Office on Drugs and Crime estimates of PWID, living with HIV, HCV, and HBV see https://www.unodc.org/wdr2015/field/4.1.1_Estimates_of_people_who_inject_drugs_living_with_HIV_HCV_and_HBV.xls

HCV genotypes in sub-Saharan Africa

Characterisation of HCV genotypes in sub-Saharan Africa is still needed despite the growing range of highly effective and potentially pangenotypic direct-acting antiviral therapies. Until universally effective pangenotypic therapies are available, the choice, duration, and cost of treatment will be influenced by the virus genotype.⁷ The distribution of HCV genotypes across sub-Saharan Africa is variable, but genotypes 1 and 4 predominate overall. In central Africa, genotype 4 predominates in the Central African Republic (82·8%), the Democratic Republic of Congo (96·8%), Gabon (91·9%), and Equatorial Guinea (60·0%). The remainder of infections include low frequencies of genotypes 1, 2, and 3, except in Equatorial Guinea where genotype 1 accounts for a third of infections. In Chad, most (84·6%) of the infected population are infected with genotype 4.¹⁸ Notably, widely heterogeneous subtypes of genotype 4 are present—for instance, in the Central African Republic, genotypes 4k and 4c predominate, with 4r and 4f also present.¹⁹ In the eastern region of Africa, genotypes 4 (50·0–68·0%), 2 (33·3%), 3 (9·5%), and 5 (11·1%) have been documented in Ethiopia, whereas in Madagascar genotypes 1 and 2 are seen equally frequently.²⁰ In the western region of Africa, genotype 4 is less frequent, with genotypes 1 and 2 being more common. Prevalence of genotype 2 ranges from 15% of infections in Nigeria, to 87% of infections in Ghana, and 98·2% of infections in Guinea-Bissau.²⁰ Genotype 1 dominates in Nigeria (85%), whereas Burkina Faso has a mixture of genotypes 2 and 3, with genotype 1 making up less than 10% of infections.²⁰ In the Gambia the situation is similar, although the frequency of genotype 1 infection is greater (19·4%) than in Burkina Faso. In southern Africa, all genotypes are found, except genotype 6. A study²¹ of the general population in South Africa found that genotype 1 was the most common genotype in blood donors (34%), and that, in the overall population, genotype 5a was the most prevalent genotype (36%), accounting for 54% of infections in black South Africans, whereas genotype 1 was seen in 43% of white South Africans. Overall, the study found that 31% of participants had genotype 1, 2% had genotype 2, 14% had genotype 3, 14% had genotype 4, 35% had genotype 5, and 4% had mixed genotypes.²¹

Recommendations for HCV genotype testing

A wide array of HCV genotypes and subtypes are found in sub-Saharan Africa and thus genotype testing remains a requirement for treatment. Proven pangenotypic regimens would eliminate the need for genotype testing and would simplify the path from testing to treatment. Pangenotypic therapies include sofosbuvir plus daclatasvir, sofosbuvir plus velpatasvir, pibrentasvir plus glecaprevir, and the pipeline therapy sofosbuvir plus ravidasvir.

HCV transmission risks in sub-Saharan Africa

The predominant and historic routes of HCV transmission are mostly parenteral and include blood and blood products (typically before 1990), injecting drug use, tissue and organ transplants, unsafe medical procedures or injection practices, health-care worker parenteral exposure (eg, needle-stick injuries), body piercings, and vertical transmission. The epidemiological role of the sexual transmission of HCV is controversial because sexual contact is considered an inefficient mode of transmission.²² Several studies^{23–28} have reported low instances of sexual transmission of HCV between HCV-serodiscordant heterosexual couples, with studies from Europe,^{24,25} the USA,^{23,26} and southeast Asia^{27,28} showing that the seroprevalence of HCV among heterosexual couples ranges from 0% to 27%. Prevalence of heterosexual transmission, however, is less than 5% when excluding partners with known parenteral transmission risks. A study²⁹ based on genotype concordance supports this infrequent occurrence of HCV sexual transmission, with HCV seroprevalence attributable to sexual contact estimated at 0·6%. However, evidence³⁰ is accumulating to support the permucosal transmission of HCV in HIV-positive MSM and in recreational drug use. This changing pattern of HCV transmission, first described in 2004, has been confirmed by case-control and cohort studies.³¹ Although the risk seems to be lower, it remains substantial in HIV-negative MSM.

Globally, most new HCV infections are in PWID or who are in high-risk groups (eg, MSM), although only 8% of PWID globally reside in sub-Saharan Africa.¹³ Unsafe blood supply in many parts of sub-Saharan Africa has contributed to HCV transmission. In the late 1990s, only 19% of blood was screened for HCV in sub-Saharan Africa, with the main reason being the prohibitive cost of laboratory testing. Additionally, inconsistent screening procedures, non-WHO prequalified test kits, and a scarcity of confirmatory nucleic acid testing of blood donations have made blood transfusion a major risk. The major risk posed is supported by the high HCV seroprevalence (17%) in patients with sickle-cell disease who have received multiple transfusions. With the aid of the US President's Emergency Plan for Aids Relief, the Global Fund, and WHO, blood safety programmes in 36 sub-Saharan African countries have been funded. Between 2000–04 and 2010–11, the median annual number of units of blood donated per country increased, with approximately 95% of blood donations screened for HBV and HCV. Overall, HCV antibody screening increased from 34% to 86%, with the median proportion of positive blood donations decreasing from 1·4% to 0·9%.³² 40 WHO-supported African countries now report³³ testing 100% of all blood donations for all transfusion-transmitted infections. Inconsistent confirmatory testing of blood donations remains an issue, as does the quality of kits used; therefore, outside urban centres and hospitals, blood-donation screening is less likely to be done.

HCV transmission in sub-Saharan Africa differs in many aspects to other parts of the world. From WHO estimates,³⁴ approximately 18% of therapeutic injections in sub-Saharan Africa are with re-used syringes or unsterilised needles, substantially increasing the risk of transmission via unsafe injection practices. Previous vaccination campaigns that used unsafe injection practices also contributed to transmission. For example, between 1920 and 1960, HCV seroprevalence significantly increased in Cameroon, coinciding with mass campaigns of vaccination and treatment for trypanosomiasis—a cohort effect that could be factored into screening programmes.³⁵ Data from the Central African Republic suggest a similar trend related to iatrogenic transmission during interventions for controlling endemic tropical diseases.¹⁹ The prevalence of vertical transmission of HCV is uncertain, but transmission risk is estimated at 10–8% in HIV–HCV co-infected mothers.³⁶ Common traditional practices including circumcision or scarification rituals with reused instruments could be an important route of transmission. In a study in Ghana,³⁷ risk factors associated with HCV infection included traditional circumcision, homebirth, tribal scarring, and hepatitis B virus (HBV) co-infection.

Recommendations on who to screen

In sub-Saharan Africa, transmission routes and risk should directly affect who should be screened when using HCV-detection programmes as a step towards elimination. Three screening approaches are possible: birth-cohort screening, general-population screening (including antenatal), and risk-factor-based screening. In sub-Saharan Africa, birth-cohort screening is not justifiable given intercountry differences. A more practical approach would be risk-factor-based screening—for instance, screening anybody who has ever received blood or blood products (using a time deadline [eg, 1990] is not recommended because the quality of the blood services varied between sub-Saharan African countries; time-specific cutoffs would need to be country dependent). Other high-risk groups to whom screening should be offered include PWID; MSM; sex workers; prisoners; health-care workers, including laboratory and support staff; HIV-positive or HBV-positive individuals; those with tattoos, including traditional practice markings; and recipients of traditional practices such as scarification and circumcision. It would also be prudent to offer screening as a part of antenatal screenings, especially in HIV-positive women, as well as children born to HCV-positive mothers. General-population screening should make use of existing community-based or facility-based testing opportunities, such as at antenatal clinics, HIV or tuberculosis clinics, or drug-treatment services. Additionally, in countries such as Cameroon and the Central African Republic, a birth-cohort effect related to programmes for treatment of tropical diseases could apply and should be considered when developing screening policies.

Suitable screening methods for HCV in sub-Saharan Africa

The aim of the WHO global health sector strategy on viral hepatitis is to decrease mortality from end-stage liver disease by 65% and reduce the incidence of new infections by 90% by 2030. Since HCV infection can be asymptomatic for decades, diagnostic screening and patients' linkage to treatment are crucial prerequisites for curing and eliminating HCV. The purpose of screening for infection is to ascertain HCV viraemia; an anti-HCV antibody test will require an additional test for HCV-core antigen (HCVcAg) or HCV RNA. Both rapid diagnostic tests and laboratory-based immunoassays must meet quality and performance standards of sensitivity and specificity. Rapid diagnostic tests are an acceptable alternative when laboratory-based services are unavailable. When a test screening for antibodies is positive, a quantitative or qualitative nucleic acid test must then be done to confirm active viraemia. Rapid diagnostic tests are attractive because they are simple, low cost, and have a rapid turnaround. Additionally, rapid diagnostic tests have the potential to improve access to HCV testing, enhance linkage to care, and reduce loss to follow-up. Rapid diagnostic tests can be blood based (eg, fingerprick blood) or saliva based, and although some variation between different products exists, they have good sensitivity and specificity when compared with gold standard laboratory-based testing.³⁸ Rapid diagnostic tests allow for point-of-care testing and will prove ideal for programmes wishing to upscale rapidly, especially if larger volumes can reduce costs. Rapid diagnostic tests using saliva tend to have lower sensitivities (94%) and higher specificities (100%) than standard reference techniques.³⁸ In December, 2016, WHO prequalified its first HCV point-of-care rapid diagnostic test, the SD BIOLINE HCV (Standard Diagnostics Inc, Gyeonggi-do, South Korea). In March, 2017, WHO also prequalified the OraQuick HCV Rapid Antibody Test (OraSure Technologies Inc, Bethlehem, PA, USA). Both tests have sensitivities and specificities that approach 100%, but collection of large-scale field data for the use of these rapid diagnostic antibody-screening tests in sub-Saharan Africa is needed.^{39,40}

Although rapid diagnostic tests and laboratory-based testing (invariably ELISA-based tests) have similar sensitivity and specificity, laboratory-based testing is more appropriate and cost-effective when laboratory resources are available.⁴¹ Laboratory testing enables high volumes of testing to be done. The HCVcAg assay is an alternative test; however, performance between different commercial HCVcAg assays varies substantially, with pooled sensitivities of 93.4% to 59.5% and specificities of 98.7% to 82.9%.⁴² HCVcAg data for genotypes 1, 2, and 3 exist but are sparse for other genotypes. An additional issue is that the sensitivity of detecting HCVcAg is impaired below 3000 IU/mL, and the lower level of detection for the most sensitive assay is

For more on the first WHO prequalified hepatitis C rapid test see http://www.who.int/medicines/news/prequal_hcv/en/

1000–3000 IU/mL.⁴² However, more than 90% of patients with HCV have viral loads above 3000 IU/mL. Detection of HCVcAg can provide confirmation of active viraemia, and can be used for monitoring treatment and to confirm SVR, relapse, or re-infection after treatment.⁴³ HCVcAg testing allows a one-step approach to detect viraemia, but can give a false-negative result in some infected individuals, hence HCVcAg assays are currently not ideal for large-scale use. The cost of nucleic acid-based testing is decreasing, but a WHO-prequalified and affordable test is needed. Pooled testing could be an applicable framework because HIV and tuberculosis services already exist across sub-Saharan Africa. Several sub-Saharan African countries have access to Gene Xpert tests (Cepheid Inc, Sunnyvale, CA, USA) for the diagnosis of tuberculosis, with HIV-nucleic acid testing also used on the same platform. Thus, countries could use this technology to incorporate HBV-nucleic acid testing (in development) and HCV-nucleic acid testing across their Gene Xpert equipment network. The Gene Xpert HCV viral load test shows good performance, with a sensitivity of 5 IU/mL, and a turnaround of 90 min.⁴⁴ Multiplex systems are also available but field studies to validate this technology in sub-Saharan Africa are required.⁴⁵

Recommendations for screening tests

Screening patients for HCV can be done using laboratory-based testing where available (ie, ELISA-based tests), or, alternatively, using high-quality rapid diagnostic tests. If the tests are positive, confirmation is required via HCV-RNA nucleic acid testing, using either qualitative or quantitative tests to establish active viraemia. HCVcAg tests remain a useful alternative to detect viraemia, but field data within sub-Saharan Africa are required to validate the method. If the costs of nucleic acid testing are equivalent to the costs of HCVcAg testing, then nucleic acid testing is the recommended option.

Fibrosis assessment in patients with HCV infection

Despite major advances with direct-acting antiviral therapy, staging of patients with fibrosis remains a necessity because it influences the duration and choice of therapy and whether ribavirin needs to be added to the regimen. Liver biopsy remains the gold standard to assess the stage of liver disease and grade of fibrosis. However, in sub-Saharan Africa the role of liver biopsy is attenuated by its limited availability, high cost, low cultural acceptability, and a shortage of liver histopathologists, and so is often limited to major teaching hospital centres. The need for biopsy diminishes linkage to care for newly identified patients and thus is not ideal. Although standardised histological scoring systems have been developed, including the METAVIR (eg, F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with septa; F3, numerous septa without cirrhosis; F4, cirrhosis), Knodell⁴⁶ and Ishak⁴⁷ scoring systems, non-invasive fibrosis testing

is a more viable alternative to liver biopsy to assess fibrosis, or as a rule in or rule out test for cirrhosis.⁴⁸

Several non-invasive fibrosis tests based on blood or serum markers exist (eg, aspartate aminotransferase-to-platelet ratio index [APRI], FibroTest [BioPredictive, Paris, France], and Fibrosis-4) in addition to vibration-controlled transient elastography (VCTE; eg, Fibroscan [Echosens, Paris, France]). The APRI and Fibrosis-4 scoring tests incorporate routine blood tests, such as for alanine aminotransferase and aspartate aminotransferase, and platelet count. These routine tests are more generally available than FibroTest and cheap. Interpretation of the tests is straightforward and they can be done in an outpatient setting. FibroTest needs a higher level of quality control than do routine blood tests with respect to laboratory requirements for its validity; additionally, apart from the test's commercial and patented nature, FibroTest is also more expensive and less readily available. The non-invasive blood tests are less discriminatory in accurately staging fibrosis than biopsy, but are good in terms of ruling in or ruling out cirrhosis. VCTE, which was approved in Europe in 2003 and in the USA in 2013, measures liver stiffness and is done using a Fibroscan. The technique has been extensively assessed and its predictive value for measuring the stages of fibrosis has been validated. Applicability of the technique in sub-Saharan Africa has been shown and it works well as a mobile tool.⁴⁹ Notably, the area under the receiver operator curve (AUROC) for Fibroscan in its assessment of cirrhosis, is consistently higher than 0.9.^{50,51} Potential issues are the high initial capital cost, the need for annual recalibration and formal training, and the restricted availability in sub-Saharan Africa. Nevertheless, to achieve the objective of HCV elimination, technologies such as VCTE, together with point-of-care diagnostic testing, offer localised services for rapid decision making and improved linkage to care. With the current economy of scale regarding the use of direct-acting antiviral therapy and the price of access to therapy throughout sub-Saharan Africa, the need to prioritise patients for therapy through assessment of fibrosis could be eliminated. Formalised staging of fibrosis might only be needed for individuals with suspected advanced cirrhosis to establish the duration and choice of direct-acting antiviral therapy and the need to continue hepatocellular carcinoma surveillance after SVR has been achieved.

Recommendations for fibrosis assessment

Although liver biopsy remains the gold standard for assessing liver fibrosis and establishing potential cofactors, access to liver biopsy in sub-Saharan Africa is restricted. Therefore, efforts to improve the availability of training to complete and interpret liver biopsies should be continued. Given the need for fibrosis assessment in patient management and the low availability of liver biopsy, non-invasive measures of fibrosis, which are either blood or VCTE based, are the recommended investigations for use

in sub-Saharan Africa. VCTE is an ideal technology, but costs and operator skill are a potentially limiting factor. The APRI score is the recommended blood-based non-invasive test, given its simplicity and availability, although the Fibrosis-4 test is a reasonable alternative.

Recommended management of HCV in sub-Saharan Africa

The WHO HCV elimination objective requires national plans, appropriate resources, and political will to expedite unrestricted access to care and treatment. When determining who requires therapy, if elimination of HCV is the objective, then all patients who are willing to be treated deserve therapy. Universal access to treatment should be established for all, except for individuals with a compelling reason not to be treated, such as those with terminal or end-stage disease. All treatment-naïve and treatment-experienced patients with compensated or decompensated HCV-related chronic liver disease who have no contraindications to treatment should be offered therapy.

Universal access to treatment requires the streamlining of therapeutic approaches. In the context of sub-Saharan Africa, extensive therapeutic options with several nuances that are neither realistic nor achievable are of no value.

The recommendations that follow and that are in table 2 are an attempt to simplify therapeutic approaches and reduce the need for complex decision making. Furthermore, these recommendations acknowledge that the availability of more complex testing (eg, subgenotyping) might not be readily available, and in these situations a standard approach should be used. These recommendations do not detract from country-specific guidelines or recommendations that might already exist. However, to achieve the objective of elimination, a harmonised approach to the management of patients with HCV should be considered to allow health-care workers with a broad range of skills to manage patients. Pangenotypic combination therapies are favoured because they preclude the need for genotype testing.⁵²⁻⁵⁵

Table 2 is a recommended treatment schedule for patients who have cirrhosis, compensated cirrhosis (ie, classified as Child–Pugh class A), those who are treatment naïve or treatment experienced, including those who have been treated with pegylated interferon and ribavirin, and those who are naïve to direct-acting antivirals. These recommendations are applicable to patients with HCV mono-infection or HIV–HCV co-infection (notably with efavirenz-based antiretroviral therapy, a common regimen in sub-Saharan Africa);

	Sofosbuvir and ledipasvir*	Sofosbuvir and daclatasvir†	Sofosbuvir and velpatasvir‡	Sofosbuvir and ribavirin§
Genotype 1a/1b¶				
Treatment naïve	12 weeks	12 weeks	12 weeks	No
Treatment experienced or cirrhosis	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	12 weeks	No
Genotype 2				
Treatment naïve	No	12 weeks	12 weeks	12 weeks
Treatment experienced or cirrhosis	No	12 weeks	12 weeks	16–24 weeks
Genotype 3				
Treatment naïve	No	12 weeks	12 weeks	No
Treatment experienced or cirrhosis	No	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	No
Genotype 4				
Treatment naïve	12 weeks	12 weeks	12 weeks	No
Treatment experienced or cirrhosis	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	12 weeks	No
Genotype 5				
Treatment naïve	12 weeks	12 weeks	12 weeks	No
Treatment experienced or cirrhosis	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	12 weeks	No

When a patient is co-infected with HCV and HIV, careful consideration must be given to drug–drug interactions with existing antiretroviral therapy. If the HCV genotype is unknown, treatment using sofosbuvir and daclatasvir is recommended. *Sofosbuvir (400 mg) with ledipasvir (90 mg). †Sofosbuvir (400 mg) with daclatasvir (60 mg); daclatasvir doses might need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. ‡Sofosbuvir (400 mg) with velpatasvir (100 mg). §Sofosbuvir (400 mg) with a bodyweight-based dose of ribavirin. ¶If the subgenotype is known, bodyweight-based ribavirin is not required for patients who have genotype 1b infection and are treatment experienced or have compensated cirrhosis. The default treatment in the absence of subgenotype is to add ribavirin for 12 weeks or extend treatment to 24 weeks without ribavirin.

Table 2: Treatment schedule for hepatitis C by genotype, treatment history, and presence of compensated cirrhosis

For potential drug–drug interactions see <http://www.hep-druginteractions.org>

however, for those who are HIV co-infected, careful consideration must be given to drug–drug interactions with existing antiretroviral therapy (all potential drug–drug interactions must be checked before initiation of direct-acting antiviral therapy). Of note, when using efavirenz-based antiretroviral therapy, sofosbuvir plus velpatasvir is contraindicated, and the dose of daclatasvir should be increased to 90 mg.

Four potential drug combinations can be used for treatment of HCV in sub-Saharan Africa (sofosbuvir plus ledipasvir, sofosbuvir plus daclatasvir, sofosbuvir plus velpatasvir, and sofosbuvir plus ribavirin; table 2), and the choice of treatment schedule is dependent on the HCV genotype. However, if genotype testing is unavailable, the default option should be to treat with pangenotypic therapy, using either sofosbuvir with daclatasvir or sofosbuvir with velpatasvir. Both pangenotypic options are generically available, although the combination of sofosbuvir with daclatasvir is favoured because it is more cost-effective and readily available. Details of recommended regimens by genotype are shown in table 2.

The cost of treating and eliminating hepatitis C in sub-Saharan Africa

The cost and affordability of treatments for HCV are important to achieve the elimination targets set out by WHO for sub-Saharan Africa. The average yearly income in sub-Saharan Africa is US\$2041 or \$5·60 per day, with three-quarters of the population living on less than \$2 per day.⁵⁶ The cost of drugs has already been substantially reduced with the availability of generics, with some companies providing access pricing for most countries in sub-Saharan Africa. Updated costs for 12-week courses of generic sofosbuvir (400 mg; \$153 in Egypt and \$72 in India) with daclatasvir (60 mg; in Egypt, \$69–183 in India), and sofosbuvir plus ledipasvir (400 mg and 90 mg, respectively; \$249–307 in India), or sofosbuvir plus velpatasvir (400 mg and 100 mg, respectively; \$550 in India) could be the benchmark of prices for generic treatments in sub-Saharan Africa. Even so, in many countries in sub-Saharan Africa, individuals bear the costs of treatment, with only a few countries paying for treatment.

Apart from drug costs, the affordability of diagnostics also warrants consideration. Approaches to streamline the treatment cascade have been previously suggested, such as those that reduce the testing and monitoring required. However, innovative funding mechanisms need to be developed to treat patients on low annual incomes. Most importantly, governments need to recognise that hepatitis C, which is entirely treatable, leads to high numbers of deaths annually. Political will in confronting these challenges is crucial. Governments could form partnerships with funders who have shown some willingness to support the global treatment of viral hepatitis, such as The Global Fund, Gavi, and Unitaid.

Recommendations for special categories of HCV-infected patients

Decompensated Child–Pugh class B and class C cirrhosis

Liver transplantation is the treatment of choice for end-stage liver disease; however, apart from a select few countries, transplantation is not available in sub-Saharan Africa. Hence, treating patients with advanced HCV-related liver disease should be considered in all circumstances. Although not specifically recommended in this paper, regimens using NS3-4A protease inhibitors—eg, simeprevir, paritaprevir, or grazoprevir—should not be used to treat patients with Child–Pugh class B or C decompensated cirrhosis because of the risk of toxic effects. Data supporting the use of direct-acting antivirals in patients who are classified as having Child–Pugh class B or C cirrhosis includes the SOLAR-1 study,⁵⁷ in which patients with HCV genotype 1 or 4 with decompensated cirrhosis received sofosbuvir plus ledipasvir for 12 or 24 weeks with ribavirin. In patients with Child–Pugh class B and C liver disease, the proportion of patients with an SVR was 87% and 86% with 12 weeks of treatment, and 89% and 87% with 24 weeks of treatment, respectively.⁵⁷ Clinically, patients improved as measured by the Child–Pugh and MELD scores. In the ASTRAL-4 study,⁵⁸ treatment of patients with Child–Pugh class B decompensated cirrhosis with genotypes 1, 2, 3, 4, and 6 using sofosbuvir plus velpatasvir for 12 weeks with ribavirin yielded an SVR in 83% of patients, whereas treatment for 12 weeks without ribavirin yielded an SVR in 94% of patients, and treatment for 24 weeks without ribavirin yielded an SVR in 86% of patients. For participants with baseline MELD scores of less than 15, 52% had improved scores and 27% had worse scores after treatment. For participants with MELD scores of more than 15, 84% had improved scores and 8% had worse scores at the end of the study, suggesting an imperative to treat those with higher MELD scores. Data for 12 weeks of treatment with sofosbuvir plus daclatasvir, with or without ribavirin, in patients with decompensated cirrhosis and HCV genotype 1 infection suggested a need for ribavirin, because the proportion of patients with an SVR who did not receive ribavirin was 50% versus 88% in those who did receive ribavirin.⁵⁹ A similar result was observed with patients who had HCV genotype 3 infection. In summary, patients with decompensated cirrhosis benefit from treatment, and patients who are classified as having Child–Pugh class B cirrhosis are more likely to benefit than are those with Child–Pugh class C.

Chronic kidney disease

The prevalence of chronic kidney disease in sub-Saharan Africa is substantial, with some instances related to HCV but most being secondary to type 2 diabetes, hypertension, and HIV.⁶⁰ For individuals in sub-Saharan Africa with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min), access to

For WHO global hepatitis report 2017 see <http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/>

haemodialysis or peritoneal dialysis is poor. For those with mild-to-moderate renal impairment (eGFR >30 mL/min), dose adjustments of sofosbuvir plus ledipasvir, sofosbuvir plus velpatasvir, and sofosbuvir plus daclatasvir are not required and standard recommendations can be followed. Stage 4 or 5 chronic kidney disease in sub-Saharan Africa poses a challenge. The efficacy of grazoprevir plus elbasvir and ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir for treating chronic kidney disease has been proven.^{61,62} However, in sub-Saharan Africa these regimens are neither widely available nor affordable and are limited to the treatment of HCV genotype 1 and 4 infections. Sofosbuvir and its metabolite, GS-331007, are renally eliminated and so are substantially elevated in patients with renal impairment, with renal function worsening in those with severe impairment when on the drug (impairment can reverse when the drug is stopped), without affecting the SVR rate. The appropriate dose of sofosbuvir for patients with stage 4 or 5 chronic kidney disease has not been established. A study⁶³ of 50 patients with mild-to-moderate renal impairment, with eGFR of 30 mL/min, who were treated with sofosbuvir 400 mg every alternate day, yielded an SVR rate of 86%. If sofosbuvir-based therapy is used, it should be done cautiously and with close monitoring. A practical consideration is that reduced sofosbuvir dosing is not practical with fixed-dose combination formulations, except for sofosbuvir plus daclatasvir.

Ribavirin-eligible patients

Ribavirin retains a role in the optimal treatment of some patients, usually those with cirrhosis or treatment experience.⁶⁴ Ribavirin is given twice daily and the dose is based on bodyweight (1000 mg/day if <75 kg, or 1200 mg/day if ≥75 kg). Use of ribavirin is complicated by the prevalence of sickle-cell disease in sub-Saharan Africa: 80% of all children born with the disease are from sub-Saharan Africa, predominantly western Africa. Furthermore, the incidence of HCV in this population is elevated because of their need for transfusions of red blood cells. A small study⁶⁵ from the Democratic Republic of Congo calculated HCV seroprevalence to be 7.9%. Another small study⁶⁶ has suggested that ribavirin can be used successfully in patients with sickle-cell disease, but avoidance of the need for transfusions during therapy is preferred.

Pregnancy

No direct-acting antiviral therapies are currently regarded as safe for use during pregnancy because data on these patients are absent. Until these data become available, women of childbearing age should be prioritised for treatment before pregnancy, and if a patient is diagnosed during pregnancy, their treatment should be deferred until after pregnancy and once breast-feeding has terminated.

Children

No direct-acting antivirals are registered for use in children infected with HCV, instead pegylated interferon with ribavirin is the standard of care. A phase 2 study⁶⁷ assessed the use of ledipasvir plus sofosbuvir for 12 weeks in the treatment of 100 adolescents who were infected with genotype 1 HCV, 80% of whom were treatment naive and 84% of whom had been infected perinatally. Overall, 98% achieved an SVR. Direct-acting antiviral therapy for children and adolescents is awaiting imminent approval.

Patients who do not respond to direct-acting antiviral therapy

Patients who do not respond to direct-acting antiviral treatment are a particular challenge in sub-Saharan Africa, because alternative regimens are not accessible. In principle, these patients require referral to a centre with related expertise. The risk of direct-acting antiviral treatment failure can be reduced by selecting the optimal treatment regimen—eg, adding on ribavirin when appropriate, and ensuring the accurate assessment of the stage of fibrosis to avoid undertreating those who have advanced fibrosis or cirrhosis. Sofosbuvir has a high barrier to resistance and can be re-used in regimens with drugs that do not share cross resistance, or with newer direct-acting antiviral drugs that are active against substitutions associated with NS5A resistance.⁶⁸ Resistance-associated substitutions selected by NS3-4A protease inhibitors tend to decline and disappear within months of treatment cessation. However, NS5A resistance-associated substitutions are replication fit and persist indefinitely. A class effect also tends to occur. In principle, when selecting a re-treatment regimen, three or four drugs should be selected and ribavirin should be added. For patients who are difficult to treat (eg, patients with cirrhosis), their treatment should be extended beyond the usual 12 weeks.⁶⁸

HBV-infected patients

In October, 2016, the US Food and Drug Administration adverse events reporting system reported⁶⁹ 29 patients with substantial recurrences of their HBV co-infection 4–8 weeks after initiating direct-acting antiviral therapy for HCV. 19 (66%) of the patients were from Japan, five (17%) from the USA, and five (17%) from outside the USA and Japan. Before direct-acting antiviral treatment, 12 of the patients were known to be positive for hepatitis B surface antigen (HBsAg) and six were known to be positive for hepatitis B core antibody (HBcAb) positive. Two patients died, one had a liver transplant, and six were admitted to hospital. A review⁷⁰ of 62920 veterans receiving direct-acting antivirals, found that only nine patients had a recurrence of their HBV co-infection, and all of these instances were mild. A subsequent meta-analysis⁷¹ advised HBV screening before starting direct-acting antiviral therapy. Given the high prevalence

Search strategy and selection criteria

We searched for references for this Series paper with no starting date restriction to July 3, 2017, using PubMed and the search terms “Africa”, “sub-Saharan Africa”, “hepatitis C”, “hepatitis C genotypes”, and “hepatitis C seroprevalence”. We also used our own files to find references. In one instance, a personal communication is cited in the body of the text. English and French articles were included in the search. We used Google to obtain some reports published since 2016—eg, the US Food and Drug Administration report. The references included in this Series paper were chosen on the basis of their relevance to the topic and our perspectives related to our countries of origin.

of hepatitis B exposure in sub-Saharan Africa, hepatitis B screening (for HBsAg, HBeAb, and HBV DNA) before starting direct-acting antiviral therapy is advised, with monitoring during therapy required. For patients who are HBsAg positive, pre-emptive initiation of antiviral treatment for HBV could be warranted, although clear data on this approach to treatment do not exist. HBV reactivation is a safety concern in patients who take direct-acting antivirals; however, the benefits of eliminating HCV outweigh any harm in those who could be at risk.

Conclusion

The goal of eliminating hepatitis C in sub-Saharan Africa is achievable. What is needed to achieve this goal is political will from governments, acknowledging the problem, and providing or enabling necessary resources. Using a combination of seamless and simple screening, diagnostic, and therapeutic approaches, and leveraging on existing infrastructure, patients could be rapidly transitioned from diagnosis and linked to care. To achieve elimination of HCV, the rules of old will no longer apply, and innovative new approaches will be needed.

Contributors

MWS drafted the manuscript. All authors contributed equally to reviewing the available literature, providing country specific perspectives, formulating consensus recommendations, and reviewing the manuscript. CWS and GD provided addition technical expertise.

Declaration of interests

We declare no competing interests.

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