Review Article

Hepatitis C Virus: Molecular Epidemiology, Treatment and Diagnosis Challenges in Sub-Saharan Africa (SSA)

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Abstract | Chronic Hepatitis C virus (HCV) infection can be considered as a silent and neglected killer, fueled by many years of inertia from government and stakeholders. Treatment of chronic HCV infection has the potential to influence the 2030 elimination target due to the increasing availability of effective pangenotypic antiviral DAAs. Understanding the extent of HCV genetic diversity is important for treatment and development of vaccine. Among the routes of HCV transmission; intravenous drug addiction or injection drug use accounts for the majority of many cases apart from hemodialysis patients, unprotected sexual intercourse, blood transfusion and vertical transmission. Therefore, there is a need for government commitment for HCV elimination program through making the DAAs available and its affordability to general population to curb the catastrophic cost of managing the epidemic. However, the diagnosis of HCV infection is faced with several challenges, therefore there is a demand for development of easy to use and inexpensive molecular methods for accurate diagnosis. The sub-Saharan Africa HCV genotypes distribution are diverse, but genotype I is the most common. This review highlights the need for more robust surveillance studies with introduction of opt-in testing at all clinics for better epidemiology the HCV disease burden more accurately.

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Introduction

Hepatitis C virus (HCV) disease is an important global public health problem. About 185 million people are currently infected with HCV (Hanafiah et al., 2013), while about 350,000 person died from liver failure and cancer caused by hepatitis C disease, with majority of cases in Africa (Mora et al., 2016). Reports have shown that HCV and Hepatitis B virus (HBV) infection accounts for large number of chronic liver disease and hepatocellular carcinoma (HCC) with an alarming number of new cases occur annually (Lavanchy, 2009). The prevalence of hepatitis C varies significantly worldwide, imposing an important disease burden in highly endemic countries such as sub-Saharan Africa (SSA) (WHO, 2017). HCV infection is commonly associated with chronic liver disease, resulting in cirrhosis, hepatocellular carcinoma (HCC) and death following viral persistence for years (McHutchison and McHutchison, 2005). Sub-Saharan Africa especially Nigeria is in dare needed of the current direct-acting antivirals (DAA) that have proved to be highly effective and potentially pangenotypic. The choice, duration, and cost of

treatment has the potential to be influenced virus genotype which is important because the proportions and distribution of HCV genotypes across sub-Saharan Africa are very diverse.

HCV genotypes distribution

HCV is a member of the *Flaviviridae* family, genus Hepacivirus that infect humans, rodents, bats, canines and horses. HCV is a single-stranded, positive-sense RNA, enveloped 55-65nm in diameter. The viral RNA genome is ~9.6 kb in length and contains a single open reading frame encoding a large polyprotein. The polyprotein is processed by viral and host proteases to give structural proteins and nonstructural proteins (Chevaliez and Pawlotsky, 2006).

HCV mainly affects liver hepatocytes but may also be present in blood mononuclear cells and dendritic cells (Alter, 2007). To date, based on the nucleotide variability in the viral genome, 7 genotypes (1-7) of HCV have been identified based on phylogenetic analysis, which are further subdivided into 84 subtypes represented as; a, b, c, d, e, f, etc., many of which were identified in high income countries (Echeverría et al., 2015; Petruzziello et al., 2016; Davis et al., 2019). Genotypes 1a, 1b and 3a are distributed globally, while genotype 1b, 3 and 6 are found predominantly in Southern and South East Asia. Genotypes 4 and 5 are mainly in Africa, genotype 4 is predominating in the Central African Republic, Democratic Republic of Congo (97%), Gabon (92%), Chad (84·6%) and Equatorial Guinea (60 %) (Petruzziello et al., 2016). In the Eastern region of Africa, genotypes 4 predominates than genotypes, 1, 2, 3, and 5. Genotype 2 predominates in Burkina faso, Togo, Ethiopia while genotype 1 has been documented in Madagascar (Smith et al., 2014; Njouom et al., 2009). In Nigeria, diverse HCV genotypes exist in the non-homogeneous studied populations from blood donors, HIV infected and general population. The identified genotypes in Nigeria are1, 2, 3, 4, and 5 including the heterogeneous subtypes (1a, 1b, 2b, 2c and 5a) Shenge et al., 2018, 2019; Okwuraiwe et al., 2012; Oni and Harrison, 1996; Sheyin et al., 2012).

The higher mutation rate of HCV, is leading to high degree of intra-host genetic diversity (Assih et al., 2018). Understanding the extent of HCV genetic diversity is important to better understand the treatment response and development of vaccine which are keys for virus elimination and better understanding forrecent and historical transmission patterns. The molecular plasticity of HCV allows rapid rearrangement of the intra-host viral population under selection pressures, while the virus genetic variability has hampered the development of a successful vaccine till now (Ralston et al., 2011).

Molecular surveillance of HCV is very important in order to identify the existing transmission cycle and networks which is a critical component of disease outbreak investigations. In addition, surveillance can provide important information about the circulating HCV lineages. However, genetic variability is important to track HCV infections and phylodynamic studies (Depledge et al., 2014). Parenteral route is the main route of transmission for HCV (intravenous drug addiction or injection drug use, where 60% out of patients are undergoing hemodialysis, unprotected sexual intercourse represent 15%, and vertical transmission (mother to child) (WHO, 2017; Compagnone et al., 2019). Transfusion of unscreened blood and blood products represents 10% and occupational about 4%. Other routes of transmission are tattooing, surgical and dental treatment, shaving, nail trimming and ear-piercing including unknown sources (MacDonald et al., 1996; WHO, 2017). In developed countries the main cause of HCV transmission is injection drug use (Depledge et al., 2014).

Current recommendation for HCV management and challenges

The WHO elimination plan for viral hepatitis including HCV requires national plans, appropriate resources, and political to expedite unrestricted access to care and treatment (WHO, 2017). So, there is a need for universal access for all, except for individuals with a compelling reason to opt out, with exceptions of those with end-stage disease or hepatocellular carcinoma (Tyson et al., 2013). Antiviral treatment for -naïve, and/or experienced patients with compensated or decompensated HCV-related liver disease with no contraindications to treatment should be offered. This treatment require streamlining of therapeutic approaches depending on the availability of the therapy that are neither realistic nor achievable (Asselah et al., 2016). To achieve the objective of elimination, a harmonized approach for management of HCV patients should be considered. Also, Pangenotypic combination therapies are favored because they preclude the need for genotype testing.

Coinfected HCV patients with HIV, careful consideration must be given to drug–drug interactions with the usage of antiretroviral therapy (Asselah et al., 2016). With unknown genotype, which is common in Africa, sofosbuvir and daclatasvir combination is recommended (Asselah et al., 2016; EASL, 2017), Sofosbuvir (400 mg) plus ledipasvir (90 mg) or Sofosbuvir (400 mg) plus daclatasvir (60 mg) or Sofosbuvir (400 mg) plus velpatasvir (100 mg) or Sofosbuvir (400 mg) with a bodyweight-based dose of ribavirin EASL, 2017. The default treatment in the absence of subgenotype is to add ribavirin for 12 weeks or extended treatment up to 24 weeks without ribavirin (EASL, 2017). However, generally, for genotype 1a, b, 2,3,4, and 5, the recommendations are Sofosbuvir (400 mg) with daclatasvir (60 mg) or Sofosbuvir (400 mg) with velpatasvir (100 mg) for 12 weeks. 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 (Asselah et al., 2016; EASL, 2017).

These treatment 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). While, for patients who are HIV co-infected and on antiretroviral therapy, sofosbuvir plus velpatasvir contraindicates efavirenz-based antiretroviral therapy, therefore the dose of daclatasvir should be increased to 90 mg (Abergel et al., 2016). However, with unavailable genotype testing, the default option should be to treat with pangenotypic therapy, using either sofosbuvir plus daclatasvir or sofosbuvir plus velpatasvir. Both of these pangenotypic drug options are available in generic formulations, while the combination of sofosbuvir with daclatasvir is preferred based on the cost and availability (Abergel et al., 2016; Asselah et al., 2016; AASLD, 2015).

The cost and affordability of treatments for HCV are important to achieve the disease elimination set targets. Apart from the disease challenges is the genetic variability which has an impact on the treatment outcome and the cost of the available drugs is not within the range of low middle-income individuals. Although the cost of pangenotypic drugs has been reduced substantially with the availability of generics formulations in SSA, The cost of generic sofosbuvir (400 mg) is $153 in Egypt and $72 in India and daclatasvir (60 mg) in Egypt is ($69) and ($183) in India for 12 weeks course. Though, this could be a good benchmark of prices for generic treatments while many countries in Africa, individuals are still bearing the cost of treatment (Terrault et al., 2018). The introduction of the DAAs may have been hampered for lack of data regarding HCV genotypes, and viral mutations. In addition, the efficacy of DAAs against the less common genotypes, such as genotype 5 and 6 are not yet well studied. Other challenges to HCV treatment in SSA including Nigeria, include antiviral high costs, a perceived complexity in treatment regimens and lack of DAA availability and pollical support for importation, licensing and distribution of medicines.

Diagnostic challenges

An important public health challenge is to reduce the diagnosis cost, because it is estimated that the rate of diagnosis of HCV infection is below 50% (Gower et al., 2014). This requires nation-wide hepatitis-specific action plans that have only been implemented in few countries (Lazarus et al., 2013). Costs for diagnosis especially viral load testing, is a major hurdle, while it is an important marker to monitor patients during antiviral therapy. Apart from rapid diagnostic tests available commercially, ELISA that has similar sensitivity and specificity, but issues of false positive and negative results are major concerns that need to be addressed and confirmed with nucleic acid-based technology (Bartenschlage et al., 2018). Thus, the need to develop less expensive diagnostic tests such as HCV viral load, decentralized HCV RNA testing and/or core antigen that are easy to use, alongside with inexpensive equipment and training. So, combinations of these tests with available DAAs may be a major step to achieve HCV elimination.

Interestingly, little is known regarding the burden of HCV infection in the general population in Nigeria, and many other countries in Africa, but the available data suggests that the seroprevalence could be higher due to inhomogeneous populations studied, and lack of data especially in high-risk groups such as PWID, MSM, and patients undergoing hemodialysis (Lanini et al., 2016). The goal of eliminating hepatitis C in SSA is achievable. However, it requires political will from governments by first, acknowledge the magnitude of the problem, and providing or enabling necessary resources such as inclusion of blood collection centers at outpatient clinics as sentinel sites to aid testing.

The knowledge of HCV genetic diversity is of great epidemiological and clinical interest, therefore it is important to improve molecular methods such as next-generation sequencing platforms and statistical approaches to unveil the transmission mechanisms (Bellocchi et al., 2019). Also, it is important to develop inexpensive molecular methods to diagnose, treat and vaccine candidate development that will eliminate HCV infections. The use of simple screening techniques with high sensitivity and specificity, or nucleic acid-based essay, therapeutic approaches, especially with leveraging on existing infrastructure, will aid for rapid transitioning of patients from point of diagnosis and linking up to care. It is also equally important that comprehensive HCV molecular studies are needed to reduce the existing gaps in intra-host genetic variability, transmission networks and genotype related treatment outcomes (Trémeaux et al., 2016; Ramachandran et al., 2018). To estimate the burden of HCV infection in SSA there is a need to start with knowing the infection status through surveillance that will measure basic epidemiological indicators and will provide useful baseline data. To achieve elimination of HCV, we suggest the need to borrow ideas from the lessons of HIV management and develop innovative approaches to facilitate target intervention programs necessary to curb HCV infection and liver related disease (Eckman et al., 2019; Umutesi et al., 2019). In order to reduce gaps within on diagnosis, a more pragmatic approach such opt-in for screening, target high-risk populations, and an expanded universal screening for general population are highly needed (Umutesi et al., 2019).

In conclusion, antiviral therapy high-cost still remain a barrier in Nigeria like many SSA countries, therefore, continued advocacy for manufacturing companies and funders to reduce antiviral therapy costs and remove gaps for DAA. Vast majority of patients infected with HCV in Africa remain undiagnosed and untreated, despite the development of well-tolerated, curative antiviral medications. The diagnosis of HCV has not kept pace with antiviral development. So, there is an urgent unmet clinical need for decentralized HCV testing that is simplified, accurate, accessible, available, affordable, and can be administered in a community setting without compromising quality. It is surprising that support for basic HCV research has not received enough attention compared to other pathogens of similar medical importance. It has become inevitable that priorities for HCV prevention treatment and research need urgent attention, and early and accessible accurate diagnosis, making the DAAs available and affordable as a starting point. However, stakeholders such as clinicians, researchers, public health experts, and advocacy groups must get involve and advance the daunting task to achieve HCV elimination target of 2030 which is achievable (Sonderup et al., 2017)

The clarion call is in an urgent need to provide HCV universal and opt-in testing at and routine clinical monitoring protocol to be available for all public hospitals. It also imperative that the government should come up with innovative funding mechanisms needed to treat patients on low incomes. Most importantly, governments need to recognize that hepatitis C, which is entirely treatable, leads to higher numbers of deaths than HIV. The necessary political to muscle in this effort in confronting these challenges is crucial and cannot be timelier than now. Government should identify and involve the stakeholders through partnerships and funders who have shown interest to support the global treatment of viral hepatitis in SSA.

Authors Contribution

J.A-O conceived the idea, developed the framework and first draft. O.J.O read the draft and made corrections, O.A encouraged the idea, participated in the second draft, made subsequent corrections and final proof reading.

Conflict of interest

The authors have declared no conflict of interest.

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