HEPATITIS

Viral hepatitis, most commonly caused by a handful of hepatotropic viruses, leads to a wide spectrum of clinical syndromes ranging from a self-limited febrile illness to chronic infection, liver failure and hepatocellular carcinoma. Hepatitis A virus (HAV) is associated with an acute, self-limited infection resulting in prompt induction of active immunity. Hepatitis B virus (HBV) has historically imposed the greatest global health burden, given the high prevalence in East Asia, India and Africa and the risk of cirrhosis and liver cancer that accompanies chronic infection.[1] While development of effective vaccines and treatment for actively infected patients has greatly improved the outlook for control of HBV, major challenges remain. Hepatitis E, although typically considered a self-limited disease, can be highly lethal during pregnancy and recent reports have documented chronic infection in immuno-compromised hosts.[2] Hepatitis D Virus, a defective entity dependent on HBV for assembly and secretion, can lead to severe acute hepatitis when superinfection with HBV occurs.[3]

Despite the relative success of efforts to control other hepatatrophic viruses, hepatitis C (HCV) is emerging as a formidable challenge. First recognized in the 1980s, HCV is now the cause of a global epidemic and in some regions of the world is the leading cause of cirrhosis, liver failure and cancer.[4-6] The World Health Organization (WHO) estimates the current worldwide HCV sero-prevalence at 2·8% (>185 million persons), a substantial increase from 2·3% (>122 million persons) in 1990.[7] Humans are the only species susceptible to HCV; it successfully evades our immune system through rapid replication and mutation and the consequent high level of intra-species diversity. High diversity both within and between strains has also thwarted efforts to produce a vaccine. While treatment options and their relative efficacy have improved with the advent of direct acting anti-viral agents, persistent social factors that limit diagnosis, access to medical

care, and timely management make it inevitable that cirrhosis and hepatocellular carcinoma (HCC) attributable to chronic HCV will continue to be a major problem for many years to come.[8]

Much of sub-Saharan Africa continues to labor under a heavy burden of infectious diseases and viral hepatitis is no exception. Unfortunately the current state of knowledge about numerous epidemiologic aspects of hepatitis is woefully inadequate, as detailed below. Evidence of high viral diversity and prolonged endemicity, [9-15] compared to other regions of the world, suggest that it first became a human infectious agent in Africa. However, the prevalence in many parts of the continent remains unknown. While there are candidate explanations for how the infection is being transmitted, in the main this critical question remains unanswered. The most complete description of the disease burden from HCV in Africa comes from Egypt where an epidemic of genotype 4 was tragically ignited through use of unsterile intravenous therapy during a campaigns against schistosomiasis.[16] Beyond these fragmentary details, little else can be said with confidence about the epidemiology of hepatitis C in what is most likely its continent of origin.

The evolutionary history of HCV

Although only detected and characterized three decades ago [17], mounting evidence suggests that HCV has been endemic in sub-Saharan Africa for several centuries. Genome sequence analysis has documented high levels of diversity for HCV genotype 1 and 2 within west and central Africa.[9-15,18-22] Recent studies in Nigeria have shown that genotype 1 originated in that region in the 12th -15th centuries, with both genotypes 1 and 2 expanding continuously over the last 200-300 years in Nigeria and then to central Africa.[9] Recent identification of new members of genus *Hepacivirus* from bats, rodents,

dogs, horses and New and Old World monkeys expands significantly the range of natural animal hosts for the HCV-related viruses and provides a theoretical explanation for the dramatic viral diversity of HCV seen in Africa and other regions.[23-26] Other recent work has identified a nonprimate hepacivirus (NPHV), originally named canine hepacivirus, [26-28] which has the greatest degree of genetic homology to HCV yet detected. Bayesian modeling suggests a divergence of NPHV and HCV within the last 500-1000 years,[28] which is consistent with prolonged endemicity and high diversity of HCV on the Africa continent.

It is hypothesized that rapid worldwide spread of the virus occurred only in the 20th century, coinciding with the introduction of blood and blood product component transfusions, the use of unsterilized needles, and the increase in intravenous drug abuse in developed countries.[4,21,29] With these newer, highly effective modes of blood-borne transmission, following a pathway similar to HIV, the more recent and well-described global epidemic of HCV was born.

Hepatitis C- Presumed Burden of Disease

For sub-Saharan Africa, seroreactivity rates range from 2·1-2·8%, with the highest rates in West Africa, viz. 2·8% (95% CI: 2·4-3·3). Age-specific prevalence rates peaked at 55-64 years of age, with estimates from 5·3-6·7%; interestingly, a unique two peak pattern was observed in West Africa, with a lower, but distinct peak apparent in the 15-19 year age range.[6]

For African regions, as well as others, a meta-analysis derived from available English language published studies from 1990-2005 served as the source for current sero-prevalence estimates. Studies using high-risk populations (i.e., known risk factors for

hepatitis, HIV infected population, intravenous drug user population) were eliminated, which likely led to conservative estimates. However, there are important limitations inherent in an attempted meta-analysis for data from Africa. Whereas estimates in the US can be derived from population-based studies (e.g., National Health and Nutrition Examination Surveys),[6] representative surveys are not available from Africa and the majority of studies are based on convenience samples, such as emergency room patients, blood donors and pregnant women. Evidentiary support for these estimates is listed as moderate, due to the limited number of data point entries per country within each sub-region.

A point of particular concern is the variability of assays used to determine seroprevalence. Over the fifteen-year interval surveyed, significant changes occurred in the diagnostic tests, resulting in variation in the sensitivity and specificity of among assays [30] and recent work has raised the possibility of high false positive rates.[31,32] Seremba et al screened 380 patients presenting to an emergency department in Uganda and found substantial variation between the rapid screen assay (RSA) and enzyme immunoassay (EIA) results. Further, of the 48 subjects positive for either one of the tests, only fourteen (29%) had detectable virus.[33] Among blood donors at a large hospital in Ghana, similar low rates of viremia were detected in seroreactive subjects; furthermore, while 3% were positive by one assay, only 1·3% were positive by two HCV assays.[13] Given the likely lower pre-test probability of infection in the studies used for the meta-analysis and apparent variation of assay precision across time and studies, the WHO estimates of the burden of HCV in Africa must viewed with great caution.

More recent studies continue to highlight the uncertainty of the reported population data as well as the distinct possibility of localized outbreaks. In two rural villages in Nigeria,

the seroprevalence rate was 15% using a RSA.[9] Of those with positive RSA results, 82% had detectable viremia and could be genotyped, suggesting not only a high rate of exposure, but a high rate of active infection. In a study in the Democratic Republic of Congo, ELISA-based sero-prevalence rates were 13% (41/299), with only 27% having detectable virus, reinforcing the concern of false positive results.[19] However, even if we accept only the patients with confirmed viremia as infected, i.e., 3·7% (11/299), this is higher than the prior meta-analysis.

Hepatitis C in Africa - Epidemiologic Knowledge Gaps

The limitations of our knowledge extend beyond the uncertainty of seroprevalence to nearly all aspects of the epidemiology of HCV in Africa. The lack of community- or population-based studies prevents us from understanding risk factors for acquisition and disease progression, a fundamental first step toward screening and prevention. While the main modes of transmission in western countries are well understood, transmission lines in Africa are a mystery. It is unclear what routes would have allowed the virus to be endemic for several centuries as suggested by the high level of diversity seen in circulating strains. While in Egypt, the phylogeny of predominantly genotype 4 strains is consistent with the exposure of a contaminated parenteral therapy for schistosomiasis,[16] the varied genotypes and high level of diversity seen in strains in sub-Saharan African do not support a similar common mode of transmission. Nonetheless, contaminated needles or related products are most often cited as the dominant modes of transmission, together with procedures such as circumcision, scarification or even use of straight razors by barbers. At least some proportion of the sharp increase in HCV during the 20th century in Africa itself must be attributable to parenteral therapies and blood products.[19,20] Other reports have highlighted higher rates of co-infection with HIV and HBV, suggesting similar transmission routes.[34,35] Sexual transmission is considered an

inefficient mode of transmission for HCV; however, whether this, or transmission occurs during child birth is not known.

Insufficient data exists on the viral genotype and phylogenetic distribution throughout the African continent as well. Detailed phylogenetic analyses are also lacking, although there have more efforts to characterize the circulating strains in the last few years.[10,13,18,20,21,36] Insight from these evolutionary studies can help elucidate transmission routes and be important in defining the process of viral-host adaptation; it will be essential to include such analyses in future epidemiologic studies.

Major gaps in our knowledge also include the extent of chronicity and character of HCV disease progression in Africa. In western countries a significant proportion of infected subjects develop chronic disease; when untreated, liver failure and cancer can ensue.[4,6,8] African Americans have a slower disease progression [37] and a higher basal interferon (IFN) response to infection.[38,39] While not fully established, it is possible that higher basal IFN confers an appropriately regulated immune response that leads to a slower progression of active disease in African Americans. Interestingly, in Africa the large proportion of confirmed seropositive individuals negative for viral RNA suggest the possibility of a higher frequency of spontaneous recovery than described in western countries.[13,20,33,40] Whether similar findings would be seen in a wide range of African populations and all viral genotypes is not known, but if true would provide an opportunity to better understand the host factors driving the indolent course of disease. Cohorts are also needed to define the rate of disease progression and risk factors for accelerated progression.

Hepatitis C - Urgent questions to be addressed in Africa

The myriad questions in need of answers regarding HCV in Africa can be clustered into several major themes that are intimately linked: a) epidemiologic features, b) host genetic factors, and c) viral genetic/diversity. A clearer and more detailed epidemiologic picture derived from population and cohort studies remains the highest priority. These studies must be designed to address current transmission routes, the rate of chronicity, and the risk co-factors for both active infection, and disease progression. Recent molecular genetic studies have identified host factors that are associated with spontaneous clearance and treatment response,[41,42] although the causal mutations and associated immunologic pathways are not well understood. Interestingly, substantial allelic variation exists between geographic populations at these gene regions,[41,42] as well as phenotypic expression of HCV outcomes.[43-46] Studying the host genetic factors in large African samples may illuminate the causal variants, or identify new gene regions associated with this phenotypic outcome to HCV exposure. Additional 'race'-based variations also are associated with disease progression, with African Americans appearing to have slower rates of natural fibrosis progression compared to non-Hispanic white groups.[37] If indeed similar findings are again found, examining the underlying genetic factors may provide knowledge on the complex interplay between the host's immune system and the mutational adaptation through which the virus sustains the infection.

Finally, increasing evidence supports the origin of at least genotypes 1 and 2 in Africa well before the emergence of the worldwide epidemic. The full extent of the ancestral history and origin in humans remains to be established. Numerous questions arise naturally out of any effort to speculate on the history of this epidemic. Is there evidence for viral-host adaptive changes during this long period of endemicity? Did the virus develop adaptive changes that led to more efficient transmission over time? Did

favorable host genetic factors enable a more symbiotic relationship between host and virus? Did prior exposures to other flaviviruses, long present on the African continent, lead to favorable evolutionary traits?

Multi-Disciplinary Translational Approach to address HCV in Africa

The armamentarium of clinical and laboratory tools now in place greatly enhance epidemiologic research and make it possible to mount a decisive attack on HCV in Africa. The evolution of large, multi-disciplinary collaborations in biomedical research provides models (Figures 1 and 2) for epidemiologists, virologists, clinicians, and geneticists to bring complementary skills to the task of defining the mode of transmission, characteristics of the viral agent, and host response. Building on lessons learned from research on influenza, SARS and HIV, this model provides the ideal opportunity to demonstrate the contribution that molecular medicine can make to translational research. Epidemiology provides the foundation on which properly designed population- based cohorts can be studied and serves as the organizing force to synthesize the laboratory and clinical data. Insights from clinical medicine, immunology, virology, and molecular genetics will all be required to describe the complex symbiotic relationship we currently share with this virus. The goal of this work should be to create the basis for a comprehensive health campaign against hepatitis and therefore must also involve local public health experts in the design and conduct of the research.

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