Journal of Virus Eradication 9 (2023) 100317

Contents lists available at ScienceDirect

Journal of Virus Eradication

journal homepage: www.sciencedirect.com/journal/journal-of-virus-eradication

Barriers that prevent adults living with HBV infection from participating in clinical research: experience from South Africa

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ARTICLE INFO

Keywords:
Hepatitis B virus
HBV
Clinical research
Trials
Ethics
Barriers
Elimination
Equity
South Africa
LMIC

ABSTRACT

High profile international goals have been set for the elimination of hepatitis B virus (HBV) infection as a public health threat by the year 2030. Developing and expanding equitable, accessible translational HBV research programmes that represent real-world populations are therefore an urgent priority for clinical and academic communities. We present experiences and insights by an expert interdisciplinary group focusing on barriers that impede adults living with HBV infection from participating in clinical studies. Our viewpoint describes barriers we have identified through working in a variety of settings across South Africa, including lack of education and awareness, experiences of stigma and discrimination, challenges for governance and data management, and a burden of complex morbidity. Through identifying these challenges, we propose solutions and interventions, highlight new approaches, and provide a framework for future research.

Abbreviations: HBV, Hepatitis B Virus; WHO, World Health Organization; HIV, Human Immunodeficiency Virus; TB, Tuberculosis; HCW, Healthcare Workers; HCV, Hepatitis C Virus; eHealth, Electronic Health.

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https://doi.org/10.1016/j.jve.2023.100317
Received 18 December 2022; Accepted 18 February 2023
Available online 23 February 2023

1. Background and context

A solid evidence base for improvements in diagnosis, stratification, treatment and prevention is needed to speed up the global elimination goals for hepatitis B virus (HBV) infection.[1] The elimination agenda is being advanced by an increasing pace of research in the cure field.[2] Over 80 million people are living with chronic HBV in the WHO Africa region,[3] and there is a compelling need for clinical HBV research in these populations. However, overall HBV research has been neglected[4,5] and comprehensive studies are predominantly established in high-income settings to capitalise on existing clinical infrastructure, provision of standard-of-care treatment, electronic patient records, and healthcare resources. The majority of translational HBV work is focused in Europe, North America and Asia, while African populations have been particularly under-represented in laboratory, clinical and implementation research.

As outcomes of infection may be influenced by the HBV genotype, host genetics, and environmental factors, approaches for risk stratification and treatment developed elsewhere need to be re-evaluated in African populations.[6] Persistent inequity in research representation risks generating data and outputs that cannot be implemented in (or are inapplicable to) populations most affected, and raises major ethical challenges for the global HBV research agenda.[7] As new agents emerge for the treatment of HBV infection, these will first be made available to people who are enrolled in care and have viraemia suppressed on existing treatment. Thus those who cannot access care provision will not be offered opportunities to engage in research, are not represented in data that influences policy and practice, and cannot access new therapies. To redress this imbalance, there is an urgent need for enhanced research representation of diverse communities affected by HBV infection.

We present a viewpoint founded on the experiences of clinical research partnerships in South Africa, allowing us to report insights representing healthcare workers, researchers, and people with lived experience of HBV infection. HBV research being undertaken in these communities has been described in previous papers, which provide a backdrop and context to our experience.[8,9] We here present our perspectives to support the development of an improved evidence-base for interventions and resources that drive enhanced representation and engagement, and to inform future research enterprise. By enhancing awareness, sharing experience, and promoting dialogue, barriers to participation in research and access to clinical care can be tackled.

2. What are the challenges?

We present our viewpoint narrative in six broad themes that can provide a framework for targeted intervention, presented in turn below.

1. **Awareness and information:** despite its endemicity in South Africa, HBV has a low profile compared to other infectious diseases that are prevalent in these populations, such as HIV and tuberculosis (TB). This is further compounded by stigma and discrimination. In individuals with a recent HBV diagnosis, or among those who have not previously attended a hepatology or infection clinic, most participants have limited or no prior awareness of HBV infection or its treatment. Knowledge among front-line healthcare workers (HCW) is also limited, so information given to patients may be inadequate, incomplete or inaccurate. This lack of information was reflected in a comment made about study participants by a study nurse 'Hep B, it's something they've never heard of - it's never mentioned in our health facilities'.
2. **Trust, confidence and communication:** patients may not trust a member of a study team approaching them for the first time regarding participation in research, in comparison to routine clinical teams with whom they more commonly have had time to develop relationships. People living with HBV infection are not well represented; advocates are lacking in local communities and in public life, and personal testimony is very limited – so there is a lack of confidence in communication, and people feel inhibited or anxious in coming forward to ask for information or support. Participants commonly expect direct feedback of individual results from clinical research, but this may not be made available in ways that are accessible. Individual results are often not available in a disaggregated form (and may be generated at a later date, not clinically validated, and only analysed in anonymised form as part of a larger dataset). However, sharing overall progress updates and research outputs is crucial, but frequently not done in a way that can be accessed by the majority of study participants.
3. **Governance aspects of research participation:** while research staff recognise the integral need to gain valid informed consent for participation in clinical research, the process is onerous, off-putting and inaccessible to some participants. In a multisite study, subject to review by several distinct research ethics committees, the volume of written information can become burdensome due to specific documentation added by different sites. Those who cannot comfortably understand written information are not equitably represented unless literacy support is provided. Although ethics committees may mandate that participants be offered paper copies of study-related documents, this is often perceived as irrelevant by participants who may also be concerned about their infection being inadvertently disclosed by having study paperwork in their possession. As reported by a study nurse, 'They say consent is too long. Signing many times they become irritated; others are unable to read and write. They complain about consent and information documents - they say it's repetition and I'm just making their houses dirty with a lot of papers they are not going to use'.
4. **Challenges in follow-up:** recruitment to studies may be dependent on patients attending one or more scheduled clinic appointments. Many patients already spend long waits to see a healthcare worker, and may not be willing to further extend their appointment to participate in research, particularly when this means time away from work, childcare or other domestic responsibilities. Travel to appointments is costly and cumbersome, which can be a further barrier to attending regular follow-up. Many patients use traditional medicines before seeking hospital-based treatment, posing challenges for prompt and consistent engagement with clinical care. Tenofovir monotherapy, the first line standard-of-care therapy for HBV, is not available in all settings, and only a minority of patients are eligible, which disincentivizes attendance for follow-up. Vaccination services for uninfected sexual partners are not widely available, missing opportunities to create awareness and household engagement in both screening and HBV prevention.
5. **Burden of morbidity:** individuals with complex health concerns may be too unwell to give informed consent, may be exhausted by conflicting healthcare needs, and may perceive HBV infection as a lower priority than competing physical, psychological and social concerns. Mental health problems are common, as reported by a study nurse: 'I find some patients depressed, having suicidal thoughts'. In some cases, alcohol excess is a specific barrier to engagement. In these instances, a multidisciplinary approach is essential to support and prioritise diverse needs. Interestingly, in patients with diagnosed HIV coinfection, education, engagement, resources and access to treatment may be better than for HBV monoinfected individuals.
6. **Information linkage:** accessing clinical results depends on consistent patient identifiers. However, different services use varied approaches, making it difficult or impossible to link healthcare records. Individuals may be mobile between regions, and even within one setting can present to different services. Inconsistent identifiers arise commonly (e.g. varied versions or spellings of name, and uncertain dates of birth), while frequent changes in contact details for patients cause problems in consistency of care and scheduling follow-up

clinic visits. This is a large burden for research staff and often results in a failure to maintain connections with patients (whether or not they are participating in research).

3. How can we drive improvements?

We have highlighted complex barriers for people living with HBV to participate in research programmes. Awareness of these challenges can provide a foundation for practical changes and for research to generate evidence to inform approaches for patient-centric solutions (Table 1).

Provision of better information and education is essential; this must be tailored to the needs of individuals and the community to make it accessible and relevant. Engagement of routine clinical teams in the research pathway provides a route to information from a trusted source, and this process could be strengthened through provision of trained counsellors, ideally linked to and representing local communities. There is growing evidence for the role of peer support, although this mainly comes from experience in management of HCV and HIV to date.[10,11] Tackling stigma through education, access to clinical care and participation in clinical trials begins to redress its impact[12]; thus there is a positive feedback loop in which reducing stigma promotes better research representation, which in turn further tackles stigma. HBV research now has the potential to inform rapid changes in clinical management; a holistic and integrated approach is of benefit across the clinical-research spectrum, for example by linking HBV initiatives to other domains (which might include maternal and child health, mental health, sexual health, and HIV services). Applying learning across these clinical areas will ultimately result in better use of resources, sharing of skills, and delivery of holistic care provision.

Table 1
Summary of barriers to participation of adults with HBV in clinical research in South Africa, with suggested strategies for tackling challenges to reduce inequity.

Domain	Barriers	Strategies
Awareness and information	> Limited education > Low profile of HBV > Stigma and discrimination > Poor patient knowledge about treatment	> Provision of accessible, relevant information and education for patients, families and healthcare workers. > Multimedia approaches to provision of information. > Peer supporters/ counsellors to provide education, including patients' knowledge about their own treatments.
Trust, confidence and communication	> Lack of relationship with research team > Poor access to real-time feedback from research	> Integrated clinical/ research pathways. > Management of expectations around participation in research. > Timely access to feedback and outputs from research programmes. > Patient involvement in planning and communicating research. > Involvement of peer supporters and community networks.
Governance	> Overwhelming/ inaccessible information and consent process	> Optimisation of amount, nature and presentation of information. > Use of images, audio and video information.
Challenges in follow-up	> Time, economic cost and disruption of appointments on work and domestic commitments > Lack of access to tenofovir monotherapy	> Reimbursement where relevant. > Streamlining of combined clinical/research appointments. > Access to therapy (reliable and affordable treatment).
Burden of morbidity	> Complex multimorbidity, including physical and mental health concerns	> Management of HBV alongside other comorbid conditions. > Integrated services (e.g. combined HIV/HBV screening and care, psychosocial support).
Information linkage	> Poor data linkage between services > Mobile populations with frequent changes in contact details.	> Improved use of smart technology to identify patients, and link them to clinical services. > Incentivisation to stay linked to care include all points in above domains.

We highlight the essential need for study documentation that is appropriate and accessible to the target population. We suggest provision of a brief patient information sheet (akin to a simple abstract of the study, aimed at a lay audience), accompanied by an infographic or flow diagram to provide a basic visual summary (an example we have generated is available on-line[13]). Provision of audio or video information may also be helpful. There is growing experience to support use of digital consent to reduce unwieldy paperwork and streamline the process.[14]

Clinical research teams should work with research participants, people with lived experience of HBV, and with ethics committees, to co-design studies,[15] with structured mechanisms to engage the HBV community and promote patient voice.[16] Management of expectations for study participants is important, so that they receive timely and relevant feedback, and can access updates and outputs from the study.

Lack of consistent access to tenofovir monotherapy is a crucial issue for many resource-limited settings, despite tenofovir being on the WHO List of Essential Medicines.[17] Advances in public health and policy are urgently needed to address this unmet demand. Maintaining patient engagement with clinical services is vital, as access to current therapies will expand and to keep patients informed about newer HBV therapies and opportunities to participate in trials. For people with significant comorbidity, providing integrated care will be important, for example building on existing clinical services that tackle both HIV and HBV, or combining HBV care with services for other chronic diseases. Enhanced opportunities for education and advocacy that are created by research programmes can be used as a platform for providing better access to diagnosis and treatment, with influence beyond the immediate scope of the study.

The HBV field offers opportunities for better integration of 'eHealth' technology. For example, capitalising on the widespread use of smartphones can provide a consistent means of linking participants to the research programme, as well as for providing education, connections to trusted care providers and/or peer support, clinic reminders and updates on the progress and outputs of the study.[18,19] As long as undertaken with consent, and worded to avoid disclosure if intercepted by an unintended recipient, this can use existing messaging platforms and does not mandate the design of bespoke apps. Optimising connectivity may allow remote follow-up, thus reducing the burden of repeat clinic visits, although there are challenges related to frequent change of mobile phone numbers. For some studies, reimbursement is important, in recognition of time invested and economic impact of participation in research, and to avoid systematic exclusion of the most deprived groups.

4. Discussion and conclusions

Our viewpoint is based on diverse interdisciplinary experience, and forms a preliminary foundation that can inform future work to formalise an evidence base for enhanced practice. Given the neglect of HBV to date, and the prevalence of knowledge gaps, poor representation, stigma, and lack of access to first line treatment, special focus is

required, although many of the themes we highlight may also be relevant to managing other health challenges. Some of our learning points may be of wide utility to clinical research, while other observations may be more specific to the local context in South Africa. Formal qualitative research in this domain is needed to represent the needs and challenges faced by different communities, and to advance insights into perspectives of researchers, clinicians, and people with lived experience of HBV. Tackling barriers to participation in research offers improved opportunities for engagement, contributes to redressing health inequity, delivers research that represents the communities with the greatest needs, and sets the scene for optimum access to new therapies as these become available.

Funding

PCM is funded by Wellcome (Grant ref. 110110/Z/15/Z and 110110/Z/15/C) and also receives funding from the UCLH/UCL NIHR Biomedical Research Centre (BRC). This work was also supported by the Francis Crick Institute which receives its core funding from Cancer Research UK, the UK Medical Research Council, and the Wellcome Trust (ref. CC2223).

Ethics

The studies that formed the backdrop for this perspective are approved by Oxford Tropical Research Ethics Committee (ref. 1–18), Stellenbosch University (ref. N17/01/013) and The University of the Free State (UFS-HSD2018/0193–0001). Specific ethical approval was not required for this viewpoint.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

PCM – funding receipt from GSK to support a PhD student (independent of the submitted work).

VM – Editorial Board for the Journal of Virus Eradication.

Data availability

No data was used for the research described in the article.

Acknowledgements

We are grateful to clinical and research staff in South Africa and the UK, and to patients approached to participate in our study in Cape Town and Bloemfontein, South Africa. This material has also been presented as a poster at the on-line Conference on Liver Disease in Africa (COLDA), 2021; https://doi.org/10.6084/m9.figshare.16685047.v1.

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