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"When to treat" in people living with hepatitis B in Africa: A discrete choice experiment assessing health worker preference

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LIST OF ACRONYMS

ALT	Alanine transferase enzyme
APRI	Aspartate aminotransferase-to-platelet ratio index
cccDNA	covalently closed circular DNA
CGHE	Coalition for Global Hepatitis Elimination
CHB	Chronic hepatitis B
DCE	Discrete choice experiment
DNA	Deoxyribonucleic Acid
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCW	Health care worker
HEPSANET	Hepatitis B in Africa Collaborative Network
HIV	Human immunodeficiency virus
LMIC	Low and middle-income countries
NNT	Number needed to treat
OOP	Out-of-pocket
PLWHBV	People living with hepatitis B virus
RT-PCR	Real-time polymerase chain reaction
TDF	Tenofovir disproxil fumarate
USD	United States dollar
WHO	World Health Organization

ABSTRACT

Title: 'When to treat' in people living with hepatitis B in Africa; A discrete choice experiment assessing health workers' preference.

Background: Chronic HBV infection presents silently with no noticeable symptoms and can take decades to lead to complications like hepatocellular carcinoma. Guidelines recommend identifying individuals at high risk and providing them with antiviral therapy. This study assessed health workers' preferences regarding when to recommend initiating antiviral therapy for people with chronic HBV infection in Africa.

Objectives: To evaluate stated treatment preference, treatment eagerness, and predict acceptance of specific treatment profiles.

Method: A single profile discrete choice experiment (DCE) was conducted among African healthcare workers (HCWs) using an online questionnaire survey. The DCE included the following attributes; benefit (number needed to treat, NNT), duration, out-of-pocket costs, and safety. We quantified the utility gain or loss generated by each attribute using a binary logistic model, evaluated treatment eagerness via a choice certainty scale with linear regression, and modeled predicted acceptance of specific treatment profiles.

Results: Increase in levels of NNT, treatment duration, cost, and safety all generated significant disutility. The effect size of the highest attribute level relative to the reference was in the order: cost (OR 0.02, 95%CI [0.01; 0.03]), benefit (OR 0.07, 95%CI [0.04; 0.10]), duration (OR 0.35, 95%CI [0.19; 0.35]), safety (OR 0.34, 95%CI [0.26; 0.44]). Attributes' impact on treatment eagerness was similar. 30% of rational participants were pro-treat-all, comprising mainly midwives and public health practitioners. 90% of HCWs will recommend treatment at a monthly cost of up to 100 USD for a benefit of 8 NNT if treatment duration is one year with rare adverse events.

Conclusion: Out-of-pocket costs, treatment benefits, duration, and safety significantly influence HCWs recommendations for initiating antiviral therapy, with out-of-pocket medication cost being the most influential factor.

Keywords: Hepatitis B, Africa, anti-viral therapy, DCE.

Introduction

Hepatitis B Virus (HBV) infection is a major public health concern. In 2019, the World Health Organization (WHO) estimated that about 296 million people globally are living with chronic HBV infection, with 1.5 million new infections annually, and an estimated 820,000 deaths.[1] The burden of HBV is disproportionately distributed, with the highest burden found in sub-Saharan African and Western Pacific regions, where 5 – 10% of the adult population is chronically infected.[2]

To eliminate viral hepatitis as a major public health threat by 2030, the WHO set a target to reduce new infections by 90% and deaths by 65% respectively.[2] These goals will require accelerated efforts that are effective and tailored to the specific contexts of different locations, populations, and settings to achieve maximum impact.

The WHO HBV guidelines published in 2015 recommend treatment in individuals with cirrhosis based on clinical evidence or aspartate aminotransferase-to-platelet ratio index (APRI) score. In the absence of cirrhosis, treatment is recommended for those who have abnormal ALT levels and elevated HBV DNA levels.[3] A recent systematic review and meta-analysis, commissioned by the WHO, confirmed that the baseline HBV DNA level is one of the most important determinants of the incidence rate of hepatocellular carcinoma (HCC) and other clinical endpoints.[4] However, applying these treatment eligibility criteria based on HBV DNA levels poses challenges as this requires real-time polymerase chain reaction assays (RT-PCR). RT-PCR is not widely accessible in LMICs because of its high cost and the limited skilled laboratory workforce.

Considering the limited access to diagnostic tests required to assess the existing treatment eligibility criteria, a “Treat All” approach has recently emerged as an attractive alternative in LMICs.[5] The idea is to offer antiviral therapy to everyone with a positive hepatitis B surface antigen (HBsAg), avoiding the need for quantification of viral load, ALT levels, and liver fibrosis stage, before initiating antiviral therapy.

Implementing a “Treat All” approach could potentially reduce the costs associated with diagnostic tests to assess treatment eligibility. However, as a trade-off, this strategy may lead to overtreatment in an important proportion of individuals with a low risk of liver disease progression. This could result in exposing them to a minor risk of side effects and placing them under a lifelong financial burden associated with antiviral therapy, particularly in countries where there is no subsidization for hepatitis care.[6] A modeling study conducted in The Gambia, a low-income country, evaluated different strategies for determining eligibility for anti-HBV treatment. The study concluded that compared to other approaches that rely on costly or

complex laboratory and clinical staging, a 'treat-all' approach would be the most effective in reducing HBV-related deaths. However, its high implementation cost prevents the strategy from being cost-effective in this specific context.[6]

Our objective was to conduct out an online questionnaire survey using a discrete choice experiment to elicit the preferences and trade-offs of prescribers in Africa. Specifically, we aimed to investigate healthcare workers' (HCWs) preferences regarding when to initiate antiviral therapy, focusing on the following attributes: the clinical benefits of antiviral therapy, the duration of antiviral therapy, the out-of-pocket costs of antiviral therapy, and the safety profile of antiviral therapy. This study provides valuable insights into the factors that weigh most heavily on healthcare workers in Africa when deciding to advise people living with chronic HBV (PLWHBV) infection to initiate antiviral treatment.

Objectives

Primary objective

1. To evaluate the stated preferences of health professionals focusing on four attributes of antiviral therapy; the clinical benefits, duration, out-of-pocket costs, and safety profile

Secondary objectives

1. To evaluate the certainty of stated treatment preferences
2. To model predicted acceptance of specific treatment profiles

Method

Study Design

This study employed a discrete choice experiment (DCE) method. DCE is a well-established quantitative method used to elicit stated preferences between hypothetical scenarios to understand people's preferences when faced with different options.[7] DCEs are well recognized as a valuable method for addressing health policy issues by utilizing the stated preferences of relevant stakeholders.[8] The assumption is that rational individuals will always choose alternatives with higher levels of benefit.

This study was a cross-sectional survey of health care workers in Africa. Participants were invited to participate in a self-administered internet-based questionnaire hosted on the REDCap platform. The experimental design presented a series of eight clinical scenarios, each featuring a distinct combination of four attributes: the clinical benefits of antiviral therapy, duration of antiviral therapy, out-of-pocket costs of antiviral therapy, and safety profile of

antiviral therapy. For each scenario, participants were asked to choose whether they would advise initiating antiviral therapy, thereby providing valuable insights into their preferences.

Study Participants

All healthcare workers (HCWs) including medical doctors, pharmacists, nurses, laboratory staff, and public health practitioners, working in Africa were eligible for the study. Survey invitations were sent via email to HCWs listed in an existing database of stakeholders involved in hepatitis B projects. This study secured collaboration with the Coalition for Global Hepatitis Elimination (CGHE) and Hepatitis B in Africa Collaborative Network (HEPSANET), which supported the dissemination of the questionnaire across the African continent. A chain-referral sampling technique, encouraging participants to share the survey within their professional network, was employed to ensure wide dissemination of the survey. At least 300 responses were expected.[9] Participation in the study was completely anonymous at all stages and informed consent was not required from participants.

Questionnaire

The DCE questionnaire was designed as a single-profile DCE and comprised four parts: (i) an introduction explaining the study rationale and describing the pros and cons of antiviral therapy and the complexity of considering multiple factors simultaneously before advising an individual on whether to initiate antiviral therapy; (ii) a detailed description of the clinical context in which choices should be made including the attributes and their levels; (iii) a discrete choice experiment with eight choice scenarios; and (iv) a short questionnaire about survey respondents.

For the DCE, participants (HCWs) were asked to imagine a clinical context in which he/she is: “A healthcare worker in a clinic situated in a low-income area, where many adults live on less than US$ 65 per month. The clinic provides care for individuals with chronic HBV infection, and he/she is responsible for prescribing antiviral treatment. The participant considered a 35-year-old adult who was incidentally found to have chronic HBV infection during a blood donation. The infected individual could be either a male or a female (who has decided not to have additional children) and does not have any symptoms, any significant past medical history, does not smoke or drink alcohol, isn’t taking any medications, and shows no signs of kidney problems.” Based on the imaginary clinical context, participants were asked to choose whether they would advise initiating antiviral therapy in eight choice tasks that differed based on varying levels of the four attributes (

Figure 1).

DCE Attributes and Levels

To define the attributes and levels of the experiment, a comprehensive review of the literature on hepatitis B was conducted, including the previous (published in 2015) and updated (in 2024) WHO guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection.[3, 4] In-depth discussions were held with experts in hepatitis B management, epidemiology, statistics, research, and general practice, to refine and improve the attributes and corresponding levels. The final DCE tool includes the following attributes;

1) **Clinical benefit of antiviral therapy (four levels)**

The primary objective of antiviral therapy for chronic HBV infection is to improve survival by preventing cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[3] Among these key clinical endpoints, this study focused on HCC. Given the variability in the risk of developing HCC based on baseline clinical parameters, such as HBV DNA levels, ALT levels, and liver fibrosis stage, it is important to individually assess the underlying risk of the event in people living with HBV. Additionally, the efficacy of treatment in preventing HCC may also vary according to the baseline clinical characteristics, such as HBV DNA levels.[10] To address the natural progression of chronic HBV infection and the efficacy of antiviral therapy concurrently, this study presents the clinical benefit of antiviral therapy as the number needed to treat (NNT) to prevent one case of liver cancer over the next 20 years.

To determine the NNT over the next 20 years for people infected with HBV but without cirrhosis stratified by HBV DNA levels, we extracted data from systematic reviews and meta-analyses. This included the incidence rate (per 100) of HCC based on the natural history and the relative risk of developing HCC in individuals treated with antiviral therapy. The 20-year cumulative incidence was calculated by relating the incidence rate with cumulative incidence, as outlined in a study conducted by Suissa et al in the following way;[11]

$$\mathbf{CI = (1 - \exp^{-IR \times t})}$$

where CI is the cumulative incidence of developing HCC up to time *t* (20 years) and IR is the incidence rate of HCC in untreated HBV-infected individuals. The NNT over 20 years was then derived using $\mathbf{1/(CI_0 - CI_1)}$, where CI_0 is the cumulative incidence of HCC in HBV-infected patients without antiviral therapy and CI_1 is the cumulative incidence of HCC in HBV-infected patients receiving antiviral therapy. CI_1 was obtained by multiplying CI_0 by the relative risk of developing HCC in individuals treated with antiviral therapy This study considered four levels of NNT as follows: 10, 50, 100, 1000.

2) Duration of antiviral therapy (two levels)

This study primarily considered tenofovir disproxil fumarate (TDF), as it is the most commonly available anti-HBV drug in Africa.[12] Current anti-HBV therapies, including TDF, often fail to achieve functional cure due to the presence of covalently closed circular DNA (cccDNA) and integrated HBV DNA.[13] As a result, complete virus elimination is rare, leading to the necessity of potentially lifelong treatment.[3] However, novel antiviral and immunomodulatory therapies that aim to provide finite treatments leading to functional cure (i.e., clearance of HBsAg) are currently undergoing clinical development.[14] This experiment considered two levels of treatment duration: infinite (20 years) and finite (1 year).

3) Out-of-pocket cost of antiviral therapy (four levels)

Following negotiations and alignments for HIV treatment pricing, the annual costs of generic tenofovir have largely declined to about US$ 30 as reported in the WHO's global report on HIV, viral hepatitis, and sexually transmitted infections.[15, 16] According to the World Bank, many of the adult population in Africa live on less than US$ 2.15 per day (about US$ 65 monthly).[17, 18] TDF is widely available and approved in many African countries for treating both HIV and HBV.[12, 19] However, while HIV programs often receive sufficient funding, resources for hepatitis programs are limited. As a result, TDF treatment for HBV does not benefit from the same level of subsidized funding from the government or donor organizations. Consequently, while HIV/HBV co-infected individuals receive free/subsidized TDF treatment through donor agencies, many individuals mono-infected with HBV must bear the out-of-pocket costs for their TDF medication, unless they have health insurance coverage.[12] This study considered four levels of treatment cost: US$ 0 monthly (free), US$ 3 monthly, US$ 50 monthly, and US$ 500 monthly.

4) Safety profile of antiviral therapy (two levels)

Like other nucleoside analogues, TDF has a good safety profile, but adverse events could occur especially with long-term use.[8] A systematic review indicated that the most frequently observed adverse events associated with nucleoside analogues include laboratory abnormalities (18.8%), gastrointestinal disorders (15.3%), infections and infestations (13.1%), general disorders (9.8%), and nervous system disorders (7.9%).[20] However, there is also the risk of serious adverse events such as bone fracture and kidney impairment associated with TDF use.[21, 22] The frequency of both mild and serious adverse events varies, ranging from rare to very common.[23] This study evaluated treatment safety by the frequency of serious adverse

events, classified into two levels: rare (estimated to occur in less than 0.1% of individuals) and common (estimated to occur in 1-10% of individuals).[23]

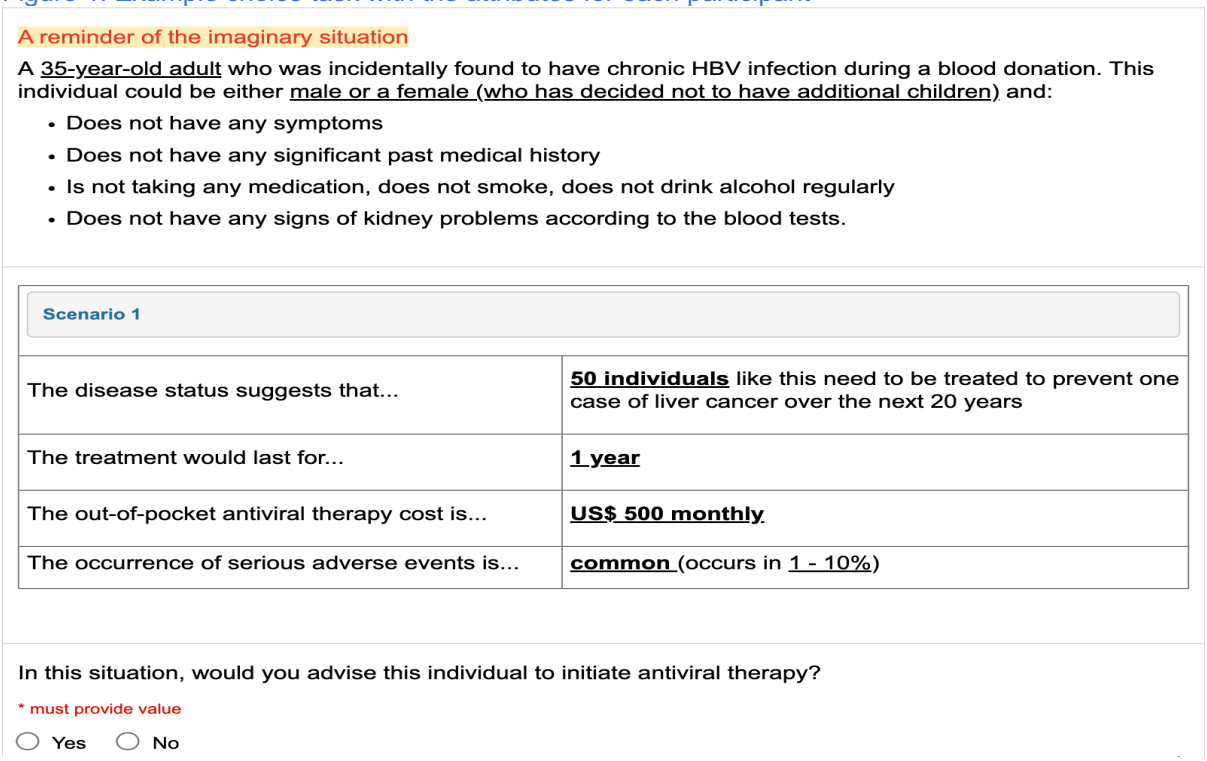
The levels set for each DCE parameter is described in

Table 1.

Table 1: Attributes and levels of the discrete choice experiment

Factor	Label	Definition	Level	Hypothesis
Clinical benefit of antiviral therapy	Benefit (NNT)	The number of individuals of this kind who would need to be treated to prevent one case of liver cancer	10 50 100 1000	Reference OR < 1 OR < 1 OR < 1
Duration of antiviral therapy	Duration	The duration of treatment	Finite (1 year) Infinite (at least 20 years)	Reference OR < 1
Out-of-pocket cost of antiviral therapy	Cost	The monthly out-of-pocket costs for antiviral treatment	Free US$ 3 per month US$ 50 per month US$ 500 per month	Reference OR < 1 OR < 1 OR < 1
Safety profile of antiviral therapy	Safety	The frequency of serious adverse events (such as kidney damage or bone fractures)	Rare (estimated to occur in less than 0.1% of individuals) Common (estimated to occur in 1-10% of individuals)	Reference OR < 1

Figure 1: Example choice task with the attributes for each participant



Experimental Design

Using STATA 17.0, the relevant combinations of attributes were crafted to obtain 16 choice tasks. In line with good DCE practice, these tasks were divided into two blocks, each containing eight choice tasks.[24] Participants were randomly assigned to one of these blocks using a randomization function in REDCap. This block experimental design was adopted for two reasons: (i) to encourage more thoughtful responses from participants by minimizing the number of choice tasks, thereby reducing the likelihood of experiencing decision fatigue, and (ii) for an efficient design ensuring responses cover the full range of choice tasks without presenting all possible choice tasks to each participant.[25] To evaluate rational responses from respondents, we identified all dominant pairs of scenarios within each block, where one scenario was superior to the other (Annex 1). Respondents were deemed “irrational” if they opted to advise against antiviral therapy for the superior scenario but choose to advise antiviral therapy for the inferior scenario within any of the identified dominant pairs.

Statistical Analysis

The statistical analysis included only complete responses from eligible participants.

Objective 1: Evaluating response patterns in rational and irrational responders

Within each block, we identified dominant pairs of scenarios where one scenario consistently showed equal or superior levels across all four attributes compared to the other scenario. In total, 7 and 11 dominant pairs of scenarios in block 1 and block 2 were identified respectively (Annex 1). Participants were classified as “irrational” if they chose “No” for a superior scenario and "Yes" for an inferior scenario within any of the predetermined dominant pairs, and “rational” otherwise. We described participant characteristics based on this classification and evaluated the difference in response patterns between rational and irrational participants using Fischer’s exact (for cell values less than 5) and chi-squared tests as appropriate. We compared the median time to complete the questionnaire between the two groups using the Mann-Whitney U test and excluded irrational participants from further analysis.

Objective 2: Estimating the impact of attributes and levels on treatment preference of rational non-uniform responders

To assess the impact of attributes on stated treatment preference, we excluded uniform responders who consistently responded "Yes" (labeled "pro-treat-all") or "No" (labeled "never-treat") across all hypothetical scenarios since these participants do not provide any information regarding the probability of making a treatment choice based on the varying attribute levels. A random effects binary logistic regression model was employed to estimate the impact of the four attributes (benefit, duration, out-of-pocket cost, and safety) on the stated treatment preference of participants. Models with fixed effects specification yielded similar results (Hausman tests comparing fixed and random effects specifications not significantly different from 0 at $p<0.05$). Results were presented as odds ratios for each attribute level. For the benefit and cost attributes (having 4 levels each), linear relationship between the attribute levels and coefficient values was assessed using a scatter diagram and fitting a regression line. We calculated average marginal effects to estimate average changes in the probability of recommending treatment for each attribute level. We hypothesized that participants' profession and involvement in hepatitis care could influence their stated treatment preferences. Specifically, we posited that the different attributes (benefit, duration, out-of-pocket costs, and safety) might weigh differently between participants from different professions, and for those involved in hepatitis care compared to those not involved. We explored the interaction between participant characteristics (profession, hepatitis care involvement) and each attribute.

Objective 3: Investigating the determinants of uniform responses (pro-treat-all and never-treat) compared to non-uniform responses

We described the characteristics of "pro-treat-all", "never-treat", and non-uniform responders and investigated the differences in their characteristics. In univariate analysis, we estimated the effect of each characteristic on participants' response patterns. Excluding the never-treat responders due to limited sample size (n = 8), a binary logistic regression model (including only covariates significant at less than 0.20 level in univariate analysis) was used to estimate the adjusted effect size of individual characteristics on participants' likelihood of being "pro-treat-all" compared to non-uniform.

Objective 4: Evaluating the treatment preference of pro-treat-all and never-treat responders using choice certainty

Since uniform responders offer limited insight into their underlying preferences, we hypothesized that the choice certainty scale provides more amplitude for expressing preferences compared to binary choices.[26] Choice certainty scales consider the level of uncertainty surrounding a hypothetical decision, potentially offering a more accurate representation of real-life decision-making processes.[26] We estimated the effect of attribute

levels on the choice certainty of pro-treat-all and never-treat responders using a random effects linear regression model. We assumed that higher choice certainty correlates with a greater likelihood of maintaining the same decision in real-life scenarios, irrespective of the choice made.[26, 27] We described the threshold benefit (NNT) level above which pro-treat-all will not recommend treatment (having fixed the levels of duration, cost, and safety attributes).

Objective 5: Development of a treatment eagerness scale to evaluate the impact of attributes on the choice certainty of all rational responders

To assess the impact of attributes on the certainty of participants' stated treatment preference, we developed a "treatment eagerness" scale by transforming the original certainty scale ranging from 0 (not certain) to 10 (perfectly certain). The new treatment eagerness scale ranged from -10 to +10, with negative scores (-10 to -1) indicating a preference against treatment ("No" choice) and positive scores (+1 to +10) indicating a preference for treatment ("Yes" choice). A score of -10 represents strong certainty against treatment, +10 represents strong certainty for treatment, and 0 indicated high level of uncertainty. We evaluated the effect of attributes on participants' treatment eagerness using a random effects linear regression.

Objective 6: Modelling predicted treatment acceptance

For non-uniform responders, we calculated the predicted treatment acceptance for specific scenarios. Assuming linearity of the coefficients and attribute levels, we computed utility for specific scenarios by summing the losses or gains for the respective combination of attribute levels using the formula:

$$\textbf{Utility} = \alpha + \beta_1 \textbf{benefit}*(\textbf{Benefit} - 10) + \beta_2 \textbf{Duration} + \beta_3 \textbf{Cost}*(\textbf{Cost} - 0) + \beta_4 \textbf{Safety}$$

where α represents the intercept, β_1, β_2, β_3, and β_4 represent the coefficients of the benefit, duration, cost, and safety attributes respectively.

We estimated the predicted treatment acceptance using the function:

$$\textbf{Predicted treatment acceptance} = 1/[1 + e^{-\textbf{utility}}]$$

A treatment acceptance probability of 70% was applied as the minimum threshold at which health professionals are willing to recommend treatment for a given treatment characteristic.

Sensitivity Analysis

We hypothesized that the survey response time of participants could influence the quality of their stated treatment preferences. The survey completion time was available for all participants, with an average of 8.7 minutes (range; 2.2 – 2029.4 minutes). We defined “fast response” as a completion time below the 25th percentile (< 6.6 minutes) of all participants' response time. To assess the potential impact of rapid response on our results, sensitivity analysis was conducted on the average marginal effects of treatment attributes on the probability of recommending treatment for rational non-uniform responders excluding “fast response” participants. All statistical analysis was conducted using STATA.

Ethics

This study was completely anonymous and did not collect any personally identifiable information. The questionnaire requested only general information, and participants were reminded not to provide any personal data. The study was granted an exemption from review by the Institutional Review Board (IRB) at Institut Pasteur (IRB2024-D-Exempt) on 5 April 2024. All collected data were securely stored on the REDCap server owned by the Institut Pasteur.

Results

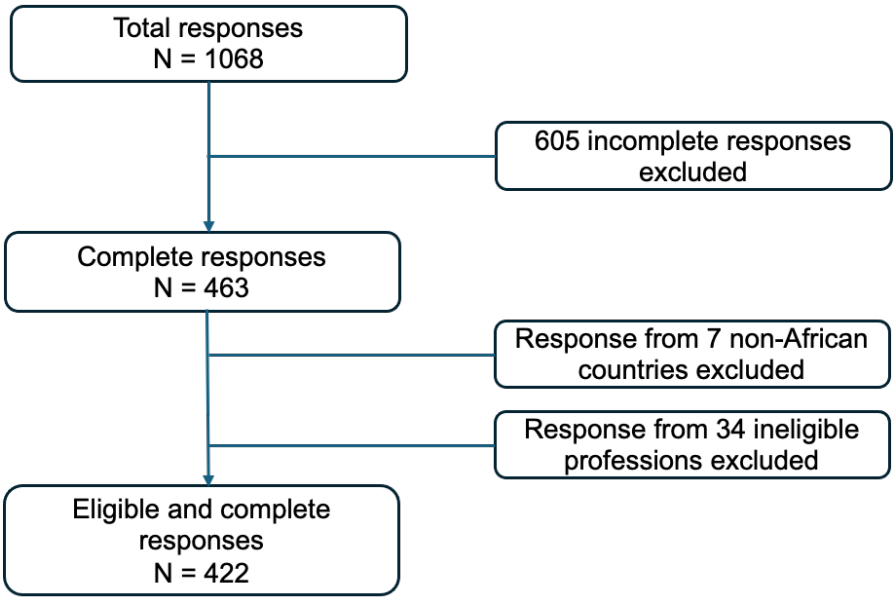


Figure 2: Participant inclusion flowchart

Participant characteristics

Among the 1068 respondents, 422 eligible participants with valid and complete responses were included in the analysis after excluding incomplete responses and 41 ineligible participants (Figure 2). Table 2 shows the distribution of participant characteristics. Most participants were between 30 and 50 years of age (67.8%), with males being predominant (62.1%). Professionally, participants included doctors (61.6%), pharmacists (7.3%), nurses (5.9%), midwives (1.9%), laboratory staff (5.2%), and public health practitioners (17.1%). Medical doctors were mostly general practitioners (47.3%), and hepatologists (30.8%), with the remainder specializing in surgery, infectious disease, and other medical specialties (dentistry, gynecology, pediatrics, and pathology). Participants worked in various healthcare settings, including national hospitals (25.8%), regional hospitals (15.6%), private hospitals (15.4%), district hospitals (11.9%), primary care (10.0%), and the public health sector (17.8%). Geographically, the participants were spread across all African regions; Central (4%), East (34.8%), North (19%), South (5%), and West (37.2%). More than two-thirds (67.1%) of the healthcare workers were involved in hepatitis care. A similar proportion (66.4%) could prescribe antiviral therapy, and 56.9% have a history of prescribing antiviral therapy.

Objective 1: Evaluating response patterns in rational and irrational responders

In the full sample (n = 422), 357 (84.6%) participants consistently responded rationally and termed “rational responders”, while 65 (15.4%) participants termed “irrational responders” made at least one irrational response across the eight choice tasks (Table 2). Participants over 50 years of age (90.7%) made more rational responses compared to younger participants. The distribution of rational and irrational responders was similar between male and female participants (84.4% vs. 85.5%). Professionally, nurses made the least rational responses (72.0%), while over 80% of the other professions were rational responders. Doctors’ medical specialty was significantly associated with the likelihood of making rational or irrational responses. Notably, medical doctors specializing in infectious diseases exhibited a higher propensity for rational responses (100%) than other medical specialties. Rational and irrational responders exhibited significantly different response patterns to the choice tasks (Annex 2). Additionally, the survey completion time of irrational responders was markedly shorter compared to rational responders (median time; 6.6 minutes vs 8.7 minutes, p=0.04) (Annex 3). This suggests that irrational responders may have insufficiently engaged in the cognitive evaluation of the choice tasks and the necessary trade-offs.

Table 2: Participant characteristics and their association with being rational or irrational responders

	Full sample (N = 422)		Rational responders (n = 357)		Irrational responders (n = 65)		
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**	**p-value**
Age group (years) **							
< 30	82	19.4	67	81.7	15	18.3	0.348
30 - 50	286	67.8	241	84.3	45	15.7	
> 50	54	12.8	49	90.7	5	9.3	
Gender *							
Male	262	62.1	221	84.4	41	15.6	0.163
Female	159	37.7	136	85.5	23	14.5	
Other	1	0.2	0.0	0.0	1	100.0	
Profession *							
Doctor	260	61.6	223	85.8	37	14.2	0.541
Pharmacists	31	7.3	25	80.6	6	19.4	
Nurse	25	5.9	18	72.0	7	28.0	
Midwife	8	1.9	7	87.5	1	12.5	
Laboratory staff	22	5.2	19	86.4	3	13.6	
Public health practitioner	72	17.1	62	86.1	10	13.9	
Other	4	1.0	3	75.0	1	25.0	
Medical Specialty *							
General practitioner	123	47.3	102	82.9	21	17.1	0.034
Hepatology	80	30.8	68	85.0	12	15.0	
Surgery	9	3.5	8	88.9	1	11.1	
Infectious disease	35	13.4	35	100.0	0	0.0	
Others	13	5.0	10	76.9	3	23.0	
Work sector *							
Public/Primary care	42	10.0	35	83.3	7	16.7	0.320
Public/District hospital	50	11.9	41	82.0	9	18.0	
Public/Regional hospital	66	15.6	60	90.9	6	9.1	
Public/National hospital	109	25.8	93	85.3	16	14.7	
Private	65	15.4	53	81.5	12	18.5	
Public health sector	75	17.8	60	80.0	15	20.0	
Other	15	3.5	15	100.0	0	0.0	
Region *							
Central	17	4.0	12	70.6	5	29.4	0.295
East	147	34.8	127	86.4	20	13.6	
North	80	19.0	66	82.5	14	17.5	
South	21	5.0	20	95.2	1	4.8	
West	157	37.2	132	84.1	25	15.9	
Hepatitis B care involvement **							
No	139	32.9	119	85.6	20	14.4	0.686
Yes	283	67.1	238	84.1	45	15.9	
Ability to prescribe antiviral therapy **							
No	142	33.6	115	81.0	27	19.0	0.143
Yes	280	66.4	242	86.4	38	13.6	
Ever prescribed antiviral therapy **							
No	182	43.1	154	84.6	28	15.4	0.993
Yes	240	56.9	203	84.6	37	15.4	

* Fischers' exact test, ** Chi-square test

Objective 2: Estimating the impact of attribute levels on treatment preference of rational non-uniform responders

In the sample comprising only rational non-uniform responders (n = 268), all attribute levels significantly impacted the treatment preferences of health professionals in a clear dose-response pattern (Table 4). Adjusting for other attributes and compared to the reference for treatment benefit (NNT 10), the odds of recommending treatment consistently decreased as the NNT increased to 50 (OR 0.47, 95% CI[0.31; 0.70]), 500 (OR 0.19, 95% CI [0.12; 0.29]), and 1000 (OR 0.07, 95% CI [0.04; 0.10]). The likelihood of recommending treatment was reduced by 0.35-fold [CI 0.19; 0.35] for a treatment duration of 20 years compared to one year. Similarly, increased out-of-pocket medication costs negatively impacted treatment recommendations. Relative to no cost, the odds of recommending treatment dropped by 65% (OR 0.35, 95% CI [0.23; 0.50]) at a cost of 3 USD, 85% (OR 0.15, 95% CI [0.10; 0.22]) at a cost of 50 USD, and by 98% (OR 0.02, 95% CI [0.01; 0.03]) at a cost of 500 USD. Similarly, an increased occurrence of serious adverse events from rare to common was associated with a decreased likelihood of recommending treatment by 0.34-fold (95% CI 0.26; 0.44). Considering the attributes as continuous given the linear correlation between the benefit and cost attribute levels and the corresponding coefficient values (Annex 7), a unit increase in both the benefit and cost attributes generated significant disutility by (β = -0.002, 95% CI[0.99; 0.99]), and (β = -0.006, 95% CI [0.99; 0.99]) respectively. Utility decreased (β = -0.052 [95% CI 0.93; 0.96]) with each additional year of treatment. Increase in the frequency of adverse events from rare to common reduced utility by β = -0.796 [95% CI 0.35; 0.56] (Table 4).

In the marginal effect analysis (Table 4, Figure 3A), the average probability of recommending treatment significantly decreased by 9% when the benefit increased from "10 NNT" to "50 NNT," by 21% for an increase to "100 NNT," and by 37% for an increase to "1000 NNT." Increasing the treatment duration from 1 year to 20 years reduced the probability of recommending treatment by 18%, and the probability decreased by 14.3% when the frequency of serious adverse events increased from rare to common. An out-of-pocket medication costs of 500 USD had the most substantial negative impact on treatment recommendations, reducing the probability by 55.9% compared to no cost (0 USD). However, when the benefit, duration, and cost attributes increased by one unit (Figure 3B), there was no substantial decrease in the probability of recommending treatment. Regarding safety, an 11.6% decrease in the probability of recommending treatment was observed when serious adverse events became common. Clearly, higher treatment benefits (low NNT), shorter duration, lower out-of-pocket cost, and rare occurrence of serious adverse events were associated with a greater likelihood of recommending treatment.

Interaction

Table 3 presents the interaction between individual characteristics (profession, involvement in hepatitis care) and continuous attribute coefficients. The utility coefficients account for the full effect, including the main effect and interaction effects specific to each profession, relative to the reference category. All professions demonstrated unwillingness (decreasing utility) to recommend treatment as the number needed to treat (NNT) increased by one unit, except for midwives who exhibited a significantly increased willingness to recommend treatment ($\beta = 0.0014$, $p < 0.01$). However, disutility among unwilling professions was significantly smaller in nurses ($\beta = -0.0002$, $p < 0.01$) and public health professionals ($\beta = -0.0006$, $p < 0.001$) than in doctors. This suggests that although nurses and public health professionals demonstrated a reduced willingness to recommend treatment with a unit increase in NNT, they were nonetheless more willing to recommend treatment compared to doctors. Pharmacists demonstrated a significantly greater willingness ($\beta = 0.0713$) to recommend treatment as treatment duration increased by one unit compared to doctors. No significant interaction was observed between profession and duration and cost attributes. Compared to health professionals not involved in hepatitis care, those involved in hepatitis care had a significantly higher loss in utility ($\beta = -0.0021$, $p<0.01$), reflecting greater reluctance among professionals involved in hepatitis care to recommend treatment as NNT increased.

Table 3: Interaction between one unit increase in attributes and individual characteristics

Characteristics			**Attribute coefficients**			
Profession	**N = 268**		**Benefit**	**Duration**	**Cost**	**Safety**
Doctor	186	**ref**	**-0.0024**	**-0.0580**	**-0.0054**	**-0.8932**
Pharmacist	18		-0.0018	-0.1032	-0.0070	0.0713 *
Nurse	12		-0.0002**	-0.0176	-0.0073	-1.1621
Midwife	3		0.0014 **	0.0315	-0.0064	-3.7601
Laboratory staff	13		-0.0014	-0.0129	-0.0082	-0.3207
Public health practitioner	33		-0.0006 ***	-0.0392	-0.0051	-0.6972
Other	3		-0.0008	0.0529	-0.0078	0.9563
Hepatitis B care involvement						
No	77	**ref**	**-0.0012**	**-0.0640**	**-0.0057**	**-0.7623**
Yes	191		-0.0021 **	-0.0469	-0.0058	-0.8103

The coefficients accounts for full effect including the main effect and the interaction effect of each sub-group

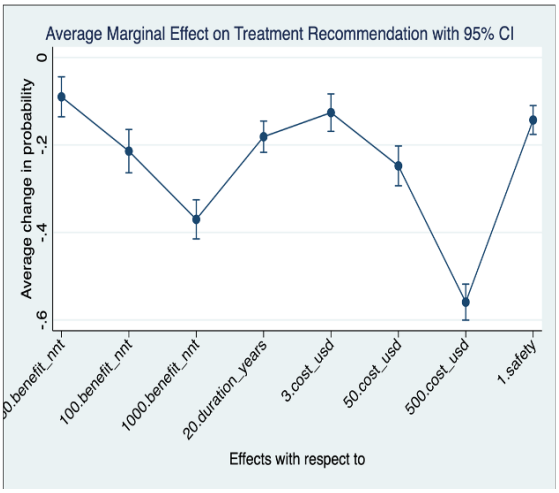
* p<0.05, ** p<0.01, *** p<0.001

Table 4: Attributes impact on treatment preference and average probability of recommending treatment in rational non-uniform responders

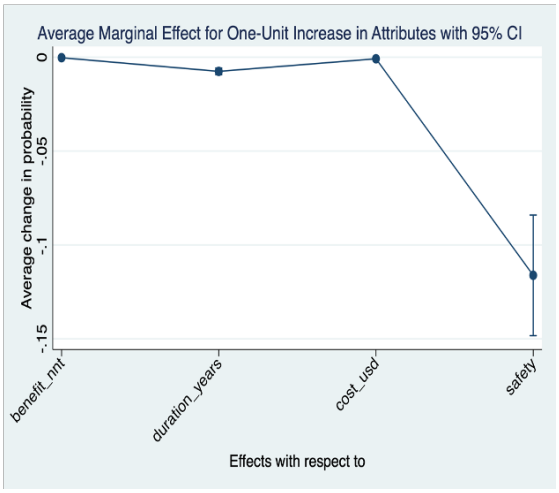
Categorical attributes						
Impact of attribute on treatment preference (RE)				**Average marginal effects analysis**		
Attributes	**OR**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**
Benefit						
10 NNT	1.00		<0.0001	ref		<0.0001
50 NNT	0.47	[0.31; 0.70]		-0.0900	[-0.13; -0.04]	
100 NNT	0.19	[0.12; 0.29]		-0.2141	[-0.26; -0.16]	
1000 NNT	0.07	[0.04; 0.10]		-0.3700	[-0.41; -0.32]	
Duration						
1 year	1.00		<0.0001	ref		<0.0001
20 years	0.35	[0.19; 0.35]		-0.1811	[-0.21; -0.14]	
Cost						
0 USD	1.00		<0.0001	ref		<0.0001
3 USD	0.35	[0.23; 0.50]		-0.1261	[-0.16; -0.08]	
50 USD	0.15	[0.10; 0.22]		-0.2478	[-0.29; -0.20]	
500 USD	0.02	[0.01; 0.03]		-0.5592	[-0.60; -0.51]	
Safety						
Rare	1.00		<0.0001	ref		<0.0001
Common	0.34	[0.26; 0.44]		-0.1430	[-0.17; -0.10]	
Continuous attributes						
Impact of attribute on treatment preference (RE)				**Average marginal effects analysis**		
Attributes	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**
Benefit	-0.0019	[0.99; 0.99]	<0.0001	-0.0003	[-0.0003; -0.0002]	<0.0001
Duration	-0.0518	[0.93; 0.96]		-0.0076	[-0.0092; -0.0058]	
Cost	-0.0057	[0.99; 0.99]		-0.0008	[-0.0008; -0.0007]	
Safety	-0.7963	[0.35; 0.56]		-0.1162	[-0.1482; -0.0840]	
RE: Random effects specification. OR: Odds ratio. 95%CI: 95% confidence interval. Ref: Reference level						

Figure 3: Average Marginal Effects with 95% CIs

A – Categorical attributes



B – Continuous attributes



Objective 3: Investigating the determinants of uniform responses (pro-treat-all and never-treat) compared to non-uniform responses

Most rational responders made non-uniform responses (75.1%), while 24.9% were uniform responders (Annex 4). Doctors (83.4%) and pharmacists (72%) predominantly responded non-uniformly, whereas midwives (57%) and public health professionals (46.8%) were most likely to provide uniform responses. Among doctors, surgeons (25%) and infectious disease specialists (20%) demonstrated a higher propensity for uniform responses than general practitioners (11.8%) and hepatologists (8.8%). Uniform responders were mostly pro-treat-all (91%), whereas the never-treat participants comprised only 9% and included primarily doctors (especially general practitioners) and pharmacists. Uniform responders mostly worked in the primary care (40%) and public health sectors (36.7%), followed by regional (23.3%) and national hospitals (20.4%), and least in the district (17.1%) and private hospitals (17%). Geographically, participants from North Africa were least likely to provide uniform responses (18.2%) compared to those from other regions; Central (33.3%), West (28.8%), South (25%), and East (23.6%).

In the unadjusted model exploring the determinants of pro-treat-all versus non-uniform responders (Table 5), profession was significantly associated with being pro-treat-all. Compared to doctors, midwives (OR 8.27, [1.76; 38.78]), public health practitioners (OR 5.45, [2.90; 10.23]), nurses (OR 3.10, [1.08; 8.88]), and laboratory staff (OR 2.86, [1.01; 8.10]) all exhibited significantly higher odds of being pro-treat-all. Pro-treat-all responders were less likely to be involved in hepatitis care (OR 0.46, [0.27; 0.75]), possess the ability to prescribe antiviral therapy (OR 0.50, [0.30; 0.84]), or have a history of prescribing antiviral therapy (OR 0.49, [0.29; 0.81]).

In the adjusted analysis (Table 5), midwives (OR 11.8, [2.17; 64.77]), public health practitioners (OR 6.58, [2.89; 14.98]), and laboratory staff (OR 3.64, [1.08; 12.24]) maintained significantly higher odds of being pro-treat-all than doctors. Conversely, hepatitis B care involvement, ability to prescribe antiviral therapy, and having a history of prescribing antiviral therapy were not significantly associated with being pro-treat-all.

This result shows that the health profession of participants was associated with being a pro-treat-all uniform responder. Never-treat responders were excluded from this analysis because of the small sample size (n = 8).

Table 5: Determinants of being a pro-treat-all responder compared to non-uniform responder

	Pro-treat-all (n = 81)			Pro-treat-all compared to non-uniform responders (n = 268)		
	Univariate analysis model			Adjusted model		
Participant characteristics	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age group (years)						
< 30	ref		0.8751			
30 - 50	0.91	[0.47; 1.72]			N/A	
> 50	0.79	[0.32; 1.90]				
Gender						
Male	ref		0.6258		N/A	
Female	0.88	[0.52; 1.47]				
Profession						
Doctor	ref		<0.0001	ref		0.0002
Pharmacist	2.07	[0.75; 5.62]		2.29	[0.75; 6.91]	
Nurse	3.10	[1.08; 8.88]		3.12	[0.99; 9.79]	
Midwife	8.27	[1.76; 38.78]		11.88	[2.17; 64.77]	
Laboratory staff	2.86	[1.01; 8.10]		3.64	[1.08; 12.24]	
Public health practitioner	5.45	[2.90; 10.23]		6.58	[2.89; 14.98]	
Other						
Medical Specialty						
General practitioner	ref		0.2434			
Hepatology	0.70	[0.24; 1.95]				
Surgery	2.36	[0.42; 13.06]			N/A	
Infectious disease	1.84	[0.65; 5.13]				
Others	3.04	[0.69; 13.35]				
Work sector						
Public/Primary care	ref		0.0597	ref		0.3369
Public/District hospital	0.31	[0.10; 0.94]		0.42	[0.12; 1.44]	
Public/Regional hospital	0.46	[0.17; 1.18]		1.13	[0.38; 3.28]	
Public/National hospital	0.43	[0.17; 1.02]		0.99	[0.35; 2.72]	
Private	0.32	[0.11; 0.89]		0.37	[0.11; 1.15]	
Public health sector	0.97	[0.39; 2.34]		0.62	[0.22; 1.68]	
Other	0.64	[0.16; 2.44]		0.47	[0.10; 2.01]	
Region						
Central	ref		0.4953			
East	0.56	[0.15; 1.98]				
North	0.41	[0.10; 1.59]			N/A	
South	0.53	[0.10; 2.72]				
West	0.74	[0.21; 2.62]				
Hepatitis B care involvement						
No	ref		0.0026	ref		0.0651
Yes	0.46	[0.27; 0.75]		0.51	[0.25; 1.04]	
Ability to prescribe antiviral therapy						
No	ref		0.0087	ref		0.4961
Yes	0.50	[0.30; 0.84]		1.34	[0.58; 3.06]	
Ever prescribed antiviral therapy						
No	ref		0.0055	ref		0.6977
Yes	0.49	[0.29; 0.81]		0.85	[0.36; 1.97]	

OR: Odds ratio. 95% CI: 95% confidence interval. N/A: Not included in multivariate model because not significant at <0.20 level in unvariate analysis

Objective 4: Evaluating the treatment preference of pro-treat-all and never-treat responders using choice certainty

4.1 Description of the choice certainty scale

In the full sample (n = 422), the mean certainty was 8.0 (SD 2.2), which remained constant after excluding the irrational responders (

Table 6). Non-uniform responders had a slightly lower mean certainty of 7.9 (SD 2.1), while uniform responders had a mean certainty of 8.2 (SD 2.2). Uniform responders, especially the

pro-treat-all responders, significantly provided more constant certainty scores than non-uniform responders (28.4% vs 10.1%; p<0.001). These participants demonstrated higher certainty and stronger confidence in their choice than non-uniform responders. However, the distribution of participants with low mean certainty (0-4), medium mean certainty (5-7), and high mean certainty (8-10) was similar across non-uniform, never-treat, and pro-treat-all participants.

4.2 Attributes impact on choice certainty of pro-treat-all and never-treat responders

The choice certainty of the pro-treat-all participants was not significantly influenced by the number needed to treat (clinical benefit) or the frequency of serious adverse events (safety attribute). However, treatment duration significantly impacted the certainty of pro-treat-all responders, causing a substantial reduction (β = -0.3551, 95% CI [-0.60; -0.10]) in their choice certainty for a treatment duration of 20 years compared to one year (Table 7). Similarly, out-of-pocket medication costs had a notable impact on the certainty level of pro-treat-all. Relative to no cost, a marked reduction in certainty was observed for out-of-pocket medication costs of 50 USD (β = -0.7175, 95% CI [-1.03; -0.40]) and 500 USD (β = -1.0570, 95% CI [-1.37; -0.74]). No significant impact on certainty was observed when the cost increased from 0 to 3 USD. This finding indicates that while the number needed to treat may be inconsequential for pro-treat-all participants, treatment duration and out-of-pocket financial implications significantly influenced the certainty of their decision to consistently recommend treatment. From the response assessing extreme NNT values (n = 76, excluding five irrational responders), the percentage of pro-treat-all who would not recommend treatment at extreme NNT levels was as follows: 5.3% at 5000 NNT, 6.6% at 10,000 NNT, 11.8% at 100,000 NNT, and 17.1% at 1,000,000 NNT. Notably, 20% of pro-treat-all responders would not recommend antiviral therapy regardless of the number needed to treat. Whereas 80% would consistently recommend antiviral therapy regardless of the number needed to treat (Annex 5).

The never-treat group was excluded from this analysis owing to the small sample size (n=8).

Objective 5: Evaluating the impact of attributes on choice certainty of all rational responders using the treatment eagerness scale

All attribute levels significantly impacted the treatment eagerness of rational responders (Table 7). Compared to the benefit reference level of 10 NNT, treatment eagerness substantially decreased for NNT 100 (β = -2.3749 [-2.97; -1.77]) and NNT 1000 (β = -4.3557 [-4.95; -3.75]), but not for NNT 50. Similarly, treatment eagerness significantly decreased for a treatment duration of 20 years (β = -2.3462 [-2.80; -1.88]) compared to one year, and as the frequency of serious adverse events became common (β = -1.6412 [-2.05; -1.22]) compared to rare. All levels of out-of-pocket medication costs significantly affected the treatment eagerness of

rational responders; 3 USD (β = -1.2469 [-1.83; -0.66]), 50 USD (β = -3.4644 [-4.05; -2.87]), and 500 USD (β = -7.2991 [-7.88; -6.71]).

Table 6: Descriptive statistics of choice certainty level

	Number of choice observations	Mean certainty	Standard deviation	% with constant certainty	% with low mean certainty (0 - 4)	% with medium mean certainty (5 - 7)	% with high mean certainty (8 - 10)
Overall (n = 422)	3376	8.0	2.2				
Rational responders (n = 357)	2,856	8.0	2.1	14.6	2.5	18.8	78.7
Non-uniform sample (268)	2,144	7.9	2.1	10.1	2.6	19.0	78.4
Uniform sample (n = 89)	712	8.2	2.2	28.1 ***	2.2	18.0	79.8
Never-treat (n = 8)	64	8.1	2.1	25 ***	0.0	25.0	75.0
Always-treat (n = 81)	648	8.2	2.2	28.4 ***	2.5	17.3	80.2

Fischers' exact test compared to non-uniform responders, *** p<0.001

Table 7: Impact of attributes on the choice certainty level of "pro-treat-all" responders and the "treatment eagerness" scale of all rational responders

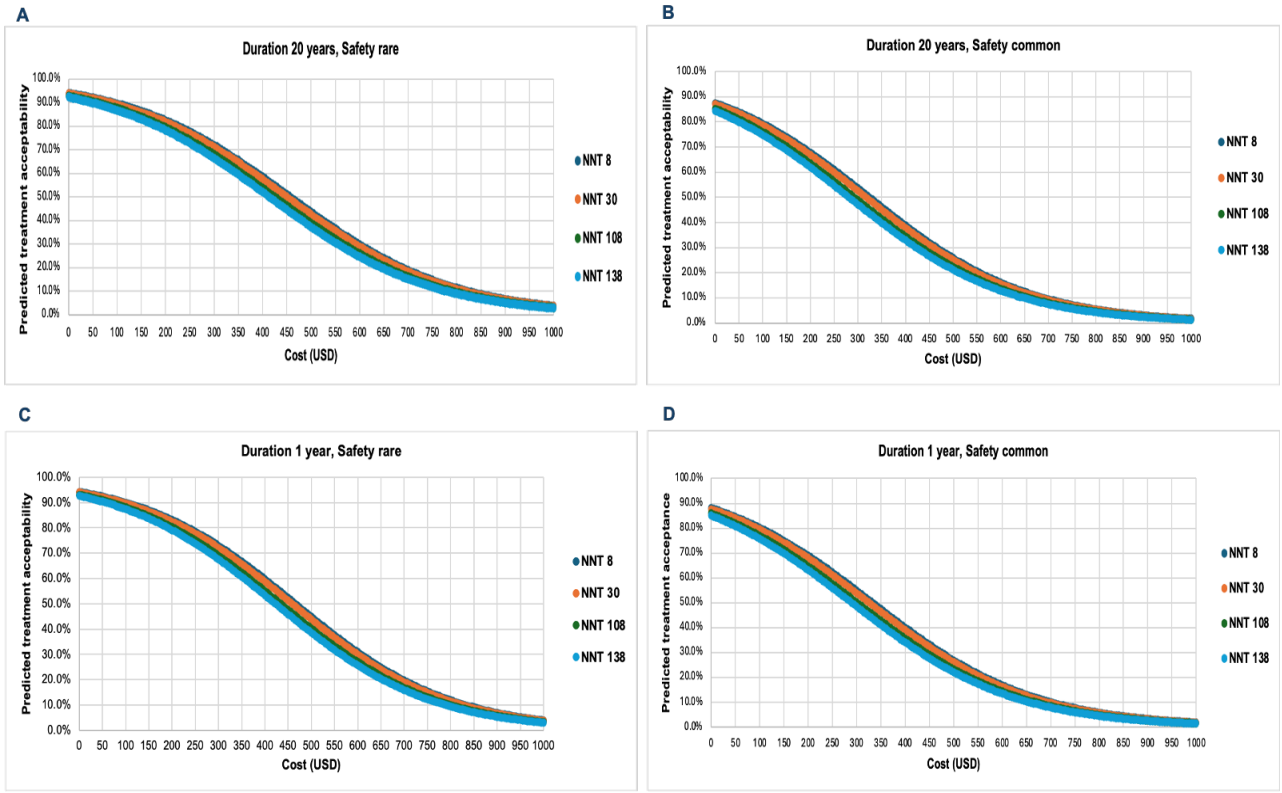
Impact of attributes on choice certainty of "pro-treat-all" responders (n = 81)				Impact of attributes on "treatment eagerness" of all rational responders (n = 357)		
Attribute	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**
Benefit						
10 NNT	ref		0.7528	ref		<0.0001
50 NNT	-0.033	[-0.34; 0.28]		-0.559	[-1.14; 0.02]	
100 NNT	-0.167	[-0.48; 0.15]		-2.374	[-2.97; -1.77]	
1000 NNT	-0.087	[-0.41; 0.23]		-4.355	[-4.95; -3.75]	
Duration						
1 year	ref		0.0056	ref		<0.0001
20 years	-0.355	[-0.60; -0.10]		-2.346	[-2.80; -1.88]	
Cost						
0 USD	ref		<0.0001	ref		<0.0001
3 USD	-0.283	[-0.59; 0.03]		-1.246	[-1.83; -0.66]	
50 USD	-0.717	[-1.03; -0.40]		-3.464	[-4.05; -2.87]	
500 USD	-1.056	[-1.37; -0.74]		-7.299	[-7.88; -6.71]	
Safety						
Rare	ref		0.6222	ref		<0.0001
Common	-0.056	[-0.27; 0.16]		-1.641	[-2.05; -1.22]	

Objective 6: Modelling predicted acceptance

Figure 4 illustrates the probability of recommending treatment by varying the treatment duration (between 1 year and 20 years), safety (from rare to common), treatment benefit (between 8 NNT, 30 NNT, 103 NNT, and 138 NNT), and out-of-pocket medication cost (ranging from 0 to 1000 USD). Assuming an antiviral therapy that guarantees 1-year treatment duration with rare occurrences of serious adverse events (Figure 4C), 90% of HCWs will recommend treatment at a monthly out-of-pocket medication cost up to 100 USD for a clinical benefit of 8 NNT, 90 USD for 30 NNT, 65 USD for 103 NNT, and 55 USD for 138 NNT. 70% of HCWs will recommend treatment at a monthly out-of-pocket medication cost of up to 325 USD, 315 USD, 290 USD, and 280 USD for similar respective benefits.

Assuming a treatment duration of 20 years with a common (1 – 10%) occurrence of serious adverse events (Figure 4B), 70% of African health professionals will recommend treatment if the out-of-pocket medication costs is 180 USD, 175 USD, 150 USD, and 140 USD for clinical benefits of 8 NNT, 30 NNT, 103 NNT, and 138 NNT respectively. With no out-of-pocket medication cost, a maximum of 87.5%, 87%, 85.3%, and 84.4% of HCWs will recommend treatment for the same respective benefit.

Figure 4: Predicted treatment acceptance for specific scenarios



Sensitivity Analysis

After the exclusion of “fast response” participants, sensitivity analysis on the marginal effect of rational non-uniform responders yielded results consistent with those obtained from the analysis that included all rational non-uniform responders (Annex 6).

Discussion

To our knowledge, this is the first DCE study examining the trade-offs that African health professionals make when recommending treatment for individuals with chronic HBV infection, specifically balancing the treatment benefits, duration, out-of-pocket costs, and safety. Analyzing the certainty level of stated preferences provided additional crucial information regarding their sensitivity to the attributes, offering more depth in expressing preferences compared to binary choices. This study revealed that all the parameters significantly influenced healthcare workers' stated preferences and treatment eagerness in the following order of priorities: out-of-pocket cost, treatment benefit, duration, and safety.

The number needed to treat (NNT), used as the metric for treatment benefit in this study, is a valuable measure that encapsulates the combined effects of the natural progression of CHB and the efficacy of antiviral therapy. NNT represents the average number of individuals to treat to prevent one occurrence of hepatocellular carcinoma (HCC). Lower NNT values, such as 10, indicate a higher clinical benefit because fewer individuals need to be treated to prevent one case of HCC. Conversely, higher NNT values, such as 1000 indicate a lower clinical benefit because more individuals need to be treated to prevent one case of HCC. Health professionals were less likely to recommend antiviral therapy when clinical benefits were lower. This aligns with previous DCE studies which have reported that treatment efficacy as an important driver of individuals' and physicians' preferences when considering antiviral therapy for viral hepatitis.[8, 28]

High out-of-pocket medication costs (OOP) had the highest impact on the HCWs' preferences, significantly reducing the average probability of recommending antiviral therapy initiation as OOP medication costs increased. This is not surprising in LMIC settings where financial constraints have been a major barrier to accessing HBV care and treatment. OOP costs may be the dominant factor limiting the initiation of antiviral therapy for persons living with HBV (PLWHBV). Hepatitis programs often lack adequate funding and dedicated financing mechanisms, coupled with weak health systems and poor health insurance in many African countries. [29] Consequently, many PLWHBV, especially those mono-infected, pay substantial fees to access HBV care and treatment.[29] Moreover, current HBV treatment is lifelong in the absence of a finite treatment that offers functional cure. This implies a long-term financial burden for HBV mono-infected individuals except those co-infected with HIV who receive free/subsidized tenofovir disproxil fumarate (TDF) treatment through funded HIV programs or donors.[12] The substantial impact of OOP costs on HCWs' stated preferences and treatment eagerness highlights the massive financial barriers to accessing hepatitis B treatment in resource-limited settings.

The marked effect of treatment duration on HCWs' choices suggests that they consider the potential challenges associated with prolonged therapy. These challenges include difficulties in maintaining medication adherence, an increased financial burden, and exposure to medication side effects. Medication-induced side effects can disrupt daily activities and affect the productivity and finances of affected HBV-infected individuals, the majority of whom already live within the World Bank's LMICs poverty line of 3 USD per day.[8, 17] Although not devoid of adverse events, TDF has a proven good safety profile and is the most commonly used anti-HBV drug in Africa.[12] Health professionals are likely to be cautious about recommending treatments with a high risk of adverse events, reflecting the significant impact of safety on their stated preference. However, the good safety profile of current anti-HBV therapy suggests why antiviral safety profile weighs the least for HCWs compared to other attributes. This corroborates reports of other studies that identified safety profile as an important driver for treatment decisions, but a less significant factor compared to other factors such as efficacy. [8, 28]

This study revealed variation in trade-offs influenced by healthcare workers' individual characteristics. Usually, medical doctors are the main prescribers of antiviral therapy and are involved in the management of complications.[12] This role engenders a holistic consideration of all factors for initiating antiviral therapy including clinical benefit, treatment duration, costs, and safety. Among the HCWs, midwives cared the least about NNT and demonstrated the highest propensity to recommend treatment with increasing NNT. Nurses and public health professionals also demonstrated a higher propensity to recommend treatment than doctors in the clinical profiles presented, indicating that NNT had less weight on their choices. Regarding safety, pharmacists were the least sensitive and exhibited a slightly higher willingness to recommend treatment, despite a lesser safety profile. This demonstrates how the diverse roles and patient care experiences of different healthcare professions influence their consideration and prioritization of various factors when advising initiation of antiviral therapy for individuals with chronic HBV infection. For instance, nurses and midwives play a crucial role in preventing mother-to-child transmission of hepatitis B and administering vaccines to newborns, positioning them as key agents in preventive care. Similarly, public health professionals, who often prioritize broader public health outcomes, may place less emphasis on NNT. Additionally, professionals involved in hepatitis care were more reluctant to recommend treatment as the clinical benefits decreased compared to those who were not involved in hepatitis care. This suggests a difference in practical experience and understanding of hepatitis management between those involved in hepatitis B care and those who are not. The deeper knowledge of the natural history of chronic HBV infection and the challenges associated with long-term management likely makes them more cautious in their recommendations.

Results using the treatment eagerness scale in rational responders were consistent with the findings from the actual stated preferences: increasing levels of NNT, treatment duration, costs, and safety decreased treatment recommendations. An interesting finding from analyzing participants' certainty is the observation that pro-treat-all participants have a preference for shorter treatment durations and lower out-of-pocket medication costs. The "Treat all" strategy, among several other strategies, has been proposed by civil societies and researchers as a potential approach to simplify HBV treatment algorithms and expand access to antiviral therapy, especially in resource-limited settings.[6, 15, 19] While the "treat all" approach might be effective, especially in terms of clinical benefits, the logistical and financial challenges, particularly due to increasing drug costs, may make it infeasible in low-income settings.[6] The concern about the cost-intensiveness of implementing the "treat-all" approach is reflected in this study. Despite pro-treat-all responders' inclination to recommend treatment regardless of the number of individuals needed to treat to prevent one case of HCC, their decisions were significantly sensitive to out-of-pocket medication cost and treatment duration.

Public health professionals and midwives exhibited a greater tendency to support the treat-all approach, although the small sample size of these subgroups limits definitive conclusions. This finding aligns with the interaction analysis which showed that public health professionals, midwives, and nurses were the least sensitive to clinical benefits (NNT). This reemphasizes how the varying roles, knowledge bases, unique perspectives, and experiences of different health professions may influence their treatment recommendations. The preventive mindset of midwives and public health professionals may foster greater openness to strategies such as treat-all even if individual clinical metrics like NNT suggest lower efficacy. However, some treat-all advocates may reconsider their stance if the clinical benefit is very low. This study found that approximately 17% (13 of 76) of pro-treat-all responders would not recommend antiviral therapy if the clinical benefit was as low as treating one million individuals with chronic HBV to prevent one occurrence of HCC. This highlights a potential sensitivity of treat-all advocates to low clinical benefits of HBV therapy.

This study aims to provide evidence to support policy and regulatory decisions for improving HBV treatment in Africa. By using the DCE method, we could predict the potential acceptability of specific treatment profiles. Assuming the development of a new treatment that offers a functional cure within one year and has a rare occurrence of serious adverse events, our predictions indicate that for a high clinical benefit of 8 NNT, 90% of HCWs would recommend treatment at a monthly OOP medication cost of up to 100 USD, while 70% of HCWs would recommend therapy at monthly OOP medication costs of up to 325 USD. While these predictions should be taken with caution, the findings of this study could be instrumental in

guiding drug pricing alignments for future antiviral therapies, especially those that can offer a functional cure against HBV. Similar methods have been used to support the development of acceptable HBV rapid diagnostic tests and interventions to promote HBV vaccine uptake. [30, 31]

This study had limitations. First, we did not randomize the order of the DCE scenarios, resulting in every participant encountering the choice task in the same sequence. This lack of randomization may introduce order effects[9, 32, 33], potentially biasing the quality of responses to some choice tasks because of the cognitive demands of completing a DCE. Therefore, these results should be interpreted with caution. Second, the generalizability of this result may be reduced due to the use of online surveys which could limit access for health professionals without internet services. Additionally, the heterogeneity arising from the diverse participants' subregions, healthcare systems, and resources could affect the generalizability beyond the study population. Third, this study did not elicit the preferences of people living with chronic HBV infection. DCEs assessing patient preferences have been conducted in high-income countries,[8, 28, 34]. Assessing patient preferences is crucial for delivering patient-centered care, addressing underlying disparities, enhancing patient satisfaction, and improving treatment adherence and outcomes. Finally, although DCEs are powerful methods for assessing preferences, the hypothetical nature of the scenarios may not accurately reflect real-life situations, potentially leading to discrepancies between stated and actual choices. This study attempted to minimize such differences by developing scenarios that closely mimic the real world.

Implications and Recommendation

The findings of this study have important implications and recommendations for addressing the substantial burden of HBV infection in Africa and accelerating efforts to achieve the global goal of eliminating viral hepatitis by 2030. Out-of-pocket medication cost is the most important factor when HCWs are considering recommending antiviral therapy initiation for PLWHBV. While progress has been made in reducing the cost of TDF (an anti-HBV drug),[16] further cost reductions are necessary to eliminate financial constraints in African LMICs where many chronic HBV-infected individuals still pay out-of-pocket. Since TDF is currently used as an antiviral medication in both HBV and HIV programs, an integrated HBV-HIV program could be a feasible approach to providing comprehensive medication coverage for both mono-infected and co-infected individuals. This integration would alleviate the OOP financial burden encountered by most mono-infected HBV individuals, as underscored by health professionals' increased willingness to recommend treatment at reduced cost. Improved funding and commitment from governments and international organizations are pivotal to achieving this. Second, while research and development of new antivirals that could potentially offer functional

and finite cures are ongoing, studies eliciting the preference of individuals living with chronic HBV infection in Africa are encouraged. Understanding the preferences of chronic HBV-infected individuals, in addition to the treatment recommendation predictions from HCWs, would be instrumental in promoting synergy and developing tailored strategies that would enhance viral hepatitis control and contribute to its elimination in the region.

Conclusion

This study provides valuable insights into the preferences of African healthcare workers' regarding when to initiate antiviral therapy, highlighting the significant impact of out-of-pocket costs, treatment benefits, duration, and safety on their decisions. Reduced out-of-pocket medication costs, high clinical benefit, finite treatment duration, and improved safety profile are critical factors that will accelerate the initiation of antiviral therapy for individuals living with chronic hepatitis B infection in Africa. Addressing these factors is essential for improving HBV treatment in Africa and advancing global efforts towards viral hepatitis elimination.

Contributions

This research was conducted at Institut Pasteur under the professional supervision of Yusuke Shimakawa. This study was completely developed from scratch. It was conceptualized by Yusuke Shimakawa, and Boms Rewhandamzi joined in developing the idea. Boms Rewhandamzi was involved in the epidemiological study design, developed the study protocol, and secured ethical approval. Boms Rewhandamzi designed the study questionnaire, established the database, and set up the study on the REDCap platform. Boms Rewhandamzi participated in meetings and made presentations that secured the buy-in of research collaborators. All data management, cleaning, statistical analysis, and manuscript writing were conducted by Boms Rewhandamzi under the supervision of Yusuke Shimakawa. This study was conducted with important inputs from Judith Mueller, Jonathan Sicsic, and MaryBeth Terry.

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Annex

Annex 1: List of dominant pairs of scenarios

Dominant pairs	Superior scenario					Inferior scenario				
	Scenario ID	Clinical benefit (NNT)	Duration (Years)	Costs (USD monthly)	Safety	Scenario ID	Clinical benefit (NNT)	Duration (Years)	Costs (USD monthly)	Safety
Block 1										
1 > 2	1	50	20	3	Rare	2	100	20	50	Common
6 > 2	6	10	1	50	Rare	2	100	20	50	Common
6 > 3						3	100	1	500	Rare
6 > 4						4	10	20	500	Common
8 > 2	8	50	20	Free	Rare	2	100	20	50	Common
8 > 5						5	1000	20	Free	Common
8 > 1						1	50	20	3	Rare
Block 2										
3 > 1	3	50	1	50	Common	1	50	1	500	Common
4 > 1	4	10	1	Free	Rare	1	50	1	500	Common
4 > 2						2	1000	20	500	Rare
4 > 3						3	50	1	50	Common
4 > 5						5	100	1	Free	Common
4 > 6						6	1000	20	50	Rare
4 > 7						7	100	1	3	Rare
4 > 8						8	10	20	3	Common
6 > 2	6	1000	20	50	Rare	2	1000	20	500	Rare
7 > 2	7	100	1	3	Rare	2	1000	20	500	Rare
7 > 6	7	100	1	3	Rare	6	1000	20	50	Rare

Annex 2: Description of response pattern between rational and irrational responders

Choice task	Benefit (NNT)	Duration (Years)	Cost (USD monthly)	Safety	Full sample (N = 422)		Rational responders (n = 357)		Irrational responders (n = 65)		p-value
					Yes, n (%)	**No**, n (%)	**Yes**, n (%)	**No**, n (%)	**Yes**, n (%)	**No**, n (%)	
Block 1 (n = 212)											
1	50	20	3	Rare	159 (75.0)	53 (23.9)	142 (80.7)	34 (19.3)	17 (47.2)	19 (52.8)	<0.001
2	100	20	50	Common	111 (52.4)	101 (47.6)	82 (46.6)	94 (53.4)	29 (80.6)	7 (19.4)	<0.001
3	100	1	500	Rare	99 (46.7)	113 (53.3)	86 (48.9)	90 (51.1)	13 (36.1)	23 (63.9)	0.162
4	10	20	500	Common	96 (45.3)	116 (54.7)	74 (42.0)	102 (58.0)	22 (61.1)	14 (38.9)	0.036
5 *	1000	20	Free	Common	133 (62.7)	79 (37.3)	100 (56.8)	76 (43.2)	33 (91.7)	3 (8.3)	<0.001
6	10	1	50	Rare	175 (82.5)	37 (17.5)	160 (90.9)	16 (9.1)	15 (41.7)	21 (58.3)	<0.001
7	1000	1	3	Common	139 (65.6)	73 (34.4)	110 (62.5)	66 (37.5)	29 (80.6)	7 (19.4)	0.038
8	50	20	Free	Rare	187 (88.2)	25 (11.8)	164 (93.2)	12 (6.8)	23 (63.9)	13 (36.1)	<0.001
Block 2 (n = 210)											
9	50	1	500	Common	95 (45.2)	115 (54.8)	84 (46.4)	97 (53.6)	11 (37.9)	18 (62.1)	0.394
10	1000	20	500	Rare	73 (34.8)	137 (65.2)	55 (30.4)	126 (69.6)	18 (62.1)	11 (37.9)	0.001
11	50	1	50	Common	159 (75.7)	51 (24.3)	142 (78.5)	39 (21.5)	17 (58.6)	12 (41.4)	0.021
12 *	10	1	Free	Rare	190 (90.5)	20 (9.5)	177 (97.8)	4 (2.2)	13 (44.8)	16 (55.2)	<0.001
13	100	1	Free	Common	173 (82.4)	37 (17.6)	151 (83.4)	30 (16.6)	22 (75.9)	7 (24.1)	0.321
14	1000	20	50	Rare	90 (42.9)	120 (57.1)	79 (43.6)	102 (56.4)	11 (37.9)	18 (62.1)	0.564
15	100	1	3	Rare	185 (88.1)	25 (11.9)	162 (89.5)	19 (10.5)	23 (79.3)	6 (20.7)	0.116
16	10	20	3	Common	157 (74.8)	53 (25.2)	140 (77.4)	41 (22.6)	17 (58.6)	12 (41.4)	0.031

* Fischers' exact test

Annex 3: Description of survey completion time by participants

	Median response time mins (range)	Normal response (≥6.6 minutes)		Fast response time (<6.6 minutes)		p-value
		n	%	n	%	
Full sample (n = 422)	8.7 (2.2 - 2029.4)	351	83.2	71	16.8	
Responder						
Rational responders (n = 357)	8.7 (2.2 - 2029.4)	302	84.6	55	15.4	<0.001
Irrational responders (n = 65)	6.5 (2.2 - 819.2) *	49	75.4	16	24.6	
Rational responders only						
Non-uniform (n = 268)	8.7 (2.2 - 2029.4)	232	86.6	36	13.4	<0.001
Uniform responders (n = 89)	8.7 (2.2 - 85.2)	70	78.6	19	21.4	
Uniform responders only						
Never-treat (n = 8)	5.5 (2.2 - 11)	4	50.0	4	50.0	
Always treat (n = 81)	10.9 (2.2 - 85.2)	66	81.5	15	18.5	

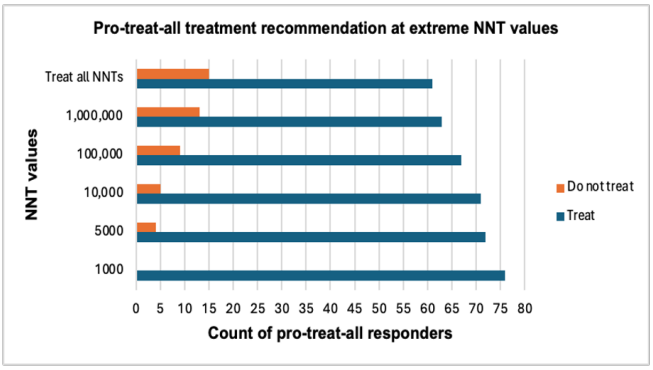
* p = 0.047, significant difference in response time between rational and irrational responders

Annex 4: Distribution of participants by non-uniform and uniform responses

						Uniform responders			
	Full sample N = 422	Non-uniform responders n = 268		Uniform responders n = 89		Never-treat responders n = 8		Pro-treat-all responders n = 81	
Characteristics	n	n	%	n	%	n	%	n	%
Age group (years)									
< 30	67	48	71.6	19	28.4	3	4.5	16	23.9
30 - 50	241	182	75.5	59	24.5	4	1.7	55	22.8
> 50	49	38	77.5	88	22.5	1	2.0	10	20.4
Gender									
Male	221	164	74.2	57	25.8	5	2.3	52	23.5
Female	136	104	16.5	32	23.5	3	2.2	29	21.3
Profession									
Doctor	223	186	83.4	37	16.6	7	3.1	30	13.5
Pharmacist	25	18	72.0	7	28.0	1	4.0	6	24.0
Nurse	18	12	66.7	6	33.3	0	0.0	6	33.3
Midwife	7	3	42.9	4	57.0	0	0.0	4	57.1
Laboratory staff	19	13	68.4	6	31.6	0	0.0	6	31.6
Public health practitioner	62	33	53.2	29	46.8	0	0.0	19	46.8
Other	3	3	100.0	0	0.0	0	0.0	0	0.0
Medical Specialty									
General practitioner	102	85	83.3	17	16.7	5	4.9	12	11.8
Hepatology	68	61	89.7	7	10.3	1	1.5	6	8.8
Surgery	8	6	75.0	2	25.0	0	0.0	2	25.0
Infectious disease	35	27	77.1	8	22.9	1	2.9	7	20.0
Others	10	7	70.0	3	30.0	0	0.0	3	30.0
Work sector									
Public/Primary care	35	21	60.0	14	40.0	2	5.7	12	34.3
Public/District hospital	41	34	83.0	7	17.1	1	2.4	6	14.6
Public/Regional hospital	60	46	76.7	14	23.3	2	3.3	12	20.0
Public/National hospital	93	74	79.6	19	20.4	1	1.1	18	19.3
Private	53	44	83.0	9	17.0	1	1.9	8	15.1
Public health sector	60	38	63.3	22	36.7	1	1.7	21	35.0
Other	15	11	73.3	4	26.7	0	0.0	4	26.7
Region									
Central	12	8	66.7	4	33.3	0	0.0	4	33.3
East	127	97	76.4	30	23.6	3	2.4	27	21.2
North	66	54	81.8	12	18.2	1	1.5	11	16.7
South	20	15	75.0	5	25.0	1	5.0	4	20.0
West	132	94	71.2	38	28.8	3	2.3	35	26.5
Hepatitis B care involvement									
No	119	77	64.7	42	35.3	4	3.4	38	31.9
Yes	238	191	80.2	47	19.8	4	1.7	43	18.1
Ability to prescribe antiviral therapy									
No	115	77	67.0	38	33.0	2	1.7	36	31.3
Yes	242	191	78.9	51	21.1	6	2.3	45	18.6
Ever prescribed antiviral therapy									
No	154	105	68.2	49	31.8	3	2.0	46	29.8
Yes	203	163	80.3	40	19.7	5	2.5	35	17.2

Annex 5: Pro-treat-all treatment recommendation at extreme NNT values

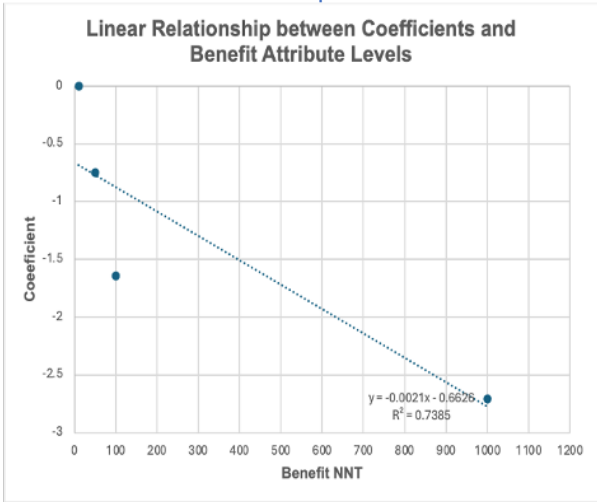
	Treat		Do not treat	
NNT value	**n**	**%**	**n**	**%**
NNT 1000	76	100.0	0	0.0
NNT 5000	72	94.7	4	5.3
NNT 10,000	71	93.4	5	6.6
NNT 100,000	67	88.2	9	11.8
NNT 1,000,000	63	82.9	13	17.1
Treat all NNTs	61	80.3	15	19.7

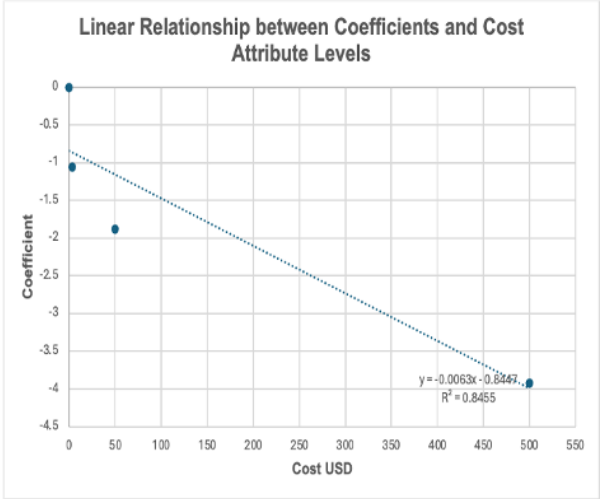


Annex 6: Sensitivity analysis assessing average marginal effects on rational responders excluding "fast response" participants

Attribute	Coefficient	95% CI	p-value
Benefit			
10 NNT	ref		<0.0001
50 NNT	-0.098	[-0.14; -0.04]	
100 NNT	-0.213	[-0.26; -0.15]	
1000 NNT	-0.373	[-0.42; -0.32]	
Duration			
1 year	ref		<0.0001
20 years	-0.185	[-0.22; -0.14]	
Cost			
0 USD	ref		<0.0001
3 USD	-0.129	[-0.17; -0.08]	
50 USD	-0.239	[-0.28; -0.19]	
500 USD	-0.564	[-0.60; -0.52]	
Safety			
Rare	ref		<0.0001
Common	-0.147	[-0.18; -0.11]	

Annex 7: Linear relationship between attribute levels and coefficients





RÉSUMÉ EN FRANÇAIS

Titre: “Quand traiter” les personnes vivant avec l'hépatite B en Afrique; Une expérience de choix discret évaluant les préférences des professionnels de santé.

Contexte: L'infection chronique par le VHB se manifeste silencieusement, sans symptômes apparents, et peut prendre des décennies avant d'entraîner des complications telles que le carcinome hépatocellulaire. Les directives recommandent d'identifier les personnes à haut risque et de leur fournir une thérapie antivirale. Cette étude a évalué les préférences des professionnels de la santé concernant le moment où il convient de recommander l'instauration d'une thérapie antivirale pour les personnes atteintes d'une infection chronique par le VHB en Afrique.

Objectifs: Évaluer les préférences thérapeutiques déclarées, l'empressement à traiter et prédire l'acceptation de profils thérapeutiques spécifiques.

Méthode: Une expérience de choix discret (ECD) portant sur un seul profil a été menée auprès d'agents de santé africains à l'aide d'un questionnaire en ligne. L'expérience de choix discret comprenait les attributs suivants : bénéfice (nombre nécessaire pour traiter, NNT), durée, coûts à la charge du patient et sécurité. Nous avons quantifié le gain ou la perte d'utilité généré par chaque attribut à l'aide d'un modèle logistique binaire, évalué l'empressement au traitement à l'aide d'une échelle de certitude de choix avec régression linéaire, et modélisé l'acceptation prédite de profils de traitement spécifiques

Résultats: L'augmentation des niveaux du NST, de la durée du traitement, du coût et de la sécurité a généré une désutilité significative. L'ampleur de l'effet du niveau d'attribut le plus élevé par rapport à la référence était dans l'ordre suivant : coût (OR 0.02, 95%CI [0.01 ; 0.03]), bénéfice (OR 0.07, 95%CI [0.04 ; 0.10]), durée (OR 0.35, 95%CI [0.19 ; 0.35]), sécurité (OR 0.34, 95%CI [0.26 ; 0.44]). L'impact des attributs sur la volonté de traitement était similaire. 30 % des participants rationnels étaient favorables au traitement de tous, principalement des sages-femmes et des professionnels de la santé publique. 90 % des travailleurs de la santé recommanderont un traitement à un coût mensuel allant jusqu'à 100 USD pour un bénéfice de 8 NNT si la durée du traitement est d'un an avec des effets indésirables rares.

Conclusion: Les coûts à la charge du patient, les avantages du traitement, sa durée et son innocuité influencent de manière significative les recommandations des travailleurs de la santé concernant l'instauration d'un traitement antiviral, le coût à la charge du patient étant le facteur le plus influent.

Mots-clés: Hépatite B, Afrique, thérapie antivirale, DCE.

N/B: This abstract was translated from English to French using DeepL Translate[35]