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ORIGINAL ARTICLE

Viral hepatitis elimination challenges in low- and middle-income countries—Uzbekistan Hepatitis Elimination Program (UHEP)

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Abstract

Background & Aims: Chronic infection with hepatitis B and C viruses (HBV & HCV) is a major contributor to liver disease and liver-related mortality in Uzbekistan. There is a need to demonstrate the feasibility of large-scale simplified testing and treatment to implement a national viral hepatitis elimination program.

Methods: Thirteen polyclinics were utilized to screen, conduct follow-up biochemical measures and treat chronic HBV and HCV infection in the general adult population. Task shifting and motivational interviewing training allowed nurses to provide rapid screening and general practitioners (GPs) to treat individuals on-site. An electronic medical system tracked individuals through the cascade of care.

Results: The use of rapid tests allowed for screening of 60 769 people for HCV and HBV over 6 months and permitted outdoor testing during the COVID-19 pandemic along with COVID testing. 13%–14% of individuals were lost to follow-up after the rapid test, and another 62%–66% failed to come in for their consultation. One stop testing and treatment did not result in a statistically increase in retention and lack of patient awareness of viral hepatitis was identified as a key factor. Despite training, there were large differences between GPs and patients initiating treatment.

Conclusions: The current study demonstrated the feasibility of large-scale general population screening and task shifting in low- and middle-income countries. However, such programs need to be proceeded by awareness campaign to minimize loss to follow up. In addition, multiple trainings are needed for GPs to bolster their skills to talk to patients about treatment.

KEYWORDS
disease eradication, epidemiology, hepatitis B, hepatitis C, prevalence, Uzbekistan

Abbreviations: aPR, adjusted prevalence ratio; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; CI, confidence interval; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; LMICs, low- and middle-income countries; LTFU, lost to follow up; REDCap, Research Electronic Data Capture; RIV, Research Institute of Virology; SVR, sustained viral response; UHEP, Uzbekistan Hepatitis Elimination Project; WHO, World Health Organization.

1 | BACKGROUND

Infection with hepatitis B (HBV) and hepatitis C (HCV) viruses is a leading cause of liver disease globally, with an estimated 1.1 million deaths attributable to viral hepatitis and resulting liver disease in 2019.[1] Globally, an estimated 296 million individuals are chronically infected with HBV, and 58 million with chronic HCV infection.[1,2] Even though effective vaccination is available to prevent HBV infection, and efficacious antiviral therapies for HBV and HCV are available for those already infected, many individuals remain untested and unaware of treatment options. This situation is even more pronounced in low- and middle-income countries (LMICs), including those in Central Asia.

Cirrhosis mortality is elevated in Central Asia as compared to the rest of the world and over half of such mortality in the region has been attributed to HBV and HCV infection. It was estimated that Uzbekistan had the seventh highest rate of cirrhosis mortality globally in 2010.[3] In 2017, Central Asia was identified as the region with the highest rate of age-standardized cirrhosis mortality globally and was one of only two regions where such mortality increased during 1990–2017.[4] Globally, cirrhosis was responsible for 26.8% fewer DALYs in 2019 than in 1990,[5] but the disability and economic impact are likely still rising in Uzbekistan.

In 2016, the estimated prevalence of chronic HBV infection (hepatitis B surface antigen positive, or HBsAg+) was 8.3% in Uzbekistan, equivalent to an estimated 2.5 million infected individuals. It was estimated that 10% had been previously diagnosed, and 0.5% (approximately 12 500) had received treatment.[6] The estimated prevalence of chronic HCV infection (HCV RNA+) in Uzbekistan was 4.3%, equivalent to 1.3 million infected individuals. It was estimated that 5% had been previously diagnosed, and 2% (approximately 26 000) had received treatment.[7] A meta-analysis of HCV prevalence in Central Asia estimated prevalence of 9.6% in Uzbekistan,[8] higher than in the other Central Asian countries.

The Uzbekistan Hepatitis Elimination Project (UHEP 1.0) was a 1-year pilot program started in December 2019 to test adults in Tashkent for chronic HBV and HCV infection and link them to care. The objective of the program was to demonstrate the feasibility of simplified testing and treatment protocols for HCV and HBV in the general population. The program incorporated several novel concepts: (1) Simultaneous screening for HCV and HBV using rapid tests at polyclinics; (2) simplification of laboratory testing requirements; (3) task shifting, or training of primary care physicians to treat HCV and HBV individuals without advanced liver disease; (4) motivational interviewing training for nurses and physicians to motivate individuals to seek treatment; (5) a dynamic operational research approach where the study protocols were modified based on real-time learnings; and (6) after September 2020, integration of viral hepatitis screening into coronavirus disease 2019 (COVID-19) testing at polyclinics.

Key Points

Large-scale hepatitis B & C screening of the general population is feasible using rapid tests and simplified test and treat guidelines. However, unless the screening campaign is complemented by an awareness campaign, the majority of the diagnosed individuals will be lost to follow up. In addition, targeted awareness campaign for general practitioners (GPs) is needed to help them communicate the need for treatment, as GPs represent the front line for most newly diagnosed individuals.

2 | METHODS

2.1 | Study site and study population

After signing a consent form, individuals were tested at 13 polyclinics in Tashkent with the goal of diagnosing and treating all individuals with an active infection.[9] Convenience sampling was used by recruiting individuals who were attending the polyclinics for other procedures or doctor visits. In the first part of the project (December 2019 to March 2020), three polyclinics were utilized to screen individuals and all who tested positive for HBV or HCV were referred to specialists at the Research Institute of Virology (RIV). After the COVID-19 pandemic and reopening of clinics in September 2020, the project was moved to 10 new polyclinics and all HBV+ and HCV+ individuals (without cirrhosis) were treated by the in-house primary care physicians.

All individuals received free HCV and HBV screening, lab tests and physician consultation. Tenofovir disoproxil fumarate and tenofovir alafenamide for HBV individuals, sofosbuvir & daclatasvir for non-cirrhotic HCV individuals and sofosbuvir/velpatasvir for cirrhotic HCV individuals were offered. Free medications were provided for individuals eligible for free healthcare & social services (10% of all individuals), as defined by the government, while others who did not meet the income/need criteria were asked to pay for their treatment at a cost below the market price.[9]

A simplified test and treat protocol were used for all HBV+ cases. Individuals were tested with an HBsAg rapid diagnostic test (Alere Determine HBsAg 2, Alere Medical Company). If individuals were HBsAg+, rapid human immunodeficiency virus (HIV) (CE HIV RDT, InTec Inc.) and rapid creatinine (StatSensor Xpress, Nova Biomedical) tests were conducted. HBsAg+ individuals with negative HIV tests and estimated glomerular filtration rate (eGFR) >30 ml/min were offered antiviral therapy, while the remaining HBsAg+ individuals were referred to a specialist for further care.

Simultaneously, incoming individuals were tested for anti-HCV antibody using an HCV rapid diagnostic test (CE HCV antibody RDT, InTec Products Inc.). Two vials of whole blood were collected from all anti-HCV-positive individuals. The first vial was used to test for HCV core antigen or PCR testing (ARCHITECT HCV Antigen Assay,

Abbott Laboratories until March 2020 and Cobas, Roche Diagnostics after September 2020) to confirm active infection (RNA+). The second vial was used to test for creatinine, aspartate aminotransferase (AST) and platelets at RIV. Individuals without evidence of cirrhosis (AST to platelet ratio index (APRI) <1.0) or eGFR >30 ml/min[10,11] were offered antiviral therapy, with the remaining individuals referred for specialist care. HCV+ individuals who came in for their physician consultation completed a detailed questionnaire that assessed their risk factors.

Throughout the study, interviews with randomly selected individuals were conducted to assess the impact of the project. In addition, 63 randomly selected HCV individuals, who initiated treatment, were brought in 12 weeks after they completed their treatment to assess sustained virologic response (SVR-12).

2.2 | Data collection

Study data were collected and managed using REDCap electronic data capture tools.[12,13] REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. Data were entered on handheld tablets linked to REDCap using rechargeable mobile 3G routers. All individuals were given a barcode with a unique patient identifier that was used to track their progress through the cascade of care including the purchase and refill of prescriptions at pharmacies.

2.3 | Training

Task shifting training was provided by the University of Maryland School of Medicine, based on the ASCEND study.[14–17] A special training module was created for treatment of HBV individuals. Motivational interviewing training was provided by the Academy for Health Coaching to teach nurses and doctors how to talk to individuals to retain them in care and seek treatment.[18] International trainers trained the first group of healthcare workers and trainers. The local trainers continued the training as additional polyclinics and healthcare workers were added.

2.4 | Confidentiality and ethical approval

All methods were carried out in accordance with relevant guidelines and regulations. Before responding to the questionnaire, all individuals provided consent for their anonymous data to be used for research purposes. The Uzbekistan Ministry of Health and national institutional review board approved all study protocols.

2.5 | Statistical analyses and sample size

All patient records were initially screened for study inclusion based on valid recording of individuals' sex, age, residence and birthplace. To make inferences for the national population, a sampling weight was assigned to each patient record based on reported projection of 2020 population for Uzbekistan by age and sex.[19]

Possible associations with chronic HBV or HCV infection were investigated using univariate and multivariate modified Poisson regression for sex, age group, residence and birthplace. The adjusted prevalence ratio (aPR) and 95% confidence intervals (95% CI) are presented in the Results section. In all analyses (univariate and multivariate), a two-sided $p < .05$ was considered statistically significant. Analyses were performed using R statistical software (version 4.0.4) and Microsoft Excel.

3 | RESULTS

A total of 62 975 individuals were tested (Figure 1) with 30 727 tested prior to the COVID-19 shutdown in March 2022, and the remaining tested after clinics opened again in September 2020. Due to lower visits to healthcare facilities after the COVID-19 pandemic, the number of polyclinics had to increase from 3 to 10 to maintain the same screening throughput. Of the total screened, 60 769 (96.5%) patient records included valid data for sex, age, residence and birthplace, and were considered for inclusion in HBV and HCV disease burden analysis.

3.1 | HBV prevalence

Of the 60 769 patient records considered for analysis, 5803 (9.5%) were missing HBsAg test results, and 1125 (1.9%) had positive HBsAg results, but reported previous awareness of infection. After excluding these, there was a total of 53 841 individuals. Of these individuals, 68.9% were female (37 080 individuals) and the 18- to 29-year-old age group was the largest with 14 320 individuals (26.6% of total).

There were 1509 individuals who were HBsAg+ and not previously aware of infection, resulting in a crude prevalence of 2.80% (95% CI 2.66–2.95) (Table 1). Age and sex standardized prevalence was estimated at 3.23% (3.07–3.38). Adjusted prevalence was estimated at more than twice the rate among males 4.39% (4.14–4.65) as compared to females 2.10% (1.93–2.28). Among both males and females, the highest adjusted prevalence was recorded among individuals aged 30–39 years (6.57% [5.99–7.19] and 2.93% [2.54–3.37]), followed by individuals aged 40–49 years (5.62% [4.99–6.33] and 2.66% [2.23–3.16]) (Figure 2 and Table 1).

Among all individuals in the HBV data set, the mean age was 41.23 [41.11–41.36], and males were younger (40.14 [39.91–40.38]) as compared to females (41.73 [41.58–41.87]). The mean age of HBV positive cases was also younger (39.01 [38.40–39.62]) than negative cases (41.30 [41.17–41.42]).

Regression analyses demonstrated that individuals aged 30–49 years experienced significantly higher rates of infection as compared to individuals aged 18–29 years, with the lowest

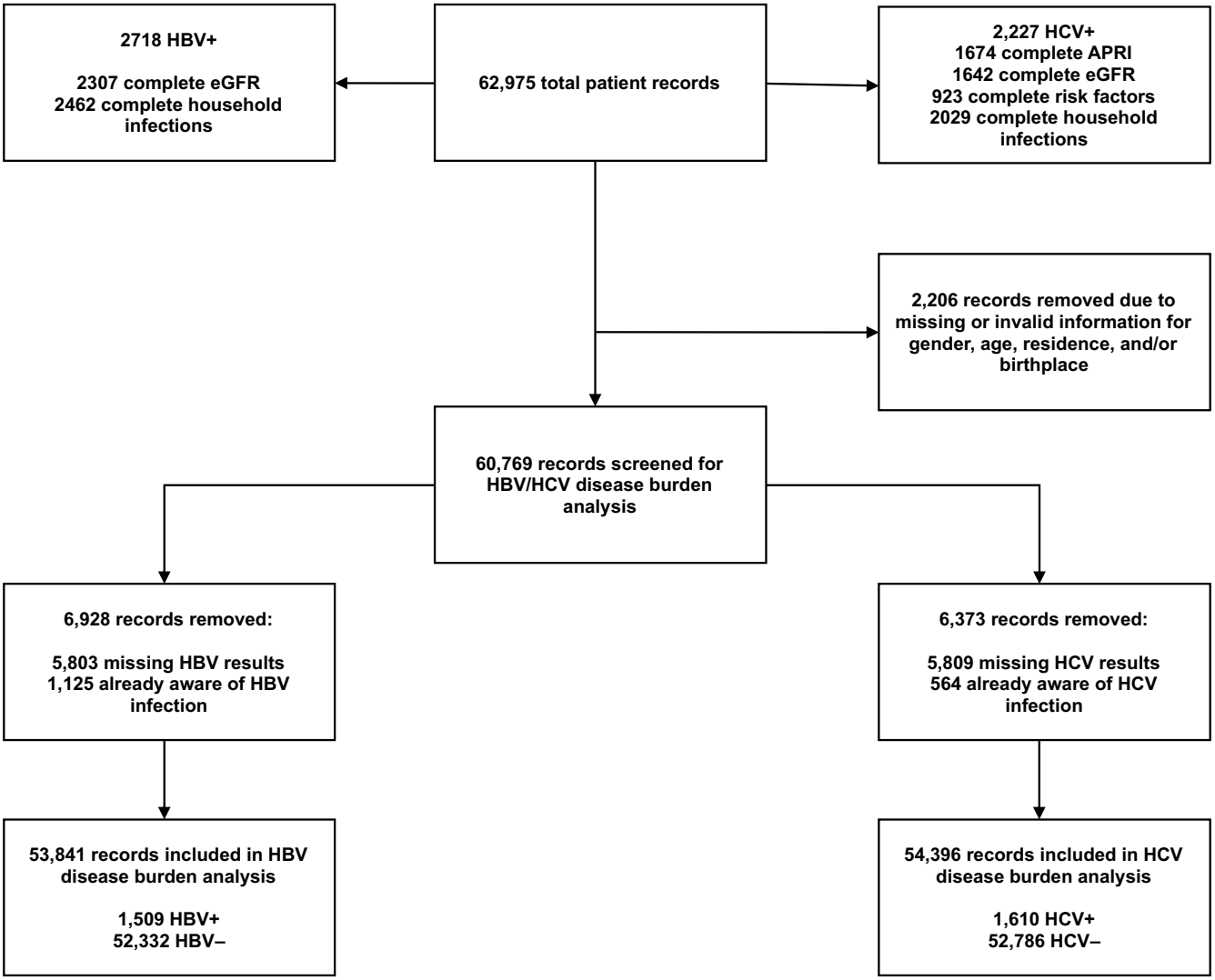


FIGURE 1 Study flowchart for UHEP patient records.

prevalence observed among individuals aged ≥60 years. HBV infection rates by district of residence varied, with significantly elevated rates observed among individuals residing outside Tashkent and outside Uzbekistan. For patient birthplace, higher prevalence was observed among individuals born in all Uzbek districts as compared to Tashkent, while prevalence among individuals born outside Uzbekistan was lower than for any Uzbek province, including Tashkent.

3.2 | HCV prevalence

Of the 60769 patient records considered for analysis, 5809 (9.6%) were missing HCV test results, and 564 (0.93%) had positive HCV results, but reported previous awareness of infection. After excluding these cases, there was a total of 54396 individuals. Of these individuals, 68.6% were female (37312 individuals) and the 18- to 29-year-old age group was the largest with 14464 individuals (23.8% of total).

There were 1610 individuals who were HCV+ and not previously aware of infection, resulting in a crude prevalence of 2.96% (2.82–3.11) (Table 1). Age and sex standardized prevalence were estimated at 3.02% (2.87–3.16). Adjusted prevalence was estimated at 38% higher among males (3.50% [3.29–3.73]) as compared to females (2.54% [2.36–2.74]). Among males, the highest adjusted prevalence was recorded among individuals aged 40–49 years (6.21% [5.55–6.95]), while for females, the highest rate was among individuals aged 60–69 years (5.13% [4.32–6.08]).

Among all individuals in the HCV data set, the mean age was 41.10 (40.98–41.23), and males were younger (39.95 [39.72–40.19]) as compared to females (41.63 [41.48–41.77]). The mean age of HCV positive cases was (48.30 [47.62–48.98]), older than negative cases (40.88 [40.76–41.01]).

Regression analyses demonstrated that older age groups experienced higher rates of HCV infection as compared to the 18–29 age group, and that HCV infection rates by district of residence varied considerably. Individuals reporting residence outside Uzbekistan had significantly elevated prevalence in univariate analysis, but this

TABLE 1 Characteristics of chronic HBV & HCV infection in Tashkent

	HBV positive	Total	Crude prevalence (%)	Adjusted prevalence (%)	Univariate		Multivariate	
HBV								
Total	1509	53841	2.80 [2.67–2.95]	3.23 [3.08–3.38]				
Sex					aPR		aPR	
Male	714	16761	4.26 [3.96–4.58]	4.39 [4.15–4.65]	2.09 [1.90–2.32]	<.001	1.92 [1.74–2.13]	<.001
Female	795	37080	2.14 [2.00–2.30]	2.10 [1.93–2.28]	Ref		Ref	
Age group								
18–29	347	14320	2.42 [2.18–2.69]	2.56 [2.33–2.81]	Ref		Ref	
30–39	533	13112	4.06 [3.74–4.42]	4.75 [4.40–5.13]	1.86 [1.64–2.10]	<.001	1.92 [1.70–2.17]	<.001
40–49	347	10290	3.37 [3.04–3.74]	4.11 [3.73–4.54]	1.61 [1.40–1.84]	<.001	1.73 [1.51–1.99]	<.001
50–59	183	8913	2.05 [1.77–2.37]	2.43 [2.09–2.81]	0.95 [0.79–1.13]		1.10 [0.92–1.31]	
60–69	71	5145	1.38 [1.09–1.75]	1.49 [1.17–1.89]	0.58 [0.45–0.74]	<.001	0.71 [0.55–0.91]	<.05
70–99	28	2061	1.36 [0.92–1.99]	1.38 [0.93–2.03]	0.54 [0.36–0.78]	<.01	0.73 [0.48–1.05]	
Residence – district								
Almazar	76	4558	1.67 [1.32–2.09]	2.06 [1.67–2.54]	0.75 [0.59–0.93]	<.05	0.83 [0.65–1.03]	
Bektemir	51	1676	3.04 [2.30–4.01]	3.10 [2.34–4.09]	1.12 [0.83–1.49]		1.23 [0.91–1.62]	
Mirabad	43	1573	2.73 [2.01–3.70]	2.97 [2.20–4.00]	1.08 [0.78–1.45]		1.05 [0.76–1.41]	
Mirzo Ulugbek	120	4853	2.47 [2.06–2.96]	2.77 [2.33–3.28]	1.00 [0.82–1.21]		0.93 [0.77–1.13]	
Sergeli	28	1298	2.16 [1.47–3.15]	2.47 [1.70–3.56]	0.90 [0.61–1.27]		0.85 [0.57–1.21]	
Uchtepa	27	1399	1.93 [1.30–2.84]	2.18 [1.48–3.19]	0.79 [0.53–1.14]		0.78 [0.52–1.12]	
Chilanzar	40	1037	3.86 [2.80–5.26]	4.30 [3.17–5.80]	1.56 [1.12–2.11]	<.05	1.46 [1.05–1.97]	<.05
Shaykhantokhur	72	4430	1.63 [1.28–2.05]	1.81 [1.45–2.26]	0.66 [0.51–0.83]	<.01	0.72 [0.56–0.91]	<.05
Yunusabad	407	16769	2.43 [2.20–2.67]	2.76 [2.51–3.03]	Ref		Ref	
Yakkasaray	49	2973	1.65 [1.23–2.19]	1.74 [1.31–2.29]	0.63 [0.47–0.83]	<.01	0.60 [0.45–0.80]	<.01
Yashnobod	109	3728	2.92 [2.42–3.53]	3.29 [2.77–3.90]	1.19 [0.98–1.44]		1.06 [0.87–1.29]	
UZB – Outside Tashkent	279	6961	4.01 [3.57–4.50]	4.63 [4.17–5.14]	1.68 [1.46–1.93]	<.001	1.56 [1.35–1.80]	<.001
Outside Uzbekistan	208	2586	8.04 [7.04–9.18]	8.80 [7.83–9.88]	3.19 [2.74–3.71]	<.001	1.84 [1.53–2.21]	<.001
Birthplace – region								
Tashkent	1061	44415	2.39 [2.25–2.54]	2.71 [2.56–2.87]	Ref		Ref	
Andizhan	25	504	4.96 [3.30–7.34]	6.17 [4.34–8.65]	2.28 [1.58–3.16]	<.001	1.74 [1.20–2.44]	<.01
Bukhara	27	644	4.19 [2.83–6.12]	4.54 [3.15–6.45]	1.67 [1.15–2.35]	<.05	1.24 [0.84–1.76]	
Fergana	37	683	5.42 [3.89–7.46]	6.54 [4.86–8.72]	2.41 [1.77–3.21]	<.001	1.92 [1.39–2.57]	<.001
Dzhizak	27	447	6.04 [4.09–8.77]	6.37 [4.46–8.97]	2.35 [1.62–3.28]	<.001	1.70 [1.15–2.40]	<.05
Namangan	26	452	5.75 [3.86–8.42]	6.81 [4.79–9.56]	2.51 [1.74–3.50]	<.001	1.90 [1.30–2.67]	<.01
Navoi	15	304	4.93 [2.89–8.18]	5.15 [3.10–8.33]	1.90 [1.12–2.98]	<.05	1.44 [0.84–2.28]	
Kashkadarya	89	1218	7.31 [5.94–8.95]	8.69 [7.25–10.39]	3.21 [2.63–3.87]	<.001	2.30 [1.85–2.83]	<.001
Samarkand	52	1172	4.44 [3.36–5.82]	5.29 [4.13–6.75]	1.95 [1.50–2.49]	<.001	1.50 [1.14–1.93]	<.01
Syrdarya	21	396	5.30 [3.39–8.12]	6.16 [4.07–9.14]	2.27 [1.48–3.32]	<.001	1.80 [1.16–2.64]	<.05
Surkhandarya	49	694	7.06 [5.32–9.29]	7.95 [6.16–10.19]	2.93 [2.24–3.77]	<.001	2.06 [1.55–2.70]	<.001
Khorezm	27	510	5.29 [3.58–7.71]	5.34 [3.63–7.75]	1.97 [1.32–2.82]	<.01	1.59 [1.05–2.29]	<.05
Republic of Karakalpakstan	16	342	4.68 [2.79–7.64]	5.48 [3.40–8.61]	2.02 [1.23–3.10]	<.01	1.59 [0.96–2.45]	
Outside Uzbekistan	37	2060	1.80 [1.29–2.49]	2.20 [1.61–2.99]	0.81 [0.59–1.09]		0.87 [0.63–1.18]	

(Continues)

TABLE 1 (Continued)

	HCV positive	Total	Crude prevalence (%)	Adjusted prevalence (%)	Univariate		Multivariate	
HCV								
Total	1610	54396	2.96 [2.82–3.11]	3.02 [2.87–3.16]				
Sex					aPR		aPR	
Male	603	17084	3.53 [3.26–3.82]	3.50 [3.29–3.73]	1.38 [1.25–1.52]	<.001	1.45 [1.32–1.61]	<.001
Female	1007	37312	2.70 [2.54–2.87]	2.54 [2.36–2.74]	Ref		Ref	
Age group								
18–29	168	14464	1.16 [1.00–1.35]	1.20 [1.04–1.38]	Ref		Ref	
30–39	260	13471	1.93 [1.71–2.18]	1.99 [1.77–2.25]	1.66 [1.39–2.00]	<.001	1.63 [1.36–1.96]	<.001
40–49	422	10448	4.04 [3.67–4.44]	4.70 [4.29–5.15]	3.92 [3.33–4.63]	<.001	3.83 [3.25–4.54]	<.001
50–59	395	8902	4.44 [4.02–4.89]	4.89 [4.42–5.41]	4.08 [3.44–4.85]	<.001	3.96 [3.34–4.72]	<.001
60–69	274	5089	5.38 [4.79–6.05]	5.46 [4.84–6.16]	4.56 [3.79–5.48]	<.001	4.42 [3.67–5.34]	<.001
70–99	91	2022	4.50 [3.66–5.52]	4.49 [3.65–5.52]	3.75 [2.91–4.78]	<.001	3.73 [2.89–4.79]	<.001
Residence – District								
Almazar	120	4570	2.63 [2.19–3.14]	2.77 [2.31–3.31]	0.81 [0.66–0.98]		0.85 [0.70–1.03]	
Bektemir	40	1678	2.38 [1.73–3.26]	2.13 [1.51–2.98]	0.62 [0.43–0.86]	<.01	0.64 [0.44–0.88]	<.05
Mirabad	72	1583	4.55 [3.60–5.72]	5.10 [4.07–6.37]	1.49 [1.16–1.88]	<.01	1.47 [1.15–1.85]	<.01
Mirzo Ulugbek	198	4852	4.08 [3.55–4.69]	4.45 [3.89–5.09]	1.30 [1.11–1.52]	<.01	1.23 [1.05–1.44]	<.05
Sergeli	26	1317	1.97 [1.32–2.92]	2.08 [1.39–3.09]	0.61 [0.40–0.88]	<.05	0.60 [0.39–0.87]	<.05
Uchtepa	38	1386	2.74 [1.97–3.78]	2.91 [2.08–4.04]	0.85 [0.60–1.17]		0.90 [0.63–1.23]	
Chilanzar	49	1025	4.78 [3.59–6.32]	4.94 [3.71–6.53]	1.44 [1.06–1.91]	<.05	1.45 [1.07–1.92]	<.05
Shaykhantokhur	100	4433	2.26 [1.85–2.75]	2.24 [1.83–2.73]	0.65 [0.52–0.80]	<.001	0.83 [0.67–1.03]	
Yunusabad	545	16790	3.25 [2.99–3.53]	3.43 [3.16–3.72]	Ref		Ref	
Yakkasaray	68	2973	2.29 [1.79–2.91]	2.41 [1.90–3.04]	0.70 [0.55–0.89]	<.05	0.64 [0.50–0.82]	<.01
Yashnobod	115	3743	3.07 [2.55–3.69]	2.96 [2.46–3.55]	0.86 [0.70–1.05]		0.84 [0.69–1.02]	
UZB – Outside Tashkent	161	7134	2.26 [1.93–2.64]	2.07 [1.77–2.43]	0.60 [0.50–0.72]	<.001	0.70 [0.58–0.83]	<.001
Outside Uzbekistan	78	2912	2.68 [2.14–3.35]	2.36 [1.89–2.95]	0.69 [0.54–0.87]	<.01	0.84 [0.64–1.08]	
Birthplace – region								
Tashkent	1287	44602	2.89 [2.73–3.05]	2.97 [2.81–3.13]	Ref		Ref	
Andizhan	26	514	5.06 [3.40–7.42]	5.32 [3.65–7.64]	1.79 [1.21–2.54]	<.01	1.81 [1.22–2.58]	<.01
Bukhara	21	661	3.18 [2.03–4.90]	2.78 [1.74–4.36]	0.94 [0.58–1.42]		0.90 [0.55–1.37]	
Fergana	20	731	2.74 [1.72–4.27]	2.27 [1.37–3.70]	0.77 [0.45–1.20]		0.74 [0.44–1.17]	
Dzhizak	9	494	1.82 [0.89–3.56]	1.50 [0.71–3.01]	0.51 [0.23–0.93]		0.60 [0.28–1.12]	
Namangan	19	468	4.06 [2.53–6.38]	3.70 [2.27–5.88]	1.25 [0.75–1.92]		1.33 [0.80–2.05]	
Navoi	9	315	2.86 [1.40–5.54]	2.54 [1.21–5.04]	0.86 [0.40–1.57]		1.00 [0.47–1.85]	
Kashkadarya	38	1297	2.93 [2.11–4.04]	2.95 [2.15–4.02]	0.99 [0.72–1.34]		1.05 [0.75–1.43]	
Samarkand	28	1198	2.34 [1.59–3.41]	2.64 [1.85–3.74]	0.89 [0.62–1.24]		0.83 [0.57–1.15]	
Syrdarya	19	411	4.62 [2.88–7.25]	5.14 [3.29–7.89]	1.73 [1.09–2.60]	<.05	1.71 [1.07–2.58]	<.05
Surkhandarya	28	737	3.80 [2.59–5.52]	3.14 [2.08–4.67]	1.06 [0.69–1.54]		1.05 [0.68–1.54]	
Khorezm	24	514	4.67 [3.08–6.97]	4.89 [3.26–7.21]	1.65 [1.08–2.39]	<.05	1.61 [1.05–2.34]	<.05
Republic of Karakalpakstan	5	364	1.37 [0.51–3.36]	1.76 [0.74–3.87]	0.59 [0.24–1.18]		0.52 [0.21–1.04]	
Outside Uzbekistan	77	2090	3.68 [2.94–4.61]	3.72 [2.95–4.69]	1.26 [0.98–1.58]		0.93 [0.73–1.17]	

Abbreviation: aPR, adjusted prevalence ratio.

risk did not remain in multivariate analysis. For patient birthplace, there was no significant difference between Tashkent and most other provinces, and no significant difference between individuals born in Tashkent and those born outside Uzbekistan.

SVR-12 among 63 randomly selected individuals who initiated treatment was 97%. Among those who did not know of their HCV infection prior to this study (33 cases), SVR-12 was 100%.

3.3 | Cascade of care

Figure 3 shows the HBV and HCV cascade of care for the whole project as well as pre- and post-COVID-19 pandemic period. The HCV cascade included the viraemic rate of 53% (50%–57%) for all the individuals who had a blood draw and 80% (72%–88%) for those who came in for a physician consultation. The latter indicated the percent of the individuals who were eligible to receive a prescription. The GPs prescription and treatment initiation patterns are summarized in Figure 4.

3.4 | APRI/eGFR/coinfection

Among a total of 2227 HCV+ individuals, there were 1674 (75%) with complete data for APRI. Mean APRI score was 0.608 (0.584–0.631). There were 42 individuals (2.5%) with APRI score ≥1.5 and 38 individuals (2.3%) with APRI score >1 and ≤1.5. Thus, expanding the cut-off for cirrhosis from 1.5 to 1.0 had a small impact on the number of individuals referred to specialists.

There were complete eGFR results for 1642 HCV+ individuals (74% of total). Mean eGFR was 81.74 (80.73–82.74) and 54 individuals (3.3%) had eGFR < 30. Among HBV+ individuals, 2307 (85% of total) had eGFR data available, and mean eGFR was 86.15 (85.41–86.88). There were 27 individuals (1.2%) with eGFR < 30.

Of those who were previously unaware of either HBV or HCV infection, there were 58 HBV/HCV coinfected persons, representing 3.86% of HBV-infected and 3.63% of HCV-infected individuals. HIV/HBV coinfection prevalence was 0.63%.

4 | DISCUSSION

The objective of this study was to demonstrate the feasibility of simplified test/treat protocols and high-throughput screening of a general population and to estimate HBV/HCV prevalence. The project and its outcomes were confounded by the COVID-19 pandemic and the shutdown of all health facilities from March to September 2020, although it also provided a new opportunity that allowed us to screen for HBV/HCV while a national screening for COVID-19 was conducted.

Our findings influenced the national viral hepatitis elimination program by identifying the age cohorts and regions to prioritize even though the study was not designed as a serosurvey. A limitation of the current study was the potential lack of representativeness of the sampled population. A substantial number of individuals were already aware of their infection and were excluded from the analysis. This was done to reduce selection bias for individuals who were seeking low-cost treatment for their infection. However, individuals who are diagnosed and have not received curative treatment do represent a portion of total prevalent cases at the national level. Therefore, exclusion of individuals with prior knowledge of infection could result in underestimation of true disease burden. Furthermore, over 80% of all individuals reported birthplace within Tashkent province. Differences may exist between regions in risk factors for infection, and the current results show that HBV prevalence was significantly elevated among individuals reporting place of birth in multiple Uzbek provinces outside of Tashkent.

Uzbekistan provides universal screening of pregnant women for HBV, HCV and HIV. In addition, universal HBV three-dose vaccination started in 1999 and universal birth dose in 2001. The HBV vaccination rate has been over 99% since 2011.[20] The impact of vaccination is seen in Figure 2 with a much lower HBV prevalence in the vaccinated age cohorts. The lower HBV prevalence among older age cohorts could be due to hepatitis D virus (HDV) coinfection[21] which has a much faster disease progression and mortality (fewer individuals are surviving their HBV/HDV co-infection). HCV transmission in Uzbekistan has historically been through blood products.[22] This study was sufficient to help prioritize regions to expand the screening and linkage to care. In 2021–2022, this project was expanded to six regions outside of Tashkent to screen 250 000 people for HBV/HCV (UHEP 2.0). The result of that study will be reported separately once complete.

Overall, we were able to demonstrate very high-throughput screening using HBV/HCV rapid tests at polyclinics, but the screening throughput dropped by 70% as the result of fewer individuals coming to health facilities once polyclinics re-opened in September 2020. We had to increase the number of polyclinics in our program from 3 (pre-COVID-19) to 10 to maintain the same screening throughput, and screening had to be conducted outdoors or in large rooms with social distancing to minimize COVID-19 transmission. The post-COVID-19 screening was combined with a national program that offered free COVID-19 testing at the polyclinics.

Opportunistic screening did result in a large loss to follow up. For HBsAg+ individuals, 14% were lost to follow up (LTFU) between two rooms (HBsAg screening and HIV/creatinine testing) and another 62% did not see a physician to discuss their test results and review their treatment options (Figure 3). Changes in these rates, pre- and post-COVID, were not statistically significant. However, we did see a statistically significant drop in physician consultation post-COVID. Pre-COVID, 47% of the individuals came in for consultation but individuals had to travel to RIV to see a physician. A random survey of 77 individuals indicated that 61% of individuals travelled ≥30 min and 31% had to travel ≥1 h to RIV. General practitioners (GPs) were trained to treat HBV individuals at the same clinic to remove this burden. This change was implemented in September 2020

when polyclinics were re-opened but any increase in linkage to care was confounded by the impact of COVID. We saw a 40% reduction in physician consultation post-COVID despite the change to GPs. Treatment rate stayed constant throughout the program.

The HCV cascade of care was very similar with 13% of the individuals lost between two rooms (HCV rapid test and blood draw). Viraemic rate for all tested was 53%, but this increased to 80% among individuals who consulted with a physician. More advanced liver disease was not the cause as individuals attending a consultation had an average APRI score that was within the confidence interval of the APRI score of all tested. Again, the percent of HCV-treated individuals pre- and post-COVID were statistically similar.

A key observation of this study was that simplifications of the cascade of care did not result in an improved patient retention in general population screening. Post-COIVD, HBV individuals were tested and treated at the same clinic on the same day whereas HCV individuals had to come back the following week to receive and review their PCR and APRI results with a physician. The loss to follow up was statistically the same between the two groups. We attribute this to our general population screening strategy. After excluding those who were previously diagnosed and motivated to engage in this program, we were left with a population that is attending a polyclinic for other reasons. Screening them for HBV and HCV without an awareness program to motivate individuals to engage in care resulted in the same loss to follow up whether a consultation was offered the same day in the same clinic or if the patient had to come back a week later.

Nearly all the donated medicine was distributed to warehoused individuals already aware of their infection and were not included in this analysis. Only 9 HBV individuals and 23 HCV individuals met the government criteria for free treatment and were unaware of their infection prior to this study.

In a survey of 203 LTFU individuals, 13% of all HBsAg+ individuals and 38% of all HCV RNA+ were treated in the private market. For HBV, 46% of the treated individuals went to a private doctor while the rest saw a doctor in our program but picked up their prescription outside of our program. For HCV, 19% of the LTFU individuals reported going to a private doctor to be treated while the rest saw a doctor in our program but picked up a prescription outside of our program. To better understand this, we conducted another survey of 73 randomly selected participants, 85% had an annual household income of ≤$2500 per year and 50% made ≤$1000 annually.

According to the World Bank, the gross domestic product (GDP) per capita in Uzbekistan was $1750 with $99 annual healthcare expenditure per capita, and 58% of total health expenditure was in the private system.[23] With 89.8 thousand doctors in the country,[24] elimination of viral hepatitis is feasible, but requires the engaging of the private healthcare system to achieve the elimination of viral hepatitis. Our small-sampled survey suggests that the public health system in this study serviced low- and middle-income individuals while the upper middle- and high-income individuals prefer to utilize private health facilities.

We estimate that 29% of all the HBsAg+ and 51% of all HCV+ RNA+ individuals were treated within our program and in the private market. The Polaris Observatory estimates that 27% of the HBsAg+ population in Uzbekistan is eligible for treatment.[25] The strategy to test and treat all HBsAg+ individuals was controversial and not endorsed by the technical advisory group (TAG). However, it was approved by the investigational review board and the Ministry of Health. The removal of all restrictions, except for HBsAg positivity, resulted in only a slightly higher treatment rate than the eligible population. In a survey of 73 individuals, 42% did not know viral hepatitis infection can lead to cancer suggesting low viral hepatitis awareness among our individuals. In September of 2020, we did start a patient awareness campaign by leaving brochures in the waiting areas where HBsAg+ and HCV antibody positive individuals waited for their follow-up tests. However, we could not measure the impact of this awareness campaign due to the large loss to follow up as the result of post-COVID-19.

A separate analysis of GPs prescription and treatment initiation (Figure 4) found treatment initiation rates between 12% and 85% of the eligible population (RNA+ for HCV and HBsAg+ for HBV) even though all physicians received the same training. A lower overall HCV treatment initiation could be explained for individuals' desire to be treated in the private market. This analysis suggests that some GPs are much more comfortable treating HBV/HCV individuals. As part of Universal Healthcare, there is a large push to task shift key healthcare interventions to the general practitioners. Our study suggests that GPs require multiple training and awareness programs to be consistently motivated to link individuals to care. Monitoring and evaluation systems like Figure 4 may be needed to assess individual physicians' performance, provide feedback and additional training.

Finally, a key observation of this study was the difficulty of engaging males into care. Even though males had a much higher prevalence rate, they accounted for 31.1% of all HBV and 31.4% of all HCV cases who came in for screening. Discussions with polyclinics confirmed that males were much less likely to come in for healthcare and the male to female ratio observed in our study was consistent with the ratio that attend polyclinics for any reason. Before March, we did meet with the religious leaders in the community, and the Ministry of Health sent a request for these leaders to talk about the importance of hepatitis screening, but that strategy was not feasible once the COVID pandemic started and large gatherings were prohibited.

There were several shortcomings with this study, including the small sample size of our surveys. However, the objective of these surveys was to get a qualitative assessment rather than a statistically significant measure (which would have required a much larger sample size). In addition, a key goal of this study was operational research where the study was modified based on learnings during the study. This meant that the study protocols changed throughout the study: specialists to GPs, screening in 3–10 polyclinics to maintain the same screening throughput and adding an awareness campaign in the middle of the study. However, the largest shortcoming was conducting this study in the middle of a pandemic that resulted in a 6-month shutdown and limited access to healthcare once the clinics were open.

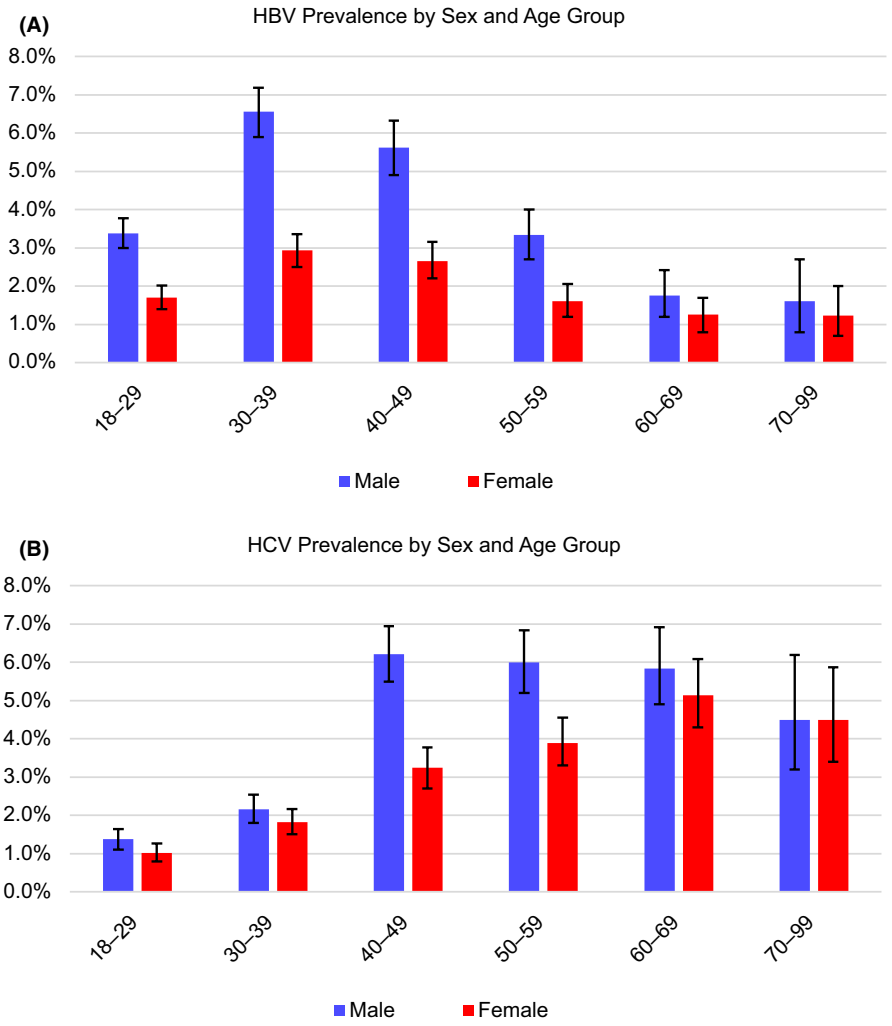
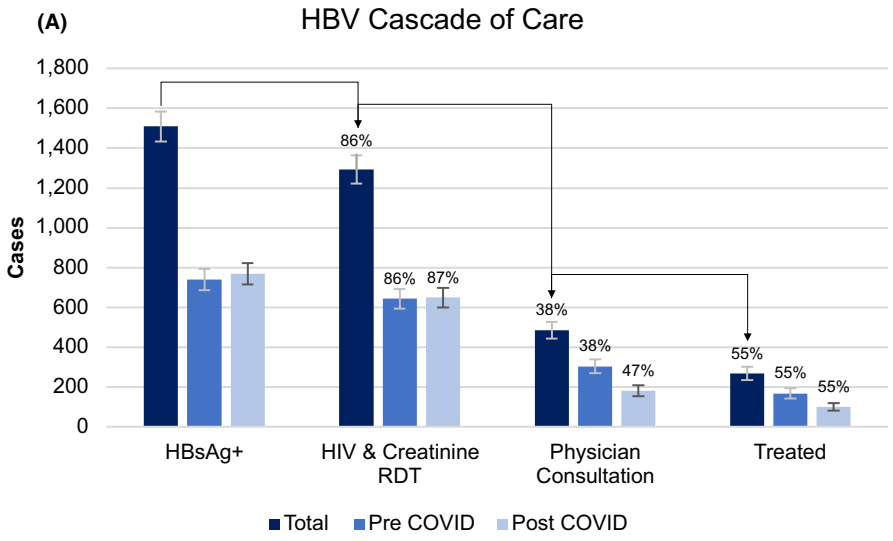


FIGURE 2 (A) HBV prevalence by sex and age group in Tashkent. (B) HCV prevalence by sex and age group in Tashkent.

Despite these shortcomings, there were many key insights that would be applicable to viral hepatitis programs in other LMICs. (1) To diagnose 90% of all HBV/HCV infections, general population screening is needed. In our study, there was no identifiable risk factor, other than dental procedures and medical injections, that would lead to a special population screening strategy. In countries where nosocomial infection is the key risk factor, universal screening is needed. (2) General population screening will result in a large loss to follow up unless it is accompanied by a large awareness campaign. (3) An awareness campaign would be highly beneficial before screening starts. This campaign should target individuals and GPs. The percentage of individuals who initiated treatment was the same pre- and post-COVID even though we saw a large drop in the number of individuals seeing physicians post-COVID. This could suggest that if the individuals are knowledgeable and motivated, they are more likely to start treatment despite barriers. In addition, as shown in Figure 4, if GPs are knowledgeable and motivated, they are also more likely to get individuals to initiate treatment. (4) Targeted awareness programs for males are needed. HBV/HCV prevalence is typically higher among males, and they do not access healthcare as often as females. Specific strategies to bring them in for screening and linking them to care are needed. (5) It might be counterintuitive, but on-site viral load and other lab tests may not be as beneficial in the general population as compared to populations already motivated to seek testing and treatment. When we compared HBV and HCV cascades of care, we expected a large difference between the two. HBV individuals were all tested on-site, and post-COVID, they were treated on-site. In comparison, the HCV individuals had to come back after 1 week to discuss the RNA and lab test results with a physician (Figure 3). In fact, the two cascades of care are nearly identical suggesting that on-site lab tests do not result in a higher linkage to care. (6) Combining viral hepatitis programs with other national programs (e.g. COVID-19, HIV or tuberculosis screening) is feasible and highly recommended. Combining our program with the national COVID-19 screening allowed us to expand to more polyclinics. Although visits to polyclinics and doctors dropped post-COVID, the rest of the cascade of care remained relatively the same. (7) In countries where a significant portion of the population gets their medical care through private healthcare (most LMICs), the private healthcare system has to be engaged to achieve the World Health Organization's (WHO) elimination targets. (8) Simplifying HBV test and treat guidelines to base treatment on HBsAg positivity does not mean every HBV patient will go on treatment. In our study, despite this change, HBV treatment remained well below HCV treatment rate. As seen with



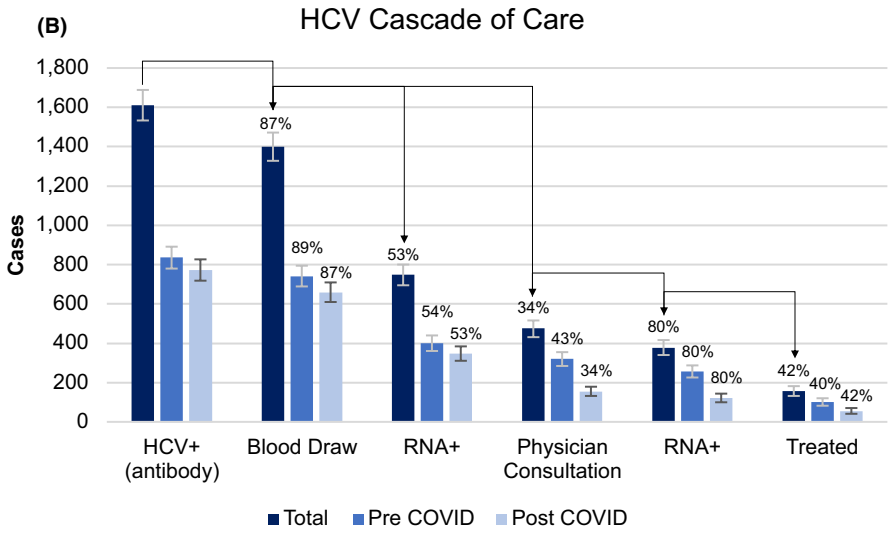


FIGURE 3 HBV and HCV cascade of care—total program, pre-COVID-19, post-COVID-19 pandemic.

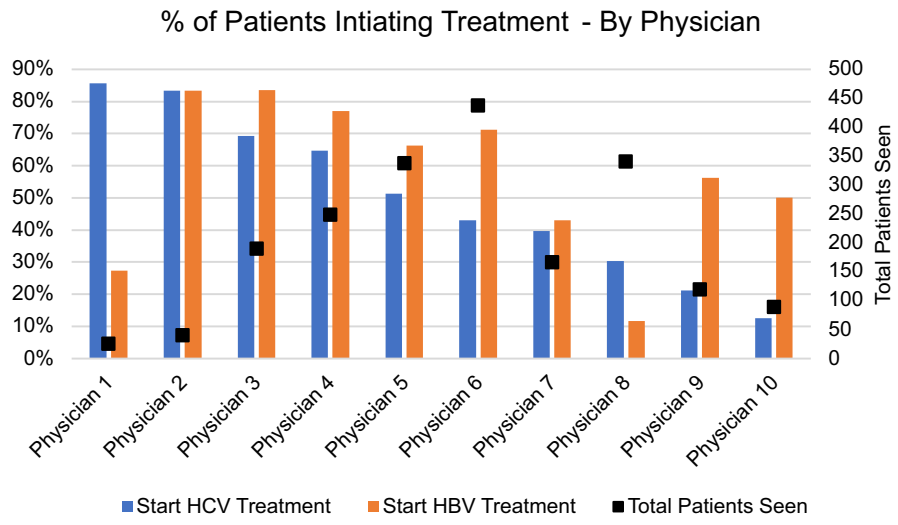


FIGURE 4 Percent of HBV/HCV individuals linked to care by general practitioner doctor.

HIV, considerable effort is needed to bring in individuals, link them to care and maintain them in care even if treatment barriers are removed. To achieve the HBV treatment targets, considerable effort will be required, as well, to improve the overall cascade of care even if all treatment restrictions are removed. (9) Governments should provide free HBV/HCV screening for their population even if they

cannot afford to provide treatment. Our study showed that large-scale screening was feasible using trained nurses. An asymptomatic individual is unlikely to seek HBV/HCV testing if they must pay for it. However, once diagnosed, we observed a consistent cascade of care for HBV and HCV for motivated and aware individuals even though nearly all our individuals had to pay for their own treatment. We did offer low treatment pricing in our program, but some individuals elected to pay higher prices for their medicine in the private market. (10) Governments should provide free HBV/HCV treatment for the portion of the population who cannot afford to pay for their treatment. In our analysis of the World Bank data, 10%–25% of populations in LMICs will cross the catastrophic healthcare expenditure limits[26] at current HBV/HCV medicine prices. This leaves 75%–90% of the population who could potentially pay for their own treatment if they are diagnosed, motivated and linked to care.

To achieve the WHO elimination targets by 2030, novel strategies are needed in LMICs. This demonstration project, as well as the UHEP 2.0 follow-on project conducted in 2021–2022, resulted in the presidential decree that was signed in 2022. This decree provided the budget, resources and IT systems for screening 1 million HBV and HCV individuals annually, HCV treatment and HBV vaccination of all healthcare workers. Properly conducted demonstration projects could be the key to expanding viral hepatitis elimination programs in low- and middle-income countries.

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CONFLICT OF INTEREST

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