

Access to antiviral therapy for chronic hepatitis B during COVID-19

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SUMMARY

OBJECTIVE: Hepatitis B is an important public health concern. Currently, the COVID-19 pandemic is a major challenge for health systems, and the access to pharmacologic and non-pharmacologic treatment of chronic diseases, such as hepatitis B, may have been affected due to the contingency measures. This study aimed to evaluate the access to antiviral therapy during the ongoing pandemic.

METHODS: This was a descriptive analysis of the access to treatment for chronic hepatitis B at a tertiary-level university hospital in São Paulo, integrated with the Brazilian health system. The study was conducted from April to December 2020.

RESULTS: Access to antiviral therapy for 225 patients was assessed. The majority of the population was male (59%). The main type of service was the *Programa Medicamento em Casa* (Home Medication Delivery Program), which was availed by 144 (64%) patients. Women had poorer access to antiviral therapy (56%, $p < 0.05$), and patients registered in the HMDP (68%, $p < 0.05$) had better access. The age group of >48 years represented 70% of the group without access to antiviral therapy. Twenty-two pharmaceutical appointments were conducted through phone calls with patients without access to antiviral therapy.

CONCLUSION: This study contributes to the rationalization of efforts in a public health crisis through the identification of groups with the highest risk of poor access to antiviral therapy and the demonstration of the benefits of a medication delivery system.

KEYWORDS: Hepatitis B. Antiviral agents. COVID-19. Public health.

INTRODUCTION

Hepatitis B is an important public health issue with significant morbidity and mortality rates. Since the beginning of the century, mortality due to viral hepatitis has increased by 22%, which is expected to increase in the absence of adequate diagnosis and treatment. Globally, hepatitis B is responsible for approximately 800,000 deaths from complications such as cirrhosis and hepatocellular carcinoma, and 3.5% of the world population is estimated to have chronic hepatitis B^{1,2}. In Brazil, 9,938 new cases and 1,728 deaths from hepatitis B were recorded in 2018³.

The main goal of antiviral therapy against hepatitis B is to achieve viral suppression to slow disease progression and prevent complications, increasing survival and quality of life^{4,5}. Currently, the Ministry of Health offers five oral drugs for the treatment of chronic hepatitis B: tenofovir (TDF), entecavir (ETV), and lamivudine (3TC)⁶. Ford et al. reported treatment adherence as one of the main factors that define the success of antiviral therapy and discussed the presence of numerous barriers, such as lack of medication. Adverse reactions can also be a

barrier to adherence^{2,7}. Abreu et al. identified an unsatisfactory rate of non-adherence (43%) when compared with experimental models, which associated rates below 65% with an additional 2.6 million deaths in a 15-year period. In a prospective study, for 3 consecutive years, a significant increase in the rate of adherence after health education to patients was noted^{8,9}.

Since March 2020, the COVID-19 pandemic has become a global challenge to health systems. The restriction measures and mobilization of health professionals may have impaired the management of chronic diseases. Supplying medications for chronic use is a priority of health services and, by extension, of the pharmaceutical service^{10,11}. The pharmacist plays an important role in fostering adherence and monitoring the efficacy and safety of current therapy to avoid unnecessary hospital visits^{10,12}.

Therefore, according to the recommendations of the official entities in the State of São Paulo, the Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo instituted contingency measures on March 18, 2020, aimed at ensuring medical care to patients through the program “HC at home”

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with the postponement of in-person medical consultations and extension of the validity of medical prescriptions.

In the midst of the COVID-19 pandemic, access to drugs may be hampered due to the adopted contingency measures and, consequently, impair the treatment of chronic diseases.

Regular and continued use of medications is essential for the success of therapy in hepatitis B. Therefore, it is necessary to investigate the access to antiviral therapy during the pandemic period and the current public health situation.

METHODS

This was a descriptive analysis of patients undergoing treatment for chronic hepatitis B who continued and discontinued antiviral therapy, given the contingency measures adopted secondary to the COVID-19 pandemic.

This study was conducted in a tertiary-level university hospital in São Paulo integrated into the Unified Health System. Patients aged >18 years, diagnosed with chronic hepatitis B, using antiviral therapy (e.g., TDF, ETV, or 3TC), and in outpatient follow-up were included. Patients co-infected with hepatitis C and human immunodeficiency virus were excluded.

Data were collected from patients regarding the prescribed antiviral therapy (e.g., TDF, ETV, or 3TC) between October 1, 2019, and April 1, 2020, and medications were dispensed by the pharmacy from April 1 to 30, 2020, through an institutional computerized system of medical records. After confirming the withdrawal or delivery of drugs, two groups were identified: group with access to antiviral therapy and group without access to antiviral therapy (Figure 1).

The members of the group without access to antiviral therapy were evaluated for possible failures in the dispensing process and were the candidates for distanced pharmaceutical consultation through phone calls. The distance pharmaceutical consultation form was applied individually and recorded in electronic medical records. After 30 days from the date of consultation and registration in the institutional system, a favorable (i.e., dispensation of treatment and continuity of antiviral therapy) or unfavorable outcome (i.e., probable treatment abandonment) was assessed.

Quantitative variables are presented as absolute values and mean±standard deviation, and qualitative variables are presented as absolute frequency (n) and relative frequency (%). The association between qualitative variables was assessed by the chi-square statistical test, with a significance set at $p < 0.05$.

According to the opinion no. 4.157.514 of the Research Ethics Committee of the institution, the study was exempt from the requirement of the informed consent form.

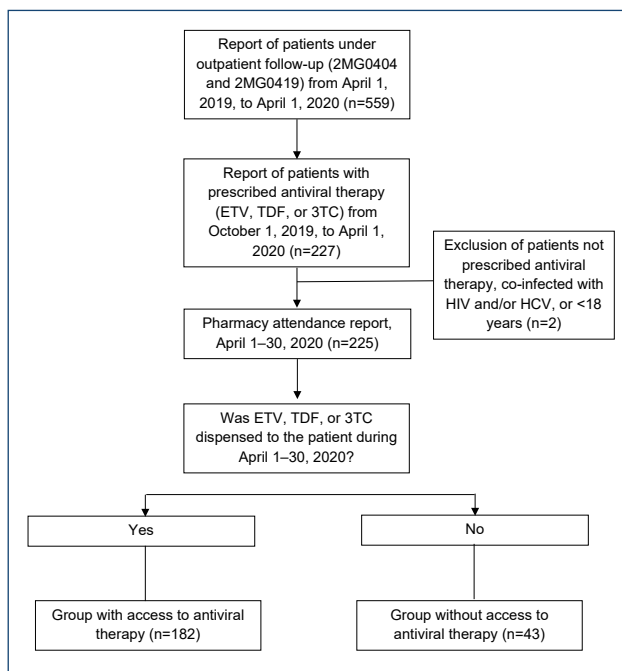


Figure 1. Flowchart of the patient enrollment process.

RESULTS

The study analyzed 225 patients who were prescribed antiviral therapy regarding their access to the prescribed medication in the proposed period. A total of 182 (80.9%) patients were identified to have access to the prescribed treatment, whereas 43 (19.1%) patients did not have access to the drug.

The general characteristics of the study participants are shown in Table 1. The largest percentage of the population is male (59%). The mean age was 55.11 ± 14.20 years. The most prescribed drug was tenofovir, being given to 181 (80.4%) patients. The main type of care in the pharmacy was the Home Medication Delivery Program (HMDP), an institutional program for the delivery of medicines at home, to 144 (64%) patients.

When analyzing the association between gender and access to antiviral therapy (Table 2), we confirmed that women had less access than men to antiviral therapy (56 vs. 44%, $p < 0.05$) during the study period.

Similarly, when comparing the groups with and without access to antiviral therapy regarding the type of care, access was higher in the group that received the drug through the HMDP, corresponding to 68% ($p < 0.05$) among those who had guaranteed access to antiviral therapy (Table 3).

The analysis of the group without access to antiviral therapy revealed that 30% experienced access failure due to the

inefficiency of the measures during the pandemic. The remaining 70% was attributed to patient non-adherence. The age group of 48–77 years corresponded to 70% of the patients in the group without access to antiviral therapy.

The pharmaceutical consultations conducted from August to December 2020 recorded the reasons reported by 22 (47%) of the 43 patients without access to antiviral therapy (Table 4): 9 (41%) did not reside in São Paulo (capital); 15 (68%) mainly used public transportation; 14 (64%) had remaining medications at home; and 5 (23%) had a “fear of leaving home.”

Table 1. General characteristics of patients with chronic hepatitis B treated with antiviral therapy at an outpatient gastroenterology clinic.

Characteristics	Total (N=225)
Sex, n (%)	
Female	93 (41.33)
Male	132 (58.67)
Age (years), mean±SD	55.11±14.20
Medications, n (%)	
Tenofovir	184 (81.78)
Entecavir	36 (16.00)
Lamivudine (tablet)	3 (1.33)
Lamivudine (suspension)	2 (0.89)
Care offered by pharmacy, n (%)	
In-person	81 (36)
Home medicine program	144 (64)

SD: standard deviation.

Table 2. Comparison of groups with and without access to antiviral therapy by sex.

Sex	With access to antiviral therapy		Without access to antiviral therapy		p-value
	n	%	n	%	
Female	69	38	24	56	0.031
Male	113	62	19	44	0.031

Table 3. Comparison of groups with and without access to antiviral therapy by care offered.

Care provided by pharmacy	With access to antiviral therapy		Without access to antiviral therapy		p-value
	N	%	N	%	
In-person	58	32	23	53	0.007
Home medicine program	124	68	20	47	0.007

DISCUSSION

The data from this study were collected at the beginning of the COVID-19 pandemic, in which there were numerous changes in social mobility due to the establishment of control measures, particularly social distancing¹³. The results indicate the difficulty of access to medications for a significant proportion of patients.

Table 4. Distance pharmaceutical consultations and responses from patients in the without access to antiviral therapy group (n=22).

Remote pharmaceutical consultations		n	%
Performed		22	51
Not performed		21	49
In which city do you currently live?	Sao Paulo	11	50
	Other	11	50
How long does it take you to travel to the Hospital das Clínicas?	30 min	1	5
	1 h	11	50
	>1 h	10	45
What means of transportation do you use to travel to the Hospital das Clínicas?	Own	7	32
	Public	15	68
Do you live alone?	Yes	10	45
	No	12	55
What medication are you using for the treatment of chronic hepatitis B?	TDF	13	59
	ETV	6	27
	3TC	0	0
	Don't know	3	14
Are you responsible for your pharmacotherapy?	Yes	22	100
	No	0	0
You were not given the drug in April for the treatment of chronic hepatitis B. Why did you not come to the Hospital das Clínicas to receive the drug?	Fear of leaving home	5	23
	Strictly complied with the social isolation recommendations	2	9
	I didn't know the pharmacy was open	0	0
	I used leftover drug at home	14	64
	Distance from hospital	0	0
	Lack of transportation	1	5
	Other	0	0
Did you have to seek emergency medical care with symptoms of COVID-19?	Yes, needed hospitalization for >24 h	1	5
	Yes, but did not need hospitalization	2	9
	No	19	86
Remote post-consultation situation	Continue antiviral therapy	20	91
	Failure to access/likely abandonment	2	9

In a survey conducted between May and June 2020 in Nigeria among study participants with chronic conditions, there was an increase from 10.6 to 35.2% in patients who had difficulty obtaining access to medications¹⁴. In Italy, the impact of COVID-19 on the management of liver diseases, including viral hepatitis, was reported, and in 23% of the patients, the onset of viral hepatitis treatment was postponed¹⁵.

Medication access hampered by the COVID-19 pandemic is an additional challenge to the WHO's target of eliminating viral hepatitis¹. Mobility restrictions and suspension of medical care during this pandemic may have contributed to poor access. In a survey by the World Hepatitis Alliance, 52% of frontline health professionals reported that patients undergoing treatment for viral hepatitis did not have access to the drug¹⁶.

Levorato et al. reported that women, in general, more frequently seek health services¹⁷. In the United States and other English-speaking European countries, men exhibit less compliance than women on the recommendations for social distancing, and those aged >45 years exhibited greater adherence to social distancing measures during this pandemic¹⁸. In this study, females and patients aged >48 years were predominant in the group without access to antiviral therapy, which may be related to better adherence to pandemic measures.

The difficulty of access was greater in those who receive the drug in person at the pharmacy, as well as in the age groups of 41–50 and 61–70 years. These data may be related to the context of the pandemic and restriction measures. The study does not exactly provide the reasons for not accessing the drug but suggests that the number of reduced medical visits and strict compliance with social distancing may have influenced the findings. The generalizability of our results is subject to

limitations such as the limited study duration and lack of data regarding the consequences of the COVID-19 pandemic on disease progression. Further investigations involving the same study population are required.

CONCLUSION

The findings from this study can contribute to the identification and monitoring of high-risk populations and those with potential difficulty in accessing treatment during a public health crisis. The efficiency of the established pandemic contingency plans was not evaluated; however, beneficial results were evident in the drug delivery system that can be expanded in similar contexts to ensure access to all patients.

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AUTHORS' CONTRIBUTIONS

MRB: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **PAR:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **SKO:** Conceptualization, Formal Analysis, Supervision, Validation, Writing – review & editing. **VBP:** Validation, Writing – review & editing.

REFERENCES

1. World Health Organization (WHO). Global hepatitis report, 2017. WHO | World Health Organization, January 01, 2017. [cited on May 02, 2020]. Available from: www.who.int/hepatitis/publications/global-hepatitis-report2017/en/
2. Ford N, Scourse R, Lemoine M, Hutin Y, Bulterys M, Shubber Z, et al. Adherence to nucleos(t)ide analogue therapies for chronic hepatitis B infection: a systematic review and meta-analysis. *Hepatology*. 2018;2(10):1160-7. <https://doi.org/10.1002/hep4.1247>
3. TabNet Win32 3.0. Casos confirmados notificados no sistema de informação de agravos de notificação - São Paulo. Brasil. n.d. [cited on May 17, 2020]. Available from: <http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sinannet/cnv/hepas.def>
4. Lieveld FI, van Vlerken LG, Siersema PD, van Erpecum KJ. Patient adherence to antiviral treatment for chronic hepatitis B and C: a systematic review. *Ann Hepatol*. 2013;12(3):380-91. PMID: 23619254
5. Ha NB, Trinh HN, Rosenblatt L, Nghiem D, Nguyen MH. Treatment outcomes with first-line therapies with entecavir and tenofovir in treatment-naïve chronic hepatitis B patients in a routine clinical practice. *J Clin Gastroenterol*. 2016;50(2):169-74. <https://doi.org/10.1097/MCG.0000000000000345>
6. Brasil. Ministério da Saúde. Protocolo Clínico e Diretrizes Terapêuticas para Hepatite B e Coinfecções. Brasília, DF: Ministério da Saúde; 2016. [cited on May 2, 2020]. Available from <http://www.aids.gov.br/pt-br/pub/2016/protocolo-clinico-e-diretrizes-terapeuticas-para-hepatite-b-e-coinfeccoes>.
7. de Fraga RS, Van Vaisberg V, Mendes LCA, Carrilho FJ, Ono SK. Adverse events of nucleos(t)ide analogues for chronic hepatitis B: a systematic review. *J Gastroenterol*. 2020;55(5):496-514. <https://doi.org/10.1007/s00535-020-01680-0>
8. Abreu RM, da Silva Ferreira C, Ferreira AS, Remor E, Nasser PD, Carrilho FJ, et al. Assessment of adherence to prescribed therapy in patients with chronic hepatitis B. *Infect Dis Ther*. 2016;5(1):53-64. <https://doi.org/10.1007/s40121-015-0101-y>

9. Abreu RM, Bassit LC, Tao S, Jiang Y, Ferreira AS, Hori PC, et al. Long-term virological and adherence outcomes to antiviral treatment in a 4-year cohort chronic HBV study. *Antivir Ther.* 2019;24(8):567-79. <https://doi.org/10.3851/IMP3338>
10. Zheng S-Q, Yang L, Zhou P-X, Li H-B, Liu F, Zhao R-S. Recommendations and guidance for providing pharmaceutical care services during COVID-19 pandemic: a China perspective. *Res Soc Adm Pharm.* 2021;17(1):1819-24. <https://doi.org/10.1016/j.sapharm.2020.03.012>
11. Kretchy IA, Asiedu-Danso M, Kretchy JP. Medication management and adherence during the COVID-19 pandemic: perspectives and experiences from low-and middle-income countries. *Res Soc Adm Pharm.* 2020;17(1):2032-6 <https://doi.org/10.1016/j.sapharm.2020.04.007>
12. Cadogan CA, Hughes CM. On the frontline against COVID-19: community pharmacists' contribution during a public health crisis. *Res Soc Adm Pharm.* 2021;17(1):2032-5. <https://doi.org/10.1016/j.sapharm.2020.03.015>
13. Aquino EML, Silveira IH, Pescarini JM, Aquino R, Souza-Filho JA, Rocha AS, et al. Social distancing measures to control the COVID-19 pandemic: potential impacts and challenges in Brazil. *Ciênc Saúde Colet.* 2020;25(suppl. 1):2423-46. <https://doi.org/10.1590/1413-81232020256.1.10502020>
14. Emmanuel Awucha N, Chinelo Janefrances O, Chima Meshach A, Chiamaka Henrietta J, Ibilolia Daniel A, Esther Chidiebere N. Impact of the COVID-19 pandemic on consumers' access to essential medicines in Nigeria. *Am J Trop Med Hyg.* 2020;103(4):1630-4. <https://doi.org/10.4269/ajtmh.20-0838>
15. Aghemo A, Masarone M, Montagnese S, Petta S, Ponziani FR, Russo FP. Assessing the impact of COVID-19 on the management of patients with liver diseases: a national survey by the Italian association for the study of the Liver. *Dig Liver Dis.* 2020;52(9):937-41. <https://doi.org/10.1016/j.dld.2020.07.008>
16. The Lancet Gastroenterology Hepatology. Eliminating viral hepatitis in the COVID-19 era: weighing challenge and opportunity. *Lancet Gastroenterol Hepatol.* 2020;5(9):789. [https://doi.org/10.1016/S2468-1253\(20\)30237-5](https://doi.org/10.1016/S2468-1253(20)30237-5)
17. Levorato CD, Mello LM de, Silva AS da, Nunes AA, Levorato CD, Mello LM de, et al. Fatores associados à procura por serviços de saúde numa perspectiva relacional de gênero. *Ciênc Saúde Colet.* 2014;19(04):1263-74. <https://doi.org/10.1590/1413-81232014194.01242013>
18. Coroiu A, Moran C, Campbell T, Geller AC. Barriers and facilitators of adherence to social distancing recommendations during COVID-19 among a large international sample of adults. *PLoS One.* 2020;15(10):e0239795. <https://doi.org/10.1371/journal.pone.0239795>

