Impact of National Centralized Drug Procurement Policy on Antiviral Utilization and Expenditure for Hepatitis B in China

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Abstract

Background and Aims: The National Centralized Drug Procurement (NCDP) policy was launched in mainland China in April 2019, with entecavir (ETV) and tenofovir disoproxil fumarate (TDF) being included in the procurement list. We conducted the current study to investigate the impact of the NCDP policy on the utilization and expenditures of antiviral therapy for chronic hepatitis B (CHB) in China. Methods: Procurement records, including monthly purchase volume, expenditure, and price of nucleos(t)ide analogs (NAs), were derived from the National Healthcare Security Administration from April 2018 to March 2021. The changes in volumes and expenditures of the first-line NAs and bid-winning products were calculated. The effects of price, volume, and structure related to drug expenditure were calculated by the Addis and Magrini (AM) Index System Analysis. Results: The purchase volume of NAs significantly increased from 134.3 to 318.3 million DDDs, whereas the expenditure sharply decreased from 1,623.41 to 490.43 million renminbi (RMB) or 241.94 million USD. The proportions of first-line NAs rose from 72.51% (ETV: 69.00%, TDF: 3.51%) to 73.09 million US dollars (USD). The proportions of first-line NAs from 1,623.41 to 490.43 million renminbi (RMB) or 241.94 million DDDs, whereas the expenditure sharply decreased from 1,623.41 to 490.43 million renminbi (RMB) or 241.94 million USD. The proportions of first-line NAs rose from 72.51% (ETV: 69.00%, TDF: 3.51%) to 73.09% (ETV: 77.42%, TDF: 17.55%). AM analysis showed that the NCDP policy decreased the expenditure of all NAs (S=0.91) but increased that of the first-line NAs in the bid-winning list (S=1.13). Assuming the population size of CHB patients remains stable and a compliance rate of ≥75%, the proportion of CHB patients receiving first-line antiviral therapy would increase from 6.36–8.48% to 11.56–15.41%. Conclusions: The implementation of the NCDP policy significantly increased the utilization of first-line NAs for CHB patients at a lower expenditure. The findings provided evidence for optimizing antiviral therapy strategy and allocating medical resources in China.

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Introduction

Chronic hepatitis B virus (HBV) infection (known as CHB) used to be highly prevalent in China. Following the implementation of universal hepatitis B vaccination of newborns and infants, the prevalence of hepatitis B surface antigen (HBsAg) in China has decreased from 9.75% to 6.1%. However, due to the large population base, it is estimated that there are still nearly 80 million persons living with chronic HBV infection in mainland China, which is the world’s most significant HBV-related disease burden. Antiviral therapy, especially with the first-line nucleos(t)ide analogs (NAs), is key to reducing HBV-related serious consequences, such as cirrhosis and hepatocellular carcinoma. However, the treatment rate and utilization of the preferred antiviral agents have been low largely due to the high cost of the first-line therapy in China.

To improve the accessibility and affordability of medicines, the General Office of the State Council of the People’s Republic of China issued the National Centralized Drug Procurement (NCDP) policy in January 2019. This is the first attempt at nationwide volume-based drug procurement in mainland China, aiming at providing patients with high-quality drugs at lower prices through economies of scale. In the first round of NCDP, eleven cities were selected as a pilot project, including four municipalities (Beijing, Tianjin, Shanghai, and
Chongqing) and seven subprovincial cities (Shenyang, Dalian, Xiamen, Guangzhou, Shenzhen, Chengdu, Xi’an), which was known as the “4+7” program. This policy was successfully implemented in the pilot cities in April 2019 (initiation period) and was then extended to all cities across mainland China in November 2019 (expansion period). The first-line antiviral agents included in the NCDP list for CHB were entecavir (ETV) and tenofovir disoproxil fumarate (TDF).

This study was conducted to assess the impact of NCDP policy on the utilization and expenditure of antiviral therapy for CHB in mainland China based on the administrative database of the National Healthcare Security Administration (NHSA).

**Methods**

**Data sources**

The procurement records of NAs ordered from Apr 2018 to Mar 2021 were retrieved from the administrative database of the NHSA. This database covers monthly purchase records of all drugs including those in the “4+7” procurement list, in every medical institution in mainland China (23 provinces, 5 autonomous regions, and 4 municipalities directly under the Central Government). Each purchase order recorded the date, province name, generic name, specification, pharmaceutical manufacturer, purchase volume, and expenditure. The NAs of interest included lamivudine (LAM), adefovir (ADV), telbivudine (LdT), ETV, and TDF. To make sure that the purchased NAs were used to treat CHB patients, LAM 150 mg or 300 mg, which is used for patients with acquired immune deficiency syndrome, was excluded. Finally, an analytical database containing 25,219 monthly aggregated purchase order records was established. Institutional ethical approval and informed consent were waived because the study did not include any data from human participants or animals.

**Drug classification**

According to the HBV treatment guidelines, the antiviral agents were categorized as first-line NAs (ETV and TDF) and non-first-line NAs (LAM, ADV, and LdT) treatment. In addition, based on the bidding results of the “4+7” program, NAs from different pharmaceutical companies were further sorted into bid-winning and non-bid-winning products. In the first round of NCDP, the ETV dispersive tablets (Tianqiang Pharmaceutical Group Co., Ltd., Chengdu, Sichuan, China) and TDF tablets (Chengdu Beite Pharmaceutical Co., Ltd., Chengdu, Sichuan, China) won the bidding. When the policy was extended to all cities, ETV dispersive tablets (Suizhou Dongri Pharmaceutical Co., Ltd., Suzhou, Jiangsu, China), ETV tablets (Beijing Biaiao Pharmaceutical Co., Ltd., Lianyungang, Jiangsu, China) and TDF tablets (Qilu Pharmaceutical Co., Ltd., Jinan, Shandong, China; Hangzhou Heze Pharmaceutical Technology Co., Ltd., Hangzhou, Zhejiang, China; and Chengdu Beite Pharmaceutical Co., Ltd., Chengdu, Sichuan, China) were also included in the list. Therefore, the bid-winning products in this study are referred to as the ETV or TDF from the bid-winning group of drugs toward more or less expensive products in terms of price, volume, or structure effect (S). Price and volume effects reflect variations due to price and volume change, respectively. Structure effects, also known as “mixed effects,” refers to the variation due to the shift within the same therapeutic group of drugs toward more or less expensive products in addition to variations caused by changes in price and purchase volume. E was calculated as:

\[
E = \sum \frac{P \times V}{P_0 \times V_0} = P \times S = P \times \left( \sum \frac{V}{V_0} \times \sum \frac{P}{P_0} \right)
\]

where 0 denotes the baseline period, 1 denotes the initial implementation or extension period. In brief, if \( P \), \( V \) or \( S \) is >1, then the price, volume, or structure effect (policy effects) increase the expenditure index; if \( P \), \( V \) or \( S \) is <1, then means that the price, volume, or structure effect decrease the expenditure index. If \( P \), \( V \) or \( S \) is equal to 1, then the price, volume, or structure effect have no impact on the expenditure index.

**Outcome variables**

The outcome variables included: (1) purchase volumes, expenditures, and prices of NAs; (2) utilization of first-line antiviral agents; (3) the number and percentage of CHB patients receiving antiviral therapy in different settings. Volume was measured by the defined daily dose (DDD), which was used to compare drug consumption. The DDD in this study referred to the average maintenance dose per day for each drug in an adult CHB patient. Expenditure data were reported in Chinese Yuan, i.e. RMB. Expenditure and price data were reported in the Chinese Yuan, i.e. RMB in the main results, and then reported in USA dollars (USD) in the supplemental information. The exchange rate of RMB to USD was 6.71 to 1 (People’s Bank of China, average exchange rate between January 31, 2018 and December 31, 2021).

The estimated number of CHB patients eligible for antiviral therapy is 25.8 million in mainland China, which was derived from the following published data: the prevalence of HBsAg in China was 6.1%, there were 86.01 million HBsAg positive persons, 30% of whom meet the treatment criteria. We calculated the increased proportions of CHB patients receiving antiviral therapy assuming that the population of CHB patients remained stable during the study period. We assumed the compliance rates of antiviral treatment ranged from 100%, 75%, 50% to 25%. Therefore, the estimated proportion of CHB patients receiving antiviral treatment was calculated as:

\[
\text{The proportion of treatment} = \frac{\text{DDD} \times \text{compliance rate} \times 100\%}{25.8 \times 10^6}
\]

**Statistical analysis**

The timeline was divided into three periods: baseline (April 2018–March 2019), initial implementation (April 2019–March 2020), and extension (April 2020–March 2021), which were defined as the previous year, the first year after, and the second year after the implementation of the NCDP policy. The total purchase volume, expenditure, and price of each antiviral agent during the three periods were described and then stratified by seven geographical regions, including North, East, Central, Southwest, Southeast, Northwest, and Northeast China. The quarterly changes of purchase volume and expenditure of each NA and the monthly proportions of first-line NAs were depicted to visualize the impacts of NCDP policy on the utilization and expenditure of HBV antiviral therapy from Apr 2018 to Mar 2021.

The Addis and Magrini (AM) index refers to the variations of drug expenditure (E) in different periods. The index is derived from changes of price effect (P), volume effect (V), and structure effect (S). Price and volume effects reflect variations due to price and volume change, respectively. Structure effects, also known as “mixed effects,” refers to the variation due to the shift within the same therapeutic group of drugs toward more or less expensive products in addition to variations caused by changes in price and purchase volume. E was calculated as:

\[
E = \sum \frac{P \times V}{P_0 \times V_0} = P \times S = P \times \left( \sum \frac{V}{V_0} \times \sum \frac{P}{P_0} \right)
\]

where 0 denotes the baseline period, 1 denotes the initial implementation or extension period. In brief, if \( P \), \( V \) or \( S \) is >1, then the price, volume, or structure effect (policy effects) increase the expenditure index; if \( P \), \( V \) or \( S \) is <1, then means that the price, volume, or structure effect decrease the expenditure index. If \( P \), \( V \) or \( S \) is equal to 1, then the price, volume, or structure effect have no impact on the expenditure index.
Results

Changes in purchase volume and expenditure for NAs for CHB

Figure 1 shows the quarterly change in purchase volumes and expenditures of HBV-related NAs from April 2018 to February 2021. After initiating the “4+7” program, especially during the extension period in November 2019, the volumes of the antiviral drugs for HBV increased from 134.3 to 318.3 million DDDs, and the expenditures significantly dropped from 1,623.41 to 490.43 million RMB (241.94 to 73.09 million USD, Supplementary Fig. 1). Compared with the total purchase volume of NAs in the baseline period (598.83 million DDDs), the purchase volume increased to 971.29 and 1,169.55 million DDDs in the initial implementation in the “4+7” program and extension periods, with an average growth rate of 41.31% and a cumulative rate of 95.31% (Table 1). Moreover, the increase in volume and the decrease in expenditure were mainly for the first-line NAs (ETV and TDF).

Changes in purchase volume and expenditure of the bid-winning NAs

The trend in quarterly volume proportions of each antiviral agent is shown in Figure 2. The proportions of first-line NAs gradually increased from 72.51% to 94.97%. The proportion of the bid-winning NAs increased from 1.20% to 51.24%. Specifically, the proportion of ETV increased from 70.66% to 77.42%. The proportion of the bid-winning ETV products increased from 1.68% to 48.92%, and the proportion of TDF dramatically increased from 3.51% to 17.55% The proportion of the bid-winning TDF products increased from 1.07% to 76.16%. Further analysis showed that the cumulative growth rate of TDF was nearly two-fold of ETV in
Fig. 2. Quarterly change of proportions of HBV-related NAs from Apr 2018 to Feb 2021. The NCDP policy was successfully implemented in the pilot cities in Apr 2019 and was then extended to all cities across mainland China in Nov 2019. Apr, April; Feb, February; HBV, hepatitis B virus; NAs, nucleos(t)ide analogs; NCDP, National Centralized Drug Procurement.
the bid-winning products (5,086.62% vs. 2,576.58%, Table 1).

Compared with the baseline, the total expenditures on HBV-related NAs in the extension period was decreased by 69.64%. Reduced purchases of ADV and ETV contributed most to the decline, with a cumulative reduction rate of 82.33% and 74.53%, respectively. While the total expenditures of the bid-winning products (the first-line NAs produced by the bidding companies) increased from 102.26 to 148.21 million RMB/year (ETV: from 82.73 to 96.29; TDF: from 19.53 to 51.91, respectively), their prices dramatically decreased (ETV: from 12.47 to 1.78 RMB; TDF: from 14.89 to 0.99 RMB per pill), which means more than 90% decrease compared with the baseline period. (Table 2). The results in USD are shown in Supplementary Table 1.

### Decomposition analysis of expenditure for NAs for HBV

The decomposition effects of price, volume, and structure on expenditure are shown in Table 3. Compared with the baseline period, decreased expenditures of all HBV-related NAs in the implementation and extension periods were mainly due to structure effects (i.e. initial implementation period, S=0.91 and extension period, S=0.13) and volume effects (implementation period, P=0.48 and extension period, P=0.20). For the first-line NAs in the bid-winning list, the increased expenditures in the initial implementation and extension periods were mainly due to structure effects (initial implementation period, S=1.07 and extension period, S=1.13) and volume effects (implementation period, V=14.11; extension period, V=27.46).

### Increase in the proportion of CHB patients receiving first-line antiviral therapy

Increase in the proportion of CHB patients receiving antiviral therapy, especially first-line antiviral therapy, was estimated in different scenarios (Table 4). Assuming the population of CHB patients remained stable during the study period,
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Fig. 3. Purchase volume (A) and expenditures (B) of hepatitis B antiviral drugs 2 years after implementing the NCDP policy by provinces in China. NCDP, National Centralized Drug Procurement.
the purchase volume of first-line NAs covered 1,255,169 (4.86%) CHB patients at baseline if antiviral treatment compliance was 100%. After implementing the NCDP policy, the proportion of CHB patients receiving first-line antiviral therapy increased to 9.28% in the implementation period and 11.56% in the extension period. The proportions of the bid-winning products increased from 0.21% in the baseline to 6.48% in the extension period. If the compliance was 75%, the proportion of CHB patients receiving first-line antiviral therapy increased to 15.41%. The proportion of the bid-winning products increased from 0.29% to 8.64%.

Discussion

This study used the NHSA administrative database to investigate the impact of NCDP policy on the volume, expenditure, and price of NAs for CHB patients in mainland China. The national purchase volume of first-line NAs, including ETV and TDF, accounted for 94.97% of all NAs. The NCDP policy decreased the expenditure of all NAs and the price of first-line NAs but increased the expenditure proportion of the first-line NAs in the bid-winning list. As a result, the proportion of CHB patients receiving first-line antiviral therapy among all treatment-eligible patients was estimated to increase from 4.86–6.49% to 11.59–15.41%, assuming a compliance rate of ≥75%. One important finding is that the NCDP policy significantly increased the purchase volume of HBV-related NAs at a lower expenditure. More importantly, the increase in volume was contributed by the first-line NAs.

Using a nationwide registry system for CHB, Shan et al. reported that the proportion of patients who received first-line NAs among patients receiving any NAs increased from 13.5% in 2003 to 79.7% in 2016. This study showed that

Table 3. Decomposition analysis for hepatitis B antiviral drugs

| Drug group | April 2018–March 2019 to April 2019–March 2020 | E | P | V | S |
|------------|-----------------------------------------------|---|---|---|---|
| Hepatitis B antiviral drugs | | 0.73 | 0.48 | 1.62 | 0.95 |
| Drugs in the bid-winning list | | 1.34 | 0.09 | 14.11 | 1.07 |
| Drugs in the non-bid-winning list | | 0.72 | 0.62 | 1.15 | 1.01 |

| Drug group | April 2018–March 2019 to April 2020–March 2021 | E | P | V | S |
|------------|-----------------------------------------------|---|---|---|---|
| Hepatitis B antiviral drugs | | 0.36 | 0.20 | 1.95 | 0.91 |
| Drugs in the bid-winning list | | 2.80 | 0.09 | 27.46 | 1.13 |
| Drugs in the non-bid-winning list | | 0.24 | 0.25 | 0.97 | 0.99 |

E, expenditure index; P, price effects; S, structure effects; V, volume effects.

Table 4. Changes in the proportion of CHB patients receiving antiviral treatment before and after the implementation of “four plus seven” policy

| Groups | April 2018–March 2019 | % | April 2019–March 2020 | % | April 2020–March 2021 | % |
|--------|-----------------------|---|-----------------------|---|-----------------------|---|
| Total NAs | | | | | | |
| Compliance rate | | | | | | |
| 100% | 1,640,626 | 6.36 | 2,661,061 | 10.31 | 3,204,251 | 12.42 |
| 75% | 2,187,502 | 8.48 | 3,548,082 | 13.75 | 4,272,335 | 16.56 |
| 50% | 3,281,252 | 12.72 | 5,322,123 | 20.63 | 6,408,502 | 24.84 |
| 25% | 6,562,505 | 25.44 | 10,644,246 | 41.26 | 12,817,004 | 49.68 |

| First-line NAsb | | | | | | |
| Compliance rate | | | | | | |
| 100% | 1,255,169 | 4.86 | 2,393,733 | 9.28 | 2,982,164 | 11.56 |
| 75% | 1,673,558 | 6.49 | 3,191,643 | 12.37 | 3,976,219 | 15.41 |
| 50% | 2,510,337 | 9.73 | 4,787,465 | 18.56 | 5,964,329 | 23.12 |
| 25% | 5,020,674 | 19.46 | 9,574,930 | 37.11 | 11,928,657 | 46.24 |

| First-line NAs in the bid-winning list | | | | | | |
| Compliance rate | | | | | | |
| 100% | 55,273 | 0.21 | 843,135 | 3.27 | 1,671,132 | 6.48 |
| 75% | 73,697 | 0.29 | 1,124,180 | 4.36 | 2,228,176 | 8.64 |
| 50% | 110,546 | 0.43 | 1,686,270 | 6.54 | 3,342,264 | 12.95 |
| 25% | 221,092 | 0.86 | 3,372,539 | 13.07 | 6,684,527 | 25.91 |

aNumber of CHB patients receiving antiviral treatment; bFirst-line NAs included entecavir and tenofovir. CHB, chronic hepatitis B; NAs, nucleos(t)ide analogs.
the proportion of ETV or TDF among all NAs increased from 72.51% to 94.97% within 2 years after the implementation of the NCDP policy, indicating that the clinical treatment behavior was consistent with international and national guidelines.\textsuperscript{11,17} The growth trend of nationwide data in NAs of the NCDP policy, suggesting that the clinical treatment rate increased from 72.51% to 94.97% within 2 years after the implementation of the policy.\textsuperscript{19–21} Without treatment scale-up, it is estimated that there will be 10 million HBV-related deaths in the next decade.\textsuperscript{22} However, the treatment rates and patient compliance are hindered by the high cost of antiviral agents and insufficient reimbursement by health insurance. As a result, high coverage of hepatitis B diagnosis and treatment has become the most challenging global target to achieve.\textsuperscript{23} In response to this challenge, the Chinese government has taken a series of measures to reduce the financial burden of CHB patients, including massive ETV and TDF price reductions through government negotiations in 2016 and listing them as national reimbursement drugs in 2017.\textsuperscript{24} This study demonstrated that the prices of bid-winning ETV and TDF were 70 RMB and 180 RMB per person-year after adopting the NCDP policy, which will further reduce the economic burden of HBV-related liver diseases.

With respect to the impact of the NCDP policy on the expansion of the treatment rate, we estimate that the proportion of CHB patients receiving first-line antiviral therapy will increase by 11.56–15.41% assuming a 75% compliance rate. This favorable change will translate into long-term clinical and public health benefits. Indeed, Li et al.\textsuperscript{24} showed that basic medical insurance coverage of first-line anti-HBV medications in Beijing of China significantly reduced the risk of developing liver-related death from 0.38% to 0.16% for patients with non-cirrhotic CHB and from 4.03% to 3.39% for those with compensated cirrhosis.\textsuperscript{24} However, there is still a big gap to the target of 80% treatment rate to achieve the goal of eliminating viral hepatitis as a public health threat by 2030 proposed by the World Health Organization.\textsuperscript{25,26} Lastly, the AM index analysis also confirmed that the structure change and price decrease, which were caused by the impact of NCDP policy on the dramatically increased purchase of the first-line NAs in the bid-winning list, contributed to the overall reduction in expenditure. Meanwhile, among all expenditures on antiviral agents, the proportion of the spending on the first-line NAs increased due to the structure change and volume increase.

Our study has several limitations. First, it was an observational study and may be subject to confounding factors that may have affected the evaluation of the NCDP policy impact on expenditures. However, we analyzed data for 3 years to minimize the lag effect. Second, calculating the increment in CHB treatment rate may be subject to bias resulting from different estimations of treatment compliance. However, considering that the medications are almost exclusively indicated for HBV and have a simple, fixed-dose regimen, the estimation of the increased proportion in treatment rate is reasonable. Lastly, as the NCDP policy has been followed for only 2 years, we did not analyze the clinical impact and cost-effectiveness in the current study.

Conclusion

The NCDP policy increased the purchase volume and decreased the price and total expenditures of NAs, thereby positively impacting the utilization of first-line NAs for CHB patients at a lower expenditure. The findings provide evidence for optimizing the strategy of government procurement of medical products or services, thereby more efficiently allocating public health resources in China.

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Conflict of interest

JJ has been an executive associate editor of Journal of Clinical and Translational Hepatology since 2021. YK has been an editorial board member of Journal of Clinical and Translational Hepatology since 2022. HY has been an editorial board member of Journal of Clinical and Translational Hepatology since 2021. The other authors have no conflict of interests related to this publication.

Author contributions

Study design, guidance in writing of the manuscript, and review of the final manuscript (YK, JJ), analysis of the data (XZ, ML), writing of the manuscript (XZ), and interpretation of the data (HY, HW, XX, XW, YS, CN, BW, SC). All authors read and approved the final manuscript.

Ethical statement

According to the Institutional Review Board of Beijing Friendship Hospital, Capital Medical University, the study did not contain individual data, so ethical review and informed consent were waived.

Data sharing statements

Additional data are available on request from the corresponding authors at jia_jd@ccmu.edu.cn and kongyy@ccmu.edu.cn.

References

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\begin{enumerate}
\item Cui F, Shen L, Li L, Wang H, Wang F, Bi S, et al. Prevention of Chronic Hepatitis B after 3 Decades of Escalating Vaccination Policy, China. Emerg Infect Dis 2017;23(5):765–772. doi:10.3201/eid2305.161477, PMID:28641829.
\item Liu J, Zhang S, Wang Q, Shen H, Zhang M, Zhang Y, et al. Seroepidemiology of hepatitis B virus infection in 2 million men aged 21–49 years in rural China: a population-based, cross-sectional study. Lancet Infect Dis 2016;16(1):80–86. doi:10.1016/S1473-3099(15)00218-2, PMID:26268687.
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