Treatment outcomes of HIV patients with hepatitis B and C virus co-infections in Southwest China: an observational cohort study

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Abstract

Background: Antiretroviral therapy (ART) has reduced mortality among people living with HIV (PLWH) in China, but co-infections of hepatitis B virus (HBV) and hepatitis C virus (HCV) may individually or jointly reduce the effect of ART. This study aimed to evaluate the impacts of HBV/HCV coinfections on treatment drop-out and mortality among PLWH on ART.

Methods: A retrospective cohort study analysis of 58 239 people living with HIV (PLWH) who initiated antiretroviral therapy (ART) during 2010–2018 was conducted in Guangxi Province, China. Data were from the observational database of the National Free Antiretroviral Treatment Program. Cox proportional hazard models were fitted to evaluate the effects of baseline infection of HBV or HCV or both on death and treatment attrition among PLWH.

Results: Our study showed high prevalence of HBV (11.5%), HCV (6.6%) and HBV-HCV (1.5%) co-infections. The overall mortality rate and treatment attrition rate was 2.95 [95% confidence interval (CI) 2.88–3.02] and 5.92 (95% CI 5.82–6.01) per 100 person-years, respectively. Compared with HIV-only patients, HBV-co-infected patients had 42% higher mortality [adjusted hazard ratio (aHR) = 1.42; 95% CI 1.32–1.54] and 5.92 (95% CI 5.82–6.01) per 100 person-years, respectively. Compared with HIV-only patients, HBV-co-infected patients had 42% higher mortality [adjusted hazard ratio (aHR) = 1.42; 95% CI 1.32–1.54], HCV-co-infected patients had 65% higher mortality (aHR = 1.65; 95% CI 1.47–1.86), and patients with both HCV and HBV co-infections had 123% higher mortality (aHR = 2.23; 95% CI 1.87–2.66).

Conclusions: HBV and HCV coinfection may have an additive effect on increasing the risk of all-cause death among PLWH who are on ART. It is suggested that there is need for primary prevention and access to effective hepatitis treatment for PLWH.

Keywords: Hepatitis C virus, Hepatitis B virus, HIV, Antiretroviral therapy, Mortality, Retrospective cohort
**Background**

Highly active antiretroviral therapy (ART) has reduced deaths among people living with HIV (PLWH) in China and globally [1–3]. However, the effectiveness of ART depends on a variety of factors. Studies have shown that comorbid hepatitis B virus (HBV) and hepatitis C virus (HCV) infections could have negative impacts on HIV treatment outcomes, but few studies have assessed their individual and joint effects simultaneously [4–6]. HBV infection may accelerate the development of AIDS with HBV X proteins upregulating HIV replication and transcription by synergizing with kappa B-like enhancers and T-cell activation signals [7, 8]. HBV or HCV coinfection is associated with a higher level of hepatic fibrosis, which may impact the liver’s detoxification function [6, 9–11]. Since some ART drugs have liver toxicity, coinfecion of HBV and HCV is a significant risk factor for death in PLWH.

Hepatitis B is endemic in China. Meta analyses showed that the prevalence of HBV infection was around 7% [12] among the adult general population of China and was double (13.7%) among people living with HIV (PLWH) [13]. Additionally, the prevalence of anti-HCV antibodies was lower among the general population (0.9%) [14], but higher among PLWH (24.7%) [13]. Triple infection of HBV, HCV and HIV occurred in about 3.5% of the population [13].

Though coinfections of HBV and HCV are common among PLWH, data on their effects on HIV treatment outcomes in China are sparse. We performed a retrospective cohort study analysis to evaluate the impacts of HBV/HCV coinfections on treatment dropout and mortality among PLWH on ART in southwestern China.

**Methods**

**Study design and study participants**

This study was designed as a retrospective cohort analysis of HIV treatment data in the Guangxi Zhuang Autonomous Region in southwest China. As of October 2020, Guangxi represented 9.3% of the total number of nationally reported HIV/AIDS cases, and this region has accumulated the third highest number of HIV cases reported in China. Sexual transmission accounted for more than 95% of reported cases in Guangxi.

The data were from the observational database of the National Free Antiretroviral Treatment Program (NFATP) of China. The study subjects were HIV patients who received free ART between 2010 and 2018 through NFATP. Physicians administering the ART at the local hospitals managed case report forms at the time of initiating ART and follow-up at 0.5, 1, 2 and 3 months, and every 3 months thereafter. The case report forms were uploaded into a web-based database hosted by Chinese Center for Disease Control (China CDC). Eligibility criteria for the subjects of this study were: (1) HIV patients who initiated free ART between 2010 and 2018; (2) at least 18 years old; (3) tested for HBV or HCV; (4) provided informed consent. The researchers in the Guangxi
Province CDC have access to all records in the NFATP for patients who lived in Guangxi Province.

Chinese free ART eligibility criteria have gone through several phases: From 2008, PLWH with CD4 cell counts lower than 350 cells/mm$^3$ were eligible for treatment; since 2014, the treatment threshold was CD4 counts below 500; and since 2016, China has provided free ART for all PLWH regardless of CD4 count. Currently, first-line regimens for free ART in China are tenofovir (TDF) or azidothymidine (AZT) + lamivudine (3TC) + efavirenz (EFV) or nevirapine (NVP). Second-line regimens are TDF + 3TC + EFV or lopinavir/ritonavir (LPV/r).

Data collection
Information about HIV patients in the electronic database NFATP includes two parts: baseline data and follow-up data. Baseline data included demographics such as age, sex, marital status and clinical characteristics such as route of HIV transmission, CD4 count (cells/mm$^3$) before ART, WHO clinic stage before ART, initial first-line ART regimen, current ART regimen and calendar year of ART initiation. Follow-up data included transferal to another clinic, cessation of ART, loss to follow-up, duration of ART, and survival status. HBV infection was tested by finding Hepatitis B surface antigens (HBsAg) and HCV infection was tested by finding antibodies of HCV.

Statistical analysis
We conducted a prospective follow-up study analysis. Time zero was defined as the date of ART initiation, and data was censored on December 31, 2019. Outcome variables included death and ART attrition. Survival status was recorded as censored if patients were still alive or transferred to another clinic. Attrition was defined as cessation of ART and loss to follow-up. Loss to follow-up or withdrawal of ART was defined as missing visits more than 90 days after the last record in a clinic. Incidence rates of mortality and attrition were calculated based on Poisson distribution and reported as the number of deaths and attritions per 100 person-years, respectively.

Cox proportional hazard models were used to evaluate the effects of baseline infection of HBV or HCV or both on death and attrition among PLWH. Competing risks for cause-specific hazard models were censored accordingly [20, 21]. Potential confounders were controlled by adjusting the model with the following baseline covariates: age, sex, marital status, route of HIV transmission, baseline CD4 count, WHO clinical stage before ART, initial first-line regimen, current ART regimen, duration of tenofovir disoproxil fumarate (TDF)-containing ART regimens, and calendar year of ART initiation.

Statistical significance was determined to have a two-sided $P \leq 0.05$. All the statistical analyses were performed using SAS V9.1 (SAS Institute Inc., Cary, NC, USA).

Results
Baseline characteristics of study patients
As of December 31, 2019, 79,245 PLWH initiated free ART between 2010 and 2018 in Guangxi, China. Excluding 291 patients under 18 years old, two without follow-up data and 20,713 without HBV and HCV testing results, a total of 58,239 individuals were eligible and included in the analysis (Fig. 1). Of those included participants, 12% died, 16% were lost to follow-up, 8% dropped out of treatment and 64% were active on treatment by the end of follow-up.

The baseline characteristics of the study patients are shown in Table 1: 6,707 (11.5%) participants had HIV-HBV co-infection, 3,828 (6.6%) had HIV-HCV co-infection, 857 (1.5%) and had triple infection. Two fifths (40.9%) of patients were over 50 years old; 68.3% were male and 63.7% were married. The majority (87.3%) of patients were infected through heterosexual intercourse, followed by homosexual intercourse (5.9%), intravenous drug use (4.9%) and other causes (1.9%). Prior to ART initiation, 59.8% of the patients had CD4 counts $\leq$ 350 cells/mm$^3$, and 5.9% of the patients were classified as WHO clinical stage III or IV. Patients with initial ART regimens of stavudine (D4T)-based, azidothymidine (AZT)-based, tenofovir disoproxil fumarate (TDF)-based and lopinavir-ritonavir (LPV/r)-based accounted for 8.5%, 33.7%, 46.8% and 10.1%.
### Table 1  Baseline characteristics of HIV patients who initiated ART between 2010 and 2018 in Guangxi, China

| Variable                        | Total | % HIV only | % HIV-HBV co-infection | % HIV-HCV co-infection | % HIV-HBV-HCV Triple infection |
|---------------------------------|-------|------------|-------------------------|------------------------|-------------------------------|
| Total                           | 58,239| 100.0      | 46,847                  | 100.0                  | 3,828                         | 100.0                        |
| **Age, years**                  |       |            |                         |                        |                               |                               |
| 18–50                           | 34,424| 59.1       | 25,731                  | 54.9                   | 4,504                         | 67.2                          | 3,404                         | 88.9                          | 785                           | 91.6                          |
| ≥ 50                            | 23,815| 40.9       | 21,116                  | 45.1                   | 2,203                         | 32.8                          | 424                           | 11.1                          | 72                            | 8.4                           |
| **Sex**                         |       |            |                         |                        |                               |                               |
| Male                            | 39,754| 68.3       | 31,097                  | 66.4                   | 4,798                         | 71.5                          | 3,110                         | 81.2                          | 749                           | 87.4                          |
| Female                          | 18,485| 31.7       | 15,750                  | 33.6                   | 1,909                         | 28.5                          | 718                           | 28.5                          | 108                           | 12.6                          |
| **Marital status**              |       |            |                         |                        |                               |                               |
| Married                         | 37,104| 63.7       | 30,197                  | 64.5                   | 4,306                         | 64.2                          | 2,136                         | 55.8                          | 465                           | 54.3                          |
| Other                           | 21,135| 36.3       | 16,650                  | 35.5                   | 2,401                         | 35.8                          | 1,692                         | 44.2                          | 392                           | 45.7                          |
| **Route of HIV transmission**   |       |            |                         |                        |                               |                               |
| Heterosexual intercourse        | 50,836| 87.3       | 42,911                  | 91.6                   | 6,118                         | 91.2                          | 1,480                         | 38.7                          | 327                           | 38.2                          |
| Homosexual intercourse          | 3,455 | 5.9        | 534                     | 1.1                    | 152                           | 2.3                           | 2,257                         | 59.0                          | 512                           | 59.7                          |
| Intravenous drug use            | 2,827 | 4.9        | 2,488                   | 5.3                    | 297                           | 4.4                           | 36                            | 0.9                           | 6                             | 0.7                           |
| Other                           | 1,121 | 1.9        | 914                     | 2.0                    | 140                           | 2.1                           | 55                            | 1.4                           | 12                            | 1.4                           |
| **CD4 count before ART, cells/mm³** |       |            |                         |                        |                               |                               |
| ≤ 350                           | 34,837| 59.8       | 28,133                  | 60.1                   | 3,853                         | 57.4                          | 2,345                         | 61.3                          | 506                           | 59.0                          |
| > 350                           | 23,402| 40.2       | 18,714                  | 39.9                   | 2,854                         | 42.6                          | 1,483                         | 38.7                          | 351                           | 41.0                          |
| **WHO clinical stage before ART** |       |            |                         |                        |                               |                               |
| I/II                            | 7,268 | 12.5       | 5,937                   | 12.7                   | 807                           | 12.0                          | 443                           | 11.6                          | 81                            | 9.5                           |
| III/IV                          | 3,447 | 5.9        | 2,831                   | 6.0                    | 397                           | 5.8                           | 198                           | 5.2                           | 31                            | 3.6                           |
| **Initial first-line ART regimen** |       |            |                         |                        |                               |                               |
| ART containing D4T              | 4,966 | 8.5        | 4,011                   | 8.6                    | 412                           | 6.1                           | 430                           | 11.2                          | 113                           | 13.2                          |
| ART containing AZT              | 19,621| 33.7       | 17,208                  | 36.7                   | 1,027                         | 15.3                          | 1,176                         | 30.7                          | 210                           | 24.5                          |
| ART containing TDF              | 27,246| 46.8       | 20,270                  | 43.3                   | 6,434                         | 69.1                          | 1,881                         | 49.1                          | 461                           | 53.8                          |
| ART containing LPV/r            | 5,863 | 10.1       | 4,862                   | 10.4                   | 101                           | 9.1                           | 319                           | 8.3                           | 72                            | 8.4                           |
| Other                           | 543   | 0.9        | 496                     | 1.1                    | 24                            | 0.4                           | 22                            | 0.6                           | 1                             | 0.1                           |
| **Current ART regimen**         |       |            |                         |                        |                               |                               |
| First-line ART                  | 45,854| 78.7       | 36,743                  | 78.4                   | 5,311                         | 79.2                          | 3,107                         | 81.2                          | 693                           | 80.9                          |
| Second-line ART                 | 12,385| 21.3       | 10,104                  | 21.6                   | 1,396                         | 20.8                          | 721                           | 18.8                          | 164                           | 19.1                          |
| **Duration of TDF-containing regimens** |       |            |                         |                        |                               |                               |
| ≤ 2 years                       | 33,115| 56.9       | 27,865                  | 59.5                   | 2,740                         | 40.9                          | 2,088                         | 54.5                          | 422                           | 49.2                          |
| > 2 years                       | 25,124| 43.1       | 18,982                  | 40.5                   | 3,967                         | 59.1                          | 1,740                         | 45.4                          | 435                           | 50.8                          |
| **Calendar year of ART initiation** |       |            |                         |                        |                               |                               |
| 2010                            | 3,515 | 6.0        | 2,518                   | 5.4                    | 437                           | 6.5                           | 425                           | 11.1                          | 135                           | 15.8                          |
| 2011                            | 4,982 | 8.6        | 3,839                   | 8.2                    | 604                           | 9.0                           | 414                           | 10.8                          | 125                           | 14.6                          |
| 2012                            | 6,226 | 10.7       | 4,876                   | 10.4                   | 700                           | 10.4                          | 537                           | 14.0                          | 113                           | 13.2                          |
| 2013                            | 6,384 | 11.0       | 5,057                   | 10.8                   | 738                           | 11.0                          | 487                           | 12.7                          | 102                           | 11.9                          |
| 2014                            | 7,290 | 12.5       | 5,755                   | 12.3                   | 883                           | 13.2                          | 558                           | 14.6                          | 94                            | 11.0                          |
| 2015                            | 8,016 | 13.8       | 6,524                   | 13.9                   | 954                           | 14.2                          | 450                           | 11.8                          | 88                            | 10.3                          |
| 2016                            | 7,421 | 12.7       | 6,170                   | 13.2                   | 823                           | 12.3                          | 349                           | 9.1                           | 79                            | 9.2                           |
| 2017                            | 7,164 | 12.3       | 5,954                   | 12.7                   | 830                           | 12.4                          | 315                           | 8.2                           | 65                            | 7.6                           |
| 2018                            | 7,241 | 12.4       | 6,154                   | 13.1                   | 738                           | 11.0                          | 293                           | 7.7                           | 56                            | 6.4                           |

**ART**, Antiretroviral therapy; **AZT**, Zidovudine; **D4T**, Stavudine; **LPV/r**, Lopinavir-ritonavir; **TDF**, Tenofovir; **HBV**, Hepatitis B virus; **HCV**, Hepatitis C virus; **HIV**, Human immunodeficiency virus
of all patients, respectively. Most patients (78.7%) used first-line ART regimens, 21.3% used second-line regimens, and 43.1% used TDF-based ART regimens for more than 2 years.

Impact of HBV and HCV co-infections on death among PLWH who initiated ART

The unadjusted and adjusted effects of HBV and HCV co-infections on death are shown in Table 2. Among 58,239 patients who initiated ART between 2010 and 2018, 6,916 deaths were observed, and the overall mortality rate was 2.95 per 100 person-years [95% confidence interval (CI) 2.88–3.02]. The crude mortality rate was 2.86% in HIV-only patients, 2.84% in HBV-co-infected, 3.89% in HCV-co-infected and 4.66% in HBV/HCV-co-infected patients. Multivariate cox models showed that compared with patients with HIV infection only, HBV co-infected patients had a 42% higher risk of death [adjusted hazard ratio (aHR) = 1.42; 95% CI 1.32–1.54; P < 0.001]; HCV co-infected patients had a 65% higher risk (aHR = 1.65; 95% CI 1.47–1.86; P < 0.001); and patients with both HIV and HCV co-infections had a 123% higher risk (aHR = 2.23; 95% CI 1.87–2.66; P < 0.001). The increase of death risk among patients with triple infection (123%) approximately equals to the sum of increases in death among PLWH with co-HBV (42%) and those with co-HCV (65%) infection. There is an additive interaction between HBV- and HCV-co-infection on mortality among PLWH.

**Impact of HBV and HCV co-infections on treatment attrition among PLWH who initiated ART**

The unadjusted and adjusted effects of HBV and HCV co-infections on treatment attrition are presented in Table 3. Among 58,329 patients, 13,872 patients dropped out from the treatment including 9,107 patients lost to follow-up and 4,765 stopping ART. The overall drop-out rate was 5.92 (95% CI 5.82–6.01) per 100 person-years. The crude drop-out rate was 5.42% in HIV-only patients, 5.13% in HBV-co-infected, 12.03% in HCV-co-infected and 12.51% in HBV/HCV-co-infected HIV patients. Multivariate cox models showed that compared to HIV-only patients, HBV co-infected patients were 34% more likely to drop out of treatment (aHR = 1.34; 95% CI 1.27–1.42; P < 0.001); HCV co-infected patients had a 73% increased risk (aHR = 1.73; 95% CI 1.61–1.87; P < 0.001); patients with both HBV and HCV co-infections had a 107%

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**Table 2** Effect of HBV and HCV co-infections on death among HIV patients who initiated ART between 2010 and 2018 in Guangxi, China

| Coinfection          | Number of HIV patients | Deaths | Person-years (PY) | Mortality rate per 100 person-years (95% CI) | HR (95% CI) | P value | aHRa (95% CI) | P value |
|----------------------|------------------------|--------|-------------------|---------------------------------------------|-------------|---------|------------|---------|
| Total                | 58,239                 | 6,916  | 234,421.19        | 2.95 (2.88–3.02)                             | Reference   | Reference|            |         |
| HIV only             | 46,847                 | 5,366  | 187,680.8         | 2.86 (2.78–2.93)                             | Reference   | Reference|            |         |
| HIV + HBV            | 6,707                  | 797    | 28,092.09         | 2.84 (2.65–3.03)                             | 0.99 (0.92–1.07) | 0.784 | 1.42 (1.32–1.54) | < 0.001 |
| HIV + HCV            | 3,828                  | 500    | 15,148.30         | 3.89 (3.59–4.20)                             | 1.35 (1.24–1.47) | < 0.001 | 1.65 (1.47–1.86) | < 0.001 |
| HIV + HBV + HCV      | 857                    | 163    | 3,500.00          | 4.66 (3.96–5.35)                             | 1.60 (1.37–1.87) | < 0.001 | 2.23 (1.87–2.66) | < 0.001 |

CI, Confidence interval; HR, Hazard ratio; aHR, Adjusted hazard ratio; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus

*a* Adjusted for Age, gender, marital status, route of HIV transmission, CD4 count before ART, WHO clinical stage before ART, initial first-line ART regimen, current ART regimen, duration of using TDF-containing regimens, calendar year of ART initiation

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**Table 3** Effect of HBV and HCV co-infections on ART attrition among HIV patients who initiated ART between 2010 and 2018 in Guangxi, China

| Variables           | Number of HIV patients | Attritions | Person-years (PY) | Attraction rate per 100 person-years (95% CI) | HR (95% CI) | P value | aHRa (95% CI) | P value |
|---------------------|------------------------|------------|-------------------|----------------------------------------------|-------------|---------|------------|---------|
| Total               | 58,239                 | 13,872     | 234,421.19        | 5.92 (5.82–6.01)                             | Reference   | Reference|            |         |
| HIV                 | 46,847                 | 10,169     | 187,680.8         | 5.42 (5.32–5.52)                             | Reference   | Reference|            |         |
| HIV + HBV           | 6,707                  | 1,442      | 28,092.09         | 5.13 (4.87–5.39)                             | 0.95 (0.90–1.01) | 0.074 | 1.34 (1.27–1.42) | < 0.001 |
| HIV + HCV           | 3,828                  | 1,823      | 15,148.30         | 12.03 (11.50–12.57)                          | 2.22 (2.11–2.33) | < 0.001 | 1.73 (1.61–1.87) | < 0.001 |
| HIV + HBV + HCV     | 857                    | 438        | 3500.00           | 12.51 (11.37–13.66)                          | 2.31 (2.10–2.54) | < 0.001 | 2.07 (1.85–2.31) | < 0.001 |

CI, Confidence interval; HR, Hazard ratio; aHR, Adjusted hazard ratio; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus

*a* Adjusted for Age, gender, marital status, route of HIV transmission, CD4 count before ART, WHO clinical stage before ART, initial first-line ART regimen, current ART regimen, duration of using TDF-containing regimens, calendar year of ART initiation
increased risk ($aHR = 2.07; 95\% CI 1.85–2.31; P < 0.001$). The increase of attrition risk among patients with triple infection (107%) equals to the sum of increases in treatment attrition among PLWH with co-HBV (34%) and those with co-HCV (73%) infection. There is an additive interaction between HBV- and HCV-co-infection on treatment attrition among PLWH.

Discussion
Our study confirmed the previous study finding that the Chinese national free ART program has significantly reduced HIV related mortality in China [15, 16]. The overall mortality rate in our study sample who started ART between 2010 and 2018 in Guangxi, China, was as low as 2.95 per 100 person-years. HBV and HCV co-infection could independently increase mortality. This is consistent with findings among the Asia–Pacific PLWH population [17]. In addition, co-infection with both HCV and HBV had an additive effect on the risk of death among PLWH.

Studies have shown that in China there is a high prevalence of HCV infection among people who inject drugs [18, 19], and injection drug use (IDU) is associated with faster HIV disease progression and increased risk of death [20, 21]. IDU is unlikely to explain the association between HCV infection and risk of death in our study, as only 4.8% of our study sample were PWID and IDU was adjusted for in assessing the association. HCV may cause hepatic fibrosis and reduce liver detoxification function [9, 10], which reduces patients’ tolerance to side effects of ART drugs and therefore increases HIV treatment dropout and increases mortality. Our study also showed that patients with HCV co-infection were more likely to have treatment attrition than those without any co-infection, and this might be one factor explaining for the increased risk of death among PLWH with HCV-co-infection.

Our study has limitations. First, HCV status was assessed by antibody testing in this study, and a positive HCV antibody test might indicate past or current infection. However, most HCV infections could become chronic as there was virtually no treatment for HCV infection. There is need for primary prevention and effective hepatitis treatment among PLWH.

Conclusions
This cohort study showed that both HBV and HCV coinfection was associated with higher mortality and treatment attrition among PLWH who were on ART. There is need for primary prevention and effective hepatitis treatment among PLWH.

Abbreviations
HVB: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; ART: Antiretroviral therapy; PLWH: People living with HIV; IDU: Injection drug use; WHO: World Health Organization; NFATP: The National Free Antiretroviral Treatment Program; aHR: Adjusted hazard ratio; CI: Confidence interval.

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Authors’ contributions
YR, JZ and HZQ designed the study. QZ, GL, HC, ZS and JL collected the data. JJ, QZ, LD, YR, JZ and HZQ analysed the data. JI, QZ, LD, AJ and HZQ draft the manuscript. All authors interpreted the results and revised the manuscript. All authors read and approved the final manuscript.
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Availability of data and materials
The datasets are available from the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate
The institutional review board of Guangxi Province CDC had reviewed and approved use of deidentified data from the NFATP observational database before conducting the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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