Driving force of COVID-19 among people living with HIV in Wuhan, China

Wei Guo, Fangzhao Ming, Yu Dong, Qian Zhang, Lian Liu, Ming Gao, Xiaoxia Zhang, Pingzheng Mo, Yong Feng, Weiming Tang and Ke Liang

Background: Although people living with HIV (PLWH) were considered to be at increased risk of SARS-CoV-2 infection, the driving force among this group of individuals is still not clear.

Methods: We investigated 1,709 PLWH through a telephone interview and identified 11 COVID-19 patients in four districts of Wuhan, China. The demographic features and major clinical characteristics of these patients were retrieved from the information management systems for COVID-19 patients of the four districts’ CDC. Statistical analysis was performed to find out the driving force of COVID-19 among PLWH.

Results: The prevalence of COVID-19 in PLWH is 0.6% (95% CI: 0.2% - 1.0%), which is comparable to the overall population prevalence in Wuhan city (0.6%). Nine out of the 11 COVID-19 patients had relatively high CD4+ T lymphocyte count (>200/μL) and undetectable HIV viral load (<20 copies/ml), and ten of them were on antiretroviral therapy. Older PLWH with low CD4+ count, got HIV infected through homosexual activity, and had been diagnosed with HIV for a long time, were more likely to develop COVID-19.

Conclusions: COVID-19 related morbidity rates were comparable between PLWH and the general population. Older age with low CD4 count, an extended period of HIV diagnosis, and treatment-naivety were potential driving forces of COVID-19 prevalence among PLWH. Strategies for preventing SARS-CoV-2 infection among PLWH with weak immune responses are required.

Background

As a highly contagious pathogen, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) rapidly spread around the world, and lead to a great number of people getting sick and even death. Inappropriate response to the emerging infectious diseases, a substantial number of studies had been conducted to succinctly summarize the clinical characteristics of COVID-19. Findings from those studies stipulated the evidential basis that chronic diseases like hypertension, chronic pulmonary diseases, diabetes, and other co-morbidities contribute to the driving forces of both COVID-19 related morbidity and fatality (Guan et al., 2020; Huang et al., 2020). In notable addition, published findings from some studies have suggestively indicated people living with HIV (PLWH) to be at a presumed higher risk of SARS-CoV-2 infection due to their compromised immunity (Etienne et al., 2020). However, very few studies have been conducted to rigorously evaluate the driving forces of SARS-CoV-2 infection among PLWH till date. Therefore, a further investigation on
the driving force of SARS-CoV-2 infection among PLWH may enable us to better protect this vulnerable group.

Between 31st December 2019 and 14th May 2020, an estimated total of 84,464 confirmed cases were reported in China of which 50,339 were reported in Wuhan and 3,869 died. Wuhan being the epidemic center of the SARS-CoV-2 pandemic provides a unique opportunity to further investigate the driving forces of COVID-19 among PLWH. Therefore, we summarized the specific situation of PLWH in four local districts of Wuhan and fortunately reached all the PLWH in clinical care within the four districts.

In this study, we investigated the prevalence of COVID-19 among PLWH and evaluated the potential factors associated with the development of COVID-19 among PLWH.

Materials and methods

Patients in four districts of Wuhan

Study participants were recruited from 4 districts in Wuhan namely Wuchang, Qingshan, Caidian, and Xinzhou. Although there are 13 districts in Wuhan, these four districts are representative of the cultural and economic center (Wuchang and Qingshan) and suburb districts (Caidian and Xinzhou). By the endpoint of patients’ follow-up on 14th May 2020, COVID-19 patients totaled 7,551 in Wuchang, 2,804 in Qingshan, 1,424 in Caidian, and 1,071 in Xinzhou (Commission., 2020). There was a total of 5,953 PLWH in care in Wuhan, of which a total 1,709 were PLWH being managed by the 4 district CDCs (910 in Wuchang, 266 in Qingshan, 321 in Xinzhou, and 212 in Caidian) [Figure 1].

The scheme of the investigation

Study participants were interviewed using telephone calls or social communication software (16th Feb-14th May) due to lockdown restrictions during the study period (23rd Jan-18th Apr). Participants were inquired about experiencing any of the typical symptoms mentioned in the previous clinical reports, such as fever, non-productive cough, dyspnea, etc.(Wang et al., 2020). The contact history with confirmed or suspected COVID-19 patients was then investigated. Participants who presented with clinical symptoms or contacted COVID-19 patients were introduced to a local designated hospital for a CT scan and nucleic acid test (NAT) for SARS-CoV-2. Diagnosis criteria for COVID-19 were according to the Diagnosis and Treatment of COVID-19 in China (the 7th edition) (National Health Commission, 2020). The criteria can be summarized as (1) epidemiologic history (such as travel or residence history in Wuhan or contact with those who infected with SARS-COV-2); (2) clinical symptoms such as fever, respiratory system symptoms, or having the imaging features of COVID-19; (3) virological or serological evidence like positive results for NAT or serological antibodies against SARS-COV-2.

Data from completed questionnaires were confirmed through a face-to-face interview from April 18th to May 14th. PLWH and COVID-19 participants’ names and identification card numbers were double-checked in their respective district CDC information management systems. Clinical records and the symptoms of COVID-19 infection with which PLWH clients had reported were retrieved from the corresponding hospitals (Guo et al., 2020).

Laboratory results acquisition

The NATs for SARS-COV-2 were performed in the local designated hospital. The usage of laryngeal swab specimens and the real-time reverse-transcription polymerase chain reaction were reported previously(Wang et al., 2020). The CT and NAT results were retrieved from the information management systems for COVID-19 patients of the four districts’ CDC. Participants’ most recent (in 3 months) CD4 + T cell count, HIV viral load, current ART regimen, and demographic information were obtained from the AIDS Comprehensive Prevention and Control Data Information Management System of the Chinese CDC.

Statistical analysis

Categorical variables were presented as count (%), and continuous variables were presented as mean ± standard deviation. Univariate and multivariable logistic regressions were used to identify the factors associated with COVID-19 prevalence among PLWH. Various factors including age, gender, CD4 + count, HIV-VL, number of days since diagnosis, number of days on ART, and ART regimen were included in the multivariable logistic regression model. Odds ratios (OR), adjusted odds ratio (AOR) with 95% confidence intervals (CI), and P-values were also reported. As both CD4 count and HIV-VL were not normally distributed, they were further log-transformed. We performed all statistical analyses using SAS 9.4.
Ethical approval

This study was approved by the Ethics Committee of Zhongnan Hospital affiliated with Wuhan University (2020062), and informed consent was obtained.

Results

Patients enrolled in the study

Overall, a total of 1,709 PLWH in the four study districts were reached and interviewed. Five participants who were living outside of Wuhan for more than six months, and three asymptomatic carriers (NAT positive and CT negative) were ruled out from the study (Figure 2). The included 1,701 participants consisted of 1484 (87.2%) males, 217 (12.8%) females, and an average age of 42 ± 14.5 years old. Most PLWH (1,406, 82.7%) ART regimens consisted of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs). Another 172 participants (10.1%) took LPV/r-based ART and 87(5.1%) took integrase inhibitors (INI) based ART (62 Dolutegravir-based, 19 Elvitegravir/Cobicistat-based, 4 Raltegravir-based, 2 Bictegravir-based). Few participants (36; 2.1%) were still treatment-naive at the time of the study.

The morbidity for COVID-19 in PLWH

Through screening interviews and medical histories retrieval from the CDC information systems, we identified 11 confirmed COVID-19 patients among the 1,701 PLWH participants. Among the 11 COVID-19 patients...
who all got HIV via heterosexual transmission routes, ten (90.9%) were males and one (9.1%) was female. The average duration of time since HIV diagnosis was 7.5 ± 3.12 years, and the average duration of time since ART initiative was 5.56 ± 2.85 years, respectively. Nine out of the 11 COVID-19/AIDS patients had a relatively high CD4 count (>200/μl) and an undetectable HIV viral load (<20 copies/ml). Among the 11 COVID-19 infected PLWH, 81.8% (nine) took NRTI + NNRTIs, one took LPV/r-based ART, one was treatment-naive. The COVID-19 related morbidity in PLWH was about 0.6% (95%CI: 0.2%-1.0%) with no significant difference between patients by different ART regimens [Table 1].

Figure 2. The scheme of the investigation. The investigation followed the scheme shown here. HIV/AIDS patients enrolled in this cohort are documented in the AIDS Comprehensive Prevention and Control Data Information Management System of the Chinese Center for Disease Control and Prevention.

Table 1. Social-demographic and status of people living with HIV in Wuhan, China, 2020 (N = 1701).

<table>
<thead>
<tr>
<th></th>
<th>Total enrolled HIV/AIDS (n = 1701)</th>
<th>COVID-19 (n = 11)</th>
<th>Without COVID-19 (n = 1690)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>42.0 ± 14.5</td>
<td>53.2 ± 12.8</td>
<td>42.0 ± 14.5</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1484(87.2%)</td>
<td>10 (90.9%)</td>
<td>1474(87.2%)</td>
</tr>
<tr>
<td>Female</td>
<td>217 (12.8%)</td>
<td>1 (9.1%)</td>
<td>216 (12.8%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>416 (24.5%)</td>
<td>4 (36.4%)</td>
<td>412 (24.4%)</td>
</tr>
<tr>
<td>Unmarried</td>
<td>854 (50.2%)</td>
<td>4 (36.4%)</td>
<td>850 (50.3%)</td>
</tr>
<tr>
<td>Widow</td>
<td>431 (25.3%)</td>
<td>3 (27.3%)</td>
<td>428 (25.3%)</td>
</tr>
<tr>
<td>Transmission route</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexual</td>
<td>1173 (69.0%)</td>
<td>10 (90.9%)</td>
<td>1163 (68.8%)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>495 (29.1%)</td>
<td>1 (9.1%)</td>
<td>494 (29.2%)</td>
</tr>
<tr>
<td>Others</td>
<td>33 (1.9%)</td>
<td>0 (0.0%)</td>
<td>33 (2.0%)</td>
</tr>
<tr>
<td>Log10(CD4)*</td>
<td>2.63 ± 0.31</td>
<td>2.50 ± 0.42</td>
<td>2.63 ± 0.31</td>
</tr>
<tr>
<td>Log10(VL)*</td>
<td>0.89 ± 1.62</td>
<td>0.41 ± 1.37</td>
<td>0.89 ± 1.62</td>
</tr>
<tr>
<td>HIV diagnosis*/100</td>
<td>16.8 ± 11.8</td>
<td>27.4 ± 11.4</td>
<td>16.8 ± 11.7</td>
</tr>
<tr>
<td>Days ART/100</td>
<td>14.5 ± 10.4</td>
<td>20.3 ± 10.4</td>
<td>14.5 ± 10.4</td>
</tr>
<tr>
<td>ART regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTI + NNRTI</td>
<td>1406(82.7%)</td>
<td>9 (81.8%)</td>
<td>1397(82.7%)</td>
</tr>
<tr>
<td>LPV/r-based</td>
<td>172 (10.1%)</td>
<td>1 (9.1%)</td>
<td>171 (10.1%)</td>
</tr>
<tr>
<td>INI-based</td>
<td>87 (5.1%)</td>
<td>0 (0.0%)</td>
<td>87 (5.1%)</td>
</tr>
<tr>
<td>None</td>
<td>36 (2.1%)</td>
<td>1 (9.1%)</td>
<td>35 (2.1%)</td>
</tr>
</tbody>
</table>

Note: *Most recent, INI: integrase inhibitors; INI-based: 62 Dolutegravir-based, 19 Elvitegravir/Cobicista-based, 4 Raltegravir-based, 2 Bictegravir –based, “: Number of days since HIV diagnosis
Six of the 11 participants were categorized as mild COVID-19 cases, three as severe, and two were critical cases who died later. All categories were determined according to the Diagnosis and Treatment of COVID-19 in China (the 7th edition) (CNH).

Factors associated with COVID-19 among PLWH
Table 1 compares the characteristics of COVID-19 infected PLWH with uninfected PLWH. The average age of 53.2 ± 14.5 among COVID-19 infected PLWH (n = 11) was significantly older (P = 0.012) than the average age of uninfected PLWH (n = 1,690). Univariate and multivariable logistic regression analyses showed older age to be associated with COVID-19 prevalence in PLWH (AOR = 1.07, 95% CI:1.02, 1.13) [Table 2]. The multivariable results also indicated that log-transformed CD4 count was negatively associated with the COVID-19 prevalence in PLWH (AOR = 0.06, 95%: CI 0.01-0.30). However, log-transformed duration of time since HIV diagnosis was positively associated with COVID-19 occurrence (AOR = 1.12, 95% CI:1.05-1.19). We also found that people who got HIV infected through heterosexual transmission routes were less likely to develop COVID-19 compared to infected through heterosexual transmission routes (AOR = 0.07, 95% CI:0.01-0.90). Treatment naivety was also marginally associated with COVID-19 occurrence compared to treatment with NRTI + NNRTIs regimen (AOR = 13.36, 95% CI:0.77-231.74) [Table 2].

Discussion
Vulnerable individuals with compromised immune systems are considered to be more susceptible to SARS-CoV-2 infection. As PLWH presents with varying extents of immunosuppression characteristics, evidence from this study may enable us to prevent COVID-19 incidence among PLWH and immunodeficient individuals. Our study extends current literature by assessing the prevalence of COVID-19 among PLWH and exploring the driving forces of COVID-19 prevalence among PLWH. We found that older age, lower CD4 count, a longer time length since HIV diagnosis and treatment status were associated with COVID-19 prevalence among PLWH.

In the current investigation, we found COVID-19 related morbidity among PLWH to be comparable to the general population in Wuhan (∼0.6%, 50 thousand/9 million by 14th May 2020). The fact that 98% of identified PLWH participants were on regular ART and had relatively normal CD4 count (over 200/µL) could have accounted for the low morbidity. As proven by other studies, effective ART progressively improves immune system functions and could reduce the risk of opportunistic infection like SARS-CoV-2 (Currier & Havlir, 2018). This plausibility is also supported by our empirical finding that showed treatment naivety to be one of the potential driving forces of the COVID-19 prevalence among PLWH. Additionally, the preventive interventions utilized to retain PLWH in care during the strict quarantine period in Wuhan may have equally contributed to the observed low disease morbidity (Li et al., 2020a; Li et al., 2020b). Effective strategies adopted during the period thoughtfully included community-based organizations arranging for trained volunteers to collect and deliver ART drugs to PLWH individually (Jiang et al., 2020). This eliminated the compelling need for PLWH to visit highly exposed hospital environments where substantial numbers of COVID-19 cases had been admitted and facilitated treatment adherence without missed doses. Moreover, those who consistently took their ART may also observe better hygiene practices including keeping social distancing, etc., which may contribute to the lower morbidity than those Treatment naivety PLWH.

Having a higher CD4 count reduced likely chances of COVID-19 prevalence in PLWH as our findings showed that PLWH with lower CD4 count were more likely to develop COVID-19. Although no published studies on driving forces of COVID-19 prevalence in HIV negative population exists, CD4 count decrease and lymphopenia reportedly correlate with COVID-19 disease severity (Chen et al., 2020; Liu et al., 2020; Xu et al., 2020a). Besides, recent researches have indicated that lymphocytes, and especially CD4+ T lymphocytes are pivotal in the dynamics of anti-SARS-CoV-2 immune responses (Grifoni et al., 2020; Zhang et al., 2020). Therefore, early CD4+ responses were considered to be protective against SARS-CoV-2, while late phase CD4+ responses amplified pathological inflammation. In addition, our findings indicated that an extended period since HIV diagnosis is also correlated with COVID-19 prevalence. The long-term exhaustion of lymphocytes in PLWH could possibly account for an imbalanced immune state and low CD4 count. Such lengthy terms of immune deficiency could make affected individuals more vulnerable to SARS-CoV-2 infection (Giamarellos-Bourboulis et al., 2020; Ong et al., 2020). Despite that, further studies are needed to better understand the immune-pathogenesis of COVID-19 in PLWH.

We also speculate homosexual spread of HIV to be a possible risk factor of COVID-19 prevalence as PLWH infected via heterosexual routes were less likely to have COVID-19. This possibility is however consistent with observations made in some previous case series.
All the COVID-19 affected PLWH in these case series were typically found to have been HIV infected through homosexual transmission routes (Blanco et al., 2020). As reasons for this complex phenomenon are unclear, further investigations are required to properly understand the behavioral characteristics of PLWH infected with HIV through both homosexual and heterosexual routes.

Moreover, COVID-19 infected PLWH tended to be older than the other PLWH. This was consistent with a previous study’s findings that older males make up a more substantial proportion of the overall COVID-19 patient population (Huang et al., 2020). In addition, our study findings revealed older age to be a risk factor for COVID-19 infection in PLWH, which is no different from the HIV-negative population (Xu et al., 2020b).

Our study has several limitations. First, even though our study included 1701 PLWH individuals, only 11 had COVID-19 cases and were included. Those PLWH living outside of Wuhan were not taken into the investigation. This may have limited the study power to identify all the driving forces of COVID-19 among PLWH, and hence our results need to be interpreted with caution. Second, the transmission routes of the COVID-19 cases could not be researched in detail. This impeded our ability to further speculate on the reasons why homosexual HIV transmission presented a higher risk for COVID-19 prevalence. Whether the number of sexual partners was associated with the driving force of HIV and COVID-19 could not elucidate as well. Third, although we identified three asymptomatic carriers, there could have been more unrevealed virus carriers due to the speculated higher infection rate in PLWH. To be able to evaluate the proportion of COVID-19 PLWH patients in all SARS-CoV-2 carriers could have helped us to better understand the immune-pathogenesis of COVID-19.

**Conclusion**

COVID-19 related morbidity rates are similar in both PLWH and the general population. Older age, low CD4 count, long-term HIV diagnosis, and treatment-naïveté are potential driving forces of COVID-19 prevalence in PLWH. Therefore, strategies to prevent SARS-CoV-2 infection among PLWH with deficient immune responses are needed.

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Authors' contribution

WT, YF, and KL have full access to all of the data. WG, YF, WT, and KL conceived the research. FM, QZ, LL, PM, XZ, MG collected all the data. DY, WG, WT, and KL analyzed the data and drafted the manuscript.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Ethics approval

This study was approved by the Ethics Committee of Zhongnan Hospital affiliated with Wuhan University (2020062), and informed consent was obtained.

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