Analysis of different levels of viral suppression in HIV-1 patients after antiviral treatment

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Research article

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Abstract

Background Though highly active antiretroviral therapy (HAART) has brought the tremendous benefits to the HIV patients, there are still some patients with low HIV replication after treatment. This study investigated the influencing factors of different levels of viral suppression in HIV-infected patients in Central China. **Methods** A total of 4424 HIV-infected patients treated in 2016 from Hunan Province were enrolled and divided into 5 groups according to the level of virus replication, characteristics and clinic indicators were analyzed. **Results** There were 3871 cases (87.5%) who maintained the viral loads under 200 copies/mL after treatment, 261 cases (5.9%) with repeated test results, 57 cases (1.3%) had sustained low-level replication of virus, and 235 cases (5.3%) had long-term high-level replication of virus. Not surprisingly, the trend of CD4 cell counts growth were correlated with the trend of viral loads declination. Age, transmission mode, CD4 cell counts baseline, the interval between test and treat and the final statues between 5 groups were significant differences ($P < 0.05$). Compared with low-level replication group, patients with clinical phase I were more likely be in complete supression group than those with clinical phase IV; Patients transmitted by hetero sex were more likely to be with repeated viral loads than those transmitted by blood transfusion or contaminated blood products or mother-to-child. If we define viral loads always less than 200 copies/mL as the criterion for positive treatment, CD4 cell counts baseline under 500 n/μL and co-infected with HBV were independent risk factors for high HIV-1 replication, but young and test & treat were independent protective factors for viral suppression. **Conclusions** Early treatment is more effective in inhibiting viral replication, but screening for incomplete viral supression patients should be a routine practice in the management and control of HIV infection.

Background

Highly active antiretroviral therapy (HAART) is the most effective method to treat AIDS at present and has been carried out for more than ten years in Hunan, central region in China. It can effectively inhibit the replication of HIV virus in patients, rebuild the immune system of the body, and improve the quality of life of patients ^[1-4]. Generally speaking, after 3 to 6 months of treatment, the level of HIV RNA in the plasma of patients can be reduced to less than 20 copies/mL ^[5-6]. The third edition of the National Guidelines for Diagnosis and Treatment of China (2015 edition) adopted the criterion of effective treatment for viral suppression < 200 copies/mL, the opposite is regarded as failure. But the current standard line for drug resistance detection in China is viral load ≥ 1000 copies/mL. As a matter of fact, after long-term treatment, a small number of HIV patients' virual loads have been maintained at 200-999 copies/mL, that is, long-term low-level replication. The mechanism and influencing factors are still unclear, leading to clinical difficult to determine the prognosis. In this study, the target patients were divided into 5 groups by retrospective analysis of different levels of viral suppression after treatment, and the factors leading to this situation were evaluated by comparing various basic data and clinical data among the groups

Materials And Methods

Samples

From January to December 2016, there were 5099 newly treated HIV-1 patients in Hunan province, of which 675 were missing follow-up data, and the remaining 4424 were included in the study. Virological indicators, or viral loads was the main criteria for judging the therapeutic effect, which accorded with the third edition of the Guidelines for Diagnosis and Treatment(2015 edition). All the values of VL were < 200 copies/mL after 6-12 months of treatment were selected as group 1; low trend in first and high trend in late with the first test value ≥ 200 copies/mL and the continues < 200 copies/mL were group 2, the opposite as group 5; all the values of VL were between 200-999 copies/mL was group 3; all the values of VL were ≥ 1000 copies/mL as group 4.

Statistical analysis

Statistical analysis was performed with SPSS for Windows version 21.0 (SPSS, Chicago, IL, USA). Continuous variables were tested using Student's t -test. Categorical variables were analyzed using the χ^2 test. Risk factors were analyzed by multinomial regression and multivariate regression. Statistical significance was denoted as $P < 0.05$.

Results

Demographic characteristics of the target patients

Samples were collected from 4424 HIV-infected patients treated in 2016. Among these, 3396 (76.8%) were male and 1028 (23.2%) were female. The mean age was 43.3 ± 15.4 years. Transmission modes were intravenous drug use (60, 1.4%) and sexual transmission (4038, 91.3%). HIV-1/TB dual infection, HIV-1/HBV dual infection, and HIV-1/HCV dual infection were found in 210 (4.7%), 144 (3.3 %), and 56 (1.3%) patients, respectively. There were 449 (10.1%) patients treated with LPV/r initially, 3967 (89.7%) patients adhered the "test & treat" policy, and 50 (1.1%) had died up to now. Demographic characteristics of HIV-infected patients enrolled in this study are summarized in Table 1.

The immunologic response among 5 groups

The immunologic indicators of 4424 target patients changed every year. In 2017, the average CD4 cell counts in every group were 370.4 ± 235.4 n/ μ L, 282.9 ± 196.3 n/ μ L, 295.3 ± 179.6 n/ μ L, 270.7 ± 183.4 n/ μ L and 327.2 ± 230.0 n/ μ L, respectively($F=13.218$, $p=0.000$). While in 2018, the average CD4 cell counts in every group were 431.4 ± 288.5 n/ μ L, 369.3 ± 219.9 n/ μ L, 356.4 ± 221.7 n/ μ L, 323.0 ± 261.6 n/ μ L and 310.5 ± 235.9 n/ μ L, respectively($F=10.476$, $p=0.000$). Except group5, the average counts of CD4⁺ T cell in ART patients improved obviously, especially in group 1. The rising trends are showed in Fig 1.

Multinomial analysis

Risk factors for different level of HIV-1 replication were analyzed by multiple logistic regression analysis. Compared with group 3, the likelihood of patients with clinical phase $\square$ appearing in group 1 was 2.499 times that of those with clinical phase $\square$ ($OR = 2.499$, $P = 0.033$). Males were 2.056 times more likely to be

in group 2 than females ($OR = 2.056$, $P = 0.043$); patients with lower CD4 cell counts baseline (< 200 n/ μ L) were 4.522 times more likely to be in group 2 than those losing CD4 cell results ($OR = 4.522$, $P = 0.011$). Patients transmitted by hetero sex were 5.494 times more likely to be in group 5 than those transmitted by blood transfusion or contaminated blood products or mother-to-child ($OR = 5.494$, $P = 0.014$); those with clinical phase I and II were 3.769 times and 3.477 times more likely to be in group 5 than those with clinical phase III ($OR = 3.769$, $P = 0.013$; $OR = 3.477$, $P = 0.028$), respectively.

Multivariate analysis

Risk factors for positive HIV-1 inhibition were analyzed by multiple logistic regression analysis. Positive suppression was defined as viral loads keeping < 200 copies/mL after treatment. Sex, age, transmission modes, HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc were used for univariate analysis. Sex, age, transmission mode, CD4 cell counts baseline, marital status, dual infection, initial regimen, and test & treat were associated with positive suppression ($P < 0.05$). After multivariate analysis, CD4 cell counts baseline under 500 n/ μ L and co-infected with HBV were independent risk factors for high HIV-1 replication, but young age and test & treat were independent protective factors for viral suppression. The results are summarized in Table 2.

Discussion

Previous studies have shown that early treatment not only benefits infected people, but also protects the general population [7]. Treatment Manual in China (4th edition) was brought out and test & treat strategy were implemented in 2016. But due to the individual

differences of patients, regimen options, drug adherence and the spread of drug-resistant strains, the therapeutic effect of some patients failed to meet expectations: failure or incomplete inhibition of virology, failure of immune reconstruction, increase of clinical risk diseases, etc [8-11]. virological indicators were suggested and used as a monitoring index to diagnose and determine the failure of antiviral therapy. After 6 months of antiviral treatment, two consecutive plasma VL > 200 copies/mL was considered virological failure [12]. In the present study, we investigated 4424 cases treated in 2016 and found that 87.5% achieved positive therapy. If add cases whose viral loads remains stable after 18 months, the ratio would rise to 93.4%, means 90% of the effective treatment targets can be achieved in Hunan, a central province in China. Among 292 patients who failed in treatment, there were three cases: 57 patients with low-level viral replication, 76 patients with high-level viral replication and 159 patients with inhibition succeeded initially, but the replication of the virus increased dramatically over time. It is important to point out that the current line of drug resistance detection for efficacy monitoring is VL ≥ 1000 copies/mL, and most analysis of influencing factors of virological failures were focused on this group. In fact, the low level of virus suppression is related to the rapid progress of HIV disease,

cardiovascular complications and the rapid spread of HIV in the region ^[13-15]. So, the patients with low-level viral replication could not be ignored.

we compared the characteristics information and found that there were no significant differences in sex, clinic phases, average CD4 cell counts baseline and dual infection between 5 groups ($P > 0.05$). The lack of HIV-VL baseline means that it was not possible to analyse the effect of initial viral replication, but not to our surprise, group 1 had the fast CD4 cell counts growth, group 4 had the slowest growth rate, while in the fifth group, the CD4 cell counts decreased after the virus replication increased dramatically. Previous studies have shown that the increase in CD4 counts reaches a plateau after 4-6 years of viral response ^[16-17], this needs to be investigated further in our cohort. It looks like age, transmission mode and the interval between test and treat were significantly different between 5 groups ($P < 0.05$). Patients in group 1 had the youngest age and the highest rate of test & treat. Sexual transmission accounts for the highest proportion of all groups. Medication adherence was an important factor associated with low viral suppression proved by other study ^[18], that's what we need to consider next. If look at the follow-up status, group 2 has the highest mortality rate while group 4 has the highest rate of loss of follow-up. These data imply a possibility that poor viral suppression can undermine confidence in continuing treatment. However, this needs to be investigated further.

Compared with group 3 and group 1, patients with the slighter clinical phase had the better viral suppression effect. Compared with group 3 and group 2, males and those with lower CD4 cell counts baseline ($< 200 \text{ n}/\mu\text{L}$) were more likely to have higher viral loads initially then decreased markedly. Compared with group 3 and group 5, patients transmitted by hetero sex were 5.494 times more likely to have lower viral loads initially then increased markedly than those transmitted by blood or mother-to-child ($OR = 5.494, P = 0.014$), it was also possible happened for those with the slighter clinical phase. To our surprise, compared with group 3 and group 4, gender, age, route of transmission, initial CD4 cell counts, marriage or not, co-infection and so forth did not differ between low and high levels of viral replication after treatment. In addition to host factors, virological factors deserve further studies, as the therapy effects depend on interaction between host, virus and drug.

Conclusions

In our study, CD4 cell counts baseline under $500 \text{ n}/\mu\text{L}$ and co-infected with HBV were independent risk factors for high HIV-1 replication. These were consistent with previous studies ^[19-20]. Young age and test & treat were independent protective factors for viral suppression. These results imply that immune function, infection state, age and treatment time influence the therapeutic effects of HAART, and point out the importance of early treatment again, but screening for incomplete viral suppression patients should be a routine practice in the management and control of HIV infection.

Declarations

Ethics approval and consent to participate

The data in this article are from the existing database of antiviral therapy in our province and the study has been approved by the Ethics Committee of Hunan Provincial Center for Disease Control and Prevention.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HE Jian-mei, ZHEN Jun and WEI Xiu-qing screened the targets from database. DING Li-sha and LI Xiang-zhong made experimental index for patients. DING Li-sha analyzed and interpreted the data with CHEN Xi, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, tables 1 and 2 are only available as a download in the supplemental files section.

Figures

Fig 1 Rising trends of CD4 cell counts among 5 groups

Figure 1

Rising trends of CD4 cell counts among 5 groups

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Tables1and2.pdf](#)