Texila International Journal of Public Health
ISSN: 2520-3134
DOI: 10.21522/TIJPH.2013.10.02.Art021

Prevalence of HIV-associated Co-infections and Clinical Characteristics among HIV/AIDS Outpatients in the Context of Dolutegravir Roll-out Program in Vietnam

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Abstract

The prevalence of significant HIV-associated co-infections and clinical data of HIV/AIDS outpatients in the context of dolutegravir (DTG) transition are sparsely reported in Vietnam. Treatments of HIV co-infection, including antifungals, anti-tuberculous drugs, and direct-acting antiviral agents for viral hepatitis C, potentially challenge the efficacy of DTG-based therapies in terms of drug-to-drug interactions. We conducted a single-center, cross-sectional study between June and October 2020 in Ho Chi Minh City, Vietnam. HIV-infected outpatients were enrolled in the study when they attended the clinic to receive medical consultations and antiretroviral therapy (ART). Descriptive analyses were performed to describe the data. A total of 406 HIV-infected participants were enrolled in the study. The prevalence of HIV co-infected with chronic viral hepatitis B and C were 9.9% and 10.6%, respectively. Approximately 22.2% of HIV-infected patients had a history of tuberculosis treatment, and roughly 9% of participants experienced invasive fungal infections, mainly cryptococcosis, taralomycosis, and Pneumocystic jirovecii pneumonia. History of sexually transmitted diseases accounted for 40.4%. At the time of DTG transition, roughly 93% of patients were clinically stable, with a median CD4 count of 603 cells/µl. Two-thirds of HIV-infected patients achieved viral suppression (HIV viral load threshold < 20 copies/ml). A total of thirteen (3.2%) patients were ongoingly undertaking protease-inhibitors-based second-line ART regimens. The ART adherence was assessed at 92.1%. The prevalence of HIV-associated co-infections is still high in the context of DTG transition in Vietnam. More effort is needed in order to achieve the UNAIDS 90-90-90 targets.

Keywords: *Dolutegravir, Invasive fungal infections, Tuberculosis, Viral hepatitis, Vietnam.*

Introduction

Although HIV incidence has significantly decreased in the antiretroviral therapy (ART) era, the World Health Organization (WHO) reported that in 2020 there were 37.7 million people living with HIV/AIDS (PLWHA) worldwide, and approximately 680,000 people died of AIDS-related diseases and 1.5 million new HIV infections [1]. There has been an increase in ART coverage worldwide in recent years, and the WHO recommended dolutegravir (DTG) as the prioritized HIV treatment in all populations [2]. Recently, dolutegravir roll-out program has been implemented sporadically in Vietnam, and this poses a positive impact on the physical well-being of HIV/AIDS patients and prolongs the life span of PLWHA. The prevalences of significant HIV co-infection and clinical data of HIV/AIDS outpatients in the context of DTG transition are sparsely reported in Vietnam [3-5]. Treatments of HIV/AIDS co-infection, including antifungals, anti-tuberculous drugs, and direct-acting antiviral

Received: 18.03.2022 ***Accepted: 11.05.2022*** ***Published on: 30.06.2022***
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agents for viral hepatitis C, potentially challenge the efficacy of DTG-based therapies in terms of drug-to-drug interactions. Therefore, more understanding in this knowledge gap will substantially improve treatments and outcomes of HIV-infected individuals in resource-limited countries. This study aimed to determine the prevalences of the critical HIV-associated co-infections, including systemic mycoses, tuberculosis, and chronic viral hepatitis B and C, and describe the major clinical characteristics among HIV/AIDS outpatients in the context of dolutegravir transition in Vietnam.

Materials and Methods

Ethics Statement

This study was approved by the Institutional Review Board of the Faculty of the Public Health, University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam. The approval number was 252, signed on 16 April 2020. All study participants completely understood the study objectives and gave their written informed consent. This study was performed in compliance with principles in the Good Clinical Practice and Helsinki Declaration.

Study Setting and Design

We conducted a single-center, cross-sectional, HIV outpatient-clinic-based study between June and October 2020 at Mai Khoi charity clinic, Ho Chi Minh City, Vietnam. Briefly, Ho Chi Minh City is the most populated area in southern Vietnam, with a population of roughly nine million people, and receives the majority of HIV/AIDS patients from all regions across the country to receive healthcare and ART regimens [6]. The study site is well representative of HIV outpatient clinics in large cities in Vietnam, with approximately 1,200 HIV-infected outpatients to receive ART routinely. The clinic provided free-of-charge medical consultations and ART for enrolled HIV-infected patients. Patients attending their routine consultations were invited to participate in the study.

Study Participants

Eligibility criteria included HIV-infected, being more than 18 years old, and currently monitored and treated at the clinic. Study participants were selected using a simple random sampling method. A total of 406 subjects were enrolled.

Study Procedures

Patients would be provided verbal information statements about this study. For those who did not want to participate continued their routine medical care. Patients who agreed to participate in the study signed the written consent forms. The study participants have continued physical examination and ART adherence assessment. The clinical data were also extracted from medical records upon participants' approvals presented in the consent forms.

Study Definitions

WHO Clinical Staging of HIV/AIDS

The clinical staging of HIV/AIDS for adults with confirmed HIV infection was defined by WHO guidelines [7]. Briefly, HIV/AIDS clinical stages are categorized into four stages: stage 1, patients are asymptomatic; stage 2 (early HIV infection), patients may present mild symptoms; stage 3 (progressive disease), patients manifest intermediate symptoms and stage 4 (AIDS), patients demonstrate severe opportunistic infections and/or other life-threatening conditions.

WHO Virological Failure

Virological failure was defined as a persistently detectable plasma HIV viral load above 1,000 copies/mL, based on two consecutive viral load measurements after 6 months with intensive ART adherence counseling [7].

ART Adherence Assessment

The ART adherence was assessed in every clinic visit of patients, based on pill counts and on times of whether or not the patients missed monthly medical consultations and took ART on those missed days. Patients who were compliant with the ART medications, more than 95% were considered as adherent. More specifically, 95% or more adherence was equivalent to missing less than two doses of the total 28 doses within 28 days, and patients also had to take ART medications within two hours before or after the fixed time indicated by physicians.

Data Collection

Demographic and Psychosocial Variables

These included age, sex, intravenous drug use, education, employment and marital status, and mental and financial support from family members.

Clinical Variables

These included WHO HIV clinical stages, recent six-month HIV viral load measurements, HIV opportunistic co-infections including the history of tuberculosis treatment and invasive fungal infections in the recent past five years, history of sexually transmitted diseases (STDs), chronic viral hepatitis B and C co-infections, any pre-existing chronic underlying diseases (diabetes, hypertension, chronic kidney insufficiency, and other underlying diseases), ART duration, treatment adherence, history of ART failure and current ART regimens.

Statistical Analysis

Statistics were summarized by using median with interquartile range (IQR) for continuous variables and frequency (%) for categorical variables. All analyses were performed with STATA statistical software, version 16.

Results

A total of 406 participants were enrolled in the study. The baseline characteristics are presented in Table 1. The median age of patients was 35 years (interquartile range (IQR), of 30-41 years), nearly one-third of participants were female. Approximately 10% of participants had a past history of intravenous drug use (IVDU), and all reported to stop IVDU practice at the study enrolment time. Nearly two-thirds of participants completed high school or above degrees. In addition, a majority of patients were working as part-time or full-time staff and receiving financial and mental support from family members. Over 60% of patients were living alone.

Table 1. Baseline Characteristics of the Study Participants (N=406)

Characteristics	**Statistics ***
Age, years	35 (30-41)
Female, gender	123 (30.3)
History of intravenous drug use, yes	40 (9.9)
Educational status	
Primary school or less	37 (9.1)
Secondary school	113 (27.8)
High school or greater	256 (63.1)
Employment status	
Full-time or part-time employed	363 (89.4)
Currently unemployed or unable to work	43 (10.6)
Marital status	
Married	160 (39.4)

Characteristics	Statistics *
Single, widowed or divorced	300 (60.6)
Financial and mental support from family members, yes	364 (89.7)

* Summary statistic is median (interquartile range, IQR) for continuous variables and frequency (%) for categorical variables

The major clinical characteristics of participants are presented in Table 2. The majority of patients were clinically stable, with 92.6% in the HIV clinical stages 1 and 2. Most patients were under well-controlled immunological status, with the recent six-month median CD4 count of 603 cells/µl, and two-thirds of patients achieved HIV viral suppression with the recent six-month HIV viral load measurements < 20 copies/ml. Among 139 (34%) individuals with detected HIV viral load levels, the median HIV viral load was 20 copies/ml, with an interquartile range (IQR) from 20 to 25 copies/ml and with a minimum of 20 to a maximum of 750 copies/ml. The median time from confirmed HIV diagnosis to study enrolments was 5.8 years (IQR, 2.9-8.4). In addition, the median time since ART initiation until study enrolment was 5.1 years (IQR, 2.2-7.7); therefore, the interval time from HIV diagnosis to ART initiation was estimated at roughly 06 months. The common underlying chronic comorbidities, including diabetes, cardiovascular diseases, and chronic kidney insufficiency, were observed in 25% of patients. The prevalences of HIV co-infected with chronic viral hepatitis B and C were 9.9% and 10.6%, respectively. In addition, HIV-Tuberculosis (TB) co-infection was seen in 22.2% of patients, and roughly 9% of participants experienced invasive fungal infections, including crytococcosis, talaromycosis, *Pneumocystic jirovecii* pneumonia. The history of sexually transmitted diseases (mainly syphilis and Herpes simplex infections) accounted for 40.4% among HIV/AIDS patients. All patients were stably treated with either the first-line or the second-line ART. Particularly, 13/406 (3.2%) participants were ongoingly prescribed the protease-inhibitors-based second-line ART regimens, and the remaining patients were undertaking the first-line ART regimens. Remarkably, 92% of patients were well-adhered to treatment.

Table 2. Clinical Characteristics of HIV-positive Study Participants (N=406)

Characteristics	Statistics
Time since confirmed HIV diagnosis, years	5.8 (2.9-8.4)
Duration of ART, years	5.1 (2.2-7.7)
WHO HIV clinical stages	
Stages 1 and 2	376 (92.6)
Stages 3 and 4	30 (7.4)
Pre-existing chronic comorbidities	100 (25)
History of STDs *	164 (40.4)
History of tuberculosis treatment	90 (22.2)
History of HIV-associated opportunistic infections	
Talaromyces marneffei infection	(3.9)
Cryptococcal neoformans meningitis	(1.2)
Toxoplasmosis	(0.7)
Esophageal candidiasis	(2.0)

Characteristics	Statistics
Other OIs **	10 (2.4)
Chronic viral hepatitis B ***	40 (9.9)
Chronic viral hepatitis C ***	43 (10.6)
CD4 counts at time of study enrolment, cells/µl	603 (401-776)
HIV viral suppression	
Undetected viral load (< 20 cps/ml)	237/376 (63)
Detected viral load (≥ 20 cps/ml)	139/376 (37)
HIV viral load measurements (cps/ml) among detected cases	20 (20-25)
Currently treated ART regimens	
First-line ART	393 (96.8)
Second-line ART	13 (3.2)
ART adherence, yes	374 (92.1)

* STDs mainly included syphilis and Herpes simplex infections

** Other OIs included Cytomegalovirus, Pneumocystic jirovecii pneumonia and other opportunistic infections

*** Chronic viral hepatitis B and C were diagnosed by positive serum HBsAg, anti-HCV

Discussion

This study clearly demonstrates the high prevalence of HIV-associated co-infections among HIV/AIDS outpatients and altogether accounted for approximately two-thirds of the whole study population. This may potentially challenge the treatment efficacy of dolutegravir in terms of drug-to-drug interactions in the context of ongoing DTG roll-out in Vietnam in order to achieve the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 targets [8]. Our study clearly shows that the most frequently observed co-infections among HIV-infected patients were tuberculosis (22.2%) and invasive fungal infections (9%). These figures are quite consistent with previous reports in Vietnam and other African countries [9-11]. Remarkably, STDs were commonly seen among HIV/AIDS patients. Particularly, STDs can potentially elevate the risks of HIV transmission to susceptible populations, affecting reproductive health and reducing the quality of life of PLWHA [12]. In addition, the prevalence of chronic viral hepatitis B and HIV co-infection in our study was quite similar to previous reports from India, European and African countries [13-17]. Remarkably, the prevalence of HIV and chronic viral hepatitis C co-infection in this study was close to the Indian population report; however, it was higher than in African populations [13, 15-17]. This could be explained that intravenous drug use was an important risk factor for HCV infection and was more prevalent among patients with HIV-HCV co-infection in our studied participants and the Indian population compared to the African cohorts [13, 15-17]. Significantly, HIV and viral hepatitis B, and C co-infections continued to be a major concern in clinical practice because they substantially contributed to the increased risks of rapid progression to end-stage liver disease and mortality [18, 19].

With regards to clinical characteristics, a majority of study participants in the studied clinic were clinically and immunologically stable, and were going on well with currently treated ART regimens. Although one-third of patients had detectable HIV viral load measurements (≥ 20 copies/ml) with the minimum to maximum levels ranging from 20 to 750 copies/ml, which did not fully meet WHO HIV virological failure criteria of more than 1,000 copies/ml. Noticeably, the ART adherence was assessed 92%. Therefore, this indicates that the insufficiency of antiretroviral

drug concentration pressure resulted from considerable drug-drug interactions between ART and other concomitant medications and/or the interference of meals on the ART absorption. These were the most driven factors not obtaining HIV viral suppression and recommended to be thoroughly assessed at every medical consultation. Nevertheless, the first-line ART failure prevalence (3.2%) in our study population was relatively lower than reports from African countries [20-24]. Nevertheless, our studied clinic did not fulfill the UNAIDS 90-90-90 targets, particularly at least 90% of HIV-infected patients under ART should achieve HIV viral suppression [8]. However, the UNAIDS 90-90-90 targets have been shown to be dramatically challenging for the resource-limited countries as well as Vietnam [25].

In compliance with WHO recommendation that DTG-based ARTs should be prioritized in all HIV populations, our clinic has recently implemented the transition from nucleoside- and non-nucleoside- reverse transcriptase inhibitors (NRTIs, NNRTIs) containing ART to DTG-based regimens for six months [2, 4]. The preliminary results showed that DTG-based ART was effective in terms of rapidly increased CD4 counts and HIV viral suppression, fewer side effects, and improved patient treatment adherence. Most importantly, the drug interactions between DTG-based ART and tuberculous drugs (rifampicin) should be paid more attention with regard to the high prevalence of HIV co-infection with tuberculosis as observed in our study population. In this regard, adjusted dolutegravir dose of 100 mg daily was shown to be effective and well-tolerated among adult patients receiving rifampicin-based TB treatment [26]. Nevertheless, dolutegravir was reported to have minimal drug-drug interactions with azole antifungals. Hence routine DTG dose of 50 mg daily was suggested to continue for patients with invasive mycoses on azole-based therapies [27, 28].

Our study findings clearly demonstrated the prevalences of significant HIV co-infections, particularly tuberculosis and systemic invasive mycoses, chronic viral hepatitis B and C, and the study also presented the major clinical challenges in antiretroviral treatments in the context of dolutegravir roll-out in Vietnam. However, there are several limitations in this study, including selection and information biases which are inherent in the cross-sectional study design.

Conclusion

The prevalences of HIV-associated co-infections are persistently high among HIV/AIDS outpatients in Vietnam. The UNAIDS 90-90-90 targets, particularly at least 90% of HIV-infected patients achieving HIV viral suppression, are still challenging in the outpatient settings in Vietnam.

Conflicts of Interest

There is no conflict of interest.

Acknowledgements

We thanked all study participants and Mai Khoi clinic staff, especially Nguyen Nhu Hieu, M.D, and nurse, Ms. Linh, who arranged appointments with patients and reserved interviewed rooms for the study staff.

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