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Prevalence of transmitted drug resistance and phylogenetic analysis of HIV-1 among antiretroviral therapy-naïve patients in Northern Vietnam from 2019 to 2022

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Abstract: Since the rapid expansion of antiretroviral therapy (ART) for HIV, transmitted drug resistance (TDR) has become a major concern in Vietnam. HIV services there are transitioning to be covered by social insurance. Access to pre-exposure prophylaxis (PrEP) is being expanded to tackle the growing HIV epidemic among men who have sex with men. Therefore, a cross-sectional study was conducted at 10 ART facilities in Northern Vietnam from 9th December 2019 to 9th June 2022 to investigate the prevalence and pattern of TDR among ART-naïve people living with HIV (PLWH). TDR mutations were defined according to the World Health Organization 2009 List of Mutations for Surveillance of Transmitted Drug Resistant HIV Strains. Mutation transmission dynamics and TDR clusters were investigated *via* phylogenetic analysis. We enrolled 391 ART-naïve PLWH. The overall TDR prevalence was 4.6%, with an annual prevalence of 6.0% in 2019/2020, 4.8% in 2021, and 1.3% in 2022. TDR mutations to non-nucleoside reverse transcriptase inhibitors (2.8%), including K103N were the most common. Less commonly, the protease inhibitor-associated mutation M46I and mutations to nucleoside reverse transcriptase inhibitors, including M184V/I, were observed. CRF01_AE was the most common subtype (77.0%). CRF07_BC (14.3%), which had been rare in Vietnam, was also observed. No genetic association was observed between HIV-1 sequences with TDR mutations. In conclusion, the overall prevalence of TDR was stably low in this region. The phylogenetic tree suggests that TDR clusters have not formed. Continuous monitoring of HIV TDR and strains is crucial to maintaining ART and PrEP efficacy.

***Keywords*:** transmitted drug resistance, mutations, phylogeny, HIV, Vietnam

Introduction

The extensive expansion of access to antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) are key components to controlling and preventing HIV infection and ending the HIV/AIDS epidemic. However, with the increased use of antiretroviral drugs, HIV drug resistance (HIVDR) has emerged, impacting the drugs' ability to block viral replication. In particular, transmitted drug resistance (TDR), which occurs when individuals are infected with an HIV strain that is already resistant to one or more drugs, compromises the efficacy of ART and PrEP, and poses a potential threat to the success of HIV elimination. A recent review found that the prevalence of TDR among ART-naïve people living with HIV (PLWH) varied regionally from 4.1% in South/Southeast Asia to 14.2% in North America between 2014 and 2019, with a rising trend in some regions (*1*).

Vietnam has made considerable progress in responding to the HIV epidemic over the past 30 years. By 2021, approximately 70% of an estimated 240,000 PLWH were receiving ART in Vietnam (*2*). The number of new infections decreased from 210,000 in 2003 to 5,700 in 2021 (*2*). In addition, according to nationally representative surveillance, the prevalence of TDR in Vietnam remained low at 5.8% (the prevalence of having any pre-treatment HIVDR) in 2017–2018 (*3*). The prevalence has been maintained below the threshold of 10% beyond which the World Health Organization (WHO) recommends changing the first-line treatment regimen (*4*).

However, in recent years, there has been a growing concern that the incidence of TDR could rise and these

gains could be reversed in Vietnam's unique context, which would hinder achievement of the 95-95-95 target (*5*) by 2025. Vietnam is currently facing a transition in the funding of HIV services, from international donor support to domestic funding using social health insurance (SHI) (*6*). This transition imposes a series of important changes on beneficiaries and providers. In particular, decentralization of HIV services and out-of-pocket costs can be barriers to continuing ART for PLWH (*7*), with potential subsequent increases in the risk of developing and transmitting HIVDR.

Increased TDR levels could have a negative impact on the efficacy of PrEP. Recently, elevated HIV prevalence in men who have sex with men (MSM) has been noted in Vietnam; HIV prevalence among MSM increased from 5.1% in 2015 to 13.2% in 2020 (*8*). To address HIV prevention in this emerging population with elevated HIV infection rates, Vietnam introduced PrEP for MSM and transgender women in 2017 (*9*). In addition, drug resistance testing is not covered by SHI due to limited testing capacity, and it is rarely performed in Vietnam for purposes other than surveillance. In this context, there is a considerable need to evaluate TDR in Vietnam. However, relevant data are limited, especially from real-world clinical settings.

HIV is a highly diverse and rapidly evolving pathogen, with multiple subtypes and recombinant forms that can differ in their transmission dynamics, virulence, and drug resistance profiles. Phylogenetic analysis is a powerful tool to study the evolutionary relationships among different HIV strains, as well as infer transmission networks and patterns within specific populations. Amid the rapidly changing dynamics of the HIV epidemic, this analysis can help identify circulating HIV strains and the distribution of TDR in ART-naïve PLWH in Vietnam. This information will be crucial for the development of targeted HIV infection prevention and control strategies.

Conducted during the transition to SHI-based HIV services and the emerging HIV epidemic among MSM in Northern Vietnam, this study aimed to investigate the prevalence and pattern of TDR among PLWH with no previous exposure to ART. We also analyzed the phylogeny of HIV strains to identify their transmission dynamics and the distribution of TDR.

Patients and Methods

Study design and participants

From 9th December 2019 to 9th June 2022, a cross-sectional study was conducted among ART-naïve PLWH from 10 provincial- or district-level facilities in Northern Vietnam. These facilities were registered in a program titled "Science and Technology Research Partnership for Sustainable Development (SATREPS)". Eligible participants were ART-naïve PLWH aged ≥16 years with confirmed HIV infection according to local guidelines. Participants were excluded if their physician deemed them likely to have a history of ART use, which would render them ineligible to participate in the study. The convenience sampling technique was applied and all patients who met the inclusion criteria were invited to take part in the study. Well-trained healthcare staff at the study sites collected the baseline characteristics of the participants.

Drug resistance testing

Drug resistance testing was performed for those with an HIV viral load (HIV-VL) > 1,000 copies/mL, following a guideline issued by the Vietnam Ministry of Health (*10*). To measure HIV-VL, two EDTA tubes of whole blood were collected from each participant to extract plasma. All plasma samples were stored at −20 °C or lower at the study sites, then transferred on dry ice or gel ice to the National Hospital for Tropical Diseases in Hanoi. The quantitative measurement of HIV-VL was carried out using two automated systems, COBAS® AmpliPrep/COBAS® TaqMan and cobas® 6800 (Roche Diagnostics, Switzerland).

First, for drug resistance testing, HIV-1 RNA purification was conducted with the QIAamp Viral RNA Mini Kit (Qiagen, Germany). Next, the PrimeScript II High Fidelity RT-PCR Kit and the PrimeSTAR GXL DNA Polymerase Kit (Takara Bio, Japan) were used to amplify the protease (1–99) and reverse transcriptase (1–560) regions of HIV-1. Then, Sanger sequencing was conducted using the 3500 Genetic Analyzer (Thermo Fisher Scientific, USA). All primers used for polymerase chain reaction and sequencing are listed in Supplemental Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=77*) (*11,12*). Finally, the sequence results were analyzed with ATGC software (Genetyx Corporation, Japan) to confirm the mixture of bases and construct consensus sequencing. The Stanford HIV Drug Resistance Mutations Database (*https://hivdb.stanford.edu/*) was used to evaluate relevant sequences associated with resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitor (PIs). TDR was determined using the World Health Organization 2009 List of Mutations for Surveillance of Transmitted Drug Resistant HIV Strains (hereafter referred to as the WHO 2009 Mutation List) (*13,14*); HIV strains with at least one TDR mutation on the list were defined as resistant.

Phylogenetic analyses

To evaluate the transmission dynamics and distribution of TDR, a phylogenetic tree was constructed. Sequences were aligned with the HIValign tool of the Los Alamos

database (*https://www.hiv.lanl.gov/content/index*) and altered by the GENETYX Parallel Editor program (Genetyx Corporation, Japan). MEGA 7 software was used to construct the phylogenetic tree from the aligned data, with the neighbor-joining method using the Kimura two-parameter model. The bootstrap replication was set as 1,000, and the clustering of sequences with a bootstrap value > 90% was considered significant.

Statistical analyses

The overall and class-specific TDR prevalence by year were calculated from 2019 to 2022. However, only nine samples were collected in December 2019. These were combined with the samples collected in 2020 for annual analysis. In addition, chi-square tests were performed to assess associations between any TDR mutation and demographic factors (*i.e*., gender, age, facility level, facility location, and route of HIV transmission). The pattern of class-specific TDR mutations was also descriptively analyzed. All statistical analysis was performed using Stata software (version 16, StataCorp, College Station, TX, USA).

Ethical considerations

The study was approved by both the Human Research Ethics Committee of the National Center for Global Health and Medicine in Japan (reference: NCGM-G-003124-02, NCGM-G-003124-03) and the Bio-medical Research Ethics Committees of the National Hospital for Tropical Diseases in Vietnam (reference:12/HDDD-NDTU, 17/HDDD-NDTU). All study participants provided written informed consent for participation and for the use and publication of their clinical and laboratory data for research. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Study participants

In total, 391 ART-naïve PLWH from 10 study sites participated in this study. Of these, 55.8% were from provincial-level hospitals and 44.2% were from district-level facilities. Their median age was 33 years old (inter-quantile range: 26–44), and the majority were male (80.0%). The main route of HIV transmission was heterosexual contact (44.0%), particularly contact with a spouse or long-term partner, followed by male homosexual contact (39.6%). The median baseline HIV-VL was 95,300 copies/mL (inter-quantile range: 37,100–273,000) with approximately half having an HIV-VL > 100,000 copies/mL (Table 1). There was no association between the baseline characteristics of

Table 1. Characteristics of study participants and prevalence of transmitted drug resistance mutations

Characteristics	*n* (%)	any TDR *n* (%)	*p* value*
Gender			0.413
Male	312 (80.0)	13 (4.2)	
Female	79 (20.0)	5 (6.3)	
Age (years)			
Median (IQR)	33 (26–44)		0.385
< 30	155 (39.6)	6 (3.9)	
30 to < 40	103 (26.3)	6 (5.8)	
40 to < 50	85 (21.8)	2 (2.4)	
≥ 50	48 (12.3)	4 (8.3)	
Facility level			0.986
Provincial	218 (55.8)	10 (4.6)	
District	173 (44.2)	8 (4.6)	
Facility location			0.150
Hanoi	319 (81.6)	17 (5.3)	
Other provinces	72 (18.4)	1 (1.4)	
Route of HIV transmission			0.838
Heterosexual contact	172 (44.0)	9 (5.2)	
MSM	155 (39.6)	6 (3.9)	
IDU	34 (8.7)	1 (2.9)	
Other/Unknown	30 (7.7)	2 (6.7)	
Baseline viral load (copies/mL)			
Median (IQR)	95,300 (37,100–273,000)	-	
200–999	2 (0.5)	-	
1,000–9,999	29 (7.4)	-	
10,000–99,999	168 (43)	-	
100,000–999,999	162 (41.4)	-	
≥ 1,000,000	30 (7.7)	-	

*Chi-squared test. TDR: transmitted drug resistance; IQR: inter-quantile range; MSM: men who have sex with men; IDU: injection drug use.

Table 2. The prevalence of transmitted drug resistance

TDR prevalence	Total *n* (%)	2019[#]/2020	2021	2022
Study participants (*n*)	391	150	165	76
Any DRM	18 (4.6)	9 (6.0)	8 (4.8)	1 (1.3)
Any NRTI DRM	5 (1.3)*	2 (1.3)	2 (1.2)*	1 (1.3)
Any NNRTI DRM	11 (2.8)*	4 (2.7)	7 (4.2)*	0 (0.0)
Any PI DRM	3 (0.8)	3 (2.0)	0 (0.0)	0 (0.0)

*One patient had drug resistance mutations to both NRTIs and NNRTIs and was classified in two categories. [#]Only nine samples were collected in December 2019, so they were combined with the 2020 samples for annual analysis. TDR: transmitted drug resistance; DRM: drug resistance mutation; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

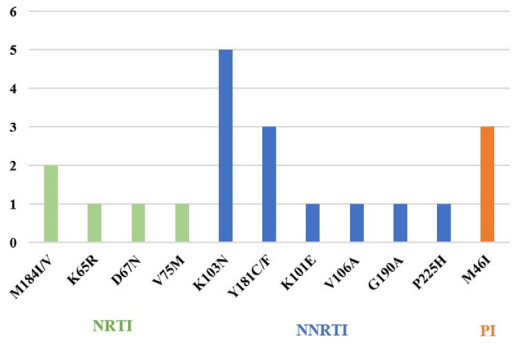

Figure 1. Drug class-specific transmitted drug resistance mutations. NRTI: nucleotide reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

the participants and the presence of any TDR mutation (Table 1).

Overall and annual prevalence of TDR

The overall prevalence of having any TDR mutation was 4.6%, with an annual prevalence of 6.0% in 2019/2020, 4.8% in 2021, and 1.3% in 2022. In addition, TDR mutations for NNRTIs were the most prevalent throughout the study period, whereas TDR mutations for NRTIs and PIs were less prevalent. One patient carried TDR mutations for both NRTIs and NNRTIs. No patient was resistant to all three drug classes (Table 2).

Drug class-specific TDR mutations are listed in Figure 1. Single mutations occurred the most frequently. The most common NNRTI-associated mutations was K103N followed by Y181C/F, K101E, V106A, G190A, and P225H. As for the NRTI-associated mutations, M184I/V was the most frequently observed, followed by K65R, D67N, and V75M. The M46I mutation, the only one associated with PI resistance, was detected in three participants.

Phylogenetic tree analysis

Phylogenetic tree analysis was conducted for the protease and reverse transcriptase regions of HIV-1 (HXB2: 2253-4229). No genetic link was observed among HIV-1 sequences with any TDR mutation in this study. The analysis revealed that the most common subtype of HIV-1 was CRF01_AE (n = 301, 77.0%), followed by CRF07_BC (n = 56, 14.3%), CRF08_BC (n = 5, 1.3%), A (n = 1, 0.3%), C (n = 1, 0.3%), and F (n = 1, 0.3%). In addition, other recombinant subtypes (n = 26, 6.6%) formed a cluster at the bottom of the phylogenetic tree (Figure 2). Among the recombinant subtypes, some sequences were nearly identical to those of CRF109_0107, whereas other sequences had a slightly different pattern of recombination. In the upper right region of the phylogenetic tree, heterosexual female participants, heterosexual male participants, and those with a history of injection drug use were abundant. This region had more TDR cases than the other regions of the phylogenetic tree. However, sequences in the upper right were diverse and could not be defined as one group (bootstrap value ≤ 90). The CRF07_BC group made a significant cluster, which was composed of mainly MSM. Sequence data are available in DDBJ/EMBL/GenBank (accession number LC765998-LC766388).

Discussion

Against the backdrop of the transition to SHI-based HIV services and the emerging HIV epidemic among MSM in Vietnam, our study evaluated the prevalence of TDR mutations among ART-naïve PLWH in Northern Vietnam from 2019 to 2022. The TDR prevalence was 4.6% overall, with a preponderance of resistance mutations to NNRTIs (2.8%) over NRTIs (1.3%) and PIs (0.8%), according to the WHO 2009 Mutation List. Our findings are consistent with previous data from Vietnam on pre-treatment PLWH (3.5% between 2009 and 2010 in three major cities (*15*); 6.4% between 2005 and 2008 in the south (*16*), and 5.8% in a nationally representative surveillance between 2017 and 2018 (*3*)). However, the stable trend in TDR prevalence observed in this study contrasts with the trend for rising TDR prevalence in Asia and low-income countries (*17,18*). One explanation for such a difference may be the successful maintenance of HIV treatment during the coronavirus disease 2019 (COVID-19) pandemic in Vietnam (*19*). The effective responses to COVID-19 at all HIV service levels to ensure the preservation of the HIV continuum of care may have contributed to stable treatment outcomes during the pandemic and prevented the development and transmission of HIVDR among PLWH.

The most common TDR mutation observed in this study was K103N in the NNRTI resistance class. This finding is consistent with those of other studies

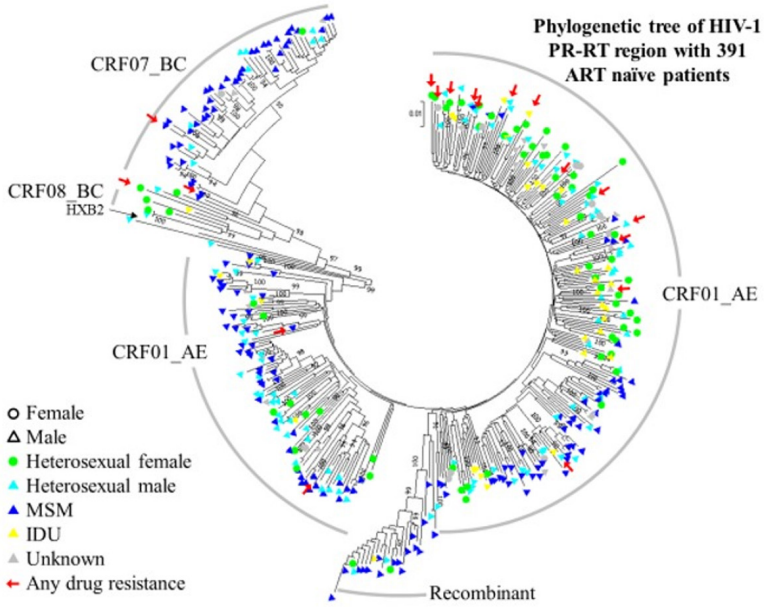

Figure 2. Phylogenetic analysis of HIV strains from antiretroviral therapy-naïve patients in Northern Vietnam from 2019 to 2022. MSM: men who have sex with men; IDU: injection drug users.

conducted in Vietnam (*3,12*) and similar to findings from other low- and middle-income countries (*20-25*). K103N and Y181C/F are drug resistance mutations that can develop in response to treatment with NNRTIs, such as nevirapine or efavirenz. These drugs have been commonly used as the first-line regimen for ART-naïve PLWH in Vietnam for many years (*26*). However, the recent introduction of integrase strand transfer inhibitors (INSTIs) such as dolutegravir (DTG) has provided a new option for the management of HIV infection. DTG has a high genetic barrier to the development of HIV drug resistance. Therefore, the expanded use of a DTG-based regimen may have contributed to the stabilization of TDR prevalence in recent years and may further reduce the prevalence in the future (*27*).

It is also noteworthy that an NRTI-related mutation, M184V/I, and a PI-related mutation, M46I, were found in 2/391 (0.5%) and 3/391 patients (0.8%), respectively. The M184V/I mutation is selected by lamivudine (3TC) and emtricitabine (FTC), one of the combination drugs (TDF-FTC) in PrEP. Therefore, while the use of PrEP is rapidly expanding in Vietnam, the M184V/I mutation may offset its benefits. However, PIs are the major class of drug used in second-line and alternative regimens for those who experience treatment failure. Given that options for second-line and third-line regimens are limited in Vietnam, the emergence of PI-associated mutations could pose challenges for the selection of an optimal ART regimen. Although the prevalence of these TDR mutations is still low, continuous monitoring of HIVDR in PLWH is necessary to ensure effective clinical management and maximize the efficacy of ART and PrEP.

In line with previous reports from Vietnam, in which CRF01_AE predominated (≥ 97%) over other subtypes (*3,12,16,28-30*), CRF01_AE was the most prevalent HIV-1 subtype observed in this study, accounting for infection in 77.0% of the participants. However, in contrast to the findings of these reports, we found that the prevalence of CRF07_BC was much higher (14.3%) and the CRF07_BC cluster consisted primarily of MSM. Notably, a similar trend was observed in a recent study in China, where the prevalence of CRF07_BC increased from 24.1% in 2007 to 40.3% in 2022 (*31*). Furthermore, in addition to the prevalent subtypes CRF07_BC and CRF08_BC in China, we also found subtype CRF109_0107, which has recently been reported in Shenzhen, China (*32*). This is the first report of the migration and expansion of these new strains from China to Northern Vietnam, especially in MSM. Further studies are needed to understand the transmission dynamics of new strains such as CRF07_BC, not only in Northern Vietnam but throughout the country. Furthermore, there was no genetic association observed between TDR cases in our study, indicating that there is no current outbreak of HIV-1-resistant strains. This may be one reason for the low prevalence of TDR in this country.

When assessing the findings of our study, one major limitation should be taken into consideration. We collected data from 391 ART-naïve PLWH in Northern Vietnam. This relatively small sample size from a specific geographical region could limit the generalizability of the findings. A larger sample size would have provided the statistical power to investigate an association between TDR and the characteristics of the study participants.

In conclusion, we found that the prevalence of

TDR was stable at a low level (4.6%) among ART-naïve PLWH in Vietnam from 2019 to 2022, during the transition to SHI-based HIV services and the emerging HIV epidemic among MSM. However, given the prevalence of M46I and M184V/I, and the emerging risk of the development of INSTI-associated mutations during the expansion of DTG use, continuous monitoring of HIVDR is crucial to maintain the efficacy of ART and PrEP and to meet the 95-95-95 target (*5*) by 2025 in Vietnam. An increase in CRF07_BC infection among MSM observed in this study may indicate rapid HIV-1 migration from Southern China to Northern Vietnam, especially among MSM.

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Meeting at which parts of the data were presented
Prevalence of baseline drug resistance mutations among people living with HIV in Northern Vietnam from 2019 to 2021, Asia-Pacific AIDS & Co-Infections Conference (APACC) 2022, Virtual Meeting, 16–18 Jun 2022.

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Conflict of Interest: SO has received research grants from ViiV Healthcare and Gilead Sciences, drug for clinical research from Gilead Sciences, and honorarium for lectures from ViiV Healthcare and Gilead Sciences. Other authors have no conflicts of interest to disclose.

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