

A Review of the Extent of HIV Drug Resistance in Vietnam

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Abstract

Background: In 2005, free antiretroviral therapy (ART) was rolled-out as a national program in Viet Nam. The estimated population of people living with HIV reached 254,000 in 2010 and this leads to increasing demand of ART in the near future. By 2009, ART coverage reached 53.7% for adults and adolescents, and 49.7% for children. This study aims to describe the prevalence of HIV acquired drug resistance (ADR) among people receiving ART and prevalence of transmitted drug resistance (TDR) among recently HIV-infected persons in Vietnam, and their associated ART coverage, antiretroviral treatment adherence and risk behaviors.

Methods: We performed a comprehensive review of published English literature containing relevant epidemiological and behavioral indicators through internet searches.

Results: Twenty-one relevant publications were included in this review. TDR prevalence among people recently infected with HIV increased from below 5% in 2006 to a higher level of 5-15% during 2007-2008 in urban Vietnam, whereas TDR prevalence among chronic antiretroviral-naïve HIV-infected adults stabilized between 6-8% across the country. About half of all adults and children with clinical or immunological criteria of therapeutic failure had evidence of developing resistance to antiretroviral drugs. Non-adherence among adults on ART ranged between 25-32% and the level of viral suppression (< 1,000 copies/ml) fluctuated from 68% to more than 83% at 12 month after initiating ART. However, relevant data concerning children were mostly absent.

Conclusion: Increasing trend of transmission of HIV drug resistance was observed in urban Vietnam, suggesting an urgency of the establishment of regular surveillance for TDR. Viral load testing and availability of second or third line ART are recommended for the early diagnosis of drug resistance and prevention of its accumulation and transmission.

Keywords: Review; HIV; Drug resistance; Vietnam

Introduction

The Vietnam's HIV epidemic remains concentrated among high-risk populations since the first case reported in late 1990. The overall HIV prevalence was estimated to be 0.44% among people aged between 15-49 years in 2010 [1]. In comparison, much higher prevalence was observed among drug users (IDU) (18.4% in 2009), female sex worker (FSW, 3.2% in 2009) since the establishment of the national HIV sentinel surveillance in 1994 [2]. However, the latest data indicated a remarkable increase of HIV prevalence among men who have sex with men (MSM, 16.7% in 2009 [2]). The estimated population of people living with HIV (PLHIV) more than doubled during the past decade, reaching approximately 254,000 in 2010 [1,2]. This is expected to lead to a high demand of antiretroviral (ARV) treatment in the near future.

Antiretroviral therapy (ART) can substantially slow AIDS disease progression and reduce morbidity and mortality among HIV-infected populations [3-5]. However, under ARV drugs pressure, people receiving ART develop drug-resistant strains of HIV, namely, acquired drug resistance (ADR). These strains can be transmitted through exchange of body fluids, and susceptible individuals are then infected with the transmitted drug resistant strains of HIV (TDR). Many developed countries, with a long history of ART implementation, reported high prevalence of both ADR and TDR, typically ranged between 35-60% [6,7] and 8-25% [8-18], respectively. Recently, several developing countries also reported increasing transmission of HIV drug resistance [19-21], despite that the overall prevalence of TDR remained low. Although ART through public out-patient clinics has been available in Vietnam for nearly ten years, it was not until 2005 Vietnam received sufficient support from the United States President's Emergency Plan for AIDS Relief and the Global Fund to Fight

AIDS, Tuberculosis, and Malaria to roll-out its free ART programs on a national level. Since then, several regional surveys reported the prevalence of HIV resistance across various populations, adherence to ART, and risk behaviors of PLHIV, revealing the emergence and transmission of HIV drug resistance. However, to our best knowledge, no review on HIV drug resistance in relation to ARV treatment in Vietnam has been published.

This review aims to describe the epidemic of the emerging drug resistant strains of HIV among people receiving ART and its transmission among recently infected individuals in Vietnam. We further estimate the coverage of ART among treatment-eligible population in both adults and children populations, and describe treatment adherence and risk behaviors among people receiving ART. The results of our study may provide an overview of HIV drug resistance in this country, determine current knowledge gaps in understanding of the transmission pattern, and recommend suitable intervention strategies for minimizing the emergence and spread of HIV drug resistance in Vietnam.

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Received November 15, 2011; **Accepted** December 25, 2011; **Published** December 30, 2011

Citation: Pham QD, Wilson DP, Zhang L (2012) A Review of the Extent of HIV Drug Resistance in Vietnam. J AIDS Clinic Res S5:001. doi:10.4172/2155-6113.S5-001

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Methods

We estimate ART coverage in Vietnam based on the available data from governmental sources. The coverage of ART among PLHIV with age over 15 years was calculated by dividing the annually reported numbers of people receiving ART by the estimated number of treatment-eligible adults and adolescents (aged 15+ years, CD4 < 200 cell/mm³) at the same year [22]. According to the World Health Organization (WHO), HIV-infected infants or children (aged 0-14 year) should be treated with ART as soon as possible after HIV-diagnosis regardless of CD4 levels or identified WHO clinical stages [23]. Hence, we divide the number of children receiving ART by the estimated population size of HIV-infected children to estimate the coverage of ART for this population. Data was collected from two reliable reports of the Vietnam Administration of HIV/AIDS Control (VAAC), Ministry of Health [1,24]. The number of adults and adolescents receiving ART by years was made publicly available at a national HIV/AIDS conference in 2010 [1], whereas a VAAC report provided the yearly estimated number of people aged over 15 years in need of ART and number of HIV-infected children [24].

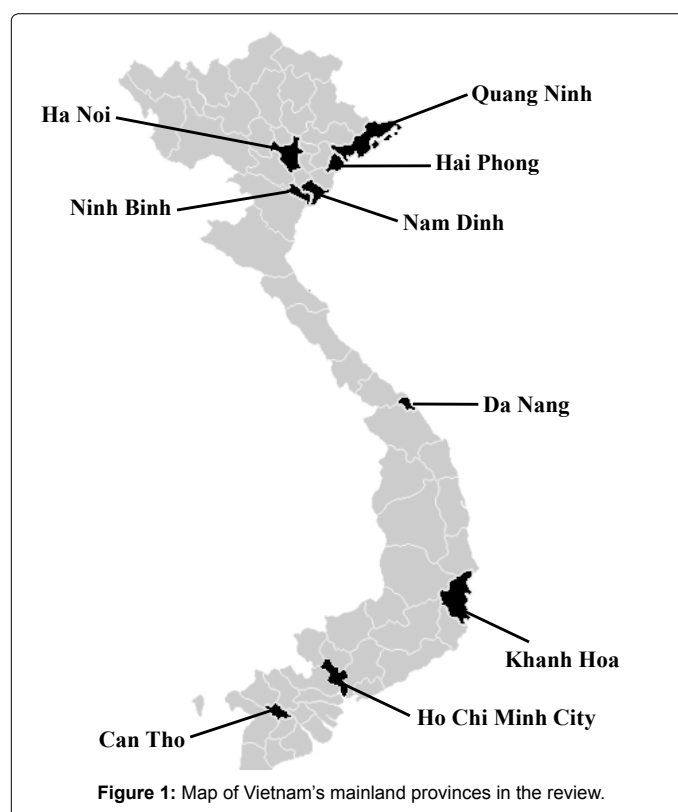
Data on the ADR prevalence, level of treatment adherence and risk behaviors among people on ART, and TDR prevalence among recently HIV-infected persons were drawn from published electronic English literature. We performed searches in October 2011 for papers on PubMed and peer-reviewed abstracts on major international conferences (International AIDS Conference, Conference on HIV Pathogenesis and Treatment - IAS, and Conference on Retroviruses and Opportunistic Infection - CROI), according to the following search terms: ('HIV') AND ('antiretroviral' OR 'ARV' OR 'ART' OR 'HAART') OR ('HIV treatment' OR 'HIV care') AND ('Vietnam'). Our review excluded studies prior to January 1, 2000 or those with sample size less than 30. A publication is included if it reported any of the prevalence of ADR, treatment adherence level or risk behaviors among people receiving ART or the prevalence of TDR among those who recently acquired HIV. Most studies investigating HIV drug resistance in Vietnam conducted a sequencing test for the specimen when its viral load level was greater than 1,000 copies/ml [25-29] and only reported the prevalence of ADR among people with a successful sequencing. However, Lee et al. [30] argued that people receiving ART with viremia less than 1,000 copies per ml is not typically associated with development of HIV drug resistance. Thus, we assume that people treated with ART who have viral load levels under this threshold harbor only wild-type HIV; this may not always be true and therefore our estimates are conservative. The prevalence of ADR is then estimated by the number of people harboring drug resistant HIV divided by number of the ART recipients having viral load testing in each published survey.

Results

The current paper reviewed twenty-one publications reporting relevant drug-resistance information including ART coverage, treatment-adherence rate and level of viral suppression during treatment, and prevalence of ADR and TDR. Of these, nineteen papers contained empirical survey data from HIV-infected populations recruited from nine Vietnamese provinces (Figure 1).

Scale-up of free ART program in Vietnam

By the end of 2004, over 21,000 HIV-infected adults and adolescents (age 15+ years) were estimated to require ART, with only approximately 500 receiving it, representing an extremely low coverage of 2.1% (range: 1.6-3.1%). The provision of ART through public sector increased nationally since 2005 when international efforts scaled-up



funding for care and treatment program in Vietnam in response to the new ARV treatment guidelines at this time. Nearly 2,700 people aged over 15 years were on ART by the end 2005. This figure dramatically scaled up to over 15,000 and 36,000 by 2007 and 2009, respectively. This corresponds to an increase of ART coverage from 8.5% (range: 6.5-12.4%) in 2005 to 32.1% (range: 24.7-45.9%) in 2007 and 53.7% (range: 42.8-75.0%) in 2009. Comparably, ART coverage among HIV-infected eligible children (0-14 years) increases in a similar rate, from 15.7% (range: 15.0-16.4%) in 2005 to 39% (range: 36.0-41.2%) in 2007 and 49.7%, (range: 47.6-52.0%) in 2009 (Table 1).

Prevalence of transmitted and acquired drug resistance of HIV

In accordance to the WHO's guidelines for TDR surveillance [31], proxy recent HIV-infected populations that are ARV -naive, such as pregnant women or attendees of voluntary counselling and testing (VCT) were monitored for TDR prevalence in Vietnam. In Ho Chi Minh City (HCMC) in 2005, one of 163 (0.6%) HIV-infected pregnant women accessing prevention of mother-to-child transmission program were diagnosed with mutations associated with resistance to nucleoside reverse transcriptase inhibitor (NRTI) [32]. Further study in this city in 2006 revealed a higher prevalence of 3.2% among VCT attendees (age < 25 years and CD4 count > 500 cells/mm³), of whom two were found be infected with HIV drug resistant mutation: one resisted non-nucleoside reverse transcriptase inhibitor (NNRTI) and the other had resistance to protease inhibitor (PI) [33]. Consistently, in 2006, among 49 adults aged 18-24 years seeking their first HIV test at VCT in Hanoi, only one person had HIV mutations, that resists both NRTI and NNRTI indicating a low TDR prevalence (< 5%) [34]. A subsequent survey in HCMC in 2007-2008 showed that up to 5% to 15% of VCT attendees aged less than 25 years developed drug resistant strains of HIV [35]. In this survey, the authors reported numerous mutations associated with

People aged 0-14 years				People aged 15+ years		
Year	Number of people on ART ^a	Estimated number of eligible people for ART (Min – Max) ^{b, d}	Coverage estimate of ART (%; Min - Max)	Number of people on ART ^a	Estimated number of eligible people for ART (Min – Max) ^{b, c}	Coverage estimate of ART (%; Min – Max)
2004	NA	2,334 (2,238 – 2,430)	NA	500	24,102 (16,392 – 21,506)	2.1 (1.6 – 3.1)
2005	428	2,727 (2,602 – 2,853)	15.7 (15.0 – 16.4)	2,670	31,359 (21,506 – 41,212)	8.5 (6.5 – 12.4)
2006	930	3,214 (3,056 – 3,373)	28.9 (27.6 – 30.4)	7,818	39,102 (27,044 – 51,159)	20.0 (15.3 – 28.9)
2007	1,462	3,749 (3,546 – 3,953)	39.0 (36.0 – 41.2)	15,173	47,516 (33,305 – 61,727)	32.1 (24.7 – 45.9)
2008	1,987	4,278 (4,074 – 4,482)	46.4 (44.3 – 48.8)	25,597	56,870 (40,628 – 73,111)	45.0 (35.0 – 63.0)
2009	2,344	4,719 (4,508 – 4,929)	49.7 (47.6 – 52.0)	36,008	67,047 (48,037 – 86,057)	53.7 (42.8 – 75.0)

ART, antiretroviral therapy.

^a Source: Presentation of Vietnam Administration for HIV/AIDS Control (VAAC), Ministry of Health: "Preliminary Results of the National Evaluation of Clinical and Immunological Response to ARV of Adult Patients in Vietnam", Ha Noi, Vietnam 2010 (24).

^b Source: Vietnam HIV/AIDS Estimates and Projections, 2007 – 2012, VAAC, Ministry of Health (1).

^c Number of HIV-infected adults and adolescents with CD4 count less than 200 cells/mm³.

^d Number of HIV-infected children.

Table 1: Scale-up of antiretroviral therapy for treatment-eligible people in Vietnam, 2004 – 2009.

Sample year	Location	Study group	Age*	N (% male)	Geno-types (RT/PR)	Prevalence of HIV drug resistance: overall and per class of antiretroviral drug								Ref
						Overall		NRTI		NNRTI		PI		
						n (%)	(95% CI)‡	n (%)	Mutation	n (%)	Mutation	n(%)	Muta-tion	
Proxy recent infection														
2005-06	HCMC†	Pregnant women	25	163 (0.0)	163/163	1 (0.6)	(0.02, 3.4)	1 (0.6)	V75M	0 (0)	-	0 (0)	-	(32)
2006	HCMC	VCT attendees	22.3	63 (46.0)	63/63	2 (3.2)	(0.9, 10.9)	0 (0)	-	1 (1.6)	G190A	1 (1.6)	M46I	(33)
2006	Ha Noi§	VCT attendees	23.0	70 (NR)	49/49	1 (<5)	NA	1 (<5)	L74V	1 (<5)	Y181C	0 (<5)	-	(34)
2007-08	HCMC§	VCT attendees	<25	73 (NR)	73/73	NR (5-15)	NA	NR	D67N, K70R, T215F, K219EQ	NR	K103N, Y181C, G190A/CS, P225HP	1 (<5)	F63Y	(35)
Chronic infection														
2001-02	HCMC	CSW, IDU, and STD patients	23.0	200 (60.5)	200/200	13 (6.5)	(3.5, 10.9)	9 (4.5)	M41L, M184V, K219Q	0 (0)	-	4 (2.0)	D30N, L90M	(67)
2005-07	HCMC	HIV-positive people with TB meningitis	NR	220 (NR)	219/219	14 (6.4)	(3.5, 10.5)	9 (4.1)	D67N, T69D, L74V, V75M, M184V, K219R	6 (2.7)	K103N, V106M, Y181C, Y188L, G190A	0 (0)	-	(37)
2007	Hai Phong	CSW, IDU, pregnant women, blood donors	NR	301 (>90.0)	273/294	8 (2.9)	(1.3, 5.7)	3 (1.1)	L74I, M184I, K219E	5 (1.8)	K103N, G190E	1 (0.3)	M46I	(68)
2008	Multi-prov-inces**	Unknown	32.0	206 (80.1)	155/173	10 (6.5)	(3.1, 11.5)	5 (3.2)	M41L, A62V, D67N, K65R, M184V, L210W, T215F	5 (3.2)	K103N, V108I, Y181C, G190A	3(1.7)	L33F M46IL	(38)
2008-09	Quang Ninh	Pre-ART people	NR	63 (NR)	63/63	4 (6.3)	(1.8, 15.5)	3 (4.8)	L74I, V75M, L210W	1 (1.6)	Y181C	0 (0)	-	(39)
2008-09	HCMC†	Pre-ART people	30	140 (NR)	140/140	NR	NA	8 (5.7)	NR	7(5.0)	NR	2 (1.3)	NR	(36)
2008-09	Multi-prov-inces††	CSW and IDU	29.0	122 (60.6)	92/92	7 (7.6)	(3.1, 15.1)	6 (6.5)	M41L, K65R, V75A/M, M184V	6 (6.5)	K103N, Y181C, G190A, P225H	0 (0)	-	(40)

N, number of participants; n, number of cases harbouring HIV drug-resistant mutation; CI, confident interval; HCMC, Ho Chi Minh City; VCT, voluntary counseling and testing; CSW, commercial sex worker; IDU, injecting drug user; STD, sexually transmitted disease; RT, reverse transcriptase gene; PR, protease gene; ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TB, tuberculosis; NR, not reported; NA, not applicable; Ref, reference.

* Median or mean age (years).

† Baseline data of a longitudinal study.

‡ 95% CI was estimated from number of people harbouring drug resistance of HIV and number of specimen with successful genotyping with both RT and PR genes.

§ Survey used the World Health Organization's methodology for surveillance for transmitted HIV drug resistance with three thresholds: <5% (low), 5-15% (moderate), >15% (high).

**Three provinces were enrolled: Ha Noi, Ninh Binh, and Nam Dinh.

†† Five provinces were enrolled: Ha Noi, Hai Phong, Da Nang, Khanh Hoa, and Can Tho.

Table 2: The prevalence of HIV drug resistance among recently and chronically HIV-infected people with antiretroviral naive in Vietnam, 2000-2009

HIV drug resistance and also highlighted the presence of resistance to PI among primarily HIV acquired population (Table 2).

In Table 2, during 2001-2009, 6.3-7.6% of ART-naive chronically HIV-infected population was associated with drug resistance of HIV across both northern and southern provinces of Vietnam [22,36-40], except Hai Phong where the prevalence was documented to be 2.9%

[41]. Among ARV drug classes, resistance to NRTI was more common than other drug classes, ranging between 1.1-4.5% in 2001-2007 and 4.8-6.5% in 2008-2009. Notably, resistance prevalence to PI was found less than 2% throughout the same period.

Ten out of eleven surveys recruiting recently and chronically HIV-infected people who were ARV-naive reported HIV mutations

Characteristics	Giang et al* (25) (N=248)	Kinh et al† (26) (N=79)	Kinh et al† (27) (N=51)	Lien et al† (29) (N=119)	Nhung et al‡ (28) (N=54)	Dean et al§ (40) (N=68)	
Sample year	2007	2008	2008	2006-2009	2008	2009	
Location	HCMC	HCMC	HCMC	HCMC	HCMC	Multi-provinces**	
Any drug resistance, N (%)	121 (49)	NR	28 (55)	66 (55)	34 (50)	5 (7)	
NRTI	Any	116 (47)	69 (87)	25 (49)	65 (55)	5 (7)	
	Any of TAM	83 (33)	NR	NR	40 (34)	2 (3)	
	M184V/I	90 (36)	NR	NR	57 (48)	4 (6)	
	K65R	11 (4)	NR	NR	9 (8)	0 (0)	
	Q151M	9 (4)	NR	NR	11 (9)	0 (0)	
NNRTI	Any	107 (43)	62 (78)	28 (55)	63 (53)	4 (6)	
	K103N	44 (18)	NR	NR	20 (17)	1 (1)	
	Y181C/I/V	43 (17)	NR	NR	35 (29)	3 (4)	
	G190A/S	42 (17)	NR	NR	21 (18)	3 (4)	
	Y188L	13 (5)	NR	NR	12 (10)	0 (0)	
PI	Any major mutation	10 (4)	4 (5)	2 (4)	2 (2)	3 (4)	0 (0)

N, number of participants; HIVDR, HIV drug resistance; ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, Non- nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; HCMC, Ho Chi Minh City; NR, not reported; TAMs is thymidine-analogue mutations, including M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E.

* Adults and children with clinical or immunological criteria of first-and second-line ART failure.

† Adults with clinical or immunological criteria of first-line line ART failure.

‡ Children with clinical or immunological criteria of first-and second-line ART failure.

§ Adults receiving ART.

** The study was conducted in Ha Noi, Hai Phong, Da Nang, Khanh Hoa, and Can Tho.

Table 3: The prevalence of acquired HIVDR and selected HIV resistant mutations among people on ART and with suspect of treatment failure in Vietnam, 2000-2009

Characteristics	Tang et al*(42) (N=100)	Trinh et al**(44) (N=288)	Quang et al*(36) (N=140)	Do et al*** (43) (N=615)
Sample year	2006-2008	2009	2008-2009	2010
Location	Ha Noi	HCMC	HCMC	Five rural and urban clinics
Poor-adherence of antiretroviral drugs, n/N (%)	6 month: 21/81(26) 12 month: 24/75 (32) (Self reported with VAS)	59/228 (25) (Self-reported)	NR	153/615 (25) (ACASI with VAS)
Viral suppression, n/N (%)	6 month: 60/76 (74) 12 month: 51/75 (68) (< 1,000 copies/ml)	175/228 (77) (< 1,000 copies/ml)	6 month: NR (76.6) 12 month: NR (83.1) (< 250 copies/ml)	NR

N, number of participants; n, frequency; HCMC, Ho Chi Minh City; ART, antiretroviral therapy; NR, not reported; VAS, a 30-day visual analogue scale for evaluating the usage of a prescribed regimen in the preceding month; ACASI, audio computer assisted self-interview.

* Longitudinal study.

** Cross-sectional study among people on ART over 1 year.

*** Cross-sectional study among people on ART.

Table 4: Summary of antiretroviral-adherent level and viral suppression among people on first-line ART in Vietnam, 2000 -2009.

resistant against specific ARV drug classes. Among NRTI-mutations, those appearing in highest frequency, of five studies, were M184I/V and thymidine-analogue mutations (TAM), including M41L, D67N, K70R, T215F, L210W, and K219E/Q. Subsequently, L74I/V was documented in four surveys. Regarding other drug classes, the three most commonly observed NNRTI-mutations were Y181C (6 studies), K103N (5 studies), and G190A (5 studies). Mutations M46I/I (3 studies) was more commonly observed than other PI-mutation patterns (Table 2).

As shown in Table 3, most relevant studies were conducted in treatment sites in HCMC. Between 2007 and 2009, ADR prevalence among people failing multiple lines of ART was similar across study population in HCMC, ranging from 49% to 55% in adults and 50% in children (aged 0-14 years) [25-29]. In this population, resistance to NRTI and NNRTI were documented to vary in wide ranges of 47-87% and 37-78%, respectively, and were more frequently observed than resistance to PI (< 5%). Of note, the proportion of ARV-resistant mutations was 33-35% for any TAM, 32-48% for M184I/V, whereas K65R and Q151M mutations were rarely found even among ART-failed persons (< 10% for both). Among NNRTI-mutations, K103N,

Y181C/I/V, G190A/S, and Y188L were mostly observed in these studies. In contrast to high level of resistance among subjects failing with ART, a study in five northern and southern Vietnamese provinces in 2009 indicated that people on ART had a markedly lower level of HIV drug resistance, for instance, 7% for overall, 7% for NRTI, 6% for NNRTI, and 0% for PI [40].

Risks factors for emergence and transmission of HIV drug resistance

Several studies investigated adherence among adults (aged over 18 years) receiving ART in Vietnam and showed that around one quarter of adults surveyed had poor adherence to HIV medications in the preceding month. During 2006-2008 in Ha Noi, this rate among 100 HIV-acquired IDU after 6 and 12 month of initiation of ART was of 26% and 32%, respectively, based on a 30-day visual analogue scale [42]. Although with different the study site, time and methodology, two other cross-sectional, clinic-based surveys in 2009-2010 also demonstrated a similar percentage of 25% self-reporting as non-adherence [43,44] (Table 4).

Only three studies have presented the virological outcome

among adult receiving ART in Vietnam (Table 4). The proportion of viral suppression (< 1,000 copies/ml) at 6 and 12 month since ART initiation among IDU who were recruited from a treatment site in Ha Noi in 2006-2008, was of 74% and 68%, respectively [42]. This figure was likely to be substantially lower than of that of an average people receiving ART. An analysis of 228 people on ART over 1 year in HCMC indicated that 77% had a viral suppression [10], and more recently published data in HCMC indicates a 77% and 83% rate of undetectable viral load (< 250 copies/ml) at the first 6 and 12 months of ART [45]. No studies have ever been conducted on adherence of ART medication and virological outcome among children receiving ART in Vietnam. Sexual risk behaviors and illicit drug use among adults on ART were also not found in available literature.

Discussion

There is limited information about the emergence of HIV drug resistance in Vietnam. No longitudinal data related to the development of ADR has been published. The available ADR prevalence was estimated through several cross-sectional, clinic-based surveys among people who are currently on ART or have failed first-line ART. We assumed that people with viral load less than 1,000 copies/ml would not have drug-resistant mutations; however, it is important to note it is possible for these viral strains to exist in such conditions [46,47]. Therefore, our estimate of the extent of drug resistance in Vietnam is a conservative under-estimate of the actual level. Despite this limitation, we determined that HIV drug-resistant mutations existed in nearly half of the ARV-treated population suspected of certain clinical and/or immunological criteria of treatment failure. The current review also indicates that approximately 25% of Vietnamese adults receiving ART were classified as non-adherent, a key risk factor for the acquisition of HIV drug resistance [48-53]. Non-adherence is caused by numerous factors. Most adults on ART were IDU (62%) [24], whose high level of active illicit drug use during therapy (30-33%) [42], directly impacts on their adherence to ARV drugs. Furthermore, widespread stigma and discrimination related to HIV infection leads to a fear of disclosure of their HIV positive status and use of ART [54]. Addressing these issues is complex but important for the health and well-being of all people affected with HIV. It is also likely that most people using a failed ART regimen would be using it for considerable time after the emergence of drug resistant mutations. Regular viral load testing and increasing the availabilities of therapeutic options should be considered as an appropriate strategy to curb the emergence and transmission of HIV drug resistance. Phillips et al. [55] showed that the introduction of viral load monitoring leads to lower prevalence of TDR among recent infections as well as reduced mortality among people on ART. It has also been estimated that if viral load tests are conducted in every second year, it would have an impact of reducing new TDR cases by more than 50% [56].

We found that ARV-resistant strains are spreading among various adult HIV-infected populations in Vietnam. The prevalence of TDR among proxy primary HIV-infected persons in HCMC increased from less than 5% before 2006 to a higher level of 5-15% in 2007-2008. This is comparable to findings from multiple cross-sectional TDR surveys in Thailand, where prevalence gradually increased beyond the threshold of 5% after 5 years of their ART program which commenced in 2002 (0% in 2003, 1.2% in 2004, 2.6% in 2005, and 5.2% in 2006) [19]. Our results suggest that the transmission of HIV drug resistance is increasing in urban areas in Vietnam, as a result of rapid scale-up of ART [57,58]. Therefore, surveillance for TDR should be regularly conducted and also expanded to urban areas with high coverage of ART [59]. In this review, several studies across the country at different time

periods further documented a similar 6-8% level of drug-resistant HIV among chronic infections. This percentage is considerably higher than that among HIV-infected individuals in a Chinese nationwide survey in 2004, in which the TDR prevalence was documented as 3.8% [60]. It is generally accepted that people with TDR are more likely to have higher rates of treatment failure during the first 12 months of treatment if their mutation resists at least one drug in their prescribed ARV regimens [61,62]. Based on these findings, we recommend a gradual scale-up in procurement of second- and third-line ART to treat the expanding population infected with TDR strains who may have failed the standard first-line ART.

Although ART services for children have been scaled up in Vietnam, little is known about the level of HIV drug resistance among children on ART in Vietnam. The rate of transmission from mother to child is as high as 14.7% in southern provinces of Vietnam [63] and 45.5% of mothers treated with dual ART for preventing transmission to their children had the M184IV mutation at delivery [32]. Hence, mother-to-child transmission of drug-resistant strains of HIV may be common in Vietnam.

Our review has a number of limitations. Firstly, most studies had small sample sizes, and conveniently selected a limited number of local sites, mostly in urban areas. This could introduce selection bias if large heterogeneities exist across the target population. Secondly, the majority of TDR surveys enrolled chronically HIV-infected persons who were ARV-naïve to estimate the TDR prevalence. This approach may underestimate the true prevalence as drug-resistant strains are more likely to revert to wide-type after 12 months of infection [64,65] and stay as minority-resistant strains (< 25%), which cannot be detected by standard polymerase chain reaction [66]. Thirdly, data may not be representative for HIV drug resistance among all people on ART in Vietnam. Most studies in the current review estimate ADR prevalence by enrolling individuals who have already experienced clinical or immunological failure of ART. These persons were more likely to harbor resistant viruses leading to an over-estimating of the actual ADR prevalence. Lastly, due to the limited available data on HIV medication adherence and risk behaviours, we could not completely describe risk factors and their association with the dynamics of drug-resistant HIV epidemics. Further studies are required to fill these gaps.

Transmission of HIV drug resistance is increasing in urban Vietnam, indicating the importance and urgency of the implementation of regular TDR surveillance. Regular viral load testing is recommended for early diagnosis of the occurrence of drug resistance and is vital for curbing the secondary transmission of HIV drug resistant strains. A gradual scale-up in procurement of second- and higher-line ART regimens to provide timely treatment for the expanding population of HIV-infected people with TDR is also essential in reducing the further spread of drug resistance strains of HIV. Further investigations for both adults and children are required to provide a more insightful understanding of the epidemic of drug resistant HIV strains and identify factors for its control.

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This article was originally published in a special issue, **Drug Resistance: HIV** handled by Editor(s). Dr. Claudia Goulston, University of Utah, USA