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National Survey of Pretreatment HIV-Drug Resistance in Thai HIV-1-Infected Adults

Abstract

Background: WHO recommended a method to estimate nationally representative pretreatment HIV drug resistance (PDR) prevalence for providing evidence in selection of first-line antiretroviral treatment regimens. This study aimed to assess PDR prevalence in Thai HIV-1 infected adults.

Methods: We conducted a cross-sectional survey among patients aged 18 years and above who were antiretroviral drug (ARV)-naïve or prior-exposed to ARVs and interrupted for more than three months. Twenty hospitals were sampled using probability proportional to size of patients initiating antiretroviral therapy. Then a consecutive enrolment of eligible patients was done during August 2016-February 2017. Plasma specimens were collected for genotyping.

Results: Of 327 patients with genotypic results, most of them were men (48.6%), naive (84.4%) and infected with HIV-1 subtype CRF01_AE (90.7%). Median CD4 count was 160cells/mm^3 and median viral load was 83,696 copies/ml. Overall PDR prevalence was 8.2% (95% CI 4.5-14.7). The prevalence was 0.2% (95% CI 0.1-0.3) for any nucleoside reverse-transcriptase inhibitors (NRTIs), 8.1% (95% CI 4.3-14.5) for any non-NRTIs (NNRTIs), 1.2% (95% CI 0.2-7.1) for any protease inhibitors (PIs), 0.1% (95% CI 0.0-0.2) for both NRTIs and NNRTIs, and 1.1% (95% CI 0.2-7.5) for both PIs and NNRTIs. The most common surveillance drug resistance mutations were Y181C (2.3%), followed by K103N (2.0%) and G190A (1.1%), respectively.

Conclusion: NNRTIs resistance prevalence was less than 10% which was a WHO recommendation's cut-off point for changing the first-line regimen. However, PDR surveillance should be conducted every three year and PDR prevention interventions should be implemented.

Keywords: Survey; Pretreatment HIV drug resistance; HIV-1; Thai

Research Article

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Abbreviations: PLHIV: People Living With HIV; HAART: Highly Active Antiretroviral Therapy; ART: Antiretroviral Therapy; ARV: Antiretroviral Drug; NNRTI: Non-Nucleoside Reverse-Transcriptase Inhibitor; NRTI: Nucleoside Reverse-Transcriptase Inhibitor; PI: Protease Inhibitor; HIVDR: HIV Drug Resistance; PDR: Pretreatment HIV Drug Resistance; ADR: Acquired HIV Drug Resistance; PrEP: Pre-Exposure Prophylaxis; PEP: Post-Exposure Prophylaxis; PMTCT: Prevention of Mother-To-Child Transmission; WHO: World Health Organization; BATS: Bureau of AIDS, TB and STIs; CI: Confidence Interval; PPS: Probability Proportional to Size; PR: Protease; RT: Reverse Transcriptase; PCR: Polymerase Chain Reaction; VL: Viral Load; SD: Standard Deviation; IQR: Interquartile Range; DRM: Drug Resistance Mutation; SDRM: Surveillance Drug Resistance Mutation; TAM: Thymidine Analogue Resistance-Associated Mutation

Introduction

Highly active antiretroviral therapy (HAART) is still the most effective treatment for HIV-infected patients. HAART reduces morbidity, mortality and increases quality of life of HIV patients. Thailand started a free of charge antiretroviral service with Zidovudine monotherapy in 1992 and changed to HAART in 1997 [1]. However, access to antiretroviral therapy (ART) was limited in some pilot sites. In 2004, Thailand implemented a national antiretroviral treatment program for people living with HIV (PLHIV) [1,2] and had expanded access to ART continuously. Until 2006, Thailand included ART service in the Universal Health Coverage scheme [3] and in October 2014, Thailand announced criteria to start ART in all HIV-infected patients, regardless of any CD4 cell count which accelerated ART access of all Thai HIV-infected patients [4]. As of September 2014, more than 260,000 PLHIV were receiving ART from ARV clinics situated nationwide [5]. The ART clinics in Thailand must provide services according to national HIV/AIDS treatment guidelines which recommend non-nucleoside reverse-transcriptase inhibitor (NNRTI)-based regimen as first-line treatment. Switching to a second-line regimen requires evidence of HIV drug resistance (HIVDR) mutation [4,6-8]. Improper use of antiretroviral drugs (ARVs), poor treatment adherence and ineffective ART program management can cause viral mutations associated with HIVDR, which can impede the efficacy of current ART regimens. There have been concerns about emergence of HIVDR due to accelerated program scale-up. To provide HIVDR prevention plan and to sustain long-term efficacy of current first-line regimens, HIVDR surveillance and monitoring of early warning indicators, which are recommended by World Health Organization (WHO) as fundamental elements

of the strategy to alert HIVDR situation [9,10], have been implemented in Thailand since 2006 [11]. Pretreatment HIV drug resistance (PDR) surveillance in Thailand has been developed continuously by consultation with WHO's experts to improve its method suitable for Thailand's context and to get better results' reliability and national representativeness. Between 2006 and 2013, Bureau of AIDS, TB and STIs (BATS), Department of Disease Control conducted four prospective cohort studies among patients initiating a first-line ART regimen in studied hospitals. The patients were tested genotyping before starting ART and during 2-3 years of a follow-up period. The results demonstrated an increasing trend of HIVDR prevalence among pretreatment cases from 1.9% in 2006 to 2.8%, 3.8%, and 5.6% in 2007, 2008, and 2013, respectively [11-13].

Other previous studies in Thailand found 2%-17.6% of HIVDR prevalence among pretreatment ARV-naïve patients during 2002 to 2011. They collected the data from sentinel sites and most of them didn't describe their sampling methods and sample size calculation clearly, sample size of some studies varied with number of patients visiting hospitals during study periods [14-20]. Thus the various prevalence rates identified from these studies depended on their study sites and methodology. In 2014, the WHO published a survey method to assess nationally representative PDR prevalence in adults initiating ART [21]. The PDR survey provides evidence to inform the selection and effectiveness of first-line regimens of ART, pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) regimens when used [21]. Thus BATS applied the WHO's concept note for this study that aimed to assess nationally representative PDR prevalence in Thai HIV-1 infected adults in order to prepare information for policy makers, HIV program managers and experts in developing the national guidelines on HIV/AIDS treatment, including making awareness of ART clinic's staff and related persons in PDR situation.

Materials and Methods

A cross-sectional survey of PDR was conducted among Thai HIV-1 infected patients aged 18 years and above who were initiating ART and were ARV-naïve or prior-exposed to ARVs and interrupted ARVs for more than three months. Prior ARV exposure was defined as

a. Previous ART for treatment of HIV infection

b. PrEP

c. PEP

d. Prevention of mother-to-child transmission (PMTCT)

e. A combination of exposures.

Sample size calculation and sampling method were conducted according to the WHO PDR surveillance concept note [21]. The sample size was calculated to estimate the prevalence of PDR outcomes with a desired confidence interval (CI) of ± 2.5% by using a 20 hospital model and assumptions of 5% of expected prevalence of HIVDR among all ART initiators [12]. We estimated a sample size of 340. We employed a two-stage cluster sampling design. The first stage involved a selection of 20 hospitals with ART service by using a sampling according to probability proportional to size (PPS) of patients initiating ART. We obtained a list of all hospitals providing ART in Thailand with their number of ART initiators during 2014 (the most recent available information at the time of survey planning) from National AIDS Program (NAP) database [5]. The hospitals where had less than 20 initiators in 2014 were excluded from a sampling table due to difficulty to reach the sample size within six-month enrolment period. Twenty-seven percent (244 from 907) of ART hospitals with 76.5% of all ART initiators in 2014 were included in the sampling table. In the second stage, consecutive eligible patients initiating ART on or after a survey start date were enrolled until the sample size of 17 patients for each sampled hospital was achieved. If any hospitals couldn't reach the required sample size, we would enroll rest number of patients from other sampled large hospitals located in the same region as on top of the required quota for those hospitals. Ethical approval of this study was obtained from The Ethics Committee for Research in Human Subjects of Department of Disease Control, Ministry of Public Health, Thailand. All patients provided written informed consents prior to enroll in this study. They would be assigned a study identification number which was used to identify the patient. The patients' information was obtained by hospital staff using a questionnaire applied to the patients and reviewing patient medical and laboratory records. Blood samples drawn from the patients before ART initiation were sent to Ramathibodi hospital for HIV-1 RNA viral load testing by using Abbott real time HIV-1 assay and Abbott m2000rt, and a WHO-designated laboratory of National Institute of Health, Department of Medical Sciences for HIVDR genotyping.

The genotyping of protease (PR) and reverse transcriptase (RT) was performed by using the in-house method [22,23]. In brief, viral RNA was isolated from plasma samples and subjected to RT-polymerase chain reaction (PCR) and nested PCR. Then sequencing was performed on an Applied Biosystems™ 3130xl DNA Analyzers. Nucleotide sequences were analyzed using Stanford HIV database algorithm, available on the Stanford HIV database website (http://hivdb.stanford.edu/hivdb/by-mutations/). Any HIVDR was defined in sequences classified as low-, intermediate- or high-level resistance according to the Stanford HIVdb algorithm with respect to one or more ARVs. Drug resistance level was classified according to the Stanford Penalty Score as high (≥60), intermediate (30-59), or low (15-29). HIV subtype was identified by the Stanford HIV database website based on the PR and RT genes.

Three hundred and forty patients were recruited between 25 August 2016 and 3 February 2017 from 20 hospitals in Thailand. We excluded 13 samples with unsuccessful genotyping due to amplification failure from low viral load (VL) (<1,000 copies/ml) from data analysis. Data analysis for all outcomes was performed in Stata Software. Data were weighted taking into account hospital-level patient accrual, the number of patients screened and the number of patients with sequences genotyped as recommended in the WHO PDR surveillance concept note [21]. Descriptive statistics such as mean with standard deviation (SD), median with interquartile range (IQR), frequency (%) were used for describing patients' characteristics. HIVDR prevalence and 95% CI were estimated divided by drug class, drug resistance mutation (DRM) and history of ARV exposure.

Citation: Lertpiriyasuwat C, Kohreanudom S, Pattaraprayoon N, Saeng-aroon S (2018) National Survey of Pretreatment HIV-Drug Resistance in Thai HIV-1-Infected Adults. J Hum Virol Retrovirol 6(1): 00190. DOI: 10.15406/jhvrv.2018.06.00190

Results

The results of 327 patients (96.2% of patients) with genotypic results were demonstrated as the following.

Demographic characteristics

Most of them were recruited from regional hospitals (39.2%), men (48.6%), educated from secondary school or higher level (62.1%), laborers or farmers (40.4%), married or having regular partner (44.3%), infected with HIV-1 subtype CRF01_AE (90.7%) and asymptomatic (53.5%). Mean age was 36.8 years (SD=11.0), median CD4 cell count was 160 cells/mm^3 (IQR 40-331) and median plasma HIV-1 RNA was 83,696 copies/ml (IQR 16,338-304,618). Eighty-four percent were ARV-naive patients and sixteen percent were prior ARV-exposed patients (Table 1). Among ARV-exposed group, 24.0% exposed ARVs for PMTCT, 66.0% exposed ART and 10.0% exposed both ARVs for PMTCT and ART. Of these, 46.0% told that they had history of poor adherence to ART or ART failure, and 8.0% had history of HIVDR.

Table 1: Demographic characteristics of 327 HIV-infected patients stratified by history of ARV exposure.

Characteristics	ARV-naïve*		Prior-exposed†		All	
	Number	(%)	Number	(%)	Number	(%)
Number of patients	276	84.4	51	15.6	327	100
Hospital Type						
Community hospital	79	28.6	28	54.9	107	32.7
Provincial hospital	81	29.4	11	21.6	92	28.1
Regional hospital	116	42	12	23.5	128	39.2
Gender						
Men	138	50	21	41.2	159	48.6
Women	87	31.5	28	54.9	115	35.2
Men who have sex with men (MSM)	46	16.7	2	3.9	48	14.7
Transgender (TG)	5	1.8	0	0	5	1.5
Age Group						
< 25 years	48	17.4	5	9.8	53	16.2
≥ 25 years	228	82.6	46	90.2	274	83.8
Mean (SD)	36.8 (11.3)		37.0 (9.3)		36.8 (11.0)	
Min-max	18.1-68.7		19.5-62.5		18.1-68.7	
Education						
Primary school or lower level or uneducated	94	34.1	30	58.8	124	37.9
Secondary school or higher level	182	65.9	21	41.2	203	62.1
Occupation						
Student	19	6.9	0	0	19	5.8
Unemployed	86	31.2	22	43.1	108	33
Laborer or farmer	108	39.1	24	47.1	132	40.4
Officer or owner	63	22.8	5	9.8	68	20.8
Business or company employee						
Marital Status						
Single	122	44.2	13	25.5	135	41.3
Married/having regular partner	123	44.6	22	43.1	145	44.3

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Widowed/divorced	31	11.2	16	31.4	47	14.4
HIV Risk Behaviors in the Past Year						
No	99	35.9	23	45.1	122	37.3
Yes	177	64.1	28	54.9	205	62.7
HIV Subtype						
CRF01_AE	250	91.2	45	88.2	295	90.7
B	18	6.6	4	7.9	22	6.8
CRF01_AE and B	5	1.8	2	3.9	7	2.2
A	1	0.4	0	0	1	0.3
Stage of HIV Infection as Enrollment Date						
Asymptomatic HIV	152	55.1	23	45.1	175	53.5
Symptomatic HIV	42	15.2	8	15.7	50	15.3
AIDS	82	29.7	20	39.2	102	31.2
CD4 Cell Count (cells/mm^3)						
< 200	156	57.6	33	66	189	58.9
200-350	49	18.1	9	18	58	18.1
>350-499	35	12.9	4	8	39	12.1
≥ 500	31	11.4	4	8	35	10.9
Mean (SD)	224.3 (223.5)		168.6 (184.2)		215.6 (218.5)	
Median (IQR)	167 (43–339)		97 (20–266)		160 (40–331)	
Min-max	1–1,345		1–729		1–1,345	
Plasma HIV-1 RNA (copies/ml)						
< 50	1	0.4	1	2	2	0.6
< 1,000	9	3.2	3	5.9	12	3.7
≥1,000	266	96.4	47	92.1	313	95.7
Mean (SD)	286,695 (494,690.2)		295,117.6 (512,897.2)		288,008.6 (496,780.4)	
Median (IQR)	88,689 (16,160–303,465)		65,925 (20,631–315,118)		83,696 (16,338–304,618)	
Min-max	< 40–2,799,102		< 40–2,544,326		< 40–2,799,102	

[*] Two participants had missing data for HIV subtype and 5 participants had missing data for CD4 cell count; [†] One participant had missing data for CD4 cell count.

SD: Standard Deviation; IQR: Interquartile Range

Prevalence of pretreatment HIV drug resistance

Overall prevalence of PDR to any drug classes among all ART initiators, regardless of prior ARV exposure was 8.2% (95% CI 4.5-14.7). Drug resistance prevalence was 0.2% (95% CI 0.1-0.3) for any nucleoside reverse-transcriptase inhibitors (NRTIs), 8.1% (95% CI 4.3-14.5) for any NNRTIs, 1.2% (95% CI 0.2-7.1) for any protease inhibitors (PIs), 0.1% (95% CI 0.0-0.2) for both NRTIs and NNRTIs, and 1.1% (95% CI 0.2-7.5) for both PIs and NNRTIs. Among ARV-naïve group, PDR prevalence was 7.3% (95%CI 3.8-13.5). The PDR prevalence divided by drug class was 0.1% (95%CI 0.0-0.2) for NRTIs, 7.2% (95%CI 3.7-13.4) for NNRTIs, and 1.3% (95%CI 0.2-7.7) for PIs. Among ARV prior-exposed group, PDR prevalence was 19.3% (95%CI 3.9-58.7). NRTIs resistance prevalence was 1.2% (95%CI 0.4-3.4) and NNRTIs resistance prevalence was 18.9% (95%CI 3.6-58.9) (Table 2).

When analyzed the PDR prevalence stratified by demographic characteristics, we found the results as follows: patients from regional hospitals had higher prevalence (73.7%, 95%CI 42.1-91.5) than those from provincial hospitals (6.1%, 95%CI 2.6-13.5); patients aged ≥ 25 years had higher prevalence (83.1%, 95%CI 54.8-95.2) than patients aged < 25 years (16.9%, 95%CI

4.8-45.2); patients infected with HIV subtype CRF01_AE had higher prevalence (91.4%, 95%CI 62.0-98.6) than those infected with HIV subtype B (0.4%, 95%CI 0.1-1.3); and patients with VL ≥ 1,000 copies/ml had higher prevalence (98.1%, 95%CI 93.5-99.5) than those with VL<1,000 copies/ml (1.9%, 95%CI 0.5-6.5); and widowed or divorced patients had lower prevalence (2.6%, 95%CI 0.9-7.2) than patients who were single (51.7%, 95%CI 23.3-79.0) or married/having regular partners (45.8%, 95%CI 19.3-74.9).

Table 2: Prevalence of pretreatment HIV-drug resistance divided by history of antiretroviral drug exposure and antiretroviral drug class some patients had resistance to more than one drug.

Antiretroviral Drug	ARV-naïve (n=276)		Prior-Exposed (n=51)		All (n=327)	
	Number	% (95%CI)	Number	% (95%CI)	Number	% (95%CI)
Any drugs	19	7.3 (3.8-13.5)	7	19.3 (3.9-58.7)	26	8.2 (4.5-14.7)
NRTIs	2	0.1 (0.0-0.2)	3	1.2 (0.4-3.4)	5	0.2 (0.1-0.3)
ABC	2	0.1 (0.0-0.2)	3	1.2 (0.4-3.4)	5	0.2 (0.1-0.3)
AZT	0	0	1	0.2 (0.1-1.0)	1	0.0 (0.0-0.1)
FTC	2	0.1 (0.0-0.2)	1	0.5 (0.1-3.2)	3	0.1 (0.1-0.3)
3TC	2	0.1 (0.0-0.2)	1	0.5 (0.1-3.2)	3	0.1 (0.1-0.3)
TDF	1	0.0 (0.0-0.1)	3	1.2 (0.4-3.4)	4	0.1 (0.1-0.3)
d4T	1	0.0 (0.0-0.1)	3	1.2 (0.4-3.4)	4	0.1 (0.1-0.3)
ddI	1	0.0 (0.0-0.1)	3	1.2 (0.4-3.4)	4	0.1 (0.1-0.3)
NNRTIs	17	7.2 (3.7-13.4)	6	18.9 (3.6-58.9)	23	8.1 (4.3-14.5)
EFV	6	4.4 (1.7-10.8)	6	18.9 (3.6-58.9)	12	5.5 (2.4-12.1)
ETR	3	3.6 (1.3-10.1)	2	1.4 (0.5-4.0)	5	3.5 (1.2-9.3)
NVP	6	4.4 (1.7-10.8)	6	18.9 (3.6-58.9)	12	5.5 (2.4-12.1)
RPV	14	6.4 (3.1-12.5)	4	2.1 (0.8-5.3)	18	6.1 (3.0-11.7)
PIs	2	1.3 (0.2-7.7)	0	0	2	1.2 (0.2-7.1)
NFV	1	1.2 (0.2-8.1)	0	0	1	1.1 (0.2-7.5)
TPV/r	1	0.1 (0.0-0.4)	0	0	1	0.1 (0.0-0.4)
NRTIs and NNRTIs	1	0.0 (0.0-0.1)	2	0.7 (0.2-3.0)	3	0.1 (0.0-0.2)
NNRTIs and PIs	1	1.2 (0.2-8.1)	0	0	1	1.1 (0.2-7.5)

NNRTI: Non-Nucleoside Reverse-Transcriptase Inhibitor; NRTI: Nucleoside Reverse-Transcriptase Inhibitor; PI: Protease Inhibitor; ABC: Abacavir; AZT: Zidovudine; FTC: Emtricitabine; 3TC: Lamivudine; TDF: Tenofovir Disoproxil Fumarate; d4T: Stavudine; ddI: Didanosine; EFV: Efavirenz; ETR: Etravirine; NVP: Nevirapine; RPV: Rilpivirine; NFV: Nelfinavir; TPV/R: Ritonavir-Boosted Tipranavir.

In addition, the prevalence was 43.3% (95%CI 17.9-72.8) among men, 18.4% (95%CI 5.8-45.3) among women, 38.3% (95%CI 13.8-70.6) among men who have sex with men, and 0% among transgender. Regarding drug resistance level detected in 26 patients, we found that high- level resistance was presented most frequently in Nevirapine and Efavirenz. Out of 18 patients detected Rilpivirine resistance, 13 patients had low-level resistance to Rilpivirine; mutations of 11 ARV-naïve patients were only E138A and mutations of one naïve patient and one prior-exposed patient were E138G. All resistance to Zidovudine, Emtricitabine and Lamivudine was high-level resistance (Figure 1). Nineteen percent of patients detected HIVDR knew HIV infection of their partners, but all of them didn't know whether their infected partners had history of HIVDR or treatment failure or poor adherence. All of 7 prior-exposed patients detected HIVDR had history of treatment with NNRTI-based regimens (Stavudine or Zidovudine+ Lamivudine+Nevirapine, Tenofovir+Lamivudine+Nevirapine or Efavirenz). Of these, three patients were detected intermediate- or high- level resistance to NNRTI drugs, especially Efavirenz and Nevirapine, three patients were detected intermediate- or high- level resistance to both NNRTIs and NRTIs, and one patient had only low-level resistance to NRTIs. In addition, four patients (57.1%) had history of poor ARV drug adherence or treatment failure.

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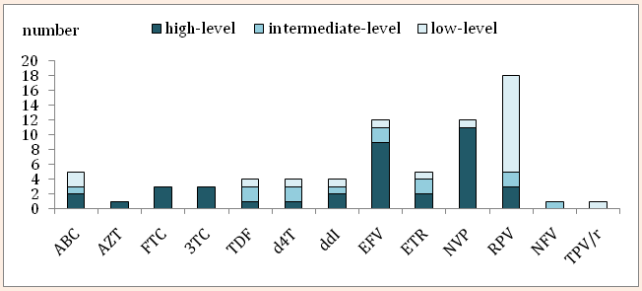

Figure 1: Number of detected pretreatment HIV-drug resistance among 26 patients divided by antiretroviral drugs and drug resistance level.

Prevalence of HIV drug resistance mutations

The prevalence of DRMs was shown in Table 3. Any surveillance drug resistance mutations (SDRMs), defined by the WHO [24], were detected as the following. The most commonly observed NRTI-SDRMs in RT were M184V/IV (0.1%, 95%CI 0.1-0.3) and K65R (0.1%, 95%CI 0.0-0.2). The most commonly observed NNRTIs-SDRMs in RT were Y181C (2.3%, 95%CI 0.6-8.1), followed by K103N (2.0%, 95%CI 0.5-7.7) and G190A (1.1%, 95%CI 0.2-7.3), respectively. Only one PI-SDRM in PR was detected, it was M46I with a prevalence of 1.1% (95%CI 0.2-7.5). Only one patient (0.3% of patients) who had history of receiving Zidovudine+Lamivudine+Nevirapine regimen presented with 4 Thymidine analogue resistance-associated mutations (TAMs) [25]: D67N, K70R, K219Q, T215IV (T215IV is a reversion mutation which occurs after patients infected with virus strains containing T215Y/F [26]), which conferred high-level resistance to all NRTIs except Lamivudine and Emtricitabine and NNRTIs. This TAM pattern was pathway 2 [27]. Of 26 patients with HIVDR, 22 patients were infected with HIV subtype CRF01_AE, 2 patients were infected with HIV subtype B, and 2 patients were infected with HIV subtype CRF01_AE and B. The prevalence of DRMs among patients with HIV subtype CRF01_AE was E138A/G, 4.0% (95% CI 1.7-9.0); Y181C, 2.6% (95% CI 0.7-8.9); V179D/E, 2.6% (95% CI 0.7-8.9); K103N, 1.5% (95% CI 0.2-8.8); G190A, 1.3% (95% CI 0.2-8.1); M46I, 1.2% (95% CI 0.2-8.2); M184V/IV, 0.1% (95%CI 0.0-0.2); and 0% (95%CI 0-0.1) for each mutation at K65R, K70R, K70T, Y115F, T215IV, K219Q, D67N, K238T, A98G, K101E, H221Y, V106M, F227L, Y188L. Both patients with HIV subtype B were detected only one mutation at E138A with prevalence of 0.7% (95% CI 0.2-2.1). Among patients with HIV subtype CRF01_AE and B, the most prevalence was K103N, 24.1% (95% CI 3.2-75.2), followed by equal prevalence of 1.4% (95% CI 0.2-10.4) for each mutation at E138G, K238N, M184V and K65R.

Table 3: Prevalence of HIV drug resistance mutations divided by history of antiretroviral drug exposure.

Drug Resistance Mutation†	ARV-naïve (n = 276)		Prior-Exposed (n = 51)		All (n = 327)	
	Number	% (95%CI)	Number	% (95%CI)	Number	% (95%CI)
NRTI						
M184V/IV	2	0.1 (0.0-0.2)	1	0.5 (0.1-3.2)	3	0.1 (0.1-0.3)
K65R	1	0.0 (0.0-0.1)	1	0.5 (0.1-3.2)	2	0.1 (0.0-0.2)
K70R	0	0	1	0.2 (0.1-1.0)	1	0.0 (0.0-0.1)
K70T	0	0	1	0.5 (0.1-1.7)	1	0.0 (0.0-0.1)
Y115F	1	0.0 (0.0-0.1)	0	0	1	0.0 (0.0-0.1)
T215IV	0	0	1	0.2 (0.1-1.0)	1	0.0 (0.0-0.1)
K219Q	0	0	1	0.2 (0.1-1.0)	1	0.0 (0.0-0.1)
D67N	0	0	1	0.2 (0.1-1.0)	1	0.0 (0.0-0.1)
NNRTI						
E138A/G*	12	4.0 (1.7-8.8)	1	0.5 (0.1-3.2)	13	3.7 (1.6-8.2)
K103N	2	0.8 (0.1-4.4)	3	17.2 (2.8-59.8)	5	2.0 (0.5-7.7)
Y181C	2	2.4 (0.6-8.9)	2	1.4 (0.5-4.0)	4	2.3 (0.6-8.1)
V179D/E*	3	2.5 (0.6-8.8)	1	1.0 (0.3-3.6)	4	2.3 (0.6-8.1)
G190A	1	1.2 (0.2-8.1)	1	0.4 (0.1-1.7)	2	1.1 (0.2-7.3)
K238T/N*	0	0	2	0.7 (0.2-3.0)	2	0.1 (0.0-0.2)
A98G*	0	0	1	0.4 (0.1-1.7)	1	0.0 (0.0-0.1)
K101E	0	0	1	0.4 (0.1-1.7)	1	0.0 (0.0-0.1)

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H221Y*	0	0	1	0.4 (0.1-1.7)	1	0.0 (0.0-0.1)
V106M	1	0.0 (0.0-0.1)	0	0	1	0.0 (0.0-0.1)
F227L*	1	0.0 (0.0-0.1)	0	0	1	0.0 (0.0-0.1)
Y188L	0	0	1	0.2 (0.1-1.0)	1	0.0 (0.0-0.1)
PI						
M46I	1	1.2 (0.2-8.1)	0	0	1	1.1 (0.2-7.5)

Some patients had more than one drug resistance mutation.

* not SDRM, defined by the WHO [24].

† This table showed drug resistance mutations interpreted by the Stanford HIV database algorithm as PI major resistance mutations or NRTI resistance mutations or NNRTI resistance mutations, but it didn't show PI accessory resistance mutations and NRTI or NNRTI or PI other mutations.

NNRTI: Non-Nucleoside Reverse-Transcriptase Inhibitor; NRTI: Nucleoside Reverse-Transcriptase Inhibitor; PI: Protease Inhibitor; SDRM: Surveillance Drug Resistance Mutation

Discussion

This study found the overall PDR prevalence was 8.2% that were higher than the results from previous HIVDR surveillance of Thailand during 2006-2013 (1.9%-5.6%) [11-13]. When compared with the PDR survey results of eleven countries studied during 2014-2016 by using the standardized methods according to the WHO PDR surveillance concept note [21], it showed that Thailand's prevalence was less than 10% like Myanmar, Columbia, Brazil and Cameroon and lower than the prevalence of seven countries (Guatemala, Mexico, Namibia, Nicaragua, Uganda, Zimbabwe and Argentina) which was greater than 10% [28]. Regarding the PDR prevalence among ARV-naïve group, this study showed 7.3% that were higher than HIVDR surveillance's result in 2013 (4.8%) [12]. Because of rapidly scaling-up of access to ART in Thailand since 2004 [1], there have been lots of HIV-infected patients accessing to ART that has resulted in an increase of spreading HIV mutations from some patients with drug failure to new ARV-naïve patients. The prevalence among ARV-naive group of our survey was below 10% like the prevalence of Myanmar, Columbia, Brazil, Namibia and Cameroon and lower than the prevalence of six countries (Argentina, Uganda, Zimbabwe, Guatemala, Mexico, Nicaragua) which was higher than 10% and surveyed during 2014-2016 [28]. We are concerning an increasing trend of NNRTI resistance; PDR prevalence rose from 4.6% in 2013 [12] to 8.1% from this study. Its increase was consistent with the drug resistance situations of all regions servicing ART in the world [28-31]. It will reduce the effectiveness of the first-line NNRTI-based ART regimens implemented according to all national HIV/AIDS treatment guidelines in Thailand [4,6-8] and WHO guidelines. If the PDR prevalence to NNRTIs among people initiating first-line ART, regardless of previous ARV drug exposure is ≥10%, the WHO recommends urgently considering non-NNRTI-containing first-line regimens. Where the use of non-NNRTI-containing regimens cannot be implemented at the population level, countries may consider using HIVDR testing to guide first-line ART regimen selection and continue VL monitoring [32]. Most of SDRMs detected from this study were Y181C, K103N and G190A which resulted in resistance to NNRTIs, especially Nevirapine and Efavirenz used as the first-line regimens. This finding was consistent with previous studies' results in Thailand [12,14]. Rilpivirine resistance was determined the highest prevalence, although Rilpivirine wasn't included in the first-line regimens of Thailand. Because 11 patients detected Rilpivirine resistance had only E138A which is a natural polymorphic mutation and occurs in 2%-13% of virus from ARV-naïve patients depending on HIV subtype, especially occurring commonly in HIV subtype C [33,34]. E138A reduces Rilpivirine susceptibility about 2-fold [35] which causes low-level resistance to Rilpivirine [25]. Prevalence of resistance to any PIs group still has been low as other countries [28] thus we can use this drug group to be second-line regimens for patients having resistance to the first-line regimens.

This study was the first nationally representative survey of pretreatment HIVDR in Thailand with its strength of using PPS method; however, it had limitations as the following. There were 663 hospitals, where had less than 20 ART initiators per hospital in 2014 and took part of 23.5% of all initiators, excluded from the sampling table, the PDR prevalence estimated in this study may be biased. In addition, this study surveyed in 51 prior-ARV exposed patients that effected the PDR prevalence among this group with wide confidence interval (19.3%, 95%CI 3.9-58.7). It needs additional surveys among this group to get larger sample size for precise results.

Conclusion and Recommendations

From this survey, we noted the increasing trend of PDR in Thailand, with dominance of NNRTI pretreatment resistance. We should raise the effort in all levels to promote PLHIV to access to ART as soon as they know their HIV status, adhere to ARVs and remain in treatment in order to reduce HIVDR and maintain the effectiveness of the current first-line regimens for the longest duration. Thailand launched a new AIDS strategy to end AIDS epidemic by 2030. One of its goal is vertical transmission should be virtually zero [36]. Thus they should organize national AIDS expert committee meetings to consider whether Thailand should select Lopinavir containing regimen as the first regimen for PMTCT instead of Efavirenz or Nevirapine containing regimens. Because this study demonstrated 5.5% resistant to Efavirenz or Nevirapine and 8.1% resistant to any NNRTIs which may affect achievement of the ending AIDS target in the future. To achieve the target of ending AIDS in 2030 [36], preventing, monitoring and responding to HIVDR are prioritized critical measures which need to be planned, written in AIDS plans and implemented

urgently in all levels to maintain current achievements, improve treatment outcomes for PLHIV, protect investments, and guarantee the long-term sustainability of care and treatment programs. The WHO recommends five strategic objectives in The Global Action Plan on HIV Resistance 2017-2021[37]. They are 1) implement high-impact interventions to prevent and respond to HIVDR, 2) monitor surveillance of HIVDR and quality of HIV treatment service delivery at ART clinics such as using early warning indicators, PDR and acquired HIVDR (ADR) surveillances, 3) develop innovative researches to have impact on minimizing HIVDR, 4) strengthen and expand laboratory capacity of VL testing and HIVDR testing, and 5) ensure governance and enabling mechanisms for supporting actions on HIVDR. National programs should perform periodic nationally representative surveys of HIVDR every three years among pretreatment HIV-infected persons, including people experiencing treatment failure and newly diagnosed infants to detect potential future increases of HIVDR in a timely manner [21,28,37]. Moreover, researches on HIVDR among key populations such as pregnant women, children aged less than 18 years, adolescents may be needed to identify HIVDR prevalence levels and trends in order to inform the selection of suitable regimens for HIV prevention and treatment among these groups. To sustain resources for continuing HIVDR surveillance, they should address the HIVDR surveillance in a national HIV/AIDS plan or integrate it to drug resistance surveillance systems of other diseases.

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Conflict of Interest

None to declare.

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