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ORIGINAL RESEARCH

High rate of HIV-1 drug resistance in treatment failure patients in Taiwan, 2009–2014

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Background: Drug resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) has been associated with loss of viral suppression measured by a rise in HIV-1 RNA levels, a decline in CD4 cell counts, persistence on a failing treatment regimen, and lack of adherence to combination antiretroviral therapy.

Objectives: This study aimed to monitor the prevalence and risk factors associated with drug resistance in Taiwan after failure of first-line therapy.

Materials and methods: Data from the Veterans General Hospital Surveillance and Monitor Network for the period 2009–2014 were analyzed. Plasma samples from patients diagnosed with virologic failure and an HIV-1 RNA viral load >1000 copies/mL were analyzed by the ViroSeq™ HIV-1 genotyping system for drug susceptibility. Hazard ratios (HRs) for drug resistance were calculated using a Cox proportional hazard model.

Results: From 2009 to 2014, 359 patients were tested for resistance. The median CD4 count and viral load (log) were 214 cells/μL (interquartile range [IQR]: 71–367) and 4.5 (IQR: 3.9–5.0), respectively. Subtype B HIV-1 strains were found in 90% of individuals. The resistance rate to any of the three classes of antiretroviral drugs (NRTI, NNRTI, and PI) was 75.5%. The percentage of NRTI, NNRTI, and PI resistance was 58.6%, 61.4%, and 11.4%, respectively. The risk factors for any class of drug resistance included age ≤35 years (adjusted HR: 2.30, CI: 1.48–3.56; $p<0.0001$), initial NNRTI-based antiretroviral regimens (adjusted HR: 1.70, CI: 1.10–2.63; $p=0.018$), and current NNRTI-based antiretroviral regimens when treatment failure occurs (odds ratio: 4.04, CI: 2.47–6.59; $p<0.001$). There was no association between HIV-1 subtype, viral load, and resistance.

Conclusion: This study demonstrated a high level of resistance to NRTI and NNRTI in patients with virologic failure to first-line antiretroviral therapy despite routine viral load monitoring. Educating younger men who have sex with men to maintain good adherence is crucial, as PI use is associated with lower possibility of drug resistance.

Keywords: antiretroviral therapy, HIV, drug resistance, treatment failure

Introduction

The introduction of highly active antiretroviral therapy (HAART) has dramatically changed the disease course of HIV infection, making it a chronic and controllable disease.[1–4] Suppression of virus replication can reduce disease progression and transmission. Monitoring HIV-1 drug resistance is essential for accessing requirements for new drugs and for stopping the spread of resistances. As such, patients with virologic failure provide a surrogate marker for treatment effectiveness.[5] Continuing with failed regimens may lead to more complex mutation patterns, the development

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of cross-resistance, and the forward transmission of drug-resistant HIV to antiretroviral therapy (ART)-naïve patients.[6]

The World Health Organization recommends monitoring for acquired HIV drug resistance in individuals receiving ART.[7] A recent review reported high drug resistance levels in patients with virologic failure and the most common resistance mutations, M184V and K103N, were found in 65% and 52% of patients, respectively.[8] However, the prevalence rate of acquired ART resistance in Asia, where routine viral load monitoring is available, remains unknown.

Genotypic drug resistance testing (GRT) before treatment can influence the rate of acquired drug resistance mutation. In the Swiss HIV Cohort Study, 28.9% of post-ART patients had detectable drug resistance mutation, whereas in the recent ART-initiator group, only 45 of 2092 (1.6%) patients with pretreatment GRT acquired drug resistance mutations on ART.[9] Thus, regular surveillance of transmitted drug resistance is important to combat drug resistance.

The prevalence of transmitted HIV resistance had recently increased to 5% in some areas of South Africa, Kenya, and Zambia, and up to 15% in Uganda.[10–12] In Asia, this rate was around 4%–12%, including 3.8% in China,[13] 7.7% in Japan,[14] 12% in South Korea,[15] 4.9% in Thailand,[16] and 8%–11.1% in northern Taiwan.[17–18] However, routine pretreatment GRT in ART-naïve patients is lacking in Taiwan because of financial constraints.

Informed strategies to prevent the development of virologic failure to first-line ART and the emergence of HIV resistance are, therefore, crucial. Although studies have been conducted on the prevalence of HIV-transmitted drug resistance in northern Taiwan,[17,18] data on the impact of epidemiologic information and drug resistance after failure to ART are unknown. This study aims to establish the prevalence of genotypic drug resistance after failure of anti-HIV therapy and to establish the clinical and viral characteristics that might be predictive of drug resistance.

Materials and methods

Ethical statement

The institutional review board of the Kaohsiung Veterans General Hospital in Taiwan approved this study (VGHKS98-CT1-08 and VGHKS13-CT4-12). The protocol complied with all ethical considerations involving human subjects, and all information obtained followed standard clinical guidelines. All of the study participants provided written informed consent.

Study design and participants

Samples covering the period 2009–2014 were obtained from a clinical HIV cohort on HIV drug resistance in adult patients at the Veterans General Hospital Surveillance and Monitor Network (VGHSMN), which consisted of branches in Taipei, Taichung, and Kaohsiung, as well as 10 veterans and other satellite hospitals. The inclusion criteria were: 1) HIV-1-infected adult aged ≥20 years; 2) HAART initiation between 1 January 2009 and 31 December 2014; and 3) treatment failure with HIV-1 viral load ≥1000 copies/mL. A standardized questionnaire was also used to collect demographic data that included age, sex, risk factors for HIV infection, CD4 count, viral load, and duration and name of ART used.

Patients with a previous history of ART exposure for prevention of mother to child transmission or for post-exposure prophylaxis were excluded. When the patients returned to the clinics, laboratory exams for CD4 cell counts (FACS Flow; Becton Dickinson and Company, Franklin Lakes, NJ, USA) and plasma viral load (Cobas Amplicor HIV-1 monitor test, version 1.5; Roche Diagnostics Corporation, Indianapolis, IN, USA) were performed. First-line ART was provided for free in designated hospital nationwide by infectious diseases physicians and supported by the HIV case managers. Treatment switches were guided by clinical, immunologic, and virologic criteria, as determined by the physician in charge.

Standard follow-up of HIV-infected patients on ART consisted of outpatient visits every 3 months, with physical examinations, CD4+ T cell count, viral load, hematology, and biochemistry. However, HIV-1 GRT was not routinely performed for patients with virologic failure. Blood samples for such patients could be sent to the Center for Diseases Control for GRT once in every 3 years or to the reference laboratory if the patient was in the VGHSMN cohort.

Genotypic drug resistance testing

Resistance testing was performed on plasma samples using the ViroSeq™ HIV-1 Genotyping System version v2.8, according to the manufacturer's instructions (Celera, Alameda, CA, USA). Antiretroviral resistance mutations were defined using the 2015 International Antiviral Society–USA (IAS–USA) HIV drug resistance algorithm,[19] while drug resistances were compared using the HIVdb program of the Stanford University HIV Drug Resistance Database. Patients were then classified as low-level, intermediate, or high-level resistance, as defined accordingly.

Statistics analysis

The Mann–Whitney *U* test was used to compare the median values of continuous variables between groups (resistance and wild virus), while the Fisher's exact test was used to compare categorical variables between the two groups. Kaplan–Meier curves were estimated to determine the association

between duration of current ART use and the development of drug resistance. A Cox proportional hazard model was used to calculate the hazard ratio (HR) for drug resistance. A two-sided $p<0.05$ was considered statistically significant. Statistical calculations were performed using the SPSS program version 12.0 (IBM Corporation, Armonk, NY, USA).

Results

From 2009 to 2014, a total of 359 patients had GRT and sequences were successfully obtained from 290 (81%). Sixty-nine did not report resistance due to low viral load (n=13), poor sample quality (n=1), and cancellation by the requesting physician due to viral re-suppression after education (n=55). The demographic data between patients with successful GRT and those without did not show any difference. Among the 359 patients, 93.6% (n=336) were male and 69.4% (n=247) were aged 20–39 years. Moreover, 73.4% (n=256) were men who had sex with men (MSM).

Upon virologic failure, the median CD4 cell count was 214 (interquartile range [IQR]: 71–367) cells/μL and the viral load was 4.5 log (IQR: 3.9–5.0). Most (90%) of the 290 patients with available GRT report had HIV subtype B, 9% had CRF01_AE, and 1% had subtype C (Table 1).

Table 1 Demographic data among HIV-1 infected patients with treatment failure (N=359)

Parameters	Number of patients (%)
Sex (N=359)	
Male	336 (93.6)
Female	23 (6.4)
Age (N=356)	
20–29	120 (33.7)
30–39	127 (35.7)
40–49	71 (19.9)
>50	38 (10.7)
Risk factor (n=349)	
Heterosexual	63 (18.1)
MSM	256 (73.4)
IDU	30 (8.5)
Any class of resistance (n=290)	
Yes	219 (75.5)
No	71 (24.5)
HIV subtype (n=290)	
Non-B	29 (10)
B	261 (90)
CD4 (cells/μL)	
Minimum	1
Maximum	1217
Median (IQR)	214 (71–367)
CD4 cutoff point (cells/μL)	
≥200	189 (52.6)
<200	170 (47.4)
Viral load (log)	
Minimum	1.30
Maximum	6.82
Median (IQR)	4.53 (3.94–4.99)
Viral load cutoff point (log)	
≥4	258 (73.1)
<4	95 (26.9)
Syphilis (n=63)	
Negative	35 (55.6)
Positive	28 (44.4)
Months on HAART	
Minimum	0.5
Maximum	168
Median (IQR)	24 (9–51)
Months of current regimen	
Minimum	0.1
Maximum	120
Median (IQR)	9 (4–20.3)
Current regimens (CR)	
NNRTI based	158 (49.8)
PI based	159 (50.2)
NRTIs in CR	
ZDV/3TC	135 (41.0)
ABC/3TC	121 (36.8)
TDF/3TC	31 (9.4)
Others	42 (12.8)
NNRTI in CR	
NVP	87 (53.7)
EFV	75 (46.3)
PIs in CR	
Boosted PI	109 (66.9)
Unboosted PI	54 (33.1)
NRTIs in initial regimens (IR)	
ZDV/3TC	152 (51.9)
ABC/3TC	98 (33.4)
TDF/3TC	14 (4.8)
Others	29 (9.9)
NNRTIs in IR	
NVP	80 (44.7)
EFV	99 (55.3)
PIs in IR	
Boosted PI	85 (71.4)
Unboosted PI	34 (28.6)

Notes: PIs in CR: Boosted PI consisted of lopinavir/ritonavir (n=77), atazanavir/ritonavir (n=21), darunavir/ritonavir (n=10), and tipranavir/ritonavir (n=1). Unboosted PI consisted of atazanavir (n=54). PIs in IR: Boosted PI consisted of lopinavir/ritonavir (n=70), atazanavir/ritonavir (n=9), indinavir/ritonavir (n=4), and nelfinavir/ritonavir (n=2). Unboosted PI consisted of atazanavir (n=31), indinavir (n=2), and ritonavir (n=1).

Abbreviations: ABC/3TC, abacavir/lamivudine; EFV, efavirenz; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IDU, intravenous drug abuser; IQR: interquartile range; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; TDF/3TC, tenofovir/lamivudine; ZDT/3TC, zidovudine/lamivudine; IR, initial regimens; CR, current regimens.

The median duration of HAART use was 24 months (IQR: 9–50.5 months). The median duration of current HAART upon presentation for GRT was 9 months (IQR: 4–20.3 months). Upon presentation for GRT, 49.8% (158/317) of the patients were under non-nucleoside reverse transcriptase inhibitor (NNRTI)-based treatment. The most commonly used nucleoside reverse transcriptase inhibitor (NRTI) backbone included zidovudine/lamivudine (41%), abacavir/lamivudine (36.8%), and tenofovir/lamivudine (9.4%). The most commonly used NNRTIs were nevirapine (53.7%, 87/162) and efavirenz (46.3%, 75/162). Booster protease inhibitor (PI) was used in 109 (66.9%, 109/163) patients with lopinavir/ritonavir (47%, 77/163), atazanavir/ritonavir (13%, 21/163), darunavir/ritonavir (6%, 10/163), and tipranavir/ritonavir (0.6%, 1/163). Unboosted PI (atazanavir) was used in 54 (33.1%) patients.

Of the 290 patients with GRT, 75.5% (n=219) had drug resistance to any of the three classes of antiretroviral drugs, including 58.6% showing resistance to NRTI, 61.4% to NNRTI, and 11.4% to PI (Figure 1). The NNRTI cross-resistance was common in 51.7% of patients who were also resistant to rilpivirine, although they had no previous exposure to this new second-generation NNRTI (Figure 2). The prevalence of IAS–USA drug resistance associated mutations in NRTI, NNRTI, and PI was 62.1%, 72.1%, and 37.2%, respectively (Figure 1). The most common NRTI drug resistance associated mutations were M184V (52.1%), L74V (13.8%), and Y115F (7.2%). For NNRTI, the most common drug resistance associated mutations were K103N (26.6%), Y181C (16.2%), V179D (14.8%), and G190A (13.4%), while for PI, these were A71V (13.1%), L10I (12.4%), A71T (11.0%), and I50L (5.9%), as shown in Figure 3.

Risk factors associated with the presence of drug-resistant strains in a single variance analysis were younger age (p=0.045), MSM (adjusted HR [aHR]: 2.171, 95% CI: 1.210–3.894; p=0.011), and NNRTI-based HARRT at failure (aHR: 4.706, 95% CI: 2.331–9.499; p<0.0001), as shown in Table 2. Risk factors for any class drug resistance in multivariate analysis included age ≤35 years (aHR: 2.30, CI: 1.48–3.56; p<0.0001), initial NNRTI-based antiretroviral (ARV) regimens (aHR: 1.70, CI: 1.10–2.63; p=0.018), and currently used NNRTI-based ARV when there is the occurrence of virological failure (odds ratio: 4.04, CI: 2.47–6.59; p<0.001), as shown in Figure 4. There were no associations among HIV-1 subtype, viral load, and resistance (Table 3).

Discussion

This study illustrates the prevalence of HIV drug resistance among HIV-infected patients with virologic failure after first-line ART in Taiwan. In particular, this study highlights the high rate of drug resistance (75.5%) and the association of younger age (<35 years), even with widely available routine viral load monitoring. More importantly, the drug resistance to tenofovir and PI is low, compared to that of NNRTIs.

The findings here are similar to the resistance data from those patients in Africa who have suffered from early failures to the first-line treatment, showing that 70% with more than one drug resistance mutation after 12 months of treatment.[10,20] Compared to other studies, the patients here had been a long duration on ART, with a median of 24 months.[20] Thus, the high prevalence of resistance in this study is likely due to a limited availability of resistance testing, leading to prolonged failure of ART and an accumulation of resistance mutations.

Most of the NRTI backbone used in this study included lamivudine and zidovudine: 52% (n=152), in the initial regimen

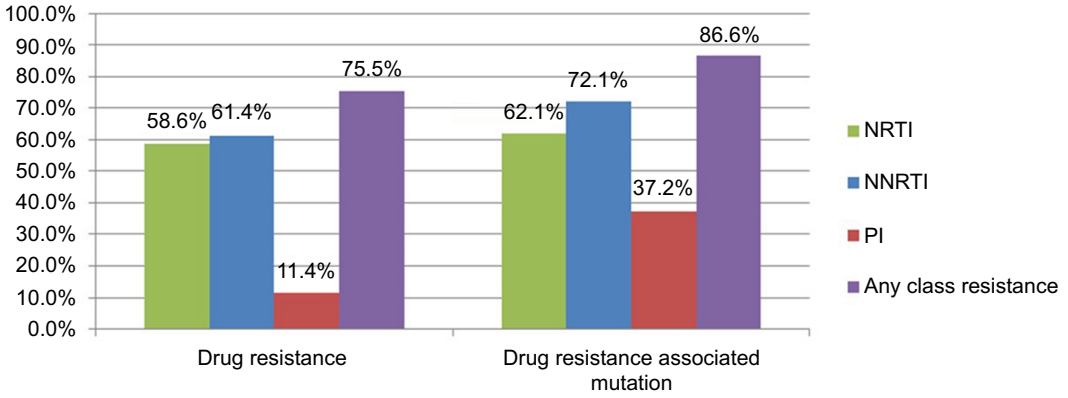

Figure 1 Percentage of IAS–USA HIV drug resistance associated mutations and drug resistance by HIVdb program of the Stanford University among 290 HIV-1 infected patients with virologic failure, 2009–2014.
Note: A high of 75.5% of patients had drug resistance to any of the three classes of ART and 86.6% of the patients harbored any of the drug resistance associated mutations.
Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

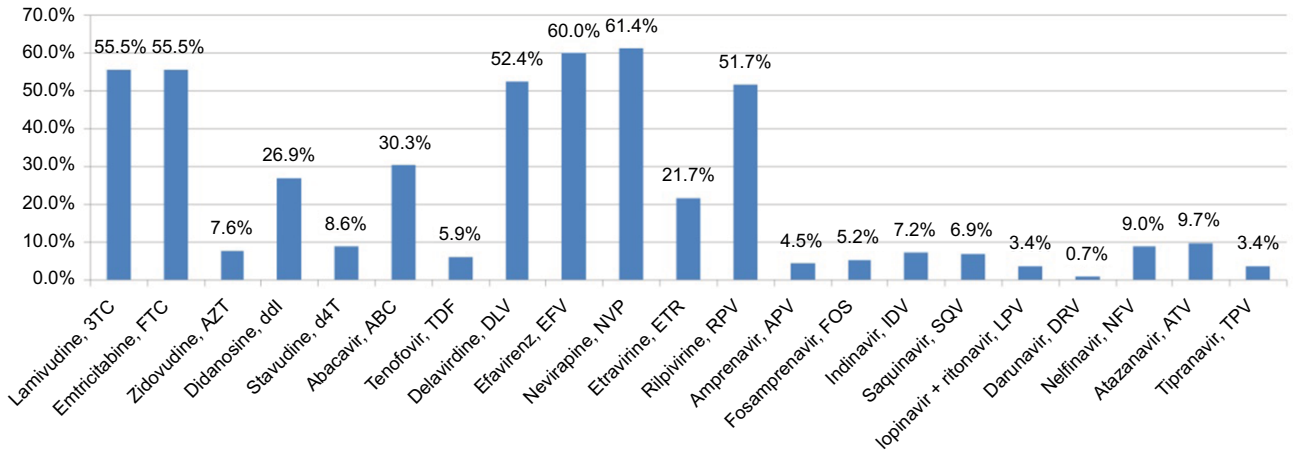

Figure 2 The prevalence of drug resistance to NRTI, NNRTI, and PI among 290 HIV-1 infected patients with virologic failure.
Note: Only 5.9% of the patients had drug resistance to tenofovir. The NNRTI cross-resistance was common and 51.7% of patients were also resistant to rilpivirine although they had no previous exposure to this new second-generation NNRTI.
Abbreviations: HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

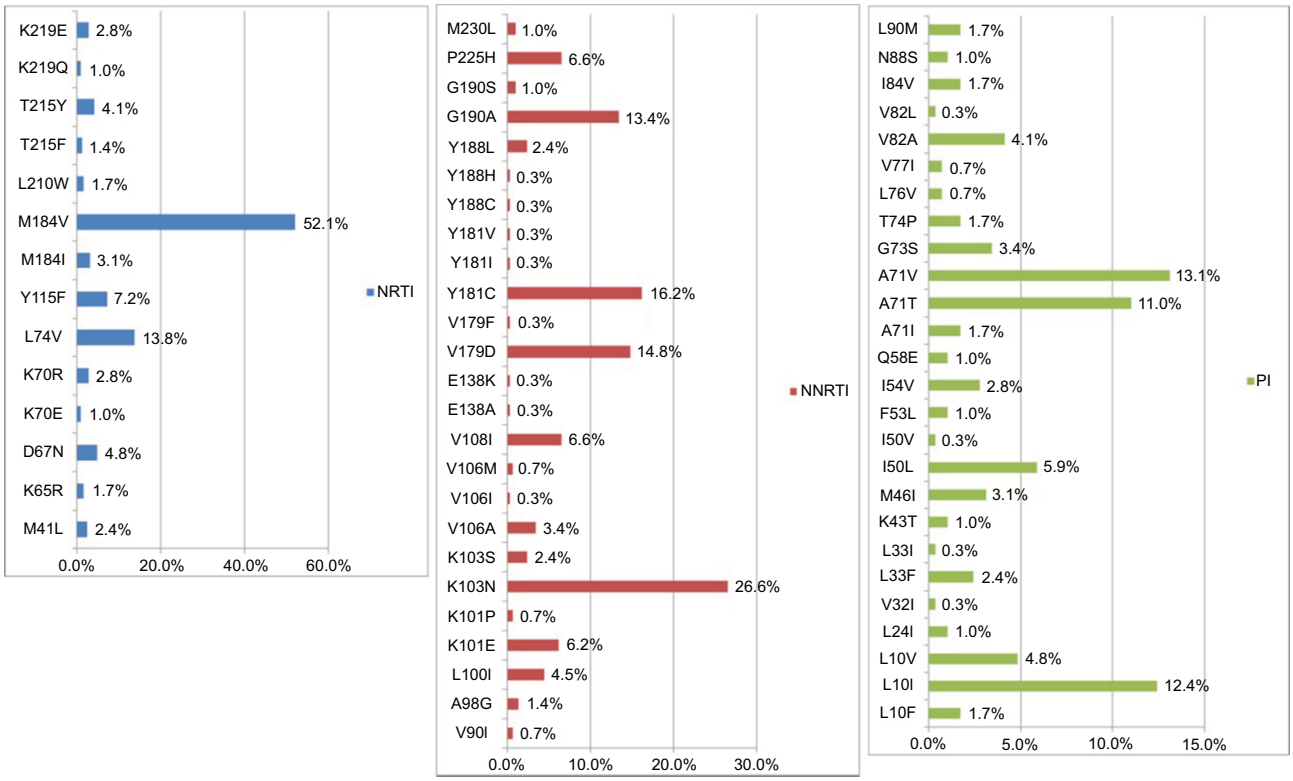

Figure 3 Percentage of ISA–USA HIV drug resistance associated mutations in NRTI, NNRTI, and PI among 290 HIV-1 infected patients with virologic failure.
Notes: The most common NRTI drug resistance associated mutations were M184V (52.1%) and L74V (13.8%). For NNRTI, the most common drug resistance associated mutations were K103N (26.6%) and Y181C, while for PI, these were A71V (13.1%) and L10I (12.4%).
Abbreviations: HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

when starting ART and 41% (n=135) in the current regimen when virologic failure occurred, explaining the predominance of M184V mutations and thymidine-associated mutations at the point of failure. In this study, the K65R mutation (1.7%) was rare, probably because tenofovir had been introduced in Taiwan in 2011 and had a restricted use in the national HIV treatment guideline initially. These results suggest that tenofovir remains a good option for second-line therapy.

The prevalence of resistance to NNRTIs was high, which was 60% for efavirenz and 61.4% for nevirapine. These

Table 2 Risk factors associated with HIV-1 drug resistance in univariate analysis

Demographic data and drug regimens	Resistance (n=219)	Nonresistance (n=71)	*p*-value	aHR	95% CI
Sex					
Male	206 (94)	65 (92)	0.422	1.463	0.535–4.003
Female	13 (6)	6 (8)			
Age (median, IQR)	33 (27–41)	34 (30–44)	0.045*		
Risk factor, n (%)					
MSM	169 (79)	44 (63)	0.011*	2.171	1.210–3.894
Non-MSM	46 (21)	26 (37)			
Viral load (log) (median, IQR)	4.6 (4.0–5.0)	4.7 (4.2–5.3)	0.085		
CD4 (median, IQR)	198 (58–364)	219 (58–343)	0.883		
HIV subtype, n (%)					
B	195(89)	66 (93)	0.495	0.612	0.225–1.670
Non-B	24 (11)	5 (7)			
Current regimen, n (%)					
NNRTI based	120 (59)	12 (23)	<0.0001*	4.706	2.331–9.499
PI based	85 (41)	40 (77)			
NRTI of current regimen					
ZDT/3TC	80 (38)	21 (37)			
ABC/3TC	80 (38)	20 (36)			
TDF/3TC	25 (12)	4 (7)			
Others	23 (11)	11 (20)			
NNRTI of current regimen					
NVP	69 (57)	7 (54)	1.000	1.16	0.354–3.516
EFV	53 (43)	6 (46)			
PIs in current regimen[a]					
Boosted PI	52 (60)	34 (83)	0.009*	0.306	0.122–0.767
Unboosted PI	35 (40)	7 (17)			
Months on HAART (median, IQR)	19 (8–52.5)	32 (15–48)	0.157		
Months on current regimen (median, IQR)	9 (5–20)	8.5 (3–19.8)	0.599		
NRTIs in initial regimen					
ZDT/3TC	86 (47)	31 (64)			
ABC/3TC	71 (39)	12 (24)			
TDF/3TC	11 (6)	1 (2)			
Others	15 (8)	5 (10)			
NNRTIs in initial regimen					
NVP	63 (49)	8 (36)	0.356	1.696	0.666–4.321
EFV	65 (51)	14 (64)			
PIs in initial regimen[b]					
Boosted PI	40 (68)	22 (79)	0.447	0.574	0.200–1.649
Unboosted PI	19 (32)	6 (21)			
Syphilis	27/59 (46)	1/4 (25)	0.622	2.531	0.249–25.768

Notes: [a]For patients who developed resistance, the current use of boosted PI when failure occurred consisted of lopinavir/ritonavir (n=29), atazanavir/ritonavir (n=15), darunavir/ritonavir (n=7), and tipranavir/ritonavir (n=1). For patients who developed resistance, the current use of unboosted PI when failure occurred consisted of atazanavir (n=35). For patients who did not develop resistance, the current use of boosted PI when failure occurred consisted of lopinavir/ritonavir (n=31), atazanavir/ritonavir (n=2), and darunavir/ritonavir (n=1). For patients who did not develop resistance, the current use of unboosted PI when failure occurred consisted of atazanavir (n=7). [b]For patients who developed resistance, the initial regimen of boosted PI when failure occurred consisted of lopinavir/ritonavir (n=32), atazanavir/ritonavir (n=6), and indinavir/ritonavir (n=2). For patients who developed resistance, the initial regimen of unboosted PI when failure occurred consisted of atazanavir (n=16), indinavir (n=2), and ritonavir (n=1). For patients who did not develop resistance, the initial regimen of boosted PI when failure occurred consisted of lopinavir/ritonavir (n=20) and atazanavir/ritonavir (n=2). For patients who did not develop resistance, the initial regimen of unboosted PI when failure occurred consisted of atazanavir (n=6). *$p<0.05$.

Abbreviations: aHR, adjusted hazard ratio; ABC/3TC, abacavir/lamivudine; EFV, efavirenz; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; TDF/3TC, tenofovir/lamivudine; ZDT/3TC, zidovudine/lamivudine.

were similar to the results of studies reported from Africa, where a high rate of resistance to first-generation NNRTIs was observed.[10,20] In the present cohort, initial and current NNRTI-based ARV was associated with the development of drug resistance and only 78.3% and 48.3% of the individual genotypes predicted full susceptibility to etravirine and rilpivirine, respectively. None of the patients here had a previous exposure to rilpivirine or etravirine. These results also impacted on the second-generation NNRTI drug choices in patients with treatment failure. Studies show that nevirapine

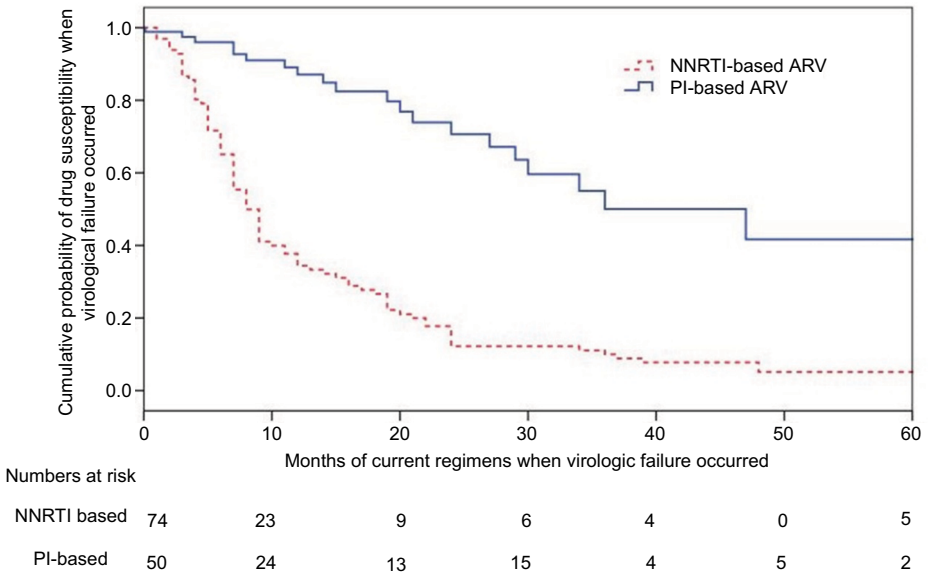

Figure 4 Kaplan–Meier curves for probabilities of developing drug resistances in patients after failure of their current regimen ($p<0.0001$, log rank test).
Notes: Patients with NNRTI-based regimen were more likely to develop virologic failure, compared to those on PI-based regimens (odds ratio: 4.04, CI: 2.47–6.59; $p<0.001$). The numbers used in the category at risk were 234. However, 290 samples were successfully tested for resistance. The detailed information for the drug prescription was not available in 56 subjects.
Abbreviations: NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 3 Risk factors associated with drug resistance in Cox regression model

Variable	Number (%)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p*-value	aHR (95% CI)	*p*-value
Total	290				
Sex					
Male	271 (93.4)	1.21 (0.53–2.76)	0.65		
Female	19 (6.6)	1			
Age (years)					
≤35	176 (60.7)	2.49 (1.64–3.79)	<0.0001	2.30 (1.48–3.56)	<0.0001
>36	112 (38.6)	1			
Route of transmission					
MSM	213 (73.4)	1.62 (0.99–2.65)	0.054		
Non-MSM	72 (24.8)	1			
HIV RNA (copies/mL)					
≤10,000	219 (75.5)	1.44 (0.86–2.40)	0.17		
>10,000	65 (22.4)	1			
CD4 count (cells/μL)					
≤200	235 (81)	1.09 (0.70–1.71)	0.70		
>200	55 (19)	1			
Initial ART regimen					
NNRTI	150 (51.7)	1.90 (1.25–2.90)	0.003	1.70 (1.10–2.63)	0.018
PI	87 (30)	0.46(0.30–0.72)	<0.0001	0.51 (0.32–0.80)	0.003
Current ART regimen					
NNRTI	135 (46.6)	4.51 (2.8–7.28)	<0.0001	4.04 (2.47–6.59)	<0.0001
PI	128 (44.1)	0.23 (0.14–0.37)	<0.0001	0.26 (0.16–0.42)	<0.0001
HIV strain					
Subtype B	260 (89.7)	1.41 (0.78–2.53)	0.26		
Non-subtype B	29 (10)	1			

Notes: Statistical analysis: Variables with a *p* value <0.20 in the univariate analysis were considered for inclusion in multivariate Cox regression models. *p* Values <0.05 were considered statistically significant. All analyses were performed using SPSS software version 12.
Abbreviations: aHR, adjusted hazard ratio; ART, antiretroviral therapy; HIV, human immunodeficiency virus; HR, hazard ratio; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

selects for the Y181C and G190A mutations and leads to reduced rilpivirine or etravirine susceptibility.[21,22] Efavirenz failure is more likely to be associated with K103N mutation and has little impact on etravirine susceptibility.[21,22] The median duration for the development of NNRTI resistance was 9 months, reflecting the low genetic barrier nature of NNRTI and poor drug compliance in the younger age group.

In this study, only 11.4% of patients developed PI resistance. The emergence of PI resistance at the time of virologic failure is uncommon in PI-naïve patients who experience virologic failure during their PI regimen. Moreover, the PI mutations can be located outside the *pol* gene, thereby underestimating the prevalence of PI resistance.[23–25] In previous studies in Taiwan, the transmitted drug resistance to PI was extremely low (<4%).[17,18] The PIs used in this study with failure were mostly lopinavir/ritonavir (60/125, 48%) and unboosted atazanavir (42/125, 33.6%). Up to 88.6% of patients did not have PI resistance on treatment failure and there was no association between unboosted PI use and the development of resistance. This might be due to the poor access to GRT and poor drug adherence.

Rates of PI resistance at the time of second-line failure are high in resource-limited settings and are associated with the duration of exposure to previous drug regimens and poor adherence.[26] A high prevalence of PI resistance was reported in four studies, two of which studied patients from Asia, especially from India (n=45, 73%)[27] and Vietnam (n=231, 59%).[28] The other two studies were from Mali (n=93, 25%)[29] and Nigeria (n=61, 62%).[30] Except for the study from India, where indinavir/ritonavir and atazanavir/ritonavir were used, the studies in these other countries used lopinavir/ritonavir for second-line therapy, similar to this study.

In this study, younger age (<35 years) is associated with the development of resistance. Several large cohort studies also report that older age is associated with better treatment outcomes,[31,32] although better adherence does not necessarily explain the lower risk of failure in this group. No data about the level of adherence was available in this study. However, 24.5% of patients who experienced virologic failure had the wild-type virus, suggesting that adherence was an important factor in virologic failure.

The resistance rates to any of the three classes of antiretroviral drugs (NRTI, NNRTI, and PI) were up to 75.5%, despite the viral load measurements taken every 3–4 months. This rate was similar to those of developing countries in which viral load monitoring was not routinely available. In an HIV clinical trial in the USA where viral load was measured regularly every 3 months, the frequency of resistance in the study subjects receiving optimal first-line regimens was 62% at virologic failure.[33] This was similar to the 70% drug resistance rate in the Pharm Access African Studies to Evaluate Resistance, where HIV plasma viral load was measured after 12 months of a first-line regimen.[10] In the ANRS (National Agency for AIDS Research) 1268 study, the overall prevalence of major drug resistance mutations after virologic failure without any RNA monitoring was 71% and 86% among those assessed after 1 and 2 years, respectively, consistent with the evidence of a modest increase in resistance without monitoring among recipients of first-line treatment in Africa.[34–36]

It is very difficult to ascribe rates of virologic failure in resource-limited settings to a lack of viral load monitoring. Patient treatment adherence, HAART regimens used, accessibility of genotypic drug resistance, duration of failing regimen before resistance testing, even challenges in providing sample transport, laboratory and clinical infrastructure, and trained personnel,[10] and competing for treatment resources – all play significant roles that weaken the efficiency of routine viral load monitoring in the prevalence of drug resistance.

Limitations

There was no data available on the baseline prevalence of HIV-transmitted drug resistance for the study population. Nonetheless, the prevalence of transmitted antiretroviral resistance was reported to be around 8%–10% in Taiwan. The duration of virologic failure under treatment was not precisely determined in all of the patients because the information was lacking in some of the patients. In patients failing ART, GRT was found to have a significant benefit on the virologic response when choosing the salvage regimens.[37–39] But the treatment outcomes for patients with virologic failures switching to another regimen were not available, making it impossible to evaluate the clinical impact of GRT. There was also no information on adherence to the ART regimen, making interpretation of the effect of age on the development of resistance more complicated. However, several large cohort studies reported that older age was associated with better treatment outcomes, although better adherence did not necessarily explain the lower risk of treatment failure in this group. Lastly, the results were from the VGHSMN cohort. Thus, it would be interesting to extend this work to the other parts of Taiwan.

Conclusion

This study demonstrates a high level of resistance to NRTI and NNRTI among patients who experienced virologic failure to first-line antiretroviral therapy even with routine viral load monitoring. It is crucial to educate younger MSM individuals to maintain good adherence to their treatment regimen. The use of PI is also associated with lower possibility of drug resistance.

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Disclosure

The authors report no conflicts of interest in this work.

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