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ORIGINAL RESEARCH

Trend of HIV Transmitted Drug Resistance After the Introduction of Single-Tablet Regimens in Southern Taiwan

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Background: The prevalence of transmitted drug resistance (TDR) after the universal implementation of STRs is unknown in Taiwan.

Objective: This study aimed to investigate the prevalence of TDR in patients with HIV-1 infection, clarify the risk factors for *pol* resistance, and compare differences in HIV drug resistance before and after the implementation of STRs in Taiwan.

Methods: Adult patients infected with HIV-1 were enrolled in this study from 2013 to 2021. Mutations associated with drug resistance were identified using the 2019 International Antiviral Society-USA list of drug resistant mutations in HIV, and drug susceptibility was assessed according to the Stanford HIV Drug Resistance Database edition 9. A logistic regression model was used to analyze the risk factors for *pol* resistance, and the differences in the prevalence of drug resistance from 2013–2016 to 2017–2021 were compared using the Mann–Whitney *U*-test. General linear regression was used to analyze temporal changes in the annual proportion of TDR overall and by type of antiretroviral drugs.

Results: A total of 369 patients were included. The prevalence rate of *pol* resistance was 9.8% (36/369). The resistance rates to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs) were 3.3%, 6.9%, 0% and 1.8%, respectively. The patients with hepatitis C infection were more likely to have *pol* resistance (aHR 5.767, CI 1.232–26.991, p=0.026). The prevalence rate of *pol* resistance did not decrease after the implementation of STRs as first-line therapy in 2017 (11.2% vs 8.7%, aHR 1.329, CI 0.667–2.645, p=0.480), and no significant temporal changes were shown in the annual proportion of TDR overall or by type of antiretroviral drug.

Conclusion: Our findings showed a stable prevalence rate of transmitted drug resistance despite the implementation of STRs as the first-line therapy in June 2016.

Keywords: HIV, transmitted drug resistance, single-tablet regimen

Introduction

Despite the wide implementation of highly active antiretroviral therapy (HAART) for people living with human immunodeficiency virus (HIV), the emergence of HIV transmitted drug resistance (TDR) can substantially increase the risk of treatment failure.[1–3] In Taiwan, HIV infection is a reportable disease. Since the first HIV-1-infected patient was diagnosed in Taiwan in 1984, the annual number of reported cases has reduced remarkably, possibly due to the promotion of HIV pre-exposure prophylaxis, implementation of treatment for prevention with no CD4 limitation, introduction of single-tablet regimen (STRs), and case management nurses.[4–6] By the end of March 2022, a total of 42,553 individuals were reported as being infected with HIV-1 in Taiwan, most of whom (28,297, 66.5%) were men who

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have sex with men (MSM) or bisexual, and 93% were aged 15–49 years.[5] The Taiwan Centers for Disease Control (CDC) has provided free voluntary counseling and testing (VCT) services since 1997 to reach the target populations most at risk of HIV infection in Taiwan.

The prevalence rate of TDR in Taiwan, where genotypic drug-resistance testing is not routinely available, is about 10–12% for nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).[7,8] HIV integrase strand transfer inhibitor (INSTI) resistance is low in HIV-1-infected treatment-naïve individuals, and routine Sanger genotypic drug-resistance testing is not recommended. However, the reported rates of TDR-associated mutations to INSTIs in Taiwan were 1.2% in northern Taiwan from 2006 to 2015,[9] and 0.9% in southern Taiwan from 2013 to 2017.[10] STRs have been associated with better drug adherence,[11] decreased risk of resistance mutations,[12] and improved quality of life compared to multiple tablet regimens.[13] However, the long-term temporal trend of resistance in high-risk HIV groups diagnosed through the VCT program after the introduction of STRs in Taiwan is unknown. Most previous studies of TDR in HIV-1-infected patients have been cross-sectional, spanned a short period of time, and used different drug resistance interpretational criteria.[14,15] No previous study has provided long-term observational resistance follow-up data or used the newest Stanford HIV Drug Resistance Database edition 9 to analyze the prevalence of resistance. Therefore, this study aimed to investigate the prevalence of TDR in HIV-infected patients newly diagnosed through the free national VCT program in southern Taiwan from 2013 to 2021, clarify the risk factors for drug resistance, and compare the trends of the prevalence of resistance before and after the introduction of STRs as the recommended regimen after June 2016.

Materials and Methods

Ethics Statement

The Institutional Review Board of Kaohsiung Veterans General Hospital, Taiwan, approved this study (VGHKS12-CT5-07, VGHKS15-CT5-10 and VGHKS16-CT11-21), which was conducted according to the Declaration of Helsinki. In addition, all of the participants provided written informed consent.

Study Design and Participants

This retrospective cohort study was conducted at Kaohsiung Veterans General Hospital, which is one of the largest medical centers in Kaohsiung City and is responsible for the health care of approximately 25% of all HIV-infected individuals in the city, and about 5% of all HIV-infected individuals in Taiwan. We enrolled individuals residing in southern Taiwan who were newly diagnosed with HIV-1 infection through the free VCT program from 2013 to 2021. The enrolled patients attended regular follow-up visits at our outpatient department, during which they were tested for viral load, CD4+ T cell count, biochemistry, and hematology every 3 months during the first year after the diagnosis of HIV, and every 6 months thereafter for the stable patients. Combination antiretroviral therapy (cART) is provided to all individuals infected with HIV-1 at no cost by the Taiwanese government. The cost of genotypic drug resistance testing is not reimbursed in Taiwan, and pretreatment testing is not mandatory. Before June 2016, the first-line cART regimens were restricted to zidovudine/lamivudine (ZDT/3TC) plus nevirapine (NVP) or efavirenz (EFV) due to financial constraints. However, after June 2016 the criteria for reimbursement were revised, and subsequently all treatment-naïve patients infected with HIV-1 were able to receive a STR. Efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla) became available in Taiwan in 2010, and in June 2016 it was recommended as the first-line cART regimen. Other recommended first-line cART regimens available in Taiwan include abacavir/dolutegravir/lamivudine (Triumeq) and emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Complera) also in June 2016, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya) in September 2018, bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) and rilpivirine/emtricitabine/tenofovir alafenamide (Odefsey) in October 2019, and doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) and dolutegravir/lamivudine (Dovato) in December 2020.

In 2007, Taiwan introduced the HIV case management nurse program at designated hospitals, and the treat-all policy for HIV-infected patients was implemented in 2016. In 2018, rapid antiretroviral therapy initiation was encouraged, and a nationwide HIV pre-exposure prophylaxis program was started. In general, most HIV-1-infected treatment-naïve patients (80%) in Taiwan are given an INSTI-based STR, and 20% are given an NNRTI-based STR.

Genotypic Drug Resistance Testing

ViroSeq HIV-1 Genotyping System version v2.8 (Celera, Alameda, CA, USA) was used to test resistance for PR/RT (*pol* gene), and in-house sequencing was used to test resistance to INSTIs (*pol* gene).[16,17] The International Antiviral Society

Table 1 Demographic Data Among Treatment-Naïve of HIV-1 Infected Patients (n=369)

Parameters		Patient Numbers (%)
Gender	Male	365 (98.9)
	Female	4 (1.1)
Age	Median (IQR)	27 (23–33)
Risk factor	Heterosexual	11 (3)
	MSM	357 (96.7)
	IVDU	1 (0.3)
pol resistance	Y	36 (9.8)
	N	333 (90.2)
pol mutation	Y	59 (16)
	N	310 (84)
HIV subtype	CRF01_AE	24 (6.5)
	B	341 (92.4)
	CRF07_BC	4 (1.1)
CD4 (cell/ul)	Minimum	0
	Maximum	1098
	Median (IQR)	311 (201–431)
CD4 cut point (cell/ul) (n=366)	< 200	89 (24.3)
	≥ 200	277 (75.7)
Viral load (Log)	Minimum	2.47
	Maximum	7.00
	Median (IQR)	4.71 (4.34–5.11)
Viral load cut point (Log) (n=367)	< 4	41 (11.2)
	≥ 4	326 (88.8)
Syphilis	Negative	253 (68.6)
	Positive	116 (31.4)
IHA-AMEBIASIS (n=341)	≦ 128	326 (95.6)
	≧ 256	15 (4.4)
TOXOPLASMA-IgG (n=365)	Negative	339 (92.9)
	Positive	26 (7.1)
CMV-IgG (n=307)	Negative	6 (2)
	Positive	301 (98)
CRYPTOCOCCUS Ag (n=308)	Negative	305 (99)
	Positive	3 (1)
HAV Ab (n=366)	Negative	316 (86.3)
	Positive	50 (13.7)
HBs Ab (n=367)	Negative	188 (51.2)
	Positive	179 (48.8)
HBs Ag (n=367)	Negative	341 (92.9)
	Positive	26 (7.1)
HBc Ab (n=367)	Negative	277 (75.5)
	Positive	90 (24.5)
HCV Ab (n=367)	Negative	358 (97.5)
	Positive	9 (2.5)

Abbreviations: HIV, human immunodeficiency virus; IHA, indirect hemagglutination; CMV, cytomegalovirus; HAV, hepatitis A virus; HBs Ab, hepatitis B surface antibody; HBs Ag, hepatitis B surface antigen; HBc Ab, hepatitis B core antibody; HCV, hepatitis C virus; IQR, interquartile range; MSM, men who have sex with men; IVDU, intravenous drug abuser; Y, yes; N, no.

(IAS)-USA 2019 mutation list[18] was used to define the clinically relevant mutations associated with drug resistance to NRTIs, INSTIs, PIs, and NNRTIs. The Stanford University HIV Drug Resistance Database (version 9, last update 2021-2-22) was used to assess resistance and subtypes. The patients with low, intermediate and high resistance were all classified as having drug resistance.[19]

Statistical Analysis

Comparisons of median values of continuous variables between groups (resistant and wild-type virus) were performed using the Mann–Whitney *U*-test. Categorical variables were compared between two groups (mutations or resistance)

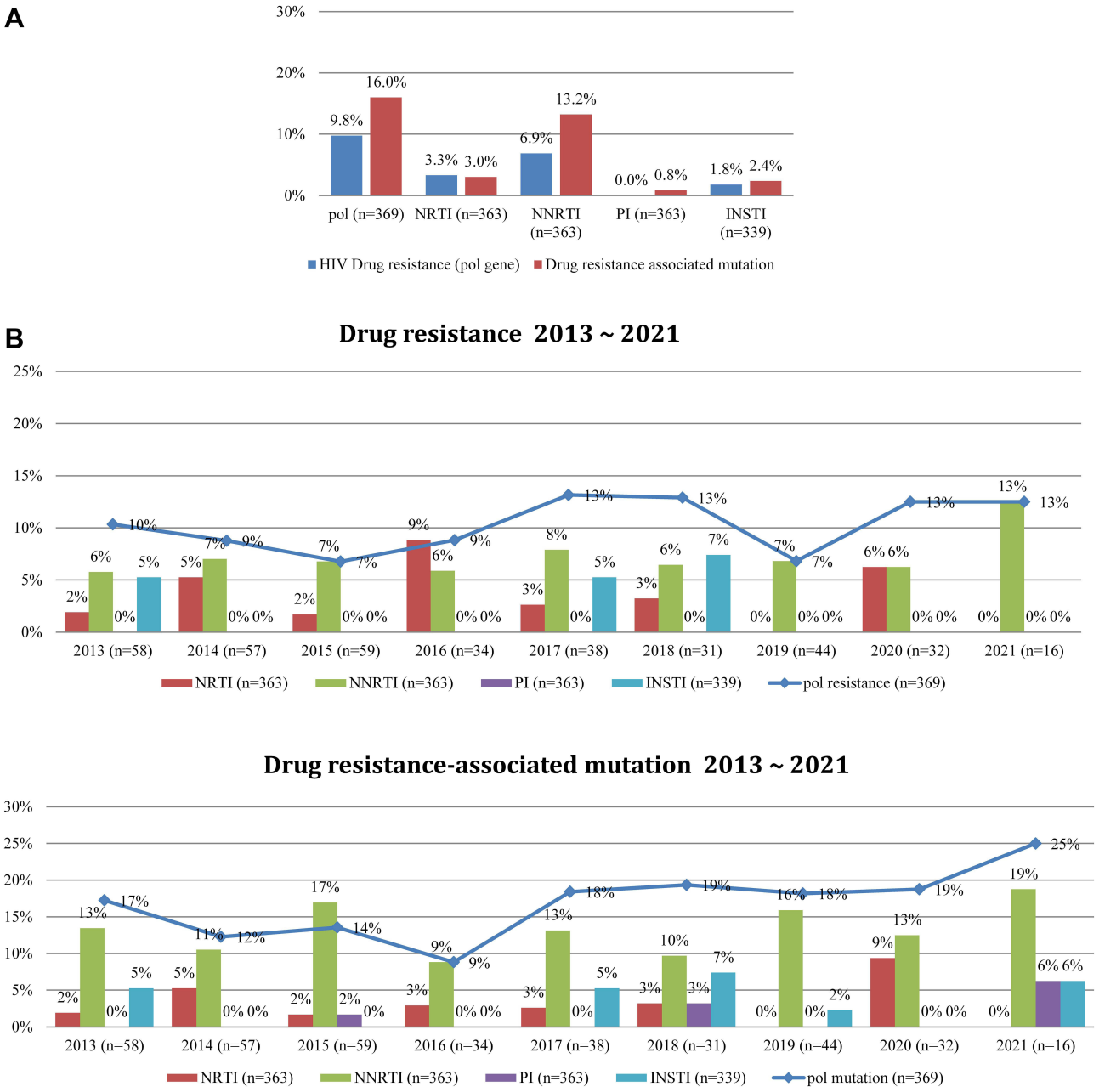

Figure 1 Prevalence of drug resistance (*pol*) and drug resistance-associated mutations (**A**) among the 369 HIV-1-infected treatment-naïve patients enrolled from 2013 to 2021 (**B**).

Abbreviations: INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

using the chi-square test or Fisher's exact test. A logistic regression model was used to analyze the odds ratios associated with *pol* resistance, and the factors in the univariate analysis with a p value of < 0.2 were further entered into a multivariate model.

General linear regression was used to analyze the temporal changes in the annual proportion of TDR overall and by type of antiretroviral drugs. A two-sided p value of < 0.05 was considered to be statistically significant. All statistical analyses were conducted using SPSS version 12.0 (SPSS Inc., Chicago, IL).

Results

A total of 369 patients were included, of whom 208 was enrolled from 2013 to 2016 and 161 were enrolled from 2017 to 2021. Their median age was 27 (interquartile range [IQR], 23–33) years. The median CD4 level was 311 (IQR, 201–431) cells/μL, and the median plasma viral load (log) was 4.71 (IQR, 4.34–5.11) copies/mL. Overall, 92.4% (341/369) of the patients had subtype B HIV-1 strains. Concurrent infection with hepatitis B was found in 7.1% (26/367) of the individuals, hepatitis C in 2.5% (9/367), syphilis in 31.4% (116/369), and amoeba (indirect hemagglutination, [IHA] ≥ 256) in 4.4% (15/341) (Table 1). The prevalence rate of *pol* resistance was 9.8% (36/369). The resistance rates to NRTIs, NNRTIs, PIs and NSTIs were 3.3%, 6.9%, 0% and 1.8%, respectively, and the mutation-associated drug resistance rates to NRTIs, NNRTIs, PIs and NSTIs were 3%, 13.2%, 0.8% and 2.4%, respectively (Figure 1). The individual prevalence rates of drug resistance to NRTIs, NNRTIs, PIs and NSTIs by year are also shown in Figure 1. The demographic information for the individuals enrolled from 2013–2016 and from 2017–2021 is summarized in Table 2. In brief, the 161 patients enrolled after the introduction of STRs (2017–2021) were older (28 (24–35) vs 26 (23–31), p=0.005), and had a lower plasma viral load (log) (4.6 (4.3–5.1) vs 4.8 (4.4–5.1), p=0.011), lower rate of subtype B HIV strain (88.2% vs 95.7%, adjusted hazard ratio [aHR] 0.338, CI 0.149–0.769, p=0.009), and lower rate of hepatitis B infection (3.1% vs 10.1%, aHR 0.286, CI 0.105–0.775, p=0.013) compared to the 208 patients enrolled from

Table 2 Comparison the Differences of Demographic Information Among 208 Patients Enrolled Between 2013 to 2016 and 161 Patients Between 2017 to 2021

	2013–2016 (n=208)	2017–2021 (n=161)	*p* value	aHR	95% C.I
Gender					
Male	208 (100)	157 (97.5)	0.035*		
Female	0 (0)	4 (2.5)			
Age (median, IQR)	26 (23–31)	28 (24–35)	0.005*		
Risk factor, n (%)					
MSM	202 (97.1)	155 (96.3)	0.770	0.767	0.243–2.425
Non-MSM	6 (2.9)	6 (3.7)			
Viral load (log) (median, IQR)	4.8 (4.4–5.1)	4.6 (4.3–5.1)	0.011*		
CD4 (median, IQR)	310 (201–432)	312 (198–429)	0.840		
Cut point of viral load (log)					
< 4	17 (8.2)	24 (15)	0.046*	0.507	0.262–0.980
≧ 4	190 (91.8)	136 (85)			
Cut point of CD4					
< 200	49 (23.7)	40 (25.2)	0.806	0.923	0.571–1.492
≧ 200	158 (76.3)	119 (74.8)			
HIV subtype, n (%)					
B	199 (95.7)	142 (88.2)	0.009*	0.338	0.149–0.769
Non-B	9 (4.3)	19 (11.8)			
pol resistance, n (%)					
Y	18 (8.7)	18 (11.2)	0.480	1.329	0. 667–2.645
N	190 (91.3)	143 (88.8)			
pol mutation, n (%)					
Y	28 (13.5)	31 (19.3)	0.153	1.533	0.877–2.680
N	180 (86.5)	130 (80.7)			

(*Continued*)

Table 2 (Continued).

	2013–2016 (n=208)	2017–2021 (n=161)	*p* value	aHR	95% C.I
NRTIs resistance, n=363					
Y	8 (4)	4 (2.5)	0.560	0.618	0.183–2.090
N	194 (96)	157 (97.5)			
NNRTIs resistance, n=363					
Y	13 (6.4)	12 (7.5)	0.835	1.171	0.519–2.641
N	189 (93.6)	149 (92.5)			
PIs resistance, n=363					
Y	0 (0)	0 (0)			
N	202 (100)	161 (100)			
INSTIs resistance, n=339					
Y	2 (1.1)	4 (2.6)	0.414	2.500	0.452–13.837
N	185 (98.9)	148 (97.4)			
INSTIs mutation, n=339					
Y	2 (1.1)	6 (3.9)	0.146	3.801	0.756–19.112
N	185 (98.9)	146 (96.1)			
Syphilis					
Y	70 (33.7)	46 (28.6)	0.311	0.789	0.504–1.233
N	138 (66.3)	115 (71.4)			
HAV Ab, n=366					
Y	22 (10.6)	28 (17.6)	0.065	1.797	0.985–3.280
N	185 (89.4)	131 (82.4)			
HBsAg, n=367					
Y	21 (10.1)	5 (3.1)	0.013*	0.286	0.105–0.775
N	186 (89.9)	155 (96.9)			
HCV Ab, n=367					
Y	5 (2.4)	4 (2.5)	1.000	1.036	0.274–3.922
N	202 (97.6)	156 (97.5)			
Amebiasis-IHA, n=341					
Y	5 (2.7)	10 (6.3)	0.122	2.376	0.794–7.105
N	177 (97.3)	149 (93.7)			
Toxoplasma gondii IgG, n=365					
Y	15 (7.2)	11 (7)	1.000	0.958	0.427–2.147
N	192 (92.8)	147 (93)			
CMV IgG, n=307					
Y	148 (99.3)	153 (96.8)	0.215	0.207	0.024–1.791
N	1 (0.7)	5 (3.2)			
Cryptococcus Ag, n=308					
Y	0 (0)	3 (1.9)	0.248		
N	149 (100)	156 (98.1)			

Note: *p<0.05.

Abbreviations: MSM, men who have sex with men; IQR, interquartile range; CI, confidence interval; aHR, adjusted hazard ratio; NTRI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor; IHA, indirect hemagglutination; CMV, cytomegalovirus; HAV Ab, hepatitis A virus antibody; HBs Ag, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; Y, yes; N, no.

2013–2016 (Table 2). The prevalence rates of drug resistance and drug resistance-associated mutations in the patients enrolled from 2013–2016 and 2017–2021 are shown in Figure 2. They were not statistically different (Mann–Whitney test). The prevalence rates of resistance to individual drugs and resistance-associated mutations are shown in Figures 3 and 4. The prevalence of tenofovir resistance was 0.8%, lamivudine 1.9%, doravirine 1.7%, and nevirapine 6.6%. There was no TDR to the second-generation INSTIs such as dolutegravir and bictegravir, however the resistance rates for raltegravir and elvitegravir

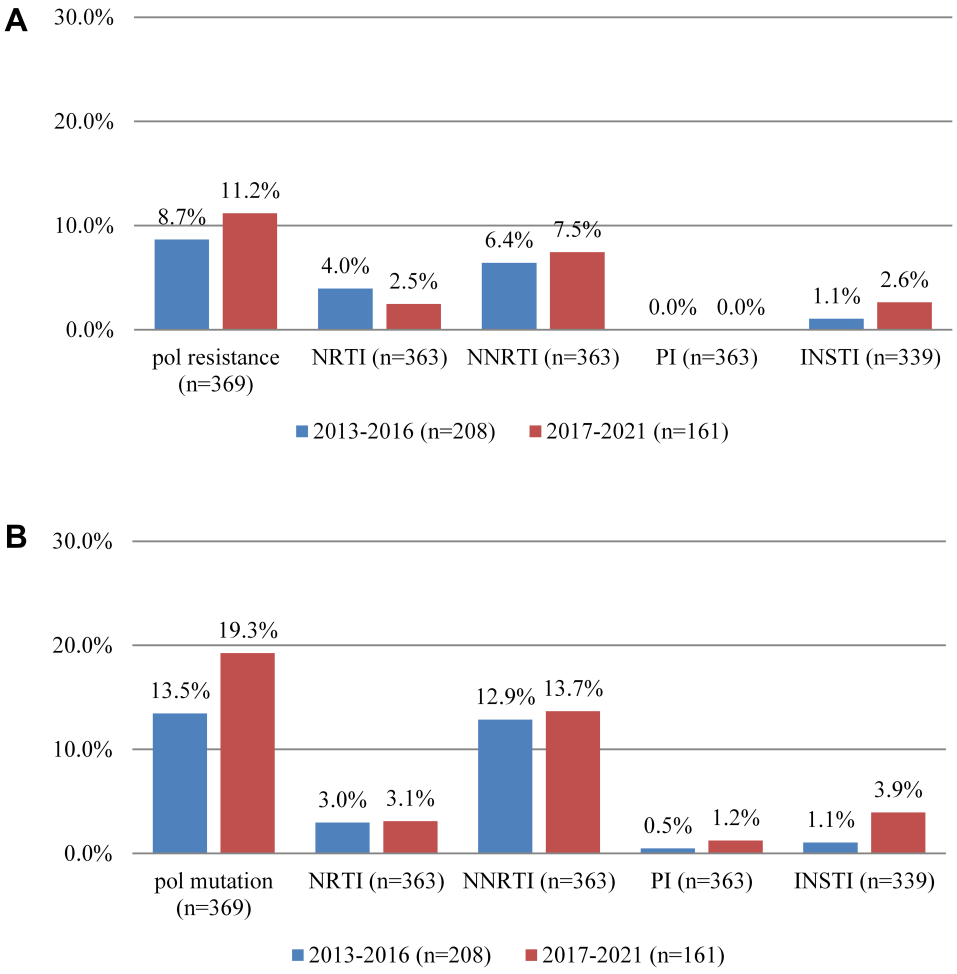

Figure 2 Comparisons of the prevalence of drug resistance (**A**) and drug resistance-associated mutations (**B**) between the two study periods (2013–2016 and 2017–2021).
Abbreviations: INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

were both 1.8% (Figure 3). The most common mutations associated with resistance to NRTIs were M184V (1.4%) and K65R (0.6%); for NNRTIs, V179D (4.1%), V106I (3%) and K103N (2.2%); for PIs, L89V (0.3%) and Q58E (0.3%); and for INSTIs, G163R (0.9%) and E157Q (0.6%). The risk factors associated with *pol* resistance are shown in Table 3. Logistic regression analysis showed that the patients with hepatitis C infection were more likely to have *pol* resistance (aHR 5.767, CI 1.232–26.991, p=0.026) (Table 4). The prevalence rate of *pol* resistance did not decrease after the implementation of STRs as the first-line therapy in 2017 (11.2% vs 8.7%, aHR 1.329, CI 0.667–2.645, p=0.480). In addition, no significant temporal changes were shown in the annual proportion of TDR mutations overall or by type of antiretroviral drug in general linear regression (Supplementary Tables 1–3).

Discussion

In this study, we found a stable trend of TDR after the universe use of STRs as the first-line therapy in our newly diagnosed HIV-1-infected patients. The total prevalence rate of *pol* resistance was 9.8% (36/369). The patients with hepatitis C infection were more likely to have *pol* resistance (aHR 5.767, CI 1.232–26.991, p=0.026).

Previous TDR prevalence studies in Taiwan have reported a drug resistance rate of around 10–12%.[7,8] However, Huang et al[15] reported a high prevalence rate of HIV TDR of 27.4% in Taiwan during 2018 to 2020 using PBMC provirus DNA genotypic testing. They could have overestimated the prevalence of TDR in Taiwan. Among the 164 patients enrolled in their study, the prevalence of TDR was 21.4% in 2018, 26.8% in 2019, and 34.1% in 2020, when the

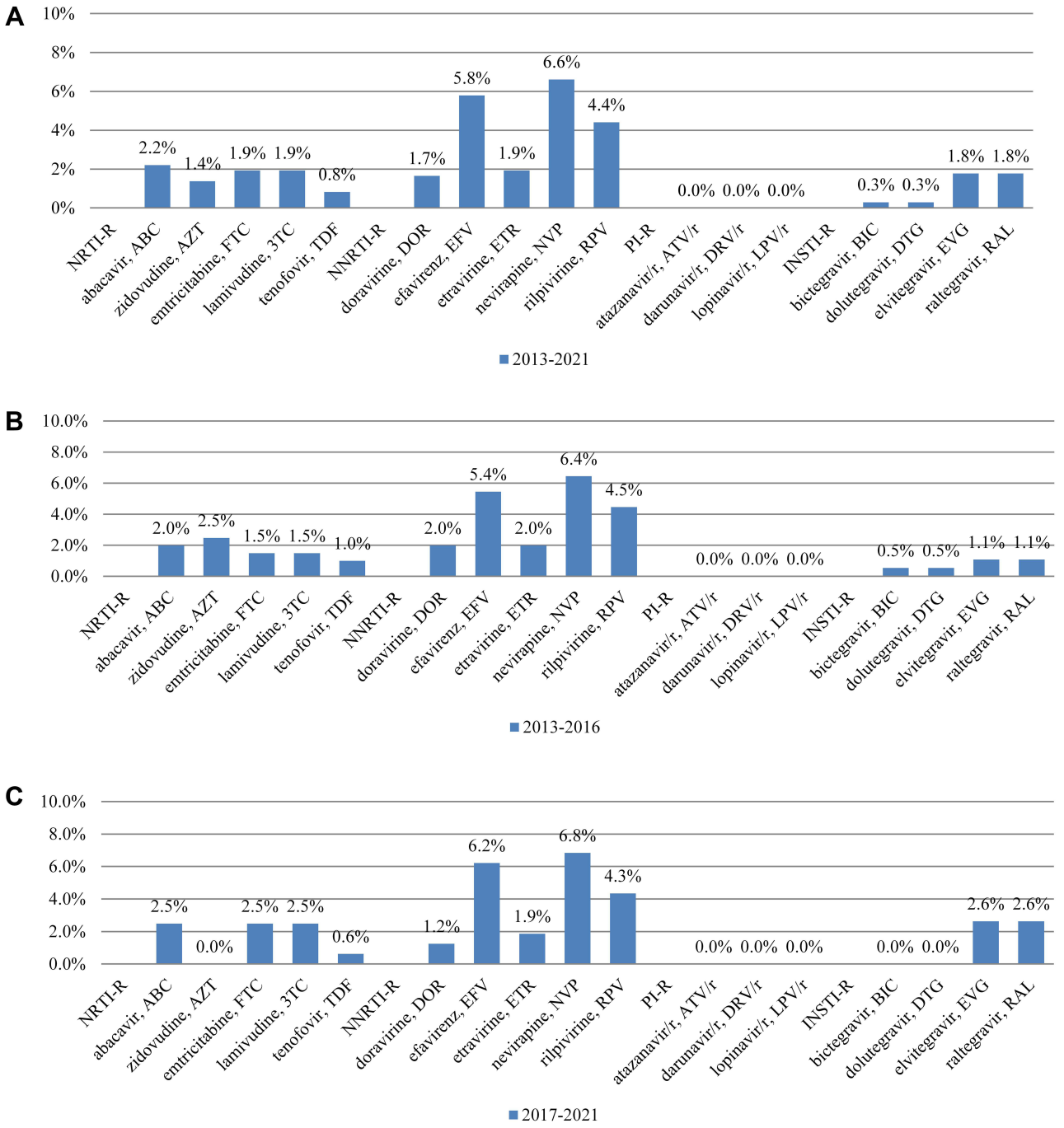

Figure 3 Differences in the prevalence of drug resistance to NRTIs, NNRTIs, PIs and INSTIs (**A**) between the two study periods (2013–2016 and 2017–2021) (**B** and **C**).
Abbreviations: STR, single-tablet regimen; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

resistance was interpreted using the Stanford University HIV drug resistance algorithm (https://hivdb.stanford.edu/). Interesting, they only compared the prevalence rate of TDR of provirus DNA with other studies using conventional plasma RNA Sanger drug resistance testing. Furthermore, they showed that the most common NNRTI mutation contributing to drug resistance was V179D/E (12.1%). However, based on the Stanford University HIV Drug Resistance algorithm (version 9, last update 2021-2-22)[19] which we used in this study, V179D/E is considered to be associated with a low level of resistance, and that it should not be considered to confer resistance if not combined with other mutations.

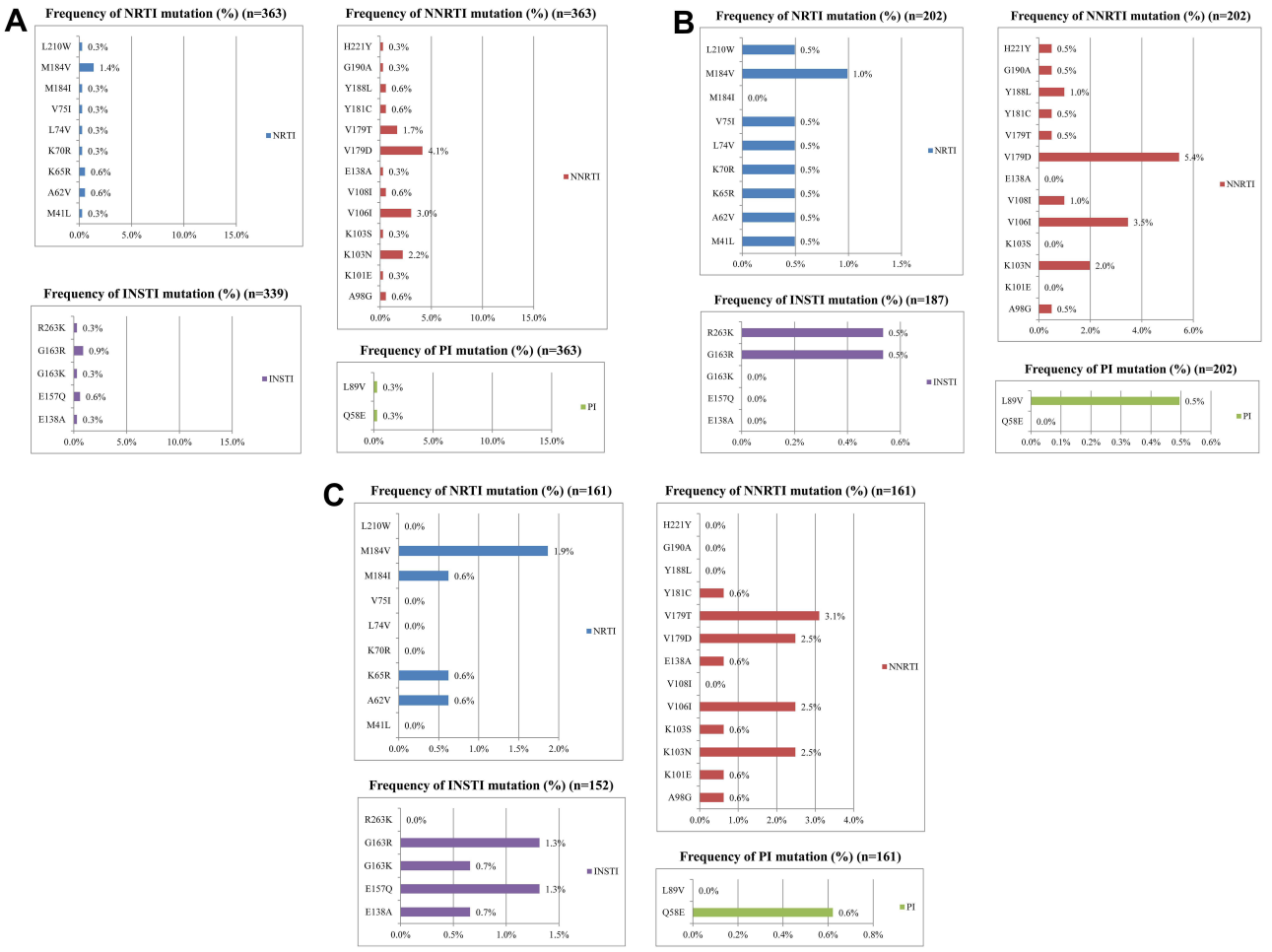

Figure 4 Differences in the prevalence of mutations associated with drug resistance to NRTIs, NNRTIs, PIs and INSTIs (**A**) between the two study periods (2013–2016 and 2017–2021) (**B** and **C**).

Abbreviations: STR, single-tablet regimen; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

It is not clear why the patients with hepatitis C infection were more likely to have *pol* resistance. None of our patients with hepatitis C infection were intravenous heroin drug abusers. It is possible that they became infected with hepatitis C through sexual contact, because HIV and hepatitis C infection share the same route of transmission through intense

Table 3 Risk Factors Associated with *pol* resistance Among 369 HIV-1 Infected Treatment Naïve Patients Enrolled Between 2013 to 2021

	***pol* Resistance (n=36)**	**Non-*pol* Resistance (n=333)**	***p* value**	**aHR**	**95% C.I**
Gender					
Male	36 (100)	329 (98.8)	1.000		
Female	0 (0)	4 (1.2)			
Age (median, IQR)	28 (24–33)	27 (23–33)	0.638		
Risk factor, n (%)					
MSM	34 (94.4)	323 (97)	0.330	0.526	0.111–2.502
Non-MSM	2 (5.6)	10 (3)			

(*Continued*)

Table 3 (Continued).

	***pol* Resistance (n=36)**	**Non-*pol* Resistance (n=333)**	***p* value**	**aHR**	**95% C.I**
Year of sampling					
2013–2016	18 (50)	190 (57.1)	0.480	1.329	0.667–2.645
2017–2021	18 (50)	143 (42.9)			
Viral load (log) (median, IQR)	4.7 (4.1–5.1)	4.7 (4.3–5.1)	0.657		
CD4 (median, IQR)	335 (236–487)	304 (198–430)	0.346		
Cut point of viral load (log)					
< 4	6 (16.7)	35 (10.6)	0.267	0.591	0.230–1.519
≧ 4	30 (83.3)	296 (89.4)			
Cut point of CD4					
< 200	6 (16.7)	83 (25.2)	0.311	1.680	0.676–4.179
≧ 200	30 (83.3)	247 (74.8)			
HIV subtype, n (%)					
B	36 (100)	305 (91.6)	0.093		
Non-B	0 (0)	28 (8.4)			
Syphilis					
Y	7 (19.4)	109 (32.7)	0.130	0.496	0.211–1.168
N	29 (80.6)	224 (67.3)			
Amebiasis-IHA, n=341					
Y	2 (6.1)	13 (4.2)	0.646	1.464	0.316–6.788
N	31 (93.9)	295 (95.8)			
Toxoplasma gondii IgG, n=365					
Y	3 (8.3)	23 (7)	0.732	1.209	0.345–4.245
N	33 (91.7)	306 (93)			
CMV IgG, n=307					
Y	30 (100)	271 (97.8)	1.000		
N	0 (0)	6 (2.2)			
Cryptococcus Ag, n=308					
Y	0 (0)	3 (1.1)	1.000		
N	30 (100)	275 (98.9)			
HAV Ab, n=366					
Y	2 (5.6)	48 (14.5)	0.199	0.346	0.080–1.486
N	34 (94.4)	282 (85.5)			
HBsAg, n=367					
Y	3 (8.3)	23 (6.9)	0.731	1.217	0.347–4.273
N	33 (91.7)	308 (93.1)			
HCV Ab, n=367					
Y	3 (8.3)	6 (1.8)	0.048*	4.924	1.177–20.606
N	33 (91.7)	325 (98.2)			

Note: *p<0.05.

Abbreviations: MSM, men who have sex with men; IQR, interquartile range; CI, confidence interval; aHR, adjusted hazard ratio; IHA, indirect hemagglutination; CMV, cytomegalovirus; HAV Ab, hepatitis A virus antibody; HBs Ag, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; Y, yes; N, no.

mucosally traumatic sexual practices.[20] Patients with HIV/hepatitis C co-infection have been reported to be more likely to show poor treatment compliance or low adherence to cART.[21]

Recently acquired hepatitis C infection has been associated with previous sexually transmitted infections, male sex, and sharing chemsex drugs among HIV-infected patients.[22] Information on chemsex was not available in our VCT clients, our patients had 31.4% concurrent infection with syphilis and we hypothesize that our patients became infected

Table 4 Risk Factors Associated with HIV Transmitted Drug Resistance Among 369 Patients Enrolled in This Study from 2013 to 2021

Variable	Number (%)	Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	P value	aHR (95% CI)	P value
HIV subtype					
B	341 (92.4)		0.093		0.998
Non-B	28 (7.6)				
Syphilis					
Y	7 (19.4)	0.496 (0.211–1.168)	0.130	0.516 (0.216–1.231)	0.136
N	29 (80.6)	1			
HAV Ab					
Y	2 (5.6)	0.346 (0.080–1.486)	0.199	0.364 (0.083–1.608)	0.183
N	34 (94.4)	1			
HCV Ab					
Y	3 (8.3)	4.924 (1.177–20.606)	0.048*	5.767 (1.232–26.991)	0.026*
N	33 (91.7)	1			

Notes: Statistical Analysis: Variables with $p<0.20$ in univariate analysis were considered for inclusion in logistic regression models. A $p<0.05$ was considered statistically significant. *$p<0.05$.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; HAV Ab, hepatitis A virus antibody; HCV Ab, hepatitis C virus antibody; Y, yes; N, no.

with hepatitis C and drug-resistant HIV during unprotected sexual behavior. Chemsex with reduced drug adherence and increased risk of drug-resistant strains may have contributed to the increased *pol* resistance in our patients.

The main strength of this study is that our study population was homogenous. They predominantly had subtype B, and they were all enrolled from the VCT program without selection bias. There are also several limitations to this study. First, this was a single center study and predominantly enrolled MSM who were our VCT clients. Therefore, our results may not apply to other populations such as heterosexuals or intravenous drug abusers. In a retrospective study analyzing the trends of antiretroviral drug resistance in treatment-naive patients with HIV-1 infections in northern Taiwan between 1999 and 2006, Chang et al reported that intravenous drug abusers and those infected with the CRF07_BC strain were at a lower risk of harboring drug-resistant viruses (4.1%).[23] Second, the policy of reimbursement for STRs as the first-line therapy was implemented in Taiwan in June 2016, and it may not be the only factor contributing to the prevalence of TDR. Other factors, such as treatment as prevention without any CD4 count or viral load limitations in 2016, and encouragement of same day/early cART implementation in 2018 may also have impacted the prevalence of resistance.[6] Finally, TDR prevalence data should be analyzed carefully. The presence of transmission clusters, different drug resistance interpretation tools, such as the French National Agency for AIDS Research (ANRS) HIV drug-resistance interpretation algorithm, HIVdb drug-resistance interpretation algorithm, IAS-USA HIV drug-resistance mutations list, Los Alamos National Laboratories HIV Sequence database, Rega Institute Drug-Resistance Interpretation Algorithm, WHO 2009 list of mutations, and even different editions of the Stanford University HIV Drug Resistance Database and also the type of drug resistance testing (provirus DNA vs plasma RNA) will all contribute to differences in the prevalence rate of TDR, making comparisons of the prevalence of drug resistance between different institutions difficult.

Conclusion

Our findings showed a stable prevalence rate of TDR despite the implementation of STRs as the first-line therapy in Taiwan in June 2016. The prevalence rate of *pol* resistance was 9.8% (36/369). The patients with hepatitis C infection were more likely to have *pol* resistance. Further large multi-center studies are needed to clarify if hepatitis C infection contributes to the increased HIV *pol* resistance.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Palella FJ, Armon C, Buchacz K, et al. The association of HIV susceptibility testing with survival among HIV-infected patients receiving antiretroviral therapy: a cohort study. *Ann Intern Med*. 2009;151:73–84. doi:10.7326/0003-4819-151-2-200907210-00003
2. Kuritzkes DR, Lalama CM, Ribaudo HJ, et al. Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naive HIV-1-infected subjects. *J Infect Dis*. 2008;197:867–870. doi:10.1086/528802
3. Wittkop L, Günthard HF, de Wolf F, et al. Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study. *Lancet Infect Dis*. 2011;11:363–371. doi:10.1016/S1473-3099(11)70032-9
4. Wu SB, Huang YC, Huang YF, Huang JC. Estimating HIV incidence, prevalence, and percent of undiagnosed infections in Taiwan using CD4 data. *J Formos Med Assoc*. 2022;121:482–489. doi:10.1016/j.jfma.2021.05.030
5. Taiwan center for diseases control HIV monthly report. Available from: https://www.cdc.gov.tw/File/Get/9dT-gsPC46au0kRYIw9Drw. Accessed April 1, 2022.
6. Huang YC, Sun HY, Chuang YC, et al. Short-term outcomes of rapid initiation of antiretroviral therapy among HIV-positive patients: real-world experience from a single-centre retrospective cohort in Taiwan. *BMJ Open*. 2019;9:e033246. doi:10.1136/bmjopen-2019-033246
7. Weng YW, Tsai HC, Lee SS, et al. Prevalence and associated factors for HIV-1 transmitted drug resistance in voluntary clients for counseling and testing in Southern Taiwan. *J Microbiol Immunol Infect*. 2016;49:487–493. doi:10.1016/j.jmii.2014.08.002
8. Lai CC, Liu WC, Fang CT, et al. Transmitted drug resistance of HIV-1 strains among individuals attending voluntary counselling and testing in Taiwan. *J Antimicrob Chemother*. 2016;71:226–234. doi:10.1093/jac/dkv284
9. Chang SY, Lin PH, Cheng CL, et al. Prevalence of Integrase Strand Transfer Inhibitors (INSTI) resistance mutations in Taiwan. *Sci Rep*. 2016;6:35779. doi:10.1038/srep35779
10. Tsai HC, Chen IT, Tsai KW, Lee SS, Chen YS. Prevalence of HIV-1 Integrase strand transfer inhibitor resistance in treatment-naïve voluntary counselling and testing clients by population sequencing and illumina next-generation sequencing in Taiwan. *Infect Drug Resist*. 2020;13:4519–4529. doi:10.2147/IDR.S273704
11. Bangsberg DR, Ragland K, Monk A, Deeks SG. A single tablet regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV+ homeless and marginally housed people. *AIDS*. 2010;24:2835–2840. doi:10.1097/QAD.0b013e328340a209
12. Cotte L, Ferry T, Pugliese P, et al. Effectiveness and tolerance of single tablet versus once daily multiple tablet regimens as first-line antiretroviral therapy - Results from a large French multicenter cohort study. *PLoS One*. 2017;12:e0170661. doi:10.1371/journal.pone.0170661
13. Airoldi M, Zaccarelli M, Bisi L, et al. One-pill once-a-day HAART: a simplification strategy that improves adherence and quality of life of HIV-infected subjects. *Patient Prefer Adherence*. 2010;4:115–125. doi:10.2147/ppa.s10330
14. Tsai HC, Chou PY, Wann SR, Lee SS, Chen YS. Chemokine co-receptor usage in HIV-1-infected treatment-naïve voluntary counselling and testing clients in Southern Taiwan. *BMJ Open*. 2015;5:e007334. doi:10.1136/bmjopen-2014-007334
15. Huang SW, Shen MC, Wang WH, et al. High prevalence of HIV-1 transmitted drug resistance and factors associated with time to virological failure and viral suppression in Taiwan. *J Antimicrob Chemother*. 2021;77:185–195. doi:10.1093/jac/dkab361
16. Canducci F, Barda B, Ceresola E, et al. Evolution patterns of raltegravir-resistant mutations after integrase inhibitor interruption. *Clin Microbiol Infect*. 2011;17:928–934. doi:10.1111/j.1469-0691.2010.03375.x
17. Canducci F, Ceresola ER, Boeri E, et al. Cross-resistance profile of the novel integrase inhibitor Dolutegravir (S/GSK1349572) using clonal viral variants selected in patients failing raltegravir. *J Infect Dis*. 2011;204:1811–1815. doi:10.1093/infdis/jir636
18. Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. update of the drug resistance mutations in HIV-1. *Top Antivir Med*. 2019;2019(27):111–121.
19. Stanford University HIV drug resistance database. Available from: https://hivdb.stanford.edu. Accessed June 2, 2021.
20. Chan DP, Sun HY, Wong HT, Lee SS, Hung CC. Sexually acquired hepatitis C virus infection: a review. *Int J Infect Dis*. 2016;49:47–58. doi:10.1016/j.ijid.2016.05.030
21. Braitstein P, Justice A, Bangsberg DR, et al. Hepatitis C coinfection is independently associated with decreased adherence to antiretroviral therapy in a population-based HIV cohort. *AIDS*. 2006;20:323–331. doi:10.1097/01.aids.0000198091.70325.f4
22. Gonzalez-Serna A, Macias J, Palacios R, et al.; HEPAVIR study group. Incidence of recently acquired hepatitis C virus infection among HIV-infected patients in southern Spain. *HIV Med*. 22;2021:379–386. doi:10.1111/hiv.13039
23. Chang SY, Chen MY, Lee CN, et al. Trends of antiretroviral drug resistance in treatment-naive patients with human immunodeficiency virus type 1 infection in Taiwan. *J Antimicrob Chemother*. 2008;61:689–693. doi:10.1093/jac/dkn002