

# 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.<sup>1–3</sup> 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.<sup>4–6</sup> 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

have sex with men (MSM) or bisexual, and 93% were aged 15–49 years.<sup>5</sup> 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).<sup>7,8</sup> 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,<sup>9</sup> and 0.9% in southern Taiwan from 2013 to 2017.<sup>10</sup> STRs have been associated with better drug adherence,<sup>11</sup> decreased risk of resistance mutations,<sup>12</sup> and improved quality of life compared to multiple tablet regimens.<sup>13</sup> 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.<sup>14,15</sup> 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).<sup>16,17</sup> The International Antiviral Society

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

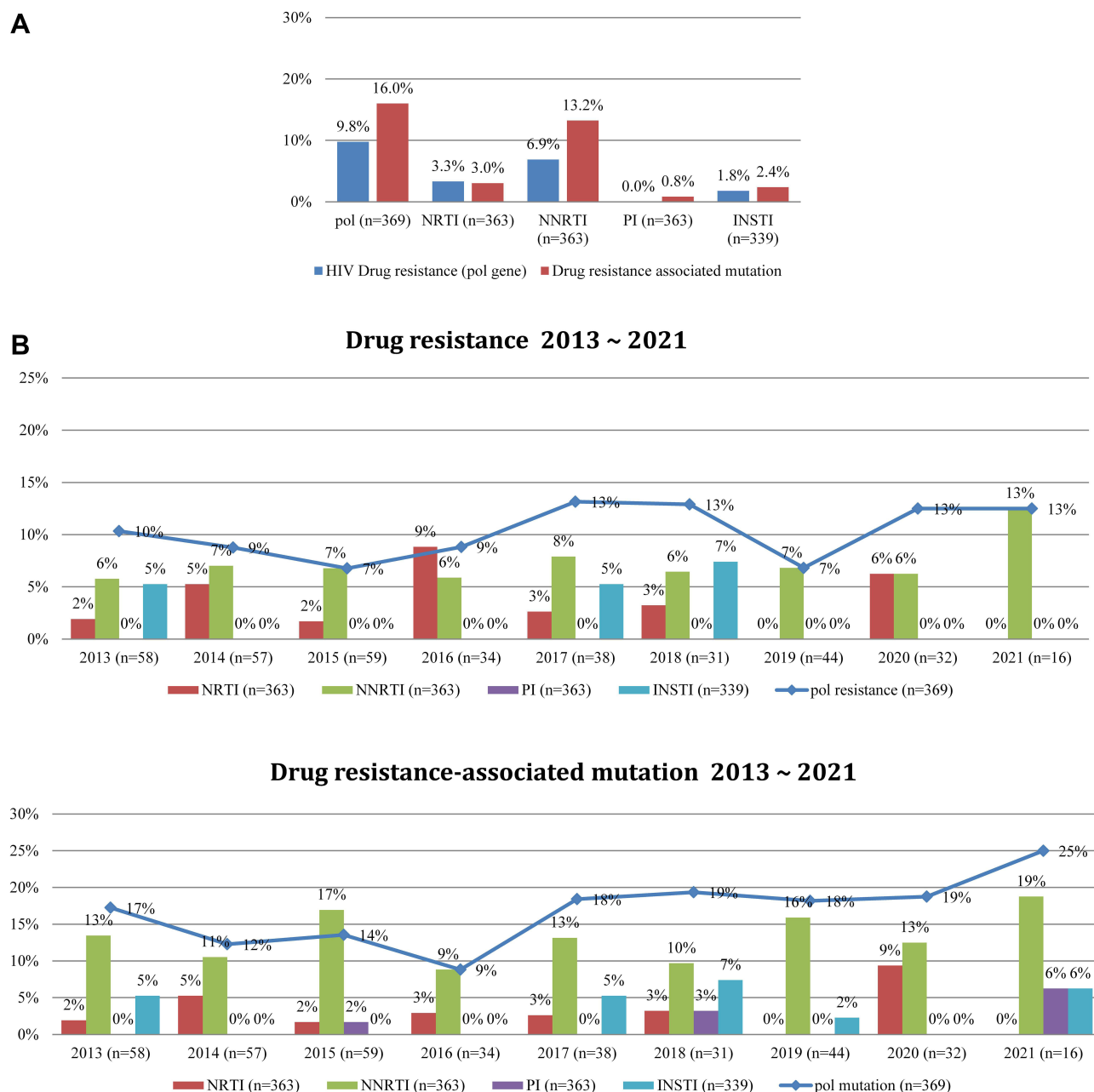
| Parameters                         |              | Patient Numbers (%) |
|------------------------------------|--------------|---------------------|
| Gender                             | Male         | 365 (98.9)          |
|                                    | Female       | 4 (1.1)             |
| Age                                | Median (IQR) | 27 (23–33)          |
| Risk factor                        | Heterosexual | 11 (3)              |
|                                    | MSM          | 357 (96.7)          |
|                                    | IVDU         | 1 (0.3)             |
| <i>pol</i> resistance              | Y            | 36 (9.8)            |
|                                    | N            | 333 (90.2)          |
| <i>pol</i> 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<sup>18</sup> 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.<sup>19</sup>

## 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 I** 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/ $\mu$ L, 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]  $\geq 256$ ) 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) | <i>p</i> 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 |
| $\geq 4$                       | 190 (91.8)        | 136 (85)          |                |       |             |
| Cut point of CD4               |                   |                   |                |       |             |
| < 200                          | 49 (23.7)         | 40 (25.2)         | 0.806          | 0.923 | 0.571–1.492 |
| $\geq 200$                     | 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)         |                |       |             |
| <i>pol</i> resistance, n (%)   |                   |                   |                |       |             |
| Y                              | 18 (8.7)          | 18 (11.2)         | 0.480          | 1.329 | 0.667–2.645 |
| N                              | 190 (91.3)        | 143 (88.8)        |                |       |             |
| <i>pol</i> 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)

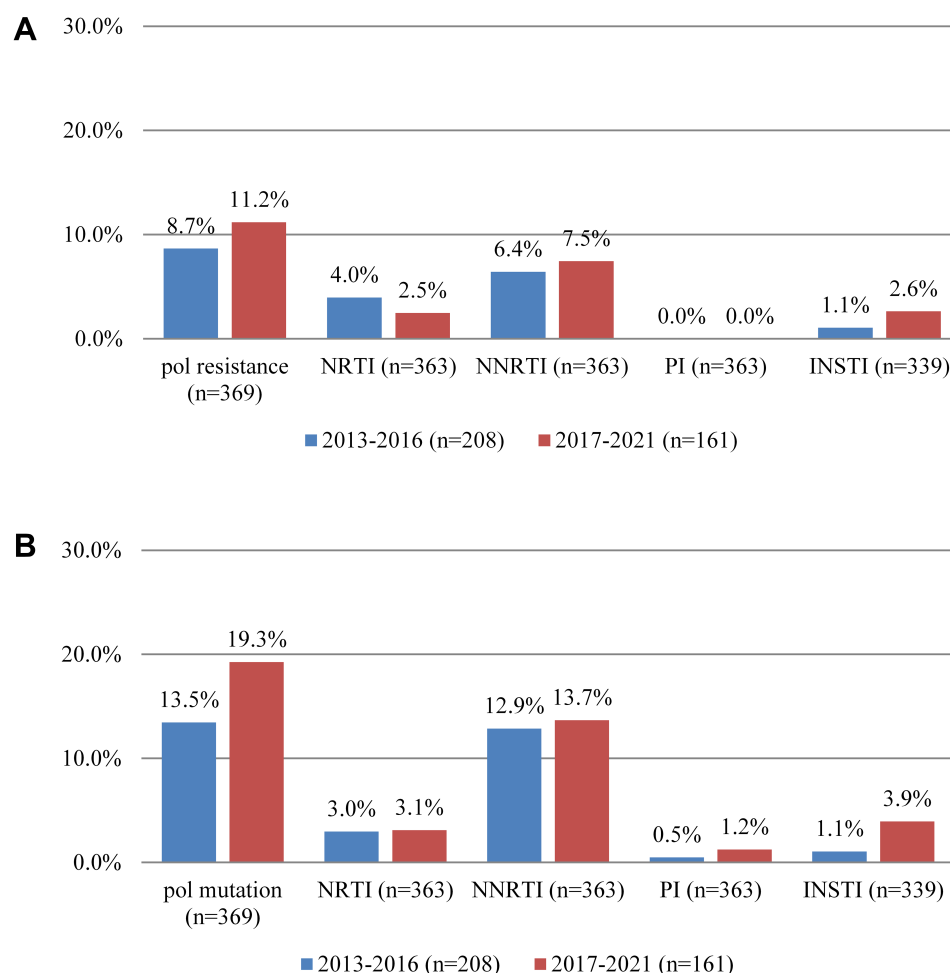
**Table 2** (Continued).

|                                     | 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)        |         |       |              |
| <i>Toxoplasma gondii</i> 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.

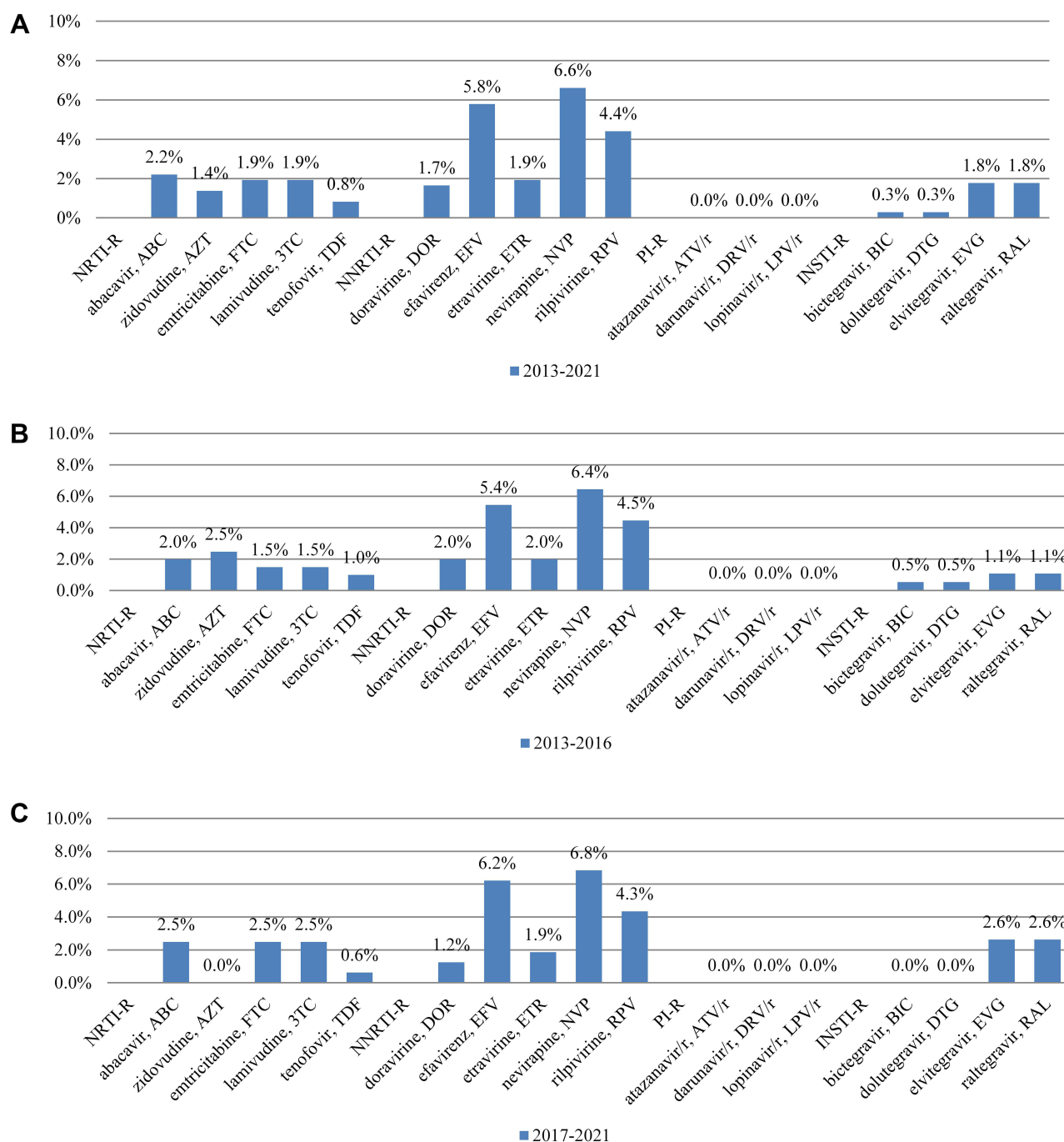
were both 1.8% (Figure 3). The most common mutations associated with resistance to NRTIs were M184V (1.4%) and K65R (0.6%); for NNRTIs, V179D (4.1%), V106I (3%) and K103N (2.2%); for PIs, L89V (0.3%) and Q58E (0.3%); and for INSTIs, G163R (0.9%) and E157Q (0.6%). The risk factors associated with *pol* 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%.<sup>7,8</sup> However, Huang et al<sup>15</sup> 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

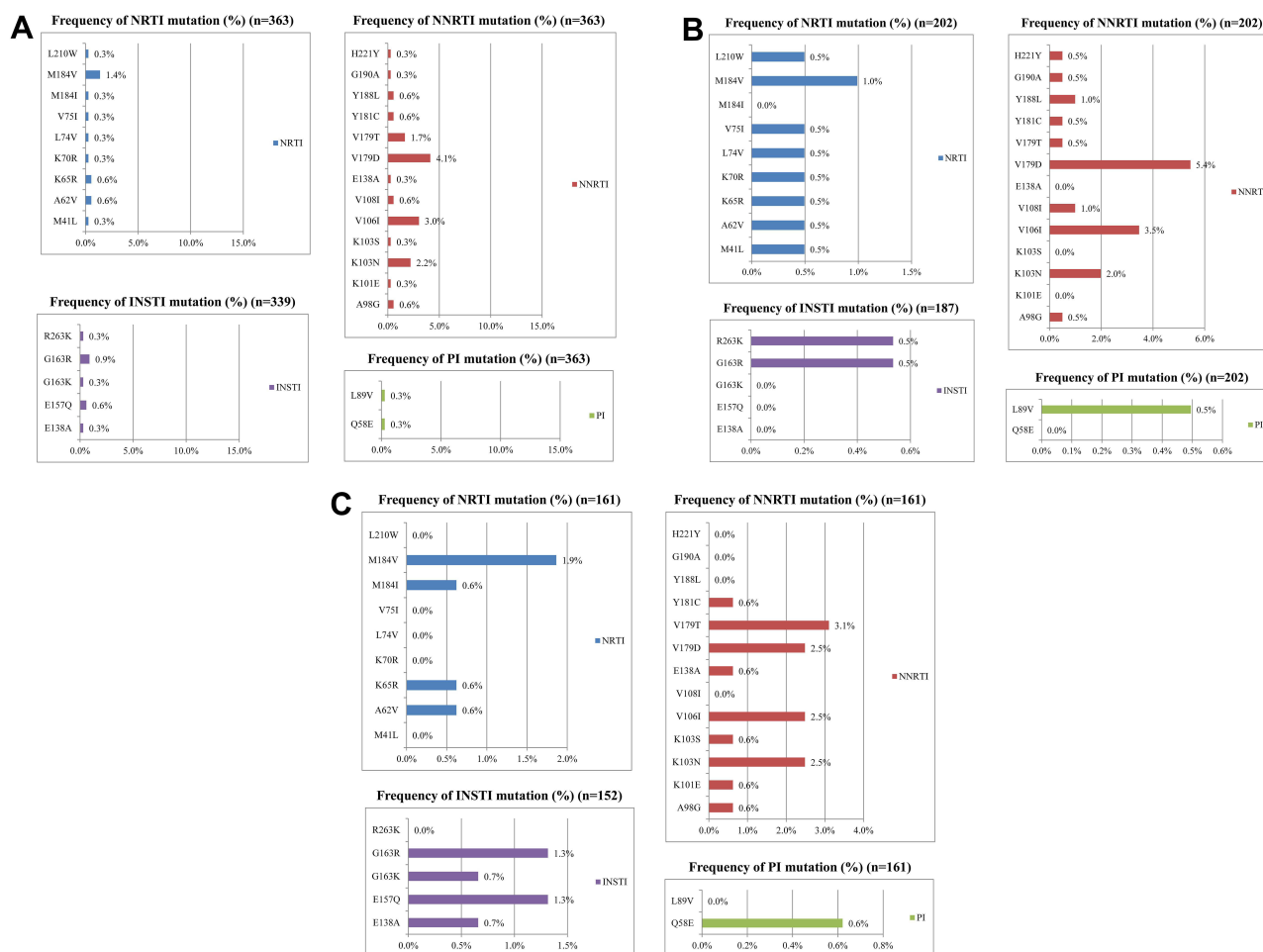




**Figure 3** Differences in the prevalence of drug resistance to NRTIs, NNRTIs, PIs and INSTIs (**A**) between the two study periods (2013–2016 and 2017–2021) (**B** and **C**). **Abbreviations:** STR, single-tablet regimen; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside 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)<sup>19</sup> 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-I Infected Treatment Naïve Patients Enrolled Between 2013 to 2021

|                    | <i>pol</i> Resistance (n=36) | Non- <i>pol</i> 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).

|                                     | <b>pol Resistance<br/>(n=36)</b> | <b>Non-pol Resistance<br/>(n=333)</b> | <b>p value</b> | <b>aHR</b> | <b>95% C.I</b> |
|-------------------------------------|----------------------------------|---------------------------------------|----------------|------------|----------------|
| 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)                            |                |            |                |
| <i>Toxoplasma gondii</i> 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.<sup>20</sup> Patients with HIV/hepatitis C co-infection have been reported to be more likely to show poor treatment compliance or low adherence to cART.<sup>21</sup>

Recently acquired hepatitis C infection has been associated with previous sexually transmitted infections, male sex, and sharing chemsex drugs among HIV-infected patients.<sup>22</sup> 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)  | I                    |         |                       |         |
| 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)  | I                    |         |                       |         |
| 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)  | I                    |         |                       |         |

**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-naïve 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%).<sup>23</sup> 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.<sup>6</sup> 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.

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