



Surveillance of transmitted HIV drug resistance among newly diagnosed, treatment-naïve individuals at a county HIV clinic in Santa Clara County



William Chan^{a,*}, Wilson Ly^{b,c}

^a School of Medicine, University of California, Irvine, CA, USA

^b School of Medicine, University of California, San Francisco, CA, USA

^c Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA, USA

ARTICLE INFO

Keywords:

Infectious disease
Antiretroviral agents
HIV
Drug resistance
Transmitted drug resistance

ABSTRACT

Introduction: To our knowledge, HIV transmitted drug resistance (TDR) patterns have not been characterized specifically in Santa Clara County (SCC), California, one of the largest counties by population in the United States. Understanding TDR here will help improve antiretroviral therapy outcomes and prevent future transmission events.

Material and methods: This is a retrospective analysis of TDR among patients establishing care at a county HIV clinic at the Santa Clara Valley Health and Hospital System. We identified 206 treatment-naïve individuals who were newly diagnosed with HIV between 2006–2013. Using these individuals, we assessed the prevalence and temporal trends of total TDR and TDR to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs).

Results: We identified a total TDR prevalence of 17.5% during 2006–2013 (7.3% NNRTI, 6.8% NRTI, 2.4% PI, 2.9% INSTI) with 1.9% exhibiting dual-class resistance. Total TDR prevalence initially ranged between 19.0–22.7% during 2006–2008 and decreased to within 10.5–16.2% during 2011–2013, though this decrease was not significant ($p = 0.42$). NRTI TDR decreased from 22.7% in 2006 to 5.3% in 2013 ($p = 0.02$), and NNRTI TDR appeared to fluctuate between 2.7–13.5% ($p = 0.96$). PI and INSTI TDR remained low, with noted E138A prevalence of 2.9%.

Conclusions: The prevalence of TDR was substantial among newly diagnosed, treatment-naïve individuals establishing care at a SCC-based county HIV clinic from 2006 to 2013. This, along with the presence of transmitted mutations associated with INSTI resistance, warrants continued surveillance of TDR in SCC and use of baseline genotyping prior to antiretroviral therapy initiation.

1. Introduction

Human immunodeficiency virus (HIV) transmitted drug resistance (TDR) occurs from the transmission of drug-resistant HIV from one individual to another [1]. The prevalence of TDR varies with geographical location in the United States (US), with some national estimates of around 14% in the last two decades [2, 3]. Among the four commonly used antiretroviral drug classes, TDR to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTIs) appear to be more common than protease inhibitor (PI) TDR [4]. There are few studies surveying integrase strand transfer inhibitor (INSTI) TDR in the US and available data suggest a low prevalence

or absence of this [5, 6, 7]. In addition, INSTI resistance mutations are not routinely included in standard baseline resistance testing, but they are expected to increase in the future as INSTIs are currently a recommended antiretroviral therapy (ART) by the US Department of Health and Human Services [8, 9].

Currently, baseline genotype testing before ART initiation is a standard of care to increase treatment success. However, these tests are limited by their sensitivity to detect resistant HIV and turnaround time of up to two weeks [9]. With regards to the sensitivity of genotype sequencing, resistant viruses may be missed as individuals with HIV may have been infected for years prior to their initial diagnosis [10]. During this time, the proportion of resistant viruses may decrease as reversion to

* Corresponding author.

E-mail address: whchan1@uci.edu (W. Chan).

<https://doi.org/10.1016/j.heliyon.2019.e02411>

Received 20 November 2018; Received in revised form 4 June 2019; Accepted 29 August 2019

2405-8440/© 2019 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

wild type occurs as a mechanism for restoring viral fitness and replicative capacity [11, 12]. As typical genotype assays are unable to reliably detect mutants amounting to less than 10–20% of the plasmatic viral population [9], low levels of resistant viruses may remain undetected and the potential for re-proliferation and treatment failure under the selective pressure of ART exists [13, 14]. Further, as fully exploring the HIV reservoir is impractical, clinicians may have to resort to their own projection or turn to epidemiological data to predict ART efficacy. This highlights the importance of characterizing local TDR patterns especially in the setting of the test-and-treat model, where newly diagnosed patients are started on ART prior to the availability of genotype results.

Knowledge of communal TDR patterns is important to effective HIV management, as newly infected, treatment-naïve patients with TDR are at an increased risk of virologic failure after initial ART [15]. TDR may also limit treatment options such as the “one-pill-once-a-day” regimens and post-exposure prophylaxis (PEP), which may complicate ART adherence and the treatment of initial HIV exposure [16, 17].

To our knowledge, TDR patterns have yet to be characterized specifically in Santa Clara County (SCC), California, one of the largest counties by population in the United States, with a population of over 1.9 million [18]. This is important, as national epidemiological data may or may not be applicable to HIV-infected persons living in SCC. The PACE (Partners in AIDS Care and Education) clinic (PC) is a county HIV clinic at the Santa Clara Valley Health and Hospital System that provides care to these individuals, many of whom are Hispanic/Latino and men who have sex with men (MSM). In the general United States HIV population, MSM also account for most new HIV diagnoses, but Blacks/African Americans are the predominant race/ethnicity affected by HIV transmission [19].

In this retrospective study, we aim to describe the prevalence and trends of HIV TDR among patients establishing care at PC.

2. Materials and methods

2.1. Study population and data collection

Through retrospective analysis of available health records at PC, we identified 206 individuals to include into our study sample (Fig. 1). Our

inclusion criteria were as follows: 1) Newly diagnosed with HIV between 2006–2013 2) Available baseline genotype data performed within 12 months of diagnosis 3) ART-naïve prior to diagnosis and baseline genotyping. The following information was collected from their health records: diagnosis date, genotype collection and result dates, genotype results, date of initial ART, baseline CD4 count (cells/ μ L), baseline plasma HIV-1 RNA Q_t PCR level or viral load (log₁₀ copies/mL), and HIV subtype. Demographic information was also collected which included sex, age at HIV diagnosis, race/ethnicity, and acquisition risk factors.

2.2. Identifying transmitted drug resistance

NRTI, NNRTI, and PI transmitted drug resistance mutations (TDRMs) were identified using the World Health Organization TDR surveillance guidelines updated in 2009 [20]. INSTI TDRMs were identified using the bolded INSTI mutations listed on the Stanford University HIV Drug Resistance Database (HIVdb version 8.8) [21]. Dual, triple, and quadruple-class resistance were defined as individuals with mutations conferring resistance to two, three, and four drug classes, respectively.

2.3. Statistical analysis

TDR prevalence was calculated from the proportion of individuals with TDR among all participants meeting inclusion criteria. 95% confidence intervals (CI) were calculated using the exact binomial method. We used the Cochran-Armitage test for trend to assess temporal trends in TDR using Stata software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.). To characterize the study sample, continuous variables were presented as medians with their interquartile ranges (IQR) and categorical variables were presented as frequencies with their proportions.

2.4. Ethics statement

The Santa Clara Valley Medical Center Institutional Review Board, Federalwide Assurance #00001437, reviewed and approved this study as a quality improvement project.

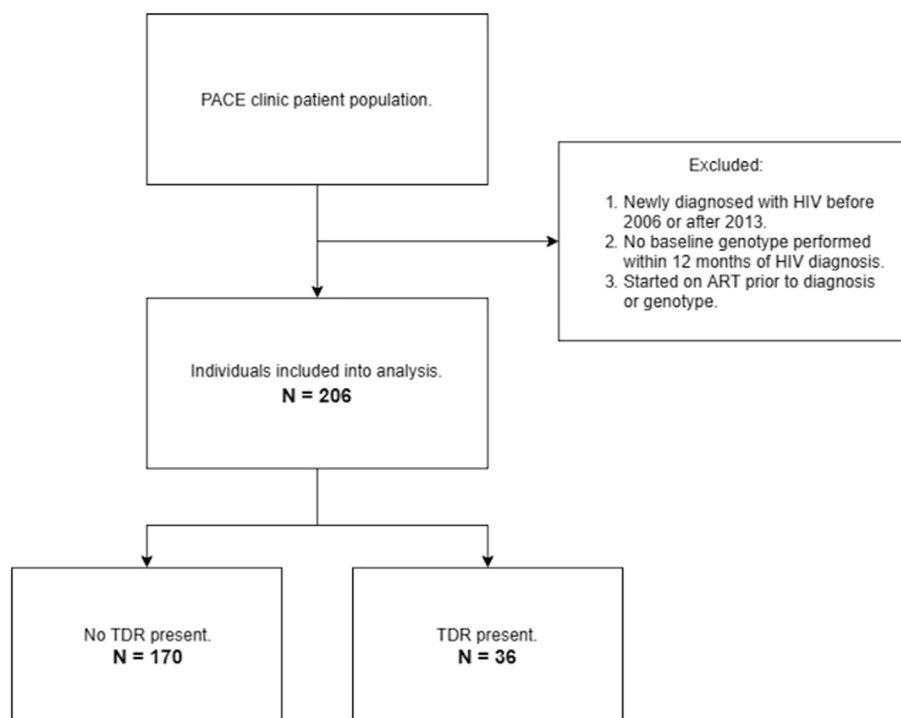


Fig. 1. Inclusion process and composition of study sample.

3. Results

3.1. Study population

206 individuals were included into our study sample, described in Table 1. The median age of all participants was 37 years (IQR 30.75–45 years). 85.0% were male with a median age of 38 (IQR 31–45), and 15.0% were female with a median age of 34 (IQR 30–43). More than half were Hispanic/Latino (51.0%), 20.9% Asian, 17.5% White, and 7.8% Black. 46.1% were MSM, 31.6% heterosexual, and 5.8% reported intravenous drug use (IVDU). We obtained baseline CD4 cell counts and viral loads for 203/206 (98.5%) individuals. The median CD4 cell count and viral load at diagnosis were 210 cells/ μ L (IQR 50–350) and 4.81 log₁₀ copies/mL (IQR 4.38–5.36), respectively. Only 37/206 (18.0%) individuals had available subtype data, and of those available 36/37 were subtype B and 1/37 was subtype C. The median time delay between diagnosis and availability of genotype data was 29 days (IQR 18–40).

3.2. Prevalence of TDR

The overall prevalence of TDR was 17.5% (95% CI: 12.6, 23.4) during 2006–2013 with 1.9% exhibiting dual-class resistance and none with triple or quadruple-class resistance (Fig. 2). Prevalence of TDR to NNRTIs was 7.3%, 6.8% for NRTIs, 2.4% for PIs, and 2.9% for INSTIs. K103N (5.8%) comprised of the majority of NNRTI TDRMs. The prevalence of individual NRTI TDRMs was low at <3%, the two most frequent being K70R (2.4%) and M41L (1.9%). The prevalence of individual PI TDRMs was generally <0.5% except for L90M (1.0%). The only mutation associated with INSTI resistance was E138A (2.9%).

Table 1

Characteristics of individuals meeting inclusion criteria. IQR = Interquartile range. IVDU = Intravenous drug use. MSM = Men who have sex with men. TDR = Transmitted drug resistance.

	No TDR	TDR	Total
Total, frequency (%)	170 (82.5)	36 (17.5)	206 (100)
Sex, frequency (%)			
Male	145 (70.4)	30 (14.6)	175 (85.0)
Female	25 (12.1)	6 (2.9)	31 (15.0)
Age, median (IQR)			
Total	37 (31–44.25)	41 (28.25–48.5)	37 (30.75–45)
Male	37 (31–44.5)	41.5 (29.5–49)	38 (31–45)
Female	34 (30.5–44)	31 (27.5–41.25)	34 (30–43)
Race/Ethnicity, frequency (%)			
Hispanic/Latino	81 (39.3)	24 (11.7)	105 (51.0)
Non-Hispanic White	28 (13.6)	8 (3.9)	36 (17.5)
Non-Hispanic Black	15 (7.3)	1 (0.5)	16 (7.8)
Asian	41 (19.9)	2 (1.0)	43 (20.9)
Pacific Islander	2 (1.0)	0 (0)	2 (1.0)
Other	2 (1.0)	0 (0)	2 (1.0)
Unknown	1 (0.5)	1 (0.5)	2 (1.0)
Risk Factor, frequency (%)			
MSM	74 (35.9)	21 (10.2)	95 (46.1)
Heterosexual	54 (26.2)	11 (5.3)	65 (31.6)
IVDU	9 (4.4)	3 (1.5)	12 (5.8)
Other	1 (0.5)	0 (0)	1 (0.5)
Unknown	35 (17.0)	4 (1.9)	39 (18.9)
CD4 Count (cells/μL)			
Median (IQR)	215 (50–380)	190 (50–330)	210 (50–350)
HIV-1 RNA Q_t-PCR (log₁₀ copies/mL)			
Median (IQR)	4.83 (4.38–5.33)	4.72 (4.38–5.44)	4.81 (4.38–5.36)
Subtype, frequency (%)			
B	30 (14.6)	6 (2.9)	36 (17.5)
C	1 (0.5)	0 (0)	1 (0.5)
Unknown	139 (67.5)	30 (14.6)	169 (82.0)
Delay Between Diagnosis and Genotype Availability (days)			
Median (IQR)	29 (18.75–41)	25.5 (15–38.75)	29 (18–40)

3.3. Temporal trends of TDR

Total TDR prevalence ranged between 19.0–22.7% during 2006–2008, dropped to 8.8% in 2009, rose again to 27.0% in 2010, then decreased to 10.5–16.2% during 2011–2013 (Fig. 3). The overall decrease was not significant ($p = 0.42$). NRTI TDR decreased from 22.7% in 2006 to 5.3% in 2013 ($p = 0.02$). The prevalence of NNRTI TDR was initially 9% in 2006, rising to over 13% in 2010, then falling to under 3% by 2012. NNRTI TDR would rise again to 10.5% in 2013, though no significant trend was observed ($p = 0.96$). PI TDR remained low and stable ($p = 0.75$). The presence of E138A, a mutation associated with INSTI resistance, was noted from 2007–2013, however no significant trend was observed ($p = 0.74$).

4. Discussion

To our knowledge, this is the first study to characterize HIV TDR patterns specifically in SCC. We identified an overall TDR prevalence of 17.5% between 2006 and 2013, which is high relative to national surveillance data collected within a similar period [2, 3]. A recent study surveying TDR in a large northern Californian cohort described a TDR prevalence of 13.9% during 2003–2016 [22]. However, the study cohort appears to best represent northern California's insured population, excluding those covered by government assistance programs (Medi-Cal) and the uninsured [23]. This highlights socioeconomic factors as potential reasons for a higher prevalence of TDR seen at PC. As PC is associated with a public hospital system, its patients often are covered by government programs (namely Medi-Cal and Ryan White) and hail from disadvantaged socioeconomic backgrounds, such as lower income households and underserved groups. It is well-documented that these circumstances are associated with poorer HIV outcomes [24], stemming from factors such as medication noncompliance and delays in diagnosis which may promote the selection and transmission of resistant HIV [10, 25, 26, 27].

Among the four classes of TDR studied, NNRTI TDR was the most prevalent, which is consistent with prior studies [4, 7, 22, 28, 29]. This may be attributable to the persistence of NNRTI resistance mutations in ART-naïve settings, compounded by the long lapse of time often seen between HIV infection to diagnosis [10, 30]. The predominance of NNRTI TDR in our study period also coincides with the usage pattern of Atripla (EFV/TDF/FTC), an Efavirenz-based, single tablet antiretroviral medication. Atripla was commonly prescribed since its approval by the US Food and Drug Administration (FDA) in 2006, and its widespread use likely led to the preeminence of NNRTI TDR (K103N in particular) [31].

We also observed a relatively high prevalence of NRTI TDR, second only to NNRTI TDR, which is consistent with several other studies of TDR in the US [4, 7, 22, 28]. Most notably, we observed a significant decrease in NRTI TDR during our study period, and this pattern appears to be driven by the thymidine analog mutations (TAMs). Thus, the higher prevalence of NRTI TDR earlier in our study period suggests that there may have been prior widespread usage of the thymidine analogs AZT and d4T [21], until 2004 when TDF/FTC (Truvada) was approved by the US FDA [32]. This likely led to a correspondent decrease in TAM prevalence and NRTI TDR, as regimens containing Truvada such as Atripla became more popular [31]. Interestingly, we would expect the subsequent appearance of TDF/FTC-associated mutations, but we only observed one case of M184V in 2006 and zero cases of K65R, which are major NRTI mutations selected for by FTC/3TC and TDF, respectively [21]. This may be due to the lower selectivity of FTC for M184V and the inhibitive action of M184V and K65R on viral fitness [33, 34]. Further, a review of K65R suggested that the mutation is uncommon, and individuals infected with subtype C HIV may be at a greater risk of acquiring the mutation [35]. Unfortunately, we were unable to fully characterize the HIV subtypes of our study sample, so it is unclear if the absence of K65R in our study is related to our subtype distribution. It is important to note, however, that subtype B is predominant in the US [36].

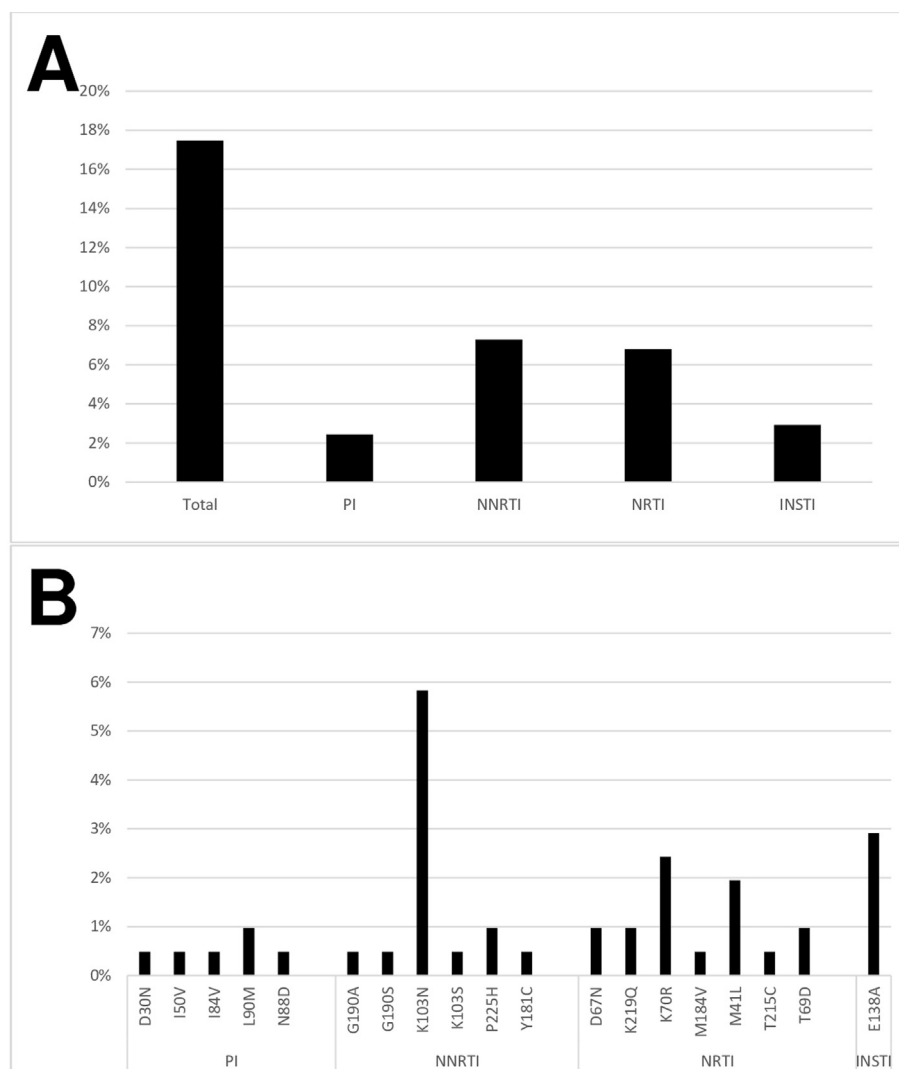


Fig. 2. Prevalence of total transmitted drug resistance (TDR) and TDR by drug class among 206 individuals meeting inclusion criteria, 2006–2013 (A). Prevalence of individual resistance mutations by drug class, 2006–2013 (B). INSTI = Integrase strand transfer inhibitor. NNRTI = Non-nucleoside reverse transcriptase inhibitor. NRTI = Nucleoside reverse transcriptase inhibitor. PI = Protease inhibitor.

The low prevalence of PI TDR and the predominance of L90M among PI TDRMs is consistent with other US-based studies [7, 22, 28]. The low prevalence of PI TDR is likely attributable to the high genetic barrier of PIs [37, 38]. We also found evidence of mutations associated with INSTI resistance, beginning in 2007 and coinciding with the approval of the INSTI Raltegravir (RAL) [39]. E138A is an accessory mutation that confers major resistance to RAL and EVG in combination with Q148 mutations [40, 41]. Although there is no indication of a significant, underlying trend, it should be noted that instances of E138A doubled in 2010–2013 compared to 2007–2009, which could be a result of increasing INSTI usage. Given our finding of a mutation associated with INSTI resistance, testing for INSTI resistance during routine genotyping should be considered.

One limitation of this study is that our study sample is not a comprehensive representation of the population at large, so our results may not fully reflect SCC's TDR patterns. Another limitation is that we relied on individuals' diagnosis dates as our time indicator for HIV acquisition, although this may be inaccurate as some individuals may have been infected for years prior to seeking care [10]. During this time, resistant HIV may have reverted to undetectable levels [11, 12], leading to an underestimation of TDR prevalence.

Despite these limitations, this study to our knowledge is the first to describe HIV TDR patterns specifically in SCC. We revealed a high prevalence of TDR with the presence of mutations associated with INSTI resistance. Our findings emphasize the importance of baseline genotyping prior to initial treatment and the continued surveillance of local TDR patterns to optimize present and future treatment strategies.

5. Conclusions

TDR prevalence is substantial among newly diagnosed, treatment-naïve individuals establishing care at the PACE clinic, a county HIV clinic in Santa Clara County, California. This, along with the presence of transmitted mutations associated with INSTI resistance, warrants close surveillance of TDR in the community and regular baseline genotyping prior to ART initiation. In addition, our findings recommend that providers should consider INSTI testing in their evaluation of newly diagnosed individuals, as these tests are often excluded during routine genotyping. Continued monitoring of local TDR patterns will update clinicians on the trajectory of drug resistance and guide future resistance testing and treatment options.

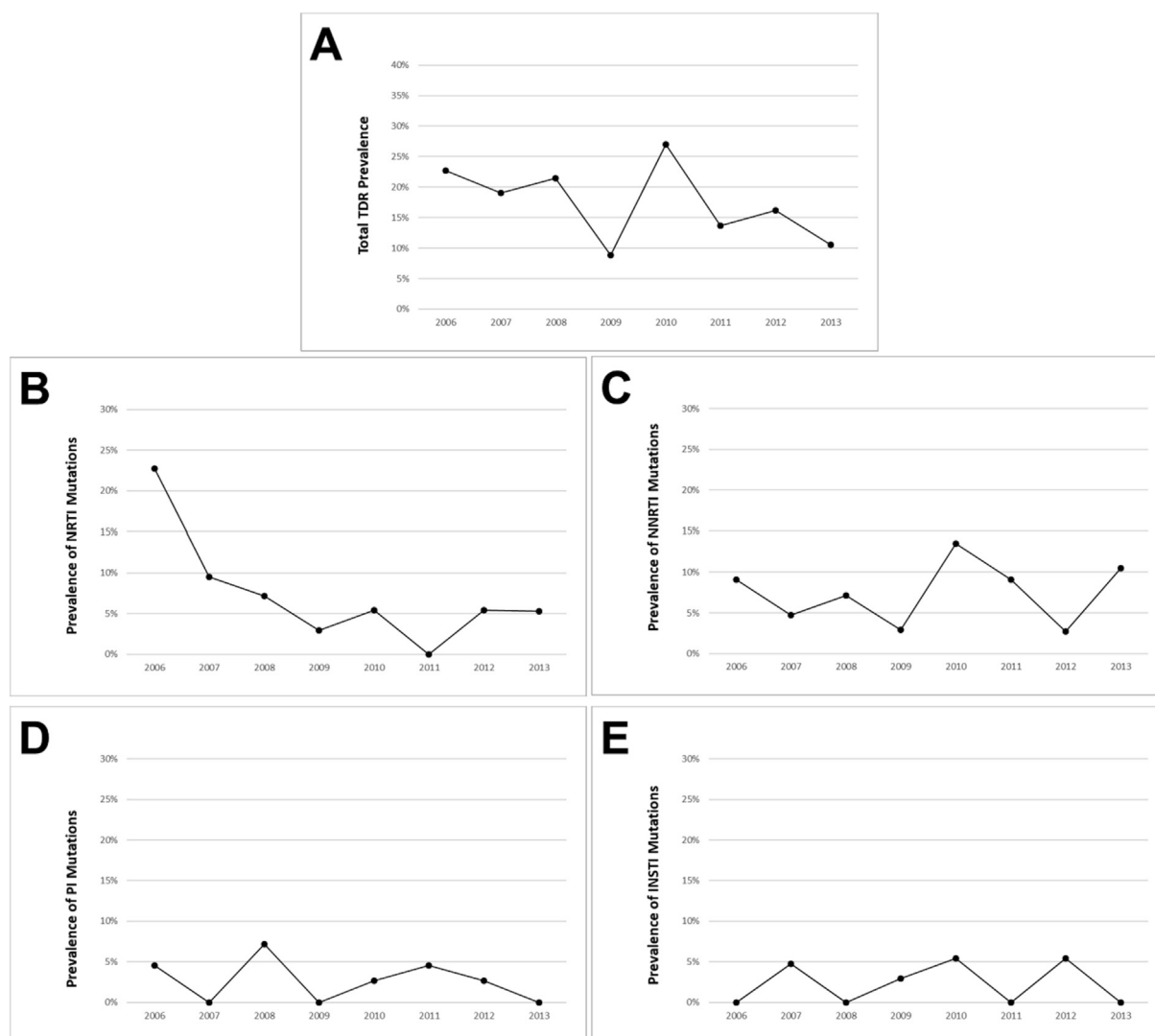


Fig. 3. Temporal trends of transmitted drug resistance (TDR) among 206 individuals meeting inclusion criteria, 2006–2013. Total TDR (A), NRTI (B), NNRTI (C), PI (D), INSTI (E). INSTI = Integrase strand transfer inhibitor. NNRTI = Non-nucleoside reverse transcriptase inhibitor. NRTI = Nucleoside reverse transcriptase inhibitor. PI = Protease inhibitor.

Declarations

Author contribution statement

William Chan, Wilson Ly: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

We thank Rajat Bansil, Pharm. D. and Shirley Chan, M.D. for their review of the manuscript and the PACE Clinic at the Santa Clara Valley Medical Center for providing the facilities to conduct this study.

References

- [1] US Department of Health and Human Services, HIV/AIDS Glossary, 2019. Retrieved from, <https://aidsinfo.nih.gov/understanding-hiv-aids/glossary/1622/transmitted-resistance>.
- [2] World Health Organization, WHO HIV Drug Resistance Report 2012 [PDF File], 2012. Retrieved from, <http://www.who.int/hiv/pub/drugresistance/report2012>.
- [3] L.L. Ross, D. Shortino, M.S. Shaefer, Changes from 2000 to 2009 in the prevalence of HIV-1 containing drug resistance-associated mutations from antiretroviral therapy-naïve, HIV-1-infected patients in the United States, *AIDS Res. Hum. Retrovir.* 34 (8) (2018) 672–679.
- [4] N.A. Margot, P. Wong, R. Kulkarni, K. White, D. Porter, M.E. Abram, C. Callebaut, M.D. Miller, Commonly transmitted HIV-1 drug resistance mutations in reverse-transcriptase and protease in antiretroviral treatment-naïve patients and response to regimens containing tenofovir disoproxil fumarate or tenofovir alafenamide, *J. Infect. Dis.* 215 (6) (2017) 920–927.
- [5] J.M. Volpe, O. Yang, C.J. Petropoulos, C.M. Walworth, Absence of Integrase Inhibitor Resistant HIV-1 Transmission in the California AIDS Healthcare Foundation Network, 2015 [Abstract]. ICAAC 2015, September 17–21, 2015, San Diego.

- [6] J.D. Stekler, J. McKernan, R. Milne, K.A. Tapia, K. Mykhalchenko, S. Holte, et al., Lack of resistance to integrase inhibitors among antiretroviral-naïve subjects with primary HIV-1 infection, 2007–2013, *Antivir. Ther.* 20 (1) (2014) 77–80.
- [7] A.M. Aldous, A.D. Castel, D.M. Parenti, Prevalence and trends in transmitted and acquired antiretroviral drug resistance, Washington, DC, 1999–2014, *BMC Res. Notes* 10 (1) (2017).
- [8] C.B. Hurt, Transmitted resistance to HIV integrase strand-transfer inhibitors: right on schedule, *Antivir. Ther.* 16 (2) (2011) 137–140.
- [9] US Department of Health and Human Services, Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents, 2018. Retrieved from, <https://aidsinfo.nih.gov/guidelines/>.
- [10] A.F. Dailey, B.E. Hoots, H.I. Hall, R. Song, D. Hayes, P. Fulton Jr., et al., Vital signs: human immunodeficiency virus testing and diagnosis delays - United States, *MMWR. Morb. Mort. Weekly Rep.* 66 (47) (2017) 1300–1306.
- [11] D.C. Boettiger, S. Kiertiburanakul, S. Sungkanuparph, M.G. Law, TREAT Asia Studies to Evaluate Resistance, The impact of wild-type reversion on transmitted resistance surveillance, *Antivir. Ther.* 19 (7) (2014) 719–722.
- [12] R.T. Gandhi, A. Wurcel, E.S. Rosenberg, M.N. Johnston, N. Hellmann, M. Bates, et al., Progressive reversion of human immunodeficiency virus type 1 resistance mutations in vivo after transmission of a multiply drug-resistant virus, *Clin. Infect. Dis.* 37 (12) (2003) 1693–1698.
- [13] J.A. Johnson, J.F. Li, X. Wei, J. Lipscomb, D. Irlbeck, C. Craig, et al., Minority HIV-1 drug resistance mutations are present in antiretroviral treatment-naïve populations and associate with reduced treatment efficacy, *PLoS Med.* 5 (7) (2008) e158.
- [14] B.B. Simen, J.F. Simons, K.H. Hullsiek, R.M. Novak, R.D. MacArthur, et al., Low-abundance drug-resistant viral variants in chronically HIV-infected, antiretroviral treatment-naïve patients significantly impact treatment outcomes, *JID (J. Infect. Dis.)* 199 (5) (2009) 693–701.
- [15] L. Wittkop, H.F. Günthard, F. de Wolf, D. Dunn, A. Cozzi-Lepri, A. de Luca, 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.* 11 (5) (2011) 363–371.
- [16] F. Raffi, Y. Yazdanpanah, F. Fagnani, C. Laurendeau, A. Lafuma, J. Gourmelen, Persistence and adherence to single-tablet regimens in HIV treatment: a cohort study from the French National Healthcare Insurance Database, *J. Antimicrob. Chemother.* 70 (7) (2015) 2121–2128.
- [17] S. Duwal, D. Seeler, L. Dickinson, S. Khoo, M.V. Kleist, The utility of efavirenz-based prophylaxis Against HIV infection. A systems pharmacological analysis, *Front. Pharmacol.* 10 (2019).
- [18] U.S. Census Bureau, 2018 Population Estimates, 2018. Retrieved from, <https://www.census.gov/quickfacts/fact/table/santaclaracountycalifornia/INC110217>.
- [19] Centers for Disease Control and Prevention, Basic HIV/AIDS Statistics, 2017. Retrieved from, <https://www.cdc.gov/hiv/basics/statistics.html>.
- [20] D.E. Bennett, R.J. Camacho, D. Otelea, D.R. Kuritzkes, H. Fleury, M. Kiuchi, et al., Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update, *PLoS One* 4 (3) (2009) e4724.
- [21] T.F. Liu, R.W. Shafer, Web resources for HIV type 1 genotypic-resistance test interpretation, *Clin. Infect. Dis.* 42 (11) (2006) 1608–1618.
- [22] S.Y. Rhee, D. Clutter, W.J. Fessel, D. Klein, S. Slome, B.A. Pinsky, et al., Trends in the molecular epidemiology and genetic mechanisms of transmitted human immunodeficiency virus type 1 drug resistance in a large US clinic population, *Clin. Infect. Dis.: an official publication of the Infectious Diseases Society of America* 68 (2) (2019) 213–221.
- [23] N.P. Gordon, Similarity of the Adult Kaiser Permanente Membership in Northern California to the Insured and General Population in Northern California: Statistics from the 2011–12 California Health Interview Survey, Kaiser Permanente Division of Research, Oakland, CA, June 2015. Available at: http://www.dor.kaiser.org/external/chis_non_kp_2011/.
- [24] J.A. Pellowski, S.C. Kalichman, K.A. Matthews, N. Adler, A pandemic of the poor: social disadvantage and the U.S. HIV epidemic, *Am. Psychol.* 68 (4) (2013) 197–209.
- [25] C.E. Golin, H. Liu, R.D. Hays, L.G. Miller, C.K. Beck, J. Ickovics, et al., A prospective study of predictors of adherence to combination antiretroviral medication, *J. Gen. Intern. Med.* 17 (10) (2002) 756–765.
- [26] US Department of Health and Human Services, HIV Treatment Adherence, 2019. Retrieved from, <https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/21/54/hiv-treatment-adherence>.
- [27] B.G. Brenner, M. Roger, J. Routy, D. Moisi, M. Ntemgw, et al., High rates of forward transmission events after acute/early HIV-1 infection, *J. Infect. Dis.* 195 (7) (2007) 951–959.
- [28] S.N. Levintow, N.L. Okeke, S. Hué, L. Mkumba, A. Virkud, S. Napravnik, et al., Prevalence and transmission dynamics of HIV-1 transmitted drug resistance in a southeastern cohort, *Open Forum Infect. Dis.* 5 (8) (2018) ofy178.
- [29] T. Panichsillapakit, D.M. Smith, J.O. Wertheim, D.D. Richman, S.J. Little, S.R. Mehta, Prevalence of transmitted HIV drug resistance among recently infected persons in San Diego, CA 1996–2013, *J. Acquir. Immune Defic. Syndr.* 71 (2) (2016) 228–236.
- [30] P. Machnowska, K. Meixnerberger, D. Schmidt, H. Jessen, H. Hillenbrand, B. Günsheimer-Bartmeyer, et al., German HIV-1 Seroconverter Study Group, Prevalence and persistence of transmitted drug resistance mutations in the German HIV-1 seroconverter study cohort, *PLoS One* 14 (1) (2019) e0209605.
- [31] M.A. Horberg, D.B. Klein, An update on the use of Atripla® in the treatment of HIV in the United States, *HIV/AIDS (Auckland, N.Z.)* 2 (2010) 135–140.
- [32] US Food & Drug Administration, Drugs@FDA: Approved Drug Products, 2006. Retrieved from, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021752s000/TruvadaTOC.cfm.
- [33] V. Svicher, C. Alteri, A. Artese, F. Forbici, M.M. Santoro, D. Schols, et al., Different evolution of genotypic resistance profiles to emtricitabine versus lamivudine in tenofovir-containing regimens, *JAIDS J. Acq. Immune Def. Syndr.* 55 (3) (2010) 336–344.
- [34] J. Deval, K.L. White, M.D. Miller, N.T. Parkin, J. Courcambeck, P. Halfon, et al., Mechanistic basis for reduced viral and enzymatic fitness of HIV-1 reverse transcriptase containing both K65R and M184V mutations, *J. Biol. Chem.* 279 (1) (2003) 509–516.
- [35] B.G. Brenner, D. Coutinos, The K65R mutation in HIV-1 reverse transcriptase: genetic barriers, resistance profile and clinical implications, *HIV Ther.* 3 (6) (2009) 583–594.
- [36] N. Bbosa, P. Kaleebu, D. Ssemwanga, HIV subtype diversity worldwide, *Curr. Opin. HIV AIDS* 14 (3) (2019) 153–160.
- [37] K.M. Doherty, P. Nakka, B.M. King, S.Y. Rhee, S.P. Holmes, R.W. Shafer, M.L. Radhakrishnan, A multifaceted analysis of HIV-1 protease multidrug resistance phenotypes, *BMC Bioinf.* 12 (2011) 477.
- [38] M.W. Tang, R.W. Shafer, HIV-1 antiretroviral resistance: scientific principles and clinical applications, *Drugs* 72 (9) (2012) e1–e25.
- [39] US Food & Drug Administration, Drugs@FDA: Approved Drug Products, 2008. Retrieved from, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/0221451sntress.cfm.
- [40] M. Kobayashi, T. Yoshinaga, T. Seki, C. Wakasa-Morimoto, K.W. Brown, R. Ferris, et al., In Vitro antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor, *Antimicrob. Agents Chemother.* 55 (2) (2011) 813–821.
- [41] M. Tsiang, G.S. Jones, J. Goldsmith, A. Mulato, D. Hansen, E. Kan, et al., Antiviral activity of bictegravir (GS-9883), a novel potent HIV-1 integrase strand transfer inhibitor with an improved resistance profile, *Antimicrob. Agents Chemother.* (2016), 01474–16.