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Prevalence of transmitted HIV drug resistance among recently infected persons in San Diego, California 1996-2013

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Abstract

Background—Transmitted drug resistance (TDR) remains an important concern when initiating antiretroviral therapy (ART). Here we describe the prevalence and phylogenetic relationships of TDR among ART-naïve, HIV-infected individuals in San Diego from 1996-2013.

Methods—Data were analyzed from 496 participants of the San Diego Primary Infection Cohort who underwent genotypic resistance testing before initiating therapy. Mutations associated with drug resistance were identified according to the WHO-2009 surveillance list. Network and phylogenetic analyses of the HIV-1 *pol* sequences were used to evaluate the relationships of TDR within the context of the entire cohort.

Results—The overall prevalence of TDR was 13.5% (67/496), with an increasing trend over the study period (p=0.005). TDR was predominantly toward non-nucleoside reverse transcriptase inhibitors (NNRTIs) [8.5% (42/496)], also increasing over the study period (p=0.005). In contrast, TDR to protease inhibitors and nucleos(t)ide reverse transcriptase inhibitors were 4.4% (22/496) and 3.8% (19/496) respectively, and did not vary with time. TDR prevalence did not differ by age, gender, race/ethnicity or risk factor. Using phylogenetic analysis, we identified 52 transmission clusters, including eight with at least two individuals sharing the same mutation, accounting for 23.8% (16/67) of the individuals with TDR.

Conclusions—Between 1996 and 2013, the prevalence of TDR significantly increased among recently infected ART-naïve individuals in San Diego. Around one-fourth of TDR occurred within

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clusters of recently infected individuals. These findings highlight the importance of baseline resistance testing to guide selection of ART and for public health monitoring.

Keywords

HIV-1; Infection; Transmission; Drug resistance; Antiretroviral therapy; San Diego

Introduction

The widespread use of combination antiretroviral therapy (ART) in the United States has resulted in a substantial reduction of HIV-related morbidity and mortality.[1] Mathematical models and clinical studies have also demonstrated that ART use reduces the risk of HIV transmission.[2-4] However, the emergence of HIV drug-resistant variants and their transmission remains a major concern to the widespread use of ART, which can lead to higher probability of early virological failure in first-line ART.[5-8]

Estimates of the rates of transmitted drug resistance (TDR) in HIV epidemic vary throughout the world. There are several reasons for this variation including differences in sampling, gender, race/ethnicity, location, time from seroconversion, duration of use of ART in the study population, and risk exposure category.[9-13] Overall, the prevalence of TDR has been reported to range from 3.4% to 25.2% among ART-naïve HIV-infected individuals in the United States [9][14-29], and has been associated with the level of drug resistance in the community as a whole, ‘community drug resistance’.[30]

Continued monitoring in the same population can provide important insights into important trends of TDR that may impact clinical practice, like which first line ART regimens should be used and if baseline drug resistance testing should be performed. Our group has monitored TDR in San Diego County since 1996 [16] and has documented TDR rates in both ART-naïve patients with an unknown duration of HIV infection [24] and those with recent infection.[16][31] Our most recent report was in 2009, which found the overall prevalence of TDR among newly diagnosed HIV-infected patients in San Diego County to be 19%.[31] The current study builds on this previous work by determining the prevalence, rate of change, and phylogenetic relationships of TDR in newly diagnosed and ART-naïve HIV-infected individuals in San Diego County from 1996 through 2013.

Methods

Study population

Individuals enrolled between June 1996 and June 2013 in the University of California, San Diego Primary Infection Resource Consortium (SDPIRC) were included in this analysis. Inclusion criteria were (1) age over 18 years, (2) HIV-infected within the previous 12 months, as determined by laboratory diagnostics, documented evolution of HIV seroconversion within the preceding 12 months or evidence of acute or early HIV infection as determined using a set of clinical, virologic and serologic criteria, and (3) no ART exposure at the time of enrollment (treatment-naïve), as previously described.[32] After informed consent, clinical demographic characteristics and laboratory data were obtained at

baseline from all participants. This study was approved by the UCSD human research protection program.

Genotypic resistance analysis

Blood specimens were collected before the initiation of therapy and within 1 month of enrollment into SDPIRC for drug resistance evaluation. Population sequencing of the partial HIV-1 *pol* coding region was performed (GeneSeq HIV-1; Monogram Biosciences, Inc., South San Francisco, CA or Viroseq v.2.0; Celera Diagnostics, Alameda, CA).[33] Genotypic analysis was performed to detect mutations in the HIV-1 *pol* gene fragment encoding protease (PR) and reverse transcriptase (RT), as previously described.[32] Major drug resistance mutations (DRM) were identified using the Stanford HIV database Calibrated Population Resistance Tool version 6.0 available on http://cpr.stanford.edu/cpr/index.html [34] based on the 2009 World Health Organization surveillance of transmitted drug resistant mutations (SDRMs) list for nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).[35] The presence of one or more major resistance mutations in any drug class was considered as TDR according to the SDRM list.

Identification of transmission clusters by network analysis

Cluster analyses were performed as previously described.[36] Briefly, the Tamura-Nei93 nucleotide substitution model (TN93) [37] was used to compute genetic distance between all sequences, and a putative link was inferred if the TN93 genetic distance between two sequences was less than 1.5%. Elucidation of transmission clusters was performed by combining these inferred linkages.[31]

HIV-1 subtyping

The HIV-1 subtypes and circulating recombinant forms (CRF) were determined using two HIV-1 subtyping tools, namely the Rega HIV-1 subtyping tool version 3.0 [38, 39] and SCUEAL [40].The discordant subtyping results between the two tools were then analyzed using phylogenetic analysis in the Treemaker tool provided by HIV LANL Sequence Database that included all reference sequences from HIV-1 subtypes and CRFs to make an informed assignment of subtype.[41]

Phylogenetic Analysis

An alignment of the 496 available sequences was created using MUSCLE [42] and further curated manually using Bioedit software version 7.2.5.[43] To avoid the effect of homoplasy (convergent evolution) of drug resistance mutations on the phylogenetic analysis, all 29 codons associated with major DRM in PR and RT were removed from all of the sequences within the alignment. Phylogenetic approaches were then used to establish transmission clusters and interrelationships among viral sequences. Global phylogenetic relationships were estimated using a maximum likelihood (ML) approach with a bootstrap analyses with 1000 replicates using the general time reversible + Gamma (GTR + Γ) model of nucleotide substitution in FastTree version 2.1.[44] Robust clusters were assessed by bootstrap support

values (≥70%) with 1000 replicates. The trees were edited and visualized using FigTree version 1.4.1.[45]

Statistical analysis

Prevalence values were calculated with a 95% Wilson score confidence interval (95% CI) for binomially distributed data. Categorical variables were compared using the χ^2 test, Fisher's exact test, or simple logistic regression analysis as appropriate. Continuous variables were compared using the Student's t-test or the Mann–Whitney U test. Multiple binomial logistic regression analysis was used to determine the factors associated with drug resistance mutations and control the potential confounders. The yearly time periods were assessed with χ^2 test for trend or the Cochran-Armitage test. All *P*-values were two-tailed tests and the statistical significance level set at $P< 0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Characteristics of subjects

A total of 496 SDPIRC participants with clinical or laboratory evidence of primary HIV infection were enrolled from 1996 through 2013. The majority of the study population was male (97%); 78% were white, 9.7% Native American, 6.8% black, 3.7% Asian, and 1.9% Pacific Islander (Table 1). The mean age of SDPIRC participants was 32 years at the time of resistance testing. The most commonly reported transmission risk factors were men who have sex with men (MSM, 90.3%) or MSM and intravenous drug use (MSM+IVDU; 3.2%), followed by heterosexual contact (2.4%). These data are consistent with the HIV epidemiology in San Diego County.[46] At enrollment, mean baseline CD4 count was 530 cell/μLand 3.4% having CD4 < 200 cell/μL. Median viral load at enrollment was 97, 808 HIV RNA copies/mL. Overall, most participants were infected with HIV-1 subtype B (97.4%). No any single HIV-1 non-B subtype represented more than 0.4% of the sample.

Overall prevalence of transmitted drug resistance (TDR)

The percentage of ART-naïve individuals with primary HIV infection enrolled in SDPIRC between 1996 and 2013 who harbored one or more DRM was 13.5% [67/496; 95% confidence interval (CI): 10.8-16.8%]. The most common major DRM identified were associated with NNRTIs resistance at 8.5% [42/496; 95% CI: 6.3-11.3%], followed by PIs at 4.4% [22/496; 95% CI: 2.9-6.7%] and NRTIs at 3.8% [19/496; 95% CI: 2.4-5.9%] (Table 3). Dual- and triple-class TDR were found in 3.8% [19/496; 95% CI: 2.4-5.9] and 1.0% (5/496; 95% CI: 0.4-2.4%) of subjects. The K103N/S, NNRTIs-associated mutation, was the most frequent mutation observed in 7.3% of individuals, while most NRTIs DRM were thymidine analogue mutations (TAM) of which the most prevalent were the T215Y/F/I/S/D/E/C/V mutations (2%), followed by M41L (1.8%), whereas M46I/L was the most common PI DRM, which was found in 1.8% of individuals (Supplementary material).

TDR trends throughout the study period

When the rates of TDR were compared among four time periods (1996-1999, 2000-2004, 2005-2009 and 2010-2013), we found a statistically significant increase over time in the

proportion of participants with TDR ($p = 0.005$; Table 2), and this significance remains when controlling for potential confounders ($p = 0.02$). When comparing resistance by ART class (Table 3 and Figure 1), TDR prevalence for NNRTIs significantly increased over the entire study period (p for trend = 0.005) that coincided with the observed increase in K103N/S mutation (p for trend = 0.005; Figure 2 and Supplementary material). In contrast, the prevalence of NRTIs and PIs TDR were apparently stable over time (p = NS). The temporal trends for specific mutations are presented in Supplementary material.

Correlates of TDR

Characteristics of individuals with and without TDR were comparable for sex, age at enrollment, ethnicity, route of transmission, CD4 cell count, plasma HIV-RNA, baseline history of alcohol use and IVDU within 90 days of SDPIRC enrollment, and year of diagnosis (Table 2). In a univariate analysis, mean baseline CD4 cell count was significantly lower among individuals with TDR ($p = 0.02$; Table2), but no difference was found in baseline median plasma viral load ($p = 0.23$; Table 2). Similarly, no significant association between TDR and other demographic factors, sexual practices, or use of recreational drugs were found. Given that only one factor was associated with TDR (baseline CD4 count), no significant associations became evident in multivariate analyses.

Phylogenetic and network analysis

A phylogenetic tree was inferred with the 496 HIV-1 partial *pol* sequences from the SD PIRC dataset (Figure 3). Given the limitations associated with phylogenetically analyzing such large numbers of sequences, we also utilized network analysis to obtain a deeper understanding of the underlying transmission network. We identified 52 transmission clusters (169 individuals, 34% of the cohort), of which 12 included at least one individual with a DRM. Of these clusters, eight (66.6%) included at least two individuals carrying the same resistance mutation, and the K103N was the concordant mutation found in seven out of these eight clusters, whereas in the remaining one cluster, L90M was the concordant mutation. Phylogenetic analysis using FastTree software was used to confirm the existence of these eight clusters, and all these clusters had bootstrap values ≥ 70% (Figure 3), supporting the findings made using the network analysis.

Focusing on the individuals with primary infection, the prevalence of TDR was not significantly different among individuals who were part of clusters and those who were not [11.8% (20/169) vs. 16.8% (47/280), respectively; $p = 0.49$]. In order to further determine the probability of having the same DRM in the same identified cluster by chance, prevalence of TDR was also compared among all individuals of each transmission cluster, which contained at least two individuals sharing the same DRM. Significant over-representation of individuals sharing the same DRM was found in 6 of 8 clusters at two different nominal p-values of 0.005 and 0.02 (data not shown). We also found strong evidence that individuals with DRM that were in a phylogenetic cluster were more likely to have a closest neighbor in the phylogenetic tree of all SD PIRC sequences with the same DRM than individuals with sequences harboring DRM who were not found within a cluster ($p = 0.002$, data not shown).

Discussion

This study estimated the prevalence of TDR among individuals with acute and early HIV infection in San Diego between 1996 and 2013. The combined prevalence of TDR to one or more drugs in the first three ART classes was approximately 13.5% over the 18 years of the study. Given the episodic nature of HIV transmission, we expected to observe year-to-year variation in TDR rates, similar to what has been shown in other recent studies [47-49]; however we did observe a significant increase in the overall rate of TDR over time. The TDR rates found from 2005-2013 mirror the most recent CDC study evaluating TDR nationally between 2007 and 2010, which reported a 16.2% rate of TDR among ART-naïve HIV-infected individuals across the United States.[29] In contrast, studies in Europe have reported stabilizing and possibly decreasing trends in TDR prevalence in recent years.[50] Similar to the CDC report, we found that the overall prevalence of TDR to NNRTIs was 8.5% in our cohort, while the CDC report by Kim et al. found the prevalence of TDR to NNRTIs to be 8.1%. Our study found that dual-class resistance and triple-class resistance was slightly higher at 3.8% and 1.0% respectively, compared to the CDC report of 2.1% and 0.5% respectively. These differences may be secondary to differences in study design where we only evaluated for TDR among individuals with recent HIV infection, while the CDC study examined individuals who were ART-naïve but the duration of infection was not always known. As such, the rates of TDR from the CDC study maybe underestimations, since TDR mutations can become undetectable over time from reversion to wild-type sequences.[51]

In our study, TDR to NNRTIs was the most frequently observed DRM, consistent with other published studies.[11] [17] In the pre-combination ART era (before 1996), TDR in the US was primarily directed to NRTIs; however, when NNRTIs became widely available in 1996 [52-56], the prevalence of recently HIV-infected individuals who had TDR to NNRTI increased over time, with the K103N the most frequently observed DRM. Specifically, 53.7% of individuals with DRM had the K103N mutation. This may be because the K103N DRM is often associated with early virologic failure with the most frequently used NNRTI efavirenz [57], has minimal effects on viral replication capacity [58] and may persist for long periods, even after discontinuation NNRTI-based therapy. [59, 60] Generally, early virologic failure to efavirenz is conferred by a single mutation, but continuation of ART during virologic failure often leads to accumulation of multiple DRM, which can lead to cross class resistance.[61]

In this study most DRM to NRTIs were TAMs T215Y/F/I/S/D/E/C/V (2%) and M41L (1.8%), which mostly confer resistance to older generation NRTIs, zidovudine and stavudine. However, the M41L alone can be a polymorphism that is not associated with reduced susceptibility to any NRTIs by itself.[62, 63] The rate of this TDR to NRTI with TAMs remained relatively stable throughout our observed study period. Since zidovudine and stavudine are rarely prescribed anymore, the persistence of these TAMs in our ART-naïve cohort suggests that these TAMs and their revertants are evidence of ongoing TDR that carries DRM that were selected for in patients receiving zidovudine or stavudine earlier in the epidemic. This hypothesis is supported by several studies that have demonstrated that

TAMs and their revertants persist for several years with little reversion to wild type amino acids in the absence of antiretroviral selection pressure.[51] [64]

The prevalence of TDR to PIs was lower than TDR to NNRTIs and NRTIs, which is consistent with other studies [64-66], and is likely the result of the high genetic barrier to develop DRM to PIs.[67, 68] According to recent version guidelines for treating HIV infection [69, 70], integrase strand transfer inhibitors (INSTIs) were listed as a “preferred” regimen for ART-naïve HIV-infected individuals. Although to date the prevalence of TDR to INSTIs has been very rare [71-73], increased use will certainly lead to increasing TDR to INSTIs. Thus, monitoring of TDR should include evaluation for integrase mutations.

In most studies, individuals with TDR appeared to have higher baseline CD4 cell count than individuals without TDR [11][74, 75]; however, our study found the opposite. This discrepancy was found in at least one other study [76], and may be due to differences between cohorts. However, this association turned to non-significant in multivariate analysis. The most recent CDC report of TDR among ART-naïve MSM in a large US study showed higher prevalence of TDR among MSM (17.4%) compared to heterosexuals.[77] In comparison, we found the prevalence of TDR among MSM to be lower at 13.4% as compared to 16.7% in the heterosexual population ($p = 0.67$, data not shown). Unfortunately, the small number of participants reporting heterosexual risk prevents us from generalizing our results to that population. These variations may reflect differences in the MSM population size, linkage or access to diagnosis and care. Since new infection among MSM still remain important factor driving HIV epidemic, especially in San Diego, TDR surveillance in this group should be regularly performed to identify and intervene on developing TDR trends.

This study had a rate of clustering with 34.1% of sequences segregating into 52 clusters. Several of these transmission clusters included individuals sharing the same DRM, in particular K103N mutation. This presence of TDR within transmission clusters accounted for almost 30% of DRM in the cohort, which may be explained by reduced time for viral reversion of DRM during clustered transmission.[78] Several remaining clusters included individuals with different resistance mutations, which may reflect reversions, or sampling bias.

As with any other observational study, our study has limitations. First, we may have had a biased sample of the local population since potential participants were not selected using random sampling methods, and thus our study population might not be representative of our overall local population. Second, although the predominant risk factor in the San Diego epidemic is MSM, the SDPIRC is even more highly focused on this population with targeted HIV testing campaigns [79], and thus MSM were most likely over-represented. Third, this study did not evaluate TDR to other classes of antiretroviral medications, like integrase inhibitors and fusion inhibitors. As the use of these agents increases, surveillance for TDR to the agents must be included. Finally, our data were not complete, and so demographic and clustering associations with TDR may have been missed.

Conclusion

Transmission of primary HIV-1 drug resistance continues to be an important public health threat. This study indicates that the prevalence of TDR has significantly increased over the past 18 years, specifically for TDR to NNRTIs. This study has also identified that TDR can occur within transmission clusters, which may be why the rate of TDR does not seem to be slowing despite the use of more effective ART over time. Taken together, this study reinforces the current recommendations for both baseline resistance testing to guide treatment decisions [68] and the early treatment recently diagnosed individuals [80], since early HIV detection and treatment can prevent transmission of HIV drug resistance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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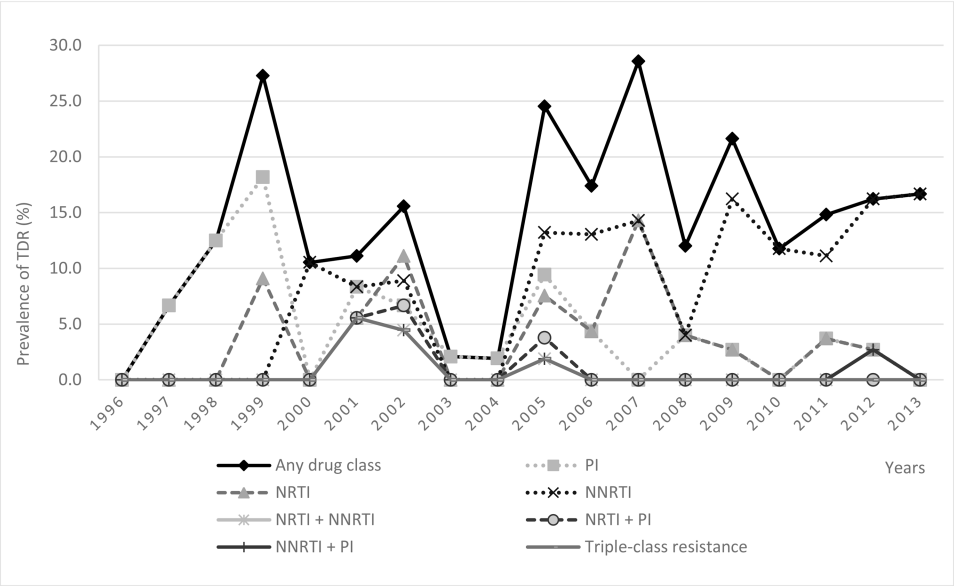

Figure 1.

Prevalence of transmitted drug resistance mutations by drug class among treatment-naïve, recently HIV-infected individuals over time.

PI, protease inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; TDR, transmitted drug resistance; Any, TDR to any drug class.

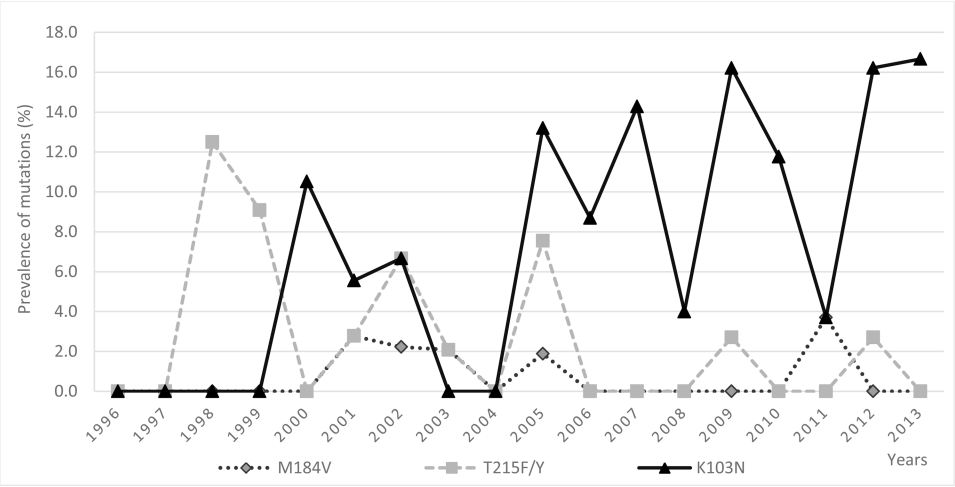

Figure 2. Prevalence of common specific resistance mutations in treatment-naïve, recently HIV-infected individuals over time

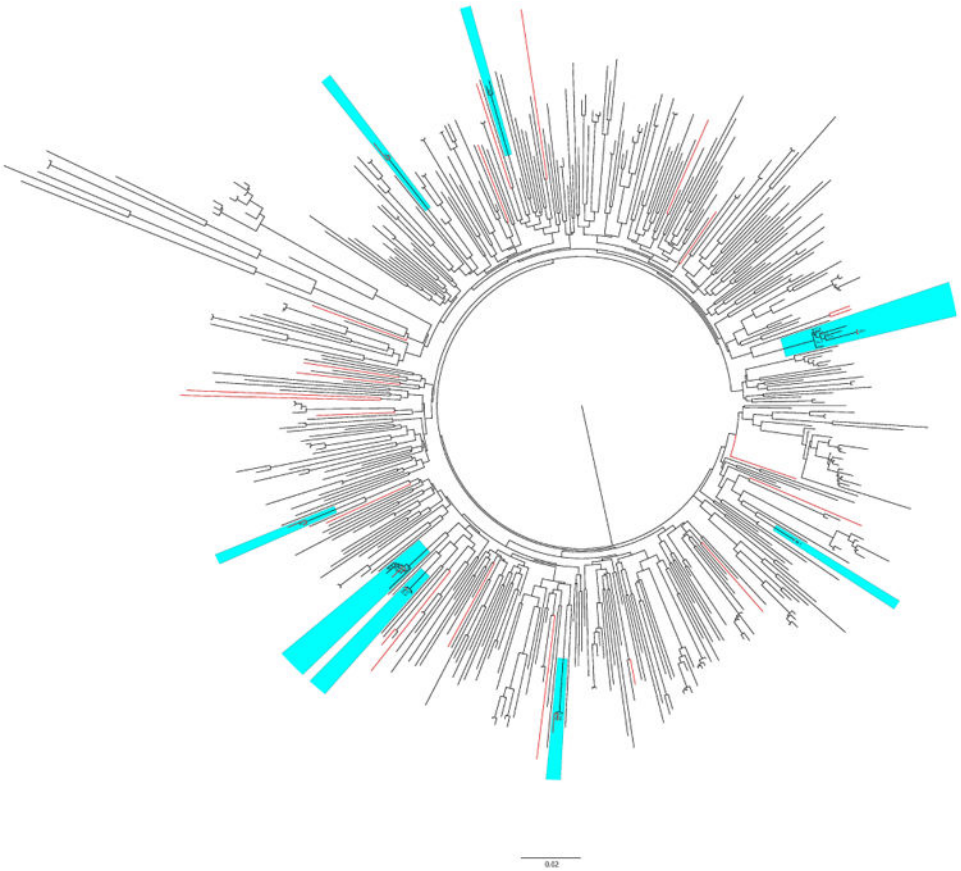

Figure 3.

The maximum likelihood phylogenetic tree of all HIV-1 *pol* sequences using GTR + Gamma nucleotide substitution model in FastTree package. Total available 496 sequences were used to reconstruct the phylogeny. Twenty-nine codons associated with resistance mutations were remove from the alignment. Bootstrap with 1000 replicated was applied to evaluate the reliability of the reconstructed tree. Bootstrap support values of ≥70% are shown at nodes on the tree. Red branches represent sequences with K103N mutation and blue box indicates identified clusters which contain at least two individuals sharing the same resistance mutation.

Table 1
Baseline characteristics of newly HIV-infected individuals

Characteristic	Number of individuals, n (%)
All patients	496 (100)
Sex	
Male	478 (96.96)
Female	15 (3.04)
Unknown	3
Age at diagnosis (Years)	
20-29	169 (39.67)
30-39	141 (33.1)
40-49	87 (20.42)
≥50	29 (6.81)
Else (Missing data & < 20)	70
Mean, years (±SD)	32.49 (±11.13)
Ethnicity	
Non-Hispanic or Latino/	230 (63.36)
Hispanic or Latino/	131 (36.09)
Other	2 (0.55)
Unknown	133
Race	
White/Caucasian	379 (77.99)
Native American	47 (9.67)
Black/African American	33 (6.79)
Asian	18 (3.7)
Pacific Islander	9 (1.85)
Unknown	10
HIV risk exposure	
MSM/MSM-IDU	464 (94.69)
Heterosexual	12 (2.45)
Bisexual/Bisexual-IDU	14 (2.86)
Unknown	6
CD4 cell count (cell/mm^3)	
< 200	17 (3.43)
200 to < 350	88 (17.74)
350 to < 500	136 (27.42)
≥ 500	255 (51.41)
Mean absolute CD4 (±SD)	530 (±222.69)
Mean percent CD4 (±SD)	28.44 (±23.42)
Viral load	

Characteristic	**Number of individuals, n (%)**
Median Viral load (copies/mL)	97808
Mean Viral load (log_{10}copies/mL) (±SD)	4.97 (±1.11)
Missing	1
Baseline alcohol 3 months before enrollment	
Yes	118 (80.27)
No	29 (19.73)
Missing	349
Baseline methamphetamine injection 3 months before enrollment	
Yes	6 (5.77)
No	98 (94.23)
Missing	392

Table 2

Characteristics of newly HIV-1-infected patients with and without transmitted drug resistance mutations

	Total	TDR	Wild type	Univariate			Multivariate		
				OR	(95%CI)	*P*-value	OR	(95%CI)	*P*-value
Patients	496	67 (13.5)	429 (86.5)						
Sex						0.97			0.08
Male	478	65 (13.6)	413 (86.4)	1	Reference		1	Reference	
Female	15	2 (13.3)	13 (86.7)	0.98	0.22-4.43		6.62	0.76-57.8	
Unknown	3			*c*			*c*		
Age						0.6			0.46
20-29	169	23 (13.6)	146 (86.4)	1	Reference		1	Reference	
30-39	141	16 (11.3)	125 (88.7)	0.81	0.41-1.61		1.15	0.5-2.66	
40-49	87	15 (17.2)	72 (82.8)	1.32	0.65-2.69		1.89	0.79-4.56	
≥ 50	29	5 (17.2)	24 (82.8)	1.32	0.46-3.81		1.9	0.56-6.5	
Unknown & ≤ 20	70			*c*			*c*		
Mean years (±SD)	32.5 (±11.13)	32.6 (±13.2)	32.5 (±10.8)			0.94[a]			
Ethnicity						0.75			0.58
Non-Hispanic or Latino/A	230	34 (14.8)	196 (85.2)	1	Reference		1	Reference	
Hispanic or Latino/A	131	21 (16)	110 (84)	1.1	0.61-1.99		1.23	0.6-2.53	
Other	2	0 (0)	2 (100)	1	-		1	-	
Unknown	133			*c*			*c*		
HIV risk exposure						0.66			0.58
MSM/MSM-IDU	464	62 (13.4)	402 (86.6)	1	Reference		1	Reference	
Heterosexual	12	2 (16.7)	10 (83.3)	1.30	0.28-6.06		2.45	0.2-30.36	
Bisexual/Bisexual-IDU	14	3 (21.4)	11 (78.6)	1.77	0.48-6.52		1.81	0.42-7.8	
Unknown	6			*c*			*c*		
CD4 cell count at enrollment (cells/mm^3)						0.23			0.55
<200	17	2 (11.8)	15 (88.2)	1	Reference		1	Reference	
200 to < 350	88	14 (15.9)	74 (84.1)	1.42	0.29-6.90		5.15	0.52-51.06	

	Total	TDR	Wild type	Univariate			Multivariate		
				OR	(95%CI)	*P*-value	OR	(95%CI)	*P*-value
350 to <500	136	24 (17.6)	112(82.4)	1.61	0.34-7.50		5.79	0.52-64.89	
≥ 500	255	27 (10.6)	228 (89.4)	0.89	0.19-4.10		5.7	0.36-89.42	
Mean absolute CD4 (±SD)	530 (±222.7)	479 (±172.3)	537 (±228.7)			0.02[a]			0.33
Mean percent CD4 (±SD)	28.44 (±23.4)	26.86 (±9.5)	28.69 (±24.8)			0.28[a]			0.85
Viral load									
Median VL (copies/ml)	97808	170000	90050			0.23[b]			
Mean log10 viral load (±SD)	4.97 (±1.1)	5.23 (±1.1)	4.96 (±1.1)			0.24[a]			0.24
Year of Diagnosis						0.005			0.02
1996-1999	40	5 (12.5)	35 (87.5)	1	Reference		1	Reference	
2000-2004	200	15 (7.5)	185 (92.5)	0.57	0.19-1.66		0.07	0.01-0.71	
2005-2009	152	32 (21.1)	120 (78.9)	1.87	0.68-5.15		0.23	0.03-2.09	
2010-2013	104	15 (14.4)	89 (85.6)	1.18	0.40-3.49		0.14	0.01-1.29	

Data are presented as number (%) of patients, unless otherwise indicated.

OR, odds ratio; CI, confidence interval; TDR, transmitted drug resistance; SD, standard deviation; Latino/A, Latino Americans; MSM, men who have sex with men; IDU, intravenous drug user; VL, viral load.

ORs were estimated using simple (unadjusted) and multiple (adjusted) logistic regression.

[a]=Two-sample t test

[b]=Wilcoxon-Mann-Whitney test.

[c]=Persons with every unknown category were excluded from logistic regression models.

Table 3

Trends of HIV-1 transmitted drug resistance throughout the study period

TDR Category	Total N=496	1996 n=6	1997 n=15	1998 n=8	1999 n=11	2000 n=19	2001 n=36	2002 n=45	2003 n=48	2004 n=52	2005 n=53	2006 n=23	2007 n=14	2008 n=25	2009 n=37	2010 n=34	2011 n=27	2012 n=37	2013 n=6	*P**
Any, n (%)	67 (13.5)	0 (0)	1 (6.7)	1 (12.5)	3 (27.3)	2 (10.5)	4 (11.1)	7 (15.6)	1 (2.1)	1 (1.9)	13 (24.5)	4 (17.4)	4 (28.6)	3 (12.0)	8 (21.6)	4 (11.8)	4 (14.8)	6 (16.2)	1 (16.7)	0.16
PI, n (%)	22 (4.4)	0 (0)	1 (6.7)	1 (12.5)	2 (18.2)	0 (0)	3 (8.3)	3 (6.7)	1 (2.1)	1 (1.9)	5 (9.4)	1 (4.3)	0 (0)	1 (4.0)	1 (2.7)	0 (0)	1 (3.7)	1 (2.7)	0 (0)	0.09
NRTI, n (%)	19 (3.8)	0 (0)	0 (0)	0 (0)	1 (9.1)	0 (0)	2 (5.6)	5 (11.1)	0 (0)	0 (0)	4 (7.5)	1 (4.3)	2 (14.3)	1 (4.0)	1 (2.7)	0 (0)	1 (3.7)	1 (2.7)	0 (0)	0.68
NNRTI, n (%)	42 (8.5)	0 (0)	0 (0)	0 (0)	0 (0)	2 (10.5)	3 (8.3)	4 (8.9)	0 (0)	0 (0)	7 (13.0)	3 (13.0)	2 (14.3)	1 (4.0)	6 (16.2)	4 (11.8)	3 (11.1)	6 (16.2)	1 (16.7)	0.005
NRTI + NNRTI, n (%)	6 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5.6)	2 (4.4)	0 (0)	0 (0)	1 (1.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.7)	0 (0)	0.43
NRTI + PI, n (%)	7 (1.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5.6)	3 (6.7)	0 (0)	0 (0)	2 (3.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.1
NNRTI + PI, n (%)	6 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5.6)	2 (4.4)	0 (0)	0 (0)	1 (1.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.7)	0 (0)	0.43
Triple-class, n (%)	5 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5.6)	2 (4.4)	0 (0)	0 (0)	1 (1.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.11

* $\chi 2$ test for linear trend, unadjusted

PI, protease inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitor