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Transmitted Drug Resistance Among Human Immunodeficiency Virus (HIV)-1 Diagnoses in the United States, 2014–2018

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Background. Transmitted human immunodeficiency virus (HIV) drug resistance can threaten the efficacy of antiretroviral therapy and pre-exposure prophylaxis (PrEP). Drug-resistance testing is recommended at entry to HIV care in the United States and provides valuable insight for clinical decision making and population-level monitoring.

Methods. We assessed transmitted drug-resistance–associated mutation (TDRM) prevalence and predicted susceptibility to common HIV drugs among US persons with HIV diagnosed during 2014–2018 who had a drug resistance test performed ≤3 months after HIV diagnosis and reported to the National HIV Surveillance System and who resided in 28 jurisdictions where ≥20% of HIV diagnoses had an eligible sequence during this period.

Results. Of 50 747 persons in the analysis, 9616 (18.9%) had ≥1 TDRM. TDRM prevalence was 0.8% for integrase strand transfer inhibitors (INSTIs), 4.2% for protease inhibitors, 6.9% for nucleoside reverse transcriptase inhibitors (NRTIs), and 12.0% for non-NRTIs. Most individual mutations had a prevalence <1.0% including M184V (0.9%) and K65R (0.1%); K103N was most prevalent (8.6%). TDRM prevalence did not increase or decrease significantly during 2014–2018 overall, for individual drug classes, or for key individual mutations except for M184V (12.9% increase per year; 95% confidence interval, 5.6–20.6%).

Conclusions. TDRM prevalence overall and for individual drug classes remained stable during 2014–2018; transmitted INSTI resistance was uncommon. Continued population-level monitoring of INSTI and NRTI mutations, especially M184V and K65R, is warranted amidst expanding use of second-generation INSTIs and PrEP.

Keywords. HIV; drug resistance; surveillance; public health; integrase inhibitor.

Human immunodeficiency virus (HIV) antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) are cornerstones of HIV treatment and prevention and essential components of the Ending the HIV Epidemic: A Plan for America (EHE) initiative [1]. Viral resistance to ART and PrEP can arise from mutations transmitted at the time of infection or acquired during exposure to suboptimal drug levels; this resistance can reduce the efficacy of ART and PrEP and represents a threat to successful HIV elimination efforts. Transmitted drug-resistance–associated mutations (TDRMs) have been described for all major drug classes and can result in delayed viral suppression or treatment failure for persons initiating ART [2]. For this reason, standard genotypic drug resistance testing is recommended at entry into care for all persons with HIV in the United States to assist with selection of an initial ART regimen [3–5].

Prior estimates of overall TDRM prevalence in the United States have ranged from 11% to 15% [6–9], with non-nucleoside reverse transcriptase inhibitors (NNRTIs) providing the largest contribution (prevalence, 6–10%) followed by nucleoside reverse transcriptase inhibitors (NRTIs; prevalence, 3–8%) and protease inhibitors (PIs; prevalence, 3–5%) [6–9]. Thymidine-analog mutations (TAMs) selected previously by NRTIs no longer in widespread use still contribute substantially to overall NRTI TDRM prevalence [6]. Few studies have assessed population-level transmitted resistance to integrase strand transfer inhibitors (INSTIs) in the United States, and reports of INSTI resistance in treatment-naive individuals have been rare [10–13].

The efficacy of approved PrEP regimens that combine tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) with emtricitabine (FTC) can be reduced by drug-resistance mutations. M184V (affecting FTC) and K65R (affecting TDF/TAF and FTC) have been associated with PrEP failure due to infection with drug-resistant virus [14–18]. INSTI resistance is also relevant to PrEP: cabotegravir, an

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investigational INSTI currently in PrEP efficacy trials, selects for mutations associated with resistance to other INSTIs used for ART [19, 20].

In the United States, all states and territories submit deidentified demographic, risk, clinical, and laboratory data for persons with diagnosed HIV infection to the National HIV Surveillance System (NHSS) at the Centers for Disease Control and Prevention (CDC). Since 2004, HIV-1 nucleotide sequence data from persons with diagnosed HIV residing in select jurisdictions have been incorporated into routine NHSS reporting. The number of participating jurisdictions has grown in recent years; as of 2018, health departments in all US jurisdictions were required to collect and submit HIV-1 nucleotide sequence data to NHSS from drug-resistance tests for all persons with diagnosed HIV in their jurisdiction. This includes the protease (PR), reverse transcriptase (RT), and integrase (IN) segments of the *pol* region. These data provide valuable insight into population-level drug-resistance patterns and can inform guidelines for clinical management of HIV and PrEP in the United States. We analyzed NHSS data to describe the prevalence of transmitted drug resistance in the United States among persons with HIV diagnosed during 2014–2018.

METHODS

We included persons with HIV infection diagnosed during 2014–2018 with a partial HIV-1 *pol* nucleotide sequence collected 3 months or earlier of HIV diagnosis and reported to NHSS by 30 June 2019, who were 13 years or older at the time of HIV diagnosis, and who had no evidence of HIV ART use prior to the date of sequence collection. HIV subtype was determined using Context-based Modeling for Expeditious Typing (COMET) version 2.2 [21]; and sequences from subtypes A, B, C, D, F, and G and circulating recombinant forms (CRF) 01 and 02 were included. Sequences were classified by whether they contained the protease and reverse transcriptase (PR-RT) region and/or the integrase (IN) region; sequences less than 500 nucleotides in length were excluded. For persons with multiple PR, RT, or IN sequences meeting the inclusion criteria, the earliest PR, RT, and IN sequence was selected. We included persons whose residence at diagnosis was in 1 of 28 US jurisdictions where 20% or more of HIV diagnoses during 2014–2018 had a sequence meeting the inclusion criteria.

We defined NRTI, NNRTI, and PI TDRMs using the previously published CDC HIV-1 surveillance mutation list [9], which includes RT and PR mutations with a prevalence of 1% or greater in treated persons and omits polymorphic mutations (prevalence ≥0.5% in treatment-naive persons). For INSTI TDRMs, we included 24 non-polymorphic mutations identified by Tzou et al [22] based on published expert lists, conservation in INSTI-naive persons, frequency in INSTI-treated persons, and contribution to reduced in vitro susceptibility: T66A/I/K, E92G/Q, G118R, F121Y, E138A/K/T, G140A/C/S, Y143C/H/R/S, S147G, Q148H/R/K, N155H, S230R, R263K. We included 5 additional rare nonpolymorphic mutations (E92V, Y143G/K, N155S/T) for a total of 29 INSTI TDRMs.

HIV-1 drug-resistance–associated mutations were identified using the Sierra Web Service version 1.1 [23]. Because all sequences were performed 3 months or less after HIV diagnosis among persons with no evidence of prior ART use, all mutations were classified as TDRMs. We reported the number of sequences with each individual mutation, with 1 or more TDRM to each individual drug class (NRTI, NNRTI, PI, and INSTI) and with 1 or more TDRM to any drug class. TDRM prevalence was calculated by dividing the number of sequences with each TDRM by the number of sequences containing the relevant gene (PR, RT, or IN). For each drug class and for select mutations with pronounced effects on commonly used drugs, we calculated the estimated annual percent change during 2014–2018 using log binomial regression.

We used the Stanford HIV Drug Resistance Database (HIVdb) genotypic resistance interpretation system, version 8.2 [24], to predict susceptibility to commonly used antiretroviral drugs. This system assigns a drug penalty score to each mutation and combination of mutations based on prevalence in treated and untreated persons, in vitro phenotypic data, published associations between genotype and virologic suppression, and expert opinion. Scores for individual mutations range from −15 to +60; higher positive numbers indicate higher resistance, 0 indicates no change to susceptibility, and negative numbers indicate increased susceptibility compared with wild-type virus. Individual mutation scores are combined to obtain a final score in 1 of 5 categories: susceptible (0–9), potential low-level resistance (10–14), low-level resistance (15–29), intermediate resistance (30–59), and high-level resistance (≥60). We determined predicted resistance for commonly used antiretroviral drugs assessed by HIVdb using the total number of sequences with 1 or more TDRM affecting the corresponding drug class as the denominator.

RESULTS

A total of 50 747 persons with diagnosed HIV infection from 28 jurisdictions (Alabama, Alaska, Arizona, California, Colorado, Connecticut, District of Columbia, Florida, Idaho, Illinois, Iowa, Louisiana, Maryland, Michigan, Montana, New York, North Dakota, Ohio, Oregon, Pennsylvania, South Carolina, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin) had a sequence included in the analysis, representing 35.4% of all HIV diagnoses in these jurisdictions during 2014–2018. Of those with an eligible sequence, 47 215 (93.0%) persons had a PR-RT sequence available and 10 319 (20.3%) had an IN sequence available; 6787 persons (13.4%) had PR-RT and IN sequences

Table 1. Characteristics of Persons With Diagnosed Human Immunodeficiency Virus (HIV) Infection With and Without an Eligible HIV-1 Nucleotide Sequence: 28 US States, 2014–2018

	New HIV Diagnoses With an Eligible Sequence		New HIV Diagnoses Without an Eligible Sequence	
Characteristics	n	%	n	%
Total	50 747	100.0	92 662	100.0
Sex at birth				
Female	8636	17.0	17 840	19.3
Male	42 111	83.0	74 822	80.7
Age at HIV diagnosis				
13–29 years	21 031	41.4	37 922	40.9
30–49 years	21 131	41.6	39 187	42.3
≥50 years	8585	16.9	15 553	16.8
Race/ethnicity				
Black/African American	19 463	38.4	37 807	40.8
Hispanic/Latino	14 731	29.0	26 450	28.5
White	13 392	26.4	22 351	24.1
Other	3161	6.2	6054	6.5
Transmission category				
Male-to-male sexual contact	35 111	69.2	60 895	65.7
IDU	2617	5.2	5585	6.0
Male-to-male sexual contact and IDU	1793	3.5	3321	3.6
Heterosexual contact	11 153	22.0	22 680	24.5
Other	72	0.1	181	0.2
US Census region				
Northeast	8189	16.1	13 226	14.3
Midwest	6134	12.1	11 575	12.5
South	23 881	47.1	45 652	49.3
West	12 543	24.7	22 209	24.0
Year of HIV diagnosis				
2014	9395	18.5	20 342	22.0
2015	9575	18.9	19 667	21.2
2016	10 923	21.5	18 215	19.7
2017	10 892	21.5	17 115	18.5
2018	9962	19.6	17 323	18.7
Stage of HIV infection at diagnosis				
Stage 1	13 202	26.0	21 838	23.6
Stage 2	18 234	35.9	24 057	26.0
Stage 3 (AIDS)	13 059	25.7	17 378	18.8
Stage unknown	6252	12.3	29 389	31.7

Abbreviation: IDU, injection drug use.

available. Characteristics of persons included in the analysis are presented in Table 1; most were male (83.0%) and reported male-to-male sexual contact as a transmission risk factor (69.2%). Demographic and risk characteristics for those with and without a sequence were similar overall, with the exception of stage of HIV infection at diagnosis; a larger proportion of new HIV diagnoses without an eligible sequence had an unknown stage of HIV infection at diagnosis (31.7% vs 12.3%). The most common HIV subtype was subtype B (n = 48,253, 95.1%), followed by subtype C (n = 606, 1.2%); no other subtype had a prevalence greater than 1.0% (data not shown).

Among the 50 747 persons with a PR-RT and/or IN sequence, 9616 (18.9%) had 1 or more TDRM to any drug class. For individual drug classes, TDRM prevalence was 0.8% (INSTI), 4.2% (PI), 6.9% (NRTI), and 12.0% (NNRTI) (Table 2). The most common individual mutations were K103N (8.6%), M41L (1.4%), and T69N (1.2%); all other mutations had a prevalence 1% or less. M184V prevalence was 0.9%. A total of 31 sequences contained K65R (prevalence, 0.1%); for 19 of 31 (61%) of these sequences, M184V/I was also detected. Among 79 total sequences with INSTI TDRMs, E138K was the most common mutation (n = 22); for 18 of 22 (82%) sequences it was the only TDRM and for 20 of 22 (91%) sequences it was the only INSTI TDRM, indicating minimal impact overall on INSTI susceptibility [25] (1 sequence also contained Q148H and G140S; another contained Q148R). A total of 1180 (2.3%) persons had

Table 2. Prevalence of Transmitted Drug Resistance-Associated Mutations by Drug Class: 28 US States, 2014–2018

INSTI *(N=10,319 IN sequences)*		
Mutation	**N**	**Prevalence, %**
Any INSTI	79	0.8
T66A	2	0.0
T66I	4	0.0
E92G	1	0.0
E92Q	8	0.1
G118R	1	0.0
E138K	22	0.2
G140A	1	0.0
G140S	7	0.1
Y143C	2	0.0
Y143H	3	0.0
Y143R	2	0.0
S147G	6	0.1
Q148H	6	0.1
Q148R	2	0.0
N155H	11	0.1
N155S	2	0.0
S230R	6	0.1
R263K	7	0.1

NNRTI *(N=47,215 PR-RT sequences)*		
Mutation	**N**	**Prevalence, %**
Any NNRTI	5,662	12.0
A98G	200	0.4
L100I	68	0.1
K101E	247	0.5
K101H	45	0.1
K101P	31	0.1
K103N	4042	8.6
K103S	355	0.8
V106A	27	0.1
V106M	36	0.1
E138Q	90	0.2
V179F	9	0.0
Y181C	411	0.9
Y181I	11	0.0
Y181V	8	0.0
Y188C	12	0.0
Y188H	14	0.0
Y188L	236	0.5
G190A	389	0.8
G190E	10	0.0
G190S	62	0.1
H221Y	142	0.3
P225H	241	0.5
L228R	102	0.2
M230L	18	0.0

NRTI *(N=47,215 PR-RT sequences)*		
Mutation	**N**	**Prevalence, %**
Any NRTI	3,258	6.9
M41L	676	1.4
E44A	5	0.0
E44D	182	0.4
A62V	143	0.3
K65R	31	0.1
D67E	12	0.0
D67G	33	0.1
D67N	284	0.6
T69A	255	0.5
T69D	152	0.3
T69N	557	1.2
K70E	31	0.1
K70R	68	0.1
L74I	31	0.1
L74V	39	0.1
V75A	8	0.0
V75I	82	0.2
V75M	21	0.0
V75T	7	0.0
F77L	20	0.0
Y115F	16	0.0
F116Y	4	0.0
Q151M	6	0.0
M184I	79	0.2
M184V	402	0.9
L210W	208	0.4
T215C	145	0.3
T215D	298	0.6
T215E	160	0.3
T215F	25	0.1
T215I	61	0.1
T215S	457	1.0
T215V	15	0.0
T215Y	53	0.1
K219E	92	0.2
K219N	25	0.1
K219Q	215	0.5
K219R	80	0.2

PI *(N=47,215 PR-RT sequences)*		
Mutation	**N**	**Prevalence, %**
Any PI	1,983	4.2
V11I	233	0.5
L23I	15	0.0
L24I	35	0.1
D30N	119	0.3
V32I	27	0.1
M46I	173	0.4
M46L	232	0.5
I47V	14	0.0
G48V	4	0.0
I50L	22	0.0
I50V	15	0.0
F53L	16	0.0
F53Y	10	0.0
I54A	1	0.0
I54L	14	0.0
I54M	5	0.0
I54T	3	0.0
I54V	69	0.1
Q58E	421	0.9
G73A	1	0.0
G73C	4	0.0
G73S	21	0.0
T74P	14	0.0
T74S	229	0.5
L76V	9	0.0
V82A	91	0.2
V82C	1	0.0
V82F	3	0.0
V82L	13	0.0
V82M	7	0.0
V82T	4	0.0
N83D	4	0.0
I84V	33	0.1
I85V	94	0.2
N88D	106	0.2
N88S	8	0.0
L90M	459	1.0

Mutations included in the analysis but not detected in any sequences: INSTI: T66K, E92V, F121Y, E138A, E138T, G140C, Y143G, Y143K, Y143S, Q148K, N155T; PI: I47A, G48M, I54S, G73T, V82S, I84A, I84C; NRTI: V75S. Abbreviations: IN, integrase; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PR, protease; RT, reverse transcriptase

TDRMs to 2 drug classes, 140 (0.3%) had TDRMs to 3 drug classes, and 1 person had TDRMs to all 4 drug classes.

Predicted resistance to common ART drugs among sequences with 1 or more TDRM is shown in Figure 1. The proportion of sequences predicted to maintain susceptibility ranged from 0% (elvitegravir) to 94.4% (darunavir/ritonavir). Predicted high-level or intermediate resistance was uncommon for dolutegravir (8/79 [10.1%]), TDF (174/3258 [5.3%]), emtricitabine/lamivudine (FTC/3TC) (468/3258 [14.4%]), abacavir (ABC) (286/3258 [8.8%]), darunavir/ritonavir (15/1983 [0.8%]), and atazanavir/

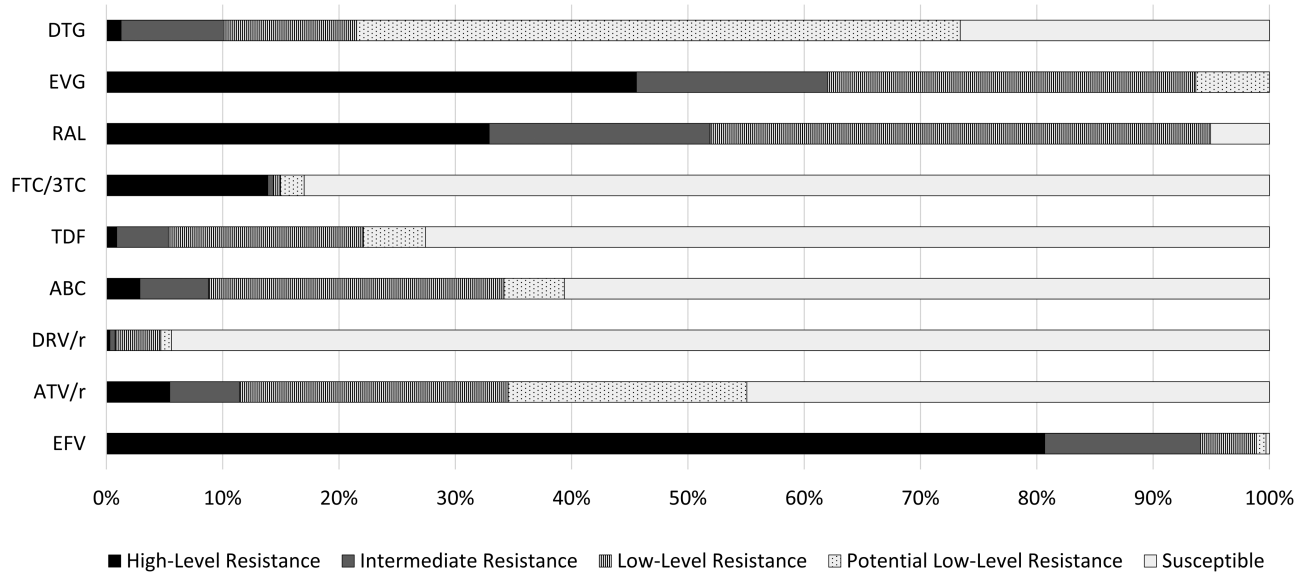

Figure 1. Predicted resistance to commonly used antiretroviral drugs among HIV-1 nucleotide sequences with ≥1 transmitted drug-resistance–associated mutation: 28 US states, 2014–2018. Resistance was predicted by HIVdb genotypic resistance interpretation system, version 8.2. Abbreviations: ABC, abacavir; ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC/3TC, emtricitabine/lamivudine; RAL, raltegravir; TDF, tenofovir.

ritonavir (227/1983 [11.4%]) but much more common for raltegravir (41/79 [51.9%]), elvitegravir (49/79 [62.0%]), and efavirenz (5327/5662 [94.1%]).

During 2014–2018, TDRM prevalence did not change significantly overall or for individual drug classes (Figure 2A). Among mutations with notable effect on first-line NRTI or INSTI and present in more than 10 sequences in the analysis, only M184V prevalence increased during the time period (estimated 12.9% increase per year; 95% confidence interval, 5.6–20.6), from 0.5% in 2014 to 0.9% in 2018 (Figure 2B).

DISCUSSION

In this study, we report transmitted HIV-1 drug resistance among more than 50 000 persons with diagnosed HIV, the largest US sample to date. We include data from 28 states where HIV nucleotide sequences from clinical drug-resistance testing were routinely reported during 2014–2018; these 28 states account for more than 70% of all HIV diagnoses in the United States each year [26]. We report for the first time the prevalence of transmitted HIV-1 drug resistance to INSTIs in a large US sample; the more than 10 000 integrase sequences in this

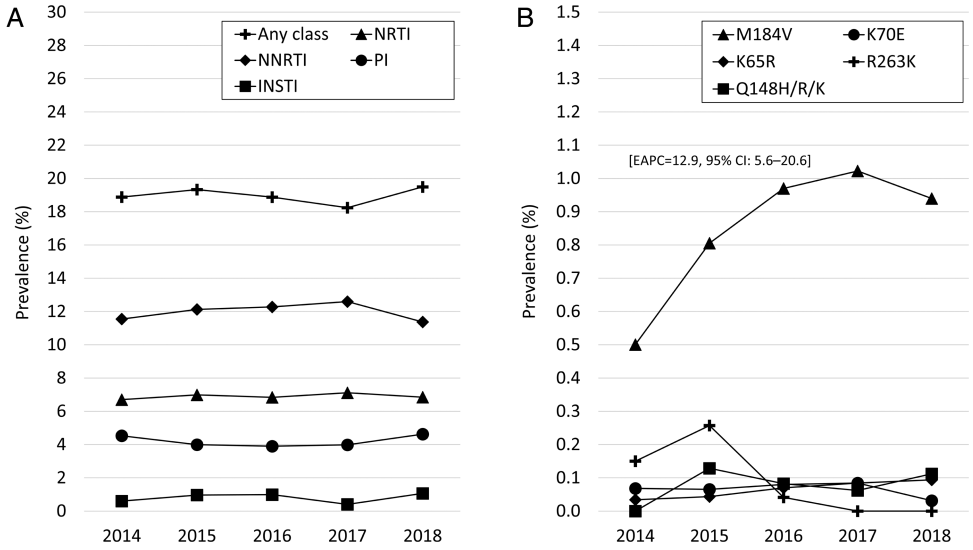

Figure 2. Transmitted drug-resistance–associated mutation prevalence by year for (*A*) individual drug classes and (*B*) key NRTI and INSTI mutations: 28 US states, 2014–2018. Key mutations include those with frequency N >10 in the analysis, and which substantially decrease susceptibility to first-line NRTIs (M184V, K65R, K70E) or INSTIs (Q148H/R/K, R263K). Abbreviations: CI, confidence interval; EAPC, estimated annual percent change; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

analysis were performed during a period of expanding INSTI use in clinical care.

Overall TDRM prevalence in this analysis was 18.9%, the highest prevalence reported to date in a large US study. Direct comparison to prior studies is complicated by differences in surveillance mutation lists used and by our inclusion of INSTI TDRMs. Our analysis used a similar method and mutation list as a prior CDC analysis of 2006 data [9], but with the addition of INSTI mutations that were a small contributor to overall TDRM prevalence. Compared with this previous study, our results suggest that US TDRM prevalence did increase between 2006 and 2014 overall (14.6% to 18.9%), for NNRTI (7.8% to 11.5%), and for NRTI (5.6% to 6.7%), with no change for PI (4.5%) [9]. However, from 2014 to 2018, TDRM prevalence did not increase or decrease overall or for individual drug classes. The low proportion of sequences with TDRMs to multiple drug classes was similar to prior US studies [7, 27] and indicates that an active ART regimen could be constructed for nearly all persons in the analysis.

Transmitted NRTI resistance in this analysis was similar to previous US studies [8, 9, 27] overall and in the prominence of TAMs, which comprised 7 of the 10 most common NRTI mutations (ie, M41L, T215S, T215D, D67N, K219Q, L210W, E44D). These mutations, selected by zidovudine (AZT) and stavudine (d4T), emerged in the 1990s and continue to be transmitted at stable levels despite infrequent use of these drugs in the current era; TAMs have minimal effects on current first-line NRTIs unless combined with other mutations.

Among non-TAM NRTI mutations, M184V, which reduces 3TC and FTC susceptibility, was most common (0.9%), and increased modestly during 2014–2018. However, M184V prevalence overall and by year remains similar to prior analyses [8, 9]. K65R, which significantly reduces susceptibility to tenofovir disoproxil fumarate (TDF) [28], tenofovir alafenamide (TAF) [29], FTC/3TC, and ABC [30], was detected infrequently in this analysis, similar to results from prior studies [8, 9]. Even fewer sequences contained both K65R and M184V/I, a mutation combination noted in prior PrEP failures. This observed prevalence likely underestimates true transmitted K65R and M184V prevalence, as both mutations decay within weeks or months in the absence of drug pressure [31–34] but can persist in minority variant strains not detected by conventional bulk sequencing [35]. Although NHSS data do not capture time since HIV infection, the large proportion of persons with stage 2 or stage 3 infection at diagnosis (Table 1) indicates a majority of people in this study had longstanding HIV infection at the time of diagnosis with ample time for the decay of transmitted resistance. Regardless, continued low prevalence of transmitted M184V and K65R is reassuring and reflects relatively low transmission fitness of these strains in addition to fast reversion dynamics. As PrEP use continues to expand, population-level monitoring of M184V and K65R can provide important insight into the potential impact of drug resistance on future PrEP efficacy.

We report low overall TDRM prevalence for INSTIs with no significant increase or decrease in prevalence during 2014–2018. Most individual INSTI mutations were detected in fewer than 10 sequences; however, high-level or intermediate resistance to the first-generation INSTIs, raltegravir and elvitegravir, was predicted for over half of the 79 sequences with 1 or more INSTI TDRM, which likely reflects their relatively low barrier to resistance and longer period of widespread use. Predicted high-level or intermediate resistance was much less common for dolutegravir. Low INSTI TDRM prevalence throughout 2014–2018 is reassuring, although conclusions about future transmitted INSTI resistance might be premature given that second-generation INSTIs have been widely used for fewer than 5 years and continued expansion of INSTI use is likely for ART and potentially for PrEP.

Transmitted NNRTI resistance prevalence (12.0%) was higher in this study than in prior large US studies [7–9], driven primarily by K103N (8.6%). K103N alone can result in failure of efavirenz-based ART and is responsible for most of the predicted high-level efavirenz resistance in this analysis. Although INSTI-based regimens have largely replaced efavirenz-based ART in the United States, K103N prevalence did not decrease during 2014–2018, reflecting longer intra-host persistence, minimal fitness cost, and more frequent transmission clustering of K103N strains compared with mutations like M184V and K65R [31, 36].

Protease inhibitor TDRM prevalence has changed very little in the past 15 years [6–9], and no significant increase or decrease was seen during 2014–2018. Predicted low, intermediate, and high-level resistance was more common for atazanavir/ritonavir (ATV/r) than for darunavir/r (DRV/r) due primarily to M46I/L, I54V, V82A, and L90M, which have minimal effect on DRV/r. This provides additional support for current ART recommendations favoring DRV/r when a regimen including a PI is needed [3].

This analysis was subject to several limitations. First, this study only includes persons with diagnosed HIV infection with a drug-resistance test performed 3 months or less after HIV diagnosis and reported to public health, and might not reflect prevalence among persons with undiagnosed HIV or those with diagnosed HIV without a drug-resistance test performed or reported. Failure to disclose or report ART use prior to a drug-resistance test could also lead to misclassification of acquired drug resistance. Second, because genotypic resistance testing of the integrase gene is recommended only when INSTI resistance is a concern, it is possible that INSTI TDRM prevalence in this analysis overestimates the true prevalence among all persons with HIV. Third, TDRM prevalence in this analysis is likely underestimated due to reversion of drug-resistant virus

to wild-type, which can occur within weeks or months of HIV infection and varies by mutation; most persons in this analysis had longstanding infection at the time of diagnosis. Finally, HIV-1 nucleotide sequence data in this analysis were generated by conventional bulk sequencing that does not characterize minority variants and might underestimate relevant TDRM prevalence.

We document a reservoir of TAMs and TDRMs to PIs and NNRTIs, which continue to be transmitted despite reduced use or discontinuation of the drugs that select for them. This persistent transmission highlights the role that undiagnosed infection and untreated persons play in HIV transmission [36–38], and underscores the importance of early diagnosis and viral suppression in reducing transmitted drug resistance. Efforts to improve diagnosis and treatment in the EHE initiative will be essential for shrinking this reservoir and preventing further transmission of drug resistance. HIV sequence data reported to public health provide valuable insight into trends in population-level drug resistance resulting from the ever-evolving landscape of clinical guidelines, prescribing practices, and public health initiatives to improve testing and treatment programs.

Standard genotypic drug-resistance testing is recommended at entry into care for all persons with HIV in the United States to assist with selection of an initial ART regimen. In a recent modeling analysis, Hyle et al [39] found such testing offered limited clinical benefit and was not cost-effective for people with HIV starting an INSTI-based regimen. These important findings must be balanced by the population-level benefit of drug-resistance monitoring, the meaningful benefit to vulnerable individuals whose resistance profile is consequential, and the miniscule cost of resistance testing relative to other costs associated with HIV treatment. Population-level monitoring of drug resistance also provides public health benefit through the identification of HIV transmission clusters and subsequent efforts to interrupt transmission and improve service delivery to people with HIV or at risk for HIV.

In conclusion, our data confirm transmitted resistance to current first-line ART remains low and support current ART and PrEP recommendations. Drug susceptibility scoring in this analysis indicates that, among sequences with 1 or more TDRM, only a subset is predicted to have intermediate or high-level resistance in practice. Amidst evolving trends in the use of these drugs for ART and PrEP, population-level monitoring remains essential for informing current and future treatment and prevention guidelines.

Notes

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Potential conflicts of interest. W. H. reports receiving royalties on licenses of patents on pre-exposure prophylaxis for HIV prevention and is listed as an inventor on patents by the US government on methods for HIV drug-resistance detection and patents on methods for HIV prevention by chemoprophylaxis, outside the submitted work. J. A. J. and W. H. are named on patents for sensitive assays for HIV-1 drug resistance. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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