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Prevalence of Transmitted HIV-1 Drug Resistance (TDR) Associated Mutations and Predicted Drug Sensitivity in Newly Diagnosed HIV-1 Patient Cohort in a Western New York, 2005-2011

Lili Dai[1,3], Supriya D Mahajan[3], Donald L Sykes[3], Alyssa Shon[2], Stanley A Schwartz[3], Ning Li[1], Hao Wu[1]* and Chiu-Bin Hsiao[2]

[1]*Center for Infectious Diseases, Beijing You'an Hospital, Capital Medical University, China*
[2]*Department of Medicine, Division of Infectious Diseases, State University of New York at Buffalo, USA*
[3]*Department of Medicine, Division of Allergy, Immunology, and Rheumatology, State University of New York at Buffalo, USA*

Abstract

HIV-1 drug resistance associated mutations can be transmitted to persons who are antiretroviral-naive, called Transmitted Drug Resistance (TDR). TDR has the potential to compromise first-line anti-retroviral therapy (ART) in HIV patients and limit the antiretroviral regimens options, which has become an important public health problem. TDR surveillance is an important strategy to monitor the emergence of genetic. TDR has been reported in the United States for many years. Current antiretroviral treatment guidelines recommend drug resistance testing after diagnosis. We did a retrospective analysis of the genotype database of ART-naïve patients from our immunodeficiency clinics at the Erie County Medical Center (ECMC) in Buffalo, New York, United States from 2005 to 2011. The prevalence of TDR in the ECMC-US cohort is still high 13.3%. The drug susceptibility is significantly reduced in 10.9% patients. The mutations were mostly "old" drug (such as AZT, D4T, EFV, NVP, SQV/r) related, while most of the "new" drugs (such as TDF, RPV, DRV/r) maintained sensitivity. The introduction of new second, third generation drugs in recent years has not brought down the prevalence of TDR significantly. The TDR prevalence rates in the United States are indicative of the fact that drug resistant mutations were generated before or at the beginning of ART and transmitted down from one generation to the other in ART naive patients, emphasizing that additional management strategies are needed to diagnose HIV infected patients earlier and to effectively treat them timely to further reduce TDR.

Keywords: TDR; Drug resistance; AIDS; HIV; Antiviral therapy

Introduction

HIV-1 drug resistance associated mutations can be transmitted to persons who are antiretroviral-naive, called transmitted drug resistance (TDR). TDR has the potential to compromise first-line anti-retroviral therapy (ART) in HIV patients and limit the antiretroviral regimens options, which has become an important public health problem. TDR surveillance is an important strategy to monitor the emergence of genetic resistance. TDR usually emerges in regions where ART has been widely available for years. TDR has been reported in the United States for many years [1-3], significant resistance has been observed to the three main antiretroviral drug classes, nucleoside reverse-transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs) and protease inhibitors (PIs). Since late 2007, several newer HIV medications, including Raltegravir, Maraviroc, Darunavir and Etravirine, were introduced, allowing for greater virologic suppression in patients on those treatment regimens. But studies have shown, that although the upward trend of the TDR rate from 2003-2007 has ceased due to the introduction of the new drugs, the TDR prevalence in 2008-2009 remained substantial, and was not significantly different than in prior years [4,5].

Several factors contribute to the occurrence of TDR in a given population, these include specific drug-resistance mutation list used to interpret resistance data, patients risky behaviors such as unprotected sex and intravenous drug use, nonadherence to treatment, current or previous ART regimens efficacy, rates of virologic suppression and HIV-1 subtype diversity. In the current study, we did a retrospective analysis of the genotype database of ART-naïve patients from our immunodeficiency clinics at the Erie County Medical Center (ECMC) in Buffalo, New York, United States since 2005 to 2011. The aim of our study is to calculate the prevalence of TDR and identify resistance patterns. We also examined whether TDR differed before and after the augment of new antiretroviral medications in late 2007 at ECMC. Characterizing the TDR in the newly diagnosed patients in ECMC would give us an insight on the effect of ART on TDR in USA in recent years, which would provide important HIV treatment guidelines for clinicians.

Materials and Methods

Study population

This study included databases from the immunodeficiency clinics in Immunodeficiency Clinic at Erie County Medical Center (ECMC), Buffalo, New York. ECMC's immunodeficiency Services is the largest and only comprehensive HIV/AIDS care center in Western New York, which has been the designated site for the testing, preventing, counseling and caring of HIV infected individuals since 1986. The cohort database has been established and maintained since 1994. We collected the genotyping data for all patients enrolled in the HIV/AIDS clinics since the genotypic resistance tests were done for all the patients

***Corresponding author:** Hao Wu, Director of Center for Infectious Diseases, Beijing You'an Hospital, Capital Medical University, Beijng, China, 10069, Tel: 716 -361-3985 (8613501253203); E-mail: whdoc900@gmail.com

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as part of routine clinical care since 2005 to 2011. The main patient inclusion criteria for the study was recent positive diagnosis (within 6 months), and no known exposure to antiretroviral drugs (ART-naïve). A total of 330 ART-naïve patients were included in the study.

Ethics statement

Informed consent was obtained from all study participants for the collection of blood samples, and subsequent analyses, and the study was approved by the Health Sciences Institutional Review Board (HSIRB) at University at Buffalo.

Data collection

Age, demographics, HIV risk factors, and ART history were collected by trained counselors using a standardized questionnaire at enrolment.

CD4 count and HIV-1 viral load

$CD4^+$T lymphocytes counts were measured in whole fresh blood on a single flow-cytometry platform on a FACScalibur instrument (Becton Dickinson, San Jose, CA, USA), according to manufacturer's instructions. Plasma HIV-1 RNA (pVL) quantification was performed on thawed plasma using the Roche Cobas Ampli-Prep/Cobas TaqMan HIV-1 test (Roche Molecular Systems, France), according to the manufacturer's instructions. For this study, the samples of $CD4^+$T lymphocytes cell counts, plasma HIV-1 RNA levels and genotype were taken at the same time of diagnosis.

Resistance analysis

HIV genotype testing was performed by commercial laboratories test kit, GenoSure™, and results were reported to the state or local health department. Only protease and reverse transcriptase sequences of the pol gene were reported. TDR was defined as the detection of 1 or more mutations in the surveillance drug resistance mutations (SDRMs) listed by the World Health Organization [6,7]. This guideline optimizes the specificity of TDR classification for epidemiologic studies by including only mutations that are rarely selected for without drug pressure, and by excluding common polymorphic mutations (includes mutations that have a prevalence of at least 1% in treated persons and omits those mutations that are ≤ 0.5% in treatment-naive persons in any subtype. ARV specific predicted resistance was calculated using code developed by Frontier Science and scores from the Stanford HIVDB algorithm, version 6.2.0. ARVs were categorized by class. Predicted resistance to specific antiretroviral drugs was defined as sequences with intermediate or high level resistance according to the Stanford HIVDB 5-point resistance scale.

Statistics

Prevalence of TDR was calculated as the number of patients with detectable SDRMs divided by the number of patients with a specific genotype. Confidence intervals (CI) were calculated using a 95% Wilson confidence interval for binomially distributed data. Data analyses were performed using a Chi-square test and differences were considered statistically significant when P values were ≤ 0.05. All statistical analyses were conducted in SPSS 14.0 software. Resistance to each ART class NRTIs, NNRTIs, and PIs was calculated by each year. To compare the odds ratio of TDR before and after the use of newer antiretroviral medications that were prescribed in late 2007, we divided patients into two groups by estimated dates of HIV infection (2005-2007 vs 2008-2011).

Results

Patient characteristics

A total of 330 patients were enrolled. All the patients were ART-naïve. The general characteristics of all the patients included in the analysis are shown in Table 1. Briefly, the median age of the patients was 40 years old (IQR 30-45), 216 patients (65.5%) were male; 122 (36.4%) patients were men who have sex with men (MSM), and 26 (7.9%) used injection drugs, 160 (48.5%) were heterosexual contact, 7 (2.1%) patients might be infected by homosexual contact or intravenous drug using, another 17 (5.1%) were others or did not know the possible infecting route; In the racial distribution, there was 36.7% Caucasian, 51.5% African American, 10% Hispanic and 1.8% Asian. The median CD4 cell count was 302 (84-532) cells/mm^3, and the viral load was 4.6 (4.0-5.3) log10 copies/ml. There was no significant difference in the demographic and clinical characteristics of the patients with TDR and without TDR.

Prevalence of TDR

According to the surveillance drug resistance mutations (SDRMs) listed by the World Health Organization, a totally of 44 patients had one or more transmitted HIV-1 drug resistance mutations (Table 2), representing an overall 13.3% prevalence of TDR. TDR to nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) were identified among 24 (7.3%) and 22 (6.7%) of the patients respectively. However the of TDR to protease inhibitors (PIs) was found in 10 (3.0%) patients. The majority of the patients with TDR displayed a single drug class resistance mutation (34 out of 44 TDR patients, representing 10% in the entire cohort). However, there were 8 (2.4%) and 2 (0.6%) patients with TDRs to two or three classes of ARV were discovered respectively.

The patterns of TDR

Among all the patients harboring resistant, the most common TDR mutations were NRTIs associated mutations (Table 3): reverse transcriptase (RT) position T215 revertants (4.5%), M41L (1.8%), L210W (1.8%), M184V (1.5%) and NNRTIs associated mutations: RT position K103N (3.6%), G190A (1.5%). Other relatively rare TDR resistance related mutations include reverse transcriptase T69D (0.9%), K219Q(0.9%), V75M (0.3%), L74V (0.3%), D67N (0.3%), K101E/P (0.6%), Y181C (0.6%), P225H (0.6%), V106A/M (0.6%), Y188L/H (0.6%), and protease L90M (0.9%), N88D (0.6%), V82A/L (0.6%), M46L/I/V (0.6%), I84V (0.3%), I50V (0.3%), D30N (0.3%).

Drug susceptibility

Based on the Stanford HIVdb algorithm, drug susceptibility was possibly significantly reduced in 36 patients (10.9%) (Table 4). Among the 15 cases (4.5%) with mutations conferring significant resistance to NRTIs, 10 (3.0%) had intermediate or high level resistance to AZT, D4T, only 3 (0.9%) and 4 (1.2%) patients were predicted to be obviously resistant to TDF and ABC. 5 patients (1.5%) were predicted to have high-level resistance to 3TC and FTC. When NNRTI mutations were present in 22 (6.7%) patients, almost all the patients were predicted to have intermediate to high-level resistance to EFV (n=21, 6.4%) and NVP (n=22, 6.7%), while quite a few patients were resistant to RPV and ETR (n=6, 1.8% and n=3, 0.9% respectively). Cases with PI resistance (n=9, 2.7%) tended to have intermediate or high-level resistance to NFV, seen in n=7, (2.1%) and SQV/r as seen in n=4 (1.2%) patients, who

	Total n=330	TDR (n=44)	No TDR (n=286)	P value
Age at genotype testing				
Mean (IQR)	40 (30-45)	39 (28-44)	40(31-46)	0.404
Sex				
Male n(%)	216 (65.5)	29 (65.9)	187 (65.4)	0.946
Estimated routes of infection				
MSM n(%)	120 (36.4)	16 (36.4)	104 (6.4)	1.000
IDU n(%)	26 (7.9)	3 (6.8)	23 (8.0)	0.779
Heterosexual contact n(%)	160 (48.5)	21 (47.7)	139 (48.6)	0.914
Others or unknown n(%)	24 (7.3)	4(9.1)	20(7.0)	0.618
Race				
white n(%)	121 (36.7)	16(36.4)	105 (36.7)	0.964
black n(%)	170 (51.5)	24(54.5)	146 (51.0)	0.666
Hispanics or Asian n (%)	39(11.8)	3(6.8)	36(12.6)	0.270
CD4 cell count (cells/mm^3)				
Mean ± SD	302 (84-532)	263(19-489)	315(117-537)	0.096
Viral load				
Mean (IQR)	4.6 (4.0-5.3)	4.7(3.9-5.1)	4.6(4.0-5.3)	0.530

Table 1: Demographic and Clinical Characteristics of HIV-Infected Patients in ECMC, Buffalo, New York, USA.

Drug Treatment	ECMC	(n=330)
	n	%
Any ARVs	**44**	**13.3**
NRTI	**24**	**7.3***
NNRTI	**22**	**6.7****
PI	**10**	**3.0**
Single Class	**34**	**10.3**
Two Class	**8**	**2.4**
NRTI-NNRTI	**4**	**1.2**
NRTI-PI	**3**	**0.9**
NNRTI-PI	**1**	**0.3**
Three Class	**2**	**0.6**

ARVs were categorized by class. Single, double or triple class resistance was defined as 1 or more TDR within one, two or three antiretroviral drug classes respectively

*The prevalence of TDR to NRTIs (7.3%) was significantly higher than that to PIs (3.0%), p=0.014 and p=0.030. and NNRTIs (6.7%);

**The prevalence of TDR to NNRTIs (6.7%) was significantly higher than that to PIs (3.0%), p=0.030

Table 2: Transmitted drug resistance by drug class in new diagnosed HIV infected patients, ECMC, Buffalo, New York, 2005-2011.

NRTI mutations	n	%	NNRTI mutations	n	%	PI mutations	N	%
T215C/D/E/F/S/Y	15	4.5	K103N/S	12	3.6	L90M	3	0.9
M41L	6	1.8	G190A	5	1.5	N88D	2	0.6
L210W	6	1.8	K101E/P	2	0.6	V82A/L	2	0.6
M184V	5	1.5	Y181C	2	0.6	M46L/I/V	2	0.6
T69D	3	0.9	P225H	2	0.6	I84V	1	0.3
K219Q	3	0.9	V106A/M	2	0.6	I50V	1	0.3
V75M	1	0.3	Y188L/H	2	0.6	D30N	1	0.3
L74V	1	0.3						
D67N	1	0.3						

Table 3: Resistant mutations by drug class in new diagnosed patients 2005-2011, ECMC, Buffalo, New York, USA.

also remained susceptible or had only a potential low-level resistance to DRV/r. Only one (0.3%) patient from this cohort was predicted to have intermediate-level resistance to LPV/r and ATV/r, two patients (0.6%) were predicted to have intermediate-level resistance to FPV/r and TPV/r. Predicted drug sensitivity were marked in Figure 1.

Prevalence of TDR before and after the introduction of newer ART regimens

We examined whether TDR differed before and after the adoption

	N	%
Total	36	10.9
NRTIs	15	4.5
3TC/FTC	5	1.5
ABC	4	1.2
AZT	10	3.0
TDF	3	0.9
NNRTIs	22	6.7
EFV	21	6.4
NVP	22	6.7
RPV	6	1.8
ETR	3	0.9
PIs	9	2.7
LPV/r	1	0.3
DRV/r	0	0
FPV/r	2	0.6
ATV/r	1	0.3
SQV/r	4	1.2

*(i) 0 to 9: Susceptible, no evidence of reduced susceptibility compared with wildtype;

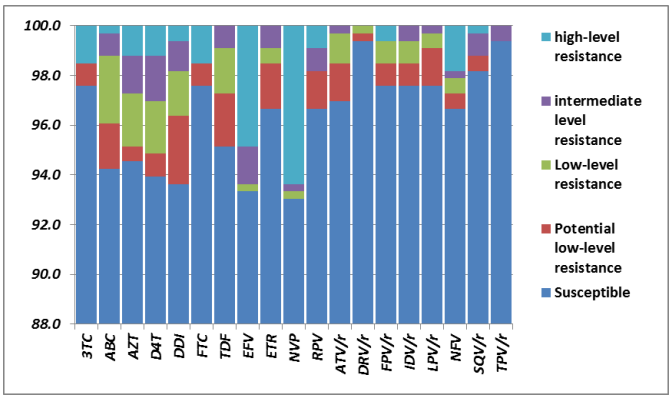
(ii) 10 to 14: Potential low-level resistance. The virus is likely to be fully susceptible yet it contains mutations that may be indicative of previous exposure to the ARV class of the drug;

(iii) 15 to 29: Low-level resistance. Virus isolates of this type have reduced *in-vitro* drug-susceptibility and/or patients with viruses of this genotype may have a suboptimal virologic response to treatment compared with the treatment of a wildtype virus;

(iv) 30 to 59: The genotype suggests a degree of drug resistance greater than low-level resistance but lower than high-level resistance;

(v) ≥ 60: the genotype is similar to that of isolates with the highest levels of *in vitro* drug resistance and/or patients infected with isolates having similar genotypes generally have little or no virologic response to treatment with the drug.

Table 4: Prevalence of predicted intermediate or high level resistance to DHHS recommended starting drugs according to the Stanford HIVDB 5-point resistance scale.



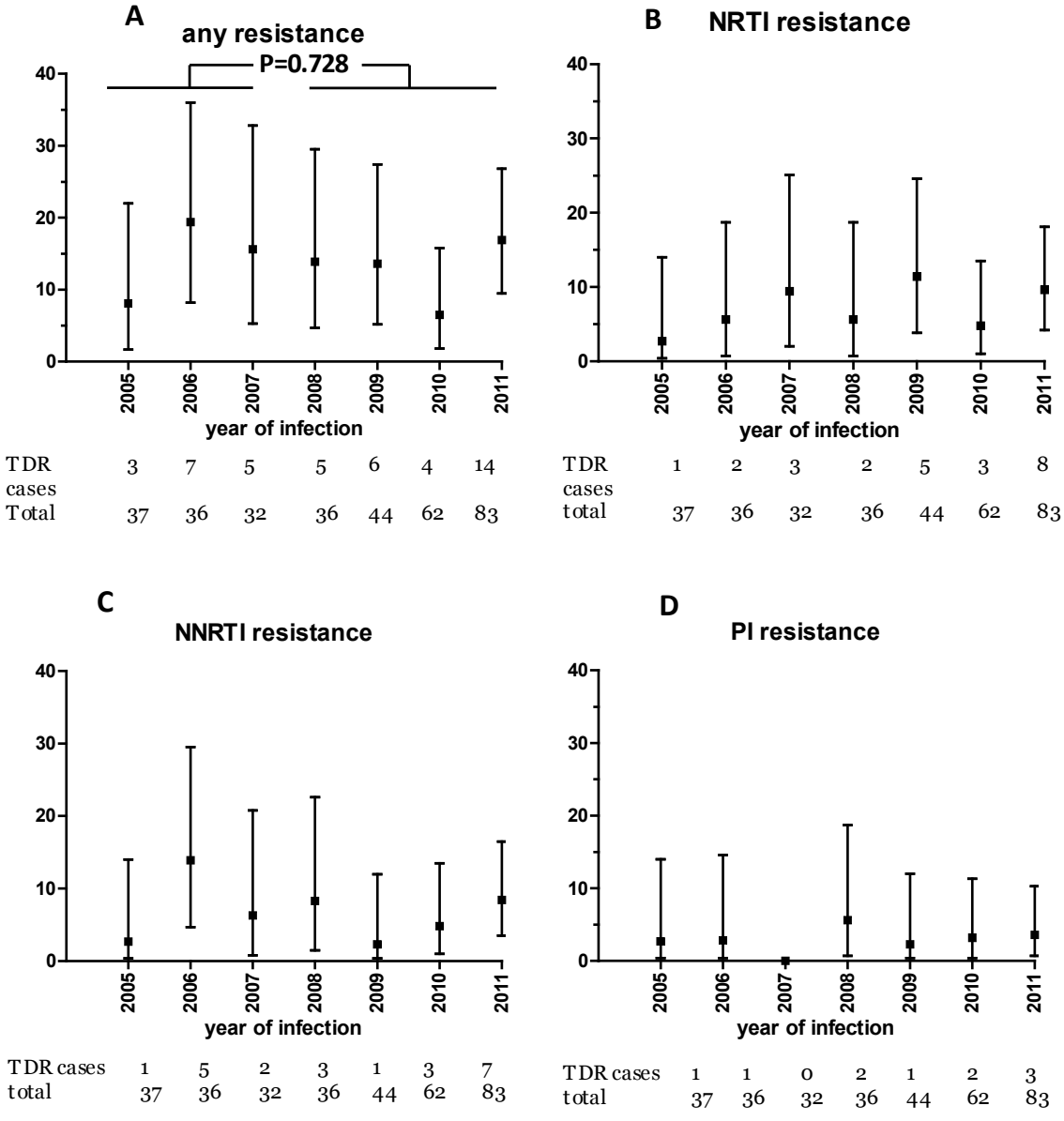
3TC: Lamivudine; ABC: abacavir ; AZT: zidovudine; D4T: Stavudine; DDI: Didanosine; FTC: Emtricitabine; TDF: Tenofovir; EFV: Efavirenz ; ETR: Etravirine; NVP: Nevirapine; RPV: Rilpivirine; ATV/r: Atazanavir+Ritonavir; DRV/r: Darunavir+Ritonavir; FPV/r: Fosamprenavir+Ritonavir; IDV/r: Indinavir+Ritonavir; LPV/r: Lopinavir/Ritonavir; NFV: nelfinavir; SQV/r: saquinavir+Ritonavir; TPV/r: Tipranavir+ Ritonavir

Figure 1: Predicted drug sensitivity of 330 new diagnosed HIV-infected patients 2005-2011, ECMC, Buffalo, New York according to the Stanford HIVDB 5-point resistance scale.

of new antiretroviral medications in late 2007. Our data from 2008-2011, shows that 12.9% (95% CI, 8.8%-18.0%) of cohort members acquired TDR. This was lower than the 14.3% prevalence seen in the group of patients enrolled in the clinic between 2005-2007 (95% CI, 8.2%-22.5%). The confidence intervals around both estimations were wide and although the TDR was lower in patients enrolled between 2008-2011 as compared to patients enrolled between 2005-2007, this difference was not statistically significant (odds ratio 1.1264, 95% CI 0.5756 to 2.2045; P= 0.7282) (Figure 2).

Discussion

TDR which is an inevitable outcome of antiretroviral therapy has important clinical and public health implications, and presents in 10-20% [8] of new HIV-1 infections worldwide. Understanding current TDR patterns can help clinicians assess the importance of genotyping antiretroviral therapy (ART)-naive patients, been informed about the selection of ART regimens, and anticipate trends that may affect the future ability to effectively treat the HIV epidemic with existing ART agents. HIV transmitted drug resistance can be influenced by factors such as prevalence of drug resistance among persons engaged



Prevalence (dot) and 95% confidence interval (vertical line) of overall transmitted drug resistance (A), NRTI resistance (B), NNRTI resistance (C), and PI resistance (D)
TDR: transmitted drug resistance; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor

Figure 2: Annual prevalence of transmitted HIV-1 drug resistance in 330 new diagnosed HIV-infected patients, 2005-2011.

in high-risk behavior, access to ART, physician prescribing practices, and proportion of HIV-infected patients achieving full suppression of plasma viremia.

The early induction of ART in the United States (US) has led to increasing transmission of HIV variants with reduced susceptibility to ARV drugs. US is reported to be one of the places where there is the highest prevalence of TDR because of the prolonged periods of ART exposure. There are currently five classes of HIV drugs available in the US, which include Entry and Fusion Inhibitors, Integrase Inhibitors, Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Nucleoside Reverse Transcriptase Inhibitors (NRTIs), and Protease Inhibitors (PIs). AZT, was the first drug used to treat HIV infection in 1987 in the US. Isolates with reduced susceptibility to AZT were first described in 1989. The NNRTs, PIs, and other NRTIs were approved by the Federal Drug Administration (FDA), which then led to the universal adoption of Highly Active Antiretroviral Therapy (HAART) or combined antiretroviral therapy (cART). But, as use of each class of ARV agents expanded, it was followed by the selection of HIV variants resistant to that ARV agent and subsequent transmission of these resistant variants occurred. It was reported that the overall TDR prevalence in the US is 14.6% [9] and that in New York State is 11.2% [10] respectively. In late 2007, several new drugs, such as Raltegravir, Maraviroc, Darunavir and Etravirine were approved by FDA, it was believed that the prevalence of TDR would be cut down by the widespread use of the new drugs. But, earlier studies have shown, that although the upward trend of the 2003-2007 TDR rate from has ceased due to the introduction of the new drugs, the TDR prevalence in 2008-2009 was not significantly different as compared to the 2003- 2007 prevalence [4,5].

In the current study, we did a retrospective analysis of 330 ART-naïve patients from our immunodeficiency clinics at ECMC in Buffalo, New York, US since 2005 to 2011. We found, the overall prevalence of TDR in these patients was 13.3%, which is similar to other reported US studies [9,10]. The prevalence of TDR to NRTIs (7.3%) and NNRTIs (6.7%) was significantly ($p<0.001$ and $p=0.002$ respectively) higher than that to PIs (3.0%).

Furthermore, with respect to the pattern of TDR, the most common mutations included the reverse transcriptase (RT) mutations such as T215/S/D/Y, M41L, L210W, M184V, K103N/S, G190A, which are mainly related to AZT,3TC, EFV, NVP, SQV/r, all of which were to these first generation drugs, however, most of the new ARV drugs, such as TDF, DRV/r, LPV/r, ATV/r showed sustained sensitivity, suggesting most of the TDR originated from the non-adequate treatment with these first generation ARV drugs in early 1990s, and not due failure of current antiretroviral therapies. As PIs use in the US was much more popular than NNRTIs, TDR related to the NRTIs and NNRTIs are more common as compared to TDR related to PIs, which is consistent with other studies [4,10,11].

There are two important sources of TDR: (1) persons who develop drug resistance mutations while on ART and subsequently transmit HIV and (2) persons who acquire TDR mutations during initial infection and maintain the mutations in the absence of ART until they transmit HIV [4]. If TDR trends are driven primarily by persons with drug-resistant HIV who are viremic despite taking ART, changes in ART can help achieve better suppression of drug resistance and rapidly decrease TDR rates. In contrast, if TDR is driven more by ART-naive individuals, the effects of novel therapies should be minimal or delayed, at least during the initial period that these drugs become widely available. Our results suggest that patients who had ART failure are not a major source of TDR. The outcome of the comparison between the rate of TDR before and after the introduction of new drugs in late 2007 in ECMC-US cohorts supports this finding. We observed no significant difference in TDR prevalence (13.8% vs 12.5%, P=0.911) before and after the introduction of new drugs. Several studies from resource rich settings such as the US, Canada and Poland also reported that despite the introduction of novel ART agents such as Raltegravir, Maraviroc, and Etravirine in late 2007, the prevalence of transmitted drug resistance in 2008-2009 remained substantial and was not significantly different from that obtained in prior years.

Early studies suggest that mutations that may result in significantly decreased fitness of HIV-1 as measured by replicative capacity are not as prevalent in ART naïve patients as compared with patients who were treatment-experienced patients, suggesting a decreased efficiency of transmission with decreased fitness. It was believed that some TDR, like M184 V and MDR variants, have an impaired fitness, which weakens the virus propagation efficiency [12]. Using mathematical modeling of the genotypes from HIV-infected patients in Los Angeles and San Diego, investigators found that drug-resistant strains were transmitted only 20% of the frequency predicted by the prevalence of drug resistance, this suggests that complex interactions between fitness of drug-resistant HIV and viral transmission remain to be elucidated. Mechanisms cited for TDR transmission include 1) archived mutation(s) in latently infected resting CD4+ T cells that reflects the transmitted strain(s), most of these TDR mutations cannot be reversed to wild-type HIV (back mutation) after the transmission to new host, as most transmitted drug-resistant variants remain detectable in plasma for over two years [12,13]. If a patient gets infected and acquires a TDR early, he or she can be an important source of TDR for a long period of time. TDR can be found in HIV proviral DNA in seminal cells, circulating monocytes, and $CD4^+$ T lymphocytes of patients with suppressed plasma HIV RNA [12]. This reflects persistence of transmitted drug resistance. 2) Significant differences exist in the composition of viruses in various body compartments and it has been hypothesized that this may be attributed to the differences in drug penetration between the compartments. Even if the virus levels in the plasma are controlled, the less ARV accessible sites such as the central nervous system and genital tract, may become predisposed to becoming reservoirs of drug-resistant variants.

Our study provides an insight on the effect of ART on TDR in USA in recent years, these observations warrant a need for a larger population study in the future. Even though most of TDR seems susceptible to the new drugs at present, the accumulation of them could cause more drug resistance in the future and it could be an important concern for the HIV treatment in the resource-limited settings where available drugs are limited.

Conclusions

The prevalence of TDR in the ECMC-US cohort is 13.3%. The drug susceptibility is significantly reduced in 10.9% patients. The mutations were mostly "old" drugs (such as AZT, D4T, EFV, NVP, SQV/r) related, while most of the "new" drugs (such as TDF, RPV, DRV/r) maintained sensitivity. The introduction of new second, third generation drugs in recent years has not brought down the prevalence of TDR significantly. This study indicates that most of the TDR in USA is transmitted from before or at the beginning of ART era by ART naive patients, emphasizing that additional improved strategy are needed to

diagnose acute/early HIV infected patients earlier and treat them in a timely fashion to further reduce TDR. Genotypic resistance testing is still necessary prior to initiation of antiretroviral therapy in ARV-naïve individuals in USA. TDR surveillance programs are necessary to closely observe the TDR prevalence in the country.

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Author Contributions

LD - Conceived experimental design and laboratory and data analysis of the patients and manuscript writing; SM -Data Analysis of the ECMC-US patient cohort and manuscript writing; DS- ECMC cohort laboratory analysis; CBH, AS -Patient enrollment, clinical evaluation of all patients in the ECMC-US cohort; SAS - clinical evaluation of patients in the ECMC-US cohort; NL- data analysis of the patients; HW-Manuscript writing and data analysis.

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