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Transmitted Drug Resistance and Antiretroviral Treatment Outcomes in Non-Subtype B HIV1- Infected Patients in South East Asia

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Abstract

Background—We compared treatment outcomes of transmitted drug resistance (TDR) in patients on fully or partially sensitive drug regimens.

Methods—Factors associated with survival and failure were analyzed using Cox proportional hazards and discrete time conditional logistic models.

Results—TDR, found in 60/1471 (4.1%) Asian treatment naïve patients, was one of the significant predictors of failure. Patients with TDR to >1 drug in their regimen were >3 times as likely to fail compared to no TDR.

Conclusion—TDR was associated with failure in the context of non-fully sensitive regimens. Efforts are needed to incorporate resistance testing into national treatment programs.

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Introduction

Transmitted drug resistance (TDR) can lead to treatment failure, and screening for HIV drug resistance (HIVDR) before antiretroviral therapy (ART) initiation is recommended in high-income countries.¹ However, such screening is not routinely done in developing countries due to infrastructure and cost constraints. Most available data on the association of TDR with treatment failure are from developed countries where HIV-1 subtype B predominates¹⁻² and similar data from settings with non-B subtypes are limited³⁻⁴.

Several threshold surveillance studies in 2005-6 revealed low prevalence of TDR (<5%) in Asia and Sub-Saharan Africa⁵⁻⁹ as compared to 8-19% prevalence in developed countries, where ART has been used longer.¹⁰⁻¹⁴ More recent TDR surveillance in Thailand showed increasing TDR trends in both heterosexual (4.9%)¹⁵ and male homosexual populations (6.8%).¹⁶ Longer-term TDR data and their impact on ART outcome from low- and middle-income Asian countries are still limited especially in South-East Asia, where circulating recombinant form (CRF)01_AE predominates.¹⁷

TASER-M (TREAT Asia Studies to Evaluate Resistance-Monitoring) is an observational cohort study designed to monitor HIVDR in Asian patients starting combination ART (cART) or switching to second-line ART upon treatment failure. In a preliminary report, Sungkanuparph et al. found that 13.8% of 682 patients had >1 primary HIVDR mutation.¹⁸ In this study we examined the effects of TDR on longitudinal treatment outcomes, such as virological failure (VF) and mortality in TASER-M patients initiating cART.

Methods

Patient Recruitment

TASER-M patients were recruited from 12 sites in Thailand (5 sites), Malaysia (3), Hong Kong (2), the Philippines and Indonesia (1 site each). Informed consent was obtained prior to enrollment and the study protocol was approved by the institutional review boards of the participating sites and coordinating centers.

Genotypic HIVDR testing and analysis

Commercial (TrueGene[®] and ViroSeq[®]) and in-house genotypic HIVDR assays⁵ were used by clinical sites depending on local availability. All laboratories participated in the TAQAS external quality assurance program.¹⁹ Resistance mutations and drug susceptibility predictions were obtained from the Stanford HIV Database algorithm (version 6.1.1).²⁰ HIV-1 subtypes were predicted by the REGA Subtyping Tool.²¹ TDR was defined as 1 amino acid mutation according to the WHO 2009 surveillance HIVDR mutation list.²²

Patients were classified into three groups: (1) 'no TDR'; (2) 'TDR with susceptible ART': TDR and full predicted susceptibility to the initial ART regimen (susceptible and potential low-level resistance by the Stanford algorithm); and (3) 'TDR with suboptimal ART': TDR and at least one initial drug with predicted reduced susceptibility (low-level, intermediate and high-level resistance by the Stanford algorithm).

Statistical analysis

For survival analysis, the endpoint was defined as all-cause mortality. Factors associated with survival were analyzed using the Cox regression model, stratified by site.

VF was defined as viral load (VL) ≥ 400 copies/ml after at least six months on cART. To account for VF occurring at the same time point among different patients due to VL assessments being scheduled annually as per protocol, regression models were analyzed using discrete time conditional logistic models, conditioned on site and time interval. Analysis time was divided into 6-monthly intervals to account for patients with VL testing outside of their scheduled annual monitoring. As such, there were seven intervals for the regression models: (1) 6-months to 1-year; (2) 1-1.5 years; (3) 1.5-2 years; (4) 2-2.5 years; (5) 2.5-3 years; (6) 3-3.5 years; and (7) 3.5-4 years.

Other covariates included age at start of cART, sex, HIV exposure mode, pre-treatment VL and CD4, initial ART, hepatitis B/C co-infection, prior AIDS diagnosis, subtype and ART adherence, obtained from the 30-day Adherence Visual Analogue Scale at each clinical visit. Factors significant in the multivariate model at the 5% level were adjusted for in the final model. Descriptive statistics were analyzed using Chi Squared/Fisher's exact test for categorical data and Kruskal-Wallis test for continuous data.

Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and STATA version 12.0 (STATA Corp., College Station, TX, USA).

Results

Of a total of 1,471 patients included, 1,411 (95.9%) were in the 'no TDR' group, 26 (1.8%) in the 'TDR with susceptible ART' group and 34 (2.3%) in the 'TDR with suboptimal ART' group (Table 1). Most patients (90.7%) received WHO-recommended first-line ART, i.e., nucleoside reverse transcriptase inhibitor (NRTI) + non-nucleoside reverse transcriptase inhibitors (NNRTI). There was no significant difference in the proportions of those who received NRTI+NNRTI vs NRTI+protease inhibitors (PI) vs NRTI only for all TDR groups ($p=0.065$). There was also no significant difference in the proportions of TDR for AE, B and other Non-B subtypes ($p=0.312$).

TDR was found in 60 patients (4.1%); 60% of which had NRTI, 43% NNRTI and 18% PI-associated mutations. The most common NRTI-associated mutation was M184V whereas the most common NNRTI- and PI-associated mutations were K103N and M46L, respectively. Two or more thymidine analogue mutations (TAMs) were found in four patients.

TDR and mortality

Of 1,471 treatment-naïve patients, there were 60 deaths. The median follow-up time was 1.8 years (IQR: 0.9-2.4) with a mortality rate of 2.4 per 100 patient-years. Factors associated with mortality in the final multivariate model were age ($p<0.001$), sex ($p=0.011$) and prior AIDS diagnosis ($p=0.004$). Patients older than 51 years when starting cART had more than four times the hazard of dying compared to those who were 30 years or younger [HR=4.53,

95%CI (1.90-10.79), $p=0.001$]. Being female provided a 62% hazard reduction compared to males [HR=0.38, 95%CI (0.18-0.80), $p=0.011$], and having prior AIDS diagnosis before initiating cART more than doubled the hazard of mortality [HR=2.3, 95%CI (1.30-4.06), $p=0.004$]. TDR was not a significant factor in determining mortality in the univariate analysis.

TDR and VF

There were 1,173 patients who had at least one VL measurement after six months from start of cART. The median frequency of VL testing was twice per patient per year (IQR: 1-3). There was no significant difference in median VL frequency across the TDR groups ($p=0.343$). Of these 1,173 patients, 120 (10%) experienced VF; 112 of the 1,122 patients (10%) in the 'no TDR' group; 1 of the 21 patients (4.8%) in the 'TDR with susceptible ART' group; and 7 of the 30 patients (23.3%) in the 'TDR with suboptimal ART' group. The 'TDR with suboptimal ART' group had most failures, with all occurring in the first year of cART.

Factors associated with VF in the adjusted model were TDR ($p=0.033$), CD4 count ($p=0.012$) and adherence ($p<0.001$) (Table 2). Patients from the 'TDR with suboptimal ART' group were more than three times as likely to fail compared to the 'no TDR' group [OR = 3.12, 95%CI (1.31-7.43), $p=0.010$]. However, there was no significant difference in the odds of failure for those from the 'TDR with susceptible ART' group compared to the 'no TDR' group [OR=0.62, 95%CI (0.08-4.68), $p=0.647$]. Patients who initiated cART at CD4 count of >200 cells/ μ l had a 59% reduction in the odds of failure compared to the group with CD4 count ≤ 50 cells/ μ l [OR=0.41, 95%CI (0.22-0.74), $p=0.003$]. Having suboptimal adherence ($<95\%$) was associated with higher odds of failure [OR = 9.37, 95%CI (5.00-17.56), $p<0.001$].

Discussion

In this Asian cohort of 1,471 ART-naïve HIV-infected patients, infected mostly with HIV-1 CRF01_AE, HIVDR mutations were found in 4.1% prior to ART initiation. Factors associated with mortality included older age, male sex and prior AIDS diagnosis but not TDR. In 1,173 patients with available VL at follow-up, 10% experienced VF. In addition to CD4 count and adherence that were significant predictors of VF, patients with TDR and taking suboptimal ART were more than three times as likely to fail cART than patients with no TDR.

The level of TDR in this study (4.1%) is slightly lower than a parallel study in sub-Saharan Africa which showed a prevalence of 5.6% TDR among a population of 2,436 patients.²³ In an earlier report, Sungkanuparph et al reported a 13.8% prevalence of primary HIVDR mutations in 682 patients of the TASER-M cohort.¹⁸ The much higher prevalence of primary HIVDR mutations in that report may be due to the use of the IAS-USA mutation list instead of the WHO mutation list as in the current study. Using the WHO mutation list for TDR, a recent survey in 466 patients from a university hospital in Bangkok found a prevalence of 4.9%¹⁵ TDR, which is similar to findings in our cross-Asian cohort.

TDR is expected to increase with time after large-scale ART rollout. This is particularly true for resource-limited settings where VL and resistance monitoring are limited. In the developed world data show a mixed picture of increased, stable and decreased TDR trends.²⁴⁻²⁶ Timing of TDR determination is also important with chronic infections having less TDR compared to acute infections²⁷⁻²⁸ due to resistance mutations reverting to wild type or becoming minor variants. In reviewing published reports of TDR from across the world during the periods before 2001, 2001-2003 and 2003-2009, Frentz et al. found that while NRTI resistance declined over time in resource-rich settings, it increased in Asia and Africa, and NNRTI resistance increased in all regions.²⁹ This was supported by a separate meta-regression analysis which showed that TDR, especially NNRTI resistance, increased significantly over time since ART rollout (2001-2011) in several regions of sub-Saharan Africa to as high as 7.4% (4.3-12.7%) although the change in TDR over time was unclear in Asia.¹⁴

The significance of drug-specific or drug class-specific TDR to treatment outcome is not fully understood, especially when one or more drugs or drug classes in the regimen are still effective. Our findings indicate that after adjusting for confounders, patients taking cART with at least one 'suboptimal' drug will have a 3.12-fold higher chance of VF compared to those without resistance. Low baseline CD4 cell count (CD4 < 50 cells/ μ l) and suboptimal adherence (adherence <95%) were also significantly associated with VF. Our findings confirm a report from Africa in different HIV-1 subtypes,³ where taking ART with at least one 'suboptimal' drug had an odds ratio of 2.13 (95% CI 1.44-3.14; $p < 0.0001$) in developing VF after a mean follow-up of 12 months, as well as a European multicohort analysis, which found that patients who had TDR to at least one prescribed drug in the first-line regimen had a hazard ratio of 3.13 (95% CI 2.33-4.20) in developing VF after 12 months.³⁰

One of the main arguments in using HIVDR testing before ART initiation is cost-effectiveness. The higher the prevalence of TDR, the more cost-effective the resistance testing is. Although the use of HIVDR testing after initial treatment failure was found to be cost-effective,³¹⁻³³ the cost-effectiveness of resistance testing before initiation of ART remains controversial, particularly when TDR prevalence is <5%.³⁴⁻³⁵ In a cost-effectiveness study in the USA where TDR was set at 8.3%, HIVDR testing before starting cART was as cost-effective as other HIV care interventions.³⁵ The cost-effectiveness is lost if prevalence of TDR is equal to or below 1%.

There are certain limitations in this study. First, only five countries were involved, thus results cannot be generalized to all of Asia. Second, TDR may be overestimated since 62% of patients were from Thailand where ART was in use longer than other countries except Hong Kong. Third, self-reporting of ART-naïve status may not be completely reliable. Fourth, our study may be underpowered due to the small number of patients with resistance mutations and the small number of endpoints. Finally, our analyses did not examine changes to ART susceptibility over time due to a limited number of follow-up genotypic sequences available.

In summary, our results show that without HIVDR testing prior to starting ART, at least 2.3% of the patients could be put on regimens with at least one drug to which the virus is resistant, especially the commonly used NNRTIs, with their low genetic-barrier to resistance. This treatment-resistance discordance resulted in significantly higher VF rates, particularly in patients with low CD4 counts and suboptimal ART adherence. Although the cost of HIVDR testing is high, the cost of second-line ART in developing countries is 4-5 times higher than first-line ART and therapy is life-long. Therefore, it is important to investigate what level of TDR will make routine HIVDR testing prior to starting ART cost-effective.

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Table 1

TASER-M patient characteristics by TDR category

	Total (%) n=1471 (100)	No TDR (%) n=1411 (95.9)	TDR with susceptible ART (%) n=26 (1.8)	TDR with suboptimal ART (%) n=34 (2.3)	P*
Age					
Median (IQR)	36 (31-44)	36 (31-44)	32 (29-38)	34.5 (30-41)	0.042
<=30	347 (23.6)	326 (23.1)	11 (42.3)	10 (29.4)	0.116
31-40	602 (40.9)	578 (41.0)	9 (34.6)	15 (44.1)	
41-50	369 (25.1)	355 (25.2)	5 (19.2)	9 (26.5)	
51+	153 (10.4)	152 (10.8)	1 (3.8)	0 (0.0)	
Sex					
Male	990 (67.3)	948 (67.2)	20 (76.9)	22 (64.7)	0.547
Female	481 (32.7)	463 (32.8)	6 (23.1)	12 (35.3)	
Exposure Category					
Heterosexual contact	1024 (69.6)	994 (70.4)	11 (42.3)	19 (55.9)	0.004
Homosexual contact	306 (20.8)	285 (20.2)	12 (46.2)	9 (26.5)	
Other	141 (9.6)	132 (9.4)	3 (11.5)	6 (17.6)	
Pre-treatment viral load (copies/ml)					
Median log VL (IQR)	5.00 (4.61-5.39)	5.00 (4.62-5.39)	5.00 (4.39-5.14)	5.06 (4.51-5.58)	0.587
<=50000	423 (28.8)	402 (28.5)	9 (34.6)	12 (35.3)	0.147
50001-250000	690 (46.9)	666 (47.2)	14 (53.8)	10 (29.4)	
250001+	358 (24.3)	343 (24.3)	3 (11.5)	12 (35.3)	
Pre-treatment CD4 (counts/uL)					
Median (IQR)	101 (33-205)	102 (34-204)	96 (32-228)	96.5 (24-214)	0.916
<=50	484 (32.9)	464 (32.9)	9 (34.6)	11 (32.4)	0.871
51-100	227 (15.4)	215 (15.2)	4 (15.4)	8 (23.5)	
101-200	347 (23.6)	336 (23.8)	5 (19.2)	6 (17.6)	
201+	372 (25.3)	355 (25.2)	8 (30.8)	9 (26.5)	
Missing	41 (2.8)	41 (2.9)	0 (0.0)	0 (0.0)	

	Total (%) n=1471 (100)	No TDR (%) n=1411 (95.9)	TDR with susceptible ART (%) n=26 (1.8)	TDR with suboptimal ART (%) n=34 (2.3)	P*
Initial cART					
NRTI+NNRTI	1334 (90.7)	1283 (90.9)	21 (80.8)	30 (88.2)	0.065
NRTI+PI	114 (7.7)	107 (7.6)	5 (19.2)	2 (5.9)	
NRTI only	23 (1.6)	21 (1.5)	0 (0.0)	2 (5.9)	
Hepatitis B co-infection					
Negative	1151 (78.2)	1109 (78.6)	18 (69.2)	24 (70.6)	0.179
Positive	141 (9.6)	132 (9.4)	3 (11.5)	6 (17.6)	
Not tested	179 (12.2)	170 (12.0)	5 (19.2)	4 (11.8)	
Hepatitis C co-infection					
Negative	1063 (72.3)	1021 (72.4)	18 (69.2)	24 (70.6)	0.135
Positive	104 (7.1)	99 (7.0)	0 (0.0)	5 (14.7)	
Not tested	304 (20.7)	291 (20.6)	8 (30.8)	5 (14.7)	
Previous AIDS					
No	934 (63.5)	897 (63.6)	15 (57.7)	22 (64.7)	0.818
Yes	537 (36.5)	514 (36.4)	11 (42.3)	12 (35.3)	
HIV Subtype					
AE	1109 (75.4)	1069 (75.8)	17 (65.4)	23 (67.6)	0.312
B	247 (16.8)	231 (16.4)	7 (26.9)	9 (26.5)	
Other Non-B	115 (7.8)	111 (7.9)	2 (7.7)	2 (5.9)	
Adherence (assessments/patient/year)					
Median (IQR)	4 (2-6)	4 (2-6)	5 (3-6)	4 (2-6)	0.676

* P refers to test of equality of proportions/medians of No TDR vs TDR with susceptible ART vs TDR with suboptimal ART for each of the patient characteristics.

Table 2

Factors associated with first viral load failure.

	No of patients	No of failures	OR	95% CI	p	* Global p
Total	1173	120				
TDR						0.033
No TDR	1122	112	1			
TDR with susceptible ART	21	1	0.62	(0.08 to 4.68)	0.647	
TDR with suboptimal ART	30	7	3.12	(1.31 to 7.43)	0.010	
Pre-treatment CD4 (counts/uL)						0.012
<=50	368	46	1			
51-100	183	19	0.88	(0.49 to 1.57)	0.662	
101-200	288	32	1.02	(0.62 to 1.68)	0.930	
201+	305	18	0.41	(0.22 to 0.74)	0.003	
Missing	29	5				
~ Adherence						<0.001
>=95%	~	71	1			
<95%	~	18	9.37	(5.00 to 17.56)	<0.001	
Missing	~	31				

* Global p is test for trend excluding missing values forCD4. Other global p-values are test for heterogeneity excluding missing values.
~Time updated covariate where each patient can contribute in more than one category.