

Deferred modification of antiretroviral regimen following treatment failure in Asia:

Results from The TREAT Asia HIV Observational Database (TAHOD)

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Introduction

The World Health Organisation (WHO) estimates that about 3 million people were receiving antiretroviral therapy at the end of 2007, nearly 950 000 more compared with the year before and a 7.5-fold increase during the past four years.

The aim of antiretroviral treatment is to suppress viral replication to below the level of detection with standard assays in plasma. For patients who experience treatment failure, second-line combination antiretroviral treatments (cART) are not readily available in many countries in Asia. The decision to change to second-line treatment regimen when treatment failure develops is crucial to preserve any remaining first-line regimen benefit and minimise risk of disease progression and death.

In this paper, we analysed antiretroviral modification following treatment failure in patients from The TREAT Asia HIV Observational Database.

Methods

This analysis was conducted using the TREAT Asia HIV Observational Database (TAHOD), a prospective cohort including more than 4,000 patients receiving care at one of 17 clinical centers in East, South, and Southeast Asia. Patients were included in this analysis if they were naïve to antiretroviral treatment, and initiated combination therapy including 3 or more drugs since 1996.

Treatment failure was defined using WHO guidelines for antiretroviral therapy for adults and adolescents. This definition integrates CD4 count, viral load measure and clinical status to guide modification of treatment. The individual date of treatment failure was identified from the database according to the guidelines. The earliest failure was included for patients with more than one type of failure during treatment.

Modification of antiretroviral treatment following treatment failure was defined as a change to (adding, stopping or substituting) at least one drug from the treatment combination received at the time treatment failure was identified. A treatment modification with duration of 14 days or less was ignored. Time to treatment modification was determined by univariate and multivariate survival analyses (Kaplan-Meier and Cox proportional hazards models).

Results

There were a total of 2446 TAHOD patients (71% male) who were treatment naïve and initiated cART since 1996. During a median treatment period of 1.97 years (interquartile, IQR 0.75 to 3.55 years), a total of 447 patients were identified with at least one type (e.g., immunological, virological, or clinical) of treatment failure (7.85 per 100 person-years, 95% confidence interval, CI 7.15–8.61).

Following treatment failure, a total of 253 patients had a treatment modification after failure, of whom, 44 modified on the same day when treatment failure was identified. During a median follow up of 0.64 years (IQR 0.15 to 1.61 years), a further 209 patients changed at least one drug. The rate of treatment modification after failure was 51.6 per 100 person-years (95% confidence interval, CI 45.6–58.4).

The rate of treatment modification was similar between patients from high- and low-income countries (Figure 1).

However, the rate of modification was higher in patients with a virological failure than those patients with either immunological failure or clinical progression (Figure 1). At the end of first year following failure, 40% patients with virological failure remained on the previous regimen, compared to close to 60% patients with either immunological failure or clinical progression.

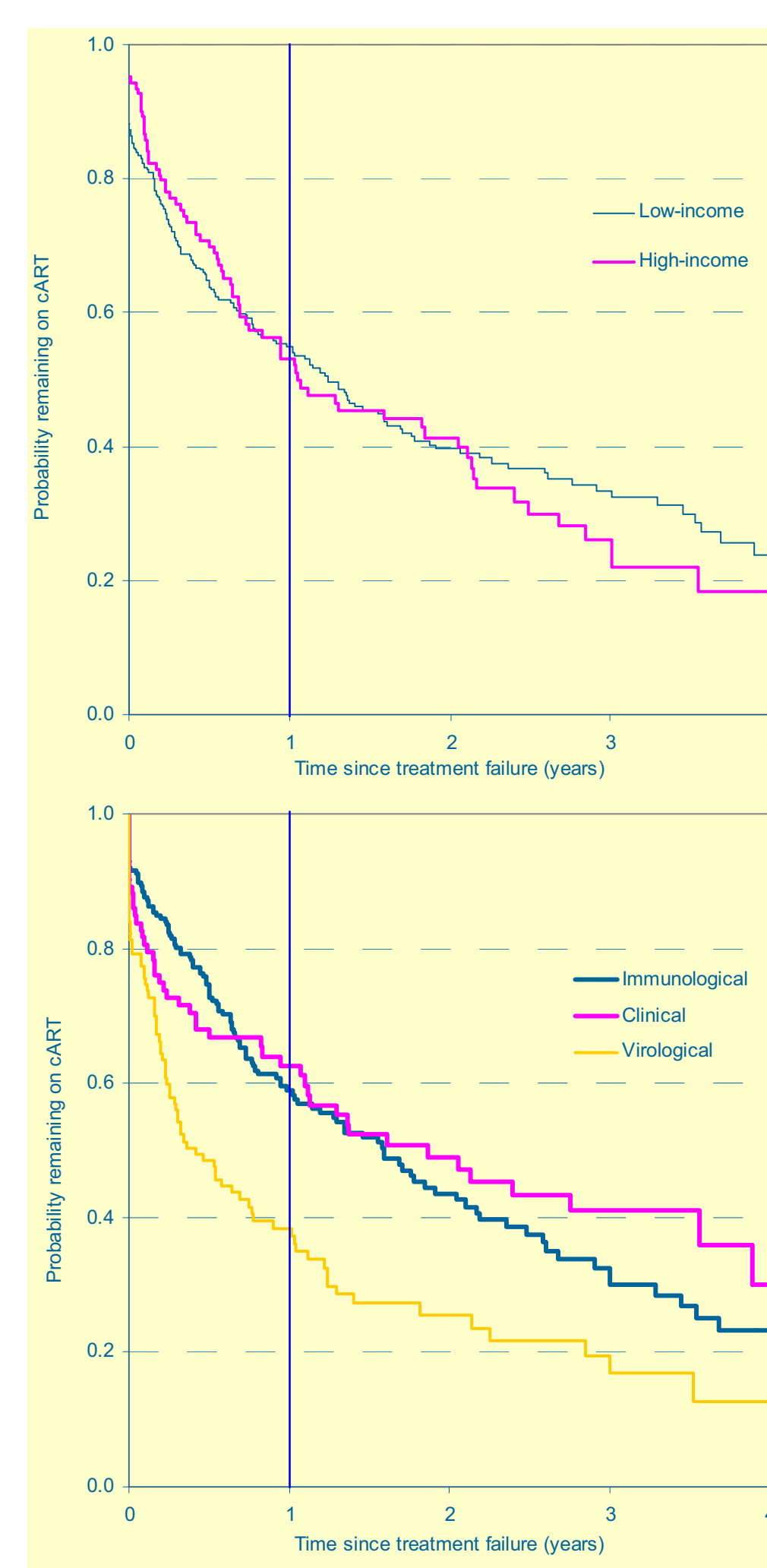


Figure 1: Time to treatment modification after treatment failure, by country income category and type of treatment failure

Of patients who modifying treatment, 24 (10% of 253) added one or more drug, 92 (36%) changed one and 137 (54%) two or more drugs. Although the rates of treatment modification were similar in patients from high- and low-income countries (adjusted hazard-ratio HR, 1.02, $p=0.891$), patients from high-income countries were more likely to have two or more drugs changed (67% vs. 49%, $p=0.009$) and to change to a protease-inhibitor-based regimen (48% vs. 16%, $p<0.001$).

Patients modify treatment regimens for different reasons. Treatment failure was only part of the reasons for modifying drugs (25% of all reported reasons, Figure 2). Patients from high-income countries were more likely to report treatment failure as the reason for stopping a drug than those from low-income countries (32% vs. 21%, $p=0.003$). There were more drugs which were reported to be stopped due to treatment failure following an identified virological failure than those following immunological failure and clinical progression (39% vs. 21% and 3%, respectively, $p<0.001$). The proportions of reporting treatment failure were similar by time from identified treatment failure (all types) to treatment modification.



Figure 2: Reported reasons for stopping a drug when treatment was modified

- a. all drugs
 b. by country income category: b-1, high-income; b-2, low-income
 c. by type of treatment failure: c-1, immunological failure; c-2, virological failure; c-3, clinical progression
 d. by time from treatment failure: d-1, up to 90 days; d-2, 91 to 180 days; d-3, 181 days or more

Table 1 shows the factors associated with time to antiretroviral treatment modification after treatment failure by univariate and multivariate Cox proportional hazards models. In the final model, the factors independently associated with treatment modification after failure included advanced CDC classification, lower CD4 count and higher HIV viral load, all at the time of treatment failure.

Table 1: Time to treatment modification following treatment failure

	No. (%) patients	Follow up (years)	No. of events	Rate (/100py)	Univariate HR	p-value	Multivariate ¹ HR (95% CI)	p-value
Total	447	490	253	51.6				
Sex								
Male	342 (77)	374	197	52.7				
Female	105 (23)	116	56	48.3	0.93	0.640	0.87 (0.63, 1.22)	0.423
Age at time of failure (years)								
<=30	119 (27)	143	63	44.2				
31–40	203 (45)	208	116	55.7	1.23	0.193	1.19 (0.86, 1.66)	0.294
41+	125 (28)	139	74	53.1	1.22	0.243	1.20 (0.84, 1.74)	0.319
Reported mode of infection								
Heterosexual contact	288 (65)	328	162	49.5				
Homosexual contact	94 (21)	117	50	42.8	0.89	0.461	0.66 (0.42, 1.05)	0.079
Injecting drug use	24 (5)	22	16	71.6	1.26	0.366	1.25 (0.67, 2.32)	0.484
Blood products	32 (7)	18	19	103.0	1.73	0.024	1.02 (0.48, 2.14)	0.968
Other/unknown	9 (2)	5	6	109.7	1.64	0.238	1.34 (0.55, 3.29)	0.519
CDC classification at time of failure								
Category A	173 (39)	192	95	49.4				
Category B	39 (9)	43	18	41.4	0.82	0.448	1.25 (0.70, 2.23)	0.444
Category C	235 (52)	255	140	55.0	1.08	0.567	1.38 (1.01, 1.87)	0.040
CD4 count (cells/μL) at time of failure								
<=50	39 (9)	29	30	104.3				
51+	349 (78)	386	192	49.7	0.56	0.003	0.61 (0.40, 0.93)	0.022
Not tested	59 (13)	75	31	41.4	0.49	0.006	0.60 (0.34, 1.05)	0.074
HIV viral load (copies/ml) at time of failure								
<400	121 (27)	169	56	33.1				
400 or more	145 (33)	107	106	99.5	2.46	<0.001	2.69 (1.90, 3.81)	<0.001
Not tested	181 (40)	215	91	42.4	1.25	0.196	1.74 (1.14, 2.66)	0.010
Antiretroviral treatment² at time of failure								
3+(NRTI+NNRTI+PI)	318 (71)	376	168	44.7				
3+(NRTI+NNRTI+PI)	100 (22)	86	61	70.4	1.37	0.038	1.28 (0.91, 1.82)	0.157
Others	29 (7)	28	24	87.5	1.83	0.006	1.58 (0.96, 2.57)	0.069
Type of treatment failure								
Immunological	242 (54)	273	123	45.0				
Virological	112 (25)	89	82	91.8	1.83	<0.001	0.90 (0.53, 1.53)	0.704
Clinical	93 (21)	128	48	37.6	0.91	0.595	1.02 (0.63, 1.65)	0.941
Country income category								
Low-income	323 (72)	346	178	51.4				
High-income	124 (28)	144	75	52.2	1.03	0.829	1.02 (0.77, 1.35)	0.891

¹ Stratified by site (except for country income category)

² Antiretroviral treatment:

3+(NRTI+NNRTI+PI), combination of three or more drugs including NRTI and NNRTI but not PI

3+(NRTI+NNRTI+PI), combination of three or more drugs including NRTI and PI but not NNRTI

Conclusion

Modification of ART regimens following treatment failure is deferred in many Asian countries. This may have implications for accumulation of drug resistance and response to second-line treatment. There is an urgent need to scale up viral load monitoring and access to second-line ART regimens in this region.

The TREAT Asia HIV Observational Database

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