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Effects of unplanned treatment interruptions on treatment outcomes– results from TAHOD

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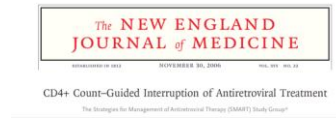
Background

* 2006 – Higher opportunistic disease and mortality in treatment interruption (TI) group.
  - Early termination.

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Background

* Post SMART – unplanned TIs still occur.

* Resource-limited settings: AEs, toxicities, drug stockouts, socio-economic factors.

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Objectives

* Determine reasons for unplanned TIs in Asian patients enrolled in TAHOD receiving ART.

* Assess how well patients responded to ART after resuming treatment.

"Predictors of treatment failure whilst receiving ART"

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TREAT Asia HIV Observational Database – TAHOD

* Longitudinal cohort study: 2003 – present
* 21 active sites from 12 countries.

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Methods

* Patients enrolled in TAHOD starting ART from 2006 onwards.
  – After the SMART study.

* At least 6 months of follow-up.

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Methods

- TI defined as no ART for more than 1 day.

- Reasons for TI
  – Stopped due to AEs
  – Stopped due to other reasons

- AEs – drug adverse reactions, toxicity, and side effects.

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Statistical Methods

- TI variable (time-updated)
  (i) No previous TI
  (ii) Previous TI due to AEs
  (iii) Previous TI due to other reasons

- Time off treatment not included in analysis
  – Not counted as risk time
- Failures whilst on ART.

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Statistical Methods

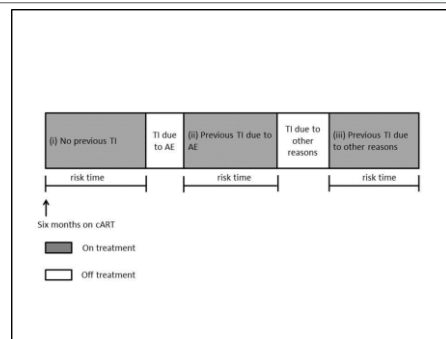- Treatment failure:

  – Clinical – CDC grade C

  – Immunological –CD4 below baseline or CD4 <100 cells/µL (confirmed 6 months).

  – Virological – VL >1000 copies/mL (confirmed 6 months).

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Sensitivity Analysis

- Treatment failure
  - no secondary confirmatory testing

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Statistical Methods

- Cox regression with gaps.

- Stratification on site.

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Results

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	Total = 4549 patients
Age at cART initiation (years)	median =34 , IQR (29-41)
Sex	
Male	3176 (69.8)
Female	1373 (30.2)
Mode of HIV exposure	
Heterosexual contact	2791 (61.4)
Homosexual contact	952 (20.9)
Injecting drug use	496 (10.9)
Other/unknown	310 (6.8)
Pre-cART viral load (copies/mL)	median =100000, IQR (31697-260000)
Pre-cART CD4 (cells/µL)	median =131, IQR (41-226)
Initial cART regimen	
NRTI+NNRTI	4103 (90.2)
NRTI+PI	401 (8.8)
Other	45 (1.0)
Hepatitis B co-infection	
Negative	3363 (73.9)
Positive	379 (8.3)
Not tested	807 (17.7)
Hepatitis C co-infection	
Negative	2839 (62.4)
Positive	616 (13.5)
Not tested	1094 (24.1)
Previous AIDS	
No	2907 (63.9)
Yes	1642 (36.1)

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Treatment interruptions

	Total (%)
TI – 5.45%	**4549 (100)**
TI	
No interruption	4303 (94.6)
At least 1 TI due to adverse events	111 (2.4)
All TI due to other reasons	135 (3.0)
Duration of TI(days)	
Interruption due to adverse events	median = 22, IQR (12-47)
Interruption due to other reasons	median = 148, IQR (27-319)

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Reasons for treatment interruptions

Due to AEs	Number of patients
Skin side effects	55
Liver toxicities	17
Drug allergies	11
GI side effects	8
Other AE/Unknown AE	25
Due to other reasons	**Number of patients**
Treatment failure	1
Clinical progression/hospitalisation	4
Patient decision/request	50
Adherence difficulties	21
Other	70

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Treatment failures

- 730 patients failed (16%)
  - 89 Virological failures
  - 501 Immunological failures
  - 175 Clinical failures
- Some with >1 type of failure on the same day.

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Factors associated with treatment failure

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			Multivariate		
	Total patients	Number with treatment failure	HR	95% CI	p
Total	4549	730			<0.001
Previous TI duration (days)					
0-30	~	690	1		
31-180	~	21	2.63	(1.68, 4.11)	<0.001
181-365	~	10	6.16	(3.23, 11.75)	<0.001
>365	~	9	9.04	(4.24, 19.25)	<0.001
Age at cART initiation (years)					0.011
≤30	1433	210	1		
31-40	1895	309	1.11	(0.93, 1.33)	0.261
41-50	860	137	1.12	(0.89, 1.41)	0.315
>50	361	74	1.56	(1.17, 2.07)	0.002
Sex					
Male	3176	541	1		
Female	1373	189	0.74	(0.62, 0.90)	0.002
Mode of HIV exposure					0.009
Heterosexual contact	2791	450	1		
Homosexual contact	952	139	0.74	(0.56, 0.98)	0.034
Injecting drug use	496	99	1.27	(0.96, 1.68)	0.089
Other/unknown	310	42	0.69	(0.49, 0.98)	0.040
Pre-cART CD4 (cells/µL)					<0.001
≤50	1169	151	1		
51-100	564	62	0.85	(0.63, 1.15)	0.289
101-200	1015	179	1.42	(1.13, 1.78)	0.002
>200	1290	269	1.75	(1.41, 2.17)	<0.001
Missing	511	69			

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Reasons for TI – adjusted for other significant variables

			Adjusted		
	Total patients	Number with treatment failure	HR	95% CI	p
Total	4549	730			
Reasons for Previous TI					0.059
No previous TI	~	668	1		
Previous TI due to AE	~	19	1.05	(0.62, 1.78)	0.853
Previous TI due to other reasons	~	43	1.86	(1.09, 3.15)	0.022

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Other non-significant variables, p >0.05

- Pre-cART VL
- Initial cART regimen
- Hepatitis B/C co-infection
- Prior AIDS diagnosis

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Sensitivity Analysis

- 1152 patients failed (25%)
  - 348 Virological failures
  - 791 Immunological failures
  - 159 Clinical failures

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Sensitivity Analysis

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	Multivariate		
	HR	95% CI	p
Total			
Reasons for Previous TI			0.009
No previous TI	1		
Previous TI due to AE	1.04	(0.69, 1.57)	0.848
Previous TI due to other reasons	1.90	(1.24, 2.92)	0.003
Previous TI duration (days)			<0.001
0-30	1		
31-180	1.84	(1.11, 3.04)	0.019
181-365	3.29	(1.75, 6.17)	<0.001
>365	10.01	(4.84, 20.74)	<0.001
Pre-cART CD4 (cells/µL)			<0.001
≤50	1		
51-100	0.49	(0.39, 0.61)	<0.001
101-200	0.60	(0.51, 0.72)	<0.001
>200	0.69	(0.59, 0.81)	<0.001
Missing			

Other covariates showed similar effects.

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Limitations

- No drug resistance information available.

- Not all ART stop reasons could be classified due to ambiguity in data.

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Conclusions

- Longer time off treatment and non-AE related TIs → treatment failure

- AE-related TIs not associated with failure possibly due to shorter time span.

- If TI is unavoidable, duration of TI should be minimised to avoid poor treatment response after cART resumption.

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Conflicts of Interest

There are no conflicts of interest.

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