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TREATASIA

Impact of the frequency of plasma viral load monitoring on treatment outcome among perinatally HIV-infected Asian children stable on first-line NNRTI-based cART

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Introduction

- **Plasma viral load (pVL) is a reliable indicator** of initial and sustained response to cART.
- **It can be measured in HIV-infected patients** at entry into care, at initiation of therapy, and on a regular basis thereafter.
  - The availability and cost are obstacles to using pVL in monitoring HIV treatment outcomes in resource-constrained settings
- **Recommendations on the optimal frequency of pVL monitoring** in HIV-infected children stable on cART are inconsistent.

Recommendations on the frequency of pVL testing

Guidelines	Recommendations
WHO[1] (2016)	pVL should be performed at 6 months and 12 months after initiating ART and every 12 months thereafter.
DHHS[2] (2016)	• In children on a stable, suppressive ARV regimen: pVL should be repeated every 3-4 months to provide enhanced monitoring of adherence and disease progression. • In current adult and adolescents guidelines: support pVL testing every 6 months for adherent patients whose viral load has been suppressed for more than 2 years and CD4 count consistently >300 cells/mm^3.
PENTA[3] (2015)	pVL can be monitored approximately every 3–4 months once the patient has been established on treatment.
Thailand[4] (2014)	pVL should be monitored every 6-12 months in patient stable on cART.

[1]WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed. 2016. [2]Panel on antiretroviral therapy and medical management of HIV-infected children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Department of Health and Human Services. [3]A Bamford, A Turkova, H Lyall, et al. Paediatric European Network for Treatment of AIDS (PENTA) guidelines for treatment of paediatric HIV-1 infection 2015: optimizing health in preparation for adult life. [4]Thailand national guidelines on HIV/AIDS treatment and prevention 2014.

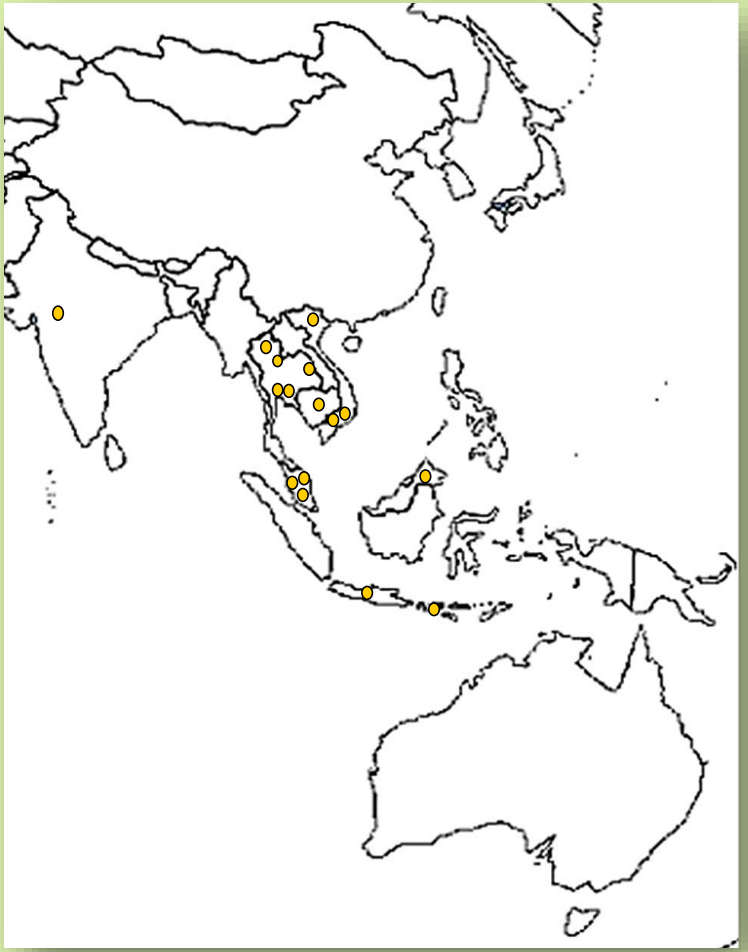
Objectives

- **To determine the impact of annual vs. semi-annual pVL testing on treatment outcomes** among perinatally HIV-infected children stable on first-line NNRTI-based cART.

- **To evaluate factors associated with treatment failure** in this population.

Methods

- **Study design:** Retrospective cohort study
- **Study cohort:** The TREAT Asia pediatric HIV Observational Database (TApHOD)
  - Sites: Cambodia (n=1), India (n=1), Indonesia (n=2), Malaysia (n=4), Thailand (n=5), Vietnam (n=3)
  - Data: 5,783 children receiving care from all 16 sites
- **Study population:** HIV-infected children enrolled in TApHOD before March 30, 2015

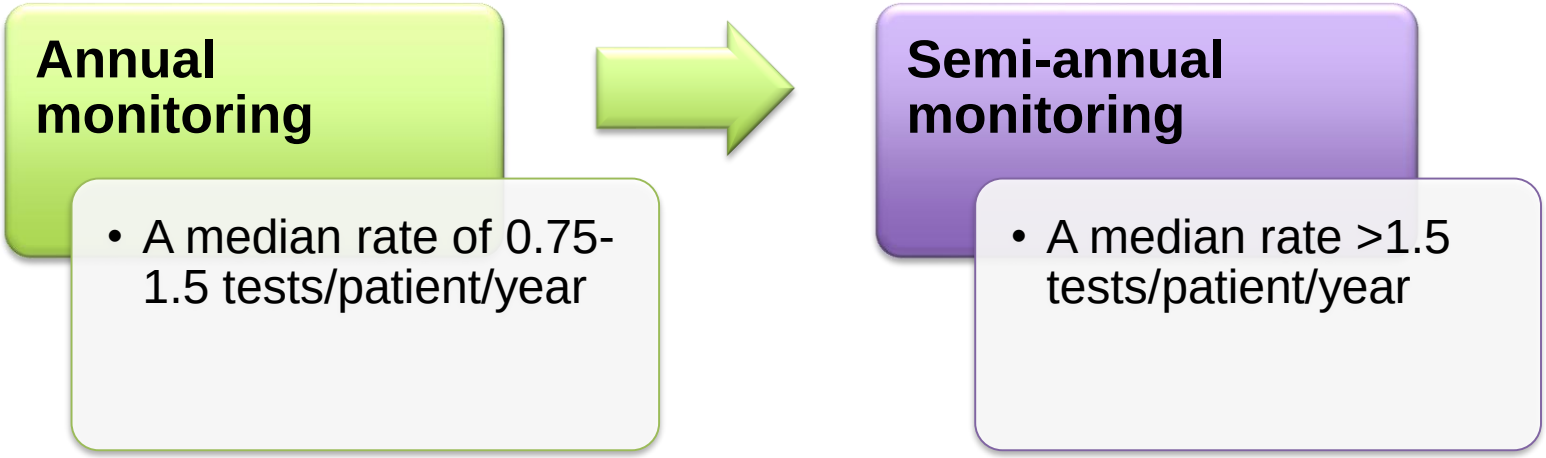


Methods

- **Inclusion criteria:**
  - Perinatally acquired HIV infection
  - Aged <18 years
  - Were receiving first-line NNRTI-based cART
  - Had a documented history of viral suppression (two consecutive pVL <400 copies/ml at least 6 months apart)
- **Exclusion criteria:**
  - Exposed to mono/dual therapy prior starting cART

Definitions

- **The frequency of pVL testing:**
  - Determined at site-level
  - Based on a median rate of pVL measurement at each clinical site over the entire follow-up period in TApHOD



******Patients from sites with a median monitoring rate <0.75 test/patient/year over the entire follow-up period in TApHOD were excluded******

Definitions

- **Treatment failure (outcome of interest):**
  - 2 consecutive pVL >1000 copies/ml, or
  - A change of antiretroviral drug class, or
  - Death

- **Loss to follow-up:**
  - Not having been seen in clinic for >12 months without documentation of transfer

Statistical analysis

- **Kaplan-Meier estimates and log-rank tests:**
  - Describe and compare the cumulative probability of detecting treatment failure by pVL monitoring frequency
  - Baseline: The date of the 2nd pVL <400 copies/ml
  - Censor: Last clinic visit
- **Competing-risks regression models:**
  - Identify factors associated with treatment failure
  - Loss to follow-up was considered a competing event
  - A 2-tail *P* <0.05 was considered statistically significant

Site-specific rates of pVL monitoring

Site name	Rate of pVL monitoring (tests/patient/year)			Monitoring category*
	Median	IQR		
Thailand #1	2.8	2.3	3.4	Semi-annual
Malaysia #1	2.8	2.3	3.2	Semi-annual
Malaysia #2	2.5	2.2	2.6	Semi-annual
Malaysia #3	2.2	1.7	2.4	Semi-annual
Thailand #2	1.4	1.1	1.8	Annual
Thailand #3	1.2	0.9	1.7	Annual
Thailand #4	1.2	0.9	1.6	Annual
Thailand #5	1.1	0.8	1.4	Annual
Cambodia #1	1.1	0.9	1.3	Annual
Malaysia #4	1.0	0.7	1.2	Annual
Vietnam #1	0.7	0.5	1.0	Less than annual
Vietnam #2	0.5	0.3	0.8	Less than annual
Vietnam #3	0.5	0.2	0.8	Less than annual
Indonesia #1	0.5	0.3	0.8	Less than annual
Indonesia #2	0.3	0.2	0.4	Less than annual
India	0.2	0.1	0.3	Less than annual

*Less than annual, <0.75 tests/patient/year; Annual, 0.75-1.5 tests/patient/year; Semi-annual, >1.5 tests/patient/year

Participant characteristics

- **Of 10 clinical sites, 1220 children were eligible**
  - 1042 children (85%) were from 6 sites which performed annual pVL monitoring
  - 178 children (15%) were from 4 sites which performed semi-annual pVL monitoring

Patient characteristics*,†	Total number of children with data	Overall	pVL monitoring	
			Annual (n = 1042)	Semi-annual (n = 178)
Age, years	1220	9.2 (6.3 - 12.0)	9.6 (6.6 - 12.2)	7.5 (4.5 - 10.0)
Sex	1220			
• Male		581 (47.6)	490 (47.0)	91 (51.1)
• Female		639 (52.4)	552 (53.0)	87 (48.9)
Orphan status	1051			
• Both parents alive		248 (23.6)	211 (22.1)	37 (38.1)
• Single parent alive		298 (28.4)	274 (28.7)	24 (24.7)
• Neither parent alive		505 (48.0)	469 (49.2)	36 (37.1)
HIV disclosure status	759			
• Disclosed		294 (38.7)	274 (41.4)	20 (20.6)
• Not disclosed		465 (61.3)	388 (58.6)	77 (79.4)
Height-for-age z-score	1175	-1.9 (-2.7 to -1.2)	-2.0 (-2.8 to -1.2)	-1.5 (-2.2 to -0.8)
• >-1.5		424 (36.1)	339 (33.6)	85 (51.2)
• -1.5 to -2.5		390 (32.0)	337 (33.4)	53 (31.9)
• <-2.5		361 (30.7)	333 (33.0)	28 (16.9)
Weight-for-age z-score	1179	-1.7 (-2.6 to -0.9)	-1.8 (-2.7 to -1.0)	-1.4 (-2.4 to -0.6)
• >-1.5		508 (43.1)	409 (40.4)	99 (59.6)
• -1.5 to -2.5		333 (28.2)	302 (29.8)	31 (18.7)
• <-2.5		338 (28.7)	302 (29.8)	36 (21.7)

*Characteristics were at baseline (date of the 2nd pVL <400 copies/ml), unless otherwise specified.
†Data were presented as n (%) for categorical data and medians (interquartile range) for continuous data.

Patient characteristics*,†	Total number of children with data	Overall	pVL monitoring	
			Annual (n = 1042)	Semi-annual (n = 178)
Most severe WHO clinical stage	1220			
• Stage 1 and 2		545 (44.7)	461 (44.2)	84 (47.2)
• Stage 3		371 (30.4)	327 (31.4)	44 (24.7)
• Stage 4		304 (24.9)	254 (24.4)	50 (28.1)
pVL at cART initiation, log_{10} copies/ml	529	5.2 (4.8 - 5.7)	5.3 (4.9 - 5.7)	5.0 (4.8 - 5.6)
• <4.3		58 (11.0)	37 (9.4)	21 (15.2)
• 4.3 to 5.0		140 (26.5)	94 (24.1)	46 (33.3)
• >5.0		331 (62.5)	260 (66.5)	71 (51.5)
cART regimen	1220			
• Nevirapine-based		786 (64.4)	689 (66.1)	97 (54.5)
• Efavirenz-based		434 (35.6)	353 (33.9)	81 (45.5)
Duration of cART use, years	1220	1.6 (1.0 - 3.0)	1.8 (1.0 - 3.0)	1.0 (0.9 - 1.8)
CD4 T-cell percentage, %	1190	26 (20 - 31)	26 (20 - 31)	26 (21 - 32)
• >30		307 (25.8)	258 (25.4)	49 (28.2)
• 20 to 30		617 (51.8)	527 (51.9)	90 (51.7)
• <20		266 (22.4)	231 (22.7)	35 (20.1)
pVL measurement, tests/patient/year	1220	1.5 (1.1 - 2.1)	1.4 (1.1 - 1.8)	2.5 (2.2 - 3.1)

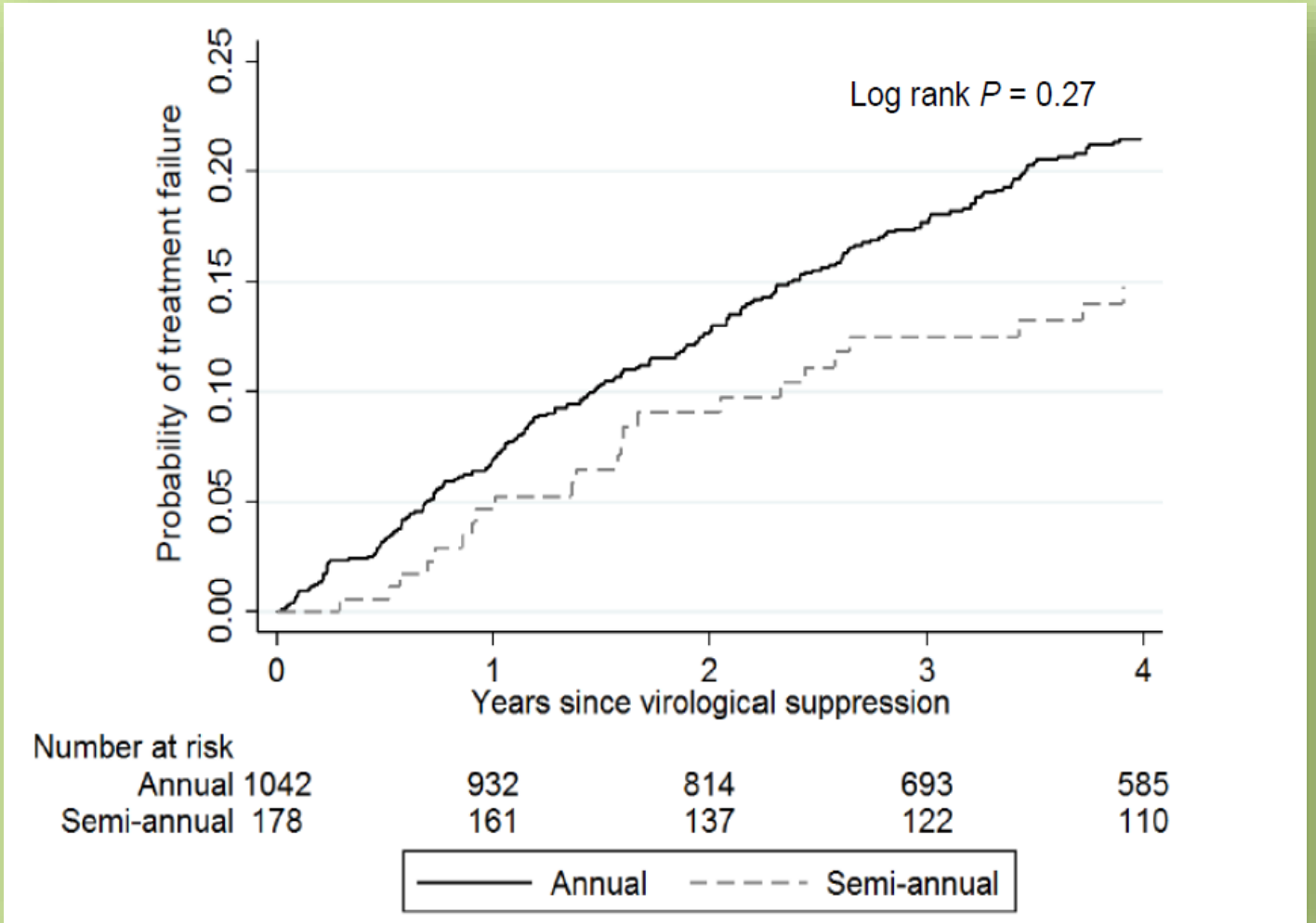
*Characteristics were at baseline (date of the 2nd pVL <400 copies/ml), unless otherwise specified.
†Data were presented as n (%) for categorical data and median (interquartile range) for continuous data.

Incidence of treatment failure

- **Median follow-up time** was 4.6 (IQR 2.2 - 6.6) years
  - 20 children (1.6%) were lost to follow-up, incidence rate of 0.4 (95%CI: 0.2-0.5) per 100 person-years of follow-up (PYFU)

- **Treatment failure developed in**
  - 258 children (25%) with annual pVL monitoring, incidence rate of 5.4 (95% CI: 4.8-6.1) per 100 PYFU
  - 40 children (23%) with semi-annual pVL monitoring, incidence rate of 4.3 (95% CI: 3.1-5.8) per 100 PYFU

Kaplan-Meier estimates of cumulative probability of detecting treatment failure by pVL monitoring frequency



Predictors of treatment failure among perinatally HIV-infected children on stable first-line NNRTI–based cART

Patient characteristics*	Univariable analysis		Multivariable analysis†	
	Crude HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Frequency of pVL measurement • **Semi-annual** • **Annual**	**Ref** **1.19 (0.86 - 1.65)**	**0.29**	**Ref** **1.12 (0.80 - 1.59)**	**0.50**
Age (per 1 yr increase)	1.09 (1.06 - 1.12)	<0.01	1.11 (1.07 - 1.14)	<0.01
Most severe WHO clinical stage • Stage 1 and 2 • Stage 3 • Stage 4	Ref 1.26 (0.96 - 1.65) 1.41 (1.07 - 1.87)	 0.09 0.02	Ref 1.31 (0.99 - 1.73) 1.43 (1.08 - 1.88)	 0.06 0.01
Duration of cART use (per 1 yr increase)	0.92 (0.85 - 1.00)	0.05	0.85 (0.77 - 0.93)	<0.01

*Characteristics represent the conditions at baseline (date of the 2nd pVL <400 copies/ml).
†Multivariable model adjusted by frequency of pVL measurement, age, orphan status, school attendance, HIV disclosure status, height-for-age z-score, pVL at cART initiation, the most severe WHO clinical stage, duration of cART, and current CD4 T-cell percentage.

Characteristics of HIV-infected children with treatment failure

Characteristics at the time of treatment failure (n = 298)*	**Total number of children with data**	**Number (%) or median (IQR)**
Age, years	298	12.6 (10.3 - 15.1)
Sex • Male • Female	298	 133 (44.6) 165 (55.4)
Height-for-age z-score • >-1.5 • -1.5 to -2.5 • <-2.5	273	-1.8 (-2.4 to -1.1) 104 (38.1) 109 (39.9) 60 (22.0)
Weight-for-age z-score • >-1.5 • -1.5 to -2.5 • <-2.5	264	-1.7 (-2.5 to -0.9) 121 (45.8) 82 (31.1) 61 (23.1)
WHO clinical stage • Stage 1 and 2 • Stage 3 • Stage 4	298	 113 (37.9) 96 (32.2) 89 (29.9)
CD4 T-cell percentage, % • >30 • 20 to 30 • <20	271	26 (19 - 31) 77 (28.4) 120 (44.3) 74 (27.3)
pVL, $\log_{10}$ copies/ml	89	4.2 (3.4 - 4.8)

*Data were presented as n(%) for categorical data and medians (interquartile range) for continuous data.

Study limitations

- **Selection bias** towards sites that have higher level of resources to perform pVL measurement in their patients.
- **Other treatment outcomes not evaluated**
  - Development of opportunistic infections, hospitalizations, drug resistance

Conclusions and discussion

- No significant difference between the rate of treatment failure detected by annual vs. semi-annual pVL monitoring in previously suppressed children.
- For suppressed children, annual pVL testing may be sufficient to monitor ART outcomes.
  - Cost savings without jeopardizing patient safety
  - Consistent with WHO 2016 recommendations
- Taking into consideration patient-level factors when determining monitoring frequency may help to balance clinical needs and program costs.

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  - AIDS Life Association, Austria