Low rate of sequential virological failure to both PI and NNRTI based regimens in HIV-1 infected patients in the Netherlands

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Abstract

Background
Although two new drug classes are now available for treatment of HIV-1 infected patients, recommended first-line regimens still consist of 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir boosted protease inhibitor (PI). Virologic failure to these 3 traditional drug classes still represents a key stage in a patients drug failure history. We aimed to get better insight in the rate of triple class virologic failure (TCVF) and its risk factors in the Netherlands.

Methods
Patients who were ART naïve at the start of cART, who started cART in or after 1998 with 2 NRTIs and either 1 NNRTI or 1 PI/r were selected from the national ATHENA HIV-1 observational cohort. Virological failure was defined as 1 viral load measurement above 500 copies/ml following at least 4 months of continuous antiretroviral therapy TCVF was defined as virological failure on 2 NRTIs, 1 NNRTI and 1 PI/r, provided the last failure was at least 4 months after switching to a new drug class. Time from the start of cART to TCVF was analysed using unadjusted and adjusted Cox regression models.

Results
In total 9211 patients were included, of which 110 experienced a TCVF (1.2%). The Kaplan-Meier estimate of the percentage of patients with TCVF at 5 and at 10 years after starting cART was 1.5% and 3.7%, respectively. A significantly higher risk of TCVF was observed in younger patients (HR for every 10 years older 0.55, 95% CI 0.44-0.68, p<0.0001). Patients originating from South-America and the Caribbean (HR 2.23, 1.26-3.96, p=0.006) and sub-Saharan Africa (HR 2.47, 1.38-4.41, p=0.002) had a higher risk of TCVF compared to patients from the Netherlands. Also, patients with lower CD4 cell counts and higher plasma viral load the start of cART had a borderline significantly higher risk of TCVF (overall p-value=0.06 and p=0.15, respectively). The risk of TCVF did not differ significantly according to calendar year of starting cART (1998-2003 vs. 2004-2010, HR 1.23, 0.79-1.91, p=0.36) nor on the initial regimen (PI-based vs. NNRTI-based, HR 1.20, 0.81-1.77, p=0.36).

Conclusion
The rate of TCVF in the Netherlands (1.5% at 5 year after starting cART) is lower than the reported rate by the PLATO II multi cohort study (3.4%) which included data from this cohort. This may be due to a smaller proportion of patients from non-European origin in our cohort, at higher risk for TCVF. The higher risk among patients with low CD4 cell counts at the start of cART and patients from sub-Saharan Africa and South-America may be due to differences in adherence and health seeking behaviour.

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Background

- Recommended first-line regimens consist of 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir boosted protease inhibitor (PI).
- Virologic failure to these 3 traditional drug classes represents a key stage in a patients drug failure history.
- In the Pursuing Later Treatment Options II (PLATO II) study[1], a European multi-cohort collaboration including data from the ATHENA cohort, 3.4% of patients experienced triple class virologic failure (TCVF) within 5 years from starting cART. However, this figure might not be representative for the Netherlands.
- We aimed to get better insight in the rate of triple class virologic failure (TCVF) and its risk factors in the Netherlands.

1. Lodwick R, Costagliola D, Reiss P, Torti C, Teira R, Dorrucci M, *et al.* Triple-class virologic failure in HIV-infected patients undergoing antiretroviral therapy for up to 10 years. *Arch Intern Med* 2010; **170(5)**:410-419.

Methods

Patient selection

- Patients >16 yr from the ATHENA national observational HIV cohort.
- ART naïve at the start of cART between 1998-2010.
- Starting with a 2 NRTI and either 1 NNRTI or 1 PI/r.

Outcome

- Time to Triple Class Virologic Failure (**TCVF**).
- **TCVF**: virological failure on 2 NRTIs, 1 NNRTI and 1 PI/r, provided the last failure was at least 4 months after switching to a new drug class.
- Virologic failure: 1 viral load measurement >500 copies/ml following at least 4 months of continuous antiretroviral therapy.

Statistical analysis

- Time from the start of cART to TCVF was analysed using unadjusted and adjusted Cox regression models. Time was censored at the date of the last viral load, CD4 cell count or clinical visit.

Table 1. *Characteristics at the start of cART of 9211 selected patients.*

	N (%)
Total	9211 (100)
Male	7318 (79)
Transmission risk group	
MSM	5156 (56)
Heterosexual	3059 (33)
IDU	345 (4)
Region of origin	
Netherlands	5069 (55)
Sub Saharan Africa	1650 (18)
W-Europe/N-America	661 (7)
HCV co-infection	695 (7)
HBV co-infection	592 (6)
Initial regimen	
NNRTi-based	6270 (68)
PI-based	2899 (32)
	Median (IQR)
Age at start cART	38.6 (32.3-45.9)
CD4 cell count (cells/mm³)	220 (100-320)
HIV RNA (copies/ml)	4.9 (4.3-5.3)

Table 2. *Unadjusted and adjusted risk estimates for the hazard of triple-class virological failure.*

	Unadjusted		Adjusted	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Female gender	1.83 (1.23-2.72)	0.003		
Transmission risk group				*0.06*
MSM	1.00			
Heterosexual contact	2.30 (1.50-3.53)	0.0001	1.14 (0.66-1.95)	0.65
IDU	2.54 (1.13-5.71)	0.02	1.59 (0.67-3.77)	0.29
Other	3.54 (1.96-6.40)	<.0001	2.25 (1.16-4.35)	0.02
Region of origin				*0.002*
Netherlands	1.00		1.00	
W-Europe/N-America	0.87 (0.31-2.44)	0.79	0.78 (0.27-2.23)	0.65
Caribbean/S-America	2.79 (1.61-4.82)	0.0002	2.23 (1.26-3.96)	0.006
Sub-Saharan Africa	4.32 (2.78-6.72)	<.0001	2.47 (1.38-4.41)	0.002
Other	0.43 (0.10-1.78)	0.24	0.28 (0.07-1.18)	0.08
Age at start of cART (per 10 yr older)	0.55 (0.44-0.68)	<.0001	0.61 (0.49-0.77)	<.0001
CD4 cell count at start of cART (cells/mm³)				*0.06*
<50	2.52 (1.46-4.33)	0.0009	2.03 (1.15-3.58)	0.01
50-200	1.60 (0.96-2.67)	0.07	1.40 (0.83-2.36)	0.21
200-350	1.00		1.00	
350-500	0.29 (0.07-1.21)	0.09	0.33 (0.08-1.41)	0.14
≥500	1.24 (0.47	0.66	1.26 (0.47-3.34)	0.65
Year of starting cART				
1998-2003	1.34 (0.86-2.08)	0.20		
2004-2010	1.00			
HIV RNA at the start of cART (copies/ml)				*0.15*
<10,000	0.67 (0.26-2.08)	0.41	0.53 (0.20-1.39)	0.20
10,000-100,000	1.00			
≥100,000	1.50 (0.96-2.35)	0.07	1.40 (0.89-2.23)	0.15
AIDS at the start of cART	1.43 (0.97-2.12)	0.07		
HCV Positive	0.49 (0.18-1.34)	0.17		
HBV Positive	1.95 (1.09-3.49)	0.02	1.89 (1.05-3.39)	0.03
Initial regimen				
2 NRTIs + 1 NNRTI	1.00			
2 NRTI + 1 PI/r	1.20 (0.82-1.75)	0.36		
cART started during pregnancy	1.97 (0.86-4.48)	0.11		

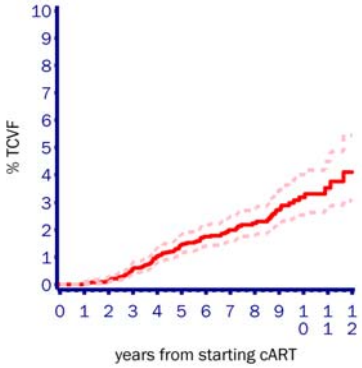

Figure 1. *Kaplan-Meier estimates of the percentage of patients with triple class virologic failure.*

Results

- Baseline characteristics of 9211 selected patients are shown in Table 1.
- During a median (IQR) follow-up of 3.7 years (1.7-6.9) 110 patients (1.2%) experienced TCVF.
- The cumulative incidence at 5 years was 1.5% and at 12 years after starting cART 4.1% (Figure 1).
- Younger age was independently associated with an increased risk of TCVF.
- Individuals from Carribean/S-America and from Sub Saharan Africa had a higher risk of TCVF compared to those from the Netherlands and W-Europe/N-America in analyses adjusted for other confounders.
- The risk was also higher individuals with a HBV co-infection and with lower CD4 cell counts at the start of cART.

Conclusions

- The rate of TCVF in the Netherlands (1.5% at 5 year after starting cART) is lower than the reported rate by the PLATO II multi cohort study (3.4%) which included data from this cohort.
- This may be due to a smaller proportion of patients from non-European origin, at higher risk for TCVF, in our cohort compared to other cohorts.
- The higher risk among patients with low CD4 cell counts at the start of cART and patients from sub-Saharan Africa and South-America may be due to differences in adherence and health seeking behaviour.