Poster 799

Improved toxicity profile of recent HAART regimens

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1. Background

Adverse effects of highly active antiretroviral therapy (HAART) can result in poorer adherence or discontinuation of treatment, thereby increasing the chance of emergence of resistance. We investigated the incidence of toxicity driven regimen changes (TDRC) in the Netherlands ATHENA observational cohort in relation to 4 pre-specified periods: 1996 (first introduction of HAART), 1997-1999 (early HAART), 2000-2001 (intermediate HAART) and 2002-2005 (late HAART) and compared differences in time to the first TDRC between HAART combinations.

2. Methods

Outcome A: Incidence of TDRC during first 3 years after starting HAART

Inclusion criteria
- ≥16 year at the start of HAART.
- Antiretroviral therapy naive.
- HAART started between July 1996-December 2005.
- 6835 patients.
- Poisson regression with a autoregressive covariance structure.
- Subdivided in periods 0-3, 3-6, 6-12, 12-24 and 24-36 months after starting HAART.

Outcome B: Time to first toxicity driven therapy change

Extra inclusion criteria
- Starting regimen includes efavirenz (EFV), nevirapine NVP) or lopinavir/ritonavir (LOP/r) combined with either tenofovir/lamivudine (TDF+3TC) or zidovudine/ lamivudine (AZT+3TC). These are the most frequently used regimens.
- HAART started in 2000-2005.
- 2345 patients
- Cox regression and Kaplan-Meier (KM) estimates.
- Time censored at date of lost to follow-up, death or stop of any drug for any reason other than toxicity.

3. Results

A: Incidence of toxicity driven therapy changes between 1996-2005

Baseline characteristics of the 6835 selected patients are shown in Table 1. During the first 3 years after starting HAART, patients were followed for a total of 16,491 person-years; of those, 14,858 person-years (90.1%) included therapy with antiretroviral drugs.

Table 1. Characteristics of 6835 patients who started HAART between 1 July 1996 and 31 December 2005.

	N	%
Male	5125	75
Female	1710	25
Transmission risk group		
MSM	3334	49
IDU	271	4
Heterosexual	2645	39
Other	585	9
Dutch origin	3629	53
CDC-C event pre-HAART	1915	28
Starting year of HAART		
1996	354	5
1997-1999	2067	30
2000-2001	1362	20
2002-2005	3052	45

	N	%
Starting combination		
Single PI	2127	31
≥ 2 PI	1824	27
NNRT	2431	36
PI+NNRT	211	3
≥ 3 NRT	224	3
	median	**IQR**
Pre-HAART		
CD4 cell count		
cells/mm^3	198	80-320
HIV-RNA		
$\log_{10}$ copies/ml	5.0	4.5-5.4
Age at starting HAART	37.3	31.5-44.4

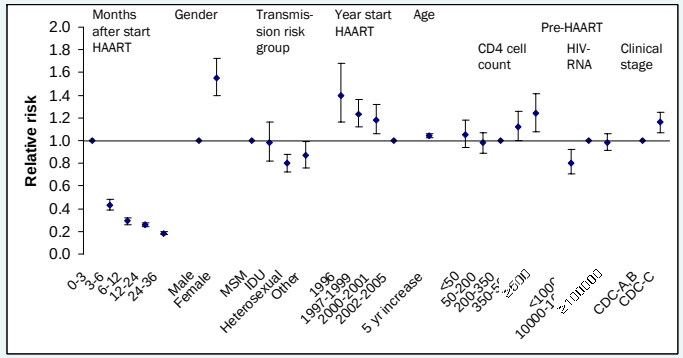

Figure 1. Variables independently associated with the number of toxicity-driven therapy changes during the first 3 years of HAART.

The overall incidence of TDRC was 23.6 (95% CI, 22.8-24.4) per 100 PYART. The incidence was highest (67.7 per 100 PYART) during the first 3 months after starting HAART; it declined to 29.5 per 100 PYART between 3 and 6 months and further declined to 13.1 per 100 PYART between 24 and 36 months after the start of HAART (p<0.0001). In multivariate analyses, the risk of a TDRC for patients starting HAART in 1997-1999 and in 2000-2001 was 1.23 (95% CI 1.12-1.36, p<0.0001) and 1.18 (1.06-1.32, p=0.003) times higher, respectively, compared to starting in 2002-2005. The relative risk for patients starting in 2000-2001 did not differ significantly from those starting in 1997-1999 (p=0.46).

B: Time to first toxicity driven therapy change

Baseline characteristics are shown in Table 2. A lower proportion of women started on regimens including LOP/r. Patients starting LOP/r had more advanced disease, higher pre-HAART HIV RNA levels, lower CD4 cell counts, and more often had a CDC-C diagnosis.

Table 2. Characteristics of 2345 patients who started HAART between 2000-2005 with regimens including NVP, LOP/r or EFV combined with either AZT/3TC or TDF/3TC.

	LOP/r, n=701 %	EFV, n=861 %	NVP, n=783 %	p-value
NRT combination				
AZT/3TC	91	53	81	<0.0001
TDF/3TC	9	47	19	
Male gender	78	76	64	<0.0001
Dutch origin	55	46	43	<0.0001
Transmission risk group				<0.0001
MSM	48	44	41	
IDU	2	10	3	
Heterosexual	40	43	49	
CDC-C event prior to the start of HAART	37	31	16	<0.0001
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	
HIV-RNA ($\log_{10}$ copies/ml)	5.1 (4.9-5.6)	5.0 (4.6-5.2)	5.0 (4.6-5.3)	<0.0001
CD4 cell count (cells/mm^3)	130 (40-220)	170 (70-260)	225 (130-314)	<0.0001

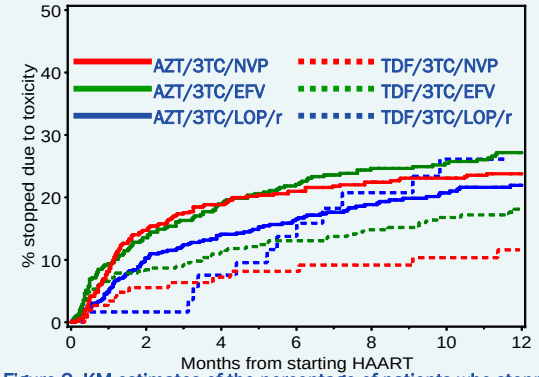

Figure 2. KM estimates of the percentage of patients who stopped the initial HAART regimen due to toxicity.

Twelve months after starting HAART, 22.3% (95% CI 20.5-24.2) of the patients had stopped at least 1 of the drugs because of toxicity. In uni- and multivariate analyses (see Figure 2 and 3), patients starting with TDF/3TC/NVP and TDF/3TC/EFV were the least likely to change the regimen because of toxicity. Time to a TDRC was significantly shorter for patients starting on AZT/3TC/NVP compared to TDF/3TC/NVP, adjusted HR 2.64 (1.50-4.66, p=0.0008) and likewise for patients starting on AZT/3TC/EFV compared to TDF/3TC/EFV, HR 1.78 (1.28-2.47, p=0.0006).

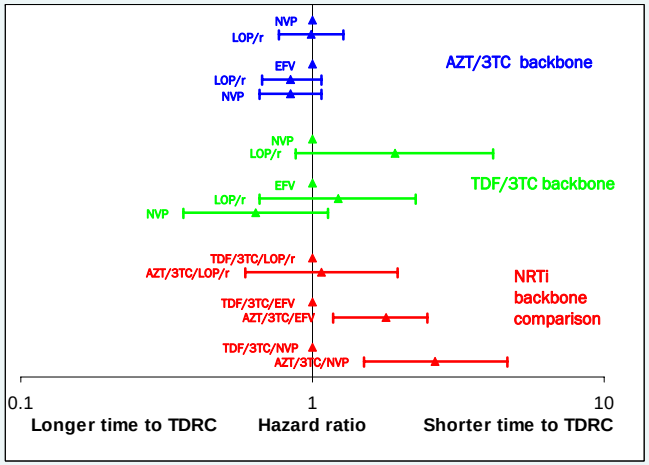

Figure 3. Adjusted hazard ratios of time to first TDRC.

Conclusions

The incidence of HAART regimen change due to toxicity has declined over time, particularly after 2002. This is most likely the result of changes in antiretroviral drugs used in HAART combinations. HAART with TDF/3TC combined with either EFV or NVP was continued for a longer period of time without treatment-limiting toxicity than an AZT/3TC NRTi backbone.