Poster 585

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Collaboration of Observational HIV Epidemiological Research Europe

Coordination: Copenhagen HIV Programme (CHIP) & Institut de Santé Publique,d'Epidémiologie et de Développement (ISPED)

Risk of extensive triple-class virologic failure of the three original antiretroviral drug classes among people followed from therapy initiation with NNRTI or ritonavir-boosted Protease Inhibitor regimens

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BACKGROUND

- This study forms part of the PLATO II project (Pursuing Later Treatment Options)
- Life expectancy in people with HIV has been estimated to be approaching that of the uninfected general population in some successfully treated population subgroups. For these potential life expectancies to be attained, viral suppression must be maintained for decades.
- Patients who have virologically failed all three original antiretroviral classes have limited treatment options. It is therefore important to monitor the rate at which this is occurring in order to anticipate the continuing need for new drugs in the future.
- In resource-limited settings, NNRTI-containing regimens are the almost universal choice for initial regimens. Second line regimens containing a PI/r are being introduced in such settings for patients who appear, by whatever means of monitoring available, to be failing first line regimens.
- In a large European multi-cohort collaboration, we studied the rate of triple class virologic failure (TCVF) in patients who started ART with 2 NRTIs and either an NNRTI or a PI/r.
- We also specifically focused on TCVF in a subgroup of patients who started a PI/r-containing regimen (as first PI) after having virologically failed a first-line NNRTI regimen.

METHODS

- COHERE (Collaboration of Observational HIV Epidemiological Research Europe) is a collaboration of most HIV observational cohorts in Europe. The 28 cohorts participating in the PLATO II project submitted data in a standardized format to one of two regional coordinating centres, where error checks were performed and duplicate records removed.
- The analysis was restricted to patients aged 16 or over, who started ART from 1998 onwards with an initial regimen of 2 NRTIs and either an NNRTI or a PI/r. Patients were followed from the start of ART to their last viral load, and were only included if they had at least 4 months of follow-up.
- Virologic failure of a drug was defined by a viral load >500 copies/ml despite at least 4 months of continuous use. TCVF was defined as virologic failure of at least 2 NRTIs, 1 NNRTI and 1 PI/r. We evaluated the risk of TCVF after starting ART.
- In further analyses we focused on a subgroup of patients who had started ART with an NNRTI-based regimen, virologically failed an NNRTI, and then subsequently started a PI/r as first PI. In these patients, we evaluated the risk of TCVF after starting a PI/r.
- In both analyses, Cox regression methods were used to investigate factors associated with the risk of TCVF.

FIGURE 1: Incidence rates (with 95% confidence interval) of triple class virologic failure (TCVF) by time from the start of ART.

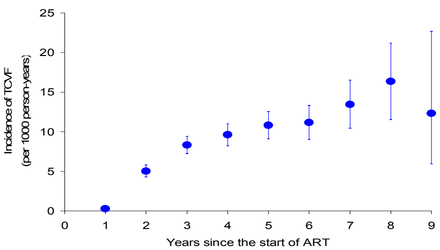
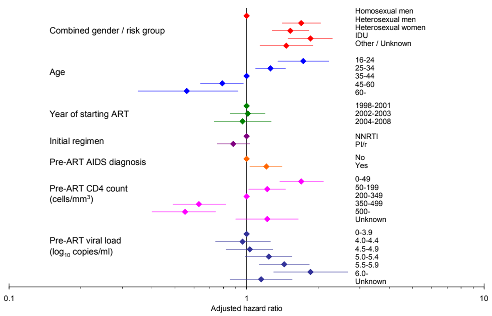
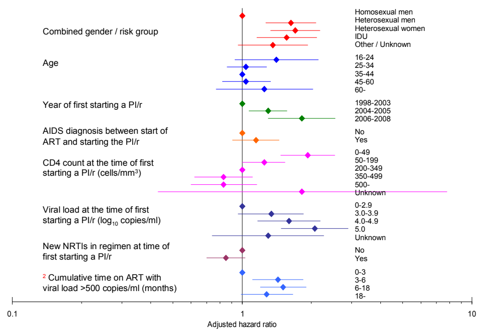


FIGURE 2: Adjusted[1] hazard ratios for triple class virologic failure after the start of ART .



[1] Adjusted for all other factors in the model.

FIGURE 3: Adjusted[1] hazard ratios for triple class virologic failure after the start of a PI/r as second line ART .



[1] Adjusted for all other factors in the model.
[2] After virologically failing an NNRTI and before first starting a PI/r.

RESULTS

Main analysis

- 45937 patients were included in the main analysis (**TABLE 1**). Patients were followed for a median (IQR) of 3.0 (1.5-5.0) years.
- 980 (2.1%) patients developed TCVF. The incidence increased in the first 3-4 years after the start of ART but began to plateau thereafter during the follow-up available (**FIGURE 1**).
- Kaplan-Meier estimates for the cumulative proportions of patients who had developed TCVF by 5 and 9 years from the start of ART were 3.4% (95% CI: 3.1%-3.6%) and 8.6% (95% CI: 7.5%-9.8%).
- Hazard ratios for factors associated with the risk of TCVF after the start of ART are shown in **FIGURE 2**. Lower pre-ART CD4 count and higher pre-ART viral load were associated with an increased risk of TCVF. A lower risk of TCVF was observed in homosexual men than in the other combined gender / risk groups, and older age at the time of starting ART was found to be associated with a lower risk of TCVF.
- There was no significant difference in the risk of TCVF according to the drug class used in the initial ART regimen (adjusted HR for PI/r compared with NNRTI: 0.88, 95% CI: 0.75-1.03, p=0.11).

Analysis of patients starting a PI/r as second line ART

- A subgroup of 2042 patients were included in the analysis of patients starting a PI/r as second line ART (**TABLE 2**).
- In these patients, the median (IQR) time from starting ART to failing an NNRTI was 0.9 (0.5-1.9) years, and the median (IQR) time from failing an NNRTI to starting a PI/r was 0.8 (0.3-2.2) years.
- Of a total of 2945 person-years of follow-up from failure of the NNRTI to initiation of the PI/r, 353 person-years (12.0%) were spent off ART, 1928 person-years (65.5%) were spent on ART with viral load >500 copies/ml, and 664 person-years (22.5%) were spent on ART with viral load ≤500 copies/ml.
- 575 (28.2%) patients developed TCVF, in all cases on the date of virologic failure of a PI/r. The Kaplan-Meier estimates of the cumulative proportions of patients who had developed TCVF by 1 and 5 years from the start of the first PI/r were 20.4% (95% CI: 18.4%-22.3%) and 46.3% (95% CI: 42.8%-49.7%).
- Hazard ratios for factors associated with the risk of TCVF after first starting a PI/r are shown in **FIGURE 3**. Lower CD4 count and higher viral load at the time of starting the PI/r were associated with an increased risk of TCVF. Patients who, between failing an NNRTI and starting the PI/r, had spent less than 3 months on ART with a viral load >500 copies/ml had a lower risk of TCVF.

TABLE 1: Characteristics at the time of starting ART (n=45937).

Characteristic		n	(%)
Combined gender / risk group	Homosexual men	16649	(36.2)
	Heterosexual men	9122	(19.9)
	Heterosexual women	10523	(22.9)
	IDU	5586	(12.2)
	Other / Unknown	4057	(8.8)
Age at the start of ART (years)	16-24	2570	(5.6)
	25-34	15467	(33.7)
	35-44	17814	(38.8)
	45-59	8516	(18.5)
	60-	1570	(3.4)
Year of starting ART	1998-2001	16509	(35.9)
	2002-2003	11474	(25.0)
	2004-2008	17954	(39.1)
Initial regimen	2 NRTIs + 1 NNRTI	29282	(63.7)
	Efavirenz	16978	(58.0)
	Nevirapine	12304	(42.0)
	2 NRTIs + 1 PI/r	16655	(36.3)
	Lopinavir/r	9638	(57.9)
	Indinavir/r	2731	(16.4)
	Saquinavir/r	1804	(10.8)
	Atazanavir/r	1279	(7.7)
	Fosamprenavir/r	1016	(6.1)
	Amprenavir/r	129	(0.8)
	Tipranavir/r	47	(0.3)
	Darunavir/r	11	(0.1)
Previous AIDS diagnosis	Yes	8976	(19.5)
CD4 count (cells/mm³)	0-49	5937	(12.9)
	50-199	13310	(29.0)
	200-349	13478	(29.3)
	350-499	5014	(10.9)
	500-	3708	(8.1)
	Unknown	4490	(9.8)
Viral load (log_{10} copies/ml)	0-3.9	7431	(16.2)
	4.0-4.4	5300	(11.5)
	4.5-4.9	9406	(20.5)
	5.0-5.4	10455	(22.8)
	5.5-5.9	6473	(14.1)
	6.0-	1528	(3.3)
	Unknown	5344	(11.6)

TABLE 2: Characteristics at the time of starting a PI/r as second line ART (n=2042).

Characteristic		n	(%)
Combined gender / risk group	Homosexual men	613	(30.9)
	Heterosexual men	465	(22.8)
	Heterosexual women	484	(23.7)
	IDU	303	(14.8)
	Other / Unknown	159	(7.8)
Age at the time of first starting a PI/r (years)	16-24	62	(3.0)
	25-34	587	(28.8)
	35-44	947	(46.4)
	45-59	382	(18.7)
	60-	64	(3.1)
Year of first starting a PI/r	1998-2003	750	(36.7)
	2004-2005	851	(41.7)
	2006-2008	441	(21.6)
AIDS diagnosis between start of ART and starting the PI/r	Yes	258	(12.6)
CD4 count at the time of first starting a PI/r (cells/mm³)	0-49	200	(9.8)
	50-199	579	(28.4)
	200-349	650	(31.8)
	350-499	351	(17.2)
	500-	256	(12.5)
	Unknown	6	(0.3)
Viral load at the time of first starting a PI/r (log_{10} copies/ml)	0-2.9	353	(17.3)
	3.0-3.9	495	(24.2)
	4.0-4.9	703	(34.4)
	5.0-	426	(20.9)
	Unknown	65	(3.2)
New NRTIs in regimen at time of first starting a PI/r	Yes	1501	(73.5)
* Cumulative time on ART with viral load >500 copies/ml (months)	0-3	536	(26.3)
	3-6	429	(21.0)
	6-18	601	(29.4)
	18-	476	(23.3)
First PI (or PI pair)	Lopinavir/r	1081	(52.9)
	Atazanavir/r	509	(24.9)
	Other single PI/r	368	(18.0)
	Double PI/r	84	(4.1)

* After virologically failing an NNRTI and before first starting a PI/r

COMMENTS

- The rate of development of TCVF was very similar according to whether ART was started with NNRTI-containing regimens or PI/r-containing regimens.
- For those patients who experienced first line virologic failure, the time to the start of a regimen containing the third class was surprisingly long at a median of 0.8 years.
- Factors in our analysis associated with slower development of TCVF after starting ART included being in the homosexual male risk group and older age, in addition to lower pre-ART viral load and higher pre-ART CD4 count. In those starting a PI/r as second-line ART, homosexual men also experienced a slower rate of TCVF, as did those with lower viral load and higher CD4 count at the time of starting the PI/r, and those who spent less than 3 months on ART with viral load >500 copies/ml after NNRTI failure.

SUMMARY AND CONCLUSIONS

- The rate of virologic failure of the three original drug classes is low, but not negligible, and does not appear to diminish with time from start of ART. If this trend continues many patients are likely to eventually need newer drugs in order to maintain viral suppression.
- The rate of triple class failure from start of a PI/r after NNRTI failure (46% with failure by 5 years overall, 55% in the heterosexual risk groups) provides a comparator for studies of response to second-line regimens in developing countries.

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