

Trends Over Time in Initial Virological Failure of First HAART: 1996 to 2002.

A Joint Cohort Analysis of 4143 Subjects.

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BACKGROUND

Triple combination antiretroviral treatment (HAART) for HIV has been in use for almost a decade. However the likelihood of initial treatment success may have changed considerably over this period, due to changes in drug options, accumulating clinical experience and increased understanding of treatment issues by patients and clinicians.

OBJECTIVE

Combining data from five observational HIV clinic cohorts in Europe and Canada, we examined the risk of initial virological failure of first HAART among antiretroviral naïve subjects, according to calendar year of starting treatment, from 1996 to 2002.

METHODS

The following HIV cohorts were included:

- Hospital Clinic i Provincial HIV cohort, Barcelona
- Frankfurt HIV cohort, Goethe University Clinic, Frankfurt
- Royal Free HIV clinic cohort, London
- Hopital de l'Archet HIV clinic cohort, Nice
- Southern Alberta HIV clinic cohort, Calgary

Subjects were selected according to the following criteria:

- started HAART (≥3 drugs including a PI, NNRTI or abacavir) naïve to ART from 1996 to 2002 at age ≥ 16 years
- ≥1 pre-HAART viral load (VL)
- potential for ≥1 year follow-up (based on last follow-up for each cohort)

Virological failure was defined as VL >500 c/mL using the first VL from 6 to 12 months after HAART initiation, including:

- A: all subjects, missing VL=failure [n=4143]**
- B: all subjects with VL measurement [n=3360]**
- C: all subjects on any ART at VL measurement [n=3111]**

CD4 response to HAART was assessed using the change from pre-HAART to the first value from 6 to 12 months after HAART initiation. An increase of <50/mm³ was defined as failure, with missing CD4=failure.

Cox regression (with fixed follow-up time) stratified by cohort was used to generate risk ratios for virological failure and CD4 response according to calendar year of starting HAART and other factors.

RESULTS

Subject characteristics

Subjects starting HAART in recent years were more likely to be women, have heterosexual risk, be older and have lower CD4 count. The most frequent starting regimen changed from a non-boosted PI to an NNRTI-including combination (Table 1).

Table 1: Demographic and clinical characteristics by calendar year of starting HAART

	Year of starting HAART						
	1996	1997	1998	1999	2000	2001	2002
N	162	841	763	735	575	599	468
%							
Women	19	20	23	26	29	28	25
Heterosexual risk	23	24	28	36	35	36	37
IDU risk	12	24	26	21	21	19	15
Previous AIDS	23	21	22	25	26	24	25
Median:							
Age at HAART	35.8	35.2	35.6	36.2	35.9	36.5	37.4
VL c/mL pre HAART	5.4	5.1	5.1	5.1	5.2	5.1	5.1
CD4 /mm ³ pre HAART	232	262	225	202	186	179	189
3rd drug in regimen, %							
Single PI: SAQ HG	13	15	3	1	0	0	0
Single PI: other	83	64	62	31	19	10	9
Ritonavir plus other PI	1	2	5	16	16	29	30
Single NNRTI	4	17	25	33	43	40	47
Abacavir	0	1	1	13	18	19	12
Combination of above	0	1	3	6	3	2	2

Trends in risk of virological failure

Overall proportions of subjects with virological failure were:

- A: 34.8% (1443/4143)**
- B: 19.6% (660/3360)**
- C: 14.4% (449/3111)**

There was a marked reduction over time in the probability of virological failure for analyses A, B and C (Table 2).

Table 2: Virological failure by calendar year of starting HAART

	Year of starting HAART						
	1996	1997	1998	1999	2000	2001	2002
% with failure							
A (M=failure)	40.1	41.9	38.5	34.0	31.5	30.4	25.4
B (exclude M)	29.7	28.1	22.1	18.1	14.5	14.7	12.3
C (on ART only)	24.8	23.0	17.3	12.4	10.0	8.0	8.4
Median weeks: HAART to VL measurement	29.9	31.1	32.1	31.3	31.9	32.1	32.4
% with no VL from 6 to 12 months	14.8	19.1	21.1	19.5	19.8	18.4	15.0
% off ART at VL measurement*	9.4	8.1	7.6	8.5	6.5	7.4	4.8

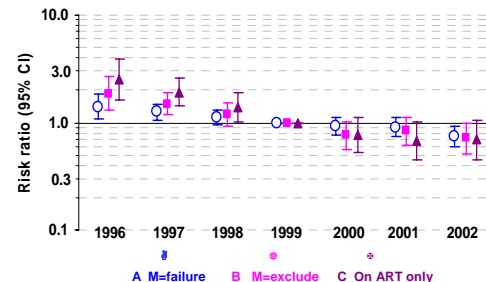
*Of those with VL measurement

Adjustment for demographic factors, pre-HAART CD4, VL and AIDS had little effect on the trend (Figure 1; Table 3). Risk of virological fell substantially from 1996 to 1999, with evidence of a further decline from 1999 to 2002 (p<0.001 for trend across 7 year period for A, B, C).

Relative reduction in failure risk was greatest when considering subjects remaining on any ART (analysis C), because reductions over time in the risks of loss to follow-up and treatment discontinuation were relatively small (Table 2).

The trend in risk of virological failure remained but was attenuated after further adjustment for type of first HAART regimen (Table 3).

Figure 1. Adjusted[§] risk ratios for virological failure by calendar year of starting HAART



[§]Adjusted for age, sex, risk group, pre-HAART VL and CD4, pre-existing AIDS, stratified by cohort. 1999 is reference category.

Table 3: Unadjusted and adjusted risk ratios for virological failure by calendar year of starting HAART

	Year of starting HAART						
	1996	1997	1998	1999	2000	2001	2002
A (M=failure)							
Unadjusted	1.31	1.25	1.13	1	0.92	0.89	0.71
Adjusted [§]	1.41	1.25	1.11	1	0.92	0.90	0.74
Adjusted plus SR [¶]	1.27	1.12	1.04	1	0.96	0.99	0.82
B (exclude M)							
Unadjusted	1.78	1.55	1.22	1	0.80	0.82	0.68
Adjusted [§]	1.86	1.50	1.19	1	0.76	0.83	0.71
Adjusted plus SR [¶]	1.48	1.22	1.06	1	0.83	0.98	0.86
C (on ART only)							
Unadjusted	2.42	1.89	1.39	1	0.80	0.66	0.66
Adjusted [§]	2.51	1.92	1.40	1	0.76	0.67	0.70
Adjusted plus SR [¶]	2.18	1.64	1.33	1	0.81	0.76	0.80

[§]Adjusted-risk ratios adjusted for age, sex, risk group, pre-HAART VL and CD4, pre-existing AIDS. [¶]Adjusted plus SR=risk ratios adjusted for all previous factors plus starting regimen as defined by 3rd drug in Table 1. All analyses stratified by cohort. 1999 is reference category

Other factors were associated with virological failure. Risk of failure was lower with older age and for homosexual compared to heterosexual, IDU and other risk groups. Risk of failure was higher with a higher pre-HAART VL and pre-existing AIDS.

Trends in CD4 response

CD4 response to treatment varied with calendar year of starting HAART. The risk of a poor response (<50/mm³ increase from baseline) fell over time (Table 4; p=0.002 for trend across 7 year period, adjusted model).

Table 4. CD4 count response by calendar year of starting HAART

	Year of starting HAART						
	1996	1997	1998	1999	2000	2001	2002
% with <50/mm ³ CD4 increase [¶]	39	43	42	40	38	36	32
Adjusted [§] risk ratios (95% CI) for <50/mm ³ increase:	1.13 (0.9,1.5)	1.10 (0.9,1.3)	1.04 (0.9,1.2)	1 (0.8,1.2)	0.98 (0.8,1.1)	0.93 (0.8,1.1)	0.82 (0.7,1.0)
Median increase [*] /mm ³	97	119	120	121	127	125	150

[¶]From pre-HAART to 6-12 months, with missing CD4=failure. [§]Adjusted for age, sex, risk group, pre-HAART VL, pre-existing AIDS, stratified by cohort. 1999 is reference category. ^{*}For median increase, subjects with no CD4 count from 6-12 months excluded.

CONCLUSIONS

Over a seven-year period of HAART use in clinical practice, the risk of initial virological failure of treatment has halved at least.

These data suggest that changes in starting regimens may not fully explain this trend. Factors such as increases in adherence and improvements in clinical management of patients starting HAART may have made an additional contribution.

For subjects starting HAART who remain on treatment, risk of initial failure is now very low, leaving little potential for further improvement. However, failure due to treatment discontinuation and loss to follow-up remains more common, suggesting scope for continued improvement in future years with simpler, less toxic regimens and increasingly effective patient care strategies.