10th European AIDS Conference / EACS 2005, Dublin, Ireland – Poster PE18.4/8

Responders to antiretroviral treatment over 500 CD4 /mm3 reach same mortality rates as general population APROCO and Aquitaine cohorts, France

C Lewden (1), Aproco and Aquitaine Study Groups
(1) ISPED - INSERM U593, 146 rue Léo Saignat, 33076 Bordeaux

CONTEXT

- Availability of combination antiretroviral therapy (CART) has resulted in
  - immune restoration in the majority of treated HIV-infected patients
  - a dramatic decrease in AIDS-related mortality
- For HIV-infected persons, having a social life that include working, having children or buying a house means obtaining insurance contracts and loans

Published studies: mortality in HIV-infected persons remains higher than in the general population

			N	Median follow-up (years)	Deaths (n)	Rates (%PY)		
Lewden JAIDS 2001	France	After HAART initiation	1157	1.9	44	2.2	Standardized Mortality Ratio	7.8 (5.7-10.4)
Keiser AIDS 2004	Switzerland	1997-2001	7037				Standardized Mortality Ratio	15.3 (14.2-16.4)
		1997-2001, HAART	5393					10.1 (9.1-11.1)
		1997-2001, HAART, non -IDU						6.8 (5.9-7.6)
Jensen-Fangel AIDS 2004	Denmark	After HAART initiation	647	3.5	53	2.7	Mortality rate ratio	7.1 (7.4-9.4)
Van Sighem JAIDS 2005	Netherlands	6 months after HAART initiation	3678		126	1.1	Standardized Mortality Ratio	
		Men, non-IDU, CD4 600/mL HIV-RNA <5log						4.3 (3.3-5.8)
		Women, non-IDU, CD4 600/mL HIV-RNA <5log						5.9 (4.4-8.2)
Jaggy Lancet 2003	Switzerland	1997-2001	3963	3.7	341	2.6	Excess Death Rate (/100 PY)	2.4 (2.1-2.7)
		Non Hepatitis C	2318		134	1.8		1.4 (1.1-1.7)
		Non Hepatitis C, CD4>250/mm³	1567		35	0.8		0.4 (0.2-0.7)

OBJECTIVE

To compare mortality rates in HIV-infected adults five years after starting a protease-inhibitor (PI) containing antiretroviral therapy to mortality in the general population, globally and according to CD4 cell count in the last year of follow-up

METHODS

Patients

HIV-infected adults starting for the first time a PI-containing treatment between 1997 and 1999 in the APROCO and Aquitaine cohorts

The ANRS CO8-APROCO Cohort
- Prospective observational multicenter study, France
- 1281 consecutive HIV-1 infected adults
- 1st PI-containing therapy in 1997-1999
- Standardized clinical and biological data : M0, M1, M4, every 4 months

The ANRS-CO3 Aquitaine Cohort
- Based on public hospital surveillance system since 1987
- HIV-infected adults in the Aquitaine region, France
- Standardized clinical and biological data collected at each hospital contact

Definitions

Response to treatment in the year preceding the last available data:

- **Favorable response:**
  - at least two CD4+ cell counts >=500/mm³
  - no CD4 cell count <500/mm³
  - no plasma HIV-RNA >=10000 copies/ml
- **"Response 350":**
  - at least 2 CD4 cell counts >=350/mm³
  - no CD4 <350/mm³
  - excluding favorable response
- **"Response 200":**
  - at least 2 CD4 cell counts >=200/mm³
  - no CD4 <200/mm³
  - excluding higher levels of response

Indirect standardization

- Death rates per 100 person-years (%PY) until 30th June 2003
  95% confidence intervals (CI) estimated by the Poisson method
- Standardized mortality ratio (SMR)
  reference : French death rates, year 1999
  stratified by age and gender
  SMR = observed deaths / expected deaths

RESULTS

Table 1. Baseline characteristics of 2279 HIV-infected adults starting a protease inhibitor-containing therapy, 1997-99

		Total (n=2279)	Men (n=1743)	Women (n=536)	p
Median age	(years)	36	37	35	<0.01
(inter-quartile range)		32-43	33-43	30-40	
HIV transmission group	(%)				
homo-bisexual		38	50	-	<0.01
heterosexual		35	25	68	
injecting drug use		20	19	26	
haemophilia, transfusion		2	2	2	
undetermined		4	5	3	
Median known duration of HIV infection	(years)	4.4	4.1	5.4	<0.01
(inter-quartile range)		0.7-8.5	0.5-8.3	2.0-9.1	
Clinical AIDS stage	(%)	21	22	17	0.01
Median CD4+ cell count	(/mm³)	270	270	270	0.20
(inter-quartile range)		137-416	128-416	163-414	
Median HIV-RNA	(log_{10} copies/ml)	4.5	4.5	4.3	<0.01
(inter-quartile range)		3.7-5.1	3.8-5.2	3.5-5.0	
HCV infection	(%)	27	25	34	<0.01
Positive HBs Antigen	(%)	6	7	2	<0.01

Abbreviations: HIV: Human Immunodeficiency Virus; AIDS: acquired immunodeficiency syndrome; AIDS stage: 1993 CDC clinical stage C; HCV: hepatitis C virus.

Table 2. Mortality rates and standardized mortality ratio (SMR) in HIV-infected adults, January 1997 - June 2003

	N	Person-years (PY)	Deaths (n)	Rates (%PY)	95%CI	SMR	95%CI
Global	2279	9332	202	2.2	(1.9-2.5)	7.8	(6.7-8.9)
Men	1743	7202	158	2.2	(1.9-2.5)	5.4	(4.6-6.3)
Women	536	2129	44	2.1	(1.5-2.7)	14.1	(10.3-18.9)
Injecting drug users	442	1741	55	3.2	(2.3-4.0)	18.6	(14.0-24.2)
Other transmission groups	1837	7591	147	1.9	(1.6-2.2)	6.4	(5.4-7.5)
HCV infected	554	2243	69	3.1	(2.4-3.8)	13.6	(10.6-17.2)
Non HCV infected	1496	6205	116	1.9	(1.5-2.2)	6.3	(5.2-7.6)
Non HIV-related deaths§	2279	9332	100	1.1	(0.9-1.3)	3.8	(3.1-4.7)
Favorable responders	**549**	**2560**	**7**	**0.3**	**(0.1-0.5)**	**1.1**	**(0.4-2.2)**
Response 350	582	2565	22	0.9	(0.5-1.2)	3.1	(1.9-4.7)
Response 200	499	2108	31	1.5	(1.0-2.0)	4.8	(3.3-6.8)
Other responses	649	2100	142	6.8	(5.7-7.9)	23.6	(19.8-27.8)

Abbreviations: HIV: Human Immunodeficiency Virus; HCV: hepatitis C virus.

§Non-HIV related death: death not related to AIDS, to an infection other than viral hepatitis and to treatment of HIV-infection or its complications

Table 3. Mortality rates and standardized mortality ratio (SMR) according to year of death in 3343 HIV-infected adults starting a protease inhibitor-containing therapy in 1996-2002

	Person-years (PY)	Deaths (n)	Rates (%PY)	95%CI	SMR	95%CI
1996	273	31	11.3	(7.4-15.3)	40.7	(27.7-57.8)
1997	1106	56	5.1	(3.7-6.4)	19.6	(14.8-25.5)
1998	2187	77	3.5	(2.7-4.3)	13.4	(10.6-16.8)
1999	2435	43	1.8	(1.2-2.3)	6.5	(4.7-8.8)
2000	2428	47	1.9	(1.4-2.5)	6.7	(4.9-8.9)
2001	2349	57	2.4	(1.8-3.1)	7.8	(5.9-10.1)
2002	2124	56	2.6	(2.0-3.3)	7.9	(6.0-10.3)
2003	495	19	3.8	(2.1-5.6)	10.9	(6.6-17.1)

CONCLUSION

We addressed the question of what level of CD4 cell count to reach overtime

Five years after having started CART, mortality still remained higher in HIV-infected patients than in the general population
especially in women, injecting drug users, hepatitis C co-infected patients

Among patients with sustained CD4 cell count over 500/mm³, mortality was similar to the general population

HIV infection with favorable response to treatment might no longer be considered as an obstacle to obtain insurance contracts and loans

Medical teams should go through all known aspects of sub optimal response to treatment, i.e. tolerance, adherence, social support or depression in order to reach sustained high CD4 cell counts in a majority of patients

Researchers should develop operational tools to improve therapeutic success

ANRS-CO3 Aquitaine Cohort Study Group

Scientific committee: J. Beylot, G. Chêne, F. Dabis, M. Dupon, M. Longy-Boursier, JL. Pellegrin, JM. Ragnaud and R. Salamon.
Methodological coordination: F. Dabis, G. Chêne, R. Thiébaut, C. Lewden and S. Lawson-Ayayi.
Medical coordination: M. Dupon, P. Mercié, JF. Moreau, P. Morlat, JL. Pellegrin, JM. Ragnaud, N. Bernard, D. Lacoste, D. Malvy and D. Neau.
Data Management and Analysis: MJ. Blaizeau, M. Decoin, S. Delveaux, C. Hannapier, S. Labarrère, V. Lavignolle-Aurillac, B. Uwamaliya-Nziyumvira, G. Palmer,D. Touchard, E. Balestre, A. Alioum, H. Jacqmin-Gadda and R. Thiébaut.

Participating physicians : *Bordeaux University Hospital*: J. Beylot, P. Morlat, N. Bernard, M. Bonarek, F. Bonnet, B. Coadou, P. Gellie, D. Lacoste, C. Routs, M. Dupon, F. Bocquentin, H. Dutronc, S. Lafarie; M. Longy-Boursier, P. Mercié, A. Aslan, D. Malvy, T. Pistonne, P. Thibaut, R. Vatan; JM.Ragnaud, D. Chambon, C. De La Taille, C. Cazorla, D. Neau, A. Ocho; JL.Pellegrin, JF. Viallard, O. Caubet, C. Cipriano E. Lazaro; P.Couzigou, L. Castera; H. Fleury, ME. Lafon, B. Masquelier, I. Pellegrin; D. Breilh; JF. Moreau, P. Blanco.
Dax Hospital: P. Loste, L. Caunègre.
Bayonne Hospital: F. Bonnal, S. Farbos, M. Ferrand.
Libourne Hospital: J.Ceccaldi, S. Tchamgoué.
Mont de Marsan Hospital: S. De Witte
Financial support:
Agence Nationale de Recherches sur le Sida (ANRS, Action Coordonnée n°7).

ANRS-CO8 APROCO-COPILOTE Study Group

Scientific Committee:
- Steering Committee : *Principal Investigators*: C. Leport, F. Raffi,
Methodology: G. Chêne, R. Salamon.
Social Sciences: J-P. Moatti, J. Pierret, B. Spire
Virology: F. Brun-Vézinet, H. Fleury, B. Masquelier,
Pharmacology: G. Peytavin, R. Garraffo
- *Other members*: F. Balereau, D. Costagliola, P. Dellamonica, C. Katlama, L. Meyer, M. Morin, D. Sicard, D. Salmon, A. Sobel,
Events Validation Committee: L. Cuzin, M. Dupon, X. Duval, V. Le Moing, B. Marchou, T. May, P. Morlat, C. Rabaud, A. Waldner-Combernoux
Observers: P. Choutet, JF. Delfraissy, J. Dormont, C. Grillot-Courvalin, M. Garré, Y. Souteyrand, JL. Vildé
Data monitoring and statistical analysis:
C.Alfaro, F.Alkaied, C.Barennes, D.Beniken, S.Boucherit, AD.Bouhnik, C.Brunet-François, V.Cailleton, MP.Carrieri, AS.Chabaud, C.Charlois-Ou, JF.Cocallemen, M. Courcoul, F. Collin, C.Droz, G.Dupouy, S.Duran, X.Duval, JL.Ecobichon, C.Egouy, V.El Fouikar, M.François, C.Jadand, V.Journot, R.Lassalle, L.Latour, JP.Legrand, S.Marrakchi, B.Matera, W.Nouioua, G.Palmer, S.Perchard, C.Petit, E.Pereira, M.Préau, C. Protopopescu, C.Roussillon, M.Savès, M.Souville, J.Surzyn, S.Tabubeau, A.Taieb, R.Thiébaut, V.Villes, E.Vincent, R.Winum, H.Zouari

Clinical Centers (coordinators): Amiens (Pr JL. Schmit), *Angers* (Dr JM. Chennebault), *Belfort* (Dr JP. Faller), Besançon (Pr JL Dupond, Dr JM. Estavoyer, Pr R. Laurent, Pr D. Vuitton), Bobigny (Pr L. Guillevin, Pr A. Kitvitzky), Bordeaux (Pr J. Beylot, Pr M. Dupon, Pr Lacut, Pr M. Le Bras, Pr M. Longy-Boursier, Pr JM. Ragnaud), Bourg-en-Bresse (Dr P. Granier), Brest (Pr M. Garré), Caen (Pr C. Bazin, Pr R. Verdon), Compiègne (Dr P. Veysseir), Corbeil Essonnes (Dr A. Devidas), Créteil (Pr A. Sobel), Dijon (Pr H. Portier), Garches (Pr C. Perronne), Lagny (Dr P. Lagarde), Libourne (Dr J. Ceccaldi), Lyon (Pr D. Peyramond), Meaux (Dr C. Allard), Montpellier (Pr J. Reynes), Nancy (Pr P. Canton, Pr T. May), Nantes (Pr F. Raffi), Nice (Pr JP. Cassuto, Pr P. Dellamonica), Orléans (Dr P. Arsac), Paris (Pr E. Bouvet, Pr F. Bricaire, Pr Cabane, Pr C. Caulin, Dr G. Cessot, Pr Frottier, Pr PM. Girard, Pr L. Guillevin, Pr S. Herson, Pr JC. Imbert, Pr JE. Malkin, Pr M. Molina, Pr G. Pialoux, Pr W. Rozenbaum, Pr D. Salmon, Pr D. Sicard, Pr F. Vachon, Pr JL. Vildé, Pr Yéni), Poitiers (Pr B. Becq-Giraudon), Reims (Pr G. Rémy), Rennes (Pr F. Cartier, Pr C. Michelet), Saint-Etienne (Pr F. Lucht), Saint-Mandé (Pr T. Debord, Pr R. Roué), Strasbourg (Pr JM. Lang), Toulon (Dr Jaubert, Dr JP. de Jaureguiberry), Toulouse (Pr B. Marchou, Pr P. Massip), Tours (Pr P. Choutet, JM Besnier).
Financial support:
Agence Nationale de Recherches sur le Sida (ANRS, Action Coordonnée n°7), Sidaction Ensemble contre le Sida and laboratories : Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Glaxo- SmithKline, Merck Sharp et Dohme, Roche.
Other supports: Collège des Universitaires de Maladies Infectieuses et Tropicales (CMIT), (ex Association des Professeurs de Pathologie Infectieuse et Tropicale-APPIT)