1497

Incidence And Risk Factors For The Occurrence Of Non-AIDS-defining Non-HAART-related Severe Clinical Events In HIV-infected Adults With Long-term Follow-up, Aproco-copilote Cohort (ANRS CO8)

T. FERRY[1], F. RAFFI [2], F. COLLIN[3], M. GARRE[4], X. DUVAL[5], P. MORLAT[6], J. CHENNEBAULT[7], G. CHENE[3], C. LEPORT[5], V. LE MOING[8], ANRS CO8 Study Group

[1]Service de Maladies Infectieuses, Hospices Civils de Lyon, Lyon, France; [2]Service de Maladies Infectieuses, Hôtel-Dieu, Nantes, France; [3]ISPED, INSERM U593, Université Victor Segalen, Bordeaux, France; [4]Service de Maladies Infectieuses, University Hospital, Brest, France; [5]Service de Maladies Infectieuses, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, Paris, France; [6]Service de Médecine Interne, Hôpital saint-André, Bordeaux, France; [7]Service de Maladies Infectieuses, Angers, France; [8]Service des Maladies Infectieuses, University Hospital, Montpellier, France.

Contact: tristan.ferry@univ-lyon1.fr

Abstract

Background. Non-AIDS non-HAART-related (NANHR) events have become the most frequent clinical events in HIV-infected patients with HAART. **Methods.** In the APROCO/COPILOTE cohort, 1281 patients were enrolled in 1997-1999 at the initiation of a protease inhibitor-containing antiretroviral regimen. All severe events (hospitalization or death) were reviewed by a validation committee. Incidence and risk factors for NANHR events were analyzed using multivariate Cox models with CD4 and plasma HIV RNA as time-dependent covariates.**Results.** Among 1231 patients (median follow-up, 7 years), 713 NANHR events were recorded (incidence of 10.5/100 patient-years). Most frequent first-occurring NANHR events were (mainly bacterial airway) infections (196 events, 27%), cancer-related (68, 9.5%), cardiovascular (68, 9.5%) and psychiatric events (61, 8.5%). They were significantly more frequent in patients older than 60 (hazard ratio [HR], 2.1; 95% confidence interval [CI], 1.3-3.2), co-infected with HCV (HR, 1.7; 95% CI, 1.4-2.1), with CD4 below 100 cells/mm3 (HR, 2.5; 95% CI, 1.8-3.6) and with plasma HIV RNA level above 10 000 copies/mL (HR, 1.9; 95% CI 1.5-2.5). Infections represented 41.5% and 42.4% of the events occurring at CD4 below 100 cells/mm3 and at plasma HIV RNA level above 10 000 copies/mL, respectively. **Conclusions.** NANHR severe clinical events, especially bacterial infections, may be favored by persistent immunosuppression and virological replication.

Background

Since 1996, in the HAART era:

- Mortality of HIV-infected patients has decreased due to the reduction of occurrence of AIDS-defining illnesses.
- Nowadays, non-AIDS non-HAART-related (NANHR) events have become the most frequent clinical events in HIV-infected patients with HAART and are the first cause of death in HAART-treated patients.
- Few data are available in the literature about risk factors for developing NANHR events.

Objectives

- To determine the incidence of NANHR events in the French national cohort ANRS CO8 APROCO/COPILOTE
- To study risk factors of NANHR events (especially immunological and virological response to HAART)

Methods

Patients. APROCO/COPILOTE (prospective observational multicenter cohort study in France) enrolled 1281 patients in 1997-1999 at the initiation of a protease inhibitor-containing antiretroviral regimen. The 1231 patients who had at least one follow-up visit after M4 were selected for the present study.

Definitions of severe clinical events and NANHR events. Each event was categorized and scored independently by two experts from the Events Validation Comittee. A clinical event was considered to be severe when:

- It required hospitalization or an extension of hospitalization,
- It led to a life-threatening condition (grade 3 or grade 4 of the standardized classification of the *Agence Nationale de Recherche contre le SIDA,*
- It led to death.

Clinical NANHR events were considered after exclusion of:

- AIDS-defining events
- Solely HAART-related events (lipodystrophy, hypersensitivity in patients treated with abacavir or nevirapine, symptomatic liver or pancreas toxicity, symptomatic anemia in patients treated with zidovudine, indinavir-related nephrolithiasis or renal colic, lactic acidosis)
- Asymptomatic biological events.

Methods

Statistical analysis. Probability of the occurrence of a first NANHR-event was estimated with the Kaplan-Meier product-limit method. Potential determinants of the occurrence of the first severe NANHR-event and the first bacterial infection were analyzed using Cox proportional-hazards regression models with plasma HIV RNA and CD4+ cell count treated as time-dependent variables.

Results

Median follow-up was 88 months (IQR, 52-102 months) and the total follow up was 7664 patients-years. During the follow up, a total of 713 severe NANHR-events were recorded in 385 patients (Table 2), leading to an incidence of NANHR events of 10.5/100 patients-years, while the incidence of AIDS-related events was 2.7/100 patients-years. Variables independently associated with a higher risk of occurrence of a first NANHR event are detailed in Table 3.

	N (%) or med (IQR)
Age (years) :	36 (31.9-42.5)
Men	949 (77.1)
Route of HIV transmission	
Men who have sex with men	480 (39.0)
Heterosexual contact	195 (15.9)
Unknown	403 (32.7)
Injection drug use	153 (12.4)
Smoking status at baseline	412 (33.5)
Time of HIV infection diagnosis at baseline (years)	4 (0.4-8.2)
No prior antiretroviral treatment at baseline	550 (44.7)
Positive HCV antibodies testing at baseline	282 (22.9)
Positive HBs antigenemia testing at baseline	59 (4.8)
Plasma HIV RNA level (log10 copies/mL) at baseline	4.5 (3.7-5.2)
CD4 cells count (per mm3) at baseline	279 (128-425)

Table 1. Characteristics at baseline, ANRS CO8 APROCO-COPILOTE, N=1231 .

	N (%)		N (%)
Bacterial infections	**167 (23.4%)**	**Cardiovascular events**	**68 (9.5%)**
Airway bacterial infections	89 (12.5%)	Ischemic events	53 (7.4%)
Intraabdominal infections	26 (3.6%)	Non-ischemic events	15 (2.1%)
Bacteremia/sepsis	15 (2.1%)	**Psychiatric events**	**61 (8.6%)**
Skin and soft tissue infections	13 (1.8%)	Depression with or without suicide attempt	50 (7%)
Urinary tract infections	9 (1.3%)	Other psychiatric disorders	11 (1.6%)
Bone and/or joint infections	5 (0.7%)	**Neurological events**	**42 (5.9%)**
Perianal abscess	5 (0.7%)	Neuropathy	17 (2.4%)
Others	5 (0.7%)	Miscellanous central neurologic events	14 (2%)
Cancer-related events	**68 (9.5%)**	Seizure	11 (1.5%)
Solid tumors	58 (8.1%)		
Hodgkin lymphoma	12 (1.7%)	**Total**	**713 (100)**

Table 2. Description of the most frequent non AIDS- non HAART related (NANHR) severe clinical events. ANRS CO8 APROCO-COPILOTE, N=1231.

Factors associated with bacterial infections were similar to those associated with all types of NANHR events with a stronger association between virological failure and occurrence of an event: compared to patients with a plasma HIV RNA < 4 $\log_{10}$ copies/ml, HR of event was 2.48 (95% CI, 1.48-4.17) when plasma HIV RNA was between 4 $\log_{10}$ and 5 $\log_{10}$ copies/mL and 4.08 (95% CI, 2.28-7.36) when plasma HIV RNA was > 5 $\log_{10}$ copies/ml.

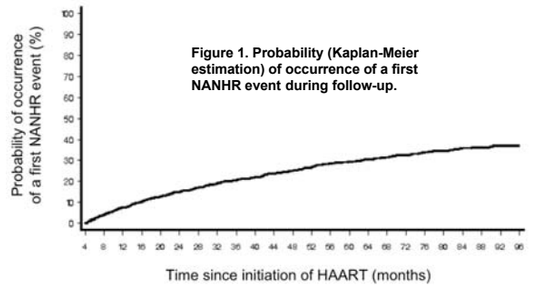

Figure 1. Probability (Kaplan-Meier estimation) of occurrence of a first NANHR event during follow-up.

Factor studied	NANHR events (n, %)	Crude relative hazard	p	Adjusted relative hazard	95% confidence interval	p
Age						
< 30	58 (28.6)	1				
30-40	168 (27.3)	0.83	0.21			
40-50	108 (39.1)	1.21	0.25	1		
50-60	30 (33.0)	1.02	0.96			
> 60	21 (48.8)	1.70	0.04	2.08	1.33-3.24	0.001
Gender						
Male	301 (31.7)	1				
Female	84 (29.8)	0.99	0.98			
Non smoker at baseline						
Yes	114 (27.7)	0.76	0.01			
No or unknown	271 (33.1)	1				
HCV antibodies at baseline						
Negative	262 (27.6)	1		1		
Positive	123 (43.6)	1.76	<0.001	1.74	1.40-2.16	<0.001
CD4+ cells count						
< 100 per mm^3		1		2.54	1.79-3.62	<0.001
100-200 per mm^3		0.30	<0.001			
200-500 per mm^3		0.35	<0.001	1		
> 500 per mm^3		0.24	<0.001			
Plasma HIV RNA level						
< 500 copies/mL		1		1		
500 - 10 000 copies/mL		0.87	0.44			
10 000 - 100 000 copies/mL		1.83	<0.001	1.90	1.46-2.47	<0.001
> 100 0000 copies/mL		3.05	<0.001			

Table 3. Factors associated with the occurrence of the 385 first NANHR severe clinical events.

Conclusions

NANHR severe clinical events:

- Have a high incidence in HAART-treated patients.
- Are independently associated with both persistent immunosuppression and virological failure (plasma HIV RNA > 10 000 copies/ml).

Along with all its other beneficial effects, the control of HIV replication may protect against the occurrence of non AIDS-events, notably bacterial infections in HAART-treated patients. These results give further arguments against interruptions of antiretroviral treatment.

ANRS CO8 APROCO/COPILOTE Study Group

Scientific Committee. ***Steering Committee-Principal Investigators:*** C. Leport and F. Raffi, ***Methodology:*** G. Chêne and R. Salamon, ***Social Sciences***: J.-P. Moatti, J. Pierret, and B. Spire; ***Virology:*** F. Brun-Vézinet, H. Fleury, and B. Masquelier, ***Pharmacology:*** G. Peytavin and R. Garraffo; ***Other members:*** D. Costagliola, P. Dellamonica, C. Katlama, L. Meyer, M. Morin, D. Salmon, and A. Sobel; ***Events Validation Committee:*** L. Cuzin, M. Dupon, X. Duval, V. Le Moing, B. Marchou, T. May, P. Morlat, C. Rabaud, and A. Waldner-Combernoux; ***Project coordination:*** F. Collin; ***Observers:*** J. F. Delfraissy, J. D ormon, P. B ursachi, M. Garré, and J. L. Vildé; ***Clinical Research Group Coordinators:*** V. Le Moing and C. Lewden; ***Data Monitoring and Statistical Analysis:*** C. Alfaro, F. Alkaied, C. Barennes, S. Boucherit, A. D. Bouhnik, C. Brunet-François, M. P . Carrieri, M. Courcoul, F. Couturier, J. L . Ecobichon, M. François, L. Iordache, V. Journot, P. Kurkdji, R. Lassalle, E. Lootvoet, J. P. Legrand, E. Pereira, M. Préau, C. Protopopescu, J. Surzyn, A. Taieb, F. Tourteau, V. Villes, and H. Zouari; ***Promotion***: Agence Nationale de Recherches sur le SIDA et les hépatites virales (ANRS, Action Coordonnée no. 7). ***Other support:*** Collège des Universitaires de Maladies Infectieuses et Tropicales, Sidaction Ensemble contre le S ida and associated pharmaceutical companies: Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Glaxo-SmithKline, Merck Sharp and Dohme, and Roche; ***Clinical Centers (coordinators):*** Amiens (Pr. J. L. Schmit), Angers (Dr. J. M. Chennebault), Belfort (Dr. J. P. Faller), Besançon (Pr. J. L. Dupond, Dr. J. M. Estavoyer, and Pr. P. Humbert), Bobigny (Pr. A. Krivitzky), Bordeaux (Pr. M. Dupon, Pr. Longy-Boursier, Pr. P. Morlat, and Pr. J. M. Ragnaud), Bourg-en-Bresse (Dr. P. Granier), Brest (Pr. M. Garré), Caen (Pr. R. Verdon), Compiègne (Dr. Y. Domart), Corbeil Essonnes (Dr. A. Devidas), Créteil (Pr. A. S obel), 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. T. May), Nantes (Pr. F. Raffi), Nice (Pr. J. P. Cassuto, Pr. P. Dellamonica), Orléans (Dr. P . Arsac), Paris (Pr. E. Bouvet, Pr. F. Bricaire, Pr. P. Bergmann, Pr. J. Cabane, Dr. G. Cessot, Pr. P. M. Girard, Pr. L. Guillevin, Pr. C. Leport, Pr. S. Herson, Pr. M. C. Meyohas, Pr. J. M. Molina, Pr. G. Pialoux, and Pr. D. Salmon), Poitiers (Pr. B. Becq-Giraudon), Reims (Pr. R. Jaussaud), Rennes (Pr. C. Michelet), Saint-Etienne (Pr. F. Lucht), Saint-Mandé (Pr. T. Debord), Strasbourg (Pr. J. M. Lang), Toulon (Dr. J. P. De Jaureguiberry), Toulouse (Pr. B. Marchou), and Tours (Pr. J. M. Besnier).