

Early Short-course HAART Initiated at the Time of Primary HIV Infection Provides  
No Sustained Benefit in Terms of Time to CD4 Decline below 350/mm<sup>3</sup>:  
Results of a Propensity Analysis within the ANRS PRIMO Cohort

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# ABSTRACT

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- ▶ **Background:** No controlled trial assessed the efficacy of early short course (ESC) HAART initiated at the time of PHI. Observational studies are prone to several biases, mainly indication bias. Using propensity analysis to control for bias in treatment assignment and prognostic imbalances, we compared the time to CD4 decline below  $350/\text{mm}^3$  after interruption of HAART in patients who received ESC-HAART vs. after enrollment in patients who received no HAART at the time of PHI diagnosis.
- ▶ **Methods:** From 1996 to 2007, 439 PHI patients were enrolled within 2 months (median 39 days) of infection in the ongoing French ANRS PRIMO cohort. Of these, 73 patients received HAART for 6-24 months after enrollment (ESC group) while 149 patients received no HAART at enrollment and remained untreated for  $\geq 3$  months (median time off treatment 14 months; deferred [DEF] group).
- ▶ **Potential selection biases** were adjusted for by developing a propensity score for ESC-HAART through a multivariate logistic regression model, which included sex, age, symptomatic primary infection, CD4 and HIV-RNA at enrollment and time between infection and enrollment. This score was then used to match patients from the 2 groups. The time to CD4 decline below  $350/\text{mm}^3$  from baseline -i.e. from enrollment in DEF patients or from treatment interruption in ESC patients- was assessed through Kaplan-Meier curves.
- ▶ **Results:** 63 patients from each group could be matched according to their propensity score. At enrollment median CD4 count was  $493/\text{mm}^3$  in ESC patients vs.  $498/\text{mm}^3$  in DEF patients; it reached  $745/\text{mm}^3$  at HAART interruption in ESC patients. CD4 counts tended to decline below  $350/\text{mm}^3$  more rapidly in DEF patients than in ESC patients in the first 10 months of follow-up from baseline but less rapidly later on (interaction term with time,  $p=0.04$ ). This led to similar cumulated proportions of patients whose CD4 count remained  $>350/\text{mm}^3$  36 months after baseline in the 2 groups (57% vs. 58%). Sensitivity analysis considering the time to CD4 decline below  $350/\text{mm}^3$  or to initiate/reinitiate treatment as the outcome led to similar results.
- ▶ **Conclusion:** Using a propensity analysis that compared patients who received ESC-HAART at the time of PHI with their matched DEF counterparts, we found that ESC-HAART initiated at the time of PHI provides no sustained benefit in terms of time to CD4 decline below  $350/\text{mm}^3$ .

# Introduction - Background

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- ▶ No controlled trial assessed the efficacy of early short-course HAART (ESC-HAART) initiated at the time of PHI
- ▶ The main objective of this study was to assess whether ESC-HAART could significantly impact the course of HIV infection, compared to deferred initiation of HAART (DEF-HAART)
- ▶ Observational studies are prone to several biases, including indication bias. Propensity analyses allow to control for bias in treatment assignment and prognostic imbalances
- ▶ Using propensity analysis, we compared the time to CD4 decline below  $350/\text{mm}^3$ 
  - ▶ after interruption of HAART in patients who received ESC-HAART
  - ▶ vs. after enrollment in patients who were assigned DEF-HAART at the time of PHI diagnosis

# The ANRS Primo Cohort

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- ▶ The ANRS Primo cohort is an ongoing multicenter cohort that was initiated in November 1996 and enrolled patients at the time of primary HIV infection
- ▶ Recent infection was confirmed by
  - ▶ incomplete Western blot (WVB) (absence of anti-p68 and anti-p34); or
  - ▶ positive p24 antigenemia or detectable plasma HIV RNA; or
  - ▶ negative or weakly reactive ELISA test
- ▶ The date of infection was estimated as
  - ▶ the date of symptom onset minus 15 days; or
  - ▶ the date of incomplete Western blot minus one month; or
  - ▶ the mid-point between a negative and a positive ELISA test
- ▶ Patients were enrolled  $\leq 3$  months following infection and were antiretroviral-naive at enrollment
- ▶ HAART was defined as a regimen containing
  - ▶ 2 NRTIs + 1 PI; or
  - ▶ 2 NRTIs + 1 NNRTI; or
  - ▶ The zidovudine + lamivudine + abacavir triple NRTI combination

# Patients and Methods

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- ▶ Of the 698 patients that had been enrolled at the time of analysis (February 2007), 451 patients had been enrolled within 2 months following infection.
- ▶ ESC-HAART regimen was defined as follows:
  - ▶ Initiation of HAART within 15 days of enrollment,
  - ▶ Duration of HAART of 6-24 months, and
  - ▶ Cessation of treatment for  $\geq 2$  months.

A total of 73 patients received ESC HAART according to these criteria.

- ▶ HAART was considered as deferred (DEF) if
  - ▶ Never initiated during follow-up (n=112 patients) or
  - ▶ Initiated more than 3 months after enrollment (n=37 patients)

A total of 149 patients received DEF HAART according to these criteria.

# Patients and Methods: statistical approach (1)

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- ▶ Propensity scores were constructed using a multiple logistic regression model to estimate the probability of belonging to the ESC group on the basis of values of selected baseline covariates known to be associated with outcome:
  - ▶ Gender and age
  - ▶ symptoms of PHI (presence versus absence)
  - ▶ CD4 T-cell count and HIV RNA at baseline
  - ▶ time between infection and enrollment
- ▶ ESC and DEF patients were matched on propensity scores using greedy matching techniques that assigned each ESC patient with the DEF patient having the nearest propensity score.
- ▶ A total of 63 matched pairs of ESC/DEF patients were obtained.
- ▶ Characteristics at enrollment of ESC and DEF patients were compared using
  - ▶ Chi-square test for qualitative variables
  - ▶ nonparametric median tests for continuous variables.

# Patients and Methods: statistical approach (2)

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- ▶ Survival analysis evaluated the impact of ESC HAART in terms of time for CD4 T-cell count level to decline below  $350/\text{mm}^3$ 
  - ▶ after cessation of HAART in ESC matched patients
  - ▶ from enrollment in DEF matched patients.
- ▶ Kaplan-Meier curves and logrank test were used to compare times to event in ESC- and DEF-HAART patients
- ▶ A proportional hazard Cox model adjusted for propensity scores was used to quantify the relative risk for CD4 decline  $<350/\text{mm}^3$  in ESC- vs DEF- HAART patients
- ▶ A significant time-by-treatment interaction was included in the Cox model

# Disposition of patients

PRIMO patients enrolled within 2 months following infection  
(N=451)

149 DEF Patients

73 ESC Patients

HAART-initiation within  
0-15 days after enrollment  
(N=256)

HAART-initiation within  
16-179 days after  
enrollment (N=8)

HAART-initiation > 3mo  
after enrollment (N=150)

## Exclusion criteria

- Initiation of non-HAART regimen (N=3)
- Neurological symptoms at PHI (N=16)
- Follow-up < 3 months after infection (N=17)
- No CD4 at enrollment (N=1)

HAART duration  
<6mo (N=38)

HAART duration  
6-24mo (N=100)

HAART duration  
>24mo (N=118)

HAART treated  
(N=38)

Never treated  
(N=112)

No cessation of  
HAART (N=24)

Cessation of HAART  
(N=76)

≥ 1 CD4 measurement  
before treatment (N=37)

No CD4 measurement  
before treatment (N=1)

No CD4 measurement  
after cessation (N=3)

≥ 1 CD4 measurement  
after cessation (N=73)

# Characteristics of ESC and DEF patients at enrollment

Characteristics	ESC patients	DEF patients	P-value
	(n=73)	(n=149)	
Time from infection to enrollment (days) *	35 (29-42)	44 (37-52)	< .01
HAART treated	73 (100)	37 (25)	< .01
Male sex	60 (82)	131 (88)	0.25
Age (years) *	34 (27-43)	33 (29-39)	0.70
Date of enrollment *	04/01 (06/00-03/03)	11/04 (01/03-11/05)	< 0.01
White non Hispanic (???)	64 (88)	130 (88)	0.97
Educational level $\geq$ university	37 (51)	71 (49)	0.70
Symptomatic PHI	64 (88)	127 (85)	0.62
CD4 T-cell count (cells/mm <sup>3</sup> ) *	492 (354-696)	580 (421-783)	0.04
HIV-1 RNA (log <sub>10</sub> copies/ml) *	5.5 (4.9-6.0)	4.9 (4.1-5.6)	< .01
HIV-1 DNA (log <sub>10</sub> copies/ml) *	3.4 (3.0-3.8)	3.2 (2.7-3.6)	< .01

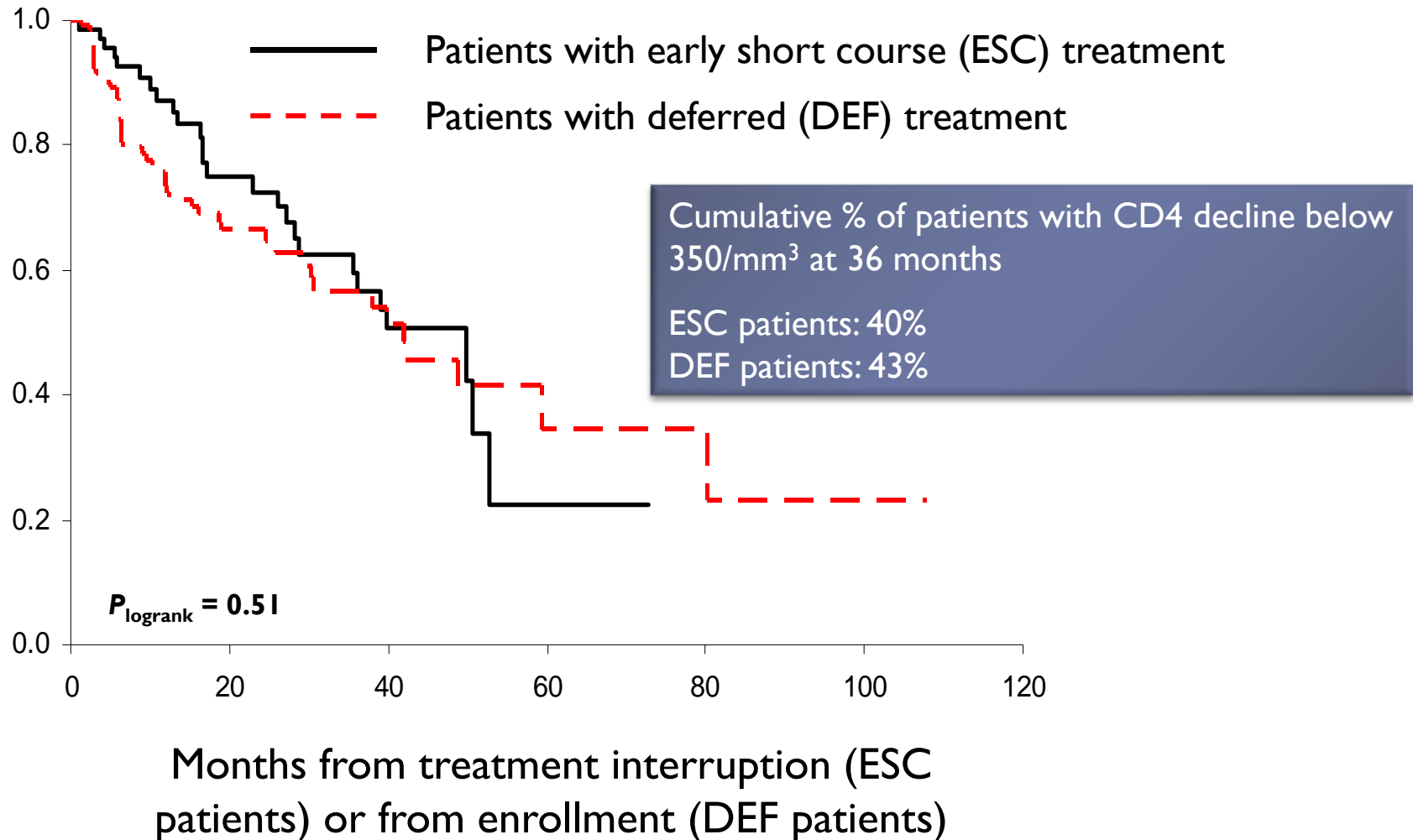
Data are no. (%) of patients except for \*: median (interquartile range).

# Compared characteristics of the 63 matched pairs of ESC/DEF patients at enrollment

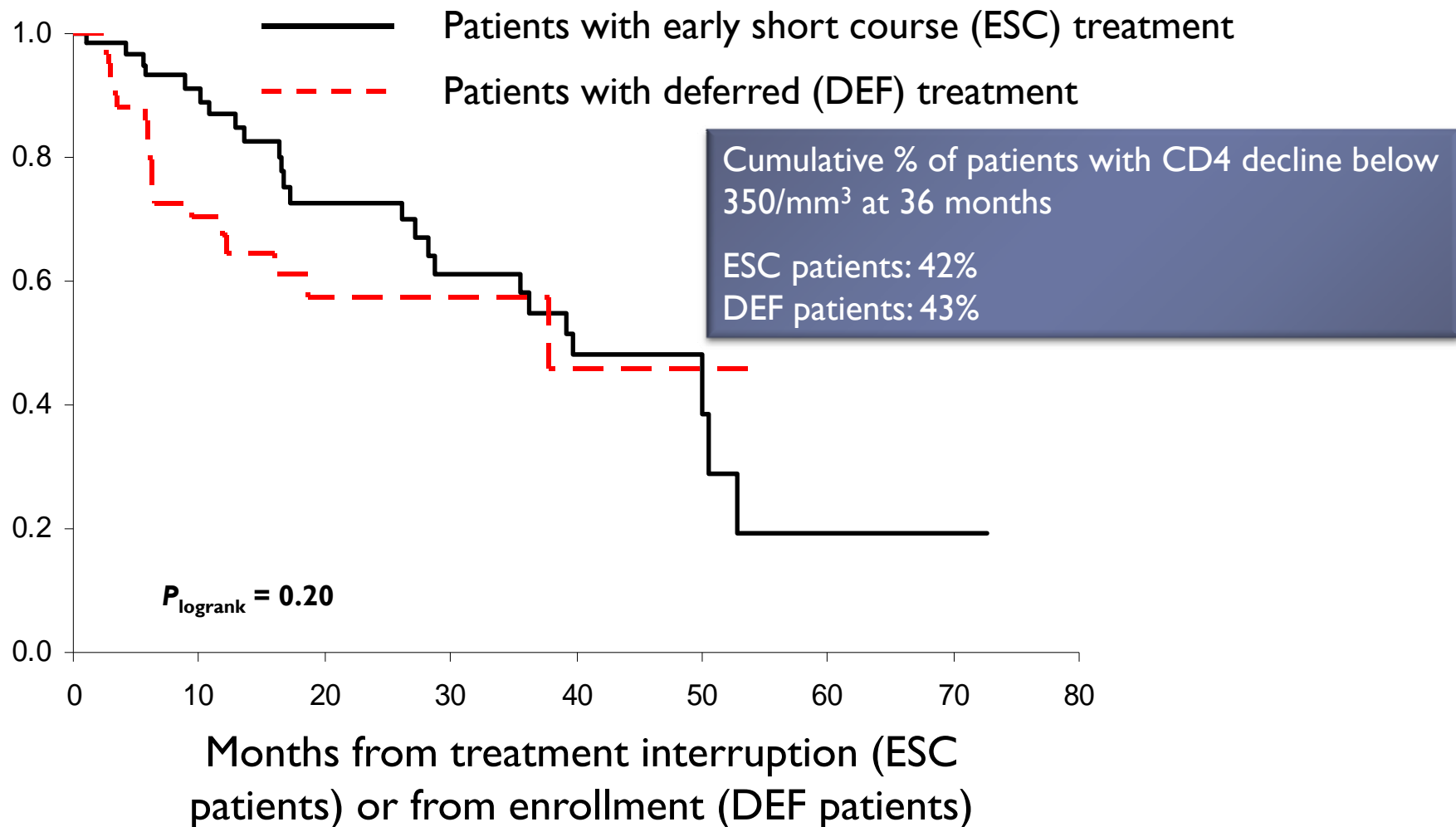
Characteristics	Matched ESC patients	Matched DEF patients	P-value
	(n=63)	(n=63)	
Time from infection (days) *	36 (30-45)	37 (32-43)	0.78
Male sex	53 (84)	52 (83)	0.81
Age (years) *	33 (27-45)	35 (27-43)	0.99
Date of enrollment *	04/01 (05/00-01/03)	04/05 (09/03-03/06)	< .01
Educational level $\geq$ university	32 (51)	27 (44)	0.42
Symptomatic PHI	55 (87)	53 (84)	0.61
CD4 count (cells/mm <sup>3</sup> ) *	493 (379-730)	498 (384-722)	0.94
HIV-1 RNA (log <sub>10</sub> copies/ml) *	5.4 (4.8-5.9)	5.2 (4.7-5.9)	0.70
HIV-1 DNA (log <sub>10</sub> copies/ml) *	3.4 (2.9-3.7) a	3.4 (3.0-3.7) b	0.71

Data are no. (%) of patients; \* median (interquartile range). HAART, highly active antiretroviral therapy; PHI, primary HIV-1 infection. a 4 missing measurements; b 11 missing measurements

# Time to CD4 T-cell count decline below $350/\text{mm}^3$ in the whole sample of patients



# Time to CD4 T-cell count decline below 350/mm<sup>3</sup> among the 63 matched patients



# Relative risk of decline of CD4 below 350/mm<sup>3</sup>: results of the Cox model

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Time from baseline	RR	95%CI	P-value
6 months	2.55	1.12-5.79	0.026
24 months	0.62	0.19-2.02	0.43

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RR, relative risk of DEF *versus* ESC patients



# Conclusion

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- ▶ The 2 major findings of this propensity analysis that compared patients who received ESC-HAART at the time of PHI with their matched DEF counterparts are the following:
- ▶ A more rapid progression to CD4  $<350/\text{mm}^3$  was observed in the DEF group only during the first 10 months, which may result from a lower CD4 count in this group at enrollment compared to CD4 count in the ESC group at the time of treatment interruption
- ▶ ESC-HAART initiated at the time of PHI provides no sustained benefit in terms of time to CD4 decline below  $350/\text{mm}^3$  on the long term, after the first 10 months of interruption

# Acknowledgments

J.M. Molina, B. Loze (St Louis - Paris) - P. Morlat, M. Bonarek, F. Bonnet, C. Nouts, I. Louis (St André - Bordeaux) - F. Raffi, V. Reliquet, F. Sauser, C. Biron, O. Mounoury, H. Hue, D. Brosseau (Hotel Dieu - Nantes) - J.F. Delfraissy, C. Goujard, J. Ghosn, MT. Rannou (Bicêtre – Le Kremlin Bicêtre) - J.F. Bergmann, E. Badsì, A. Rami, M. Diemer, M.Parrinello (Lariboisière - Paris) - P.M. Girard, D. Samanon-Bollens, P. Campa, M. Tourneur, N. Desplanques (St Antoine - Paris) - J.M. Livrozet, F. Jeanblanc, P. Chiarello, D. Makhloufi (E. Herriot - Lyon) - A.P. Blanc, T. Allègre (CHG - Aix en Provence) - J. Reynes, V. Baillat, V. Lemoing, C. Merle de Boever, C. Tramoni (Gui de Chauliac - Montpellier) - A. Cabié, G. Sobesky, S. Abel, V. Beaujolais (CHU - Fort de France) - G. Pialoux, L. Slama, C. Chakvetadze, V. Berrebi (Tenon - Paris) - P. Yeni, E. Bouvet, I. Fournier, J. Gerbe (Bichat - Paris) - C. Trepo, K. Koffi, C. Augustin-Normand, P. Miaillhes, V. Thoirain, C. Brochier (Hotel Dieu - Lyon) - R. Thomas, F. Souala, M. Ratajczak (Pontchaillou - Rennes) - J. Beytoux, C. Jacomet, F. Gourdon (G. Montpied - Clermont-Ferrand) - E. Rouveix, S. Morelon, C. Dupont, C. Olivier (A. Paré - Boulogne) - O. Lortholary, B. Dupont, J.P. Viard, A. Maignan (Necker - Paris) - J.M. Ragnaud, I. Raymond (Pellegriin - Bordeaux) - C. Leport, C. Jadand, C. Jestin, P. Longuet, S. Boucherit (Bichat - Paris) - D. Sereni, C. Lascoux, F. PrevotEAU (St Louis - Paris) - A. Sobel, Y. Levy, JD. Lelièvre, AS. Lascaux, S. Dominguez, C. Dumont (H. Mondor - Créteil) - H. Aumaitre, B. Delmas, M. Saada, M. Medus (St Jean - Perpignan) - L. Guillevin, D. Salmon, T. Tahì (Cochin - Paris) - Y. Yazdanpanah, S. Pavel, MC. Marien (CH Dron - Tourcoing) - B. Drenou, G. Beck-Wirth, C. Beck, M. Benomar (E. Muller - Mulhouse) - C. Katlama, R. Tubiana, H. Ait Mohand, A. Chermak, S. Ben Abdallah (Pitié-Salpêtrière - Paris) - M. Bentata, F. Touam, (Avicenne - Bobigny) - B. Hoen, C. Drobacheff, A. Folzer (St Jacques - Besançon) - P. Massip, M. Obadia, L. Prudhomme, E. Bonnet, F. Balzarín (Purpan - Toulouse) - E. Pichard, J.M. Chennebault, P. Fialaire, J. Loison (CHR - Angers) - P. Galanaud, F. Boué, D. Bornarel (Béclère - Clamart) - R. Verdon, C. Bazin, M Six, P. Ferret (CHR Côte de Nacre - Caen) - L. Weiss, D. Batisse, G. Gonzales-Canali, D. Tisne-Dessus (HEGP - Paris) - A. Devidas, P. Chevojon, I. Turpault (Corbeil Essonnes) - A. Lafeuillade, A. Cheret, G. Philip (Chalucet - Toulon) - P. Morel, J. Timsit (St Louis - Paris) - S. Herson, N. Amirat, A. Simon, C. Brancion (Pitié-Salpêtrière - Paris) - J. Cabane, O. Picard, J. Tredup, N. Desplanques (St Antoine - Paris) - A. Stein, I. Ravault (La Conception - Marseille) - C. Chavanet, M. Buisson, S. Treuvelot (Bocage - Dijon) - P. Choutet, P. Nau, F. Bastides (Bretonneau - Tours) - T. May, L. Boyer, S. Wassoumbou (CHU - Nancy) - E. Oksenhendeler, L. Gérard (St Louis - Paris) - L. Bernard, P. De Truchis, H. Berthé (R. Poincaré – Garches) - Y. Domart, D. Merrien (CH - Compiègne) - A. Greder Belan, (A. Mignot - Le Chesnay) - M. Gayraud, L. Bodard, A. Meudec (IMM Jourdan - Paris) - C. Beuscart, C. Daniel, E. Pape (La Beauchée - St Brieuc) - P. Vinceneux, A.M. Simonpoli, A. Zeng (L. Mourier - Colombes) - L. Fournier (M. Jacquet - Melun) - J.G. Fuzibet, C. Sohn, E. Rosenthal, M. Quaranta (L'Archet - Nice) - P. Dellamonica, S. Chaillou, M. Sabah (L'Archet - Nice) - B. Audhuy, A. Schieber (L. Pasteur - Colmar) - P. Moreau, M. Niault, O. Vaillant (Bretagne Sud - Lorient) - G. Huchon, A. Compagnucci (Hotel-Dieu - Paris) - I. De Lacroix Szmania, L. Richier (Intercommunal - Créteil) - I. Lamaury (Abymes - Pointe à Pitre) - F. Saint-Dizier, D. Lamaury (Ducuing – Toulouse) - J.A. Gastaut, M.P. Drogoul, I. Poizot Martin, G. Fabre (St Marguerite – Marseille) - G. Lambert de Cursay, B. Abraham, C. Perino (CH - Brives) - P. Lagarde, F. David (CH - Lagny) - J. Roche-Sicot, J.L. SarauX, A. Leprêtre (S. Veil - Eaubonne) - B. Fampin, A. Uludag, A.S. Morin (Beaujon – Clichy) - O. Bletry, D. Zucman (Foch - Suresnes) - A. Regnier (CH - Vichy) - JJ. Girard (CH - Loches) - D.T. Quinsat, L. Heripret (CH - Antibes) - F. Grihon (Haute Vallée de l'Oise - Noyon) - D. Houlbert (CH - Alençon) - M. Ruel, K. Chemlal (CH - Nanterre) - F. Caron, Y. Debab (C. Nicolle - Rouen) - F. Tremollières, V. Perronne (F. Quesnay - Mantes La Jolie) - G. Lepeu, B. Slama (H. Duffaut - Avignon) - P. Perré (Les Oudairies - La Roche sur Yon) - C. Miodovski (Paris) - G. Guermontprez, A. Dulioust (CMC Bligny - Briis s/Forges) - P. Boudon, D. Malbec (R. Ballanger - Aulnay s/bois) - O. Patey, C. Semaille (CH - Villeneuve St Georges) - J. Deville, G. Remy, I. Béguinot (Reims)