DOI: 10.1111/hiv.12344
HIV Medicine (2016), **17**, 471–478

SHORT COMMUNICATION

Host and disease factors are associated with cognitive function in European HIV-infected adults prior to initiation of antiretroviral therapy

A Winston,[1] W Stöhr,[2] A Antinori,[3] A Arenas-Pinto,[2] JM Llibre,[4,5] H Amieva,[6] A Cabié,[7] I Williams,[8] G Di Perri,[9,10] MJ Tellez,[11] J Rockstroh,[12] A Babiker,[2] A Pozniak,[13] F Raffi[14] and L Richert[6,15] for the NEAT 001/Agence Nationale de Recherche sur le SIDA (ANRS) 143 Study Group*

[1]Department of Medicine, Imperial College London, London, UK, [2]MRC Clinical Trials Unit at University College London, London, UK, [3]Clinical Department, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy, [4]HIV Unit and Lluita contra la SIDA Foundation, University Hospital Germans Trias i Pujol, Badalona, Spain, [5]Universitat Autonoma de Barcelona, Barcelona, Spain, [6]Centre Inserm U897-Epidemiologie-Biostatistique, University of Bordeaux, ISPED, Bordeaux, France, [7]Department of Infectious and Tropical Diseases and INSERM CIE802, University Hospital of Fort-de-France, Fort-de-France, Martinique, France, [8]Centre for Sexual Health and HIV Research, Mortimer Market Centre, University College London, London, UK, [9]Laboratory of Clinical Pharmacology and Pharmacogenetics (2), Unit of Infectious Diseases, University of Turin, Turin, Italy, [10]Department of Medical Sciences, Amedeo di Savoia Hospital, Turin, Italy, [11]Infectious Diseases Unit, Internal Medicine, Hospital Clinico Universitario, Madrid, Spain, [12]Department of General Internal Medicine I, University Hospital of Bonn, Bonn, Germany, [13]Chelsea and Westminster NHS Foundation Trust, London, UK, [14]CMIT, Paris, France and [15]CHU de Bordeaux, Pole de sante publique, and CIC1401-EC (Clinical Epidemiology), Bordeaux, France

Objectives

Deficits in cognitive function remain prevalent in HIV-infected individuals. The aim of this European multicentre study was to assess factors associated with cognitive function in antiretroviral therapy (ART)-naïve HIV-infected subjects at the time of enrolment in the NEAT 001/Agence Nationale de Recherche sur le SIDA (ANRS) 143 study.

Methods

Prior to starting ART, seven cognitive tests exploring domains including episodic memory, verbal fluency, executive function and psychomotor speed were administered with scores standardized to *z*-score using the study population sample mean and standard deviation. The primary measure was overall *z*-score average (NPZ). We assessed associations between baseline factors and test results using multivariable regression models.

Results

Of 283 subjects with baseline cognitive assessments, 90% were male and 12% of black ethnicity. Median (interquartile range) age, years of education, years of known HIV infection, baseline CD4 count and baseline HIV RNA were 39 (31, 47) years, 13 (11, 17) years, 1 (0, 4) years, 344 (279, 410) cells/μL and 4.74 (4.28, 5.14) $\log_{10}$ HIV-1 RNA copies/mL, respectively. Forty per cent were current smokers. Factors significantly associated with poorer overall cognitive performance in multivariable models included older age, shorter duration of education, black ethnicity, lower height, and lower plasma HIV RNA.

Conclusions

In this large, European-wide, ART-naïve population with relatively preserved immunity and early HIV infection, cognitive function scores at the time of ART initiation were associated with demographic and HIV-disease factors.

Correspondence: Dr Alan Winston, Clinical Trials, Winston-Churchill Wing, St Mary's Hospital, London W2 1NY, UK. Tel: +44203 3121603; fax: +44203 3126123; e-mail: a.winston@imperial.ac.uk

*See Appendix 1.

Keywords: antiretroviral naïve, cognitive, HIV, neuropsychological tests
Accepted 19 August 2015

Introduction

Subsequent to the introduction of effective combination antiretroviral therapy (ART), the incidence of the severe forms of HIV-associated brain disease has declined dramatically [1]. However, milder forms of HIV-related brain disease, known as HIV-associated cognitive disorders, remain prevalent [2]. Prevalence rates of HIV-associated cognitive impairment, usually assessed in antiretroviral-treated populations, vary widely between cohorts from < 10% [3,4] to > 50% [2] of people living with HIV (PLWH). These discrepancies may be attributable to differences in normative data sets and in the definitions of cognitive impairment utilized, where rates are lower in reports only including subjects with symptoms of memory impairment, relative to rates based purely on neuropsychiatric test results.

Several risk factors have been implicated in the development of HIV-associated cognitive disorders, including HIV-disease factors [5], the type of ART utilized [6] and concomitant medical conditions [7]. The effects these different risk factors have on cognitive function during the different stages of HIV infection remain largely unknown. The aim of this study was to assess factors associated with cognitive function in HIV-infected adults electively commencing ART for the first time in a large European study.

Methods

Subject selection

Antiretroviral-naïve adults entering the NEAT 001/Agence Nationale de Recherche sur le SIDA (ANRS) 143 study between August 2010 and September 2011 [8] were eligible to participate in this neurocognitive substudy in sites in France, Spain, Italy, Belgium, Germany, Ireland and the UK.

Subjects were required to have a CD4 lymphocyte count < 500 cells/μL or symptomatic HIV infection. Detailed inclusion criteria have been previously described [8]. Specific substudy exclusion criteria were current or past opportunistic infections or tumours of the central nervous system (CNS), non-HIV-related major neurological or psychiatric disorders, active recreational drug use and linguistic difficulties. Human ethics committee approval was gained at all participating sites and all subjects provided written informed consent.

Study procedures

Standardized neuropsychological assessments were undertaken at baseline and after 96 weeks by trained study staff. Here were report the baseline results of the neuropsychological assessments prior to commencing ART. Specifically, these assessments comprised the Trail Making Test (TMT) parts A and B (attention and mental flexibility), the Digit Symbol Substitution Test (psychomotor speed), the Backwards Digit Span Test (working memory), the Free and Cued Selective Reminding Test (retrieval ability and episodic memory), Semantic and Formal Fluency Tests (verbal fluency) and the Frontal Assessment Battery (frontal executive function). These tests were specifically chosen to assess the cognitive domains reported to be predominantly affected in chronic HIV infection [9] and were feasible to undertake within a multicentre clinical study. In addition, a short questionnaire was used to assess the patient's own perception of cognitive abilities, and difficulties in coping with complex activities of daily living were investigated with Lawton's questionnaire of Instrumental Activities of Daily Living.

Statistical analysis

The primary outcome of this analysis was a composite neurocognitive score (NPZ) which was calculated from the seven neuropsychological tests in participants with one or fewer missing tests. For this, raw test scores were first transformed to *z*-scores by subtracting the mean and dividing by the standard deviation (SD) of the study sample. The signs for the TMTs were reversed so that for all tests a score above zero denotes above-average and a score below zero denotes below-average cognitive function within the study population. The NPZ was then calculated as the average of the seven individual *z*-scores.

Linear regression modelling was performed to assess associations of demographic and HIV-related factors and laboratory results at baseline with neurocognitive test performance. We evaluated the following factors: age, gender, ethnicity (white, black or other), years of education, country of enrolment (France, Spain, UK, Italy or other), smoking (never smoked, previously smoked but stopped or current smoker), years since first positive HIV serology, HIV stage and CD4 cell count nadir; CD4 cell count, HIV RNA, body height and weight, diastolic blood pressure, aspartate transaminase (AST) concentration, total

cholesterol concentration, high-density lipoprotein (HDL) cholesterol concentration, estimated glomerular filtration rate (eGFR; estimated with the Cockcroft–Gault formula) and glucose concentration at baseline; CNS-related disorder at screening and hepatitis C status (any marker positive). TMT-A and B scores were $\log_{10}$-transformed. Some factors had missing values (< 4%), and these were imputed via multiple imputation from available cognitive test scores and other co-factors using the STATA (version 13.1: STATA, Timberlake Analytics, Washington DC, USA) mi impute command to create 10 simulations which were then combined using Rubin's rules.

Results

Of 283 subjects who completed baseline cognitive assessments, 90% were male and 12% of black ethnicity. Mode of HIV acquisition was men who have sex with men (MSM) in 196 subjects (69%), heterosexual sexual acquisition in 65 (23%), injecting drug use in seven (2%), and other/unknown in 15 (5%). The mean duration of known HIV infection was 1 year (range 0–4 years). In 48 (17%), 35 (13%), 79 (28%) and 119 (42%) subjects, the duration of known HIV infection was ≤ 3 months, 3–6 months, 6–24 months and > 24 months, respectively. Details of baseline results are shown in Table 1. These baseline characteristics did not show any clinically relevant differences from those of subjects enrolled in the NEAT 001/ANRS 143 trial who were not recruited for this substudy at the participating sites.

Results of individual neurocognitive tests [median (interquartile range)] were as follows: Free Selective Reminding Test: total number of words recalled, 34 (30–38); Frontal Assessment Battery: cumulative score, 17 (16–18); Digit Symbol Substitution Test: correct marks, 51 (40–60); TMT A: 33 (26–43) s; TMT B: 61 (48–90) s; Backwards Digit Span Test: 4 (3–5) digits; semantic and semantic and formal fluency tests: total number of words, 34 (29–40). Mean NPZ was 0.0 by definition (SD = 0.7) in 273 of 283 participants with one or fewer missing tests. One hundred participants (36%) had at least one cognitive complaint and 19 (7%) required help in at least one activity of daily living.

Factors significantly and independently associated with poorer overall cognitive performance included older age, shorter duration of education, black ethnicity, lower height, and lower plasma HIV RNA (Table 1). These associations were largely consistent across individual cognitive domains (data not shown). The following factors were not associated with NPZ or with any of the individual tests exploring cognitive function: current or nadir CD4 cell count, blood pressure, and smoking.

Discussion

In this cohort of European treatment-naïve HIV-infected subjects, we identified older age, shorter duration of education, black ethnicity, lower height, and lower plasma HIV RNA as factors independently associated with poorer overall cognitive performance.

The underlying pathogenesis of HIV-associated cognitive disorders remains unclear. Traditional risk factors such as older age and fewer years of education have been associated with poorer cognitive performance in several cohorts of PLWH [5,7,10]. Ethnicity is also described as a factor closely associated with cognitive function results, which may be related to cultural background and a lack of normative data for differing ethnic groups [10,11]. Studies of cohorts where the majority of PLWH have been receiving ART have reported differing associations with cognitive function, including the presence of comorbidities [7], CD4 lymphocyte count at nadir [5] and the type of ART utilized [12]. In a large study assessing cognitive function in treatment-naïve PLWH with CD4 lymphocyte cell counts > 500 cells/μL, demographic factors, comorbidities and duration of known HIV infection are reported to be associated with cognitive function [13].

Our study adds to this field given that limited data exist on the factors associated with cognitive function in naïve subjects electively commencing ART for the first time with a median CD4 lymphocyte cell count of approximately 350 cells/μL. As with other cohorts, we observed associations of traditional demographic risk factors such as age and education with cognitive performance. We did not observe an association between CD4 lymphocyte cell count and cognitive function. By the nature of the group we studied, namely participants who were all about to commence ART according to treatment guidelines at this time (2010 to 2011), the range of CD4 lymphocyte counts was relatively narrow (interquartile range 258–381 cells/μL), which may have limited our ability to detect associations between CD4 lymphocyte count and cognitive parameters. The relationship between greater height and improved cognitive performance has not been reported in HIV-infected populations thus far. However, it has been described in non-HIV-infected cohorts, where the association between greater height and improved cognitive function in adults has been thought to be related to childhood nutrition [14] or gender effects [15].

The association we have observed between lower pretreatment plasma HIV RNA and poorer cognitive performance is unexpected. This association was present for many individual cognitive domains and was not

Table 1 Baseline characteristics and factors associated with neurocognitive function.

		Association with neurocognitive function: multivariable model[‡]			
Factor	**Description[†]**	**Change in NPZ-7 (95% CI)**	**Unit change of cofactor**	***P*-value**	**Overall *P***
Age (years)	39 (31–47)	−0.21 (−0.29 to −0.12)	Per 10 years	<0.001*	
Education (years)	13 (11–17)	0.23 (0.14 to 0.31)	Per 5 years	<0.001*	
Ethnicity					
White/other	248 (87.6%)				
Black	35 (12.4%)	−0.48 (−0.70 to −0.26)	*vs.* white/other	<0.001*	
Gender					
Male	255 (90.1%)			0.313	
Female	28 (9.9%)	0.14 (−0.13 to 0.41)	*vs.* male		
Years since first positive HIV serology	1 (0–4)	0.02 (−0.00 to 0.04)	Per year	0.084	
CD4 count nadir (cells/μL)	330 (259–381)	0.02 (−0.09 to 0.14)	Per 100 cells/μL	0.664	
CD4 count (cells/μL)	344 (279–410)	−0.01 (−0.11 to 0.09)	Per 1 cells/μL	0.902	
HIV RNA (log_{10} copies/mL)	4.74 (4.28–5.14)	0.18 (0.07 to 0.30)	Per 1 log_{10} copies/mL	0.002*	
Height (cm)	175 (171–180)	0.16 (0.05 to 0.27)	Per 10 cm	0.006*	
Weight (kg)	72 (64–80)	0.05 (−0.03 to 0.13)	Per 10 kg	0.239	
Diastolic blood pressure (mmHg)	74 (66–80)	−0.01 (−0.08 to 0.06)	Per 10 mmHg	0.833	
AST (IU/L)	26 (21–32)	0.28 (−0.14 to 0.71)	Per 1 log_{10} IU/L	0.193	
Total cholesterol (mmol/L)	4.2 (3.6–4.8)	0.06 (−0.02 to 0.13)	Per 1 mmol/L	0.126	
HDL cholesterol (mmol/L)	1.0 (0.9–1.2)	0.16 (−0.07 to 0.39)	Per 1 mmol/L	0.171	
eGFR (mL/min/1.73 m^2)	112 (98–131)	−0.01 (−0.04 to 0.03)	Per 10 mL/min/1.73 m^2	0.732	
Glucose (mmol/L)	4.7 (4.3–5.1)	0.05 (−0.05 to 0.15)	Per 1 mmol/L	0.315	
CNS-related disorder at screening	16 (5.7%)	0.04 (−0.26 to 0.34)	*vs.* no disorder	0.792	
Country					
France	114 (40.3%)		*vs.* France		0.436
Spain	26 (9.2%)	−0.14 (−0.39 to 0.11)		0.271	
UK	56 (19.8%)	−0.10 (−0.30 to 0.10)		0.320	
Italy	68 (24.0%)	0.07 (−0.12 to 0.25)		0.477	
Other countries	19 (6.7%)	0.03 (−0.25 to 0.32)		0.823	
Smoking					
Never smoked	142 (50.2%)				0.098
Stopped	30 (10.6%)	0.23 (0.01 to 0.45)	*vs.* never smoked	0.037*	
Current	111 (39.2%)	0.01 (−0.14 to 0.15)		0.938	
HIV stage					
Stage A	248 (87.6%)				0.580
Stage B	27 (9.5%)	0.10 (−0.13 to 0.33)		0.388	
Stage C	8 (2.8%)	−0.10 (−0.50 to 0.30)	*vs.* stage A	0.621	
Hepatitis C, any marker positive	10 (3.5%)	−0.04 (−0.39 to 0.31)	*vs.* no marker positive	0.812	

AST, aspartate transaminase; CI, confidence interval; CNS, central nervous system; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.
[†]Number (percentage) or median (interquartile range).
[‡]$n = 273$ individuals included, of whom 40 had at least one imputed value.
*$P < 0.05$.

driven by a particular test. Several explanations may account for this finding. One such possible explanation is recruitment bias. The NEAT 001/ANRS 143 study assessed a novel nucleoside-sparing ART strategy [8], the efficacy of which was not established at the time of enrolment in the trial. Clinicians may thus have had concerns about entering into such a randomized study subjects whom they considered the most challenging to treat (i.e. those with high viral loads and/or presenting comorbidities) and in whom standard first-line ART would therefore be the clinician's preferred choice. While patients with low viral load may have been extensively entered into the trial irrespective of any comorbidity, including neurocognitive impairment, individuals with high plasma HIV RNA may have been enrolled preferentially if they had few or no comorbidities, i.e. no neurocognitive impairment. Our cohort also included subjects with a relatively short duration of known HIV infection (median time since first known positive HIV serology of 1 year). The effects of high plasma HIV RNA over longer periods of time on cognitive function can therefore not be ascertained from this study. Another possible explanation for this finding is related to immune activation. A small proportion of subjects achieve and sustain control of HIV replication without ART. Despite this control of virus, immune activation is present in these so-called HIV controllers [16]. It is possible that in antiretroviral-naïve subjects with low, but not undetectable, HIV plasma viraemia immune activation may be high and this could drive

neuroinflammation, a potential pathogenic mechanism underlying HIV-associated cognitive impairment [17].

We have assessed cognitive function utilizing internal means and SDs rather than using external normative means to standardize results. This has advantages for our interpretation of the results which is not dependent on appropriate normative data sets which would have been challenging to obtain for this European-wide study. This means that we were not able to determine the prevalence of cognitive impairment in HIV-infected subjects not yet on ART in this study, which was not the aim of our study. Strengths of our study include its relatively large sample size, the inclusion of only ART-naïve participants and assessment of subjects across several European countries. Furthermore, we assessed cognitive performance in all subjects entering this study, not limiting our observations to those with symptoms of cognitive impairment. Our findings within this specific group add to our understanding of cognitive function prior to the initiation of ART and aid our understanding and interpretation of changes in cognitive function that may occur after the initiation of ART.

Acknowledgements

We thank the NEAT 001/ANRS 143 study participants and their partners, families and caregivers and the staff from all the centres taking part in the trial. We thank the European AIDS Treatment Group for their collaboration. We thank Jesper Kjar, CHIP, Copenhagen, Denmark, and Valerie Journot, CMG-EC, Inserm U897, Bordeaux, France, for their contributions to the data management set-up.

Conflicts of interest and sources of funding: NEAT is a project awarded the Instituto Superiore di Sanita–Rome by the European Union under the Sixth Framework Programme, project number LSHP-CT-2006-037570. The trial was also supported by Gilead Sciences, Janssen Pharmaceuticals, and Merck Laboratories, and The French National Institute for Health and Medical Research–France Recherche. Nord&Sud Sida-HIV Hepatites (Inserm-ANRS) is the sponsor and a funder of the trial. All authors declare no conflicts of interest.

Appendix 1: NEAT 001/ANRS 143 Study Group

Trial Development Team (TDT)

Belgium: Nikos Dedes (Brussels); France: Genevieve Chene, Laura Richert (Bordeaux), Clotilde Allavena, Francois Raffi (Nantes) and Brigitte Autran (Paris); Italy: Andrea Antinori, Raffaella Bucciardini and Stefano Vella (Rome); Poland: Andrzej Horban (Warsaw); Spain: Jose Arribas (Madrid); UK: Abdel G Babiker, Marta Boffito, Deenan Pillay and Anton Pozniak (London).

Trial Steering Committee (TSC)

Belgium: Xavier Franquet and Siegfried Schwarze (Brussels); Denmark: Jesper Grarup (Copenhagen); France: Genevieve Chene, Aurelie Fischer, Laura Richert, Cedrick Wallet (Bordeaux), Francois Raffi (Nantes), Alpha Diallo, Jean-Michel Molina, and Juliette Saillard (Paris); Germany: Christiane Moecklinghoff (Janssen Pharmaceuticals; Freiburg) and Hans-Jurgen Stellbrink (Hamburg); Italy: Stefano Vella (Rome); Netherlands: Remko Van Leeuwen (Amsterdam); Spain: Jose Gatell (Barcelona); Sweden: Eric Sandstrom (Stockholm); Switzerland: Markus Flepp (Zurich); UK: Abdel G Babiker, Fiona Ewings, Elizabeth C. George, Fleur Hudson, and Anton Pozniak (London); USA: Gillian Pearce, Romina Quercia, Felipe Rogatto (Gilead Sciences; Foster City, CA), Randi Leavitt, and Bach-Yen Nguyen (Merck Laboratories; Whitehouse Station, NJ).

Independent Data Monitoring Committee (IDMC)

Germany: Frank Goebel (Munich); Italy: Simone Marcotullio (Rome); UK: Abdel Babiker, Fiona Ewings, Elizabeth C. George, Fleur Hudson, Navrup Kaur, Peter Sasieni, Christina Spencer-Drake (London) and Tim Peto (Oxford); USA: Veronica Miller (Washington, DC).

Trial Management Team (TMT)

France: Clotilde Allavena and François Raffi (Nantes); Italy: Stefano Vella (Rome); UK: Anton Pozniak (London).

CMG-EC, INSERM U897 Coordinating Unit, Bordeaux, France

Geneviève Chêne, Head of Coordinating CTU, Member, Bordeaux, France; Fabien Arnault, Coordinating CTU Representative, Member, Bordeaux, France; Céline Boucherie, Bordeaux CTU Representative, Observer, Bordeaux, France; Aurélie Fischer, Coordinating CTU Representative, Member, Bordeaux, France; Delphine Jean, Bordeaux CTU Representative, Observer, Bordeaux, France; Virginie Paniego, Coordinating CTU Representative, Member, Bordeaux, France; Felasoa Paraina, Bordeaux CTU Representative, Observer, Bordeaux, France; Laura Richert, Coordinating CTU Representative, Member, Bordeaux,

France; Elodie Rouch, Bordeaux CTU Representative, Observer, Bordeaux, France; Christine Schwimmer, Coordinating CTU Representative, Member, Bordeaux, France; Malika Soussi*, Bordeaux CTU Representative, Observer, Bordeaux, France; Audrey Taieb, Bordeaux CTU Representative, Observer, Bordeaux, France; Monique Termote, Coordinating CTU Representative, Member, Bordeaux, France; Guillaume Touzeau, Coordinating CTU Representative, Member, Bordeaux, France; Cédrick Wallet, Bordeaux CTU Representative, Member, Bordeaux, France.

MRC Clinical Trials Coordinating Unit, London, UK

Abdel G. Babiker, Trial Statistician, Member, London, UK; Adam Cursley, MRC CTU Representative, Observer, London, UK; Wendy Dodds, MRC CTU Representative, Member, London, UK; Fiona Ewings, Trial Statistician, Member, London, UK; Elizabeth C. George, Trial Statistician, Member, London, UK; Anne Hoppe, MRC CTU Representative, Observer, London, UK; Fleur Hudson, MRC CTU Representative, Member, London, UK; Ischa Kummeling, MRC CTU Representative, Observer, London, UK; Filippo Pacciarini, MRC CTU Representative, Observer, London, UK; Nick Paton, MRC CTU Representative, Observer, London, UK; Charlotte Russell, MRC CTU Representative, Observer, London, UK; Kay Taylor, MRC CTU Representative, Observer, London, UK; Denise Ward, MRC CTU Representative, Observer, London, UK.

CHIP Coordinating Unit, Copenhagen, Denmark

Bitten Aagaard, CHIP CTU Representative, Observer, Copenhagen, Denmark; Marius Eid, CHIP CTU Representative, Observer, Copenhagen, Denmark; Daniela Gey, CHIP CTU Representative, Member, Copenhagen, Denmark; Birgitte Gram Jensen, CHIP CTU Representative, Observer, Copenhagen, Denmark; Jesper Grarup, CHIP CTU Representative, Member, Copenhagen, Denmark; Marie-Louise Jakobsen, CHIP CTU Representative, Observer, Copenhagen, Denmark; Per O. Jansson, CHIP CTU Representative, Member, Copenhagen, Denmark; Karoline Jensen, CHIP CTU Representative, Member, Copenhagen, Denmark; Zillah Maria Joensen, CHIP CTU Representative, Observer, Copenhagen, Denmark; Ellen Moseholm Larsen, CHIP CTU Representative, Observer, Copenhagen, Denmark; Christiane Pahl, CHIP CTU Representative, Observer, Copenhagen, Denmark; Mary Pearson, CHIP CTU Representative, Member, Copenhagen, Denmark; Birgit Riis Nielsen, CHIP CTU Representative, Observer, Copenhagen, Denmark; Søren Stentoft Reilev, CHIP CTU Representative, Observer, Copenhagen, Denmark.

Amsterdam Medical Center Coordinating Unit, Amsterdam, the Netherlands

Ilse Christ, AMC CTU Representative, Observer, Amsterdam, the Netherlands; Desiree Lathouwers, AMC CTU Representative, Member, Amsterdam, the Netherlands; Corry Manting, AMC CTU Representative, Member, Amsterdam, the Netherlands; Remko Van Leeuwen, AMC CTU Representative, Member, Amsterdam, the Netherlands.

ANRS, Paris, France

Alpha Diallo, Pharmacovigilance Representative, Member, Paris, France; Bienvenu Yves Mendy, Pharmacovigilance Representative, Member, Paris, France; Annie Metro, Pharmacovigilance Representative, Member, Paris, France; Juliette Saillard, Sponsor Representative, Member, Paris, France; Sandrine Couffin-Cadiergues, Sponsor Representative, Observer, Paris, France.

ISS, Rome, Italy

Anne-Laure Knellwolf, NEAT Management Representative, Observer, Rome, ltaly; Lucia Palmisiano, NEAT Management Representative, Member, Rome, ltaly.

Local CTUs

GESIDA, Madrid, Spain: Esther Aznar, Cristina Barea, Manuel Cotarelo, Herminia Esteban, Iciar Girbau, Beatriz Moyano, Miriam Ramirez, Carmen Saiz, Isabel Sanchez and Maria Yllescas; ISS, Rome, Italy: Andrea Binelli, Valentina Colasantid, Maurizio Massella and Lucia Palmisiano; University of Athens Medical School, Greece: Olga Anagnostou, Vicky Gioukari and Giota Touloumi.

Study Investigators

Austria: Brigitte Schmied (National Coordinating Investigator), Armin Rieger and Norbert Vetter; Belgium: Stephane De Wit (National Coordinating Investigator), Eric Florence and Linos Vandekerckhove; Denmark: Jan Gerstoft (National Coordinating Investigator) and Lars Mathiesen; France: Christine Katlama (National Coordinating Investigator), Andre Cabie, Antoine Cheretf, Michel Dupon, Jade Ghosn, Pierre-Marie Girard, Cécile Goujard, Yves Lévy, Jean-Michel Molina, Philippe Morlat, Didier Neau, Martine Obadia, Philippe Perre,

Lionel Piroth, Jacques Reynes, Pierre Tattevin, Francois Raffi, Jean Marie Ragnaud, Laurence Weiss, Yazdanpanah Yazdan, Patrick Yeni and David Zucman; Germany: Georg Behrens (National Coordinating Investigator), Stefan Esser, Gerd Fätkenheuer, Christian Hoffmann, Heiko Jessen, Jürgen Rockstroh, Reinhold Schmidt, Christoph Stephan and Stefan Unger; Greece: Angelos Hatzakis (National Coordinating Investigator), George L Daikos, Antonios Papadopoulos and Athamasios Skoutelis; Hungary: Denes Banhegyi (National Coordinating Investigator); Ireland: Paddy Mallon (National Coordinating Investigator) and Fiona Mulcahy; Italy: Andrea Antinori (National Coordinating Investigator), Massimo Andreoni, Stefano Bonora, Francesco Castelli, Antonella D'Arminio Monforte, Giovanni Di Perri, Massimo Galli, Adriano Lazzarin, Francesco Mazzotta, Torti Carlo and Vincenzo Vullo; the Netherlands: Jan Prins (National Coordinating Investigator), Clemens Richter, Dominique Verhagen and Arne Van Eeden; Poland: Andrzej Horban (National Coordinating Investigator); Portugal: Manuela Doroana (National Coordinating Investigator), Francisco Antunes, Fernando Maltez and Rui Sarmento-Castro; Spain: Juan Gonzalez Garcia (National Coordinating Investigator), José López Aldeguer, Bonaventura Clotet, Pere Domingo, Jose M. Gatell, Hernando Knobel, Manuel Marquez, Martin Pilar Miralles, Joaquin Portilla, Vicente Soriano and Maria-Jesus Tellez; Sweden: Anders Thalme (National Coordinating Investigator), Anders Blaxhult and Magnus Gisslen; UK: Alan Winston (National Coordinating Investigator), Julie Fox, Mark Gompels, Elbushra Herieka, Margaret Johnson, Clifford Leen, Anton Pozniak, Alastair Teague and Ian Williams.

Endpoint Review Committee (ERC)

Australia: Mark Alastair Boyd (Sydney); Denmark: Jesper Grarup, Per O Jansson, Nina Friis Møller, Ellen Frøsig and Moseholm Larsen (Copenhagen); France: Philippe Morlat (Bordeaux), Lionel Piroth (Dijon) and Vincent Le Moing (Montpellier); Netherlands: Ferdinand W. N. M. Wit, Chair (Amsterdam); Poland: Justyna Kowalska (Warsaw); Spain: Juan Berenguer and Santiago Moreno (Madrid); Switzerland: Nicolas J. MuHller (Zurich); UK: Estée Török (Cambridge), Frank Post (London) and Brian Angus (Oxford).

Substudy Working Groups

Virology Working Group: Vincent Calvez (Coordinator), Charles Boucher, Simon Collins, David Dunn (Statistician), Sidonie Lambert, Anne-Geneviève Marcelin, Carlo Federico Perno, Deenan Pillay and Ellen White (Statistician).

Pharmacology and Adherence Working Group: Marta Boffito (Coordinator), Adriana Ammassari, Andrea Antinori and Wolgang Stoehr (Statistician).

Immunology Working Group: Brigitte Autran (Coordinator), Reinhold Ernst Schmidt, Michal Odermarsky, Colette Smith and Rodolphe Thiébaut (Statistician).

Toxicity, Including Co-infection Working Group: Jose Arribas (Coordinator), Jose Ignacio Bernardino De LaSerna, Antonella Castagna, Stephane De Wit, Xavier Franquet, Hans-Jackob Furrer, Christine Katlama, Amanda Mocroft (Statistician) and Peter Reiss.

Quality of Life Working Group: Raffaella Bucciardini (Coordinator), Nikos Dedes, Vincenzo Fragola, Elizabeth C. George (Statistician), Marco Lauriola, Rita Murri, Pythia Nieuwkerk, Bruno Spire, Alain Volny-Anne and Brian West.

Neurocognitive Function Working Group: Hélène Amieva (Coordinator), Andrea Antinori, Josep Maria Llibre Codina, Laura Richert, Wolfgang Stöhr (Statistician) and Alan Winston.

Pharmaco-economics Working Group: Francesco Castelli (Coordinator), Marco Braggion (Statistician) and Emanuele Focà.

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