Evaluation of Subcutaneous Proleukin (Interleukin-2) in a Randomized International Trial (ESPRIT): Geographical and Gender Differences in the Baseline Characteristics of Participants

ESPRIT Research Group* and Writing Group: S.L. Pett,[1] H. Wand,[1] M.G. Law,[1] R. Arduino,[2] J.C. Lopez,[3] B. Knysz,[4] L.C. Pereira,[5] S. Pollack,[6] P. Reiss,[7] and G. Tambussi[8]

[1]National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia; [2]University of Texas Medical School of Houston, Houston, Texas, USA; [3]Hospital Universitario Gergorio Maranon, Servicio de Micobiologica y Enf. Infecciosas, Madrid, Spain; [4]Medical University of Wroclaw, Department of Infectious Diseases, Wroclaw University School of Medicine, Poland; [5]Instituto de Infectologia Emillio Ribas, Sao Paulo, Brazil; [6]Rambam Medical Center, Immunology Allergy and AIDS Institute, B. Rappaport Faculty of Medicine, Technion, Haifa, Israel; [7]Academisch Medisch Centrum – Amsterdam, Amsterdam, The Netherlands; [8]Ospedale San Raffaele, Divisione Malattie Infettive - Centro San Luigi, Milano, Italy

Background: ESPRIT, is a phase III, open-label, randomized, international clinical trial evaluating the effects of subcutaneous recombinant interleukin-2 (rIL-2) plus antiretroviral therapy (ART) versus ART alone on HIV-disease progression and death in HIV-1–infected individuals with CD4+ T-cells ≥300 cells/μL. **Objectives:** To describe the baseline characteristics of participants randomized to ESPRIT overall and by geographic location. **Method:** Baseline characteristics of randomized participants were summarized by region. **Results:** 4,150 patients were enrolled in ESPRIT from 254 sites in 25 countries. 41%, 27%, 16%, 11%, and 5% were enrolled in Europe, North America, South America, Asia, and Australia, respectively. The median age was 40 years, 81% were men, and 76%, 11%, and 9% were Caucasian, Asian, and African American or African, respectively. 44% of women enrolled (*n* = 769) were enrolled in Thailand and Argentina. Overall, 55% and 38% of the cohort acquired HIV through male homosexual and heterosexual contact, respectively. 25% had a prior history of AIDS-defining illness; *Pneumocystis jirovecii* pneumonia, *M. tuberculosis*, and esophageal candida were most commonly reported. Median nadir and baseline CD4+ T-cell counts were 199 and 458 cells/μL, respectively. 6% and 13% were hepatitis B or C virus coinfected, respectively. Median duration of antiretroviral therapy (ART) was 4.2 years; the longest median duration was in Australia (5.2 years) and the shortest was in Asia (2.3 years). 17%, 13%, and 69% of participants began ART before 1995, between 1996 and 1997, and from 1998 onward, respectively. 86% used ART from two or more ART classes, with 49% using a protease inhibitor–based regimen and 46% using a nonnucleoside reverse transcriptase inhibitor–based regimen. 78% had plasma HIV RNA below detection (<500 cp/mL). **Conclusion:** ESPRIT has enrolled a diverse population of HIV-infected individuals including large populations of women and patients of African-American/African and Asian ethnicity often underrepresented in HIV research. As a consequence, the results of the study may have wide global applicability. **Key words:** *AIDS-defining illnesses, ESPRIT, HIV, progression of disease, recombinant interleukin-2*

For correspondence or reprints contact: Dr. Sarah L. Pett, MRCP, FRACP, National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Level 2, 376 Victoria St., Sydney, NSW 2010, Australia. Email: spett@nchecr.unsw.edu.au

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*For members of the ESPRIT Research Group see Appendix A.

Despite the enormous benefits of combination antiretroviral therapy (ART) in HIV-infection, there are a number of limitations to its efficacy and durability including the failure to eradicate virus.[1,2] Moreover, incomplete viral suppression, in some cases due to poor adherence but also due to different potency of ART regimens and different pharmacokinetic profiles, can lead to loss of viral control and development of drug-resistant viral strains.[3] In addition, ART is associated with cumulative toxicities, including significant metabolic disturbances, which impact on body habitus and have the potential to accelerate atherosclerosis.[4,5] Furthermore, many toxicities may be exacerbated by coinfection with hepatitis B virus (HBV) and hepatitis C virus (HCV).[6]

Current ART guidelines[7] echo uncertainty regarding initiation and duration of ART and contrast markedly with previous statements recommending early institution of therapy aimed at suppression of plasma virus to undetectable levels. This is in large part due to the recognition that there are long-term toxicities associated with ART and, as a consequence, alternative approaches for clinical management are needed. A number of phase I/II randomized studies of subcutaneous recombinant interleukin-2 (SC rIL-2) have established that intermittent dosing cycles of rIL-2 in combination with ART increase CD4+ T-cell counts significantly more than ART alone.[8–15] Naïve CD4+ T cells are preferentially expanded, including a unique subset of CD4+ CD25+ naïve T cells, and may remain elevated for many years without further rIL-2 dosing.[16,17] Kovacs et al.[18] have recently described two mechanisms that contribute to this: increased proliferation of CD4+ T cells and to a lesser extent CD8+ T cells during rIL-2 dosing coupled with prolonged survival of these naïve CD4+ T cells and the central memory pool of CD4+ T cells. None of the earlier studies of rIL-2 therapy in HIV infection has been powered to show that the rIL-2–induced CD4+ T cell increases are associated with additional clinical benefit compared to the use of ART alone, although the pooled analysis[19] implied a clinical benefit of rIL-2. To this end, there are two ongoing, fully enrolled, phase III, open-label, randomized studies, ESPRIT (Evaluation of Subcutaneous Proleukin® in a Randomized International Trial)[20] and SILCAAT (Subcutaneous Recombinant, Human Interleukin-2 in HIV-Infected Patients with Low CD4+ Counts Under Active Antiretroviral Therapy),[21] comparing the clinical impact, with respect to AIDS-defining illnesses (ADI) and death in HIV-1–infected patients, of intermittent dosing cycles of SC rIL-2 with ART versus ART alone over at least 5 years of follow-up. In order to understand the impact of rIL-2 in a broad population of people with HIV, the ESPRIT trial recruited from a diverse population of patients around the world who had access to combination ART – including intermittent (i.e., a noncontinuous supply) access – and who were being cared for in a variety of clinical practice settings. To be as inclusive as possible, there were relatively few inclusion and exclusion criteria; exclusions included patients in whom receipt of rIL-2 might represent a potential safety issue (i.e., concurrent malignancy requiring cytotoxic chemotherapy); use of systemic corticosteroids, immunosuppressants, or cytotoxic agents within 45 days prior to study randomization; any CNS abnormality that required ongoing treatment with antiseizure medication; current or historical autoimmune/inflammatory diseases; pregnancy; or breastfeeding. The present article describes the baseline characteristics overall and for selected subgroups of participants in ESPRIT.

MATERIALS AND METHOD

Study Population

Prior to the initiation of ESPRIT, four ESPRIT phase II Vanguard studies were conducted. In all, 729 patients were enrolled; of these, 638 were enrolled into ESPRIT as described in the article by Tavel and colleagues.[22] In ESPRIT, eligible patients were HIV-infected adults (≥18 years) with CD4+ T-cell count of ≥300 cells/μL (within 45 days of randomization) and on or starting combination ART. In the Vanguard studies and version 1.0 of the protocol, patients had Centers for Disease Control and Prevention (CDC) category A/B HIV disease at enrollment; version 2.0 of the protocol allowed the enrollment of CDC category C patients providing they had no active ADI for 12 months.

The trial is being conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use–Good Clinical Practice (ICH-GCP) guidelines. ESPRIT has been approved by the institutional review board for each participating site and is sponsored by the National Insti-

Table 1. Number of sites and patients enrolled in ESPRIT by geographic region

	Europe[a] (*n*; % of total enrollment)	Asia[b] (*n*; % of total enrollment)	North America[c] (*n*; % of total enrollment)	South America[d] (*n*; % of total enrollment)	Australia[e] (*n*; % of total enrollment)	Total (*n*)
Sites	103	12	99	16	24	254
Patients enrolled	1,690 (41%)	474 (11%)	1,129 (27%)	652 (16%)	205 (5%)	4,150

[a]Europe as described by participant countries (no. of sites, no. of patients enrolled): Austria (2 sites, *n* = 3); Belgium (1 site, *n* = 80); Denmark (5 sites, *n* = 72); France (22 sites, *n* = 182); Germany (10 sites, *n* = 266); Ireland (1 site, *n* = 4); Italy (8 sites, *n* = 104); Netherlands (6 sites, *n* = 54); Norway (1 site, *n* = 8); Poland (4 sites, *n* = 100); Portugal (3 sites, *n* = 107); Spain (16 sites, *n* = 308); Sweden (2 sites, *n* = 7); Switzerland (1 site, *n* = 10); United Kingdom (20 sites, *n* = 328); Morocco (1 site, *n* = 26).

[b]Asia as described by participant countries (no. of sites, no. of patients enrolled): Israel (3 sites, *n* = 64); Japan (3 sites, *n* = 25); Thailand (5 sites, *n* = 365; Singapore (1 site, *n* = 20).

[c]North America as described by participant countries (no. of sites, no. of patients enrolled): USA (85 sites, *n* = 988); Canada (14 sites, *n* = 141).

[d]South America as described by participant countries (no. of sites, no. of patients enrolled): Argentina (13 sites, *n* = 554); Brazil (3 sites, *n* = 98).

[e]Australia as described by no. of sites, no. of patients enrolled (24 sites, *n* = 205).

tute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). Informed consent has been obtained from all patients.

Trial Design

ESPRIT is a randomized, open-label, clinical endpoint study of intermittent SC rIL-2 plus ART versus ART alone. Patients were randomized on a 1:1 basis to receive intermittent open-label SC rIL-2 with ART or ART alone. The primary endpoint is HIV progression of disease or death. The definition of the former includes all conditions classified in the CDC category C 1993 revised classification[23] plus 12 other conditions that have been associated with HIV-related immunodeficiency.[24] Details of the study design including the sample size justification and statistical methodology have been published.[20]

SC rIL-2 Treatment

In ESPRIT, the induction phase consists of SC rIL-2 at a starting dose of 7.5 MIU given twice daily for 5 consecutive days every 8 weeks for three dosing cycles. Following induction, patients are given further rIL-2 dosing cycles to achieve or sustain the CD4+ T-cell "goal." The latter is based upon entry CD4+ T-cell count, that is, a doubling of baseline CD4+ T-cell count if entry CD4+ was between 300–499 cells/μL or CD4+ ≥1000 cells/μL if entry CD4+ T-cell count was ≥500 cells/mL. All patients are seen every 4 months for the duration of the study.

Statistical Analyses

Summary statistics – frequency distributions, means, medians, and interquartile range (IQR) – are used for describing the cohort overall and by geographic region, age, gender, coinfection with hepatitis B and C, and duration and type of ART. Analyses were performed using Statistical Analyses Software (SAS) Version 8.2 (SAS Institute, Cary, North Carolina, USA) and STATA Release 8.0 (STATA Corporation, College Station, Texas, USA) software.

RESULTS

Overall Baseline Characteristics

ESPRIT was fully enrolled with 4,150 patients in May 2003. These patients were accrued from 254 sites in 25 different countries across six continents (**Table 1**). The majority of clinical sites were in Europe (including one site in Morocco; *n* = 103) and North America (*n* = 99). The percentages of patients enrolled by sites in Europe, North America, South America, Asia, Australia, and Africa were 41%, 27%, 16%, 11%, 5%, and 0.6%, respectively. The median age was 40 years, and 19% of patients were women (**Table 2**). Overall, 76%, 11%, and 9%

Table 2. Baseline characteristics of the ESPRIT cohort grouped by geographic region

Characteristic	Europe, including Morocco	Asia	North America	South America	Australia	Total
Age, yrs [median (IQR)]	41 (36–48)	35 (31–40)	42 (36–48)	37 (33–44)	43 (37–49)	40 (35–47)
Female [*n* (% of region's total)]	252 (15%)	228 (48%)	117 (10%)	164 (25%)	8 (4%)	769 (19%)
Male, age <35 yrs [*n* (% of region's total)]	236 (33%)	87 (12%)	198 (28%)	165 (23%)	34 (5%)	720
Male, age 35–44 yrs [*n* (% of region's total)]	665 (44%)	122 (8%)	441 (29%)	208 (14%)	81 (5%)	1,517
Male, age >45 yrs [*n* (% of region's total)]	537 (47%)	37 (3%)	373 (33%)	115 (10%)	82 (7%)	1,144
Female, age <35 yrs [*n* (% of region's total)]	74 (22%)	142 (41%)	39 (11%)	84 (25%)	4 (1%)	343
Female, age 35–44 yrs [*n* (% of region's total)]	135 (44%)	71 (23%)	50 (16%)	52 (17%)	2 (1%)	310
Female, age >45 yrs [*n* (% of region's total)]	43 (37%)	15 (13%)	28 (24%)	28 (24%)	2 (1%)	116
All, age <35 yrs [*n* (% of region's total)]	310 (18%)	229 (48%)	237 (21%)	249 (38%)	38 (19%)	1,063
All, age 35–44 yrs [*n* (% of region's total)]	800 (47%)	193 (41%)	491 (43%)	260 (40%)	83 (40%)	1,827
All, age >45yrs [*n* (% of region's total)]	580 (34%)	52 (11%)	401 (36%)	143 (22%)	84 (41%)	1,260
White [*n* (% of region's total)]	1,559 (92%)	41 (9%)	727 (64%)	585 (90%)	186 (90%)	3,098 (76%)
Acquisition of HIV via IVDU [*n* (% of region's enrollment)]	229 (14%)	18 (4%)	97 (9%)	83 (13%)	5 (2%)	432 (10%)
Baseline CD4+ T-cell count, cells/μL [median (IQR)]	442 (365–563)	422 (361–510)	513 (410–664)	447 (361–574)	450 (370–572)	458 (373–588)
Baseline CD4+, % [median (IQR)]	23 (19–29)	21 (17–27)	27 (21–33)	24 (19–30)	23 (18–28)	24 (19–30)
Nadir CD4+ T-cell count, cells/μL [median (IQR)]	153 (62–244)	265 (158–352)	265 (147–374)	200 (100–314)	176 (84–256)	199 (92–310)
Median difference (baseline – nadir) CD4+ T-cell count, cells/μL	304 (213–396)	192 (62–305)	268 (148–396)	260 (165–368)	287 (206–380)	277 (172–382)
Prior AIDS events	565 (33%)	58 (12%)	171 (15%)	182 (28%)	61 (30%)	1,037 (25%)
HIV RNA <400 cp/mL	1,327 (79%)	260 (55%)	767 (68%)	352 (54%)	127 (62%)	2,833
HBV sAg +ve	97 (6%)	36 (8%)	59 (5%)	24 (4%)	12 (6%)	228 (5.5%)
HCV +ve	283 (17%)	34 (7%)	113 (10%)	84 (13%)	9 (4%)	523 (13%)
Duration of ART, yrs [median (IQR)]	4.8 (2.7–7.0)	2.3 (0.5–4.2)	4.0 (2.1–6.7)	3.6 (1.9–5.3)	5.2 (3.9–8.8)	4.2 (2–6)
BMI, kg/m^2 [median (IQR)]	23.2 (21.6–25.3)	21.8 (20.1–24.0)	25.1 (23.2–27.6)	24.1 (22.4–25.7)	23.5 (21.8–25.8)	24.0 (22.0–26.0)

Note: ART = antiretroviral therapy; BMI = body mass index; IVDU = intravenous drug use; IQR = interquartile range; HBV sAg +ve = hepatitis B virus surface antigen positive; HCV +ve = hepatitis C virus positive.

were of Caucasian, Asian, and African-American/African ethnicity. HIV was acquired through male homosexual sex in 55% of men and was heterosexually acquired in 38% of patients; 10% of patients reported intravenous drug use (IVDU) alone as a mode of HIV transmission. In the mixed categories where more than one risk factor for disease acquisition was reported, male homosexual/IVDU and heterosexual/IVDU risks were reported in 1% and 3%, respectively. Blood products were reported as the sole means of HIV transmission in 50 patients (1% of the total).

The median duration of HIV infection was 6 years (median IQR 3–10 years). Median nadir and baseline CD4+ T cells were 199 cells/μL and 458 cells/μL (24%), respectively; median difference in CD4+ T cells (baseline minus nadir) was 277 cells/mL. Twenty-five percent of patients had a history of prior ADI. The most common prior ADIs recorded, in descending order of frequency, were *Pneumocystis carinii (jirovecii)* pneumonia (PCP), *M. tuberculosis*, esophageal candida, Kaposi's sarcoma, cytomegalovirus (CMV) infection, cerebral toxoplasmosis, disseminated *Herpes zoster*, and HIV-wasting syndrome. Non-category C ADI made up 12% of all ADIs reported at baseline. In comparing those participants with prior ADI to those without, the median age was older at 42 years versus 39 years ($p \leq .0001$), CD4+ T-cell nadir was significantly lower at 62 versus 239 cells/μL ($p \leq .0001$), and baseline CD4+ T cells were also lower at 418 versus 472 cells/μL ($p \leq .0001$), respectively. The median duration of ART use was 4.2 years (median IQR 2–6 years) (**Table 2**); 17%, 13%, and 69% of patients commenced ART in the pre-highly active antiretroviral therapy (pre-HAART; 1994–1995), early HAART (1996–1997), and late HAART (1998+) eras, respectively. Seventy-eight percent, 16%, and 5% had a viral load below the level of quantification (<500 copies/mL), between 500–9,999 copies/mL, or ≥10,000 copies/mL, respectively. The majority of patients (50%) were taking a three-drug combination, with 14%, 2%, and 0.4% on 4, 5, and ≥6 drug combinations, respectively. Fourteen percent, 77%, and 9% of patients were on drugs from one, two, and three classes of ART, respectively. Forty-six percent were on ART containing nonnucleoside reverse transcriptase inhibitors (NNRTIs) and 49% were on a protease inhibitor (PI)–based regimen; 15% were using ritonavir-boosted PI (**Table 3**). Overall, 18% were reported as having peripheral lipodystrophy (thinning of the face, limbs, or upper trunk) and 9% as having accumulation of fat in the abdomen, neck, or breasts. Ten percent had dyslipidaemia that was being treated with lipid-lowering medication; 2% had diabetes mellitus that was being treated with oral hypoglycaemic agents or insulin, and 5% had hypertension that required drug treatment. Less than 1% of patients gave a history of prior myocardial infarction or stroke. The most common prophylaxes used were against PCP and Herpes simplex in 6% and 5% of the cohort, respectively.

At baseline, 14% (n = 585), 37% (n = 1,536), and 36% (n = 1,494) of the patients did not have results for hepatitis B virus surface antigen (HBV sAg), hepatitis B virus surface antibody (HBV sAb), and hepatitis B virus core antibody (HBV cAb) status, respectively. Of those for whom these data were available, 6% were HBV sAg positive and 31% were HBV cAb positive. Thirteen percent were HCV coinfected, and 28 (0.8%) had dual infection with HBV and HCV (defined as hepatitis C antibody and HBV sAg positive). Overall, 17% (n = 680) had received a full course of hepatitis B vaccinations and 83% (n = 3,410) had not. There was no difference in the HBV sAb status in those reporting a full course of hepatitis B vaccination compared to those who were not vaccinated or were non-completers (36% vs. 31%, respectively). Six percent of those with HCV coinfection had received vaccination against HBV; however, 51% (n = 265) of patients with HCV coinfection were also HBV cAb positive, indicating past exposure and immunity to HBV. Median weight of the cohort was 72 kg (IQR 65–93 kg) equivalent to a median body mass index (BMI) of 24 kg/m^2 (IQR 22–26 kg/m^2).

Baseline Characteristics by Geographic Region

The baseline characteristics of the ESPRIT patients according to their geographic region of enrollment are described in **Table 2**. Key differences were that patients enrolled in Asia and Argentina were younger and 48% of patients enrolled in Asia and 25% in South America were female. Moreover, 44% (n = 336) of all women enrolled (n = 769) were enrolled in Thailand and Argentina, equating to 54% and 25% of each of these country's total enrollment into ESPRIT, respectively. Eighty-one percent of patients enrolled in Asia were infected through heterosexual sex compared to much lower rates in

Table 3. Baseline characteristics by duration of ART

	ART duration ≤2 yrs (*n* = 928)	ART duration 2–4 yrs (*n* = 1,030)	ART duration 4–6 yrs (*n* = 999)	ART duration >6 yrs (*n* = 1,138)	Total[a]
No. of ART drugs in use at baseline					
None	2 (0.2%)	1 (0.1%)	—	2 (0.2%)	5
1	37 (4%)	36 (4%)	33 (3%)	25 (2%)	131
2	462 (50%)	335 (33%)	280 (28%)	184 (16%)	1,261
3+	424 (46%)	653 (63%)	668 (67%)	869 (76%)	2,614
5+	3 (0.3%)	6 (0.6%)	18 (1.8%)	58 (5%)	85
Classes of ART drugs in use at baseline					
None	2 (0.2%)	1 (0.1%)	—	2 (0.2%)	5
1	206 (22%)	120 (12%)	147 (15%)	89 (8%)	562
2	697 (75%)	875 (85%)	771 (77%)	825 (73%)	3,168
3	23 (2%)	34 (3%)	80 (8%)	217 (19%)	354
4	—	(3%)	1 (0.1%)	5 (0.4%)	6
Use of NNRTI	437 (47%)	467 (45%)	413 (41%)	575 (51%)	1,892
Use of PI	306 (33%)	473 (46%)	527 (53%)	701 (62%)	2,007
Use of ritonavir-boosted PI	58 (6%)	99 (10%)	167 (17%)	294 (26%)	618
Peripheral fat loss +/- fat accumulation	25 (3%)	161 (16%)	257 (26%)	398 (35%)	841
Dyslipdaemia treated with lipid-lowering agents	24 (3%)	90 (9%)	119 (12%)	247 (22%)	480
Hypertension treated with anti-hypertensives	21 (2%)	49 (5%)	50 (5%)	92 (8%)	212
HIV RNA <400 cp/mL	582 (63%)	772 (75%)	671 (67%)	776 (68%)	2,801
Baseline CD4+ T-cell count, cells/μL [median (IQR)]	449 (374–577)	478 (380–607)	464 (367–588)	446 (370–562)	
Nadir CD4+ T-cell count, cells/μL [median (IQR)]	274 (176–377)	196 (90–310)	185 (80–280)	149 (65–248)	
Median difference (baseline – nadir) CD4+ T-cell count, cells/μL	200 (98–298)	297 (188–398)	290 (199–392)	306 (210–411)	
CD4+ T-cell slope in the 12 months prior to study entry	118 (-50, 284)	51 (-106, 200)	-0.24 (-158, 161)	37 (-122,175)	

Note: ART = antiretroviral therapy; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

[a]Data missing on 55 people and 5 people were not on any ART at baseline.

the other regions: 28%, 36%, 49%, and 6% in Europe, North America, South America, and Australia, respectively. IVDU as the route of HIV acquisition was most commonly reported in Europe (14%) and South America (13%). In countries with more than 20 patients enrolled, the highest rates of HIV acquisition via IVDU were in Poland (56%), Spain (32%), Italy (30%), Israel (16%), and Argentina (14%), with much lower rates in the other northern European countries (≤3%), Australia (2%), Canada (6%), Brazil (5%), and Thailand (2%).

In those countries with at least 20 patients enrolled, the longest duration of HIV-infection (i.e., the time since their first positive HIV test) was in patients enrolled in France (9.5 years), Australia (9 years), and Belgium (8.4 years). The time since first HIV diagnosis was shortest in Asia (3 years; median IQR 2–6 years), which is mostly due to the large number of patients enrolled in Thailand (77% of total enrollment from Asia) where the median duration was 3 years. Thirty-three and 30% of patients enrolled in Europe and Australia, respectively, had a prior ADI. In contrast, 15% of those in North America and 12% of those in Asia had a prior ADI. PCP was the most common prior ADI in all continents. Prior PCP was most common in Europe (n = 201; 12%), South America (n = 75; 11%), and Australia (n = 22; 11%). *M. tuberculosis* was the second most commonly recorded previous ADI; the highest percentages were recorded in patients enrolled in South America (n = 39; 6%), Europe (n = 95; 6%), and Asia (n = 25; 5%). In Europe, 30% of patients with prior tuberculosis were enrolled in Spain (n = 28). Forty-eight percent of the 1,037 participants who reported prior ADI were enrolled from four countries: United Kingdom (n = 144), Argentina (n = 142), Spain (n = 118), and Germany (n = 90).

Baseline CD4+ T-cell count and percentage at enrollment were highest in North America (513 cells/μL and 27%, respectively). Nadir CD4+ T cells were lowest in Europe (153 cells/mL) and Australia (176 cells/mL). The median difference between nadir and baseline CD4+ T cells was lowest in Asia (192 cells/μL). The median duration of ART use was shortest in Asia (median 2.3 years) and South America (median 3.6 years). In countries enrolling more than 20 patients, use of NNRTI-based regimens at study entry was highest in Spain (n = 308; 66%) and lowest in Denmark (n = 17; 24%). Ritonavir-boosted PI use at study entry was highest in some Northern European countries (Denmark [29% of 72 enrolled], Germany [27% of 266 enrolled], Belgium [26% of 80 enrolled], and Austria [23% of 34 enrolled]), Australia (27% of 205 enrolled), and some sites in North America. The lowest use of ritonavir-boosted PI at study entry was in Morocco (0% of 26 enrolled), Netherlands (7% of 54 enrolled), and Thailand (7% of 365 enrolled); however, 66 (18%) patients in Thailand were enrolled between 1997 and 1998 prior to the widespread use of either ritonavir-boosted PI or NNRTI.

Europe and Argentina had the highest rates of HCV coinfection, mirroring the highest IVDU rates (**Table 2**). HBV coinfection rates were highest in Asia (8%) and Europe (6%). Use of prophylaxis against *Herpes* infections was highest in the United States, Australia, and the United Kingdom and was lowest (≤1%) in Argentina, Brazil, and Thailand. All patients had BMI in the normal range (18.5–24.9 kg/m^2), aside from those in North America where median BMI was just in the "overweight" range (**Table 2**). BMI was lowest in Asia (21.8 kg/m^2), which was in part due to the large number of women (44% of participants), many of whom were enrolled in Thailand.

Baseline Characteristics by Gender and Age

The baseline characteristics by age and gender in the different regions are shown in **Tables 2** and **4**. Twenty-six percent of the women versus 7% of the men enrolled were Asian; 53% of the women and 80% of the men were Caucasian. The women enrolled were younger than the men (median age 36 vs. 41 years); 15% and 34% of the women and men enrolled, respectively, were more than 45 years old. Women had been diagnosed more recently than the men (median 5 years; IQR 3–9 years). Nadir CD4+ T cells were significantly higher in women than men (232 vs. 190 cells/μL; $p \leq .0001$), although baseline CD4+ T cells at study entry were similar. Twenty-seven percent of men versus 18% of women ($p < .0001$) had a prior ADI at baseline. In men, the highest rates of prior ADI occurred in those between the ages of 35–44 years and over 45 years; these two age groups also had the lowest nadir CD4+ T-cell counts and the longest duration of ART use. The median duration of ART use was 3.9 years in women and 4.3 years in men. Forty percent and 39% of women were on an NNRTI or PI at baseline compared to 47% and 51% of men, respectively, a significant difference for both pa-

Table 4. Baseline characteristics of the ESPRIT by age group and gender

	Male (<35 yrs)	Male (35–44 yrs)	Male (>45yrs)	Female (<35 yrs)	Female (35–44 yrs)	Female (age >45 yrs)	All (<35 yrs)	All (35–44 yrs)	All (>45 yrs)
White [*n* (% of total in each age group)]	513 (71%)	1202 (79%)	973 (85%)	151 (44%)	184 (59%)	75 (65%)	664 (62%)	1,386 (76%)	1,048 (83%)
Acquisition of HIV via IVDU [*n* (% of total in each age group)]	84 (12%)	201 (13%)	57 (5%)	31 (9%)	49 (16%)	10 (9%)	115 (11%)	250 (14%)	67 (5%)
Baseline CD4+ T-cell count, cells/μL [median (IQR)]	474 (380–607)	460 (372–591)	446 (369–573)	469 (382–594)	436 (367–566)	455 (376–567)	470 (380–599)	456 (371–584)	448 (370–572)
Baseline CD4% [median (IQR)]	25 (20–32)	23 (19–29)	22 (18–28)	26 (21–34)	25 (20–31)	24 (19–31)	26 (20–33)	24 (19–30)	23 (18–29)
Nadir CD4+ T-cell count, cells/μL [median (IQR)]	253 (147–350)	174 (72–288)	175 (85–270)	260 (153–371)	204 (100–313)	210 (97–305)	256 (149–356)	180 (77-292)	179 (85–274)
Median difference (baseline – nadir) CD4+ T-cell count, cells/μL	247 (129–354)	293 (191–397)	290 (191–383)	245 (105–363)	254 (145–367)	257 (151–388)	244 (121–356)	289 (182–392)	289 (189–384)
Prior AIDS events	98 (14%)	439 (29%)	361 (32%)	41 (12%)	71 (23%)	27 (23%)	139 (13%)	510 (28%)	388 (31%)
HIV RNA <400 cp/mL	478 (66%)	1073 (71%)	829 (72%)	164 (48%)	210 (68%)	79 (68%)	642 (60%)	1283 (70%)	908 (72%)
HBV sAg +ve	— (—)	108 (7%)	63 (5%)	— (—)	13 (4%)	4 (3%)	— (—)	121 (7%)	67 (5%)
HCV +ve[a] [*n* (% of total in each group)]	97 (14%)	222 (15%)	87 (8%)	37 (11%)	68 (22%)	12 (11%)	134 (13%)	290 (16%)	99 (8%)
Duration of ART, yrs [median (IQR)]	2.7 (1.3–4.6)	4.5 (2.6–6.5)	5.0 (3.0–7.9)	2.3 (1.2–4.4)	4.3 (2.2–6.5)	3.9 (2.2–6.2)	2.5 (1.3–4.5)	4.5 (2.5–6.5)	4.9 (2.9–7.8)
BMI, kg/m^2 [median (IQR)]	23.6 (21.8–25.6)	24.0 (22.1–25.9)	24.4 (22.6–24.5)	21.9 (20.2–24.0)	22.7 (20.6–25.7)	23.9 (22.0–27.3)	23.1 (21.1–25.2)	23.8 (21.8–25.9)	24.4 (22.5–26.5)

Note: IDVU = intravenous drug use; HBV sAg +ve = hepatitis B virus surface antigen positive; ART = antiretroviral therapy; BMI = body mass index.
[a]Data missing on 49 patients.

rameters. Fewer women than men had dyslipidaemia being treated with lipid-lowering drugs (4% vs. 12%). In women, peripheral lipodystrophy and accumulation of fat in the abdomen, neck, or breasts was reported in 15% and 11%, respectively, which was significantly less than in men for both parameters.

Baseline Characteristics by Duration of ART

These are summarized in **Table 3** and have been discussed in the overall results. Patients treated with ART for the longest duration (i.e., over 6 years) were more likely to be taking drugs from four or more classes of antiretrovirals compared to patients on treatment for 4 years or less at study entry. Rates of virological suppression (<400 cp/mL) were lowest in those on ART for ≤2 years (63%) and highest (75%) in those on ART for 2–4 years. PI use, including ritonavir-boosted PI, at study entry was highest in the heavily treated group (>6 years of ART) and lowest in those treated for ≤2 years; the latter group had a higher use of NNRTI (47%) compared to PI use (33%) and greater use of single class ART (22%) compared to patients on ART for more than 2 years. The nadir CD4+ T-cell count of patients treated for <2 years was significantly higher (median 274 cells/μL) than that of patients treated for 6 years (median 149 cells/μL). Fat accumulation/loss and dyslipdaemia requiring treatment with lipid-lowering agents correlated with duration of ART exposure, with the highest rates in those with ART of ≥6 years' duration.

Baseline Characteristics by HBV or HCV Infection

These are summarized in **Table 5**. All those with HBV and/or HCV coinfection were over 35 years of age. Twenty-two percent and 11% of those with HCV or HBV coinfection, respectively, were women. Hepatitis C coinfection mirrored IVDU as a mode of HIV acquisition in 61% of patients; in contrast, HBV coinfection was not closely correlated with IVDU (11%).

DISCUSSION

ESPRIT is the largest trial of an experimental agent in HIV infection to date. Patients were enrolled from 254 sites in 25 countries on six continents. This wide global coverage, coupled with a protocol designed to be as inclusive as possible, has led to the enrollment of a diverse population of HIV-infected patients across a wide variety of clinical settings. It is hoped that as a consequence the results will have greater global applicability. Many prior trials have been criticized for excluding certain HIV-infected populations, such as the nontrialing of new agents in women of child-bearing potential; patients with hepatitis B or C coinfection with or without ongoing IVDU, and patients from Asian, African American, and other ethnicities traditionally underrepresented in clinical research.[25] In light of these criticisms and especially because there may be gender- and ethnicity-related differences related to therapeutic response and toxicity of HIV treatments, the Food and Drug Administration (FDA) is now permitted to place a hold on the licensing of investigational agents if, for example, there are insufficient efficacy and safety data in women.[26]

ESPRIT, compared to many other large intervention studies involving antiretroviral therapy, differs in terms of the sheer magnitude of the study population (n = 4,150), larger numbers of female patients, and enrollment of relatively large numbers of patients of non-white ethnicity and with hepatitis C coinfection. Exclusions were minimal and were predominantly for safety reasons. Moreover, while the ESPRIT entry criteria excluded women who were pregnant or breastfeeding at the time of enrollment for safety reasons, the protocol allows pregnancy on study provided no SC rIL-2 was administered until the pregnancy was over. The baseline demographics are very similar to some of the other large observational studies, such as the ART collaboration cohort[27] and EuroSIDA,[28] in the countries where these cohort studies are being conducted; the implication is that the ESPRIT patients are representative of the general population of HIV-infected patients in these countries.

We hypothesize that duration of known HIV infection (i.e., time from first positive test), prior ADI, and access to ART may have influenced patient selection for ESPRIT participation in different settings. For example, in Australia, patients had been diagnosed with HIV longer, had lower nadir CD4+ T-cell counts, had high rates of prior ADI, and had longer duration of ART. In contrast, patients in Thailand had been diagnosed with HIV infection

Table 5. Baseline characteristics by coinfection with HBV and HCV[a]

Characteristic	HBV sAg +ve	HBV sAg -ve	HCV +ve	HCV -ve	HBV and/or HCV -ve
No. (% of total enrollment)	228 (6%)	3,337 (80%)	523 (13%)	2,925 (70%)	3,673 (89%)
Age, yrs [median (IQR)]	41 (37–46)	40 (35–47)	39 (35–44)	41 (35–47)	40 (35–47)
Female[b]	26 (11%)	621 (19%)	117 (22%)	503 (17%)	657 (18%)
Caucasian [*n* (% of total)]	158 (69%)	2,542 (76%)	438 (84%)	2,199 (75%)	2,797 (76%)
Afro-American/African	32 (14%)	315 (9%)	41 (8%)	302 (10%)	358 (10%)
Asian	33 (14%)	332 (10%)	25 (5%)	302 (10%)	359 (10%)
Acquisition of HIV via IVDU [*n* (% of total)]	24 (11%)	353 (11%)	321 (61%)	65 (2%)	365 (105)
Baseline CD4+ T-cell count, cells/μL [median (IQR)]	425 (357–551)	460 (373–590)	450 (370–554)	460 (372–594)	459 (371–589)
Nadir CD4+ T-cell count, cells/μL [median (IQR)]	196 (81–296)	193 (90–298)	178 (81–284)	199 (90–301)	195 (90–300)
Median difference (baseline – nadir) CD4+ T-cell count, cells/μL	258 (145–364)	285 (180–388)	284 (177–371)	280 (177–388)	281 (178–385)
Prior AIDS events	65 (29%)	837 (25%)	126 (24%)	744 (25%)	930 (25%)
HIV RNA <400 cp/mL	163 (71%)	2,356 (71%)	363 (69%)	2,077 (71%)	2,583 (70%)
Duration of ART, yrs [median (IQR)]	4.6 (2.3–7.4)	4.1 (2.2–6.3)	4.7 (2.5–7.0)	4.1 (2.1–6.3)	4.2 (2.2–6.4)
BMI, kg/m^2 [median (IQR)]	24 (22–26)	23 (22–25)	24 (22–26)	24 (22–26)	24 (22–26)

Note: HBV sAg +ve = hepatitis B virus surface antigen positive; HBV sAg -ve = hepatitis B virus surface antigen negative; HCV = hepatitis C virus; IQR = interquartile range; IVDU = intravenous drug use; ART = antiretroviral therapy; BMI = body mass index.

[a]Data on HBV sAg status and HCV status missing in 585 and 702 patients, respectively.

[b]Data on hepatitis B status missing in 14 female patients.

more recently, had lower rates of prior ADI, had higher nadir CD4+ T-cell counts, and had shorter duration of ART. Therefore, patients enrolled in ESPRIT in Australia were more likely to have been treated before combination ART was widely used (i.e., with monotherapy); although these patients were virologically suppressed at ESPRIT baseline, they might be expected to have fewer treatment options (at least at the time of ESPRIT enrollment) if virological failure were to occur. In contrast, patients enrolled in Thailand would have access to one or two combination antiretroviral regimens with more limited access to future regimens in the event of virological failure. In both cases, rIL-2 might have been viewed as a way of maintaining a higher CD4+ T-cell count so that when or if virological rebound occurred in the absence of an antiretroviral regimen that could achieve durable

viral suppression, patients would potentially remain well for longer as a consequence of having higher CD4+ T-cell counts.

The use of single class ART at study entry mirrored by lack of use of PI and NNRTI-based regimens was more common in women than in men. Limited access to ART in countries in which large numbers of women were enrolled and the enrollment of ESPRIT Vanguard patients in 1997–1999 – a time when dual nucleoside therapy was the recommended treatment in local ART guidelines – offer some insights into this finding. In addition, the entry requirement of a CD4+ T-cell count ≥300 cells/μL may have affected the choice of ART at baseline, especially if this count was higher than the recommended level for ART commencement that was set by treatment guidelines in the country of enrollment. Overall, however, across the entire cohort, approximately equal numbers of patients were on a PI- or NNRTI-based combination at baseline, which reflects adherence with the International AIDS Society-USA (IAS) guidelines at the time that ESPRIT was enrolling patients (2000–2003).[29] Longer duration of ART correlated with clinical and metabolic manifestations of the HIV-lipodystrophy syndrome. The lowest nadir CD4+ T cells, highest percentage of patients with prior ADI, and longest duration of antiretroviral use were seen in patients enrolled in Europe and Australia. These findings suggest that patients with advanced immunodeficiency as exemplified by low nadir CD4+ T cells (<100 cells/μL), irrespective of whether they had developed an ADI, were treated with ART in accordance with what ART was available at that time and were "rescued" clinically as a consequence. The magnitude of immune restoration as illustrated by median difference between the baseline and nadir CD4+ T-cell count did not appear to be negatively impacted by lower nadir CD4+ T-cell count. In Asia, the degree of immune restoration was lowest despite these patients having the highest nadir CD4+ T-cell counts; this may have been a consequence of incomplete immune restoration at the time of enrollment due to shorter duration of ART or virological failure. The low overall use of any kind of opportunistic infection (OI) prophylaxis reflects the high entry CD4+ T-cell counts of the study participants and in patients with a previously low CD4+ T-cell nadir might reflect the withdrawal of primary or secondary prophylaxis in accordance with the IDSA guidelines.[30]

Reported hepatitis B coinfection rates were lower than expected, particularly in countries where HBV is endemic. HCV but not HBV rates mirrored reported rates of IVDU; this suggests transmission through routes other than IVDU for HBV, if the reporting of IVDU was accurate. The relatively low rates of HBV (and to some extent HCV) coinfection in the ESPRIT cohort may be explained by patients not meeting the inclusion criteria with respect to liver transaminases within protocol-defined ranges (≤5 x the upper limit of normal) or investigator anxiety regarding the potential impact of rIL-2 on those with liver disease.

ESPRIT has enrolled patients from a large number of clinical sites on six continents. Moreover, groups often underrepresented in HIV clinical trials, such as women and patients of Asian and African-American/African ethnicity, have been enrolled in relatively large numbers. As a consequence, the acceptability of rIL-2 will be able to be evaluated in these different populations. Furthermore, the highly heterogenous patient sample will aid the broad generalizability of results to all patients with HIV infection.

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APPENDIX A

ESPRIT Study Group: An International Steering Committee that includes the Executive Committee and representatives from National and Regional Coordinating Centers oversee the trial. Co-chairs of the ESPRIT study are Donald I. Abrams and David A. Cooper. Representatives from each national group and key committees are named below. Past and current members of the International Steering Committee are in bold typeface.

Executive Committee: Donald I. Abrams, David A. Cooper, Janet H. Darbyshire, William R. Duncan, Sean Emery, H. Clifford Lane, Sandra Lehrman, Jens D. Lundgren, James D. Neaton.

Argentina National Coordinating Center: Liliana Aguilar, Eleonora Betina Angel, Silvia Aquilia, Waldo Belloso, Jorge Benetucci, Victor Bittar, Pedro Cahn, Arnaldo Casiro, Jorge Contarelli, Jorge Corral, Lucia Daciuk, Daniel David, Ines Ferrari, Diego Fridman, Viviana Galache, Graciela Guaragna, Silvina Ivalo, Hector Laplume, Maria B. Lasala, Roberta Lattes, Jaime Lasovsky, Gustavo Lopardo, **Marcelo Losso,** Leonardo Lourtau, Sergio Lupo, Aldo Maranzana, Cristina Marson, Lucila Massera, Marisa del Lujan Sanchez, Carla Somenzini, Mariel Tocci.

Australia National Trial Coordinating Center: Sally Algar, Jonathan Anderson, David Austin, David Baker, Kathy Blavius, Mark Bloch, Michael Boyle, David Bradford, Leah Carrall, Andrew Carr, John Chuah, Michael Curry, Clive D'Arcy-Evans, Pauline Dobson, Nicholas Doong, Wendy Ferguson, **Robert Finlayson, Martyn French,** Julian Gold, Philip Habel, Jennifer Hoy, Jeff Hudson, Robyn James, Sarangapany Jeganathan, Jenny Leung, Kaye Lowe, Karen MacRae, Simon Mallal, Marilyn McMurchie, Nicholas Medland, Anne Mijch, Samantha Miller, Jo Murray, David Orth, Julie Patching, Ruth Primrose, Dick Quan, Michael Rawlinson, Hugo Ree, Robyn Richardson, Gary Rogers, Janine Roney, Norman Roth, David Shaw, Tuck Meng Soo, David Sowden, Alison Street, Alan Street, Robyn Vale, Claudio Villella, Allen Walker, Ashley Watson, Ngaire Wendt, Helen Wood, David Youds.

Austria National Trial Coordinating Center: Alexander Aichelburg, Armin Rieger, Norbert Vetter.

Belgium National Trial Coordinating Center: Nathan Clumeck, Stèphane De Wit, Kabamba Kabeya, Elizabeth O'Doherty.

Brazil National Trial Coordinating Center: Caritas Relva Basso, Cristiane de Sales Amorim, David Salamão Lewi, Tamara Newman Lobato Souza, **Luiz Carlos Pereira,** Mariliza da Silva.

Canada National Trial Coordinating Center: Jonathan Angel, Pierrette-Rolande Bouchard, Fran Clark, Jeff Cohen, Mimose Dambreville, Michele Ellis, Stephan Fiset, Andrea Foster, Christopher Fraser, Susan Gagnon, Janet Gilmour, Richard Guenette, Heather Haldane, Nanci Hawley-Foss, Susan Hyndman, Lynn Johnston, Nathalie Jubinville, Francoise Juneau, Lynn Kelleher, Lyne LaPointe, Judy Latendre-Paquette, Adeline Lindemulder, Laura Mashinter, Eric Lefebvre, Nancy McFarland, Chantal Morisseau, Robert O'Neill, Alain Piche, Edward Ralph, Danielle Rouleau, **Jean-Pierre Routy**,

Roger Sandre, Shelley Schmidt, Stephen Shafran, Fiona Smaill, Dale Stromberg, Jean-Marc Trepanier, Sylvie Trottier, Susanne Veal, Sharon Walmsley, Karl Weiss, Kurt Williams, Mavis Young, Barbara Zaleschuk, Don Zarowny.

Denmark National Trial Coordinating Center: Bente Baadegaard, Finn Black, Kirsten Boedker, **Jan Gerstoft**, Lene Jensen, Lars Mathiesen, Henrik Nielsen, Court Pedersen, Dorthe Petersen.

France National Trial Coordinating Center: Jean-Pierre Aboulker, Adyb Baakili, Nafissa Bengrait, Maryse Bensalem, Huguette Berthe, Martin Bloche, Claude Bazin, Francois Boue, Elisabeth Bouvet, Christiane Brancon, Catherine Capitant, Carole Ceppi, Christine Cheneau, Anne Coutellier, Jean Marie Chennebault, Fabienne Coquet, Pierre De Truchis, Anne-Marie Delavalle, Veronique Frixon-Marin, Jean-Albert Gastaut, Francois Delfraissy, Muriel Eliaszeicz, Herve Gallais, Jean-Albert Gataut, Jacques Gilquin, Gustavo Gonzalez-Canali, Chrisiane Gaudebout, Cecile Goujard, Bruno Hoen, Patricia Honore, Bernard Jarousse, Jean-Marie Lang, Benedict Lefebvre, Yves Levy, Jocelyne Loison, Aline Maignan, Jean-Luc Meynard, Christophe Michon, Martin Mole, Laurence Marsal, Sophie Matheron, Emmanuel Mortier, Eric Oksenhendler, Sandrine Poirier, Catherine Picard-Dahan, Isabelle Ravaux, Francois Raffi, Gilles Raguin, Jacque Reynes, Willy Rozenbaum, Dominique Salmon, Anne Simon, Gabriella Spiridon, Jean-Paul Viard, Michele Vidal, **Laurence Weiss**, David Zucman.

Germany National Trial Coordinating Center: Frank Bergmann, Norbert Brockmeyer, Gerd Faetkenheuer, Stefan Fenske, Daniela Gey, Frank-Detlef Goebel, Martina Goetsch, Martin Hartmann, Hartwig Klinker, Gisela Kremer, Kathleen Mantzsch, Stefan Mauss, Juergen Rockstroh, Jessica Rotty, Ellen Rund, Katrin Schneider, Dirk Schuermann, **Schlomo Staszweski**, Klaus Tilmann, Martin Vogel.

Israel National Trial Coordinating Center: Zvi Bentwich, Goldstain Drora, Eynat Kedem, Ruth Lang, Itzic Levi, Shlomo Maayan, Eli Magen, Merav Mamorsky, Anat Pilpul, **Shimon Pollack**, Zev Sthoeger, Hadas Vered, Israel Yust.

Ireland National Trial Coordinating Center: Fiona Lyons, **Fiona Mulcahy**, Annette Rochford.

Italy National Trial Coordinating Center: Fernando Auiti, Gioacchino Angarano, Davide Bertelli, Teresa Bini, Raffaele Bruno, Gian Pietro Cadeo, Giampietro Carosi, Antonella D'Arminio Monforte, Sergio Del Giacco, Massimo Di Pietro, Roberto Esposito, Gaetano Filice, Gabriella Gavazzeni, Giovanni Guaraldi, Francesco Indiveri, Adriano Lazzarin, Francesco Mazzotta, Lorenzo Minolli, Maria Montroni, Mauro Moroni, Silvia Nozza, Guiseppe Pastor, **Guido Poli**, Enzo Raise, Sergio Romagnani, Vega Rusconi, Paolo Sacchi, Fredy Suter, **Giuseppe Tambussi**, Umberto Tirelli.

Japan National Trial Coordinating Center: Helen Fraser, Aikichi Iwamoto, Yoshida Kikuchi, Masahiko Mori, Tetsuya Nakamura, Takashi Odawara, **Shinichi Oka**, Takuma Shiasaka, Misao Takano, Junichiro To, Chisato Ueta.

Morocco National Trial Coordinating Center: Kamal El Filali, **Hakima Himmich**.

Netherlands National Trial Coordinating Center: W. Blok, J. Borleffs, B. Bravenboer, W. Bronveld, F. Claessen, Maurice Duurvoort, J. Ferwerda, P. Frissen, Nicolette Hulshoff, Job Juttman, R. Kauffmann, P. Koopmans, F. Kroon, Selwyn Lowe, M. Leemhuis, P. Meenhorst, **Peter Reiss**, S. Reinders-Folmer, C. Richter, Rick Santegoets, Marijke Schoemaker, G. Schrey, Herman Sprenger, Jacob Ten Veen, Judith Tessalaar, M. van der Ende, H. van der Vall, Arne van Eeden, Remko van Leeuwen, Joost Vermeulen, Reinier W. ten Kate, Renee van Boxtel, Arne van Eden, Bernadette van de Ven, Piet van der Meulen, C. ten Napei, R. Vriesendrop.

Norway National Trial Coordinating Center: Johann Bruun.

Poland National Trial Coordinating Center: Elzbieta Bakowska, Marek Beniowski, Anna Boron-Kaczmarska, Jacek Gasiorowski, Andrzej Gxadysz, **Andrzej Horban**, Brygida Knysz, Elzbieta Mularska, Magdelena Pynka, Aleksandra Szymczak.

Portugal National Trial Coordinating Center: Isabel Aldir, **Francisco Antunes**, Manuela Doroana, Luís Duque, Kamal Mansinho, Inez Pinto, Emilia Valadas, Jose Vera.

Singapore National Trial Coordinating Center: Anushia Panchalingham, **Poh Lian Lim**, **Nick Paton**, Bernard Peperstraete, Jorge Villacian.

Spain National Trial Coordinating Center: Rosario Alcazar-Caballero, Julio Arrizabalaga, Emilio Bouza, Concepcion Cepeda, Xabier de Barron, Miguel Cervero Jimenez, Bonaventura Clotet, Luis Cortes, Pere Domingo, Pompeyo Fernandez, **Eduardo Fernandez-Cruz**, Montserrat Fuster, Jose Gatell, Paloma Gijón, Ignacio Gil, Juan Gonzales-Lahoz, Alicia Gonzalez, Manuel Hernandez, Jose Iribarren, Miguel Jimenez, Hernando Knobel, Agathe Leon, **Juan Carlos Lopez**, Angeles Lozano, Paco Lopez, Jose Moreno, Rosa Munoz, Belen Padilla, Angeles Parras, Antoni Pastor, Jose Pedreira, Julio Pristo, Jose Pena, Victor Roca, Rafael Rubio, Jose Sanchez de Rivera, Jesus Sanz, Lara Tamargo, Rafael Torres.

Sweden National Trial Coordinating Center: Pehr O. Pehrson, **Eric Sandström**.

Switzerland National Trial Coordinating Center: Enos Bernasconi, Vanina Gurtner, Lorenzo Magenta.

Thailand National Trial Coordinating Center: Chureeratana Bowonwatnuwong, Mark Boyd, Ploenchan Chetchotisakd, Thesinee Chuenyam, Chris Duncombe, Pacharee Kantipong, **Praphan Phanuphak**, Vithaya Pongsurachet, **Kiat Ruxrungtham**, Samroeng Seekaew, Surapol Suwanagool, Wichai Techasathit, Jaturaporn Wankoon.

U.K. National Trial Coordinating Center: Aderonke Adebiyi, Diana Aldam, Ian Alexander, Brian Angus, Tristan Barber, Sue Bonnington, Chris Care, Anne Carroll, David Cornforth, Oscar Donaldson, Laurance Druiff, Philippa Easterbrook, Beverley Edwards, Chris Ellis, Ikbale Erradey, Kamal El Filali, Martin Fisher, Ray Fox, **Brian Gazzard**, Allan Harrison, Sandra Herman, Lisa Heald, Christopher Higgs, Hakima Himmich, Isabelle Jendrulek, Margaret Johnson, Lucy Judges, Fatimah Karim, George Kinghorn, Julie Laurenti, Christine Lee, Clifford Leen, Ken Legg, Fiona Lyons, Raymond Maw, Alisdair MacConachie, Sinead McKernan, Lorna McLean, Andrew McMillan, Sifiso Mguni, Sheila Morris, Fiona Mulchay, Dee Mullan, Scott Mullaney, Maurice Murphy, Andrew Nunn, Edmund Ong, Maxine Owen, Adrian Palfreeman, Nicky Perry, Barry Peters, Anton Pozniak, Annette Rochford, Agnes Ronan, Cecilia Skinner, Carol Stroud, Martin Takawira, Norbert Tamm, Rachel Thomas, Thynn Thynn Yee, An Vanthuyne, Mark Wansborough-Jones, Jonathan Weber, David White, Ed Wilkins, Martin Wiselka, Ian Williams, Mike Waugh, Joyce Wotherspoon, Mike Youle.

U.S. Chicago National Trial Coordinating Center: Margaret Doyle, Edward Goodwin, **Roberta Luskin-Hawk**, James Sullivan, Rita Verheggen.

U.S. CPCRA National Trial Coordinating Center: Donald Abrams, John Baxter, Carroll Child, David Cohn, Pam Cooper, Wafaa El-Sadr, Martha Farrough, Evelyn Fisher, Luis Fuentes, Edward Goodwin, Fred Gordin, Carol Graeber, Mary Ellen Kelly, Jay Kostman, Ann Labriola, Kelly Lattanzi, Rodger MacArthur, Linda Makohon, Norman P. Markowitz, Diane Mastro-Polak, Vinnie Mitchell, David Mushatt, George Perez, Corey Rosmarin, Jack R. Rouff, Jennifer Saldanha, James Sampson, Robert Sawyer, Barbara Standridge, James Sullivan, Bentley Sweeton, Ellen Tedaldi, Melanie Thompson, Patricia Valencia, Gwen Verlinghieri, Janice Walker, Vicky Watson.

U.S. Department of Defense National Trial Coordinating Center: Adam Armstrong, Susan Banks, David Blazes, Anthony Barile, Linda Coelho, Marilyn Dennis, Hannah Flaks, Joyce Gilcrest, Kathleen Gittens, Sheila Hooper, M. J. Humphries, Katherine Spooner, Cindy L. Tamminga, Jean Vita, **Scott A. Wegner**, Glenn Wortmann.

U.S. Department of Veterans Affairs National Trial Coordinating Center: Nicole Bisby, William Blake, Sheldon Brown, Phillippe Chilliade, Teresa Cole, Katherine Elliot, Christiane Geisler, Matthew Goetz, Elizabeth Gomez-Perez, **Fred Gordin**, Jami Helman, Nancy Klimas, Ann Labriola, Ronald Nahass, Dirk LeFlore, Barbara Marston, Maria Obregon, Jennifer Petrolati, David L. Pitrak, Robert

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U.S. NIAID National Trial Coordinating Center: Rick Davey, Bill Barrick, Doreen Chaitt, Barbara Hahn, Cliff Lane, Dennis Martell, Laura McNay, Julia Metcalf, April Powers, Jorge A. Tavel.

U.S. Portland National Coordinating Center: Karen Loveless, Norma Martinez, Sue Peterson, **James Sampson,** Suzanne Sweek.

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Chiron Corporation: Greg Baigent, William Capra, Anne-Marie Duliege, Linda Fitzgerald, Marthin Kwakkelstein, Jean Maral, Mary O'Hara, David Sahner, Claire Weber.

International Drug Distribution (CTS Inc., Durham, North Carolina):
Christine Adam-Perchec, Nigel Barron, Mary Louise Bell, Sandra Dolan, Julie Eckstrand, Steven Hicks, George McAuley.

SAIC Frederick, Inc. (specimen repository): Sharon Beck, Shawn Brown, Adam Rupert.