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Design paper

The Evaluation of Subcutaneous Proleukin® (interleukin-2) in a Randomized International Trial: rationale, design, and methods of ESPRIT

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Abstract

The Evaluation of Subcutaneous Proleukin® in a Randomized International Trial (ESPRIT) is a large ongoing randomized trial of subcutaneous interleukin-2 (IL-2) plus antiretroviral therapy versus antiretroviral therapy alone in patients with HIV (human immunodeficiency virus) disease and CD4 cell counts of at least 300 cells/mm^3. The primary objective is to determine whether the addition of IL-2 to combination antiretroviral therapy improves morbidity and mortality. The aim is to recruit 4000 participants and follow them for an average of 5 years. Eligible subjects will be recruited at 275 investigational sites in 23 countries around the world. Coupled with broad eligibility criteria this will ensure widely applicable results. A range of secondary objectives will also be addressed in this setting that will include the conduct of observational studies and nested substudies with a public health focus. This article describes the rationale supporting the trial in addition to reviewing the study design, coordination, and governance.

Keywords: Interleukin-2; HIV; Clinical endpoint study

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Introduction

Much progress has been made in understanding the pathogenesis and natural history of HIV (human immunodeficiency virus) disease. Equally important advances have also been made in the treatment of HIV infection, with impressive reductions in morbidity and mortality reflecting the more widespread use of combination antiretroviral therapy where these drugs are available [1]. Several consensus statements that guide the use of combination antiretroviral therapy recommend that the optimal objective is to render plasma levels of HIV RNA undetectable and to maintain this response for as long as possible [2–4]. The majority of these recommendations are derived from research that has evaluated new therapeutic developments on the basis of changes in surrogate markers of HIV infection: principally, increases in CD4 cell count and decreases in plasma HIV RNA. This overwhelming reliance upon laboratory surrogates for a chronic disease that has an average natural history of 10 years without treatment has resulted in growing concern that treatments are being used ineffectively. Similar concerns arise from the use of surrogate markers as the primary efficacy variable for therapies in a number of other chronic illnesses, such as interferon for early-stage hepatitis C infection, calcium-channel blockers for hypertension, and lipid-lowering agents for overall mortality.

Substantial issues remain unanswered regarding combination antiretroviral therapy and the clinical strategy that guides its use. First, the treatments do not result in eradication of HIV making treatment a lifelong commitment. Second, for many patients virologic control cannot be maintained. Estimates from urban clinics indicate that as few as 40% of patients attain undetectable virus load in the first year [5]. This relatively poor response frequently arises from adherence difficulties or poor absorption. Virus replication in the presence of antiretroviral therapy increases the risk of generating drug resistance, and this not only limits the efficacy of individual drugs, but may also affect the sensitivity of the virus to other drugs in the same class. Third, immunologic responses in some patients with adequate control of HIV replication are suboptimal. Fourth, accumulating data indicate that the long-term use of combination antiretroviral therapy is often associated with profound alterations in normal metabolism [6–9], and the potential exists that these changes may be associated with increased risks of cardiovascular and liver disease, diabetes, and other morbidities.

The incomplete recovery of immune function after the initiation of combination antiretroviral therapy, particularly in patients with more advanced disease, constitutes the basis for arguing that these treatments should be introduced early in the course of disease, before significant loss of immune repertoire has occurred. This plausible hypothesis has never been examined in randomized controlled trials [10]. The use of combination antiretroviral therapy in the patient group with more recent infection presents a dilemma: Do the benefits outweigh the risks, and can a favorable response be maintained over the long term?

The capacity of recombinant interleukin-2 (IL-2) to selectively increase the CD4 cell count of individuals with HIV infection has been established in a number of phase I/II randomized controlled trials [11–21]. When used in combination with antiretroviral therapy the increases in CD4 cell count are significantly greater than those seen with antiretroviral therapy alone. Depletion of CD4 T lymphocyte numbers is the principal pathological mechanism that results in clinical immunodeficiency in HIV infection. This has raised the attractive prospect that IL-2 therapy may be used in patients with early-stage HIV disease to preserve

immunological function [22]. If this were to occur then a significant additional strategy for the treatment of HIV infection would be available. This hypothesis can be adequately evaluated only in a randomized controlled study with clinical endpoints conducted over a long period of time. Such a study would also generate substantial long-term data to describe the safety profile of IL-2 in this clinical setting.

The Evaluation of Subcutaneous Proleukin® in a Randomized International Trial (ESPRIT) tests the hypothesis that IL-2 therapy in combination with antiretroviral therapy in patients with less severe immunodeficiency (CD4 cell counts $\geqslant$300 cells/mm^3) will prevent CD4 T cell depletion and result in fewer AIDS-defining illnesses and improved survival compared to antiretroviral therapy alone. This paper describes the rationale, design, and methods of the ongoing ESPRIT study.

Study objectives

The primary objective of ESPRIT is to compare the rates of HIV disease progression, including death, over an average of 5 years of follow-up in groups of patients randomly assigned to receive IL-2 therapy or no IL-2 in addition to combination antiretroviral therapy. The primary endpoint is new or recurrent HIV disease progression or death. HIV disease progression is specifically defined as any clinical event satisfying the diagnostic criteria for AIDS-defining events [23] with the following additional diseases: extrapulmonary *Pneumocystis carinii* disease, multidermatomal herpes zoster ($\geqslant$10 lesions in a noncontiguous site), American trypanosomiasis (Chagas) of the central nervous system, *Penicillium marneffei* disease, visceral leishmaniasis, non-Hodgkin's lymphoma of any cell type, Hodgkin's lymphoma, bartonellosis, microsporidiosis ($>$1 month's duration), nocardiosis, invasive aspergillosis, and *Rhodococcus equi* disease. These additional diagnoses have been added to reflect life-threatening opportunistic infections and cancers that are encountered in the setting of HIV immunodeficiency in some of the countries that are participating in ESPRIT.

The study is designed to address a number of secondary objectives, including comparing the effects of two treatment strategies on changes in CD4 cell count and percent, plasma HIV RNA, and antiretroviral treatment changes over an average of 5 years. Secondary analyses will also assess whether the effect of IL-2 on progression to AIDS (acquired immunodeficiency syndrome) is qualitatively different for subgroups of patients defined by their location, demographics, baseline and nadir CD4 cell counts, baseline plasma HIV RNA, prior HIV-disease progression events, and the type and duration of prior antiretroviral therapy at entry. In addition, the study is designed to compare the effects of IL-2 or no IL-2 on the development of grade 4 signs and symptoms (modified National Cancer Institute guidelines) and on the development of selected hepatic, metabolic, and cardiovascular conditions.

Secondary outcome measures include serious HIV-disease progression events known to be associated with an increased risk of death and evidence of advanced immunodeficiency [24]; survival; absolute and percent CD4 cell count; plasma HIV RNA levels; changes in antiretroviral therapy; grade 4 signs and symptoms; pattern of use of opportunistic infection prophylaxes; and hepatic, metabolic, and cardiac conditions.

Trial design

ESPRIT is a multicenter, international, phase III, open-label randomized trial of IL-2 in patients with HIV-1 infection and absolute CD4 cell counts ⩾300 cells/mm^3. Additional eligibility criteria are listed in Table 1. Four thousand eligible patients will be randomly assigned to receive IL-2 or no IL-2 in equal proportions (1:1). Randomization is stratified by individual clinical site. The central coordinating facility prepares all randomization schedules. Regional coordinating centers use a computerized on-line system to issue treatment assignments. The study is open-label since it is impractical to use placebo injections and maintain blinding due to the side effects of IL-2. Recombinant subcutaneous IL-2 is to be administered at a dose of 7.5 million international units (MIU) twice daily for 5 consecutive days every 8 weeks. Administration of IL-2 is specified at three cycles in the first 6 months after randomization with flexibility thereafter. All patients must receive combination antiret-

Table 1. ESPRIT eligibility criteria

Inclusion	Exclusion
Documentation of HIV-1 infection by any licensed ELISA test and confirmed by a second method, e.g., Western Blot; or any one of the following at any time: detectable HIV p24 antigen, quantifiable plasma HIV RNA, or detectable proviral DNA	Prior IL-2 therapy
Absolute CD4 cell count ⩾300 cells/mm^3 within 45 days prior to randomization (for postsplenectomy patients, also a CD4 cell percentage >20%)	Concurrent malignancy requiring cytotoxic chemotherapy
No evidence of active clinical disease for at least 1 year, in the judgment of the clinician for any protocol-specific HIV-disease progression event	History of an AIDS-defining illness or any of the conditions listed as modified HIV-disease progression events within the last 12 months
Age ⩾18 years	Use of systemic corticosteroids, immunosuppressants, or cytotoxic agents within 45 days prior to study randomization
Laboratory values (within 45 days prior to randomization):	Any CNS abnormality that requires ongoing treatment with antiseizure medication
—AST or ALT ⩽5× ULN	Current or historical autoimmune/ inflammatory diseases including:
—Total or direct bilirubin ⩽2× ULN (patients with hyperbilirubinemia arising from Gilbert's syndrome or indinavir therapy may have serum bilirubin <5× ULN)	—Inflammatory bowel disease
—Creatinine ⩽2.0 mg/dl (177 μmol/L)	—Psoriasis
—Platelet count ⩾50,000/mm^3	—Optic neuritis
On or initiating combination antiretroviral therapy at the time of randomization. This can include approved or investigational agents administered through routine care or through clinical trials or expanded access programs	—Any autoimmune/inflammatory diseases with potentially life-threatening complications
Signed, informed consent	Pregnancy (for women of childbearing potential, a negative pregnancy test is required within 14 days of randomization)
	Breastfeeding

ELISA = enzyme-linked immunosorbent assay; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal range; CNS = central nervous system.

roviral therapy during their IL-2 treatment cycle, with the choice of therapy at the discretion of the treating clinician. Combination antiretroviral therapy is defined as a minimum of two antiretroviral drugs. Patients are to be followed for an average of 5 years (range: 4–6 years) or until 320 primary endpoints have occurred. Longer follow-up may be required. During the study, patients in the control group will not be given IL-2 if they experience a primary endpoint. If IL-2 is found to be effective in reducing the rate of HIV-disease progression, including death, all patients will be offered IL-2 at study termination.

Participants are recruited from 275 clinical sites in 23 countries from North and South America, Europe, Australia, and Asia. The 23 participating countries are: Argentina, Australia, Belgium, Canada, Denmark, France, Germany, Greece, Ireland, Israel, Italy, Japan, the Netherlands, Norway, Poland, Portugal, Singapore, Spain, Sweden, Switzerland, Thailand, the United States, and the United Kingdom.

Prior to the initiation of ESPRIT the study group performed randomized phase II trials using an identical protocol at centers in Argentina [18], Thailand [19], and Houston and another similar trial design in the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) network in the United States [20]. The ESPRIT vanguard studies were performed to assess the feasibility of the design with the intent that enrolled patients would be followed for clinical outcomes as part of ESPRIT. A total of 729 patients were enrolled in these studies. The methodology and procedures for reconsenting these trial participants for ESPRIT are the subject of a separate article [25].

IL-2 dosing

The regimen of IL-2 employed in ESPRIT has been extensively studied in a range of phase I and phase II studies. The immunopharmacologic basis of the regimen has been summarized in previous publications [11–14,17–21]. In summary, intermittent dosing based on a regimen of 5 consecutive days every 8 weeks of subcutaneous IL-2 selectively expands peripheral CD4 cell numbers. This expansion is thought to arise from the expression of the CD25 molecule by CD4 cells in the absence of cognate antigen as a step in promoting proliferation of this cell type. More detailed evaluations of cell turnover and longevity in the setting of IL-2 therapy and HIV infection are presently under way. The starting dose was selected on the basis of a number of phase II studies that revealed consistent and significant increases in CD4 cell number were attainable in the majority of patients within the first three cycles. Patients randomly assigned to the IL-2 treatment group will receive a regimen consisting of 7.5 MIU, delivered by subcutaneous injection, twice daily for 5 consecutive days every 8 weeks. Time between cycles is counted from the first day of one cycle to the first day of the next. IL-2 therapy may not be given any more frequently than every 6 weeks and, for the first three cycles, the maximum length of time between cycles should not exceed 11 weeks. After completion of the third cycle, administration of further IL-2 is to be guided on an individual basis through periodic monitoring of CD4 cell count relative to baseline. As a guide, patients who enter the study with CD4 cell counts between 300 and 500 cells/mm^3 will be encouraged to receive additional cycles of IL-2 therapy to maintain their CD4 level greater than twice baseline. Patients entering the study with CD4 cell counts $>$500 cells/mm^3 will be encouraged to receive additional cycles of therapy to maintain their CD4 cell count

>1000 cells/mm^3. All IL-2 patients who do not attain these desired CD4 cell count outcomes 1 month after completion of the third cycle will be encouraged to continue treatment with IL-2 every 8 weeks until the desired CD4 cell count outcome is attained. For patients who reach this threshold, further cycles of IL-2 therapy can be postponed until the count drops below the threshold level. Patients who do not achieve at least a 50 cell/mm^3 increase in CD4 cell count after six cycles of therapy may choose to discontinue IL-2 therapy.

Combination antiretroviral therapy during at least the 5 days during which IL-2 therapy is administered is a requirement of the ESPRIT protocol. Investigators are encouraged to use their national guidelines to determine the nature of therapy used and the strategy they employ for management of these interventions. Local or national guidelines are also recommended to direct the use of prophylaxes for opportunistic infections.

Sample size and statistical considerations

The sample size to yield the required 320 primary endpoints for the study has been estimated as 4000 patients with an average follow-up period of 5 years. The primary analysis will be intent to treat, using the stratified log-rank statistic with strata defined by the participating international group. A number of assumptions were made in the calculation of sample size.

The first assumption was that IL-2 therapy would result in a 50% reduction in the rate of HIV-disease progression or death among fully compliant patients. The rationale for this estimate is based upon a number of data sources. Previous studies of IL-2 therapy in similar patient populations indicate that in ESPRIT, recipients of IL-2 will experience a 200–300 cells/mm^3 greater CD4 cell count increase than recipients of combination antiretroviral therapy alone [11–21]. A CD4 cell count difference of this magnitude is estimated to be associated with a 60–80% difference in the risk of HIV-disease progression (Abdel Babiker, personal communication; Jens Lundgren, personal communication) [26]. In a pooled analysis of randomized phase II trials of IL-2 therapy with follow-up extending to 2.5 years, the hazard ratio for the risk of disease progression to AIDS or death was 0.60 (95% CI: 0.30 to 1.19). This difference in clinical outcome was associated with an average difference in CD4 cell count of 215 cells/mm^3 [27].

The next assumption is that HIV-disease progression events will account for 80% of primary endpoints. The remaining events will be deaths. It is assumed that 50% of deaths will be unrelated to HIV disease and treatment, thus reducing the expected treatment difference from 50% to 45% among fully compliant patients.

It is not anticipated that all patients will be fully compliant, and therefore the desired effect of therapy on CD4 cell count will not be realized. Accordingly, the sample size estimate has been increased to preserve power. We have assumed that because of variability in compliance, only 50% of IL-2 recipients will experience the full benefit of treatment, 25% will experience partial benefit, and 25% will experience no benefit. Combining these assumptions yields a reduction in the expected rate of HIV-disease progression from 45% to 28%. It was also assumed that IL-2 use among the no-IL-2 treatment group in ESPRIT would be negligible in most countries. In the United States (25% of the overall cohort) we have included a correction that assumes that some 25% of the no-IL-2 group will use some IL-2 during follow-up. As a consequence of this assumption the hypothesized treatment difference

for the study primary endpoint is further reduced from 28% to 27%. This estimated treatment effect and a type I error of 0.05 (two-sided) and a type II error of 0.20 (power=0.80) determined the required number of primary events.

The estimated cumulative clinical event rate in the control arm is 10%. Estimates of clinical event rates for this patient population were derived from a number of data sources [26–34]. All these data are consistent in indicating that only a small percentage of clinical events will occur during the first 2 years of the study and that the annual risk of AIDS/death increases markedly with increasing follow-up. Data from published studies of HIV protease inhibitor treatment in patients with more advanced HIV disease indicate that cumulative 5-year event rates in the no-IL-2 treatment arm of ESPRIT will be as high as 12.5% [33,34]. Observational data from the EuroSIDA cohort are consistent with this estimate indicating an annual event rate of 1.3 cases per 100 patient-years (Jens Lundgren, personal communication). It is unclear how the clinical event rates will change in the lifetime of ESPRIT, but we have assumed that there will be some increase as a consequence of the failure rate being reported for patients treated with HIV protease inhibitors. An increase in the annual event rate to 2.6% for years 3–5 would result in a cumulative event rate of 10% for the entire study. While most of the data used to make estimates of clinical event rate reflect cohorts of patients in North America, Australia, and Europe, less information is available for patients with early HIV disease in other participating countries. While these other countries will contribute 15% of the ESPRIT cohort, there are data indicating that the rates and patterns of events are not likely to be substantially different (Laura Astaraloa, personal communication) [35–49].

Patients will be enrolled over a 2-year period and followed for a minimum of 4 years. Average follow-up will be 5 years and will range from 4 to 6 years. It is unreasonable to assume that there will be no losses to follow-up (patients for whom the endpoint status is unknown) in a trial of this duration. The results of the trial could be seriously biased if the losses to follow-up are associated with the development of HIV-disease progression. With a relatively low anticipated event rate, losses must be kept to an absolute minimum. If losses occur and are uninformative, treatment comparisons will not be biased, but there will be loss of power. To maintain power the sample size for ESPRIT has been increased. Table 2 summarizes study sample-size estimates for several scenarios based upon different cumulative 5-year event rates and annual losses to follow-up (to preserve 80% power to detect a 27% reduction in study primary endpoint between treatment groups). Considerable effort has been focused upon developing methodologies at all sites to maintain contact with all randomized patients. This includes obtaining contact details for relatives and access to social security numbers and other unique identifiers for contact tracing if necessary. We intend to follow all patients for at least primary endpoint variables irrespective of their adherence to assigned therapy in the trial.

Based upon these estimates a sample size of 4000 patients (2000 assigned to IL-2 and 2000 assigned to no IL-2) followed for an average of 5 years will be the goal. The sample size and follow-up period are projected to yield the required 320 endpoints for the study [40].

Time-to-event methods [41] including stratified proportional hazard models, log-rank tests, and Kaplan–Meier cumulative event curves will be used to summarize the major outcomes of HIV-disease progression including death, serious HIV-disease progression including death, and survival. These analyses will be stratified by participating international group.

Table 2. Sensitivity of sample size to assumptions concerning control group event rate and losses to follow-up

% Losses to follow-up per year (cumulative %)	Sample size		
	Cumulative event rate after 5 years (%) in the control group		
	7.5	10	12.5
0	4700	3530	2820
2 (10)	5070	3800	3040
3 (15)	5280	3960	3160

A major focus of secondary analyses will be the identification of additional surrogate markers for HIV-disease progression. These will take the form of nested case-control studies on plasma and sera samples that are taken at annual time points from all participants. In these studies, samples from patients who experience HIV-disease progression will be evaluated for a range of laboratory parameters. This validation process requires the conduct of clinical endpoint trials like ESPRIT. For patients developing HIV-disease progression, proximal CD4 cell count and plasma HIV RNA data will be summarized. In addition, Cox models with CD4 cell counts and plasma HIV RNA levels as time-dependent covariates will be used to summarize the association of changes in these markers with HIV-disease progression events [43,44].

Extensive descriptive and analytic observational analyses are planned for patients in the no-IL-2 treatment group, reflecting the unique geographical and cultural opportunity presented in ESPRIT.

Study evaluations and data collection

All patients will be followed until a common closing date irrespective of the continued use of IL-2. All patients will have baseline and enrollment data recorded at the time of randomization. All clinical centers use identical case record forms (CRFs) in English, although some procedural documentation has been translated into local languages. There is a single study database located in Minnesota.

Patients in both treatment groups will be seen every 4 months (± 2 months) for routine follow-up consisting of a targeted history and clinical evaluation, concomitant treatments including antiretroviral therapy changes, absolute and percent CD4 cell count (and any interim values), plasma HIV RNA levels (using the locally available assays), and documentation of all interim results. Annual visits will require the collection of slightly more intensive data, focusing on a targeted history and clinical examination with review of viral hepatitis status.

For IL-2-treated patients, the following additional information will also be collected every 4 months for each IL-2 treatment cycle initiated: toxicities resulting in dose reduction or cycle interruption, assessment of adherence to daily injections, most recent CD4 cell count prior to initiation of IL-2 cycle, and negative pregnancy test for women of childbearing potential within 14 days of the start of the cycle.

In addition to routine scheduled follow-up, the following events are to be reported as soon as the clinical site is aware of the event: HIV-disease progression, including detailed diagnostic documentation; grade 4 events (signs and symptoms), including details of IL-2 ther-

apy use where appropriate; serious adverse experiences (IL-2 treatment group only), which will be reported in fulfillment of reporting requirements of the U.S. Food and Drug Administration; and death. Serious adverse experiences need only be reported during or within 8 weeks of the most recent treatment with IL-2.

At baseline all patients are required to provide whole blood from which plasma, sera, and buffy coats are prepared for central storage at a single repository. These materials will be used for future virologic and immunologic research. Plasma will be obtained from all patients on an annual basis throughout the study.

For a subsample of 1500 patients, peripheral blood mononuclear cells will be viably cryopreserved at baseline and at yearly intervals thereafter for future virologic and immunologic research.

Organizational structure and governance

A trial of this size has required considerable focus on organizational structure and governance. This focus has developed over a period of years during which the study evolved. An academic group prepared a concept for the study in mid-1996. Over the next 18 months this group held a number of meetings at which the concept was refined through discussions with a large number of international colleagues representing most of the countries that now participate in the trial. The investigators who prepared the initial concept formed an executive committee (EC) that represents the interests of the larger international group that serves as an international steering committee (ISC). The establishment of these two central bodies was completed in January 1998, and shortly thereafter an unsolicited grant was submitted to the U.S. National Institutes of Health (NIH) through the National Institute of Allergy and Infectious Diseases (NIAID). The grant received initial review in July 1998 and was resubmitted in revised format in November 1998. Following a second review in March 1999 the grant was awarded to the University of Minnesota in September 1999.

The EC meets face to face at least three times per year and holds fortnightly conference calls. It is responsible for the day-to-day management of the trial and for preparation and planning of ISC meetings. The ISC, which is composed of the EC, national principal investigators, representatives of NIAID and Chiron Corporation, and community representatives, meets at least twice yearly. The EC is responsible for communications with the Data and Safety Monitoring Board (DSMB) convened by NIAID.

Logistically, the study is organized around a single, central coordinating center at the University of Minnesota, where all study materials are prepared and released (Fig. 1). The Minnesota center is also responsible for communications with the endpoint review committee (ERC), who will review all HIV-disease progression events that occur during the trial. The Minnesota Center liaises with four regional coordinating centers (RCCs) based in Copenhagen, London, Minneapolis, and Sydney. In turn, each of these RCCs is responsible for the management of ESPRIT in a number of countries or sites within their respective regions. Participating countries are organized with national trial coordinating centers (NTCCs) that for the most part are the focus for trial-related activities among national groups of investigational sites. NTCCs are either established centers of excellence in the conduct of clinical trials in HIV medicine or academic centers at which the national principal investigator is located.

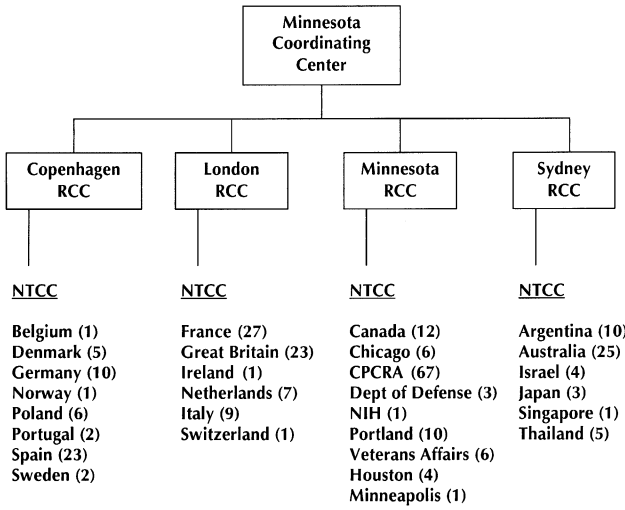

Fig. 1. ESPRIT coordination (numbers in parentheses are numbers of sites in each NTCC; RCC = regional coordinating center, NTCC = national trial coordinating center).

All members of the EC and the clinical investigators participating in ESPRIT are blinded to interim treatment differences in clinical outcome as well as surrogate markers. Two statisticians, one at the Minneapolis RCC and one at the London RCC, prepare interim analyses for the DSMB and participate in closed sessions of that group. Members of the EC attend the open session of DSMB meetings. During the open session, the EC addresses questions about trial conduct, including enrollment, losses to follow-up, and protocol adherence. The operating procedures of the NIAID DSMB have been previously described [44].

This structure is designed to ensure the timely and consistent transfer of information and materials between sites and their representative groups at a national, regional, and central level. The process is enhanced through the use of a study-specific, password-protected website that contains a great deal of study-related information and downloadable materials [45]. This website provides immediate access to authorized users to virtually all study documentation, updated recruitment statistics (including basic demography of the randomized cohort), follow-up statistics, details of the participant sites, and records of the complex regulatory process for site and protocol registration. A public website is also available that provides universal access to trial and site-specific information to potential participants and referring practitioners [46].

Site monitoring is scheduled to occur at least annually and will be conducted by staff from each NTCC to ensure familiarity with language and local culture. It is also expected that staff from each RCC will visit all participant sites in their region on an annual basis. Staff from NIAID will perform independent audits of all sites at least once during the conduct of the study.

Data collection and transmission

CRFs have been prepared and distributed to all sites. Sites are encouraged to submit all completed CRF pages as soon as all information has become available and all internal qual-

ity assurance checks have been completed. This approach encourages accuracy and currency. Two systems have evolved to allow for the transmission of CRF data. The first is direct transmission by fax of CRF pages to the Minnesota coordinating center, where CRF data are then keyed by double data entry and subjected to computer interrogation for validity checks. Queries arising from the data-entry process are then returned to sites from the coordinating center with copies to the respective NTCC so that staff can assist as required with query resolution. The second model involves sites transmitting their completed CRF pages to the NTCC in the first instance before transmission onward to the Minnesota coordinating center for data entry and validity checking. Resulting queries are again sent to sites directly with copies to the NTCC and respective RCC group. The latter process is likely to yield greater pre-entry accuracy since there are more review steps with an expected penalty of extended turnaround of data between sites and the database.

The key performance indicators are accuracy and currency of data. The majority of site payments are linked to receipt by the Minnesota coordinating center of completed CRF pages.

Data monitoring

An endpoint review committee (ERC) has been formed with responsibility for review of all HIV-disease progression events that occur during the conduct of the study. The ERC will ensure that site-reported events are sufficiently robust diagnoses when measured against established criteria for confirmed or possible diagnosis. The ERC will be blinded to treatment assignment during their review. A trained health-care professional on staff at the Minnesota RCC will assess initial reports. Two members of the ERC will review all events, and the certainty of the report will be rated as probable or definite. Any disagreement will be adjudicated through other members of the ERC.

The independent DSMB will meet twice each year to review interim analyses. O'Brien–Fleming boundaries [47] and the Lan–DeMets spending function [48] will be used as monitoring guidelines for the primary endpoint comparisons. The DSMB will also consider results from other studies and recommend early termination or modification of ESPRIT only when there is clear and substantial evidence of benefit or harm. The EC or DSMB may consider early termination of the trial for reasons of poor accrual, less than anticipated CD4 cell count differences between treatment groups, or excessive loss to follow-up.

Financial arrangements

The primary award was made by the NIH to the University of Minnesota. The University of Minnesota in consultation with RCC and NTCC principal investigators and their colleagues developed algorithms for the dispersal of monies for ESPRIT-related activities. Two types of subcontracts exist between the University of Minnesota and other participant groups: one with RCC groups and one with NTCC groups. The former is based primarily on the role of the RCC groups in site coordination, reflecting site numbers. The latter is focused primarily upon costs for patient-care activities as described in the protocol and is based upon projected recruitment numbers. All contracts have been simplified with uniform reimbursement rates across all countries.

Study drug distribution

The distribution of study drug to 275 clinical sites in 23 countries with adherence to regulatory requirements and the need for temperature control during transport and site storage was identified as an area requiring specialist advice and infrastructure. The EC issued a request for application (RFA) to a number of contract research organizations. The contract was awarded 6 months after the RFA issue date. Study drug is distributed from two centers (one in the United States and one in Europe) that receive supplies from the manufacturer. From these centers, IL-2 is distributed directly to participant sites in North America and Europe. In Argentina, Australia, Israel, Japan, and Thailand the study drug is forwarded to a single clinical pharmacy under the control of the NTCC principal investigator. Using uniform guidelines the local NTCC group then undertakes distribution of study drug to participating sites. These different approaches reflect the different requirements for importation in these countries.

Substudies

Given the enormous amount of data that will be collected in this large cohort of patients over a long period of time from geographically and culturally different settings, ESPRIT provides a unique opportunity to conduct investigational protocols with public health implications or additional biomedical relevance to HIV disease in substudies. The EC also realized that there would be considerable interest among participating investigators in conducting research on a smaller scale reflecting their particular areas of academic interest. There are two types of substudies in ESPRIT: RCC-coordinated studies and investigator-driven ancillary studies. The EC determines into which category of effort a proposal is placed. In addition, it is anticipated that the vast repository of plasma, sera, leukocytes, and viably cryopreserved peripheral blood mononuclear cells that are to be derived from trial participants will be of some importance in identifying possible surrogates for an immunologic therapy in HIV disease.

RCC-coordinated substudies can be initiated by any ESPRIT study group member who then develops a proposal that is reviewed by the EC. A steering committee is then formed. The infrastructure to support the conduct of the substudy is provided by the parent trial as far as is possible. Selected datasets from the main database will be made available to the substudy steering committee. Staff from the designated RCC groups will perform all the implementation and coordination of the study and analysis.

Investigator-driven ancillary studies are conducted by one or more investigators, usually in close proximity, and are designed to include relatively few participants. The EC reviews the protocol to ensure that conduct of the substudy would not interfere with the parent study and reserves the right to veto the initiation of the substudy. These substudies will not automatically have access to the main database, and RCC staff will not routinely provide assistance for the conduct of the research.

At this time a number of RCC-coordinated substudies are implemented or close to implementation. The first examines, in two separate protocols, the serological responses of ESPRIT patients in either treatment arm to vaccination with either influenza vaccine or tetanus and pneumococcus vaccines. In both studies, the basis of the investigation is to determine whether IL-2 results in quantitatively different serological responses to routine vaccinations that are known to generate impoverished antibody titers in most individuals with HIV infection.

Substudies examining the evolution of lipodystrophy syndrome in the setting of ESPRIT patients and also whether IL-2 results in different outcomes for the management of hepatitis B or C/HIV-coinfected individuals have been developed. Both these are significant issues in the clinical management of HIV infection, and ESPRIT provides an ideal opportunity to examine these questions in a large international, randomized trial of IL-2 therapy.

In a further reflection of the unique features of ESPRIT, a substudy of ethical issues associated with the conduct of clinical trials outside the United States is being performed with partial sponsorship through the NIH. This study will require the conduct of telephone interviews with chairs of institutional review boards and research ethics committees who have reviewed and approved the trial and who have been required to obtain cooperative project assurance accreditation from the U.S. Office of Protection of Research Subjects Risk (OPRR) for their institution. The substudy will also interview a substantial number of site investigators and trial participants from all 23 countries.

Discussion

The research environment in which ESPRIT was established reflects an improved understanding of HIV pathogenesis and more frequent use of combination antiretroviral therapies earlier during HIV disease, although this paradigm is again changing [49]. For the most part studies of antiretroviral therapies have focused upon short-term virologic outcomes and largely ignored the need to establish unequivocally that expensive, toxic, and noncurative therapies and treatment strategies make a difference to clinical outcome. IL-2 is a chemical messenger of the immune system that can induce substantial increases in CD4 cell count and therefore might have the capacity to delay further the development of immunodeficiency in individuals with HIV disease. IL-2 therapy is associated with side effects, some of which may be treatment limiting, and the long-term impact of IL-2 upon virologic measures is unknown. In the absence of laboratory surrogates that unequivocally demonstrate that the expanded CD4 population arising from the use of IL-2 therapy is immunologically competent, the only way to establish the impact of IL-2 on HIV disease is through the conduct of a randomized, clinical endpoint study. In patients with largely asymptomatic HIV disease in whom HIV-disease progression event rates are low, such a trial presents significant challenges to design and implementation.

IL-2 therapy results in a number of side effects that, over the short term at least, have been well described [14,15,17–21]. The majority of these side effects reflect constitutional symptoms and signs such as fever, headache, malaise, arthralgia, myalgia, nausea, vomiting, and diarrhea. These are self-limiting toxicities that resolve with cessation of the therapy and can be readily managed with a clinical strategy of prophylactic medications and dose reduction. Other side effects arise as a consequence of the induction of capillary leak resulting in third spacing of body fluids that can result in edema and weight gain. Careful monitoring of fluid intake and urinary output is required with prompt cessation of IL-2 therapy necessary when evidence of poor renal output is encountered. IL-2 therapy is associated with often marked neuropsychological changes such as depression, lability, and confusion. The long-term side-effect profile of IL-2 therapy is not known, and ESPRIT will generate substantial data in this

regard. Regular reviews of interim data by the DSMB are of critical importance in ensuring the safety of trial participants in light of incident side effects. This review will extend to monitoring plasma HIV RNA load to ensure that the long-term impact of IL-2 therapy is not deleterious to trial participants.

ESPRIT tests the hypothesis that IL-2 can preserve immune function in individuals with HIV infection if it is given before they are at significant risk from the opportunistic diseases and cancers that are hallmarks of advanced immunodeficiency and AIDS. ESPRIT allows recruitment of individuals with nadir CD4 cell counts <300 cells/mm^3 provided that they have subsequently experienced an increase above this level as a result of antiretroviral therapy. A CD4 cell count threshold of 300 cells/mm^3 was selected as being the limit above which HIV-disease progression events are not normally expected to occur. It was also selected since preliminary data had indicated that at this level there was an excellent responsiveness in terms of CD4 cell count increase [14]. By setting a goal for CD4 cell count at twice baseline or >1000 cells/mm^3 the study is designed to assess whether maintenance of these levels of CD4 cell count prevents morbidity and mortality. The alternative question that could be asked about IL-2 therapy in HIV disease is whether individuals with already significant immunodeficiency could experience clinical benefit through expansion of their CD4 cell count. This question is being addressed in another clinical trial (SILCAAT) that is recruiting HIV-infected patients with CD4 cell counts of 50–299 cells/mm^3 at entry.

ESPRIT was not designed with an eligibility criterion based upon plasma HIV RNA since in the proposed patient population there are no data suggesting, at least in the short term, that HIV viral load changes following administration of IL-2. ESPRIT initially excluded patients with prior AIDS-defining illnesses (including the expanded protocol definition of disease progression events). This decision was reached on the basis that the loss of immune function was of such severity that IL-2 might not reasonably be expected to restore those elements lost prior to the development of AIDS. In light of recent data that indicate that clinically significant immunoreconstitution may be possible under the influence of antiretroviral therapy a decision was made to extend ESPRIT recruitment to patients with prior AIDS-defining illnesses who have CD4 cell counts of $\geqslant 300$ cells/mm^3. Importantly, in these patients it is known that some prophylactic medications can be withdrawn and the risk of opportunistic diseases is no different from those individuals with no prior AIDS-defining illness [50–52]. However, to be eligible for ESPRIT patients are required not to have had any AIDS-defining illness or HIV-disease progression event for at least 12 months.

For the funding agency involved, ESPRIT represents a significant investment at a time when there is considerable uncertainty about the feasibility of such a study. This uncertainty is driven primarily by the relative paucity of clinical events in optimally treated HIV-infected individuals. There is growing concern, however, that the benefits of antiretroviral therapy may be only transient and new approaches to treatment are needed. We should also be mindful of the need for therapies that can be delivered in countries of the developing world where HIV/AIDS continues to cause significant morbidity, mortality, and social problems largely because expensive antiretroviral therapy cannot be delivered. It might be that simple and accessible regimens of antiretroviral therapy, or even intermittent antiretroviral therapy, in combination with infrequent IL-2 therapy could offer an attractive alternative to complex multidrug regimens of antiretroviral therapy alone.

By engaging a large international group of 23 countries recruiting from 275 clinical sites we believe that ESPRIT has the capacity to recruit sufficient patients while representing broad geographical and cultural settings. By employing widely applicable eligibility criteria with minimal exclusions and flexible approaches to IL-2 dosing and management of combination antiretroviral therapies, some of the difficulties associated with recruitment and retention of patients in HIV clinical trials have been addressed. By restricting the frequency and content of routine follow-up to an absolute minimum and attempting to reflect routine clinical care as closely as possible ESPRIT avoids an overwhelming responsibility being placed upon patients and site personnel that would be burdensome over the projected average 5 years of follow-up. We are aware of the importance of maintaining adequate follow-up of patients who are randomized in ESPRIT and have invested significantly in the development of systems to facilitate this requirement. Specifically, we have invested substantially in training for each RCC, NTCC, and all site personnel. This is delivered at the RCC level by a central training faculty employing a train-the-trainer approach. In this way we have ensured that information given to all study teams is consistent across the many different organizations and groups who are involved in ESPRIT. The training faculty is also responsible for updating training materials to accommodate the variable start-up of NTCC and site activities.

ESPRIT was funded in September 1999, at which time participant sites commenced preparation of regulatory paperwork required for the investigational new drug application and also by OPRR at the U.S. Department of Health and Human Services. This process has proven to be very challenging and has delayed the commencement of recruitment at the majority of sites. The requirement for an additional layer of regulatory requirements in addition to those that are necessary in each national group has clearly proven difficult to organize and complete in a timely fashion. Also troublesome to expediting the approval of the study was the absence of a single agency that was prepared to provide participant sites with indemnity. After discussion this was resolved by Chiron Corporation allowing the research group to use their existing insurance arrangements to provide the necessary cover. The initial recruitment period is 2 years commencing 2 months after the date of funding, and this remains the target. Enrollment actually began in March 2000 after a 5-month planning and training period. These experiences should help guide future endeavors of a similar nature. In a little over a year, some 258 of the 275 sites have completed the required regulatory requirements to reconsent vanguard patients and/or enroll new patients. Cumulative figures for site and patient recruitment are shown in Fig. 2. Recruitment at the end of July 2001 stood at 1850 patients (comprising 638 from the vanguard studies and 1212 as new enrollments). As of August 2001 four of the original vanguard sites had not yet obtained reconsent for $\geqslant$90% of their vanguard cohorts [25]. As such, 91 (from a total of 729) vanguard study patients will not contribute to the overall study total in terms of the primary endpoint. Baseline characteristics of the trial cohort are summarized in Table 3.

For patients with HIV infection, ESPRIT also represents significant challenges. The study does require a long-term commitment at a time of considerable uncertainty. Patients also have to address the issue of randomization in this study, which results in 50% not getting IL-2. ESPRIT does not provide IL-2 on a compassionate basis to patients in the control arm who experience a disease progression event during the trial. This is particularly troubling to many. There are no data to indicate that this potentially toxic drug affects progression of HIV disease. If

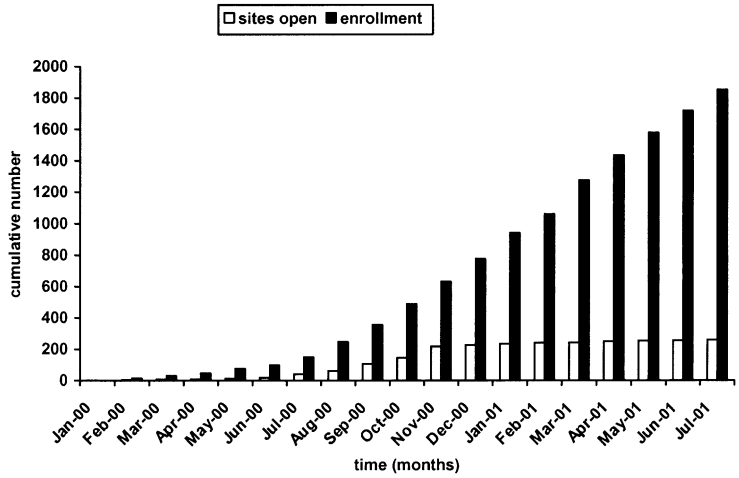

Fig. 2. Cumulative number of sites open for recruitment and cumulative patient recruitment (as of July 31, 2001).

such information existed, then the trial would be unnecessary. There is therefore no rationale to support the provision of open-label IL-2 to patients with progression of disease. If new data from other trials come to light indicating that such benefit is reasonably likely in a patient group with significant immunodeficiency, then this stipulation may be changed. Similarly, the ESPRIT study is subject to twice-yearly interim analyses with independent DSMB review that will include a review of data from other studies of IL-2 therapy. As soon as ESPRIT, or any other study of IL-2 therapy, has confirmed the role of IL-2 a decision can be made about open-label provision of IL-2 to all involved. Notwithstanding these provisions it should be clear that participation in any clinical trial is in part an act of altruism with no immediate benefit, particularly to control patients, and with potential risks, particularly to IL-2 patients.

Table 3. Baseline characteristics[a] of the ESPRIT cohort as of July 31, 2001

	Regional Coordinating Center				
Parameter	Copenhagen	London	Minnesota	Sydney	Total
Number of patients	154	273	764	494	1685
Median CD4 cell count (mm^3)	450	465	529	460	489
Median nadir CD4 cell count (mm^3)	191	185	285	254	248
HIV RNA (% undetectable)	60	62	64	56	61
Mean age (years)	42.7	41.7	41.4	37.6	40.4
Female (%)	9.1	13.9	10.5	33.8	17.7
Ethnicity					
% Asian	0.6	1.5	0.7	34.9	10.9
% Black	5.8	4.4	19.5	1.9	10.5
%White	93.5	92.3	70.1	60.7	73.3
% Other	0.0	1.8	9.7	2.5	5.3

[a]For those patients with baseline data submitted.

The ESPRIT study group believes that larger, long-term randomized trials are needed in HIV medicine and that there is a critical need to engage more investigators in these efforts. International networks have the potential to establish the necessary infrastructure and enhance the science. In addition to addressing an important clinical question, we believe that the ESPRIT study will be a model for the development of such international networks.

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Appendix: ESPRIT study group

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