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Design paper

An open-label randomized clinical trial of novel therapeutic strategies for HIV-infected patients in whom antiretroviral therapy has failed: rationale and design of the OPTIMA Trial

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Abstract

OPTIMA (**OPT**ions **I**n **M**anagement with **A**ntiretrovirals) is a clinical trial with a factorial randomization to evaluate the hypotheses that *mega-antiretroviral therapy (ART) consisting of five or more anti-HIV drugs* compared to *standard-ART consisting of four or fewer anti-HIV drugs* and a *3-month antiretroviral drug-free period (ARDFP)* compared to *no ARDFP* will delay the occurrence of new or recurrent acquired immunodeficiency syndrome events or death, and prove to be more cost-effective in treating human immunodeficiency virus-infected individuals previously exposed to ART drugs from the current three main classes. The aim is to randomize 1700 participants to four treatment

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strategy arms: (1) *ARDFP + standard-ART*; (2) *ARDFP + mega-ART*; (3) *no ARDFP + standard-ART*; (4) *no ARDFP + mega-ART*. The planned study duration is 3.5 years with 2.5 years of intake and a minimum 1 year of follow-up. The OPTIMA Trial was initiated in June 2001 at 30 U.S. Department of Veterans' Affairs hospitals, 22 hospitals in Canada, and 25 hospitals in the United Kingdom. This is the first large-scale, multicenter, randomized controlled trial to compare the relative efficacy of these different therapeutic strategies. We discuss the rationale behind the OPTIMA Trial design as well as the issues arising from the conduct of a trial that involves three national clinical trial agencies. © 2003 Elsevier Inc. All rights reserved.

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Introduction and background

Combination antiretroviral drug treatment regimens, commonly referred to as highly active antiretroviral therapy (HAART), have resulted in a substantial decrease in the incidence of acquired immunodeficiency syndrome (AIDS) and death in persons with human immunodeficiency virus (HIV) infection [1–3].

The duration of response to these antiretroviral regimens is usually limited by either the emergence of viral resistance or the development of toxicity, and there is increasing evidence from clinical practice that standard therapy fails a significant proportion of patients [4]. Furthermore, subsequent treatment options are narrowed by the problem of drug resistance, which is further complicated by the existence of variable levels of cross-resistance within each of the three main classes of antiretroviral drugs [5,6]. An effective virologic and immunologic response in retreatment may be elicited by changing as many drugs of the combination as possible, particularly if a new class of drug is used and if the virologic breakthrough is of lower degree or shorter duration. In practice, unfortunately, the response to switching therapy to three or four new drugs after failure on the first treatment is often transient. Once a prolonged and significant virologic failure occurs on two different HAART regimens that have included all three classes of drugs, few obvious treatment options are available, uncertainty as to the best choice exists, and the optimal management of such patients remains unclear. The clinical dilemma posed in selecting treatments for patients facing this situation is the focus of the Options In Management with Antiretrovirals (OPTIMA) Trial.

Two novel approaches have been recently tried in patients for whom first- and second-line HAART regimens have failed: (1) a strategy of *mega-antiretroviral therapy (ART)* comprised of five or nine drugs) [7,8] and (2) a temporary cessation of antiretroviral therapy (known variously as “*drug-free period*”, “*drug holiday*”, or “*structured treatment interruption*”) [9–11].

The first question addressed by the OPTIMA Trial is whether there is a difference in effectiveness between mega-ART and standard-ART regimens. Mega-ART is an experimental treatment strategy that has met at least some success as defined by virologic response. Virologic response to therapy has been validated on efficacy in initial treatment studies, with less cumulative toxicity, fewer drugs and less acute toxicity, and more sensitive HIV than in salvage therapy, with more cumulative toxicity of past treatments, more drugs and more

acute toxicities, and less sensitive HIV. As efficacy is related to both anti-HIV activity and toxicity of treatment, past validation of surrogate markers of activity are likely to be not as valid in this context. Essentially, the strategy is to treat with as many antiretroviral drugs as possible (defined in this study as five or more) and maintain them for as long as possible. Associated toxicity, though frequent, is manageable in many patients by supportive medication or drug substitution [7–9]. There are no mega-ART randomized controlled trials with clinical endpoints.

The second question addressed by the proposed trial is the clinical utility of a 3-month antiretroviral drug-free period (ARDFP). The potential value of an ARDFP, in the presence of multidrug resistance, is not only the respite from pill taking, reduced drug-related toxicity, and improved quality of life, (QOL) but also the possibility that the antiretroviral activity and efficacy of a subsequent HAART regimen may be improved relative to such a regimen initiated without an interruption. In one small study, in the absence of pressure from drugs, most of the resistant virus population returned to wild-type and was thus sensitive to drugs reintroduced after the ARDFP [12]. Whether the rebound viremia and partial reversion to wild-type, sensitive HIV is offset by relief of drug toxicity and subsequent response to retreatment is unknown. Enhanced virologic response to mega-ART has been observed in patients with at least 1 month of ARDFP in spite of an expected fall in CD4 counts during the ARDFP [13,14]. In addition, it is possible that a temporary ARDFP may provide the patient with an improved QOL without seriously affecting long-term survival or may improve survival even with a standard-ART regimen because the patient is better able to tolerate the new therapy. The concept of treatment interruptions has been supported by Department of Health and Human Services therapeutic guidelines, which state “For patients with no rational alternative options who have virologic failure with return of viral load to baseline (pre-treatment levels) and declining CD4 T-cell count, there should be consideration for discontinuation of antiretroviral therapy” [15]. The optimum duration of an ARDFP, however, is not known.

Objectives and hypotheses

The OPTIMA Trial aims to evaluate the clinical effect of (1) mega-ART compared to standard-ART and (2) a 3-month ARDFP compared to no ARDFP in the management of patients for whom previous HAART therapy has failed. The impact of mega-ART and ARDFP on costs of treatment for the patients and quality-adjusted life years (QALY) will also be determined; lifetime costs and outcomes will be modeled to determine the cost-effectiveness of these strategies.

Study design

The 2 × 2 open-label randomized study design (Fig. 1) provides the advantage of simultaneously assessing two novel HIV/AIDS treatment strategies: ARDFP and mega-ART. Further, the use of multiple settings in different “therapeutic cultures” will allow for generalizability

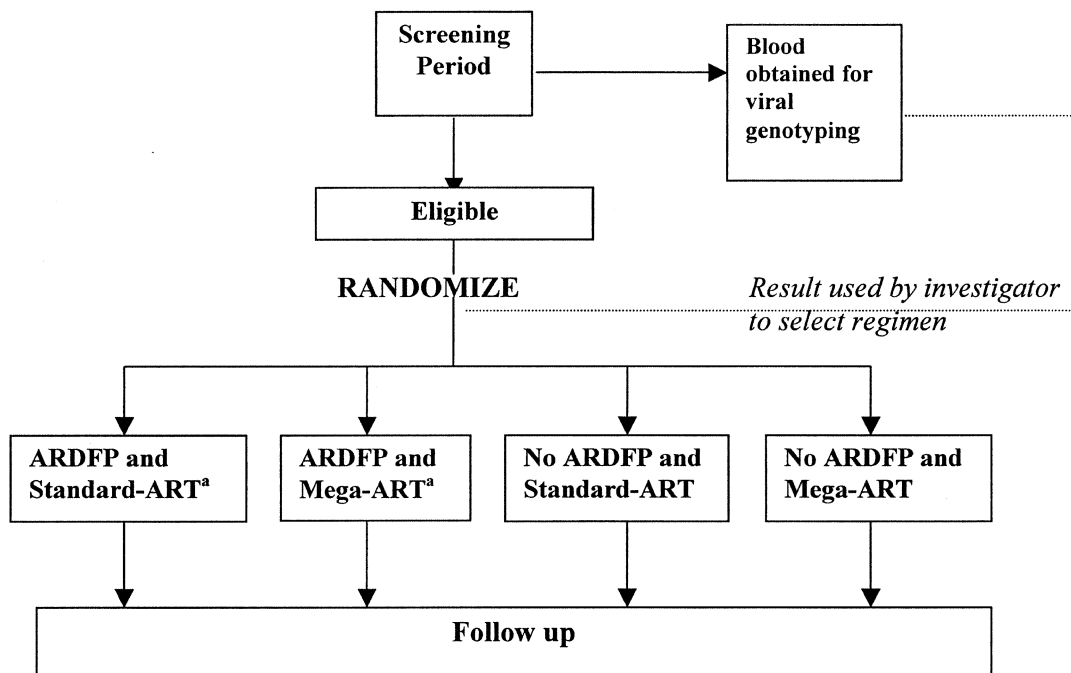


Fig. 1. Schematic for OPTIMA Trial. ^aThe assignment to standard-ART or mega-ART is released at the end of the ARDFP.

of the findings and provide evidence that will facilitate management of HIV disease in this group of patients.

The urgent need for clinically relevant guidance for managing HIV disease in patients with immunologically advanced disease justifies the OPTIMA Trial. Patients with CD4 counts under 300 cells/mm³ who have exhausted effective therapeutic options are the focus of this trial because they are at greatest risk for clinical progression and are least likely to benefit from a strategy of waiting for newer, more effective treatments to become available. OPTIMA seeks evidence for the best clinical strategy for these patients among approaches that are becoming commonly employed by clinicians.

The study design includes randomization to an ARDFP of an intended 3-month duration. This particular length of ARDFP was chosen for several reasons. Accumulating evidence indicates that the time for reversion to predominance of wild-type virus is about 10 weeks. Further, there is preliminary evidence that return of viral fitness takes slightly longer [12]. While some patients may remain clinically stable off ART for longer periods, there are legitimate safety concerns raised by mandating a longer ARDFP. Given available knowledge, a 3-month or longer ARDFP appears most likely to accrue the desired benefits in QOL and viral transformation without introducing unjustifiable risk to patients.

Even though blinded studies might be generally preferable, an open-label design was selected for several reasons:

1. The logistics of blinding regimens involving several of 17 currently available antiretroviral medications would be extremely complex.

2. Blinded clinicians would be unable to make necessary adjustments for the numerous and varied drug interactions that might occur with different regimens.
3. Blinding would subject patients randomized to standard-ART to an artifactual pill schedule and excess pill burden that could obscure the differential impact of the approaches on adherence and on QOL.

However, given an unblinded study, there is a legitimate concern about detection bias. To mitigate against this, objective clinical endpoints of death, AIDS events, and major adverse events are used and will be adjudicated by a blinded endpoint review committee. Differential intensity of investigation between unblinded arms could still give rise to detection bias.

Fortunately, the study outcomes are sufficiently acute that they will declare themselves within a short time of clinical onset even if missed at a research visit where earlier detection might have occurred. Most events are likely to be diagnosed between scheduled study visits and captured during follow-up. However, to minimize any residual detection bias, the standardized follow-up examination/diagnostic schedule across all arms of the study will be used to uncover those endpoints that may not yet have become overt.

Choice of endpoints

The selection of firm clinical criteria as primary endpoints for OPTIMA ensures that the results of the trial will have practical significance for patients and clinicians. Mortality and new or recurrent AIDS events were chosen as the primary endpoints.

An increase in the frequency of recurrence of AIDS events is anticipated as an important consequence of antiretroviral treatment that is failing and may be an important safety indicator for evaluation of the drug-free period. Differences in frequency of recurrence of clinical manifestations of AIDS-related conditions may therefore help distinguish between clinical effectiveness of the treatment strategies chosen.

All-cause mortality is always a meaningful endpoint in comparisons of both efficacy and effectiveness as well as in evaluating the safety of randomized strategies. Death rates, while insufficient to stand alone as a primary endpoint, are expected to be higher in this population of failing patients with advanced disease than in similar patient groups that retain effective treatment options. Even though conditions other than AIDS-related events are likely to contribute to study-related deaths, this does not detract from their clinical relevance within the primary endpoint. The definition of these endpoints is uniform in the clinical practices of each collaborating country (see section on Outcome measures).

The use of surrogate markers (e.g., CD4 and/or plasma viral load) would not be appropriate in the context of this trial, since the effect of the two treatment strategies on such markers might not be predictive of the clinical benefit of the strategies. For example, a decline in the CD4 levels or an increase in viral load during the ARDFP (which could be expected) would not be a reliable predictor of the eventual clinical benefit that could follow the resumption of antiretroviral therapy at the end of the ARDFP. Therefore, reaching a surrogate endpoint might not necessarily reflect the true effect of the treatment strategies on the clinical outcome; on the contrary, this might declare an eventually beneficial treatment

strategy ineffective. However, tracking surrogate marker responses may permit their restandardization and validation in this context.

Adherence

The concern for potential nonadherence to medical regimens within the respective randomized strategies exists and it could confound the interpretation of study outcomes. Indeed, inadequate adherence is likely to have been the basis for failure of prior regimens used by many patients eligible for OPTIMA. Counseling regarding adherence is a routine element of clinical care during ART therapy. However, apart from directly observed therapy, there is no gold standard for measurement of adherence. Since this is impractical, a standardized patient questionnaire, which has previously shown good correlation with reductions in viral load, will be used to assess adherence. Prescription refill records will also be tracked to provide further evidence that an intended strategy is being followed.

Advances in HIV/AIDS management

Cognizant of rapid changes in HIV/AIDS management, the OPTIMA design is open to new treatments as they become available. At the same time, though, it addresses a central issue that will remain clinically relevant for many years to come: how to best manage patients for whom all available therapies have failed.

The rapid process of new drug development has challenged all HIV treatment studies in the past. However, it is unlikely in the face of multiclass drug resistance and cross-resistance within drug classes that new drugs within existing classes (nucleoside reverse transcriptase inhibitors [NRTI], nonnucleoside reverse transcriptase inhibitors [NNRTI], and protease inhibitors [PI]) will offer enough antiviral activity to overcome existing virological and immunological failure.

Potential new classes of drugs include fusion inhibitors, which are currently in clinical trials, and integrase inhibitors, which may be 2 or 3 years away from broad availability and are not likely to be any more effective in rescue than currently available drugs [16]. No single agent or class of agents is likely to succeed as monotherapy against HIV because of its high mutational rate. The problem of sequential resistance to individual drugs and classes is unlikely to disappear and may be expected to increase as the rate of transmission of resistant virus during primary infection increases. Thus, the availability of integrase inhibitors to patients already resistant to or intolerant of currently available medications is unlikely to offer more than a temporary respite. In addition, immune modulators and therapeutic vaccines may emerge as new treatment options. Nevertheless, if new classes of drugs become available during the course of this study, possibly through compassionate access, their benefit will depend on the efficacy of concurrent treatment with existing agents. In patients with multiple drug resistance, the strategy that would potentially be determined by this study would likely incorporate such new drugs. In order to enhance the validity of this trial, we will encourage the inclusion of new agents into the standard- and mega-ART regimens as the agents become available.

Study population

The intent of the trial is to include patients with advanced HIV disease and in whom regimens that have included all three main classes of anti-HIV drugs have failed or in whom resistance to all three classes of antiretroviral agents is present.

Patients are being recruited from 77 clinical sites in the three participating countries (30 sites in the United States, 22 in Canada, and 25 in the United Kingdom).

The study was initiated with a set of eligibility criteria; however, since the rate of randomization to OPTIMA has been below projected levels, the eligibility criteria were revisited. It was clear that the initial eligibility criteria were rather restrictive, so in order to stimulate accrual and ensure that OPTIMA would meet its accrual targets, the criteria were eventually modified. Table 1 provides the initial and revised eligibility criteria for OPTIMA.

The last three of the original inclusion criteria were modified to reflect current clinical practice, and a clarification of the six exclusion criteria condensed them to four. The inclusion criterion defining failure to HIV drug classes was extended to include genotypic or phenotypic evidence of resistance, and the inclusion criterion defining recent continuous antiretroviral treatment was clarified to include a recent change in regimen as long as it was taken for 4 weeks and was shown to have failed.

Also, the exclusion criteria were simplified to combine intolerance to multiple drugs and likelihood of poor compliance. The prohibition against a current regimen containing five or more antiretroviral drugs has been deleted.

Randomization

Randomization will allocate patients (1) to either a 3-month ARDFP or no ARDFP and (2) to either a mega-ART regimen (five or more drugs) or to a standard-ART regimen (up to four drugs).

A central randomization list was prepared for the whole trial with variable block size used for individual large sites or groups of smaller sites within each country and stratified by screening CD4 cell count ($CD4 \leq 100$ or $CD4 > 100$). Each country is responsible for its own randomization process and patients in each country are randomized by telephone or fax through that country's trial coordinating center (Canadian HIV Trials Network Data Center, VA Cooperative Studies Program Coordinating Center, UK-MRC Clinical Trials Unit).

Patients are randomized to either mega-ART or standard-ART and will start treatment either immediately or following an ARDFP. For patients randomized to ARDFP, assignment to standard- or mega-ART is not communicated by the coordinating center until the end of the ARDFP (i.e., the time of drug reinitiation) since immediate knowledge of their eventual drug allocation could influence the initial phase of the study.

Sample size

The goal of the trial is to randomize 1700 patients. The sample size estimated for this study was based upon a number of assumptions:

1. standard-ART event rate at year 1 is 20%, with a 25% increase annually thereafter until the end of the study;

Table 1. Old versus revised eligibility criteria

Initial criteria	Revised criteria
Inclusion criteria	Inclusion criteria
1. Signed informed consent	1. Ability to provide informed consent
2. Age 18 years or more	2. Age of 18 years or more
3. HIV infection confirmed by ELISA or Western blot or detectable HIV viral load at any time	3. Serologic or virologic diagnosis of HIV infection
4. Had failure ^a of at least two different multidrug regimens, which included drugs of all classes that the patient can tolerate	4. Had failure ^b of at least two different multidrug regimens that included drugs of all three classes that the patient can tolerate or laboratory evidence of resistance ^c to drugs in each of the three classes
5. Had at least 3 months of continuous HAART and is still on treatment	5. Had at least 3 months of current ART and are still on treatment (unless a new failure ^b , defined as 3 below)
6. Two most recent (which can include screening) results (on current ART) of either: CD4+ T-cell count <100 cells/mm ³ and pVL >5,000 copies/mL; or 100 ≤ CD4 ≤ 200 cells/mm ³ and pVL > 10,000 copies/mL	6. Two most recent results (which can include screening) on current ART of CD4 count ≤300 cells/mm ³ or ≤15%, and plasma viral load ≥5,000 copies/mL (Roche Amplicor, v1.0), or ≥2,500 copies/mL (by bDNA: Bayer v3.0/Chiron v3.0, or PCR: Roche Amplicor/Monitor/COBAS v1.5)
Exclusion criteria	Exclusion criteria
1. Pregnancy, intention of becoming pregnant, or breastfeeding	1. Pregnancy, breastfeeding or planned pregnancy
2. In the opinion of the investigator, mega-ART is contraindicated e.g., by intolerance to multiple drugs	2. Likelihood of poor protocol follow-up or if mega-ART is not feasible (due to significant intolerance of many ARV drugs)
3. Current (within 3 months) ART regimen containing five or more drugs (ritonavir at doses 100–200 mg bid for pharmacokinetics reasons is not counted)	3. Serious, uncontrolled major opportunistic infection within 14 days of screening
4. Serious, uncontrolled opportunistic infection within 14 days of screening	4. Likelihood of early death due to non-HIV disease
5. Presence of other significant, underlying disease (non HIV-related) likely to cause early death	
6. Likelihood of poor compliance	

^a For regimens after advent of pVL testing, failure is defined as either: (1) failure to suppress viral load after 24 weeks of therapy, or (2) a rebound of at least 0.5 log₁₀ in viral load from nadir; for regimens in the therapeutic era before viral load testing was available, failure is defined as CD4 decline >50% from peak or progression of HIV disease. Treatment termination due to toxicity or nonadherence is not considered to be a failure.

^b Failure (since availability of viral load tests) is defined as: (1) failure to suppress plasma viral load after 24 weeks of therapy, or (2) a rebound of at least 0.5 log₁₀ in plasma viral load from nadir, or, (3) a less than 1.0 log₁₀ drop in plasma viral load after at least 4 weeks continuous treatment with a current new multidrug regimen, or (in the therapeutic era before viral load testing was available) failure is defined as: CD4 decline >50% from peak treatment response, or below pretreatment level, or clinical progression of HIV disease.

^c Resistance (this could be from screening susceptibility test) is defined either as: (1) genotypic (defined as the presence of primary mutations associated with resistance to at least two drugs in each class), or (2) phenotypic evidence of three-class resistance.

2. two-sided type I error (α) = 0.05;
3. loss to follow-up at 3.5 years will be 10%;
4. drop-in (standard to mega) is 5% during year 1 and increases 10% every year thereafter; and
5. dropout (mega to standard) is 20% during year 1 and decreases 50% every year thereafter.

Under the above assumptions, 652 disease progression events (including death) are expected to occur. The unadjusted hazard reduction is assumed to be 30%. However, taking into consideration losses to follow-up and crossover rates, a 22% relative reduction in the hazard of progression will be detected with 93% power.

Eligibility criteria changes and lower event rates: impact on power and number of events

The revision of eligibility criteria led to a revision of the assumptions about event rates; using the revised eligibility criteria of CD4 cell count and plasma viral load, AIDS event/death rates obtained from two European and one U.S. cohort were lower than those used in the original OPTIMA assumptions (unpublished observations).

With all other original assumptions maintained (see above), a reduced number of events ($n = 450$) is expected to occur and a 22.7% relative reduction in the hazard of progression will be detected with 80% power (unadjusted hazard reduction was assumed to be 30%).

Allocated treatment strategies

Treatment regimens

All available and approved antiretroviral medications can be used for treatment of patients in this study. The intent of the trial is to maintain the patients on the allocated treatment strategy unless there is a new or recurrent AIDS-defining event or medical contraindication to the assigned therapy. However, if warranted, the study medications will be discontinued according to established guidelines. Since patients are assigned to a strategy, individual drugs may be withdrawn and/or substituted without necessarily changing the allocated strategy.

Length of follow-up

The planned recruitment period is 2.5 years and follow-up is to extend to 1 year after the last patient has been randomized. This leads to a median follow-up of about 2 years.

The aim is to follow every patient until death or study closure. Whenever possible patients will continue to be followed according to the study procedures even if they have withdrawn from allocated strategies.

Outcome measures

The primary outcome measure is the time to new or recurrent AIDS event or death. The secondary outcome is the time to development of a new non-HIV-related serious adverse event.

Both primary and secondary outcomes are assessed through the collection of data on case report forms.

The costs per QALY of (1) *mega-ART* and (2) *ARDFP* (followed by either standard or *mega-ART*), for managing the care of patients for whom previous standard-ART therapy has failed, is the main health economics outcome. QOL measures will be collected using patient-completed questionnaires.

Other outcome measures collected using both case report forms and patient-completed questionnaires include the incidence of grade 3 or 4 clinical or laboratory events and changes in virological and immunological markers (CD4 and plasma viral load) as well as process measures including hematologic profiles, electrolytes, renal, liver and pancreatic function, and lipid levels.

Screening, baseline, and follow-up assessments

Fig. 2 indicates the follow-up schedule for randomized patients and Table 2 indicates the assessments. In the event that a scheduled clinic visit cannot be completed due to hospitalization, intercurrent illness, or logistical constraints, the patient or family is contacted by phone by the local site personnel. When necessary, the patient's primary care physician is contacted to provide necessary clinical information. The coordinating center in each country regularly provides each site with (1) a report of missing forms and (2) an accounting of those forms that contain incomplete or inconsistent information.

Vital status and date of death of patients are verified by regular follow-up or by using national HIV databases. AIDS-defining events are assessed clinically and adjudicated using well-established evaluation guidelines by an independent endpoints review committee that is blinded to the patients' treatment allocation.

Site coordinators follow each randomized patient at their clinical center; missed follow-up visits are noted.

Trial management

The management of the trial is shared between the three countries. The Canadian HIV Trials Network, the MRC-UK Clinical Trials Unit, and the VA Cooperative Studies Program Coordinating Center (CSPCC-West Haven) are responsible for the day-to-day operation

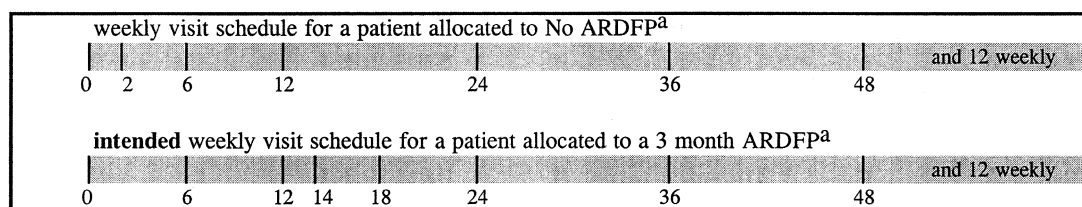


Fig. 2. OPTIMA Trial follow-up visit schedule. ^aARDFP is a 3-month antiretroviral drug-free period.

Table 2. OPTIMA case report form completion schedule

Case report form	Time of case report form completion							At time of event
	Screening	Entry baseline	Weeks after randomization			Weeks after ART initiation		
			6 ± 2 ^a	12 ± 2	q12 ± 4	2 ± 1	6 ± 2 ^a	
Informed consent	X							
Screening (urinary pregnancy test, viral load, CD4, CD8 and blood collected for storage)	X							
Eligibility verification		X						
Baseline medical history and physical examination		X						
Complete ART history		X						
Laboratory evaluations (viral load, CD4, CD8, and blood collected for storage)		X	X	X	X	X	X	
MOS-HIV		X	X	X	X			
Health utilities index		X	X	X	X			
EuroQoL		X	X	X	X			
U-Titer ^b (US-VA ONLY)		X	X	X	X			
“On-study” ART		X						
“On-study” OI and concomitant medications		X						
Follow-up visit			X	X	X	X	X	
HIV medication adherence			X	X	X	X	X	
Changes in ART medications								X
Changes in OI and concomitant medications								X
AIDS event/death								X
Adverse events (grade 3 or 4)								X
Serious adverse events								X

OI = opportunistic infection.

^a For patients randomized to no ARDFP, these visits are on the same date.

^b Computer application.

within their country. This includes handling randomization, orienting and monitoring clinical sites, ensuring quality and timeliness of data, and dealing with site-specific issues. The study is being conducted according to country-specific good clinical practice (GCP) guidelines and standard operating procedures.

The OPTIMA organizational/management structure involves, besides the coordinating centers of each of the three collaborating countries, a number of committees (see appendix).

It is overseen by an independent trial steering committee, which provides general oversight of the trial conduct, accrual, retention, quality and data systems, and management in accordance with the protocol and in light of reports or recommendations from any of the other trial committees, which include the trial management committee, endpoint review committee, and the data and safety monitoring board (DSMB). At regular intervals the trial steering committee also reviews and considers relevant information or developments in the field of HIV therapy and in legal, statutory, or regulatory requirements.

An independent DSMB composed of independent experts in the fields of virology, HIV/AIDS, clinical trial methodology, and ethics monitors the trial. Interim monitoring reports to the DSMB focus on patient intake, adherence to the allocated treatment strategy and the protocol, baseline assessment of study participants, completeness of data retrieval, and adverse events. In addition efficacy and safety are assessed as part of the interim monitoring. According to its terms of reference, the DSMB meets every 6 months; however, the DSMB has the authority to call as many meetings as it deems necessary and is thus not restricted by a fixed meeting schedule.

The trial management committee oversees the day-to-day management of the trial, resolving questions about eligibility, enrollment, randomization, regimen determination, length of drug free periods, grading and disposition of toxicities and adverse events, and determination of endpoint questions that need resolution by the endpoints review committee.

Data collection and management

Data collection is facilitated through the use of case report forms designed using an optical character recognition software package (Teleform Elite version 7.0, by Cardiff Software, Inc.).

The data collected in the OPTIMA Trial is managed at the country level as well as at the trial level using a uniform set of guidelines and procedures. The coordinating center in each of the three participating countries is responsible for the data collection from the participating sites in that country. Once collected, processed, and verified, data are then sent to the Canadian coordinating center to be merged into the trial database and to generate the analysis data files to be used for report generation and statistical analyses.

Interim analysis

There will be two full interim analyses for the primary endpoint, when 175 and 350 events have accumulated. The Haybittle-Peto method will be used for monitoring with a p -value of 0.001 for the interim analysis and p -value of 0.05 for the final analysis [17].

Final analysis

Analysis of primary outcome

The analysis of the primary endpoint (time to new or recurrent AIDS event or death) will be according to original treatment assignment, regardless of adherence (intent-to-treat).

The primary comparisons will be the main effects: standard-ART versus mega-ART and ARDFP versus no ARDFP. These comparisons will be made using the stratified log-rank test for time-to-event analysis, for example, when comparing standard- and mega-ART analysis will be stratified by ARDFP status [18].

Multivariate (adjusted) comparisons will be performed using the Cox proportional hazards regression [18]. The Cox analysis will allow for adjustment for pertinent covariates such as virological and immunological markers, composition and duration of previous antiretroviral regimens, and baseline drug resistance profiles. Estimates of the relative risk will be obtained from the Cox analysis. The Cox regression will also be used to identify subsets of patients for whom the effect of the treatment strategies are more or less pronounced. The subgroups of particular interest are defined by country, ART history (duration of therapy and initial drugs used), and the CD4 level strata incorporated into the design of the trial.

If the primary analyses of main effects show a significant difference between the strategies, secondary analyses will compare the pairwise treatment strategy comparisons. In order to provide some control for multiplicity for these secondary analyses, the Hochberg procedure, a sequentially rejective variation of the Bonferroni procedure, will be used to determine the significance at a type I error of 0.05 (two-sided) [19].

Qualitative interactions between the main effects (ART and ARDFP) are not anticipated. If, however, such interactions are found, then no main effects will be reported. Quantitative interactions, which are more likely to be present, will be assessed prior to the analysis of the main effects; these main effects will nonetheless be reported.

Analysis of secondary outcomes

One of the secondary outcome measures is time to development of a new non-HIV-related serious adverse event. Analysis of secondary outcome will be similar for that of the primary endpoint, except for adjustment for multiple comparisons (Hochberg adjustment, two-sided type I error 0.05) [19]. Further, changes in CD4 T-cell counts, viral load, and resistance will also comprise secondary endpoints.

The other important secondary outcome is QOL as measured by the Medical Outcomes Study HIV survey [20], Health Utilities Index Mark 2/3 [21], and EuroQoL [22]. One of the rationales for an ARDFP is improved QOL with minimal or nonsignificant impact on survival. Since standard- and mega-ART may have differential effects on QOL and may conceivably have similar effects on length of QOL, careful assessment of QOL is critical. Analyses comparing standard-ART versus mega-ART will examine the entire follow-up period; for comparisons of ARDFP versus no ARDFP, analyses will also examine the initial 3 months when these differential strategies are to be applied.

Multiple approaches in the calculation and analysis of QOL data will be used and explored to address the main methodological challenges: (1) use of different tools for QOL measurement and (2) effects of censoring due to loss to follow-up and death. Every attempt will be made in the data collection process to minimize missing QOL data and to ascertain the reasons why QOL measurements were not obtained as a basis for determining what type of assumptions are reasonable for the analysis (i.e., missing completely at random versus missing at random versus missing not at random).

Health economic analysis

Resources such as hospital care, medication, outpatient visits, and long-term care will be collected for all patients in each strategy arm. These QOL values will be utilized in combination with resource utilization to calculate incremental cost-effectiveness between treatment strategies.

The confidence region surrounding the cost-effectiveness ratio will be estimated using appropriate statistical methods, including bootstrap and Monte-Carlo analyses, to generate cost-effectiveness acceptability curves [23]. These curves represent a plot of the probability of one strategy being more cost-effective than the other two at each possible critical cost-effectiveness threshold, that is, under all different assumptions about the threshold cost per QALY, which defines cost-effectiveness.

Other analyses

Further analyses will include:

1. changes in CD4 cell counts over the follow-up period;
2. changes in plasma HIV RNA (\log_{10} HIV RNA) at follow-up visits and average change from nadir over the duration of follow-up will be assessed both graphically and by applying longitudinal methods where appropriate [24];
3. comparison of 12-month versus baseline viral resistance among treatment strategy groups (for patients with viral loads dictated by drug-resistance assays detection limits); and
4. comparison of use of antiretrovirals by treatment strategy arm.

Current status

Most of the implementation issues and problems encountered at the beginning of the trial have been overcome. These issues were related to regulatory requirements at the local sites as well as at the national level. The requirements vary across countries and from site to site, and as a result the start-up was not simultaneous at all the sites involved. Following approval at the national level, the study had to be approved by the local institutional review/ethics boards; approval times varied within each country and across countries. Approval and adoption of the revised protocol v1.1 was expedited in all three countries.

Another feature of the trial is that the dynamic nature of the population has affected the accrual rate. Patients fall in and out of eligibility over a short period of time thus requiring increased efforts at identifying and screening patients at the appropriate time.

Each of the three participating countries has its own database that is then merged in Canada. A lot of time and effort has been dedicated to ensuring a smooth implementation of data management procedures and processes.

The trinational nature of this trial meant close collaboration between the three governmental organizations and funding agencies. The details of planning the trial and taking it through a scientific review process agreed upon by all three agencies and the mechanics and logistics of funding study-related meetings and activities has been a tedious yet successful process.

Originally, a total of 77 sites were involved in OPTIMA (22 in Canada, 25 in the United Kingdom, and 30 in the United States). The first patient was randomized on August 9, 2001. Accrual prior to the change in eligibility criteria was at the 12% level.

At present there are 72 participating sites recruiting patients in the three countries; of these, 60 are operating under protocol v1.1 (21 in Canada, 15 in the United Kingdom, and 24 in the United States); at the remaining 12 sites approval for v1.1 is pending. There are three sites in the United States that are no longer screening and randomizing patients but are in patient follow-up status. All sites in the United States, United Kingdom, and Canada will be fully implemented over the next few months.

Prior to the changes in eligibility criteria, there were a total of 81 patients enrolled in the three countries. Since the change in eligibility criteria and the adoption of protocol v1.1 (May–March 2002), an additional 103 patients have been randomized (data as of March 21, 2003) to bring the total number randomized to 184. This increase in randomizations is clearly attributable to the change in the entry criteria.

At randomization, 84 patients had CD4 counts less than or equal to 100 cells/mm³, 67 patients had CD4 counts between 100 and 200 cells/mm³, and 33 had a CD4 count of greater than 200 cells/mm³.

Discussion

A 2 × 2 factorial design was selected for this trial since it allows for the efficient and simultaneous evaluation of the two treatment strategies. The main drawback of such a design is the potential for interaction between the two factors under examination (mega/standard-ART and ARDFP/no ARDFP). However, we do not anticipate such an interaction to be *qualitative* (change in direction); if present, this interaction will more likely be *quantitative* (change in magnitude). It is possible that the difference between mega-ART and standard-ART may be greater in the presence of than in the absence of ARDFP. The factorial design will indeed allow for the assessment of the presence of interaction, although the power to detect this interaction is low. Analysis to look for interaction will allow for detection of large differences between the groups.

In calculating sample size, conservative estimates of event rates derived from observational studies were used. In order to establish the feasibility of the accrual of 1700 patients, site surveys were undertaken in all three countries. Results of these surveys were consistent in suggesting that the accrual of 1700 patients was feasible. However, an inherent difficulty in estimating the numbers of eligible incident cases is the fact that there are few prevalent cases. The window of OPTIMA eligibility is very short since if, for example, a patient fulfills the OPTIMA criteria, some action is bound to be taken, which in turn could make the patient no longer eligible for OPTIMA. As a result these incidence estimates were mostly based on past experience.

Patient enrollment has been slow due to several factors identified by the study team. Upon reassessment the original eligibility criteria were excessively restrictive, thereby unnecessarily excluding a high proportion of patients who were considered to be appropriate for enrollment. For example, in actual experience, the CD4 cutoff level of 200 cells/mm³ for eligibility was

found to be too low. The eligibility criteria were therefore simplified and broadened. Surveys carried out in all three countries suggested that with the new eligibility criteria, the pool of eligible patients would increase by 40%. Further, screening data collected in the United States suggested the number of patients who could now be randomized would increase by over 150%. At the same time, data from recent cohorts suggest that the event rates are lower than what was originally hypothesized. Although there may be a reduction in conservatively estimated event rates, the power of the trial will continue to be at a reasonable level.

In designing the trial the timing of disclosure of the ART allocation for patients randomized to ARDFP was considered. It was determined that disclosure of the ART assignment (standard or mega) upon randomization to the ARDFP would likely jeopardize the adherence to and, consequently, the duration of the ARDFP. It was therefore decided to provide the ART assignment at the end of the ARDFP. This might pose some logistical obstacles since in some cases, prescriptions of mega-ART might be delayed at the participating site level and the patients might not be able to receive mega-ART regimens for a few days after disclosure of the ART allocation. In an attempt to minimize the time from ART assignment to initiation, it was decided to provide the ART allocation as close to the end of the ARDFP as possible, giving sites enough time to deal with any potential logistical time delays.

Initially the primary and secondary endpoints were comprised into a composite endpoint. It became clear, however, that the potential for differential impact of the proposed strategies on the outcomes would prevent the delineation of how and to what extent these strategies influenced each component individually. In turn, this would complicate the interpretation of outcomes. Moreover, if the effect of a strategy on disease progression is in the opposite direction to its effect on the serious adverse events, then combining these two endpoints would require a much larger sample size and may mask the strategy effect on either endpoint. The consideration of two separate primary endpoints was also presented as problematic, so it was decided to have the “efficacy” endpoint as primary and the “safety” endpoint as secondary.

The choice of endpoints was also a major issue in the design of this trial. The selection of clinical endpoints, whose definition is uniform in the clinical practices of the collaborating networks, will translate into practical significance for patients and clinicians. The use of surrogate endpoints in this trial could lead to incorrect conclusions about the true impact of the treatment strategies on clinical outcomes.

Further, bias in ascertainment of the endpoints will be minimal since the events are all unambiguous clinical illnesses that will cause the patient to seek medical care during the course of the study. The potential difference in the intensity of investigation of clinical symptoms could perhaps be more evident during the ARDFP and might lead to a shorter time lag in the detection of the clinical events. In order to assess such potential bias, the frequency and results of diagnostic tests performed in mega- and standard-ART patients will be compared.

In order to ensure that this potential for detection bias is further minimized, standard protocols are used to address the common patient symptom presentations seen in this population. Symptoms are recorded for all enrolled patients, irrespective of treatment allocation, throughout the study. Manuals of operation were developed to standardize trial procedures.

Definitive diagnostic methods already used in clinical practice and trials are used in patient evaluation in OPTIMA, irrespective of treatment assignment. Guidelines for presumptive

diagnosis of diseases indicative of AIDS used in previous trials are also used in the context of the OPTIMA Trial. Uniform and standard trialwide use of such up-to-date guidelines and diagnostic methods further minimizes the potential for detection bias in the trial.

OPTIMA is a clinical management trial comparing treatment strategies and is not intended to test the efficacy of individual drugs (none of which alone are likely to have considerable effects). In this context, the overriding need is for individualization rather than consistency of retreatment regimens. Factors that will influence and guide regimen decisions include treatment history, drug intolerance, drug choices and their expected toxicities, and measures of HIV susceptibility. Although it would be ideal to standardize the process of selecting treatment regimens across the trial, this will not be possible even though each clinician will likely be consistent in their selection of mega- or standard-ART regimens for patients with similar ART drug history and/or resistance patterns. Changes in treatment strategy during the conduct of the trial will not be recommended prior to patients reaching a trial endpoint.

The flexibility allowed in selecting ART medications within the randomized ART strategy will lead to a greater degree of heterogeneity, which could in turn lead to a larger standard error for the difference in outcomes between the groups. However, this heterogeneity will not bias the comparison of the treatment strategies in terms of clinical endpoints. It should also be noted that since there is no determined combination of ART medications that is known to be the most efficacious within these strategies, this heterogeneity in regimen selection is inherent to the therapeutic management of these patients.

This trial will be using antiretroviral medications that are available in routine care or through compassionate use programs or other open-label access to new HIV drugs. There is obviously a potential risk of poor compliance to the allocated strategy. For instance, patients allocated to ARDFP may resume drug therapy earlier than 3 months should they experience disease progression and precipitous decline in CD4 counts at the 6-week visit. There are no set criteria established by the protocol that mandate interruption or early termination of the ARDFP. However, the investigators are free to terminate the ARDFP at any time if, in their judgment, it is clinically warranted. Since there is no safety data on the effect of transient declines in CD4 count or elevations in HIV viral load when appropriate prophylaxis is maintained, the study encourages investigators not to use surrogate markers as the sole rationale for early termination of the ARDFP.

Similarly, patients on mega-ART may stop treatment or reduce the numbers of drugs because of presumed drug toxicity. Patient noncompliance and nonadherence to anti-HIV drug therapy, a universal problem in therapy and trials, may be relatively more operative in this trial since the study population will be selected based on treatment failure. This is often due to past nonadherence to therapies, whether through noncompliance, drug intolerance, or other factors that may still be present in individual cases. The best way to deal with nonadherence is by counseling and either identifying prompts or eliminating obstacles to adherence. The same standard of clinical practice will be followed for all study volunteers, regardless of allocation. The DSMB will closely monitor adherence to allocated regimens by treatment groups and advise the trial steering committee as necessary. Since there is no consensus about or guidelines for the best treatment strategies for such patients, clinicians should not have great difficulty urging patients to remain on their allocated treatment strategy.

The rapid process of new drug development has challenged all HIV treatment studies. However, it is unlikely, in the face of multiclass drug resistance and cross-resistance within

drug classes, that new drugs within existing classes (NRTI, PI, NNRTI) or even in individual new drug classes will offer enough antiretroviral activity to overcome existing virological and immunological failure. Potential new classes of drugs include the fusion and integrase inhibitors. T20, an injectable oligopeptide fusion inhibitor, can produce over a tenfold reduction in plasma viremia compared to monotherapy but resistance rapidly emerges [16]. Integrase inhibitors, which may be 3 years away from broad availability, are not likely to be any more effective in rescue than currently available drugs. Immune modulators and therapeutic vaccines may emerge as new treatment options. Nevertheless, if new classes of drugs become available during the course of this study, possibly through compassionate access, their benefit will depend on the efficacy of concurrent treatment with existing agents. In patients with multiple drug resistance, such new drugs could be incorporated in the treatment strategy that was deemed optimum through results of the OPTIMA Trial. In order to enhance the validity of this trial, the inclusion of new agents into the standard- and mega-ART regimes will be encouraged as the agents become available.

Lastly, the problem of serial combination drug treatment failures will undoubtedly continue in practice. This trial will retain lasting relevance in principle for the foreseeable future of ART.

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Appendix: OPTIMA study team

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Trial steering committee

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