



# An Open-Label Randomization Clinical Trial of Novel Therapeutic Strategies for Patients in Whom Antiretroviral Therapy Has Failed: Rationale and Design of the OPTIMA Trial



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## BACKGROUND

Highly-active antiretroviral therapy (HAART) has resulted in a substantial decrease in the incidence of AIDS and death in persons with the human immunodeficiency virus (HIV) infection. However, there are certain limitations of HAART:

- (a) Duration of response to HAART regimens is usually limited by either the emergence of viral resistance or the development of toxicity.
- (b) Subsequent treatment options are narrowed by the problem of drug resistance and cross-resistance within each of the three main classes of anti-retroviral drugs.

Two novel approaches have been recently tried in patients for whom first and second line HAART regimens have failed: (a) a strategy of *mega-ART* (comprised of 5 to 9 drugs) and (b) a temporary cessation of anti-retroviral therapy (known variously as 'drug-free period', 'drug-holiday', 'structured treatment interruption').

*Mega-ART*, is an experimental treatment strategy that has met at least some success, as defined by virologic response. Essentially, the strategy is to treat with as many anti-retroviral drugs as possible and maintain them for as long as possible. Associated toxicity, though frequent, is manageable in many patients by supportive medication or drug substitution.

The potential value of an anti-retroviral drug-free period (ARDFP), in the presence of multi-drug resistance, is not only the respite from pill-taking, some drug-related toxicity and improved quality of life, but also the possibility that the anti-retroviral activity and efficacy of a subsequent HAART regimen may be improved relative to such a regimen initiated without an interruption. The concept of treatment interruptions has been supported by Department of Health and Human Services (DHHS) THERAPEUTIC GUIDELINES. The optimum duration of an ARDFP, however, is not known.

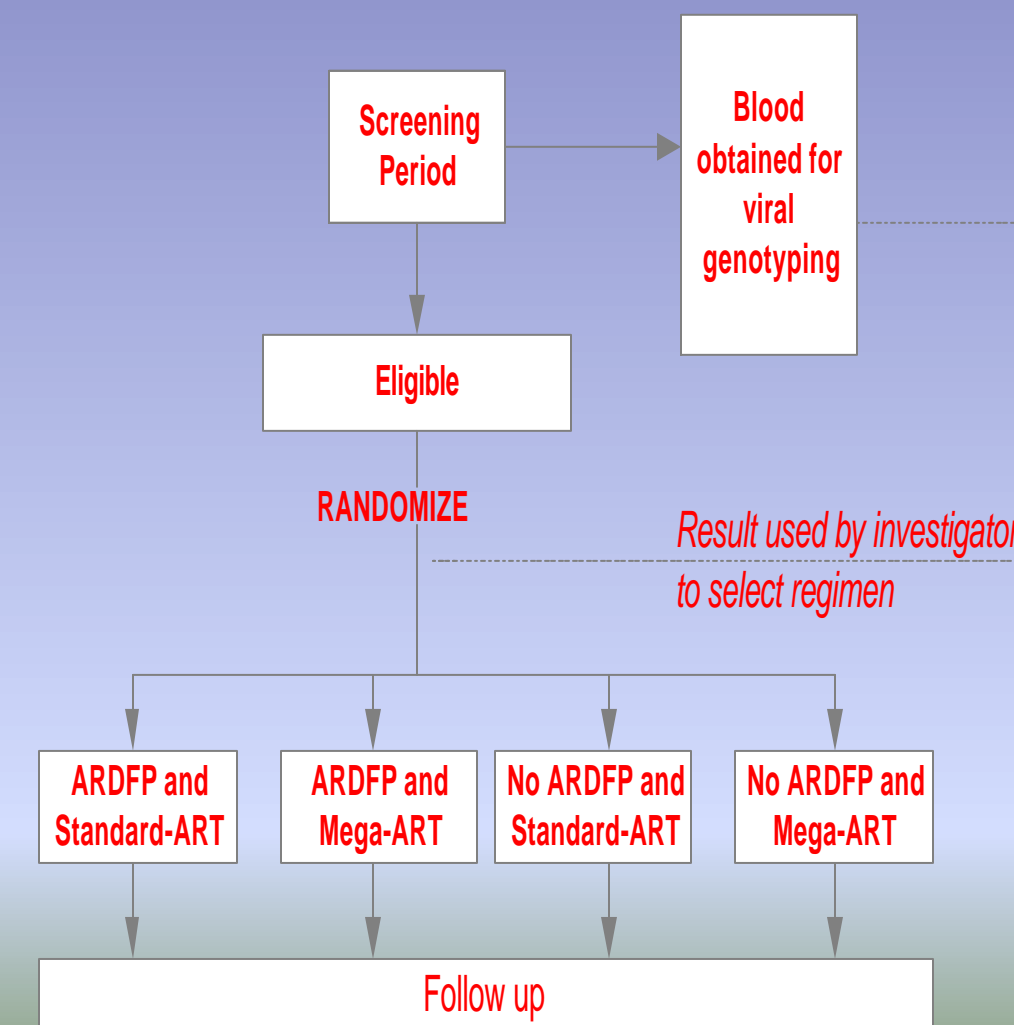
## QUESTIONS ADDRESSED BY OPTIMA

- Is there a difference in effectiveness between *mega-ART* and *standard-ART* regimens?
- What is the clinical utility of an anti-retroviral drug-free period (ARDFP)?

## OBJECTIVES AND HYPOTHESES

- To evaluate the clinical effect of (a) *mega-ART* compared to *standard-ART* and (b) an ARDFP compared to *No ARDFP*, in the management of patients for whom previous HAART therapy has failed.
- To determine the cost-effectiveness of these strategies.

## STUDY DESIGN



## Study Population

Patients with advanced HIV disease will be enrolled at 30 participating sites in the US, 22 in Canada and 25 in the UK. The initial, rather restrictive, eligibility criteria were revisited in February, 2002 and subsequently modified.

## INCLUSION CRITERIA

### Initial Inclusion Criteria

- Signed Informed Consent
- Age 18 years or more
- HIV infection confirmed by ELISA or Western Blot or detectable HIV viral load any time
- Had failure\* of at least two different multi-drug regimens, which included drugs of all classes that the patient can tolerate
- Had at least 3 months continuous HAART and is still on treatment
- Two most recent (which can include screening) results (on current ART) of either:
  - CD4+ T-cell count <100 cells/mm<sup>3</sup> and pVL > 5,000 copies/ml; or
  - 100 ≤ CD4 ≤ 200 cells/mm<sup>3</sup> and pVL > 10,000 copies/ml

\*For regimens after advent of pVL testing, failure is defined as, either: (a) failure to suppress viral load after 23 weeks of therapy, or (b) a rebound of at least 0.5 log<sub>10</sub> in 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 non-adherence is not considered to be a failure.

### Revised Inclusion Criteria

- Ability to provide informed consent
- Age 18 years or more
- Serologic or virologic diagnosis of HIV infection
- Had failure\* of at least two different multi-drug regimens that included drugs of all 3 classes that the patient can tolerate or laboratory evidence of resistance\*\* to drugs in each of the 3 classes
- Had at least 3 months continuous ART and are still on treatment (unless a new failure\*, defined as (c) below)
- Two most recent results (which can include screening) on current ART of: CD4 count ≤ 300 cells/mm<sup>3</sup> or ≥ 15%, and plasma viral load ≥ 5,000 copies/ml (Roche Amplicor, v1.0), or PCR: Roche Amplicor Monitor/COBAS v1.5).

\*Failure (since availability of viral load tests) is defined as:

- failure to suppress plasma viral load after 24 weeks of therapy, or
- a rebound of at least 0.5 log<sub>10</sub> in plasma viral load from nadir, or
- a less than 1.0 log<sub>10</sub> drop in plasma viral load after at least 4 weeks continuous treatment with a current new multi-drug 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

\*\*Resistance (this could be from screening susceptibility test) is defined either as:

- genotypic (defined as the presence of primary mutations associated with resistance to at least 2 drugs in each class), OR
- phenotypic evidence of 3-class resistance.

## EXCLUSION CRITERIA

### Initial Inclusion Criteria

- Pregnancy, intention of becoming pregnant, or breast-feeding
- In the opinion of the investigator, *Mega-ART* is contra-indicated e.g. by intolerance to multiple drugs
- Current (within 3 months) ART regimen containing ≥ 5 drugs (ritonavir at doses 100-200mg bid for pharmacokinetic reasons is not counted)
- Serious, uncontrolled opportunistic infection (OI) within 14 days of screening
- Presence of other significant, underlying disease (non HIV-related) likely to cause early death
- Likelihood of poor compliance

### Revised Exclusion Criteria

- Pregnancy, breast-feeding or planned pregnancy
- Likelihood of poor protocol follow-up or if *Mega-ART* is not feasible (due to significant intolerance of many ARV drugs)
- Serious, uncontrolled major opportunistic infection (OI) within 14 days of screening
- Likelihood of early death due to non-HIV disease

## Sample Size

The sample size (1700) estimated for this study was based on these assumptions:

- Standard-ART Event rate at Year 1 is 20%; with a 25% increase annually thereafter
- Two-sided Type I error ( $\alpha$ ) = 0.05
- Loss to follow-up at 3.5 years will be 10%
- Drop-in (Standard to Mega) is 5% Year 1; increases 10% every year thereafter
- Drop-out (Mega to Standard) is 20% Year 1; decreases 50% every year thereafter

Under these assumptions, 652 disease progression events (including death) are expected to occur and a 22% relative reduction in the hazard of progression (power = 93%).

Under the modified eligibility criteria (and lower event rates) and all other original assumptions maintained, 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 (power=80%).

## Randomization

With a central randomization list (variable block size and stratified by screening CD4 cell count (CD4 ≤ 100 or CD4 >100), patients are randomized to either *mega-ART* (≥5 drugs) or *standard-ART* (≤ 4 drugs) 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 re-initiation).

## Allocated Treatment Strategies

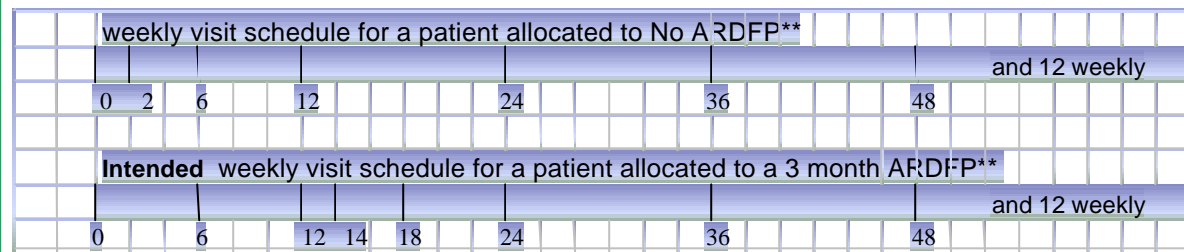
### Treatment Regimens

All available and approved antiretroviral medications can be used 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 contraindications 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.

## Patient Evaluations

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

Vital status and date of death of patients are verified by regular follow-up or by using national HIV databases. AIDS-defining events will be assessed clinically and adjudicated using well-established evaluation guidelines by the independent Endpoints Review Committee that will be blinded to the patients' treatment allocation.



\*\*ARDFP is antiretroviral drug free period

Case Report Form (CRF)	TIME OF CASE REPORT FORM COMPLETION					
	Screening	Entry/ Baseline	Weeks after Randomization			At time of Event
			6+2*	12+2	12+4	
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
RO5 HIV	X	X	X	X	X	
Health Utilities Index	X	X	X	X	X	
EuroQoL	X	X	X	X	X	
U-Titer** (US-VA ONLY)	X	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

\*For patients randomized to No ARDFP, these visits are on the same date

\*\*Computer application

## Data Collection and Management

Data collection is facilitated, at the country level, through the use of Case Report Forms (CRF) designed on an optical character recognition software package (Teleform® Elite v 7.0, by Cardiff Software, Inc.). Once collected, processed and verified, data are sent to the Canadian coordinating center where they are merged to generate the analysis data files.

## Outcome Measures

Primary: Time to new or recurrent AIDS event or death.

Secondary: Time to development of a new non-HIV related serious adverse event.

Health Economics Outcome: The costs per QALY of (a) *mega-ART* and (b) ARDFP (followed by either standard or *mega-ART*)

Other: Incidence of Grade 3 or 4 clinical or laboratory events; changes in virological and immunological markers; process measures including hematologic profiles, electrolytes, renal, liver and pancreatic function and lipid levels

## Analysis

### Interim Analysis

There will be 2 full interim analyses for the primary endpoint, when 250 and 500 events have accumulated. The Haybittle-Peto method will be used for monitoring with a p-value of 0.001.

### Final Analysis

#### Primary Outcome

Analysis will be done according to original treatment assignment, regardless of adherence (intent-to-treat), to compare (using stratified log-rank test; p-value of 0.05) the main effects of

(a) Standard-ART vs *Mega-ART* and

(b) Antiretroviral Drug-free Period (ARDFP) vs No Antiretroviral Drug-Free Period (No ARDFP).

#### Secondary Outcomes

This analysis will be similar for that of the primary endpoint, except for adjustment for multiple comparisons (Hochberg adjustment, two-sided Type I error 0.05).

#### Health Economic Outcomes

Standard-ART will be compared to *Mega-ART* during the entire follow-up period; ARDFP vs No ARDFP comparisons will also examine the initial 3 months when these differential strategies are to be applied. Cost-effectiveness comparisons will be made between treatment strategies.

### Other analyses

- Changes in virologic and immunologic variables during the follow-up period
- Comparison of 12-month vs. baseline viral resistance among treatment strategy groups
- Comparison of use of antiretrovirals by treatment strategy arm

## Trial Management

Trial management is shared between the three countries. The study is being conducted according to country-specific Good Clinical Practice (GCP) guidelines and standard operating procedures.

The OPTIMA organizational/management structure is described below.

**Trial Steering Committee (TSC):** General oversight of the trial conduct, accrual, retention, quality and data systems, and management

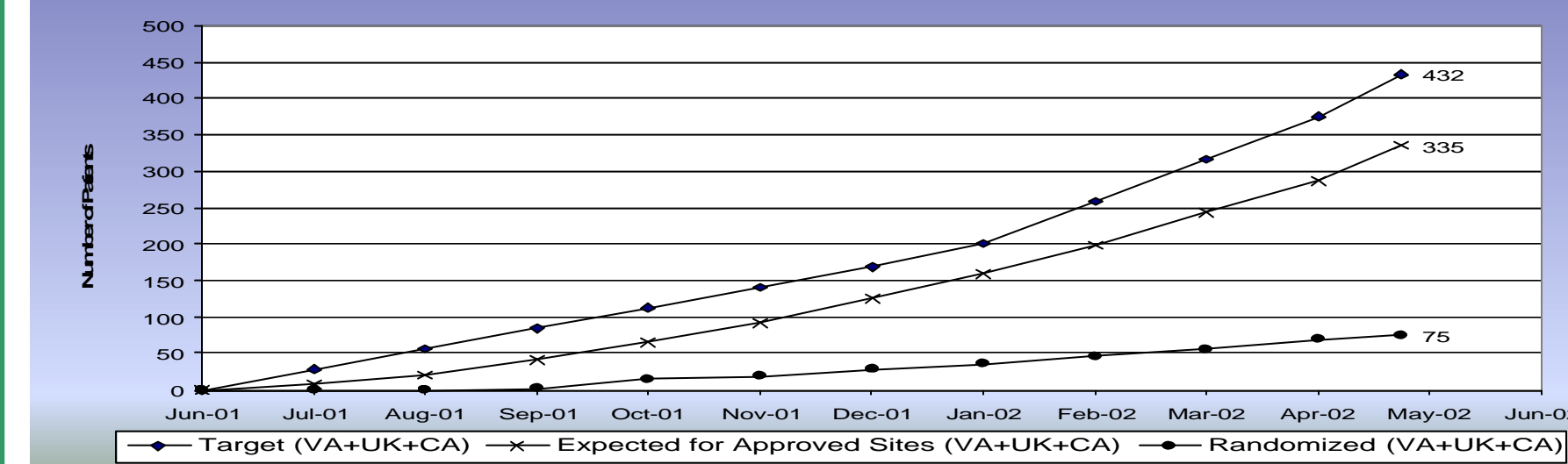
**Trial Management Committee (TMC):** Day-to-day management of the trial, eligibility issues, enrollment, randomization, regimen determination, length of drug free periods, grading and disposition of toxicities and adverse events, and determination of endpoint questions that need resolution by the ERC.

**Endpoint Review Committee (ERC):** Trial endpoint review and adjudication

**Data and Safety Monitoring Board (DSMB):** Interim trial monitoring focusing on patient intake, adherence to the allocated treatment strategy and the protocol, baseline assessment of study participants, completeness of data retrieval, efficacy and safety.

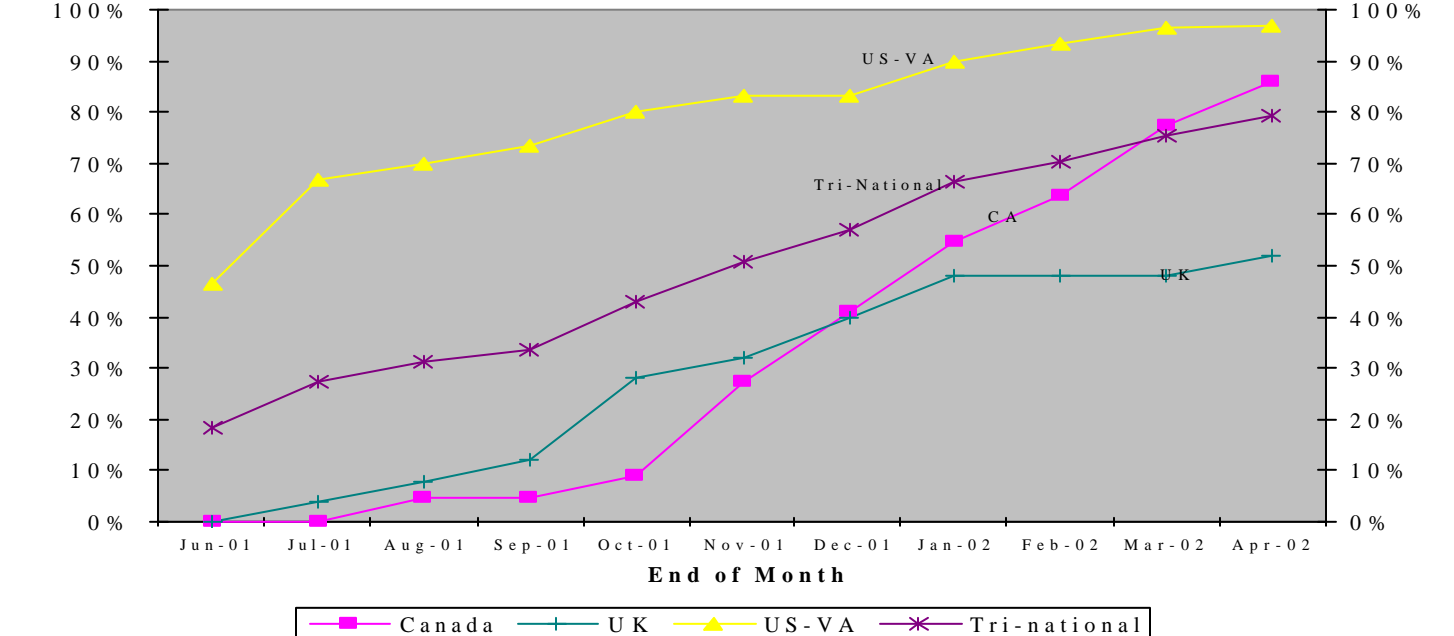
## CURRENT STATUS

Patient enrollment has been slow due to (a) excessively restrictive eligibility criteria, (b) IRB approval processing times.



Currently there are a total of 62 clinical sites that have been approved by their local ethics/IRB board and are actively participating in the OPTIMA trial.

## Percentage of Approved Sites



## Trial Management Committee

Martin Schechter, M.D. (Chair); Lawrence R. Deyton, M.D. (Cochair); Janet Darbyshire, OBE, M.D., FRCP (Cochair); Sheldon Brown, M.D.; Mark Holodniy, M.D.; Tassos C. Kyriakides, Ph.D.; Doug Owens, MD; Wei Yu, Ph.D.; William Cameron, M.D., Joel Singer, Ph.D.; Aslam Anis, Ph.D.; Brian Gazzard, M.D., FRCP; Mike Youle, M.D.; Malcolm Hooker, M.D.; Abdel Babiker, Ph.D.; Mark Sculpher, Ph.D.

## Trial Steering Committee

Professor Alasdair Breckenridge (Chair); Paul Volberding, M.D.; Mark Wainberg, Ph.D.; Kevin Schulman, M.D.; Don McIver; Simon Collins; Maggie Atkinson; Peter Peduzzi, Ph.D. (ex-officio); Isabelle Schmid, Ph.D. (ex-officio).

## Data Safety Monitoring Board

Dame Anne McClaren (Chair); Professor Vern Farewell; Mary A. Foulkes, Ph.D.; Deborah Cotton, M.D., MPH; Andreas Laupacis, Ph.D.

## Endpoints Review Committee

Richard T. Davey, Jr. M.D. (Chair); Tim Peto, M.D.

## Tri-National Funders Committee

John R. Feussner, M.D.; Isabelle Schmid, Ph.D.; Joe McNamara, Ph.D.

## ACKNOWLEDGEMENT

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OPTIMA is the initial trial of the newly established Tri-national program involving the above three agencies.