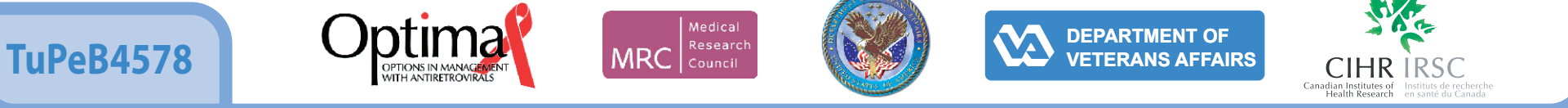


BASELINE CHARACTERISTICS, ANTIRETROVIRAL RESISTANCE PROFILE AND CLINICAL EVENTS IN THE OPTIMA TRIAL: A PRELIMINARY REPORT

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ABSTRACT
Background: The OPTIMA trial is a collaboration between the U.S. Department of Veterans Affairs, U.K. MRC and Canadian CIHR. OPTIMA is an ongoing strategy trial for patients with virologic failure and multi-drug resistant (MDR) virus.
Methods: Patients (target N=504) with HIV RNA >2,500 copies/mL, CD4 <300/mm³ on ARV therapy are randomized in a 2 by 2 factorial to a 3-month antiretroviral drug free period (ARDFP) vs. no ARDFP followed by a new standard ART (≤4 ARVs) or MegaART (>5 ARVs) versus no ARDFP (immediate change to new ARV regimen of standard vs. MegaART). AIDS events/death and adverse events are recorded for primary and secondary endpoints, respectively.
Results: 264 patients (96% male, mean age 48) have been enrolled thus far. Baseline mean HIV RNA = 4.72 log₁₀/mL and CD4 = 126 cells/mm³. ARV history included >2 PI (64%), NNRTI (96%) and NRTI (100%). Broad virtual phenotypic resistance to all ARV classes was seen. To date, there has been no loss to follow-up and the overall crossover rate is 6%. There have been 65 new or recurrent AIDS events, 23 deaths (9 AIDS related), 286 Grade 3/4 AEs in 69 patients, 75 of which lead to an ARV regimen change in 30 patients. Ongoing analysis by the DSMB has determined that there are no safety concerns.
Conclusions: Although still blinded to treatment strategy, an ARDFP has not resulted in safety concerns. The clinical response to standard or MegaART, whether preceded by an ARDFP or not, will continue to be examined.

METHODS (continued)
*** Failure (since availability of viral load tests) is defined as:**
 (a) failure to suppress plasma viral load after 24 weeks of therapy, or
 (b) a rebound of at least 0.5 log₁₀ in plasma viral load from nadir, or
 (c) a loss of 1.0 log₁₀ 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:**
 (a) genotypic (defined as the presence of primary mutations associated with resistance to at least 2 drugs in each class), OR
 (b) phenotypic evidence of 3-class resistance
EXCLUSION CRITERIA:
 1) Pregnancy, breast-feeding or planned pregnancy
 2) Likelihood of poor protocol follow-up or if Mega-ART is not feasible (due to significant intolerance of many ART drugs)
 3) Serious, uncontrolled major opportunistic infection (OI) within 14 days of screening. Likelihood of early death due to non HIV disease

TABLE 2 Antiretroviral Therapy History

class	number	total
0*	3	3
1	33	64
2	64	137
3	43	280
4	57	337
5	56	393
>5	25	418
Total Number		280
Median		3
0	10	10
1	164	174
2	89	263
>2	17	280
Total Number		280
Median		1
0	0	0
1	1	1
2	8	9
3	28	29
4	71	75
5	83	88
6	66	72
7	18	26
>7	5	13
Total Number		280
Median		5
0	273	273
1	7	280
Total Number		280
Median		0

* data not yet available from clinical sites. NOTE: Combivir is counted as two drugs (AZT and 3TC). Tivdir is counted as three drugs (AZT, 3TC, and ABC)

TABLE 6 AIDS Events and Death

	TOTAL N	%
Number Randomized	289	
Number Assessed	274	
AIDS Events		
Total Number of AIDS Events	74	
Total Number of New AIDS Events	45	
Total Number of Recurrent AIDS Events	27	
Total Number of Pending AIDS Events	2	
Total Number of Patients having New or Recurrent AIDS Event	48	17.5
Survival		
Total Number of Deaths	37	
Definitely/Probably HIV Related	4	
Uncertain HIV or ART-Related	4	
Unlikely HIV or ART-Related	3	
Pending	26	
Total Number of Patients having New or Recurrent AIDS Event or Death	62	22.6
Total Follow-up Time (in years)*	320.9	
Total at Risk Follow-up Time (years)+	283.1	
Primary outcome rate per 100 person-years	21.9	

* Follow-up calculated as time from randomization to last assessment or death
 + Follow-up at risk calculated as time from randomization to first AIDS event, death, or last assessment.

INTRODUCTION
 Combination anti-retroviral drug treatment regimens, commonly referred to as highly-active antiretroviral therapy (HAART), have resulted in substantial decrease in the incidence of AIDS and death in persons with the human immunodeficiency virus (HIV) infection (1,2,3).

The duration of response to these anti-retroviral 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 a significant proportion of patients experience toxicity. 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 anti-retroviral drugs [5,6]. An effective virologic and immunologic response in re-treatment 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 3 or 4 new drugs after failure on the first treatment, is often transient. Once a prolonged and significant virologic failure on HAART regimens that have included several 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 OPTIMA trial.

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) [7,8] and (b) temporary cessation of anti-retroviral therapy (known variously as 'drug-free period', 'drug-holiday', 'structured treatment interruption') [9,10].

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 not so valid in this context. Essentially, the strategy is to treat with as many anti-retroviral drugs as possible (defined in this study as 5 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 [7,8]. There are no mega-ART randomized controlled trials with clinical endpoints.

The second question addressed by the proposed trial is the clinical utility of an anti-retroviral drug-free period (3-month ARDFP). The potential value of an ARDFP in the presence of multi-drug resistance is not only a respite from 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. 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 re-introduced after the ARDFP [11]. Whether the rebound viremia and partial reversion to wild-type, sensitive HIV is offset by relief of drug toxicity and subsequent response to re-treatment is unknown. Enhanced virologic response to mega-ART has been observed in patients with at least one month of ARDFP in spite of an expected fall in CD4 counts during the ARDFP [12,13,14]. However, one study has shown no virologic advantage and increased clinical endpoints, but no difference in survival after an ARDFP [15]. It is possible that a temporary ARDFP may provide the patient with an improved quality of life without adversely affecting long-term survival, or possibly even improving survival even with a standard-ART regimen. The patients are better able to tolerate the new therapy. The concept of treatment interruptions has been supported by Department of Health and Human Services (DHHS) 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 counts, an anti-retroviral drug free period may be considered as an alternative therapy" [16]. The optimum duration of an ARDFP, however, is not known.

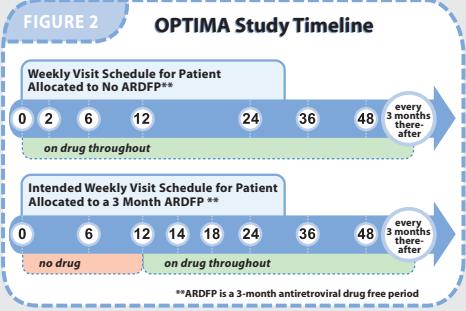
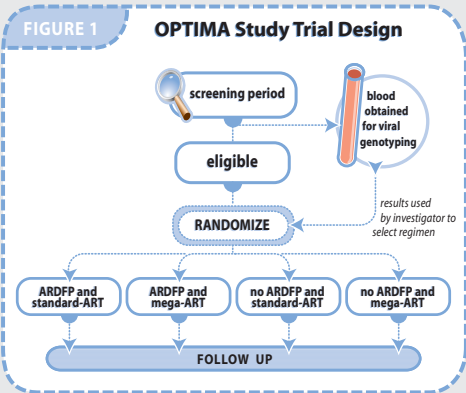


FIGURE 3 Virtual Phenotype Results

ARV	3TC	ABC	DTG	DDC	DDI	IDV	TDF	NRTI
Patient Number (N)	225	197	213	200	199	226	206	
Fold Change (FC) Cutoff	4.5	3.0	1.75	2.0	2.0	4.0	3.0	
IC ₅₀ mean FC	10.8	3.0	1.6	1.8	2.2	10.8	1.6	
25th percentile IC ₅₀ FC	2.4	1.5	0.9	1.1	1.1	1.6	0.9	
75th percentile IC ₅₀ FC	47.4	4.3	1.8	2.4	1.7	17.6	2.0	

ARV	DLV	EFV	NVP	NNRTI
Patient Number (N)	232	238	238	
Fold Change (FC) Cutoff	10	6	8	
IC ₅₀ mean FC	67.7	128	45.1	
25th percentile IC ₅₀ FC	2.8	23	38	
75th percentile IC ₅₀ FC	142	242	60	

ARV	IDV	APV	LPV	NFV	RTV	SQV	PI
Patient Number (N)	220	215	202	220	220	221	
Fold Change (FC) Cutoff	3.0	2.0	2.5	4.0	3.5	2.5	
IC ₅₀ mean FC	10.4	4.5	18.2	18.1	48.2	9.2	
25th percentile IC ₅₀ FC	0.9	0.7	0.8	1.3	0.8	0.7	
75th percentile IC ₅₀ FC	19.4	4.8	37.3	31.9	101.0	10.0	

*Indicates number of baseline samples which had a definitive susceptible or resistant fold change, and excludes those with interpretation only (i.e. Resistance likely, unlikely or possible)

METHODS
 OPTIMA is a 2x2 open randomized study of patients with advanced HIV disease in whom ART, including all three classes of anti-HIV drugs, have failed. Randomization will allocate patients (a) either to an ARDFP of at least 3 month duration or to 'no ARDFP' and (b) to either a 'mega-ART' (≥3 reverse transcriptase inhibitors, 1 non-nucleoside reverse transcriptase inhibitor and 2 protease inhibitors used in therapeutic doses) and a conventional strategy of up to 4 anti-HIV drugs (Standard-ART). For purposes of this trial, dual protease combinations involving ritonavir for pharmacokinetic reasons (in doses of 100-200 mg bid) will be counted as one drug. Hydroxyurea is not being used as an anti-cancer drug for this study but may be used at the investigator's discretion. The choice of anti-HIV drugs used during this trial will be at the discretion of the clinician and will be chosen according to the patient's previous drug history, history of drug intolerance and drug susceptibility assessment (determined by genotypic resistance testing).

The second comparison is between an intended 3-month ARDFP and 'no ARDFP'. The ARDFP is intended to be a minimum of 3 months in duration. There may be some patients who remain stable and feel well during the ARDFP and who may wish to extend the ARDFP duration. This will be permitted at the clinician's discretion as long as 6-week safety assessments after the re-initiation of ART are performed. Figure 2 shows the scheduled visits and study timeline.

Virtual phenotyping, vP, (BC Center for Excellence and Virco, Mechlen, Belgium) is performed on all subjects during the screening process prior to randomization. A central randomization list is prepared, however, each country is responsible for its own randomization processes. Patients will be randomized by telephone randomization or fax through the Canadian HIV Trials Network Data Center, the VA Cooperative Studies Program Coordinating Center or the UK-MRC Clinical Trials Unit.

Patients are randomized to either mega-ART or Standard-ART and start treatment either immediately or following a 3-month ARDFP. For patients randomized to ARDFP, knowledge of their eventual drug allocation could influence the initial phase of the study. Consequently, for this group of patients, assignment to standard- or mega-ART will not be communicated by the data center until the time of drug reintroduction.

The variety of drugs, which might be used in the trial, is too large to allow for the use of a blinded treatment methodology. Objective end-points, especially suitable for open studies, will be used to measure the efficacy of outcomes. The primary end-point is the incidence of a new or recurrent AIDS-defining illness or death, and are adjudicated by a blinded Endpoint Review Committee.

The primary and secondary endpoints are:
Primary Endpoint:
 1. Time to new or recurrent AIDS event or Death
Secondary Endpoint:
 1. Time to development of a new non-HIV related serious adverse event
 Other outcomes that will be assessed are:
 1. Quality of Life
 2. Incidence of grade 3 or 4 clinical or laboratory adverse events
 3. Changes in CD4 counts, viral load and resistance
 Process measures including hematologic profiles, electrolytes, renal function, liver function, pancreatic function, and lipid levels

This is a clinical management trial comparing strategies involving ARDFPs and numerous drugs; as such, this trial 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 re-treatment regimens. Factors that influence and guide regimen decisions include treatment history, drug intolerance, available choices and their expected toxicities, and measures of HIV susceptibility. Although standardization of the process of selecting treatment regimens would be ideal 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. Changes in treatment strategy will not be recommended prior to patients reaching a trial end-point.

This is an open randomized study using drugs 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 because of concern over disease progression and the 6-week visit for ARDFP patients could allow earlier re-initiation of ART in patients who experience a precipitous decline in CD4 counts. Similarly, patients on mega-ART may stop treatment because of presumed drug toxicity. The same standard of good 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 Steering Committee as necessary. Since there is no consensus (or guidelines) about the best treatment strategies for such patients, clinicians should not have great difficulty supporting patients to remain on their allocated treatment strategy.

INCLUSION CRITERIA:
 Patients will be eligible for enrollment in OPTIMA if they have:
 1) Ability to provide Informed Consent
 2) Age of 18 years or more
 3) Serologic or virologic diagnosis of HIV infection
 4) 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
 5) Had at least 3 months of current ART and is still on treatment (unless a new failure*, defined as (c) below)
 6) Two most recent results (which can include screening) on current ART of:
 CD4+T-cell count ≥ 300 cells/mm³ or E 15%, and plasma viral load >5,000 copies/ml (by 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)

TABLE 1 Baseline Demographic Characteristics

	N	%
Total	289	
Mean Age (SD)	47.8	8.26
Age Categories (%)		
31 - 40	51	18
41 - 50	120	39
51 - 60	96	33
> 60	16	6
Gender (%)		
Male	276	96
Female	7	2
Race / Ethnicity:		
white	146	51
black	102	35
asian	2	1
hispanic	28	10
other	11	4
Mode of Infection:		
blood transfusion	26	9
heterosexual	62	21
IV drug use	37	13
MSM	142	49
other	14	5
unknown	8	0
AIDS at Entry	282	98
OI Medications for Prophylaxis		
anti-PCP	203	70
CMV drug use	2	1
antibacterial	93	32
antifungal	53	18
Virological Markers		
<5k	34	12
5-50k	103	37
50-100k	50	18
>100k	94	33
HIV RNA copies/ml		
Total	281	
mean log ₁₀ (SD)	4.63	0.77
Immunological Markers		
N	289	
mean	130	
min	1	
max	654*	
SD	107	
median	119	

* maximum CD4 > 400 cells/mm³ as the randomisation CD4 is the CD4 count closest to baseline and may not be the CD4 count from screening

TABLE 3 Frequency of RT and PR Gene Mutations

PR MUTATIONS	N	%	RT MUTATIONS	N	%
10F	28	12	41L	120	54
10I	95	43	44D	36	16
10V	16	7	62V	11	5
20M	12	5	65R	7	3
20R	27	12	67N	81	36
24I	12	5	69D	34	15
30N	10	4	70R	39	17
32I	14	6	74V	56	25
33F	40	18	77L	12	5
33I	4	2	100L	28	13
33V	5	2	103N	116	52
36I	79	35	106M	1	0.5
46I	75	34	108I	26	12
46L	27	12	115F	15	7
47V	14	6	118I	72	32
48V	7	3	151M	10	4
50V	11	5	181C	43	19
54V	78	35	181I	3	1
54L	9	4	184V	114	51
54M	12	5	184I	6	3
63P	177	80	188L	24	11
71V	96	43	190S	17	8
73S	21	9	190A	34	15
77I	78	35	210W	81	36
82A	65	30	215Y	117	52
82F	8	4	215F	31	14
82S	5	2.2	219Q	28	13
82T	11	5	225H	8	4
84V	47	12	-	-	-
88D	12	5	-	-	-
88S	1	0.5	-	-	-
90M	120	54	-	-	-

TABLE 4 First ART Regimen On-Study

number of classes	number of drugs	total
1	1	1
2	2	1
3	3	9
4	4	6
5	5	2
Total Amount		19
2	2	1
3	3	58
4	4	45
5	5	70
6	6	10
Total Amount		184
3	3	6
4	4	22
5	5	31
6	6	7
Total Amount		39

TABLE 5 Grade 3 and 4 Adverse Events (Events that led to a change in anti-HIV treatment)

GRADE	EVENT	TOTAL
3	Anemia	5
3	Dyspepsia, retrosternal pain, gastritis, esophagitis	2
3	Dysphagia	4
3	Fatigue, tiredness, asthenia, malaise	4
3	Fever of unknown origin	2
3	Generalised allergy, hypersensitivity reaction	1
3	Hospitalization for other surgery	2
3	Infective skin conditions	1
3	Neutropenia	2
3	Pancre	