

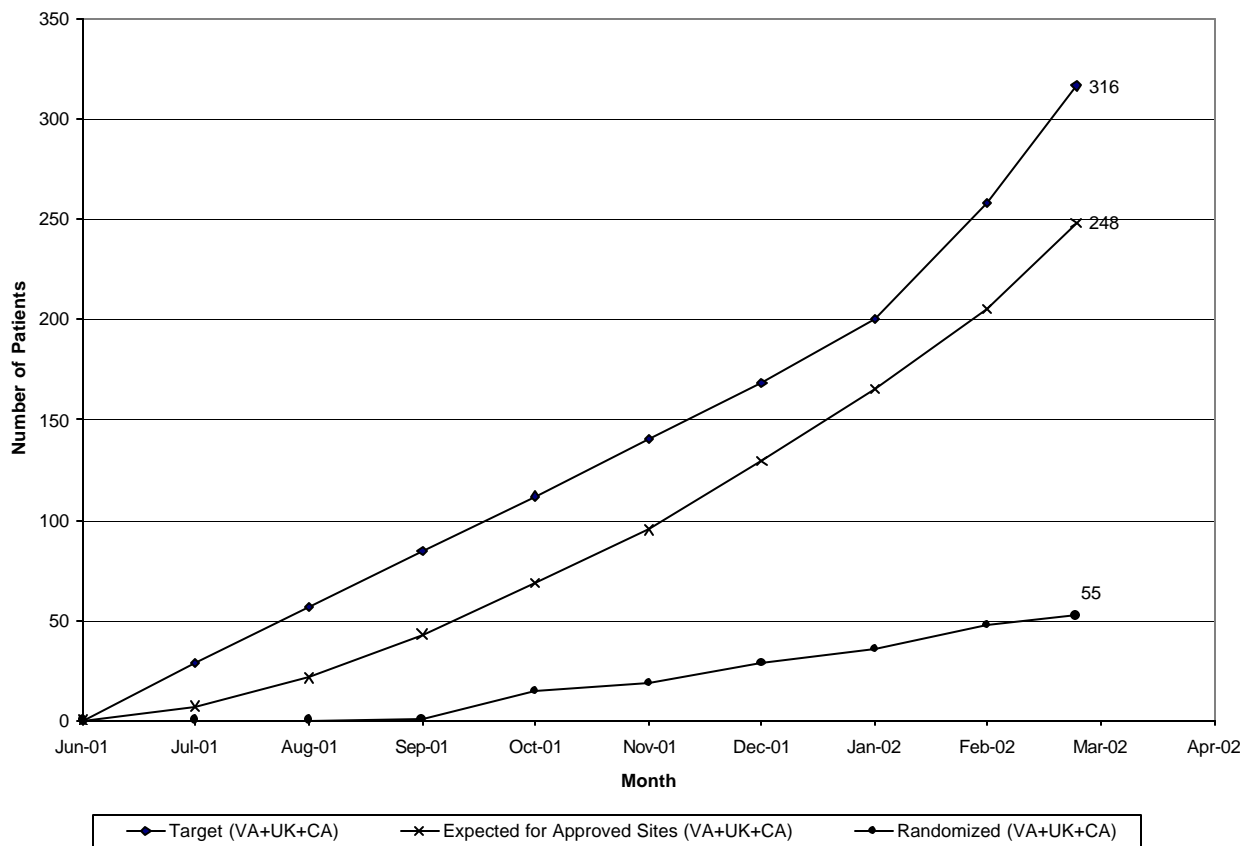
1. **Title of Study:** Tri-National Trial 1: Options in Management with Anti-Retrovirals (TNT-1: OPTIMA)
2. **Principal Investigator, Co-Investigators:**
Canada: Bill Cameron
UK: Brian Gazzard, Mike Youle
US-VA: Sheldon Brown, Mark Holodniy
3. **Trial Sites:** US: 30 Department of Veterans Affairs hospitals; UK: 25 clinical centers; Canada: 22 centers
4. **Patient Population:** 1700 patients from the three countries with advanced HIV disease who demonstrate virologic and immunologic failure on at least 2 ARV regimens. Eligibility criteria have been recently amended. Eligible participants have baseline HIV pVL >5,000 and absolute CD4 \leq 300 or CD4% \leq 15, are multiply drug experienced, and are failing their current antiretroviral regimen.
5. **Study Design:** Randomized, 2X2 factorial design. Randomization to an intended 12 week antiretroviral drug free period or no antiretroviral drug-free period, followed by either standard (4 or fewer anti-HIV drugs) or mega (5 or more anti-HIV drugs) anti-retroviral therapy.
6. **Assays :** Baseline genotyping; plasma and PBMC banking at each follow-up visit
7. **Numbers currently enrolled/anticipated enrollment:** 55 enrolled/1700 anticipated.
8. **Endpoints:** 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.
9. **Results:** OPTIMA is early in accrual. There are no results to report at this time.
10. **Willingness to consider multicenter collaboration:** This is a tri-national, multi-center trial.
11. **Obstacles perceived to be hampering pace of work:** Slow accrual has led to relaxation of strict inclusion criteria; ethics/IRB board approval process; (*plot below*)
12. **Anticipated completion date :** December 2004

Changes in Inclusion Criteria

<u>Old inclusion criteria</u>	<u>New Inclusion Criteria</u>
<ol style="list-style-type: none"> 1) Signed Informed Consent 2) Age 18 years or more 3) HIV infection confirmed by ELISA or Western Blot or detectable HIV viral load at any time 4) Had failure* of at least two different multi-drug regimens, which included drugs of all classes that the patient can tolerate 5) Had at least 3 months continuous HAART and is still on treatment 6) Two most recent (which can include screening) results (on current ART) of either: <div style="margin-left: 20px;">CD4+ T-cell count < 100 cells/mm³ and pVL > 5,000 copies/ml;</div> <div style="text-align: center; margin-left: 20px;">or</div> <div style="margin-left: 20px;">100 ≤ CD4 ≤ 200 cells/mm³ and pVL > 10,000 copies/ml</div> <p><i>*for regimens after advent of pVL testing, failure is defined as, either: (a) failure to suppress viral load after 24 weeks of therapy, or (b) 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 non-adherence is not considered to be a failure.</i></p>	<ol style="list-style-type: none"> 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 are still on treatment (unless a new failure*, defined as c) below) 6) Two most recent results (which can include screening) on current ART of: <div style="margin-left: 20px;">CD4 count ≤ 300 cells/mm³ 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).</div> <p><i>*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 less than 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 pre-treatment level, or clinical progression of HIV disease</i> <i>**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</i></p>

Changes in Exclusion Criteria

<u>Old Exclusion Criteria</u>	<u>New Exclusion Criteria</u>
<ol style="list-style-type: none"> 1. Pregnancy, intention of becoming pregnant, or breast-feeding 2. In the opinion of the investigator, <i>Mega-ART</i> is contraindicated e.g. by intolerance to multiple drugs 3. Current (within 3 months) ART regimen containing ≥ 5 drugs (ritonavir at doses 100-200mg bid for pharmacokinetic reasons is not counted) 4. Serious, uncontrolled opportunistic infection (OI) within 14 days of screening 5. Presence of other significant, underlying disease (non HIV-related) likely to cause early death 6. Likelihood of poor compliance 	<ol style="list-style-type: none"> 1. Pregnancy, breast-feeding or planned pregnancy 2. Likelihood of poor protocol follow-up or if <i>Mega-ART</i> is not feasible (due to significant intolerance of many ARV drugs) 3. Serious, uncontrolled major opportunistic infection (OI) within 14 days of screening 4. Likelihood of early death due to non-HIV disease



Percentage of Approved Sites

