

ABSTRACT

**Background:** Both AIDS and non-AIDS events have significant clinical and quality of life (QOL) consequences for HIV+ patients. In this study we evaluate the type, frequency and QOL implications of such events in patients with advanced AIDS having few treatment options.  
**Methods:** OPTIMA is an ongoing trial of alternative treatment strategies in patients with advanced HIV disease (CD4 < 350 cells/mm<sup>3</sup>) and evidence of resistance to 3 classes of antiretroviral (ARV) medications. Three groups were identified: (I) AIDS-related events (AIDS), (II) patients with non-AIDS serious adverse events (SAE's), and (III) a random control group having no serious clinical event (No Event). Using the Medical Outcomes Study HIV (MOS-HIV) QOL instrument, both the physical health status (PHS) and mental health status (MHS) scores were calculated at baseline, pre-event, and post-event. SAE coinciding with AIDS events and events with missing MOS-HIV data were excluded from the analysis. Student's t-test was used to evaluate statistical differences between mean QOL scores.  
**Results:** OPTIMA has enrolled 255 patients - median CD4 = 115 cells/mm<sup>3</sup>, median follow-up = 11 months as of December 2003. Of 23 deaths, 9 were due to AIDS, 5 were not AIDS related and 9 remain to be adjudicated. Of the reported 167 SAE's in 67 patients and 65 AIDS events in 35 patients, QOL data from 79 events were evaluable. Mean pre-event scores and those from patients without events were similar to baseline scores for PHS and MHS (39.7 and 46.2, respectively). Compared to patients without events, PHS scores declined with SAE's and MHS scores declined for both SAE's and AIDS events (Table).

Pre- vs. Post-Event Mean Scores by Groups				
Comparison Groups	AIDS (Group I)	SAE (Group II)	No Event (Group III)	p-value
<b>PHS</b>				
I vs II	-1.417	-3.106		0.354
I vs III	-1.417		-0.293	0.452
II vs III		-3.106	-0.293	<b>0.034</b>
<b>MHS</b>				
I vs II	-5.524	-2.58		0.217
I vs III	-5.524		1.295	<b>&lt;0.001</b>
II vs III		-2.58	1.295	<b>0.026</b>

PHS and MHS declines from pre-event to post-event status did not differ between SAE and AIDS events. However, significant declines in PHS scores were associated with SAE's (<3.106, p=0.09) and in MHS with AIDS events (-5.524, p=0.006).  
**Conclusion:** In patients with advanced multi-drug resistant HIV, non-AIDS SAE's occurred more often than AIDS related events. The impact of non-AIDS events on quality of life is equal to or greater than AIDS events in this population.

INTRODUCTION

There is evidence that, since the advent of HAART, non-AIDS illnesses are as important to overall morbidity as AIDS-defining conditions.<sup>1</sup> Treatment experienced patients with advanced HIV disease and multi-drug resistant virus have the highest risk of progression of AIDS. AIDS illnesses might therefore be expected to dominate morbidity in such patients. The present study evaluates the contribution of AIDS defining conditions versus non-AIDS morbidity in patients at highest risk for progression of AIDS due to lack of confident anti-retroviral treatment options. The effect of AIDS and non-AIDS morbidity on quality of life in these persons were also compared.

OPTIMA: STUDY

OPTIMA is the first study of the Tri-National Trials collaboration between the Canadian Institutes of Health Research (CIHR), the United Kingdom Medical Research Council (UK-MRC), and the United States Veterans Health Administration (VHA).<sup>2</sup> OPTIMA evaluates alternate treatment strategies in subjects with advanced multi-drug resistant HIV disease having few treatment options.

- Eligibility:**
- CD4 = 400 cells/mm<sup>3</sup>, HIV RNA > 5,000 copies/mL.
  - Evidence of multi-drug resistance or intolerance to NRTI, NNRTI, and PI classes.
- Intervention:**
- Randomization in a 2 X 2 factorial design to:**
- three month anti-retroviral drug free period (ARDFP) vs no ARDFP followed by:
  - four or fewer ARV drugs (Standard ART) vs five or greater ARV drugs (Mega-ART)
- Endpoints:**
- Primary: New AIDS-defining events or death
  - Secondary: Non-AIDS Serious Adverse Events (SAE).

Other measures for analysis gathered at scheduled visits include laboratory tests of immunological and virological status, safety measures, quality of life (QOL) instruments including the Medical Outcomes Survey (MOS-HIV), and extensive Health Economics data.

# The Impact of Non-AIDS Serious Adverse Events Equals or Exceeds that of AIDS Outcomes in Patients with Advanced Multi-Drug Resistant HIV Disease.

S.T. Brown\*<sup>1,2</sup>, J. Singer<sup>3</sup>, A. Anis<sup>3</sup>, H. Sun<sup>3</sup>, T.C. Kyriakides<sup>4</sup>, B.J. Angus<sup>5,6</sup>, K. Swanson<sup>7</sup>, W. Cameron<sup>8</sup>, A. Babiker<sup>6</sup>, M. Holodniy<sup>9</sup>, and The OPTIMA Study Team

Bronx VA<sup>1</sup>; Mt. Sinai Sch. Med, NY, NY, USA<sup>2</sup>; HIV Clin. Trials Network, Vancouver, Canada<sup>3</sup>; VA Cooperative Studies Program Coordinating Ctr, West Haven, CT, USA<sup>4</sup>; Univ. of Oxford, Headington, Oxford, UK<sup>5</sup>; Med. Res. Council Clin. Trials Unit, London, UK<sup>6</sup>; VA Cooperative Studies Program, Albuquerque, NM, USA<sup>7</sup>; Ottawa Hosp, Ottawa, Canada<sup>8</sup>; and VA Palo Alto, Palo Alto, CA, USA<sup>9</sup>



sharon.brown@optima.ca  
 Phone: (713) 584-9000, or 6666 Fax: (713) 741-4606

METHODS

Data Sources

Unblinded data from the OPTIMA study were analyzed. The data set was closed on 12/16/04.

Data elements used:

- Baseline demographics
- Baseline HIV characteristics
- Serious Adverse Events classified by MedDRA\*
- AIDS defining illnesses, new and recurrent\*\*
- Summary scores of Quality of Life using MOS-HIV\*\*\* in 2 domains:

- Physical Health Status (PHS)
- Mental Health Status (MHS)

Comparative Impact of Clinical Events on Quality of Life (QOL)

QOL comparisons were made between groups having non-AIDS related Serious Adverse Events (SAE) and AIDS related events (AIDS). An additional comparison group without serious clinical events was randomly identified (No Event).

Events excluded from QOL analysis:

- Concurrent AIDS and SAE events (<3 months between events)
- No pre-event or post-event MOS-HIV available
- Death concurrent with event or before follow-up
- No follow-up

Concurrent (<3 mos.) SAE's or concurrent AIDS events were evaluated but were treated as single events for QOL assessments. Multiple but non-concurrent events from the same patient were evaluated as unique events.

Statistical Analysis

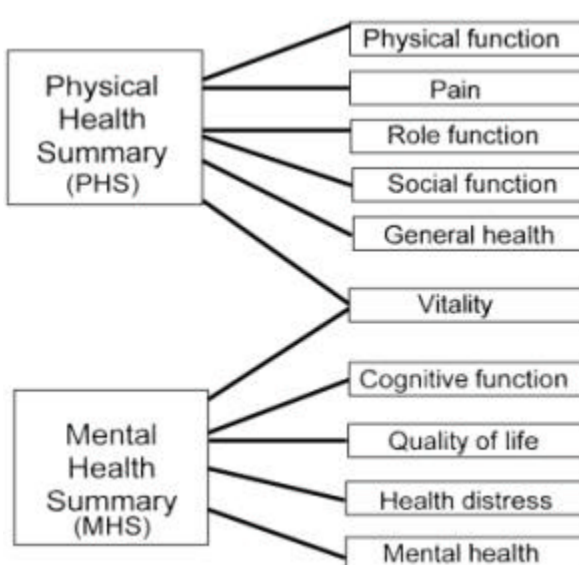
Mean PHS and MHS scores were calculated for each group - SAE, AIDS, and No-Event - at baseline of entry into study, at nearest visit prior to event (Pre-Event), and at first study evaluation following the event (Post-Event). Significance of differences between means was determined using Student's t-test.

\*SAE's in OPTIMA are defined and reported according to the ICH Harmonized Tripartite Guidelines for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (1994). New or recurring AIDS conditions identified by clinical investigators are recorded in addition to SAE's. Clinical events are subsequently classified according to the standardized MedDRA<sup>†</sup> dictionary to facilitate comparisons across sites and countries and with other studies adopting this format. Sites are individually queried for supportive primary source documentation when uncertainty arises during classification. Final adjudication for all primary endpoint events as AIDS-related or not is made by an Endpoint Review Committee.

\*\*1993 CDC guidelines for diagnosis of presumptive and definitive AIDS defining events.

\*\*\* Participants in OPTIMA complete the Medical Outcomes Survey - HIV (MOS-HIV) at baseline and all research follow-up appointments (every 3 months). The MOS-HIV is a standardized validated instrument containing 30 questions that are classified into 11 dimensions of health status. We calculated two summary scores for physical health status (PHS) and mental health status (MHS) using the scoring algorithm developed by Revicki et al<sup>4</sup>. (See Figure)

PHS and MHS Scoring Algorithm



Baseline Demographics of Patients Enrolled in OPTIMA (n=255)

	n (%)
Mean Age (SD)	48.0(8.31)
Gender (%):	
Male	249(98)
Female	6(2)
Race:	
White	126(49)
Black	91(36)
Asian	2(1)
Hispanic	27(11)
Other	3(1)
Pending*	6(2)
Mode of Infection:	
Blood	24(9)
Heterosexual	57(22)
IDU	34(13)
MSM	121(47)
Other	14(5)
Pending*	5(2)

\* Data pending as of 12/03

Baseline HIV Characteristics of Patients Enrolled in OPTIMA (n=255)

	n (%)
AIDS at entry	250(98)
CD4 at entry	
CD4 <= 100	116(45.5)
100 < CD4 <= 200	83(32.5)
CD4 > 200	54(21.2)
Median CD4 (SD)	111(103)
HIV RNA copies/ml	n (%)
<5k	16(6)
5-50k	105(42)
50-100k	47(19)
>100k	81(33)
Mean Log (SD)	4.72 (.62)
OI Prophylaxis	
Anti - PCP	180(71)
CMV	2(1)
Antibacterial	87(34)
Antifungal	45(18)

Total < 255 (100%) due to pending data

OPTIMA patients were heavily drug experienced, failing their current ARV regimen, and immunologically at risk for progression of HIV disease.

RESULTS

There was no difference between groups in pre-event QOL assessments.

Pre-Event PHS and MHS Scores Between Groups.

Comparison	AIDS (1)	SAE (2)	No Event (3)	p-value
<b>PHS</b>				
1 vs 2	39.42	39.6		0.924
1 vs 3	39.42		41	0.346
2 vs 3		39.6	41	0.339
<b>MHS</b>				
1 vs 2	48.27	47.11		0.658
1 vs 3	48.27		46.98	0.61
2 vs 3		47.11	46.98	0.951

AIDS events adversely effected Mental Health Scores and SAE's adversely effected Physical Health Scores

(Post-event - Pre-event)

Groups	n	PHS		MHS	
		Mean	p-value	Mean	p-value
AIDS	31	-1.417	0.279	-5.524	0.006
SAE	48	-3.106	0.009	-2.580	0.092
No Event	73	-0.293	0.700	1.295	0.200

Pre- and post-event scores were similar for AIDS and SAE events. Compared to No Event, SAE's adversely effected PHS scores and AIDS adversely effected MHS scores.

Comparison of Mean Change in PHS and MHS (Post-event - Pre-event) among groups

Comparison	AIDS (1)	SAE (2)	No Event	p-value
<b>PHS</b>				
1 vs 2	-1.417	-3.106		0.354
1 vs 3	-1.417		-0.29	0.452
2 vs 3		-3.106	-0.29	0.034
<b>MHS</b>				
1 vs 2	-5.524	-2.58		0.217
1 vs 3	-5.524		1.295	0.0007
2 vs 3		-2.58	1.295	0.026

CONCLUSIONS

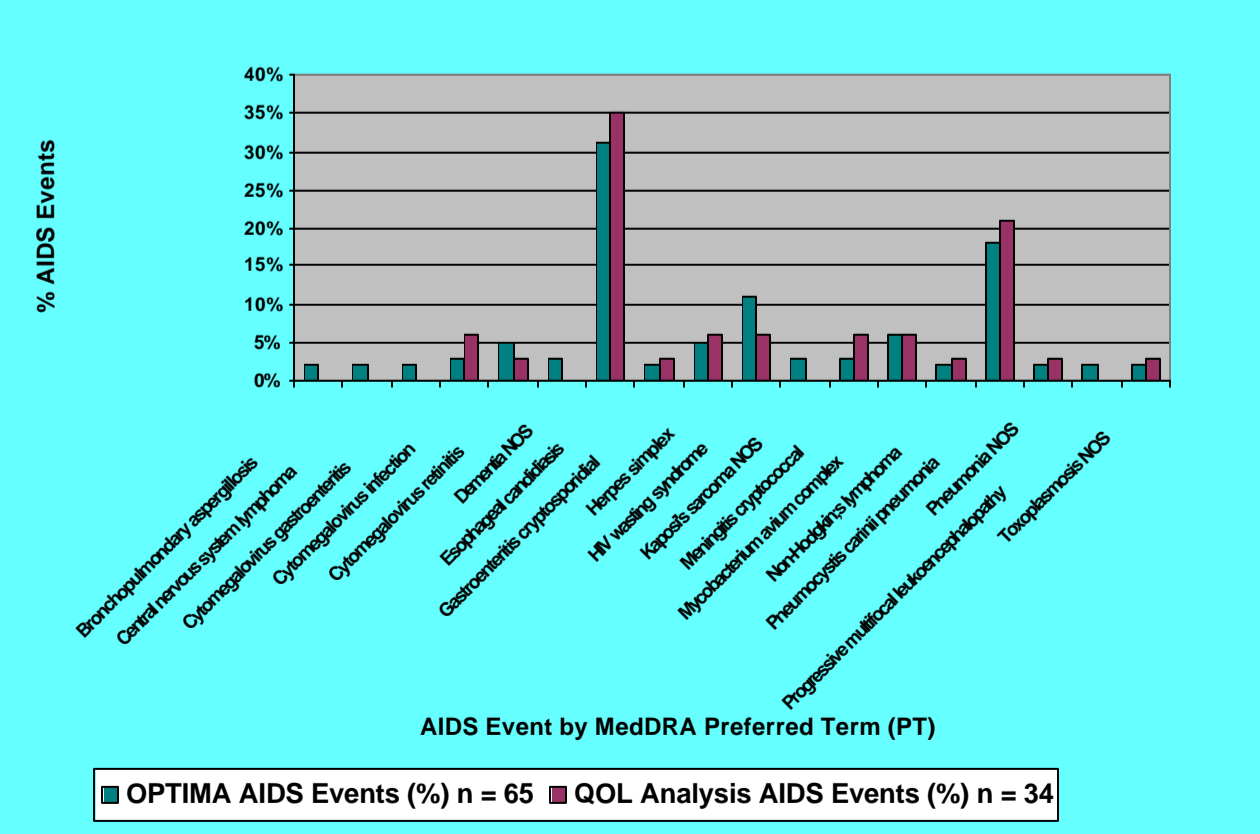
In patients with advanced HIV having limited treatment options:

- The frequency of non-AIDS serious adverse events is greater than the frequency of AIDS defining illnesses.
- Adverse effects of AIDS events and non-AIDS SAE's on physical and mental health status are similar.
- Significant declines in physical health status are associated with non-AIDS SAE's
- Significant declines in mental health status are associated with AIDS events.
- Non-AIDS serious adverse events are more frequent and associated with similar declines in quality of life as AIDS events.

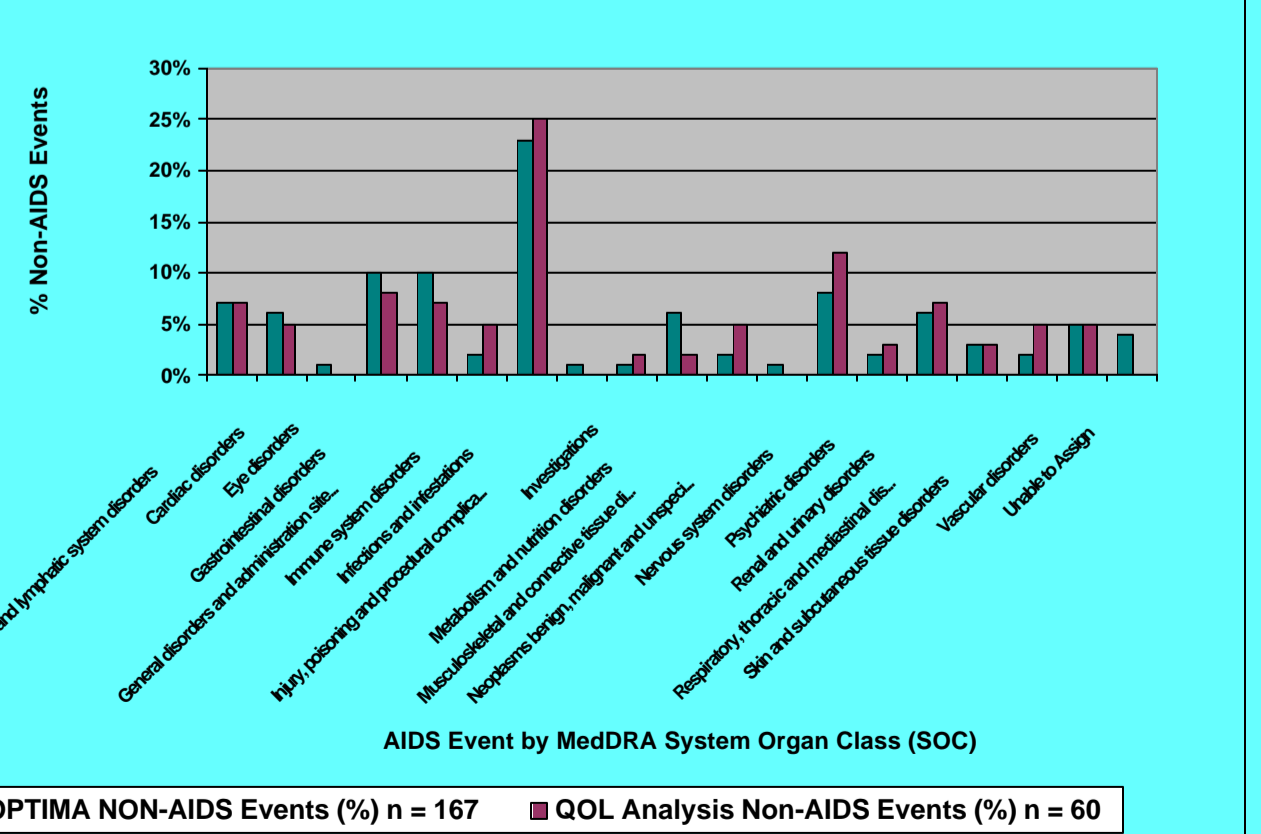
REFERENCES

- Reister, R. B. et al. "Grade 4 events are as important as AIDS events in the era of HAART." *J Acquir Immune Defic Syndr*, 34.4 (2003): 379-86.
- Kyriakides, T. C. et al. "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." *Control Clin Trials*, 24.4 (2003): 481-500.
- Anonymous. Medical Dictionary For Regulatory Activities Terminology (MedDRA) Version 5.0 Introductory Guide. Technical document.
- Revicki, D. A., S. Sorensen, and A. W. Wu. "Reliability and validity of physical and mental health summary scores from the Medical Outcomes Study HIV Health Survey." *Med Care*, 36.2 (1998): 126-37.

ALL OPTIMA vs QOL: AIDS Events



ALL OPTIMA vs QOL: Non-AIDS SAE's



The frequency of AIDS and SAE events selected for QOL analysis were similar to the OPTIMA study as a whole.