The Development of AntiRetroviral Therapy in Africa (DART) trial

Cost Effectiveness Analysis of Routine Laboratory or Clinically Driven Strategies for Monitoring Anti-Retroviral Therapy in Uganda and Zimbabwe

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Objectives

- To estimate the mean total cost per patient for LCM and CDM groups over the 6 year DART trial
- To identify the main cost drivers of managing patients on ART randomised to LCM or CDM strategies
- To estimate incremental costs and cost-effectiveness of LCM compared to CDM over the trial period
- To explore alternative scenarios of ART management

Methods

- Primary and secondary estimation of costs of healthcare service items
- Health care sector - provider perspective
- All prices in Ugandan shillings and Zimbabwean dollars were converted to 2008 USD($)
- Costs for research components were separated from ART delivery and not included in analysis (e.g. research data collection, administrative costs not associated with patient management)

Economic data collection

Unit costs	Source/derivation
ART – first- and second-line therapy	Untangling the Web of Antiretroviral Price Reductions, MSF, 11th Edition, July 2008, 88 pp.
CD4 cell counts	Micro costing & from Rosen, 2008
12-weekly haematology and biochemistry tests for toxicity	Conservative estimates including reagents, salary staff, equipment and overheads building costs*
Other investigations including X-rays	Literature and secondary sources – country specific
DART visits	Micro costing – site specific
Health centre visits	Micro costing – site specific
Concomitant medications	National prices – country specific
Per diem hospital cost	Adam, et al. in 2008 US$

* Overheads and building costs were apportioned with respect to overall expenditure of the hospital and might underestimate the real costs. In addition, plausible ranges were derived from the literature and national reference laboratory prices.

Analysis - 1

- Intention-to-treat approach
- Individual patient data from the DART database on:
  - CD4 cell counts
  - routine 12-weekly biochemistry/haematology tests
  - clinical driven toxicity monitoring tests
  - chest x-rays
  - scheduled and unscheduled DART clinic and health centre visits
  - hospital in-patient days
- Additional summary data on concomitant medications
- Mean costs per patient
  - total cost of resources used by all patients in that arm for the whole trial period divided by number of patients in that arm

Analysis - 2

- Survival differences between arms were estimated using the Kaplan-Meier survival curves
- Cost and benefits were synthesised in the form of incremental cost per life year gained
- Incremental cost effectiveness ratio (ICER) =

$$\frac{\textit{incremental average costs}}{\textit{incremental average survival}}$$

- Costs and benefits were discounted at 3% pa and adjusted for censoring (Bang and Tsiatis, 2000)
- 95% confidence intervals for difference between means were calculated using bootstrapping percentile method

First and second-line therapy

Main antiretrovirals used in first-line therapy*

Drug	Average price US$ 2008	
	Per day	Per year
ZDV	0.442	**161**
3TC	0.174	**64**
NVP	0.600	**219**
TDF	0.567	**207**
ABC	1.296	**473**

Annual cost per patient:
ZDV + 3TC + TDF = $432
ZDV + 3TC + NVP = $444
ZDV + 3TC + ABC = $698

Main antiretrovirals used in second-line therapy*

Drug	Average price US$ 2008	
	Per day	Per year
ddI 400mg	0.789	**288**
EFV	0.650	**237**
LPV/r 133/33 mg	1.824	**666**

Annual cost per patient:
ddI + EFV + LPV/r = $1,191

* Untangling the Web of Antiretroviral Price Reductions, MSF, 11th Edition, July 2008, 88 pp.

Standard monitoring tests

Efficacy Monitoring	US$ 2008
CD4 count	**8.8**
Toxicity monitoring	**US$ 2008**
Haematology panel *Haemoglobin, MCV, white cell count, total lymphocytes, neutrophils & platelets*	**5.3**
Biochemistry panel *Urea, creatinine, bilirubin, AST & ALT*	**29.5**

Observed costs

HEALTHCARE RESOURCE UTILISATION	MEAN TOTAL PER PATIENT COSTS* US$ 2008		
	LCM N = 1656	CDM N = 1660	Difference LCM - CDM
First-line therapy (SD)	1451 (603)	1470 (603)	-19
Second-line therapy (SD)	406 (964)	265 (718)	+141
CD4 monitoring (SD)	175 (57)	0 (0)	+175
Standard 12-weekly haematology /biochemistry toxicity monitoring (SD)	699 (216)	23 (65)	+676
Clinically indicated non-routine tests (SD)	41 (82)	51 (133)	-10
DART clinic visits (SD)	414 (195)	405 (197)	+9
Health centre visits (SD)	53 (56)	55 (64)	-1
Nights in hospital (SD)	141 (347)	177 (444)	-35
Concomitant medications	46	48	-2
Overall costs [95% confidence interval]**	**3425**	**2493**	**+932 [+851,+1013]**

* Total cost US$/number of patients in each arm ** 95% CI estimated with bootstrapping percentile method

Observed costs and benefits

	LCM N = 1656	CDM N = 1660	Difference (LCM – CDM)
Overall mean total costs US$ 2008 [95% confidence interval]*	$3425	$2493	$932 [$851, $1013]
Overall survival days** [95% confidence interval]*	2000	1959	41 [-15, +95]
Incremental Cost Effectiveness Ratio [95% confidence interval]*	$8313 [$3867, Dominated]		

* 95% CI estimated with bootstrapping percentile method

** Estimated through the area under the Kaplan-Meier survival curve, with censoring applied at the longest observed time of the arm whose maximum observed time occurs first

Adjusted and discounted costs and benefits

	LCM N = 1656	CDM N = 1660	Difference (LCM – CDM)
Overall mean total costs US$ 2008 - Adjusted for censoring and discounted at 3% [95% confidence interval]*	$3318	$2405	$913 [$783, $1095]
Overall survival days** - Discounted at 3% [95% confidence interval]*	1863	1827	37 [-10, +83]
Incremental Cost Effectiveness Ratio - Adjusted for censoring and discounted at 3% [95% confidence interval]*	$9016 [$3835, Dominated]		

* 95% CI estimated with bootstrapping percentile method

** Estimated through the area under the Kaplan-Meier survival curve, with censoring applied at the longest observed time of the arm whose maximum observed time occurs first

Sensitivity analysis: minimal monitoring

Modifications from adjusted and discounted costs and benefits:

- *12-weekly CD4 cell count routinely performed from the 2nd year on ART*
- *no routine (12-weekly) haematology and biochemistry tests for toxicity*

	LCM N = 1656	CDM N = 1660	Difference (LCM – CDM)
Overall mean total cost US$ 2008 – Adjusted for censoring and discounted at 3% [95% confidence interval]*	$2599	$2382	$217 [$95, $334]
Overall survival days** - Discounted at 3% [95% confidence interval]*	1863	1826	37 [-10, +83]
Incremental Cost Effectiveness Ratio - Adjusted for censoring and discounted at 3% [95% confidence interval]*	$2146 [$721, Dominated]		

* 95% CI estimated with bootstrapping percentile method

** Estimated through the area under the Kaplan-Meier survival curve, with censoring applied at the longest observed time of the arm whose maximum observed time occurs first

Sensitivity analysis: minimal resource and cost

Modifications from "adjusted and discounted" costs and benefits:

1) starting 12-weekly CD4 monitoring from the 2nd year on ART
2) no routine (12-weekly) haematology and biochemistry tests for toxicity
3) lower price of CD4 monitoring ($7.1)
4) lower annual price ($874) for second-line therapy

	LCM N = 1656	CDM N = 1660	Difference (LCM – CDM)
Overall mean total cost US$ 2008 – Adjusted for censoring and discounted at 3% [95% confidence interval]*	$2519	$2348	$171 [$98, $328]
Overall survival days** - Discounted at 3% [95% confidence interval]*	1863	1826	37 [-10, +83]
Incremental Cost Effectiveness Ratio - Adjusted for censoring and discounted at 3% [95% confidence interval]*	$1693 [$647, Dominated]		

* 95% CI estimated with bootstrapping percentile method

** Estimated through the area under the Kaplan-Meier survival curve, with censoring applied at the longest observed time of the arm whose maximum observed time occurs first

Sensitivity analysis: CD4 count costs

- At current costs ($7.1 - $8.8), CD4 testing is not cost effective

- We sought to establish the cost per test at which CD4 monitoring would be cost effective

  (ICER of $1200 ~3 times GDP per capita; WHO Commission on Macroeconomics and Health)

  CD4 count would have to cost $3.8 or less for ART management with 12-weekly CD4 monitoring from the 2nd year to be cost effective

Analyses in progress

- Cost effectiveness analysis by site
- Sub-group analysis by
  - baseline CD4 cell counts/WHO staging
  - baseline HIV RNA
  - age and sex
- Impact on household resources at 48-months and, for a sample of DART patients, travel costs
- Modelling of lifetime costs and benefits
  - including benefits in terms of Quality Adjusted Life Years (QALYs) using observed utility values from a sample of DART trial patients

Conclusions

- Routine laboratory monitoring for toxicity or efficacy (using CD4 count testing) is a key cost driver for ART programmes
- Costs need to be weighed against benefits in resource allocation
- Routine toxicity monitoring is particularly expensive, was without benefit and should be re-appraised by policy makers
- Routine 12-weekly CD4 monitoring was not cost-effective
- Sensitivity analysis suggests the cost of a CD4 count needs to drop below $3.80 to be cost effective at a 12-weekly frequency from the 2nd year on ART