

# Antiretroviral therapy can be delivered safely and successfully without routine laboratory monitoring in Africa



In 2005 Heads of States and Governments at the UN World Summit committed to the goal of Universal Access to treatment for HIV/AIDS by 2010.<sup>i</sup> At the end of 2007 only 3 million, just 31% of people who needed antiretroviral therapy (ART) globally, had access to it. By end 2008, this figure had increased to 4 million (42%), but still falls short of the goal. Inevitably the majority of those who remain in need of treatment live in low- and middle-income countries.<sup>ii</sup>

One barrier to ART roll-out in resource-constrained settings is the perception that all patients on treatment need routine laboratory tests – to maximise the effectiveness and minimise the side effects of the antiretroviral therapy. This is a major obstacle, particularly in rural areas, because these laboratory tests need substantial infrastructure (eg machines, electricity, reagents, supply chain), and trained personnel, which can be very costly to set up and then maintain.

The Development of AntiRetroviral Therapy in Africa (DART) Trial investigated whether it is safe and effective to deliver ART without the use of routine laboratory blood tests. In a parallel economic analysis, the costs and benefits of delivering ART with and without routine laboratory blood tests were compared from a public healthcare provider perspective. The trial did use laboratory services: participants were assessed with laboratory tests for eligibility to start ART; and laboratory tests were used for diagnosis if they fell ill, including with possible drug side effects.

The results of the trial show that doing laboratory tests routinely (every 3 months) to monitor ART toxicity and side effects makes no difference to patients over an average of 5 years; and is very costly.

Providing CD4 testing to patients on ART to monitor the ongoing effectiveness of first-line ART had no benefit during the first 2 years on ART. After the second year, 3-monthly CD4 tests resulted in a small but significant reduction in death (3 percentage points), largely as a result of earlier switching to second-line ART; but was also a costly intervention.

The cost-effectiveness analysis (CEA) showed that use of routine laboratory testing, as used in DART in Uganda and Zimbabwe, is not cost-effective. Analyses including other data suggest that the additional life-years gained from a management strategy based on routine laboratory tests are not proportionate to the lives lost due to lack of access to ART.

The challenge for ART programmes is to maintain and support individuals on ART (including second-line ART) as well as continuing to expand access to ART to the large number still in immediate need. The global financial and economic crisis presents a further challenge that gravely threatens achieving the goal of universal access by 2010. One way of addressing this challenge is to use existing funding better by seeking ways to make treatment programmes more efficient and cost effective, in order to get higher impact and value for money.<sup>iii</sup> The results of the DART trial can make a substantial contribution to this debate.

## Key Points

1. Life-saving ART can be delivered in Africa without the use of routine laboratory monitoring.
2. More than half of those who need ART in sub-Saharan Africa do not have access to it.
3. DART results suggest that saving costs by delivering ART without laboratory monitoring, particularly monitoring for toxicity, could enable more people to be treated.





The DART trial is the largest HIV treatment trial ever undertaken in Africa to date. It took place between 2003 and 2009 and followed a total of 3316 adults with HIV in Uganda and Zimbabwe over an average of 5 years. Participants who gave full informed consent were randomised into one of two groups.

**Criteria for joining the trial:**

- Symptomatic HIV disease.
- CD4 cell count <200 cells/mm<sup>3</sup>.
- Never previously on ART.
- No indications that ART should not be started.

3316 patients were randomised to one of 2 groups

**Laboratory and Clinical Monitoring (LCM):**  
12-weekly CD4 tests monitor ART effectiveness.

12-weekly full blood counts, liver and renal function tests monitor for drug side-effects.

The Doctor receives the results of these tests and uses them to inform the ongoing care of the patient.

1656 patients

**Clinically Driven Monitoring (CDM):**  
Patients have the same CD4, full blood count, renal and liver function tests at the same frequency as the LCM.

The Doctor never sees the CD4 test results and only sees full blood count, liver and renal function test results if requested for clinical management\*

Treatment decisions are made on the basis of clinical indicators.

1660 patients

Recruitment and randomisation to the trial took place over 2 years. Patients were followed for 4-6 years until December 2008. On exiting the trial all patients transferred to national ART programmes.

*\* as a protocol safety criteria, any result that was seriously abnormal but had not been requested was also sent back to the doctor*

Current WHO guidelines recommend starting ART in adults with clinical symptoms when the CD4 count has fallen to below 350 cells/mm<sup>3</sup>, and that it should always be started regardless of clinical symptoms when the CD4 count falls below 200 cells/mm<sup>3</sup>.<sup>v</sup> DART participants had an average CD4 count of 83 cells/mm<sup>3</sup> when they started ART, and all had symptoms of HIV-related disease. Data from a historic cohort in Entebbe, Uganda followed before ART was available and with similar characteristics as DART participants suggest that without ART less than 10% would be alive at 5 years.

Survival in DART overall was 88% at 5 years, showing the dramatic impact of ART. By trial group, 87% participants in the Clinically Driven Monitoring (CDM) group and 90% in the Laboratory and Clinical Monitoring (LCM) group were alive, a difference of only 3 percentage points.

Several WHO-recommended triple-drug regimens were used in DART. First-line ART consisted of a class of drugs known as Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI's) used alone or in combination with Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI's).<sup>vi</sup> Second-line regimens were based on boosted Protease Inhibitor (bPI). Self-reported adherence to the drugs throughout the trial was extremely high at 98% across both groups.

At the end of the trial 81% and 78% of participants in the two groups respectively were still on first-line ART and the average CD4 count was over 330 cells/mm<sup>3</sup>. After the first year, slightly more LCM than CDM participants switched to second-line ART. From the third year, disease progression to AIDS or death was slightly, but statistically significantly, faster in the CDM group, and by the end of 5 years there was just a 3 percentage point difference in deaths. This sequence of events implies that the use of CD4 counts was identifying first line treatment failure earlier, and thus leading to earlier switching from first to second-line therapy from the 2nd year of treatment.

The CEA compared the costs and benefits of delivering ART according to the LCM and CDM strategies, using an ICER (expressed as costs per life-year saved) to identify which strategy for ART monitoring was more economically viable. Results indicate that the cost of a CD4 count would have to drop below US\$4 in order for regular 12-weekly CD4 monitoring tests started from the 2nd year of ART to be a cost-effective strategy – assuming that survival benefits with LCM in DART can be replicated without routine toxicity monitoring. Routine toxicity monitoring is particularly expensive, and provides no benefit; its automatic incorporation into ART programmes should be questioned.

*The data seriously question the need to provide routine biochemistry and haematology laboratory monitoring of ART in treatment programmes in Africa*

#### Cost-Effectiveness

The Incremental Cost-Effectiveness Ratio (ICER) represents the ratio of the costs of a therapeutic intervention compared to the alternative, such as doing nothing or using the best available option to the net effect of the intervention. If an ICER equals more than 3 times GDP, it is not considered to be cost-effective according to WHO criteria.<sup>iv</sup>

CD4 counts are used to decide when a person with HIV infection should start first-line ART. They are also used to monitor ongoing treatment effectiveness once ART has been started, in particular to help identify treatment failure and guide when to switch to second-line therapy.



### Adapting Treatment Strategies for Resource-Limited Settings

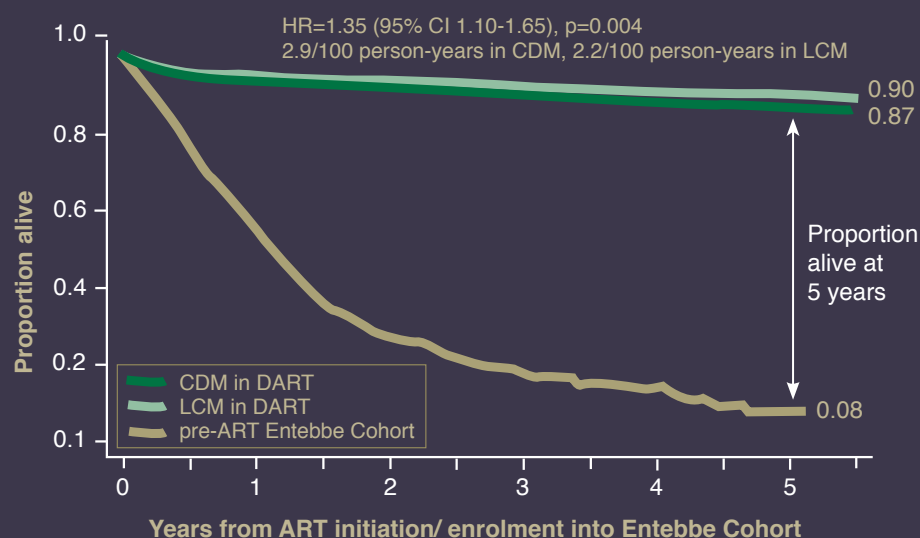
In resource-rich countries, where laboratory infrastructures are well developed, a person on ART will have regular blood tests to assess ART effectiveness and drug side-effects.

In resource-limited countries of sub-Saharan Africa 65% of the population lives in rural areas and access to healthcare is severely limited; people may have to walk for days to reach the nearest health facility with a laboratory. Infrastructure and resources for laboratory investigations are limited and need to be used in ways that maximise their impact. There is also concern that health resources have been concentrated on key diseases such as HIV, TB and malaria, to the detriment of other areas of healthcare.

DART provides evidence that ART can be delivered without expensive routine blood tests. This opens up the possibility for ART to be delivered locally by suitably trained and supervised healthcare workers and precious laboratory capacity targeted towards the diagnosis of serious HIV-related illnesses and other conditions including chronic non-infectious diseases, other infections and cancer.

*If budgets are fixed, there is a real danger that treatment of newly diagnosed patients, who are unwell, will suffer. DART clearly shows that scarce laboratory resources would be better diverted from routine laboratory monitoring to treating more people; laboratory tests could then be used to diagnose illnesses in people who are unwell.*

*At the most basic level, DART demonstrates how good well-delivered ART is at keeping people on therapy healthy and alive. Effective delivery of ART requires well supervised and properly supported clinical teams with uninterrupted access to first- and second-line anti-HIV medicines.*



DART had exceptional levels of participation with only 7% loss-to-follow-up over 5 years. Survival in DART is among the best reported from any trial, ART programme or study in Africa. Historical comparisons show that as few as 10% of people with HIV infection would be alive after 5 years without ART.

### Policy Recommendations:

- Priority should be given to widening access to first and second-line drugs to treat HIV infection.
- Resources are best focused on strengthening healthcare systems (including laboratories for diagnosing acute illnesses) and training Healthcare workers to deliver high quality care in rural areas. This benefits the health infrastructure for all, not just those with HIV.
- Monitoring disease progression with CD4 counts is of measurable but relatively small benefit which was only seen after the 2nd year of ART. For CD4 monitoring to be practical and cost-effective resources should be given to develop cheaper, point-of-care CD4 tests. This will also aid initial diagnoses of HIV and help to inform when treatment should be started.
- Routine monitoring for the side-effects of Antiretroviral Therapy (ART) is costly and of no additional benefit over and above clinical monitoring of the patient. Routine haematology and biochemistry testing should not be considered an essential element of HIV treatment in resource-limited settings.
- Efforts should also be focused on ensuring long term adherence to ART.

## DART – A Unique Public-Private Clinical Research Partnership on HIV/AIDS in Africa

DART was funded by the UK Medical Research Council, the UK Department for International Development and the Rockefeller Foundation. Drugs were provided by GlaxoSmithKline, Gilead Sciences, Boehringer-Ingelheim and Abbott. The pharmaceutical companies also funded some of the substudies which looked in more detail at specific issues related to delivering ART in Africa.

The Joint Clinical Research Centre and Infectious Diseases Institute in Kampala, MRC/Uganda Virus Research Institute Research Unit on AIDS in Uganda, Entebbe and University of Zimbabwe Clinical Research Centre in Harare collaborated with the MRC Clinical Trials Unit and Imperial College, London to carry out the research.

This unique partnership shared expertise and resources, has produced high quality research and has built research capacity in Africa. Many of the investigators are now considered to be leading researchers in the HIV field and their trial clinics in Africa are considered to be national centres of excellence.

Annie Katuregye, a DART participant, visits the grave of her husband who died from AIDS 18 years ago. She hopes that taking part in clinical research will help to bring life-saving treatment to villages like the one where her husband is buried.



## Community Understanding and Participation in DART

DART has been a landmark trial in Africa in many ways, not only the numbers involved and its length, but for the way the patient communities were involved and engaged.

Participants were fully informed of the trial and its implications before enrolling on the trial, in line with Good Clinical Practice guidelines.

More than this, participation in the clinical trial created a strong community spirit. Many participants have become HIV activists in their local communities, encouraging their peers to be tested for HIV, and to seek treatment when they become unwell. Their example has helped to reduce the stigma that is still associated with positive HIV status and to disseminate HIV prevention messages. Groups such as the Positive Voices Association (POVOA), formed from DART participants, collect funds for a basket fund which helps people living with HIV start small scale income generating activities.



## References

- i UN Resolution adopted by the General Assembly – 60/262 Political Declaration on HIV/AIDS [http://data.unaids.org/pub/Report/2006/20060615\\_HLM\\_PoliticalDeclaration\\_ARES60262\\_en.pdf](http://data.unaids.org/pub/Report/2006/20060615_HLM_PoliticalDeclaration_ARES60262_en.pdf)
- ii As defined by WHO, UNICEF and UNAIDS.
- iii “The Global Economic Crisis and HIV prevention and Treatment Programmes: Vulnerabilities and Impact” UNAIDS, June 2009
- iv Commission on Macroeconomics and Health. Macroeconomics and health: investing in health for economic development. Boston: Center for International Development at Harvard University, 2001
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## Credits:

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