DART and laboratory monitoring of HIV treatment

The DART Trial Team (Jan 9, p 123)[1] compares quarterly laboratory and clinical monitoring of patients on antiretroviral therapy (ART) with clinically driven monitoring and conclude that routine laboratory testing for toxic effects has no benefit. This conclusion has caused debate about the value of laboratory tests in countries struggling with limited resources.

We find the DART Trial Team's interpretation misleading. Despite an impressive 93% retention rate and home visits for the 1–2% of missed scheduled visits over the 5-year study period, DART patients in the clinically driven monitoring group had a 31% higher risk of death or WHO stage 4 event than the laboratory and clinical monitoring group. These risks may well be higher in real-life settings. Crowded clinics, overstretched staff, and high loss to follow-up without home visits are the realities of burgeoning treatment programmes in many countries today. Clinically monitored DART patients received test results when needed to diagnose serious adverse drug effects. Hence, programmes modelled on DART clinical monitoring will still need to build, staff, and equip laboratories to provide essential tests.

Laboratory tests are important to improve the quality of ART care. Although expanding access to ART remains a global priority, it is equally important to continue to maintain access to laboratory tests as a part of high-quality care. These elements will ensure the long-term sustainability of treatment for both patients and national programmes.

We declare that we have no conflicts of interest.

*Trevor Peter, Duncan Blair, Mike Reid, *Jessica Justman*
jj2158@columbia.edu

Clinton Health Access Initiative (CHAI), Boston, MA, USA (TP, DB); and International Center for AIDS Care and Treatment Programs (ICAP), Mailman School of Public Health, Columbia University, New York, NY 10032, USA (MR, JJ)

1 DART Trial Team. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial. *Lancet* 2010; **375:** 123–31.

The DART Trial Team[1] present clinical data from Africa showing a 3% survival benefit with laboratory monitoring compared with clinical monitoring alone in the care of HIV-infected patients. These results prioritise expansion of antiretroviral therapy (ART) to all those in need over the laboratory assessment of those currently on ART.[2]

As much as access to ART needs to be a top priority, we offer a few notes of caution when interpreting the lessons learned from the DART trial.[3] Several factors related to study design and support may have contributed to the minimal difference in survival between the laboratory and clinical monitoring groups. These include: the provision of free medical care and diagnostic tests for episodes of illness throughout the trial,[4] support such as access to ART adherence counselling, and high-quality clinical monitoring in a study setting. We believe that these factors may have led to the high level of adherence to ART, low loss-to-follow-up rates, and relatively high survival rates.

Without these components, we believe that the 3% difference in mortality between the laboratory and clinical monitoring groups in the DART study would have been higher. As the lessons from DART spur a scale-up of desperately needed HIV-treatment programmes, adequate and deliberate attention should be paid to structural and programmatic factors that were crucial for the success seen in DART, including access to free basic primary care, robust counselling, support services to patients on ART, and clinical quality assurance protocols.

We declare that we have no conflicts of interest.

**Shilpa Sayana, Rishi Manchanda, Homayoon Khanlou, Jorge Saavedra, Peter Reis, Michael Weinstein*
ssayana@gmail.com

Department of Medicine, AIDS Healthcare Foundation, Los Angeles, CA 90028, USA

1 DART Trial Team. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial. *Lancet* 2010; **375:** 123–31.
2 Phillips A, Oosterhout JV. DART points the way for HIV treatment programmes. *Lancet* 2010; **375:** 96–98.
3 Sayana S, Manchanda R, Khanlou H, et al. DART: avoid a different standard of care? *J AIDS* 2010; **53:** 153–54.
4 Taverne B, Laniece I, Desclaux A, Vinard P. Free antiretroviral medication for patients in Africa: the indispensable precondition for universal access. International Conference on AIDS; Bangkok, Thailand; July 11–16, 2004; abstr TuPeE5414.

Authors' reply

The DART trial used laboratory services to guide the start of antiretroviral therapy (ART), and to investigate and manage clinical episodes on ART in all participants. The question we addressed was not whether laboratories are necessary, but rather how best to use them.

The only difference between the clinically driven monitoring and laboratory and clinical monitoring groups was the *routine* availability of haematology or biochemistry panels, and CD4 cell counts, every 12 weeks after starting ART in the laboratory and clinical monitoring group. DART clearly showed that routine laboratory tests for toxic effects did not significantly affect any primary or secondary toxicity outcomes. This finding does not mean these toxicity tests are unimportant, but rather that doing them according to clinical need is just as effective as doing them routinely. Of note, less than 3% of haematology or biochemistry tests done in the clinically driven monitoring group were requested by clinicians to inform management.

By contrast, the risk of HIV-related WHO stage 4 events or deaths was significantly (31–35%) higher in the clinically driven monitoring group than in the laboratory and clinical monitoring group. That these differences were driven by routine CD4 monitoring, not laboratory monitoring for toxic effects, is supported by the facts that (1) there was no difference in toxicity outcomes

The printed journal includes an image merely for illustration

Giacomo Pirozzi/Panos Pictures

or drug-related deaths, (2) switch to second-line regimens occurred earlier in the laboratory and clinical monitoring group, and (3) consequently less person-time was spent with low CD4 counts in the laboratory and clinical monitoring group. Our conclusion is that, where possible, routine CD4 counts would probably improve ART outcomes. However, since the difference between groups was small in absolute terms (particularly compared with benefits of ART itself), lack of availability should never be a barrier to accessing ART.

It was essential that DART was done in centres providing good clinical care: the free care including long-term uninterrupted ART and adherence counselling no doubt contributed to low losses to follow-up (7% at 6 years), enabling us to robustly assess the *additional* effect of routine laboratory monitoring by clinicians adequately trained and supported to act on test results. Trevor Peter and colleagues' argument that the risks associated with clinically driven monitoring "may well be higher in real-life settings" assumes that health-care workers in situations where they are less able to provide high-quality clinical care are somehow able to act *more* appropriately on routine laboratory results than those in settings where they can provide high-quality care.

Substantial CD4 count variability, both natural and laboratory-related, and complexity around interpretation of tests for toxicity monitoring mean that simple rules for acting on routine test results are unlikely ever to be optimal. We would strongly argue that clinicians providing the best clinical care are also best able to interpret and act on routine laboratory results; that routine laboratory results are no substitute for good clinical care; and that "crowded clinics [with] overstretched staff" are in no position to use routine laboratory data optimally to improve the care of their patients. Thus, although the overall risks of WHO stage 4 events or death may be higher under poorer clinical care with or without routine laboratory monitoring, differences in outcomes between routine and clinically driven laboratory monitoring would, if anything, be even smaller than seen in DART.

Currently 2·9 million individuals are receiving ART in sub-Saharan Africa.[1] We agree that, without any access to laboratory services, even when sick, outcomes would be poorer than in DART, which is why we strongly argued for continuing development of laboratory services to meet clinical needs. However, *routinely* providing haematology or biochemistry tests to all these patients during a lifetime on ART would require enormous resources in terms of personnel, infrastructure, reagents, etc—with no benefit on toxicity outcomes across the range of WHO-recommended first-line ART regimens. Focusing on diagnosis and management of opportunistic infections, clinically driven laboratory monitoring for toxic effects, and targeted CD4 cell counts where practical, will lead to greater benefits for all.

We declare that we have no conflicts of interest.

*A S Walker, P Mugyenyi, P Munderi, D M Gibb, C F Gilks
asw@ctu.mrc.ac.uk

HIV Group, MRC Clinical Trials Unit, London NW1 2DA, UK

1 WHO. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Geneva: World Health Organization, 2008.

Mexico's conditional cash transfer programme

Lia Fernald and colleagues (Dec 12, p 1997)[1] analyse the effect on children's cognitive development of the total amount of cash received by the household's beneficiary of a conditional cash transfer programme in Mexico several years after its inception. Their results are, however, hard to interpret because the amount of cash accumulated depends entirely on factors that need not be random and reflect individual behaviour. For example, a household with two children, one aged 10 years and enrolled in primary school and one aged 13 years and enrolled in secondary school will get more cash than an otherwise identical household whose 13-year-old has not made it to secondary school because of grade repetition or past interruptions. Thus, a household with children better suited to school, because of higher ability or better development, receives more cash because they progressed more in school and tended to drop out less; the reverse causation, from cognitive development and academic success to cash, rather than vice versa, is obvious.

Although Fernald and colleagues qualify their results and do not claim causality when looking at the association between the amount of cash received and outcomes, we are concerned that these associations, together with the interpretation offered in their Summary, may be misconstrued as evidence on the effect of the level of cash transfers (over and above treatment status) and may be used to guide policy, without a real evidence base. To deal with this problem, in a webappendix and in other work, Fernald and colleagues suggest the use of potential grant as an instrumental variable. This is subject to the same concern, because potential grant is a deterministic function of treatment status and family composition (that are among the covariates used in the analysis) and of initial academic achievement. The importance of cash transfer schemes requires that further research takes place to establish the effect of the amount of the transfer and the nature of conditionality.

We declare that we have no conflicts of interest.

*Orazio Attanasio, Costats Meghir, Norbert Schady
o.attanasio@ucl.ac.uk

Department of Economics, University College London, London WC1E 6BT, UK (OA, CM); Institute for Fiscal Studies, London, UK (OA, CM); and Inter-American Development Bank, Washington, DC, USA (NS)

1 Fernald LCH, Gertler PJ, Neufeld LM. 10-year effect of Oportunidades, Mexico's conditional cash transfer programme, on child growth, cognition, language, and behaviour: a longitudinal follow-up study. *Lancet* 2009; **374:** 1997–2005.