

Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial



DART Trial Team*

Summary

Background HIV antiretroviral therapy (ART) is often managed without routine laboratory monitoring in Africa; however, the effect of this approach is unknown. This trial investigated whether routine toxicity and efficacy monitoring of HIV-infected patients receiving ART had an important long-term effect on clinical outcomes in Africa.

Methods In this open, non-inferiority trial in three centres in Uganda and one in Zimbabwe, 3321 symptomatic, ART-naive, HIV-infected adults with CD4 counts less than 200 cells per μL starting ART were randomly assigned to laboratory and clinical monitoring (LCM; $n=1659$) or clinically driven monitoring (CDM; $n=1662$) by a computer-generated list. Haematology, biochemistry, and CD4-cell counts were done every 12 weeks. In the LCM group, results were available to clinicians; in the CDM group, results (apart from CD4-cell count) could be requested if clinically indicated and grade 4 toxicities were available. Participants switched to second-line ART after new or recurrent WHO stage 4 events in both groups, or CD4 count less than 100 cells per μL (LCM only). Co-primary endpoints were new WHO stage 4 HIV events or death, and serious adverse events. Non-inferiority was defined as the upper 95% confidence limit for the hazard ratio (HR) for new WHO stage 4 events or death being no greater than 1.18. Analyses were by intention to treat. This study is registered, number ISRCTN13968779.

Findings Two participants assigned to CDM and three to LCM were excluded from analyses. 5-year survival was 87% (95% CI 85–88) in the CDM group and 90% (88–91) in the LCM group, and 122 (7%) and 112 (7%) participants, respectively, were lost to follow-up over median 4.9 years' follow-up. 459 (28%) participants receiving CDM versus 356 (21%) LCM had a new WHO stage 4 event or died (6.94 [95% CI 6.33–7.60] vs 5.24 [4.72–5.81] per 100 person-years; absolute difference 1.70 per 100 person-years [0.87–2.54]; HR 1.31 [1.14–1.51]; $p=0.0001$). Differences in disease progression occurred from the third year on ART, whereas higher rates of switch to second-line treatment occurred in LCM from the second year. 283 (17%) participants receiving CDM versus 260 (16%) LCM had a new serious adverse event (HR 1.12 [0.94–1.32]; $p=0.19$), with anaemia the most common (76 vs 61 cases).

Interpretation ART can be delivered safely without routine laboratory monitoring for toxic effects, but differences in disease progression suggest a role for monitoring of CD4-cell count from the second year of ART to guide the switch to second-line treatment.

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Introduction

The unprecedented expansion of antiretroviral therapy (ART) in Africa has been achieved in settings with poor health infrastructure, and often without access to routine laboratory monitoring for toxic effects or efficacy. Whether treatment programmes should provide laboratory monitoring or focus resources on continuing to expand access to first-line and second-line ART is a crucial debate in the present economic crisis.^{1,2}

In resource-rich countries, patients receiving ART have routine (typically every 3 months) tests to monitor efficacy and toxic effects. This testing is not mandated in public health ART rollout³—the approach underpinning many African treatment programmes—because it needs high-technology laboratory services and substantial resources. In fact, the effect of routine laboratory monitoring, in addition to good clinical care, has been

formally assessed only in one trial in Uganda (data not published⁴). This information is crucial for policy makers and implementers. If routine laboratory tests do not add significant benefit, ART programmes would be open to decentralisation with long-term follow-up in local clinics rather than distant hospitals, providing that consistent and good quality care could be provided. Laboratory services could be targeted to assessment for ART eligibility and to diagnosis and management of opportunistic infections or clinical toxicity, rather than being done routinely.

The Development of AntiRetroviral Therapy in Africa (DART) trial was therefore designed to investigate whether delivery of ART with or without routine monitoring of CD4-cell counts for efficacy, and haematology and biochemistry for safety, led to similar outcomes in HIV-infected patients receiving ART who had already fulfilled clinical and CD4-count criteria to start ART.

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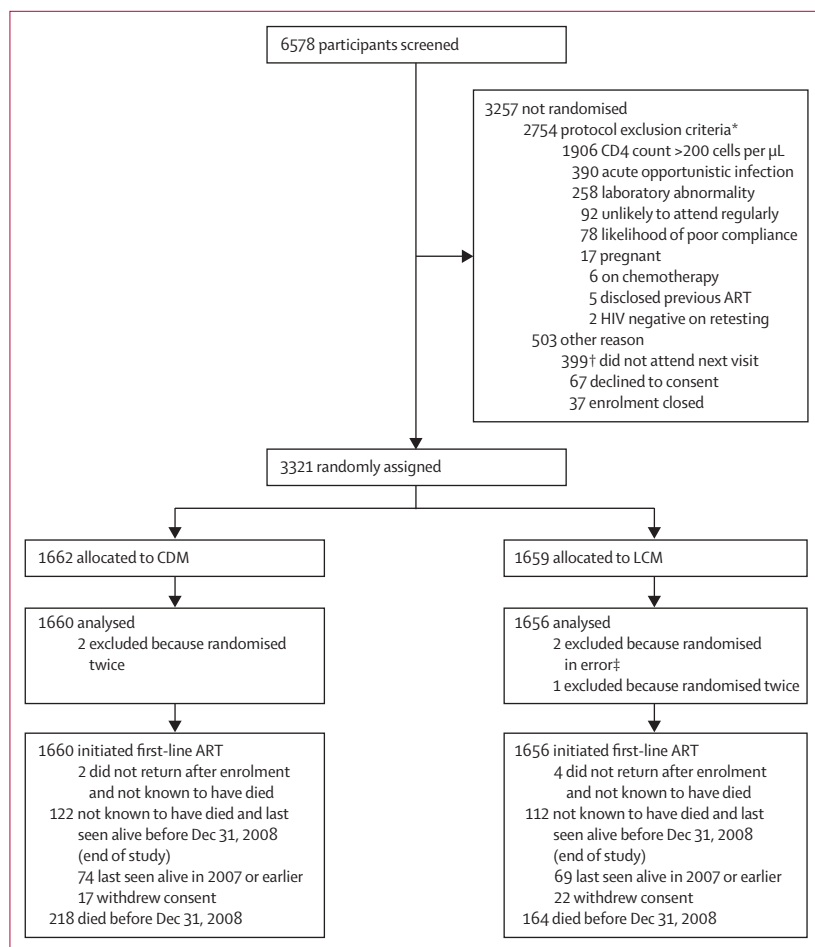


Figure 1: Trial profile

CDM=clinically driven monitoring. LCM=laboratory and clinical monitoring. ART=antiretroviral therapy. *Main reason for ineligibility. †221 (55%) participants subsequently returned and were rescreened. ‡One participant had taken ART before starting the trial, and was not prescribed trial drugs or followed up; one individual without a consent form at monitoring defaulted before 8 weeks.

Methods

Study design and participants

DART was an open randomised trial enrolling symptomatic (WHO stage 2–4) HIV-infected adults (≥ 18 years) with CD4 counts less than 200 cells per μL who reported no previous ART apart from to prevent mother-to-child transmission. Participants were enrolled between Jan 15, 2003, and Oct 24, 2004, from centres in Uganda (Medical Research Council/Uganda Virus Research Institute [UVRI] Uganda Research Unit on AIDS, Entebbe; Joint Clinical Research Centre, Kampala; and satellite Infectious Diseases Institute, Mulago) and Zimbabwe (University of Zimbabwe, Harare). Exclusion criteria were: cannot, or unlikely to attend regular follow-up (eg, usual residence too far from study centre); likelihood of poor compliance; presence of acute infection (patients could be admitted after recovery of an acute infection) or on intensive phase of antituberculosis therapy; receiving chemotherapy for

malignant disease; laboratory abnormalities that were a contraindication for the patient to start ART (eg, haemoglobin concentration < 80 g/L, neutrophils $< 0.50 \times 10^9/\text{L}$, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] more than five times the upper limit of normal, grade 3 renal dysfunction [creatinine > 360 $\mu\text{mol}/\text{L}$ or urea more than five times the upper limit of normal]); and pregnancy or breastfeeding. Participants gave written consent both for screening and, if eligible, enrolment. The trial was approved by research ethics committees in Uganda, Zimbabwe, and the UK.

Randomisation and masking

At enrolment all participants received triple-drug ART (co-formulated zidovudine-lamivudine [GlaxoSmithKline, Ware, UK] plus tenofovir disoproxil fumarate [Gilead Science, Foster City, CA, USA], abacavir [GlaxoSmithKline, Ware, UK], or nevirapine [Boehringer Ingelheim, Ingelheim, Germany]) and were randomly assigned to receive clinically driven monitoring (CDM) or laboratory plus clinical monitoring (LCM) for toxic effects (haematology and biochemistry) and efficacy (CD4-cell counts). HIV viral loads were not done in real-time, in accordance with WHO guidelines⁵ and national norms. The hypothesis was that CDM would result in similar outcomes to LCM (non-inferiority). 600 participants were randomly assigned to different first-line ART regimens in the nested Nevirapine OR Abacavir (NORA) substudy (placebo-controlled to NORA primary endpoint of toxicity at 24 weeks⁶); all other participants received open-label first-line ART. A further partial factorial randomisation within DART comparing structured treatment interruptions with continuous ART in 813 participants with CD4 counts greater than 300 cells per μL after 48 or 72 weeks on continuous ART ended in March, 2006.⁷

Randomisation was stratified by centre, screening CD4 count (0–99 vs 100–199 cells per μL), and first-line ART (tenofovir disoproxil fumarate vs nevirapine vs randomisation in NORA). The computer-generated sequentially numbered randomisation list (with variable block sizes) was prepared by the trial statistician and securely incorporated within the database at each trial centre, connected to but not located within each clinical centre, allowing trial managers to access the next number but not the whole list. Randomisation was undertaken by clinicians phoning the local trials centre.

Procedures

All participants saw a doctor and had a routine full blood count with white cell differential, lymphocyte subsets (CD4, CD8), and liver and renal function tests (bilirubin, urea, creatinine, AST/ALT) at screening, weeks 4 and 12, and then every 12 weeks. All results for LCM participants were returned to clinicians, whereas results after enrolment for CDM participants were returned only if requested for clinical reasons (reviewed and authorised

by each centre project leader) or if there was grade 4 laboratory toxic effects (protocol safety criteria, grades defined in protocol according to minor modifications of the AIDS Clinical Trials Group criteria⁸). No total lymphocyte or CD4-cell counts were returned for participants assigned to CDM. For all participants, diagnostic investigations and other laboratory tests (apart from CD4-cell count and total lymphocytes for CDM) could be requested, and concomitant drugs prescribed, as clinically indicated. All participants received ART and were reviewed by a nurse every 4 weeks (with use of a standard symptom checklist).

Antiretroviral drugs could be substituted, preferably within class, for adverse events. The decision to switch to second-line ART (with a ritonavir-boosted protease inhibitor) was based on clinical criteria in both groups (new or recurrent WHO stage 4 event; or WHO stage 3 event such as candidosis or weight loss at clinician discretion), or on laboratory criteria for LCM (confirmed CD4 count <100 cells per μL on ART [<50 cells per μL before July, 2006]). Following WHO guidelines,⁹ switching before 48 weeks was discouraged.

Participants were followed up under CDM or LCM strategies until Dec 31, 2008. At their next visit in January, 2009, participants assigned to CDM received all masked results, and those with low CD4-cell counts (following WHO guidelines⁹) were switched to second-line ART.

Study outcomes

The co-primary endpoints were (1) progression to a new WHO stage 4 HIV event or death,¹⁰ and (2) serious adverse events, which were defined as events not related only to HIV and either fatal, life-threatening, causing unplanned or prolonged admission to hospital, causing permanent or significant disability, or other important medical conditions.¹¹ Laboratory or clinical grade 4 adverse events did not have to be reported as serious adverse events unless they met one of these criteria. Secondary endpoints were: mortality; progression to a new or recurrent WHO stage 4 HIV event or death; any grade 3 or 4 adverse events; number and class of antiretroviral drugs received; time to second-line regimen; adherence measured by questionnaire and pill counts; CD4-cell counts; HIV RNA viral load and resistance (done retrospectively); and cost-effectiveness (reported separately). All WHO stage 4 events, deaths, and serious adverse events were reviewed against prespecified criteria by an Endpoint Review Committee with an independent chair and members, all of whom were masked to randomised allocation.

Statistical analysis

Interim data for safety, adherence to randomised strategies, and efficacy of CDM and LCM were reviewed regularly by an independent Data Safety and Monitoring Committee, which met every 9–12 months (seven

	Clinically driven monitoring (n=1660)	Laboratory and clinical monitoring (n=1656)
Centre		
Entebbe, Uganda	511 (31%)	509 (31%)
Joint Clinical Research Centre, Uganda	499 (30%)	498 (30%)
Infectious Disease Unit, Uganda	151 (9%)	149 (9%)
Harare, Zimbabwe	499 (30%)	500 (30%)
Women	1064 (64%)	1092 (66%)
Reported likely transmission route sex between men and women	1648 (99%)	1639 (99%)
Age (years), median (range)	36 (18–73)	36 (18–67)
CD4-cell count (cells per μL), median (range)	86 (1–199)	86 (0–199)
0–49 cells per μL	555 (33%)	554 (33%)
HIV-1 RNA (\log_{10} copies per mL)*	5.4 (0.7)	5.4 (0.7)
WHO stage		
2	310 (19%)	363 (22%)
3	948 (57%)	916 (55%)
4	402 (24%)	377 (23%)
Previous oral or oesophageal candidosis	856 (52%)	831 (50%)
Weight (kg)	57.6 (10.6)	57.9 (10.6)
Body-mass index (kg/m^2)	21.7 (3.9)	21.7 (3.8)
Haemoglobin (g/L)	115 (17)	115 (18)
Glomerular filtration rate ($\text{mL}/\text{min}/1.73 \text{ m}^2$)†	95.0 (35.0)	92.3 (28.9)
On co-trimoxazole prophylaxis at or before randomisation	1034 (62%)	1014 (61%)
First-line ART: zidovudine and lamivudine plus		
Tenofovir disoproxil fumarate	1237 (75%)	1232 (74%)
Abacavir (randomised in NORA‡)	150 (9%)	150 (9%)
Nevirapine (randomised in NORA‡)	150 (9%)	150 (9%)
Open-label nevirapine	123 (7%)	124 (7%)
Identified at any time (including after baseline) as having previously received ART for any reason§	65 (4%)	65 (4%)
Antiretroviral drugs to prevent mother-to-child transmission (% of women)¶	38 (4%)	23 (2%)

Data are n (%) or mean (SD), unless otherwise indicated. ART=antiretroviral therapy. NORA=Nevirapine OR Abacavir substudy. *968 patients (not chosen at random; 473 in CDM group vs 495 in LCM group); all participants randomised in NORA plus a substudy in participants receiving tenofovir disoproxil fumarate as first-line treatment.¹² †Calculated according to the Cockcroft-Gault formula¹³ and adjusted for body surface area. ‡Nested factorial randomised substudy, blinded to 24 weeks. §Including ART to prevent mother-to-child transmission, disclosure of previous ART during the trial (unsolicited or solicited at switch to second-line treatment), presence of any nucleoside reverse transcriptase inhibitor or non-nucleoside reverse transcriptase inhibitor mutation or major protease inhibitor mutation on baseline resistance test (467 [14%] patients assayed to date; 225 in CDM group vs 242 in LCM group), or disclosure from specific question on 4-year form (2741 patients completed; 1348 in CDM group vs 1393 in LCM group). ¶Single-dose nevirapine (n=56; 33 in CDM group vs 23 in LCM group) or zidovudine (n=5; five in CDM group vs none in LCM group).

Table: Characteristics at randomisation (ART initiation)

meetings in total). The Haybittle-Peto criterion, $p < 0.001$,¹² was the statistical guide for considering recommending stopping or modifying the trial.

The planned sample size of 3300 adults followed up for 4–6 years provided 80% power to establish that CDM was not inferior to LCM. Non-inferiority was defined as the upper 95% confidence limit for the hazard ratio (HR; CDM:LCM) for new WHO stage 4 events or death being no greater than 1.18, which is equivalent to a yearly rate of progression of no more than 11.8 per 100 person-years in CDM compared with a predicted rate of 10.0 per 100 person-years in LCM.

Kaplan-Meier plots, log-rank test, and proportional hazards models, stratified by randomisation stratification factors, were used to compare randomised groups for time-to-event outcomes, censoring at the earlier of Dec 31, 2008, or last follow-up. Categorical variables were compared between randomised groups with χ^2 or exact tests, and continuous variables with *t* tests or rank-sum tests. All comparisons between groups were as randomised (intention to treat). Baseline values were those nearest to but before and within 42 days of randomisation. Generalised estimating equations (independent correlation structure) were used to compare laboratory measurements and adherence across randomised groups over time, with the closest measurement to each scheduled visit within equally spaced intervals. All *p* values are two-sided.

This study is registered, number ISRCTN13968779.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

See Online for webappendix

Figure 1 shows the trial profile. 3321 participants were enrolled. Three participants randomised twice (at different centres) were included from their first randomisation, and two with major eligibility violations were excluded, leaving 3316 participants in the final intention-to-treat analysis (figure 1). Baseline characteristics were similar between groups (table).

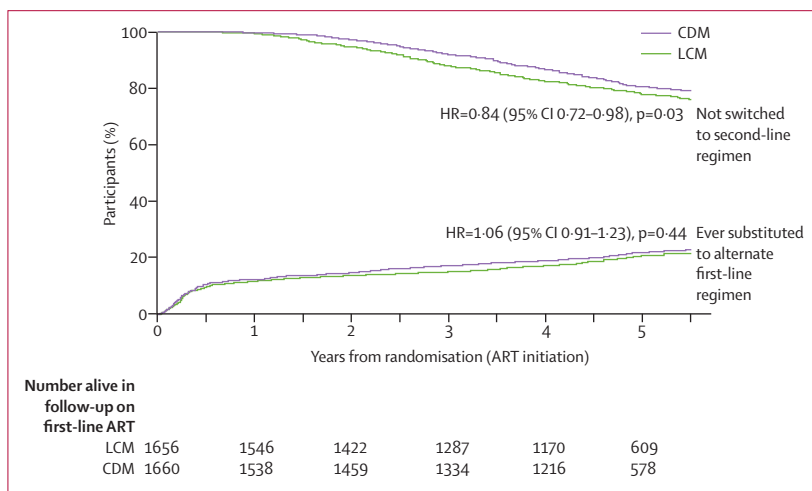


Figure 2: Substitution in first-line ART and switch to second-line ART

Percentages of participants still on first-line antiretroviral therapy (ART) and ever substituted to an alternate first-line regimen were estimated with cumulative incidences (deaths on first-line therapy were treated as competing risks, as was switch to second-line ART for first-line substitutions). Cause-specific hazard models in which deaths (and switch to second-line ART for first-line substitutions) are censored were used to calculate hazard ratios, stratified by randomisation factors. HR=hazard ratio. CDM=clinically driven monitoring. LCM=laboratory and clinical monitoring.

Median follow-up to Dec 31, 2008, or the time last seen alive was 4.9 years (IQR 4.4–5.3) in the CDM group and 4.9 years (4.5–5.3) in the LCM group. Follow-up was 14937 person-years (7404 person-years in CDM group and 7533 in LCM group; maximum 6 years), of which only 6 person-years in 12 participants (five in CDM group, seven in LCM group) was spent off the allocated monitoring strategy (viral load and/or CD4-cell count [CDM only] monitoring elsewhere but still providing follow-up data through medical records). Only 234 (7%) participants were lost to follow-up before Dec 31, 2008, and not known to have died (figure 1). Completeness of nurse visits every 4 weeks and doctor visits every 12 weeks was high and similar in both groups (nurse visits 97.7% [95 271/97 525] in CDM group vs 97.8% [97 066/99 221] in LCM group; doctor visits 98.7% [40 525/41 056] vs 98.8% [41 086/41 602]).

Clinicians managing participants assigned to CDM could request individual results from the routine biochemistry or haematology panels (every 12 weeks) for clinical reasons. These haematology or biochemistry panels could also be requested, if clinically indicated, at intervening nurse visits every 4 weeks and extra patient-initiated visits in both groups. Most of the tests done from these panels were undertaken at routine visits every 12 weeks (<8% at nurse/extra visits for haematology and <5% for biochemistry panels; webappendix p 1). In the CDM group, very few (<4%) individual results were released (webappendix p 1), most often haemoglobin, neutrophils, creatinine, and urea. Overall, more additional investigations were requested during nurse or extra visits in the LCM group than in the CDM group: 812 (49%) participants assigned to CDM and 965 (58%) to LCM had one or more additional haematology tests (*p*<0.0001); and 639 (38%) assigned to CDM and 683 (41%) to LCM had one or more additional biochemistry tests (*p*=0.11). 635 (38%) CDM and 633 (38%) LCM participants had one or more other (non-routine panel) blood tests (*p*=0.99), mostly other biochemistry (eg, electrolytes).

At Dec 31, 2008, or last clinic visit, 1346 (81%) people receiving CDM versus 1295 (78%) receiving LCM were still on first-line ART, including 288 (17%) CDM and 281 (17%) LCM participants who had substituted one or more first-line drugs (rates 7.4 [95% CI 6.8–7.5] and 7.6 [7.0–8.3] per 100 person-years, respectively). Adverse events led to 859 of 1037 (83%) first-line substitutions (427 in CDM group and 432 in LCM group; participants could substitute more than once in first-line treatment), with the remainder due to concomitant antituberculosis therapy (81 [8%]; 44 in CDM group and 37 in LCM group) or other reasons (eg, pregnancy; data not shown). Adherence by self-reported questionnaire every 4 weeks was similar in both groups, with 3.5% (3164/90 233) reports in the CDM group versus 3.3% (2995/91 979) in the LCM group of missing pills in the last 4 days (*p*=0.14), and 8.5% (7692/90 929) versus 7.8% (7256/92 656) in the last 28 days (*p*=0.45).

Overall, 314 (19%) people receiving CDM versus 361 (22%) receiving LCM switched to second-line ART (figure 2). Switching was more frequent in the LCM group than in the CDM group in the second (HR 0.48 [95% CI 0.33–0.71]) and third (0.77 [0.58–1.01]) years after starting ART, but was more similar in the fourth (0.90 [0.67–1.20]), fifth (1.36 [0.98–1.88]), and sixth (1.10 [0.44–2.73]) years (overall heterogeneity p value over years on ART $p=0.001$). 6% of follow-up time to last ART assessment (471/7397 person-years) was spent on second-line treatment in CDM group versus 9% in LCM group (700/7528 person-years).

459 (28%) CDM participants versus 356 (21%) LCM participants had a new WHO stage 4 event or died (6.94 [95% CI 6.33–7.60] and 5.24 [4.72–5.81] per 100 person-years, respectively). The absolute difference of 1.70 per 100 person-years (95% CI 0.87–2.54) translated into a relative HR of 1.31 (95% CI 1.14–1.51; $p=0.0001$; figure 3). The upper (but not lower) 95% confidence limit was greater than the predefined non-inferiority margin of 1.18.

New WHO stage 4 event-free survival at 5 years was 72% (95% CI 70–74) in the CDM group versus 78% (76–80) in the LCM group, and the number needed to monitor for 1 year to avoid one event was 59. 62% (408/654) of all new WHO stage 4 events and 65% (248/382) of deaths occurred in the first 2 years. In a prespecified subgroup analysis, event rates were similar in CDM and LCM groups during the first 90 days (29.6 [95% CI 24.7–35.5] vs 30.8 [25.7–36.8] per 100 person-years), 90 days to 1 year (7.2 [5.8–8.9] vs 7.0 [5.6–8.7] per 100 person-years), and the second year (5.4 [4.3–6.7] vs 4.4 [3.4–5.6] per 100 person-years) on ART. From the third year, event rates continued to decrease in both groups, but were 1.5–2.0-fold higher in the CDM than in the LCM group (6.0 [4.8–7.5] vs 3.1 [2.3–4.2] per 100 person-years in the third year, 4.9 [3.8–6.3] vs 2.6 [1.8–3.6] per 100 person-years in the fourth year, 4.3 [3.2–5.9] vs 2.1 [1.4–3.2] per 100 person-years in the fifth year; heterogeneity $p=0.001$). 65% of the difference between CDM and LCM in time to first new WHO stage 4 event or death was explained by adjusting for latest CD4-cell count, suggesting that the later switching leading to lower CD4-cell group in the CDM group was driving the differences between groups.

Similar results were obtained for new or recurrent WHO stage 4 event-free survival (HR 1.27 [95% CI 1.11–1.46]; $p=0.0004$). Oesophageal candidosis (178/452 [39%] in CDM group vs 100/328 [30%] in LCM group), cryptococcosis (87/452 [19%] vs 69/328 [21%] LCM group), and extrapulmonary tuberculosis (76/452 [17%] vs 72/328 [22%]) were the most common new or recurrent WHO stage 4 events, with the largest difference between groups in oesophageal candidosis.

218 (13%) CDM versus 164 (10%) LCM participants died (2.9 [95% CI 2.6–3.4] vs 2.2 [1.9–2.5] per 100 person-years, respectively; absolute difference 0.77 per 100 person-years [0.25–1.28], figure 3). 5-year

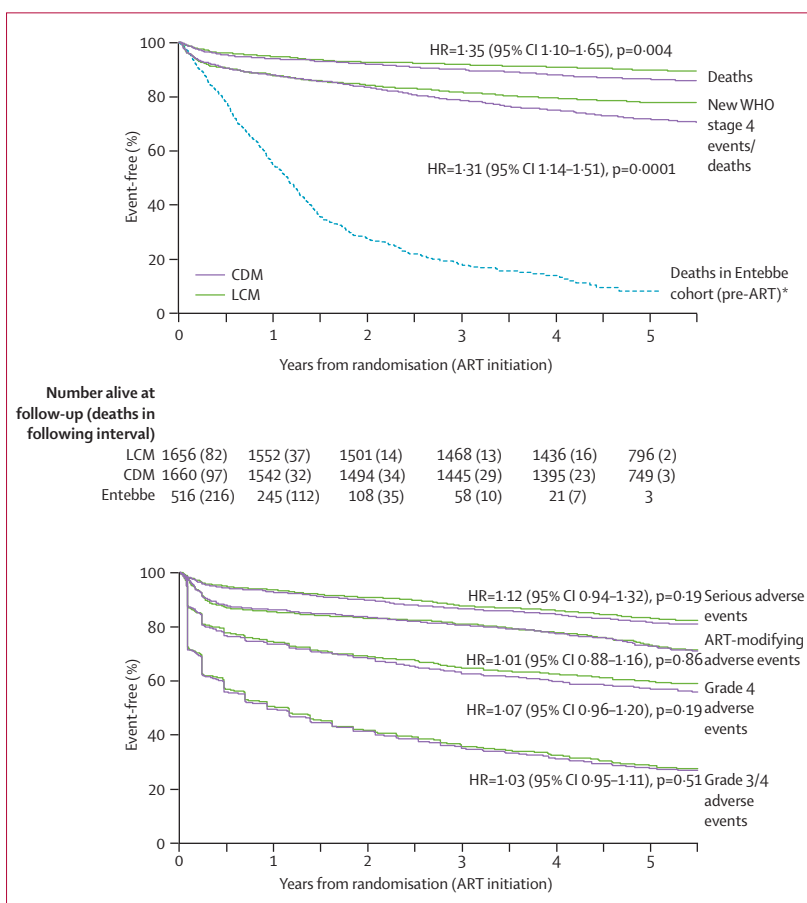


Figure 3: Clinical disease progression (A) and adverse events (B)

All hazard ratios were stratified according to randomisation factors, and p values were calculated with the log-rank test. Number needed to monitor for 1 year to avoid one (first) event was 130 (death) and 59 (new WHO stage 4 event of death) participants. Survival p values were 0.95 at 1 year, 0.92 at 3 years, and 0.90 at 5 years for laboratory and clinical monitoring (LCM) group; 0.94, 0.90, and 0.87 for clinically driven monitoring (CDM) group; and 0.55, 0.18, and 0.08 for the Entebbe²⁵ cohort, respectively. HR=hazard ratio. ART=antiretroviral therapy. *Data from HIV-infected population of similar disease stage between 1996 and 2000.

survival with ART was 87% (95% CI 85–88) in the CDM group versus 90% (88–91) in the LCM group, and the number needed to monitor for 1 year to avoid one death was 130. 105 deaths in the CDM group versus 71 in the LCM group were judged to be mainly HIV-related; and eight versus 11 deaths to be mainly drug-related (ART or concomitant).

CD4-cell counts increased throughout the trial (figure 4), with 82% (551/672) of CDM and 86% (623/728) of LCM participants having CD4 counts greater than 200 cells per μ L at week 264 (5.1 years, $n=1400$). Median CD4 counts for the 2337 participants last seen alive on first-line ART was 339 cells per μ L (IQR 225–467) in the CDM group and 372 cells per μ L (251–499) in the LCM group, with 81 of 1178 (7%) versus 22 of 1159 (2%), respectively, having CD4 counts less than 100 cells per μ L (figure 4). More CDM than LCM participants also had low CD4-cell counts at death on first-line treatment. At switch to second-line treatment,

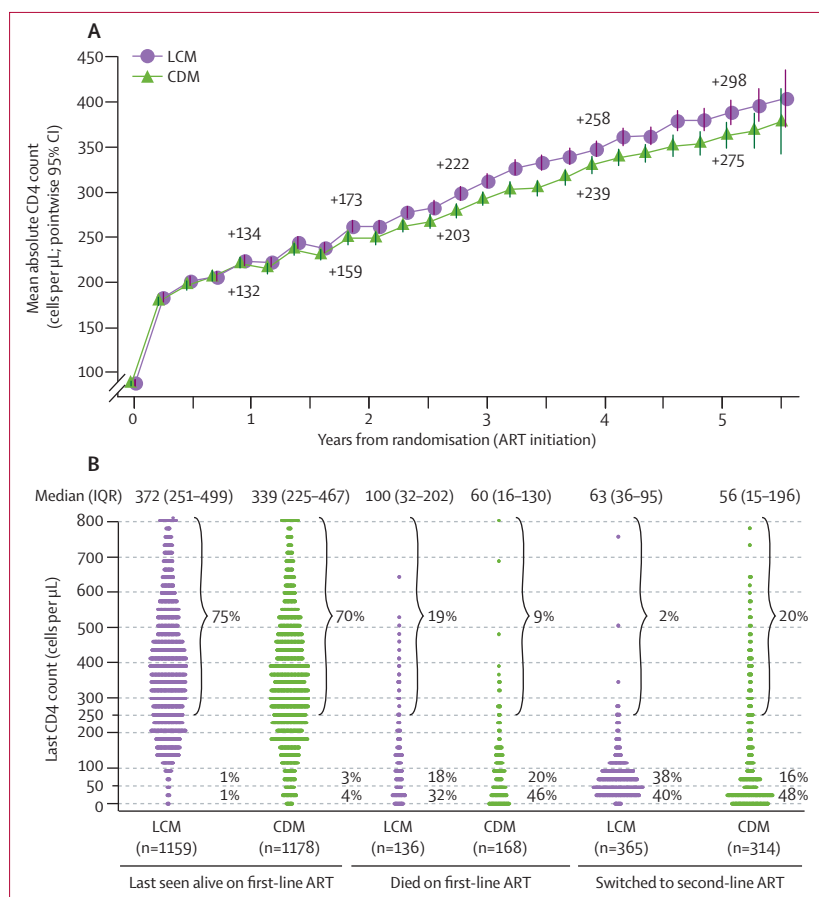


Figure 4: CD4-cell counts

(A) Mean absolute CD4-cell count with time (unadjusted). CD4-cell counts were done every 12 weeks—small decreases at weeks 60, 84, and 108 are a result of the structured treatment interruption randomisation (terminated). Increase in mean CD4 count in the first 12 weeks was 102 cells per μL (95% CI 98–106) in clinically driven monitoring (CDM) group versus 103 cells per μL (99–107) in laboratory and clinical monitoring (LCM) group ($p=0.77$). Mean increase per year was subsequently 35 cells per μL (33–37) in CDM group and 42 cells per μL (40–44) in LCM group ($p<0.0001$). (B) Last CD4-cell count on first-line antiretroviral therapy (ART) or at switch to second-line ART. Number of deaths was 82 during the first year on first-line ART and 37 in the second year in LCM group and 97 during the first year on first-line ART and 32 in the second year in CDM group.

151 of 314 (48%) CDM versus 145 of 361 (40%) LCM participants had CD4 count less than 50 cells per μL ; 64 (20%) CDM participants who switched did so with CD4 counts greater than 250 cells per μL compared with only seven (2%) LCM participants.

Despite large differences in the number of laboratory toxicity tests in the two groups, the proportion of participants having one or more serious adverse events (co-primary endpoint) was similar (283 [17%] in CDM group vs 260 [16%] in LCM group; figure 3). The most common type was hospital admissions (266/650 serious adverse events: 155 in CDM and 111 in LCM groups), and the most common diagnosis was anaemia (137/650 serious adverse events: 76 in CDM and 61 in LCM groups, webappendix p 2). 422 (25%) CDM participants and 416 (25%) LCM participants had adverse events leading to first-line or second-line ART modification (HR 1.01 [95% CI 0.88–1.16]; $p=0.86$), with anaemia the most common

cause (312/1252 modifications; 173 in CDM group vs 139 in LCM group) followed by lipodystrophy or lipoatrophy (113 vs 128) and neutropenia (81 vs 124). Similar proportions of participants had one or more grade 3 or 4 adverse events (1168 [70%] in CDM group vs 1151 [70%] in LCM group) or grade 4 adverse events (683 [41%] vs 643 [39%]). However, most grade 3–4 adverse events (2617/3533 [74%] vs 2024/3024 [67%]) and many individual grade 4 adverse events (592/1223 [48%] vs 442/1004 [44%]) were laboratory toxicity without clinical symptoms, most frequently neutropenia.

Discussion

DART was designed as a large non-inferiority trial with sufficient power to establish whether routine toxicity and efficacy monitoring on ART had an important long-term effect on clinical outcomes in Africa. The results clearly show that first-line ART can be delivered safely without routine biochemistry and haematology monitoring for toxic effects, but that routine CD4-cell count monitoring has a small but significant benefit in terms of disease progression and mortality, probably owing to slightly earlier switching to second-line ART.

In the original trial design, clinically relevant inferiority was predefined as a small increase in new WHO stage 4 events or death from 10 per 100 person-years in the LCM group to 11.8 per 100 person-years in the CDM group. To show that the effect of CDM was no more than this increase was regarded as an acceptable definition of non-inferiority; given the likely costs of routine laboratory monitoring, small differences would be unlikely to be cost effective and given the potential of CDM to allow wider ART rollout in Africa. CDM was clearly not non-inferior, with a significant increase recorded in disease progression and death. However, since the 95% CI for the co-primary endpoint new WHO stage 4 event or death included our predefined non-inferiority margin, we also cannot formally state that CDM was inferior.

CDM in DART was not implemented as no laboratory monitoring—all participants had a CD4-cell count done to establish eligibility for ART, and participants assigned to CDM could have investigations and blood tests (apart from CD4-cell count) that are necessary to manage clinical episodes, as could be feasible outside a trial setting. Indeed, with well supervised and supported clinical care that is freely available to participants, 87% survival at 5 years was achieved in the CDM group—much better than predicted given that a third of participants had CD4 count less than 50 cells per μL at ART initiation, and among the best reported in Africa^{16–18} and worldwide.^{19,20} This finding clearly shows that good ART outcomes with low mortality can be attained without routine laboratory monitoring.

Irrespective of monitoring strategy, overall survival at 5 years was 88% (death rate 2.56 per 100 person-years). The huge survival benefits from ART are well documented by historical comparison within the Entebbe centre¹⁷

(figure 3). More than 80% of participants started ART with triple nucleoside reverse transcriptase inhibitors, allaying concerns that these regimens have suboptimum clinical efficacy. High loss to follow-up can underestimate mortality, but with the very high retention sustained through 6 years, we are confident that the trial results are robust. Although quality of care might vary between ART programmes, and rarely matches that provided in well resourced clinical trials, we see no reason why the additional effect of routine laboratory monitoring should depend on the level of care provided. If anything, the interpretation of routine laboratory results by less well trained and supervised health-care workers with little access to diagnostic services and in-patient facilities would tend to weaken the usefulness of the results and provide relatively less benefit than the small differences recorded here.

Routine haematology and biochemistry toxicity laboratory monitoring did not affect time to first serious adverse event, grade 3–4 or 4 adverse event, or ART-modifying toxic effects. First-line substitution rates were similar across groups, with about 20% of participants using alternative or substituted first-line regimens at 5 years. These results should be generalisable to all currently used first-line regimens, given that stavudine toxic effects are mostly clinical (ie, would not be likely to be affected by routine laboratory monitoring for toxic effects) and that more than 900 DART participants took nevirapine, 547 from the start of ART. The number of additional tests done was generally greater in the LCM group than in the CDM group, suggesting that routine monitoring promotes, rather than prevents, extra tests being done.

Routine efficacy monitoring with CD4 tests every 12 weeks had no discernible effect in the first year on ART, but resulted in higher rates of switch to second-line therapy from the second year on ART, small but significant decreases in the proportion of person-years spent with low CD4-cell counts, and lower rates of HIV disease progression and death from the third year on ART (but not before) than in CDM. Of note, a fifth of participants assigned to CDM with clinically-identified failure had CD4 counts greater than 250 cells per μL , confirming previous reports that laboratory and clinical failure criteria do not always agree.^{21,22} Although small compared with the effect of ART, the identified benefits of CD4-cell count monitoring are highly unlikely to be attributable to chance, and further assessment of less frequent CD4 measurements (eg, every 6 months) and targeted CD4-cell counts to confirm immunological failure at suspected clinical failure is needed. All DART participants had CD4-cell counts measured before ART initiation and were screened for haematological and biochemical abnormalities. DART cannot therefore inform the debate about use of CD4-cell counts to establish eligibility for ART or the value of routine pre-ART laboratory screening.

In a parallel, individual-patient, cost-effectiveness analysis (data not published), routine laboratory

monitoring every 12 weeks for toxic effects was particularly expensive. In the LCM group, early switching to second-line ART, although lowering costs of hospital admissions, resulted in significantly greater costs of second-line drugs. Therefore overall costs of CDM were much lower than were those of LCM, and LCM, as implemented in DART, was not cost effective on the basis of present WHO recommendations for sub-Saharan Africa of three times gross domestic product per head²³—about US\$1200 in Uganda and Zimbabwe. Further continuing sensitivity analyses are exploring the cost-effectiveness of scenarios, including routine CD4-cell count but not laboratory monitoring for toxic effects while on ART. If budget constraints necessitate choices in where best to allocate scarce resources, our data suggest that a greater public health effect would be gained from widening access to ART for untreated patients with low CD4-cell counts who are at high risk of mortality rather than providing routine laboratory monitoring for people already receiving ART.

DART has several potential limitations. Randomisation was open, although members of the Endpoint Review Committee were masked to allocation. Although clinicians were encouraged to report all potential endpoints, WHO stage 4 events might have been under-reported in LCM participants with higher CD4-cell counts; however, this would reduce differences between groups in event-free survival. In the few instances in which CDM participants reported obtaining external CD4-cell counts during the trial, clinicians remained masked. In a survey at DART exit, only 81 of 1281 (6%) CDM participants reported having CD4-cell counts done privately, half having only one test. Finally, real-time viral load testing was not feasible when DART started. Detailed analyses of viral load and resistance assays undertaken on stored specimens are in progress, and will inform the debate about how best to use these tests in ART programmes in Africa.

Few studies are available with which to compare DART results. The randomised HBAC trial compared clinical monitoring with CD4-cell monitoring and with CD4-cell plus virological monitoring in more than 900 patients followed up for 3 years.⁴ Investigators reported that the use of routine CD4-cell count monitoring was associated with fewer new AIDS-defining events or death than was clinical monitoring alone, which is a similar finding to DART. However, switching rates were highest in the clinical group, making interpretation difficult. A modelling study also projected very small differences between virological, CD4-cell count, and clinical monitoring strategies to 5 years.²⁴

DART results have major implications for ART programmes in Africa at a time when there is uncertainty about long-term funding and sustainability and when most people still cannot access treatment.²⁵ We have shown that routine laboratory monitoring for toxic effects in HIV patients receiving ART has no benefit. ART can be

delivered safely with good quality clinical care, allowing treatment delivery to be decentralised. Small differences in disease progression suggest a role for CD4-cell testing from the second year on ART to guide the switch to second-line ART and should encourage accelerated development of simpler, cheaper, point-of-care CD4 tests. Laboratories will remain important for assessment of eligibility for ART, in terms of CD4-cell count and contraindications for specific drugs, and for diagnosis and management of opportunistic infections and clinical toxicity. With less need to provide routine monitoring, particularly for toxicity, funding can be focused on drug procurement, strengthening of diagnostic laboratory services, and training and supervision for health-care workers to foster quality clinical monitoring, to support scale-up of ART rollout to rural Africa where 60% of the HIV-infected population live.

Contributors

The DART trial was designed by C F Gilks, P Mugenyi, J Hakim, A Reid, D Bray, J H Darbyshire, D M Gibb, and A G Babiker. The trial was undertaken in Uganda by P Mugenyi, H Grosskurth, E Katabira, C Kityo, P Munderi, and F Ssali; and in Zimbabwe by J Hakim and A Reid. The trial was coordinated in the UK by D M Gibb, C F Gilks, A G Babiker, and A S Walker. A S Walker and A G Babiker wrote the trial analysis plan, which all authors then reviewed; and A S Walker did the analyses. All authors contributed to interpretation of the data. A S Walker wrote the first draft of the paper with D M Gibb, A G Babiker, J H Darbyshire, and C F Gilks. All authors revised the report critically and approved the final version.

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Conflicts of interest

All members of the Analysis and Writing Committee declare that they have no conflicts of interest.

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