

Monitoring of HIV viral loads, CD4 cell counts, and clinical assessments versus clinical monitoring alone for antiretroviral therapy in rural district hospitals in Cameroon (Stratall ANRS 12110/ESTHER): a randomised non-inferiority trial



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Summary

Background Scaling up of antiretroviral therapy in low-resource countries is done on the basis of decentralised, integrated HIV care in rural facilities; however, laboratory monitoring is generally unavailable. We aimed to assess the effectiveness and safety of clinical monitoring alone (CLIN) in terms of non-inferiority to laboratory and clinical monitoring (LAB).

Methods We did a randomised, open-label, non-inferiority trial in nine rural district hospitals in Cameroon. Eligible participants were adults (≥ 18 years) infected with HIV-1 group M (WHO disease stage 3–4) who had not previously received antiretroviral therapy, and were followed-up for 2 years by health-care workers in routine activities. We randomly assigned participants (1:1) to CLIN or LAB (counts of HIV viral load and CD4 cell every 6 months) groups with a computer-generated list. The primary outcome was non-inferiority of CLIN to LAB in terms of increase in CD4 cell count with a non-inferiority margin of 25%. We did all analyses in participants who attended at least one follow-up visit. This trial is registered with ClinicalTrials.gov, number NCT00301561.

Findings 238 (93%) of 256 participants assigned to CLIN and 221 (93%) of 237 assigned to LAB were eligible for analysis. CLIN was not non-inferior to LAB; the mean increase in CD4 cell count was 175 cells per μL (SD 190, 95% CI 151–200) with CLIN and 206 (190, 181–231) with LAB (difference -31 [-63 to 2] and non-inferiority margin -52 [-58 to -45]). Furthermore, in the predefined secondary outcome of treatment changes, 13 participants (6%) in the LAB group switched to second-line regimens whereas no participants in the CLIN group did so ($p < 0.0001$). By contrast, other predefined secondary outcomes were much the same in both groups—viral suppression (< 40 copies per mL; 465 [49%] of 952 measurements in CLIN vs 456 [52%] of 884 in LAB), HIV resistance (23 [10%] of 238 participants vs 22 [10%] of 219 participants), mortality (44 [18%] of 238 vs 32 [14%] of 221), disease progression (85 [36%] of 238 vs 64 [29%] of 221), adherence (672 [63%] of 1067 measurements vs 621 [61%] of 1011), loss to follow-up (21 [9%] of 238 vs 17 [8%] of 221), and toxic effects (46 [19%] of 238 vs 56 [25%] of 221).

Interpretation Our findings support WHO's recommendation for laboratory monitoring of antiretroviral therapy. However, the small differences that we noted between the strategies suggest that clinical monitoring alone could be used, at least temporarily, to expand antiretroviral therapy in low-resource settings.

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Introduction

Scaling up of antiretroviral therapy in low-resource countries has mostly been achieved through the public-health approach promoted by WHO.^{1,2} Taking into account the need for such treatment and the financial and infrastructural restrictions of health facilities, this approach recommends treatment of all patients with an advanced stage of HIV disease even if viral loads and CD4 cell counts are not available. A mathematical modelling study suggested that use of antiretroviral therapy without monitoring of viral loads or CD4 cell counts would not have distinct detrimental effects on survival of patients or development of resistance.³ Nevertheless, in the home-based AIDS care (HBAC) trial⁴

in Uganda disease progression to death or new AIDS-defining event was faster in patients who were provided antiretroviral therapy without monitoring of viral load and CD4 cell count than in those who had such tests. Furthermore, the Development of AntiRetroviral Therapy in Africa (DART) trial⁵ in Uganda and Zimbabwe showed that routine monitoring of the CD4 cell counts has a small but significant benefit in terms of disease progression and mortality.

The revised 2010 WHO guidelines⁶ recommend use of viral-load measurements (if available) to detect or confirm treatment failure and to inform the decision to switch to second-line regimens (in addition to immunological and clinical monitoring). However, evidence to support this

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recommendation is scarce in low-resource settings. Moreover, the WHO scale-up strategy is based on decentralised, integrated delivery of HIV care in rural districts where most people live, but local health facilities generally have low-grade equipment.¹⁷ In this study, we aimed to assess non-inferiority of an exclusively clinical monitoring strategy compared with a clinical monitoring strategy plus laboratory monitoring (including of viral load) in terms of effectiveness and safety in patients who had not had antiretroviral therapy and were followed up in rural district hospitals in Cameroon.

Methods

Study design and participants

We did a randomised, controlled, open-label, non-inferiority trial in nine rural district hospitals in Cameroon. Participants were recruited between May 23, 2006, and Jan 31, 2008, and followed up for 24 months by hospital health-care workers involved in routine activities. Patients were eligible if they were 18 years or older and had confirmed HIV-1 group M infection, WHO clinical stage 3 or 4, or WHO clinical stage 2 with a total lymphocyte count of fewer than 1200 cells per μL . Patients were ineligible if they were unlikely to attend follow-up in district hospitals regularly, for example because they lived far away from the hospital or had difficulty in accessing it. Other exclusion criteria were HIV-1 serotypes O or N or HIV-2 infection, active tuberculosis and total lymphocyte count of more than 1200 cells per μL , active malignant disease (apart from mucocutaneous Kaposi's sarcoma), active psychiatric disorders, hepatocellular insufficiency, previous antiretroviral therapy, present intake of corticosteroids, immunomodulators, or other experimental drugs, or pregnancy. The protocol was approved by the National Ethics Committee of Cameroon and the Institutional Ethics Committee of the French Institut de Recherche pour le Développement. All patients provided written informed consent.

Randomisation and masking

Participants were randomly allocated (1:1) at enrolment to receive either laboratory and clinical monitoring (LAB; measurement of viral load and CD4 cell count every 6 months, plus clinical monitoring every 3 months) or clinical monitoring alone (CLIN; every 3 months); both groups had haematological and biochemical tests. The computer-generated, sequentially numbered randomisation list with block sizes of 100 was prepared centrally and only visible to the project supervisor (GL-B). For every eligible participant, the project supervisor allocated a monitoring strategy to the local doctor who initiated antiretroviral therapy. Participants, health-care workers, and data analysers were not masked to group allocation.

Procedures

Participants attended clinical visits at weeks 0 and 2, months 1 and 3, and every 3 months thereafter. At week 2

and months 3, 9, 15, and 21, nurses assessed participants in the CLIN group and, in the case of adverse events, referred them to doctors for care. Systematic appointments with doctors were scheduled for all other visits. Participants in the LAB group were supposed to be seen by doctors for all study visits. Participants could also attend clinics at any time that they felt unwell. Clinical staging of HIV disease was based on the 2006 revised WHO classification.⁸ Treatment failure was defined in the LAB group as a persistent viral load of more than 5000 copies per mL on two consecutive samples, 3 months apart, and by persistent (new or recurrent) WHO stage 3 or 4 adverse event in the CLIN group after the first 6 months. Clinical and biological adverse events were graded according to the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) toxic effects scale.⁹

CD4 cell counts (FACSCount device, Becton Dickinson, Mountain View, CA, USA) and plasma viral loads (RealTime HIV-1 assay, Abbott Molecular, Des Plaines, IL, USA) were recorded at baseline and every 6 months thereafter. We assessed genotypic mutations associated with antiretroviral drug resistance with the Abbott Viroseq assay (Celera Diagnostics, Alameda, CA, USA) when the viral load was higher than 5000 copies per mL on two consecutive samples or when the patient's last viral load was higher than this threshold. We tested samples that had a viral load of more than 5000 copies per mL and, if positive, corresponding baseline samples. Mutations were classified as minor or major by use of the ANRS consensus statements on antiretroviral drug resistance version from July, 2010.¹⁰ We assessed CD4 cell counts, viral load, and resistance in a reference HIV laboratory in Yaoundé (Cameroon). All results for participants in the LAB group were returned immediately to doctors. Results for participants in the CLIN group were retained at the reference laboratory until month 24.

The first-line antiretroviral regimen was stavudine (or zidovudine), lamivudine, and nevirapine (or efavirenz), at the treating doctor's discretion. Treatment change was allowed in case of drugs-related adverse events or failures. The second-line regimen was lopinavir, ritonavir, and two nucleoside reverse transcriptase inhibitors (NRTIs). Tenofovir, emtricitabine, didanosine, and abacavir became available during the study. Treatment was dispensed once per month at district hospitals' pharmacies. We assessed adherence to treatment at months 1, 3, 6, and every 6 months thereafter through community health workers on the basis of patients' responses about dose-taking for the previous 4 days, adjusted for responses about the preceding 4 weeks.^{11,12} Participants who did not attend scheduled appointments were phoned or visited at home.

The primary outcome was mean increase in CD4 cell count from treatment initiation to month 24. Secondary outcomes were viral-load suppression, mortality, new or

recurrent WHO stage 3 or 4 adverse events, HIV resistance mutations, loss to follow-up, adherence, treatment changes, clinical and biological side-effects related to antiretroviral drugs, effect on patients' daily life, acceptability by patients and health-care workers of the particular strategy, and cost-effectiveness. Effects on patients' daily life, acceptability by patients and health-care workers, and cost-effectiveness will be reported separately.

Statistical analysis

We initially calculated a total sample size of 340 participants to obtain 80% power to show a non-inferior increase in CD4 cell counts in the CLIN group compared with the LAB group, at a 5% significance level.¹³ We made this calculation on the basis of results from a previous study in Yaoundé in which the mean increase in CD4 cell count with laboratory monitoring was 140 cells per μL (SD 130).¹⁴ The Shapiro ($p=0.78$) and skewness ($p=0.56$) tests confirmed that the distribution of the CD4 increase was normally distributed. CD4 cell count increases in the CLIN group were prespecified as non-inferior to those in the laboratory-monitoring group if the difference was 25% or less. This difference was regarded as clinically acceptable because of expected financial and infrastructural difficulties in implementation of laboratory monitoring in rural facilities for many years to come, and because of the urgent need to scale-up antiretroviral therapy. We initially assumed a maximum of 20% of participants would die or be lost to follow-up and the total sample size was increased to 430. After the trial began, we noted a higher-than-anticipated rate of deaths in both groups and reassessed the rate of participant discontinuation as 25%; 454 participants were then needed to maintain statistical power.

The independent data safety and monitoring board (based in Paris, France) met every 12 months to review interim data for recruitment of patients and follow-up, safety, and effectiveness. An interim analysis of the increase in CD4 cell count and mortality was done on June 9, 2009, when 50% of randomly allocated participants had reached month 24. The data safety and monitoring board subsequently advised the investigators to continue the trial without any change.

We did all analyses for participants who were randomly allocated to monitoring groups and had at least one follow-up visit. No patients switched groups. We compared the difference between the two groups in terms of mean increase in CD4 cell count from baseline to 24 months by comparison of the lower limit of the 95% CI for the reported difference to the upper limit of the 95% CI for the non-inferiority margin (ie, -25% of the mean increase in CD4 cell counts in the LAB group). Because such an analysis with two bilateral 95% CIs resulted in an α coefficient of less than 5% (predefined value for the sample size calculation), we repeated it with 90% CIs to obtain an α close to 5%.

The primary analysis was done with all participants who attended at least one follow-up visit and a last-

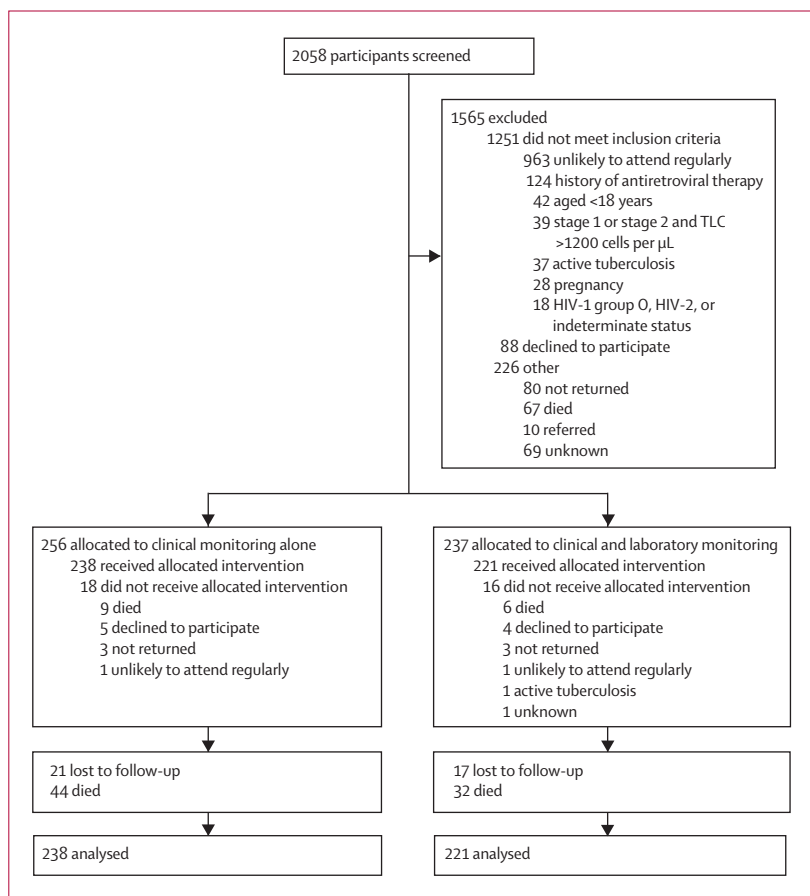


Figure 1: Trial profile
TLC=total lymphocyte count.

observation carried forward imputation was applied for participants whose CD4 data were missing at 24 months. The secondary analysis only involved participants with available CD4 data at 24 months. The proportion of participants with viral load of fewer than 40 copies per mL was compared between both groups with mixed-effect logistic regression models. The primary analysis regarded missing data as failure whereas the secondary analysis only included available data. We compared proportions at 24 months with standard logistic regression. We did survival analyses with the Kaplan-Meier method and Cox proportional hazard models. We double-entered and checked data with Microsoft Access and analysed data with Stata version 10.1.

This trial is registered with ClinicalTrials.gov, number NCT00301561.

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

We randomly allocated 493 patients to intervention groups (figure 1); of whom 238 (93%) of 256 in the CLIN group and 221 (93%) of 237 in the LAB group attended at least one follow-up visit. The most frequent reason for ineligibility was presumed difficulty in regular attendance of the district hospital, especially for patients living far away (60%). Baseline characteristics were balanced between groups (table 1).

Median follow-up was 24 months (IQR 19–24) for patients in the CLIN group and 24 months (23–24) in the LAB group ($p=0.47$). Overall follow-up in the CLIN group was 385.9 person-years and 369.0 person-years in the LAB group. Completeness of visits was lower in the CLIN group (2106 [80%] of 2618 visits) than it was in the LAB group (2035 [84%] of 2431; $p=0.003$). 21 (9%) of

238 participants in the CLIN group and 17 (8%) of 221 participants in the LAB group were lost to follow-up (incidence of 5.2 per 100 person-years for the CLIN group and 4.3 per 100 person-years for the LAB group; incidence rate ratio [IRR] 1.20, 95% CI 0.59–2.47; $p=0.60$). In the CLIN group, 1087 (93%) of 1172 visits at months 0, 1, 6, 12, 18, and 24 were done by doctors (ie, 7% by nurses alone), and 736 (79%) of 934 visits at 2 weeks and 3, 9, 15, and 21 months were done by nurses alone (21% by doctors alone or with nurses). In the LAB group, 1846 (91%) of 2035 visits were done by doctors (9% by nurses alone).

37 (16%) of 238 participants in the CLIN group and 37 (17%) of 221 participants in the LAB group substituted at least one antiretroviral drug because of treatment-related adverse events, yielding an incidence of 10.8 per 100 person-years for CLIN and 11.1 per 100 person-years for LAB (IRR 0.97, 95% CI 0.60–1.58; $p=0.90$). 13 (6%) of 221 participants in the LAB group switched to second-line regimens after a median follow-up of 18 months (IQR 17–20; incidence 3.6 per 100 person-years) because of treatment failure, whereas no participants in the CLIN group did so ($p<0.0001$). Switching occurred after a median time of 8 months (IQR 6–10) from the first viral load of more than 5000 copies per mL. Overall, 33 (15%) of 221 participants in the LAB group had confirmed viral loads of more than 5000 copies per mL, of whom 22 (67%) had resistance (including the 13 participants who switched). Virological failure was due to adherence issues only for the 11 participants without resistance. Self-reported complete adherence, for the whole study period, was 63% (672 of 1067 measures) in the CLIN group and 61% (621 of 1011) in the LAB group ($p=0.47$) and, at 24 months, was 57% (91 of 161) in the CLIN group and 56% (87 of 155) in the LAB group ($p=0.94$).

In the primary analysis, the mean increase in CD4 cell count from baseline to month 24 was 175 cells per μL (SD 190, 95% CI 151–200) in participants in the CLIN group and 206 cells per μL (190, 181–231) in participants in the LAB group (figure 2); the mean difference was therefore -31 cells per μL (95% CI -63 to 2). The lower limit of the 95% CI for the reported difference was lower than was the upper limit of the 95% CI for the non-inferiority margin (-52 cells per μL , -58 to -45). The analysis on the basis of 90% CIs also did not show non-inferiority (-58 to -3 for the reported difference and -57 to -46 for the non-inferiority margin).

At month 24, 165 (69%) of 238 participants in the CLIN group and 169 (76%) of 221 participants in the LAB group had available CD4 cell counts and were therefore included in the secondary analysis. The mean increase in CD4 cell count was 220 cells per μL (SD 187, 95% CI 192–249) in the CLIN group and 245 cells per μL (187, 217–274) in the LAB group (figure 2). The lower limit of the 95% CI for the reported difference (mean -25 cells per μL , 95% CI -64 to 14) was also lower than the upper

	Clinical monitoring group (n=238)	Laboratory plus clinical monitoring group (n=221)
Sex		
Female	166 (70%)	158 (71%)
Male	72 (30%)	63 (29%)
Age (years)	36 (30–44)	37 (31–45)
Level of education*		
No formal education	5 (2%)	5 (2%)
Primary school	106 (46%)	95 (45%)
Secondary school or higher	117 (51%)	112 (52%)
Marital status†		
Married or cohabiting	78 (34%)	62 (29%)
Divorced or separated	5 (2%)	8 (4%)
Widowed	28 (12%)	31 (15%)
Single	118 (52%)	111 (53%)
Time taken to reach district hospital‡		
<30 min	110 (49%)	83 (40%)
30–60 min	60 (27%)	74 (36%)
>60–120 min	37 (16%)	31 (15%)
>120 min	18 (8%)	17 (8%)
Head of the household§		
No	138 (61%)	122 (58%)
Yes	88 (39%)	90 (42%)
Economically active¶		
No	99 (49%)	91 (47%)
Yes	105 (51%)	104 (53%)
Water supply*		
Private tap or mineral water	41 (18%)	27 (13%)
Public tap	14 (6%)	20 (9%)
Fitted well or bored well with pump	121 (53%)	121 (57%)
Purchase or unfitted well or spring	43 (19%)	41 (19%)
Other	8 (4%)	4 (2%)
WHO clinical stage		
2	1 (1%)	0
3	174 (73%)	163 (74%)
4	63 (26%)	58 (26%)
Bodyweight (kg)	55 (49–60)	55 (49–61)

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limit of the 95% CI for the non-inferiority margin (−61 cells per μL , 95% CI −68 to −54). The analysis done on the basis of 90% CIs again did not show non-inferiority (−58 to 7 for the reported difference and −67 to −56 for the non-inferiority margin).

During follow-up, viral load was fewer than 40 copies per mL in 465 (49%) of 952 measurements in the CLIN group and in 456 (52%) of 884 measurements in the LAB group, if missing data were regarded as failure (odds ratio [OR] 0.78, 95% CI 0.44–1.39, $p=0.40$; figure 2). At month 24, 111 (47%) of 238 participants in the CLIN group and 115 (52%) of 221 participants in the LAB group had an undetectable viral load (OR 0.81, 95% CI 0.56–1.16; $p=0.25$). In the secondary analysis done on the basis of available data only, the proportion of follow-up viral loads of fewer than 40 copies per mL was 65% in both groups (465 of 717 measurements in CLIN and 456 of 703 measurements in LAB; OR 0.96, 95% CI 0.61–1.52, $p=0.88$; figure 2). At month 24, the proportion of undetectable viral loads was 66% in participants in the CLIN group and 68% in participants in the LAB group (OR 0.93, 95% CI 0.59–1.47; $p=0.76$). Of the 13 participants in the LAB group who switched to second-line regimens, six had a viral load of more than 5000 copies per mL at month 24, one had a viral load of 2385 copies per mL, one had a viral load of 41 copies per mL, and three had a viral load of fewer than 40 copies per mL (one patient was lost to follow-up and testing was not done for the other patient).

Genotypic resistance was assessed in 34 (14%) of 238 participants in the CLIN group and 33 (15%) of 221 participants in the LAB group with viral loads of more than 5000 copies per mL during follow-up. Major mutations associated with antiretroviral drug resistance were detected from the baseline samples of two male participants in the LAB group and were excluded from further analyses. Analyses of the patients' last samples with high viral load showed the presence of major mutations in 23 (10%) of 238 participants in the CLIN group and 22 (10%) of 219 participants in the LAB group ($p=0.89$, table 2). All 45 participants had resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs), specifically nevirapine and efavirenz. 17 (7%) of 238 participants in the CLIN group and 18 (8%) of 219 participants in the LAB group also had resistance to NRTIs, specifically to lamivudine and emtricitabine. Groups did not differ in terms of the number of drugs to which the participants had resistance.

44 (18%) of 238 participants in the CLIN group died (11.5 deaths per 100 person-years), as did 32 (14%) of 221 in the LAB group (8.8 deaths per 100 person-years)—hazard ratio of 1.31 (95% CI 0.83–2.06, $p=0.25$; figure 3). Survival at month 24 was 81% (95% CI 75–85) in the CLIN group and 85% (80–89) in the LAB group.

85 (36%) of 238 participants in the CLIN group and 64 (29%) of 221 participants in the LAB group had

	Clinical monitoring group (n=238)	Laboratory plus clinical monitoring group (n=221)
(Continued from previous page)		
Body mass index (kg/m^2)	19.9 (18.4–21.8)	20.1 (18.2–22.1)
CD4 cell count (cells per μL)	179 (68–323)	182 (96–345)
HIV-1 viral load (\log_{10} copies per mL)	5.6 (5.3–6.1)	5.6 (5.0–6.0)
Haemoglobin (g/L)	98 (85–110)	96 (85–112)
Neutrophils (cells per μL)	1665 (1050–2890)	1750 (960–2700)
Platelets (cells per μL)	204 000 (157 000–268 000)	211 000 (169 000–278 000)
Aspartate aminotransferase (IU/L)	28 (20–42)	30 (20–44)
Alanine aminotransferase (IU/L)	19 (12–31)	20 (13–32)
Amylase (IU/L)	81 (60–108)	79 (60–105)
Creatinine ($\mu\text{mol}/\text{L}$)	80 (62–97)	80 (62–106)
Blood glucose (mmol/L)	5.0 (4.3–5.8)	5.1 (4.3–5.9)
Total cholesterol (mmol/L)	3.1 (1.9–4.2)	3.1 (1.8–4.3)
Triglycerides (mmol/L)	1.1 (0.6–1.6)	1.0 (0.6–1.7)
Initial antiretroviral regimen		
Stavudine, lamivudine, and nevirapine	153 (64%)	151 (68%)
Stavudine, lamivudine, and efavirenz	44 (18%)	38 (17%)
Zidovudine, lamivudine, and nevirapine	22 (9%)	12 (5%)
Zidovudine, lamivudine, and efavirenz	19 (8%)	20 (9%)
Co-trimoxazole prophylaxis	230 (97%)	211 (95%)

Data are n (%) or median (IQR). *Data missing for 19 participants. †Data missing for 18 participants. ‡Data missing for 29 participants. §Data missing for 21 participants. ¶Data missing for 60 participants. ||Data missing for one participant.

Table 1: Baseline characteristics of participants

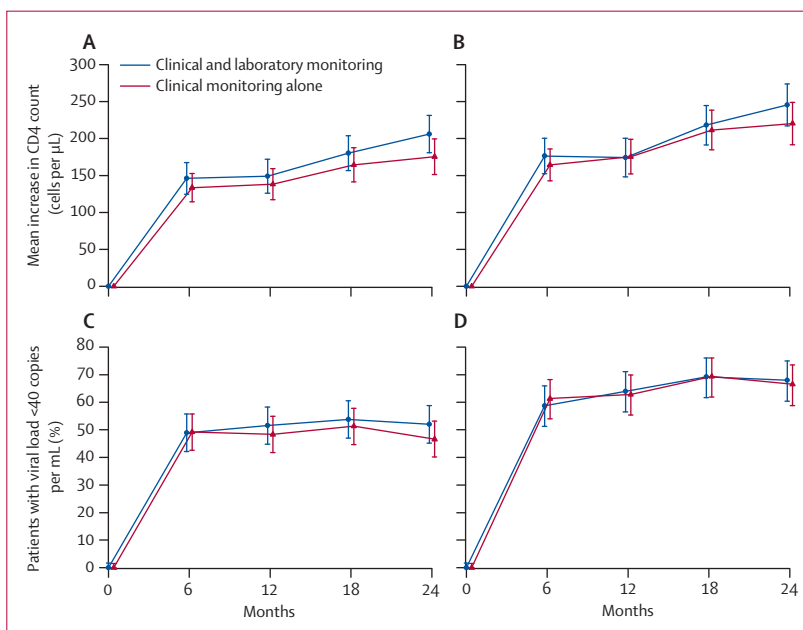


Figure 2: Immunovirological responses to antiretroviral therapy

Mean increase in CD4 cell count from the last-observation carried forward imputation method (A) and from reported data only (B). Proportion of participants with plasma HIV-1 viral load below 40 copies per mL, regarding missing data as failure (C) and from reported data only (D). Vertical bars are 95% CIs.

disease progression to new or recurrent WHO stage 3 or 4 adverse events or death; incidence was 26.6 per 100 person-years for CLIN and 19.9 per 100 person-years

	Clinical monitoring group (n=238)	Laboratory plus clinical monitoring group (n=219)
Overall	23 (10%)	22 (10%)
Non-nucleoside reverse transcriptase inhibitors	23 (10%)	22 (10%)
Nevirapine	3	0
Nevirapine and efavirenz	15	17
Nevirapine, efavirenz, and etravirine	5	4
Nevirapine, efavirenz, and etravirine*	0	1
Nucleoside reverse transcriptase inhibitors	17 (7%)	18 (8%)
Lamivudine/emtricitabine	11	15
Lamivudine/emtricitabine and abacavir	1	0
Lamivudine/emtricitabine, stavudine, and zidovudine	2	2
Lamivudine/emtricitabine, stavudine, zidovudine, abacavir, and tenofovir*	1	0
Lamivudine/emtricitabine, stavudine, zidovudine, abacavir, and didanosine	0	1
Lamivudine/emtricitabine, stavudine, abacavir, tenofovir, and didanosine*	2	0

Data are n (%) or n. *Possible resistance.

Table 2: Genotypic resistance to antiretroviral therapy

for LAB (HR 1·30, 95% CI 0·94–1·80, $p=0\cdot11$; figure 3). Survival without new or recurrent WHO stage 3 or 4 adverse events at month 24 was 63% (95% CI 56–69) in the CLIN group and 69% (62–75) in the LAB group. 51 (21%) of 238 participants in the CLIN group and 40 (18%) of 221 participants in the LAB group had WHO stage 3 adverse events, whereas 18 (8%) of 238 participants and 12 (5%) of 221 participants, respectively, had WHO stage 4 adverse events. 28 (12%) of 238 participants in the CLIN group had WHO stage 3 or 4 adverse events after the first 6 months but none of these events persisted as defined for clinical failure.

Grade 3 or 4 toxic effects related to antiretroviral therapy were reported in 46 (19%) of 238 participants in the CLIN group (60 events; incidence 13·9 per 100 person-years) and 56 (25%) of 221 participants in the LAB group (69 events; 18·2 per 100 person-years); hazard ratio 0·77 (95% CI 0·52–1·14, $p=0\cdot19$; figure 3). Laboratory side-effects predominated in both groups (52 [87%] of 60 events in the CLIN group and 58 [84%] of 69 events in the LAB group).

Discussion

Clinical monitoring alone is not non-inferior to clinical monitoring plus laboratory monitoring in terms of mean increase in CD4 cell count to 2 years. Moreover, more patients followed up with the LAB strategy switched to second-line treatment than did those in the CLIN group; antiretroviral resistance was detected in all cases. By contrast, the two monitoring strategies did not differ in terms of viral suppression, emergence of HIV resistance, mortality, disease progression, adherence, loss to follow-up, or incidence of toxic effects. Survival at 24 months was very similar between groups.

Thus, although the immunological recovery was good with both monitoring strategies compared with other studies in Africa,^{14–17} we cannot confirm that CLIN would not result in substantially reduced effectiveness when compared with that of LAB follow-up.¹⁸ Notably, the difference in methodology (non-inferiority test for immunological outcome vs superiority test for viral suppression) explains the apparent contradiction between the failure to show the non-inferiority of the CD4 cell count increase with CLIN and the equivalent virological effectiveness between the two strategies.

Detection of treatment failure with CLIN, leading to switching of antiretroviral therapy is a key issue. Although 12% of participants in the CLIN group had WHO stage 3 or 4 adverse events after the first 6 months and 10% of participants had HIV resistance, none was switched to a second-line regimen on the basis of our clinical definition—several possible reasons for this finding exist. First, the adverse events that occurred during the study were reversed because of adherence interventions combined with adequate care. Second, the patients with adverse events subsequently died or were lost to follow-up. Third, our study only lasted 2 years, but clinical diagnosis of treatment failure frequently occurs after 2 years. Finally, adverse events might have been underdiagnosed because of the difficulty of use of the WHO clinical staging of HIV disease for health-care staff who are inexperienced (most of them in our trial) or had little experience in HIV-related care¹⁹ and a heavy workload or little laboratory support. The poor sensitivity of clinical criteria for detection of treatment failure has already been reported, for example in South Africa.²⁰

In participants monitored with the LAB strategy, switching to second-line regimens occurred late after the first detectable viral load (median time 8 months) because of the difficulty for the health-care workers and participants to adapt the scheduled follow-up and because of laboratory constraints (ie, remoteness of our rural district hospitals from the laboratory in Yaoundé and logistical constraints). Furthermore, eight of 13 participants who switched to second-line regimens still had virological failure at month 24 (two were not assessed), probably because of adherence issues. Nonetheless, although the LAB strategy was not perfect, failure to show non-inferiority of CLIN suggests a potential benefit of LAB.

In the absence of LAB, especially monitoring of viral load, late clinical diagnosis of treatment failure leads to the accumulation of genotypic drug-resistant mutations that might compromise the efficacy of second-line regimens and favour the transmission of antiretroviral-resistant HIV strains.^{21,22} In our trial, the rates of resistance were similar between the two monitoring strategies but notably these results were only reported in the first 2 years. As expected in a trial (although the patients were managed by non-specialist health-care

workers in rural district hospitals), the rates of overall resistance (10%) were lower than were those in a routine HIV/AIDS outpatient clinic in Yaoundé (17% at month 24 in one study²³ and 16% after a median follow-up of 10 months in another²⁴).

Participants in both groups were reviewed by nurses instead of doctors in accordance with the WHO recommendation of task shifting.¹ This practice was unlikely to bias our comparison because participants in both groups were mostly reviewed by doctors, almost all doctors (and nurses) were initially inexperienced in HIV care, many doctors were transferred to other health facilities during the study and were replaced by others (who in turn were generally inexperienced), nurses were trained before and during the study with the doctors, and task shifting is effective.^{25–28} The joint management of patients by doctors and nurses in our trial suggests applicability of our findings to routine care.

In addition to our trial, the HBAC⁴ and DART⁵ trials have compared CLIN with different strategies that combine laboratory monitoring for ART in low-resource countries (panel). Nevertheless, our study is distinct for several reasons. First, viral load and CD4 cell count were measured every 6 months, as recommended by WHO.⁶ Second, participants were managed by local non-specialist health-care workers in rural district hospitals in which scale-up of antiretroviral therapy is underway. Third, antiretroviral therapy was started on the basis of WHO clinical criteria alone (ie, CD4 cell count was not used), in accordance with routine clinical practice in most settings. Finally, the emergence of HIV resistance was assessed.

Weaknesses of our study were the fairly short follow-up and small sample size. Inferiority of immunological recovery with clinical monitoring or significant differences between the two monitoring strategies for secondary outcomes (eg, disease progression) might have been reported with a longer follow-up or more participants. The exclusion of patients who were unlikely to attend regularly might reduce external validity because these patients are supposed to be less adherent and at higher risk of treatment interruption and HIV resistance; laboratory monitoring would therefore have allowed early detection of treatment failure and promote the switch to second-line regimens in a higher proportion of patients. However, increased adherence to these more complex regimens and subsequent follow-up is doubtful as shown by the fact that only three of 13 patients who switched to second-line regimens had undetectable viral loads at month 24. The large size of randomisation blocks could explain the difference in the number of participants between the clinical and laboratory groups. However, the groups were similar regarding all baseline characteristics. The study nurses and doctors were not blinded to study group; this is unlikely to have introduced any bias into assessment of outcomes (including the more subjective

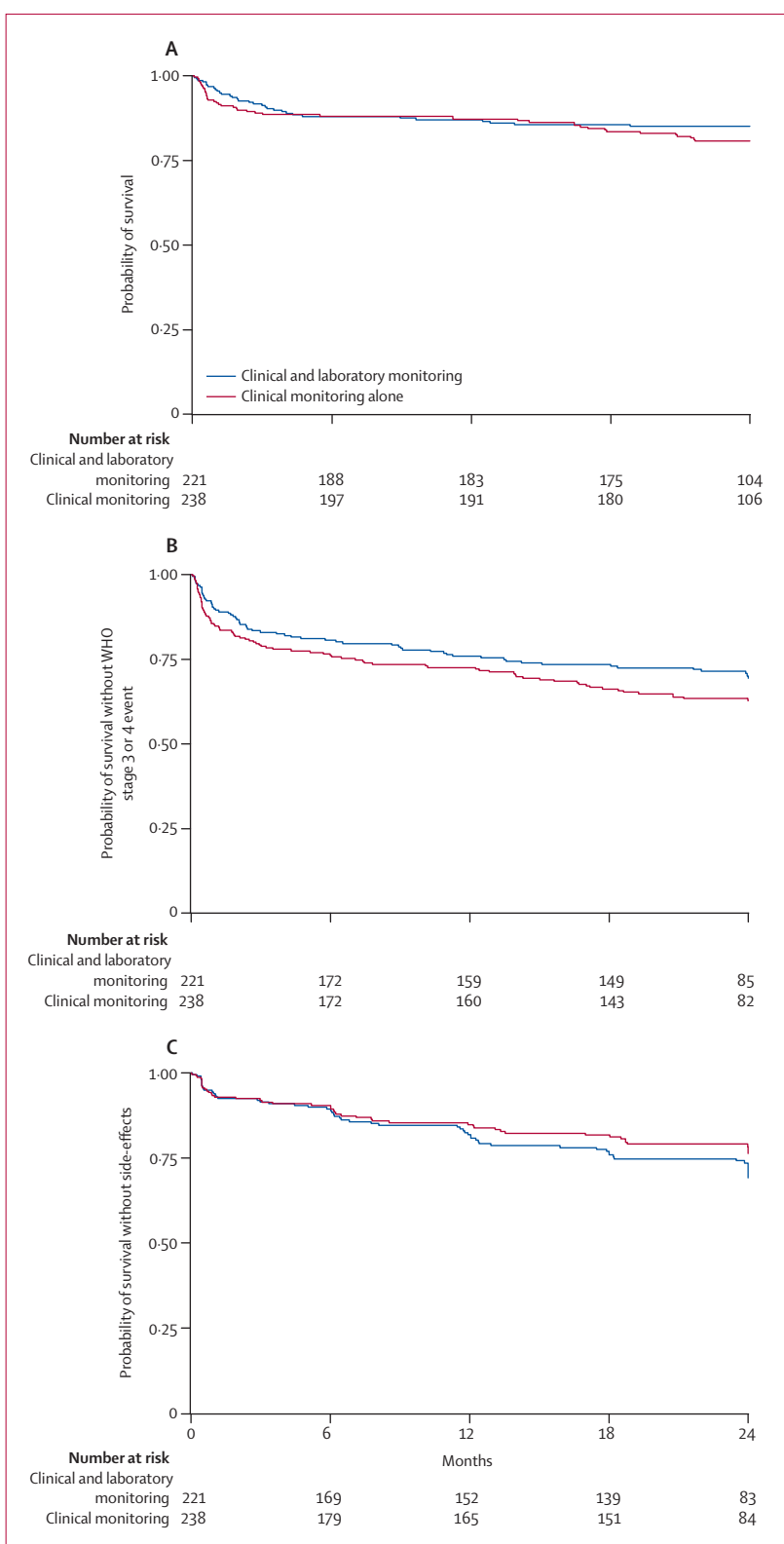


Figure 3: Kaplan-Meier curves of survival probability

Overall survival probability (A). Survival without new WHO stage 3 or 4 adverse events (B). Survival without grade 3 or 4 antiretroviral drugs-related side-effects (C).

Panel: Research in context**Systematic review**

We searched the Medline database from Aug 1, 1998, to Nov 23, 2010, without language restrictions, for randomised controlled trials that compared clinical monitoring of antiretroviral therapy with laboratory monitoring with the search terms “antiretroviral”, “laboratory” OR “biologic” OR “biological” OR “viral load” OR “CD4”, “monitoring”, “Africa” OR “resource-limited” OR “resource-poor” OR “resource-constrained” OR “developing”, and “trial”. We identified two randomised trials, the DART trial⁵ in Uganda and Zimbabwe and a cluster trial²⁹ in Zambia. We discussed the findings of the DART trial here, but the report of the second trial only included the study design, implementation, and baseline cohort characteristics. We also searched abstracts from major conferences and identified the home-based AIDS care (HBAC) trial⁶ in Uganda.

Interpretation

Our results support the WHO recommendation for laboratory monitoring of antiretroviral therapy when possible to improve quality of HIV care. This finding underlines the need for the development of simple and affordable point-of-care tests or alternative methods for viral-load measurement. In the meantime, the few overall differences that we noted between clinical and laboratory monitoring suggest that clinical monitoring alone could be used, at least temporarily, to expand antiretroviral therapy (which is the top priority) in low-resource settings that have financial and infrastructural constraints.

outcomes such as WHO stage 3 or 4 events) owing to local organisation.

Thus, the inability to show non-inferiority of immunological recovery and detect a need to switch to second-line treatment with CLIN supports the WHO recommendation for laboratory monitoring of antiretroviral therapy when possible to improve the quality of HIV care. Nevertheless, we suggest that the overall differences between the two strategies are small, and that CLIN could be used in patients who are antiretroviral therapy naive to expand treatment (which is the top priority) and to take into account financial and infrastructural constraints in low-resource settings. Some amount of laboratory monitoring at the programmatic scale should almost always be undertaken. Operational research (including laboratory measurements) to establish the overall success of the programmes is at least as crucial as provision of individual scale clinical monitoring.

Contributors

CL, CK, and ED designed and coordinated the trial. CL did the statistical analysis and wrote the first draft of the report. CK and GL-B coordinated the implementation of the trial. GL-B, SB, MPC, J-MM, MD, and SK contributed to data collection. AFA did the main laboratory analyses. JBTM and NM contributed to the data analysis of the primary outcome. All authors contributed to the interpretation of data and reviewed the report.

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Conflicts of interest

We declare that we have no conflicts of interest.

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