The DART Trial: ‘The Doctor’s Dilemma’ revisited

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Treatment of HIV infection in developing countries, particularly those in Africa, is still a major challenge to healthcare systems with limited laboratory resources. While drug costs have fallen to levels where antiretroviral therapy is now possible in these countries, questions remain regarding the effect of scarce laboratory resources on treatment monitoring and, hence, outcome. The DART trial aimed to measure the effect of laboratory monitoring. This randomized controlled trial evaluated the differences between routine laboratory monitoring and monitoring driven by clinical events, and was conducted between January 2003 and December 2008 at sites in Uganda and Zimbabwe. The results indicate that clinically driven monitoring is likely to be more cost-effective in this resource-limited situation.

Keywords: HIV, HAART, resource-limited countries, cost-effectiveness

With the advent of treatment regimens that efficiently suppress HIV replication, a disease that was universally fatal became a manageable condition. In places with broad access to antiretroviral therapy (ART), it is now possible to significantly lower the burden of the disease and reduce costs through the treatment of related conditions, such as opportunistic infections.

Treatment of HIV infection in developing countries, particularly in Africa, is still a major challenge to healthcare systems. Infected individuals in these countries exert increasing pressure on health services with limited laboratory resources for diagnosis and follow-up of patients. Some argue that broader access to ART in resource-constrained settings is not feasible given the high cost of drugs, poor socioeconomic conditions that are likely to be associated with poor adherence and the lack of laboratory infrastructure to provide optimal monitoring. However, in recent years, competition from generic manufacturers has led to sharp decreases in drug prices. Reports indicate that adherence to treatment in developing countries is at least as good as in developed countries. On the other hand, there are scant data to determine whether the limited availability of laboratory monitoring significantly affects clinical outcomes.

The DART trial was designed to evaluate the need for routine laboratory monitoring in African adults who fulfilled clinical and immunological criteria for ART initiation. DART was an open label, randomized, non-inferiority study conducted in Uganda and Zimbabwe between January 2003 and December 2008. The primary endpoints referred to efficacy (development of a new WHO stage 4 event/AIDS or death) and safety (development of any serious non-HIV-related adverse event). The study design is shown in Figure 1. Briefly, participants were randomized to receive quarterly routine laboratory monitoring [laboratory and clinical monitoring (LCM) arm] or laboratory monitoring driven by clinical events [clinically driven monitoring (CDM) arm]. Viral load (VL) monitoring was not provided to either group. In the LCM arm, switch to a second-line regimen was triggered by the occurrence of pre-defined clinical or immunological events. For patients in the CDM arm, treatment changes were driven by clinical events only. Switching treatment before 48 weeks was discouraged in both arms.

Some 6578 patients were screened, and 3316 patients were randomized to either the CDM or LCM arm and included in the final intention-to-treat analysis. Both arms were comparable with respect to baseline characteristics (Table 1). After a median follow-up of 4.9 years for both arms, 81% in the CDM arm and 78% in the LCM arm were still on first-line treatment; 17% in both arms had substituted one or more components of the initial ART regimen, largely because of adverse events (AEs).

Four hundred and fifty-nine (28%) patients in the CDM arm and 356 (21%) patients in the LCM arm developed a new or recurrent WHO stage 4 clinical condition, or died; 62% of the WHO stage 4 conditions and 65% of the deaths occurred in the first 2 years of...
The absolute difference was 1.70 per 100 person-years [95% confidence interval (CI) 0.87–2.54], with a relative hazard ratio of 1.31 (95% CI 1.14–1.51; \( P = 0.0001 \)). Although statistically significant, the upper 95% confidence limit was greater than the pre-defined margin for non-inferiority of 1.18.

The rate of development of new WHO stage 4 conditions was similar between the two arms during the first 2 years of treatment. Event rates decreased thereafter in both arms, but were 1.5- to 2-fold higher in the CDM arm (\( P = 0.001 \)). This is not surprising, since a new or recurrent WHO stage 4 event was the only condition driving the switch to second-line ART in the CDM arm. Therefore, participants randomized to this arm had to develop such an event before therapy could be changed, whereas participants in the LCM arm could have regimen changes prompted by a decline in CD4 counts, a strong predictor of the development of new clinical events.

The 5 year survival rate was 87% in the CDM arm and 90% in the LCM arm. There were 218 and 164 deaths in the CDM and LCM arms, respectively (hazard ratio for death in CDM arm = 1.35, 95% CI 1.10–1.65; \( P = 0.004 \)), an extraordinary result given the advanced stage of the disease at study entry (median CD4 count of 86 cells/mm\(^3\)). These results are even more impressive when compared with historical controls from the pre-ART era. In a large cohort followed between 1996 and 2000 in a Ugandan site that took part in DART, the 5 year survival rate for patients with similar baseline CD4 counts was 8%.\(^7\) It should be noted that in DART, the first-line regimens used were not the ones generally recommended in developed countries. Most patients received regimens containing three nucleoside analogue reverse transcriptase inhibitors, which have been shown to be virologically inferior to non-nucleoside reverse transcriptase inhibitor- or protease inhibitor (PI)-based regimens.\(^8,9\) Second-line treatment, which included a boosted PI, was prescribed for only 22% and 19% in the CDM and LCM arms, respectively. Thus, it is reasonable to assume that PI use was not the main reason for the excellent 5 year survival rates in both arms. Given the 87% and 90% survival rates at 5 years in the CDM arm and LCM arm, respectively, it is likely that the impact on prognosis of routine VL monitoring, were it available, would have been modest, at best.

### Figure 1. DART study design.

#### Table 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>LCM arm (N=1656)</th>
<th>CDM arm (N=1660)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>1092 (66)</td>
<td>1064 (64)</td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>36 (18–67)</td>
<td>36 (18–73)</td>
</tr>
<tr>
<td>CD4 cell count, cells/mm(^3), median</td>
<td>86 (0–199)</td>
<td>86 (1–199)</td>
</tr>
<tr>
<td>&lt;50 CD4 cells/mm(^3), n (%)</td>
<td>554 (33)</td>
<td>555 (33)</td>
</tr>
<tr>
<td>HIV-RNA, log(_{10}) copies/mL, mean ± SD(^a)</td>
<td>5.4 ± 0.7</td>
<td>5.4 ± 0.7</td>
</tr>
<tr>
<td>WHO stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>363 (22)</td>
<td>310 (19)</td>
</tr>
<tr>
<td>3</td>
<td>916 (55)</td>
<td>948 (57)</td>
</tr>
<tr>
<td>4</td>
<td>377 (23)</td>
<td>402 (24)</td>
</tr>
<tr>
<td>On co-trimoxazole before/at ART, n (%)</td>
<td>1014 (61)</td>
<td>1034 (62)</td>
</tr>
<tr>
<td>ART, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZDV/3TC/TDF</td>
<td>1232 (74)</td>
<td>1237 (75)</td>
</tr>
<tr>
<td>ZDV/3TC/ABC</td>
<td>150 (9)</td>
<td>150 (9)</td>
</tr>
<tr>
<td>ZDV/3TC/NVP</td>
<td>274 (16)</td>
<td>273 (16)</td>
</tr>
<tr>
<td>Identified at any time (including post-baseline) as having previously received ART, n (%)</td>
<td>65 (4)</td>
<td>65 (4)</td>
</tr>
<tr>
<td>Previous ART for PMTCT, no. of women (% of women)</td>
<td>23 (2)</td>
<td>38 (4)</td>
</tr>
</tbody>
</table>

\( ZDV, \) zidovudine; 3TC, lamivudine; TDF, tenofovir; ABC, abacavir; NVP, nevirapine; PMTCT, prevention of mother-to-child-transmission.\(^a\) Measured in a subset (n=968) at baseline only.

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3316 ART-naive adults with WHO stage 2, 3 or 4 HIV disease, CD4 <200 cells/mm\(^3\) initiating ART

Randomized

**LCM arm**
- 12 weekly biochemistry, full blood and CD4 counts
- Other investigations and concomitant medications if clinically indicated
- Switch to second-line treatment for new/recurrent WHO stage 4 condition OR new/recurrent multiple WHO stage 3 conditions OR CD4 <100 cells/mm\(^3\)

**CDM arm**
- Biochemistry, full blood returned only if clinically indicated or in case of grade 4 toxicity
- CD4 count never returned
- Other investigations and concomitant medications if clinically indicated
- Switch to second-line treatment for new/recurrent WHO stage 4 condition OR new/recurrent multiple WHO stage 3 conditions
There are limited long-term data on co-trimoxazole prophylaxis efficacy in Africa. In DART, it was provided at the discretion of clinicians to 60% of participants at study entry and 27% after ART initiation. Prophylaxis was associated with a significant reduction in the risk of overall mortality in the first 12 weeks of ART [odds ratio (OR) 0.41, 95% CI 0.27–0.65], a benefit that was sustained through to week 72 (OR 0.56, 95% CI 0.37–0.86).10 Given that co-trimoxazole use was not randomized, it is not possible to rule out prescription bias. In addition to a significant reduction in the incidence of malarial and bacterial infections, there was a reduction in the number of deaths through other causes among those who were prescribed co-trimoxazole prophylaxis. Furthermore, the impact on survival was the same among patients with CD4 cell counts above or below 200 cells/mm$^3$ during the first 72 weeks of follow-up. After this period, however, a survival benefit was no longer observed, irrespective of the CD4 cell count. Guidelines for the prevention of opportunistic infections in HIV-infected patients in the developed world usually recommend that co-trimoxazole prophylaxis be discontinued once the CD4 counts has remained >200 cells/mm$^3$ for >3 months.11 Results from DART suggest that in Africa the positive impact of co-trimoxazole prophylaxis is maintained for the first 72 weeks of ART, even after the CD4 cell count has risen to >200 cells/mm$^3$.

A separate analysis from DART has cast doubts on the cost-effectiveness of routine laboratory monitoring to prevent the morbidity and mortality that can be associated with drug toxicities.12 In DART, routine performance of biochemistry and haematology tests every 12 weeks cost almost US$700 per patient, as compared with US$175 for CD4 cell monitoring. Given that the incidence of serious AEs was similar in both arms (283 (17%) in the CDM arm and 260 (16%) in the LCM arm), regular laboratory monitoring did not seem to contribute to their prevention. It should be noted that serious laboratory abnormality results were promptly made available to patients in both arms. However, very few results needed to be released (<4%) and more additional investigations were requested during nurse or extra visits in the LCM arm than in the CDM arm (P<0.0001).

There are concerns about the long-term effects of tenofovir on renal function, particularly in patients with prior kidney disease. DART provided an excellent opportunity to investigate the risk of renal impairment in an African population using tenofovir-based combinations. The study found that severe decreases in glomerular filtration rates (GFRs) were infrequent across all treatment regimens. Overall, after 192 weeks of follow-up, 75/2618 (2.9%) patients developed severe GFR impairment on current or after past tenofovir use versus 14/698 (2.0%) who had never taken tenofovir (P=0.21), with no significant difference between the study arms.13 Two deaths were associated with renal impairment and considered to be related to ART, both in patients receiving tenofovir. This is a low event rate, since >2100 participants received tenofovir.

It has been suggested that inadequate laboratory monitoring might be associated with a higher frequency of selection of resistant viruses, due to delays in identification of virological failure. NORA was a substudy of DART that compared nevirapine with abacavir, both in combination with zidovudine and lamivudine. After 48 weeks of follow-up there was more extensive genotypic resistance in both treatment groups than is generally reported in randomized clinical trials. Of the 89 samples obtained at week 48 from patients with a plasma VL of >1000 copies/mL, one or more major resistance mutations were detected in 88% and 82% of the abacavir and nevirapine groups, respectively (P=0.5).14 Thymidine-associated mutations (TAMs) were significantly more common and more numerous in the abacavir than in the nevirapine group, and the median number of TAMs was relatively small. None of the patients whose viruses were shown to harbour resistance mutations had been considered a treatment failure by immunological or clinical criteria, a finding that underscores the importance that targeted VL measurement might have to prevent selection and transmission of resistance mutations.15

In resource-limited settings, access to ART is still the most important issue. Although coverage has dramatically increased in the past few years (~4 million individuals on treatment at the end of 2009), <50% of those in immediate need of therapy are receiving it.16 Moreover, because the epidemic continues to grow unabated, for every patient who starts ART in developing countries, two individuals become infected with HIV.

Another major impediment is the lack of appropriate laboratory support. Thus, strategies that do not rely on a sophisticated infrastructure but allow ART to be safely delivered to a larger number of individuals are desperately needed. In this context, the results of DART are of enormous importance. Despite having enrolled patients with very advanced HIV disease, the limited number of therapeutic options available and the high background mortality in the economically deprived settings where DART was conducted, it was possible to achieve survival rates that are not dissimilar from those reported from developed countries. These results likely reflect strong commitment to therapy by study participants, which is reflected in the very low loss to follow-up rate (7% in 5 years).

It can be argued that more rigid laboratory monitoring and earlier switch to second-line treatment might impact survival. The higher survival rate in the LCM arm apparently lends support to this contention. Nonetheless, the 3% gain in survival rate after 5 years of follow-up must be weighed against the costs incurred by this strategy. To avoid one AE per year required monitoring 59 patients, while avoiding one death per year required monitoring 130 patients. On the other hand, for every US$1 million spent on ART over a 5 year period, the LCM strategy would allow 292 patients to be treated, whereas the CDM strategy would provide treatment for 401 patients, a difference of 109 patients receiving therapy. Thus, mirroring ‘The Doctor’s Dilemma’, the CDM strategy could potentially increase the number of patients on ART by almost 40%, while condemning 3% to a potentially avoidable death.

Transparency declarations
None to declare.

References


