

Opportunities for improving the efficiency of paediatric HIV treatment programmes

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Objectives: To conduct two economic analyses addressing whether to: routinely monitor HIV-infected children on antiretroviral therapy (ART) clinically or with laboratory tests; continue or stop cotrimoxazole prophylaxis when children become stabilized on ART.

Design and methods: The ARROW randomized trial investigated alternative strategies to deliver paediatric ART and cotrimoxazole prophylaxis in 1206 Ugandan/Zimbabwean children. Incremental cost-effectiveness and value of implementation analyses were undertaken. Scenario analyses investigated whether laboratory monitoring (CD4⁺ tests for efficacy monitoring; haematology/biochemistry for toxicity) could be tailored and targeted to be delivered cost-effectively. Cotrimoxazole use was examined in malaria-endemic and non-endemic settings.

Results: Using all trial data, clinical monitoring delivered similar health outcomes to routine laboratory monitoring, but at a reduced cost, so was cost-effective. Continuing cotrimoxazole improved health outcomes at reduced costs. Restricting routine CD4⁺ monitoring to after 52 weeks following ART initiation and removing toxicity testing was associated with an incremental cost-effectiveness ratio of \$6084 per quality-adjusted life-year (QALY) across all age groups, but was much lower for older children (12+ years at initiation; incremental cost-effectiveness ratio = \$769/QALY). Committing resources to improve cotrimoxazole implementation appears cost-effective. A healthcare system that could pay \$600/QALY should be willing to spend up to \$12.0 per patient-year to ensure continued provision of cotrimoxazole.

Conclusion: Clinically driven monitoring of ART is cost-effective in most circumstances. Routine laboratory monitoring is generally not cost-effective at current prices, except possibly CD4⁺ testing amongst adolescents initiating ART. Committing resources to ensure continued provision of cotrimoxazole in health facilities is more likely to represent an efficient use of resources.

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Introduction

Despite large funding increases for HIV/AIDS programmes in developing countries over the past decade, the availability of paediatric antiretroviral therapy (ART) lags behind that for adults. In the region most affected by HIV/AIDS – sub-Saharan Africa – only 32% of 1.6 million children in need of ART in 2013 received it [1]. A priority for HIV/AIDS programmes must be to reduce this large treatment gap. Economic studies can help identify how limited available resources can be cost-effectively used to meet the health needs of HIV-infected children.

The Anti-Retroviral Research for Watoto (ARROW) trial (ISRCTN24791884) was a large, long-term strategy trial in children starting ART in Africa. The two randomizations considered here showed that: routine 3-monthly CD4⁺ monitoring provided some health benefit over clinical monitoring, but only after the first year on ART; however, event rates were low, survival was high and monitoring for toxicity offered no benefit [2]; continuous cotrimoxazole prophylaxis significantly reduced hospitalizations for malaria and other infections among children aged above 3 years and who were stable on ART [3].

This study uses clinical effectiveness and resource-use data collected in the trial to investigate strategies for monitoring children on ART and use of cotrimoxazole prophylaxis, with the aim of identifying potential efficiency gains in paediatric HIV programmes to maximize health outcomes from limited available resources.

Methods

Trial summary and clinical effectiveness

In this trial, 1206 previously untreated HIV-infected children/adolescents meeting WHO 2006 criteria [4] for ART initiation were enrolled from three centres in Uganda (Joint Clinical Research Centre, Kampala; Paediatric Infectious Diseases Clinic/Baylor Uganda, Mulago; MRC/UVRI Uganda Research Unit on AIDS, Entebbe) and one in Zimbabwe (University of Zimbabwe Clinical Research Centre, Harare).

For the monitoring randomization, all 1206 children were randomized to laboratory and clinical monitoring (LCM; 12-weekly CD4⁺, haematology, biochemistry) or clinically driven monitoring (CDM; no CD4⁺, haematology/biochemistry, if needed, for clinical management). Median follow-up [inter-quartile range (IQR)] was 4.0 years (3.7–4.4) and only 3% were lost to follow-up/withdrew consent (i.e. were last seen before the study end and were not known to have died) [2]. For the cotrimoxazole prophylaxis randomization, 1012 children

(>3 years) on ART for more than 96 weeks following enrolment to the monitoring trial were approached for randomization (61 had died, were lost to follow-up or withdrew; 113 were not approached). Two hundred and fifty-two children were not randomized, mostly because their caregivers strongly believed cotrimoxazole was beneficial. Seven hundred and fifty-eight were randomized to continue or stop cotrimoxazole and were followed for a median of 107 weeks (96–117); less than 1% were lost to follow-up [3].

In the monitoring randomization, the primary endpoint (first WHO 4 event/death) rate was lower in the first year on ART in the CDM group than in the LCM group (4.1 vs. 5.8/100 child years; $P=0.2$) [2]. However, this was likely due to chance because neither group was switched to second-line ART before 48 weeks. In contrast, in years 2–5, WHO 4/death rates were significantly higher in the CDM than in the LCM group (1.3 vs. 0.4/100 child years; $P=0.002$), suggesting benefit of 3-monthly CD4⁺ monitoring in the LCM group. Adverse events and ART substitutions for toxicity were infrequent and similar in both groups.

Children stopping cotrimoxazole after 96 weeks on ART had significantly higher rates of hospitalization/death compared to those continuing cotrimoxazole [hazard ratio 1.64, 95% confidence interval (CI) 1.14, 2.37, $P=0.007$], but mortality was low and similar in both groups. Increased hospitalizations in the stop-cotrimoxazole group were for infections (such as pneumonia, meningitis and sepsis) and malaria. Significant differences in hospitalization/death were evident at even the highest CD4⁺ values and were similar in Uganda and Zimbabwe (despite differences in malaria endemicity), across all ages and in both monitoring arms [3].

Ethics approval was received for the economics study in Uganda by the National Council for Science and Technology and the Institutional Review Boards of Joint Clinical Research Council and Baylor College of Medicine; and in Zimbabwe by the Medical Research Council Institutional Review Board.

Cost and outcome estimation

Healthcare costs were estimated taking a health system perspective using the ‘ingredients’ approach [5]. Resource use data were collected on case report forms in the ARROW trial on nurse/doctor visits (routine and non-routine), antiretroviral drugs, other/concomitant medications, monitoring tests (CD4⁺ cell count, biochemistry, haematology), radiographs and blood transfusions; items not expected to be incurred for roll-out of interventions were omitted.

Resource-use items from the ARROW centres in Zimbabwe/Uganda and representative national unit costs/prices were combined to estimate the total costs

of the strategies. Some unit costs were drawn from micro-costings undertaken as part of the Development of Anti-Retroviral Therapy in Africa (DART) trial [6], which compared LCM vs. CDM in adults at the same centres where the ARROW trial was conducted. Results were qualitatively similar across sites, and pooled results are presented for a typical sub-Saharan African country using the 2012 prices.

Outcomes were evaluated in terms of quality-adjusted life-years (QALYs), a generic measure combining both mortality and morbidity effects of interventions [5] (main text) and life-years gained (online supplement, <http://links.lww.com/QAD/A602>). As there are currently no published QALY weights for HIV-infected children in Africa, we used results from a model of health state utilities for HIV-infected adults in high-income countries (see eTable one for details, <http://links.lww.com/QAD/A602>) [7,8].

Resource use, costs and health outcomes (QALYs) were estimated per 6-month time-period over 228 weeks (4.4 years) and 104 weeks (2.0 years) from the monitoring and cotrimoxazole randomizations, respectively. This time-point was chosen to ensure all WHO 4 events/deaths were included, and that most children had complete data over the follow-up period. Missing data for costs and QALYs, due to unavailable CD4⁺ tests within a 6-month period, loss to follow-up before the trial end, or when trial closure was before children reached 228 or 104 weeks follow-up, respectively, were estimated using multiple imputation by chained equations using predictive mean matching [9]. Mean CD4⁺% was used to estimate QALYs when there were multiple CD4⁺% values within a 6-month period.

The expected lifetime cost and health outcomes for sub-Saharan African children alive and on ART are still largely unknown. To estimate the long-term impacts of interventions, in a further analysis, we assumed those alive at trial end live for another 25 years, resulting in an additional 13.93 discounted QALYs (assumed QALY weight of 0.8; discounted at 3% per annum) and incur costs after the trial end of \$200 per year (much lower than current costs of providing paediatric ART; discounted at 3%), regardless of the randomization strategy [10]. This scenario can be considered as representing the maximum potential for the more effective, more expensive alternatives to be cost-effective in the long term.

Monitoring strategies (cost-effectiveness analysis)

For the monitoring strategies it was anticipated the more effective alternative (LCM) would be more costly than the less effective alternative (CDM). Cost-effectiveness was estimated by comparing incremental cost-effectiveness ratios (ICERs – the additional cost per QALY gained) of LCM vs. CDM, to a cost-effectiveness threshold [5].

The cost-effectiveness threshold represents the opportunity costs of committing resources to fund interventions in terms of health gains forgone due to resources being unavailable for the provision of alternative investments [11]. It is, therefore, crucial to have a reasonable estimate of the threshold as a basis to determine whether an intervention offers value for money in a particular healthcare system.

To capture uncertainty, results are estimated probabilistically and, for some scenarios, are presented across a range of cost-effectiveness thresholds in the form of cost-effectiveness acceptability curves (CEACs) [12]. These show the probability that an alternative is cost-effective at different levels of the threshold based upon modelled variation in patient outcomes observed.

It is challenging to assess how low ICERs should be for interventions to represent cost-effective use of finite healthcare resources. The WHO deem an intervention offering a unit of health gain (DALY-averted) at under three times gross domestic product (GDP) per capita to be 'relatively cost-effective' and less than GDP per capita 'highly cost-effective' [13]. In 2009, GDP per capita was estimated to be US\$523 in Uganda and US\$324 in Zimbabwe [14], resulting in upper thresholds of US\$1569 in Uganda and US\$972 in Zimbabwe. However, GDP-based thresholds do not adequately reflect opportunity costs, and a number of commentators believe the WHO-recommended thresholds are too high [15].

An alternative is to assess other ways in which resources can be used to generate health gains in the population. In situations when HIV treatment coverage gaps remain for both adult and paediatric ART, one option is to compare estimated ICERs with those estimated in other studies for the provision of ART with clinical monitoring versus no ART because resources could instead be used to close the ART coverage gap. Other studies have estimated these at \$600/QALY [16], \$590/LYG [17] and \$628/QALY [18] for adults. In this study, we therefore choose to assess ICERs against a benchmark of \$600 to determine whether there is a possibility the interventions may be cost-effective relative to widening ART provision.

A number of scenario analyses were undertaken to investigate conditions under which the interventions are more likely to be cost-effective. These included: restricting trial resource use and event data to after week 12 (from when the first routine measurements in LCM occurred) and week 52 (after which LCM was shown to be more effective, amounting to a strategy of introducing laboratory monitoring after 1 year on ART); removing the costs of toxicity monitoring that had no impact on adverse event outcomes and undertaking age sub-group analyses (<3, 3–6, 7–11 and 12+ years) to allow the youngest children, preadolescents and adolescents to be

considered separately. It is also likely that CD4⁺ monitoring costs will decrease in the future, as point-of-care alternatives become available, so we also investigated how a 50% reduction in CD4⁺ monitoring costs would affect cost-effectiveness.

Cotrimoxazole strategies (value of implementation analysis)

A cost-effectiveness analysis was undertaken to compare continuing versus stopping cotrimoxazole prophylaxis once children are stabilized on ART. However, since cotrimoxazole is low-cost even within the context of sub-Saharan Africa, it was expected that continuation would be cost-effective. Despite its low cost and attempts to ensure widespread provision, frequent stock-outs in health facilities have nevertheless been reported [19], indicating failure of health systems to deliver cotrimoxazole reliably to patients. This suggests that further interventions (depending on context) may be beneficial to improve implementation. Possible options include strengthening procurement systems [20,21], improving drug supply chains and tracking systems [22] or paying providers based on provision of cotrimoxazole [23].

Most initiatives to improve implementation will require financial investment and policymakers must consider the resources they might commit within the context of other competing calls on their budgets. A value of implementation analysis was undertaken to investigate under what conditions such implementation initiatives are likely to prove worthwhile [24,25]. A cost-effectiveness threshold of \$600 was assumed to reflect the opportunity costs of healthcare resources (described previously). An upper bound for how much policymakers should be willing to spend to ensure continuous cotrimoxazole prophylaxis to children on ART was estimated using the measure of incremental net monetary benefit [(difference in QALYS × threshold) – difference in costs] (see eMethods for a full explanation). Importantly, grade 3/4 toxicity did not differ in the continue/stop cotrimoxazole arms of the trial. This analysis represents a conservative estimate of the value of improving

cotrimoxazole implementation because external benefits in terms of supply of other drugs, including to other patient groups, are also likely to occur.

Results

Resource-use items associated unit costs/prices are presented in Table 1 (see eTables 2 and 3, <http://links.lww.com/QAD/A602> for antiretroviral and other/concomitant medication units costs/prices).

Monitoring strategies

Estimated total costs, QALYs and ICERs are presented by monitoring strategy in Table 2, relating to the period of trial follow-up. Estimates are based upon imputed values when data are missing (see eTable 4 on missing data, <http://links.lww.com/QAD/A602>). Counts of resource use and disaggregated costs, based on available case data, are provided in eTables 5 and 6 (<http://links.lww.com/QAD/A602>).

Using all data from initial randomization through patient follow-up to 228 weeks, the mean total costs of delivering ART with LCM (\$2327.9) were greater than that with CDM (\$1775.3). LCM offered fewer QALYs (3.9 vs. 4.0), predominantly because of the early imbalance in deaths (27 LCM vs. 13 CDM in the first year on ART). CDM therefore 'dominated' LCM, being more effective and less costly, and LCM was not cost-effective.

Restricting the analysis from 12 weeks after ART initiation to 228 weeks, mean total costs per patient were \$2132.9 (LCM) and \$1608.8 (CDM); driven overwhelmingly by higher monitoring costs with LCM (\$647 vs. \$19 CDM), representing 30% of total costs in the LCM strategy (eTable 6, <http://links.lww.com/QAD/A602>). More than half of this cost derived from routine laboratory monitoring for toxicity (haematology/biochemistry) which was shown to have no benefit [2].

Table 1. Unit costs/prices.

| Resource item | Unit cost/price | Source |
|--------------------------------------|--|--------|
| Nurse visits (routine) | \$4.59 (Entebbe), \$3.71 (JCRC), \$9.43 (Harare), \$3.71 (PIDC) | [6] |
| Doctor visits (routine) | \$4.59 (Entebbe), \$3.71 (JCRC), \$9.43 (Harare), \$3.71 (PIDC) | [6] |
| Other healthcare visits | \$3.67 (Entebbe), \$9.95 (JCRC), \$9.83 (Harare), \$9.95 (PIDC) | [6] |
| Antiretroviral therapy costs | Various (costed individually, by patient, based upon length of time on regimens – see eTable2, http://links.lww.com/QAD/A602) | [26] |
| Concomitant medications | Various (costed individually, by patient, based on non-ART drug prescriptions (see eTable 3, http://links.lww.com/QAD/A602)) | [27] |
| Hospitalizations (per inpatient day) | \$34.95 (all centres) | [7] |
| CD4 ⁺ tests | \$17.77 (Entebbe), \$11.33 (JCRC), \$18.82 (Harare), \$11.33 (PIDC) | [6] |
| Haematology panel tests | \$7.27 (Entebbe), \$8.02 (JCRC), \$13.87 (Harare), \$11.33 (PIDC) | [6] |
| Biochemistry panel tests | \$13.12 (Entebbe), \$12.01 (JCRC), \$13.76 (Harare), \$12.01 (PIDC) | [6] |
| Radiographs | \$7.19 (all centres) | [7] |
| Blood transfusions | \$20.02 (all centres) | [27] |

JCRC, Joint Clinical Research Centre; PIDC, Pediatric Infectious Diseases Clinic.

Table 2. Results (base case and alternative uses of laboratory monitoring).

| | LCM | CDM |
|--|---------------|---------------|
| Base case: using all trial data from randomization (week 0) to 228 weeks | | |
| Costs, mean (SD), US\$ | 2327.9 (24.6) | 1775.3 (20.1) |
| QALYs, mean (SD) | 3.9 (.03) | 4.0 (.02) |
| Incremental cost-effectiveness ratio (ICER) | | CDM dominates |
| Evaluated from 12 weeks after initial randomization to 228 weeks | | |
| Costs, mean (SD), US\$ | 2132.9 (20.2) | 1608.8 (18.5) |
| QALYs, mean (SD) | 3.80 (.02) | 3.79 (.02) |
| Incremental cost-effectiveness ratio (ICER) | | \$49 497/QALY |
| Evaluated from 12 weeks after initial randomization to 228 weeks; excluding toxicity testing | | |
| Costs, mean (SD), US\$ | 1815.0 (17.7) | 1592.3 (18.0) |
| QALYs, mean (SD) | 3.80 (.02) | 3.79 (.02) |
| Incremental cost-effectiveness ratio (ICER) | | \$21 023/QALY |
| Evaluated from 52 weeks after initial randomization | | |
| Costs, mean (SD), US\$ | 1659.4 (14.4) | 1243.2 (14.1) |
| QALYs, mean (SD) | 3.2 (.00) | 3.1 (.01) |
| Incremental cost-effectiveness ratio (ICER) | | \$13 896/QALY |
| Evaluated from 52 weeks after initial randomization; excluding toxicity tests | | |
| Costs, mean (SD), US\$ | 1412.9 (12.8) | 1230.6 (13.7) |
| QALYs, mean (SD) | 3.2 (.00) | 3.1 (.01) |
| Incremental cost-effectiveness ratio (ICER) | | \$6084/QALY |
| Evaluated from 52 weeks after initial randomization; excluding toxicity tests and with 50% reduction in CD4 ⁺ monitoring costs ^a | | |
| Costs, mean (SD), US\$ | 1303.5 (12.4) | 1230.6 (13.7) |
| QALYs, mean (SD) | 3.2 (.00) | 3.1 (.01) |
| Incremental cost-effectiveness ratio (ICER) | | \$2431/QALY |

CDM, clinically driven monitoring; ICER, incremental cost-effectiveness ratio; LCM, laboratory and clinical monitoring; QALY, quality-adjusted life-year. Results are based upon multiple imputation by chained equations using predictive mean matching [9], where cost and QALY data per period of analysis are missing assumed at random. ^aBase case 'fully loaded' CD4⁺ test costs are \$17.8 in Entebbe, \$11.3 in JCRC/PIDC, \$18.8 in Harare. The 50% reduction on these fully loaded costs results in CD4⁺ test costs of \$8.9 in Entebbe, \$5.7 in JCRC/PIDC, \$9.4 in Harare.

Mean QALYs were 3.80 (LCM) and 3.79 (CDM), leading to an ICER per QALY of \$49 497.

In weeks 52–228, mean total costs and QALYs were \$1659 and 3.16 (LCM) vs. \$1243 and 3.13 (CDM), leading to an ICER per QALY of \$13 896. Removing toxicity tests led to ICERs of \$21 023 and \$6084 in weeks 12–228 and 52–228, respectively.

In weeks 52–228, after removing toxicity tests, the ICERs in those initiating ART aged below 3, 3–6, 7–11 and 12+ years were \$26101, \$6277, \$5093 and \$769, respectively (see Table 3). If, in a future scenario, the costs of CD4⁺ monitoring were to fall by 50% (to \$9.4 in Zimbabwe and \$7.3 in Uganda; 'full loaded' costs reflecting capital costs and personnel time as well as consumables), these ICERs would fall to \$11 697, \$2251, \$2248 and LCM (without toxicity tests) dominating CDM, respectively (see eTables 7 and 8, <http://links.lww.com/QAD/A602> for results using the measure of life-years gained).

Cost-effectiveness acceptability curves, based on costs and health outcomes in weeks 52–228, are presented in Fig. 1, for the two selected scenarios for which routine laboratory monitoring is more likely to be cost-effective for some healthcare systems: removing costs of toxicity testing, for all trial participants; removing costs of toxicity testing and reducing costs of CD4⁺ testing by 50%, for all trial participants and by age sub-groups. These show that LCM is very unlikely to be cost-effective at thresholds

below \$2000, overall and within sub-groups, with the exception of CD4⁺ testing alone for adolescents (aged 12+), especially when testing costs are reduced.

Including increments for additional QALYs and costs for children alive at trial end led to ICERs for introducing routine CD4⁺ monitoring from 52 weeks, without toxicity testing, for ages below 3, 3–6, 7–11 and 12+ years of \$2728, \$957, \$680 and \$319 per QALY, respectively (see eTable 9, <http://links.lww.com/QAD/A602>).

Cotrimoxazole strategies

Continuing cotrimoxazole for children on long-term ART led to persistent reductions in hospitalizations and prescriptions of non-ART drugs, with accompanying reductions in costs that exceeded the costs of providing cotrimoxazole itself. Stopping cotrimoxazole is both more costly and less effective than continued provision, so is not cost-effective.

Using all available trial data, mean total health sector costs and QALYs over 104 weeks follow-up were \$947.3 and 1.867 (stopping) vs. \$926.5 and 1.872 (continuing) (Table 4). The main driver of higher costs with stopping cotrimoxazole was hospitalization costs (\$43 with stopping, \$24 with continuing), estimated based upon available use data (see eTables 10 and 11, <http://links.lww.com/QAD/A602>). The cost reduction was similar in both Uganda (\$21), a malaria-endemic country, and Zimbabwe (\$18), a non-malaria-endemic country.

Table 3. Cost-effectiveness results of laboratory monitoring strategies (age sub-group analyses).

| | LCM | CDM |
|--|---------------|----------------------------------|
| Age sub-group analyses; evaluated from 52 weeks after initial randomization, no toxicity monitoring | | |
| Under 3-year-olds | | |
| Costs, mean (SD), US\$ | 1392.1 (19.8) | 1191.5 (16.6) |
| QALYs, mean (SD) | 3.17 (.00) | 3.16 (.01) |
| Incremental cost-effectiveness ratio (ICER) | | \$26 101/QALY |
| 3–6-year-olds | | |
| Costs, mean (SD), US\$ | 1392.2 (19.2) | 1224.9 (18.3) |
| QALYs, mean (SD) | 3.2 (.00) | 3.1 (.01) |
| Incremental cost-effectiveness ratio (ICER) | | \$6277/QALY |
| 7–11-year-olds | | |
| Costs, mean (SD), US\$ | 1459.6 (22.2) | 1257.3 (19.9) |
| QALYs, mean (SD) | 3.2 (.01) | 3.1 (.02) |
| Incremental cost-effectiveness ratio (ICER) | | \$5093/QALY |
| 12+-year-olds | | |
| Costs, mean (SD), US\$ | 1340.7 (34.0) | 1282.4 (49.8) |
| QALYs, mean (SD) | 3.14 (.01) | 3.07 (.06) |
| Incremental cost-effectiveness ratio (ICER) | | \$769/QALY |
| Age sub-group analyses; evaluated from 52 weeks after initial randomization, no toxicity monitoring and fully loaded CD4 ⁺ monitoring costs reduced by 50% ^a | | |
| Under 3-year-olds | | |
| Costs, mean (SD), US\$ | 1281.4 (19.3) | 1191.5 (16.6) |
| QALYs, mean (SD) | 3.17 (.00) | 3.16 (.01) |
| Incremental cost-effectiveness ratio (ICER) | | \$11 697/QALY |
| 3–6-year-olds | | |
| Costs, mean (SD), US\$ | 1284.9 (18.3) | 1224.9 (33.6) |
| QALYs, mean (SD) | 3.2 (.00) | 3.1 (.01) |
| Incremental cost-effectiveness ratio (ICER) | | \$2251/QALY |
| 7–11-year-olds | | |
| Costs, mean (SD), US\$ | 1346.6 (21.3) | 1257.3 (19.9) |
| QALYs, mean (SD) | 3.2 (.01) | 3.1 (.02) |
| Incremental cost-effectiveness ratio (ICER) | | \$2248/QALY |
| 12+-year-olds | | |
| Costs, mean (SD), US\$ | 1247.1 (37.3) | 1282.4 (49.8) |
| QALYs, mean (SD) | 3.14 (.01) | 3.07 (.06) |
| Incremental cost-effectiveness ratio (ICER) | | LCM (without toxicity) dominates |

CDM, clinically driven monitoring; ICER, incremental cost-effectiveness ratio; LCM, laboratory and clinical monitoring; QALY, quality-adjusted life-year. Results are based upon multiple imputation by chained equations using predictive mean matching, [9] where cost and QALY data per period of analysis are missing assumed at random. ^aBase case 'fully loaded' CD4⁺ test costs are \$17.8 in Entebbe, \$11.3 in JCRC/PIDC, \$18.8 in Harare. The 50% reduction on these fully loaded costs results in CD4⁺ test costs of \$8.9 in Entebbe, \$5.7 in JCRC/PIDC, \$9.4 in Harare.

The incremental net monetary benefit (INMB) for continuous provision of cotrimoxazole depends upon the cost-effectiveness threshold. At a threshold of \$600, INMB per patient is \$24 over 2 years of trial follow-up; or equivalently \$12 per patient-year. This means that if policymakers can ensure that cotrimoxazole is provided by use of some implementation initiative costing below \$12 per patient-year (over and above the estimated \$6.51 per patient-year procurement cost of cotrimoxazole [28]), this would represent value for the health system. This indicates health systems should be willing to invest notable resources to improve continuity of cotrimoxazole provision (e.g. in a district with 2000 children on ART an investment of up to \$24 000 would be worthwhile).

Discussion

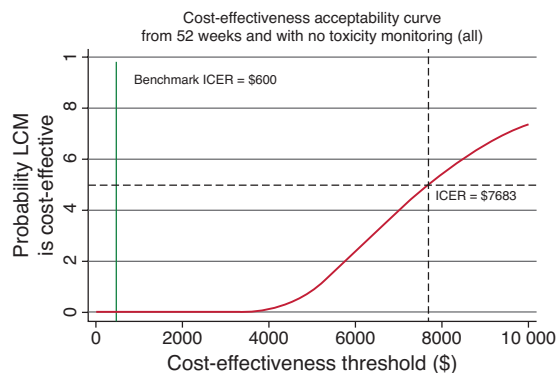
Healthcare systems in sub-Saharan Africa are severely resource-constrained and cannot meet all the health needs of HIV-infected children. Policymakers must make

difficult decisions as how best to use available resources to generate health gains. Paediatric ART is just one intervention competing for resources; other interventions, such as those aimed at HIV prevention (including from mother to child), HIV diagnosis and also non-HIV health interventions, hold equally important claims. Ensuring efficient provision of paediatric ART is important because it ensures resources committed to paediatric HIV treatment are used to greatest effect.

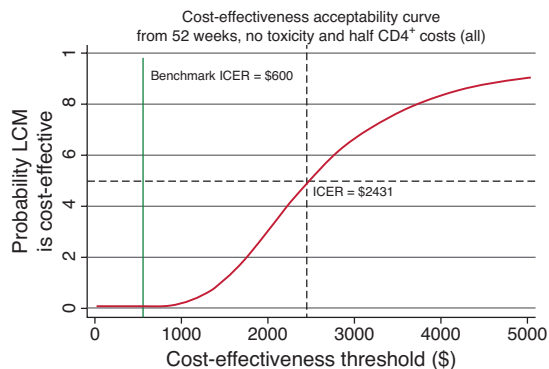
The study uses data from the ARROW trial to inform when efficiencies may be gained in tailoring paediatric ART programmes. A randomized trial design has advantages compared to other (i.e. observational) data sources since the design removes confounding and selection bias giving results strong internal validity. The trial showed that CDM (no CD4⁺, haematology/biochemistry, if needed, for clinical management) delivers impressive health outcomes similar to those achieved with routine LCM (12-weekly CD4⁺, haematology, biochemistry), which provided only small additional health gain at substantial additional cost. Conversely, continued

CEACS with no toxicity monitoring (a), and no toxicity monitoring and half CD4 costs

(a) CEAC: all trial participants, with no toxicity monitoring

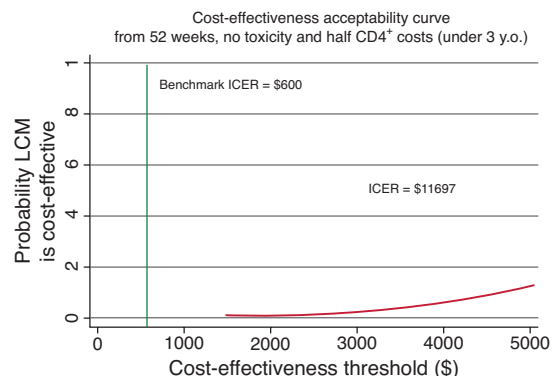


(b) CEAC: all trial participants, with no toxicity monitoring and half CD4⁺ test costs

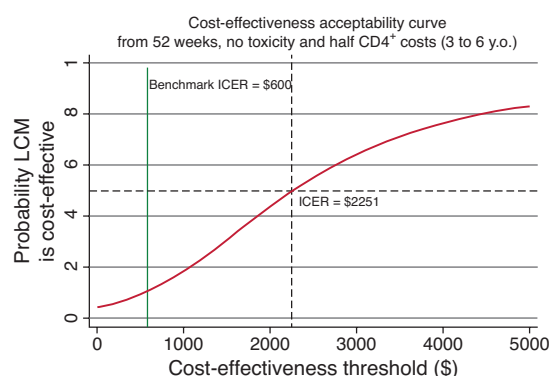


CEACS with no toxicity monitoring and half CD4⁺ costs: age subgroup analyses

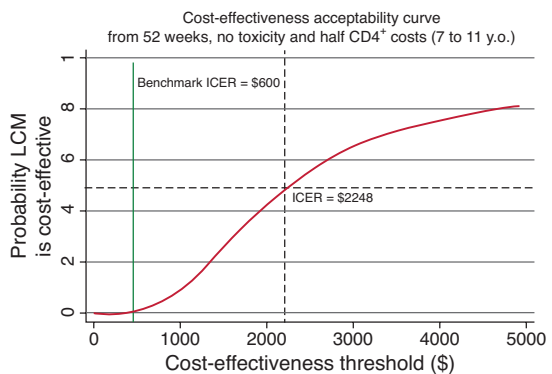
(c) Under 3 year olds



(d) 3 to 6 year olds



(d) 7 to 11 year olds



(e) 12+ year olds

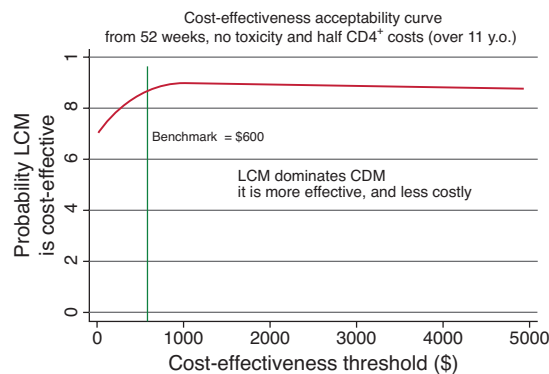


Fig. 1. Cost-effectiveness acceptability curves of alternative approaches to monitoring. (a) LCM, laboratory and clinical monitoring (12-weekly CD4⁺, haematology, biochemistry). CDM, clinically driven monitoring (no CD4⁺; haematology/biochemistry, if needed, for clinical management). ICER, incremental cost-effectiveness ratio (the cost per QALY-gained from LCM compared to CDM). The ‘cost-effectiveness threshold’ represents the maximum a healthcare system should be willing to pay for an additional QALY. The ‘Benchmark ICER’ is an indicative cost-effectiveness threshold (in these analyses marked at \$600; based upon studies indicating this is a reasonable ICER for adult ART compared to no-ART). (b) The cost-effectiveness acceptability curves (CEACs) show the probability (marked on the Y-axis) that LCM is cost-effective compared to CDM at alternative cost-effectiveness thresholds (marked on the X-axis) based upon modelled variation in observed outcomes, under the different scenarios. Two selected scenarios are: (a) LCM with CD4⁺ monitoring only; (b–e) LCM with CD4⁺ monitoring only and CD4⁺ testing costs halved, for all trial participants and for age subgroups. Results show LCM is very unlikely to be cost-effective at thresholds below \$2000, except CD4⁺ testing for adolescents (aged 12+), especially when testing costs are reduced.

Table 4. Cost-effectiveness results for cotrimoxazole randomization (base case analyses and country sub-analyses).

| | Continue cotrimoxazole | Stop cotrimoxazole | Difference in means |
|--|------------------------|--------------------|---------------------|
| Base case: Zimbabwe and Uganda results pools | | | |
| Costs, mean (SD), US\$ | 926.5 (15.1) | 947.3 (17.0) | 20.7 |
| QALYs, mean (SD) | 1.87 (.00) | 1.87 (.01) | -0.01 |
| Incremental cost-effectiveness ratio (ICER) | | Continue dominates | |
| Country sub-analyses | | | |
| Zimbabwe | | | |
| Costs, mean (SD), US\$ | 1082.4 (30.1) | 1100.6 (35.8) | 18.2 |
| QALYs, mean (SD) | 1.88 (.00) | 1.86 (.02) | -0.02 |
| Incremental cost-effectiveness ratio (ICER) | | Continue dominates | |
| Uganda | | | |
| Costs, mean (SD), US\$ | 875.3 (16.1) | 896.2 (18.4) | 20.9 |
| QALYs, mean (SD) | 1.87 (.00) | 1.87 (.00) | 0.00 |
| Incremental cost-effectiveness ratio (ICER) | | Continue dominates | |

QALY, quality-adjusted life-year. Results are based upon multiple imputation by chained equations using predictive mean matching, [9] where cost and QALY data per period of analysis are missing assumed at random.

provision of cotrimoxazole prophylaxis, for children stabilized on long-term ART, was effective at reducing hospitalizations and prescriptions of non-ART drugs from malaria and other infections, resulting in health gains and cost savings.

It is assumed the trial findings are generalizable to other (non-trial) healthcare settings. Non-trial healthcare facilities may struggle to achieve health outcomes as good as those reported in the ARROW trial, which, whilst designed as a pragmatic trial, was conducted in centres which were mostly (3/4) already providing paediatric ART and had research capability. However, the major concern is whether the incremental effectiveness of alternatives in the ARROW trial is informative for national-level policymaking. For the incremental effectiveness of LCM compared to CDM to be greater in non-trial settings than is reported in the ARROW trial, non-trial healthcare centres would have to be able to implement routine laboratory monitoring relatively more successfully than managing patients clinically compared to ARROW trial centres, which is unlikely.

For the monitoring randomization, analyses using all ARROW trial data showed that LCM is 'dominated' by CDM (being both more costly and less effective). This result is likely due to chance since early outcome differences could not have resulted from any differences in management between the two arms [2]. Restricting to outcomes beyond 12 weeks from randomization, or from 1 year, when excess disease progression/death in the CDM arm became more evident, LCM offers some benefits, but at considerable cost. Removing the costs of routine toxicity monitoring, which was costly and offered no health gains, and so should not be supported by policymakers, led to lower estimates of the cost-per-QALY gains (ICERs) resulting from LCM compared to CDM.

Age sub-group analyses showed that LCM appears to offer greatest value when targeted to children 12+ years

old, and may even dominate CDM in this group if provided without toxicity monitoring and assuming lower future cost of CD4⁺ tests. This result is potentially important: it likely reflects the greater treatment adherence challenges observed among adolescents compared with younger children, with routine CD4⁺ monitoring being able to identify complete non-adherence, which can be more easily concealed with CDM.

There have been no previous studies investigating the cost-effectiveness of paediatric ART monitoring approaches in Africa [29]. Results from this study can be compared to others investigating the cost-effectiveness of laboratory monitoring for adults on ART. A cost-effectiveness analysis of the DART trial, evaluating similar strategies to those in the ARROW trial, showed LCM was very unlikely to be cost-effective for adult patients [6]. A combined analysis of three mathematical models, investigating a wide range of monitoring alternatives, but particularly focused on whether viral load monitoring would be cost-effective, found that committing resources to the expansion of ART coverage is likely to generate greater health gains than more complex and expensive monitoring approaches in most circumstances [30]. Viral load monitoring was not investigated in the current study, but the good health outcomes reported amongst children in the ARROW trial mean that the potential for it to add additional health gains (and hence be cost-effective) is low.

Routine laboratory monitoring is recommended for children in both Uganda and Zimbabwe. Until recently, this has been using CD4⁺ and toxicity testing, but now routine viral load monitoring is recommended [31,32]. However, programmatic data show that in practice routine laboratory testing is not widely available and ART is provided using an approach in effect equivalent to CDM [19]. Similarly, cotrimoxazole prophylaxis is not available at many facilities [19]. There are then distinctions between current 'recommendations' and

current 'practice' in both the countries. This study aims to inform policy so that it may suitably affect practice and be expected to improve population health outcomes.

For the cotrimoxazole randomization, continued use of cotrimoxazole prophylaxis was shown to offer health gains and reduce health sector costs through reduced infections, in both malaria-endemic Uganda, and in non-malaria-endemic Harare, Zimbabwe. The policy dilemma is not, therefore, whether cotrimoxazole should be continued – it should – but how much to spend on implementation initiatives and health systems strengthening to ensure its continued availability in health centres.

The value of implementation analysis indicates health systems should be willing to invest substantial amounts, well beyond the cost of the drug itself, to ensure availability of cotrimoxazole, suggesting efforts to improve drug supply are likely to be of value. It also highlights an important insight that health systems can generate health gains for their populations, not only by purchasing interventions, but also (and perhaps more so) by identifying and determining how barriers to the provision and receipt of those interventions can be overcome. Further research in this direction is likely to prove fruitful.

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Conflicts of interest

M.S. has undertaken consultancy for pharmaceutical manufacturers, some of whom produce therapies for HIV.

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