## MAJOR ARTICLE

# Clinical outcomes in children living with HIV treated for non-severe tuberculosis in the SHINE Trial

**Chishala Chabala[1,2,3], Eric Wobudeya[4], Marieke M. van der Zalm[5], Monica Kapasa[2], Priyanka Raichur[6], Robert Mboizi[4], Megan Palmer[5], Aarti Kinikar[6], Syed Hissar[7], Veronica Mulenga[1,2], Vidya Mave[6], Philippa Musoke[4], Anneke C. Hesseling[5], Helen McIlleron[3], Diana Gibb[8], Angela Crook[8\*], Anna Turkova[8\*] on behalf of the SHINE trial team[+]**

[1]University of Zambia, School of Medicine, Department of Paediatrics, Lusaka, Zambia; [2]University Teaching Hospital-Children's Hospital, Lusaka, Zambia; [3]University of Cape Town, Faculty of Health Sciences, Department of Medicine, Division of Clinical Pharmacology, Cape Town, South Africa; [4]Makerere University-John Hopkins Hospital Research Collaboration, Mulago Hospital, Kampala, Uganda; [5]Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa; [6]Byramjee Jeejeebhoy Medical College- Johns Hopkins University Clinical Research Site, Pune, India; [7]Indian Council of Medical Research - National Institute for Research in Tuberculosis, Chennai, India; [8]Medical Research Council–Clinical Trials Unit at University College London, Institute of Clinical Trials and Methodology, London, United Kingdom

***Background:*** Children living with HIV(CLWH) are at high risk of tuberculosis(TB) and face poor outcomes, despite antiretroviral treatment(ART). We evaluated outcomes in CLWH and HIV-uninfected children treated for non-severe TB in the SHINE trial.

***Methods:*** SHINE was a randomized trial that enrolled children aged <16 years with smear-negative, non-severe TB who were randomized to receive 4 vs 6 months of TB treatment and followed for 72 weeks. We assessed TB relapse/recurrence, mortality, hospitalizations, grade ≥3 adverse events by HIV status, and HIV virological suppression in CLWH.

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*Joint senior authorship

+Study team members are listed in the acknowledgments.

**Corresponding Author:** Chishala Chabala; (cchabala@gmail.com). University of Zambia, School of Medicine, Department of Paediatrics, P.0 Box 50110, Ridgeway, Lusaka, Zambia

*Results:* Of 1204 enrolled, 127(11%) were CLWH, of similar age (median(IQR) 3.6(1.2, 10.3) vs. 3.5(1.5, 6.9)years, p= 0.07), but more underweight (WAZ; -2.3(-3.3, -0.8) vs -1.0(-1.8, -0.2), p<0.01) and anemic (hemoglobin 9.5(8.7, 10.9) vs 11.5(10.4, 12.3)g/dl, p<0.01) compared to HIV-uninfected children. 68(54%) CLWH were ART-naïve; baseline median CD4 count 719(241-1134) cells/mm$^3$, CD4% 16(10-26)%). CLWH were more likely to be hospitalized (aOR=2.4(1.3-4.6)) and die (aHR(95%CI) 2.6(1.2,5.8)). HIV status, age <3 years (aHR 6.3(1.5,27.3)), malnutrition (aHR 6.2(2.4,15.9)) and hemoglobin <7g/dl(aHR 3.8(1.3,11.5) independently predicted mortality. Among children with available VL, 45% and 61% CLWH had VL<1000copies/ml at weeks 24 and 48, respectively. There was no difference in the effect of randomized treatment duration (4 vs 6 months) on TB treatment outcomes by HIV status (p for interaction=0.42).

*Conclusions:* We found no evidence of a difference in TB outcomes between 4 and 6 months of treatment for CLWH treated for non-severe TB. Irrespective of TB treatment duration, CLWH had higher rates of mortality and hospitalization than HIV-uninfected counterparts.

**Key words:** Tuberculosis, antiretroviral therapy, children living with HIV, viral suppression.

## BACKGROUND

Children living with HIV(CLWH) are disproportionately affected by tuberculosis (TB). Annually, approximately 1.3 million children develop TB, resulting in 214,000 deaths: most cases going undiagnosed and untreated [1, 2]. Among children and adolescents aged <15 years dying from TB, 10% are living with HIV [3]. Antiretroviral therapy (ART) confers significant benefits, reducing the incidence of TB in CLWH [4, 5]. However, despite good immune recovery and viral suppression following ART initiation, the risk of developing TB in CLWH remains higher compared to HIV-uninfected counterparts [6] and ART may take up to 2 years to fully realize its potential for protection against TB[4].

Without ART, CLWH have five times higher risk of death compared to their uninfected peers[5, 7, 8]. Diagnostic challenges hamper early identification of TB in CLWH, leading to frequent late presentation with severe TB and advanced HIV disease, particularly in high TB endemic settings[9, 10]. HIV/TB coinfection is associated with worse HIV treatment outcomes and is among several factors that contribute to virological failure in individuals living with HIV in Sub-Saharan Africa [11]. Children concurrently treated for TB and HIV had 10 to 20% lower rates of viral suppression, with this risk persisting during the first year of ART treatment[12-14].

Treatment of TB in CLWH is complicated by drug-drug interactions (DDIs) and overlapping toxicities between antiretroviral and rifampicin-based anti-TB regimens. In low- and middle-income countries, treatment options for children with HIV/TB are limited and rifabutin, frequently used in high income countries to substitute rifampicin, is not available. Overlapping toxicities from

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co-treatment increase the risk of adverse events (AEs) which may affect adherence and TB and HIV treatment outcomes [15-17].

In the SHINE (ISRCTN63579542) trial, children with non-severe TB, randomized to receive shorter (4-month) or standard (6-month) treatment were followed-up for 72 weeks and assessed for unfavorable outcomes[18]. The trial found that 4 months was non-inferior to standard 6 months treatment in children with non-severe TB[19]. Here, we report on clinical outcomes in CLWH compared to HIV-uninfected children and describe HIV virological suppression at 24 and 48 weeks in CLWH.

## METHODS

### Study design and population.

SHINE trial(ISRCTN63579542), a non-inferiority trial, enrolled children aged <16 years with non-severe TB following written informed consent from parents/guardians. Children of known HIV-status with symptomatic non-severe, smear-negative intrathoracic TB or peripheral lymphadenitis were included. Non-severe respiratory TB was defined based on the Wiseman criteria [19, 20], as respiratory disease confined to a single lobe(opacification of <1 lobe) with none of the following on chest X-ray(CXR); cavities, miliary disease pattern, complex pleural effusions and significant airway compression. TB diagnosis was made by site clinicians based on clinical features, TB contact history, CXR findings, mycobacterial testing results.

We conducted a secondary analysis of TB treatment outcomes, mortality, hospitalizations, and grade ≥3AEs in CLWH compared to HIV-uninfected children. TB treatment outcome was defined as unfavorable if any of the following occurred; death(all-cause), treatment failure, TB treatment change, restart or extension, TB recurrence or loss to follow-up by 72 weeks [19]. Other clinical outcomes were death, hospitalizations by 72 weeks, grade ≥3 AEs during and up to 30 days after treatment, and viral suppression at 24 and 48 weeks in CLWH. Severity of AEs were graded following established criteria [21].

### Study procedures and interventions.

Eligible children with presumptive TB were screened and had a clinical evaluation including TB symptoms, contact history and a physical examination. Details of TB evaluation and initiation procedures are published elsewhere [18, 19]. At enrolment, respiratory samples and/or lymph node aspirates (if clinically indicated) were obtained for smear microscopy, Xpert(Xpert, Cepheid) and mycobacterial culture. CXRs were performed to inform diagnostic certainty, TB disease severity classification and to establish trial eligibility. An independent expert review committee retrospectively adjudicated TB status as confirmed, unconfirmed or unlikely for all enrolled children from available clinical, radiological and laboratory results using standard criteria[18, 22].

In addition, a separate independent endpoint review committee (ERC), blinded to treatment allocation, reviewed clinical events suggestive of treatment failure or TB recurrence and all deaths.

At enrolment blood samples were obtained for hematology and chemistry in all children and for CLWH CD4 cell count and HIV-1 viral load (VL) testing (if it was part of standard of care in the country). Children were seen at weeks 2, 4-weekly until week 28 and then 3-monthly up to week 72. At each visit, clinical evaluations were performed to detect new AEs, treatment failures or recurrence of TB. CD4 cell count were repeated at weeks 24 and 48. HIV-1 VL was repeated at the intervals specified by national recommendations. Acute illnesses, hospitalizations and deaths were documented throughout follow-up.

Antituberculosis treatment (rifampicin, isoniazid, pyrazinamide and/or ethambutol) was administered according to randomization arm (4 or 6 months duration) and dosed as per WHO-recommended weight-bands using fixed-dose-combination tablets(Macleods Pharmaceuticals, India) [23].

ART was provided in accordance with WHO 2016 treatment guidelines[24] and respective national recommendations. ART comprised of two nucleoside-reverse-transcriptase inhibitors (lamivudine with abacavir, zidovudine or tenofovir DF) plus efavirenz (EFV)- or lopinavir/ritonavir(LPV/r). For antituberculosis co-treatment, LPV/r was super-boosted (if single-formulated ritonavir was available) or the daily dose of LPV/r was doubled.

**Statistical analysis**

Baseline characteristics were compared using chi-square and t-tests. Heterogeneity of the effect of the randomized duration of treatment on TB outcomes assessed at the end of treatment was formally tested between CLWH and HIV-uninfected children by inclusion of a treatment by HIV status interaction term in a binary risk difference model. The interaction was tested by use of a likelihood ratio test comparing models with and without the interaction term, with p<0.1 considered evidence of a different effect (4 vs 6 months) between CLWH and HIV-uninfected children. For this comparison, we included outcomes from week 16 onwards (before week 16, treatment in the randomized groups was the same).

Logistic regression and Cox proportional hazards (CPH) models were fitted to investigate baseline predictors of clinical outcomes including age, sex, randomization arm, clinical sites, WAZ and TB disease characteristics in CLWH versus the HIV-uninfected children. Mortality was fitted as a time-to-event outcome (CPH models, summary measure hazard ratio (HR)); other outcomes were fitted as binary (logistic regression, summary measure odds ratio (OR)). All multivariable models included HIV status, age, country, TB confirmation and randomized duration of treatment. Other factors found to be significant (p<0.1) in the univariable model were also included.

In CLWH cohort, timing of ART, ART regimens and viral suppression <1000ml copies/ml at 24 and 48 weeks were assessed.

**Ethical considerations**

The study was approved by the Ethics committees and regulatory authorities in Zambia, Uganda, South Africa and India and by the sponsor (University College London) ethics committee.

## RESULTS

Of the 1,204 children enrolled in the trial, 127(11%) were CLWH, majority from Zambia (91, 72%) and Uganda (31, 24%)(table 1). Of CLWH, two-thirds (65%) had advanced or severe HIV disease (before the TB episode); median(IQR) baseline CD4% and CD4 cell counts of 16%(10, 26) and 719(241, 1134) cells/mm3 respectively. At enrolment, 68(54%) of the CLWH were ART-naïve (table 2). Baseline HIV1 VL was available for 23 children; median (IQR) baseline HIV1 VL was 89973(1864 to 587977) copies/ml; (4(17%) had VL <1000). Most started ART within 2-8 weeks after starting TB treatment; 2 died before ART initiation and in 9 ART status data were missing.

CLWH were of similar median(IQR) age compared to HIV-uninfected children (3.6(1.2, 10.3) vs 3.5(1.5-6.9) years), but were more underweight (weight-for-age z-score(WAZ); -2.3(-3.3, -0.8) vs -1.0(-1.8, -0.2), p<0.001) and had lower hemoglobin counts (9.5(8.7, 10.9) vs 11.5(10.4, 12.3) g/dl, p<0.001.). CLWH had a higher proportion of mixed (pulmonary and lymph node) TB disease (42% vs 28%, p<0.001) compared to the HIV-uninfected children. Overall, 165(14%) children had bacteriologically confirmed TB by Xpert MTB/RIF or culture, with a significantly smaller proportion (8, 6%) in CLWH compared to HIV-uninfected children (165, 15%, p=<0.01) (Table 1).

Overall, 92% of the children in the trial had favorable TB treatment outcomes. In the modified intention-to-treat population, the adjusted absolute risk difference of an unfavorable outcome (4-month vs 6-month arm) was −4.3% (in favour of 4-months, 95% CI, -14.9 to 6.2 in CLWH) and 0.0% (95% CI, -1.8 to 1.8) in HIV-uninfected children, with no heterogeneity in the effect of randomized duration of treatment (4 vs 6 months ATT) on TB treatment outcomes by HIV status (test for interaction, p=0.42))(Table 3).

Unfavorable TB treatment events were more frequent in CLWH (n=24, 19%) compared to HIV-uninfected children (n=69, 6%; adjusted HR 2.4(1.3, 4.2))(table 4). Across both groups, in addition to HIV status, age <3 years (aHR(95%CI) = 3.0(1.7, 5.2)), being underweight (WAZ≤-2)(aHR 1.8(1.1, 2.9)) and anemic (Hb<7g/dl)(aHR(95%CI) =4.6(2.1, 10.3)) were independently predictive of unfavorable TB outcomes(supplementary table 1).

Of 113 children with at least one hospitalization in 72 weeks of follow-up, 18(14%) were among CLWH compared to 95(9%) in HIV-uninfected children. Overall, the risk of hospitalization was more than twice as high among CLWH compared to HIV-uninfected children (aHR (95% CI)

=2.4(1.3-4.6))(table 4). In both groups, age <3 years (aOR(95% CI)= 1.8(1.2,2.9)) also predicted hospitalization (supplemental table 1).

Of the 31/1204(3%) deaths in the trial (Uganda=17/376(5%), Zambia=13/364(4%), S.Africa=1/315, 0/149=India), 12(39%) occurred before week 16. Thirteen (13/127(10%)) were among CLWH and 18/1077(2%) in HIV-uninfected children (aHR (95%CI) 2.6(1.2,5.8)). Pneumonia (n=6) followed by seizures (n=2), septicaemia (n=2), diarrhoeal disease (n=2), hypotension/shock and trauma(n=3) were the common causes of death (supplemental table 2). As adjudicated by the ERC, blinded to trial arm, 7/13(54%) deaths among CLHIV and 6/18(33%) in HIV-uninfected children were due to TB. The median(IQR) time to death 4.6(2.1,7.0) was shorter in CLHIV than in HIV-uninfected children 6.6(1.8,8.8) months (Table 4, Supplemental Figure 1). Independent of HIV status, age <3 years (aHR (95%CI)= 6.3(1.5,27.3)), underweight (aHR(95%CI)= 6.2(2.4,15.9)) and anemic (aHR(95%CI) = 3.8(1.3,11.5)) had higher risks of mortality (supplemental table 1).

Seventy-four children experienced at least one grade 3 or 4 AE, reported up to 30 days after the last dose of TB treatment. Grade ≥3 AEs reported in ≥5% were pneumonia or chest infection (29(25%)) children, deranged liver function (11(10%)), diarrheal diseases (7(6%)), epilepsy or seizures (6(5%)). CLWH were more likely to experience a grade ≥3 AE compared to HIV-uninfected (aHR(95% CI)= 4.6 (2.1, 9.9))(table 4). In both groups, children <3 years had a higher risk of experiencing a grade ≥3 AE than older children (aOR(95% CI)= 2.1(1.2,3.6))(supplemental table 1).

HIV-1 VL results were available for 65/119(55%) and 82/115(71%) CLWH at weeks 24 and at week 48 respectively; 45%(week-24) and 61%(week-48) had VL <1000 copies/ml. A higher proportion of children receiving EFV-based ART were virologically suppressed compared to those on LPV/r-based ART at week 48 (29/41(71%) vs 20/40(50%), p=0.056).

**DISCUSSION**

Our findings show that overall unfavorable TB treatment outcomes were more frequent in CLWH compared to children without HIV. However, when comparing randomized duration of TB treatment, there was no difference in unfavourable outcomes between 4 and 6 months in CLWH. Thus, there was no evidence to suggest that CLWH with non-severe TB needed longer treatment duration than HIV-uninfected children and both groups can receive the shorter 4 months of treatment. CLWH were at higher risk of hospitalizations and grade ≥3 AEs compared to the HIV-uninfected group. Mortality was infrequent in the entire study population, but as expected the risk was higher in CLWH and time to death was sooner. Viral suppression in CLWH was suboptimal with only 61% having VL <1000 at 48 week. Children on LPV/r-based ART had a trend towards worse VL responses compared to those on EFV-based regimens.

Our results concur with the many pediatric studies reporting worse TB treatment outcomes in CLWH compared to HIV-uninfected children, particularly in the presence of severe TB disease [25-30]. We only enrolled children with non-severe TB, and despite overall excellent treatment outcomes, HIV co-infection increased the risk of unfavorable TB outcomes, as observed in cohorts with a wider spectrum of disease [7, 8, 25, 26]. Similarly risk of hospitalization and death was significantly higher in CLWH. Despite this, the rate of mortality in SHINE was similar or lower to the reported mortality in under-fives in the respective countries in 2020 (India 4%, S.Africa 3%, Uganda 4% and Zambia 6%) [31]. Among CLWH, >10% died compared to <2% in the HIV-uninfected. Mortality rates for children with TB vary widely, from <1% in the Netherlands to 13% in Nigeria, with higher rates reported in children with severe forms of TB[7, 8, 25-28, 32]. Observational studies of children with HIV/TB co-infection have reported higher mortality rates of 10% to 20%, with worse outcomes in ART-naïve populations[5, 9, 10, 33]. In our cohort, less than half of the CLWH were on ART at the time of TB diagnosis and over 80% were on ART by end of intensive phase. While higher ART coverage reduces the risk of mortality in CLWH with TB, it does not eliminate it [34, 35]. Deaths in individuals with TB often occur in the first few months of treatment, particularly in those with HIV infection, where rapid progression of TB can occur even in the absence of immune compromise[34-36].

There were few grade ≥3 AEs observed in the trial. However, CLWH had a five-fold risk of experiencing an AE. After chest infections, elevated liver enzymes were the most common treatment related AEs [19]. Transient and asymptomatic transaminitis is commonly observed in children on TB treatment and represents hepatic adaptation to TB treatment and is often reversible[37].

Our study showed that children aged <3 years, with or without HIV, faced a significant risk of experiencing unfavorable TB outcomes, hospitalization, death, and AEs. Of note, among CLWH, a higher proportion were underweight and anemic compared to HIV-uninfected. Being underweight was an independent predictor of poor clinical outcomes, emphasizing the critical role of inadequate nutrition in contributing to unfavorable outcomes regardless of HIV status in children with TB. Younger age and undernutrition were previously identified as risk factors for TB-associated mortality; our study emphasizes that this remains relevant even in children with non-severe TB disease [34, 38, 39]. Furthermore, anemia(Hb<7g/dl) independently predicted unfavorable TB outcomes, hospitalizations, and mortality, irrespective of HIV status. Anemia is frequently observed in children from low- and middle-income countries, often associated with undernutrition [40], and it commonly complicates HIV infection [41]. Notably, it is a prevalent comorbidity with TB and linked to poor TB treatment outcomes [42, 43].

Among CLWH with available HIV-1 VLs, viral suppression was suboptimal after one year of follow-up. This could be due insufficient duration of ART since only half of the children were established on ART at the time of enrolment and ART initiation times varied. Previous studies suggested that children co-treated for TB around the time of ART initiation had low rates of virological suppression[12-14, 44]. Another possible reason could be biased selective targeting of

VL testing in children with suspected non-adherence to ART. We observed a trend towards better viral suppression in children receiving EFV-based ART compared to those on LPV/r-based ART. South African studies reported lower rates of viral suppression in children receiving ritonavir-boosted LPV/r-based ART who were cotreated for TB[13, 14]. For children aged <3 year, super-boosted LPV/r is the preferred strategy to overcome the interaction with rifampicin. However, not all sites implemented LPV/r super-boosting during the SHINE trial due to the non-availability of single-formulated ritonavir. In Zambia, double-dosing of LPV/r or switching to EFV in children ≥3 years was practiced for rifampicin cotreatment in the absence of single-formulated ritonavir. However, LPV/r double-dosing was previously associated with suboptimal lopinavir concentrations with rifampicin cotreatment[45]. Drug resistance mutations to protease inhibitors are infrequent despite virological failures, suggesting that other treatment-related factors (in particular adherence difficulties) are likely the main contributors to non-viral suppression[46], especially that pediatric formulations of LPV/r are poorly palatable and require twice-daily administration[13, 47, 48]. The currently recommended dolutegravir (DTG)-based ART, associated with high rates of viral suppression and excellent safety, is considered the preferred treatment option for CLWH with HIV/TB despite requiring twice daily dosing in children with HIV/TB [49] . DTG was not available for paediatric use at the time of the trial.

This study has several limitations including lack of generalizability to children with severe TB disease. The trial aimed to evaluate the non-inferiority of 4-month vs 6-months in children with non-severe TB and therefore CLWH with severe TB were excluded. Secondly, assessment of viral suppression in CLWH may have been affected by missing VL results. In this pragmatic trial, VLs were done as per national recommendations, which did not mandate frequent VL testing. Nevertheless, our findings align with observations in other cohorts that suggest suboptimal VL suppression in CLWH diagnosed with TB and starting ART[12, 13]. Despite these limitations, this trial had a considerable number of CLWH and excellent follow-up of up to 72 weeks, allowing comprehensive documentation of the clinical outcomes. TB diagnoses were thoroughly evaluated using well-defined criteria and independent expert review[20, 22].

We found no evidence of a difference between 4 and 6 months of treatment for CLWH being treated for non-severe TB. Acknowledging the interaction test was under-powered and the analysis can only be considered exploratory, it was nevertheless reassuring that along with all the other subgroup analyses performed, the results were consistent with the overall trial findings[19]. Benefits of TB treatment shortening include improved treatment adherence, minimal losses to follow-up and fewer AEs associated with prolonged TB treatment. Efforts should focus on equipping health services and providers with the capacity to appropriately determine TB disease severity and identify children that can benefit from the shorter regimen. In addition, patient-centered management should include the identification of potential risk factors such as anemia and undernutrition that are likely to impact treatment outcomes. Early HIV diagnosis, access to ART and comprehensive patient care that includes nutritional support can improve outcomes and reduce the risk of poor outcomes in CLWH.

## CONCLUSION

In conclusion, our study highlights that CLWH with non-severe tuberculosis had a higher risk of poor clinical outcomes compared to HIV-uninfected children. We found no significant differences in TB treatment outcomes between CLHIV and HIV-uninfected receiving 4 vs. 6 months TB treatment, providing reassurance that CLWH and receive shorter 4 months TB treatment if they have non-severe TB.

S Rohini, M Revathy. Institute of Child Health and Hospital for Children, Chennai: Sarath Balaji, S Elilarasi. Government Stanley Medical College and Hospital, Chennai: J Ganesh, MA Aravind

Local Site Monitors: Sylvia Mulambo, Hope Mwanyungwi , Dharati Tapse, Manasi Sane, Amina Abdullah, Sarah Nakalanzi, Cynthia Mukisa Williams

Radboud University Medical Center, Nijmegen, Netherlands: Rob Aarnoutse University of York: Paul Revill, James Love-Koh, Simon Walker

SHINE Trial Steering Committee Members: Peter Mugyenyi (Chair), Janet Darbyshire, Polly Clayden, Peter Donald,Varinder Singh,Malgosia Grzemska*, Soumya Swaminathan, *Replaced by Sabine Verkuijl and Annemieke Brands in March 2020

SHINE Independent Data Monitoring Committee Members: Tim Peto (Chair), Alwyn Mwinga, Katherine Fielding

SHINE Endpoint Review Committee Members: Stephen M. Graham (Chair), Steven B. Welch, James A. Seddon, Elizabeth Whittaker, Suzanne Anderson, Louis Grandjean

*Keywords:* HIV, tuberculosis, Antiretroviral treatment, Mortality, Adverse events, Viral suppression.

*Lay summary:* We compared outcomes between children with and without HIV treated for non-severe TB. Regardless of treatment duration (4 or 6 months), children with HIV had similar TB outcomes but had higher mortality and hospitalization rates than their HIV-uninfected counterparts.

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**Table 1. Baseline characteristics on the participants by HIV status**

| Participants' characteristic | HIV positive (n=127) | HIV negative (n=1,077) | Total (N=1,204) | p-value* |
|---|---|---|---|---|
| Age (years) | 3.6 (1.2, 10.3) | 3.5(1.5, 6.9) | 3.5 (1.5,7.0) | 0.07 |
| Female | 63(49.6) | 520 (48.3) | 583(48.4) | 0.78 |

| | | | | |
|---|---|---|---|---|
| Weight-for-age Z-score | -2.3 (-3.3, -0.8) | -1.0 (-1.8, -0.2) | -1.0 (-1.9, 0.3) | <0.01 (t-test) |
| Hemoglobin count (g/dL) | 9.5 (8.7, 10.9) | 11.5 (10.4, 12.3) | 11.3(10.1, 12.2) | <0.01 (t-test) |
| Alanine aminotransferase | 20.2(13.8, 35.2) | 15.0 (12.0, 20.8) | 15.7(12.0, 21.4) | <0.01 (t-test) |
| *Site of disease (n, %) | | | | |
| Pulmonary only | 74 (58.3) | 730 (67.8) | 804 (66.8) | <0.01 |
| Pulmonary and lymph node | 53 (41.7) | 300 (27.9) | 353 (29.3) | |
| Lymph node only | 0 (0) | 40 (3.7) | 40 (3.3) | |
| Other | 0 (0) | 7(0.7) | 7 (0.6) | |
| Tuberculosis status | | | | |
| Bacteriologically confirmed | 8 (6.3) | 157 (14.6) | 165 (13.7) | 0.01 |
| Unconfirmed | 95 (74.8) | 698(64.1) | 1,039 (65.9) | |
| Unlikely | 24(18.9) | 222(20.6) | 246(20.4) | |
| Anti-TB drugs dosing weight band (Kg) | | | | |
| 3.0 to 3.9 | 2 (1.6) | 1 (0.1) | 3 (0.3) | <0.01 |
| 4.0 ≤ 7.9 | 35 (27.6) | 145 (13.5) | 180 (15.0) | |
| 8.0 ≤ 11.9 | 29 (22.8) | 284 (26.4) | 313(26.0) | |
| 12.0 ≤15.9 | 10 (7.9) | 231 (21.5) | 241(20.0) | |
| 16.0 ≤ 24.9 | 31 (24.4) | 266 (24.7) | 297(24.7) | |
| ≥25.0 | 20 (15.8) | 150 (13.9) | 170(14.1) | |
| Site/country | | | | |
| Zambia | 91 (71.6) | 273 (25.3) | 364 (30.2) | <0.001 |
| Uganda | 31(24.4) | 345 (32.0) | 376 (31.2) | |
| South Africa | 5 (3.9) | 310(28.8) | 315 (26.2) | |
| India | 0 (0) | 149(13.8) | 149 (12.4) | |
| Randomization arm | | | | |
| 4 months | 65 (51.2) | 537 (49.9) | 602 (50.0) | - |
| 6 months | 62 (48.8) | 540 (50.1) | 602 (50.0) | |

Data presented as number of participants (%) or median (interquartile range); *p-value from Chi-square test unless otherwise stated

* Intrathoracic lymph node was classified as pulmonary TB while peripheral lymph node disease without any respiratory symptoms or abnormal chest x-ray findings was classified as lymph node disease.

**Table 2: Clinical characteristics of participants living with HIV.**

| Clinical characteristic (N=127) | Frequency (n, %) |
|---|---|
| HIV treatment status at baseline | |
| Naïve | 68(53.5) |
| On ART | 59(46.5) |
| WHO immunological classification* (n=88) | |
| Not significant | 21 (24.4) |
| Mild | 8 (9.3) |
| Advanced | 8 (9.3) |
| Severe | 49 (57.0) |
| CD4 count (cell/L) (n=95) | |
| <200 | 19(20.0) |

| | |
|---|---|
| ≥200-350 | 10(10.5) |
| ≥350-500 | 7 (7.4) |
| ≥500 | 59 (62.1) |
| **CD4 % (n=86)** | |
| <15 | 34 (39.5) |
| ≥15 | 52 (60.5) |
| **ART Regimen(n=116)** | |
| EFV-based | 60(51.7) |
| LPV-based | 43(37.1) |
| NVP-based | 13(11.2) |

*WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children[50].

## Table 3. Subgroup analysis of TB outcomes and randomized treatment duration by HIV status

| | CLHV | | HIV negative | | |
|---|---|---|---|---|---|
| | *4 Month* | *6 Month* | *4 Month* | *6 Month* | *Total* |
| Total randomised | 65 | 62 | 537 | 540 | 1204 |
| *Unassessable** | *6* | *8* | *24* | *21* | *59* |
| *Did not reach week 16* | *4* | *5* | *11* | *11* | *31* |
| **Favourable** | **55 (93%)** | **48 (89%)** | **501 (98%)** | **507 (98%)** | **1111 (97%)** |
| **Unfavourable** | **4 (7%)** | **6 (11%)** | **12 (2%)** | **12 (2%)** | **34 (3%)** |
| Total Assessable | 59 | 54 | 513 | 519 | 1145 |
| **Difference from control in unfavourable rate** | **- 4.3%** | | **0.03%** | | |
| 95% confidence interval | (-14.9 to 6.2) | | (-1.8 to 1.9) | | |

*Test for interaction‡ p-value= 0.42*

*Reasons for unassessable include not reaching week 16 and late exclusions for drug resistant TB; ‡Test for interaction compares the effects (risk difference) of treatment duration on TB outcomes, comparing CLHV and HIV-negative children.

## Table 4. Mortality, hospitalizations, and non-fatal grade ≥3 adverse events by HIV Status

| *Clinical Outcomes* | *HIV positive N=127* | *HIV negative N=1077* | *Adjusted\* hazard ratio (95% CI)* |
|---|---|---|---|
| **TB treatment outcomes** | | | |
| *Unfavorable* | 24 (18.9) | 69 (6.4) | 2.4 (1.3,4.2) |
| *Favorable* | 103 (81.1) | 1008 (93.6) | |
| **Mortality** | | | |
| *Dead* | 13 (10.2) | 18 (1.7) | 2.6 (1.2,5.8) |
| *Alive* | 114 (89.8) | 1059 (98.3) | |

|  |  |  | Adjusted** odds ratio (95% CI) |
|---|---|---|---|
| *Hospitalization* |  |  |  |
| *Yes* | 18 (14.2) | 95 (8.8) | 2.4 (1.3,4.6) |
| *No* | 109 (85.8) | 982 (91.2) |  |
| *AEs (Grade ≥3 )* |  |  |  |
| *Yes* | 24 (18.9) | 71 (6.6) | 4.4 (2.3,8.5) |
| *No* | 103 (81.1) | 982 (93.4) |  |

*Adjusted for age, hemoglobin count, weight-for-age z-score, bacteriological confirmation, country and randomized TB treatment duration

**Adjusted for age, weight-for-age z-score, bacteriological confirmation, site of tuberculosis disease, hemoglobin count, country and randomized TB treatment duration