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Deliverable 3.5

Empirical treatment against cytomegalovirus and tuberculosis in severe pneumonia in HIV-infected infants: a randomized controlled clinical trial

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This document compiles the analyses corresponding to the EMPIRICAL clinical trial according to its protocol and statistical analysis plan. The information included confidential information.

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1. Synopsis

Sponsor	Servicio Madrileño de Salud (SERMAS)/Fundación para la Investigación Biomédica Hospital Universitario 12 de Octubre (FI+12)
Name of Investigational Medical Product	Intervention A: Valganciclovir Intervention B: Isoniazid, rifampicin pyrazinamide, and ethambutol
Title of the study	Empirical treatment against cytomegalovirus and tuberculosis in HIV-infected infants with severe pneumonia: a multicenter, open-label randomized controlled clinical trial
Trial participants	Servicio Madrileño de Salud (SERMAS)/Fundación para la Investigación Biomédica Hospital Universitario 12 de Octubre (FI+12), Université de Bordeaux (UoB), Institut national de la santé et de la recherche médicale (INSERM), Penta Foundation (PENTA), Radboudumc University (RUMC), Instituto de Salud Global Barcelona (ISGlobal), University of Lincoln, Programme PAC-CI, Malawi-Liverpool Wellcome Trust Clinical Research Programme (MLW)/Liverpool School of Tropical Medicine (LSTM), Centro de Investigação em Saúde da Manhiça/Fundação Manhiça (CISM-FM), Eduardo Mondlane University (UEM), Makerere University, HerpeZ, University of Zimbabwe, Lilongwe Medical Relief Fund Trust (LMRFT).
Publication	Primary manuscripts under peer review at the time of final report finalisation
Study period	5 years: 4 years of enrollment, 1 year of follow-up
Primary Objective	To compare the impact on 15-day and 1-year mortality of combined systematic empirical treatment against tuberculosis (TB) and cytomegalovirus (CMV) plus Standard of Care (SoC) versus SoC in infants living with HIV (ILHIV) with severe pneumonia
Summary of results	A total of 563 infants were randomised in a 2×2 factorial design and 558 included in the final analyses. Empirical valganciclovir was associated with a reduction in early mortality, with the strongest effect observed during the first month following randomisation. The treatment effect attenuated over time and was neutral by one year. Sensitivity and time-varying analyses supported a stronger early effect. Valganciclovir was generally well tolerated and was not associated with an increased overall risk of serious adverse events. Empirical tuberculosis treatment (eTB-T) did not reduce all-cause mortality compared with clinically or microbiologically guided TB treatment (TB-T). No differences were observed in oxygen duration or cumulative hospitalisation days. eTB-T was not associated with increased adverse events. Competing-risk analyses suggested a reduction in TB-related mortality with eTB-T, but this did not translate into a reduction in overall mortality.
Conclusions	In ILHIV hospitalised with severe pneumonia, a 15-day course of empirical valganciclovir reduced early mortality and demonstrated an acceptable safety profile, although the benefit attenuated over one year. eTB-T was not superior to non-eTB-T strategies under enhanced trial conditions. These findings support consideration of empirical CMV treatment in this high-risk population and highlight the need to strengthen TB diagnostics and comprehensive post-discharge care strategies.

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2. Ethics and Administrative Structure

The EMPIRICAL trial was conducted in accordance with the ethical principles of the Declaration of Helsinki, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (E6), and all applicable national regulatory requirements in participating countries.

Prior to study initiation, the protocol, informed consent forms, and all relevant study documentation were reviewed and approved by the appropriate Institutional Review Boards (IRBs) or Ethics Committees at each participating site (Annex 1). Regulatory approvals were obtained from national competent authorities where required. No participant was enrolled before written informed consent was obtained from the parent or legal guardian.

The trial sponsor was Servicio Madrileño de Salud (SERMAS), acting through Fundación para la Investigación Biomédica del Hospital Universitario 12 de Octubre. The study was funded by the European & Developing Countries Clinical Trials Partnership (EDCTP, RIA2017MC-2013).

An Independent Data Safety Monitoring Board (IDMC) was established prior to enrolment. The IDMC consisted of independent experts with clinical, statistical, and ethical expertise. The IDMC reviewed accumulating safety data at predefined intervals (6-monthly) and provided recommendations regarding continuation, modification, or termination of the trial. No recommendation for early termination was issued during the conduct of the study.

2.1. Monitoring activities

Monitoring activities were conducted in accordance with Good Clinical Practice standards. The Clinical Trial Unit (CTU) of Fundación para la Investigación Biomédica Hospital Universitario 12 de Octubre served as the central coordinating centre and was responsible for oversight of study conduct, monitoring, data management, and regulatory compliance. Participant confidentiality was maintained throughout the trial. Participants were identified in the database using unique study identification numbers. No directly identifiable personal information was stored in the central study database. All study records will be retained for the period required by applicable regulatory standards.

The sponsor maintained appropriate insurance coverage to provide compensation in the event of study-related injury.

All substantial protocol amendments were submitted to and approved by the relevant Ethics Committees and regulatory authorities prior to implementation.

2.1.1. Site initiation and qualification

Prior to participant enrolment, all sites underwent qualification and pre-study assessment by the Clinical Trial Unit (CTU). A formal site initiation visit was conducted at each centre by representatives of a Contract Research Organisation (CRO) acting on behalf of the Sponsor. Site initiation visits included training on study procedures, administration and safety monitoring of investigational products, data entry procedures, and reporting requirements.

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2.1.2. On-site monitoring

Primary monitoring activities were performed by a designated CRO under the responsibility of the Sponsor. Monitoring was conducted according to a predefined Monitoring Plan. Sites received regular on-site monitoring visits throughout the recruitment and follow-up periods, including initiation and close-out visits. The frequency of visits was adapted according to recruitment activity and site performance.

Monitoring activities included:

- Verification of written informed consent
- Confirmation of eligibility criteria
- Source data verification (SDV) of key efficacy and safety variables
- Review of serious adverse event reporting
- Verification of investigational medicinal product accountability
- Review of pharmacy records
- Verification of primary and secondary endpoint data
- Assessment of protocol adherence
- Inspection of study-related facilities, including pharmacy, clinical areas, and laboratories

Monitors were granted direct access to relevant source documents, including medical records, laboratory reports, and pharmacy logs, in accordance with confidentiality requirements and prior caregiver consent. Monitoring findings were documented in written monitoring reports following each visit. Identified discrepancies were communicated to the site for resolution. Sites were responsible for addressing and resolving all queries within predefined timelines. Protocol deviations and breaches were documented by site investigators and/or monitors and reported according to standard operating procedures.

2.1.3. Central monitoring and data quality control

In addition to on-site monitoring, central data review and quality control procedures were implemented by the CTU Data Management Team (DMT).

Central monitoring activities included:

- Verification of data format and range checks
- Identification of missing, inconsistent, or implausible values
- Cross-checking of serious adverse event data
- Validation of eligibility criteria and key baseline variables
- Outlier detection and clinical consistency checks

Standard data editing procedures were applied across sites to ensure harmonisation of datasets. Queries generated through central data review were communicated to sites for clarification or correction. Double verification procedures were implemented for critical data elements, including deaths and serious adverse events.

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Quality control reviews were conducted at regular intervals during the study to ensure completeness and accuracy of the central database. Central data review generated data queries which were tracked and resolved in collaboration with study sites prior to database lock. All critical data fields underwent verification prior to final data cleaning.

3. Investigators and Study Administrative Structure

The EMPIRICAL trial was conducted as a multicentre study across sites in Mozambique, Uganda, Zimbabwe, Zambia, Malawi, and Ivory Coast. The enrolling centres are summarized in Table 1.

Overall scientific responsibility for the study rested with the Chief Investigator, who oversaw trial design, conduct, interpretation of results, and preparation of study reports. The Scientific Coordinator supported the development of the protocol and contributed to the overall scientific oversight of the project.

Operational management of the trial was coordinated by the Trial Management Group, which included the Chief Investigator, Scientific Coordinator, Trial Coordinator, Safety Coordinator, Trial Statistician, and Data Manager. The group met regularly to review recruitment progress, safety data, protocol adherence, and operational matters.

At each participating site, a Principal Investigator was responsible for local implementation of the study, including participant recruitment, informed consent procedures, adherence to protocol, reporting of adverse events, and compliance with regulatory requirements.

Safety oversight was supported by a designated Safety Coordinator who reviewed serious adverse events and ensured timely reporting to relevant authorities.

An independent Endpoint Review Committee adjudicated causes of death using prospectively collected clinical, laboratory, and sociodemographic data. When disagreement occurred between primary adjudicators, a third reviewer provided final determination.

Statistical analyses were conducted according to a pre-specified Statistical Analysis Plan finalised prior to database lock. Data management was centralised at the Clinical Trial Unit using a secure electronic data capture system. Data quality was ensured through programmed validation checks, monitoring visits, and resolution of data queries.

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Table 1. Enrolling centres

Partner/institution	Hospitals	City (Country)	Role
Universidade Eduardo Mondlane	Hospital Central de Maputo	Maputo (Mozambique)	Enrolling centre
	Hospital Geral de Mavalane	Maputo (Mozambique)	Enrolling centre
	Hospital Provincial da Matola	Matola (Mozambique)	Enrolling centre
	Hospital Central da Beira	Beira (Mozambique)	Enrolling centre
	Hospital Geral Jose Macamo	Maputo (Mozambique)	Enrolling centre
	Hospital Central de Nampula	Nampula (Mozambique)	Enrolling centre
Centro de investigação de Saúde de Manhiça	Hospital Distrital da Manhiça*	Manhiça (Mozambique)	Enrolling centre
	Hospital Provincial de Xai-Xai*	Xai-Xai (Mozambique)	Enrolling centre
Makerere University	China Uganda Friendship Hospital	Naguru (Uganda)	Enrolling centre
	Jinja Regional Referral Hospital	Jinja (Uganda)	Enrolling centre
	Mbarara hospital**	Mbarara (Uganda)	Enrolling centre
Herpez	University Teaching Hospital	Lusaka (Zambia)	Enrolling centre
	Arthur Davidson Children´s Hospital	Ndola (Zambia)	Enrolling centre
Malawi- Liverpool Wellcome Trust	Queen Elizabeth Central Hospital*	Blantyre (Malawi)	Enrolling centre
	Chikwawa District Hospital*	Blantyre (Malawi)	Referral
	Thyolo District Hospital*	Blantyre (Malawi)	Referral
	Chiradzulu District Hospital*	Blantyre (Malawi)	Referral
Lilongwe Medical Relief Fund Trust	Kamuzu Central Hospital&	Lilongwe (Malawi)	Enrolling centre
PACCI	Cocody University Hospital^	Abidjan (Ivory Coast)	Enrolling centre
	Treichville^	Abidjan (Ivory Coast)	Enrolling centre
	Angre^	Abidjan (Ivory Coast)	Enrolling centre
University of Zimbabwe	Harare Central Hospital	Harare (Zimbabwe)	Enrolling centre
	Parirenyatwa	Harare (Zimbabwe)	Enrolling centre
	Marondera Hospital+	Marondera (Zimbabwe)	Enrolling centre

^Recruitment stopped in year 1; *Recruitment stopped in year 2; ** Recruitment stopped in year 4 before the planned day; & Recruitment started in year 2; +Recruitment started in Year 3.

4. Introduction

Pneumonia remains the leading cause of death among ILHIV, particularly in sub-Saharan Africa. Despite improvements in prevention of mother-to-child transmission and increased availability of antiretroviral therapy (ART), early mortality in infants with advanced HIV disease remains unacceptably high. Mortality rates in ILHIV hospitalised with severe pneumonia have been reported to approach or exceed 30–40% in the short term, with additional mortality occurring after discharge.

The current World Health Organization (WHO) SoC for severe pneumonia in ILHIV includes empirical treatment for bacterial pathogens and *Pneumocystis jirovecii*, as well as supportive care and ART. However, CMV infection and TB are both highly prevalent in this population and are frequently underdiagnosed due to limited access to reliable diagnostic tools in resource-limited settings.

Post-mortem studies and minimally invasive autopsy investigations have identified CMV and TB as major contributors to mortality in infants with HIV-associated pneumonia. CMV viraemia is common in this

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population and has been associated with severe respiratory disease and increased mortality. Similarly, TB may present with non-specific clinical features, and a substantial proportion of cases may remain unrecognised at the time of hospital admission. These diagnostic limitations may result in missed therapeutic opportunities.

The rationale for the EMPIRICAL trial was therefore to evaluate whether systematic empirical treatment against CMV (with valganciclovir) and/or eTB-T (isoniazid, rifampicin, pyrazinamide, and ethambutol) could reduce short-term and long-term mortality in HIV-infected infants hospitalised with severe pneumonia.

To efficiently evaluate both interventions within the same population, a 2×2 factorial design was selected. As described in the protocol, factorial trials allow the simultaneous investigation of two interventions that target different biological mechanisms, while preserving efficiency and enabling formal assessment of potential interaction between treatments. This design permitted estimation of the independent (marginal) effects of empirical CMV treatment and eTB-T, provided no significant interaction between the interventions was observed.

Empirical valganciclovir was evaluated in a phase II framework, as antiviral treatment for CMV had shown efficacy in other clinical contexts but had not been previously tested for this specific indication. In contrast, eTB-T was evaluated in a phase III framework. Because the trial used a 2-by-2 factorial design to evaluate both strategies within the same population and to assess their independent effects on mortality, the study was operationally conducted as a phase III trial overall. The planned total sample size was 624 participants, calculated to provide 80% power at a two-sided alpha level of 0.05 to detect the anticipated reductions in mortality. The sample size calculation incorporated an estimated 5% loss to follow-up and assumed no detrimental interaction between the two interventions.

The EMPIRICAL trial was therefore designed to address two clinically important and mechanistically distinct therapeutic hypotheses within a single, coordinated multinational study, with mortality as the primary endpoint and safety carefully monitored throughout.

5. Study objectives

5.1. Primary objective

Primary aim is:

To compare the impact on 15-day and 1-year mortality of combined systematic empirical treatment against TB and CMV plus SoC versus SoC in HIV-infected infants with severe pneumonia.

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5.2. Secondary objectives

CLINICAL

- To compare the impact on 15-day and 1-year mortality of systematic empirical valganciclovir plus SoC versus SoC in HIV-infected infants with severe pneumonia.
- To compare the impact on 15-day and 1-year mortality of systematic eTB-T plus SoC versus SoC in HIV-infected infants with severe pneumonia.
- To compare the cumulative days on oxygen-therapy from randomization until discharge of the intervention arms versus SoC.
- To compare the cumulative number of days of hospitalization 1 year after randomization of the intervention arms versus SoC.

PHARMACOVIGILANCE

- To evaluate the safety of empirical valganciclovir and eTB-T in HIV-infected infants hospitalized with severe pneumonia of the intervention arms versus SoC.

EPIDEMIOLOGICAL

- To know the prevalence of CMV infection in HIV-infected infants hospitalized with severe pneumonia.
- To know the prevalence of confirmed and unconfirmed TB in HIV-infected infants hospitalized with severe pneumonia.
- To know the incidence of confirmed and unconfirmed TB in HIV-infected children hospitalized with severe pneumonia during a 1-year follow-up.
- To know the prevalence of CMV infection and confirmed and unconfirmed TB in HIV-infected children hospitalized with severe pneumonia that died.

MOLECULAR RESPONSE TO TREATMENT

- To assess the decrease of the quantitative CMV viral load in blood and saliva in HIV-infected infants hospitalized with severe pneumonia treated with valganciclovir.

TB DIAGNOSIS

- To assess the diagnostic accuracy of TB-LAM for the diagnosis of confirmed TB (reference: positive Xpert MTB/RIF Ultra in feces and/or nasopharyngeal aspirate (NPA)).

ECONOMIC EVALUATION

- To analyze the cost-effectiveness of the proposed treatment strategies in each context.

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6. Investigational Plan

6.1. Study design

EMPIRICAL was a multicentre, open-label, randomised, controlled, Phase II–III clinical trial conducted using a 2×2 factorial design.

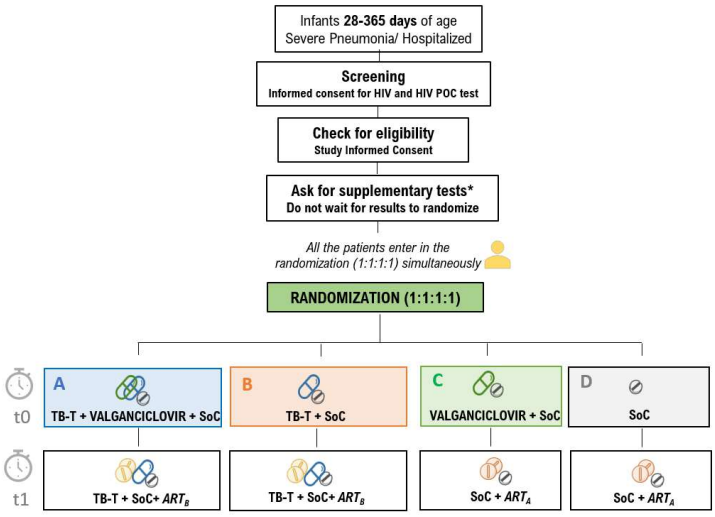
Eligible participants were randomised in a 1:1:1:1 ratio to one of four treatment groups:

1. SoC (SoC) alone
2. SoC plus eTB-T
3. SoC plus valganciclovir
4. SoC plus eTB-T and valganciclovir

The factorial design allowed simultaneous evaluation of two therapeutic strategies targeting distinct biological mechanisms: unrecognised TB and CMV infection. This approach permitted estimation of the independent (marginal) effect of each intervention, provided no clinically relevant interaction between treatments was observed. The trial was open-label due to the logistical and ethical complexities of administering multidrug TB therapy and valganciclovir in resource-limited hospital settings. However, outcome assessment of mortality was objective. In addition, causes of death were adjudicated independently by an Endpoint Review Committee.

Participants were followed from randomisation through hospitalisation and up to one year after enrolment. Clinical assessments were conducted at scheduled visits, and adverse events were systematically recorded throughout follow-up.

Figure 1. Flowchart of randomization scheme



CMV: Cytomegalovirus; **TB-T**: Tuberculosis treatment; **POC:** Point of care

t0: First 24h after screening
t1: +15days after randomization in naïve patients

***Supplementary tests**: Blood test (full blood cell count, blood chemistries, PCR for CMV), Chest X ray, Saliva CMV PCR test, Urine TB LAM, Nasopharyngeal aspirate and Stools (Xpert MTB/RIF Ultra).
SoC: Standard of Care (ceftriaxone + cotrimoxazole + prednisolone)
ART: Antiretroviral treatment.
- ART_A: First line ART
- ART_B: ART compatible with TB-T

Participants who are already on ART when admitted will continue on ART during admission as part of their Standard of Care. ART will be adapted to trial schedule if necessary.

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6.2. Study population

Participants were eligible for enrolment if they met all inclusion criteria and none of the exclusion criteria at the time of randomisation.

Infants were eligible if they were aged between 28 and 365 days, had confirmed HIV infection, and were hospitalised with severe pneumonia requiring parenteral antibiotic therapy. Severe pneumonia was defined according to WHO criteria and included clinical signs such as hypoxia, respiratory distress, or requirement for oxygen supplementation. Participants were required to have a parent or legal guardian able and willing to provide written informed consent. Exclusion criteria included a clinical or microbiological diagnosis of TB at the time of screening, previous TB-T, close contact with TB, pure wheezers, active malignancies, current immunosuppressive medications, weight <2·5 kg, haemoglobin <6 g/dL, or neutropenia <500/mm3. A complete list of the eligibility criteria is in the Table 2.

Table 2. Eligibility criteria

SCREENING CRITERIA
Infants living with HIV from 28 to 365 days of age, admitted with pneumonia.
INCLUSION CRITERIA. Must fulfil all five (5)§
1.Age 28 days to 365 days of age
2.Pneumonia defined as chest indrawing or fast breathing for age, for infants 28 to 60 days of age ≥60 breaths per minute, and for infants 61 to 365 days of age, ≥50 breaths per minute.
3.Current hospitalization with pneumonia with criteria for parenteral antibiotics (1 or more criteria) a) Chest indrawing with HIV infection b) No improvement with oral treatment. c) One or more danger signs according to WHO [35–37] - Central cyanosis or saturation of O_2 <90% - Severe respiratory distress, e.g., grunting or very severe chest indrawing - Signs of pneumonia with a general danger sign: - Unable to drink or breastfeed - Persisting vomiting - Convulsions in the last 24 hours - Lethargic or unconscious - Stridor while calm - Severe malnutrition
4.HIV-confirmed infection (with at least one molecular method: DNA PCR or RNA PCR/viral load).
5.Informed consent obtained
EXCLUSION CRITERIA
1.Clinical TB (pulmonary or extrapulmonary) diagnosis, defined as the necessity of TB-T prescribed by a physician, at the moment of randomization.
2.Known bacteriologically confirmed TB case (at least one biological specimen positive by culture or Xpert MTB/RIF) at the moment of randomization.
3.Patient previously treated for TB or currently on treatment for TB.
4.Documented evidence of close TB exposure (household contact of a patient with documented TB during the lifetime of the child, or currently receiving TB-T).
5.Pure wheezers defined as a clear clinical improvement after a bronchodilator test (give a challenge of a rapid-acting inhaled bronchodilator for up to three times 15-20 minutes apart. Count the breaths and look for chest indrawing again, and then re-classify.
6.Active malignancies.
7.Systemic immunosuppressive medications. Steroids will be considered to be immunosuppressing only if >2 mg/kg of prednisone or equivalent during >15 days.
8.Evidence of condition other than HIV and pneumonia which precludes, to the judgment of the clinical researcher, enrolment in this trial due to risk for the patient
9.Less than 2.5 kg of weight.
10.Haemoglobin <6 g/dL in the screening blood test or in a test done in the last 48 hours. Transfusion is permitted to achieve >6 g/dL if the patient's state allows it.
11.Neutropenia <500 /mm^3 in the screening blood test or in a test done in the last 48 hours. Repeating the test is allowed to check eligibility.

Abbreviations: PCR: Polymerase Chain Reaction; TB: tuberculosis; TB-T: TB treatment;
§Patients should be enrolled as soon as possible after admission; however, it was admissible to include patients at any time during admission as long as they fully filled the inclusion criteria and none of the exclusion criteria at the time of recruitment. Patients who are referred from other centres can be recruited. Children already on antiretroviral treatment can be enrolled.

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6.3. Participants Recruitment

Recruitment commenced after completion of site initiation and regulatory approvals in participating countries. The study originally planned to enrol 624 participants based on pre-specified sample size calculations.

A total of 816 infants were assessed for eligibility. Of these, 253 were not randomised. Reasons for non-randomisation included clinical or microbiological TB diagnosis at baseline, prior TB-T, documented TB exposure, haematological abnormalities, contraindications to study treatment, weight below eligibility thresholds, resolution of disease prior to randomisation, death prior to randomisation, enrolment in another study, transfer to another facility, and other screening failures. A total of 563 participants were randomised in a 2×2 factorial design.

Within the factorial allocation:

- 142 participants were assigned to SoC only.
- 142 participants were assigned to SoC plus eTB-T.
- 141 participants were assigned to SoC plus valganciclovir.
- 138 participants were assigned to SoC plus both eTB-T and valganciclovir.

For the marginal comparisons:

- 284 participants were assigned to arms without valganciclovir and 279 to arms with valganciclovir.
- 283 participants were assigned to arms without eTB-T and 280 to arms with eTB-T.

Following randomisation, a small number of participants were excluded from the intention-to-treat (ITT) analyses because they were subsequently determined not to fulfil eligibility criteria. As shown in the CONSORT diagrams, 2 participants in the non–valganciclovir arms and 3 in the valganciclovir arms were excluded from the ITT analysis. Similarly, 1 participant in the non-eTB-T and 4 in the eTB-T arms were excluded from ITT analysis for not fulfilling eligibility criteria. These counts refer to the same five participants, shown separately by marginal allocation within each factorial comparison

The final ITT populations therefore comprised:

- 282 participants in the non–valganciclovir arms and 276 in the valganciclovir arms.
- 282 participants in the non-eTB-T arms and 276 in the eTB-T arms.

Recruitment was discontinued before reaching the planned target sample size due to logistical and operational constraints, not due to interim efficacy or safety findings. Follow-up was conducted for up to one year after randomisation. Loss to follow-up during the study period is detailed in the CONSORT flow diagrams (Figures 2 and 3), including numbers completing 15-day and one-year follow-up.

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Figure 2. CONSORT Flow diagram for marginal valganciclovir comparison

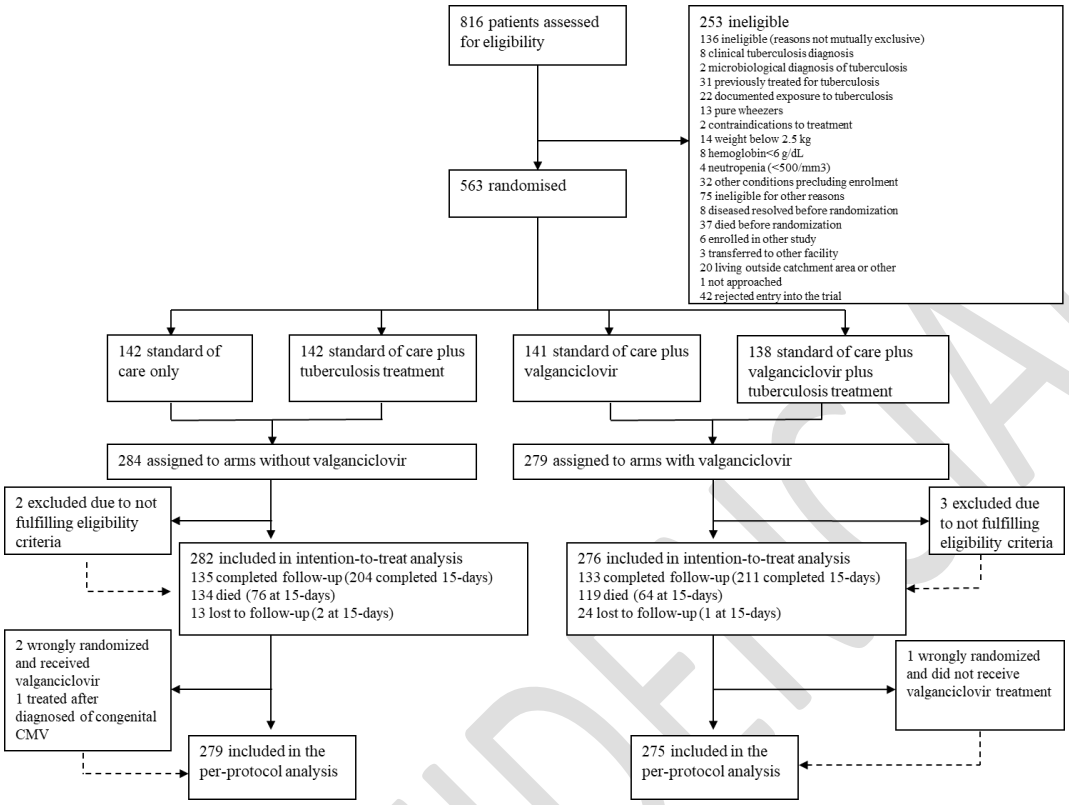

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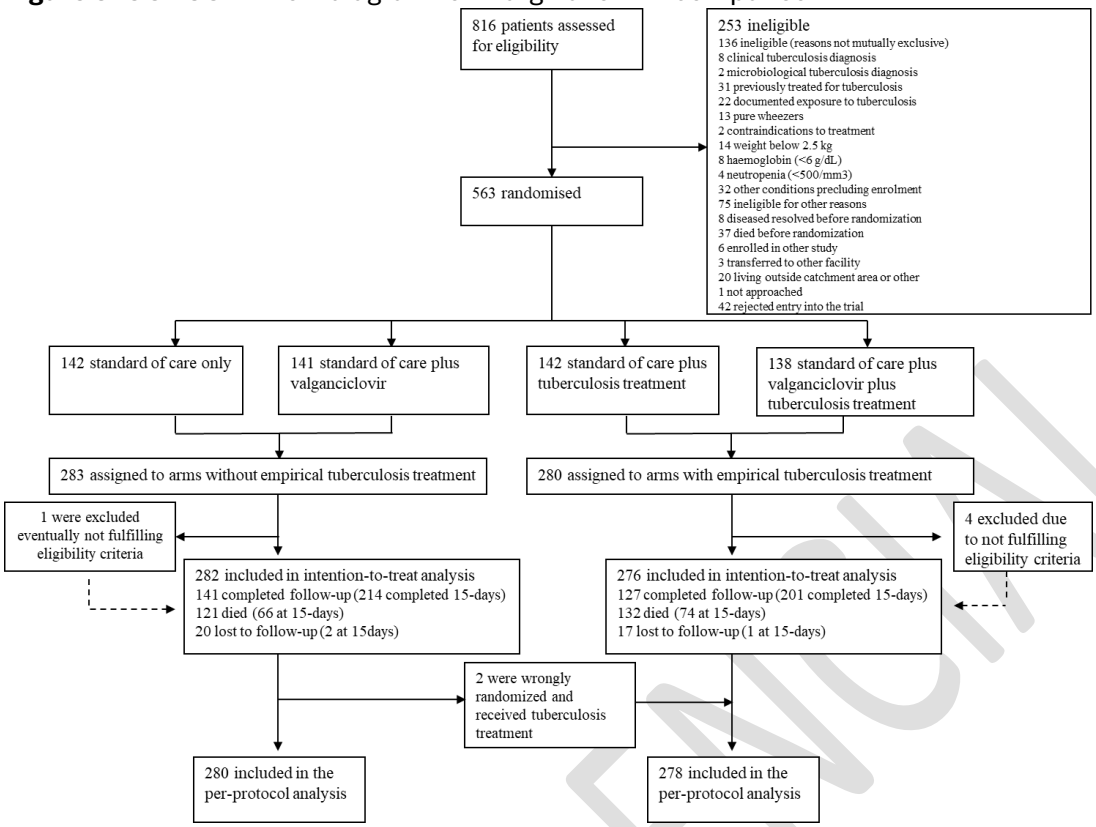
Figure 3. CONSORT Flow diagram for marginal eTB-T comparison



6.4. Randomization and allocation procedures

Participants who met all eligibility criteria were randomised in a 1:1:1:1 ratio to one of the four treatment groups within the 2×2 factorial design. Randomisation was performed centrally using a computer-generated allocation sequence using REDCap to ensure concealment and prevent selection bias.

The randomisation schedule was generated by the trial statistician prior to study initiation. Randomisation was stratified by study site and by baseline disease severity, as defined in the protocol, to ensure balance of treatment allocation across clinically relevant strata. Severe cases were defined by at least one of the following criteria: i) unable to drink/breastfeed, ii) persistent vomiting, iii) having convulsions, iv) lethargic or unconscious, v) stridor while calm, vi) severe malnutrition, vii) central cyanosis, or viii) oxygen saturation below 90%. Variable block sizes were used within each stratum to maintain allocation concealment.

Treatment assignment was implemented through a secure electronic system accessible to authorised site personnel. Once eligibility was confirmed and informed consent obtained, site investigators entered participant details into the system and received the allocated treatment assignment. Allocation concealment was maintained until the moment of assignment.

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6.5. Study treatments

6.5.1. Standard of Care

All participants received SoC for severe pneumonia in ILHIV in accordance with national WHO guidelines applicable at each study site.
SoC included antibiotics for bacterial pneumonia initiated according to WHO recommendations and for *Pneumocystis jirovecii* pneumonia, treatment consisted of cotrimoxazole (trimethoprim 8 mg/kg per dose plus sulfamethoxazole 40 mg/kg per dose) administered three times daily for 21 days, together with adjunctive prednisolone administered as 2 mg/kg daily for 7 days, followed by 1 mg/kg daily for 7 days, and 0.5 mg/kg daily for a further 7 days (total duration 21 days).
ART was administered according to local guidelines. In ART-naïve participants, ART was initiated 15 ± 7 days after enrolment. For participants receiving TB-T, ART regimens were adjusted to account for potential drug–drug interactions according to national recommendations.
Supportive care, including oxygen supplementation, fluid management, and nutritional support, was provided as clinically indicated. Regardless of randomisation arm, TB-T was initiated as part of SoC if clinical, radiological, or microbiological findings after randomisation suggested or confirmed TB.

6.5.2. Empirical TB treatment

Participants randomised to eTB-T received a standard first-line TB treatment. The intensive phase consisted of a fixed-dose dispersible tablet containing rifampicin, isoniazid, and pyrazinamide (75/50/150 mg), together with ethambutol 100 mg dispersible tablets, administered for two months. This was followed by a continuation phase consisting of a fixed-dose dispersible tablet containing rifampicin and isoniazid (75/50 mg), administered according to WHO-recommended paediatric weight bands. Dosing was based on weight at initiation and adjusted as necessary during follow-up.
Tb-T was administered orally or via nasogastric or orogastric tubes. The investigational products were manufactured by Macleods (Maharashtra, India).
Participants allocated to non-empirical TB arms could receive TB-T during follow-up if clinically indicated, using the same formulations and dosing schedules.

6.5.3. Empirical Valganciclovir

Participants randomised to valganciclovir received oral valganciclovir suspension (powder for suspension, 50 mg/mL).
Valganciclovir was administered at a dose of 16 mg/kg per dose twice daily for 15 days. Administration occurred orally or via nasogastric or orogastric tubes. The product was manufactured by Roche (Basel, Switzerland).
Dose modifications or temporary interruptions were permitted in the event of clinically significant haematological or biochemical abnormalities, according to predefined safety criteria.

6.5.4. Treatment compliance

Compliance with study treatments was assessed through review of medication administration records during hospitalisation and caregiver report during follow-up visits. Drug interruptions, discontinuations, and modifications were documented in the case report forms.

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6.6. Study procedures

Participants were assessed at baseline prior to randomisation, during hospitalisation, and at scheduled follow-up visits up to one year after enrolment.

6.6.1. Baseline assessments

At enrolment, demographic data, medical history, and clinical examination findings were recorded. Baseline laboratory investigations included complete blood count, liver function tests, renal function tests, CD4 cell percentage, and HIV-1 RNA viral load. Weight-for-length z-scores were calculated using WHO Child Growth Standards.

Diagnostic investigations for TB were performed at baseline and included urine lipoarabinomannan (TB-LAM), nasopharyngeal aspirate Xpert MTB/RIF Ultra, stool Xpert MTB/RIF Ultra. Results from *M. tuberculosis* cultures made following the local recommendations were collected. These investigations were conducted irrespective of treatment allocation.

Plasma and saliva CMV viral load was measured at baseline using quantitative PCR assays.

6.6.2. Hospitalisation

During hospitalisation, participants were monitored daily for clinical status, requirement for respiratory support, oxygen supplementation, and occurrence of adverse events. Administration of study treatments and concomitant medications was documented.

Laboratory monitoring was performed according to protocol-defined schedules to monitor for haematological toxicity and biochemical abnormalities.

6.6.3. Post-discharge follow-up

After discharge, participants were followed at scheduled visits up to 12 months after randomisation. Follow-up visits included clinical assessment, documentation of interim hospitalisations, recording of adverse events and serious adverse events, and laboratory testing as per protocol schedule.

Vital status was assessed at each visit. For participants who did not attend scheduled visits, attempts were made to contact caregivers by telephone or home visit where feasible.

Procedures among the different visit schedules is summarized in Figure 4.

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Figure 4. Trial assessment schedule

Action		Staff member	Screening	Enrollment and randomization	Post-randomization							
Day			0	0	visit day +3	discharge visit	visit day +15	visit day +30	visit day +60	visit day +90	visit day +180	visit day +360
							±3 days	±3 days	±7 days	±14 days	±21 days	±21 days
SCREENING												
Pre-screening and Screening log, inclusion assessment, information, IC screening		Site investigators	X									
Screening for HIV, anemia and neutropenia		Site investigators	X									
ENROLLMENT												
Informed Consent		Site investigators		X								
Physical exam		Site investigators		X	X	X	X	X	X	X	X	X
Ask for supplementary tests		Site investigators		X	X	X	X	X	X	X	X	X
Randomization		Site investigators		X								
INTERVENTION												
Fixed-dose INH+RF+PZA prescription (2 mo)		Site investigators		X	X	X	X	X				
Fixed-dose INH+RF prescription (4 mo)		Site investigators							X	X	X	
Ethambutol prescription (2 mo)		Site investigators		X	X	X	X	X				
Valganciclovir prescription (15 days)		Site investigators		X	X							
STANDARD OF CARE												
ART prescription		Site investigators					X	X	X	X	X	X
Antimicrobials for pneumonia prescription		Site investigators		X	X							
Cotrimoxazole prescription		Site investigators		X	X	X	X					
Cotrimoxazole prophylaxis		Site investigators						X	X	X	X	X
Steroids prescription		Site investigators		X	X	X	X					
FOLLOW-UP												
Clinical Research Form (CRF)		Site investigators		X	X	X	X	X	X	X	X	X
Evaluation of adherence		Site investigators		X	X	X	X	X	X	X	X	X
Serious adverse event form		Site investigators		X	X	X	X	X	X	X	X	X
Data entry		Data manager		X	X	X	X	X	X	X	X	X
PHARMACY												
Dispense of drug, accountability, registry drug er		Pharmacist		X	X	X	X	X	X	X	X	X
SUPPLEMENTARY TESTS												
Image												
Chest Radiograpy		Radiology		X								
Labs												
HIV-PCR		Phlebotomist/nurse	X				X					
Whole blood EDTA	CD4 count and %	Phlebotomist/nurse		X							X	X
	Full Blood Count	Phlebotomist/nurse	X			X	X	X			X	X
	Viral Load	Phlebotomist/nurse		X					X		X	X
Whole blood	Chemistry	Phlebotomist/nurse		X		X	X	X	X	X	X	X
Labs (Microbiology)												
Saliva	CMV PCR	Phlebotomist/nurse		X			X					
Blood	CMV PCR	Phlebotomist/nurse		X			X					
NPA	TB Xpert Ultra	Phlebotomist/nurse		X								
Urine	TB-LAM	Phlebotomist/nurse		X								
Faeces	TB Xpert Ultra	Phlebotomist/nurse		X								
Pharmacokinetics												
Whole Blood	PK1	Phlebotomist/nurse							X			
Whole Blood	PK2	Phlebotomist/nurse							X			
Whole Blood	PK3	Phlebotomist/nurse			X							
Whole Blood	PK4	Phlebotomist/nurse										
Immune response ancillary study												
Blood	IF gamma IGRA	Phlebotomist/nurse		X								
NPA	Cytokine levels	Phlebotomist/nurse		X			X					

6.6.4. Outcome ascertainment

The primary outcome was all-cause mortality. Deaths occurring during hospitalisation or during follow-up were documented, and causes of death were adjudicated by an independent Endpoint Review Committee using prospectively collected clinical and laboratory data. Participants were followed from randomisation until death, completion of one-year follow-up, loss to follow-up, or withdrawal of consent.

6.7. Sample Size determination

The planned total sample size was 624 participants. This calculation was based on assumptions regarding baseline mortality rates in ILHIV hospitalised with severe pneumonia and anticipated treatment effects for both investigational interventions. For short-term mortality, baseline mortality was estimated at approximately 35%. For one-year mortality, baseline mortality was estimated at approximately 41%, accounting for early and post-discharge deaths.

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The study was powered at 80% with a two-sided alpha level of 0.05 to detect clinically meaningful reductions in mortality for each intervention independently within the factorial design framework. The sample size calculation assumed no clinically significant interaction between eTB-T and valganciclovir. An allowance for approximately 5% loss to follow-up was incorporated into the final sample size determination.

Recruitment was discontinued, after four years of recruitment, before reaching the planned target due to logistical and operational constraints, including the COVID-19 pandemic.

6.8. Statistical methods

6.8.1. General Principles

All primary analyses were conducted according to the ITT principle, including all participants randomised and with available outcome data. Safety analyses included all participants who received at least one dose of study intervention.

The trial was designed as a 2×2 factorial study, allowing simultaneous evaluation of eTB-T and valganciclovir. The primary estimands were the marginal effects of:

- eTB-T versus no eTB-T
- Valganciclovir versus no valganciclovir

Before estimating marginal effects, a formal statistical test for interaction between the two interventions was performed. In the absence of a statistically significant interaction, marginal treatment effects were estimated pooling across the factorial arms.

6.8.2. Primary outcome

The primary outcome was all-cause mortality from the time of randomisation until death or censoring at the last follow-up visit. Survival probabilities were estimated using Kaplan–Meier methods, and differences between treatment groups were assessed using log-rank tests.

Hazard ratios (HRs) and corresponding 95% confidence intervals were estimated using flexible parametric survival models based on the Royston–Parmar approach, in which the baseline hazard was modelled using restricted cubic splines. Cox proportional hazards models were also fitted for comparison. The proportional hazards assumption was evaluated graphically and through statistical testing. Short-term mortality (15-day) and long-term mortality (1-year) were additionally analysed as binary outcomes using logistic regression models.

Multivariable models were initially adjusted for clinically prespecified baseline covariates, including recruitment country, baseline CD4 T-cell percentage, baseline HIV-1 viral load, age at HIV diagnosis, baseline oxygen saturation, and baseline nutritional status. In addition, baseline haemoglobin concentration, family status, days from hospitalisation to randomisation, and cotrimoxazole prophylaxis were evaluated post hoc as potential confounders. CD4 percentage and viral load were not treated as time-dependent covariates because follow-up measurements were frequently missing, largely as a

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consequence of early mortality. To obtain a parsimonious and clinically meaningful model while maintaining numerical stability, a two-step modelling strategy was applied. First, backward elimination was performed in Cox proportional hazards models fitted across multiply imputed datasets to identify a reduced set of predictors. Second, the final flexible parametric survival models were fitted using this reduced covariate set. For each co-primary model (cross-sectional time points and time-to-event different best-fitting model were obtained).

Within the factorial design framework, a formal test for interaction between eTB-T and valganciclovir was conducted prior to estimation of marginal treatment effects.

6.8.3. Secondary outcomes

Cumulative days of hospitalisation and cumulative days of oxygen supplementation during follow-up were analysed as count outcomes.

Given the presence of overdispersion in the distribution of these variables, negative binomial regression models were used to estimate incidence rate ratios (IRRs) and corresponding 95% confidence intervals. An offset term equal to the logarithm of individual follow-up time was included in the models to account for differences in observation time between participants.

6.8.4. Safety analysis

Adverse events (AEs) and serious adverse events (SAEs) were summarised by treatment group. The proportion of participants experiencing at least one event was compared using logistic regression models. Given the recurrent nature of adverse events, IRRs were estimated using zero-inflated Poisson regression models. These models accounted for excess zeros and overdispersion in event counts.

Laboratory toxicities, including neutropenia, anaemia, and thrombocytopenia, were analysed similarly using both binary and count-based approaches. All hypothesis tests were two-sided with a significance level of 0.05. Confidence intervals were calculated at the 95% level.

6.8.5. Subgroup and exploratory analyses

Subgroup analyses were conducted to evaluate potential heterogeneity of treatment effects according to baseline characteristics, including age, nutritional status, immunological status, and viral load.
Time-varying effects of valganciclovir were explored using flexible parametric models with interaction terms.

6.8.6. Handling of missing data

Missing baseline covariate data were handled using multiple imputation by chained equations (MICE) under the assumption that data were missing at random (MAR). The imputation model included all variables used in the primary multivariable analyses, treatment allocation, and the outcome variable (time-to-death indicator and follow-up time) to preserve associations between predictors and outcome.

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Appropriate imputation models were specified according to variable type. Continuous variables were imputed using predictive mean matching, and categorical variables were imputed using logistic or polytomous regression models as appropriate. A total of 50 imputed datasets were generated. Estimates from analyses performed within each imputed dataset were combined using Rubin's rules to obtain pooled effect estimates and standard errors. Patterns and proportions of missing data for baseline variables are summarised in Table S1. Variables included in the imputation model and their respective imputation methods are detailed in Table S2.

As a sensitivity analysis, the primary models were re-estimated using complete-case data only. The consistency of effect estimates between multiply imputed and complete-case analyses was assessed to evaluate robustness of conclusions to missing data assumptions.

6.8.7. Sensitivity analysis

Pre-specified sensitivity analyses were conducted to evaluate the robustness of the primary findings. These included:

- Exclusion of deaths occurring within 48 hours of randomisation
- Per-protocol analyses excluding patients with randomisation errors
- As-treated analyses accounting for treatment crossover
- Time-varying effects for valganciclovir
- Complete-case analyses to assess the impact of multiple imputation

Because visual inspection of Kaplan–Meier curves for valganciclovir suggested early separation followed by later convergence, a sensitivity analysis allowing for non-proportional hazards was conducted. The flexible parametric survival model was extended to include a spline-based time-varying coefficient (TVC) for treatment. The baseline log-cumulative hazard was modelled using a restricted cubic spline with three degrees of freedom. The time-varying coefficient for treatment was specified using a two-degree-of-freedom spline. Model complexity (baseline and TVC degrees of freedom) was selected using Akaike's Information Criterion (AIC), applying a $\Delta AIC \leq 2$ parsimony rule. The selected specification was then applied across multiply imputed datasets. A likelihood ratio test comparing the selected time-varying coefficient model with the proportional hazards model of identical baseline complexity was used to evaluate evidence against proportional hazards. Time-specific hazard ratios were derived using the delta method on the log-hazard ratio scale and pooled across imputations.

Additional exploratory analyses conducted after completion of the primary analyses are described separately in the Efficacy Evaluation section and are clearly identified as post hoc.

6.8.8. Database lock and final analysis

All efficacy and safety analyses were conducted using the final locked database. The Statistical Analysis Plan was finalised prior to database lock and prior to unblinding of treatment allocation. Data cleaning procedures included on-site monitoring, central data review, query resolution, and verification of protocol deviations. Database lock was formally documented on 13th February 2025, after which no further modifications to the clinical data were permitted.

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6.9. Safety Assessment and Monitoring

In this trial, the principles ICH-GCP require that both, investigators and the Sponsor follow specific procedures when notifying and reporting AEs in clinical trials. These procedures are described in this section of the protocol. The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of ICH-GCP, applying to this trial protocol are given below.

6.9.1. Definitions

The AEs, SAEs, adverse reactions (ARs), and suspected unexpected serious adverse reactions (SUSARs) were defined and reported in accordance with ICH-GCP guidelines and applicable regulatory requirements. The intensity of AEs was graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events (Version 2.0, Table S3).

In this trial, AEs included:

- Exacerbation of a pre-existing illness
- An increase in the frequency or intensity of a pre-existing episodic event or condition
- A condition (even though it may have been present before the start of the trial) was detected after trial drug administration
- Continuous and persistent disease or a symptom present at baseline that worsens following administration of the study treatment

And AEs did not include:

- Medical or surgical procedures; the condition that led to the procedure was the AE
- Pre-existing disease or a condition present before treatment that did not worsen
- Hospitalisations where no untoward or unintended response had occurred, e.g., elective cosmetic surgery, social admissions
- Overdose of medication without signs or symptoms

6.9.2. Severity grading (DAIDS)

When an AE or AR occurred, the investigator responsible for the patient's care first assessed whether the event was serious, using the definition given above and the toxicity grading in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, Version 2.0. When the event was serious, the site's IP or delegated staff notified the Central Trial Unit (CTU) within one working day, registered the AE in the electronic system, and reported it by mail to the CTU in an anonymised form.

6.9.3. Causality assessment

The investigators at each site assessed the causality of all AEs and ARs related to the trial therapy using the definitions above. There were five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality assessment was unrelated or unlikely to be related, the event is classified as an AE. If the causality was assessed as possible, probable or definitely related, then the event was classified as an AR. If a SAE was considered to be related to an IMP, the protocol detailed rules for discontinuing or modifying the dose of the IMP.

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6.9.4. Expectedness

All ARs were classified by the site PI's or delegate as expected or unexpected, if an AR was one that had not been previously reported in the current SmPC, or one that was more frequent or more severe than previously reported. The protocol defined a SAR assessed as being unexpected as a SUSAR. No unexpected AR or SUSARs were reported in this trial. In the absence of blinded interventions, no formal analysis was conducted.

6.9.5. Dose modifications and discontinuation criteria

Anaemia: valganciclovir was withheld at any moment if haemoglobine count reproducibly decreased to <6 g/dl. Once the haemoglobin count was ≥6 g/dL, valganciclovir was resumed at the standard dose.

Neutropenia: If the absolute neutrophil count reproducibly decreased to ≤500 cells/mm3, valganciclovir was withheld until neutrophils recovered to >750 cells/mm3; thereafter, the drug was resumed at the standard dose.

Thrombocytopenia: valganciclovir was withheld if the platelet count reproducibly decreased to ≤50,000/mm3. Once the platelet count was ≥50,000/mm3, valganciclovir at the standard dose was resumed.

Hepatotoxicity: if ALT levels were ≥5 times the upper limit of normal (with or without symptoms) or ≥3 times normal in the presence of symptoms (including nausea, vomiting, right upper quadrant pain, or lethargy), all TB-T were discontinued immediately, and the patient was evaluated carefully in accordance with local practice.

6.9.6. IDMC

According to the protocol, Independent Data and Safety Monitoring Committee (IDMC) meetings are scheduled every 6 months during the clinical trial. Throughout the study, seven IDMC meetings were held to review the safety reports generated. After each review, it was recommended that the study be continued without changes. During the last IDMC meeting, as enrolment had concluded and no safety issues or concerns had emerged, the IDMC recommended that no further IDMC meetings be held and that an informative presentation of the final results be provided, which was delivered on May 20th, 2025. At the end of the study period, the final safety report described enrollment and safety data for the 558 participants included in the analysis, covering the entire study period (46 months of trial recruitment and 12 months of follow-up).

7. Study population

7.1. Disposition of Participants

A total of 816 infants were assessed for eligibility. Of these, 253 were not randomised. Reasons for non-randomisation included clinical or microbiological TB at baseline, prior TB-T, documented TB exposure,

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haematological abnormalities, contraindications to study medication, weight below eligibility thresholds, clinical improvement prior to randomisation, death prior to enrolment, enrolment in another study, transfer to another facility, and other screening failures. A total of 563 participants were randomised in a 2×2 factorial design.

Following randomisation, five participants were excluded from the main analysis population because they were subsequently determined not to fulfil eligibility criteria. The ITT population therefore comprised 558 participants.

Within the factorial design, participants were allocated across four treatment groups. For the primary estimands, analyses were performed according to marginal randomised allocation to each intervention. Specifically, participants randomised to valganciclovir-containing arms were compared with those randomised to non–valganciclovir arms, and participants randomised to eTB-T arms were compared with those randomised to non-eTB-T arms.

In the ITT population, 276 participants were allocated to valganciclovir arms and 282 to non–valganciclovir arms. Similarly, 276 participants were allocated to eTB-T arms and 282 to non-eTB-T arms.

Participant flow from screening through randomisation, follow-up at 15 days and one year, and inclusion in the analysis populations is presented in the clinical trial flow diagrams.

7.2. Recruitment

Participants were enrolled from March 2020 to January 2024, in 19 hospitals in six African countries: Ivory Coast, Malawi, Mozambique, Uganda, Zambia, and Zimbabwe. The 1-year follow-up for defined outcomes closed in January 2025. Participants were infants with confirmed HIV infection (new or prior diagnoses), aged 28 to 365 days, hospitalised with severe pneumonia defined as chest indrawing or tachypnoea (≥60 breaths/minute for infants aged 28–60 days and ≥50 breaths/minute for those aged 61–365 days), and at least one criterion for parenteral antibiotic therapy. These criteria included chest indrawing, no improvement with oral treatment, or one or more WHO-defined danger signs: central cyanosis or oxygen saturation <90%, severe respiratory distress, inability to drink, persistent vomiting, convulsions within the previous 24 hours, lethargy or unconsciousness, or severe malnutrition. Exclusion criteria included a clinical or microbiological diagnosis of TB at screening, previous TB-T, TB close contact, pure wheezers, active malignancies, immunosuppressive medications, weight <2.5 kg, haemoglobin <6 g/dL, or neutropenia <500/mm3. Caregivers provided signed informed consent before enrolment. A total of 563 participants were enrolled from 816 screened. Among the 253 excluded participants, eight were excluded due to clinical TB diagnosis, two due to microbiological TB diagnosis at screening, 31 received TB-T previously, 22 due to documented exposure to TB and the rest for other reasons. After excluding five patients who did not meet the eligibility criteria, 558 were included in the analyses.

7.3. Baseline characteristics

Baseline demographic and clinical characteristics of the 558 participants included in the ITT population are summarised in Table 3. Randomisation assigned 276 participants to valganciclovir-containing arms (140 to valganciclovir plus SoC and 136 to valganciclovir plus eTB-T plus SoC) and 282 to non–

valganciclovir arms (142 to SoC alone and 140 to eTB-T plus SoC). Similarly, 276 participants were allocated to eTB-T arms and 282 to non-eTB-T arms. Baseline characteristics were balanced across the four treatment groups and across marginal factorial comparisons (Table 4 and Table 5), consistent with the stratified randomisation by study site and disease severity.

The median age at randomisation was 4.4 months (interquartile range [IQR] 3.2–7.4), and 274 participants (49%) were female. Most participants (395, 71%) were newly diagnosed with HIV during the hospitalisation that led to study enrolment; only 160 of 558 participants (29%) were aware of their HIV status prior to admission. Most infants (432, 77%) were antiretroviral therapy (ART)-naïve at baseline. Participants initiated ART at a median age of 4.3 months (IQR 2.6–6.9). The median time from hospital admission to randomisation was 2.0 days (IQR 1.0–4.0). A total of 512 of 558 participants (92%) had received Bacillus Calmette–Guérin (BCG) vaccination.

Participants were severely ill at enrolment. Oxygen saturation below 90% at admission was observed in 334 participants (60%). Severe immunosuppression was common, with a median CD4 T-cell percentage of 15.3% (IQR 9.6–23.2). Baseline HIV viral load was high, with a median value of 6.3 log10 copies/mL (IQR 5.6–7.0), and 83% of participants had viral loads above 5 log10 copies/mL. Malnutrition was frequent. Acute moderate-to-severe malnutrition (weight-for-length Z score below –2) was present in 217 participants (41%), including a substantial proportion with severe malnutrition.

Baseline CMV plasma viral load measurements were available for 490 participants. Among these, 403 (82%) had detectable CMV DNA, with a median CMV viral load of 4.2 log10 copies/mL (IQR 3.0–5.3).

TB diagnostic investigations were systematically performed at baseline. A total of 141 participants (25%) had evidence of TB based on baseline diagnostic testing. Of these, 127 were positive by urine TB-LAM assay (62 [49%] grade +1; 47 [37%] grade +2; 12 [9%] grade +3; and 6 [5%] grade +4), 10 by nasopharyngeal aspirate Xpert MTB/RIF Ultra assay, 19 by stool Xpert MTB/RIF Ultra assay, and one by routine gastric culture.

During follow-up, initiation of post-randomisation TB-T occurred in a substantial proportion of participants allocated to the non-eTB-T arms. Among the 282 participants allocated to non-eTB-T arms, 132 (47%) initiated TB-T after randomisation at a median of 4.0 days (IQR 3.0–15.0). In 55 of these 132 participants (42%), treatment was initiated following a positive microbiological test performed at baseline; in the remaining cases, treatment was initiated based on clinical or radiological findings suggestive of TB.

At one year of follow-up, among participants who completed follow-up, 67 of 269 (25%) had undetectable HIV viral loads. The cumulative incidence of HIV viral suppression was 1% (95%CI 0–2%) overall. The cumulative incidence of HIV viral suppression was 1·5% (95%CI 0–3%) in the non–eTB-T group and 1·0% (95%CI 0–1·5%) in the eTB-T group (Gray's test p=0·6786).

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Table 3. Demographic and Clinical Characteristics at Baseline (factorial-group analyses)

Characteristic	*SoC (N=142)*	*Empirical TB-Treatment + SoC (N=140)*	*Valganciclovir + SoC (N=140)*	*Valganciclovir + Empirical TB-Treatment + SoC (N=136)*
Demographic characteristics				
Enrolling country— no. (%)				
Mozambique: Institution 1	51 (35.9)	50 (35.7)	50 (35.7)	49 (36.0)
Uganda	34 (23.9)	35 (25.0)	34 (24.3)	34 (25.0)
Zimbabwe	19 (13.4)	17 (12.1)	18 (12.9)	18 (13.2)
Zambia	18 (12.7)	19 (13.6)	18 (12.9)	16 (11.8)
Malawi: Institution 2	8 (5.63)	9 (6.43)	9 (6.43)	9 (6.62)
Malawi: Institution 1	9 (6.34)	7 (5.00)	8 (5.71)	8 (5.88)
Mozambique: Institution 2	3 (2.11)	3 (2.14)	2 (1.43)	2 (1.47)
Ivory Coast	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Median age [IQR] — months	4.1 (3.2–6.8)	4.5 (3.2–7.8)	4.4 (3.1–7.2)	4.6 (3.3–7.6)
Female sex— no. (%)	68 (47.9)	71 (50.7)	70 (50.0)	65 (47.8)
Family situation— no. (%)				
Both parents alive	110 (77.5)	110 (78.6)	109 (77.9)	106 (77.9)
Orphaned/absent mother	1 (0.70)	0 (0.0)	2 (1.43)	2 (1.47)
Orphaned/absent father	30 (21.1)	25 (17.9)	26 (18.6)	22 (16.2)
Caregivers other than parents	0 (0.0)	4 (2.86)	2 (1.43)	5 (3.68)
Unknown	1 (0.70)	1 (0.71)	1 (0.71)	1 (0.74)
Clinical characteristics				
Oxygen saturation <90% at arrival — no. (%)	82 (58.2)	80 (57.6)	86 (62.8)	87 (64.9)
Respiratory support— no. (%)				
No	20 (14.2)	20 (14.3)	22 (15.7)	19 (14.0)
Nasal cannula	74 (52.5)	77 (55.0)	85 (60.7)	84 (61.8)
CPAP/MV	47 (33.3)	43 (30.7)	33 (23.6)	33 (24.3)
New HIV diagnosis— no. (%)				
No	36 (25.4)	41 (29.3)	49 (35.0)	34 (25.0)
Yes	106 (74.6)	99 (70.7)	88 (62.9)	102 (75.0)
Unknown	0 (0.0)	0 (0.0)	3 (2.14)	0 (0.0)
ART naïve — no. (%)	112 (78.9)	109 (77.9)	103 (73.6)	108 (79.4)
HIV RNA logs — copies/mL	6.5 (5.9–7.0)	6.4 (5.6–7.0)	6.0 (5.4–6.8)	6.3 (5.7–6.9)
Median HIV RNA >5logs copies/mL — no. (%)	113 (83.7)	115 (85.2)	105 (78.9)	113 (85.0)
Median CD4 % — cell/mm^3	15.0 (8.9–21.0)	19.0 (11.6–27.0)	16.0 (10.0–23.0)	13.6 (8.40–22.0)
Severe immunosuppression (CD4<25%)	99 (83.2)	81 (66.9)	90 (77.6)	86 (78.2)
Median baseline Weight for Length Z score ¶	-1.2 (-2.5–0.2)	-1.4 (-3.1–-0.2)	-1.5 (-3.1–-0.4)	-1.7 (-3.3–-0.4)
Baseline severe malnutrition (≤ -3SD or oedematous malnutrition) — no. (%)	28 (20.0)	41 (29.3)	41 (29.7)	42 (31.3)
Baseline moderate malnutrition (≤-2SD->-3SD) — no. (%)	27 (19.3)	17 (12.1)	14 (10.1)	19 (14.2)
Median CMV viral load in plasma logs — copies/mL	3.9 (2.9–5.1)	4.2 (3.0–5.2)	4.2 (3.0–5.2)	4.3 (3.3–5.5)
Medical History				

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Characteristic	*SoC (N=142)*	*Empirical TB-Treatment + SoC (N=140)*	*Valganciclovir + SoC (N=140)*	*Valganciclovir + Empirical TB-Treatment + SoC (N=136)*
Median days from hospitalization to randomization	2.0 (1.0–5.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)
Immunization schedule complete for age— no. (%)	101 (71.1)	108 (77.1)	109 (77.9)	104 (76.5)
Breastfeeding — no. (%)				
Never	2 (1.41)	3 (2.14)	3 (2.14)	3 (2.21)
Exclusive	79 (55.6)	61 (43.6)	70 (50.0)	55 (40.4)
Mixed	50 (35.2)	54 (38.6)	57 (40.7)	59 (43.4)
Weaned	11 (7.75)	22 (15.7)	10 (7.14)	19 (14.0)
Prophylaxis with cotrimoxazole — no. (%)				
Yes but stopped	13 (9.15)	15 (10.8)	4 (2.88)	4 (2.94)
Ongoing	30 (21.1)	38 (27.3)	39 (28.1)	43 (31.6)
Never	96 (67.6)	85 (61.2)	94 (67.6)	89 (65.4)
Unknown	3 (2.11)	1 (0.72)	2 (1.44)	0 (0.0)
Baseline ART regimen — no. (%)				
None	112 (79.4)	109 (79.0)	103 (76.3)	108 (81.8)
2 NRTI + Lopinavir/r	16 (11.3)	6 (4.35)	12 (8.89)	5 (3.79)
3 NRTI	0 (0.0)	8 (5.80)	0 (0.0)	4 (3.03)
2 NRTI + Nevirapine	1 (0.71)	0 (0.0)	2 (1.48)	0 (0.0)
2 NRTI + Dolutegravir	12 (8.51)	15 (10.9)	18 (13.3)	15 (11.4)
Unknown	1 (0.7)	2 (1.4)	5 (3.6)	10 (7.0)

Percentages may not total 100 due to rounding. ART: antiretroviral therapy, CMV: Cytomegalovirus, CPAP: continuous positive airway pressure, HIV-1: human immunodeficiency virus type 1, IQR: interquartile range, Lopinavir/r: Lopinavir and ritonavir, MV: Mechanical ventilation, NRTI: Nucleoside reverse-transcriptase inhibitors, SD: Standard deviation. Mozambique Institution 1: Universidade Eduardo Mondlane-Maputo and linked hospitals (in Maputo City, Maputo Province, Sofala, and Nampula provinces), Mozambique Institution 2: CISM-Manhiça and linked hospitals (in Maputo Province (Manhiça) and Gaza (Xai-Xai) provinces), Malawi Institution 1: Malawi- Liverpool Wellcome Trust (Blantyre), Malawi Institution 2: Lilongwe Medical Relief Fund Trust (Lilongwe). The z-scores were calculated using the WHO Child Growth Standards.

Table 4. Demographic and Clinical Characteristics at Baseline by Receipt of Empirical Valganciclovir Treatment

Characteristic	*Total N=558*	*Valganciclovir (N=276)*	*Non–valganciclovir (N=282)*
Demographic characteristics			
Enrolling country— no. (%)			
Mozambique: Institution 1	200 (35.8)	99 (35.9)	101 (35.8)
Uganda	137 (24.6)	68 (24.5)	69 (24.5)
Zimbabwe	72 (12.9)	36 (13.0)	36 (12.8)
Zambia	71 (12.7)	34 (12.3)	37 (13.1)
Malawi: Institution 2	35 (6.3)	18 (6.5)	17 (6.0)
Malawi: Institution 1	32 (5.7)	16 (5.8)	16 (5.7)
Mozambique: Institution 2	10 (1.8)	4 (1.5)	6 (2.1)

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Characteristic	*Total N=558*	*Valganciclovir (N=276)*	*Non–valganciclovir (N=282)*
Ivory Coast	1 (0.2)	1 (0.4)	0 (0.00)
Median age [IQR] — months	4.4 (3.2–7.4)	4.6 (3.1–7.3)	4.3 (3.2–7.5)
Female sex— no. (%)	274 (49.1)	135 (48.9)	139 (49.3)
Family situation— no. (%)			
Both parents alive	435 (78)	215 (77.9)	220 (78)
Orphaned/absent mother	5 (0.9)	4 (1.5)	1 (0.4)
Orphaned/absent father	103 (15.5)	48 (17.4)	55 (19.5)
Caregivers other than parents	11 (2.0)	7 (2.5)	4 (1.4)
Unknown	4 (0.7)	2 (0.7)	2 (0.7)
Clinical characteristics			
Oxygen saturation <90% at arrival — no. (%)	334 (60.6)	172 (63.2)	162 (57.9)
Respiratory support— no. (%)			
No	81 (14.5)	41 (14.9)	40 (14.2)
Nasal cannula	320 (57.5)	169 (61.2)	151 (53.7)
CPAP/MV	156 (28.0)	66 (23.9)	90 (32.0)
New HIV diagnosis— no. (%)			
No	160 (28.7)	83 (30.1)	77 (27.3)
Yes	395 (70.8)	190 (68.8)	205 (72.7)
Unknown	3 (0.5)	3 (1.1)	0 (0.0)
ART naïve — no. (%)	432 (77.4)	211 (76.4)	221 (78.4)
HIV RNA logs — copies/mL	6.3 (5.6–7.0)	6.2 (5.5–6.9)	6.4 (5.7–7.0)
Median HIV RNA >5logs copies/mL — no. (%)	446 (83.2)	218 (82.0)	228 (84.4)
Median CD4 % — cell/mm^3	15.3 (9.6–23.2)	15.0 (9.0–23.0)	16.0 (9.7–24.0)
Severe immunosuppression (CD4<25%)	356 (76.4)	176 (77.9)	180 (75.0)
Median baseline Weight for Length Z score ¶	-1.5 (-3.0–(-0.2))	-1.6 (-3.2–0.4)	-1.3 (-2.8–(-0.0))
Baseline severe malnutrition (≤ -3SD or oedematous malnutrition) — no. (%)	152 (27.5)	83 (30.5)	69 (24.6)
Baseline moderate malnutrition (≤-2SD->-3SD) — no. (%)	77 (13.9)	33 (12.1)	44 (15.7)
Median CMV viral load in plasma logs — copies/mL	3.9 (2.8–5.0)	4.1 (3.0–5.0)	3.8 (2.7–5.0)
Medical History			
Median days from hospitalization to randomization	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)
Immunization schedule complete for age— no. (%)	422 (75.6)	213 (77.2)	209 (74.1)
Breastfeeding — no. (%)			
Never	11 (2.0)	6 (2.2)	5 (1.8)
Exclusive	265 (47.5)	125 (45.3)	140 (49.6)
Mixed	220 (39.4)	116 (42.0)	104 (36.9)
Weaned	62 (11.1)	29 (10.5)	33 (11.7)
Prophylaxis with cotrimoxazole — no. (%)			
Yes but stopped	36 (6.5)	8 (2.9)	28 (10.0)
Ongoing	150 (27.0)	82 (29.8)	68 (24.2)

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Characteristic	*Total N=558*	*Valganciclovir (N=276)*	*Non–valganciclovir (N=282)*
Never	364 (65.5)	183 (66.5)	181 (64.4)
Unknown	6 (1.1)	2 (0.7)	4 (1.4)
Baseline ART regimen — no. (%)			
None	432 (77.4)	211 (76.5)	221 (78.4)
2 NRTI + Lopinavir/r	39 (7.0)	17 (6.2)	22 (7.8)
3 NRTI	12 (2.2)	4 (1.5)	8 (2.8)
2 NRTI + Nevirapine	3 (0.5)	2 (0.7)	1 (0.4)
2 NRTI + Dolutegravir	60 (10.8)	33 (12.0)	27 (9.6)
Unknown	12 (2.2)	9 (3.3)	3 (1.1)

Table 5. Demographic and Clinical Characteristics at Baseline by Receipt of empirical TB-T

Characteristic	*Empirical TB-T (N=276)*	*No empirical TB-T (N=282)*
Demographic characteristics		
Enrolling country — no. (%)		
Mozambique: Institution 1	99 (35.9)	101 (35.8)
Uganda	69 (25)	68 (24.1)
Zimbabwe	35 (12.7)	37 (13.1)
Zambia	35 (12.7)	36 (12.8)
Malawi: Institution 2	18 (6.5)	17 (6.0)
Malawi: Institution 1	15 (5.4)	17 (6.0)
Mozambique: Institution 2	5 (1.8)	5 (1.8)
Ivory Coast	0 (0.00)	1 (0.2)
Median age [IQR] — months	4.5 (3.2–7.8)	4.2 (3.1–7.1)
Female sex— no. (%)	136 (49.3)	138 (48.9)
Family situation— no. (%)		
Both parents alive	216 (78.3)	219 (77.7)
Orphaned/absent mother	2 (0.72)	3 (1.1)
Orphaned/absent father	47 (17.0)	56 (19.9)
Caregivers other than parents	9 (3.3)	2 (0.7)
Unknown	2 (0.72)	2 (0.7)
Clinical characteristics		
Oxygen saturation <90% at arrival — no. (%)	167 (61.2)	168 (60.4)
Respiratory support— no. (%)		
No	39 (14.1)	42 (14.9)
Nasal cannula	161 (58.3)	159 (56.6)
CPAP/MV	76 (27.5)	80 (28.5)
New HIV diagnosis— no. (%)		
No	75 (27.2)	85 (30.1)
Yes	201 (72.8)	194 (68.8)

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Characteristic	*Empirical TB-T (N=276)*	*No empirical TB-T (N=282)*
Unknown	0 (0.0)	3 (1.1)
ART naïve — no. (%)	217 (78.6)	215 (76.2)
HIV RNA logs — copies/mL	6.3 (5.6–7.0)	6.28 (5.6–7.0)
HIV RNA >5logs copies/mL — no. (%)	228 (85.1)	218 (81.3)
Median CD4 % — cell/mm^3	15.9 (10.0–25.0)	15.0 (9.0–21.9)
Severe immunosuppression (CD4<25%)	176 (77.9)	180 (75.0)
Median baseline Weight for Length Z score ¶	-1.5 (-3.2–0.3)	-1.36 (-2.8–(-0.1))
Baseline severe malnutrition ¶(<-3SD)— no. (%)	76 (27.7)	64 (23.0)
Baseline moderate malnutrition (≤-2SD->-3SD) — no. (%)	36 (13.1)	41 (14.7)
TB microbiologically confirmed— no. (%)	68 (28.6)	73 (25.9)
Urinary TB-LAM positive— no. (%)	62 (26.1)	65 (25.8)
NPA Xpert MTB/RIF Ultra positive— no. (%) ¥	4 (1.5)	6 (2.1)
Stool Xpert MTB/RIF Ultra positive— no. (%)	9 (3.5)	10 (3.8)
M. TB positive culture— no. (%)	0 (0.0)	1 (3.0)
Medical History		
Days from hospitalization to randomization	2.00 (1.00–4.00)	2.00 (1.00–4.00)
Immunization schedule complete for age— no. (%)	212 (76.8)	210 (74.5)
BCG immunization— no. (%)	258 (93.5)	253 (89.7)
Breastfeeding — no. (%)		
Never	6 (2.2)	5 (1.8)
Exclusive	116 (42.0)	149 (52.8)
Mixed	113 (40.9)	107 (37.9)
Weaned	41 (14.9)	21 (7.5)
Prophylaxis with cotrimoxazole — no. (%)		
Yes but stopped	19 (6.9)	27 (6.1)
Ongoing	81 (29.5)	69 (24.6)
Never	174 (63.3)	190 (67.6)
Unknown	1 (0.4)	5 (1.8)
Baseline ART regimen — no. (%)		
None	217 (78.6)	215 (76.2)
2 NRTI + Lopinavir/r	11 (4.0)	28 (9.9)
3 NRTI	12 (4.3)	0 (0.0)
2 NRTI + Nevirapine	0 (0.0)	3 (1.1)
2 NRTI + Dolutegravir	30 (10.9)	30 (10.6)
Unknown	6 (2.2)	6 (2.1)
TB treatment post-randomization— no. (%)	-	132 (46.8)
Randomisation error	-	2 (0.7)
Following clinical decision	-	75 (26.6)
Due to positive TB-LAM— no. (%)	-	53 (18.8)
Due to positive NPA Xpert MTB/RIF Ultra— no. (%)	-	2 (0.7)

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Characteristic	*Empirical TB-T (N=276)*	*No empirical TB-T (N=282)*
Due to positive Stool Xpert MTB/RIF Ultra— no. (%)	-	0 (0)
Due to positive *M. TB* culture— no. (%)	-	0 (0)
Time from randomization to TB-T post-randomization	-	4.0 (3.0–15.0)

Percentages may not total 100 due to rounding. ART: antiretroviral therapy, CPAP: continuous positive airway pressure, HIV-1: human immunodeficiency virus type 1, IQR: interquartile range, Lopinavir/r: Lopinavir and ritonavir, MV: Mechanical ventilation, NPA: nasopharyngeal aspirate, NRTI: Nucleoside reverse-transcriptase inhibitors, SD: Standard deviation. TB-T: TB treatment. Mozambique Institution 1: Universidade Eduardo Mondlane-Maputo and linked hospitals (in Maputo City, Maputo Province, Sofala, and Nampula provinces), Mozambique Institution 2: CISM-Manhiça and linked hospitals (in Maputo Province (Manhiça) and Gaza (Xai-Xai) provinces), Malawi Institution 1: Malawi- Liverpool Wellcome Trust (Blantyre), Malawi Institution 2: Lilongwe Medical Relief Fund Trust (Lilongwe). The z-scores were calculated using the WHO Child Growth Standards. The total number of positive confirmatory tests does not equal 141 because individual participants could have multiple positive tests. The data of rifampicin resistance was recorded in 9 participants, and only one was detected to be resistant.

7.4. Protocol deviations

A total of 318 protocol deviations were reported since the start of enrollment. From those, 116/318 (36.5%) have been reported as serious protocol deviations. Most of the deviations were related to missed visits or to missing samples that the teams were not able to obtain at the prespecified timepoints, resulting in missing values. Deviations were reported to the Ethical Boards and Regulatory Authorities.

7.5. Treatment exposure and compliance

Among participants allocated to valganciclovir who survived, the median duration of treatment received was 14.0 days (IQR 14–15), consistent with the planned 15-day treatment course. Twenty participants discontinued valganciclovir before completing the planned course. Among these participants, the median duration of treatment received was 7.0 days (IQR 6.0–13.5). Eight of 276 participants (3%) allocated to valganciclovir had at least one missed dose. Among these participants, the median number of missed doses was 7.5 (IQR 5.5–9.25).

Among participants allocated to the eTB-T arms who survived, the median duration of treatment received was 180 days (IQR 180–180), consistent with the planned treatment duration. Twelve participants discontinued eTB-T before completing the planned course. Among these participants, the median duration of treatment received was 75.5 days (IQR 21.8–114.3). Overall, 6 of 276 participants (2%) allocated to eTB-T received less than 50% of the planned treatment duration. Missed doses were infrequent. A total of 54 of 276 participants (20%) had at least one missed dose of eTB-T. Among these participants, the median number of missed doses was 3 (IQR 2–6) for isoniazid, rifampicin, and pyrazinamide, and 3 (IQR 2–5) for ethambutol.

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8. Efficacy Evaluation

8.1. Analysis Populations

8.1.1. Intention-to-treatment population

The primary efficacy analyses were conducted in the ITT population, defined as all randomised participants except those subsequently determined not to fulfil eligibility criteria. This population comprised 558 participants.

Within the factorial design, efficacy analyses were performed according to marginal randomised allocation. Treatment effects were estimated by comparing participants allocated to valganciclovir-containing arms with those allocated to non–valganciclovir arms, and by comparing participants allocated to eTB-T arms with those allocated to non-eTB-T arms. In the ITT population, 276 participants were allocated to valganciclovir arms and 282 to non–valganciclovir arms. Similarly, 276 participants were allocated to eTB-T arms and 282 to non-eTB-T arms.

8.1.2. Per-protocol population

Per-protocol analyses were conducted separately for valganciclovir and eTB-T to account for intervention-specific deviations.

For the valganciclovir comparison, the per-protocol population excluded four participants due to randomisation errors. Three participants were excluded because of human errors during data entry in the electronic randomisation system. One additional participant was excluded due to a positive CMV result consistent with congenital CMV infection, which led to a clinical decision to prescribe valganciclovir outside the randomised allocation. The resulting per-protocol population comprised 279 participants in the non–valganciclovir arms and 275 participants in the valganciclovir arms.

For the eTB-T comparison, the per-protocol population excluded two participants due to randomisation errors related to incorrect data entry in the electronic randomisation system. In addition, six participants allocated to the eTB-T arms who received less than 90 days (50%) of the planned TB-T duration were excluded from the per-protocol analysis. The resulting per-protocol population comprised 280 participants in the non-eTB-T arms and 278 participants in the eTB-T arms.

The safety population included all randomised participants who received at least one dose of study treatment. All primary efficacy analyses were conducted according to the modified ITT principle unless otherwise specified.

8.2. Primary outcomes

The primary outcome of the EMPIRICAL trial was all-cause mortality, evaluated through three complementary co-primary analyses:

- Short-term mortality at 15 days after randomisation
- Long-term mortality at one year after randomisation

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- Time-to-death during one-year follow-up

These analyses were conducted within the factorial design framework.

Overall, 253 participants (45%) died during the 1-year follow-up (Table 6); 154 of 253 (61%) died during the initial hospitalisation, representing an inpatient mortality rate of 28% (154 of 558). The remaining 99 deaths (39%) occurred after discharge and during follow-up. Thirty-seven participants (7%) were lost to follow-up at one year.

Table 6. Characteristics of patients who died

	All – Case Fatality Risk/site ***N=253***
Enrolling country— no. (%)	
Mozambique: Institution 1	98/200 (49.0)
Uganda	50/137 (36.5)
Zimbabwe	27/72 (37.5)
Zambia	38/71 (53.5)
Malawi: Institution 2	17/35 (48.6)
Malawi: Institution 1	17/32 (53.1)
Mozambique: Institution 2	5/10 (50.0)
Ivory Coast	1/1 (100)
Cause— no. (%)	
Severe pneumonia	120 (47.4)
Sepsis	41 (16.2)
Gastroenteritis and colitis	16 (6.3)
TB	14 (5.5)
Other*	62 (24.5)
Median time to death— d	11.0 (3.0–66.0)
≤48h— no. (%)	62 (24.5)
≤15 days	140 (55.3)
Median age at death— m	5.4 (3.6–8.7)

Percentages may not total 100 because of rounding. * Other causes of death were malnutrition (2), acidosis (2), anaemia (2), encephalitis (2), HIV resulting in multiple infections (1), hypoglycemia (1), hypovolemic shock (1), pulmonary hypertension (1), car accident (1), congenital malformation of heart (1), convulsions (1), disseminated intravascular coagulation (1), malaria (1), cerebral cryptococcosis (1), systemic inflammatory response (1), and unknown cause (43). Mozambique Institution 1: Universidade Eduardo Mondlane-Maputo and linked hospitals (in Maputo City, Maputo Province, Sofala, and Nampula provinces), Mozambique Institution 2: CISM-Manhiça and linked hospitals (in Maputo Province (Manhiça) and Gaza (Xai-Xai) provinces), Malawi Institution 1: Malawi- Liverpool Wellcome Trust (Blantyre), Malawi Institution 2: Lilongwe Medical Relief Fund Trust (Lilongwe).

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8.2.1. Interaction between interventions

Given the factorial design of the trial, empirical valganciclovir and eTB-T (eTB-T) were first analysed within the same multivariable survival model, including an interaction term between the two interventions.

There was no evidence of interaction between empirical valganciclovir and eTB-T (adjusted hazard ratio for interaction 1.19 [95% CI 0.73–1.95]; heterogeneity p=0.4836). Therefore, treatment effects for each intervention are presented as marginal comparisons.

8.2.2. Short-term mortality (15-days)

At 15 days after randomisation, 140 of 558 participants (25%) had died.

Among participants allocated to the valganciclovir arms, 64 of 276 (23%) died within 15 days, compared with 76 of 282 (27%) in the non–valganciclovir arms. The adjusted odds ratio (aOR) for death at 15 days in participants allocated to valganciclovir was 0.75 (95% CI 0.50–1.13, p=0.171), adjusted for age at HIV diagnosis, baseline HIV viral load, baseline CD4 percentage, baseline oxygen saturation, and recruitment country.

Among participants allocated to the eTB-T arms, 74 of 276 (27%) died within 15 days, compared with 66 of 282 (23%) in the non-eTB-T arms. The aOR for death at 15 days in the eTB-T arms was 1.24 (95% CI 0.83–1.84, p=0.282), adjusted for baseline oxygen saturation, baseline HIV viral load, baseline CD4 percentage, and recruitment country.

Table 7. Primary endpoint: coefficients of the short-term (15-days mortality) analysis for the valganciclovir comparison. Logistic regression coefficients.

	Analysis	Odds Ratio	Lower 95% CI	Upper 95% CI
Valganciclovir (Ref=No)	Unadjusted	0.81	0.55	1.19
Valganciclovir (Ref=No)	Adjusted	0.75	0.50	1.13
Age at HIV diagnosis (days)	Adjusted	0.99	0.99	0.99
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	1.91	0.98	3.72
Baseline percentage CD4	Adjusted	0.98	0.96	1.00
Baseline oxygen saturation (Ref: >90%)	Adjusted	2.1	1.32	3.24
Country: Zambia (Ref: Mozambique)	Adjusted	1.38	0.73	2.59
Country: Zimbabwe (Ref: Mozambique)	Adjusted	0.51	0.24	1.10
Country: Uganda (Ref: Mozambique)	Adjusted	1.49	0.86	2.60
Country: Malawi (Ref: Mozambique)	Adjusted	1.48	0.78	2.80

Due to an extremely small sample size (n=1), the Ivory Coast site was excluded from multivariable models to avoid overfitting and unstable estimates. Ref: Reference category; Model was initially adjusted by country, sex, age at HIV diagnosis, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral treatment, baseline haemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.

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Table 8. Primary endpoint: coefficients of the short-term (15-days mortality) analysis for the eTB-T comparison. Logistic regression coefficients.

	Analysis	Odds Ratio	Lower 95% CI	Upper 95% CI
Empirical TB-T (Ref=No)	Unadjusted	1.20	0.84	1.70
Empirical TB-T (Ref=No)	Adjusted	1.24	0.83	1.84
Baseline oxygen saturation (Ref=>90%)	Adjusted	2.15	1.37	3.36
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	1.91	0.98	3.71
Baseline % CD4	Adjusted	0.98	0.96	0.99
Country: Uganda (Ref Moz)	Adjusted	1.27	0.75	2.15
Country: Malawi (Ref Moz)	Adjusted	1.38	0.74	2.60
Country: Zambia (Ref Moz)	Adjusted	1.23	0.66	2.29
Country: Zimbabwe (Ref Moz)	Adjusted	0.49	0.23	1.04

** Due to extremely small sample size (n=1), the Ivory Coast site was excluded from multivariable models to avoid overfitting and unstable estimates. Ref: Reference category; Mlw: Malawi; Moz: Mozambique. Model was initially adjusted by country, sex, age at HIV diagnostic, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral treatment, baseline hemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.*

8.2.3. Long-term mortality (1-year)

In the valganciclovir arms, 119 of 276 participants (43%) died during one-year follow-up, compared with 134 of 282 (48%) in the non–valganciclovir arms. The aOR for death at one year in participants allocated to valganciclovir was 0.88 (95% CI 0.61–1.28, p=0.500), adjusted for baseline HIV viral load, baseline CD4 percentage, and baseline oxygen saturation.

In the eTB-T arms, 132 of 276 participants (48%) died during one-year follow-up, compared with 121 of 282 (43%) in the non-eTB-T arms. The aOR for death at one year in the eTB-T arms was 1.22 (95% CI 0.84–1.77, p=0.293), adjusted for baseline oxygen saturation, baseline HIV viral load, and baseline CD4 percentage.

Table 9. Primary endpoint: coefficients of the long-term (1-year mortality) analysis for the valganciclovir comparison. Logistic regression coefficients.

	Analysis	Odds Ratio	Lower 95% CI	Upper 95% CI
Valganciclovir (Ref=No)	Unadjusted	0.81	0.55	1.19
Valganciclovir (Ref=No)	Adjusted	0.88	0.61	1.28
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.81	1.61	4.90
Baseline percentage CD4	Adjusted	0.97	0.95	0.99
Baseline oxygen saturation (Ref: >90%)	Adjusted	2.10	1.32	3.24

Ref: Reference category; Model was initially adjusted by country, sex, age at HIV diagnosis, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral treatment, baseline haemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.

Table 10. Primary endpoint: coefficients of the long-term (1-year mortality) analysis for the eTB-T comparison. Logistic regression coefficients.

	Analysis	Odds Ratio	Lower 95% CI	Upper 95% CI
Empirical TB-T (Ref=No)	Unadjusted	1.20	0.84	1.70
Empirical TB-T (Ref=No)	Adjusted	1.22	0.84	1.77
Baseline oxygen saturation (Ref=>90%)	Adjusted	1.83	1.24	2.71
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.70	1.56	4.66
Baseline % CD4	Adjusted	0.97	0.95	0.99

Model was initially adjusted by country, sex, age at HIV diagnostic, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral treatment, baseline hemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.

8.2.4. Time-to-event analysis (during 1-year)

Time-to-death during the one-year follow-up period was analysed using Kaplan–Meier methods and flexible parametric survival models.

Kaplan–Meier curves showed higher survival probability in participants randomised to valganciclovir arms, with the magnitude of effect diminishing over time. Participants allocated to valganciclovir had a 21% lower hazard of death compared with those not allocated to valganciclovir (aHR 0.79, 95% CI 0.62–1.01; p=0.0678). The model was adjusted for baseline nutritional status, baseline HIV viral load, baseline oxygen saturation, days from hospitalisation to randomisation, and recruitment site (Figure 5, Table 11).

Kaplan–Meier curves did not show higher survival probability in participants randomised to eTB-T arms. Participants allocated to eTB-T arms did not have lower mortality compared with those not allocated to eTB-T (aHR 1.12, 95% CI 0.87–1.43; p=0.3868). The model was adjusted for baseline HIV viral load, baseline CD4 percentage, baseline oxygen saturation, and recruitment country (Figure 6, Table 12).

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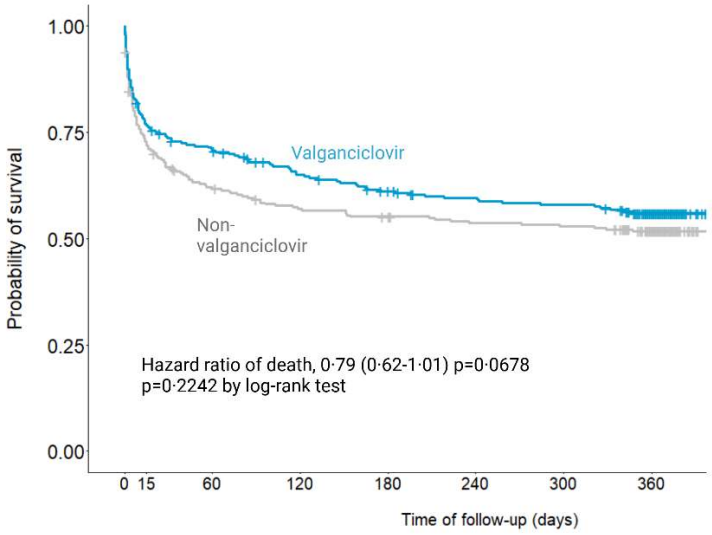
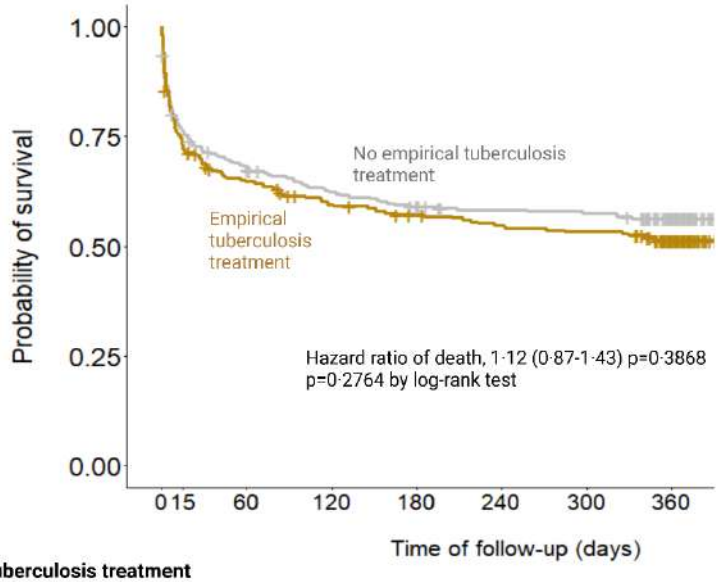
Figure 5. Kaplan-Meier curves for valganciclovir comparison



Non- Valganciclovir								
At Risk	282	204	171	155	149	143	141	108
Censored	0	2	5	7	8	10	10	53
Events	4	79	107	120	125	129	131	134
Valganciclovir								
At Risk	276	211	192	170	157	147	143	107
Censored	0	1	4	10	14	19	19	59
Events	6	65	81	96	106	110	114	119

Figure 6. Kaplan-Meier curves for empirical tuberculosis treatment comparison



No empirical tuberculosis treatment								
At Risk	282	214	198	170	160	151	149	110
Censored	0	2	4	7	9	15	15	60
Events	5	67	91	105	114	116	118	121
Empirical tuberculosis treatment								
At Risk	276	201	174	155	146	139	135	105
Censored	0	1	5	10	13	14	14	52
Events	5	77	97	111	117	123	127	132

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Table 11. Primary endpoint: coefficients of the time to event (mortality) analysis for valganciclovir comparison.

	Analysis	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
Valganciclovir (Ref=No)	Unadjusted	0.86	0.67	1.1	0.231
Valganciclovir (Ref=No)	Adjusted	0.79	0.62	1.01	0.068
Malnutrition: moderate (Ref=No)	Adjusted	0.90	0.61	1.33	0.599
Malnutrition: severe (Ref=No)	Adjusted	1.29	0.97	1.71	0.079
Baseline oxygen saturation (Ref=>90%)	Adjusted	1.50	1.14	1.99	0.004
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.10	1.33	3.32	0.001
Baseline % CD4	Adjusted	0.98	0.96	0.99	0.005
Days from hospitalization to randomization	Adjusted	0.99	0.96	1.02	0.648
Country: Uganda (Ref Mozambique)	Adjusted	0.83	0.58	1.18	0.298
Country: Malawi (Ref Mozambique)	Adjusted	1.04	0.70	1.54	0.845
Country: Zambia (Ref Mozambique)	Adjusted	1.25	0.86	1.82	0.246
Country: Zimbabwe (Ref Mozambique)	Adjusted	0.74	0.48	1.15	0.185

Due to an extremely small sample size (n=1), the Ivory Coast site was excluded from multivariable models to avoid overfitting and unstable estimates. Ref: Reference category; Model was initially adjusted by country, sex, age at HIV diagnosis, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral treatment, baseline haemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.

Table 12. Primary endpoint: coefficients of the time to event (mortality) analysis for eTB-T comparison.

	Analysis	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
Empirical TB-T (Ref=No)	Unadjusted	1.15	0.90	1.47	0.276
Empirical TB-T (Ref=No)	Adjusted	1.12	0.87	1.43	0.387
Baseline oxygen saturation (Ref=>90%)	Adjusted	1.47	1.12	1.94	0.006
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.10	1.33	3.32	0.001
Baseline % CD4	Adjusted	0.98	0.96	0.99	0.006
Country: Uganda (Ref Moz)	Adjusted	0.87	0.62	1.24	0.444
Country: Malawi (Ref Moz)	Adjusted	1.04	0.70	1.54	0.844
Country: Zambia (Ref Moz)	Adjusted	1.24	0.85	1.81	0.259
Country: Zimbabwe (Ref Moz)	Adjusted	0.73	0.47	1.14	0.165

** Moz corresponds to Mozambique. Due to extremely small sample size (n=1), the Ivory Coast site was excluded from multivariable models to avoid overfitting and unstable estimates. Ref: Reference category; Mlw: Malawi; Moz: Mozambique. Model was initially adjusted by country, sex, age at HIV diagnostic, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral treatment, baseline hemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.*

8.3. Secondary outcomes

8.3.1. Cumulative days of oxygen supplementation during the first admission

Participants in the valganciclovir arms had fewer days with supplementary oxygen therapy during the first admission (rate ratio, 0.78 [95% CI, 0.55–1.10; p=0.1084]) (Table 13).
The participants in eTB-T arms had similar days with supplementary oxygen therapy during the first admission (rate ratio, 1.03, 95%CI 0.73–1.45; p=0.8329) (Table 14).

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Table 13. Incidence rate ratio of days on supplemental oxygen during the first admission for valganciclovir comparison

	Analysis	Incidence Rate Ratio	Lower 95% CI	Upper 95% CI
Valganciclovir (Ref=No)	Unadjusted	0.73	0.52	1.03
Valganciclovir (Ref=No)	Adjusted	0.78	0.55	1.10
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	3.11	1.90	4.97
Baseline weight for height	Adjusted	0.95	0.88	1.03
Country: Uganda (Ref Mozambique)	Adjusted	0.46	0.30	0.76
Country: Malawi (Ref Mozambique)	Adjusted	1.11	0.63	2.02
Country: Zambia (Ref Mozambique)	Adjusted	1.06	0.61	1.90
Country: Zimbabwe (Ref Mozambique)	Adjusted	0.70	0.41	1.22

Incidence Rate Ratios were calculated using a negative binomial regression including an offset of time of follow-up. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.

Table 14. Incidence rate ratio of days on supplemental oxygen during the first admission for eTB-T comparison

	Analysis	Incidence Rate Ratio	Lower 95% CI	Upper 95% CI	p-value
Empirical TB-T (Ref=No)	Unadjusted	1.03	0.73	1.46	0.847
Empirical TB-T (Ref=No)	Adjusted	1.03	0.73	1.45	0.833
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.85	1.75	4.52	$4.4\ 10^{-7}$
Baseline weight for height	Adjusted	0.98	0.90	1.06	0.647

Incidence Rate Ratios were calculated using a negative binomial regression including an offset of time of follow-up. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.

8.3.2. Cumulative days of days of hospitalization during the follow-up

The participants in valganciclovir arms had fewer cumulative days of hospitalisation over 1-year of follow-up (rate ratio, 0.77, 95%CI 0.60–0.99; p=0.0212) (Table 15).

The participants in eTB-T arms had similar cumulative days of hospitalisation over 1-year of follow-up (rate ratio, 1.06, 95%CI 0.83–1.37; p=0.5821) (Table 16).

Table 15. Incidence rate ratio of cumulative days of hospitalization during 1-year follow-up for valganciclovir comparison

	Analysis	Incidence Rate Ratio	Lower 95% CI	Upper 95% CI
Valganciclovir (Ref=No)	Unadjusted	0.75	0.58	0.96
Valganciclovir (Ref=No)	Adjusted	0.77	0.60	0.99
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.48	1.76	3.45
Baseline weight for height	Adjusted	0.92	0.86	0.97
Country: Uganda (Ref Mozambique)	Adjusted	0.74	0.54	1.03
Country: Malawi (Ref Mozambique)	Adjusted	0.87	0.56	1.36
Country: Zambia (Ref Mozambique)	Adjusted	0.97	0.64	1.45
Country: Zimbabwe (Ref Mozambique)	Adjusted	0.68	0.46	1.03

Incidence Rate Ratios were calculated using a negative binomial regression including an offset of time of follow-up. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.

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Table 16. Incidence rate ratio of cumulative days of hospitalization during 1-year follow-up for eTB-T comparison

	Analysis	Incidence Rate Ratio	Lower 95% CI	Upper 95% CI	p-value
Empirical TB-T (Ref=No)	Unadjusted	1.08	0.84	1.39	0.511
Empirical TB-T (Ref=No)	Adjusted	1.06	0.83	1.37	0.582
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.57	1.82	3.57	$8.4\ 10^{-10}$
Baseline weight for height	Adjusted	0.92	0.87	0.98	0.007
Country: Uganda (Ref Mozambique)	Adjusted	0.75	0.54	1.04	0.055
Country: Malawi (Ref Mozambique)	Adjusted	0.89	0.57	1.39	0.054
Country: Zambia (Ref Mozambique)	Adjusted	1.01	0.67	1.53	0.972
Country: Zimbabwe (Ref Mozambique)	Adjusted	0.75	0.54	0.99	0.030

Incidence Rate Ratios were calculated using a negative binomial regression including an offset of time of follow-up. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.

8.4. Subgroup analysis

Subgroup analyses were conducted to explore potential heterogeneity of treatment effects across clinically relevant baseline characteristics. Subgroups were defined according to birth sex, age category, baseline oxygen saturation, oxygen supplementation at baseline, nutritional status, ART status, degree of immunosuppression, recruitment country, and microbiological findings at baseline, including TB and CMV status.

Treatment effects within each subgroup were estimated using flexible parametric survival models consistent with the principal time-to-event analysis. Models were fitted across multiply imputed datasets to account for missing baseline data. Due to the limited number of events within several subgroups, no additional covariate adjustment was performed in the subgroup models. Interaction terms between treatment allocation and subgroup variables were evaluated to assess statistical evidence of heterogeneity. Confidence intervals presented for subgroup analyses were not adjusted for multiplicity. These analyses were exploratory in nature, and the width of the confidence intervals should not be interpreted as confirmatory hypothesis testing.

Subgroup analyses for valganciclovir showed HR estimates below unity in several subgroups, consistent with the overall time-to-event analysis. In some categories, including younger age groups and participants with severe malnutrition, point estimates suggested a greater relative reduction in mortality; however, confidence intervals overlapped unity in multiple subgroups (Figure 7).

Subgroup analyses for eTB-T did not demonstrate consistent evidence of heterogeneity in treatment effect across examined baseline characteristics. HR estimates were generally close to unity across categories of sex, age, oxygen saturation, nutritional status, ART status, immunosuppression status, country, and baseline TB diagnostic status (Figure 8).

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Figure 7. Subgroup analysis for valganciclovir comparison

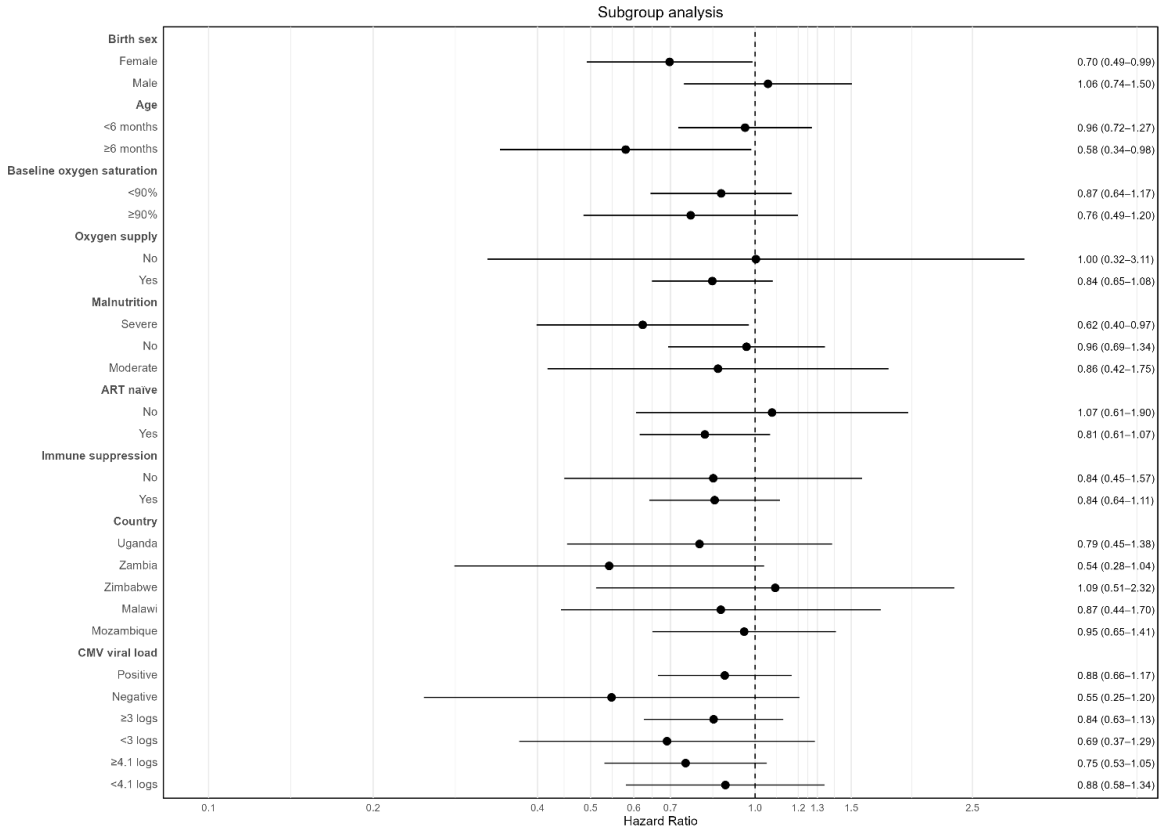
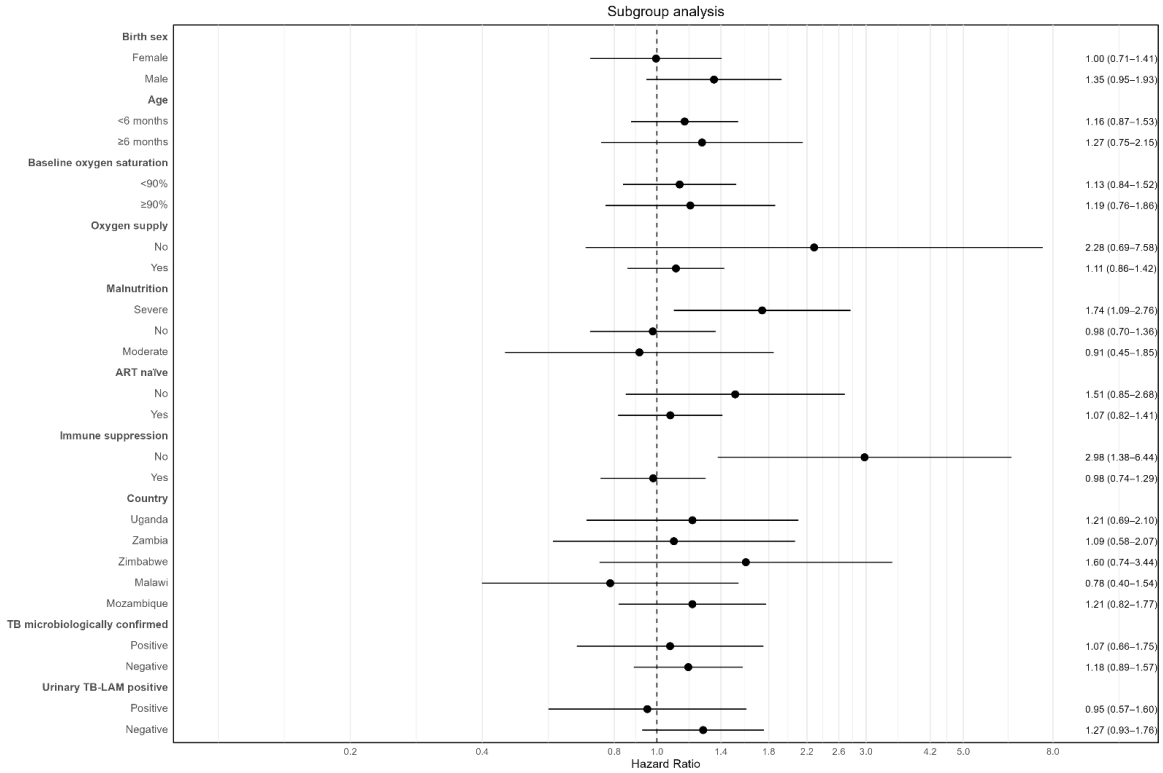


Figure 8. Subgroup analysis for eTB-T comparison



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8.5. Sensitivity analysis

8.5.1. Per-protocol analysis

Per-protocol analyses were performed separately for each intervention, reflecting the different protocol deviations applicable to valganciclovir and eTB-T.

The per-protocol analysis for valganciclovir yielded effect estimates consistent with the ITT analysis, with no material change in direction or magnitude of treatment effect (Table 17). Similarly, the per-protocol analysis for eTB-T showed results consistent with the ITT findings (Table 18).

Table 17. Primary endpoint: coefficients of the time to event (mortality) analysis in the per-protocol analysis for valganciclovir comparison

	Analysis	Hazard Ratio	Lower 95% CI	Upper 95% CI
Valganciclovir (Ref=No)	Unadjusted	0.87	0.68	1.11
Valganciclovir (Ref=No)	Adjusted	0.80	0.62	1.03
Malnutrition: moderate (Ref=No)	Adjusted	0.92	0.62	1.37
Malnutrition: severe (Ref=No)	Adjusted	1.30	0.98	1.72
Baseline oxygen saturation (Ref=>90%)	Adjusted	1.49	1.13	1.97
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.07	1.31	3.28
Baseline percentage CD4	Adjusted	0.98	0.96	0.99
Days from hospitalization to randomization	Adjusted	0.99	0.96	1.02
Country: Uganda (Ref: Mozambique)	Adjusted	0.81	0.57	1.16
Country: Malawi (Ref: Mozambique)	Adjusted	1.03	0.70	1.53
Country: Zambia (Ref: Mozambique)	Adjusted	1.24	0.85	1.82
Country: Zimbabwe (Ref: Mozambique)	Adjusted	0.75	0.49	1.17

Due to an extremely small sample size (n=1), the Ivory Coast site was excluded from multivariable models to avoid overfitting and unstable estimates. Ref: Reference category; Model was initially adjusted by country, sex, age at HIV diagnosis, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral treatment, baseline haemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.

Table 18. Primary endpoint: coefficients of the time to event (mortality) analysis in the per-protocol analysis for eTB-T comparison

	Analysis	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
Empirical TB-T (Ref=No)	Unadjusted	1.12	0.88	1.44	0.354
Empirical TB-T (Ref=No)	Adjusted	1.09	0.85	1.40	0.500
Baseline oxygen saturation (Ref=>90%)	Adjusted	1.48	1.12	1.96	0.006
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.15	1.36	3.39	0.001
Baseline % CD4	Adjusted	0.98	0.96	0.99	0.004
Country: Uganda (Ref Moz)	Adjusted	0.87	0.62	1.23	0.429
Country: Malawi (Ref Moz)	Adjusted	1.02	0.69	1.52	0.919
Country: Zambia (Ref Moz)	Adjusted	1.26	0.87	1.83	0.226
Country: Zimbabwe (Ref Moz)	Adjusted	0.70	0.47	1.14	0.114

** Moz corresponds to Mozambique. Due to extremely small sample size (n=1), the Ivory Coast site was excluded from multivariable models to avoid overfitting and unstable estimates. Ref: Reference category; Mlw: Malawi; Moz: Mozambique. Model was initially adjusted by country, sex, age at HIV diagnostic, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral*

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treatment, baseline haemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.

8.5.2. Cox proportional models

Sensitivity analyses were conducted using Cox proportional hazards models in place of flexible parametric survival models. Effect estimates were comparable across modelling approaches, and conclusions were unchanged (Table 19 and 20).

Table 19. Coefficients for Cox proportional model for the valganciclovir comparison

	Analysis	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
Valganciclovir (Ref=No)	Unadjusted	0.86	0.67	1.10	0.223
Valganciclovir (Ref=No)	Adjusted	0.79	0.61	1.02	0.067
Malnutrition: moderate (Ref=No)	Adjusted	0.90	0.61	1.34	0.606
Malnutrition: severe (Ref=No)	Adjusted	1.29	0.97	1.71	0.081
Baseline oxygen saturation (Ref=>90%)	Adjusted	1.51	1.14	1.99	0.004
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.10	1.33	3.32	0.002
Baseline CD4%	Adjusted	0.98	0.96	0.99	0.005
Days from hospitalization to randomization	Adjusted	0.99	0.96	1.03	0.643
Country: Uganda (Ref Mozambique)	Adjusted	0.83	0.58	1.18	0.297
Country: Malawi (Ref Mozambique)	Adjusted	1.04	0.70	1.53	0.867
Country: Zambia (Ref Mozambique)	Adjusted	1.25	0.85	1.83	0.248
Country: Zimbabwe (Ref Mozambique)	Adjusted	0.74	0.48	1.15	0.185

Due to an extremely small sample size (n=1), the Ivory Coast site was excluded from multivariable models to avoid overfitting and unstable estimates. Ref: Reference category; Model was initially adjusted by country, sex, age at HIV diagnosis, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral treatment, baseline haemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.

Table 20. Coefficients for Cox proportional model for the eTB-T comparison

	Analysis	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
Empirical TB-T (Ref=No)	Unadjusted	1.14	0.90	1.47	0.278
Empirical TB-T (Ref=No)	Adjusted	1.12	0.87	1.43	0.386
Baseline oxygen saturation (Ref=>90%)	Adjusted	1.47	1.12	1.94	0.006
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.14	1.36	3.38	0.001
Baseline % CD4	Adjusted	0.98	0.96	0.99	0.005
Country: Uganda (Ref Moz)	Adjusted	0.87	0.62	1.23	0.440
Country: Malawi (Ref Moz)	Adjusted	1.03	0.70	1.53	0.868
Country: Zambia (Ref Moz)	Adjusted	1.24	0.85	1.80	0.262
Country: Zimbabwe (Ref Moz)	Adjusted	0.73	0.47	1.14	0.165

** Moz corresponds to Mozambique. Due to extremely small sample size (n=1), the Ivory Coast site was excluded from multivariable models to avoid overfitting and unstable estimates. Ref: Reference category; Mlw: Malawi; Moz: Mozambique. Model was initially adjusted by country, sex, age at HIV diagnostic, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral treatment, baseline hemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.*

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8.5.3. Excluding deaths that occurred within the first 48h

To evaluate whether very early deaths influenced treatment effect estimates, a sensitivity analysis was conducted excluding participants who died within the first 48 hours after randomisation. Time-to-event models were re-fitted using the same covariate adjustment strategy as in the primary analysis.

After exclusion of deaths occurring within 48 hours, participants allocated to valganciclovir had a 24% lower hazard of death compared with those not allocated to valganciclovir (adjusted hazard ratio [aHR] 0.76, 95% CI 0.58–1.00; p=0.0500). This estimate was consistent in direction with the primary analysis (Table 21). In the time-varying treatment effect model restricted to participants surviving beyond 48 hours, the adjusted hazard ratio at day 15 was 0.68 (95% CI 0.47–0.97; p=0.0336), indicating persistence of an early treatment effect after exclusion of very early deaths.

For eTB-T, exclusion of deaths occurring within the first 48 hours did not materially alter the estimated treatment effect. The adjusted hazard ratio remained close to unity (aHR 1.21, 95% CI 0.91–1.61; p=0.199), consistent with the primary analysis. The direction and magnitude of association were unchanged (Table 22).

Overall, exclusion of deaths occurring within the first 48 hours did not change the interpretation of the primary findings for either intervention.

Table 21. Primary endpoint: coefficients of the time to event (mortality) analysis excluding deaths occurred within 48 hours for valganciclovir comparison

	Analysis	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
Valganciclovir (Ref=No)	Unadjusted	0.85	0.64	1.13	0.276
Valganciclovir (Ref=No)	Adjusted	0.76	0.58	1.00	0.050
Malnutrition: moderate (Ref=No)	Adjusted	0.96	0.64	1.44	0.846
Malnutrition: severe (Ref=No)	Adjusted	1.26	0.93	1.71	0.140
Baseline oxygen saturation (Ref=>90%)	Adjusted	1.41	1.05	1.90	0.022
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.13	1.31	3.45	0.002
Baseline % CD4	Adjusted	0.98	0.96	0.99	0.009
Days from hospitalization to randomization	Adjusted	1.00	0.97	1.04	0.835
Country: Uganda (Ref Mozambique)	Adjusted	0.83	0.57	1.21	0.329
Country: Malawi (Ref Mozambique)	Adjusted	0.96	0.62	1.47	0.849
Country: Zambia (Ref Mozambique)	Adjusted	1.19	0.79	1.79	0.403
Country: Zimbabwe (Ref Mozambique)	Adjusted	0.69	0.43	1.11	0.124

Due to an extremely small sample size (n=1), the Ivory Coast site was excluded from multivariable models to avoid overfitting and unstable estimates. Ref: Reference category; Model was initially adjusted by country, sex, age at HIV diagnosis, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral treatment, baseline haemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.

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Table 22. Primary endpoint: coefficients of the time to event (mortality) analysis excluding deaths occurred within 48 hours for eTB-T comparison

	Analysis	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
Empirical TB-T (Ref=No)	Unadjusted	1.26	0.95	1.67	0.115
Empirical TB-T (Ref=No)	Adjusted	1.21	0.91	1.61	0.199
Baseline oxygen saturation (Ref=>90%)	Adjusted	1.40	1.02	1.92	0.040
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.09	1.27	3.44	0.004
Baseline % CD4	Adjusted	0.98	0.96	0.99	0.032
Country: Uganda (Ref Moz)	Adjusted	0.74	0.50	1.11	0.144
Country: Malawi (Ref Moz)	Adjusted	0.84	0.53	1.32	0.448
Country: Zambia (Ref Moz)	Adjusted	0.94	0.60	1.48	0.791
Country: Zimbabwe (Ref Moz)	Adjusted	0.62	0.38	1.02	0.061

** Moz site 1 corresponds to Mozambique Maputo site. Due to extremely small sample size (n=1), the Ivory Coast site was excluded from multivariable models to avoid overfitting and unstable estimates. Ref: Reference category; Mlw: Malawi; Moz: Mozambique. Model was initially adjusted by country, sex, age at HIV diagnostic, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral treatment, baseline haemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.*

8.5.4. Time-varying effect of valganciclovir

Given that Kaplan–Meier survival curves for valganciclovir demonstrated early separation with subsequent convergence over time, suggesting potential attenuation of treatment effect, a sensitivity analysis was conducted allowing for time-varying treatment effects. Model complexity was selected using Akaike's information criterion with a ΔAIC ≤ 2 parsimony rule. A likelihood-ratio test comparing the TVC model with the proportional hazards model yielded p=0.087.

There was borderline statistical evidence against the proportional hazards assumption (likelihood ratio test p=0.087). In the time-varying model, the adjusted hazard ratio at day 15 was 0.60 (95% CI 0.41–0.87; p=0.0063). Estimated hazard ratios increased over time, suggesting attenuation of the treatment effect during later follow-up. These findings are consistent with an early treatment effect that diminishes over time (Figure 9).

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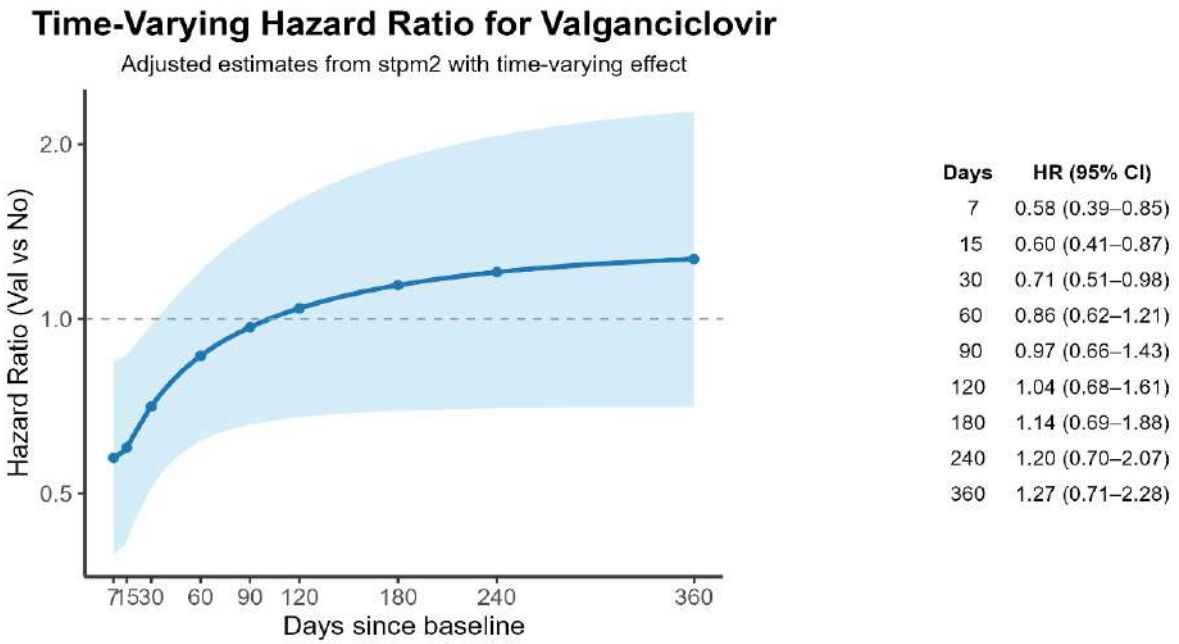
Figure 9. Time-varying effects model estimates at study time points (time-varying hazard ratio for valganciclovir)



Days	HR (95% CI)
7	0.58 (0.39–0.85)
15	0.60 (0.41–0.87)
30	0.71 (0.51–0.98)
60	0.86 (0.62–1.21)
90	0.97 (0.66–1.43)
120	1.04 (0.68–1.61)
180	1.14 (0.69–1.88)
240	1.20 (0.70–2.07)
360	1.27 (0.71–2.28)

Adjusted estimates from stpm2 with time-varying effect. HR: Hazard ratio. CI: confidence interval. Val: valganciclovir

8.5.5. Handling of missing data

Primary analyses were conducted using multiply imputed datasets to account for missing baseline covariates. As a sensitivity analysis, the primary time-to-event models were re-estimated using complete-case data only.

For valganciclovir, complete-case analyses also yielded effect estimates consistent with those from the multiply imputed models. The direction of treatment effect and overall conclusions remained unchanged (Table 23).

For eTB-T, the adjusted hazard ratio obtained in the complete-case analysis was similar in direction and magnitude to that observed in the multiply imputed analysis. No material change in statistical significance or overall interpretation was observed (Table 24).

These findings indicate that the primary efficacy results were robust to the handling of missing baseline covariates.

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Table 23. Primary endpoint: coefficients of the time to event (mortality) analysis in the complete-case analysis (without missing imputation) for valganciclovir comparison

	Analysis	Hazard Ratio	Lower 95% CI	Upper 95% CI
Valganciclovir (Ref=No)	Unadjusted	0.86	0.67	1.1
Valganciclovir (Ref=No)	Adjusted	0.80	0.62	1.02
Malnutrition: moderate (Ref=No)	Adjusted	0.94	0.64	1.38
Malnutrition: severe (Ref=No)	Adjusted	1.31	0.99	1.73
Baseline oxygen saturation (Ref=>90%)	Adjusted	1.51	1.14	1.99
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	1.93	1.26	2.95
Baseline percentage CD4	Adjusted	0.98	0.96	0.99
Days from hospitalization to randomization	Adjusted	0.99	0.96	1.02
Country: Uganda (Ref Mozambique)	Adjusted	0.83	0.58	1.18
Country: Malawi (Ref Mozambique)	Adjusted	1.05	0.71	1.55
Country: Zambia (Ref Mozambique)	Adjusted	1.23	0.85	1.80
Country: Zimbabwe (Ref Mozambique)	Adjusted	0.75	0.48	1.16

Due to an extremely small sample size (n=1), the Ivory Coast site was excluded from multivariable models to avoid overfitting and unstable estimates. Ref: Reference category; Model was initially adjusted by country, sex, age at HIV diagnosis, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral treatment, baseline haemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.

Table 24. Primary endpoint: coefficients of the time to event (mortality) analysis in the complete-case analysis (without missing imputation) for eTB-T comparison

	Analysis	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
Empirical TB-T (Ref=No)	Unadjusted	1.15	0.90	1.47	0.271
Empirical TB-T (Ref=No)	Adjusted	1.18	0.90	1.54	0.227
Baseline oxygen saturation (Ref=>90%)	Adjusted	1.51	1.12	2.04	0.007
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.25	1.36	3.73	0.002
Baseline % CD4	Adjusted	0.98	0.96	0.99	0.004
Country: Uganda (Ref Moz)	Adjusted	0.90	0.62	1.30	0.570
Country: Malawi (Ref Moz)	Adjusted	1.06	0.71	1.60	0.768
Country: Zambia (Ref Moz)	Adjusted	1.16	0.75	1.81	0.497
Country: Zimbabwe (Ref Moz)	Adjusted	0.86	0.54	1.37	0.532

** Moz corresponds to Mozambique. Due to extremely small sample size (n=1), the Ivory Coast site was excluded from multivariable models to avoid overfitting and unstable estimates. Ref: Reference category; Mlw: Malawi; Moz: Mozambique. Model was initially adjusted by country, sex, age at HIV diagnostic, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral treatment, baseline haemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.*

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8.6. Post-hoc and exploratory analysis

8.6.1. Time-Specific Landmark Analysis for Valganciclovir Effect

A post-hoc landmark analysis was conducted to explore the temporal pattern of the association between valganciclovir and mortality at predefined time points during follow-up (Table 25). At 15 days, mortality was 23% in the valganciclovir group and 27% in the non–valganciclovir group. The adjusted risk ratio (RR) was 0.81 (95% CI 0.61–1.08). The number needed to treat (NNT) ranged between approximately 10 and 17 across time points (Table S4).

Overall, this landmark analysis suggests that the mortality reduction associated with valganciclovir was most pronounced during the early months following randomisation and diminished over time. As this analysis was conducted post hoc, findings should be interpreted cautiously.

8.6.2. Valganciclovir as-treated analysis

A post-hoc as-treated analysis was conducted excluding participants who discontinued valganciclovir treatment (Table S5). In this analysis, the aHR for death among participants who received valganciclovir as treated was 0.80 (95% CI 0.62–1.03), compared with participants not receiving valganciclovir. This estimate was similar in magnitude and direction to that observed in the ITT analysis. Unadjusted estimates showed a hazard ratio of 0.87 (95% CI 0.68–1.12). After multivariable adjustment, the association remained in favour of valganciclovir but did not reach conventional statistical significance.

Overall, the as-treated analysis yielded results consistent with the primary ITT findings. Given the potential for bias inherent to as-treated analyses, these results should be interpreted as exploratory.

8.6.3. Post-hoc Analysis for eTB-T: Exclusion of Participants in the non–eTB-T Arms Who Initiated TB-T After Randomisation Following a Positive Microbiological Test

A post-hoc analysis was conducted to explore the potential impact of post-randomisation initiation of TB-T in the non–eTB-T arms. Participants allocated to the non–eTB-T arms who initiated TB-T after randomisation following a positive microbiological TB test (TB-LAM or Xpert MTB/RIF Ultra) were excluded from this analysis. A total of 55 participants were excluded.

After exclusion of these participants, Kaplan–Meier survival estimates remained similar between groups (Figure S1). No statistically significant difference in all-cause mortality was observed between participants allocated to eTB-T and those not allocated to eTB-T (log-rank p=0.6429). This analysis suggests that post-randomisation initiation of TB-T in the non–eTB-T arms did not materially influence the overall findings. However, because this analysis excludes participants after randomisation and therefore disrupts the original randomisation balance, results should be interpreted as exploratory.

8.6.4. Post-hoc Analysis for eTB-T: Exclusion of Participants in the non–eTB-T Arms Who Initiated TB-T After Randomisation Following a Positive Microbiological Test and those with early post-randomisation TB-T initiation based on clinical diagnosis (<4 days)

A post-hoc analysis was conducted to further explore the potential impact of post-randomisation initiation of TB-T in the non–eTB-T arms. In this analysis, participants allocated to the non–eTB-T arms who initiated

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TB-T after randomisation following a positive microbiological TB test (TB-LAM or Xpert MTB/RIF Ultra) were excluded. In addition, participants who initiated TB-T within the first 4 days after randomisation due to a TB clinical diagnosis were also excluded, as early initiation may have reflected clinical suspicion of TB not fully captured during screening.

In total, 55 participants were excluded due to post-randomisation microbiological confirmation, and an additional 31 participants were excluded due to very early initiation of TB-T. After these exclusions, Kaplan–Meier survival curves remained similar between participants allocated to eTB-T and those not allocated to eTB-T (Figure S2). No statistically significant difference in all-cause mortality was observed between groups (log-rank p=0.4373).

These findings suggest that early post-randomisation initiation of TB-T in the non–eTB-T arms did not materially alter the overall conclusions. As this analysis modifies the originally randomised population and excludes participants based on post-randomisation events, results should be interpreted as exploratory.

8.6.5. Post-hoc Analysis for eTB-T: Comparison Among Participants with Negative Baseline TB Tests and those who were clinically decided non-treated

A further post-hoc analysis was conducted to compare survival among participants with negative baseline TB tests who received eTB-T versus those with negative baseline tests in whom a clinical decision was made not to initiate TB-T.

Among participants with negative baseline TB tests, 51 of 137 (37%) participants receiving eTB-T died during follow-up, compared with 69 of 147 (47%) participants in whom a clinical decision was made not to treat for TB. Kaplan–Meier survival curves are shown in Figure S3. The log-rank test yielded a p-value of 0.0503.

This exploratory comparison suggests a potential survival difference in favour of eTB-T within this selected subgroup. However, as this analysis was conducted post hoc and is based on a redefined, non-randomised comparison, results should be interpreted cautiously.

8.6.6. Post-hoc Analysis for eTB-T: Cause-specific mortality analyses using competing-risk models

A post-hoc competing-risk analysis was conducted to separately evaluate TB–related and non–TB-related mortality according to allocation to eTB-T. TB-related death was defined as any death in which TB was adjudicated by the independent Endpoint Review Committee as an underlying, immediate, or contributing cause, based on prospectively collected clinical, laboratory, and sociodemographic data. Non–TB-related deaths were treated as competing events in the TB-related mortality analysis, and vice versa. Subdistribution HRs and 95% CIs were estimated using Fine–Gray models, with follow-up truncated at 180 days, corresponding to the planned duration of TB-T. Models were adjusted for baseline HIV-1 viral load category (≥5 vs <5 $\log_{10}$copies/mL), baseline CD4 percentage, baseline oxygen saturation, and recruitment country. Estimates were pooled across multiply imputed datasets using Rubin's rules.

Within 180 days of follow-up, allocation to eTB-T was associated with a lower hazard of TB-related death (aHR 0.57, 95% CI 0.34–0.90), suggesting a potential reduction in mortality directly attributable to TB. In contrast, no reduction was observed in non–TB-related mortality (aHR 1.19, 95% CI 0.97–1.44) (Table S6; Figure S4).

These findings suggest that while eTB-T did not reduce overall all-cause mortality in the primary analysis, it may have been associated with a reduction in deaths specifically attributed to TB.

9. Safety Evaluation

9.1. Overall Adverse Events description

A total of 2,049 AEs were reported during follow-up in 544 of 558 participants (97%). Of these, 995 (49%) occurred in participants allocated to valganciclovir and 1,054 (51%) in those not allocated to valganciclovir (p=0.0668). Regarding eTB-T allocation, 966 AEs (47%) occurred in participants assigned to eTB-T and 1,083 (53%) in those not assigned to eTB-T (p=0.0104).

9.2. Serious Adverse Events

9.2.1. Overall Serious Adverse Events Description

A total of 928 SAEs were reported in 451 participants during follow-up. Among these, 480 of 928 (52%) occurred in 231 participants assigned to valganciclovir arms and 448 of 928 (48%) in 220 participants not assigned to valganciclovir (p=0.1495). The mean number of repeated SAEs per participant was 2.0 (SD 1.5). Participants assigned to valganciclovir did not have higher odds of experiencing at least one SAE compared with those not assigned to valganciclovir (OR 0.64 [95% CI 0.35–1.16]; p=0.1419) (Table 25).

In the eTB-T comparison, 442 of 928 SAEs (48%) occurred in 194 participants assigned to eTB-T arms and 486 (52%) in 189 participants assigned to non–eTB-T arms (p=0.1579). The mean number of repeated SAEs was 3.5 (SD 2.8). There was no increased odds of experiencing any SAE in the eTB-T arms compared with non–eTB-T arms (OR 0.91 [95% CI 0.41–2.03]; p=0.8127). Participants assigned to eTB-T had lower odds of presenting a TB diagnosis classified as an SAE during follow-up (OR 0.38 [95% CI 0.27–0.55]) (Table 26).

Table 25. Adverse events odds ratio and incidence rate ratio (95% confidence interval) of infants assigned to arms with empirical valganciclovir, compared to infants assigned to arms with no empirical valganciclovir during the entire follow-up

	Valganciclovir (N=276) n (%)	Non–valganciclovir (N=282) n (%)	Number of repeated events, mean (SD)	Odds Ratio (95%CI), p-value	Incidence Rate Ratio (95%CI), p-value
Serious Adverse Events	231 (83.7)	220 (78.0)	2 (1.5)	0.64 (0.35-1.16), p=0.1419	0.71 (0.62-0.81), p<0.0001
Adverse Events	271 (98.2)	273 (96.8)	3.8 (2.9)	0.91 (0.21-3.89), p=0.8990	1.15 (1.06-1.26), p=0.0020
Neutropenia events	86 (31.2)	57 (20.2)	1.2 (0.3)	0.77 (0.44-1.37), p=0.3805	1.48 (1.07-2.06), p=0.0187
Anaemia events	173 (62.7)	159 (56.4)	1.2 (0.5)	1.49 (0.77-2.86), p=0.2329	1.34 (1.10-1.64), p=0.0041
Thrombocytopenia events	52 (18.8)	45 (16.0)	1.1 (0.4)	0.54 (0.28-1.03), p=0.0617	0.55 (0.35-0.86), p=0.0099

	Valganciclovir (N=276) n (%)	Non–valganciclovir (N=282) n (%)	Number of repeated events, mean (SD)	Odds Ratio (95%CI), p-value	Incidence Rate Ratio (95%CI), p-value
Any infectious disease requiring antimicrobial treatment	215 (77.9)	212 (75.2)	1.8 (1.1)	0.77 (0.43-1.38), p=0.3820	0.80 (0.69-0.93), p=0.0042

Number of participants with at least one event were described. Mean number of repeated events were described. The median time from enrolment to AEs occurrences was 5.0 [IQR 1-15] days in valganciclovir arms and 5.0 [IQR 2-15] days in non–valganciclovir arms. Estimates were calculated using a zero-inflated Poisson model.

Table 26. Adverse events odds ratio and incidence rate ratio (95% confidence interval) of infants assigned to arms with eTB-t, compared to infants assigned to arms with non eTB-T during the entire follow-up

	Empirical TB treatment (N=276) n (%)	Non Empirical TB treatment (N=282) n (%)	Number of repeated events, mean (SD)	Odds Ratio (95%CI), p-value	Incidence Rate Ratio (95%CI) ¥, p-value
All Adverse Events (other than TB*)	262 (97.5)	267 (97.5)	3.5 (2.8)	0.91 (0.41-2.03), p=0.8127	1.26 (1.11-1.69), p<0.00001
Serious Adverse Events (other than TB*)	194 (70.3)	189 (67.0)	1.9 (1.3)	1.19 (0.82-1.73), p=0.3523	1.07 (0.91-1.25), p=0.4313
Elevation of transaminases	72 (26.1)	74 (26.2)	1.2 (0.4)	0.93 (0.54-1.37), p=0.7434	0.97 (0.62-1.53), p=0.9090
Anaemia	163 (59.1)	169 (59.9)	1.3 (0.5)	0.93 (0.65-1.32), p=0.6879	1.05 (0.86-1.28), p=0.6450
Thrombocytopenia	52 (18.8)	45 (16.0)	1.1 (0.3)	1.29 (0.82-2.04), p=0.2611	0.97 (0.63-1.48), p=0.8802
TB diagnosis	76 (27.5)	138 (48.9)	1 (0.1)	0.38 (0.27-0.55), p<0.0001	0.85 (0.59-1.25), p=0.4135
IRIS	13 (4.7)	11 (3.9)	0 (0)	1.32 (0.57-3.08), p=0.5140	-
Any infectious disease requiring antimicrobial treatment (other than TB)	161 (58.3)	176 (62.4)	1.6 (1)	0.85 (0.60-1.21), p=0.1369	1.12 (0.92-1.36), p=0.2548

Number of participants with at least one event were described. Mean number of repeated events were described. The median time from enrolment to AEs occurrences was 24.0 [IQR 7-93] days in eTB-T arms and 23.0 [IQR 7-102] days in No eTB-T arms. ¥ Estimates were calculated using a zero-inflated Poisson model. * 218 TB events in 215/558 participants, 29 of them presenting TB as unique event

9.2.2. Serious Adverse Reactions (SARs)

Of the 928 reported SAEs, 39 events (4%) were classified as SARs, defined as SAEs considered at least possibly related to the investigational medicinal product.

The 39 SARs comprised:

- 20 cases of anaemia
- 6 cases of neutropenia
- 2 cases of thrombocytopenia
- 1 case of leukopenia

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- 8 cases of elevated transaminases
- 1 case of skin eruption
- 1 case of bilateral blindness

Of the 39 SARs, 23 resolved shortly after treatment discontinuation or completion. Eight participants died from causes unrelated to the SARs before resolution could be documented. One participant completed study follow-up with clinical improvement but without full resolution of anaemia at the time of last assessment. No suspected unexpected SUSARs were reported during the trial.

The distribution of participants experiencing at least one SAR according to treatment allocation is presented in Table 27. Overall, 6% of participants experienced at least one SAR during follow-up. By treatment group, SARs occurred in 4% of participants assigned to eTB-T alone, 7% of participants assigned to valganciclovir alone, and 1% of participants assigned to the combined intervention. The narrative and description of each SAR is presented in Table S7.

Table 27. Distribution of participants experiencing at least one SAR

	ALL	Empirical TB-T	Valganciclovir	Empirical TB-T + Valganciclovir
Total number of SARs	39	5 (13%)	10 (26%)	24 (62%)
Participants with at least 1 SAR	34/558 (6%)	5/140 (4%)	10/140 (7%)	19/136 (14%)

9.2.3. Deaths

A total of 253 participants among 558 analyzed (45%) died. Most of the deaths (200, 79%) were in-hospital deaths reported by health workers, 51 (20%) were at-home deaths reported by relatives, and 2 (1%) deaths were certified at the primary care health centre level. The deaths summary and causes of death were previously described in the primary outcome sections.

The description of deaths reported during the study period are presented in Table S8.

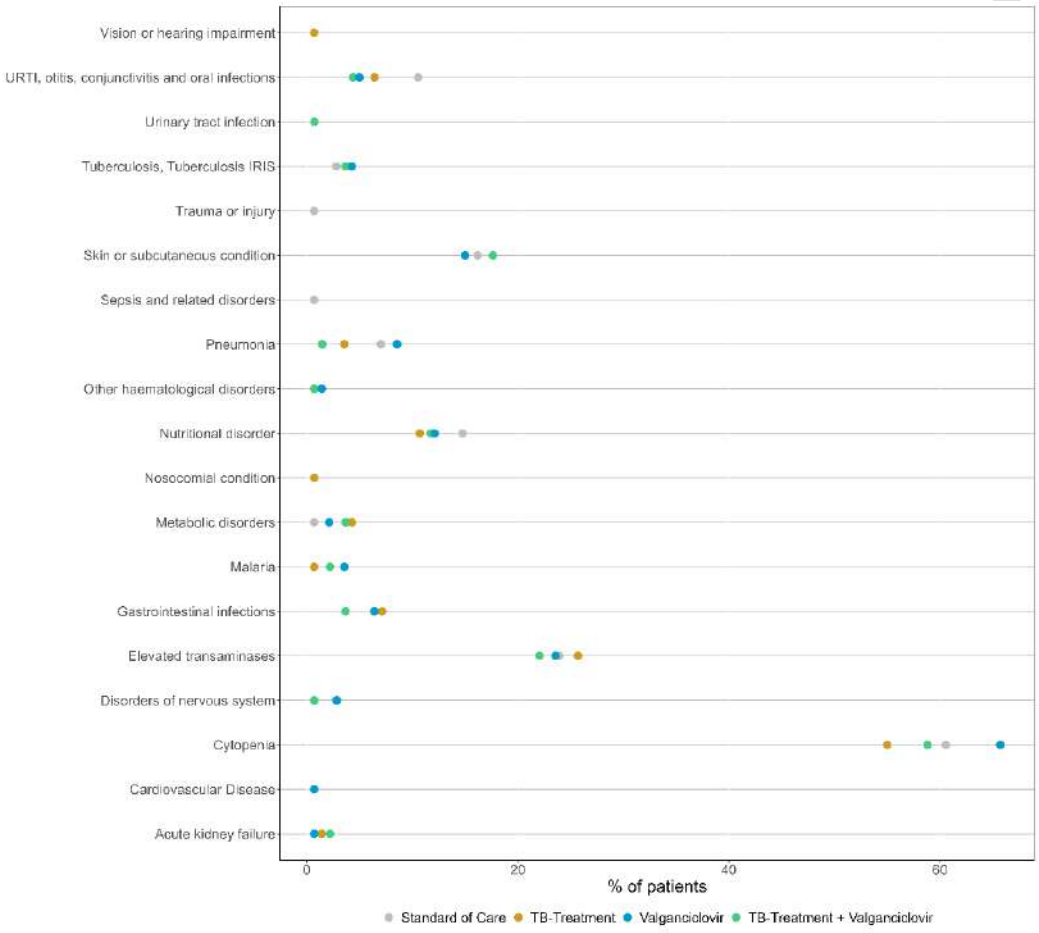
9.3. Notable Adverse Events

A total of 1,121 distinct non-serious notable AEs were reported during the study follow-up, occurring in 388 participants who experienced at least one notable event. These events included predefined categories of clinical interest such as cytopenias, liver-related abnormalities, renal events, neurological events, and infections requiring antimicrobial treatment.

When analysed according to marginal treatment allocation, participants assigned to the valganciclovir arms did not have higher odds of experiencing any notable AE, including neutropenia, anaemia, or thrombocytopenia, compared with participants not assigned to valganciclovir (OR 0.91 [95% CI 0.21–3.89]; p=0.8990). Similarly, participants assigned to eTB-T did not have higher odds of experiencing any

notable AEs, including elevated transaminases, anaemia, or thrombocytopenia, compared with those not assigned to eTB-T (OR 0.91 [95% CI 0.41–2.03]; p=0.8127). Among participants who experienced at least one notable AE, those assigned to the eTB-T arms had a higher incidence rate of recurrent events compared with participants in the non–eTB-T arms, as estimated using negative binomial models accounting for follow-up time. The percentage of participants experiencing at least one notable AE by treatment allocation is presented in Figure 10. Across treatment groups, neutropenia, anaemia, and elevated transaminases were the most frequently reported categories of non-serious notable AAE.

Figure 10. Percentage of participants with adverse events other than severe according to treatment allocation



9.4. Intensity of adverse events by organ classes

The most common type of grade 4 AE was an infectious disease, such as pneumonia, gastroenteritis, or colitis. Another common grade 4 AE reported was a new diagnosis of TB (considered per protocol a life-threatening condition), more commonly reported among children allocated to the valganciclovir arm group and SoC. The majority of cytopenias and liver function alterations (elevated ALT) reported as AR were categorized between grades 1 and 3, considered as non-serious. Figure 11 shows the grade counts of all AEs and SAEs, divided by treatment arm, with the horizontal axis representing frequency.

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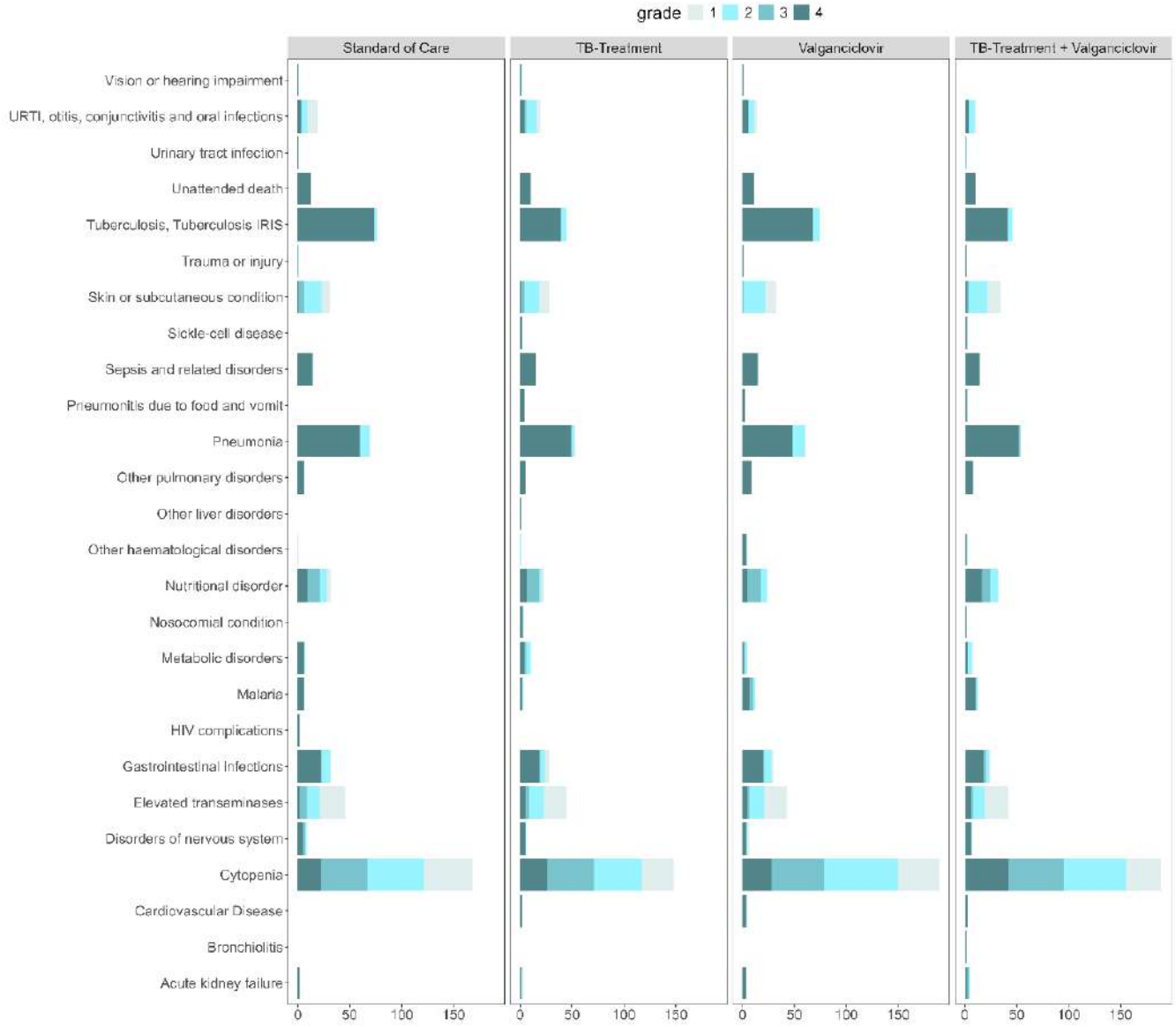
Figure 11. Notable adverse events according to DAIDS grading



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9.5. Laboratory abnormalities

9.5.1. Neutropenia

Forty-six participants receiving valganciclovir had neutropenia during the first 15 days of follow-up being 12 grade 3 or 4, and 26 participants among those allocated to non-valganciclovir arms, four with grade 3 or 4. Those receiving valganciclovir had 1.98 (95% CI 1.19–3.38) times higher odds of developing neutropenia (Table 28). Most neutropenia events were grade 1 or 2, resolved similarly across groups, and were not associated with increased infections or deaths, but led to valganciclovir discontinuation in 11 of 46 (24%) infants (Table 29).

Table 28. Participants with one or more Adverse Events during the first 15 days of follow-up

	Valganciclovir (N=276)	Non–valganciclovir (N=282)	p-value
Serious Adverse Events— no. (%)	174 (63.0)	181 (64.2)	0.848
Adverse Events— no. (%)	233 (84.4)	233 (82.6)	0.647
Neutropenia events— no. (%)	46 (16.7)	26 (9.2)	0.013
Any grade 3 or 4§	12 (4.3)	4 (1.4)	0.069
Anaemia events — no. (%)	101 (36.6)	78 (27.7)	0.030
Any grade 3 or 4	66 (23.9)	57 (20.2)	0.341
Thrombocytopenia events — no. (%)	23 (8.3)	30 (10.6)	0.433
Any grade 3 or 4	6 (2.2)	9 (3.2)	0.630
Renal function alterations— no. (%)	3 (1.1)	4 (1.4)	0.999
Any grade 3 or 4	1 (0.4)	3 (1.1)	0.624
Infectious disease requiring antimicrobial treatment — no. (%)	155 (56.2)	166 (58.9)	0.575
Any grade 3 or 4	149 (54.0)	160 (56.7)	0.570
Valganciclovir discontinued— no. (%)	20 (7.3)	-	-

Percentages may not total 100 because of rounding. § 72 events of neutropenia in 72 participants. Of those neutropenia cases, 16/72 were grade 3 or 4, and 9 had an unknown outcome.

Table 29. Neutropenia events occurred during the first 15 days of follow-up according to valganciclovir treatment

	Neutropenia events in Non valganciclovir arms *N=26*	Neutropenia events in valganciclovir arms *N=46*	p-value
Adverse Event type			1.000
Serious Adverse Event	2 (7.69%)	5 (10.9%)	
Any other registrable Adverse Event	24 (92.3%)	41 (89.1%)	
Grade			0.959
1-2	22 (84.6%)	34 (73.9%)	
3-4	4 (15.4%)	12 (26.1%)	
Event time occurred	14.5 [9.25;15.0]	14.0 [7.25;15.0]	0.341
Event duration	15.0 [12.0;23.0]	21.5 [14.0;44.0]	0.136
Action:			0.189

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	Neutropenia events in Non valganciclovir arms *N=26*	Neutropenia events in valganciclovir arms *N=46*	p-value
None	22 (84.6%)	31 (67.4%)	
Medical intervention	1 (3.85%)	0 (0.00%)	
Valganciclovir discontinued	-	11 (23.9%)	
Outcome			0.269
Resolved	21 (80.8%)	42 (91.3%)	
Unknown	5 (19.2%)	4 (8.70%)	
Resolved after 1 month	16 (61.5%)	29 (63.0%)	0.999
Resolved after 2 months	20 (76.9%)	32 (69.6%)	0.692
Death	10 (38.5%)	14 (30.4%)	0.664
During the neutropenia event	0 (0.0%)	0 (0.0%)	
During the neutropenia event (+2day)	0 (0.0%)	1 (2.2%)	
Number of infectious diseases requiring antimicrobial treatment			0.999
0	24 (92.3%)	44 (95.7%)	
1	1¥ (3.85%)	1§ (2.17%)	
2	1* (3.85%)	1*£ (2.17%)	

*TB; ¥ Fungal infection; £ Sepsis; § Lower respiratory tract infection

9.5.2. Anaemia

Hundred and one participants receiving valganciclovir had anaemia during the first 15 days of follow-up being 66 grade 3 or 4, and 78 participants among those allocated to non-valganciclovir arms, being 57 grade 3 or 4. Those participants receiving valganciclovir had an OR=1.40 (95%CI 0.97–2.02) for anaemia during the first 15 days (Table 28) compared to those in the non–valganciclovir arm. Anaemia events resolved similarly across groups, were not associated with increased deaths, but led to valganciclovir discontinuation in 10 of 102 (10%) infants.

A total of 163 participants receiving eTB-T had anaemia during the entire follow-up and 169 among those allocated in the non-eTB-T, with an OR of 0.93 (95% CI, 0.65–1.32) for anaemia during the entire follow-up period compared with participants in the non-eTB-T arm.

Table 30. Anaemia events occurred during the first 15 days of follow-up according to valganciclovir treatment

	Anaemia events in non valganciclovir arms *N=79*	Anaemia events in valganciclovir arms *N=102*	p-value
Adverse event type			0.189
Serious Adverse Event	23 (29.1%)	20 (19.6%)	
Any other registrable adverse event	56 (70.9%)	82 (80.4%)	
Grade			0.382
1-2	22 (27.8%)	36 (35.3%)	
3-4	57 (72.2%)	66 (64.7%)	
Event time occurred	38.0 [14.0;166]	20.0 [8.00;131]	0.322
Event duration	15.0 [12.0;23.0]	21.5 [14.0;44.0]	0.136
Action:			
None	28 (35.4%)	43 (42.2%)	0.445
Medical intervention	49 (62.0%)	56 (54.9%)	0.417

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	Anaemia events in non valganciclovir arms *N=79*	Anaemia events in valganciclovir arms *N=102*	p-value
Hospitalization	2 (2.53%)	1 (0.98%)	0.581
Valganciclovir discontinued	-	10 (9.80%)	-
Outcome			0.188
Resolved	43 (54.4%)	48 (47.1%)	
Continuing treatment	3 (3.80%)	11 (10.8%)	
Condition worsening	0 (0.00%)	2 (1.96%)	
Unknown	33 (41.8%)	41 (40.2%)	
Resolved after 1 month	19 (24.1%)	27 (26.5%)	0.842
Resolved after 2 months	28 (35.4%)	32 (31.4%)	0.676
Death	28 (35.4%)	35 (34.3%)	0.999
During the anaemia event	10 (12.7%)	10 (9.80%)	0.713
During the anaemia event (+2day)	11 (13.9%)	11 (10.8%)	0.680

9.5.3. Thrombocytopenia

Twenty-three participants receiving valganciclovir had thrombocytopenia during the first 15 days of follow-up, being six grade 3 or 4, and 30 participants among those allocated to non-valganciclovir arms, being nine grade 3 or 4. Those participants receiving valganciclovir had an OR=0.74 (0.40-1.35) for thrombocytopenia during the first 15 days (Table 28).

Fifty-two participants receiving eTB-T had thrombocytopenia during the entire follow-up, compared with 45 among those allocated to the non-eTB-T arm, with an OR of 1.29 (95% CI, 0.82–2.04) for thrombocytopenia during the entire follow-up period compared with participants in the non-eTB-T arms (Table 26) and during treatment period (Table 31).

Table 31. Participants with one or more Adverse Events during the 180 days of TB treatment

	Empirical TB (N=276)	Non-Empirical TB (N=282)	p-value
Serious Adverse Events— no. (%)	207 (75.0)	224 (79.4)	0.251
Adverse Events— no. (%)	262 (94.9)	270 (95.7)	0.797
Neutropenia— no. (%)	61 (22.1)	69 (24.5)	0.575
Any grade 3 or 4	21 (7.61)	23 (8.16)	0.934
Anaemia — no. (%)	142 (51.4)	145 (51.4)	0.999
Grade 3 or 4— no. (%)	97 (35.1)	85 (30.1)	0.242
Thrombocytopenia — no. (%)	48 (17.4)	40 (14.2)	0.356
Grade 3 or 4— no. (%)	16 (5.80)	9 (3.19)	0.200
Leukopenia— no. (%)	2 (0.72)	3 (1.06)	0.999
Grade 3 or 4— no. (%)	2 (0.72)	1 (0.35)	0.620
Lymphocytopenia— no. (%)	0 (0.00)	1 (0.35)	0.999
Any renal functions alterations— no. (%)	9 (3.26)	5 (1.77)	0.394
Grade 3 or 4— no. (%)	5 (1.81)	4 (1.42)	0.750
Any liver functions alterations— no. (%)	68 (24.6)	69 (24.5)	0.999
Grade 3 or 4— no. (%)	15 (5.43)	14 (4.96)	0.953

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	Empirical TB (N=276)	Non-Empirical TB (N=282)	p-value
Elevation of transaminases— no. (%)	68 (24.6)	69 (24.5)	0.999
Grade 3 or 4— no. (%)	15 (5.43)	14 (4.96)	0.953
Any neurologic alterations— no. (%)	8 (2.90)	8 (2.84)	0.999
Grade 3 or 4— no. (%)	7 (2.54)	4 (1.42)	0.519
Any infectious disease requiring antimicrobial treatment other than TB — no. (%)	151 (54.7)	154 (54.6)	0.999
Grade 3 or 4— no. (%)	128 (46.4)	134 (47.5)	0.853
Any suspected IRIS— no. (%)	13 (4.71)	11 (3.90)	0.793
TB discontinued— no. (%)	12 (4.3)	-	-

Percentages may not total 100 because of rounding. SAEs denote Serious adverse events and AEs adverse events.
*The Severe adverse reactions are anaemia (20), elevated transaminases (8), leukopenia (1), neutropenia (6), skin eruption (1), thrombocytopenia (2), and vision or hearing impairment (1).

9.6. Adverse events leading to treatment modification or discontinuation

Neutropenia occurred in 72 participants during the first 15 days of follow-up, and led to valganciclovir discontinuation in 11 of 46 (24%) infants (appendix p22). Anaemia occurred in 179 participants during the first 15 days of follow-up and led to valganciclovir discontinuation in 11 of 101 (10%) infants.

Elevated transaminases occurred in 146 participants and led to discontinued TB-T in 12 participants. Participants in the eTB-T arms who survived received a median of 180 days of treatment (IQR 180–180). Those who discontinued treatment (n=12) received a median of 75.5 days (IQR 21.8–114.3).

10. Discussion and Overall Conclusions

10.1. Summary of key findings

The EMPIRICAL trial evaluated two empirical treatment strategies in infants hospitalised with severe HIV-associated pneumonia: empirical valganciclovir and eTB-T. The trial was conducted in high-burden settings where early mortality remains substantial and diagnostic uncertainty is frequent. The results demonstrate differential effects for the two interventions.

Empirical valganciclovir was associated with a reduction in early mortality. The survival benefit was most pronounced within the first four weeks following randomisation and progressively attenuated over time, becoming neutral by the end of one-year follow-up. This temporal pattern is consistent with the 15-day treatment duration and suggests that the intervention exerted a short-term antiviral effect rather than a sustained long-term modification of disease trajectory. Time-to-event analyses using flexible parametric models confirmed non-proportional hazards, with a stronger effect observed during the early treatment window. Sensitivity analyses, including exclusion of deaths occurring within the first 48 hours and per-protocol analyses, yielded results consistent in direction and magnitude with the primary findings. The benefit of valganciclovir was supported by a 23% reduction in hospitalisation days over time.

In contrast, eTB-T did not demonstrate superiority over not receiving e-TB-T in reducing all-cause mortality. No differences were observed in secondary outcomes including oxygen requirement during the index admission or cumulative hospitalisation days during follow-up. These findings apply to infants in whom TB was not clinically suspected at enrolment, as individuals with high baseline probability of TB were excluded by design.

10.2. Interpretation of valganciclovir findings

The early mortality reduction associated with valganciclovir is biologically plausible. CMV infection was highly prevalent in this population, with high baseline plasma viral loads and a substantial proportion of infants exceeding previously reported thresholds associated with CMV pneumonia.

The attenuation of benefit over time likely reflects the multifactorial nature of mortality in this population. Infants enrolled in EMPIRICAL were severely immunocompromised, frequently newly diagnosed with HIV, and experienced high rates of persistent viraemia, malnutrition, and co-infections. These factors may have diluted any sustained impact of short-course CMV-directed therapy. In addition, CMV viral rebound after cessation of treatment may have contributed to diminishing effect over longer follow-up. The findings raise the hypothesis that extended antiviral therapy or post-treatment prophylaxis could potentially sustain benefit, although such strategies require formal evaluation.

The high mortality observed within the first 48 hours of admission further contextualises the findings. A proportion of participants died before study medications could plausibly exert clinical effect, which may have attenuated the overall magnitude of benefit. Exclusion of these early deaths did not materially alter conclusions but strengthened the early hazard reduction associated with valganciclovir.

10.3. Interpretation of eTB-T findings

The absence of mortality benefit with eTB-T likely reflects a combination of trial design factors and clinical realities. A substantial proportion of participants in the non–eTB-T arms initiated TB-T during follow-up, reducing separation between groups. The trial incorporated enhanced diagnostic procedures, including systematic TB-LAM testing and structured clinical evaluation, which likely improved case detection relative to routine care and further limited contrast between arms.

Although competing-risk analyses suggested a reduction in TB-related mortality among infants assigned to eTB-T, this did not translate into a reduction in overall mortality. Cause-of-death attribution in this population is inherently challenging, and the open-label design may have influenced diagnostic and attribution patterns. Moreover, mortality in this cohort was driven by multiple coexisting conditions, and the proportion of deaths attributable exclusively to TB may have been insufficient for empirical treatment alone to meaningfully alter all-cause mortality.

Post-hoc analyses suggested that among infants with negative baseline TB tests, those receiving eTB-T had improved survival compared with those in whom TB-T was clinically withheld. However, these exploratory findings must be interpreted cautiously given the non-randomised nature of these comparisons and potential residual confounding.

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10.4. Safety considerations

Both interventions were generally well tolerated. Valganciclovir was associated with an increased frequency of early neutropenia, consistent with its established safety profile, but these events were largely mild or transient and were not associated with excess infection-related mortality. There was no evidence of increased SAEs overall in the valganciclovir arms. eTB-T was not associated with increased hepatotoxicity, cytopenias, or other SAEs compared with non–eTB-T arms. No unexpected SARs were identified. The overall benefit–risk balance of valganciclovir appears favourable in the context of early mortality reduction, whereas eTB-T did not demonstrate additional clinical benefit under the enhanced diagnostic conditions of this study.

10.5. Limitations

The open-label design may have influenced clinical decision-making and AEs reporting, although mortality as the primary outcome is objective and unlikely to be affected by observer bias. Variability in SoC regimens across sites reflects real-world practice and was addressed through stratification and adjustment by site. High early mortality limited availability of longitudinal immunological and virological measurements, restricting time-dependent modelling. The long duration of follow-up relative to the short valganciclovir treatment window contributed to non-proportional hazards, which were addressed analytically using flexible parametric models. Multiple secondary and exploratory analyses were performed without formal multiplicity adjustment, and these results should therefore be interpreted with caution.

10.6. Overall conclusions

In infants hospitalised with severe HIV-associated pneumonia, a 15-day course of empirical valganciclovir reduced early mortality and demonstrated an acceptable safety profile, although the benefit attenuated over longer follow-up. eTB-T did not reduce all-cause mortality compared with clinically or microbiologically guided strategies implemented under enhanced diagnostic conditions. These findings support consideration of empirical CMV treatment in this highly vulnerable population while underscoring the importance of strengthening TB diagnostics and delivering comprehensive, integrated care, including post-discharge strategies to address the persistently high mortality risk.

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11. Appendix

11.1. Data availability and repository information

In accordance with the EDCTP open science policy, deidentified individual participant data (IPD) and corresponding data dictionaries have been deposited in the public repository Zenodo.

Data related to the empirical tuberculosis treatment (eTB-T) analyses are available at: https://doi.org/10.5281/zenodo.18541280

Data related to the empirical valganciclovir analyses are available at: https://doi.org/10.5281/zenodo.17878166

Access to the datasets is granted upon reasonable request, subject to applicable ethical and regulatory considerations to ensure participant confidentiality.

11.2. Tables

Table S1. Variables included in the imputation models

Variable	Details	Missing values, n (%)	Imputation method
Enrolling country	Zambia Zimbabwe Ivory Coast Uganda Malawi: Institution 1 Malawi: Institution 2 Mozambique: Institution 1 Mozambique: Institution 2	0	-
Age	Numeric Range (0-11.8)	0	-
Birth sex	Male Female	0	-
Family situation	Both parents alive Orphaned by mother Orphaned by father Caregivers other than parents Unknown	0	-
Oxygen saturation <90% at arrival	0: More or equal 90 1: Less than 90	7 (1.2)	PMM
Respiratory support	No Nasal cannula CPAP/MV	1 (0.2)	polyreg
New HIV diagnosis	No Yes Unknown	0	-
HIV RNA logs	Numeric Range (1.3-7.9)	22 (3.9)	PMM
CD4 % — cell/mm3	Numeric Range (0-57)	53 (9.5)	PMM
Baseline Weight for Height Z score	Numeric Range (-10.6-3.8)	6 (1.1)	PMM

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Days between admission and randomization	Numeric Range (0-34)	5 (0.9)	PMM
Immunization schedule for his/her age	No Yes	0	-
Breastfeeding	Never Exclusive Mixed Weaned	0	-
Prophylaxis with cotrimoxazole	Yes but stopped Ongoing Never Unknown	2 (0.4)	PMM
ART regimen after enrolment	None 2 NRTI + Lopinavir/r 3 NRTI 2 NRTI + Nevirapine 2 NRTI + Dolutegravir	4 (0.7)	polyreg
Treatment allocation	TB-T + SoC Valganciclovir + SoC TB-T +Valganciclovir SoC	0	-
Deviation of growth	No Yes Unknown	2 (0.4)	polyreg
Weight loss	No Yes Unknown	0	-
Total lymphocytes	Numeric Range (0-40.5)	4 (0.7)	PMM
Total neutrophils	Numeric Range (0.2-45.6)	0	-
Haemoglobin	Numeric Range (4.7-10.3)	0	-
Birth weight	Numeric Range (1.0-5.0)	114 (20.4)	PMM
Death	No Yes	0	-
Time of follow-up	Numeric Range (0.1-365.1)	0	-

HIV: human immunodeficiency virus, SoC: SoC, NRTI: Nucleoside reverse-transcriptase inhibitors, TB-T: TB treatment. Mozambique Institution 1: Universidade Eduardo Mondlane-Maputo and linked hospitals (in Maputo City, Maputo Province, Sofala, and Nampula provinces), Mozambique Institution 2: CISM-Manhiça and linked hospitals (in Maputo Province (Manhiça) and Gaza (Xai-Xai) provinces), Malawi Institution 1: Malawi- Liverpool Wellcome Trust (Blantyre), Malawi Institution 2: Lilongwe Medical Relief Fund Trust (Lilongwe).

Table S2. Overview of missing values

Characteristic	*Total N=558*	*Valganciclovir (N=276)*	*Non–valganciclovir (N=282)*	Empirical- TB (N=276)	Non-Empirical TB (N=282)
Demographic characteristics					
Enrolling country	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Age	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Female sex	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Family situation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Clinical characteristics					
Oxygen saturation <90% at arrival	7 (1.2)	5 (1.8)	2 (0.7)	3 (1.1)	4 (1.4)
New HIV diagnosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ART naïve	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HIV RNA logs	22 (3.9)	10 (3.6)	12 (4.3)	8 (2.9)	14 (5.0)

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Characteristic	*Total N=558*	*Valganciclovir (N=276)*	*Non–valganciclovir (N=282)*	Empirical- TB (N=276)	Non-Empirical TB (N=282)
CD4 % — cell/mm^3	53 (9.5)	29 (10.5)	24 (8.5)	26 (9.4)	27 (9.6)
Baseline Weight for Height Z score	6 (1.1)	4 (1.5)	2 (0.7)	2 (0.7)	4 (1.4)
CMV viral load in plasma	68 (12.1)	37 (13.4)	31 (11.0)	-	-
Medical History					
Days between admission and randomization	5 (0.9)	4 (1.5)	1 (0.4)	2 (0.7)	3 (1.1)
Immunization schedule for his/her age	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Breastfeeding	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Prophylaxis with cotrimoxazole	2 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Baseline ART regimen	4 (0.7)	1 (0.4)	3 (1.1)	6 (2.2)	6 (2.1)

All results given as number of missing cases (percent; %). No missing values for site of recruitment, age, sex, family situation, HIV diagnosis status, immunization schedule or type of breastfeeding.

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Table S3. Safety definitions

AE	Adverse Event
AR	Any untoward and unintended response to an IMP related to any dose administered. Response to an IMP means that there is a reasonable possibility that there is a causal relationship between the AE and the medication, i.e., that relationship cannot be excluded.
Notable AE	1. All Neurological AEs 2. All Liver-related AEs 3. All Renal-related AEs 4. All Cytopenia AEs 5. All Infections that require antimicrobials 6. Any relevant AE to the judgment of the researcher. These AEs usually are included in grade 3 and 4 adverse events. However, not necessarily all 3 AEs are relevant to the judgment of the researcher. Opposite, Grade 4 AEs are, by definition, potentially life-threatening. Therefore, all grade 4 AEs will be classified as SAEs.
SAE	1. Results in death 2. Is life-threatening: The term life-threatening in the definition of a serious event refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction. Grade 4 AEs are, by definition, potentially life-threatening. Therefore, all grade 4 AEs are SAEs (see below for grade 4 AEs). 3. Requires hospitalization or prolongation of existing hospitalization: Hospitalization is defined as an in participant admission, regardless of the length of stay, even if the hospitalization is a precautionary measure for continued observation. Hospitalizations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.
SAE	4. Results in persistent or significant disability or incapacity 5. Consists of a congenital anomaly or birth defect 6. Is another important medical condition: Medical judgment
SAR	Serious Adverse Reaction
SUSAR	A Suspected Unexpected Serious Adverse Reaction is an AR in which nature or severity is not consistent with the information about the IMP in question set out in the Summary of Product Characteristics (SmPC) or Investigator Brochure (IB) for that product.

Table S4. Risk ratios for mortality at predefined time intervals post-treatment with valganciclovir and Number Needed to Treat (NNT) for the different time points

Time point	**Valganciclovir N=276**	**No-valganciclovir N=282**	**Unadjusted**		**Adjusted***		**NNT**
	Cum. No. of deaths (%)		Risk Ratio (95% CI)	p-value	Risk Ratio (95%CI)	p-value	
15 days	64 (23.2)	76 (27)	0.85 (0.64-1.14)	0.272	0.81 (0.61-1.08)	0.152	19.9
30 days	73 (26.4)	93 (33)	0.79 (0.61-1.03)	0.081	0.77 (0.60-0.99)	0.039	12.9
60 days	80 (29)	106 (37.6)	0.76 (0.60-0.97)	0.028	0.75 (0.59-0.94)	0.015	10.5
90 days	88 (31.9)	114 (40.4)	0.78 (0.63-0.98)	0.032	0.76 (0.61-0.94)	0.013	10.15
120 days	96 (34.8)	120 (42.5)	0.81 (0.66-1.00)	0.054	0.79 (0.65-0.97)	0.023	11.33
180 days	106 (38.4)	125 (44.3)	0.86 (0.71-1.05)	0.142	0.84 (0.69-1.02)	0.079	14.27
360 days	119 (43.1)	134 (47.5)	0.90 (0.75-1.08)	0.277	0.88 (0.74-1.05)	0.152	17.42

*Poisson regression models with robust standard errors (Huber-White estimators) were used to estimate adjusted risk ratios and 95% confidence intervals (95%CI). Models included the following covariates a priori identified as potential confounders: baseline nutrition status, baseline HIV-1 viral load category (≥5 vs. <5 $\log_{10}$ copies/mL), baseline oxygen saturation, days from hospitalization to randomization, and recruitment site (due to extremely small sample size n=1, the Ivory Coast site was excluded from multivariable models to avoid overfitting and unstable estimates). Estimates were pooled across multiple imputed datasets using Rubin's rules

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Table S5. Primary endpoint: coefficients of the time to event (mortality) analysis in the as-treated analysis for valganciclovir analysis (excluding participants who discontinued valganciclovir)

	Analysis	Hazard Ratio	Lower 95% CI	Upper 95% CI
Valganciclovir (Ref=No)	Unadjusted	0.87	0.68	1.12
Valganciclovir (Ref=No)	Adjusted	0.80	0.62	1.03
Malnutrition: moderate (Ref=No)	Adjusted	0.95	0.63	1.41
Malnutrition: severe (Ref=No)	Adjusted	1.31	0.98	1.74
Baseline oxygen saturation (Ref=>90%)	Adjusted	1.52	1.14	2.01
Baseline HIV viral load ≥5logs (Ref <5logs)	Adjusted	2.04	1.29	3.22
Baseline percentage CD4	Adjusted	0.98	0.96	0.99
Days from hospitalization to randomization	Adjusted	0.99	0.96	1.02
Country: Uganda (Ref Mozambique)	Adjusted	0.88	0.61	1.26
Country: Malawi (Ref Mozambique)	Adjusted	1.05	0.71	1.56
Country: Zambia (Ref Mozambique)	Adjusted	1.26	0.86	1.84
Country: Zimbabwe (Ref Mozambique)	Adjusted	0.73	0.46	1.15

Due to an extremely small sample size (n=1), the Ivory Coast site was excluded from multivariable models to avoid overfitting and unstable estimates. Ref: Reference category; Model was initially adjusted by country, sex, age at HIV diagnosis, oxygen saturation, baseline malnutrition, family situation, current breastfeeding, immunization, cotrimoxazole prophylaxis, baseline antiretroviral treatment, baseline haemoglobin, and days from hospitalization to randomization. Best best-fitting model is presented in this table after variable selection by backward stepwise AIC.

Table S6 Competing-risk analysis of TB-related and non–TB-related mortality within 180 days of follow-up, according to eTB-T allocation

Mortality Cause: TB	Hazard Ratio	Lower 95% CI	Upper 95% CI
Empirical TB-T (Ref=No)	0.57	0.34	0.90
Baseline HIV viral load ≥5logs (Ref <5logs)	1.51	1.44	1.57
Baseline oxygen saturation (Ref=>90%)	0.99	0.98	0.99
Mortality Cause: Other causes no-TB			
Empirical TB-T (Ref=No)	1.19	0.97	1.44
Baseline HIV viral load ≥5logs (Ref <5logs)	1.56	1.52	1.59
Baseline oxygen saturation (Ref=>90%)	0.98	0.98	0.99

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Fine–Gray subdistribution hazard models accounting for competing risks, with follow-up truncated at 180 days (corresponding to the planned duration of TB-T). TB-related death was defined as having TB recorded as an underlying, immediate, or contributing cause of death, based on adjudication by an independent expert panel. Non–TB-related death was treated as a competing event in the TB-related mortality model, and vice versa. Models were adjusted for baseline covariates as shown in the table and recruitment country. Estimates were pooled across 50 multiply imputed datasets using Rubin's rules. Participants without death were censored at the end of follow-up.

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Table S7. Description of all episodes of Serious Adverse Reactions

SAR	Relatedness to IMP	Treatment allocation*	Action	Outcome
Anemia	Probably related to valganciclovir	TB-T+Val	Medical Intervention†	Resolved
Anemia	Possibly related to valganciclovir	TB-T+Val	Val discontinued	Unknown◊
Anemia	Possibly related to valganciclovir	TB-T+Val	Medical intervention† & VLG discontinued	Unknown◊
Anemia	Possibly related to valganciclovir	Val	Medical Intervention†	Resolved
Anemia	Possibly related to valganciclovir	TB-T+Val	Medical Intervention†	Unknown◊
Anemia	Possibly related to valganciclovir	Val	Medical Intervention†	Resolved
Anemia	Possibly related to valganciclovir	TB-T+Val	Medical Intervention†	Resolved
Anemia	Possibly related to valganciclovir	Val	Medical Intervention†	Unknown◊
Anemia	Probably related to valganciclovir	Val	Medical intervention† & VLG discontinued	Resolved
Anemia	Possibly related to valganciclovir	TB-T+Val	Medical Intervention†	Continuing treatment
Anemia	Possibly related to valganciclovir	Val	Medical intervention† & VLG discontinued	Resolved
Anemia	Possibly related to valganciclovir	TB-T+Val	Medical intervention† & VLG discontinued	Resolved
Anemia	Probably related to valganciclovir	Val	Medical intervention† & VLG discontinued	Resolved
Anemia	Probably related to valganciclovir	TB-T+Val	Medical intervention† & VLG discontinued	Continuing treatment
Anemia	Possibly related to valganciclovir	TB-T+Val	Medical intervention† & VLG discontinued	Resolved
Anemia	Possibly related to valganciclovir	Val	Medical Intervention†	Pending
Anemia	Possibly related to valganciclovir	Val	Hospitalization	Pending
Anemia	Possibly related to valganciclovir	Val	Medical Intervention†	Pending
Anemia	Probably related to valganciclovir	TB-T+Val	Medical intervention†	Resolved
Anemia	Possibly related to valganciclovir	TB-T+Val	Medical intervention† & VLG discontinued	Resolved
Blindness	Possibly related to Ethambutol	TB-T	TB-T discontinued	Unknown◊
Elevated transaminases	Possibly related to TB-T	TB-T	TB-T discontinued	Resolved
Elevated transaminases	Possibly related to TB-T	TB-T+Val	None	Resolved
Elevated transaminases	Probably related to isoniazid or ethambutol	TB-T+Val	None	Resolved
Elevated transaminases	Probably related to isoniazid or rifampicin	TB-T	TB-T discontinued	Resolved

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Elevated transaminases	Probably related to isoniazid or rifampicin	TB-T+Val	TB-T discontinued	Resolved
Elevated transaminases	Definitely related to isoniazid or rifampicin	TB-T+Val	TB-T discontinued	Unknown◊
Elevated transaminases	Possibly related to isoniazid or rifampicin	TB-T	TB-T discontinued	Resolved
Elevated transaminases	Possibly related to isoniazid or rifampicin	TB-T+Val	TB-T discontinued	Unknown◊
Leukopenia	Probably related to valganciclovir	TB-T+Val	Val discontinued	Resolved
Neutropenia	Probably related to valganciclovir	TB-T+Val	None	Resolved
Neutropenia	Possibly related to valganciclovir	TB-T+Val	Val discontinued	Resolved
Neutropenia	Possibly related to valganciclovir	TB-T+Val	Follow-up	Resolved
Neutropenia	Probably related to valganciclovir	TB-T+Val	Follow-up	Pending
Neutropenia	Probably related to valganciclovir	TB-T+Val	Val discontinued	Resolved
Neutropenia	Probably related to valganciclovir	TB-T+Val	Follow-up	Resolved
Skin eruption	Possibly related to Isoniazid	TB-T	Hospitalization, TB-T discontinued	Resolved
Trombocytopenia	Probably related to valganciclovir	Val	Medical intervention† Hospitalization	Unknown◊
Trombocytopenia	Possibly related to valganciclovir	TB-T+Val	Medical intervention† & VLG discontinued	Resolved

*Treatment allocation: TB-T+V – anti-TB treatment and valganciclovir; TB - anti-TB treatment. †Medical Intervention: iron and haemoglobin follow-up. ◊ Unknown: the child died due to other conditions before this Serious adverse reaction resolution.
a. Anaemia outcome unknown: Participant with Hb of 9.0 g/dl at enrolment, allocated to combined treatment, developed a grade 3 anaemia under valganciclovir treatment on day 6 with Hb=7.7 which got worse on day 15, Hb=6.3 (grade 4). This anaemia was possibly related to the IMP and then, valganciclovir was discontinued. On day 30, the Hb=6.9 and the child continued his follow-up as per protocol. Five months after enrolment, before the visit +180d, the mother communicated to the team that he died at home, of unknown causes, without resolution of the anaemia. b. Anaemia outcome unknown: Participant with Hb of 8.5 g/dl at enrolment, allocated to combined treatment, developed hospital-acquired sepsis on day 6 with WBC=29.000 cells/mm (92% neutrophils), Hb=4.9 (Grade 4) and platelet count of 97000 (Grade 2) and finally died before anaemia resolution. Although anaemia was likely caused by sepsis, valganciclovir toxicity could not be excluded as the child was under that treatment. c. Anaemia outcome unknown: Participant with Hb of 7.7 g/dl at enrolment, allocated to combined treatment, developed a grade 4 anaemia (Hb=4.3) under valganciclovir treatment on day 9, in the context of a worsening of severe pneumonia. Anaemia was considered possibly related to valganciclovir. The Hb improved up to 6.9 after transfusion but the baby died on day +10 after enrolment without resolution of the anaemia, due to severe pneumonia. d. Anaemia outcome unknown: Participant with Hb of 9.2 g/dl at enrolment, allocated to valganciclovir, developed a grade 4 anaemia (Hb=5.2) under valganciclovir treatment on day 15. Anaemia was considered possibly related to valganciclovir and it was discontinued for the last dose of the IMP course as per protocol. The Hb improved up to 9.2 g/dl after transfusion, with a later worsening of the anaemia not related to the IMP, as it had been discontinued, but the baby died on day +28 after enrolment without resolution of the anaemia, due to sepsis. e. Blindness, outcome unknown. Child allocated to TB-T, who developed blindness on day 12 of treatment. Ophthalmology reviewed the child and revealed a normal retina but with severe optic nerve inflammation with exudates all around the optic nerve. Though optic neuritis is difficult to evaluate one year of age, ethambutol was discontinued as per protocol. The child died without resolution of this SAE. f. Elevation of transaminases, outcome unknown: Participant 11 months old randomized to TB-T + valganciclovir with normal ALT at enrolment who was discharged 9 days after enrolment presenting elevated ALT (124 UI/L, grade 1) considered possibly related to the TB-T. After one week (visit +15d), the ALT became normal. The TB-T was stopped on the visit for +30 days due to a grade 3 elevated ALT (374, x 8.3 upper normal limit) with no associated symptoms. The participant was recalled for assessment and hepatitis screen, which was negative and the ALT became normal one month later after stopping TB-T. When TB drugs were re-introduced transaminases elevated again, ALT grade 3 and AST grade 4, and the patient was diagnosed with drug-induced liver injury and stopped TB-T permanently. The child died two months after enrolment due to pneumonia not considered related to the IMP and without resolution of the elevated transaminases. g. Elevation of transaminases, outcome unknown: Participant 3 months old newly diagnosed with HIIV randomized to TB-T + VLG, TB LAM negative, Gen Xpert in NPA also negative and Stool for gene x pert MTB/Rif Ultra MTB Detected trace and RIF Indeterminate. Due to this, she was

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diagnosed with TB. However, after a few days of admission, the mother was discharged against medical advice but took the study medications. The patient was seen on day +15d and a grade 4 AST and the TB-T was stopped (686 U/L, x 17 upper normal limit). A plan was made for monitoring the patient's clinical well-being and liver function tests until it was possible to re-challenge the antiTB medications but the mother refused this follow-up. On day +30, the child was seen and he didn't have new symptoms of illness and ALT was 103 U/L (no data on AST). However, two days later, the baby was admitted to the hospital due to severe respiratory distress and died with a diagnosis of severe pneumonia considered not related to the IMP nor elevated transaminases. The child died before resolution of this SAR. h. Thrombocytopenia outcome unknown: The participant in this study was initially randomized to receive valganciclovir, but tested positive for TB via a urine Lipoarabinomannan (LAM) test conducted as part of the study. The participant started TB-T on day 4 (the day of discharge), and had a platelet count of 338 x10^9 at discharge. On day 15, one day after completing valganciclovir treatment, the platelet count dropped to 117 x10^9, but the participant remained clinically stable and platelets were closely monitored. On day 75, the participant presented with elevated transaminases (>13 times the upper normal limit), and TB-T was stopped. After four weeks with no TB-T, the clinical team reintroduced TB-T one drug at a time. A control performed on day 112 showed a platelet count of 58 x10^9, prompting a transfusion of blood and platelets. Despite the transfusion, the participant's condition worsened, and they developed spontaneous bleeding with conjunctival haemorrhage and epistaxis. On day 122, after the second transfusion, the participant went into pulmonary oedema and was given a stat dose of furosemide. One day later, the participant was in severe respiratory distress and required oxygen via a facemask. Despite efforts to treat the participant, he went into respiratory arrest and died without resolution of the thrombocytopenia. TB was determined to be the cause of death, and it was not considered related to the investigational medicinal product (IMP).

Table S8. Deaths description

Record ID	Age	Cause	Time since enrolment	Arm	Description
20001-1	4 months	Severe pneumonia	1 day	eTB-T	Participant admitted due to severe pneumonia with respiratory rate of 55 bpm and oxygen saturation of 89%. The infant died before study drugs could be initiated with severe pneumonia as the assigned cause of death. Death not related to IMP.
20001-2	8 months	Sepsis	1 day	Standard of care	Participant admitted with severe pneumonia and severe acute malnutrition, with a respiratory rate of 48 bpm and oxygen saturation of 88%. The condition of the participant deteriorated the day after admission and died. The suspected cause of death was sepsis. Death not related to IMP.
20001-5	3 months	Severe pneumonia	2 days	Standard of care	Participant admitted due to severe pneumonia with respiratory rate of 63 bpm and oxygen saturation of 88%. The participant deteriorated later on but finally died in the first 48h after enrolment due to severe pneumonia. Death not related to IMP.
20001-6	4 months	Sepsis	15 days	eTB-T	Participant admitted with severe pneumonia, with no improvement over time and then managed as sepsis. On day 15, he started desaturation on Continuous Positive Airway Pressure (CPAP) (88%) and increased respiratory rate (68 bpm). He was passing blood clots via the nasogastric tube and Vitamin k was given and blood ordered for transfusion. The death was certified after unsuccessful resuscitation. The suspected cause of death was sepsis. Death not related to IMP.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20001-7	4 months	Sepsis	99 days	Valganciclovir	Participant admitted to hospital on day 30 visit, hospitalized and managed for sepsis & anaemia. She received blood transfusion and ceftriaxone with no improvement. Anti-TB treatment was started out of randomization following clinical diagnosis of pulmonary TB, with initial improvement of the respiratory symptoms, but with persistent fever. Sepsis due to S aureus (MRSA) was suspected, although all blood cultures (x3) were negative, and vancomycin was prescribed and given for 10 days. On day 90 visit participant was still hospitalized with worsening anaemia and leucocytosis. Urine culture showed E. coli species sensitive to piperacillin/tazobactam and nitrofurantoin, but, the participant died before the culture results came out. Death not related to IMP.
20001-8	18 months	Miliary tuberculosis	347 days	eTB-T + Valganciclovir	Participant randomized to combined treatment, with regular follow-up until visit +180-days visit with some not serious AEs, reported and solved in short time. The initial screening of TB was negative. She completed Valganciclovir at visit +15 and TB-T at visit +180d and was on ART and cotrimoxazole prophylaxis. 11 months after enrolment, she was admitted to the hospital with severe acute malnutrition and gastroenteritis. During admission the participant was not improving and started to be spastic in all 4 limbs and posterior deterioration, with respiratory distress, bilateral lung infiltrates and TB LAM in urine was positive. TB-T was again started together with antibiotics but the participant finally died with suspected diagnosis of miliar tuberculosis. Death was not considered to be related to the IMP.
20001-10	3 months	Severe pneumonia	3 days	eTB-T + Valganciclovir	Participant developed severe respiratory distress and was moved to the Paediatric Intensive Care Unit (PICU) the day after enrolment. There, she was initially put on CPAP but was desaturating with grunting respirations and was intubated and put on ventilator support at 48h of enrolment. She still kept on desaturating, suffering cardiopulmonary failure. Resuscitation was attempted but the baby died on the third day of enrolment. Death not related to IMP.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20001-11	3 months	Sepsis	37 days	Standard of care	Participant admitted to hospital due to severe pneumonia and enrolled in the study, randomized to standard of care commenced on ATT based on clinical decision and was discharged after 10 days of admission. He attended the visit +15 days without problem but presented to the hospital 11 days after the visit +15days with fever and difficulty breathing and had severe anemia and thrombocytopenia. He received a blood transfusion and started on IV antibiotics and CPAP which was managed as sepsis and started on ceftriaxone but continued to spike and switched to second line antibiotic, ciprofloxcin. Blood culture showed no growth and the child worsening his condition and finally died.
20001-15	8 months	Unknown	118 days	Standard of care	Participant in regular follow-up until visit +90. Four months after enrolment, the mother of the participant called study staff and informed them of the death of participant. The exact cause of death of the participant could not be ascertained, as the baby was brought in dead to the local hospital (not study hospital) and the attending physician did not have information concerning the events surrounding the death. Death was not considered to be related to the IMP.
20001-19	4 months	Sepsis	11 days	Standard of care	Participant randomized to standard of care arm with positive TB-LAM at visit 0, therefore diagnosed with TB and started TB-T 5 days after randomization. Nine days after enrolment, she developed worsening fever and diarrhea, he/she was started on piperaciline-tazobactam too, showing pancytopenia and signs of sepsis. She finally died. Death was not considered to be related to the IMP.
20001-20	9 months	Unknown	15 days	eTB-T	Participant randomized to TB-T, diagnosed of severe acute malnutrition complicated with severe pneumonia, with respiratory rate of 64 bpm and SpO2 87%. She started nutritional treatment and standard of care treatment for pneumonia in these children and the IMP. The baby clinically improved in the following days and on day 13th after admission, the mother requested discharge to home. The mother was counselled to continue the hospital admission but she declined to stay. She signed to leave the hospital against medical advice on file. The following day, the study team contacted the family via phone and she reassured that the child was doing well. The following morning, day 15th after enrolment, the study team contacted the

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					family and the informed that the child had died at home, was found dead on the bed with unknown circumstances. Exact cause of death was unknown. Death was not considered to be related to the IMP.
20001-21	9 months	Disseminated intravascular coagulation	2 days	Valganciclovir	Participant randomized to receive valganciclovir, started also treatment with standard of care treatment for pneumonia in these children and quinine, as rapid malaria test was positive. She has a history of cough and difficult breathing, SpO2 86% and respiratory rate of 88bpm. The day after enrolment, he faced an aspiration episode during feeding, causing deterioration of his baseline condition, desaturation and need of oxygen via face mask, and metronidazole, hydrocortisone and nebulized salbutamol was added to the initial treatment. He was transferred to intensive care unit, where he started bleeding from the nose and mouth and later demised, two days after enrolment. The death was considered unlikely related to the IMP.
20001-23	9 months	Severe pneumonia	2 days	eTB-T + Valganciclovir	Participant diagnosed on admission with severe pneumonia, severe acute malnutrition and oral candidiasis. In spite of the interventions for these conditions and the IMP, the clinical situation deteriorated with worsening respiratory distress and finally died in the first 48h after enrolment. Death was not considered to be related to the IMP.
20001-25	10 months	Sepsis	0 days	eTB-T	Participant was admitted with sepsis and severe acute malnutrition in a child already diagnosed with HIV. She responded poorly to IV antibiotics and had crackles on examination with severe respiratory distress and enrolled in the study and was randomized to tuberculosis treatment (TB-T) but died on the same day. Death was not considered to be related to the Investigational Medical Product (IMP).
20001-26	4 months	Sepsis	57 days	Valganciclovir	Participant admitted to hospital due to severe pneumonia and enrolled in the study, randomized to valganciclovir and discharged after 8 days of admission. He attended the visit +15 days and presented mild neutropenia and elevation of transaminases that were resolved

Record ID	Age	Cause	Time since enrolment	Arm	Description
					without problem. but presented to the hospital 11 days after the visit +15days with fever and difficulty breathing and had severe anemia and thrombocytopenia. One month after the day +30days, the baby was seen for an unscheduled visit and was admitted to hospital for severe malnutrition with sepsis, and, a few hours after admission the participant demised from sepsis-related causes. Death was not considered to be related to the IMP.
20001-28	8 months	Unknown	3 days	eTB-T	Participant admitted with history of acute gastroenteritis in a child with severe malnutrition and respiratory distress. Enrolled into empirical study and randomized to TB-T. After enrolment, the baby had a sudden change of condition with difficulties breathing, fever, severe pallor and vomiting all feeds. On day 1 post enrolment, the hemoglobin dropped to 4.5g/dl and received a blood transfusion. However, the condition continued to deteriorate despite the transfusion and escalation of oxygen therapy. The sickly test result came out positive but the child worsened the condition, and despite resuscitative measures the patent demised. Death was not considered to be related to the IMP.
20001-29	7 months	Unknown	71 days	eTB-T + Valganciclovir	Participant enrolled in the study and randomized to receive TB-T and valganciclovir, presented with one-month history of fever associated with weight loss and cough and diagnosed to have sickle cell disease during the initial stay in the hospital. He was discharged 15 days and came in for +30- and +60-days visits with no complaints. The child was scheduled to visit for +90 days but didn't come. Efforts to reach the participant on phone were unsuccessful but when was possible to contact the family, the mother reported that the participant developed difficulties in breathing and was admitted to a rural hospital and died on the same day. Clinical records to register the cause of dead was not obtained. Death was not considered to be related to the IMP.
20001-32	3 months	Sepsis	2 days	eTB-T	Participant randomized to TB-T arm and managed for severe pneumonia with congenial syphilis on X-pen and ceftriaxone. Unfortunately, the participant continued to require oxygen therapy which was escalated to Continuous positive airway pressure (CPAP) and mechanical ventilation. He was also started on adrenaline infusion for septic shock. Unfortunately, 2 days after enrolment, the participant went into cardiopulmonary failure

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					and died. Death was not considered to be related to the IMP.
20001-33	6 months	Unknown	154 days	Standard of care	Participant randomized to Standard of care and managed for severe pneumonia and malnutrition. The participant started TBT for clinical diagnosis of TB (LAM positive and RX suggestive of TB infection). However, she responded poorly to ATT, and evaluated for drug resistant TB with possible poor compliance. At day 75 after enrollment, the participant was admitted to the hospital due to pneumonia and received antibiotics, oxygen, and nutritional rehabilitation. At day 127, during a follow-up visit after hospital discharge, the medical team observed respiratory distress signs and recommended a new admission, which was rejected by the family. The participant then died at home one month later, with the mother reporting that the child was in her usual state of health until a day prior to death when the participant coughed extensively. Death was not considered to be related to the IMP.
20001-34	4 months	Severe pneumonia	1 day	Standard of care	Infant male 3 months old, newly diagnosed HIV positive, enrolled in the empirical study and randomized to receive standard of care treatment. He presented with complaints of cough for 3 days, fever for 3 days, diarrhea for 2 days, and difficulty breathing for 1 day. Participant was put on CPAP following no response to oxygen by nasal prong and started treatment with penicillin and gentamicin, cotrimoxazole and prednisolone. The same day of enrolment, the participant's condition was noted to have deteriorated with grunting respirations and a drop in SP02 on CPAP, requiring resuscitation twice and finally died. Death was not considered to be related to the IMP.

Record ID	Age	Cause	Time since enrolment	Arm	Description
20001-36	3 months	Gastroenteritis and colitis	1 day	Valganciclovir	Female 2 months old, randomized to receive valganciclovir treatment and presented with cough and difficulties in breathing for 2 days associated with difficulty feeding and nasal congestion and was diagnosed with severe pneumonia. She commenced on penicillin, gentamycin, high dose septrin, prednisolone and oxygen and was escalated to CPAP. She later developed severe watery diarrhea but didn't respond to iv fluids and died.
20001-39	5 months	Sepsis	28 days	eTB-T	Participant was randomized to TB-T arm after being admitted for severe pneumonia and new diagnosis of HIV. He initially showed a clinical improvement on IV antibiotics and TB-T and remained stable during 20 days, still admitted. After that, the participant's condition and developed difficulties in breathing and was desaturated on room air and had diarrhea and clinically septic. His condition continued to deteriorate despite being on meropenem and finally died. Death was not considered to be related to the IMP.
20001-40	4 months	Unknown	284 days	eTB-T+ Valganciclovir	Participant enrolled in the study and randomized to Valganciclovir/ TB arm, completing both treatments without challenges. She was diagnosed with TB and sickle cell anemia during the study follow-up and attended follow-up visits for +180 days, clinically stable. The study team received a notification from the mother after her death. She reported that the child was well and active and suddenly started with fever, cough, diarrhea, and vomiting and developed seizures. The family took her to the nearest hospital where she was certified dead. No related to IMP
20001-43	3 months	Sepsis	6 days	Standard of care	The participant was admitted to the hospital for severe bronchiolitis/pneumonia and was randomized to receive standard of care 2 days after admission. On day 2 after randomization, the participant's respiratory distress worsened, requiring mechanical ventilation. However, the participant did not respond well to treatment and died at day 6 after recruitment. Death was not considered to be related to the IMP.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20001-46	8 months	Unknown	115	Standard of care	The participant was randomized to receive standard of care treatment and initiated TB-T based on a clinical diagnosis. The participant was seen on several follow-up visits, including at discharge, day 15, and day 30. However, on day 41, the participant had an unscheduled visit for fever and rash and was subsequently admitted for pneumonia with an allergic skin reaction. The participant improved and was discharged after six days of admission. The participant was then seen on Visit 60 with no complaints, but subsequently missed the 90th visit despite attempts by the study team to contact the family by telephone and at home, without success. It was not until four months later that the study team was able to reach the mother by telephone and was informed that the child had died on the 115th day after a day of fever. Death was not considered to be related to the IMP.
20001-47	3 months	Severe pneumonia	2 days	Valganciclovir	3-month-old female, admitted with severe acute pneumonia. randomized to valganciclovir 4 days after admission. status deteriorated on day 7 postadmission with increased respiratory distress and participant died 2 days after randomization. Death was not considered to be related to the IMP.
20001-51	7 months	Tuberculosis	24 days	Valganciclovir	Participant 7 months old admitted to the hospital with severe acute pneumonia. She was randomized to receive valganciclovir one day after admission. The participant responded well to treatment and was discharged from the hospital on the day after she was randomized. However, on day 19 after randomization and day 3 post-admission, the participant was diagnosed with severe acute malnutrition and presumptive pulmonary tuberculosis infection. She began treatment for TB, but two days later her respiratory condition worsened and she required oxygen therapy and CPAP. Despite these interventions, the participant did not improve and sadly passed away on day 24 after randomization. Death was not considered to be related to the IMP.
20001-52	4 months	Sepsis	10 day	Standard of care	The participant was admitted to the hospital with Pneumonia / Pneumocystis jirovecii pneumonia (PCP) with meningitis. She was randomized to receive standard of care treatment and was also treated for a

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					presumptive tuberculosis infection. However, on day 5, her condition worsened and she required an escalation of antibiotics. On day 7, she began receiving mechanical ventilation due to respiratory failure, and she was subsequently managed for septic shock with inotropic support. Despite these interventions, the participant continued to deteriorate and unfortunately passed away on day 10 after being randomized. Death was not considered to be related to the IMP.
20001-54	3 months	Unknown	62 days	Valganciclovir	Participant randomized to receive valganciclovir and completed the course of the IMP without challenges. The baby was diagnosed with pulmonary TB on day 15 based on clinical findings and started TB-T as standard of care. She didn't attend the day 30 visit. The study team contacted the mother who informed her that the baby was admitted to another hospital and died there of unknown cause. She could not give more details on the clinical situation of the baby. The death was not considered related to the IMP.
20001-55	11 months	Severe acute malnutrition	17 days	eTB-T+ Valganciclovir	Participant 11 months old randomized to combined treatment being treated for severe acute malnutrition and severe pneumonia in a newly diagnosed HIV. Since the admission, the condition improved, tolerated therapeutic food but lately deteriorated with episodes of vomiting in the past five days. The child refused to be fed and the mum did not accept the use of a nasogastric tube (NGT) but agreed after counseling. The child developed worsening respiratory distress following one episode of vomiting while the tube was dislodged (the child aspirated after vomiting) and started gasping. Resuscitation was attempted but was not successful and finally died. The death was not considered related to the IMP.
20001-56	11 months	Sepsis	33 days	eTB-T	Participant 11 months old randomized to the TB treatment arm with a diagnosis of severe pneumonia. During the first admission, the baby developed sepsis and TB meningitis and was successfully treated for those conditions and discharged 15 days after enrolment. However, the baby was readmitted on day 33 after enrolment due to sepsis, clinically unstable and died the same day of

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					readmission. The cause of death was considered sepsis and not related to the IMP.
20001-57	9 months	Sepsis	2 days	Standard of care	Participant 9 months old randomized to standard of care arm, treated for severe pneumonia, acute diarrheal disease, and severe acute malnutrition in a newly diagnosed HIV participant. He was also diagnosed with pulmonary tuberculosis due to clinical findings and started TB-T soon after enrolment. Despite these diagnoses and their appropriate treatments, he continued to have high fevers, diarrhea, respiratory distress requiring continuous positive airway pressure (CPAP), and also developed seizures. First-line antibiotics were changed to meropenem and continued on anti-tuberculosis therapy but the baby continued to deteriorate and died two days after enrolment. The death was not considered related to IMP
20001-61	3 months	Severe pneumonia	7 days	eTB-T+ Valganciclovir	3 month old infant randomized to TB-T+VAL admitted with severe pneumonia, presenting with high fever and S02 of 80% room air. Already known HIV patient under ART. Subsequent on day 2 post-admission condition deteriorated with severe respiratory distress and oxygen was escalated to high flow. However condition deteriorated further with no improvement and finally died due to severe pneumonia. The death was not considered related to the IMP.
20001-62	9 months	Sepsis	2 days	eTB-T	9-month-old infant, randomized to TB arm with an admission diagnosis of severe pneumonia, sepsis, and severe acute malnutrition. He showed poor response to first-line antibiotic and anti-tuberculosis therapy. 2 days after admission, he developed diarrhea and was treated for shock with intravenous bolus fluids, ciprofloxacin and CPAP with poor response. Unfortunately, despite resuscitation, he died. The death was not considered related to the IMP.
20001-65	10 months	Unknown	50 days	Standard of care	Participant was 10 months old randomized to standard of care being treated for severe pneumonia and being discharged after 3 days. He didn't attend the follow-up visits and was lost to follow-up for more than 2 months and the mother came to report that the patient had died at home without giving a specific date and time. The death was not considered related to the IMP.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20001-66	2 months	Severe pneumonia	1 day	eTB-T	Participant 2 months old randomized to the TB treatment arm, presented with a 1-week history of cough, fever, difficulty breathing and with a diagnosis of severe pneumonia. condition deteriorated despite all interventions and died. The cause of death was considered severe pneumonia and not related to the IMP.
20001-69	3 months	Severe pneumonia	2 days	eTB-T	Participant 3 months old with severe pneumonia and randomized to TB treatment arm. The day after enrolment his condition worsened he developed severe respiratory distress and desaturating while on mechanical ventilator support. He was re-intubated and placed back on the ventilator machine. Unfortunately, his condition continued to deteriorate and died on the second day after enrolment due to severe pneumonia. The death was not considered related to the IMP.
20002-2	7 months	Severe pneumonia	15 days	eTB-T	Participant admitted and managed as severe pneumonia. Initially, there was some clinical improvement although the participant remained ill with respiratory distress and spiking temperatures of above 39°C. 15 days after enrolment, the participant's condition was reported to have suddenly deteriorated and he deceased. The suspected cause of death was pneumonia. Death not related to IMP.
20002-3	2 months	Severe pneumonia	**2 days**	Valganciclovir	Participant recently diagnosed with HIV infection and admitted with severe pneumonia. On day 2 of admission, there was marked deterioration (seizures and signs of hypoxia) and was transferred to the PICU. There, he was intubated and put on mechanical ventilation but finally died. Death unlikely related to IMP.
20002-4	2 months	Severe pneumonia	32 days	eTB-T + Valganciclovir	Infant admitted due to severe pneumonia and discharged recovered on day 21. On Day 30 visit, the infant presented with shortness of breath, refusing to breastfeed for a one-day duration and weight loss. No investigation was registered. Impression of severe pneumonia probably due to P.*jirovecii* (PCP), community-acquired pneumonia and oral candidiasis were made with differential diagnosis of TB-related IRIS. The baby was immediately transferred to the hospital for admission and management as per the diagnosis above. However, two days later, the baby deceased. Death not related to IMP.

Record ID	Age	Cause	Time since enrolment	Arm	Description
20002-6	3 months	Severe pneumonia	28 days	eTB-T	Participant who had little clinical improvement in the first days of admission. Chest X-ray and CT scan done before day 15, showed right upper lobe consolidation and right lower lobe collapse. ART was started but the participant remained unwell, in respiratory distress and oxygen-dependent. CMV viral load that was collected on day 18 was 4275980 copies per ml but the participant's condition deteriorated and she deceased the same day that the result came. Death not related to IMP.
20002-9	5 months	Severe pneumonia	100 days	Valganciclovir	Participant discharge from the hospitalization related to enrolment on day 7. The day after she was readmitted after having presented with a day's history of a continuous cough and grunting of sudden onset and TB-T treatment was started following a clinical diagnosis of TB. She tested positive for SARS CoV-2 the week after this second admission and was managed accordingly. ART was started the day 20 after enrolment together with anti-failure treatment for cor-pulmonale. She was discharged on Anti-TBs, Furosemide and Captopril, Cotrimoxazole and ART. She was seen for her day 60 visit, and was well with no complaints, but she had a grade 4 neutropenia and participant was re-called to the clinic for change the AZT for double dose LPV/r and for cotrimoxazole prophylaxis to be with-held. At that visit, the participant had symptoms of severe pneumonia and was admitted again and put under anti-failure treatment for cor-pulmonale, antibiotics and ART and oxygen per nasal prongs were given. She had initial clinical improvement but deteriorated again about 2 weeks post-admission. The participant was put on bubble CPAP and had severe respiratory distress, reduced air entry and crepitations. Meropenem was started but the child demised in hospital after unsuccessful CPR. Death not related to IMP.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20002-10	3 months	Severe pneumonia	2 days	Standard of care	The participant was a new diagnosis of HIV, admitted with severe pneumonia and treated with standard of care. The child deteriorated the same day of admission, and was put on CPAP. The day 2 after enrolment, TB-T was started out of randomization as clinical diagnosis but the participant's condition continued to deteriorate and finally died in the first 2 days of admission. Death not related to IMP.
20002-12	7 months	Severe pneumonia	121 days	eTB-T	Participant that was discharged 17 days after enrolment. During this period cotrimoxazole was stopped due to a generalized non-severe rash, suspected to be a cutaneous reaction to this drug. The TB-T was stopped on the visit +30 days due to a grade 3 elevated ALT (283.6, x6.3 upper normal limit). Once TB-T was stopped, weekly ALTs were done until the ALT levels normalized. At visit +60d, Isoniazid 50mg was reinitiated after a normalization of ALT levels. A close follow-up of ALT was done, being normal and Rifampicin 75mg was then reinitiated. A further control was done a week after the reintroduction of Rifampicin and ALT showed again a raised X3 upper normal limit (Grade 2) and thus TB-T was again stopped. The participant remained ART naïve. The participant was asymptomatic in liver toxicity. After this AR, the participant was followed every week to control ALT and four months after enrolment, he was diagnosed of upper respiratory tract infection by the clinical team, which worsened the day after and was admitted with a differential diagnosis of bronchiolitis versus pneumonia. She was managed on oxygen per nasal prongs, Normal saline nebulisations, and iv ceftriaxone without improvement. A further deterioration in the respiratory situation caused desaturation on oxygen and she was put on bubble CPAP and started treatment high dose cotrimoxazole and steroids but the child worsened and suffered a cardio-pulmonary arrest where resuscitation was done, being unsuccessful, and death was certified on that day, 121 days after enrolment without being under any IMP treatment in the previous weeks prior the death. The death was considered not related to the IMP.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20002-15	3 months	Unknown	175 days	Valganciclovir	Participant was admitted due to severe pneumonia and randomized to valganciclovir arm. The baby responded well to treatment and was discharged 8 days after enrolment. He developed severe neutropenia that was resolved in a few days. He also had a hospitalization due to bronchiolitis which was also resolved. The participant attended the follow-up visits +15, +30, +60 and +90 days without complaints but missed the day +180 visit and was not been reachable. The mother met the study staff by coincidence and reported that the participant deceased a few months earlier after suffering a flu-like illness but no clinical records were available to understand the cause of death. Death was not considered to be related to the IMP.
20002-17	3 months	Severe pneumonia	1 day	Standard of care	Participant with initial signs of severe pneumonia, respiratory rate of 76 bpm, SpO2 of 76% on 2L O2. The respiratory situation of the baby was worsening the same day of admission, needing buble CPAP without improvement and finally dying the day after enrolment. The death was considered not related to the IMP.
20002-23	5 months	Severe pneumonia	13 days	eTB-T	Participant treated as severe pneumonia, SpO2 of 74% on room air, with initial improvement. Twelve days after enrolment, the participant's condition was deteriorated, with poor feeding and vomiting. The day after, the participant went into cardiopulmonary arrest, cardiopulmonary resuscitation was unsuccessful, and the participant deceased. The death was considered not related to the IMP.
20002-25	8 months	Unknown	325 days	eTB-T+ Valganciclovir	Participant enrolled to TB+T and valganciclovir arm. The participant attended follow-up visits after the initial admission without any complaints. However, during the visit on day +180, it was noted that the participant had experienced weight loss and edema. She was weaned off the study on December 29th, 2021, and was admitted to the hospital with a diagnosis of kwashiorkor for 13 days. After discharge, she was being followed up at a nearby hospital and receiving nutritional rehabilitation. However, she required readmission on day +277 for 15 days. The

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					participant's mother reported that the participant never fully recovered after the discharge, and sadly, the child passed away one month after being discharged, while at home. Death was not considered to be related to the IMP.
20002-29	3 months	Severe pneumonia	1 day	Valganciclovir	At the enrolment visit, the participant was critically ill, had central and peripheral cyanosis and in respiratory distress with respiratory rate of 68 bpm, SpO2 of 54- 63% on bubble CPAP, subcostal, and intercostal recessions. On examination of the chest there was reduced air entry to the left upper zone, dullness to percussion of the left upper zone and scanty crepitations on the right side. The participant was lethargic. Approximately an hour after enrolment and before IMP could be administered, the participant went into cardio-pulmonary arrest, resuscitation was tried but was unsuccessful. The participant was certified dead on the same day. The death was considered not related to the IMP.
20002-31	3 months	Severe pneumonia	32 days	eTB-T + Valganciclovir	This is a 3-month-old male who was admitted for severe pneumonia treated with high dose cotrimoxazole, penicillin and gentamycin and enrolled into the study and randomized to TB-T plus Valganciclovir arm, which were initiated on the same day. The participant remained sick and in hospital and visits +15 and +30 days were done during the admission. During the visit on day +30, the child was critically ill, in respiratory distress and died a few days later with the same diagnosis as on admission. Death was not considered to be related to the IMP.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20002-36	4 months	Unknown	113 days	eTB-T + Valganciclovir	This was a 7-month-old male participant who was admitted into hospital for severe pneumonia and was a new diagnosis of HIV infection. He was enrolled on the study and randomized to TB-T plus valganciclovir arm. He was immediately initiated on the valganciclovir and TB-T, together with high dose cotrimoxazole and ceftriaxone. The participant had improved but was still O2 dependent and febrile when the mother insisted on being discharged against medical advice 10 days after enrolment. IMP was supplied and instructions were given on how to administer the drugs. They were advised to report to their nearest health care facility as soon as they reached their destination. A discharge visit was conducted on that day and the participant and caregiver left the hospital and promising to come for subsequent visits at the site clinic. Although site staff remained in contact with her, she did not attend her visits and missed day +15, +30 and +60 visits. The participant was initiated on the continuation phase of TB-T at the local hospital (not the enrolment hospital) but was never started on ART despite being seen at that hospital on a few occasions. 3 months after enrolment, the site staff received a message from the caregiver that the participant had deceased during the night after refusing feeds for a week. The cause of death is unknown as the caregiver had not sought medical attention for the child's illness. Death was not considered to be related to the IMP.
20002-38	5 months	Unknown	271 days	eTB-T	A 14-month-old participant was randomized to the TB-T arm and seen on several follow-up visits, including at discharge, day 15, day 30, day 60, day 90, and day 180. At the last visit on day 180, the participant had no complaints. The caregiver called the clinic to report that the child had suddenly died on day 271 while being carried on their mother's back. The child allegedly had a seizure and immediately died. There was no history of preceding illness. Death was not considered to be related to the IMP.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20002-39	8 months	Unknown	208 days	Standard of care	The participant was randomized to receive standard of care treatment and was seen on several follow-up visits, including at discharge, day 15, and day 30, day 60 and day90. However, on day 180 the participant missed the visit. The clinical team try to contact the caregiver without success, but the aunt was contacted and reported that the mother had relocated to another city and that child passed away but the cause of death was unknown by the aunt. Death was not considered to be related to the IMP.
20002-40	3 months	Severe pneumonia	2 days	eTB-T + Valganciclovir	This is a 2-month-old male who was admitted for severe pneumonia treated with high dose cotrimoxazole, ampicillin and gentamycin and enrolled into the study and randomized to TB-T plus valganciclovir arm, which were initiated on the same day of enrolment. The caregiver informed us that the child was refusing food for a week and they did not seek medical attention for the child's illness before that admission. The child remained critically ill, in respiratory distress and died after 2 days of admission. Death was not considered to be related to the IMP.
20002-43	9 months	Severe pneumonia	4 days	eTB-T + Valganciclovir	This is a 9-months-old female who was admitted for severe pneumonia and treated with high dose cotrimoxazole, ampicillin and gentamycin and quickly changed to ceftriaxone because of critically sick and was enrolled into the study and randomized to TB-T plus valganciclovir arm, which were initiated on the same day of enrolment. The participant was very sick and continued to deteriorate and finally died. Death was not considered to be related to the IMP.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20002-45	3 months	Severe pneumonia	1 day	eTB-T + Valganciclovir	10-week-old who was enrolled into the study and randomized to TB-T + valganciclovir. One day after randomization the participant condition deteriorated and she deceased. Death was not considered to be related to the IMP.
20002-47	3 months	Severe pneumonia	152 days	Standard of care	5-month-old participant randomized to valganciclovir arm during an admission for pneumonia. The child's condition improved, and she was discharged home on day 20 to continue cotrimoxazole prophylaxis and initiate ART at the local clinic. However, the caregiver did not take the child for ART initiation, and scheduled study visits were not done as the career had verbally withdrawn consent for follow-up visits. On day 89, the caregiver called the clinic to inform them that the child was unwell. The caregiver re-consented to continue with the study follow-up, and the child was admitted to the hospital with a diagnosis of severe pneumonia and oral candidiasis. The child was started on intravenous ceftriaxone, oral erythromycin, fluconazole, cotrimoxazole, phenobarbitone, and oxygen via nasal prongs. One month later, the participant started on TB-T, but there was no clinical improvement with conventional antibiotics and TB-T. Unfortunately, the participant passed away on day 152 after 64 days of admission. Death was not considered to be related to the IMP.
20002-49	2 months	Severe pneumonia	11 months	eTB-T	Participant 2 months old randomized to the TB treatment. Initially diagnosed with severe pneumonia and discharged one week after the enrolment. After the discharge, the child continued the follow-up and was readmitted due to severe pneumonia 3 months after enrolment. The child didn't come for the visit +180d and was seen in an unscheduled visit after missing day 180 visit by over 40 days. She was noted to be severely malnourished. One month before completing the follow-up, the child was seen in the clinic of enhanced adherence counseling and was treated for an upper respiratory tract infection. She was admitted later on in the day after she had

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20002-56	4 months	Anemia	84 days	Standard of care	started grunting. She deceased shortly after admission due to severe pneumonia. It was not considered related to the IMP Participant 4 months old randomized to the TB treatment. Initially diagnosed with severe pneumonia and pulmonary tuberculosis, improving the respiratory condition over time. At enrolment, hemoglobin was 10.3, progressively worsening in successive visits (visit day 30 was 8.8 g/dl grade 2, visit day 60 Hb 6.6g/dl Grade 3) and one month after visit +60d, the baby was readmitted with severe anemia of 4.9 g/dl which continued deteriorating up to 2.1 g/dl without finding out the cause of anemia or other condition behind it. The child died the same day of Hb was 2.1 g/dl. It was not considered related to the IMP
20002-62	2 months	unknown	25 days	eTB-T	Participant 2 months old with severe pneumonia and randomized to TB treatment arm who was discharged stable 12 days after enrolment. A few days before the day +30d, the mother phoned to inform that the child had died on their way to the hospital. The baby had grunting. No further information available. The death was not considered related to IMP
20002-64	10 months	Severe pneumonia	1 day	Standard of care	10-month-old infant with HIV-newly diagnosed, severe pneumonia and severe edematous malnutrition, enrolled in EMPIRICAL five days after admission, randomized to standard of care arm. Clinically deteriorated with worsening respiratory distress a few hours after enrolment and finally died due to severe pneumonia. The death was not considered related to IMP
20002-66	11 months	Severe pneumonia	84 days	eTB-T + Valganciclovir	Participant 11 months old randomized to TB-T + valganciclovir with normal ALT at enrolment who was discharged 9 days after enrolment presenting elevated ALT (124 UI/L, grade 1) considered possibly related to the TB-T. After one week (visit +15d), the ALT became normal. The TB-T was stopped on the visit for +30 days due to a grade 3 elevated ALT (374, x 8.3 upper normal limit) with no associated symptoms. The participant was recalled for assessment and hepatitis screen, which was negative and the ALT became normal one month later after stopping TB-T. When TB drugs were re-introduced transaminases elevated again, ALT grade 3 and AST grade 4, and the patient was diagnosed with drug-induced liver injury and stopped TB-T permanently. The child died two

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					months after enrolment due to pneumonia not considered related to the IMP and without resolution of the elevated transaminases.
20002-67	4 months	Severe pneumonia	7 days	Valganciclovir	4-month-old infant admitted with severe pneumonia and randomized to valganciclovir arm. At enrolment, he was critically ill and admitted into ICU and was saturating well on bubble CPAP + face mask. All TB investigations were negative. He suddenly deteriorated after a session of chest physiotherapy and deceased after resuscitation attempts. The cause of death was attributed to severe pneumonia and was not related to IMP.
20003-1	7 months	Unknown (unattended death)	5 days	Valganciclovir	Participant enrolled and moved from emergency room to hospital ward after enrolment in stable condition under standard of care treatment and valganciclovir. On day 3 visit, the child was in a similar clinical situation to the day of admission, with no signs of worsening. No more notes available on the clinical situation of the baby, but the team on shift the day 5 after enrolment found the baby dead and was not attended by any clinician surrounded the time of death. The last dose of valganciclovir was given 9h before the death. Death not related to IMP.
20004-2	5 months	Severe pneumonia	**2 days**	eTB-T	The participant was admitted with severe pneumonia, likely due to PCP and severe acute malnutrition. The child was randomized to TB-T and received the first dose. However, she deteriorated and passed on. Death not related to IMP.
20004-4	2 months	Unknown	5 months	Valganciclovir	Two months-old baby admitted due to severe pneumonia, enrolled on the study and randomized to the correspondent IMP. Standard of care treatment with antibiotics was started. Due to the critical condition, the baby was admitted for more than a month and clinically diagnosed with TB because not improvement under standard of care treament, though all investigations were negative. The study visits +15d and +30 days were done during the admission. The child developed anemia and elevation of transaminases, which was resolved before death. During the visit +90days, the baby was found sick and was admitted due to gastroenteritis and later was discharged. Before the next visit (+180 days) the mother called a team member and informed them that the participant had developed a cough and later on died at home, so exact cause of death is unknown.

Record ID	Age	Cause	Time since enrolment	Arm	Description
20004-5	5 months	Unspecified convulsions	**1 day**	Valganciclovir	Participant admitted due to severe pneumonia and started IMP. The day after admission (two doses of IMP received), the infant presented a generalized tonic-clonic convulsion with no incontinence seen together with a spike of fever of 39°C. Management of the convulsion was started immediately by providing rectal diazepam 3mg and a second dose 5 minutes later because of persistency of convulsion. The episode lasted about 8 minutes from the start of the treatment, stopping after the second dose of diazepam. However, the participant stopped breathing shortly afterward. Cardiopulmonary resuscitation (CPR) was started but this was futile. Death, whose cause was considered due to convulsions, was unlikely related to IMP.
20004-7	12 months	Severe pneumonia	28 days	eTB-T	Participant discharged on day 12th after enrolment and readmitted on day 27 with fever, cough, vomiting and diarrhoea for 1 week of progress and deep breathing, chest indrawing and crepitation bilaterally. The child was diagnosed with pediatric HIV/AIDS, severe acute non-edematous malnutrition, severe malaria, gastroenteritis and severe bronchopneumonia and treatment with ceftriaxone, resomal and F75 was started, in addition to artesunate due to a malaria rapid test positive although blood smear was negative. However, there was no improvement on the above treatment and he passed away 4.5 hours after admission on day 28. Death not related to IMP.
20004-10	10 months	Severe pneumonia	42 days	eTB-T	Participant enrolled and initially managed for Severe Acute non-edematous Malnutrition, PCP and Bacterial Pneumonia. The standard of care antibiotics was changed after 1 week to IV Flucloxacillin-Amoxicillin and Ciprofloxacin due to persistent intermittent fever and difficulty in breathing with mild improvement and started with ready to use therapeutic feeds and ART. On day 27 of admission she still had high grade fever, cough, difficulty in breathing and worsened the general status and the respiratory auscultation, but was able to feed orally. She was diagnosed with pediatric HIV/AIDS, Severe Acute non-edematous Malnutrition and Severe Bronchopneumonia. Antibiotics were changed to Piperacillin-Tazobactam and metronidazole was added to the treatment because of lack of improvement. Blood cultures were negative. On day 39 she continued with persistent fever, difficulty in breathing and bilateral crepitation and had a

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					severe hyponatremia that was corrected with oral sodium and continued antibiotics. On Day 40, she was diagnosed of moderate pulmonary hypertension and treatment with furosemide and digoxin was started and the antibiotic changed to Meropenem. She had occasional vomiting of feeds on coughing and 3 episodes of loose motions. On day 42, she still had cough and difficulty in breathing with bilateral crepitation and low saturation (64-69%) on oxygen therapy and finally died without never been discharged. Death was unlikely related to IMP.
20004-12	11 months	Severe pneumonia	**2 days**	Standard of care	11 months old baby who was enrolled and started standard of care treatment for severe pneumonia. The participant developed worsening respiratory distress 2 days after enrolment, and was put on CPAP but died a few hours after that. Death not related to IMP.
20004-13	12 months	Severe pneumonia	7 days	eTB-T	11-month old female infant enrolled in the trial and received standard of care and anti-TB, being stable the first days. The day 6, the participant developed respiratory distress and looked lethargic, and SoC antibiotics were changed to Flucloxacillin+Amoxicillin and Ceftriaxone. On day 7, the participant's breathing worsened following aspiration of vomitus and finally died that day. Death not related to IMP.
20004-14	4 months	Unknown (unattended death)	51 days	Standard of care	Participant discharged after 14 days from the hospitalization related to the enrolment. On day 51, the mother of the participant called study staff and informed them of the death of participant. The exact cause of death of the participant could not be ascertained. The mother had reported having stopped all treatment except ART following advice from a "Prophet."

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20004-19	4 months	Unknown	14	eTB-T	Participant was admitted with respiratory distress, SpO2 of 88% and respiratory rate of 58 bpm. The baby was treated as severe pneumonia + IMP during 11 days, with improvement from the initial condition and was discharged at home. Two days after enrolment, the father called study staff and informed about the death of the participant at home, without knowing how to explain more detail on the circumstances surrounding the death. Then, the exact cause of death is unknown. The death was considered unlikely related to the IMP.
20004-22	3 months	Severe pneumonia	2 days	Standard of care	The participant was being managed for severe pneumonia on standard of care treatment with oxygen therapy by nasal prongs. However, participant's condition worsened two days after admission, was put on CPAP but unfortunately died. The death was considered not related to the IMP.
20004-25	7 months	Severe pneumonia	3 days	eTB-T + Valganciclovir	Participant admitted with severe pneumonia, very sick-looking, with respiratory rate 86 bpm, in respiratory distress, and oxygen saturation of 77% on room air. He was put on oxygen therapy by CPAP, standard of care treatment for severe pneumonia in HIV children and nasogastric tube inserted for feeding. The IMP started the same day. The baby improved during the initial hours after admission, reaching 100% oxygen saturation on room air, but on day 3 after enrolment, the difficulty in breathing worsened and oxygen saturation was 54% on non-rebreather mask at 10L/minute. The child later got cardiorespiratory arrest, cardiopulmonary resuscitation was initiated but child died that day. The death was considered unlikely related to the IMP.
20004-27	5 months	Severe pneumonia	126 day	Valganciclovir	5 months old baby was admitted for more than a month and clinically diagnosed with TB because not improvement under antibiotics. The study visit +15d was done during the admission. The child developed an elevation of transaminases due to the TB-T. During the visit +30, +6- and +90 days, the baby attended the visits with no complaints. Before the next visit (+180 days), the participant's parent called to inform the study staff that their child had passed on following a respiratory infection. The child had been taken to a nearby health centre and diagnosed with pneumonia but did not

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					improve on treatment and passed on. Death was not considered to be related to the IMP.
20004-28	4 months	Unspecified malaria	332 days	Valganciclovir	Participant randomized to valganciclovir. The participant attended the study follow-up visit (+15, +30, +60, +90 and +180). During the follow-up, the participant was hospitalized twice, one on day 47, for 8 days due to pneumonia and again on day 253 for 15 days due to malaria, with a good recovery. However, the participant's mother called the study team to inform them that the participant had passed away on day 322 due to malaria. The participant had been admitted to a rural health center and diagnosed with malaria but unfortunately died on the same day. Death was not considered to be related to the IMP.
20004-30	5 months	Severe pneumonia	1 day	Standard of care	Participant enrolled in the study with diagnosis of severe pneumonia and diarrhea with jaundice and pallor. Randomized to standard of care with malaria screening negative. The baby was acutely sick looking, with respiratory rate of 100 bpm and SpO2 91% under oxygen therapy. The day of enrolment was transferred to the intensive care unit and was put on CPAP as the condition was critical and finally died on the first day of admission. The death was considered not related to the IMP.
20004-32	1 month	Severe pneumonia	3 days	eTB-T + Valganciclovir	1-month-old baby, a newly diagnosed pediatric HIV/AIDS participant who was admitted due to severe pneumonia. The day after enrolment, the participant experienced worsening respiratory distress and was put on CPAP without improvement and finally died. Death was not considered to be related to the IMP.
20004-33	3 months	Severe pneumonia	13 days	eTB-T	3-mont old newly diagnosed pediatric HIV, ART-naive participant admitted due to severe pneumonia. She was started on IV ceftriaxone and prednisolone, and IMP was also initiated. However, the child experienced worsening respiratory distress due to inadequate oxygenation and was transferred to ICU in the referral hospital for further management without noticing any improvement and finally

Record ID	Age	Cause	Time since enrolment	Arm	Description
					passed away. Death was not considered to be related to the IMP.
20004-35	5 months	Sepsis	5 days	eTB-T+ Valganciclovir	The child was five months old second born of the mother who had been off ART for over two years. The child was unwell for about a month with a cough, fevers and altered feeding habits. A week prior to admission the symptoms worsened with additional difficulty in breathing and vomiting. On admission had features of severe pneumonia and severe acute malnutrition and managed with valganciclovir, antibiotics, steroids, TB-T, oxygen and therapeutic feeds. Over the course of admission, the clinical condition improved gradually but started to be deteriorated again overnight, without any health worker witnessing events and the mother reported that the child had passed on soon after starting the deterioration without having time to be attended by any health worker, who arrived when the child was already dead. Death was not considered to be related to the IMP.
20004-38	5 months	Meningitis/Encephalitis	35 days	eTB-T	Infant 4-months old admitted because of severe pneumonia, who developed blindness on day 12 of treatment. Ophthalmology reviewed the child and revealed a normal retina but with severe optic nerve inflammation with exudates all around the optic nerve. Though optic neuritis is difficult to evaluate at one year of age, drugs related to hepatotoxicity were discontinued as per protocol. He also developed other clinically diagnosed neurological symptoms such as mild hearing loss and dysphonia. The participant was admitted for 22 days after enrolment and the +15-day visit was done during admission and later was discharged. However, 5 days later, the child was readmitted with febrile convulsions and antibiotics and anticonvulsants were restarted without improving the clinical condition and died in the hospital. Death was not considered to be related to the IMP.
20004-40	6 months	Severe pneumonia	44 days	eTB-T	Infant 6 months old was admitted because of severe pneumonia. The participant was admitted for 18 days after enrolment and the +15-day visit was done during admission without showing improvement. On day 18 after enrolment, the family left the hospital against medical advice. The team followed up with the family by phone and the father informed them that the baby was worsening his respiratory

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					clinical condition and was advised to visit the hospital but while on their way to the hospital, the father noticed that the child had died. Death was not considered to be related to the IMP.
20004-42	11 months	Severe pneumonia	10 days	eTB-T + Valganciclovir	Infant male 11-months old was admitted because of severe pneumonia and severe acute malnutrition managed with antibiotics and oxygen therapy by nasal prongs and therapeutic food but the infant did not improve despite the treatment and finally died during the admission. Death was not considered to be related to the IMP.
20004-43	5 months	Severe pneumonia	3 days	eTB-T	Infant male 5-months old was admitted because of severe pneumonia, and a new diagnosis of HIV and severe acute malnutrition managed and managed for severe pneumonia and severe acute malnutrition-non-edematous with I.V cotrimoxazole, ceftriaxone, prednisolone, oxygen therapy and therapeutic food. Despite that treatment, the baby experienced worsening respiratory distress and was put on CPAP and passed a few days after enrolment. Death was not considered to be related to the IMP.
20004-45	5 months	Sepsis	0 days	eTB-T + Valganciclovir	This child was admitted with high-grade fevers and difficulty in breathing. On assessment had severe pneumonia, severe acute malnutrition and septic shock. Was managed with IV fluids and oxygen in the form of CPAP. The child unfortunately passed on shortly before study drugs were initiated. Death was not considered to be related to the IMP.
20004-47	4 months	Sepsis	13 days	Valganciclovir	4-month-old female infant being managed for severe pneumonia, myocarditis with left ventricular systolic dysfunction, congestive cardiac failure, and severe acute malnutrition non-edematous when enrolled into the study, under treatment with antibiotics, furosemide and study drugs with no improvement. Her condition deteriorated showing severe pallor and anemia but no compatible blood was found in the health facility. The same day that the condition worsened, the participant went into respiratory failure and cardiac arrest and died after initiating cardiorespiratory

Record ID	Age	Cause	Time since enrolment	Arm	Description
					resuscitation. Death was not considered to be related to the IMP.
20004-49	2 months	Unknown	46 days	Standard of Care	A 2-month-old male infant enrolled in the study and managed for severe pneumonia was admitted for 20 days, and also diagnosed with TB with a TB LAM +1. TB-T was started and the child developed an elevation of transaminases that were resolved. The baby improved her condition and was discharged. Five days after being discharged, the mother informed the study team via a phone call that the child developed vomiting and later passed on that day at home. Death was not considered to be related to the IMP.
20004-50	9 months	Unknown	163 days	Valganciclovir	Participant was randomized to receive valganciclovir and initiated TB-T on day 7 due to clinical suspicion during admission for recruitment. The participant attended all scheduled follow-up visits at days +15, +30, +60, and +90, and was managed for pneumonia on an outparticipant basis on day +57. The participant did not report any other complaints during the follow-up period. However, the participant's mother called the study team to report that the participant had passed away suddenly on day 163. The mother informed the team that the participant had not experienced any health concerns before the death. Death was not considered to be related to the IMP.
20004-57	7 months	Severe pneumonia	7 days	Standard of Care	A 7-month-old male infant newly diagnosed with HIV, enrolled on the study, being managed for severe pneumonia, and severe acute malnutrition, and started on TB-T following diagnosis of Pulmonary tuberculosis based on radiological findings. A few days after admission, the mother reports deterioration in the child's condition, spiking fevers and worsening breathing and clinicians confirmed respiratory distress with severe chest in-drawing and severe pallor, with hemoglobin of 6.1 g/dl, but, no compatible blood at the facility laboratory. Seven days after enrolment, the participant's condition continued to deteriorate and finally died. Death was not considered to be related to the IMP.

Record ID	Age	Cause	Time since enrolment	Arm	Description
20004-60	3 months	Severe pneumonia	2 days	eTB-T + Valganciclovir	A 2-month-old male infant enrolled in the study and managed for severe pneumonia presenting poor weight gain, cough associated with difficulty in breathing, fevers, and oral thrush. The day after enrolment, he developed convulsions and desaturating on CPAP. Continually deteriorating with episodes of apnea, grunting, and stopped breathing. He was resuscitated but not successfully and finally died. Death was not considered to be related to the IMP.
20004-62	3 months	Severe pneumonia	6 days	eTB-T	A 3-month-old infant enrolled in the study and managed for severe pneumonia and meningitis with antibiotics who developed worsening respiratory distress during admission and finally died. Death was not considered to be related to the IMP.
20004-63	9 months	Gastroenteritis and colitis	72 days	Standard of Care	Participant randomized to standard of care. On day 39, the participant was diagnosed with malnutrition and admitted to the hospital for 23 days. On day 72, the participant's mother contacted a team member to report that the participant had been admitted to the hospital due to diarrhea and had passed away on the same day of admission. Death was not considered to be related to the IMP.
20004-65	8 months	Gastroenteritis and colitis	4 days	eTB-T + Valganciclovir	A 9-month-old male infant, newly diagnosed with HIV, was admitted with a history of cough for 1 month associated with difficulty in breathing for 3 weeks, progressive weight loss, diarrhea for 3 weeks, oral sores for 3 weeks, with no improvement to oral medication for cough and diagnosed with severe pneumonia and enrolled on the study. He was also clinically diagnosed with pulmonary tuberculosis because of clinical findings and started treatment with antibiotics, TB-T and therapeutic food. The mother reported the child was vomiting feeds, and passing loose motions, with general body weakness and severe dehydration was found without resolution despite intravenous fluid and finally died. Death was not considered to be related to the IMP.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20004-66	4 months	Severe pneumonia	5 days	eTB-T	A 4-month-old infant enrolled in the study and managed for severe pneumonia with antibiotics. The baby was diagnosed with TB because of a TB LAM +1 and TB-T was started. A few days after admission the child's condition worsened, with severe respiratory distress, central cyanosis and severe crackles and started gasping. Resuscitation was done with a bag and mask and chest compression for 30 minutes with no positive response and finally died. Death was not considered to be related to the IMP.
20004-73	3 months	Severe pneumonia	5 days	Standard of Care	A 3-month-old infant who was newly diagnosed with HIV was admitted to the hospital with a history of cough for 3 weeks, difficulty in breathing, diarrhea for three days, oral sores, and reduced appetite for feeds. On day 5, the infant's breathing and feeding difficulties worsened and required oxygen therapy, CPAP, and a nasogastric tube for feeding. The infant's condition continued to deteriorate, and death was confirmed on day 5. Death was not considered to be related to the IMP.
20004-74	4 months	Severe pneumonia	6 days	eTB-T	The participant was randomized to TB-T during admission for pneumonia. Unfortunately, the child's respiratory condition worsened, and the participant passed away on day 6. Death was not considered to be related to the IMP.
20004-77	10 months	Severe pneumonia	96 days	Standard of Care	A known HIV-positive participant who was on ART was randomized to standard of care during admission for severe pneumonia, severe acute malnutrition without edema, and oral candidiasis. The participant-initiated TB-T on day 1 due to clinical criteria and showed improvement, leading to discharge 14 days after enrollment. However, on day 22, the participant was readmitted for 15 days with a diagnosis of acute diarrhea with some dehydration and severe acute malnutrition without edema. On day 90, the participant had a third admission due to severe pneumonia and severe acute malnutrition without edema. During this admission, the participant received IV ceftriaxone, F75 and Resomal, and continued with TB-T and ART. Unfortunately, the participant's condition deteriorated six days after admission, with the participant vomiting and experiencing worsening

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					breathing, leading to death. Death was not considered to be related to the IMP.
20004-78	2 months	Sepsis	1 days	Valganciclovir	A 57-day-old infant was admitted with a recent onset of fever, cough, and difficulty breathing. The parents had been newly diagnosed with HIV. Further assessment revealed that the child was severely malnourished and had extensive oral candidiasis. The infant was admitted and treated for severe pneumonia, possibly secondary to PCP, as well as severe malnutrition. Unfortunately, the participant developed septic shock and passed away one day after admission. Death was not considered to be related to the IMP.
20004-87	3 months	Severe pneumonia	2 days	Valganciclovir	A 3-month-old infant who had been recently diagnosed with HIV was admitted with severe pneumonia (probably Pneumocystis jirovecii). Despite being on oxygen therapy, the participant's respiratory distress worsened, and the child also refused to breastfeed. On examination, the infant exhibited severe conjunctival pallor, and as a result, a blood transfusion was administered. Unfortunately, the participant passed away on the second day after randomization. Death was not considered to be related to the IMP.
20004-88	7 months	Acute Gastroenteritis	218 days	eTB-T+ Valganciclovir	Participant 7 months old randomized to the combined arm, was initially diagnosed with severe pneumonia and managed with good response. The baby did not present any complication during the follow-up and was visited up to visit +180 days, being clinically stable. 7 months after enrolment, the baby presented with a history of passing loose watery non-bloody stools, associated with general body weakness and on examination, the baby was severely dehydrated. He was admitted into the hospital and managed for acute watery diarrhea with severe dehydration with IV fluids, zinc sulphate, IV antibiotics but the treatment was not successful and the baby died a few hours after admission. The death was not considered related to the IMP.

Record ID	Age	Cause	Time since enrolment	Arm	Description
20004-89	7 months	Gastroenteritis and colitis	46 days	eTB-T	Infant randomized to the TB-Treatment arm who was subsequently diagnosed with tuberculosis due to a positive LAM test at recruitment. At day 45 the participant was readmitted with a history of vomiting and watery stools and was diagnosed with severe acute malnutrition (non-edematous) and acute gastroenteritis. Treatment with F75, Resomal, Cloxacillin, and Ceftriaxone was initiated, but unfortunately, the participant's condition deteriorated, and they passed away on the day of admission. Death was not considered to be related to the IMP.
20004-95	10 months	Meningitis/Encephalitis	16 days	Standard of Care	10-month-old infant, newly diagnosed with HIV, admitted with severe pneumonia, was randomized to the Standard of Care arm in the EMPIRICAL Trial. During the admission, the infant was diagnosed with severe pneumonia, pulmonary tuberculosis, cryptococcal meningitis, and severe acute malnutrition. Unfortunately, the participant's condition worsened, and they experienced sudden onset seizures, high-grade fevers, and progressive loss of consciousness. On day 16, the infant also suffered from vomiting, which resulted in aspiration. Despite emergency resuscitation efforts, the participant did not survive. Death was not considered to be related to the IMP.
20004-99	3 months	Severe pneumonia	1 day	Standard of Care	3-month-old infant newly diagnosed with HIV, admitted with severe pneumonia (Pneumocystis Jirovecii pneumonia). The infant was managed with oxygen therapy using C-PAP, IV Cotrimoxazole, IV Ceftriaxone 500mg OD X 5/7, IV Cloxacillin, and received a blood transfusion. Unfortunately, the participant's condition continued to deteriorate and passed away on the same day. Death was not considered to be related to the IMP.
20004-101	3 months	Severe pneumonia	4 days	eTB-T+ Valganciclovir	Participant 3 months old randomized to the combined arm, newly diagnosed pediatric HIV/AIDS participant presented with a history of cough, fever and difficulty in breathing. He was managed for severe pneumonia but soon after enrolment developed worsening respiratory distress and died within the first days after enrolment due to severe pneumonia. The death was not considered related to the IMP.

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20004-102	3 months	Severe pneumonia	2 days	Standard of care	Participant 3 months old randomized to Standard of care, newly diagnosed pediatric HIV/AIDS participant presented with a history of cough, fever and difficulty in breathing. He was managed for severe pneumonia but soon after enrolment developed worsening respiratory distress and died within 48h after enrolment due to severe pneumonia. The death was not considered related to the IMP.
20004-104	2 months	Severe pneumonia	1 day	Valganciclovir	Reviewed a 2-month-old, newly diagnosed with HIV, admitted on 9/2/2023 with a history of cough for 2 weeks associated with difficulty in breathing for 1 week, refusal to breastfeed, and general body weakness. He was managed as severe pneumonia and pulmonary TB but the baby's condition deteriorated, with worsening difficulty in breathing until gasping. Resuscitation was unsuccessfully attempted and the baby died due to severe pneumonia. The death was not considered related to the IMP.
20004-108	6 months	Hypovolemic shock	8 days	Standard of care	Participant 6 months infant old randomized to Standard of care, with a TB LAM positive, was managed for severe acute malnutrition and TB meningitis. The baby was critically sick, vomiting and refusing to breastfeed, and resomal. Her condition deteriorated progressively, being unconscious, with cold extremities, hemodynamically unstable, and finally gasping. Resuscitation attempts were unsuccessful and the baby died. The cause of death was considered hypovolemic shock and not related to the IMP.
20004-110	10 months	Severe pneumonia	3 days	eTB-T+ Valganciclovir	Participant 10 months old randomized to combined treatment with a diagnosis of severe pneumonia in a newly diagnosed pediatric HIV/AIDS participant. She was managed for severe pneumonia and non-edematous severe acute malnutrition. Three days after the enrolment, the baby developed worsening respiratory distress and died. The cause of death was considered severe pneumonia and not related to the IMP.
20004-115	2 months	Pneumonitis due to food and vomit	3 days	eTB-T	Participant 2 months old randomized to TB-Treatment with a diagnosis and being managed as severe pneumonia. Three days after the enrolment, the baby stopped breathing while the mother was feeding through an NGT. The baby presented as unresponsive no pulse, no breathing movements, and had copious secretions

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					from nose and mouth containing milk feeds and watery content. Resuscitation was attempted but was not successful and finally died. The death was not considered related to the IMP.
20004-120	6 months	Acute Gastroenteritis	12 days	Valganciclovir	Noted 6 months old male infant, an HIV participant randomized to the valganciclovir treatment, was managed for severe pneumonia, pulmonary tuberculosis, and severe acute malnutrition. Participant's condition suddenly deteriorated a few days after enrolment, with participant passing profuse watery stools associated with body weakness and inability to feed orally and died. Efforts to resuscitate the participant were unsuccessful. The death was considered due to acute gastroenteritis and not related to the IMP.
20004-133	3 months	Severe pneumonia	2 days	eTB-T+ Valganciclovir	A 3-month-old male infant admitted with severe pneumonia and randomized to the TB-T + valganciclovir arm. He was managed for severe pneumonia, and pulmonary TB, clinically diagnosed as all TB investigations were negative. He started the trial medications in addition to the standard of care treatment that involved oxygen therapy by non-rebreather mask but the child deteriorated and finally died. The cause of death was attributed to severe pneumonia and was not related to IMP.
20004-134	8 months	Pneumonitis due to inhalation of food and vomit	27 days	eTB-T	An 8 months old female infant, newly diagnosed with HIV and initiated on ART (ABC/3TC/DTG) for the last 4 days, admitted with history of productive cough and fever with associated vomiting, failure to feed and loss of weight. Reported history of fast breathing for the previous two days. She was lethargic on admission and managed for severe pneumonia, pulmonary tuberculosis, clinically diagnosed as all TB investigations were negative, and severe acute malnutrition (Non- Edematous) and randomized to the TB-Treatment arm. The child clinical continued to deteriorate with severe difficulty in breathing, vomiting of feeds and restlessness. The day of death, the child suddenly experienced episodes of vomiting which led to aspiration. Emergency resuscitation was initiated but unfruitful. The cause of death was attributed to

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					pneumonitis due to inhalation of food and vomit and not related to IMP.
20004-135	2 months	Unknownn	12 days	eTB-T+ Valganciclovir	A 2-month-old newly diagnosed pediatric HIV/AIDS infant, randomized to the TB + valganciclovir arm. He was managed for severe pneumonia with IV ceftriaxone, IV cotrimoxazole, prednisolone, oxygen therapy by nasal prongs, and started on anti-TB drugs and valganciclovir. He clinically improved on the above treatments and was discharged from the hospital 4 days after enrolment in good general condition. However, following failed attempts to reach the participant, the team was informed by the mother that the baby had passed 8 days after being discharged, and the cause of death was unknown the mother did not provide this information but not considered related to the IMP.
20005-1	3 months	Severe pneumonia	**1 day**	Valganciclovir	Participant admitted with severe pneumonia, severe respiratory distress on CPAP and severe subcostal recessions. Before they could take the Nasopharyngeal Aspirate (NPA), urine, saliva and start the IMP, the infant arrested, CPR was done but was unsuccessful and death was confirmed, with PCP as the suspected cause of death. Death not related to IMP.
20005-2	3 months	Severe pneumonia	**1 day**	eTB-T + Valganciclovir	Participant admitted with severe pneumonia, afebrile but in severe respiratory distress, saturating at 93 % on CPAP and respiratory rate of 70 bpm at the time of enrolment. Valganciclovir and TB-T were properly given by the mum through the feeding nasogastric tube, under the observation of a clinical researcher. The baby was then noted to be unresponsive by the ward nurses and they called the clinician who upon reviewing the participant noted that they had no signs of life, and death was confirmed. Cause of death was considered due to PCP. Death unlikely related to IMP.
20005-3	4 months	Severe pneumonia	159 days	eTB-T + Valganciclovir	This participant was discharged after the hospitalization when she was enrolled and was doing fine up to visit +90 days. A few weeks before the scheduled 180-days visit, the mum called the study team informing that the child is having difficulties in breathing and she was

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					advised to visit the enrolling hospital or the nearby hospital if the situation worsened. The mum took the baby to the health center where she received an injection (not documented in the health passport book) and was sent back home. She noticed that the baby became breathless and took her to the health center and from there was referred to the main hospital but the baby died before the ambulance came. Death was confirmed at the health center and was unlikely related to the IMP.
20005-8	3 months	Severe pneumonia	13 days	Standard of Care	Participant requiring CPAP at enrolment without improvement, despite being on PCP treatment and initiating antiretroviral therapy on day 7 after enrolment. On day 12 after enrolment, the participant was still on CPAP with a worsening clinical condition, saturating at 48-57 % on CPAP and the same day, worsening up to present gasping respirations on day 13. Bag and mask ventilation was done and later CPR but no improvement. Death was confirmed that day. Death was not related to the IMP.
20005-9	12 months	Unknown	197 days	eTB-T+ Valganciclovir	Participant admitted with severe pneumonia and after randomization, new diagnosis of TB was done through TB urine LAM and stool gene Xpert, and the participant also started TB-T. The participant was on regular follow-up up to the day 180 visit. During this visit the participant was almost completing his TB-T but he had chronic malnutrition which was being managed as outparticipant. A month later (7 months after enrolment), the study team called mum to check on how her baby was doing, she then informed that the baby had died a few days before in a local hospital. The study team tried to get information from the family and the clinical team at the local hospital on the circumstances surrounding the death but was not possible to get more information. Therefore, the exact cause of death is unknown. The death was considered not related to the IMP as the baby was not under IMP at the time of death.
20005-10	6 months	Acute gastroenteritis	66 days	eTB-T	Participant discharge after 9 days following the admission related to enrolment. After the visit +60 days, the participant was admitted to the hospital again due to gastroenteritis, with high fever and severe dehydration. The child started with respiratory failure the same day of readmission and died. Death was not related to the IMP.

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20005-12	3 months	Severe pneumonia	3 days	eTB-T + Valganciclovir	Participant enrolled requiring CPAP since admission, whose respiratory distress worsened after two days of enrolment, with lower saturation. The child had also dark colored stool without vomiting, abdominal pain or distension and omeprazole was started under suspicion of GI bleeding although dark stools were not seen by the clinical team, but PCV dropped to 17%. The respiratory condition of the baby worsened over time and finally died after 3 days of admission. Death was unlikely related to the IMP.
20005-14	6 months	HIV disease resulting in multiple infections	**2 days**	Standard of care	Participant enrolled in critical condition, receiving standard of care treatment, depending on CPAP and with metabolic acidosis and worsening electrolyte imbalances. Investigations found severe anemia and thrombocytopenia and a blood transfusion was ordered. However, the nurses found the baby dead when they went to review the baby a few hours later. She died the day after admission. Death was not related to the IMP.
20005-17	5 months	Gastroenteritis	14 days	eTB-T+ Valganciclovir	Participant randomized to combined arm, with respiratory rate of 32 bpm and SpO2 of 92% on 0.5 lpm of oxygen on admission. The child improved soon and was discharged four days after enrolment. Due to the valganciclovir, mum had to come to clinic every two days to come and change criobox for the drug, and nine days after discharge, we found the baby with shortness of breath and very dehydrated. The mum informed us that the baby had episodes of loose stools during the three previous days. The baby was admitted with diagnosis of gastroenteritis and severe dehydration, with respiratory rate of 44 bpm, heart rate of 150 beats/min, SpO2 of 99% on room air and temperature of 35.8°C and severe metabolic acidosis in the investigations. IV fluids and antibiotics were started and adding CPAP some hours after admission as the child worsened and continued to be severely acidotic. He died one day after this admission. The death was considered not related to the IMP.
20005-19	6 months	Unspecified anemia	85 days	eTB-T + Valganciclovir	Participant randomized into the TB-T +valganciclovir. During the enrolment visit, the participant was confirmed to have tuberculosis through urine LAM of +2 and chest X-ray. The participant progressed well and was discharged nine days after enrolment. The participant was later re-admitted 11 days later due to TB-IRIS, a week after initiating ART and

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					was in hospital for 3 weeks and later discharged. He was doing the follow-up and progressing well since the last discharge but was readmitted one week before the death and with history of shortness of breath, vomiting and 4 seizure episodes. The participant was then admitted to the ward with a diagnosis of meningitis and super imposed pneumonia and started on Ceftriaxone and fluconazole while continuing his TB-T and ARTs. Drug-induced hepatitis was suspected due to elevated ALTs and TB-T was stopped. The day before the death, the child was improving and ceftriaxone was stopped because the participant had no signs of active infection except for his oxygen dependence. On the day of the death, the infant was noted to have worsening respiratory distress and pale. A transfusion was started and one hour later the child died. Death was not considered to be related to the IMP.
20005-23	3 months	Severe pneumonia	8 days	TB-T	A 3-month-old infant enrolled in the study and was randomized into the TB-T. During the enrolment visit, the participant was very sick on oxygen via CPAP ventilation, saturating at 98%, had a respiratory rate of 40 breaths per minute and blood pressure of 63/35 mmHg. During day 3 visit on 24 January 2022, we noted that the baseline ALT prior to starting TB-T was 6 times higher than the UNL, and after discussing with the PI and the consultant pediatrician on the ward, a decision was made to stop all medication including the TB-T except high dose cotrimoxazole and prednisolone. We also noted that the infant also had persistent thrombocytopenia which was noted on the serial FBC. While on the ward the infant remained sick and not improving in a constant state of lactic acidosis and severe hypoxia despite CPAP ventilation and transfusion. On day seven after the admission, he deteriorated and went into apnea. Bag and mask ventilation were immediately initiated. The participant then went into cardiac arrest and CPR was done with 3 rounds of adrenalin, but it was not successful. Death was not considered to be related to the IMP.
20005-24	4 months	Tuberculosis	123 days	Valganciclovir	A 5-month-old infant was enrolled in the Empirical trial and randomized to valganciclovir. The TB LAM done at enrolment was positive and the child was diagnosed with respiratory tuberculosis, starting TB-T. We continued to follow up with the participant during the scheduled visit after discharge, four days after the initial admission. Two months

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					later, during a follow-up visit, the participant had elevated transaminases >13 times the UNL, and TB-T was stopped. The participant was later reviewed and showed an improved level of ALT, but still ~10 times the UNL. The study team, therefore, did not start the participant on TB-T but continued to monitor the LFTs every 3-5 days. After this event, the mum reported that baby had developed persistent high fevers and vomiting. All septic screens were not remarkable, and we decided the fevers were because of the TB which was not being treated. The follow-up ALT was still high but improving ~5 times the upper normal limit. After 4 weeks of no TB-T and trying to correct the hepatotoxicity and after consulting with the TB office, the TB-T was reintroduced one drug at a time but the ALT worsened again and developed spontaneous bleeding despite being transfused twice with whole blood and platelets. The participant continued with severe respiratory distress and was on oxygen via facemask and finally died. Death was not considered to be related to the IMP.
20005-26	3 months	Tuberculosis	19 days	Standard of Care	A 3-month-old infant was enrolled in the Empirical trial and randomized to the standard of care arm. During the enrolment visit, the participant was oxygen dependent and CPAP, saturating at 76%, had a respiratory rate of 62. The Gene Xpert and TB LAM results of the sample taken at enrolment came positive and TB diagnosis was done and TB-T was started. The TB-T started after starting ART when the results were available. The day after starting the TB-T the child deteriorated and went into respiratory failure but regained spontaneous respirations after resuscitation. An arterial blood gas was done which showed severe lactic acidosis and the participant was also having bloody secretions from NGT. We suspected the events after starting TB-T could be TB-IRIS since TB-T was started after ART. The child worsened his condition and finally died. Death was not considered to be related to the IMP.
20005-28	5 months	Tuberculosis	2 days	Valganciclovir	A 5-month-old infant was randomized to receive valganciclovir. During the enrollment visit, the participant was experiencing severe respiratory distress and required oxygen support. The following day, the participant's respiratory distress worsened, and despite increasing the oxygen concentration, the participant remained hypoxic. Consequently,

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					Continuous Positive Airway Pressure (CPAP) was initiated. Later that afternoon, the results of the nasopharyngeal aspirate and stool samples came back positive for TB, and the urine LAM test was positive with a score of +1. Based on these findings, a microbiological diagnosis of TB was made, and we planned to initiate TB-T the following day. Unfortunately, the participant passed away before treatment could be initiated. Death was not considered to be related to the IMP.
20005-29	2 months	Tuberculosis	2 days	eTB-T	2-month-old infant randomized to TB treatment. During the enrolment visit, the participant was in severe respiratory distress and oxygen-dependent via CPAP. On the following day, the clinical team reviewed the results of the nasopharyngeal aspirate (NPA) for TB screening, which came back positive. The participant continued on the randomized TB-T. However, the participant's respiratory distress continued to worsen, despite being on maximum CPAP settings. The team tried to alleviate the symptoms by adding clonidine 2mg stat and regular suctioning but without success. Unfortunately, the participant passed away at the end of the day. Death was not considered to be related to the IMP.
20005-31	8 months	Sepsis	85 days	eTB-T+ Valganciclovir	9-month-old infant randomized into TB-T and valganciclovir. TB was bacteriologically confirmed at enrollment and participant was continued on the randomized treatment arm. The participant was discharged one week after enrolment and during the follow-up visits, the participant seemed to be improving clinically and had no issues. A few months after enrolment, the mother informed the study team that the participant had been admitted to another hospital due to severe acute malnutrition with gastroenteritis and dehydration. During that admission, the participant's condition worsened, developing, acute respiratory distress. First-line antibiotics were changed and a transfer to the enrolling hospital was planned for more advance but before the transfer, the participant was arrested and efforts to resuscitate the participant were unsuccessful. The death was considered due to sepsis and not related to the IMP.
20005-32	3 months	Pulmonary Tuberculosis	5 days	Standard of Care	3-month-old infant enrolled andomised into standard of care arm. On enrollment, the participant was in severe respiratory distress,

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					with a respiratory rate of 86 breaths, saturating at 97% on CPAP. On day 3, TB LAM performed came positive +1, and the stool gene Xpert had trace MTB detected. TB diagnosis was confirmed, and the patient was started on TB treatment on that day. However, his clinical condition worsened, and he was transferred to the intensive care unit to escalate care. CPAP was continued, and the participant was kept NPO but started on IV maintenance IV fluids. However, the child remained hypoxic on CPAP despite being put on maximum settings, and on day 5, the participant went into respiratory arrest, which was also followed by a cardiac arrest. Resuscitation was unsuccessful and death was confirmed.
20006-1	5 months	Severe pneumonia	114 days	Valganciclovir	Participant doing well during the follow-up up to +90-days visit. A few days after that visit, the baby was admitted to the enrolling hospital due to severe pneumonia and was transfer to another enrolling hospital in the capital, because of intubation requirements. There, the baby was admitted to PICU, intubated, developed some neurological symptoms compatible with meningitis, and had respiratory failure and died. Death not related to the IMP.
20006-2	3 months	Severe pneumonia	5 days	Standard of care	Participant newly diagnosed with HIV and enrolled and managed with standard of care treatment. Within 72 hours of recruitment, the participant presents a clinical worsening of their ongoing pneumonia with the resumption of fever and worsening respiratory distress. The participant was transferred to the referral hospital for the optimization of respiratory support. At the arrival at the referral hospital (also enrolling hospital for this trial) the participant was admitted to the intensive unit care and started mechanical ventilation. The day after arrival to that hospital, the participant suffered cardiorespiratory arrest and was unsuccessfully resuscitated. Death not related to the IMP.
20006-7	2 months	Unknown	223 days	eTB-T	An infant was randomly assigned to receive TB-T and was confirmed to have TB with LAM at enrollment. The child completed visits at discharge, 25, 30, and 60 without any issues. However, the child was lost to follow-up after that. On month 4 after enrollment, the team was able to contact the mother who reported that the child was doing well. Unfortunately, on day 223, the mother informed the team that the child had passed away. The mother stated that the child had become ill a few days before

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					passing away and had visited the clinic but was sent home. Death was not considered to be related to the IMP.
20006-8	4 months	Severe pneumonia	8 days	eTB-T	Infant four months old, admitted in Xai-Xai hospital due to bronchopneumonia, enrolled in the study and randomized to TB-T. After four days of admission, the baby was better and was discharged and was asked to come back for follow-up after 48h because of elevated ALT. The child came back after 48h after discharge with fever and respiratory distress and admitted again with diagnosis of severe pneumonia, initiating standard antibiotic for this condition. The baby deteriorated and 3 days later from the second admission, died. Death was not considered to be related to the IMP.
20006-9	10 months	Severe pneumonia	297 days	Standard of Care	A 19-month-old participant with a diagnosis of bronchopneumonia and HIV was recruited Xai-Xai Provincial Hospital and randomized to the Standard of Care arm. The study team conducted monthly follow-ups to monitor the participant due to their comorbidities, with the last follow-up visit taking place after 180 days. On day 297, the participant was admitted to the pediatric emergency department of Xai-Xai Provincial Hospital with a diagnosis of watery diarrhea. The participant's clinical condition worsened, with persistent vomiting and diarrhea, a refusal to eat, asthenia, an occasional dry cough, and respiratory difficulty, but no fever. The participant was medicated with sweetened water, ampicillin, and gentamicin. However, thirty minutes after admission, the participant experienced cardiorespiratory arrest and was unsuccessfully resuscitated. Death was not considered to be related to the IMP.
20007-5	5 months	Severe pneumonia	3 days	Standard of care	This participant was transferred from another hospital because of a serious condition that required intensive intervention. On the day of recruitment for the study, the child was intubated. He evolved with worsening respiratory insufficiency due to severe pneumonia and signs of sepsis with declining oxygen saturation on maximal vent settings. Cause of death was considered severe pneumonia and was not related to IMP.

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20007-8	9 months	Severe pneumonia	9 days	eTB-T + Valganciclovir	Participant developed a pneumothorax and pneumo-mediastinum after enrolment in the study and was sent to the PICU where the pneumothorax was drained, but they were unable to get the participant off of the ventilator due to his underlying severe pneumonia. He developed hemodynamic instability and had several cardiorespiratory arrests on the day of death before he finally expired. He was still on the study IMPs at the time of death, but they were considered unlikely related to the cause of death.
20007-9	5 months	Gastroenteritis	93 days	Standard of care	Participant doing well during the follow-up up to +90-days visit. 6 days after that visit, the mother informed the study team that the child died at home. She reported that the child developed diarrhea with the condition worsened the day before death, but the family decided to wait to take her to the health center until the following day. When the father went to wake her the following day, he found her dead in bed. Death not related to the IMP.
20007-10	4 months	Unknown (unattended death)	18 days	Valganciclovir	Participant enrolled in the study and discharged seven days after enrolment. After the visit +15 days, the mother called the study nurse reporting that the child was sleeping and then seemed to startle and had associated respiratory distress and died at home. On physician phone follow-up, the mother confirmed that the child was well when she went to bed and had no respiratory symptoms or fever. The cause of death was unknown. Death not related to the IMP.
20007-11	3 months	Unknown (unattended death)	27 days	eTB-T	Participant enrolled in the study and discharged seven days after enrolment. After the visit +15 days, the uncle called the study nurse reporting that the child was well all day yesterday without fever, respiratory symptoms, convulsions, or any other abnormality. She cried a bit when they put her in bed, but went to sleep without problem. During the night they found her dead in bed. The cause of death was unknown. Death not related to the IMP.
20007-13	4 months	Severe pneumonia	**1 day**	eTB-T + Valganciclovir	Participant transferred to the PICU after enrolment due to cardiorespiratory failure and was intubated. Overnight developed hemodynamic instability with hypoxemia despite 100% FIO2, and was started on vasopressor therapy with dopamine. He had cardiopulmonary arrest the same day of enrolment and attempts at reanimation were unsuccessful. Death deemed to be a result of severe initial presentation and not participation in the study. Death not related to the IMP.

Record ID	Age	Cause	Time since enrolment	Arm	Description
20007-14	9 months	Severe pneumonia	**1 day**	eTB-T	Participant enrolled and followed by site physician until the end of the enrolment day, being the child stable. Overnight the central oxygen at the hospital ran out and there was a prolonged period where the child was on room air. The nurse was eventually able to obtain an oxygen tank and connect the child (along with another participant) to the tank supply, but the child died shortly thereafter. Clearly this was a very sick child with untreated HIV, marasmus, candida, severe pneumonia and renal insufficiency, but we believe the interruption of oxygen to be the principal cause of death. He did receive first doses of TB medications at enrolment but death was not considered to be related to the IMP.
20007-16	5 months	Severe pneumonia	3 days	Standard of care	Participant enrolled and sent to the PICU because of pneumothorax, which was drained and put on mechanical ventilation. The child had progressively worsening oxygen saturations and respiratory distress and finally died. Death was not considered to be related to the IMP.
20007-17	5 months	Sepsis	101 days	eTB-T + Valganciclovir	Participant doing well during the follow-up up to +90-days visit. After that visit, the child was readmitted for nutritional rehabilitation therapy and develop a septic clinical picture and was transferred to the PICU. Despite critical care interventions including dopamine, CPAP, and a blood transfusion, the child died in the early morning of the day after. Death was not considered to be related to the IMP.
20007-20	7 months	Unknown	166 days	eTB-T + Valganciclovir	Participant in regular follow-up completing visit +90. The mother reported that child was doing well up to the day of death, four days before the scheduled visit on day +180 days. The day of death, the baby suddenly had bloody stools and later began passing blood from rectum, had no other symptoms, no previous history of bleeding or use of traditional treatment. He was taken to local health center where he was somewhat better, prescribed unknown syrup and sent home. On the way home child became very pale and died on same day. He was on TB-T per randomization with Rifampicin/Isoniazid but the death was not considered to be related to the IMP.
20007-21	11 months	Sepsis	3 days	eTB-T	Participant who was stable on admission, from a respiratory standpoint but was reported to have developed dyspnea starting the day 2 after enrolment. The child maintained good oxygen saturations without needing to increase supplemental oxygen. However, he had cardiorespiratory arrest with an unsuccessful

Record ID	Age	Cause	Time since enrolment	Arm	Description
					reanimation attempt by the resident who was on call during the night. This seems like a probable case of sepsis with metabolic acidosis in the context of advanced HIV and severe malnutrition/kwashiorkor. Death deemed not related to participation in the study or TB-T (IMP).
20007-22	4 months	Pulmonary TB	7 days	eTB-T + Valganciclovir	This child was originally admitted to the hospital with new diagnosis of HIV, anemia, oral candida, and severe pneumonia/PCP. The child was transferred to the PICU with pneumohemothorax and treated with CPAP, chest drain, ceftriaxone, cotrimoxazole (therapeutic), and prednisolone. The child improved, with resolution of the pneumohemothorax and removal of the chest drain, but still continued in serious condition on TB meds, VGC, PCP treatment, and Ciprofloxacin. The NPA Xpert was positive and susceptible to Rifampicine. She had cardiorespiratory arrest on the day 7and attempts at reanimation were unsuccessful. This death is likely related to her advanced disease and not to participation in this study or IMP.
20007-23	6 months	Severe pneumonia	4 days	eTB-T + Valganciclovir	Participant who was enrolled and had bronchoaspiration when the mother was unaware that the NG tube had been dislocated from the stomach and gave milk. The respiratory status worsened after this event and the child was transferred to the PICU with respiratory failure and was placed on CPAP but finally died. Death was not considered to be related to the IMP.
20007-25	7 months	Severe pneumonia	132 days	Valganciclovir	Participant who developed anemia and thrombocytopenia reported as probably related to valganciclovir, both resolved shortly after finalizing the treatment. The baby was under regular follow-up until visit +90 days, with several episodes of elevation of ALT that were not considered related to the IMP. Four months after enrolment, the child came in for unscheduled visit with history of fever, intense cough, refusal to feed and 2 episodes of vomiting. He was in respiratory distress, with grunting, increased respiratory effort and lethargy, oxygen saturation between 87-92% on room air. Screening of TB and COVID-19 were done, being all negative. The child continued worsening during hospitalization in regular ward, with persistent severe cough and dyspnea, inability to feed, occasional fever, and falling SpO2 levels under high oxygen volumes. One week after this

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20007-29	9 months	Meningitis/Encephalitis	321 days	Standard of Care	admission, he was transferred to intensive care unit with respiratory acidosis in critical condition. He was intubated, started on mechanical ventilation and inotropic drugs, died a few hours later. Medical team attributed death to respiratory failure secondary to severe pneumonia and severe immune suppression (HIV and Marasmus). Child enrolled and randomized to Standard of care with multiple adverse events during follow-up, including new diagnosis of TB, HIV encephalopathy among others. 10 months after enrolment, admitted for severe pneumonia, on the third day of admission, the clinical condition deteriorated with decreased level of consciousness (3/15 GCS) and fever. Not clinically stable for Lumbar Punction. Decided to start Acyclovir and second course of TB-T for possible meningoencephalitis (TB Meningitis). Chest X-ray at admission with a possible miliary pattern. The child finally died a few days after admission died and the death was attributed to meningoencephalitis. Death was not considered to be related to the IMP.
20007-32	6 months	Systemic Inflammatory response	15 days	eTB-T + Valganciclovir	Participant with signs of pneumonia, respiratory rate 60 bpm with SpO2 95%. She was initially on oxygen, with worsening respiratory status with dyspnea, irritability, and vomiting a week after enrolment, when the infant was transferred to the intensive care unit and CPAP was initiated. Antibiotic was changed from ceftriaxone to piperacillin/tazobactam. A few days later the participant had a continuous deterioration of clinical status and fluconazole was added, with addition of vancomycin. Two weeks after enrolment, the participant developed a clinical picture consistent with disseminated intravascular coagulation and septic shock with upper respiratory tract bleeding and despite transfusion of blood products and fluid boluses, ended up dying in the intensive care unit 15 days after enrolment.
20007-33	7 months	Metabolic Acidosis	77 days	Standard of care	Participant discharged at home nine days after enrolment but re-admitted one week later due to marasmus and anemia and clinical diagnosis of TB due to poor weight gain. TB-T started and ART was changed as per protocol. The baby did the visits +30 and +60 still admitted to the hospital with little improvement. Nine days after the visit +60d, the baby had fever, nasal congestion and diarrhoea and COVID-19 was positive. The study team transferred the baby to the referral

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					COVID-19 treatment hospital (non-study hospital). The baby was followed by the study team in the COVID-19 treatment hospital, kept TB-T initiated clinical diagnosis and was stable with no dyspnea and with good oxygen saturation at room air (97-100%), but had occasional vomiting after feeding and diarrhea. 66 days after enrolment, still admitted to the COVID-19 treatment centre, the child's mother requested assistance after noticing that he had stopped breathing and his eyes had turned with no response upon stimulus. The mother referred that he was well earlier that morning and that she had fed him at around 6am after administration of his medication. Later that morning the participant worsened with abrupt breathing difficulty that led to death, no medical staff was present inside the isolation ward when this occurred. The study team believed that this death may have been more likely caused by metabolic acidosis as a result of poorly managed dehydration seeing as this participant presented vomiting and diarrhoea (gastroenteritis) as well as malnutrition which can mask the signs of dehydration leading to cardiorespiratory arrest and death. The death was considered not related to the IMP.
20007-36	2 months	Congenital malformation of the heart	9 days	eTB-T + Valganciclovir	Participant diagnosed of pneumonia and after a few days of persistent cyanosis and hypoxemia, the infant was diagnosed with likely Tetralogy of Fallot based on cardiac echo. This was a difficult diagnosis as at the time of admission, the mother did not report chronic symptoms. The decision was made to continue study meds at this time as there may well be a lung infection in the context of severe immune suppression (CD4=22%). Child was also on propranolol, morphine, and oxygen. Surgical evaluation at an specialized hospital was planned when the child can be stabilized. However, the infant remained gravely ill and cyanosis and hypoxia, developing severe metabolic acidosis that led to cardiorespiratory arrest nine days after enrolment. Resuscitation attempts were unsuccessful. The death was considered not related to the IMP.
20007-37	7 months	Sepsis	1 day	Valganciclovir	Participant with signs of severe sepsis at the time of recruitment and developed shock with acute renal insufficiency and oliguria. He remained in care in the emergency department of the hospital on dopamine and IV fluids after recruitment. The medical team there reported

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					his death during the first day of admission. The death was considered not related to the IMP
20007-38	8 months	Severe pneumonia	2 days	eTB-T	Child enrolled and randomized to TB-T with quick clinical deterioration after recruitment. It was placed on CPAP during the night on the ward and was in the "ronda" (system where sick participants are followed overnight). There was no ventilator available in the ICU, and the child expired two days after enrolment.
20007-40	4 months	Acidosis	9 days	eTB-T	Participant randomized to TB-T, admitted with signs of pneumonia, with respiratory rate of 60 bpm and SpO2 of 82%, with no improvement over time. Eight days after enrolment, the child developed signs of sepsis and persistence of respiratory symptoms with high oxygen requirements. The day after, nine days after enrolment, he had cardiorespiratory failure having been resuscitated successfully and transferred to the intensive care unit. The infant was critically ill, intubated with respiratory and inotropic support. This critical condition continued after resuscitation and evolved with metabolic acidosis and second episode of cardiorespiratory failure on the same day than the first, this time with unsuccessful resuscitation attempts. The death was considered not related to the IMP
20007-42	2 months	Sepsis	1 day	Standard of care	Participant admitted with severe anaemia, pneumonia, sepsis and oral candidiasis, randomized to standard of care. He was transferred to the intensive care unit from the regular ward due to worsening of the respiratory condition, with dyspnea, moaning, respiratory effort and bradycardia. It was decided to intubate him and start mechanical ventilation, he was administered venous expansion with saline solution, and dopamine, followed by dobutamine and adrenaline. He didn't resist and had a cardiorespiratory arrest, and death was declared during the first day of enrolment. The death was not considered related with IMP.
20007-44	2 months	Severe pneumonia	0 day	eTB-T + Valganciclovir	Participant admitted very acutely sick, diagnosed with severe pneumonia and randomized to combined treatment. The infant was severely ill requiring high oxygen volumes. Later on the same day the child worsened with increased respiratory distress, fever and falling oxygen saturation levels (81% on 10L/min O2). The same day of enrolment had respiratory failure and died. Cardiopulmonary resuscitation unsuccessful. The death was considered not related to the IMP.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20007-47	4 months	Sepsis	23 days	eTB-T	Participant randomized to TB-T, initially responding well to the treatment and was discharged 11 days after enrolment. He was clinically well at visit +15 day, but re-admitted five days later of this visit with acute gastroenteritis with moderate dehydration. Two days later, 20 days after enrolment, the child was gravely ill in the urgent care ward with clinical picture consistent with sepsis or meningitis and was admitted although lumbar puncture was not done due to the severity of the clinical condition. Differential diagnosis included cerebral hemorrhage given thrombocytopenia (child had opisthotonus). TB-T were stopped as a precaution given new onset jaundice, but it was more likely related to sepsis. 23 days after enrolment, the baby died. This death was not considered to be related with the IMP.
20007-50	4 months	Severe pneumonia	3 days	eTB-T	Child four months old admitted due to Severe Pneumonia, AIDS, Oral thrush, and marasmus, recruited into the study the next day and randomized to TB-T. The mother referred 1-week history of cough, fever, refusal to feed and progressive breathing difficulty. The child was taken to the local health center where she was medicated with oral Amoxicillin and Paracetamol without clinical improvement. 1 day before admission, the child was taken to a traditional healer and treated with local treatment and traditional medication (unspecified) having gotten progressively worse when the mother decided to bring the child to the hospital. The child was supposedly on ART (ABC/3TC+LPV/r) having been diagnosed on 28/06/21 (at 1 month) but with serious adherence deficits, possibly not medicating. At admission, the child was gravely ill with difficulty breathing and started on IV antibiotics, PPJ treatment, oxygen mask, Fluconazole and TB study meds (per randomization). The day after, the child's respiratory condition worsened and was taken to the emergency department for better monitoring but unfortunately died the next morning due to respiratory failure. Resuscitation maneuvers were unsuccessful. Death was not considered to be related to the IMP.
20007-53	4 months	Gastroenteritis and colitis	42 days	eTB-T + Valganciclovir	Child was admitted due to severe pneumonia and was discharged from the hospital 20 days after admission, clinically stable. During the following-up on day 30, the child had fever, oral

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					thrush, anemia, and diarrhea, malaria test was negative. The family was told to get readmitted but the mother refused to claim that she was not feeling well to stay at the hospital and take care of the child, and also refused to get admitted once she was not fine so the team could take care of her also. She went back home but the team asked her to come after few days or in case the child's condition get worse but without success, she never showed up and when the team called her she used to say she was not feeling well to go to the hospital. She came to the hospital to say that the child has passed away 48hrs ago and that he was having severe diarrhea. Death was not considered to be related to the IMP.
20007-55	2 months	Severe pneumonia	5 days	Standard of Care	Child admitted with severe pneumonia and randomized to standard of care, on oxygen through admission, and had clinical deterioration 5 days after admission. The baby had cardiorespiratory arrest with an unsuccessful attempt at resuscitation. Death was not considered to be related to the IMP.
20007-56	3 months	Sepsis	48 days	Valganciclovir	Child enrolled and randomized to valganciclovir and discharged after 15 days. The bay was readmitted 4 days before the death with signs of severe respiratory infection and was prescribed treatment for PPJ, but without improvement. The team decided to start TB-T, with a blood culture was requested and the result came out with septic infection, started vancomycin, but the child's condition was only worsening and the child passed away. Death was not considered to be related to the IMP.
20007-57	4 months	Sepsis	16 days	Standard of Care	Child 4 months old admitted to HGJM with severe pneumonia and randomized to Standard of care. During admission, did not have a good clinical evolution, and continued with a persistent cough, fever and worsening respiratory condition with increasing oxygen requirements. TB-T was initiated out-of-randomization due to a lack of response to Standard of care (SoC) antibiotics and PCP treatment - all TB testing done during admission was negative. The child had clinical deterioration the day before the death with fever, dehydration (due to gastroenteritis), oxygen desaturation, grunting, and hypotension. Had cardiorespiratory arrest later that day with unsuccessful attempt at resuscitation. Death attributed to Severe sepsis/septic shock. Death was not considered to be related to the IMP.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20007-59	4 months	Sepsis	16 days	eTB-T + Valganciclovir	Participant was admitted to the hospital already in critical condition with severe pneumonia, malnutrition, oral candidiasis. He developed malaria, anemia, thrombocytopenia and sepsis. Was treated with blood transfusions, dopamine, vancomycin and artesunate, other than study meds and SoC antibiotics, but didn't respond to treatment which ended in death. Death not related to participation in study, attributed to sepsis/septic shock. Death was not considered to be related to the IMP.
20007-60	4 months	Severe pneumonia	3 days	Valganciclovir	Child initially admitted due to enteritis with bloody stools, no evidence of intestinal intussusception and randomized to valganciclovir. On 3rd day of admission, child started having breathing difficulty, enteritis was resolved. Mother was HIV tested and returned a positive result (new diagnosis), ordered PCR for the child which was also positive. On recruitment, urine-LAM was positive (2+) and the child was started on TB-T out of randomization. During admission, child was with persistent and increasing oxygen requirements. Had clinical deterioration on 06/11/21 with worsening respiratory symptoms and fever. The baby had cardiorespiratory arrest with unsuccessful attempt at resuscitation. Death attributed to respiratory failure due to severe Pneumonia/PCP/TB. Death was not considered to be related to the IMP.
20007-62	7 months	Unknown	93 days	Standard of Care	Child randomized to Standard of care, and admitted for three weeks. On the date of the visit +30days, one week after being discharged, the family did not return to the follow-up visit. Multiple contact attempts were made to contact the family after this, asking the family to bring the child for a follow-up visit. At first it was informed that the family decided not to take the medication from the hospital and that the child is fine (informed us by the grandmother of the child with whom we made contact). After this incident the family rejected all of our contact attempts and on the day of the death contact with the grandmother was made possible. She informed that the child died on the date two months earlier Referred that the child had fever and cough. She did not know of any other clinical information about the child. Death was not considered to be related to the IMP.
20007-63	4 months	Severe pneumonia	8 days	Standard of Care	Child admitted with severe pneumonia, oral thrush was already on ART at admission, PCR+

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					at 1 month. Did not have a good clinical evolution during hospitalization. Worsened one week after admission with increased work of breathing, intense cough, grunting and falling oxygen saturation (89%) on 5L oxygen. Ordered new CXR which showed progressive infiltrates on right lung field. Started on Vancomycin, increased oxygen to 15L, suspended oral intake. Thought about starting TB meds due to 1+ Urine-LAM and poor clinical evolution, delayed to try and see if Vancomycin would be effective. Had cardiorespiratory arrest during early hours of 23/11/21, first episode with successful CPR but a couple of hours later had a second occurrence with unsuccessful resuscitation attempts. Death attributed to severe pneumonia due to advanced HIV infection. Death was not considered to be related to the IMP.
20007-66	11 months	Gastroenteritis and colitis	205 days	eTB-T + Valganciclovir	Child randomized to combined treatment, admitted with malnutrition with combined Marasmus and Kwashiorkor and discharged after 10 days from admission. Doing a normal follow-up but readmitted after visit +180d, due to severe malnutrition, fever and acute gastroenteritis with severe dehydration. During admission, the child was started on therapeutic F75 milk but developed lactose intolerance due to which a change in the diet was made. Nevertheless, the child persisted with diarrhea and vomiting on 22/06/22 and was again becoming severely dehydrated. The day before the death, the child worsened with refusal to feed and a clinical scenario suggestive of paralytic ileus. Oral intake was suspended and the child was put on IV fluids only. The child became hemodynamically unstable and had cardiorespiratory arrest with unsuccessful reanimation attempts. Death not related to study participation, it was attributed to acute gastroenteritis with dehydration associated with severe malnutrition and advanced HIV disease. Death was not considered to be related to the IMP.
20007-68	3 months	Severe pneumonia	10 days	eTB-T + Valganciclovir	Participant after recruitment maintained severe respiratory distress with hypoxemia on room air, with oxygen saturation of 57% needing to increment oxygen and change to usage of nasal bubble CPAP. The participant was on Ceftriaxone, Co-trimoxazole, HRZE and valganciclovir. Due to the continuation of the respiratory distress, Ceftriaxone was substituted with Imipenem/Cilastatin.

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					However, there was no improvement and the participant maintained respiratory distress and passed away due to respiratory failure. Death was not considered to be related to the IMP.
20007-69	3 months	Unknown	347 days	eTB-T	Child who was randomized to TB-T arm at HCM, did visit 60 with bad adherence to the treatment and became a LTFU missing visit 90. Child later came back, after abandoning the treatment for two months, and continued TB-T + restarted ART treatment. At visit day 210 (ART visit) (last contact with the child), became a LTFU once more. At day 275 the mother contacted the team asking ART transfer for a nearby health care center. Team agreed and asked the mother to come back for visit 360. After this, the team was not able to contact the mother again during the next months until 391 days after enrollment were the mother referred that the child died on day 347. According to the information the mother could share, the child started developing diarrhea and vomits before death. Clinical team are suspecting possible gastroenteritis with dehydration and metabolic acidosis, pneumonia and sepsis as differential diagnosis for the cause of death. This child had bad ART adherence and probably abandoned the treatment again. Death was not considered to be related to the IMP.
20007-71	11 months	Sepsis	258 days	Valganciclovir	A participant was randomized to receive valganciclovir. The child had a successful first admission and completed the required follow-up visits, but needed to be readmitted several times for various issues. At day 48 after enrollment, the child was diagnosed with Pulmonary TB during a clinical readmission. At day 60, the child was readmitted again due to diarrhea and fever with severe dehydration. On day 245, the child was admitted with Acute Gastroenteritis (AGE) and Pneumonia. On the next day evolved with tonic-clonic seizures with no consciousness loss and gastrointestinal bleeding through nasogastric tube being immediately transferred to Pediatric Intensive Care Unit (PICU) with severe condition in shock and 6/15 Glasgow Coma Scale (GCS). Expansion with albumin, Nacl were made, benefited from Red blood cell concentrate and platelets transfusion and were accoupled to CPAP and septic shock were stablished. A cardiac echography revealed myocarditis. Child returned to the wards with improved peripheral perfusion, but with low

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					consciousness level due to neurologic sequels. At ward evolved with focal seizures maintaining GCS at 5/15, Phenytoin and sodium Valproate were added to Vancomycin, Ceftriaxone, Fluconazole, Digoxin and Furosemide that was ongoing. On the night of the 258th, unfortunately, the participant passed away. Death was not considered to be related to the IMP.
20007-72	3 months	Sepsis	8 days	eTB-T	Child started presenting symptoms of severe respiratory infection, lab investigation was made and came back with anemia, thrombocytopenia, malaria test was also made and came out positive, started treatment but without improvement. The respiratory distress started worsening and the child started saturating less than 80% even with 5L of O2 which lead to death. Death was not considered to be related to the IMP.
20007-74	5 months	Sepsis	21 days	Valganciclovir	Child randomized to valganciclovir, admitted due to severe pneumonia and discharged 13 days after enrolment. The participant re-admitted on 20/01/22 at HGM Pediatric emergency department with 3-day history of fever, diarrhea and vomiting. The child's parents decided to wait and administer traditional medication before taking the child to the hospital. On readmission, the child was in critical condition, septic, with severe dehydration and clinical signs of shock. During the clinical observation the child had cardiorespiratory failure and was successfully reanimated, during which the child had a presumable Broncho aspiration. A few hours later the child had a second episode of cardiorespiratory failure and later died. Death attributed to septic shock secondary to gastroenteritis. Death not related to study participation. Death was not considered to be related to the IMP.
20007-75	3 months	Severe pneumonia	11 days	eTB-T	Child admitted with severe pneumonia and oral thrush. Both mother and child were newly diagnosed with HIV on this admission, recruited and randomized to TB-T. During admission, the child did not have a good clinical evolution with worsening of respiratory symptoms on high volumes of oxygen through the mask. Changed antibiotic regimen to Vancomycin after 10 days of Ceftriaxone with no response. The child worsened with increased work of breathing, grunting and hypoxemia, SpO2 = 80% on 15L of oxygen, was transferred to PICU in critical condition. There, the child was intubated during which the child

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					had cardiac arrest, was successfully reanimated and started on mechanical ventilation. clinical team at PICU started the child on Ganciclovir which was available to PICU and administered one dose. Child later died on same day as transfer due to respiratory failure, CPR attempts were unsuccessful. Death not related to participation in study, probably due to severe pneumonia (PCP) with advanced HIV infection. (VL>10,000,000 cp/mL, CD4=236 (9%)). Death was not considered to be related to the IMP.
20007-76	7 months	Sepsis	29 days	Valganciclovir	Participant admitted due to severe pneumonia, severe acute malnutrition that developed severe anemia and randomized to valganciclovir. Participant required transfusions of pRBC, and platelets. Later in the admission the participant developed signs of left-sided heart failure related to anuric renal failure secondary to sepsis and died. Death was not considered to be related to the IMP.
20007-77	4 months	Unknown	88 days	Standard of Care	Child randomized to standard of care and discharge 6 days after admission. Three months later, the child's mother contacted the team referring that the baby had fever, we asked her to come in for a consult but she refused and preferred to go to the local health center where she was prescribed Paracetamol. The team was trying to contact the mother for updates on the child's condition for the past week but her number was not reachable. Finally, we were able to talk to her and she informed us that the child had died a few days earlier at Xai-Xai while traveling on her way to Gaza where she was going to meet the child's dad with unknown cause as the child did not die in a health facility. Death was not considered to be related to the IMP.
20007-78	4 months	Severe pneumonia	6 days	eTB-T + Valganciclovir	Child admitted severely ill with severe pneumonia and marasmus and randomized to combined treatment. During admission didn't have a favorable clinical evolution with falling oxygen saturations (<90%) on 15L of oxygen through the mask and persistent breathing difficulties and died 6 days after enrolment. The death not related to participation in the study. Death was not considered to be related to the IMP.
20007-80	3 months	Severe pneumonia	22 days	Standard of Care	Child admitted with severe pneumonia, was a new HIV diagnosis at admission and randomized to standard of care. During hospitalization developed increasing respiratory distress, the participant was already on bubble nasal C-PAP but the children

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					worsening and was transferred to the pediatric intensive care unit, intubated and put on assisted mechanical ventilation due to respiratory failure. Four days after admission the participant was weaned from the ventilator and disconnected from the ventilator and restarted on CPAP, later transferred back to the breastfeeding ward when clinical condition stabilized after 8 days in PICU. One week later, the participant clinical condition deteriorated once more with difficulty breathing, increased work of breathing, cyanosis, severe hypoxemia and bronchospasm and was once again transferred to PICU in critical condition. Administered Furosemide and Morphine at admission with some improvement. The antibiotics were changed due to recurrent fever and started on Aminophylline drip due to bronchospasm. Ordered a Pulmonary CT with findings suggestive of stasis/aspiration pneumonia and a few days later, despite all these treatment changes, the child died. Death was not considered to be related to the IMP.
20007-83	8 months	Gastroenteritis and colitis	14 days	eTB-T+ Valganciclovir	The child was admitted and randomized to combined treatment with diarrhea which started getting worse three days after admission, including vomiting. Due to malnutrition, therapeutic milk was started, but the child's condition didn't improve but didn't worse for some days. On the day of the death, his clinical condition suddenly got worse, with dyspnea, tremors, chest indrawing and diarrhea, and went into cardiac arrest, CPR was done but without success and he passed away. Death was not considered to be related to the IMP.
20007-84	7 months	Gastroenteritis and colitis	3 days	Standard of Care	Child with severe diarrhea which have started a day before with lack of appetite and fever, and randomized to standard of care. The day before the death, had two convulsive fever episodes and started respiratory distress, and was transferred to the emergency room. The day after he went into cardiac arrest, CPR was done but with no success and the child passed away. Death was not considered to be related to the IMP.
20007-92	10 months	Severe pneumonia	0 days	eTB-T	Minor transferred from malnutrition ward, to the emergency due to difficulty of breathing, was then recruited for TB-T with O2 saturation of 94, with DAG Marasmus but stable. The same day of the admission, the baby started having difficulty breathing, the mother was trying to feed the child when he suddenly aspirated and went into cardiac arrest, CPR

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					was done but with no success and the child passed away. Death was not considered to be related to the IMP.
20007-93	3 months	Sepsis	5 days	Standard of Care	This child was admitted to PICU, intubated and started on mechanical ventilation before recruitment. The mother and child were both newly diagnosed with HIV on admission. The child was enrolled in the study and randomized to standard of care. During admission, the clinical condition of this participant did not improve with increasing oxygen requirements and suboptimal oxygen saturations. Arterial blood gases showed respiratory acidosis. Three days after admission, the child registered fever and generalized seizures and started anti-convulsive medication. A follow-up FBC showed worsening anemia with Hb=7.5 g/dL and a blood transfusion was ordered. The day before the death, the child had clinical deterioration with anuria and hemodynamic instability. He did vasoactive agents and various volume expansions in an attempt to correct this. Unfortunately, the next day the child had a respiratory failure and died after unsuccessful resuscitation attempts. Death was not considered to be related to the IMP.
20007-94	5 months	Severe pneumonia	3 days	Valganciclovir	Child 5 months old with cough, fever and dyspnea for a period of 5 days, was admitted due to severe pneumonia and randomized to valganciclovir and was intubated and ventilated. The participant had never improved due to respiratory failure, the X-ray revealed an image of pulmonary bole or pneumatocele. He had submitted to vasopressor treatment and bronchodilators and sedation. The state of respiratory failure and hypoxemia persisted despite mechanical ventilation. Death was not considered to be related to the IMP.
20007-95	3 months	Sepsis	5 days	eTB-T + Valganciclovir	Child admitted with severe pneumonia, both mother and child were new HIV diagnosis at admission. The participant was recruited at PICU with hypoxemia and randomized to combined treatment. Before admission, the mother had administered an unknown traditional medication which may have contributed to the child's critical condition. During hospitalization, the participant did not have a good clinical evolution with persistent hypoxemia and fever. A blood culture was collected and the results were only received after the participant died) positive for Enterobacter spp resistant to Ceftriaxone and Tetracycline. The child developed a clinical

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					scenario of septic shock with bradycardia, respiratory arrest and decreased renal output. The participant was successfully reanimated and intubated to start mechanical ventilation. Later that night, the child had cardiorespiratory failure and died. Death was attributed to Severe pneumonia, Sepsis/septic shock and advanced HIV infection with severe immune suppression. Death was not considered to be related to the IMP.
20007-96	9 months	Sepsis	1 days	Valganciclovir	Child admitted at HGJM due to AGE with severe dehydration and later on developed bronchopneumonia. Was new diagnosis of HIV at admission and already severely ill at recruitment with signs of sepsis and renal injury. The baby was randomized to valganciclovir. On the night of recruitment, the child had clinical deterioration with signs of septic shock, and started on adrenaline infusion/drip. 1 day after recruitment, the child worsened clinically, with hypoxemia, hypothermia and hypotension and died after unsuccessful reanimation attempts (less than 24 hours after recruitment). Death attributed to septic shock. Death was not considered to be related to the IMP.
20007-97	3 months	Severe pneumonia	2 days	eTB-T	Child with new HIV diagnosis at recruitment. This participant presented hypoxemia at recruitment with O2 saturations at 66% without oxygen but 99% with 5L/min of oxygen through the mask and was randomized to TB-T. The day after of enrolment, the child deteriorated with worsening of respiratory symptoms, fever and hemodynamic instability. The Oxygen flow was increased to 10L/min due to falling oxygen saturations (84%) on 5L/min and IV fluids were administered. Around midnight the child had cardiorespiratory failure after the mother had administered milk through the nasogastric tube with plenty milk reflux. All resuscitation attempts failed and the child was declared to have died two days after enrolment, probably related to broncho-aspiration associated with severe pneumonia and advanced HIV. Death was not considered to be related to the IMP.
20007-98	4 months	Severe pneumonia	78 days	eTB-T + Valganciclovir	Child randomized to TB-T and valganciclovir who successfully followed the study visits until visit 60. At visit 60 was admitted at the hospital with a history of food refusal an episode of tonic-clonic seizures. At admission was prostrate, hypotonic, sub febrile with tachypnea, groans and cold extremities. A blood count was performed which revealed WBC of 14700u/l (Neut 12300/ul and Lym

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					1200/ul), PLT 96000/ul and Hb 8.2g/dL and capillary blood glucose of 1.6mmol/l promptly corrected and an expansion with lactate ringer was made, child was transferred to PICU with Meningoencephalitis diagnosis and started therapy with Ceftriaxone, Vancomycin, Paracetamol and Midazolam SOS. The participant evolved with 2 episodes of watery dejection, fever, dyspnea with subcostal retraction, cold and cyanotic extremities, having been expanded with albumin no showing improvement, it was decided to initiate vasoactive therapy with dopamine infusion. FBC requested revealed Hb 8.7g/dL and PLT 44000 with no active bleeding, RBC transfusion was performed. Some days after, the respiratory condition was standing out it was decided to initiate PCP treatment with Cotrimoxazole and Prednisolone. At day 74 after enrolment, at afternoon clinical round was found out that the mother left the hospital with the child . On day 79 HCB team found out that the child died on 78 night at home. Death was not considered to be related to the IMP.
20007-99	3 months	Severe pneumonia	4 days	Standard of Care	Child was admitted with cough, fever and respiratory distress and oral candidiasis. Was already known as HIV positive on ART (ABC+3TC+DTG), in addition to that started treatment with penicillin, nystatin and cotrimoxazole prophylaxis during the admission. Was recruited to Standard of care and started treatment with prednisolone and CTX treatment and urine TB-Lam was positive (3+), started TB-T. Two days after enrolment got worse with severe respiratory distress, irritability, fever, difficult feeding. The team suspended penicillin and started Ceftriaxone treatment. Had clinical deterioration on three days after admission with worsening of respiratory symptoms and later had a cardiorespiratory arrest with unsuccessful attempt at resuscitation. Death attributed to respiratory failure due to severe Pneumonia/PCP/TB. Death was not considered to be related to the IMP.
20007-105	1 months	Severe pneumonia	9 days	eTB-T + Valganciclovir	Child enrolled to the study during an admission for pneumonia. Two days after enrollment, the child experienced an increase in respiratory distress, most likely due to inflammation of the larynx, and exhibited symptoms such as stridor and hypersalivation. The child was given four doses of IV hydrocortisone to alleviate the

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					symptoms. On day 9, the child's condition worsened with respiratory distress, a respiratory rate of 66, and an oxygen saturation level of 88% on room air, which increased to 98% with 4 liters of oxygen. That evening, the child aspirated during feeding, likely due to the clinical condition of laryngotracheomalacia, and went into cardiac arrest. Despite aspiration and CPR, the child passed away. Death was not considered to be related to the IMP.
20007-107	4 months	Severe pneumonia	11 days	Standard of Care	The child's condition began to worsen after recruitment, with a decrease in oxygen saturation, severe dyspnea, cyanosis, diarrhea, fever, and difficulty feeding. As a result, a nasogastric tube was inserted. A GeneXpert fecal test conducted as part of the study revealed that the child was positive for rifampicin-resistant tuberculosis, and treatment was initiated with levofloxacin, cycloserine, linezolid, and clofazimine. On the afternoon of day 10, the child's condition deteriorated further, with generalized hypotonia, oxygen saturation of 45% on room air, and pallor. A hemogram was performed, revealing a hemoglobin level of 7.9, and a blood transfusion was administered. On day 11, the child's breathing difficulties increased, leading to respiratory failure. Despite CPR, the child passed away. Death was not considered to be related to the IMP.
20007-108	3 months	Severe pneumonia	4 days	Valganciclovir	Child born prematurely with a birth weight of 1500g, twin died at birth. Mother died after a few weeks due to unknown condition (probably related to HIV) - at the same time child got admitted due to failure to thrive and HIV was diagnosed. Started ART, and after one week stopped at local health center because the weight was below 3000g. After one month without ART child came for admission due to pneumonia and anemia - presenting with dyspnea, cough and hypoxia and was enrolled in the clinical trial. Didn't have a good clinical evolution with persistent cough and increased work breathing, became septic and had an episode of bronchoaspiration. A control FBC was done at the same date, that showed a WBC of 22000/uL and severe anemia of 6.7g/dL. The clinicians decided to start Azitromycin and a blood transfusion was done. At day 4 after enrolment, the child worsened clinically and had an episode of cardiorespiratory arrest. Reanimation

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					attempts were unsuccessful and death was declared at 18:45h. Clinical team attributed death to respiratory failure due to severe pneumonia and advanced HIV disease. Note: We received the post transfusional FBC that revealed Hb of 18.4g/dL (HCT: 58.5%). We believe the child might have been accidentally overtransfused by the nursing team and that this polycythemia might have contributed to the child's death. Death was not considered to be related to the IMP.
20007-109	4 months	Severe pneumonia	1 days	eTB-T + Valganciclovir	Child enrolled to study with known HIV status on ART for the previous two months. At admission, the child presented with severe pneumonia having previously been treated at the local health center with Amoxicillin with no clinical improvement. During hospitalization, presented with low oxygen saturations (71%) on room air, was started on PCP treatment and supplementary oxygen via face mask at 5L/min with good oxygen saturations up to 99%. On second day of admission the child worsened clinically with increased work of breathing and hypoxemia. Child had respiratory failure on the same day and was declared dead after unsuccessful reanimation attempts. Death attributed to severe pneumonia/PCP and advanced HIV. Death not related to study participation.
20007-110	7 months	Severe pneumonia	4 days	eTB-T	Child admitted with severe pneumonia and hypoxemia and randomized to TB-T. Started treatment and oxygen therapy as per protocol but didn't have good clinical evolution during admission with persistent breathing difficulties, grunting and low oxygen saturation. Child worsened and died on day 4 with respiratory failure secondary to severe pneumonia. CPR attempts were unsuccessful. Death attributed to severe pneumonia/PCP and advanced HIV. Death not related to study participation.
20007-111	4 months	Sepsis	22 days	Standard of Care	The child was admitted with a diagnosis of severe bacterial pneumonia, stage IV HIV/AIDS according to WHO, and oral candidiasis. Two days after admission, the child was recruited and randomized for the SOC. TB-LAM, and GeneXpert tests, both of which were negative. However, due to the child's persistent difficulty breathing, cough, and radiological

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					appearance, the clinicians decided to start TB-T on day 9 after enrollment. Despite treatment, the child's condition continued to deteriorate. On day 14, a hemogram was performed, revealing a low hemoglobin count of 6.2, and a blood transfusion was administered. On day 22, the child began to exhibit signs of sepsis, such as low peripheral perfusion and a temperature of 35.5°C. The sepsis protocol was initiated with fluid therapy and dobutamine, but unfortunately, the child passed away. Death was not considered to be related to the IMP.
20007-112	3 months	Sepsis	2 days	Valganciclovir	Child randomized for valganciclovir treatment. One day after enrollment, the child's condition started to deteriorate, with difficulty breathing, a dry cough, and oxygen saturation dropping to 83% on room air and 91% with 5L of oxygen. The child was also receiving artesunate treatment for malaria. Although the TB LAM test came back positive, TB-T was not started at that time. On the morning of day 2, the child showed signs of multiorgan failure, including cold extremities, decreased pulse rate, and a temperature of 34.4°C. A hemogram was taken for control, but the chest X-ray could not be obtained due to the child's critical condition. The child's respiratory distress continued to worsen, and the doctor initiated a dose of 7.5 micrograms/kg/h of Dobutamine, but unfortunately, the child's condition continued to decline, eventually leading to cardiac arrest. CPR was performed, but the child did not survive. Death was not considered to be related to the IMP.
20007-118	3 months	Severe pneumonia	11 days	Valganciclovir	Child admitted with severe Pneumonia, in admission was with dyspnea, 02 sat 84%RA, crackles on pulmonary auscultation and pale extremities, child was putted on C-PAP and blood transfusion was made. During her admission the respiratory condition deteriorated with bronchospasm crisis treated with punctual doses of adrenaline and salbutamol nebulizer. At day 8 after enrolment, the crisis became more intense and frequent, child developed central cyanosis, it was decided to put her on C-PAP with 6l of oxygen, the condition was stabilized. At day 10, child got in respiratory distress with severe bronchospasm, multiples cycles of adrenaline and salbutamol were made, hydrocortisone was given with no improvement. Child developed hypoglycemia on day 11, dawn that was corrected with Dxt10%, later child had 2

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20007-121	9 months	Unknown	117 days	eTB-T + Valganciclovir	cardiac arrest successfully resuscitated, it was decided to give one more shot of hydrocortisone, alternate 4/4h adrenaline and salbutamol nebulizer, and later the child had a 3rd cardiac arrest unsuccessfully resuscitated. Death was not considered to be related to the IMP. 9 month-old infant was randomized to TB treatment + Valganciclovir arm and did study visits per protocol until visit +90 with good adherence to the treatment. According to the information the mother could share, the child started to look very pale on 12/02/23 but didn't give much importance to that. However, on 14/02/23 the child started with difficulty breathing, no fever or other symptoms. The mother went to the local health center, where the child did not received medication but was transferred to the recruitment hospital. At the hospital, the child arrived dead. We were not able to get more information from the transfer guide. The death was not considered related to the IMP.
20007-124	3 months	Severe pneumonia	15 days	Valganciclovir	Child with severe pneumonia recruited at HGM but later transferred to HCM for better care. Was already on ART but with very bad adhesion. Since admission the child had hypoxemia with increased need for supplemental oxygen. On day of death, had an episode of respiratory failure and was successfully reanimated. A blood gas was drawn with acidosis (pH 6.8). Had a second episode of respiratory failure and cardiac arrest later the same day and died at around 7 pm. Parents refused participation in MIA substudy. Death attributed to severe pneumonia, sepsis and advanced HIV disease. Death not related to participation in the study.
20007-125	4 months	Severe pneumonia	20 days	Standard of Care	Minor recruited on to SoC, since admission the child had hypoxemia with increased need for supplemental oxygen, urine-LAM and GeneXpert's were all negative. At day 15, the physician decided to start TB-T due to his clinical condition of increased respiratory distress and severe cough. At day 18 and 19 child's condition deteriorated with diarrhea, fever, respiratory distress, dyspnea and difficult feeding, the team put NGT for feeding. However, the infant evolved with dehydration,1 episode of focal convulsion, midazolam was administered and also IV rehydration therapy. At day 20, the infant developed generalized weakness, maintained dyspnea, gasometry was done and showed PH=6.8 and elevated pCO2 and lactate, dobutamine was started due

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					to the severity, from 2pm to 6pm he had 4 cardiac arrest with resuscitation but the last one at 6pm CPR was done unsuccessfully and the child passed away at 6:25pm. Death was not considered to be related to the IMP.
20007-128	5 months	Septic Shock	80 days	eTB-T	5 month-old infant was randomized for the TB arm. Since recruitment, the mother has been showing HIV status denial, first requested discharge against medical advice, then kept delaying antiretroviral therapy (ART) initiation and missed some TB doses. The child missed visit +30 and on visit +60 was re-admitted with a story of fever for 4 days and burn wounds on the child's chest, associated with food refusal and inconsolable cry. At admission, the child presented with fever and lethargy with signs of poor perfusion. Fluid resuscitation was started. During 1st-hour observation, the child had 2 episodes of tonic-clonic seizures and kept with poor perfusion, so the child was transferred to the pediatric intensive care unit (PICU) with Septic shock with a possible skin focus and started treatment with ceftriaxone, hydrocortisone, salbutamol, midazolam, ranitidine, dopamine in perfusion and paracetamol. The participant evolved with other episodes of seizures and remained with poor perfusion and periods of hyper and hypothermia. The child was diagnosed with viral encephalitis and phenytoin and acyclovir were added to the previous treatment. The participant received blood and albumin transfusion. The child kept deteriorating with oxygen desaturation requiring initially CPAP and then intubation. The child presented signs of decompensated anemia and bleeding and underwent several transfusions of blood, Vitamin K, and platelets. The antibiotic treatment was escalated to Imipenem/Cylastatin and Amikacin. A few days later a cardiac arrest was successfully resuscitated. Amikacin was suspended and Vancomycin was initiated. The child kept unstable, with focal seizures, spikes of hyperglycemia, with low O2 sat whenever it was tried to reduce the FiO2, and periods of bradycardia needing Adrenaline perfusion. Four days later the child became hyporeactive and bradycardic with severe hypothermia, it was decided to empirical correction of hypokalemia and hyponatremia, increase the FiO2 to 100% with no improvement, and the same day the child had a cardiac arrest unsuccessfully resuscitated.

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					The death was not considered related to the IMP.
20007-131	12 months	Septic Shock	117 days	eTB-T + Valganciclovir	12 month-old infant was randomized for the TB arm and followed the study visits until visit 30. However, the child missed visit 60 and almost missed visit 90, but was readmitted due to severe malnutrition on after that date. During this admission, it was discovered that the child had never started ART and likely wasn't taking TB medication. The clinical team decided to restart treatment. In the first week, the child improved, gained weight, and transitioned to nutritional rehabilitation. IV antibiotics were replaced with oral Amoxicillin. However, when the child's milk was changed to Nan, they developed lactose intolerance symptoms, lost weight, and returned to the stabilization phase. Pre-Nan milk was used as lactose-free milk wasn't available. A week later, the child developed fever, but malaria tests were negative. Full blood test (FBC) revealed WBC 40 200 cells/ul (Lym 12 500 neutrophils not reported), Hgb 6.2g/dL, and a blood culture revealed Klebsiella sensitive to Imipenem. The child was transferred to the PICU with septic shock. In the PICU, blood transfusions were given, and Dopamine was added due to poor perfusion. Over the next few days, the child's condition deteriorated, resulting in multiple organ failure, acute renal failure, metabolic acidosis, severe hypothermia, and hypoglycemia. Thrombocytopenia and anemia worsened despite transfusions. Two days later, the child's consciousness level decreased, and they had seizures that didn't respond to Diazepam. Phenytoin and hydrocortisone were added to the treatment. The day after, another FBC showed WBC 15 600cells/uL Hgb 6.9g/dL, PLT 6 000cells/ul and platelets concentrate, and plasma were administered. During the night, the child had a cardiac arrest and received resuscitation and adrenaline but could not be revived. The death was not considered related to the IMP.
20007-132	8 months	Unknown	159 days	Valganciclovir	8 month-old infant that was recruited and randomized to valganciclovir, had positive LAM result, starting TB out of randomization 2 days after recruitment, improved respiratory condition and was discharged four days later. The mother provided her father as a contact for appointment reminders but had difficulty reaching him as he lived outside Beira City.

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					The child missed visits 15, 30, and 60, returning for V90 when was admitted due to pneumonia. After discharge, a one-month follow-up was recommended. The child's mother faced adherence challenges due to family stigma, secretly administering medication due to discomfort about the child's HIV status. At the time for visit 180 the grandfather informed us that the child passed away in mid-July from an unspecified respiratory disease that began suddenly at night with respiratory distress. The death was not considered related to the IMP.
20007-135	9 months	Hypoglycemia	34 days	Standard of Care	9-month-old infant randomized to Standard of care and admitted for over a month with multiple comorbidities. Started TB-T out of randomization and completed all standard of care as per protocol, having also started ART. The child had persistent anemia and thrombocytopenia, even after many corrections, and evolved with transaminases elevation, with the need to stop the TB-T. The clinical team was still investigating the cause of the bicytopenia and transaminase elevation when the child evolved with bleeding from one of the eyes (at admission with leukoma on both eyes) and needed an urgent evisceration. After the surgery child started developing hypoglycemia and being on treatment with Piperacillin + Tazobactam. During the last days, the child had two episodes of seizures deemed related to hypoglycemia, where punctual corrections were done with dextrose, and the clinical team maintained an IV serum with dextrose reinforcement to run for 24 hours. 5 days after the surgery the child started having fever, low oxygen saturation with crackles, and rhonchus at auscultation. Started oxygen and azitromycin treatment due to possible nosocomial pneumonia. Had one more episode of hypoglycemia (glucometer reported low) during the morning - and a correction was done immediately. By the end of the day, the child went into a cardiorespiratory arrest. The glucose measured was reported low (by the glucometer). Correction with dextrose and reanimation attempts were done without success. Death was attributed to Hypoglycemia and clinicians also mentioned pneumonia as the cause of death. Caretakers

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					denied participation in the MIA substudy. The death was not considered related to the IMP.
20007-136	6 months	Sepsis	112 days	eTB-T + Valganciclovir	6 month-old infant was randomized to TB-T-VAL and followed the study visits per protocol (+15, +30, +60, +90). Anemia (grade 2) and thrombocytopenia (grade 2) were detected and monitored during the follow-up. 3 months after recruitment was admitted, with a history of 5 days of diarrhea, difficulty breathing, oral thrush, and some signs of Shock. His clinical condition kept deteriorating since admission with low O2 saturation, and a decreased level of conscience. The child received treatment with dobutamine, ceftriaxone, nystatin, and zinc sulfate and maintained the TB-treatment (2DFC) cotrimoxazole prophylactic and ART. One day after admission, nutritional evaluation was done, which revealed severe malnutrition (Marasmus), F100 was prescribed, and at 7 pm his condition continued to get worse, Glasgow scale was 3/15, with NGT, hyporeactive pupils, pulmonary auscultation with vesicular murmurs, weak pulse, moderate cold extremities, maintained dobutamine 7,5. The same night child went into cardiac arrest, CPR was done and adrenaline was also administered 3 times during resuscitation but without success and he passed away. The death was not considered related to the IMP.
20007-139	4 months	Pneumonia	1 days	eTB-T	4 month-old infant admitted with severe pneumonia and hypoxemia was randomized to TB-T. Started treatment and oxygen therapy as per protocol but didn't have good clinical evolution during admission with persistent breathing difficulties and low oxygen saturation. When the child got worse, the clinical team decided to increase the O2 given to the child to 10-15L/min (during the child's recruitment). Eventually, the child worsened with dyspnea and died the next day with respiratory failure secondary to severe pneumonia. CPR attempts were unsuccessful. The death was not considered related to the IMP.
20007-140	3 months	Pneumonia	8 days	Valganciclovir	3 month-old infant was randomized to VAL and was transferred on the same date to the reference Hospital (HCM). Admitted with severe respiratory symptoms. Developed some diarrhea during admission and had clinical deterioration after 3 days, with mixed

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					acidosis. The clinical team started treatment with azitromycin and the child was admitted to PICU. Once there, due to severe respiratory distress, the child was intubated and completed to the mechanical ventilator. Started treatment with aminophylline, dopamine, midazolam, and fentanil. After getting hemodynamically stable, dopamine and aminophylline were suspended. One week after the admission the child was aggravated with a decrease in the consciousness level (3/15 Glasgow scale), midazolam and fentanil were suspended. The next day the child evolved with decreased O2 saturations and eventually, the child went into a cardiorespiratory arrest. Reanimation attempts were made but were unsuccessful. Death was attributed to pneumonia. A minimally invasive autopsy was performed. The death was not considered related to the IMP.
20007-145	4 months	Unknown	7 months	eTB-T	4 month-old infant was randomized to TB treatment and has been an LTFU for around two months during the visit 180d time range. Before becoming an LTFU, child was already severely ill and the mother always denied admission. Finally when the child was admitted for malnutrition, pneumonia, and liver alterations by the beginning was discharged, still with severe malnutrition. Control was scheduled for the following week. During that visit, the child had lost weight and was with diarrhea, without a good clinical condition. The mother denied admission. A few days later, the mother came with the child already dead. The mother said that the child continued with diarrhea during the previous days and was lethargic. According to what the mother referred the team attributed the death to hypovolemic shock related to the AGE and malnutrition in the context of advanced HIV disease. The death was not considered related to the IMP.
20007-148	6 months	Unknown	8 monhts	eTB-T + Valganciclovir	6 month-old infant was randomized for the TB-T + valganciclovir arm, treated as severe pneumonia and discharged one week later. Urine TB lam was positive after the discharge and child was readmitted due to severe pneumonia and anemia and the mother reported that she never gave the TB-T and after discussion, the team decided to restart the TB-T. The child at visit 90 presented with a

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20007-149	3 months	unknown	56 days	eTB-T	history of intermittent fever for a week, malaria test was positive but the mother refused to be admitted, prescribed coartem together with Iron sulfate for anemia, and started 2DFC. The day +120 after the enrolment, the child was clinically stable without complaints according to the mother. After that visit, the mother didn't come to the hospital, the team tried to contact her since then, without success and they never came to follow up, after many trials in contacting them, his father finally picked the call and reported the child's death that happened 2 months ago and without giving any additional information about the child's death. The death was not considered related to the IMP. 3 month-old infant was randomized to TB-T. Urine LAM positive at recruitment. The infant followed the study visits per protocol until visit 30. At visit 30, the child was clinically stable, without any complaint, her vital signs were all normal, a control hemogram was done and revealed hemoglobin of 6.6g/dL, after talking to the mother, and counseling for a blood transfusion, mother refused to stay, saying that she needed to talk to the father of the child for permission, and she promised to come back after a week. The team contacted her after a week requesting to come to the hospital for control but she said, that the father didn't allow her to come, and she would come only on visit 60. Tried to contact her again without success. After that date, the mother called the study team to report the death of the child 2 days ago with respiratory distress. According to her, the child started presenting with difficulty breathing two days earlier, with no fever, cough, or any other abnormal symptoms, she didn't take the child to the hospital due to her availability and wanted to take the child on the next morning. But overnight, her difficulty breathing deteriorated and the child passed away while they were getting ready to go to the hospital. The death was not considered related to the IMP.
20007-150	3 months	Severe pneumonia	3 months	Standard of care	3 month-old infant randomized for the standard of care arm admitted with severe pneumonia and anemia improved respiratory condition ended up being discharged one week after enrolment. Mother requested to do ART at the same local health center she was

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					doing, a transfer. letter was given for that purpose on discharge day. Returned for visit 15, 30 with no intercurrences said that child was doing treatment. On visit 60 child presented oral candidiasis, and weight loss when requested child vaccination card to evaluate growth chart, it was noticed that the child had missing vaccines, visits to the health center and when requested when was the last time she went to pick up ART meds she confessed that she never went there. Child has been in local center for controls after birth once only. ART was started at the central hospital for better control, candidiasis was treated mother was advised to follow the vaccination program. When returned for the visit +90d, the mother presented no complaints, said that child was doing well, but when observed he was septic, febrile, pale, jaundiced, dyspneic with nasal flaring and chest indrawing, pulmonary auscultation with bilateral crackles. On next day the child respiratory condition got worsen was placed on CPAP, it was also noticed that child had troubles swallowing impressing swallowing muscles discoordination/weakness. The next morning, the child had a respiratory arrest requiring manual ventilation and aminophylline, dextrose 10%and in bolus were also administered empirically, started developing bradycardia atropine was added and then had cardiac arrest, unsuccessfully resuscitated. The death was not considered related to the IMP.
20007-154	6 months	Pneumonitis aspiration	28 days	Valganciclovir	6 month-old infant randomized to valganciclovir. The participant was admitted since recruitment doing nutritional rehabilitation due to severe malnutrition, for almost a month. Treatment was being done with therapeutic milk and porridge meals with plumpy nut. The child was also on TB-T and clinically stable after finishing Val and PPJ treatment. Before death, the Mother mentioned that the child was not playing and after feeding sometimes had postprandial vomiting or food refusal that started around one week ago. The mother called the clinical team informing them that the child was having difficulty breathing after she finished feeding the porridge meal. When the clinical team arrived, they found the child gasping with food content coming from her nostrils and mouth. Aspiration was attempted and the child entered into a cardiorespiratory arrest.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20007-159	9 months	Unknown	5 months	eTB-T	The child was reanimated without success and death was declared due to bronchoaspiration. The death was not considered related to the IMP. 9 month-old infant that was recruited and randomized to TB-T arm who did the treatment per protocol missing one month to finish. The parents were in HIV diagnoses denial fact the delayed ART initiation, which was started around visit 90 when child was re-admitted due to Hemiparesis. After the visit +90d , the mother returned with the child to collect the IMP and informed they would travel to another province and would be able to return for the visit +180d. In the process of reaching the mother for visit +180d, she informed that the child had passed away one month earlier. According to her the child had fever 3 days ago and they went to the hospital because the child was too weak, did some tests, including malaria, which was negative but didn't know the results or name of other tests. The next day, she was informed the child died. No respiratory symptoms were reported. The death was not considered related to the IMP.
20007-162	3 months	Unknown	45 days	Standard of care	3-month-old infant randomized to standard of care and started treatment with CTZ, ceftriaxone, and prednisolone, TB-lam and genexperts all negative. During admission child recovered well, without complications until discharge. The visit +30d was done without complaints. 15 days later, the mother contacted the team informing the death of the child which occurred in a district hospital. She said the child was admitted with bronchopneumonia which deteriorated after a few days. The team couldn't get more information from the mother. The death was not considered related to the IMP.
20007-163	2 months	Pneumonia	5 days	eTB-T	2 month-old infant randomized to TB-T arm was admitted since recruitment with severe respiratory symptoms. Was transferred the day recruited to the reference hospital (HCM) for better care. The child evolved maintaining severe chest indrawing, fast (high) respiratory rate, nasal flaring, and lethargy. Had low O2 saturation without oxygen, with a necessity to maintain oxygen by mask at 10L/min. On day 4 after admission, the child developed metabolic acidosis, with hyponatremia and hypoglycemia, despite correction with IV fluids, the child maintained a bad general

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					condition with dyspnea and lethargy. The next morning, the child developed low oxygen saturation even with 15l/min, and went into cardiac arrest. Reanimation attempts were made without success. A minimal invasive autopsy was performed. The death was not considered related to the IMP.
20007-166	4 months	Severe pneumonia	8 days	eTB-T+ Valganciclovir	4 month-old infant was randomized to TB-T-valganciclovir and admitted with severe pneumonia coming transferred from a private clinic with almost one-week complaints of cough, fever and ultimately difficulty breathing. Child and parents newly identified with HIV infection at this admission. At admission child was dyspneic with nasal flaring, chest indrawing, O2 sat 54% room air, pulmonary auscultation with crackles and started treatment per the protocol and placed on CPAP. During admission the clinical condition got worse with lot more effort to breathe, reducing reactiveness, and saturating lower than 50 % with CPAP, nasogastric tube for feeding was added, the case was discussed with PICU for intubation, denied per poor prognosis. There, the child had an episode of bronchospasm with peripheral cyanosis, was given high doses of hydrocortisone, and was left with salbutamol aerosol. The next day started with small bleeding from the nasogastric tube, gastric lavage with cold saline was done and vitamin K was administered stopping for that moment. Later at afternoon child had a cardio-respiratory arrest unsuccessfully resuscitated. The death was not considered related to the IMP.
20007-171	7 months	Unknown	2 months	Valganciclovir	7 month-old infant randomized to valganciclovir and discharged one week after enrolment. After that, the child had 2 readmissions, one due to pneumonia and the second one due to clinical tuberculosis diagnosis, repeated urine lam which came back positive +1, and started TB-T. The mother didn't come to the hospital for visit +60d, the team tried to contact her every day but without success. Two months after enrolment, the mother called the team to report the child's death a few days earlier. According to her, the child started getting sick a week before, she took her to the local health center were they prescribed some medications but she couldn't tell the names.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					3 days after starting treatment, child's condition didn't improve and she started noticing some skin lesions like vesicles that ruptured and serous liquid came out, she didn't take the child to the hospital and she passed away the next day.. The death was not considered related to the IMP.
20007-172	3 months	Severe pneumonia	1 day	eTB-T	3 month-old infant was randomized to TB-T, admitted with severe Pneumonia (02 sat under 80%, fast breathing up to 80 cpm, chest indrawing, nasal flaring), previously treated as outpatient twice in the past 2 weeks with no improvement. The child was transferred to PICU due and o severe distress respiratory, aggravated with respiratory acidosis, cyanosis and poor peripheral perfusion. Blood transfusion, dopamine in perfusion accoupled to CPAP were part of the treatment. The day after enrolment, the child had a cardio-respiratory arrest unsuccessfully resuscitated. The death was not considered related to the IMP.
20007-174	7 months	Unknown	28 days	Valganciclovir	7 months infant recruited and randomized to valganciclovir arm with a good evolution during admission and the v15 follow-up, with no complaints. On the visit +30 day, the mother informed the team that the child passed away the night before at home. She said that the child was doing fine, with no pathological symptoms, and when she laid the child in bed to sleep, when she came back 3 hours later, the child was not breathing. no other information was shared. The death was not considered related to the IMP as the child was not under valganciclovir.
20007-176	3 months	Severe pneumonia	6 days	Valganciclovir	3 month-old infant randomized to valganciclovir admitted with fever, cough, and dyspnea and severe hypoxemia which improved with 10L oxygen through the mask but worsened every time the child got agitated. After having TB lam +1 started TB-T. The day after enrolment, the child started aggravating with shock signs - cyanosis, and cold extremities and the cinical team started dobutamine in perfusion but the clinical condition worsened and the child died of respiratory failure attributed to severe pneumonia and septic shock, after unsuccessful CPR attempts. The death was not considered related to the IMP.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20007-177	3 months	Pneumonia	1 day	eTB-T	3 month-old infant was randomized to TB-T, was admitted with severe hypoxemia which improved with 10L oxygen through the mask but worsened every time the child got agitated. Both the child and the mother were new HIV diagnoses during this admission and all TB investigations were negative. The child's clinical condition worsened hours after admission and died of respiratory failure attributed to severe pneumonia after unsuccessful CPR attempts. The death was not considered related to the IMP.
20007-180	2 months	Severe pneumonia	2 months	Valganciclovir	2 month-old infant randomized to Val treatment and started the treatment with valganciclovir, ceftriaxone, prednisolone and CTZ right away, All TB lab tests came back negative. 2 days after recruitment mother abandoned the hospital without any medications and never return. The team couldn't contact her all this time because she didn't give any contact. now coming transferred from a local health center with a history of fever and cough for one week which deteriorated with difficult breathing for 3 days and yellowish aqueous diarrhea for also 3days without mucus or blood on it 5 times daily. at the health center was administered a dose of ampicillin and gentamycin. On admission child was dyspneic, pale, and very dehydrated, and with fever. Correction of the dehydration was done and also blood transfusion. The day after the child's clinical condition continued to deteriorate with difficulty breathing and the clinician decided to add prednisolone to the treatment but had 2 cardiac arrests, CPR was done successfully but maintained some signs of hypoperfusion, and dobutamine 0.8ml was added. A few hours The death was attributed to severe pneumonia and not considered related to the IMP.
20007-181	3 months	Severe pneumonia	2 days	TB-T	3 month-old infant randomized to TB-T arm was admitted since recruitment with severe pneumonia characterized by severe chest indrawing, tachypnea, oxygen saturation below 80% without oxygen, and with a necessity of having a nasogastric tube for food intake and received a blood transfusion. Evolved with worsening of the clinical condition entering into a cardiac arrest. The death was attributed to severe pneumonia and not considered related to the IMP.

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20007-187	4 months	Severe pneumonia	18 days	Standard of care	Participant 4 months old admitted on with severe respiratory distress and moderate gastroenteritis without dehydration, randomized to standard of care arm. Started treatment with ceftriaxone, prednisolone, and CTZ, but her clinical condition was deteriorating with difficult breathing, hypoxemia of 50% to 60% at room air that improved with 6L to 10L of O2, persistent cough, and intermittent fever some days. TB labs were all negative at recruitment. Due to her clinical condition, the team decided to suspend ceftriaxone after 14 days and prescribed Vancomycin together with TB-treatment clinical diagnosis, urine lam repeated on the 30th and came back negative. 18 days after enrolment, the child's respiratory distress deteriorated and she went into cardiac arrest, CPR was done together with 2 times administration of atropine, but without success, unfortunately, the hospital didn't have adrenaline and the child passed away. The child died due to severe pneumonia and was not considered related to the IMP.
20007-191	4 months	Severe pneumonia	2 days	Standard of care	Participant 4-months old admitted with severe hypoxemia and randomized to standard of care and started treatment with ceftriaxone, CTZ, and prednisolone. Was in critical condition since recruitment with severe respiratory distress, low O2 saturation of 50 to 60% at room air which improves with 10L of O2 through the face mask and NG-tube for feeding, All lab protocols were done at recruitment and all results (urine and genexpert NPA and stool) came back negative, no x-ray was taken due to his critical condition. The child's clinical condition worsened 48h after admission and the team decided to add aminophylline to improve his respiratory distress but without success and the child died of respiratory failure attributed to severe Pneumonia, after unsuccessful CPR attempts. The death was not considered related to the IMP.
20007-194	2 months	Severe pneumonia	28 days	eTB-T	Participant 2 months old diagnosed with severe pneumonia and randomized to TB-T. TB LAM was positive. The respiratory condition got worse with necessity to be accoupled to CPAP and start diet per a nasogastric tube and Vancomycin was added to the standard of care treatment. On the day

Record ID	Age	Cause	Time since enrolment	Arm	Description
					of death, the child broncho-aspirated during feeding time, and had a cardio-respiratory arrest reanimated with CPR and Adrenaline unsuccessfully. The death was not considered related to the IMP.
20007-200	2 months	Severe pneumonia	7 days	Standard of care	Participant 2 months old diagnosed with severe pneumonia and randomized to standard of care. All TB lab results came back negative. The child's clinical condition continued to deteriorate and on 5 days after enrolment had an intermittent fever and low O2 saturation of 53-60% room air and improved with 7L by mask. Due to difficult feeding, the clinical team decided to introduce a nasogastric tube and therapeutic milk F100 was also added into the diet. The next day child's clinical condition worsened with respiratory distress and 7 days after enrolment had a cardiac arrest, CPR was done unsuccessful and the child died attributed to severe pneumonia. The death was not considered related to the IMP.
20008-4	6 months	Gastroenteritis and colitis	2 days	Standard of Care	5-month-old male infant hospitalized at Kamuzu Central Hospital (KCH) with an acute history of cough and difficulty breathing. He was randomized to Standard of care four days after admission when HIV diagnosis was done. On hospitalization, a diagnosis of severe pneumonia and severe malnutrition was made and standard of care antibiotics regimen of intravenous benzyl penicillin and gentamicin and therapeutic feeds with diluted F-100 milk. Due to deterioration before the enrolment, antibiotic was scale up to ceftriaxone, high dose cotrimoxazole and prednisolone was also commenced to cover for Pneumocystis jirovecii pneumonia. HIV diagnosis was done and the child was enrolled into the study. Two days after enrolment, the mother of the child reported that the child had been having vomiting and passing loose stool. The mother had already been administering rehydration fluids, however it was noted that she had been administering standard oral rehydration salts (ORS) solution. On assessment, the participant had a capillary refill time of less than 3 seconds, well-felt pulses and warm peripheries and hence was assessed as not being in shock. The mother was advised to switch from administering standard ORS to RESOMAL (rehydration solution for malnutrition) and the ward call team advised to review the participant regularly. Per history reported by KCH children's ward nurse attending to the

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					participant in that night, the participant continued to be passing loose stools and vomiting during the night and gradually became weaker despite attempts to give Resomal orally. Due to this gradual weakening of the participant the nurse called the clinical officers and doctors on call on the ward to review the participant. Unfortunately, when the on-call clinicians came to review the participant within the night, the found the child with no respiratory effort and not heart beat and hence was pronounced dead. Death was not considered to be related to the IMP.
20008-5	3 months	Tuberculosis	9 days	Valganciclovir	3-month-old female infant hospitalized at Kamuzu Central Hospital (KCH) with an acute history of cough, difficulty in breathing, fever and oral thrush with unknown HIV status. On hospitalization, a diagnosis of severe pneumonia was made and standard of care antibiotics regimen and oxygen support via nasal prongs was commenced. The day after admission was tested positive for HIV, which came positive and was enrolled for the study and randomized to valganciclovir and also high dose cotrimoxazole and prednisolone to cover for Pneumocystis jirovecii pneumonia was added. The same day of enrolment, the urine LAM results came out positive 2+ and a diagnosis of tuberculosis was made and TB-T was commenced following this diagnosis. The baby deteriorated with fever and low PS02 concentration and was transferred to high dependency unit for close monitoring. On assessment. Other reasons of low oxygen saturation were role out and the baby needed a transfusion of packed red blood cells to increase peripheral oxygenation. The following days the participant continued to require oxygen support via a cylinder. The signs of respiratory distress lessened over these days but it was not possible to reduce oxygen support without the participant desaturating. The 7-day course of ceftriaxone was assessed as completed and the medication was stopped. On the day 9, the participant was noted to have redeveloped difficulties in breathing and PSO2 saturation hovering over the range of 67%-90%. Oxygen flow was initially increased to 10L/min, then to CPAP and the antibiotic was scaled up to Piperacillin-Tazobactam to cover for possible nosocomial infection. Despite the bCPAP, PSO2 and other clinical features of the participant continued to deteriorate and bag mask ventilation was

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					commenced for respiratory support together with cardiopulmonary resuscitation with bag-mask ventilation and chest compressions later on but the participant did not survive. Death was not considered to be related to the IMP.
20008-7	11 months	Pulmonary hypertension	212 days	eTB-T	A 10-month-old infant was admitted to Kamuzu Central Hospital (KCH) with severe pneumonia and severe acute malnutrition. There was no known history of tuberculosis (TB) contact, and a COVID-19 nasal swab rapid test on the date of hospitalization came back negative. One day before the enrollment, the mother and child were diagnosed with HIV and enrolled in the EMPIRICAL study, with the participant randomized into TB-T. During the EMPIRICAL study enrollment visit, a urine LAM assay was performed, and the result was positive. The guardian absconded from the hospital at day 22 after enrollment, and efforts to locate them were unsuccessful. At day 89, the study team identified the participant's mother in the resuscitation area of Children's Ward A with a cough and shortness of breath. The participant had severe malnutrition and was saturating at 89%. This was the first rehospitalization since enrollment in the EMPIRICAL study. An echocardiogram revealed pulmonary hypertension, and the participant was started on Sildenafil. The participant had defaulted on antiretroviral therapy but was recommenced after a counseling session. It was also noted that TB-T had been recommenced after the participant absconded from the hospital. The participant also had a convulsion related to hypoglycemia. After three weeks of continuous oxygen dependency, the participant was discharged. The participant was rehospitalized at day 124, due to difficulty breathing and hypoxemia, and severe pulmonary hypertension. The participant was on oxygen supply for close to 3 months, and attempts to wean off oxygen were unsuccessful. At day 212, the participant experienced a cardiorespiratory arrest and was pronounced dead despite attempts at cardiopulmonary resuscitation. Death was not considered to be related to the IMP.
20008-8	8 months	Unknown	60 days	Standard of Care	7-months old child was hospitalized at Kamuzu Central Hospital (KCH) for diagnosis severe pneumonia with mild pleural effusion and severe anemia were made and standard of care antibiotics regimen of intravenous benzyl penicillin and gentamicin were started. On the

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					same day, the child was noted to have peripheral oxyhemoglobin saturation of 77% on room air, and hence oxygen support via nasal prongs was commenced. Hemoglobin was checked on the same day and was 3.5g/dL, the child was hence transfused whole blood. 3 days after admission, the baby was tested for HIV and was positive and then enrolled in the study, randomized to standard of care, and treatment with ceftriaxone, high-dose cotrimoxazole, and prednisolone were also commenced. The participant was clinically diagnosed with pulmonary TB based on Chest-Xray findings and TB-T was started the day after randomization, despite TB LAM and Xpert being negative. The baby also started antiretroviral therapy. The baby was discharged one week after enrolment. On the day 15 visit, neutropenia was detected which was corrected on day 30th. The death was reported telephonically to the study team two months after enrolment, by the mother of the study participant. She reported that in the early morning hours three days earlier, the child developed sudden onset of cough when they were at the church. She went home to collect the health passport for the child and the child died on their way to the hospital on the same day. Death was not considered to be related to the IMP.
20008-9	2 months	Severe pneumonia	10 days	Valganciclovir	2-month-old male infant was hospitalized at Kamuzu Central Hospital (KCH) with a 3-day history of cough, difficulty breathing, fever and vomiting. He had been born as a premature baby with a low birthweight of 1.8 kilograms. On review and inquiry of vaccination history he had never received any dose of any vaccine since birth. On hospitalization, a diagnosis of severe pneumonia was made and was commenced on intravenous ceftriaxone, high dose cotrimoxazole for possible for Pneumocystis jirovecii pneumonia and oxygen support via nasal prongs. Four days after enrolment, the HIV PCR came out positive and was enrolled into the study and randomized to valganciclovir. The baby also started antiretroviral therapy. All TB investigations came out negative. From time of hospitalization the participant was not able to be weaned off from oxygen support. On all attempts to do so observed peripheral oxygen saturations were noted to be less than 88%. An echocardiogram was performed to investigate

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					for possible congenital heart disease, this came out normal. Due to ongoing oxygen dependency and lack of improvement, on day 10 from admission, flucloxacillin was added to the antibiotic regimen to cover for staphylococcal lung infection. With ongoing lack of improvement on Day 14, a blood culture was performed; antibiotic upscale to intravenous Imipenem and a repeat chest x-ray was performed. The chest x-ray showed progression of infiltrates and consolidation bilaterally. The participant received a blood transfusion to optimize oxygenation. Due to ongoing increased effort of breathing and hypoxemia the participant was transferred to the high dependency unit in the morning to continue on bubble continuous positive airway pressure (CPAP) non-invasive ventilatory support but the same day he suffered two cardiorespiratory arrests and did not survive. Death was not considered to be related to the IMP.
20008-10	8 months	Tuberculosis	14 days	Standard of Care	A 7-month-old female infant was hospitalized at Kamuzu Central Hospital (KCH) with a history of cough, difficulty breathing, and passing loose stool. On hospitalization, diagnoses of acute gastroenteritis, severe malnutrition, and pneumonia were made. Standard of care antibiotics regimen for pneumonia of intravenous benzylpenicillin and gentamicin and therapeutic food with F-75 was commenced. 3 days after admission, the HIV test came out positive and the child was enrolled in the study and randomized to standard of care. The TB LAM came out positive +3, a diagnosis of TB was done and the baby started TB-T. Despite all the treatment, the participant did not recover and died due to tuberculosis 17 days after enrolment. Death was not considered to be related to the IMP.
20008-12	6 months	Severe pneumonia	59 days	eTB-T + Valganciclovir	This 7-month old participant was hospitalized at Kamuzu Central Hospital (KCH) with a diagnosis of pneumonia and enrolled into Empirical study 1 day after admission and randomized to TB-T + valganciclovir). He was discharged from this hospitalization at 4 days after enrollment. At day 48, the child was re-admitted to KCH with a history of coughing for 5 days and a day of difficulties in breathing. With diagnosis of pneumonia and Severe Acute Malnutrition. He was commenced on Benzylpenicillin and oxygen therapy and F75 feeds. At day 5 after admission, the participant was removed from

Record ID	Age	Cause	Time since enrolment	Arm	Description
					nasal prong oxygen support (day 6 of this hospitalization) due to lack of resolution of clinical features of pneumonia (chest indrawing and fast breathing for age) the intravenous antibiotics were switched from benzylpenicillin and gentamicin to ceftriaxone. At day 53, the mother reported that since commencing antiretrovirals (ART), the baby regularly vomits soon after taking a dose. The ART clinical care providers from KCH were consulted to assist in the challenge of ART intolerance that had been reported during this hospitalization. In the morning of day 56, worsening of the respiratory symptoms, a blood culture was done, intravenous antibiotics were switched from ceftriaxone to meropenem a nasogastric tube was inserted for rehydration. The blood culture came out negative at 48 hours. Full blood count had raised white cell count of 26,900/uL, normal haemoglobin of 10.6 g/dL and platelet count of 525,000/uL. In the afternoon of day 58, the participant was noted to have developed increased effort of breathing and fever. Due to worsened respiratory distress the participant was transferred to the children`s ward high dependency unit (HDU), commenced on high dose cotrimoxazole and prednisolone to cover for possible pneumocystis jirovecii pneumonia, commenced on continuous positive airway pressure (CPAP) non-invasive ventilation. At 4:40 hours of day 59, the participant had cardiorespiratory arrest. Death was not considered to be related to the IMP.
20008-14	3 months	Severe pneumonia	5 days	Valganciclovir	3-month-old male infant was hospitalized at Kamuzu Central Hospital (KCH) with a history of cough, difficulty breathing. On hospitalization, a diagnosis of severe pneumonia was made. Standard of care antibiotics regimen for pneumonia, Ceftriaxone was commenced. He was saturating at 72% on room air and was started on oxygen therapy. This is his second admission to the hospital as he was also admitted at a rural hospital for two weeks with the same illness, which was not resolving. There is no history of a known TB contact. COVID-19 nasal swab rapid test on date of hospitalization came out negative. HIV rapid test on the mother came out positive. She was not known to be HIV positive prior to this testing. Following this, HIV PCR test on the infant (study participant) came out positive from the same date. Screening procedures for

Record ID	Age	Cause	Time since enrolment	Arm	Description
					the EMPIRICAL study were performed after 4 days of admission, including the HIV PCR test and full blood count on the infant. Full blood count has white count of 2230/uL, Haemoglobin of 12.4 g/dL and platelet count of 598,000/uL. On the day 5 of admission the participant was enrolled into the EMPIRICAL study and randomized into the valganciclovir arm. As part of the EMPIRICAL study enrollment visit investigations, urine LAM assay was performed and result came out positive. Standard tuberculosis treatment was started at day 1 after enrolment. Nasopharyngeal aspirate, stool sample for gene TB Xpert ultra results were negative. Due to severe respiratory distress the child was transferred to children's ward high dependency unit (HDU) at day 4, where he was commenced on oxygen at a higher flow rate of 10 litres per minute to maintain oxygen saturation above 90%. On transfer to the HDU the intravenous antibiotic regimen was stepped up from ceftriaxone to meropenem. Due to a decreasing trend of oxygen saturation (down to 70%) at day 5, the participant was commenced on continuous positive airway pressure (CPAP) non-invasive ventilation, but unfortunately the participant had a respiratory arrest with peripheral oxygen saturation of down to 20% and bradycardia. Cardiopulmonary resuscitation (CPR) efforts were unsuccessful. The death was not related to the study medications or participation. It is attributed to immunosuppression from HIV infection. Death was not considered to be related to the IMP.
20008-16	5 months	Tuberculosis	10 days	eTB-T	4-month-old male infant was hospitalized at Kamuzu Central Hospital (KCH) with a history of cough, difficulty breathing and fever. On hospitalization, diagnoses of pneumonia was made and Standard of care antibiotics regimen for pneumonia of intravenous benzyl penicillin and gentamicin was commenced. There was no history of a known TB contact. COVID-19 nasal swab rapid test on date of hospitalization came out negative. HIV rapid test on the mother came out positive. She was not known to be HIV positive prior to this testing. Following this, HIV PCR test on the infant (study participant) was conducted and came out positive from the same date. At 2 days after admission, the participant was enrolled into the EMPIRICAL study and randomized into the TB-T arm. As part of the

Record ID	Age	Cause	Time since enrolment	Arm	Description
					EMPIRICAL study enrollment visit investigations, urine LAM assay was, the result came out positive. Nasopharyngeal aspirate and stool sample gene TB Xpert ultra results were negative. The respiratory condition worsened and participant died 10 days after enrolment. Death was not considered to be related to the IMP.
20008-18	3 months	Unknown	42 days	Standard of Care	A 2-month-old infant was admitted to the hospital with pneumonia. There was no history of contact with TB. A COVID-19 nasal swab rapid test on the day of admission yielded a negative result. The infant was known to be HIV-exposed and was diagnosed with HIV on the day after admission. The participant was enrolled in the EMPIRICAL study and randomly assigned to the standard of care arm on the following day. Despite being treated, the infant showed no signs of improvement and was clinically judged to have TB, which was confirmed later. TB-t began on day 6 after enrollment, but on day 17, the guardian left the ward without notice. The participant was traced three times, but the guardian refused to provide TB-T at home, opting instead for traditional medicine. Sadly, the child passed away at home on day 42. The death was not related to the study medication or participation.
20008-20	7 months	Severe pneumonia	3 days	eTB-T	Six months-old female child hospitalized (KCH) with an acute history of cough, fever and vomiting. On hospitalization, diagnoses of severe pneumonia and sever acute malnutrition were made and standard of care antibiotics regimen of intravenous benzyl penicillin and gentamicin were started. A nasogastric tube (NGT) was inserted for feeding and resomal challenge was administered for rehydration for the vomiting. The peripheral oxyhemoglobin saturation was 83% on room air and hence oxygen support via nasal prongs was commenced. She also had difficulties in breathing. Full blood count came out with a white cell count of 4, 200 /ul, hemoglobin of 8.1g/dl, neutrophils 2780/ul and platelet count of 152, 000/ul. The child was later transferred from resuscitation bay of the children's ward to high dependency unit (HDU) because the child developed signs of increased effort of breathing and antibiotics were scaled up from benzyl penicillin and gentamicin to intravenous ceftriaxone and cotrimoxazole and prednisolone to cover for pneumocystis

Record ID	Age	Cause	Time since enrolment	Arm	Description
					jirovecii pneumonia. At the third day of admission, the participant was enrolled into the EMPIRICAL study and randomized into the TB-T arm, urine LAM was negative, CD4 260 with 29.21 CD4 percentage, nasopharyngeal aspirate and stool Xpert MTB/RIF ultra-not detected. The child did not improve to the interventions and treatments administered and died 3 days after enrolment. Death was not considered to be related to the IMP.
20008-21	3 months	Severe pneumonia	1 days	Valganciclovir	Three months-old male child, was hospitalized at Kamuzu Central Hospital (KCH) with an acute history of cough, difficulty in breathing and vomiting. The mother did not know that she was HIV positive until this admission. On hospitalization, a diagnosis of severe pneumonia was made and standard of care antibiotics regimen of intravenous benzyl penicillin and gentamicin were started. His peripheral oxyhemoglobin saturation was 88% on room air and hence oxygen support via nasal prongs was commenced. On the second day of admission as part of routine HIV testing services at KCH, an HIV PCR test was done on the participant (child) and this came out positive. One day after, the antibiotics were scaled up from benzyl penicillin and gentamicin to intravenous ceftriaxone (at 80mg/kg per day) plus azithromycin. High dose cotrimoxazole (120mg/kg/day) and prednisolone to cover for pneumocystis jirovecii pneumonia was also commenced. The child was transferred from pneumonia bay to resuscitation bay of the children's ward, as was noted to have an increased work of breathing and a nasogastric tube was inserted for feeding. Then later he was transferred to high dependency unit (HDU) because the child developed signs of increased effort of breathing. The participant was enrolled into the EMPIRICAL study 2 days after admission. She was randomized into the valganciclovir arm with continuing standard of care antibiotics for severe pneumonia in an HIV infected infant. urine LAM was negative, Alt 24 U/L, AST 81 U/L Creatinine 0.24mg/dL CD4 225 with 8.75 CD4 percentage, nasopharyngeal aspirate and stool Xpert MTB/RIF ultra-not detected. The child did not improve to the interventions and treatments administered died 1 day after enrolment. Death was not considered to be related to the IMP.

Record ID	Age	Cause	Time since enrolment	Arm	Description
20008-21	3 months	Severe pneumonia	1 days	Valganciclovir	Three months-old male child, was hospitalized at Kamuzu Central Hospital (KCH) with an acute history of cough, difficulty in breathing and vomiting. The mother did not know that she was HIV positive until this admission. On hospitalization, a diagnosis of severe pneumonia was made and standard of care antibiotics regimen of intravenous benzyl penicillin and gentamicin were started. His peripheral oxyhemoglobin saturation was 88% on room air and hence oxygen support via nasal prongs was commenced. On the second day of admission as part of routine HIV testing services at KCH, an HIV PCR test was done on the participant (child) and this came out positive. One day after, the antibiotics were scaled up from benzyl penicillin and gentamicin to intravenous ceftriaxone (at 80mg/kg per day) plus azithromycin. High dose cotrimoxazole (120mg/kg/day) and prednisolone to cover for pneumocystis jirovecii pneumonia was also commenced. The child was transferred from pneumonia bay to resuscitation bay of the children's ward, as was noted to have an increased work of breathing and a nasogastric tube was inserted for feeding. Then later he was transferred to high dependency unit (HDU) because the child developed signs of increased effort of breathing. The participant was enrolled into the EMPIRICAL study 2 days after admission. She was randomized into the valganciclovir arm with continuing standard of care antibiotics for severe pneumonia in an HIV infected infant. urine LAM was negative, Alt 24 U/L, AST 81 U/L Creatinine 0.24mg/dL CD4 225 with 8.75 CD4 percentage, nasopharyngeal aspirate and stool Xpert MTB/RIF ultra-not detected. The child did not improve to the interventions and treatments administered died 1 day after enrolment. Death was not considered to be related to the IMP.
20008-24	2 months	Severe pneumonia	0 days	Valganciclovir	2-month-old female infant was hospitalized with severe pneumonia and critical condition and newly diagnosed with HIV, randomized to Valganciclovir. There was no history of a known Tuberculosis (TB) contact. COVID-19 nasal swab rapid test on date of hospitalization came out negative. The baby was transferred to PICU for better management and CPAP. The participant's condition continued deteriorated and finally died. The cause of death was considered

Record ID	Age	Cause	Time since enrolment	Arm	Description
					severe pneumonia and it was assessed as not related to the study medications or participation. The death was not considered related to the IMP.
20008-25	3 months	Tuberculosis	1 day	eTB-T	3-month-old male infant was hospitalized due to severe pneumonia and newly HIV participant, and was commenced on bubble CPAP. There was no history of a known Tuberculosis (TB) contact. He was randomized into the TB treatment. The TB LAM and Xpert were both positive. The day after enrolment, the participant kept on desaturating down to around 67% and having increased effort of breathing (grunting, very fast breathing) despite being on CPAP. Due to this, additional oxygen therapy via facial mask was added on top of the CPAP and the participant was transferred to high high-dependence unit and there the participant had cardiorespiratory arrest. Resuscitation was attempted including adrenaline but it was not successful and the baby died. chest compressions, bag-mask ventilation and adrenaline without return of cardiac output nor efforts of respiratory activity. The death was considered due to tuberculosis and not related to the IMP. The death was not considered related to the IMP.
20008-26	4 months	Tuberculosis	0 days	Standard of care	3-month-old male infant was hospitalized due to severe pneumonia, and was commenced on bubble CPAP. There was no history of a known Tuberculosis (TB) contact. She was randomized into the standard of care arm. The TB LAM was positive. The participant kept on desaturating down to around 76% and having increased effort of breathing despite being on CPAP and died. The death was considered due to tuberculosis and not related to the IMP.
20008-33	3 months	Tuberculosis	38 days	eTB-T+ Valganciclovir	Participant 3 months old newly diagnosed with HIIV randomized to TB-T + valganciclovir, TB LAM negative, Gen Xpert in NPA also negative and Stool for gene x pert MTB/Rif Ultra MTB Detected trace and RIF Indeterminate. Due to this, she was diagnosed with TB. However, after a few days of admission, the mother was discharged against medical advice but took the study medications. The patient was seen on day +15d and a grade 4 AST and the TB-T was stopped (686 U/L, x 17 upper normal limit). A

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					plan was made for monitoring the patient's clinical well-being and liver function tests until it was possible to re-challenge the antituberculosis medications but the mother refused this follow-up. On day +30, the child was seen and he didn't have new symptoms of illness and ALT was 103 U/L (no data on AST). However, two days later, the baby was admitted to the hospital due to severe respiratory distress and died with a diagnosis of severe pneumonia considered not related to the IMP nor elevated transaminases. The child died before resolution of this event.
20001-70	9 months	Severe pneumonia	2 days	eTB-T+ Valganciclovir	A 9-month-old female infant admitted with severe pneumonia and sepsis randomized to the TB-T + valganciclovir arm. She was clinically managed for those conditions and stayed admitted to the hospital for ~1 month. After being discharged and until visit 180 days, the child had multiple hospitalisations due to severe acute malnutrition (SAM) or fever of unknown origin and was again discharged, without recovery of SAM. One month after visit day +180, the child was admitted again due to a gastrointestinal haemorrhage in the context of sepsis and severe pneumonia. She was clinically managed in the hospital but finally died. The cause of death was attributed to sepsis and was not related to IMP.
20002-68	9 months	Unknown	321 days	Valganciclovir	A 9-month-old female infant was admitted with severe pneumonia and randomised to the valganciclovir arm. She was discharged 48h later in good clinical condition. She missed all consequent follow-up visit and ony came on day +180d. She was clinically fine with no unfavourable condition and no AEs. A few days before the visit+360d, the nurse telephoned the father to remind him about the day 360 visit. He informed us that the child had died 2 monts ago (10 months after enrollment). He referred that she had been well on the previous day, but the day of death, she woke up lethargic and not playing. On the way to hospital she died. The cause of death was unknown.
2007-182	3 months	Road car accident	241 days	eTB-T+ Valganciclovir	A 3-month-old male infant was admitted due to severe pneumonia and randomised to TB-T + valganciclovir. She stayed in the hospital for 5 weeks. After discharge, he came regularly to visits. He developed anemia and thrombocytopenia after completing valganciclovir treatment, and was not attributed to it. Four months after enrollment, he was admitted due to severe pneumonia and

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					marasmus and discharged again. After visit +180d, this child was taken by the grandmother to live with her in Inhambane. The child did not attend the scheduled ART visits, and the team had been attempting to contact her without success. No more clinical information is available since the visit +180). Once they managed to contact them, and the child was on ART according to the mother, doing well and agreed to bring the child for a control since the medication was ending. A few days later, the day +241 after enrolment, the child and grandmother had both unfortunately died in a car accident on the way to Maputo, as the mother informed the team. This death was not attributed to participation in the study.
2007-196	3 months	Unknown	342 days	eTB-T+ Valganciclovir	3-month-old female infant, randomised to TB+Val, started the treatment right away. During admission, the child showed improvement and was discharged one week later, starting ART as per guidelines. She did visit 30,60, and 90 days accordingly without any complications, but she passed by the hospital a month later for ART control and to request a transfer to a local hospital since she was moving to another place, and the team also decided to give her 2DFC to complete until V180. Unfortunately, she missed V180, and the team lost contact with her since she lost her phone. After many attempts, the team got in touch with the child's uncle, who was also living in another district. He sent a contact from a neighbour of the child's mother, with whom we could speak to the mother. She came to the hospital on day +234 for an unscheduled visit (during which CD4 and VL were also collected), and she told the team that the child had completed the TB treatment accordingly. The team scheduled the next visit +360d and continued to call the family for check-up. On day 335, the team talked to the mother, and she said that she (mother) was very sick and didn't have a way of taking the child to the hospital, but the child was fine. A few days later, the child's mother called the team to report the child's death the day before (day +342). She reported diarrhea in the last 4 days, but she couldn't take her to the hospital due to her physical condition. Unfortunately the team couldn't get more information regarding the death.
2007-198	5 months	Severe Pneumonia	145 days	eTB-T+ Valganciclovir	5-month-old male infant, randomised to TB+Val, started the treatment right away. During admission, the child showed improvement and

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Record ID	Age	Cause	Time since enrolment	Arm	Description
					was discharged a few days. He developed mild anaemia and neutropenia, probably related to valganciclovir, which soon resolved, and mildly elevated transaminases, probably related to TB-T, which did not require any action. He visited 30 and 60, accordingly, without any complications, but on day +90, she was admitted due to severe pneumonia, which was clinically managed in the hospital, improved and discharged. He was followed up as outpatient, some weeks after discharge, when he had symptoms of a common cold (cough and increased respiratory rate) with no signs of severity or fever, the parents were instructed to contact the team if the child worsened. This child had ART adherence issues, as demonstrated by the last two viral loads (v60 and v90), which showed levels exceeding 10,000,000 copies/mL. On day +145, the parents called us to say the child had a severe cough and difficulty breathing that started on the same day. They self-medicated with Chlorpheniramine and Salbutamol syrup at home but the child only got worse. The parents were instructed to take the child to a hospital where the child arrived gravely ill, with severe dyspnea, hypoxemia (SpO2 at 48% on room air), dehydrated, wheezing, and hyporeactive. FBC showed WBC of 37,130/µL, Hb of 7.9 g/dL and platelets of 115,000/µL. Gastric lavage was done through an NG tube with plenty of dark gastric content suggestive of traditional medication coming out with a little bit of blood. The child started treatment with Oxygen, IV Ceftriaxone, and Nebulized Salbutamol. A few hours later, the child had cardiorespiratory failure and died the same day. This death was attributed to Severe Pneumonia (or PCP) associated with advanced HIV disease and sepsis. MIA not available, death is not related to study participation.
2007-201	6 months	Unknown	71 days	eTB-T	6-month-old female infant, admitted with severe Pneumonia and was randomized to TB-T arm. All protocol samples were collected, TB Lam came back positive +2.GeneXperts came back negative. She started the treatment right away. During admission, the child showed improvement and was discharged a few days later. In V15, which came back with ALT of 170.08 UI/L (4.25xUNL) and AST of 408.94 (10xUNL), with the UNL being 40.00. The child had no signs of hepatitis (no jaundice), but has had hepatomegaly since recruitment. After discussing with the mother, it was confirmed

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Record ID	Age	Cause	Time since enrolment	Arm	Description
20008-35	2.5 months	Tuberculosis	151 days	eTB-T	that the mother had been giving traditional medication to the child since discharge. Some weeks later, the mother contacted the team to inform that the child started having bloody diarrhea and the child was admitted. Control biochemistry showed an ALT of 116,71 (2.9x UNL) and AST of 234,29 (5.85 xUNL). The child received a blood transfusion, and the control showed an ALT of 61,0 (1.5xUNL) and AST of 120,93 (3,02xUNL). Child was also on Fluconazole after admission, the team wanted to stop this medication, but due to this result, it was decided to maintain the treatment. After 12 days of admission, the child was discharged to continue the treatment ambulatory.This child was seen on v60 with Bronchopneumonia and severe malnutrition (marasmus) requiring admission. The mother refused admission and signed the physical consent that she accepts responsibility for denying admission (against medical advice). We discovered that the mother had abandoned all hospital treatment (PPJ, TBT and ART) and was giving traditional medication for at least one week. After trying to negotiate with the mom, she agreed to come for a control. The following days after v60, we attempted to contact the mother to see how the child was doing, but her phone was mostly offline or she did not answer our calls. The team was able to talk to the mother who informed us that she went to Gaza (another province of Mozambique) for traditional treatment and was not coming for the control at HCM. The team tried to convince the mother to come to the hospital but again with no success. On day 72, the team was finally able to contact a family member of the mother, who informed us that the child died the day before, and the mother was not available to talk. Unfortunately, no other information was shared. 2.5-month-old female infant, was hospitalized at Kamuzu Central Hospital (KCH) with a history of cough, fever, difficulty breathing and problems with feeding with peripheral oxygen saturation of 72% on room air and chest indrawing. She was clinically managed as severe pneumonia was made, and a standard of care antibiotics regimen of intravenous Ceftriaxone was started and put on bubble continuous positive airway pressure (CPAP) non-invasive ventilation. There was no history of a known Tuberculosis (TB) contact. HIV was confirmed 5 days after admission, other standard of care treatment for severe pneumonia in HIV patients was started and the patient was enrolled in

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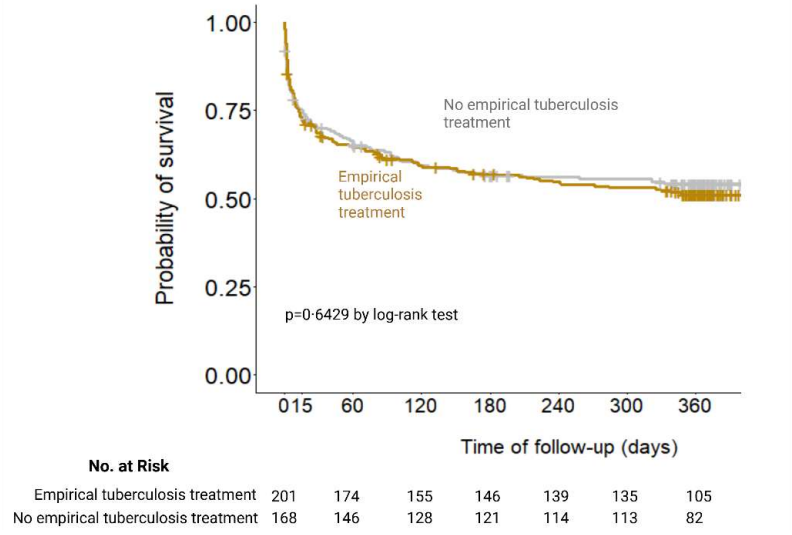
Record ID	Age	Cause	Time since enrolment	Arm	Description
					EMPIRICAL and randomised into the TB treatment arm (Arm B). As part of the EMPIRICAL study enrolment visit investigations, the urine lipoaribomannan (LAM) assay result was 2+ from the urine LAM 4+ full scale strip. Stool for gene x pert negative. HIV viral load was 3116480 and CD4 count was 189 cells. The child improved and was discharged one week later. After a visit of +15d, the study participant had missed follow-up study visits. Efforts were made to trace participant for study visits and continuity of study drugs (TB treatment). Such efforts have not been fully successful as the mother of the participant is in denial of the HIV infection diagnosis and is opting to resort for religious and prayer cure rather than medications. These efforts have involved contact and tracing via Baylor Centre of Excellence ART clinic, though not successful at the time. The participant was brought in dead to the hospital on day +151. The cause of death was considered tuberculosis, not related to participation in the study.

11.3. Figures

Figure S1 Post hoc analysis of all-cause mortality excluding participants in the non–eTB-T arms who initiated TB treatment after randomisation following a positive microbiological TB test



Kaplan–Meier estimates of survival among participants assigned to empirical TB treatment (eTB-T) and no empirical TB treatment. Participants in the non–eTB-T arms who initiated TB treatment after randomisation following a positive microbiological TB test (TB LAM or Xpert MTB/RIF Ultra performed on nasopharyngeal aspirate or stool samples) were excluded from this analysis. A total of 55 participants were excluded. Survival curves were compared using the log-rank test.

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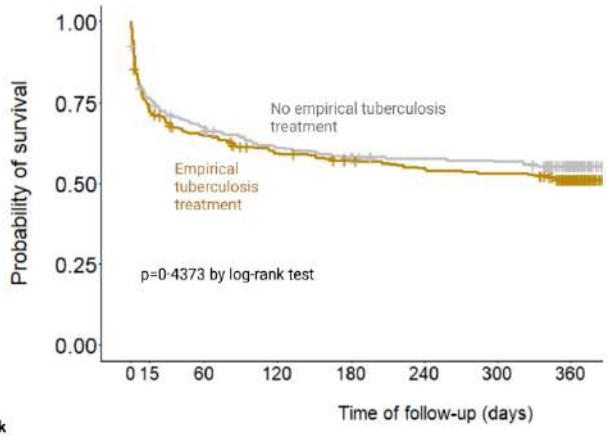
Figure S2 Post hoc analysis of all-cause mortality excluding participants in the non–eTB-T arms who initiated TB treatment after randomisation following a positive microbiological TB test or within the first 4 days after randomisation



No. at Risk								
Empirical tuberculosis treatment	276	201	174	155	146	139	133	105
No empirical tuberculosis treatment	244	185	161	143	135	128	123	90

Kaplan–Meier estimates of survival among participants assigned to empirical TB treatment (eTB-T) and no empirical TB treatment. A total of 55 participants in the non–eTB-T arms who initiated TB treatment after randomisation following a positive microbiological TB test (TB LAM or Xpert MTB/RIF Ultra performed on nasopharyngeal aspirate or stool samples), as well as 31 participants who initiated TB treatment within the first 4 days after randomisation, were excluded from this analysis. Survival curves were compared using the log-rank test.

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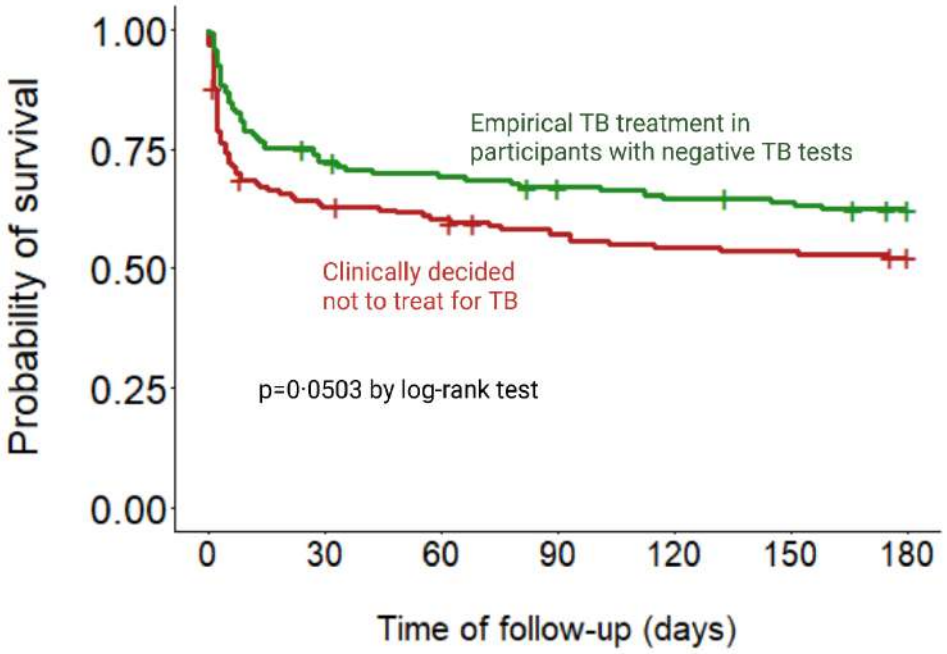
Figure S3: Post-hoc survival analysis comparing eTB-T among participants with negative baseline TB tests versus clinical decision not to treat for TB.



Clinically decided not to treat for TB								
At Risk	147	97	91	86	80	76	75	72
Censored	0	2	2	3	5	5	5	78
Events	5	49	54	58	62	66	67	69
Empirical TB treatment in participants with negative TB test								
At Risk	137	103	98	93	89	84	82	78
Censored	0	0	1	2	5	5	6	86
Events	1	34	38	42	45	48	49	51

TB, tuberculosis. The Figure compares participants who received eTB-T with those in whom a clinical decision was made not to treat for TB. Survival probabilities are shown over 180 days of follow-up. Tick marks indicate censoring. Group differences were assessed using the log-rank test.

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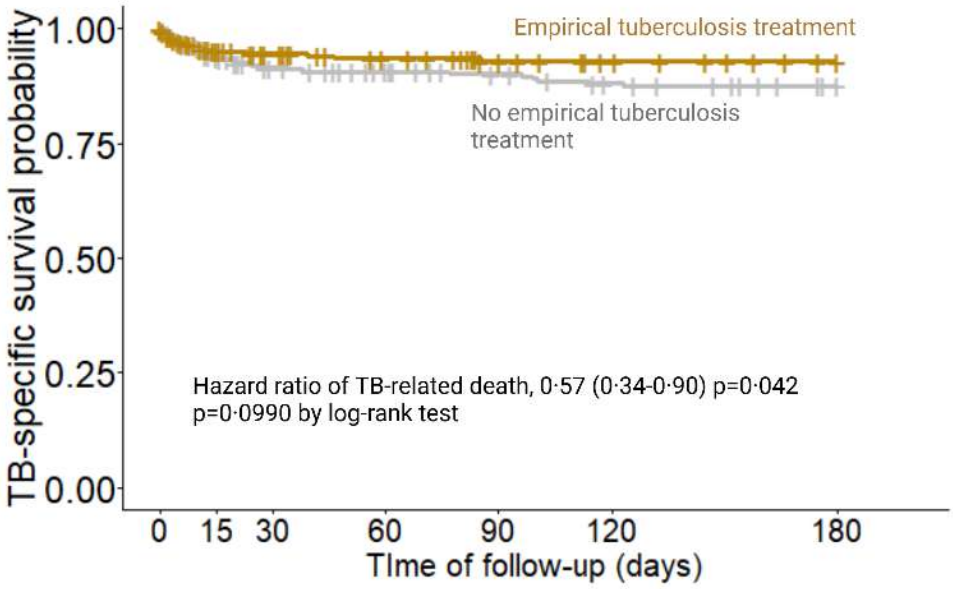
Figure S4 TB-specific mortality



No empirical tuberculosis treatment							
At Risk	282	214	199	189	179	170	160
Censored	0	52	62	70	79	84	253
Events	0	15	20	22	23	27	28
Empirical tuberculosis treatment							
At Risk	276	201	187	174	163	155	146
Censored	0	63	76	87	97	105	260
Events	0	12	13	15	16	16	16

TB-specific survival was estimated using a competing-risk framework. TB-related death was defined as TB being adjudicated by an independent expert panel as an underlying, immediate, or contributing cause of death, based on integration of prospectively collected antemortem clinical, laboratory, and sociodemographic data. Non–TB-related deaths were treated as competing events. Hazard was adjusted by baseline HIV-1 viral load, baseline CD4 percentage, baseline oxygen saturation, and country.

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Annex 1. Ethics Committee Aprovals

Name of the committee	Country	Last Renewal date	REFERENCE NUMBER
Joint Research Ethics Committee (JREC)	Zimbabwe	29 July 2024; 12 June 2025	JREC/169/19
Medical Research Council of Zimbabwe	Zimbabwe	25 January 2024; 17 March 2025	MRCZ/A/2511
Research Council of Zimbabwe	Zimbabwe	16 February 2024; 18 February 2025	No 05065; No 05396
Medicines Control Authority of Zimbabwe	Zimbabwe	09 June 2025	B/279/5/202/2025
Medicine Research and Ethics Committee	Uganda	25 June 2024	REC REF No. 2019-115
National Drug Authority	Uganda	13 February 2024	CTC 0119/2024
Biomedical Research Ethics Committee, University of Zambia	Zambia	30 July 2025	059-2019
Comité Nacional de Bioética para a Saúde (CNBS)	Mozambique	05 June 2024	Ref: 335/CNBS/24
National Health Sciences Research Committee (NHSRC)	Malawi	01 November 2024	AN 2654
Pharmacy and Medicines Regulatory Authority (PMRA)	Malawi Kamuzu	09 August 2024	III/12052021129 PMPB/CTRC/II-
College of Medicine Research and Ethics Committee (COMREC)	Malawi Lilongwe	14 August 2024	P.06/19/2712
UNC-CH Institutional Review Board (Biomedical IRB)	USA Kamuzu	22 July 2024; 06 March 2025	Study #: 21-0836 ID 475574

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