Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary material

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Supplementary Methods

(a) Further details of trial centres and participants

The REALITY (Reducing EArly mortaLITY) trial recruited adults and older children from Zimbabwe (University of Zimbabwe Clinical Research Centre, UZCRC), Uganda (Joint Clinical Research Centre sites in Mbarara, Mbale, Gulu and Fort Portal, overseen by Kampala), Malawi (Department/College of Medicine and Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre), and Kenya (KEMRI Wellcome Trust Research Programme and Academic Model for the Prevention and Treatment of HIV/AIDS (AMPATH) Centre at Moi Teaching Referral Hospital (MTRH)). UZCRC is a research centre in urban Harare, and recruited patients from city clinics providing ART and hospitals in the city. Other centres were research centres co-located with regional referral hospitals in provincial towns, and recruited patients from these hospitals and their associated ART clinics, and also from other local hospitals and ART programmes. Participants from these centres were therefore from peri-urban and rural locations.

In some centres, for some patients a pre-screening CD4 count was available for other ART programmes, clinics or the hospitals. Otherwise, patients who were admitted to hospital or with any symptoms were prioritised for screening in some centres. All participants had to provide consent to be screened as additional blood was taken. Therefore the number not eligible based on CD4 ≥100 cells.mm^3 in the CONSORT diagram (Figure 1) is of those who went through formal screening consent and completed a screening case record form.

(b) Further details of enhanced prophylaxis randomization

At the time the trial was designed (2012) and started (2013), isoniazid prophylaxis (isoniazid preventative therapy, IPT) had been demonstrated to have benefit in HIV-infected patients, but had been variably included in national guidelines and was rarely used within programmes even when national guidelines suggested it could be used. In Kenya, Uganda, and Zimbabwe guidelines recommended that isoniazid prophylaxis should be used with ART but did not specify when it should be started, and in Zimbabwe in particular guidelines said that it should be started if TB could be confidently excluded which was challenging in low-resourced settings. In Malawi, guidelines recommended that isoniazid prophylaxis should be taken before ART was initiated but should be stopped at ART initiation. Of note, in clinical practice, isoniazid prophylaxis was not being used on the ground in any of the countries participating in the trial when it started. There was also uncertainty around the timing of initiation of IPT and ART, potentially due to concerns about pill burden. For example, even current guidelines in Zimbabwe recommend that IPT should be initiated within 3 months of ART initiation and when there is reasonable certainty that the patient is free from active TB.

REALITY therefore took a pragmatic approach to addressing the question: "should isoniazid/pyridoxine be initiated at the same time as ART in highly immunocompromised patients starting ART or not", otherwise following national/local guidelines for use of isoniazid preventative therapy (IPT).

Therefore in centres in countries where isoniazid was recommended for participants on ART in the national programme, REALITY participants randomised to standard-of-care prophylaxis were prescribed isoniazid/pyridoxine prophylaxis from 12 weeks after initiating ART (Kenya, Uganda, Zimbabwe: Supplementary Figure 2). In centres in countries where isoniazid was not recommended for participants after starting ART, REALITY participants randomised to standard-of-care prophylaxis received co-trimoxazole alone (Malawi: Supplementary Figure 2). This ensured consistency between standard-of-care in the local centre and the standard-of-care randomised prophylaxis group. Where isoniazid prophylaxis was being taken as standard-of-care, REALITY participants were to take it continuously for the duration of

REALITY once started, unless national or local guidelines recommended a maximum duration (eg 24 weeks in Kenya and Zimbabwe).

When the trial started (2013), none of the national guidelines recommended primary fluconazole prophylaxis either with or without cryptococcal antigen testing.

In addition, the protocol specified a pragmatic approach in participants already taking prophylaxis **or treatment** at the screening visit, for example

- Those already receiving or needing tuberculosis treatment and/or courses of antibiotics for lung disease at randomization would continue or start these, respectively, regardless of randomised allocation. If randomised to enhanced prophylaxis they would receive additional fluconazole, azithromycin and albendazole from ART initiation. If their tuberculosis treatment stopped before 12 weeks in REALITY, they would continue with isoniazid prophylaxis from this timepoint. If their tuberculosis treatment stopped after 12 weeks in REALITY, they would receive isoniazid prophylaxis if standard-of-care in the local centre.
- Those already receiving fluconazole for secondary cryptococcal prophylaxis at randomization would continue to receive this throughout trial participation, regardless of randomised allocation. If randomised to enhanced prophylaxis they would receive additional isoniazid, azithromycin and albendazole from ART initiation, and would continue fluconazole after 12 weeks in REALITY.
- Those already receiving isoniazid prophylaxis, for example due to tuberculosis case contacts (elicited at screening), would continue it regardless of randomised allocation. If randomised to enhanced prophylaxis they would receive additional fluconazole, azithromycin and albendazole from ART initiation.

In summary, patients already receiving treatment or prophylaxis for tuberculosis or cryptococcal disease, or azithromycin for treatment of sepsis, could be enrolled, but would continue their pre-existing treatment/prophylaxis, and only receive other prophylaxis according to randomization. Furthermore, any patient who became eligible for immediate isoniazid prophylaxis after trial recruitment, for example, if another household contact was diagnosed with tuberculosis, was to start it immediately and not wait until 12 weeks post-randomization.

Following national guidelines, all children received routine de-worming at 24 and 48 weeks post-enrolment irrespective of randomization.

The enhanced-prophylaxis intervention included fluconazole, and therefore the protocol included pregnancy (or intention to become pregnant within the first 12 weeks in the trial) as an exclusion criteria. At the time the protocol was submitted for ethical approval (2012) there were significant concerns that fluconazole could be associated with higher risks of spontaneous abortion and stillbirth. Increased risk of spontaneous abortion with lower doses of fluconazole used to treat candidiasis has recently been demonstrated[1], with non-significantly increased risk of stillbirth. An earlier study[2] suggesting no evidence of increased risk of birth defects was not published when the protocol was submitted. As REALITY tested additional interventions given as well as standard ART, it was judged that the potential risks from fluconazole outweighed the potential benefits, and therefore that pregnant women should not be included.

(c) Antiretroviral therapy and raltegravir dosing

National HIV treatment guidelines from all countries recruiting patients into the trial followed WHO recommendations to initiate ART with 2NRTI+NNRTI. Adults initiated tenofovir-disoproxil-fumarate+emtricitabine or zidovudine+lamivudine, with nevirapine or efavirenz, according to physician choice and local standard-of-care. Children initiated

abacavir+lamivudine or zidovudine+lamivudine, with nevirapine or efavirenz, following WHO dose recommendations.

Adults received 400mg raltegravir twice-daily. Adolescents aged 12-18 years and children aged 6-11 years weighing ≥25kg received the standard adult dose of raltegravir (400mg film-coated tablet twice-daily). Children 5-11 years could also receive 6 mg/kg twice-daily of a chewable tablet which could be divided into equal halves. The chewable tablet and the film-coated tablet formulations are not bioequivalent. Children weighing 10 to <14kg received 0.5 chewable tablets am and 1 pm; 14 to <20kg 1 chewable tablets am and pm; 20 to <28kg 1.5 chewable tablets am and pm; 28 to <40kg 2 chewable tablets am and pm; and 40+kg 3 chewable tablets am and pm.

(d) Further details of Ready-to-use Supplementary Food (RUSF) randomization
The RUSF intervention was a lipid-based paste made with maize-soya-sorghum aiming to provide an additional 1000 kCal daily in adults and adolescents (2 x 92g foil packets daily), and an additional 500 kCal daily in children (1 x 92g foil packet daily), and was purchased from Valid International. It was fortified with multi-vitamins and multi-minerals (approx 1xRecommended Daily Allowance (RDA)), so that centres which provided these routinely to children did not provide additional multivitamin tablets for the 12 weeks in which trial RUSF was used.

Standard-of-care nutritional support followed current local practice in each centre, based on criteria for body mass index (BMI) and/or mid-upper arm circumference (MUAC) and/or availability of supplements at the time of randomization. Adults and children with mild-moderate malnutrition did not receive any nutritional support following national guidelines at the time the trial was recruiting, except in Kilifi where those with BMI<18.5 received Plumpy Soy or Acha Mum (2 sachets daily). Management of adults with severe malnutrition initiating ART varied across centres: most were provided with micronutrients and advice on food. Additional Ready to Use Therapeutic Food (RUTF) (different multi-vitamin and multi-mineral content to RUSF) was provided to severely malnourished adults with BMI<16-18 or MUAC<16cm in some centres when it was available locally. Any adult, adolescent or child requiring therapeutic feeding according to standard-of-care received this regardless of randomization (estimated <5%). Participants eligible for or receiving food products from national programmes transitioned onto the study product when they finished it if randomised to the enhanced nutritional support and still <12 weeks from randomization.

(e) WHO-based symptom checklist for tuberculosis
At the screening visit, structured questions elicited the presence of current cough (>14 days), fever, night sweats, weight loss/poor weight gain, and recent contact with a TB case. Any patients reporting cough, fever or night sweats were investigated further following national guidelines.

(f) Further details of endpoint ascertainment
SAEs were defined following the International Committee for Harmonization as events which led to death, were life-threatening, caused or prolonged hospitalisation (excluding elective procedures), caused permanent disability, or were other medical conditions or with a real, not hypothetical risk of one of the previous categories.

Clinical narratives used by the Endpoint Review Committee (ERC) to adjudicate endpoints were written by the treating physician and reviewed by the centre Principal Investigator before submission to the coordinating centre. There the Trial Manager and/or Data Manager

reviewed all the clinical narratives to ensure that no information relating to trial drugs had been inadvertently included, before passing them to the blinded ERC for review.

HIV-1 RNA VL was assayed blinded to randomization using the Roche COBAS Ampliprep/Taqman v2.0 in Uganda (Joint Clinical Research Centre (JCRC)), the NucliSENS EasyQ HIV-1 v2.0 in Zimbabwe (UZ-CRC, samples run at the Flow Cytometry Centre, Harare) and the Abbott m2000sp/rt 0.6mls protocol in Kenya (samples from AMPATH, Eldoret and KEMRI, Kilifi) and Blantyre (samples run at John Hopkins Research Project Laboratory, Malawi), with lower limit of detection of 20-50 copies/ml.

Bioimpedance analysis was measured using a TANITA BC-420MA machine.

(g) Sample size calculation from the trial protocol

The trial was powered to detect main effects of each of the three interventions. 1800 adults and children provided at least 80% power to detect a 50% relative reduction in 24 week all-cause mortality from 7% to 3.5%, or a 60% relative reduction from a lower mortality of 5% to 2% (two-sided alpha=0.05) allowing 5% lost to follow-up by 24 weeks, and incorporating a single inflation factor[3] to allow for the factorial design (rates in groups receiving multiple interventions would be lower than those in any single group if more than one intervention is effective) and 5% lost to follow-up at 48 weeks. The sample size calculation assumed that at least one of the three interventions tested would be ineffective and not therefore impact sample size, and therefore only a single inflation factor was used. For 90% power, the detectable reductions were 7% to 3% and 6% to 2.2% respectively. If ~10% of patients were already receiving isoniazid/fluconazole prophylaxis or ready-to-use therapeutic food at randomization, the study design retained >80% power to detect slightly larger reductions from 7% to 3% (57% reduction). Randomising 400 children provided at least 80% power to detect a 0.29 greater absolute increase in weight-for-age from 0 to 24 weeks with any intervention, based on other assumptions above.

Each intervention targeted a different mechanism of action (anti-HIV, anti-infection, anti-malnutrition/malabsorption), so, a priori, important interactions - the effect of one intervention varying substantially according to receipt or not of a second intervention – were considered less likely. Any interactions that could exist were considered more likely to be quantitative (slightly smaller/larger effects) rather than qualitative (effect on one background, no effect on another). The most plausible possible quantitative interactions identified were:

(1) that enhanced-prophylaxis itself could improve appetite and thus weight gain as much as the provision of trial RUSF through the prevention of oral/oesophageal candidiasis, TB and treatment of worms. However, it was not clear whether such patients would have access to additional calories without trial RUSF, and whether such an effect would impact mortality was unknown.

(2) that greater antiretroviral efficacy and also greater potential for side-effects of nevirapine would occur with enhanced-prophylaxis because fluconazole may increase nevirapine levels (at least at treatment doses). However, it was not known whether this would occur at the much lower dose of 100mg used for prophylaxis, and whether this could impact mortality was unknown).

There were no other drug-drug interactions identified between the study interventions.

(h) Statistical methods

Time-to-event analyses measured time from randomization, censored at the last clinical follow-up if the outcome had not occurred. The primary analyses stratified for randomization stratification factors (stratified logrank test and stratified Cox regression); results from secondary unstratified analyses were very similar (data not shown). Lost-to-follow-up was

defined as not being seen in the clinic for more than 3 months (91 days). There was no adjustment for multiple secondary outcomes.

Analyses of causes of death, and all time-to-event outcomes which did not include all-cause mortality, used competing risks methods. These estimated the probability of the event (analogous to Kaplan-Meier) using cumulative incidence functions, and estimated the effect of randomised group on the subdistribution hazard corresponding to the cumulative incidence function[4]. These analyses were conducted unstratified, as stratification is not possible with the estimating equation approach used for estimation. All endpoints based on new disease occurrences (e.g. time to new tuberculosis disease) included events identified as cause of death by the Endpoint Review Committee if these had not already been reported as new disease events before death. To identify grade 4 AEs either definitely/probably or definitely/probably/possibly related to any prophylaxis drugs, the Endpoint Review Committee were asked to adjudicate a relationship to all possible study interventional drugs (fluconazole, isoniazid, albendazole, azithromycin and pyridoxine) to avoid providing them with details of interventional drugs actually received which would unblind them. The Endpoint Review Committee were also asked to adjudicate a relationship to co-trimoxazole (dapsone where co-trimoxazole contraindicated) (the Endpoint Review Committee were not blinded to these non-interventional drugs). An unblinded clinical reviewer reviewed the grade 4 laboratory only (no clinical event associated) events for relatedness to drugs actually received. In analysis, grade 4 AEs related to fluconazole, isoniazid, albendazole, azithromycin, pyridoxine and cotrimoxazole were defined as those related to any of these drugs received within 30 days prior to the event.

CD4, weight and BMI were compared between randomized groups over time using generalized estimating equations (GEE) (independent correlation structure) with randomized group, adjusting for stratification factors and scheduled visit week as categorical independent variables. The closest measurement to each scheduled visit date within equally spaced windows was used as the measurement at each scheduled visit. Continuous measurements were modeled using change from baseline as the outcome in a normal GEE model. Adherence measures were modeled as dichotomous outcomes in a binomial GEE model. Baseline values were those nearest to but before and within 42 days of randomization.

(i) Death rate

To estimate a continuously varying death rate (hazard) we used flexible parametric models based on the standard Weibull model[5,6]. The underlying model has monotonic (ie always increasing or always decreasing) hazard, but the flexible parametric models introduce additional terms in the hazard linearization (via natural cubic splines) which allow the death rate to increase and then decrease or vice versa. The Akaike Information Criterion (AIC) was used to identify the number of interior knots for the natural cubic splines (between 0 and 4)[6]. AIC-based selection of the underlying model was performed adjusted for randomised group as an explanatory factor, then also allowing the variation in death rates over time to differ according to group (AIC used to identify number of interior knots for natural cubic splines for any departures from the baseline hazard (between 1 and number of interior knots identified for baseline hazard)). This analysis was not stratified for randomization stratification factors. The best fitting model according to AIC was with 2 interior knots at the 33rd and 67th percentiles of the uncensored survival times, plus 2 boundary knots at their minimum and maximum, and randomised group included as an explanatory variable only (i.e. proportional effect of randomized group on the hazard throughout follow-up). The same modelling strategy was used to identify the best flexible parametric model to describe the cause-specific risk of death from unascertained causes and cryptococcus. For unascertained causes, the best fitting model according to AIC was with 1 interior knot at the 50th percentile of the uncensored survival times, plus 2 boundary knots at their minimum and maximum, and randomised group included as an explanatory variable only. For cryptococcus, the best fitting model was with 1

interior knot at the 50th percentile, 2 boundary knots, and randomized group included as an explanatory variable only.

(j) Subgroup analyses

We pre-specified in the protocol ten subgroup analyses for the primary endpoint by the other factorial randomizations and stratification factors (age </≥13 years, centre), and also by country, baseline CD4 (0-24, 25-49, 50-99 cells/mm^3), initial backbone NRTI, initial NNRTI, Tuberculin Skin Test (TST) status (positive vs negative), and BMI<20 (adults) or weight-for-age<-1 (children). TST was not performed and therefore this subgroup analysis was not done, leaving nine pre-planned subgroup analyses.

We also conducted nine additional exploratory subgroup analyses for the primary endpoint by country, sex, age group (5-17, 18-29, 30-39, 40+ years; or pooling 18+ to maximise power to detect differences between adults and adolescents/children), VL (<100,000, 100,000-999,999, ≥1,000,000 copies/ml), white cell count (0-<3, 3-<4, ≥4 $x10^9$/L), neutrophil count (0-<1, 1-<2, ≥2 $x10^9$/L), WHO stage, and whether isoniazid or fluconazole was prescribed at randomization as treatment (rather than prophylaxis within the intervention).

Subgroup analyses were conducted to assess consistency of effects across different patient characteristics. The primary method of assessing interactions was an interaction test within a Cox proportional hazards regression. For the continuous factors (baseline CD4, $\log_{10}$(VL), white cell count and neutrophils) we used both categorization and natural cubic splines (five knots at the 10^{th}, 25^{th}, 50^{th}, 75^{th}, and 90^{th} centiles) to test for interactions. Subgroup analyses were conducted unstratified to avoid losing information from small strata with no events in one randomised group. No formal adjustment for multiple testing was made for subgroup analyses.

(k) Economic analyses

Health was measured using quality-adjusted life-years (QALYs), a generic health outcome measure which captures both survival duration and health-related quality-of-life (HRQoL) reflected as weights between 1 (good health) and 0 (death).

Supplementary Results

1791(99.2%) patients initiated ART on the day of randomization: delays of up to 15 days in the remainder were predominantly due to initiation of tuberculosis treatment. 894(98.7%) of the 906 patients randomised to enhanced-prophylaxis initiated all components of it on the day of randomization. At randomization, 271(15.0%) participants had active tuberculosis and continued or initiated full anti-tuberculosis therapy. 25(1.4%) participants had active cryptococcus and continued or initiated full anti-cryptococcal therapy.

12664/12944 (97.8%) scheduled visits before death/loss-to-follow-up were completed.

Use of antibiotics other than azithromycin prophylaxis in the enhanced-prophylaxis group and cotrimoxazole/dapsone prophylaxis in both groups was greatest in the first 12 weeks after ART initiation (Supplementary Figure 1c) but was similar between groups (2.9% and 3.1% person-time in the trial through 12 weeks in the enhanced-prophylaxis and standard-prophylaxis groups respectively; compared to 0.7% and 0.9% respectively from 12-48 weeks).

Acceptability of prophylaxis was similar between the enhanced-prophylaxis and standard-prophylaxis groups (Supplementary Figure 3b/c), with, for example, 98.3% versus 98.6% reporting that taking prophylaxis drugs did not interfere with their everyday life much or at all between weeks 8-12; and 97.9% versus 97.3% reporting prophylaxis drugs as easy, or neither easy nor difficult, to take.

Of the 42 tuberculosis-related deaths, 13 (6 enhanced-prophylaxis, 7 standard-prophylaxis) had active tuberculosis disease at enrolment and 29 (14 enhanced-prophylaxis, 15 standard-prophylaxis) did not. Of the 17 deaths from cryptococcus, 1 (standard-prophylaxis) had active cryptococcus disease at baseline and 16 (4 enhanced-prophylaxis versus 12 standard-prophylaxis) did not. Rates of death from cryptococcus (Supplementary Figure 4c) showed similar patterns to all-cause mortality, with greatest risk in the standard-prophylaxis group between 1-4 weeks, but risk remaining elevated through at least 8 weeks. Only 9/225 (4%) deaths were adjudicated to have probable/definite relationships to ART or prophylaxis drugs (2 enhanced-prophylaxis versus 7 standard prophylaxis; Supplementary Table 1). In the first 24 weeks, deaths were greatest from TB, other causes and unknown causes, with differences predominantly in unknown deaths (Table S1b). 188 of the 225 deaths were in the first 24 weeks. After 24 weeks, deaths were more commonly from unknown causes and severe bacterial infections. Median (IQR) last CD4 before death was 36 (18-69) cells/mm^3 for deaths from 0-24 weeks vs 65 (39-115) cells/mm^3 for deaths from 24-48 weeks (p=0.002). 43/184 (23.4%) deaths in the first 24 weeks had last VL<50 copies/ml, vs 15/36 (41.7%) subsequently (p=0.04) (remainder did not have any VL available). Of the 15 deaths after week 24 with last VL<50 copies/ml, 7 still had CD4 <100 cells/mm^3, and 6 CD4 100-200 cells/mm^3.

There was no evidence that mortality benefits depended on pre-ART VL (p=0.35/0.18 using categorical/continuous interactions), white cell count (p=0.67/0.71) or neutrophil count (p=0.33/0.78). Two adolescents and one child aged 6 years died (1 standard-prophylaxis, 2 enhanced prophylaxis, interaction p=0.47). All remaining deaths occurred in adults.

Enhanced-prophylaxis significantly reduced ERC-adjudicated IRIS-compatible events (p=0.001). TB IRIS events occurred in 38/906 (4.2%) enhanced-prophylaxis versus 69/899 (7.7%) standard-prophylaxis (p=0.002 Fisher's exact test). Cryptococcal IRIS events occurred in 10 (1.1%) versus 21 (2.3%) (p=0.047) and other IRIS events of known aetiology in 17 (1.9%) versus 14 (1.6%) (p=0.72) (IRIS events of unknown aetiology occurred in six patients).

Six enhanced-prophylaxis patients developed cryptococcal disease after 12 weeks (range 13.6-24 weeks post ART initiation). Their last prior CD4 was median 72, range 23-95 cells/mm^3; all 6 patients had last VL <50 copies/ml.

Bioimpedance analysis demonstrated that the trend towards greater weight gain associated with enhanced-prophylaxis was due to greater increases in fat (global p=0.007 for change in fat mass (kg) vs p=0.97 for change in muscle mass (kg), Supplementary Figure 6a, 6b). Basal metabolic rate decreased significantly in both randomized groups at week 4, but there was no evidence of difference between randomized groups at this timepoint (p=0.38) or overall (global p=0.70, Supplementary Figure 6c).

Figure S1 Isoniazid, fluconazole and antibiotics received over time

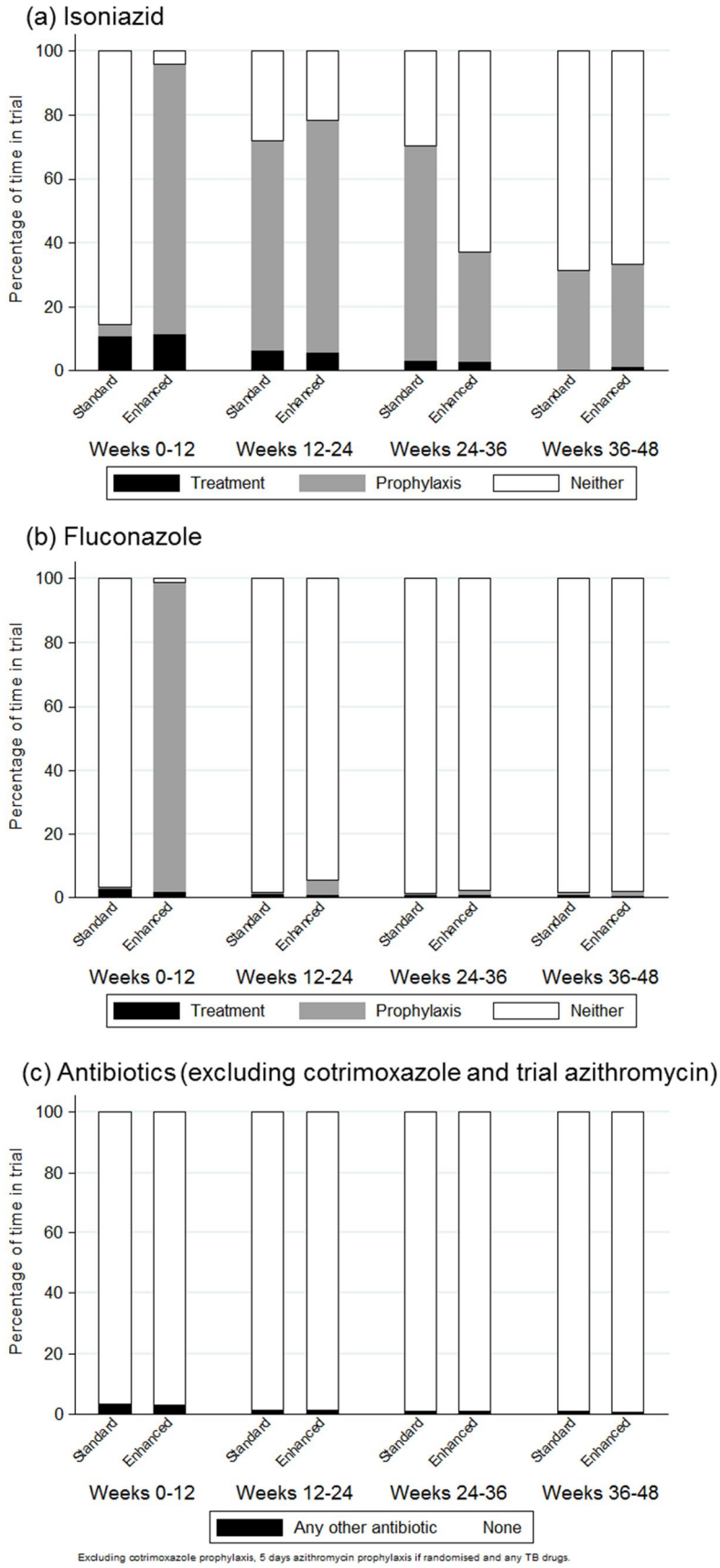


Figure S2 Isoniazid received over time by country/

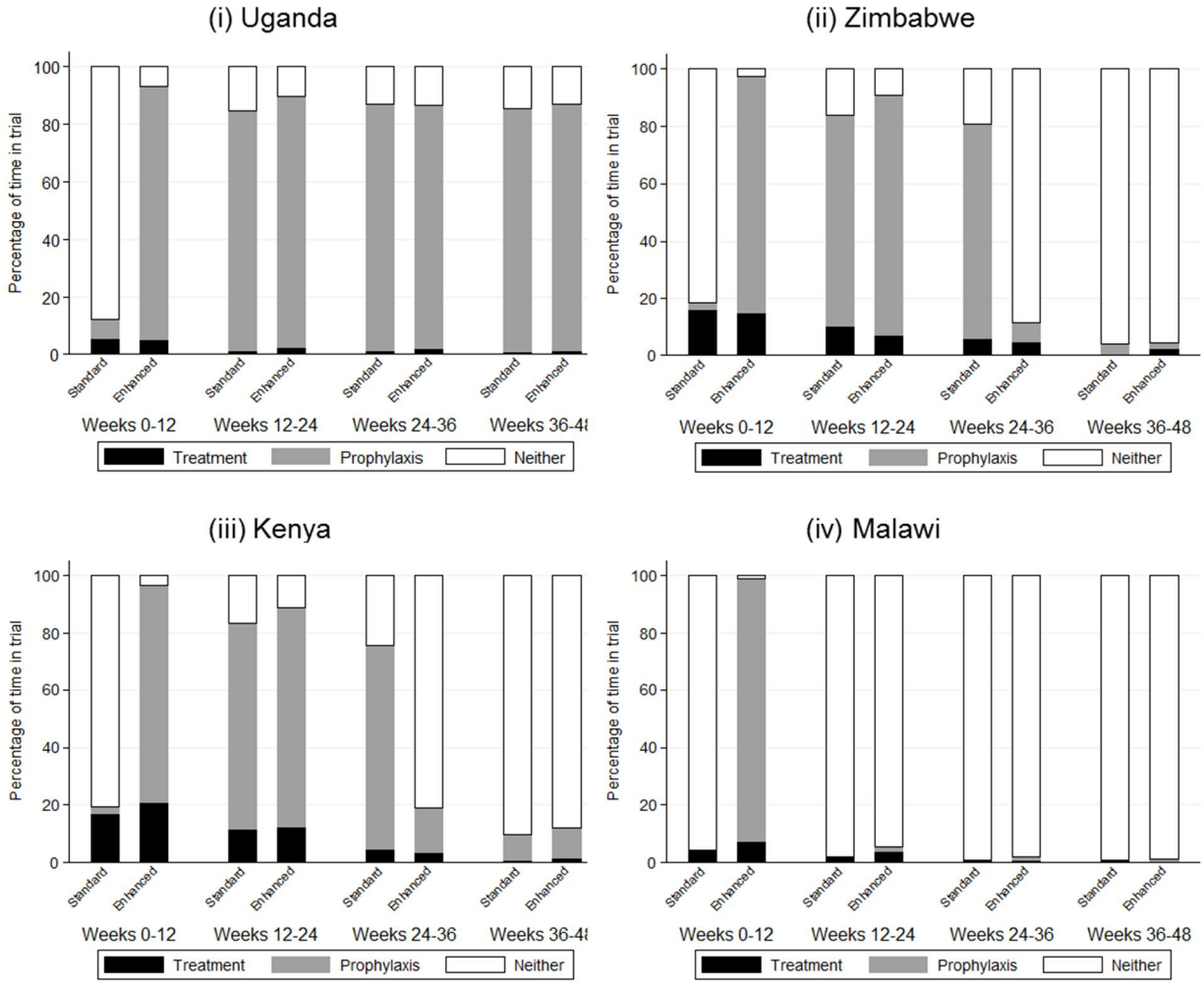
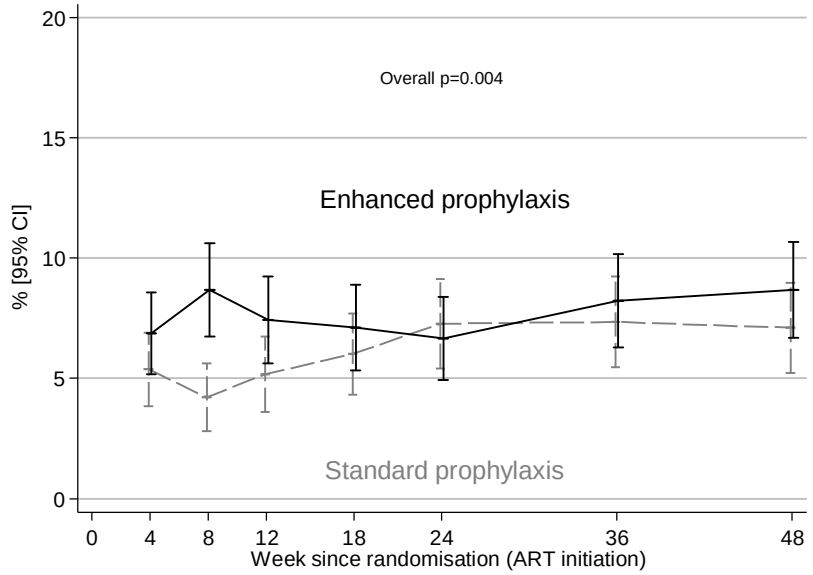


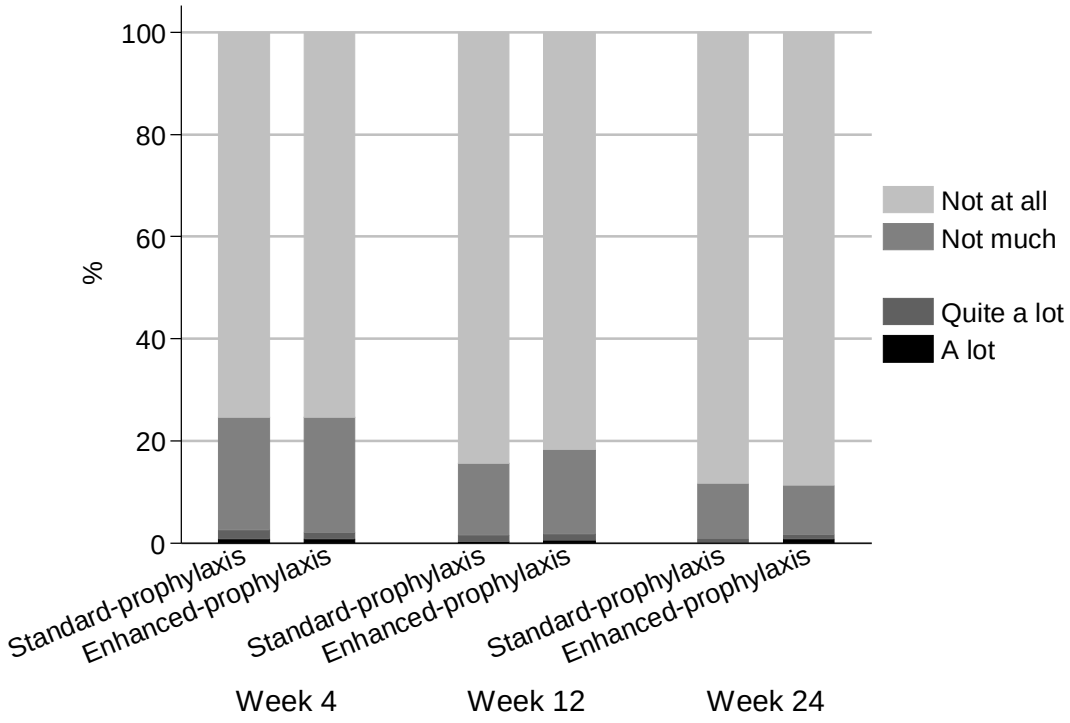
Figure S3 Self-reported adherence and acceptability

(a) percentage reporting missing doses of any of the prophylaxis drugs (including co-trimoxazole) in the last 4 weeks

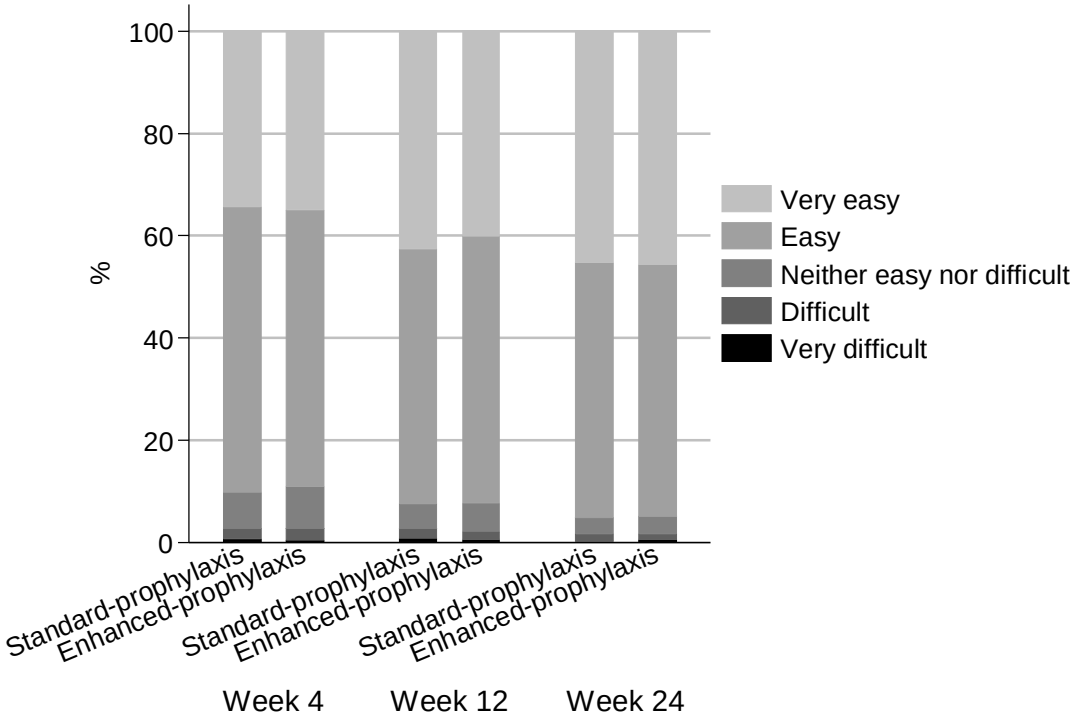


Percentage							
Enhanced	6.9%	8.7%	7.4%	7.1%	6.7%	8.2%	8.7%
Standard	5.4%	4.2%	5.2%	6.0%	7.3%	7.3%	7.1%
p	*0.18*	*0.0002*	*0.047*	*0.44*	*0.71*	*0.48*	*0.19*

(b) acceptability of prophylaxis drugs: how much does taking prophylaxis drugs interfere with your everyday life?



(c) acceptability of prophylaxis drugs: how easy do you find it to take prophylaxis drugs every day?



(d) percentage reporting missing doses of any ART drugs in the last 4 weeks

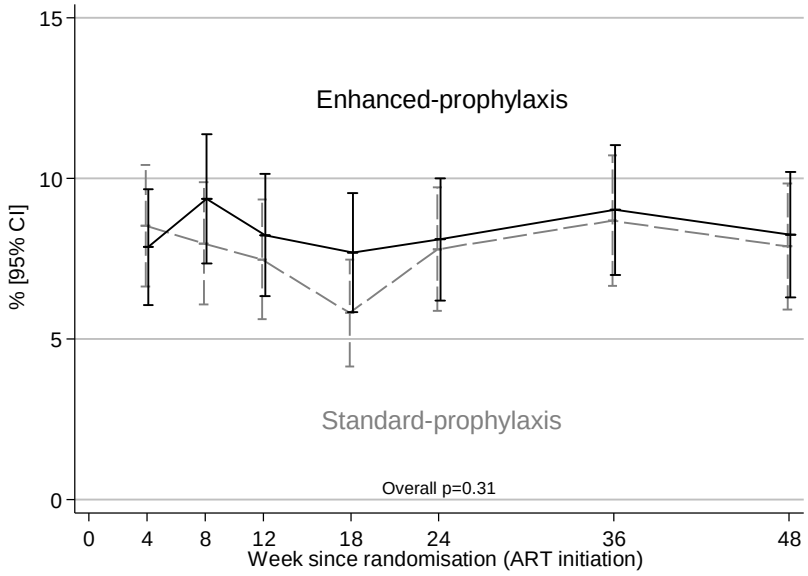
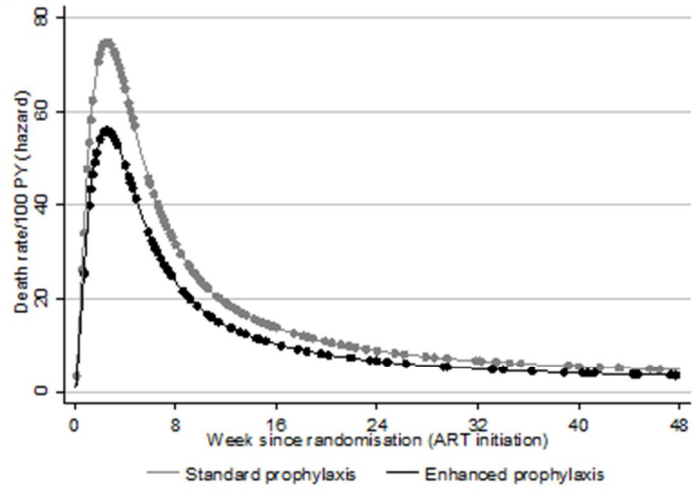
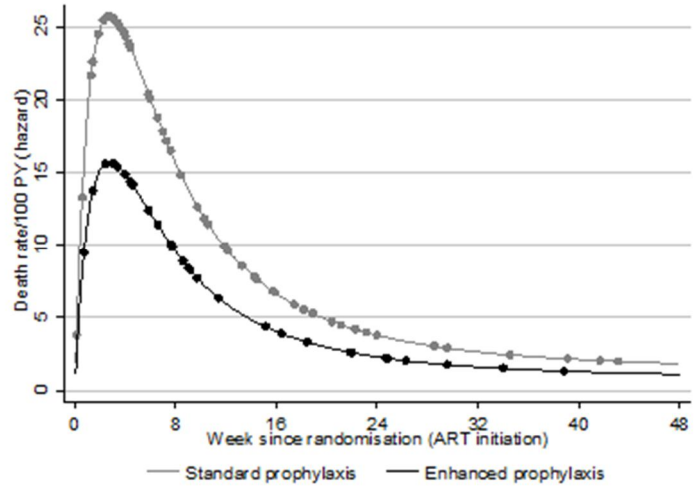


Figure S4 Mortality rates over time from ART initiation

(a) All-cause



(b) Of unknown cause



(c) From cryptococcus

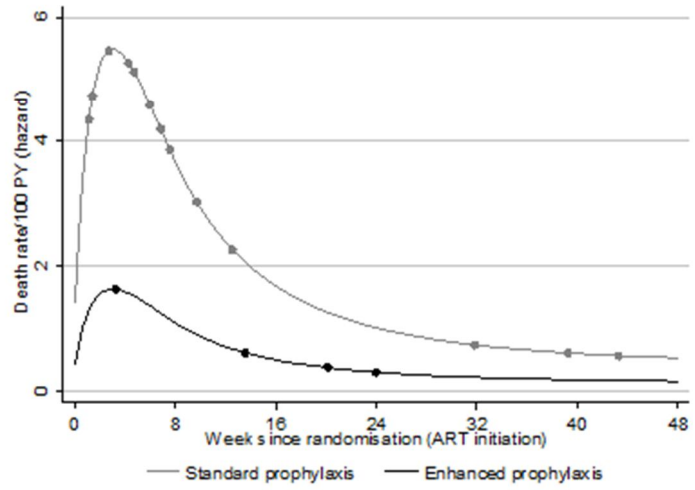
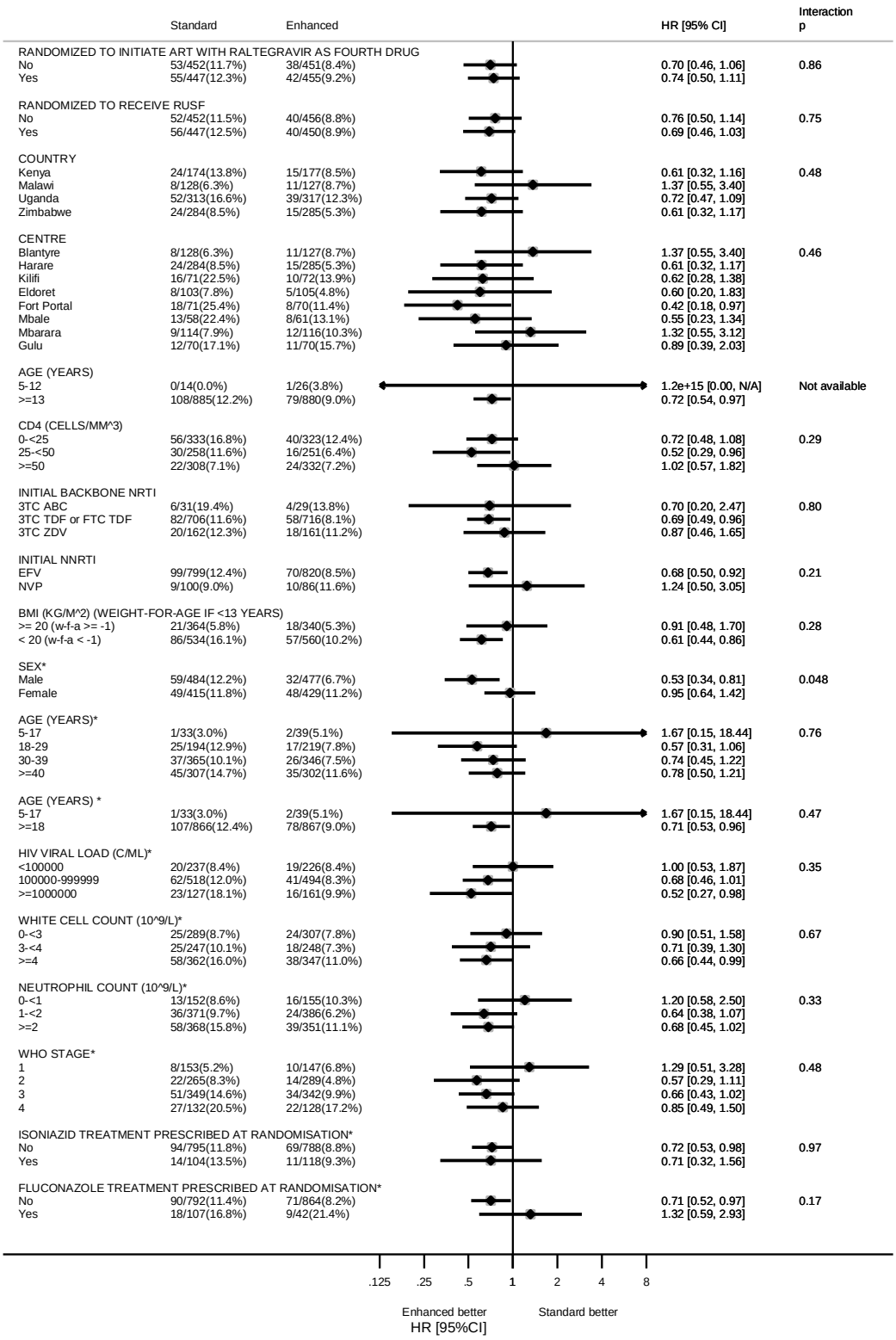
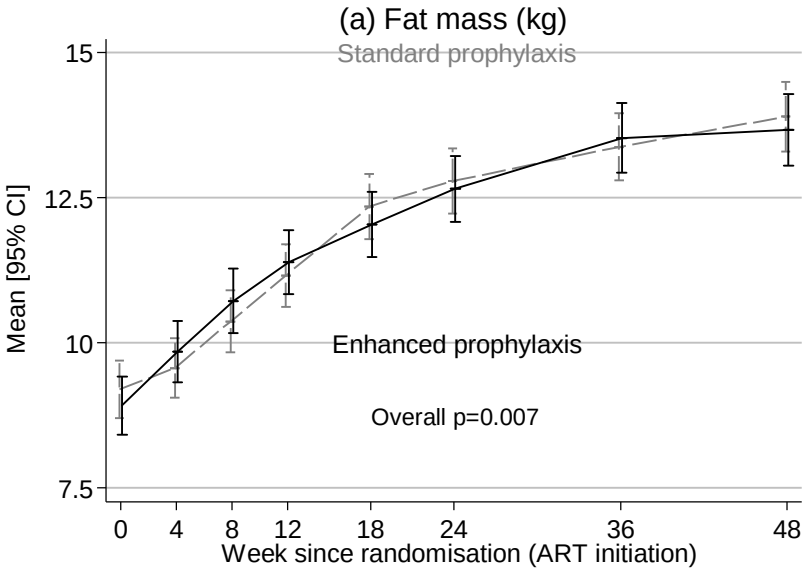


Figure S5 Subgroup analyses for mortality through 24 weeks (primary endpoint)

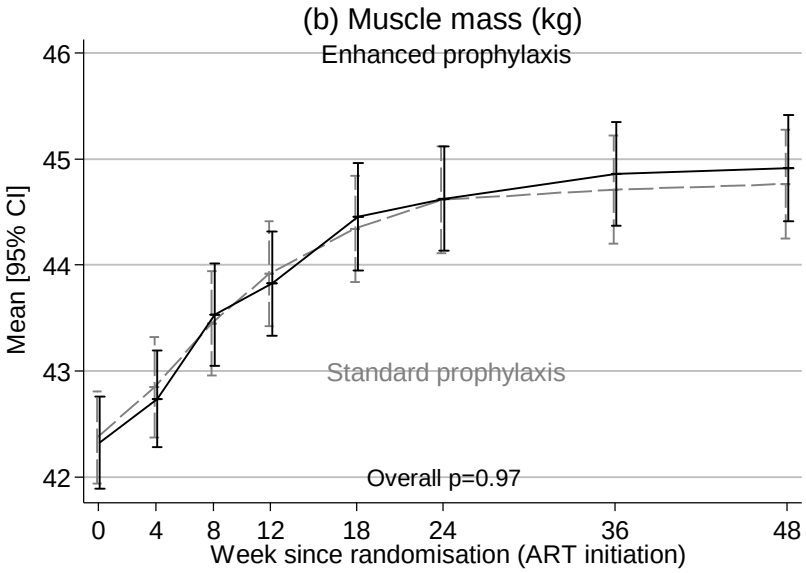


* exploratory analysis

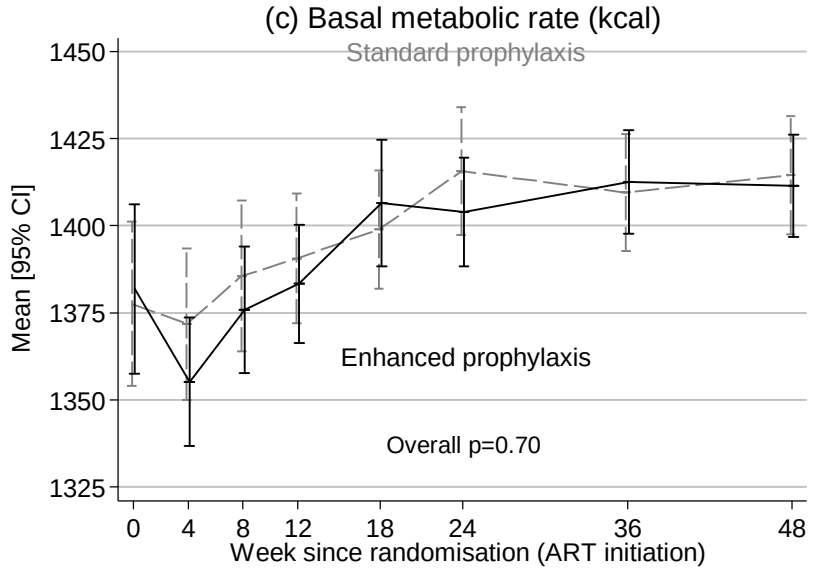
Figure S6 Body parameters



Mean change from baseline							
Enhanced	+0.7	+1.6	+2.2	+2.8	+3,5	+4.3	+4.5
Standard	+0.3	+0.9	+1.8	+2.8	+3.2	+3.8	+4.2
p	*0.0002*	*<0.0001*	*0.004*	*0.58*	*0.08*	*0.04*	*0.24*



Mean change from baseline							
Enhanced	+0.3	+1.0	+1.2	+1.8	+2.0	_+2.2	+2.2
Standard	+0.3	+1.0	_+1.4	+1.7	+2.0	_+2.1	+2.2
p	*0.79*	*0.79*	*0.17*	*0.34*	*0.96*	*0.63*	*0.85*



Mean change from baseline							
Enhanced	-58.8	-32.8	-25.9	-3.9	-4.6	+2.1	+2.3
Standard	-42.9	-29.6	-18.8	-5.4	+2.2	+6.7	+12.6
p	*0.38*	*0.88*	*0.70*	*0.96*	*0.70*	*0.80*	*0.56*

Note: p-values compare change from baseline across randomised groups

Table S1 Characteristics at enrolment (full table)
*

Factor	Standard Px (N=899)	Enhanced Px (N=906)	All (N=1805)
Country			
Kenya	174 (19.4%)	177 (19.5%)	351 (19.4%)
Malawi	128 (14.2%)	127 (14.0%)	255 (14.1%)
Uganda	313 (34.8%)	317 (35.0%)	630 (34.9%)
Zimbabwe	284 (31.6%)	285 (31.5%)	569 (31.5%)
Male	484 (53.8%)	477 (52.6%)	961 (53.2%)
Age (years)	36 (30-42) [5-78]	36 (29-42) [6-71]	36 (29-42) [5-78]
5-17 years	33 (3.7%)	39 (4.3%)	72 (4.0%)
WHO stage			
1	153 (17.0%)	147 (16.2%)	300 (16.6%)
2	265 (29.5%)	289 (31.9%)	554 (30.7%)
3	349 (38.8%)	342 (37.7%)	691 (38.3%)
4	132 (14.7%)	128 (14.1%)	260 (14.4%)
Current TB disease	135 (15.0%)	136 (15.0%)	271 (15.0%)
Current cryptococcal disease	12 (1.3%)	13 (1.4%)	25 (1.4%)
Current candida disease	53 (5.9%)	46 (5.1%)	99 (5.5%)
CD4* (cells/mm^3)	36 (16-60)	38 (16-64)	37 (16-63)
0-24 cells/mm^3	333 (37.0%)	323 (35.7%)	656 (36.3%)
25-49 cells/mm^3	258 (28.7%)	251 (27.7%)	509 (28.2%)
HIV viral load (c/ml) (N=1763)	250000 (92000-544240)	242110 (97140-640840)	246130 (94000-595880)
≥100,000 c/ml	645/882 (73.1%)	655/881 (74.3%)	1300/1763 (73.7%)
<1000 c/ml**	10/882 (1.1%)	4/881 (0.5%)	14/1763 (0.8%)
Haemoglobin (g/l) (N=1800)	112 (96-127)	111 (95-128)	112 (96-127)
Creatinine clearance† (ml/min) (N=1793)	97.1 (77.8-120.1)	97.3 (76.6-121.9)	97.3 (77.3-121.1)
Weight* (kg) (N=1800)	52.6 (46.4-59.2)	52.4 (46.0-59.4)	52.5 (46.3-59.3)
BMI (kg/m^2) (N=1797)	19.3 (17.4-21.5)	19.1 (17.1-21.3)	19.2 (17.2-21.4)
<18 kg/m^2	307/898 (34.2%)	318/899 (35.4%)	625/1797 (34.8%)
Days from screening to enrolment (ART initiation)	5 (2-8)	5 (2-8)	5 (2-8)
Hospitalised at enrolment	10 (1.1%)	12 (1.3%)	22 (1.2%)
Initiated ART with efavirenz	799 (88.9%)	820 (90.5%)	1619 (89.7%)
Initiated ART with tenofovir/ emtricitabine backbone	706 (78.5%)	716 (79.0%)	1422 (78.8%)
Standard ART regimen (excluding adjunctive raltegravir)			
Tenofovir/emtricitabine/efavirenz	681 (75.8%)	697 (76.9%)	1378 (76.3%)
Zidovudine/lamivudine/efavirenz	87 (9.7%)	92 (10.2%)	179 (9.9%)
Zidovudine/lamivudine/nevirapine	75 (8.3%)	69 (7.6%)	144 (8.0%)
Abacavir/lamivudine/efavirenz	26 (2.9%)	29 (3.2%)	55 (3.0%)
Tenofovir/emtricitabine/nevirapine	21 (2.3%)	17 (1.9%)	38 (2.1%)
Other	9 (1.0%)	2 (0.2%)	11 (0.7%)
Randomized to initiate ART with raltegravir as fourth drug	447 (49.7%)	455 (50.2%)	902 (50.0%)
Randomized to receive RUSF	447 (49.7%)	450 (49.7%)	897 (49.7%)
Isoniazid received pre-randomization‡, n(%) [median days			

since started]			
Prophylaxis	1 (0.2%) [1]	2 (0.2%) [36]	3 (0.2%) [14]
Treatment	76 (8.5%) [16]	98 (10.8%) [18]	174 (9.6%) [17]
Fluconazole prescribed pre-randomization‡, n(%) [median days since started]			
Prophylaxis	0 (0.0%)	9 (1.1%) [9]	9 (0.5%) [9]
Treatment	95 (10.6%) [6]	101 (11.1%) [7]	196 (10.9%) [6]
Isoniazid prescribed at randomization			
Prophylaxis	9 (1.0%)	784 (86.5%)	793 (43.9%)
Treatment	104 (11.6%)	118 (13.0%)	222 (12.3%)
Not prescribed	786 (87.4%)	4 (0.4%)	790 (43.8%)
Fluconazole prescribed at randomization			
Prophylaxis	1 (0.1%)	863 (95.3%)	864 (47.9%)
Treatment	107 (11.9%)	42 (4.6%)	149 (8.3%)
Not prescribed	791 (88.0%)	1 (0.1%)	792 (43.9%)
Azithromycin prescribed at randomization			
Prophylaxis	1 (0.1%)	906 (100.0%)	907 (50.2%)
Treatment	13 (1.4%)	0 (0.0%)	13 (0.7%)
Not prescribed	885 (98.4%)	0 (0.0%)	885 (49.0%)
Albendazole prescribed at randomization			
Prophylaxis (single dose)	1 (0.1%)	906 (100.0%)	907 (50.2%)
Treatment	4 (0.4%)	0 (0.0%)	4 (0.2%)
Not prescribed	894 (99.4%)	0 (0.0%)	894 (49.5%)
Co-trimoxazole/dapsone prescribed at randomization			
Co-trimoxazole prophylaxis	877 (97.6%)	889 (98.1%)	1766 (97.8%)
Co-trimoxazole treatment	3 (0.3%)	1 (0.1%)	4 (0.2%)
Dapsone prophylaxis	16 (1.8%)	16 (1.8%)	32 (1.8%)
Neither co-trimoxazole nor dapsone prescribed	3 (0.3%)	0 (0.0%)	3 (0.2%)
Any other antibiotics prescribed at randomization	122 (14.6%)	76 (8.4%)	198 (11.0%)

* mean of screening and enrolment values. Eligibility required screening CD4 to be <100 cells/mm^3, so baseline can be above 100 depending on the CD4 at enrolment.

** potentially indicating undisclosed prior ART: median CD4 76 cells/mm^3 in these participants.

† estimated using Cockcroft Gault, normalised to 1.73m^2

‡ remainder were not prescribed

Note: showing n(%) or median (IQR) [range]. As an indicator of imbalance, P>0.15 for all comparisons of baseline characteristics between groups.

Table S2a Primary and secondary causes of deaths through 48 weeks

	Standard prophylaxis	Enhanced prophylaxis	Total
Main cause of death – Infections			
Tuberculosis	**22**	**20**	**42**
Acute abdomen; Tuberculosis – abdominal	0	1	1
Tuberculosis – abdominal	1†	0	1
Tuberculosis - disseminated/military	11	11	22
Tuberculosis - disseminated/miliary; Chronic diarrhoea not investigated	0	1	1
Tuberculosis - disseminated/miliary; Hepatic failure - acute	1	0	1
Tuberculosis - disseminated/miliary; Hepatic failure - acute; Renal failure - acute	1*	0	1
Tuberculosis - disseminated/miliary; Kaposi's sarcoma cutaneous	0	1	1
Tuberculosis - disseminated/miliary; P falciparum malaria	1	0	1
Tuberculosis - disseminated/miliary; Pancytopenia, bone marrow depression	0	1	1
Tuberculosis - disseminated/miliary; Renal failure - acute	1	0	1
Tuberculosis – meningitis	2	2	4
Tuberculosis – other	0	1	1
Tuberculosis - pulmonary - smear positive	4	2	6
Cryptococcus	**13**	**4**	**17**
Cryptococcal meningitis	12	4	16
Cryptococcal meningitis; Cirrhosis	1	0	1
Bacterial infection	**15**	**18**	**33**
Acute diarrhoea not investigated	0	1	1
Aspiration pneumonia; Tuberculosis - pulmonary - smear negative or not done	0	1	1
CNS abscess	0	1	1
Chest infection	0	1	1
Gastroenteritis	0	1	1
Gastroenteritis; Hyponatraemia	0	1	1
Meningitis lumbar puncture diagnosed – no organism (no culture)	1	0	1
Meningitis no lumbar puncture	1	0	1
Mycobacterial disease - atypical disseminated	0	1	1
Pneumonia - other bacterial	0	2†	2
Pneumonia no organism identified	2	1	3
Presumed septicaemia/bacteremia - no organism	0	1	1

	Standard prophylaxis	Enhanced prophylaxis	Total
Presumed septicaemia/bacteremia - no organism; Renal failure - acute	1	0	1
Presumed septicaemia/bacteremia - no organism; Renal failure - acute; Anaemia with clinical symptoms	1	0	1
Presumed septicaemia/bacteremia - no organism; Renal failure - chronic	0	1	1
Presumed septicaemia/bacteremia - no organism; Septic abortion; Anaemia with clinical symptoms	0	1	1
Presumed septicaemia/bacteremia - no organism; Visceral abscess; Tuberculosis - pulmonary - smear negative or not done	0	1	1
Presumed septicaemia/bacteremia - not investigated	4†	0	4
Presumed septicaemia/bacteremia - not investigated; Anaemia with clinical symptoms	1	1	2
Presumed septicaemia/bacteremia - not investigated; Lower urinary tract infection (UTI), cystitis; Diabetes - Type II	1	0	1
Presumed septicaemia/bacteremia - not investigated; Pneumonia no organism identified; Pancytopenia, bone marrow depression	1	0	1
Presumed septicaemia/bacteremia - not investigated; Stevens-Johnson Syndrome	0	1*	1
Presumed septicaemia/bacteremia - not investigated; Tuberculosis - abdominal	1	0	1
Presumed septicaemia/bacteremia - not investigated; Tuberculosis - disseminated/miliary	0	1	1
Presumed septicaemia/bacteremia - not investigated; Tuberculosis - pulmonary - smear positive	0	1	1
Pyomyositis - infection	1	0	1
Main cause of death - Other	**23**	**22**	**45**
CNS			
Brain syndrome**/indeterminate intracerebral lesions	5	2	7
Brain syndrome**/indeterminate intracerebral lesions; Diabetes - Type II; Anaemia with clinical symptoms	1	0	1
Brain syndrome**/indeterminate intracerebral lesions; Renal failure - acute; Anaemia with clinical symptoms	0	1	1
Encephalitis – presumed infectious	0	1	1
Encephalopathy – unspecified	0	1	1
Progressive multifocal leukoencephalopathy	0	1	1
Lower Respiratory Tract			
Lung syndrome††	0	1†	1
Cardiovascular			
Congestive cardiac failure	0	1	1
Cardiomyopathy; Tuberculosis - disseminated/miliary	0	1	1
Pulmonary embolism; Deep vein thrombosis; Candidiasis of oesophagus, trachea, bronchi or lungs	0	1	1
Stroke, cerebrovascular accident	1	0	1
Stroke, cerebrovascular accident; Salmonella bacteraemia - NON typhi	1	0	1
Gastrointestinal			

	Standard prophylaxis	Enhanced prophylaxis	Total
Haematemesis; Peptic/gastric/duodenal ulcer; Overdose (not suicide attempt)	1*	0	1
Haematemesis; Wasting syndrome uninvestigated; Alcohol related	0	1	1
Hepatic			
Acute hepatitis	1*	0	1
Cardiomyopathy; Tuberculosis - disseminated/miliary	0	1	1
Hepatic encephalopathy; Hepatitis B; Tuberculosis - disseminated/miliary	0	1	1
Hepatic failure – acute	1	0	1
Hepatic failure - acute; Tuberculosis - pulmonary - smear positive; Renal failure - acute	1*	0	1
Hepatitis cause unknown; Tuberculosis - lymph nodes	1	0	1
Renal			
Renal failure - acute; Acute diarrhoea not investigated	0	1	1
Renal failure - acute; Chronic diarrhoea not investigated	1	0	1
Renal failure - acute; Gastroenteritis	0	2	2
Renal failure - acute; Tuberculosis - other	1	0	1
Renal failure - chronic; HIV associated nephropathy	1*	0	1
Skin			
Hypersensitivity reaction	0	1	1
Haematological			
Anaemia with clinical symptoms	1*	0	1
Anaemia with clinical symptoms; Renal failure - acute	1	1	2
Biochemical			
Metabolic disorder - other; Candidiasis of oesophagus, trachea, bronchi or lungs	0	1	1
Systemic			
Wasting syndrome uninvestigated	0	1	1
Wasting syndrome uninvestigated; Gastroenteritis	0	1	1
Tumours			
Kaposi's sarcoma - other; Presumed septicaemia/bacteremia - not investigated	0	1	1
Kaposi's sarcoma cutaneous	1	0	1
Kaposi's sarcoma lymph nodes	2	0	2
Non Hodgkin lymphoma	1	0	1
Other Solid tumour	0	1	1
Non-HIV related			
Traumatic	1	0	1

	Standard prophylaxis	Enhanced prophylaxis	Total
Main cause of death - unknown	**54**	**34**	**88**
Death, cause unknown	39	26	65
Death, cause unknown; Anaemia with clinical symptoms	1	0	1
Death, cause unknown; Brain syndrome**/indeterminate intracerebral lesions	1	0	1
Death, cause unknown; Candidiasis of oesophagus, trachea, bronchi or lungs	0	1	1
Death, cause unknown; Dysphagia, difficulty swallowing	1	0	1
Death, cause unknown; Hepatic failure - acute; Tuberculosis - pulmonary - smear negative or not done	1	0	1
Death, cause unknown; Kaposi's sarcoma - other	1	0	1
Death, cause unknown; Pancreatitis	1	0	1
Death, cause unknown; Pancytopenia, bone marrow depression	0	1	1
Death, cause unknown; Presumed septicaemia/bacteremia - not investigated; Renal failure - acute	0	1	1
Death, cause unknown; Renal failure - acute; Tuberculosis - lymph nodes	0	1*	1
Death, cause unknown; Secondary/Tertiary syphilis; P falciparum malaria	0	1	1
Death, cause unknown; Severe weight loss (>10%)	1	0	1
Death, cause unknown; Stevens-Johnson Syndrome	1	0	1
Death, cause unknown; Stroke, cerebrovascular accident	0	1	1
Death, cause unknown; Tuberculosis - disseminated/miliary	1	1	2
Death, cause unknown; Tuberculosis - pulmonary - smear negative or not done	1	0	1
Death, cause unknown; Tuberculosis - pulmonary - smear positive	2	1	3
Death, cause unknown; Wasting syndrome uninvestigated	3*	0	3

Where secondary cause(s) of death were adjudicated by the Endpoint Review Committee, these are provided after the primary cause of death (e.g. 'death, cause unknown; Stevens-Johnson Syndrome,' denotes that the primary cause of death was unknown and the secondary cause was Stevens-Johnson Syndrome)

*One definitely/probably related to antiretroviral/antimicrobial drugs.

†One aged <18 years at enrolment.

** Brain syndrome describes an event of comparable clinical severity to other HIV-associated cerebral events such as toxoplasmosis or cryptococcal meningitis, but where tests or investigations were not done, precluding even a presumptive diagnosis.

†† Lung syndrome describes an event of comparable clinical severity to other HIV-associated respiratory events such as severe pneumonia, but where tests or investigations were not done, precluding even a presumptive diagnosis.

Table S2b Primary cause of death through 0-24 and 24-48 weeks

		Standard prophylaxis (N=899)	Enhanced prophylaxis (N=906)	Total (n=1805)
Not known to have died		772 (85.9%)	808 (89.2%)	1580 (87.5%)
Died 0-24 weeks	Total	108 (12.0%)	80 (8.8%)	188 (10.4%)
	TB	22 (2.4%)	17 (1.9%)	39 (2.2%)
	Cryptococcal disease	10 (1.1%)	4 (0.4%)	14 (0.8%)
	Severe bacterial infections	9 (1.0%)	12 (1.3%)	21 (1.2%)
	Other	19 (2.1%)	19 (2.1%)	38 (2.1%)
	Cause unknown	48 (5.3%	28 (3.1%)	76 (4.2%)
Died 24-48 weeks	Total	19 (2.1%)	18 (2.0%)	37 (2.0%)
	TB	0 (0.0%)	3 (0.3%)	3 (0.2%)
	Cryptococcal disease	3 (0.3%)	0 (0.0%)	3 (0.2%)
	Severe bacterial infections	6 (0.7%)	6 (0.7%)	12 (0.7%)
	Other	4 (0.4%)	3 (0.3%)	7 (0.4%)
	Cause unknown	6 (0.7%)	6 (0.7%)	12 (0.7%)

Note: no evidence of variation in the effect of enhanced-prophylaxis vs standard-prophylaxis on mortality between 0-24 weeks and 24-48 weeks (interaction p=0.49). See Figure S4a for mortality risk over time from ART initiation.

Table S3 Secondary and other outcomes through 48 weeks

	Standard prophylaxis N (%) [events]	Enhanced prophylaxis N (%) [events]	Total N (%) [events]	p
Death	127 (14.1%) [127]	98 (10.8%) [98]	225 (12.5%) [225]	0.04
New WHO 4 event or death	181 (20.1%) [237]	138 (15.2%) [182]	319 (17.7%) [419]	0.006
New WHO 3 or 4 event or death	224 (24.9%) [341]	179 (19.8%) [270]	403 (22.3%) [611]	0.008
New tuberculosis disease*	92 (10.2%) [116]	64 (7.1%) [80]	156 (8.6%) [196]	0.02
New cryptococcal disease*	23 (2.6%) [37]	9 (1.0%) [14]	32 (1.8%) [51]	0.01
New candida disease (oesophageal or oral)*	23 (2.6%) [23]	10 (1.1%) [13]	33 (1.8%) [36]	0.02
New presumptive severe bacterial infection*	33 (3.7%) [50]	42 (4.6%) [61]	75 (4.2%) [111]	0.32
Any serious adverse event	219 (24.4%) [299]	191 (21.1%) [239]	410 (22.7%) [538]	0.08
New hospitalization*	186 (20.7%) [247]	154 (17.0%) [184]	340 (18.8%) [431]	0.03
Grade 4 AE*	191 (21.2%) [274]	162 (17.9%) [230]	353 (19.6%) [504]	0.09
Grade 3 or 4 AE	336 (37.4%) [565]	322 (35.5%) [488]	658 (36.5%) [1053]	0.31
Grade 4 AE definitely, probably or possibly related to prophylaxis drugs	69 (7.7%) [78]	62 (6.8%) [74]	131 (7.3%) [152]	0.50
Grade 4 AE definitely or probably related to prophylaxis drugs	8 (0.9%) [9]	13 (1.4%) [15]	21 (1.2%) [24]	0.27
AE leading to prophylaxis drug discontinuation*	14 (1.6%) [14]	14 (1.5%) [16]	28 (1.6%) [30]	0.97
IRIS	108 (12.0%) [111]	67 (7.4%) [69]	175 (9.7%) [180]	0.001

* secondary outcome

Note: Table shows number of patients with one or more episode (% of patients) [number of episodes]
(e.g., '2 (20.0%) [3],' would indicate a total of 3 episodes in 2 patients). No evidence of interaction with other factorial randomizations (p>0.1; 39 tests) except for AEs leading to prophylaxis drug discontinuation (higher in standard prophylaxis+no-RUSF and enhanced prophylaxis+RUSF than standard prophylaxis+RUSF and enhanced prophylaxis+no-RUSF; p=0.03).

Table S4 Serious adverse events

	Standard prophylaxis N=899 N (%) [events]	Enhanced prophylaxis N=906 N (%) [events]	Total N=1805 N (%) [events]	p
Body system				
Any	**219 (24.4%) [299]**	**191 (21.1%) [239]**	**410 (22.7%) [538]**	**0.10**
CNS	**23 (2.6%) [25]**	**26 (2.9%) [26]**	**49 (2.7%) [51]**	**0.77**
Acute altered conscious level	1	0	1	
Acute focal neurological event without fever, Cryptococcal disease serum CRAG +ve only	1	0	1	
Disorientated/confusion	2	1	3	
Dizziness	0	1	1	
Encephalitis – presumed infectious	0	2	2	
Encephalopathy – unspecified	0	1	1	
Encephalopathy – unspecified, Stroke, cerebrovascular accident	0	1	1	
Epilepsy, fits, convulsions	1	0	1	
Headache	1	1	2	
Hemiparesis	1	1	2	
Raised intracranial pressure	0	1	1	
Meningitis – other	0	1	1	
Meningitis lumbar puncture diagnosed – no organism (no culture), HIV associated nephropathy, Anaemia with no clinical symptoms	0	1	1	
Meningitis lumbar puncture diagnosed – no organism (no culture), Pneumonia no organism identified, Candidiasis of oesophagus, trachea, bronchi or lungs, Neutropenia	1	0	1	
Meningitis no lumbar puncture	1	0	1	
Myelopathy	0	1	1	
PML	1	1	2	
Peripheral neuropathy - motor only, Metabolic disorder - other	0	1	1	
Peripheral neuropathy - sensory & motor	1	0	1	
Pyogenic meningitis - no organism	2	0	2	
Pyogenic meningitis - organism	0	1	1	
Stroke, cerebrovascular accident	3	2	5	
Stroke, cerebrovascular accident, Cardiomyopathy, Tuberculosis - disseminated/miliary	0	1	1	

Stroke, cerebrovascular accident, Salmonella bacteraemia - NON typhi	1	0	1	
Toxoplasmosis of the brain	0	2	2	
Other CNS disease	0	2	2	
Brain syndrome/indeterminate intracerebral lesions	7	1	8	
Brain syndrome/indeterminate intracerebral lesions, Anaemia with clinical symptoms	0	1	1	
Brain syndrome/indeterminate intracerebral lesions, Anaemia with clinical symptoms, Hypoglycaemia, Raised creatinine	1	0	1	
Brain syndrome/indeterminate intracerebral lesions, Presumed septicaemia/bacteraemia - not investigated, Lung syndrome, Renal failure - acute, Anaemia with clinical symptoms	0	1	1	
Brain syndrome/indeterminate intracerebral lesions, Tuberculosis - pulmonary - smear positive	0	1	1	
Psychiatric	**8 (0.9%) [8]**	**4 (0.4%) [4]**	**12 (0.7%) [12]**	**0.26**
Depression	1	0	1	
Psychosis, mania	6	3	9	
Psychosis, mania, Neutropenia	1	0	1	
Psychosis, mania, Tuberculosis - pulmonary - smear positive, Pneumonia no organism identified	0	1	1	
Lower Respiratory Tract	**10 (1.1%) [12]**	**19 (2.1%) [21]**	**29 (1.6%) [33]**	**0.13**
Candidiasis of oesophagus, trachea, bronchi or lungs	1	1	2	
Chest infection	1	1	2	
Pleural effusion - other, Pneumonia no organism identified	0	1	1	
Pneumonia - *Pneumocystis jirovecii*	0	1	1	
Pneumonia - *Pneumocystis jirovecii*, Anaemia with no clinical symptoms	0	1	1	
Pneumonia - other bacterial	0	1	1	
Pneumonia - other bacterial, Anaemia with clinical symptoms	0	1	1	
Pneumonia no organism identified	6	11	17	
Pneumonia no organism identified, Ascites, Hepatitis B	0	1	1	
Pneumonia no organism identified, Hypotension/shock/toxic shock	0	1	1	
Pulmonary embolism, Deep vein thrombosis	3	0	3	
Lung syndrome, Anaemia with clinical symptoms	1	1	2	
Cardiovascular	**7 (0.8%) [8]**	**6 (0.7%) [8]**	**13 (0.7%) [16]**	**0.79**
Chest pain	1	0	1	
Cardiomyopathy, Tuberculosis - disseminated/miliary	0	1	1	
Congestive cardiac failure, Cardiomyopathy, Anaemia with clinical symptoms	0	1	1	

Congestive cardiac failure, HIV Associated Cardiomyopathy , Other cardiovascular, Deep vein thrombosis	1	0	1	
Congestive cardiac failure, Pancytopenia, bone marrow depression	0	1	1	
Deep vein thrombosis	3	3	6	
Deep vein thrombosis, Anaemia with clinical symptoms	2	0	2	
Deep vein thrombosis, Candidiasis of oesophagus, trachea, bronchi or lungs, Gastroenteritis	0	1	1	
Deep vein thrombosis, Lymphadenopathy	1	0	1	
Deep vein thrombosis, Pleural effusion - Tuberculosis	0	1	1	
Gastrointestinal	**17 (1.9%) [20]**	**15 (1.7%) [15]**	**32 (1.8%) [35]**	**0.73**
Abdominal or epigastric pain	1	0	1	
Acute abdomen, Tuberculosis - abdominal	0	1	1	
Appendicitis	0	1	1	
Dysphagia, difficulty swallowing	1	1	2	
Gastroenteritis	4	8	12	
Gastroenteritis, Hepatitis cause unknown	0	1	1	
Gastroenteritis, Raised creatinine	1	0	1	
Gastroenteritis, Renal failure - acute	1	0	1	
Haematemesis	1	0	1	
Indigestion, oesophageal reflux, gastritis, ulcerative oesophagitis	4	0	4	
Pancreatitis	1	1	2	
Per rectal bleeding (fresh blood and/or malaena)	1	0	1	
Vomiting	4	2	6	
Vomiting, Abdominal or epigastric pain	1	0	1	
Diarrhoeal	**3 (0.3%) [3]**	**4 (0.4%) [4]**	**7 (0.4%) [7]**	**1.00**
Acute diarrhoea not investigated	1	2	3	
Chronic diarrhoea not investigated, Oral candida	0	1	1	
Chronic diarrhoea not investigated, Renal failure - acute	1	0	1	
Chronic diarrhoea not investigated, Septicaemia with organism (unspecified), Pancytopenia, bone marrow depression	1	0	1	
Chronic diarrhoea with *Cryptosporidia*	0	1	1	
Wasting Syndrome	**1 (0.1%) [1]**	**1 (0.1%) [1]**	**2 (0.1%) [2]**	**1.00**
Severe weight loss (>10%)	1	0	1	
Severe weight loss (>10%), Anaemia with clinical symptoms, Raised creatinine	0	1	1	
Hepatic	**6 (0.7%) [7]**	**7 (0.8%) [7]**	**13 (0.7%) [14]**	**1.00**

Acute hepatitis	2	5	7	
Acute hepatitis, Candidiasis of oesophagus, trachea, bronchi or lungs, Anaemia with clinical symptoms	0	1	1	
Hepatic encephalopathy, Hepatic failure - chronic, Tuberculosis - disseminated/miliary, Hepatitis B	0	1	1	
Hepatic failure - acute	1	0	1	
Hepatic failure - acute, Tuberculosis - pulmonary - smear negative or not done, Wasting syndrome uninvestigated	2	0	2	
Hepatic failure - acute, Tuberculosis - pulmonary - smear positive, Renal failure - acute, Hepatitis B, Neutropenia	1	0	1	
Jaundice	1	0	1	
Renal	**10 (1.1%) [11]**	**10 (1.1%) [10]**	**20 (1.1%) [21]**	**1.00**
HIV associated nephropathy	1	0	1	
HIV associated nephropathy, Tuberculosis - pulmonary - smear positive	1	0	1	
Haematuria, Anaemia with clinical symptoms	0	1	1	
Pyelonephritis	1	2	3	
Pyelonephritis, Renal failure - acute	0	1	1	
Renal failure - acute	4	0	4	
Renal failure - acute, Acute diarrhoea not investigated, Intravascular haemolysis	0	1	1	
Renal failure - acute, Acute diarrhoea not investigated, Oral candida	2	0	2	
Renal failure - acute, Anaemia with clinical symptoms	0	1	1	
Renal failure - acute, Anaemia with clinical symptoms, Tuberculosis - lymph nodes, Kaposi's sarcoma lymph nodes, Overdose (not suicide attempt), Peripheral neuropathy - sensory & motor	0	1	1	
Renal failure - acute, Gastroenteritis	0	1	1	
Renal failure - acute, Gastroenteritis, Anaemia with clinical symptoms	0	1	1	
Renal failure - acute, Pyelonephritis	1	0	1	
Renal failure - acute, Raised AST, Raised ALT	0	1	1	
Renal failure - acute, Tuberculosis - other, Oral candida	1	0	1	
Genitourinary	**1 (0.1%) [1]**	**2 (0.2%) [2]**	**3 (0.2%) [3]**	**1.00**
Lower urinary tract infection (UTI), cystitis, Neutropenia	0	1	1	
Lower urinary tract infection (UTI), cystitis, Raised creatinine, Hypertension	1	0	1	
Vaginal bleeding	0	1	1	
Musculoskeletal	**1 (0.1%) [1]**	**0 (0.0%) [0]**	**1 (0.1%) [1]**	**0.50**
Pyomyositis - infection	1	0	1	
Skin	**1 (0.1%) [1]**	**2 (0.2%) [2]**	**3 (0.2%) [3]**	**1.00**

Hypersensitivity reaction	0	2	2	
Hypersensitivity reaction, Epilepsy, fits, convulsions	1	0	1	
Haematological	**18 (2.0%) [21]**	**14 (1.5%) [14]**	**32 (1.8%) [35]**	**0.48**
Anaemia with clinical symptoms	16	7	23	
Anaemia with clinical symptoms, Gastroenteritis	0	1	1	
Anaemia with clinical symptoms, Gastroenteritis, Neutropenia	1	0	1	
Anaemia with clinical symptoms, Headache	0	1	1	
Anaemia with clinical symptoms, Hemiparesis	0	1	1	
Anaemia with clinical symptoms, Neutropenia	1	1	2	
Anaemia with clinical symptoms, Neutropenia, Tuberculosis - pulmonary - smear positive	0	1	1	
Anaemia with clinical symptoms, Renal failure - acute	1	0	1	
Anaemia with clinical symptoms, Skin abscess, Neutropenia	1	0	1	
Anaemia with clinical symptoms, Thrombocytopenia	1	0	1	
Anaemia with no clinical symptoms, Neutropenia, Thrombocytopenia	0	1	1	
Pancytopenia, bone marrow depression	0	1	1	
Biochemical	**0 (0.0%) [0]**	**2 (0.2%) [2]**	**2 (0.1%) [2]**	**0.50**
Metabolic disorder - other, Candidiasis of oesophagus, trachea, bronchi or lungs	0	1	1	
Raised bilirubin, Raised liver enzymes	0	1	1	
Systemic	**7 (0.8%) [8]**	**6 (0.7%) [6]**	**13 (0.7%) [14]**	**0.79**
Wasting syndrome uninvestigated	3	2	5	
Wasting syndrome uninvestigated, Abdominal or epigastric pain	1	0	1	
Wasting syndrome uninvestigated, Acute hepatitis	1	0	1	
Wasting syndrome uninvestigated, Gastroenteritis	0	1	1	
Wasting syndrome uninvestigated, Oral candida	1	0	1	
Stevens-Johnson Syndrome	1	1	2	
Stevens-Johnson Syndrome, Presumed septicaemia/bacteraemia - not investigated	0	1	1	
Dehydration, Tuberculosis - abdominal	0	1	1	
Dehydration, Vomiting	1	0	1	
Specific Infections	**106 (11.8%) [121]**	**71 (7.8%) [84]**	**177 (9.8%) [205]**	**0.005**
Cryptococcal meningitis	22	9	31	
Cryptococcal meningitis, Anaemia with no clinical symptoms	0	1	1	
Cryptococcal meningitis, Cirrhosis, Candidiasis of oesophagus, trachea, bronchi or lungs	1	0	1	

Cryptococcal meningitis, Raised ALT	1	0	1	
Cryptococcal meningitis, Renal failure - acute	1	0	1	
Cryptococcal meningitis, Renal failure - acute, Anaemia with clinical symptoms	1	0	1	
Cryptococcal meningitis, Tuberculosis - disseminated/miliary	0	1	1	
Tuberculosis - meningitis	1	1	2	
Tuberculosis - meningitis, Candidiasis of oesophagus, trachea, bronchi or lungs	0	1	1	
Tuberculosis - meningitis, Pneumonia no organism identified, Oral candida	1	0	1	
Pleural effusion - Tuberculosis	1	0	1	
Pleural effusion - Tuberculosis, P falciparum malaria	1	0	1	
Tuberculosis - pulmonary - smear negative or not done	5	1	6	
Tuberculosis - pulmonary - smear negative or not done, Aspiration pneumonia	0	1	1	
Tuberculosis - pulmonary - smear negative or not done, Hepatitis cause unknown	1	0	1	
Tuberculosis - pulmonary - smear negative or not done, Neutropenia	1	0	1	
Tuberculosis - pulmonary - smear negative or not done, Pneumonia - other bacterial	0	1	1	
Tuberculosis - pulmonary - smear negative or not done, Severe malnutrition, Pneumonia - other bacterial, Anaemia with clinical symptoms	1	0	1	
Tuberculosis - pulmonary - smear positive	8	6	14	
Tuberculosis - pulmonary - smear positive, Anaemia with clinical symptoms	1	1	2	
Tuberculosis - pulmonary - smear positive, Oral candida	2	0	2	
Tuberculosis - pulmonary - smear positive, Pneumonia no organism identified	1	0	1	
Tuberculosis - pulmonary - smear positive, Renal failure - acute, Anaemia with clinical symptoms, Hyponatraemia	1	0	1	
Tuberculosis - pulmonary - smear positive, Tuberculosis - lymph nodes	0	1	1	
CMV retinitis	0	2	2	
Tuberculosis - abdominal	2	4	6	
Tuberculosis - abdominal, Anaemia with no clinical symptoms, Acute hepatitis	0	1	1	
Tuberculosis - abdominal, Peripheral neuropathy - sensory & motor, Ulcer, decubitus ulcer	1	0	1	
Cutaneous warts, Human Papillomavirus	0	1	1	
Tuberculosis - lymph nodes	6	0	6	
Tuberculosis - lymph nodes, Acute hepatitis, Rash, urticaria	1	0	1	
Tuberculosis - lymph nodes, Anaemia with clinical symptoms	1	0	1	
Tuberculosis - lymph nodes, Jaundice	1	0	1	
Tuberculosis - lymph nodes, Renal failure - acute	1	0	1	
Mycobacterial disease - atypical disseminated	0	1	1	

Tuberculosis - disseminated/miliary	16	12	28	
Tuberculosis - disseminated/miliary, Acute hepatitis	1	1	2	
Tuberculosis - disseminated/miliary, Anaemia with clinical symptoms	2	1	3	
Tuberculosis - disseminated/miliary, Anaemia with clinical symptoms, Presumed septicaemia/bacteraemia - no organism, Renal failure - acute	1	0	1	
Tuberculosis - disseminated/miliary, Ascites, Pleural effusion - other, P falciparum malaria	1	0	1	
Tuberculosis - disseminated/miliary, Candidiasis of oesophagus, trachea, bronchi or lungs	0	1	1	
Tuberculosis - disseminated/miliary, Chronic diarrhoea not investigated, Acute hepatitis	0	1	1	
Tuberculosis - disseminated/miliary, Hepatic failure - acute, Anaemia with clinical symptoms	1	0	1	
Tuberculosis - disseminated/miliary, Hepatic failure - acute, Renal failure - acute, Candidiasis of oesophagus, trachea, bronchi or lungs	1	0	1	
Tuberculosis - disseminated/miliary, Kaposi's sarcoma cutaneous	0	1	1	
Tuberculosis - disseminated/miliary, Neutropenia	1	0	1	
Tuberculosis - disseminated/miliary, Oral candida	1	0	1	
Tuberculosis - disseminated/miliary, Pneumonia - other bacterial	1	0	1	
Tuberculosis - disseminated/miliary, Pneumonia no organism identified	0	1	1	
Tuberculosis - disseminated/miliary, Pneumonia no organism identified, Anaemia with no clinical symptoms, Visceral abscess	0	1	1	
Tuberculosis - disseminated/miliary, Pneumonia no organism identified, Jaundice	0	1	1	
Tuberculosis - disseminated/miliary, Presumed septicaemia/bacteraemia - no organism, Hypokalaemia, Purpura, bruising, petechiae, Thrombocytopenia, Low albumin	1	0	1	
Tuberculosis - disseminated/miliary, Presumed septicaemia/bacteraemia - not investigated	0	3	3	
Tuberculosis - disseminated/miliary, Presumed septicaemia/bacteraemia - not investigated, Anaemia with clinical symptoms	1	0	1	
Tuberculosis - disseminated/miliary, Presumed septicaemia/bacteraemia - not investigated, Pancytopenia, bone marrow depression	0	1	1	
Tuberculosis - disseminated/miliary, Pure red cell aplasia	0	5	5	
Tuberculosis - disseminated/miliary, Raised liver enzymes	3	0	3	
Tuberculosis - disseminated/miliary, Renal failure - acute	1	1	2	
Tuberculosis - disseminated/miliary, Thrombocytopenia	1	0	1	
Tuberculosis - other	0	1	1	

Tuberculosis - other, Candidiasis of oesophagus, trachea, bronchi or lungs, Hypophosphataemia	1	0	1	
Cryptococcal fungaemia	1	0	1	
Presumed septicaemia/bacteraemia - no organism	3	2	5	
Presumed septicaemia/bacteraemia - no organism, Anaemia with clinical symptoms	0	1	1	
Presumed septicaemia/bacteraemia - no organism, Anaemia with clinical symptoms, P falciparum malaria	0	1	1	
Presumed septicaemia/bacteraemia - no organism, Candidiasis of oesophagus, trachea, bronchi or lungs	1	0	1	
Presumed septicaemia/bacteraemia - no organism, Disorientated/confusion, Hypoglycaemia	1	0	1	
Presumed septicaemia/bacteraemia - no organism, Renal failure - acute, Pancytopenia, bone marrow depression	1	0	1	
Presumed septicaemia/bacteraemia - no organism, Renal failure - chronic	0	1	1	
Presumed septicaemia/bacteraemia - no organism, Visceral abscess, Candidiasis of oesophagus, trachea, bronchi or lungs	0	1	1	
Presumed septicaemia/bacteraemia - not investigated	4	2	6	
Presumed septicaemia/bacteraemia - not investigated, Anaemia with clinical symptoms	1	1	2	
Presumed septicaemia/bacteraemia - not investigated, Anaemia with clinical symptoms, Neutropenia	0	1	1	
Presumed septicaemia/bacteraemia - not investigated, Brain syndrome/indeterminate intracerebral lesions	1	0	1	
Presumed septicaemia/bacteraemia - not investigated, Diabetes - Type II, Disorientated/confusion	1	0	1	
Presumed septicaemia/bacteraemia - not investigated, Lower urinary tract infection (UTI), cystitis	1	0	1	
Presumed septicaemia/bacteraemia - not investigated, Pancytopenia, bone marrow depression	1	1	2	
Presumed septicaemia/bacteraemia - not investigated, Pneumonia no organism identified	1	0	1	
Presumed septicaemia/bacteraemia - not investigated, Renal failure - acute, Anaemia with clinical symptoms, Thrombocytopenia	0	1	1	
Presumed septicaemia/bacteraemia - not investigated, Tuberculosis - abdominal	1	0	1	
Presumed septicaemia/bacteraemia - not investigated, Tuberculosis - disseminated/miliary	0	1	1	
Presumed septicaemia/bacteraemia - not investigated, Tuberculosis - pulmonary -	0	1	1	

smear positive				
Presumed septicaemia/bacteraemia - not investigated, Wasting syndrome with investigations	0	1	1	
P falciparum malaria	2	4	6	
P falciparum malaria, Anaemia with no clinical symptoms, Neutropenia	1	0	1	
P falciparum malaria, Neutropenia	1	1	2	
Histoplasmosis, Anaemia with clinical symptoms	1	0	1	
Tumours	**13 (1.4%) [16]**	**9 (1.0%) [9]**	**22 (1.2%) [25]**	**0.40**
Primary CNS lymphoma	1	0	1	
Kaposi's sarcoma pulmonary	1	0	1	
Kaposi's sarcoma mucosal	0	1	1	
Kaposi's sarcoma cutaneous	6	1	7	
Kaposi's sarcoma cutaneous, Anaemia with clinical symptoms	2	0	2	
Kaposi's sarcoma lymph nodes	1	1	2	
Kaposi's sarcoma lymph nodes, Nephrotic syndrome	1	0	1	
Non Hodgkin lymphoma	1	0	1	
Benign tumour	1	0	1	
Other Solid tumour	0	3	3	
Kaposi's sarcoma - other	1	1	2	
Kaposi's sarcoma - other, Acute hepatitis	0	1	1	
Kaposi's sarcoma - other, Anaemia with clinical symptoms	1	0	1	
Kaposi's sarcoma - other, Presumed septicaemia/bacteraemia - not investigated	0	1	1	
Abscess	**1 (0.1%) [1]**	**2 (0.2%) [2]**	**3 (0.2%) [3]**	**1.00**
CNS abscess	0	1	1	
CNS abscess, Pyogenic meningitis - no organism	1	0	1	
Skin abscess	0	1	1	
Non HIV Related Deaths	**1 (0.1%) [1]**	**0 (0.0%) [0]**	**1 (0.1%) [1]**	**0.50**
Traumatic	1	0	1	
Other	**32 (3.6%) [32]**	**22 (2.4%) [22]**	**54 (3.0%) [54]**	**0.17**
Non-fatal trauma	1	2	3	
Death, cause unknown	31	20	51	
Unknown	**1 (0.1%) [1]**	**0 (0.0%) [0]**	**1 (0.1%) [1]**	
Unknown Reason For Hospitalization	1	0	1	

Note: Table shows number of patients with one or more episode (% of patients) [number of episodes]
(e.g., '2 (20.0%) [3],' would indicate a total of 3 episodes in 2 patients)

Table S5 Adverse events (any grade) leading to discontinuation of prophylaxis drugs

	Standard prophylaxis N (%)	Enhanced prophylaxis N (%)	Total N (%)
Discontinued prophylaxis drugs due to an adverse event	**14 (1.6%)**	**14 (1.5%)**	**28 (1.6%)**
hepatotoxicity	3 (0.3%)	5 (0.6%)	8 (0.4%)
hepatitis	1 (0.1%)	1 (0.1%)	2 (0.1%)
raised ALT/AST	0 (0.0%)	1 (0.1%)	1 (0.1%)
renal and liver insufficiency	1 (0.1%)	0 (0.0%)	1 (0.1%)
renal failure	2 (0.2%)	0 (0.0%)	2 (0.1%)
erythema, generalised	0 (0.0%)	1 (0.1%)	1 (0.1%)
hypersensitivity	4 (0.4%)	1 (0.1%)	5 (0.3%)
itchiness	0 (0.0%)	2 (0.2%)	2 (0.1%)
neutropenia	0 (0.0%)	1 (0.1%)	1 (0.1%)
pancytopenia	1 (0.1%)	0 (0.0%)	1 (0.1%)
pancytopenia/anaemia	0 (0.0%)	2 (0.2%)*	2 (0.1%)
pure red cell aplasia	0 (0.0%)	1 (0.1%)*	1 (0.1%)
peripheral neuropathy	1 (0.1%)	0 (0.0%)	1 (0.1%)
allergic to sulphur	1 (0.1%)	0 (0.0%)	1 (0.1%)

*One patient discontinued due to pancytopenia/anaemia, subsequently restarted, then discontinued due to pure red cell aplasia

Table S6: Unit costs and costs of the trial intervention (2016 $US)

	Zimba-bwe	Uganda	Malawi	Kenya	Source
Costs of trial prophylaxis drugs					
	Per day	Per day	Per day	Per day	
Albendazole (400mg)	1.000	0.100	0.290	0.040	Trial centres
Azithromycin (500mg)	4.470	0.264	0.562	0.156	Trial centres
Fluconazole (100mg)	0.086	0.051	0.330	0.031	Trial centres
Fixed dose combination of co-trimoxazole (800/160mg), isoniazid (300mg) and pyridoxine (25mg)	0.038	0.057	0.026	0.054	Trial centres & WHO-International Drug Price Indicator Guide
Co-trimoxazole (800/160mg)	0.009	0.009	0.009	0.009	WHO-International Drug Price Indicator Guide
Isoniazid (300mg) and pyridoxine (25mg)	0.029	0.048	0.017	0.045	Trial centres
Trial intervention (12 weeks)*	33.766	10.492	33.004	7.960	Trial centres & WHO-International Drug Price Indicator Guide
Cotrimoxazole (12 weeks)**	0.756	0.756	0.756	0.756	WHO-International Drug Price Indicator Guide
Primary and secondary care resource use					
	Per day	Per day	Per day	Per day	
Inpatient stay	5.33	5.299	2.504	8.196	WHO Choice
Clinic visit	1.082	1.067	0.606	1.572	WHO Choice
Other concomitant medications	Various	Various	Various	Various	WHO-International Drug Price Indicator Guide
Antiretrovirals	Various	Various	Various	Various	Global Fund

Table S7: Costs and health related quality of life

		Standard prophylaxis	Enhanced prophylaxis	Difference
Resource use item				
Albendazole	Mean (SD)	$0.011 (0.132)	$0.595 (1.685)	$0.584
Azithromycin	Mean (SD)	$0.114 (1.030)	$8.632 (11.663)	$8.518
Fluconazole	Mean (SD)	$1.91 (15.088)	$8.802 (11.029)	$6.892
FDC	Mean (SD)	$5.891 (5.699)	$8.212 (6.822)	$2.321
Co-trimoxazole	Mean (SD)	$1.469 (0.963)	$1.127 (0.998)	$-0.342
All concomitant medications, costing trial drugs at actual within-country prices*	Mean (SD)	$16.73 (19.84)	$34.79 (20.96)	$18.06
All concomitant medications, costing trial drugs at minimum per drug across countries*	Mean (SD)	$12.30 (13.10)	$16.52 (13.75)	$4.22
Antiretrovirals	Mean (SD)	$172.07 (103.73)	$176.83 (101.82)	$4.76
Hospitalisations	Mean (SD)	$17.41 (53.09)	$13.13 (46.98)	$-4.28
Clinic visits	Mean (SD)	$8.43 (3.71)	$8.71 (3.60)	$0.28
Total costs (actual within country trial drug costs)	Mean (SD)	$214.64 (117.96)	$233.46 (115.14)	$18.81
Total costs (minimum trial drug costs across countries)	Mean (SD)	$210.22 (116.75)	$215.19 (113.15)	$4.97
Health impact				
QALYs	Mean (SD)	0.7125 (0.2475)	0.7372 (0.2180)	0.0247
Life years	Mean (SD)	0.7954 (0.2791)	0.8261 (0.2497)	0.0307

* see Supplementary Table 5
Note: FDC=fixed dose combination

Supplementary References

1. Molgaard-Nielsen D, Svanstrom H, Melbye M, Hviid A, Pasternak B. Association Between Use of Oral Fluconazole During Pregnancy and Risk of Spontaneous Abortion and Stillbirth. *JAMA* 2016; **315**(1): 58-67.
2. Molgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. *N Engl J Med* 2013; **369**(9): 830-9.
3. Babiker AG, Walker AS. Statistical issues emerging from clinical trials in HIV infection. In: Geller N, ed. Advances in clinical trial biostatistics: CRC Press; 2003.
4. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association* 1999; **94**(446): 496-509.
5. Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Statistics in Medicine* 2002; **21**: 2175-97.
6. Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. *The Stata Journal* 2009; **9**(2): 265-90.