

Full Title of trial:

A randomised placebo-controlled double-blind phase III trial to determine the effects of metformin versus placebo on the incidence of diabetes in persons living with HIV with pre-diabetes in Tanzania.

Short title: Metformin Treatment for Africa

Acronym: META trial

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Signature: Date: 29th January 2026



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(Chair of TSC for final protocols and amended final protocols)

GENERAL INFORMATION

This document describes a trial of metformin in HIV-positive persons with pre-diabetes and provides information about trial procedures. The protocol should not be used as an aide-memoire or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial. Problems relating to this trial should be referred to the relevant Chief Investigator.

Compliance: The trial will be conducted in compliance with MRC Good Practice Guidelines. The trial will adhere to the Liverpool School of Tropical Medicine (LSTM) Governance and Ethics Committee, the UCL Research Ethics Committee and the NIMR Research Ethics Committee. In addition to the regulatory requirements of the Tanzanian Medicines and Medical Devices Authority (TMDA).

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The trial partners are:

- The Liverpool School of Tropical Medicine (LSTM), UK. A research institution with a clinical trials unit and trial governance. LSTM has been the trial sponsor and activity co-ordinator from the trial start to the novation of the grant to UCL. Following novation of the grant to UCL, LSTM remains a trial partner.
- MRC/UVRI Uganda Research Unit (MRC/UVRI). A research centre who will provide technical support.
- National Institute for Medical Research (NIMR), Muhimbili Centre. A research centre who will provide research support in Tanzania and undertake management of all trial data.
- Research and Training Unit, Shree Hindu Mandal, and Shree Hindu Mandal Hospital, not-for-profit health care provider. They will provide clinical expertise as well as operations support.
- Amana Regional Referral Hospital, Temeke Regional Referral Hospital, Mwananyamala Regional Referral Hospital, Mbagala Hospital, Mnazi Moja Hospital and Shree Hindu Mandal Hospital. These will be trial sites.
- University College London (UCL), Institute for Global Health, London, UK. Following novation of the grant from LSTM, UCL will be the Sponsor and will co-ordinate trial activity.
- Barcelona Institute for Global Health, ISGlobal.
- University College Dublin, School of Medicine
- University of Umea, Department of Epidemiology and Global Health
- University of Liverpool, Institute of Life Course and Medical Sciences

In addition, we will work closely with Ministry of Health in Tanzania.

The trial sponsor is the Liverpool School of Tropical Medicine, and following novation of the grant to UCL, UCL will be the Sponsor.

Trial Monitor: Trial Management group based at Liverpool School of Tropical Medicine and following novation of the grant, at UCL.

The trial will be conducted in compliance with the protocol, GCP and regulatory requirements

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Abbreviations

ART	Antiretroviral Treatment
CRF	Case Report Form
CVD	Cardiovascular disease
DTG	Dolutegravir
EFZ	Efavirenz
GFR	Glomerular Filtration Rate
HbA1c test	Haemoglobin A1c / Glycated Haemoglobin test
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
LSTM	Liverpool School of Tropical Medicine.
MRC/UVRI	MRC/UVRI Uganda Research Unit
NIMR	National Institute of Medical Research, Tanzania
NCDs	Non-Communicable Diseases
NIHR	National Institute for Health Research
NIMR	National Institute for Medical Research
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OGTT	Oral Glucose Tolerance Test
PI	Protease Inhibitor
TASO	The AIDS Support Organisation.
TDF	Tenofovir
UCL	University College London

WHO	World Health Organisation
ZDV	Zidovudine
3TC	Lamivudine

1 SUMMARY

1.1 Summary of trial design

This protocol describes a phase III randomised double-blind placebo-controlled trial to evaluate the use of metformin in persons living with HIV on antiretroviral treatment (ART) with pre-diabetes. We will determine whether metformin can prevent or delay the progression to diabetes in this group. This study follows a phase II trial that tested feasibility and changes in glycaemia.

Metformin is the recommended first line drug for persons with diabetes and HIV-infection in the UK, Africa and elsewhere. Metformin has also been evaluated in persons with HIV infection on ART who have lipodystrophy and metabolic syndrome (but who do not have diabetes or pre-diabetes). Based on the evidence, and our ongoing phase 2 study, we believe that metformin is safe for use in persons living with HIV on ART who have pre-diabetes. Our purpose is to conduct a phase III trial and generate efficacy data as well as data on safety and health economics.

Participants will be adults living with HIV and on ART and confirmed to be pre-diabetic using the Oral Glucose Tolerance Test (OGTT) and fasting blood glucose, with no contraindication to metformin. The trial will be done at Centres where good clinical cover will be provided. 2100 patients will be randomised 1:1 to the intervention or control group:

Intervention: Metformin hydrochloride 2000 mg per patient per day.

Control: Matching Placebo

All participants will continue to take their ART.

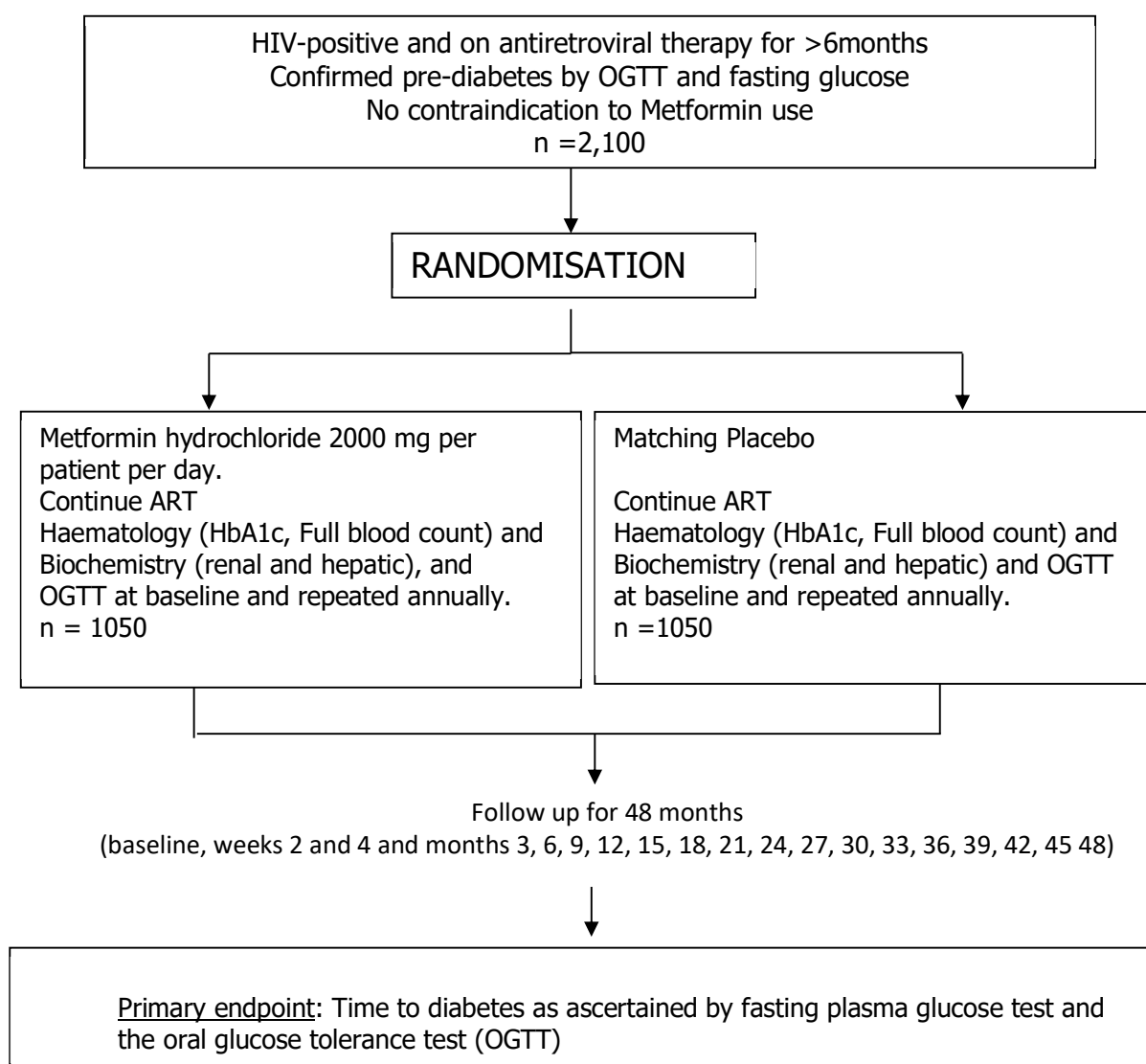
The primary outcome measure is the time to diabetes. We will define this by the gold standard oral glucose tolerance test. We will compare the incidence of the primary outcome between the metformin and control arm over a 4-year follow-up in an intention-to-treat (ITT) analysis. Secondary endpoints will include incidence of diabetes as diagnosed using other markers of glycaemia, adverse events and cost-effectiveness.

The study will be based in Dar es Salaam in Tanzania, at well functioning hospitals experienced in international-level clinical trials research, collaborating with NIMR and the Shree Hindu Mandal Research and Training Centre. Most of the recruitment will be done at 4 hospitals where we are currently conducting a phase II randomised trial of metformin versus placebo; 2 additional sites will also be available.

Recruitment is estimated to be complete within 6-12 months. Participants will be followed up for a duration of up to 4 years after recruitment. The study is funded by an EDCTP2 grant that was held at LSTM at the trial start and subsequently moved to UCL, and by an EDCTP3 grant held at ISGlobal; and in partnership with the NIMR Muhimbili Medical Research Centre and with the Shree Hindu Mandal Hospital.

1.2 FLOW DIAGRAM

Figure 1: Trial entry, randomisation and treatment



2 BACKGROUND

2.1 Introduction

Diabetes burden. Diabetes is a serious chronic condition associated with diffuse complications and an increased risk of premature death, imposing enormous financial pressure on national health care systems and national economies. An estimated 460 million adults worldwide were living with type 2 diabetes mellitus (hereon referred to as diabetes) in 2019, and this is rising rapidly¹. Diabetes doubles the risk of developing cardiovascular disease (CVD), is a major cause of end-stage renal disease and the commonest cause of non-traumatic amputation and blindness globally. Sub-Saharan Africa has a prevalence of 5%, projected to rise to ~10% in the next two decades - the highest-global increase. In Africa, diabetes affects younger people than in high-income countries and is having a massive impact on the continent². In 2019, the Africa Region had the highest estimate of the proportion of diabetes related deaths under the age of 60 years (73.1%)¹.

Why is pre-diabetes important? Persons who develop diabetes first pass from a phase of normal glucose through to impaired glucose tolerance, known as pre-diabetes³. Recent studies have shown that pre-diabetes strongly predicts the risk of developing diabetes; studies in different populations have shown that 10-20% of subjects with prediabetes progress to clinical diabetes each year⁴⁻⁶, and 70% of these individuals can expect to go on to develop overt diabetes during their lifetime⁷. The US Diabetes Prevention Program study⁴ was the largest study of pre-diabetes. Table 1 shows the diabetes incidence, which is almost 4 times higher among those with fasting glucose of 6.1-6.9 mmol/L than those with lower fasting glucose, who were diagnosed as pre-diabetic under the ADA (American Diabetes Association) definition.

Table 1. Rates of diabetes incidence among persons identified with pre-diabetes in the US Diabetes Prevention Programme.

Test	mg/dl	mmol/L	Diabetes incidence per 100 person-years *
Fasting Glucose	95-109	5.3 – 6.1	6.4 (based on n=2174)
	110-125	6.1 – 6.9	22.3 (based on n=1060)
Oral Glucose Tolerance Test (OGTT), mmol/L	140-153	7.8-8.5	4.3 (based on n=1049)
	154-172	8.6 – 9.6	6.6 (based on n=1103)
	173-179	9.6 -11.1	12.3 (based on n=1082)

* these are figures reported in the control group.

Further, prediabetes is not only a reservoir of new diabetes cases to come – it, like diabetes, elevates microvascular and macrovascular disease risk⁸⁻¹⁰. A study from the USA spanning 25

years showed that cardiovascular and renal risks were highly prevalent in adults with pre-diabetes, irrespective of the definitions (of pre-diabetes) used¹¹. A recent systematic review, involving 129 studies and over 10 million participants shows that pre-diabetes is associated with a 13% increased risk of all cause mortality¹².

The prevalence of pre-diabetes in HIV-infection, as defined by WHO criteria, is high (Table 2). Several other studies done in Africa using the American Diabetes Association criteria (which define pre-diabetes from a lower threshold) have reported even higher pre-diabetes prevalence figures in the population living with HIV¹³⁻¹⁵.

Table 2. Prevalence of prediabetes, as defined using the WHO definition, among persons living with HIV in Africa.

Region	Study population	Pre-diabetes definition	Prevalence
Cape Town, South Africa ¹⁶	N=940 (393 ART naïve, 439 on first-line ART, 108 on 2 nd line ART)	Fasting plasma glucose 6.1 – 6.9 mmol/l	18% in ART naïve 22% first line ART 26% second line ART
Jimma, Ethiopia ¹⁷	N=393 aged 21-75 years (mean 38); 72% on ART.	Fasting blood glucose 6.1 6.9 mmol/L	19.6%
Mwanza, Tanzania ¹⁸	N=273, mean age 42y on ART	Fasting glucose 6.1-6.9 mmol/L/ or OGTT 7.8 - 11.0 mmol/L	22.3%

ART – antiretroviral therapy, OGTT - oral glucose tolerance test

In preparation for the proposed phase 3, we are conducting the META phase 2 trial, among people living with HIV with pre-diabetes. We are screening people living with HIV for glycaemia using the gold standard, the oral glucose tolerance test (OGTT). We purposely screened participants living with HIV-infection who were overweight (728/975 (75%) had BMI $\geq$ 25), and found that a staggering 313/975 (32%) had an oral glucose tolerance test (OGTT) of between 7.8-11.0 mmol/L (*unpublished*).

Persons living with HIV-infection might be at high risk of diabetes: Two large studies have suggested that the risk of diabetes is even higher among HIV-positive persons than among HIV-seronegative persons. In a cross-sectional study of 15,000 adults in Italy, diabetes prevalence was two-fold higher among HIV-positive than among HIV-seronegative persons¹⁹. In North America, the incidence of diabetes was 4.1 fold (95% CI 1.9, 9.2) higher among HIV-positive men on ART compared with seronegative men²⁰ during a 4-year period of follow-up.

Data from Africa are limited, and mostly come from small studies that have flaws in the study design and that have used different diagnostic criteria. In a recent systematic review that brought these together, eight studies reported the prevalence of diabetes among HIV-infected and uninfected persons, but the prevalences varied so greatly that meta-analysis could not be

performed. A further seven studies reported on the incidence of diabetes among persons living with HIV but none of these studies had a control group of HIV-uninfected persons.²¹

In a cohort study conducted in Nigeria, 2452 persons who did not have diabetes were followed up and 130 (5.3%, 95% CI 4.2%, 6.3%) newly developed diabetes in just 12 months²².

In the META phase 2 trial, 975 HIV-infected participants with a median age 47 years were screened, of whom 75% had BMI $\geq$ 25 as mentioned above. We found 65 (7%) had an OGTT $\geq$ 11.1 mmol/L.

The mechanisms for the increased risk of diabetes among persons living with HIV, if true, are unknown, but may relate to the infectious/inflammatory process of HIV itself²³⁻²⁵ or result from the toxicity of antiretroviral therapy (ART)²⁶; two classes of ART, nucleoside reverse transcriptase inhibitors (NRTIs)^{27,28} and protease inhibitors^{29,30} have been implicated.

Data on pre-diabetes are weaker. While we know that the prevalence of pre-diabetes among persons living with HIV is high (Table 1), we do not know whether the pre-diabetes prevalence is higher among persons living with HIV than among HIV-seronegative persons. There have been no direct comparisons of the prevalence of pre-diabetes between HIV-infected and HIV-seronegative persons.

How can diabetes be prevented? There are two approaches: lifestyle changes and pharmacological agents. Most of the evaluation of these approaches have been done in Western countries (i.e. in HIV-uninfected populations). These studies have demonstrated that progression from prediabetes to diabetes can be delayed by lifestyle changes. The Malmo Study³¹, the Da Qing study in China³², the Finnish Diabetes Prevention Study³³⁻³⁵ the US Diabetes Prevention Program/Diabetes Prevention Programme Outcomes Study⁴ all demonstrated significant delay in diabetes progression with lifestyle interventions³⁶. However, these interventions involved frequent one-to-one patient consultations with trained professionals over a prolonged period of follow-up. **The interventions have not been reproducible in real world clinical practice and are unlikely to be practical in Africa.** They are costly to implement, time intensive and difficult for patients to maintain, and the weight loss achieved tends to be regained over time^{4,35,37,38}. In this trial, we therefore do not plan to evaluate a lifestyle intervention. However, participants in both groups will receive basic advice on diet and exercise.

In randomised trials, delays in progression to diabetes among HIV-uninfected persons have also been demonstrated with pharmacological agents including Acarbose³⁹, Rosiglitazone⁴⁰, Pioglitazone⁴¹ and metformin⁴²⁻⁴⁴. Of these agents, metformin has been in clinical use for decades. Table 2 shows all three comparative studies that have evaluated metformin in pre-diabetes. **In a meta-analysis combining data from these three trials, metformin reduced development of diabetes by 35% (95% CI 0.22, 0.45)⁴³ compared with control.** In the US study (the Diabetes Prevention Program/Diabetes Prevention Programme Outcomes Study³), open-

label follow-up of the cohort for 15 years suggests that a substantial beneficial effect of metformin was sustained over time.⁴⁵

The effects of metformin on glycaemia in pre-diabetes in African persons, including those who are HIV-infected, have not been quantified.

Table 3. Efficacy of metformin in (HIV-uninfected) persons with prediabetes in reducing the incidence of diabetes as reported in trials.

Region	RCT design	Population of prediabetes patients	Length of trial follow-up time	No (%) who became diabetic (reported by authors)		Odds ratio (fixed) taken from meta analysis (95% CI) ⁴⁴
				Metformin	control	
US ⁴	Metformin versus placebo, double blind.	Age>25y Fasting glucose 5.3-6.9 mmol/ or 7.8-11.0 mmol/l after 2-h glucose load	2.8 years	233/1073 (21.7)	313/1082 (28.9)	0.68 (0.56, 0.83)
China ⁴²	Metformin versus placebo, double blind.	Age>25y. Fasting glucose 6.1-6.9 mmol/l or 7.8-11.0 mmol/l after 2-h glucose load	12 months	1/33 (3.0)	6/37 (16.2)	0.16 (0.02, 1.42)
India ⁴⁴	open label, Metformin versus standard care	Age 35-55y Fasting glucose 6.1-6.9 mmol/l or 7.8-11.0 mmol/l after 2-h glucose load	30 months	52/128 (40.6)	73/133 (54.9)	0.56 (0.34, 0.92)

Experience from the phase 2 trial of metformin versus placebo

From 12th November 2019 through to July 24th 2020, we screened 1,279 patients living with HIV-infection who had been in HIV care for at least 6-months for the META phase 2 trial (a double blind placebo controlled trial testing a daily dose of metformin at 2000mg). Overall, 384 patients were eligible and 364 were enrolled following written informed consent. Of the 20 who were not enrolled, 14 declined as they reported not being ready to start medication or that they needed to discuss with family; 1 was disabled and the caretaker did not think it would be possible to take part and in 5 cases there had been misunderstanding of the eligibility criteria by study staff and they were not offered recruitment. The median age of participants enrolled was 47 years (range 20-85 years). Thus far, 7 participants have withdrawn because of minor adverse events, and a further 8 patients did not attend after the enrolment visit and have been lost to follow-up.

Table 4 shows the overall characteristics of the participants at baseline and at the 6-month stage. Thus far (29th September 2020), 119/364 (33%) have been followed up through to 6 months.

Table 4. Characteristics of participants enrolled in the META trial.

Indicator	Baseline (n=364)	6 months (n=119)
Female, number (%)	299 (82%)	101 (85%)
Age, median (IQR)	47 (42 – 52)	47 (44 – 53)
Weight, median (IQR) KG	79 (68 – 89)	79 (69 – 87)
BMI, median (IQR)	31.2 (27.2 – 34.9)	30.8 (27.4 – 35.2)
Fasting glucose	6.4 (5.8 – 6.7)	5.9 (5.3 – 6.5)
HbA1c *	5.6 (5.2 – 6.1)	5.6 (5.2 – 6.1)
OGTT	8.1 (7.4 – 9.3)	7.9 (6.9 – 8.7)

* missing for n=1 at baseline

2.1.1 Trial setting

We plan to conduct the study in up to 6 health facilities in Dar es Salaam, shown below, together with minimal estimates of the patient load at each facility (Table 5).

Table 5. Estimated enrolment by site.

Centre	No. on ART and in regular care, Aug 2017	No. newly initiated on ART monthly	Minimum no. estimated with pre- diabetes	No. assumed will be available for recruitment
Mwananyamala *	6990	210	580	520
Temeke *	5990	150	480	430
Amana *	6270	150	500	450
Mbagala	4600	120	370	340
Mnazi Moja	4360	100	350	320
Hindu Mandal Hospital *	3200	100	200	150

Note: these data were collected in Aug 2017. In Feb 2019, we re-checked and cohort was only marginally larger. The number on ART is those in regular care. Those who have died, were lost or attend erratically have been excluded.

* these sites recruited and managed patients for the phase 2.

We have recruited and managed participants at 4 of the 6 sites. The prevalence of raised glycaemia was much higher than the assumptions in table above (31% had fasting glucose 6.1 – 6.9 mmol/L and 32% had an OGTT of 7.8-11.1 mmol/L). Therefore, we estimate that recruitment should be completed within 6-12 months at these 4 sites, but we will open up the remainder 2 sites if needed. It is important we have the option to expand recruitment since, for example, Covid-19 may disrupt supplies of re-agents or patient attendance at health facilities.

All of these facilities have good clinical care capacity and are reasonably close to each other. They also have excellent relations with the patients, patient groups and the communities.

Identifying persons with pre-diabetes for the trial. We will screen patients attending the HIV clinics for routine HIV care with oral glucose tolerance testing. We will also test using HbA1c testing. This is not recommended by WHO as its utility is unknown in Africa, and screening will advance knowledge. We feel that a single fasting blood glucose is unreliable.

As in the phase 2 study, persons identified with diabetes during our screening will be referred to the diabetic clinic in the hospital and offered treatment according to the national treatment guidelines.

2.1.2 Investigational product/ intervention(s)

We will use the products as tested in the phase 2 study:

Intervention arm: Metformin hydrochloride 2000 mg per patient per day, while continuing to take ART.

Glucophage SR 2000 mg as made by Merck.

Control arm: matching placebo per patient per day, while continuing to take ART.

2.2 RATIONALE AND OBJECTIVES.

2.2.1 Rationale for using metformin

Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity thus increasing peripheral glucose uptake and utilisation⁶. Currently, Metformin is the only pharmacologic agent recommended for use in the prevention or delay of diabetes (type 2) among high-risk individuals⁴⁶⁻⁴⁸. The National Institute of Health and Care Excellence (NICE) in the UK recommends offering metformin to patients at high risk of developing Type 2 Diabetes where HbA1c or fasting plasma glucose levels have deteriorated despite participation in intensive lifestyle change programmes or if they are unable to participate in such a programme⁴⁷. Economic models showed that metformin is particularly cost effective in people whose BMI is over 35 (when their blood test results have deteriorated). There has been no evaluation of Metformin's use in Africa in any population.

Safety

Metformin is well tolerated and associated with relatively mild gastrointestinal side effects, including diarrhoea, nausea, vomiting, abdominal bloating, abdominal pain, flatulence and anorexia. These are reported to occur in 20% to 30% of patients receiving metformin therapy, usually occurring at the onset of therapy and disappearing spontaneously.⁴⁹

Rare side effects include lactic acidosis; decrease of Vitamin B12 absorption and subsequent decrease in serum levels; abnormal taste; skin redness and itching; liver function test abnormalities or hepatitis with or without jaundice resolving upon discontinuation of Metformin. It does not lead to hypoglycaemia except very rarely, usually when used in association with other glucose lowering agents.

Below we review the literature first and then provide data from the META phase 2 study (i.e. from the setting for the phase 3 trial).

Metformin associated lactic acidosis

The reported incidence of metformin associated lactic acidosis in clinical practice (which by nature includes patients presenting sick) is estimated to be low (<1 case per 10,000 patient years).⁵⁰ Risk factors for the development of lactic acidosis with metformin use are thought to include poor renal function, impaired liver metabolism, and other conditions causing increased production of lactate (chronic heart failure, sepsis and reduced tissue perfusion) and there are restrictions applied to the use of the drug in patients with these conditions. However, it has recently been suggested that the contraindications to use are too conservative, thus denying patients the potential benefit of metformin therapy.^{50,51}

A Cochrane review has evaluated the risk of fatal or non-fatal lactic acidosis with the use of metformin. It comprised more than 347 comparative trials and cohort studies in patients with type 2 diabetes of at least one month duration, evaluating metformin alone or in combination with other treatments compared to placebo or any other glucose-lowering therapy and found **no cases of fatal or non-fatal lactic acidosis in 70,490 patient years of metformin use or in 55,451 patients-years in the non-metformin group.**⁴⁹ Further, using Poisson statistics, the upper limit for the true incidence of lactic acidosis per 100,000 patient-years was 4.3 cases in the metformin group and 5.4 cases in the non-metformin group.⁴⁹ There was no difference in lactate levels, either as mean treatment levels or as a net change from baseline, for metformin compared to non-metformin therapies.

Antiretroviral therapy associated lactic acidosis.

Data on the incidence of lactic acidosis among persons living with HIV on ART are weak and come mostly from case-studies and small-scale studies. The increased risk of hyperlactataemia¹

¹ Hyperlactataemia is defined as a mild-to-moderate increase in serum lactate (2-5 mmol/l), with normal pH value and bicarbonate level (pH≥7.35 and bicarbonate concentration ≥20 mmol/l)

and lactic acidosis² appears to be among persons living with HIV taking ART combinations with NRTIs (nucleoside reverse transcriptase inhibitors).⁵² The NRTIs associated with comparatively high risk for causing hyperlactataemia are stavudine (d4T), didanosine (ddl) and zalcitabine⁵³; but stavudine was phased out in Africa several years ago and ddl and zalcitabine are not available in Africa. Further, this risk is thought to be only elevated in a short window period - between about 4 months and 2 years following ART initiation⁵⁴ - and among patients with any condition that impairs renal function, including dehydration or sepsis or other intercurrent illness.

Longitudinal data are very limited. Overall, symptomatic hyperlactataemia is thought to occur in about 0.4% to 0.9% of persons on NRTI therapy; lactic acidosis occurs in an estimated 0.1% to 0.4% patients⁵⁴.

Recent changes to drug safety warnings for nucleoside analogues include warnings that lactic acidosis and severe hepatomegaly with steatosis have been reported with use of lamivudine and zidovudine (*Combivir*).

At Hindu Mandal Hospital in Tanzania, a cohort of 800 adult patients living with HIV have been followed up for more than 3 years. Approximately 90% of the cohort are on emtricitabine, tenofovir and efavirenz. Less than 10% are on combivir and efavirenz.

In Uganda, our collaborator TASO has a cohort comprising 7224 adults at one of its 10 clinical sites (TASO Mulago, Kampala). Of these 4670 (65%) are on emtricitabine, tenofovir and efavirenz and the remainder on AZT (zidovudine) and ABC (abacavir). Follow-up of the cohort exceeds 5 years. Thus, at the two study sites where we have close links, we have a follow-up of at least 40,000 person years. Not a single case of lactic acidosis has been observed.

Risk of lactic acidosis in patients on metformin and antiretroviral therapy

It is unclear whether co-administration of metformin is a risk factor, as according to the Southern African HIV Clinicians Society Guidelines⁵⁴. Although metformin is first line therapy for the treatment of type 2 diabetes in patients on antiretroviral therapy, there is little evidence beyond case studies available on the risks of developing lactic acidosis in this patient group. Previous trials that have used metformin in patients living with HIV on antiretroviral therapy have found metformin to be well tolerated. These studies have all been small (number treated with metformin $\leq$ 100 persons) of short duration (up to 12 months), have used a range of doses of metformin, and have all been conducted in the US or Europe⁵⁵⁻⁶². These studies did not generally include patients who were diabetic or prediabetic and were rather investigating the effects of metformin on lipodystrophy or other cardiovascular risk indices. No cases of lactic

² Lactic acidosis is defined as persistently and remarkably elevated serum lactate level (generally >5 mmol/l) associated with metabolic acidosis ($\text{pH} < 7.35$ and bicarbonate concentration < 20 mmol/l)

acidosis were found. There are no data in African populations on the incidence of metformin associated lactic acidosis in the population of people living with HIV and diabetes. **Based on the evidence from high-income settings, and noting that in a clinical trial, patients who might be at increased risk of lactic acidosis will be excluded at the outset, the incidence in our study population is likely to be extremely low.**

In consultation with the Molecular and Clinical Pharmacology Group (Prof Saye Khoo; personal communication) at the University of Liverpool we were advised prior to the start of the phase 2 trial, that the risk of lactic acidosis was minimal with the NRTI's in use today, and there appears to be no epidemiological evidence of an interaction between metformin and the NRTIs in use in Tanzania and Uganda, including AZT and 3TC (lamivudine) primarily because they are metabolised differently, as outlined in the University of Liverpool's HIV Drug interactions website (<https://www.hiv-druginteractions.org>).

Safety evidence from the phase 2 META trial. The trial started on 5th November 2019 and enrolment was completed on 24th July 2020. Follow-up is now continuing. A total of 364 persons with pre-diabetes and HIV-infection were enrolled. As at the end of September 2020, a total of 20 adverse events at grade 3 (15), grade 4 (3) or grade 5 (2) were reported. All 20 adverse events were unrelated (17) or unlikely related to metformin (3). Most (13) were events detected at enrolment and were still present at the patients week 2 visit (they had not deteriorated following enrolment into the study and start of the study drugs); 3 events were related to incidental findings, and the remaining 4 events were related to HIV disease.

Longterm use of Metformin and Vitamin B12 deficiency The association between Vitamin B12 deficiency and long term use of metformin has been established.^{63,64} The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. A recent change to the safety information for Metformin indicated that people who have been taking high dose metformin for at least 3 years should be investigated for Vitamin B12 deficiency, particularly in the case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), or should have B12 supplementation.⁶⁵ There is little evidence of the prevalence on Vitamin B12 deficiency in the Tanzanian population, with one available study reporting low levels of serum vitamin B12 in 12.5% of patients with type 2 diabetes taking metformin therapy.⁶⁶ Consultations with diabetologists familiar with the Tanzanian setting suggest that low levels of B12 are not common and that supplementation with long term metformin use does not generally occur (K. Ramaiya; Personal Communication).

As trial subjects will have been taking high dose metformin for a period of up to 4 years, we seek to establish whether Vitamin B12 deficiency is common in the trial population, and more prevalent in participants in the metformin group. To this end we will test Vitamin B12 levels in a

selection of participants, randomly distributed between metformin and placebo groups, at trial exit. We will include all participants who have anaemia based on their last full blood count results who are still in trial follow up. In addition we will randomly select 10% of people who are still in follow up in the trial, balanced by gender and allocation to have the Vitamin B12 test.

As we do not have baseline Vitamin B12 values for these participants, we will not be able to determine how much metformin use is associated with reduced Vitamin B12 levels in individuals. We will be able to analyse the difference in Vitamin B12 levels between those in the placebo arm and those in the metformin arm. Samples will be analysed at the Muhimbili National Hospital Reference laboratory as with other trial samples, and the normal ranges as determined by the laboratory for the Tanzanian population will be used. Blood samples will be taken as per the trial SOP, maintained in a cooled sample box and transported to the laboratory for testing on the same day.

As these tests will be done at the trial end, participants identified with low Vitamin B12 levels will be contacted through the HIV Care clinics and offered Vitamin B12 supplementation. These actions will be taken together with the HIV care clinicians, who will be provided with all relevant information.

2.2.2 Objectives

Our aim is to conduct a phase III randomised trial to provide definitive data on the effectiveness, including cost-effectiveness, of metformin in preventing diabetes among HIV-positive individuals with pre-diabetes. The trial is designed to inform health policy across sub Saharan Africa. It will be large and simple with about 2000 participants enrolled and followed-up for 4 years.

The principle question that the trial addresses is: can the use of metformin either prevent progression to diabetes or delay the onset of diabetes among patients living with HIV and impaired glucose tolerance (Prediabetes)?

We will also observe safety and report on any adverse events. As discussed, the likelihood of observing any cases of lactic acidosis in this phase III is close to zero. Nonetheless, we will have a strict protocol in place to detect lactic acidosis in the study cohort.

Primary objective

- i. To conduct a phase III randomised placebo-controlled double-blind trial to determine the efficacy of metformin in reducing the incidence of diabetes among people living with HIV infection and pre-diabetes.

Secondary objectives

- i. To determine the costs incurred by the health service with the use of metformin (in relation to placebo) and to relate these to quality of life. To determine also the costs associated with accessing care for patients in the two arms of the trial
- ii. To compare diagnostic indicators for diagnosing diabetes in persons living with HIV
- iii. To determine the safety and relative tolerability of metformin in persons living with HIV
- iv. To determine the prevalence and incidence of glycaemia related complications (including retinopathy, neuropathy and nephropathy) in patients living with HIV and prediabetes.

The endpoints of the trial are:

Primary endpoint:

A challenge is that the (clinical) diagnosis of diabetes varies considerably between clinical centres across Africa, and the diagnostic utility of markers of raised glucose is much less understood. For example, as mentioned above, WHO advises against the use of HbA1c. It is also impossible to know, in the case of fasting glucose, whether patients have actually fasted or indeed the size of the meal that they had the night before, which may affect their readings even if they have fasted. Ability to diagnose clinical diabetes and start patients on treatment and/or lifestyle programmes has been set back following COVID-19, which has resulted in resource constraints in health care delivery.

Our primary endpoint was chosen following extensive consultation with clinical and public health experts in Africa. We also have many secondary endpoints, which shed light on the utility of glycaemic markers.

The **primary outcome** is the incidence of diabetes using the gold standard method for the diagnosis of diabetes. This will be determined with up to 48 months of follow-up.

There might be other beneficial effects of metformin – e.g. as an anti-inflammatory that reduces the incidence of HIV-associated clinical events and mortality but detecting such effects in a clinical trial would be hugely challenging.

Trial participants will be tested for glycaemia annually by the oral glucose tolerance test (OGTT) and HbA1c and when indicated clinically (e.g. if they present with symptoms). In addition, participants will be offered a routine fasting blood glucose 6-monthly.

The diagnosis of diabetes will be by **oral glucose tolerance testing**, which is the gold standard, and using WHO criteria (i.e. once a participant is considered to have reached a fasting plasma glucose ≥ 7.0 mmol/L or ≥ 11.1 mmol/L two hours following oral glucose load).⁶⁷ Use of fasting plasma glucose alone could miss those with isolated postprandial hyperglycaemia (the frequency of which is unknown in Africa). The utility of HbA1c as a diagnostic tool in Africa is unclear since the high prevalences of anaemia (including from malaria, haemoglobinopathies and HIV), as is found in Tanzania, could confound test results.

The participant will be determined to have reached the primary endpoint if they have a blood glucose 2-hr post glucose load (OGTT) ≥ 11.1 mmol/L or if they have 2 consecutive fasting blood glucose levels ≥ 7.0 mmol/L (at least one of which must be done alongside a 2-hr post glucose load test).

We need to be reasonably sure that patients have fasted adequately but knowledge of the accuracy of reporting of fasting by patients is limited. We hypothesise, based on experience in the phase 2 study and with management, that participants are more likely to fast when they come to clinic for a much longer investigation (i.e. when they have a 2-hr post glucose load test). Therefore, this criteria is made explicit in the definition of the primary endpoint.

We anticipate the following scenarios in which the participant will be found to have reached the endpoint:

- a) At the annual OGTT, the participant is found to have a 2-hour post load blood glucose value of ≥ 11.1 mmol/L.
- b) At the annual OGTT, the participant has a fasting blood glucose ≥ 7.0 mmol/L and a 2-hour post load blood glucose value of < 11.1 mmol/L. They will be asked to return a week later for a repeat fasting blood glucose. If the fasting blood glucose is < 7.0 they will remain in the study. If the fasting blood glucose is ≥ 7.0 mmol/L they will have reached the endpoint.

In cases where participants do not return in a timely manner, we will use any 2 consecutive fasting glucose tests (provided at least one is done with a 2-hour post glucose test).

- c) At the interim fasting blood glucose test, if this is ≥ 7.0 mmol/L the participant will be asked to return a week later. If the second fasting blood glucose is ≥ 7.0 mmol/L then an OGTT will be done and regardless of the OGTT result the participant will be determined to have reached the endpoint.

- d) At the interim fasting blood glucose test, if this is ≥ 7.0 mmol/L the participant will be asked to return a week later. If the second fasting blood glucose is < 7.0 mmol/L, the participant will remain in the trial and be tested again at the annual OGTT.

Secondary outcomes

These will be defined in detail in the statistical analysis plan. They will include: diagnoses of diabetes as according to each of the indicators alone (2 hr post glucose load of 11.1 mmol/L or more, fasting glucose of 7.0 mmol/L or more or HbA1c of 48mmol/mol (6.5%) or more). For the fasting blood glucose, the endpoints will include single values measured when an oral glucose tolerance is done, and 2 consecutive values. An endpoint comprising diabetes as indicated by any one of these indicators will also be considered.

An Endpoints Review Committee will be formed to establish diagnosis of diabetes in cases that are not easily diagnosed by an algorithm. This will be based typically on assessments of glycaemia, symptoms or clinical complications of. The endpoint review committee will include 2 specialist physicians: the physician who did the initial diagnosis and a second specialist not involved with the clinical management of the patient. Where there is disagreement, a 3rd physician will be invited.

Findings of the Endpoint Review Committee will be combined with the primary endpoint classification above to form an additional secondary endpoint.

Other secondary outcomes will include determining safety, the prevalence and incidence of glycaemia related complications (including retinopathy, neuropathy and nephropathy) in those with prediabetes, time to diabetes-free survival, cost consequences, health-related quality-of-life, and cost-effectiveness.

Adverse events are discussed below. These will be assessed by the Adverse Events Review Committee, which will include members of the Endpoints Review Committee but will be larger. They will assign the final diagnosis of the adverse event and its likely link to study product.

Health Economics. Societal costs, i.e., patients' out-of-pocket expenses, costs associated with lost productivity, and health services and social care resource use costs will be collected. Patients will be asked to complete both the EuroQol EQ-5D and the 12-Item Short Form-12 (SF-12) health survey questionnaire and responses will be converted to health-related quality of life utility values. Outcomes will be quality adjusted life years (QALYs), direct and indirect cost changes per patient, and cost per diabetes case prevented.

In ancillary studies we will compare diagnostic methods for diabetes in participants living with HIV.

3. SELECTION OF CENTRES/CLINICIANS

The study will be conducted largely at the facilities used in the phase 2 trial, as mentioned above. These facilities provide comparatively high quality clinical care. There will be at least one research physician at specialist registrar level at each site, supported by diabetes and infectious disease consultants.

The study will also have a clinical monitor, independent of the research team, who will contribute to the assessment of adverse and serious adverse events.

Training of study clinic teams on the new research protocol will be conducted prior to the start of recruitment. The study teams will oversee the coordination of the clinical trial at the study site, supervising the clinical care of patients, and ensuring compliance with the study protocol and good clinical practice.

The research team in Tanzania will be supported by clinical researchers and clinical trialists from the UK. The trial will also be monitored by an independent data safety monitoring committee, which will include at least one consultant diabetologist and at least one infectious diseases consultant.

4. SELECTION OF PATIENTS

4.1 Patient inclusion criteria.

- i) Adult HIV-positive persons on antiretroviral therapy (ART) for at least 6 months and considered stable on treatment (i.e. in regular attendance for care). Considered by the clinical team to be in regular care with a plasma viral load of less than 1000 copies per ml taken within the last 12 months.
- ii) Either impaired fasting glucose (≥ 6.1 to ≤ 6.9 mmol/L) and/or impaired glucose tolerance at 2 hours (≥ 7.8 to < 11.10 mmol/L)
- iii) Planning to remain in the area for > 12-months
- iv) Written informed consent

4.2 Patient exclusion criteria

- i) Pregnant women
- ii) Patients who were participants of the META Phase II study
- iii) Renal disease or renal dysfunction (eGFR<45)

-
- iv) Signs and symptoms of any form of acute metabolic acidosis including lactic acidosis and diabetic ketoacidosis
 - v) Other acute conditions with:
 - a. the potential to alter renal function including: dehydration, severe infection or shock
 - b. the potential to cause tissue hypoxia including decompensated heart failure, respiratory failure, recent myocardial infarction, shock
 - vi) Congestive heart failure requiring pharmacological treatment
 - vii) Clinical evidence of liver disease
 - viii) Evidence of alcoholism or acute alcohol intoxication
 - ix) Known hypersensitivity to metformin or any excipients associated with the preparation (in this case: Magnesium stearate, sodium carboxymethylcellulose, hypromellose)
 - x) Other acute conditions requiring hospital admission or emergency clinical intervention, including blood pressure >180/110 mmHg, haemoglobin <6.5g/dL for women or haemoglobin <7.0g/dL for men (grade 3); white cell count <1.5 x 10⁹ cells/mm³(grade 3) and any baseline liver function derangements at grade 4 according to DAIDS criteria.

There are two common definitions of pre-diabetes: the World Health Organisation (WHO) definition and the American Diabetes Association definition. The American Diabetes Association defines pre-diabetes at lower levels of glycaemia than the levels recommended by WHO. We have chosen the WHO definition as that is widely accepted across Africa.

The higher risk of diabetes with increasing levels of blood glucose are demonstrated in the US Diabetes Prevention Program ⁴, the largest study of pre-diabetes (Table 1 above). Diabetes incidence increased sharply with increasing fasting glucose level among persons with pre-diabetes.

We will also restrict to patients who have been on antiretroviral therapy for at least 6 months and who have achieved viral load suppression (<1000 copies/ml) as per the National Guidelines for the management of HIV/AIDS (2019)⁶⁸. Those who have newly initiated antiretroviral therapy or have high viral load or other very high clinical or laboratory markers (including severe hypertension)⁶⁹, have a comparatively high frequency of adverse events, which are often linked to their HIV-infection. Excluding them will minimise the number of adverse events reported to the study and ensure that health services focus on their immediate clinical issues. When these are resolved, the individuals will be invited to re-screen for the trial if recruitment is continuing.

We have excluded patients in whom metformin is contraindicated

(<https://www.medicines.org.uk/emc/product/6298/smpc>). Metformin is not teratogenic but pregnant women will be excluded as gestational diabetes/ dysglycaemia requires specialist management. We have excluded those with known renal or liver disease, heart failure or those hypersensitive to metformin – this number will be small. Median age of patients in HIV programmes is around 30 years, when the prevalence of pre-diabetes is already high. Therefore, we have not included a minimum age as an inclusion criterion.

We do not propose to have NRTIs as an exclusion criteria as there is no clear evidence that co-administration of metformin would increase risk of lactic acidosis, as described above. Having minimal inclusion and exclusion criteria will ensure greater generalisability.

We propose to use oral glucose tolerance testing, as that is the gold standard for diagnosing diabetes. We will be measuring HbA1c and fasting glucose also, so that we can assess the utility of these measures in this population.

4.2.1 Number and source of subjects

We have been working at most of the study sites (for the phase 2 study). We will provide general information about the metformin phase 3 trial to all patients attending the HIV-clinics.

Two thousand and one hundred patients will be enrolled from the study sites. Patients attending the government health facilities who have been on ART for at least 6-months will be screened for the study. Those eligible will be invited to join following written informed consent.

In the phase 2 study, we deliberately started enrolment very slowly in early November 2019 and from about Dec 20th 2019 stopped new recruitment for a month because of holidays in the country. We then had considerable disruption from Covid-19. One of our sites (Amana Hospital) was closed on 9th April 2020 just as we reached a good recruitment rate. We had a period of 5 weeks when recruitment into research studies was suspended in the country by regulatory authorities (because of a partial lockdown). Following that, when recruitment resumed, we had difficulty in procuring supplies for consumables, particularly for oral glucose tolerance testing as Covid-19 had disrupted supply chains. At any one time, we were recruiting at most at 2 of the 4 hospitals where recruitment was done. Despite these challenges we enrolled 360 participants by the 24th July 2020.

In the phase 3, we will start recruitment at Temeke, Amana, Mwananyamala and Hindu Mandal Hospitals at roughly the same time and anticipate that recruitment will take 6-12 months to complete. Two further health facilities (Mbagala and Mnazi Moja) will be kept in reserve in case recruitment is slower than anticipated. We have a good knowledge and working relations with other hospitals also, including Kibaha Hospital and Sinza Hospital, as further reserves.

4.3 Screening procedures and pre-randomisation investigations

Patients stable on ART will be contacted during their routine HIV clinic appointments. They will be given an information sheet about the metformin study and asked to give written consent for screening. For those who consent, we will arrange a return visit when participants will attend having fasted, i.e. not eaten or drunk anything except water for 8 hours before their appointment). We will screen participants with an oral glucose tolerance test. Those found to have diabetes will be referred and offered treatment according to national guidelines. Persons with pre-diabetes will be invited to join the trial if they fulfil the other inclusion criteria and do not fulfil the exclusion criteria.

Screening procedures: At screening, the following information will be recorded onto patient case record forms: Patient identifiers, eligibility according to each inclusion and exclusion criterion, clinical examination data (height, weight, and blood pressure).

Laboratory investigations to be conducted at screening will be: Fasting blood sugar, 2-hour blood sugar measurement (after consuming 75g of sugar solution), and urine β hcg (if applicable). Point of care HbA1c will be performed in selected participants as part of the screening. This will be to address the secondary question of comparison of diagnostic indicators for diabetes. All participants who are enrolled in the trial will have a point of care HbA1c measurement. Patients who are acutely ill at the time of screening may be re-screened for enrolment after resolution of the acute illness. In addition, if after the completion of the OGTT, study staff are not convinced that a patient was adequately fasted, they may ask the patient to return for a repeat OGTT. The repeat OGTT may not occur within 72 hours of the first OGTT. Pregnant women will be excluded as gestational diabetes/ dysglycaemia requires specialist management.

Patients suspected of Covid-19 will be referred to the government Covid-19 services for a PCR test and managed accordingly. Tanzania has not had a lock-down but early on in the pandemic, it closed a major hospital (Amana) to general presentations and converted it a Covid-19 only hospital. However, the infection appears to be much less severe than in high-income countries and neither Amana Hospital or Hindu-Mandal Hospital, a not-for-profit private hospital which serves older more wealthier people, have had many presentations of Covid-19. The Johns Hopkins estimates that to date there have been 509 cases of coronavirus and 21 deaths from Covid 19 in Tanzania. This will be an under-estimate because of limited testing but it does seem that the Covid-19 disease burden is limited within Tanzania. In the neighbouring countries, Kenya has the highest death toll of approximately 700 confirmed deaths to date. The other neighbouring countries including Uganda, Kenya, Rwanda, Zambia, Malawi, Mozambique, Burundi, DRC generally have confirmed numbers of deaths of less 200 in total to date (end September 2020). Although the burden is low in Tanzania, clinical staff will be trained to identify suspected Covid-19 among patients and refer them to appropriate facilities for testing.

Informed signed consent will be obtained just before randomisation. Patients will be required to consent to be randomised to either metformin treatment or the placebo control group.

Enrolment procedures: Patient's eligibility for enrolment will be confirmed after diagnosis of pre-diabetes following the oral glucose tolerance test.

At enrolment, clinical history and physical examination details will be recorded as well as results of all screening investigations. The following information will be recorded onto patient case record forms: Patients residence and contact details; medical history; including date when they started on ART and regimens, presence of other non-communicable diseases, full list of current medications, last viral load and a full clinical examination (including weight, waist circumference and height).

In addition to the oral glucose tolerance test (fasting glucose and repeat glucose measurement 2hrs after oral glucose loading), point of care glycated haemoglobin test (HbA1c) and malaria rapid diagnostic test conducted during screening, and further laboratory investigations to be conducted at enrolment will be: a full blood count, liver function tests, renal function tests, and a lipid profile. In a proportion of patients, fasting insulin laboratory measurement will be conducted on the sample collected for blood chemistry. In addition, attending clinicians will be able to conduct additional clinical assessments, monitoring and order any further tests as appropriate in the patients' management, and invite patients back to clinic for assessment.

A trial register of all patients who are eligible and invited to join the trial, will be maintained as part of the EDC. Those accepting will have name, date of birth, date of randomisation and trial number recorded. Those who refuse will have initials, age, and reason for refusal recorded.

As the follow up period for some participants can be extended beyond 36 months to up to 48 months, participants who have reached the 36th month visit will be asked if they wish to continue in the trial for up to a further 12 months, and informed that all trial activity will finish by May 2026. This will only apply to approximately 500 participants who will have reached 36 months follow up prior to September 2025. Written informed consent will be taken from these participants to continue their participation in the trial. The remaining participants will have completed 36 months follow up or less by May 2026 and no new consent will be required.

5. RANDOMISATION

The trial is double-blinded to minimise bias.

Randomisation will be stratified by sex to ensure that at least one third enrolled are men and one third are women. The other one third can be men or women. This is essential in order to ensure that study findings are generalisable. In the phase 2, we struggled to identify men as they tend to avoid seeking health care (a problem that is common in most settings and most health conditions).

Both the active drug and the placebo are being supplied by the Merck Group for the current phase 2. The placebo is identical in appearance and texture. The active drug – metformin – is a slow release formulation, which is well tolerated. Patients will be on a cocktail of drugs (for HIV-infection and any related conditions). Unmasking as a result of occurrence of side-effects is therefore less likely than would be the case in a HIV-uninfected cohort or if we used standard metformin.

In the phase 2, we initiated metformin (or placebo) at 2000 mg per day and noted that mild adverse events occurred in approximately 55% of participants and usually resolved after 2 weeks. In the phase 3, to ensure better tolerability, we will start patients at 1000mg per day and titrate up at 2 weeks to 2000mg per day. For patients in whom this is not possible (e.g. if mild adverse events remain at 2 weeks), we will continue their dose at 1000 mg until week 4. At 4 weeks, they will be titrated up to 2000mg daily. We are not expecting any patient who will not be able to tolerate 2000mg per day, based on the experience acquired in the phase 2. However, clinical staff will have the opportunity to maintain participants at lower than 2000 mg per day if indicated clinically.

The greater issue for participants in the phase 2 was the number, and to a degree, the size of the pills, rather than the minor early side effects. Therefore, in the phase 3 we will strengthen the adherence counselling provided to participants.

Patients in both arms will also be provided with standard diet and lifestyle advice, delivered in the local language (Swahili).

Eligible participants will be randomised to the intervention arm or control arm using permuted block randomisation with varying block sizes of 4, 6 and 8 persons chosen at random using the SAS software. This method will ensure a balanced allocation of subjects among treatment groups. Patients fulfilling the eligibility criteria will be randomised sequentially.

Each participant will have a unique randomisation code. They will be given appropriate study drug supplies at regular intervals and appointments will be at baseline, 2 weeks, 4 weeks and months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48. Drug refills will be prepared in advance of the participants' attendance, with the final refill provided at the last visit before study end in May 2026.

If there is disruption to these routine appointments (e.g. because of Covid-19), we may move some schedules to 6-monthly and/or conduct home visits to deliver drugs, provide adherence

support and collect data and samples, if acceptable to the participant. As part of our wider programme, our research group is involved in major studies evaluating community-based HIV and non-communicable disease care and we have the ability to modify care of participants in accordance with temporary changes in local practice brought about by pandemics.

5.1 Randomisation practicalities

A randomisation schedule will be created by an independent statistician (based at the LSTM) using permuted-block randomisation of variable size. It will be integrated into the Electronic Data Capture system (see section 10 on Data Management), as done in the phase 2.

When a patient is confirmed to be eligible via the screening process and has consented to being enrolled, the consent will be entered into the Electronic Data Capture system and the patient will be allocated the next available trial number for their site. The trial number assigned to that participant will be used on all trial documents and will identify the pre-labelled coded study medication (Metformin or placebo). This number is unique and should not be used for any other participant.

With respect to patients who are part of the META Phase II trial, they will continue their treatment and follow up in the Phase III in the groups that they have already been randomised to.

5.2 Randomisation codes and unblinding

The independent trial statistician responsible for the schedule will maintain the randomisation codes, a copy of which will be held by the trial pharmacist. Unblinding will be discouraged during treatment; if however, a trial clinician considers it necessary for a participant's allocated treatment to be unblinded this should first be discussed with the local chief investigator or a clinical deputy. If unblinding is considered appropriate, the reason for unblinding should be recorded in the Electronic Data Capture system and in the unblinding register held in the trial office. This register should not include the details of the allocated treatment arm.

If it is considered appropriate to unblind a participant an unblinding form should be completed and sent to the independent statistician, or in their absence to the pharmacist. Unblinding information will be kept confidential to clinical staff responsible for the patient. The unblinding form will be entered on the database.

In the event of adverse drug reactions considered to be possibly related to study drug, study drug will be discontinued immediately in the affected patient. Unblinding will not be done unless it is required in the interest of patient safety, for example in the case of a potential metformin related lactic acidosis. The specific event will then be managed according to a pre-established SOP (standard operating procedure).

Any code break intentional or accidental will be documented and will include as a minimum the date, time, reason for unblinding, name of the person requesting and person breaking the code.

Care will be taken when filing documentation and communicating an unblinding event to ensure that the trial team are not unblinded unnecessarily.

6. TREATMENT OF PATIENTS

6.1 Trial treatment

Eligible participants will be randomised to receive either treatment with extended release metformin hydrochloride 2000 mg per patient per day, or daily matching metformin placebo tablets. The follow-up schedule is given in detail in section 7.1.

6.2 Trial product(s)

Merck will supply Metformin and the matching placebo. We have chosen to use the same metformin dose as for diabetes (which maximally enhances insulin sensitivity) and which has been used in other diabetes prevention trials. As discussed above, we will start patients on a low dose and titrate up to reduce the risk of minor side effects.

The placebo will be supplied also by Merck and will be identical in appearance, shape and weight as the active drug. These will be packed and labelled by NIMR research staff for use at the study sites. The label will include information on who the participant should contact in the event of the occurrence of severe adverse events, which might be related to taking the study medication.

6.2.1 Use of placebo

There is currently no available pharmacological treatment for patients living with HIV and prediabetes for the prevention of progression to diabetes. The evidence for the efficacy of metformin is based on data from high and middle-income countries and in non-HIV-infected populations. The HIV population differs in that there is additional impact from the antiretroviral therapies that the patients are taking, and possibly also differing patient behaviours.

People with prediabetes and HIV are a diverse group, differing in the HIV-related therapies they are taking, duration of living with HIV and duration on therapy, as well as differing in the uptake of lifestyle change advice that they are offered; all of which could affect their risk of progressing to diabetes. By randomly assigning subjects to active treatment and placebo groups, that diversity is spread equally between the groups. In large trials, such as ours, this ensures that the two study arms have patients with near identical characteristics, except that one has received an active treatment and the other a placebo. Thus, any effect observed can then be attributed to the treatment being tested.

6.3 Follow-up of patients

The duration of follow-up following randomisation is up to 48 months. All participants will have been on antiretroviral therapy for at least 6-months. Their routine appointments at the HIV-clinics will usually be scheduled at 3-monthly intervals by the health facility. Thus, patients will be seen at enrolment (week 0) and subsequently at weeks 2 and 4, and then at 3 months and 3-monthly thereafter by the study team. We have included extra visits at 2 and 4 weeks following enrolment into the trial to the patients' routine schedule of visits. These extra visits are intended to re-enforce adherence to study drugs, to re-enforce their understanding of side effects and the actions that they need to take if these occur and to examine the participant clinically. The participants will be seen by a study physician.

Renal and liver function and haematology testing will be repeated at 3 months, 12 months and then annually (months 24, 36 and 48), or the following visit if the annual visit is missed, to monitor safety.

Patients will be provided with sufficient packs of 2000 mg tablets (or placebo), with 1 week of extra tablets to allow for the possibility of patients attending a few days late for their appointments. Patients will be requested to return their unused tablets at scheduled clinic visits in order to monitor their adherence (discussed below).

As mentioned above, we will adapt follow-up schedules to 6-monthly or conduct home visits where possible in the event of disruption (e.g. due to a pandemic).

Recording and monitoring of adverse events

Adverse events will be recorded by the attending physician. In addition to adverse and serious adverse events, we will classify lactic acidosis and the classical signs of lactic acidosis as adverse events of special interest. These signs comprise: abdominal or stomach discomfort, decreased appetite, diarrhoea, fast or shallow breathing, a general feeling of discomfort, muscle pain or cramping; and unusual sleepiness, fatigue, or weakness.

We will also classify any clinical signs of hepatomegaly with steatosis as an adverse event of special interest. While this condition often does not have any clinical signs and symptoms, it may present with an enlarged liver on examination, and symptoms of fatigue and right upper abdominal pain. The risk of developing this condition is higher in patients who are obese and who have type 2 diabetes or metabolic syndrome. Although metformin is not associated with this condition, the underlying liver disease may predispose to the development of lactic acidosis.

Each time a reportable adverse event is recorded by the attending physician, he/she will notify the site trial co-ordinator who will convene a meeting of the Adverse Events Review Committee. This will comprise the trial co-ordinator, the attending clinician, the senior Tanzania

investigator (co-chief investigator), the UK trial co-ordinator and at least one study specialist diabetologist. The physicians may be deputised by suitably qualified clinicians. The meeting may be virtual or face-to-face. A minimum of 3 clinicians must attend. The meeting will usually be within a few hours and no later than 24 hours from the recording of the adverse event.

The likelihood that serious adverse events and adverse events of special interest are linked to the metformin will be assessed by the committee.

The attending physician will manage the patient promptly. For example, he/she may invite the patient back to clinic if the adverse event has shown up in blood test results done after the patient has left clinic. The clinical management strategy will be reviewed by the Adverse Events Review Committee and finalised. The diagnosis and grading will also be finalised for reporting purposes.

These details will be checked further by an independent clinically qualified monitor when he/she visits the site. This review will usually be done in bulk – i.e. all patients who have had an event will be reviewed together by the independent monitor.

Non-reportable adverse events such as incidental findings at baseline or adverse events at grade 1 or 2 will be managed by the attending physician. All such clinical events will be reviewed at clinical meetings of clinicians, which will be conducted daily prior to the start of the clinic. Management strategy of these events/conditions will be reviewed jointly at these meetings.

The trial co-ordinator based in the UK and trial co-ordinator based in Tanzania will also review entered data regularly to check for non-reportable and reportable adverse events to ensure that a management strategy has been discussed.

When there is disagreement about the diagnosis of the event and its likely link to the medication, the information will be sent promptly to Prof John Wilding, who is the chair of the independent Data and Monitoring Committee for the trial.

Both the serious adverse events and adverse events of special interest, including all hospitalisations and deaths will be reported to the sponsor within 24 hours of site becoming aware of the event and to the ethics committees within the rules / timelines that the particular ethics committee specifies (those of special interest will usually be reported to the sponsor within an hour, although 24 hours is the maximum) . In addition, as a further measure, the adverse events of special interest will also be reported to the Data Safety Monitoring Committee within 24 hours of their receipt by the sponsor. The Data Safety Monitoring Committee includes 2 senior physicians and a clinical trialist. The adverse events of special interest will be directed to Prof John Wilding, a senior diabetologist and chair of the Data Safety Monitoring Committee, who will consult the other members as needed.

In addition to the real-time monitoring, we will collate all adverse events (divided by adverse events, serious adverse events and adverse events of special interest) for the independent Data Safety Monitoring Committee at 3-monthly intervals. They will meet at these intervals to discuss trends and other safety aspects of the trial.

6.4 Measures of adherence

Patients will receive adherence advice each time they visit the study clinic. Provision of adherence support with drugs is essential to achieve the optimal efficacy. Work done by our group shows that limited support repeated during the initial period following initiation of treatment is a highly effective means of linking and retaining patients in care⁷⁰.

We will monitor adherence to the study medications by interview, as used in the phase 2 trial, which were adapted from previous HIV trials.

Additional measures for adherence support trialled in the phase II study include training of the nurses about the research process and importance of fully informing the participants about the study, frequent contact early on, particularly on the first 1-2 weeks following enrolment, regular engagement thereafter to support adherence such as culturally appropriate interactions (regular calls & counseling), enhanced communication strategies (e.g. use of expert patients) and forming partnership with the patient through patient representatives attending steering committee meetings.

6.5 Antiretroviral therapy and non-trial treatment

All participants will be treated with concomitant antiretroviral treatment in line with the national programme guidelines. Other medication(s) or treatments as necessary for the management of HIV related illnesses or other chronic disease conditions will be documented and evaluated for compatibility with administered study drugs.

7. ASSESSMENTS AND FOLLOW-UP

7.1 Schedule for follow-up / Flow Chart

The duration of follow-up post randomisation is up to 48 months. Patients will attend for scheduled post enrolment (week 0) assessments at the study clinics at weeks 2, 4, 3 months and 3-monthly thereafter. Patients stable on antiretroviral therapy usually attend the clinic every 3 months to collect their antiretroviral medication and receive clinical or laboratory monitoring. The study visits will coincide with routine visits for HIV care where possible. For any additional visits, we will cover transport costs.

The study will send text reminders of appointments. Patients who miss appointments will be contacted by phone or by home visit if necessary within 2 weeks and encouraged to attend. This service is not currently available within the health services.

Crucially, participants will also be encouraged to report to the study clinics whenever they are ill in between scheduled follow-up visits. They will be given a phone number to call if they wish to discuss their symptoms with clinical staff. In the information provided to patients (both written and verbal), we will educate patients about the signs and symptoms that should trigger a self-referral. This will include symptoms related to lactic acidosis, which will trigger an immediate self-referral. When patients suspect symptoms of lactic acidosis or have conditions that could increase their risk (e.g. dehydration, hypotension, breathlessness), they will be asked to stop medication immediately and to present immediately to the clinic or nearby hospital. The study clinics are open 24 hours a day, 7 days a week and have comparatively high clinical cover at all times. Study participants will be identified as being in the trial from their clinical records, from a study appointment card and from the trial information sheet and they will have access to expedited care when they self-refer.

At each follow up assessment, the following will be performed:

- An adherence assessment,
- Medical history and symptom check to detect intercurrent illness
- Clinical examination by a physician and record of events since last visit
- Full blood count, liver function tests, renal function tests, HbA1c test, malaria rapid diagnostic test and OGTT as indicated by protocol schedule.
- Any or other clinical investigations as indicated by patient's clinical state

Renal and liver function testing and haematology tests will be repeated at month 3, 12, 24, 36 and 48 unless baseline blood tests indicate any abnormalities, in which case blood monitoring will occur more frequently (usually every 3 months). HbA1c and oral glucose tolerance testing will be repeated 12 monthly, unless otherwise indicated. Table 6 charts the procedures over the course of the follow-up.

Table 6. Procedures planned over the course of follow-up.

Procedure	Screening Visit (week -2 to -4)	Enrolment Visit (week 0)	Weeks 2 & 4	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	Month 27	Month 30	Month 33	Month 36	Month 39	Month 42	Month 45	Month 48/ Final visit if prior to month 48
Consent for Screening	x																		
Consent for Enrolment		x												x	x				
History & Physical Examination*		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Fasting blood sugar		x			x		x		x		x		x		x		x		x
OGTT		x					x				x				x				x
Full Blood Count		x		x			x				x				x				x
Biochemistry renal and liver		x		x			x				x				x				x
Lipid tests		x																	x
Insulin		x																	x
HbA1c test		x					x				x				x				x

Vitamin B12																			X
Malaria rapid diagnostic test		x																	X
Adherence assessment		x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
Study drug prescription/refill		x	x	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x

** These assessments will be done by a doctor. Participants will also be asked about clinical events and any adverse events since their previous visit.*

7.2 Procedures for assessing safety

Haematological and biochemistry events will be assessed through scheduled and clinically driven laboratory tests done in the Muhimbili National Hospital Laboratory, Dar es Salaam. The DAIDS toxicity-grading tables will be utilized to grade laboratory measured parameters. (Appendix 3). In addition, as discussed above lactic acidosis and the symptoms that relate to this will be classified as adverse events of special interest.

7.3 Loss to follow-up

All subjects will be followed up for up to 48 months in the trial. Participants will be sent text message reminders prior to their appointment. If they fail to show, then they will be contacted by phone or by home visit if phoning is not possible, in order to understand the reasons and reschedule another appointment within a week. In addition to protocol-scheduled assessments, participants will also be encouraged to report to the study clinics whenever they are acutely ill, as noted in section 7.1.

Participants will be declared lost to follow-up if after their last scheduled attended appointment, they do not attend 3 consecutive appointments meaning they are without IMP for 6 months, and are not reachable. If they are reachable but do not attend 3 consecutive appointments and are without IMP for 6 months, they will be considered withdrawn.

7.4 Pregnancy

In the event of a trial participant becoming pregnant, confirmed by an urine pregnancy test, the participant will be taken off the IMP and put onto a different follow up schedule. They will be referred to Antenatal services if they have not already attended. The participant will be asked if we can contact them for information on the outcome of the pregnancy. This will be done at approximately 3 months after the expected end date of the pregnancy.

If a pregnancy is reported or diagnosed at or near the final scheduled study visit (ie, close to or at the point of trial closure), the planned 3-month post-pregnancy follow-up will not be conducted due to insufficient time. The follow-up contact was to document pregnancy outcomes and is not related to participant safety monitoring, however safety reporting obligations remain unchanged. The outcome section of the Pregnancy Follow-Up Case Report Form will be marked as *“not assessable due to study closure”*.

7.5 Follow up of participants who have reached the primary endpoint

When a participant is found to have reached the primary endpoint, as described in section 2.2.2, the participant will be taken off the IMP. As the primary endpoint is also considered to be the point at which a diagnosis of diabetes is likely, the participant will then be referred to the diabetes clinic at the hospital they currently attend. Information on the tests and results will be included in the referral letter and the local clinician may be contacted if the participant agrees. The participant will be put onto a different follow up schedule, with one further appointment to

determine the outcome of the referral to the diabetes clinic and whether the participant accessed diabetes care. If a participant reaches the end point at or near their final scheduled study visit(ie, close to or at the point of trial closure), the planned 6-month post-referral follow-up visit will not be conducted due to insufficient time. This visit is intended solely to document routine clinical outcomes following referral and is not related to participant safety monitoring, however safety reporting obligations remain unchanged. In such cases, referral to the diabetes clinic will still be completed in accordance with the protocol. The Diabetes Referral Follow-Up Case Report Form will be completed to document that the referral was made, and the outcome section will be marked as *“not assessable due to study closure”*.

7.6 Trial closure

Study follow up will be for 48 months following randomisation. The trial will be considered closed after the last patient enrolled has completed 48 months of follow up, or by May 2026. The study will unblind once data have been cleaned. Trial exit procedures will include documenting exit date and data on an exit form. Clinical care of the enrolled patients will continue at the health facilities.

8. WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, trial follow-up and data collection.

8.1 Withdrawal from trial intervention

Withdrawal from blinded trial allocation has been covered in section 6.4 and will be recorded on an unblinding form. Patients may in addition be withdrawn from study treatment for the following reasons:

- i. Patient withdraws consent.
- ii. Patient becomes pregnant (confirmed by pregnancy test)
- ii. Unacceptable toxicity.
- iii. Intercurrent illness which prevents further treatment.
- iv. Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion.

No additional patients will be recruited to replace those patients who withdraw from the study. For participants who are pregnant will be taken off study medication and referred to the antenatal clinic for further management. Follow up of any patients so withdrawn from the study intervention and clinical data recording will continue unless the patient has explicitly also withdrawn consent for follow-up.

8.2 Withdrawal from the trial completely

If a patient wishes to withdraw from trial treatment, study teams will nevertheless explain the importance of remaining on trial follow-up or failing this, of allowing routine follow-up data to be used for trial purposes. If the patient explicitly states their wish not to contribute further data to the study, the study team will document this on a withdrawal of consent form.

9. STATISTICAL CONSIDERATIONS

9.1 Method of Randomisation

Patients will be randomly allocated to one of the two treatment arms using random permuted blocks of variable size. A randomisation list will be generated in SAS by an independent statistician who will keep the codes.

Randomisation will be stratified by sex to ensure a minimum of 1/3 of participants from each sex as mentioned above. Participants will fall into one of two groups in each strata. Each will have a unique code for their treatment allocation (metformin or placebo).

The pharmacists will prepare the dispensing of the study drugs into dispensing bottles and label the bottle with the code and the study ID. This will be quality controlled. At least two persons will be involved with dispensing and labelling with oversight from a third person.

9.2 Outcome Measures

The study's primary endpoint is the time to diabetes as ascertained by the oral glucose tolerance test.

9.3 Sample size

9.3.1 Sampling strategies. This will be a randomised controlled trial. Consecutive patients fulfilling the criteria will be invited to join.

9.3.2 Sample size determination

There have been no studies of diabetes incidence in persons living with HIV. We have therefore inferred from HIV-uninfected cohorts. In HIV-uninfected persons with pre-diabetes, the annual diabetes incidence is 10-20%^{4,5,7} and 70% can expect to go on to develop overt diabetes during their lifetime⁵. (See Table 1 above, which is based on a large clinical trial cohort).

Conservatively, we will assume that the annual incidence of diabetes in our HIV-infected pre-diabetes participants will be 5% (i.e. less than half that reported elsewhere).

In 3 RCTs, metformin reduced diabetes incidence^{4,42,44,71}. **In a meta analysis combining data**

from these 3 trials⁴³ (Table 7), metformin reduced diabetes by 35% (95% CI 0.22, 0.45) compared with control. Our study population will have a higher levels of glycaemia than that of patients studied in this meta analysis and evidence suggests clearly that the effect size will be greater will be greater in this group⁷¹⁻⁷³.

Conservatively, we will power the trial to detect a 30-35% relative reduction in diabetes incidence.

Table 7. Efficacy of metformin in reducing the incidence of diabetes reported in trials.

Region	RCT design	Population of prediabetes patients	Duration of follow - up time	No (%) who became diabetic (reported by authors)		Odds ratio (fixed) taken from meta analysis (95% CI) ⁴³
				Metformin	control	
US ⁴	metformin versus placebo, double blind.	Age>25y Fasting glucose 5.3-6.9 mmol/or 7.8-11.0 mmol/l after 2-h glucose load	2.8 years	233/1073 (21.7)	313/1082 (28.9)	0.68 (0.56, 0.83)
China ⁴²	metformin versus placebo, double blind.	Age>25y. Fasting glucose 6.1-6.9 mmol/l or 7.8-11.0 mmol/l after 2-h glucose load	12 months	1/33 (3.0)	6/37 (16.2)	0.16 (0.02, 1.42)
India ⁴⁴	open label, metformin vs standard care	Age 35-55y Fasting glucose 6.1-6.9 or 7.8-11.0 mmol/l after 2-h glucose load	30 months	52/128 (40.6)	73/133 (54.9)	0.56 (0.34, 0.92)

Note: diabetes defined as fasting glucose ≥ 7.0 mmol/l or ≥ 11.1 mmol/l after 2-h glucose load.

Table 8 shows the sample sizes per arm.

Table 8. Number of participants needed **per arm** overall to detect relative differences in the incidence of diabetes between the two study arms. Calculations assume a 5% two-sided significance level and that each participant will be followed for 3 years.

Assumed annual incidence of diabetes in the control group	80% power			90% power		
	5%	10%	15%	5%	10%	15%
Relative reduction in diabetes incidence in the metformin arm						
25%	1326	663	442	1802	901	601
30%	874	437	291	1192	596	397
35%	608	304	203	832	416	277
40%	439	220	146	605	302	202

Losses to follow-up: We have achieved low losses to follow-up in previous trials involving persons living with HIV initiating ART in Uganda and Tanzania (Jinja trial, 10% withdrew or lost from care over 3-years of follow-up; and Dar es Salaam REMSTART trial, 2% lost over 12 months). In the phase 2 as at end September 2020, a total of 21/364 (5.8%) patients have ended participation in the study. Of these 3 fulfilled late exclusion criteria (2 pregnant, 1 moved away), 1 was withdrawn by the clinician due to development of a severe illness, 10 participants did not return after enrolment and 7 withdrew due to side effects.

We anticipate that the losses will be lower in the phase 3. We will be titrating the dose and providing more adherence support. We will restrict recruitment to participants with HIV viral suppression and excluding those who are found to have baseline very low haemoglobin or white cell counts or who have abnormal liver enzyme values. We are also restricting to people aiming to remain in the area for 12 months or more (as opposed to 6 months in the phase 2).

We will aim for 2100 total (1050 per arm). With this number, even if losses are as high as 10%, we will still have over 80% power to detect a 30% relative reduction in diabetes incidence (justification of a maximum 10% loss to follow-up is provided below). If the effect is larger, say a 35% relative reduction, power will exceed 90%.

We have discussed power with policy makers. Although our view is that the effect size will likely be larger than 35%, having high power to detect a smaller reduction is important as the intervention may still be cost-effective at this level and could be scaled up with relative ease.

These sample size calculations have been cross-validated by simulation.

New timelines:

Due to the delays experienced in recruiting participants and the need to stop recruitment early (with n=1691 participants randomised) we are extending the follow up period to up to approximately 48 months.

It is possible that we will only see the benefits of metformin after sustained use and this was why we wanted to continue follow up for 3 years. If we had been able to recruit rapidly, as planned originally, follow-up of each individual to 3 years would have led to a neat easy to manage and easy to analyse dataset. If we are to follow up each participant for 3 years, as planned, it will mean continuing follow-up to December 2026. However, given the urgent need for the findings, we propose to end the study earlier in May 2026 and continue follow up of all participants to this date. This would mean that the most recent participants recruited (in the second half of 2023) would have a follow-up of a minimum of 2 years. We estimate that the follow-up will comprise: 915 participants followed for a minimum of 2 years (those recruited in 2023), 1058 participants followed for a minimum of 3 years (recruited in 2022) and 126 participants followed for up to 4 years (recruited in 2021). This would mean little or no loss to power from our original trial design. We anticipate that the effect size will also be unchanged, the lower follow-up being compensated by increased follow-up to 4 years of some participants.

10 DATA MANAGEMENT

Data will be collected and managed electronically as in the phase 2 using an in-house developed electronic data capture system, from here referred to as “the EDC”. The EDC

provides realtime rule-based data collection, query management, reporting and monitoring. It emulates Good Clinical Practice Guidelines (based on ICH guidelines) by tracking the user name, date/time, system version and device for each data record created or modified and storing a snapshot of the full data record prior to each modification in a separate audit trail.

All data will be treated as strictly confidential and will in no circumstances be made publicly available.

For data sharing, summary tables, continuous progress reports or presentations during various meetings will be provided and accessed online in the web based database, and credentials will be given to authorized officers representing stakeholders as deemed necessary by stakeholders consultations. Otherwise, generated information will be shared through the project website for public use and online workspace for scientific project network. Before data transfer takes place, we will make sure that the Data Transfer Agreement (DTA) is signed by NIMR and LSTM, as a requirement by the ethical committee in Tanzania. The copy of DTA is attached. When transferring data to LSTM in London, the encryption software will be applied. In addition we will make sure that no names of participant in the database, and individual record will be identified by given unique number (ID).

10.1 Data Collection and Quality Assurance.

Potential participants are screened for eligibility on the EDC in realtime. Eligible and consenting participants are registered on the system, allocated a unique study identifier, and connected to adaptive pre-defined follow-up and data collection schedules. Trial data is collected and entered against the unique study identifier at point-of-care into electronic case record forms (CRFs). Each electronic CRF has embedded skip logic and inter- and intra-form validation checks that give feedback to the user to resolve inconsistencies in realtime .

In the rare event of a system outage, sites will be prepared with paper CRFs as backup.

Research staff receive protocol specific EDC training, make valuable contributions to the electronic representations of the CRFs and the embedded data validation strategy, have access to user support and an issue tracking system.

Data management staff will provide on-going user support, communicate any EDC issues they are unable to resolve to developer staff, monitor the completeness of submitted data for each participant, and report on trial progress to the study team. Select analytical staff, granted access to the raw dataset, will report on more complex data-related issues by conducting interim mock statistical analyses.

Independent monitoring will be conducted to maximise quality of data and adherence to procedures. The UK team at LSTM will visit the site in Tanzania regularly and conduct monitoring of procedures and data quality on at least a 3-monthly basis. The Governance

Manager at LSTM will also visit the sites at least once and conduct an independent audit of procedures, data collection and assess data quality. (See also Section 16)

The monitoring will adhere to Good Clinical Practice Guidelines (based on ICH guidelines). The following data should be verifiable from source documents: all signed consent forms; dates of visits including laboratory results; eligibility and baseline values for all study subjects; all clinical endpoints; all serious / severe adverse events; routine patient clinical and laboratory data; dates drug dispensed; drug adherence (both for ART and for blinded study medication) and details of all concomitant medication.

10.2 Data Security

The Electronic Data Capture will be accessed by site research staff online. Access to the EDC's user facing components is restricted to authorized users and permissions within the system are granted as needed per user account through groups and roles. All data are submitted and received over encrypted channels where sensitive data values are individually encrypted prior to submission and storage and decrypted only for use by the EDC's user facing components.

Trial data are stored on cloud servers, deployed with industry standard security (Firewall, private network access to the database, drive encryption, field-level database encryption, etc). With this approach, sensitive information is rendered unusable, unreadable, or indecipherable to unauthorized individuals for "data in use" (e.g. data being analyzed by statisticians), "data in motion" [e.g. data being transferred between data entry and storage points] and "data at rest" (e.g. data in storage in the database). Backup and disaster recovery includes 4-hourly data archiving, encrypted archives stored in multiple locations, daily server snapshots, active system error detection, notification and reporting, and frequent mock restorations.

Physical documents, such as participant consents, will be stored in locked cabinets at secure locations.

10.3 Data Availability, Access and Sharing

As data are submitted and validated in realtime, raw data are technically available immediately after submission. However, access to any aspect of the data management system is granted on a need only basis and requires approval from the PI -- be it the user facing components, the system data servers, the trial database, data encryption keys, or EDC application settings.

Trial data and other clinical information will not be released without written permission, except as necessary for monitoring by the trial monitors.

Note: In the META phase 2, data collected from a patient on a particular day are available in a clean final format ready for analysis within a day or so. We will aim to have data up-to-date within about 2 days of collection so that ethics committees, our Data Safety Monitoring Board can be viewing up to date information.

11 ANALYSIS PLAN.

Data will be analysed using SAS and STATA. Findings will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Primary analyses will be based on the intention-to-treat population and secondary analyses will be based on the per-protocol population.

The primary endpoint will be analysed using a Poisson regression model with the study arm as the predictor. Incidence rate ratio and its 95% confidence interval will be derived from the Poisson regression model. Incidence rates will also be calculated as the number of incident cases divided by the person-time in years, with person-time calculated from randomisation to either i) when diabetes occurred, ii) study end at 3 years, iii) death or time last seen if lost to follow-up. The timing of diabetes will be estimated as the mid-point between two oral glucose tolerance tests, one indicating diabetes and the other below this threshold.

Time to event data (eg, from randomisation to the occurrence of the first diabetes) will be summarised using Kaplan-Meier curves and compared using a log-rank test. Cox model will be used to calculate the hazard ratio between two arms and its 95% confidence interval, In secondary analysis of the primary endpoint, we will adjust for covariates, defined apriori (age, sex, and baseline oral glucose tolerance test result) using the Poisson regression model. Per protocol analysis will be done and defined as according to reported adherence to the intended allocation. Subgroup analysis of primary endpoint will also be performed using the Poisson model on the prespecified subgroup variables (age, sex, and baseline oral glucose tolerance test result).

Other secondary outcomes will be analysed using generalized linear models depending on their distributions. Mean difference with its 95% confidence interval will be derived for a continuous outcome and odds ratio with its 95% confidence interval will be estimated for a binary outcome.

Adverse events will be summarised using number and percentage of subjects with an adverse event.

The analysis will be led by a Prof of Biostatistics at LSTM (Prof Duolao Wang). A statistician based at NIMR Tanzania will verify the analysis. This is standard practice and is also part of capacity development. A detailed analysis plan will be described in full in the statistical analysis plan and prepared soon after the study starts and finalized before the data lockup.

Interim review of efficacy. Our initial proposed total sample size is n=2100 participants, each followed for 36 months. Following the end of enrolment, we have a revised sample size of n=1634 followed for between 2 and 4 years.

Our estimate of efficacy, used in the sample size calculations, is based on data from high and middle-income countries and in non-HIV-infected populations. It is possible that in our study population, the effect might be greater, if for example, adherence to study products (metformin or placebo) is very high. In the event that efficacy is greater than estimated, and the trial is able to demonstrate this very clearly at an earlier time than planned currently, we would want to consider early stopping of the trial. This could enable all people with pre-diabetes to benefit from the intervention in a shorter time frame (through changes in health policy and practice).

Thus, an interim review of data will be done by the independent Data and Safety Monitoring Committee. This will be done when at least 80% of the participants have been followed up for at least 2 years. This is beyond the half-way stage to ensure that the efficacy estimate calculated at this time is statistically stable. Early stopping will be considered if the significance level is $p=0.001$ or lower (i.e. using the Haybittle-Peto boundary). Conducting the interim review at this low significance level will ensure that the statistical penalty of the interim review on the final statistical analysis is negligible. The norm is to conduct final analyses of such trials at a significance level of 0.05.⁷⁴

Other knowledge that may have come to light since the start of the trial, will be taken into account before a final decision to stop is made by the steering committee. For example, if our effect estimate differs from that of other studies, there might be a case for continuing our trial, to show more definitively the difference between our finding and that of other studies.

12. ETHICAL CONSIDERATIONS AND APPROVAL

12.1 Ethical considerations

The study will abide by the principles of the Declaration of Helsinki.

The trial we propose will be hospital or clinic based allowing close clinical supervision and care of patients. Patient information will include education on recommended lifestyle changes and pharmacological agents.

Participants will be free to withdraw from the trial after enrolment if they do so wish, without compromising their care.

Persons identified with diabetes or hypertension or those who develop diabetes will be offered treatment by health services in accordance with national treatment guidelines. We will stock buffer drugs supplies for diabetes to ensure that there are no drug shortages during the trial period.

12.2 Ethical approval

Ethical approval for this protocol will be sought from the following committees:

- The research ethics committee of the sponsor at the Liverpool School of Tropical Medicine
- In Tanzania from the NIMR Research Ethics Committee (NatHREC) and guidance will be sought from the Tanzania Medicines and Medical Devices Authority (TMDA).

13. DISSEMINATION

The study will be conducted in partnership with the Ministry of Health in Tanzania and results will be reported to them as well as published in an international journal. We will also feed the results back to all participants on a one-to-one basis when they return for routine HIV follow-up. If the patient is not in the area, we may discuss on the phone and provide written material to the patient if they request this.

The Deputy Director of Preventive Services (Dr Janneth Mghamba) and the national programme managers for HIV control (Dr Angela Ramadhani) and for non-communicable diseases (Dr Sarah Maongezi) are partners on our wider research programme on the prevention and management of HIV-infection, diabetes and hypertension, and on this phase III trial. They have met with the research group every 3-6 months for the last 3 years and sit on the operations steering committee.

Also, on our steering committee in Tanzania is a patient representative who is the vice chair of the Tanzania Diabetes Association (Mr Ramadhan Mongi – diabetic since 1978).

14. POTENTIAL LIMITATIONS; ANTICIPATED PROBLEMS

This is a large simple randomised controlled trial with a clear objective endpoint. The design was chosen to minimise potential bias. We will select patients already identified with HIV-infection who are under regular follow-up. Thus, we anticipate enrolment and follow-up will both be high.

Covid-19 caused major disruption in the early part of 2020 but since about May 2020, there have been very few cases of coronavirus identified. Tanzania suspended research activity briefly but there has not been a lock down, and life has returned to normal for the vast majority of people. Therefore, we do not expect major disruption from Covid-19 and have the experience of working through many problems in the unlikely event of any other disruption.

15. TIME FRAME

We would like to start this trial in January 2021. We anticipate enrolment will take between 6-12 months based on our experience within the phase II study and knowledge of the patient group in Tanzania.

16 Trial Monitoring

The purposes of trial monitoring are to verify that:

- The rights and well-being of human subjects are protected.
- The reported trial data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement

16.1 Extent and nature of monitoring

The site will be visited at regular intervals in order to monitor the conduct of the trial. These visits will be made by the Trial Monitor/Manager. We will be supported by a clinical trials group at the Liverpool School of Tropical Medicine, later UCL – comprising a senior trials manager, 3-4 statisticians, 2 data managers, and a governance team; the latter group conducts trials monitoring including pharmacovigilance monitoring. The frequency of monitoring visits will be according to need but will be no less than every 6 months in each centre.

The personnel at the sites are all trained in data collection. Nonetheless, we will repeat training in Good Clinical Practice. As part of this, the governance office will visit the sites to supplement training. They will also conduct an independent audit of all procedures, including data collection, sample handling, informed consent. Independent monitoring will also be conducted by the East Africa Clinical Trials Monitoring Group.

16.2 Site monitoring

At monitoring visits, the data entered in the in CRFs and EDC database will be checked against available source data according to the procedures described in the trial monitoring plan filed in the Trial Master File. Data stored will be checked for missing or unusual values (range checks) and checked for consistency within participants over time.

Particular attention will be given to:

(a) Verifying, for the study drugs:

- I. That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
- II. That the study drugs are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

- III. That subjects are provided with necessary instruction on properly taking study medication.
- IV. That the receipt and use of study drugs at the trial sites are controlled and documented adequately.

(b) Verifying that the local investigator follows the approved protocol and all approved amendment(s), if any.

(c) Verifying that written informed consent was obtained before each subject's participation in the trial.

(d) Ensuring that the Principal Investigator has received the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(e) Ensuring that the local investigator and the investigator's trial staff are adequately informed about the trial.

(f) Verifying that the local investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the local investigator/institution, and have not delegated these functions to unauthorized individuals.

(g) Verifying that the local investigator is enrolling only eligible subjects.

(h) Reporting the subject recruitment rate.

(i) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

(j) Verifying that the local investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(k) Checking the accuracy and completeness of the EDC entries, source documents and other trial-related records against each other.

17 SAFETY REPORTING

17.1 Definitions

The definitions of the EU Directive 2001/20/EC Article 2 based on ICH GCP apply in this trial protocol. These definitions are given in the Table 9.

Table 9: Definitions of different types of clinical events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (or Investigator brochure) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • results in death • is life-threatening* • requires hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect
Adverse event of special interest	Any clinical signs of lactic acidosis including: hyperventilation, tachycardia, low blood pressure, altered mental status (confusion to coma). Any participant showing a combination of symptoms of indicating potential lactic acidosis including: abdominal or stomach discomfort, decreased appetite, diarrhoea, fast or shallow breathing, a general feeling of discomfort, muscle pain or cramping; and unusual sleepiness, fatigue, or weakness. Any signs or symptoms of hepatomegaly with steatosis including complaints of fatigue and right upper abdominal pain, and findings of enlarged or tender liver on examination.

17.1.1 Clarifications and Exceptions

The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an serious adverse event.

Medical judgement should be exercised in deciding whether an adverse event/adverse reaction is serious in other situations. Important adverse event/adverse reaction that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Adverse events of special interest should also be considered serious.

17.1.2 Trial Specific Exceptions to Expedited SAE Notification and Reporting:

Due to the seriousness of the disease in this study, the following situations that fulfill the definition of an SAE are excluded from expedited notification on an SAE form and should be reported on the specific case report form.

- Elective hospitalisation to simplify treatment or procedures
- Elective hospitalisation for pre-existing conditions that, in the investigator's opinion, have not been exacerbated by trial treatment.

17.2 Institution/Investigator Responsibilities

All non-serious adverse event/adverse reaction, whether expected or not, should be recorded in the toxicity (symptoms) section of the case report form and sent to NIMR Medical Research Centre in Dar es Salaam within one month of the form being due. SAEs/SARs should be notified to the NIMR Dar es Salaam and to the sponsor, LSTM/UCL. The serious adverse events and adverse events of special interest in any study clinic in Tanzania should reach the sponsor within the timeframe agreed with the Sponsor .

The severity (i.e. intensity) of all adverse event/adverse reaction (serious and non-serious) in this trial should be graded using the Division of AIDS Table for Grading the severity of Adult and Paediatric Adverse Events, Corrected Version 2.1, July 2017.

A flowchart is given at the end of this section to help explain the notification procedures. Any questions concerning this process should be directed to the trial coordinator in the first instance.

17.2.1 Investigator Assessment

(a) Seriousness

When an adverse event/adverse reaction occurs the investigator responsible for the care of the patient must first assess whether the event is serious using the definition given in Table 9. If the event is serious and not exempt from expedited reporting, then an SAE form must be completed and the NIMR Dar es Salaam notified as well as the trial sponsor, LSTM/UCL, as stated above. All events of special interest shall be considered as serious and must be reported in the same way.

(b) Causality

The Investigator must assess the causality of all serious events/reactions in relation to the trial therapy using the definitions in Table 10. There are 5 categories: unrelated, unlikely, possible, probable and definitely related. If the causality assessment is unrelated or unlikely to be related the event is classified as a SAE. If the causality is assessed as either possible, probable or definitely related then the event is classified as a SAR.

As discussed above, in addition to the assessment of causality by the investigator, the independent clinical monitor must also make an independent assessment. If there is disagreement between the two, then the final assessment must be made by a senior member of the data safety monitoring board .

Table 10: Definitions of causality

Relationship	Description	Event Type
Unrelated	There is no evidence of any causal relationship	SAE
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	SAE
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after	SAR

	administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

(c) Expected

If the event is a SAR the Investigator must assess the expectedness of the event. The definition of an unexpected adverse reaction (UAR) is given in Table 9. Potential toxicities associated with Metformin are:

- Skin rash / hypersensitivity reaction
- Hepatotoxicity
- Gastrointestinal disturbances
- Lactic acidosis

If a SAR is assessed as being unexpected it becomes a SUSAR.

(d) Notification

NIMR Tanzania and the Trial Sponsor (LSTM/UCL) should be notified within one working day of the investigator becoming aware of an event that requires expedited reporting. Investigators should notify the NIMR and LSTM/UCL of all SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration. SARs and SUSARs and adverse events of special interest must be notified to the LSTM/UCL and NIMR indefinitely (i.e. no matter when they occur after randomisation).

As discussed above, the data safety monitoring committee must also be notified (by LSTM/UCL) of all adverse events of special interest within 24 hours.

Notification Procedure:

1. The SAE form must be completed by the Investigator (named on the signature list and delegation of responsibilities log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the

absence of the responsible investigator the form should be completed and signed by a member of the site trial team. The responsible investigator should subsequently check the SAE form, make changes as appropriate, sign and then re-submit to NIMR and LSTM as soon as possible. The initial report shall be followed by detailed reports as appropriate.

2. SAE reporting will occur within the Electronic Data Capture system with automatic notifications being sent to LSTM/UCL and NIMR study co-ordinators. Backup paper based systems will also be available, in which case the SAE form will be sent as an email attachment to LSTM/UCL and to NIMR.
Email: NIMR Tanzania, email sokoinale@yahoo.co.uk and LSTM/UCL, email anupam.garrib@lstmed.ac.uk or a.garrib@ucl.ac.uk
3. Follow-up: Patients must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. Follow-up information should be noted on a further SAE form by ticking the box marked 'follow-up' and sending to NIMR Tanzania/LSTM/UCL as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient must be identified by trial number, date of birth and initials only. The patient's name should not be used on any correspondence.
4. Staff at the institution must notify the ethics committee of the event (as per the institutions standard local procedure).
5. Adverse events must also be reported to the Data Safety and Monitoring Committee. **In addition, we will classify lactic acidosis and suspected cases of lactic acidosis as adverse events of special interest.** These events will be reported in real-time (within 24 hours) to the Data and Safety Monitoring Committee. They will also receive a collated monthly summary for them to review aggregated data.
6. All serious adverse events (grades 4, 5 and selected grade 3 events), will be reported to the on-site Clinical Monitor and, if necessary, to data and safety monitoring committee, that will decide a final diagnosis of the adverse event and the likelihood that that event was related to the drugs.

17.3 NIMR and LSTM/UCL Responsibilities

Medically qualified staff at the NIMR and LSTM/UCL and the Chief Investigator (or a medically qualified delegate) will review all adverse event reports received and provide a causality assessment.

NIMR and LSTM/UCL are responsible for the reporting of SUSARs and other SARs to the regulatory authorities and the research ethics committees as appropriate. NIMR and LSTM/UCL will also keep all investigators informed of any safety issues that arise during the course of the trial.

SAE NOTIFICATION

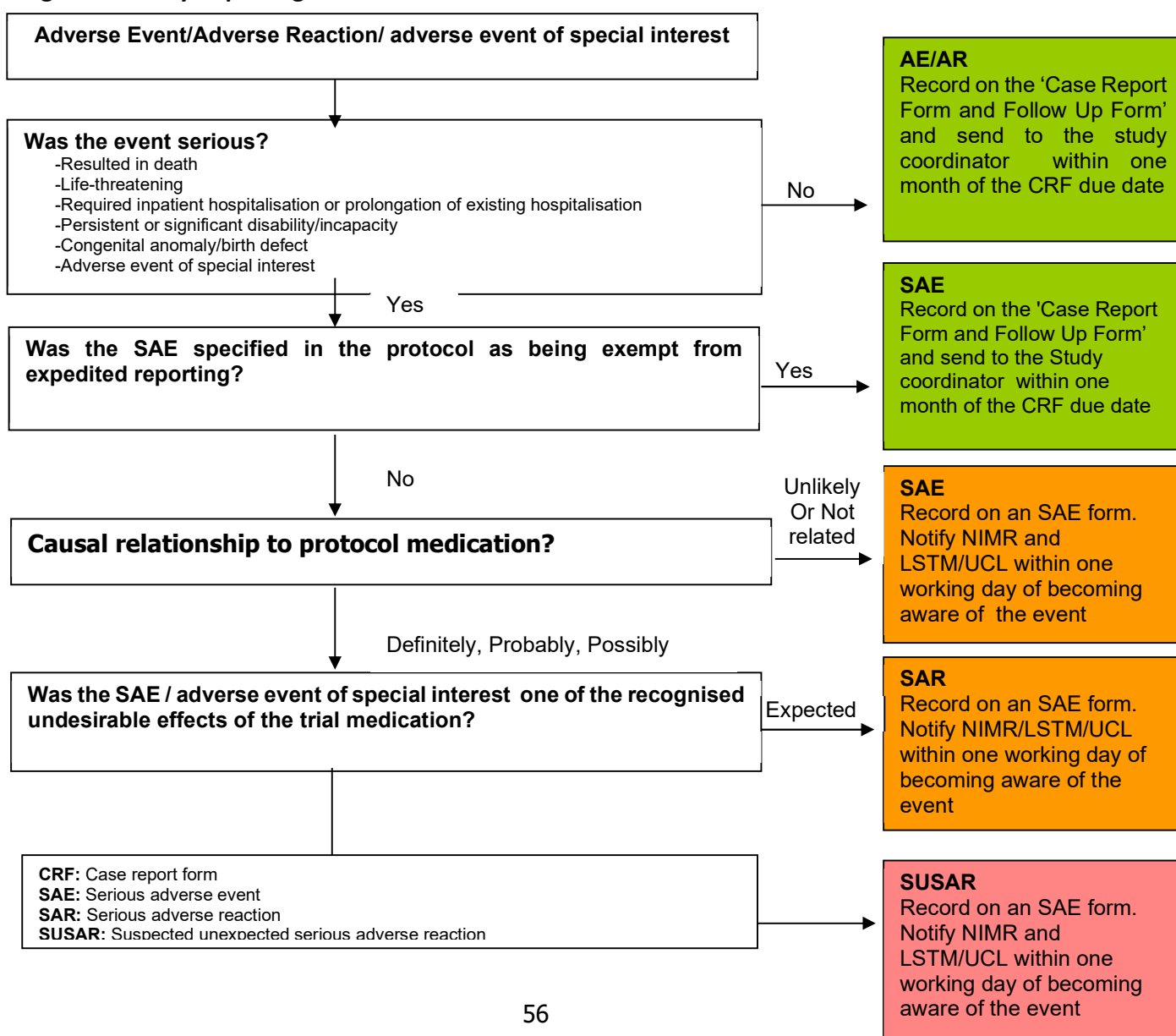
Within one working day of becoming aware of an SAE, please complete an SAE notification form in the EDC and inform the Country Study Coordinator and LSTM/UCL at:

Tanzania: sokoinele@yahoo.co.uk

LSTM: Anupam.garrib@lstmed.ac.uk

UCL: a.garrib@ucl.ac.uk

Figure 3: Safety Reporting Flowchart



19 INDEMNITY

All personnel involved in the trial will be expected to be indemnified by their employing authority. Patients will be indemnified, for non- negligent harm, through a separate policy taken out by Liverpool of School of Tropical Medicine, which will be transferred to UCL.

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APPENDIX 1: Participant information sheet (General)

PARTICIPANT INFORMATION SHEET

Study Title: Prevention of diabetes in Africa: a randomised placebo-controlled double-blind phase III trial of Metformin in HIV-infected persons with pre-diabetes.

Local Principle Investigators: Dr Kaushik Ramaiya and Prof Sayoki Mfinanga

Sponsor: Liverpool School of Tropical Medicine./ University College London

Introduction

The National Institute for Medical Research – Muhimbili Medical Research Centre (NIMR), the Liverpool School of Tropical Medicine (LSTM) and the Institute of Global Health at University College London have formed a partnership. They will conduct a research study to test a new way of preventing diabetes in people living with HIV.

You are being invited to take part in a research study. Before you decide it is important for you to understand, why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part. Thank you for reading this.

What is the purpose of the study?

Adult onset diabetes has been on the increase in people with HIV. Before full diabetes develops, most people have mildly increased sugar levels in their blood, a condition known as prediabetes. Our study will test whether a drug called Metformin can delay or prevent people with prediabetes from developing diabetes

Metformin is a drug that is already routinely used to treat diabetes, including in people infected with HIV, but currently not offered to people with prediabetes. However, it has been tested in this way in studies involving people with pre-diabetes and without HIV living in Europe and America. The drug was shown to be effective in preventing diabetes in those studies. However, Metformin has not been tested in large numbers of persons with pre-diabetes in Africa, including those who are living with HIV.

Between 2019 and 2021, we have been conducting a small study to test whether Metformin might work in persons living with HIV- who have pre-diabetes in controlling their blood sugar. This study showed that the drug was very safe. There were no serious events reported that could likely be linked to Metformin.

Why have I been chosen?

You have been approached today to ask you to join this study for two reasons. Firstly, you are a person living with HIV, who is receiving regular care –and have regularly come to the HIV clinic where we can meet you. Secondly, diabetes and pre-diabetes are very common among people living with HIV and we want to find ways of preventing diabetes in this group.

We will test you to see if you have slightly raised blood sugar (i.e. pre-diabetes). Two-thousand patients altogether will be enrolled in this study.

How can I join the study?

After reading this information sheet you will be asked to give your agreement to be screened. We will ask you some questions about your health to see if you could join the study. If you are then eligible, we will ask you to sign a form that you agree to do the screening tests. For screening, you will be asked to attend another appointment and asked not to eat or drink anything, except water, for at least 8 hours before your study appointment. At this fasting appointment, you will be seen by a doctor and, after the procedure described below, you will be told whether you are eligible for the study. If you are eligible we will ask you to sign a study consent form if you choose to participate.

Do I have to take part?

Your participation is entirely voluntary. It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive at the clinic.

What will happen to me if I take part?

The study will last for over 36 months. After you have given your written agreement to participate in the study, you will be requested to attend the study clinic in 2 weeks, 4 weeks and then at your routine HIV 3-monthly appointments, as well as whenever you feel ill. A transport refund will be provided to you to attend the special study clinic appointments. This will be calculated based on how much it costs for you to get here and return home using public transport.

We will also send text messages to remind you about your appointment times.

Once you agree to the study, we will perform the following procedures described below.

Screening Procedures:

To measure your blood sugar level at the screening appointment, you will be asked not to eat or drink anything, except water, for at least 8 hours before your appointment. We will take blood after you have been fasting and then see how your body responds when you drink a sugary drink. This is known as the oral glucose tolerance test (or OGTT for short) and it is the best test for accurately working out the amount of sugar that a person has in their blood.

When you come to the clinic after fasting, you will be requested to give a urine sample of 25 mls and a blood sample of 10 mls (about 1 tablespoon) from which the fasting glucose will be measured for the first time, as well as a different blood sugar test called the HbA1c, and other baseline laboratory tests including full blood count, renal function test, liver function tests, lipid profile and malaria rapid tests.

You will then be asked to drink a 250 mls glass of flavoured sugar water. After 2 hours, we will take a blood sample of about 4 mls (one teaspoon) to see how your body is dealing with the sugar.

The procedure (the oral glucose tolerance test) will be repeated every 12 months after you have started the study. We will do 6-monthly blood tests to check your kidneys and liver. The blood samples given will be used for monitoring your condition during the study. After they have been analysed, any remaining blood left over will be destroyed by the laboratory. Your results will be communicated back to the study doctors/nurses, and will urgently communicated to you via phone if there is something that require medical attention or you will get them at your subsequent clinic visit. The study staff will explain to you about your results, if found abnormal you will be followed up closely.

At your clinic visits, we will ask you questions about how often you have taken the study drug, if you have experienced any side effects, attended any health care facility during the last visit, whether you have taken any drugs apart from the IMP and ART, any change in your ART regimen, and about your health. A doctor / study nurse will examine you. They will measure your blood pressure, weight, body temperature, and heart rate and examine you to see if you have abdominal tenderness, enlarged liver, and jaundice. If you think that you may be unwell, we may request some extra investigations depending on the possible medical condition. We will also examine you and do some extra tests to check if your body has developed any effects of having a slightly raised sugar level. This will include an examination of the nerves in your feet and may include a check of your eyes.

What will the results mean?

When your blood sugar is tested, there will be three (3) possible readings:

- I. You sugar level is raised but lower than for a diabetes diagnosis – you have pre-diabetes. We will then invite you to be in our study.
- II. Your sugar level will be normal. We will not invite you to be in our study.
- III. Your sugar level is high. You have diabetes. We will not invite you to be in our study.

Everyone will be given information about diabetes.

If we find you already have diabetes, then you cannot join our study. However, we will ask you to go to the diabetes clinic and see one of the doctors there. There you will receive the usual care for diabetes. We will give you a note to take to the diabetes clinic, which will explain that you have diabetes (this is called a referral slip). Likewise, if we suspect that, you have any other condition; we will refer you to the appropriate clinic.

If you have pre-diabetes and are eligible to join the trial, we will discuss with you what will happen in the study and what you would have to do. If you would like to discuss with your family or friends, about whether or not to take part, you can do this and return to the clinic within two weeks to start on the trial.

What sort of study is this?

We will conduct a randomised clinical trial or RCT. About 2100 persons who are living with HIV and found to be pre-diabetic will be enrolled.

Once you have agreed to enter the trial, you will be allocated to one of two treatment groups:

- Metformin treatment group (will take Metformin tablets 4 tablets daily).
- Placebo group (will take placebo or dummy tablets 4 tablets daily).

For the first 2 weeks you will be asked to take 2 tablets, and thereafter you will be asked to take 4 tablets once a day in the evening.

There are equal chances of either treatment group being the one you will receive. Allocating treatment this way is done by the computer and means that the groups of people getting each treatment will be similar.

Neither you nor your doctor will know which treatment group you are in because all the treatments will look the same (although, if your doctor needs to find out he/she can do so).

The Metformin will be given at the dose as used in most people with diabetes. The placebo treatment is a tablet, which looks like the Metformin treatment, but it is not. It contains no active ingredient. Everyone will be asked to take his or her medication (either Metformin or placebo) the same number of times (once a day for 36 months). All other care will be provided as usual.

We will test the blood of those enrolled into the study, to work out whether the drug brings down the blood sugar levels. We will do these tests at the beginning of the study, and at the end of each year of follow up in the study, that is at months 12, 24 and 36. We will also measure your height once, and your fasting blood sugar, weight and blood pressures at each visit.

We know that this treatment can help control blood sugar, but we do not know by how much. We will analyse the information we have collected after most patients have had 2 years of treatment. Depending on what we find, for example if one group is doing much better than another, we might take the decision to stop the trial early.

What are the possible disadvantages and risks of taking part?

You may have temporary discomfort, bruising or redness of the skin when we take blood from your arm. About one out of ten people have mild nausea or an upset stomach with the sugary drink.

Metformin can commonly cause nausea, vomiting, diarrhoea, loss of appetite, and an abnormal taste in the mouth. This may be present at the start of treatment but will mostly disappear on its own.

Very rarely metformin may cause a condition called lactic acidosis. This causes, tummy ache, diarrhoea, vomiting, muscular pain or cramps, unusual tiredness or sleepiness or body weakness, fast or difficult breathing, fast or irregular heartbeat. If you have this you must come to the emergency department of the clinic straight away, or go to your nearest hospital immediately. **You must not take any more metformin until you have been seen by someone at the clinic.** We will reimburse you any transport costs for any such visit.

If you are sick and have very bad diarrhoea or vomiting, a high fever or cannot eat or drink much, you should stop taking the metformin and come to the clinic. When you have seen someone at the clinic, they will tell you when to start taking metformin again. Again, we will reimburse you transport costs for any such visit.

You should not take too much alcohol while taking metformin, as this may also make it more likely that you might develop lactic acidosis.

Very rarely metformin can make your blood sugar go too low. If this happens, you will feel hungry, dizzy, shaky, headache, sweating, becoming easily irritated or have a fast or pounding heartbeat. If this happens, you should have a sweet drink or snack or eat your main meal. You should let the clinic know if this happens.

If you think that you might be pregnant, you should let the clinic know as soon as possible. The study staff will be able to give you a pregnancy test. If you are pregnant we will refer you to the antenatal clinic. Although metformin can be used in pregnancy, it would be best to stop your participation in the study.

The study clinic team is accessible to you in event of any ill health. If you go and see doctors or nurses at any other clinic or hospital, you must tell them that you are taking metformin as part of this study.

What are the possible benefits of taking part?

The information we get from this study could eventually help us to treat future patients with HIV infection better. If Metformin could prevent diabetes in persons with prediabetes, it could be an important way of tackling diabetes. You will also be given information about diabetes prevention through improving diets and increasing exercise. This way, your chances of getting diabetes may be reduced. If after we test your blood sugar, you discover you have diabetes, you will not be invited to join the study. However, you will have the information on which to seek services and we will facilitate that the doctors at the diabetes clinic see you.

What happens when the research study stops?

After the research stops, you will continue to receive your HIV care here at the clinic and the study team will advise you on the findings of this study.

The findings of this study will be published in an international peer reviewed journal. We will also tell the Ministry of Health in Tanzania the results at one of our routine meetings with them.

When the study is over, we will feedback the information on what we find to you at one of your HIV appointments. We will write this in the form of a leaflet which we will share with you.

You will be asked to stop taking the medication when the study ends. Depending on the findings in the study, we will make recommendations to the Ministry of Health about whether this treatment should be provided to patients with prediabetes and HIV.

There may be further studies that will follow this trial or be related to the work we are doing in this trial. If there is a study that is relevant to you, we would like to tell you about it and ask you if you would like to join. If you agree to be in this study, when you sign the consent form, we will ask your permission to tell you about any further studies in the future.

What will happen to the samples I give?

The blood samples given will be used for monitoring your condition during the study. After they have been analysed, any remaining blood left over will be destroyed by the laboratory.

Reimbursements/Compensation

We will reimburse you for travel costs – between Shs 5,000 and Shs 10,000, depending on how much it costs you to get here. In addition, on those appointments when we ask you to do the oral glucose tolerance test, we will compensate you an additional Shs 10,000 for the extra time that we will be asking you to spend at the clinic on those days.

What will happen to my data (the information we are collecting about you)?

We will be using information collected from you in order to undertake this study. We are responsible for looking after your information and using it properly. We will use the minimum

personally-identifiable information possible. We will keep the information we have collected in the study for 10 years after the study has finished. It will be stored securely in x.

Will my taking part in this study be kept confidential?

If you consent to take part in the research, your medical information may be seen by staff of the NIMR, for purposes of analysing the results. All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. The regulatory authorities may also check that the study is being carried out correctly. Your name, however, will not be displayed on any of this information outside the study clinic and you cannot be recognised from it.

The NIMR, the Liverpool School of Tropical Medicine (LSTM) and the Institute for Global Health/UCL is carrying out this study. The study is funded by a grant from the European and Developing Countries Clinical Trials Partnership (EDCTP). Data sharing will be provided and accessed online in a web-based database, and only people who are authorized to view it are allowed access. NIMR, LSTM and UCL have signed an agreement about sharing and protecting this information as required by the ethical committee in Tanzania. When any information is transferred we will make sure it is encrypted so that no one except those who are authorised are able to see it. In addition, we will make sure that no names of any participant are in the database. All people will be identified by a number instead.

What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions.

The Sponsor, Liverpool School of Tropical Medicine/UCL, is ultimately responsible for the safe conduct of the study and the well-being of participants. Any unforeseen circumstances will be reported to the Sponsor and dealt with appropriately.

If you experience harm or injury as a result of taking part in this study, you may be eligible to claim compensation. If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the META 3 Study Tanzania Principal Investigator, Prof Sayoki Mfinanga Tel no +255784755632 or Dr. Sokoine Kivuyo. Tel no. +255763244779. The emergency telephone number is: +255-22-2152232.

All personnel involved in the study will be indemnified.

As study Sponsor, LSTM/UCL has insurance to cover this research study, which includes compensation cover in the event that any claims arise from participation in the study. If you are harmed and the insurer pays for the necessary medical costs, usually you will be asked to accept that insurance payment as full settlement of the claim for medical costs.

However, accepting this offer of insurance cover does not mean you give up your right to make a separate claim for other losses based on negligence, in a Tanzanian court. It is important to follow the study doctor's instructions and to report straightaway if you have a side effect from the study medicine.

Who has reviewed the study?

This study was given a favourable ethical opinion by National Health Research Ethics sub-committee (NatHREC) in Tanzania and by the LSTM Research Ethics Committee in the UK. The The Tanzanian Medicine and Medical Devices Authority (TMDA) has also reviewed and approved this study.

Contact Details

Please feel free to ask the doctors, nurses and counsellors about anything that you feel you have not understood. You can also contact the study teams on the telephone numbers below.

Dr Sokoine Kivuyo Tel no. +255763244779.

Dr Kaushik Ramaiya Tel no +255713618495

Dr Sayoki Mfinanga Tel no +255784755632

The emergency telephone number: +255-22-2152232

The ethical oversight of this clinical study in Tanzania is performed by the NatHREC Research Ethics Committee. They can be contacted on Tel +255 222121400/390 in case you have any ethical concerns or questions about your rights or welfare as a participant on this research study.

Thank you for taking the time to read this form and for considering joining the study

APPENDIX 1a: Signature page for consent to participate in the study

Study Title: Prevention of diabetes in Africa: a randomised placebo-controlled double blind phase III trial of Metformin in HIV-infected persons with pre-diabetes.

Local Principle Investigator: Dr Kaushik Ramaiya and Prof Sayoki Mfinanga

Sponsor: Liverpool School of Tropical Medicine/UCL.

Participant Study ID --

I have read /been read the information sheet concerning the Metformin-prediabetes study and understand what will be required of me if I take part in the study. My questions concerning this study have been answered by:

I understand that at any time, I may withdraw from this study without giving a reason and without affecting my normal care and management. I understand that I will have to continue taking my antiretroviral drugs plus either Metformin or placebo during the study. I voluntarily agree to take part in the study.

If there are research studies in the future that are related to my participation in this trial, research staff can approach me to tell me about these.

☐ I agree

☐ I do not agree

PARTICIPANT'S CONSENT

My signature (or thumbprint) below confirms that I freely agree to take part in the study.		
		_ _ _ / _ _ _ / _ _ _ _ _ _
Participant's Name	Participant's Signature/Thumbprint	Date

IMPARTIAL WITNESS in the event the participant is unable to read

I confirm that I saw the participant being informed about the Metformin-Prediabetes study. She/he freely consented verbally and by marking this form confirms to this consent.		
		_ _ _ / _ _ _ / _ _ _ _ _ _
Witness Name	Signature	Date

INVESTIGATOR / DESIGNEE

As Investigator or individual properly delegated by the investigator, I have fully informed the participant of all aspects of the Metformin-Prediabetes study.		
		_ _ _ / _ _ _ / _ _ _ _ _
Investigator/Designee Name	Signature	Date

Metformin treatment for Africa (the META trial)

Consent form for screening; Tanzania (Version 1.0) for use with Participant Information Sheet General_v3.0;
(Protocol version 5.2) 29th January 2026

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APPENDIX 2: Signature page for consent to screening for the META Trial

Prevention of diabetes in Africa: a randomised placebo-controlled double blind phase III trial of Metformin in HIV-infected persons with pre-diabetes.	
Local Principal Investigator: Dr Kaushik Ramaiya and Prof Sayoki Mfinanga	Sponsor: Liverpool School of Tropical Medicine/UCL.
Participant Study ID □□□□-□□□□□□	Site:
You have been invited to participate in screening for the Metformin treatment for Africa (META) Trial. This is a trial to test a new way of preventing diabetes in people living with HIV. To see if you are eligible to join the trial, we will do certain tests to see if you have slightly raised blood sugar (also called <i>pre-diabetes</i>). You have been provided with the Patient Information Sheet (PIS) which explains the illness and the META trial in more detail, and we encourage you to read through this document and discuss with your friends/ family before deciding whether to participate or not. You should ask your study doctor or nurse any questions you might have about the trial. The procedures and tests that need to be done are as follows:	
Fasting blood sugar	To measure your blood sugar level at the screening appointment, you will be asked not to eat or drink anything, except water, for at least 8 hours before your appointment. When you come to the clinic after fasting, you will be requested to give and a blood sample of 10 mls from which the blood sugar will be measured for the first time.
Oral glucose tolerance test (OGTT)	You will then be asked to drink a 250 mls glass of flavoured sugar water. After 2 hours, we will take a finger-prick blood sample to see how your body is dealing with the sugar.
Urine tests	When you arrive at the clinic you will be asked to give a urine sample which will be tested for sugar, blood and protein and also a pregnancy test if applicable.
Blood tests	The blood sample that is taken when you arrive will also be used for a malaria rapid tests and, if you are eligible and decide to join the trial, may also be used for a different blood sugar test called the HbA1c, and other baseline laboratory tests.

PARTICIPANT'S CONSENT		
My signature (or thumbprint) below confirms that I freely agree to take part in the screening for the META Trial.		

Metformin treatment for Africa (the META trial)

Consent form for screening; Tanzania (Version 1.0) for use with Participant Information Sheet General_v3.0;
(Protocol version 5.2) 29th January 2026

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Participant's Name	Participant's Signature/Thumbprint	Date
IMPARTIAL WITNESS in the event the participant is unable to read		
I confirm that I saw the participant being informed about the screening for the META Trial. She/he freely consented and by marking this form confirms to this consent.		
Witness Name	Participant's Signature/Thumbprint	Date
INVESTIGATOR / DESIGNEE		
As Investigator or individual properly delegated by the investigator, I have fully informed the participant of all aspects of the screening for the META Trial.		
Participant's Name	Participant's Signature/Thumbprint	Date

APPENDIX 3a: Patient information sheet for continuation in the META trial beyond 36 months

Study Title: Prevention of diabetes in Africa: a randomised placebo-controlled double-blind phase III trial of Metformin in persons living with HIV and pre-diabetes.

Local Principal Investigators: Dr Kaushik Ramaiya and Prof Sayoki Mfinanga

Sponsor: University College London

Introduction

The National Institute for Medical Research – Muhimbili Medical Research Centre (NIMR), and the Institute of Global Health at University College London and the Liverpool School of Tropical Medicine have formed a partnership. They are conducting a research study to test a new way of preventing diabetes in people living with HIV.

You have been taking part in this research study called the META Trial (Metformin Treatment for Africa Trial). We are asking you if you will continue taking part in this trial beyond the 3 years/ 36 months that we initially asked you to participate in. Before you decide it is important for you to understand, why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to continue taking part. Thank you for reading this.

What is the purpose of the study?

Adult onset diabetes has been on the increase in people with HIV. Before full diabetes develops, most people have mildly increased sugar levels in their blood, a condition known as prediabetes. Our study is testing whether a drug called Metformin can delay or prevent people with prediabetes from developing diabetes.

Metformin is a drug that is already routinely used to treat diabetes, including in people living with HIV, but currently not offered to people with prediabetes. However, it has been tested in this way in studies involving people with pre-diabetes and without HIV living in Europe and America. The drug was shown to be effective in preventing diabetes in those studies. However, Metformin has not been tested in large numbers of persons with pre-diabetes in Africa, including those who are living with HIV.

Between 2019 and 2021, we conducted a small study to test whether Metformin might work in helping control blood sugar of people living with HIV who have pre-diabetes. This study showed that the drug was very safe. There were no serious events reported that could likely be linked to Metformin.

Why have I been chosen?

You have been approached today to ask if you will continue your participation in this study for a longer time. When we started this study we planned to follow everyone for a period of 3 years/36 months. We had planned on recruiting 2100 people to join this trial. We were not able to get the full number of people to join the trial because it was taking a long time to do the screening process and we have run out of time. We would therefore like to have people in the study for a longer time to be sure we have enough information to fully answer the question of whether metformin works to prevent diabetes in people living with HIV.

Do I have to take part?

Your participation is entirely voluntary. It is up to you to decide whether or not you wish to stay in the study. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive at the clinic.

What will happen to me if I take part?

The study will be finishing by May 2026. We will ask you to stay in the study until this time or until you have been in the study for 4 years/48 months. The 3-monthly visits you have been doing will continue as they have during the study. The transport refund will continue as before. We will also send text messages to remind you about your appointment times as before.

If you agree to stay in the study, we will perform the procedures described below:

- At your clinic visits, we will ask you questions about how often you have taken the study drug, if you have experienced any side effects, attended any health care facility during the last visit, whether you have taken any drugs apart from the IMP and ART, any change in your ART regimen, and about your health.
- A doctor / study nurse will examine you. They will measure your blood pressure, weight, body temperature, and heart rate and examine you to see if you have abdominal tenderness, enlarged liver, and jaundice. If you think that you may be unwell, we may request some extra investigations depending on the possible medical condition.
- At the end of each 12 months in the trial and at your last trial appointment, we will ask you for blood samples that will be used for tests of your kidneys, liver and the fats in your blood as we have been doing during the trial, and for some participants we will add in a test of insulin levels (only if you had this at the start of the study) and Vitamin B12 levels in the blood. The blood samples given will be used for monitoring your condition during the study. After they have been analysed, any remaining blood left over will be destroyed by the laboratory. Your results will be communicated back to the study doctors/nurses and will be urgently communicated to you via phone if there is something that requires medical

attention, or you will get them at your next clinic visit. The study staff will explain to you about your results, and if anything abnormal is found you will be followed up closely. These results will be shared with your HIV care team so that they can also follow up the test results when the trial is over.

- You will be asked to do the blood sugar testing at the end of the participation on the study, as you have done at the end of each year you have been in the study so far. This is the oral glucose tolerance test, where you are asked to come to the clinic fasted (having nothing to eat or drink for at least 8 hours before your study appointment. Your blood sugar is checked on arrival at the clinic and you are then given a sugar drink. You are asked to wait for 2 hours and will have your blood sugar measurements taken after this time.
- We will ask you some questions about your quality of life at the end of your participation in the study.
- We will also examine you and do some extra tests to check if your body has developed any effects of having a slightly raised sugar level. This will include an examination of the nerves in your feet and may include a check of your eyes.

What do I need to do to stay in the study?

After reading this information sheet you will be asked to give your agreement to continue participating in the trial beyond the 3 years we initially asked you for. You will be asked to continue taking the tablets as you have been previously in the study.

What are the possible disadvantages and risks of taking part?

As you have been taking the drugs for some time, it is unlikely that you will have any new side effects of taking the drugs.

You may have temporary discomfort, bruising or redness of the skin when we take blood from your arm. About one out of ten people have mild nausea or an upset stomach with the sugary drink.

Very rarely metformin may cause a condition called lactic acidosis. This causes, tummy ache, diarrhoea, vomiting, muscular pain or cramps, unusual tiredness or sleepiness or body weakness, fast or difficult breathing, fast or irregular heartbeat. If you have this you must come to the emergency department of the clinic straight away, or go to your nearest hospital immediately. **You must not take any more metformin until you have been seen by someone at the clinic.** We will reimburse you any transport costs for any such visit.

If you are sick and have very bad diarrhoea or vomiting, a high fever or cannot eat or drink much, you should stop taking the metformin and come to the clinic. When you have seen someone at the clinic, they will tell you when to start taking metformin again. Again, we will reimburse you transport costs for any such visit.

You should not take too much alcohol while taking metformin, as this may also make it more likely that you might develop lactic acidosis.

Very rarely metformin can make your blood sugar go too low. If this happens, you will feel hungry, dizzy, shaky, headache, sweating, becoming easily irritated or have a fast or pounding heartbeat. If this happens, you should have a sweet drink or snack or eat your main meal. You should let the clinic know if this happens.

If you think that you might be pregnant, you should let the clinic know as soon as possible. The study staff will be able to give you a pregnancy test. If you are pregnant we will refer you to the antenatal clinic. Although metformin can be used in pregnancy, it would be best to stop your participation in the study.

The study clinic team is accessible to you in event of any ill health. If you go and see doctors or nurses at any other clinic or hospital, you must tell them that you are taking metformin as part of this study.

What are the possible benefits of taking part?

The information we get from this study could eventually help us to treat future patients with HIV infection better. If Metformin could prevent diabetes in persons with prediabetes, it could be an important way of tackling diabetes. You will also be given information about diabetes prevention through improving diets and increasing exercise. This way, your chances of getting diabetes may be reduced. If when we test your blood sugar, we think you may have diabetes, you will not be invited to join the study. However, you will have the information on which to seek services and we will facilitate that the doctors at the diabetes clinic see you.

What happens when the research study stops?

After the research stops, you will continue to receive your HIV care here at the clinic and the study team will advise you on the findings of this study.

The findings of this study will be published in an international peer reviewed journal. We will also tell the Ministry of Health in Tanzania the results at one of our routine meetings with them.

When the study is over, we will feedback the information on what we find to you at one of your HIV appointments. We will write this in the form of a leaflet which we will share with you.

You will be asked to stop taking the medication when the study ends. Depending on the findings in the study, we will make recommendations to the Ministry of Health about whether this treatment should be provided to patients with prediabetes and HIV.

There may be further studies that will follow this trial or be related to the work we are doing in this trial. If there is a study that is relevant to you, we would like to tell you about it and ask you

if you would like to join. If you agree to be in this study, when you sign the consent form, we will ask your permission to tell you about any further studies in the future.

What will happen to the samples I give?

The blood samples given will be used for monitoring your condition during the study. After they have been analysed, any remaining blood left over will be destroyed by the laboratory.

Reimbursements/Compensation

We will reimburse you for travel costs – between Shs 5,000 and Shs 10,000, depending on how much it costs you to get here. In addition, on those appointments when we ask you to do the oral glucose tolerance test, we will compensate you an additional Shs 10,000 for the extra time that we will be asking you to spend at the clinic on those days.

What will happen to my data (the information we are collecting about you)?

We will be using information collected from you in order to undertake this study. We are responsible for looking after your information and using it properly. We will use the minimum personally-identifiable information possible. We will keep the information we have collected in the study for 10 years after the study has finished.

Will my taking part in this study be kept confidential?

If you consent to take part in the research, your medical information may be seen by staff of the NIMR, for purposes of analysing the results. All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. The regulatory authorities may also check that the study is being carried out correctly. Your name, however, will not be displayed on any of this information outside the study clinic and you cannot be recognised from it.

The NIMR, the Institute for Global Health/UCL and the Liverpool School of Tropical Medicine (LSTM) is carrying out this study. The study is funded by a grant from the European and Developing Countries Clinical Trials Partnership (EDCTP). Data sharing will be provided and accessed online in a web-based database, and only people who are authorized to view it are allowed access. NIMR, LSTM and UCL have signed an agreement about sharing and protecting this information as required by the ethical committee in Tanzania. When any information is transferred we will make sure it is encrypted so that no one except those who are authorised are able to see it. In addition, we will make sure that no names of any participant are in the database. All people will be identified by a number instead.

What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions.

The Sponsor, UCL, is ultimately responsible for the safe conduct of the study and the well-being of participants. Any unforeseen circumstances will be reported to the Sponsor and dealt with appropriately.

If you experience harm or injury as a result of taking part in this study, you may be eligible to claim compensation. If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the META 3 Study Tanzania Principal Investigator, Prof Sayoki Mfinanga Tel no +255784755632 or Dr. Sokoine Kivuyo. Tel no. +255763244779. The emergency telephone number is: +255-22-2152232.

All personnel involved in the study will be indemnified.

As study Sponsor, UCL has insurance to cover this research study, which includes compensation cover in the event that any claims arise from participation in the study.

If you are harmed and the insurer pays for the necessary medical costs, usually you will be asked to accept that insurance payment as full settlement of the claim for medical costs. However, accepting this offer of insurance cover does not mean you give up your right to make a separate claim for other losses based on negligence, in a Tanzanian court. It is important to follow the study doctor's instructions and to report straightaway if you have a side effect from the study medicine.

Who has reviewed the study?

This study was given a favourable ethical opinion by National Health Research Ethics sub-committee (NatHREC) in Tanzania and by the Research Ethics Committee at UCL and at LSTM in the UK. The The Tanzanian Medicine and Medical Devices Authority (TMDA) has also reviewed and approved this study.

The trial protocol and previous amendments have been reviewed and approved by:

- The Liverpool School of Tropical Medicine (LSTM)
- National Health Research Ethics sub-committee (NatHREC), Tanzania
- Tanzanian Medicine and Medical Devices Authority (TMDA).

Contact Details

Please feel free to ask the doctors, nurses and counsellors about anything that you feel you have not understood. You can also contact the study teams on the telephone numbers below.

Dr Sokoine Kivuyo Tel no. +255763244779.

Dr Kaushik Ramaiya Tel no +255713618495

Dr Sayoki Mfinanga Tel no +255784755632

The emergency telephone number: +255-22-2152232

The ethical oversight of this clinical study in Tanzania is performed by the NatHREC Research Ethics Committee. They can be contacted on Tel +255 222121400/390 in case you have any ethical concerns or questions about your rights or welfare as a participant on this research study.

Thank you for taking the time to read this form and for considering staying in the study.

APPENDIX 3b: Signature page for consent to remain in the META Trial beyond 36 months

Prevention of diabetes in Africa: a randomised placebo-controlled double blind phase III trial of Metformin in persons living with HIV and pre-diabetes.	
Local Principal Investigator: Prof Sayoki Mfinanga and Prof Kaushik Ramaiya	Sponsor: UCL.
Participant Study ID □□□□-□□□□□□	Site:
I have read /been read the information sheet concerning the META study and understand what will be required of me if I remain in the study for an additional follow up period. I understand that at any time, I may withdraw from this study without giving a reason and without affecting my normal care and management. I understand that I will have to continue taking my antiretroviral drugs plus either Metformin or placebo during the study. I voluntarily agree to take part in the study. If there are research studies in the future that are related to my participation in this trial, research staff can approach me to tell me about these. ☐ I agree ☐ I do not agree The procedures and tests that need to be done are as follows:	
Fasting blood sugar	When you come to the clinic after fasting, you will be requested to give and a blood sample of 10 mls from which the blood sugar will be measured for the first time.
Oral glucose tolerance test (OGTT)	You will then be asked to drink a 250 mls glass of flavoured sugar water. After 2 hours, we will take a finger-prick blood sample to see how your body is dealing with the sugar.
Urine tests	At your final visit, you will be asked to give a urine sample which will be tested for sugar, blood and protein and also a pregnancy test if applicable.
Blood tests	You will have laboratory tests for monitoring done at the last visit, and at any other visit if there is any indication of any abnormality. At the final visit your blood sample will also be used for a malaria rapid test, a different blood sugar test called the HbA1c and, for some participants, a Vitamin B12 test.
Clinical examination	You will be examined by the study doctors and nurses at each time you visit the study clinic.

PARTICIPANT'S CONSENT		
My signature (or thumbprint) below confirms that I freely agree to take part in the META Trial.		
Participant's Name	Participant's Signature/Thumbprint	Date
IMPARTIAL WITNESS in the event the participant is unable to read		
I confirm that I saw the participant being informed about the continuation of participation in the META Trial. She/he freely consented and by marking this form confirms to this consent.		
Witness Name	Participant's Signature/Thumbprint	Date
INVESTIGATOR / DESIGNEE		
As Investigator or individual properly delegated by the investigator, I have fully informed the participant of all aspects of the screening for the META Trial.		
Participant's Name	Participant's Signature/Thumbprint	Date

Appendix 4: Toxicity table

Extracted from: DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS VERSION 2.1, July 2017. [DAIDS Adverse Event Grading Tables | DAIDS Regulatory Support Center \(RSC\) \(nih.gov\)](#)

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
Major clinical conditions: Cardiovascular				
Arrhythmia (by ECG or physical examination) <i>Specify type, if applicable</i>	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities¹ Hypertension (with the lowest reading taken after repeat testing during a visit) ≥ 18 years of age	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated

Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Dermatologic				
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus³ (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash <i>Specify type, if applicable</i>	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
Endocrine and Metabolic				
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)

Lipoatrophy^{4 4} Definition:	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy^{5 5}	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Gastrointestinal				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension <i>Report only one</i>	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)

Diarrhea ≥ 1 year of age	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Musculoskeletal				
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Neurologic				

Altered Mental Status (for Dementia, see <i>Cognitive, Behavioral, or Attentional Disturbance</i> below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) <i>Specify type, if applicable</i>	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) <i>Specify type, if applicable</i>	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA
Psychiatric				

Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Respiratory				
Dyspnea or Respiratory Distress <i>Report only one</i>	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)
Sensory				
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
Systemic				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA

Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain⁹ (not associated with study agent injections and not specified elsewhere) <i>Specify location</i>	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
INJECTION SITE REACTIONS				
Injection Site Pain or Tenderness <i>Report only one</i>	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness¹² <i>Report only one > 15 years of age</i>	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm ² surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm ² surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm ² surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
Laboratory values: Chemistries				
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; g/L)	3.0 to < LLN 30 to < LLN	≥ 2.0 to < 3.0 ≥ 20 to < 30	< 2.0 < 20	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
ALT or SGPT, High <i>Report only one</i>	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High <i>Report only one</i>	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High <i>Report only one</i>	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; mmol/L)	16.0 to < LLN 16.0 to < LLN	11.0 to < 16.0 11.0 to < 16.0	8.0 to < 11.0 8.0 to < 11.0	< 8.0 < 8.0
Bilirubin Direct Bilirubin¹³, High <i>> 28 days of age</i>	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
Creatinine, High <i>*Report only one</i>	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance¹⁴ or eGFR, Low <i>*Report only one</i>	NA	< 90 to 60 ml/min or ml/min/1.73 m ² OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m ² OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m ² OR ≥ 50% decrease from participant's baseline or dialysis needed

Glucose (mg/dL; mmol/L) Fasting, High	110 to 125 6.11 to < 6.95	> 125 to 250 6.95 to < 13.89	> 250 to 500 13.89 to < 27.75	≥ 500 ≥ 27.75
Nonfasting, High	116 to 160 6.44 to < 8.89	> 160 to 250 8.89 to < 13.89	> 250 to 500 13.89 to < 27.75	≥ 500 ≥ 27.75
Glucose, Low (mg/dL; mmol/L) ≥ 1 month of age	55 to 64 3.05 to <3.55	40 to < 55 2.22 to < 3.05	30 to < 40 1.67 to < 2.22	< 30 < 1.67
< 1 month of age	50 to 54 2.78 to < 3.00	40 to < 50 2.22 to < 2.78	30 to < 40 1.67 to < 2.22	< 30 < 1.67
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipid Disorders (mg/dL; mmol/L) Cholesterol, Fasting, High ≥ 18 years of age	200 to < 240 5.18 to < 6.19	240 to < 300 6.19 to < 7.77	≥ 300 ≥ 7.77	NA
LDL, Fasting, High ≥ 18 years of age	130 to < 160 3.37 to < 4.12	160 to < 190 4.12 to < 4.90	≥ 190 ≥ 4.90	NA
Triglycerides, Fasting, High	150 to 300 1.71 to 3.42	>300 to 500 >3.42 to 5.7	>500 to < 1,000 >5.7 to 11.4	> 1,000 > 11.4
Uric Acid, High (mg/dL; mmol/L)	7.5 to < 10.0 0.45 to < 0.59	10.0 to < 12.0 0.59 to < 0.71	12.0 to < 15.0 0.71 to < 0.89	≥ 15.0 ≥ 0.89
Vitamin B12	>187pmol/L	<187pmol/L ³		
Haematology				
Hemoglobin16, Low (g/dL; mmol/L) ¹⁷ ≥ 13 years of age (male only)	10.0 to 10.9 6.19 to 6.76	9.0 to < 10.0 5.57 to < 6.19	7.0 to < 9.0 4.34 to < 5.57	< 7.0 < 4.34
≥ 13 years of age (female only)	9.5 to 10.4 5.88 to 6.48	8.5 to < 9.5 5.25 to < 5.88	6.5 to < 8.5 4.03 to < 5.25	< 6.5 < 4.03
Platelets, Decreased (cells/mm3; cells/L)	100,000 to < 125,000 100.000 x 109 to < 125.000 x 109	50,000 to < 100,000 50.000 x 109 to < 100.000 x 109	25,000 to < 50,000 25.000 x 109 to < 50.000 x 109	< 25,000 < 25.000 x 109

³ Based on laboratory normal values from the Muhimbili National Hospital Central Pathology Laboratory.

WBC, Decreased (cells/mm ³ ; cells/L) > 7 days of age	2,000 to 2,499 <i>2.000 x 10⁹ to 2.499 x 10⁹</i>	1,500 to 1,999 <i>1.500 x 10⁹ to 1.999 x 10⁹</i>	1,000 to 1,499 <i>1.000 x 10⁹ to 1.499 x 10⁹</i>	< 1,000 <i>< 1.000 x 10⁹</i>
Urinalysis				
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

APPENDIX 5: PROTOCOL AMENDMENTS**Amendment 1; Protocol version 3.0 dated 7th December 2021**

1. Cover page, authorised by: Protocol signed again to revise date of signature for Prof. Shabbar Jaffar and date updated to 7th December 2021. Version number updated to 3.0
2. Updating of information on the study team (page 2)
We have updated the names of clinicians, statisticians and health economists to reflect changes to the study team as a result of making new collaborations and team members who have moved to new positions.
3. Clarification of criteria for diagnosis of diabetes (page 20)
We have stated in the protocol that diagnosis of diabetes made using the WHO accepted values for fasting blood glucose and 2-hr post glucose load values. Correction of signs ($\geq$) to clarify exact values to make this diagnosis is made on page 20 and 21.
4. Study monitor (page 21)
There will be a monitor for the trial who will work across sites rather than a monitor at each clinic site.
5. Changes to the inclusion and exclusion criteria (page 22 and 23):
 - a. Current inclusion criteria limit eligible participants to those with a viral load measure of < 400 copies/ml taken within the last 6 months. Since the start of the COVID pandemic, intervals between appointments in the HIV clinics have increased from 3 to 6 months for many stable patients, and we have found that viral load measurements have been taken less frequently. We would like to change this criterion to include participants with a viral load measure of <1000 copies/ml taken within the last 12 months. This will also be more in line with the viral load testing algorithm in the National Guidance⁶⁸.
 - b. Clarification of exact values that are included and excluded for fasting blood glucose and 2-hour post glucose load values.
 - c. Exclusion of participants who were part of the META Phase II study. These participants were due to be included in the study, but due to the delay in the start of the phase III trial, it was decided that this was no longer possible. In order to prevent re-randomisation of META II participants, in whom the residual effect of metformin (if this was their allocation) could have an impact on their glucose control in the phase III, it was decided after discussion with the DSMC that these participants should be excluded from the phase III.
 - d. Current national guidance on the hypertension management, describes hypertensive urgency as a systolic blood pressure of >180mmHg and/or a diastolic blood pressure of >110mmHg. This is a lower blood pressure cut off than we have included in our criteria, it is appropriate to change the criteria we have used to be consistent with national guidance⁶⁹.

6. Removal of section describing the inclusion of the phase II participants (page 24)
As described above, it was originally expected that the phase II and phase III studies would overlap, and participants in META phase II could be incorporated in their allocated groups into the phase III study. Due to delays in the start of the phase III trial, the phase II trial had completely finished all patient contact and participants had been off trial drugs for some time. It was not felt to be appropriate to rerandomize these participants for inclusion into the phase III trial.
7. Screening and enrolment procedures (page 25)
 - a. Removal of waist circumference measure from the screening procedures and moving this to the enrolment procedures.
 - b. Early experience in the screening procedures, raised a concern that there are a few cases where the clinical staff were not sure, from the results of the OGTT, that the participant had fasted properly. In this case a patient may appear to be eligible for the study, but if the staff have concerns about whether a patient has properly fasted, we felt that the safest course would be to repeat the OGTT before enrolling the patient. After discussion with local clinicians, we have included an option in this case for the clinician to ask the patient to return for a second OGTT. A minimum of 3 days must have passed before the OGTT can be repeated.
 - c. Clarification on addition of insulin testing (page 26). A fasting insulin laboratory measurement will be conducted in a proportion of patients, included in the sample already taken for blood chemistry. No additional samples are required for this test.
8. Clarification that the trial register will be maintained as part of the electronic data capture (EDC) system rather than as a separate paper document at each site (page 26).
9. Timeline of reporting of serious adverse events (page 31).
Serious adverse events and adverse events of special interest will be reported within 24 hours of the site becoming aware of the event, rather than within 24 hours of diagnosis. This is because the site may only be informed or become aware of an event sometime after it has occurred.
10. Correction of omissions in the follow schedule (page 32 and 33)
This is to correct the follow up schedule description in the text of the protocol to match that outlined in the Study Flow Diagram (page 10).
11. Change and further detail on the definition of loss to follow up (page 34)
Following experiences gained during the META phase II trial, in particular the fact that follow up schedules for people living with HIV were changed as a response to the COVID pandemic i.e. patients are allowed longer intervals between appointments, the definition of loss to follow up has been changed to increase the amount of time a participant may be

given before being declared lost to follow up. Clarification is also provided on the definitions of withdrawals.

12. Clarification of follow up and withdrawal of participants who become pregnant during the trial (page 35).

In the phase II trial, participants who become pregnant were taken off the trial drug, and this will continue in the phase III trial. This is because diagnostic criteria for gestational diabetes overlap with those of prediabetes in non-pregnant individuals. In addition, if a participant develops gestational diabetes during pregnancy, they may be required to take metformin for the management of this condition. Participants will therefore be withdrawn from study but asked to remain in the study in follow up. An addition has been made to the protocol to make it clear that pregnant women fall into the group that may be withdrawn from the study and to describe the procedures to be followed.

13. Removal of Appendix 2 (page 67)

This is the separate patient information sheet that was written for participants who were part of the META Phase II study and were to be enrolled into the phase III study. As this is no longer going to happen, we have removed this version of the participant information sheet.

Amendment 2; Protocol version 4.0 dated August 2023

1. Cover page, authorised by: Protocol signed again to revise date of signature for Prof. Shabbar Jaffar and date updated to 31st August 2023. Version number updated to 4.0
2. Updating of information on the study team (page 2)
We have updated the names of clinicians, statisticians and health economists to reflect changes to the study team as a result of making new collaborations and team members who have moved to new positions, including the change of institution of the PI and some of the trial team members from LSTM to UCL.
3. Following the move of the PI from LSTM to the Institute of Global Health at UCL, the Sponsor role for the trial will be taken over by the Faculty of Population Sciences, under which the Institute of Global Health falls. The trial insurance will remain in place and be transferred to UCL. LSTM remains a partner in the trial.
4. Correction of an error in the flow diagram (page 9)
In the flow diagram, the frequency of OGTT testing was incorrectly listed as 6-monthly. This is planned to be done annually as described in table 6 (page 33) which details the frequency of all investigations in the trial.
5. Change in the frequency of fasting glucose measurements (page 19)

Following meeting with the Endpoint Review Committee, we are changing the frequency of routine fasting glucose measurements from 3-monthly to 6-monthly. As we would not expect to see changes in the blood glucose levels early in the trial, and based on the experience with these routine tests so far, we do not perceive any additional benefit to doing the fasting blood glucose levels this frequently. This change will spare the participants the additional fingerprick every 6 months, and is still twice the level of monitoring that would routinely be done.

6. Further detail on criteria for determination of the endpoint (page 19/20)

We provide further detail on how the endpoint will be determined to ensure consistency throughout the trial. As stated in the protocol the endpoint is determined using the WHO diagnostic criteria for diabetes of fasting blood glucose (≥ 7.0 mmol/l) and 2-hr post glucose load values (≥ 11.1 mmol/l). We clarify that two consecutive fasting blood glucose measurements of ≥ 7.0 mmol/l must be present for the endpoint to be reached, and a single measurement of 2-hr post glucose load of ≥ 11.1 mmol/l will be accepted for the endpoint to be reached. We provide a description of the actions to be taken during follow up to determine if the endpoint has been reached.

7. Correction of the white cell count value in the exclusion criteria (page 22)

The exclusion criteria state that participants who have a white cell count of grade 3 according to the DAIDS criteria in the baseline blood tests will be late excluded from the trial. This was incorrectly stated as a value of $> 2.0 \times 10^9$ cells/mm³ (this is actually grade 2) and has been corrected to read white cell count $< 1.5 \times 10^9$ cells/mm³ (grade 3).

8. HbA1c tests during screening

HbA1c testing had been included during the screening procedures in order to answer a secondary question of the comparison of diagnostic tests of diabetes. As we have screened almost 5000 participants for the trial so far we feel we have sufficient data to answer this question. HbA1c testing will only be done for those who are enrolled into the trial.

9. Written consent for screening (page 24)

In this trial and in the preceding phase II trial, consent for undergoing screening has been taken verbally. However, following a monitoring visit from the ethics committee in Tanzania, it was requested that we take written consent for screening procedures. We have therefore included this in the protocol and prepared a consent form for this (Appendix 2b) as well as included it in a revised patient information sheet (version 3.0; page 58).

10. Change in monitoring schedule (page 32/33)

Following a review of the blood results from the monitoring schedule and the reporting of adverse events, we have determined that there are some blood tests that do not need to be done as frequently as we had planned to do them. In those participants that do not have

any baseline abnormalities, we are not picking up incidental abnormalities in the monitoring. We propose to reduce the frequency of full blood count, renal and liver function testing to baseline, 3-months and then 12, 24 and 36 months; lipid testing to at the start and the end of the trial. For those who have an abnormality at baseline, more frequent testing (3-6 monthly, or at an interval determined by the condition) will still be done.

11. Follow up schedule for participants who reach the endpoint or who become pregnant (page 34)

Further details are provided on the follow up schedule of those who have come off the IMP but are still in follow up in order to determine either the outcome of the pregnancy or the outcome of the diagnosis of diabetes. Following the stopping of the IMP, the participants who have reached these endpoints will have one further follow up appointment 6 months later.

Amendment 3; Protocol version 5.0 dated 11th June 2024

1. Cover page of protocol signed again to revise date of signature for Prof. Shabbar Jaffar and date updated to 11 June 2024. Version number updated to 5.0.
2. Due to delays experienced in the trial, initially with the disruption caused by the covid pandemic and the delays to the regulatory processes, slower recruitment due to the changes in the functioning of HIV clinics post-covid where people were accessing care in the community rather than at health facilities, and shortages in consumables that slowed recruitment we were unable to screen and recruit the 2100 participants we had planned to recruit. After discussions with the Trial Steering Committee and the DSMC, and the proposed plan to increase follow up time as outlined in point 3, it was decided to terminate the recruitment in March 2024. With the available funding and the time left to us in the grant, we would not have been able to recruit the additional participants and follow them for the 36 years as planned.
3. In order to preserve the power of the trial, we propose increasing the follow up time of some participants to up to 48 months. With additional funding from EDCTP3, we are able to continue follow up of participants for an additional 12 months following the original grant end date. This would mean that the most recent participants recruited would have a follow-up of just 2 years but others would be followed up for 4 years. We estimate that the follow-up will comprise:
 - 915 participants followed for 2 years
 - 1058 participants followed for 3 years
 - 126 participants followed for 4 years

4. Participants who agree to the extended follow up beyond the 36 months originally stated in the consent form, will be reconsented. A consent form and signature page is added to the protocol in Appendix 3.
5. The monitoring schedule (page 35) is updated to reflect the additional visits between 36 and 48 months of follow up. The same testing schedule as has been previously applied will be applied to this additional year, including annual OGTT, biochemistry and haematology testing. Any exit investigations or CRFs will be applied to the final visit of the participant occurring at month 48 or the last scheduled visit prior to February 2026.
6. Clarification that for the primary outcome, at least one of the fasting blood glucose measures should have been collected alongside a 2-hour post load glucose test. This does not change the definition of the primary endpoint or the outline of the scenarios in which we anticipate to have the primary endpoint reached, but serves to make clear our experience that participants are more likely to fast when they come to clinic for a much longer investigation (i.e. when they have a 2-hr post glucose load test). Therefore, this criteria is made explicit in the definition of the primary endpoint.
7. Further information is provided on the secondary outcomes. They will include: diagnoses of diabetes as according to each of the indicators alone (2 hr post glucose load of 11.1 mmol/L or more, fasting glucose of 7.0 mmol/L or more or HbA1c of 48mmol/mol (6.5%) or more). For the fasting blood glucose, the endpoints will include single values measured when an oral glucose tolerance is done, and 2 consecutive values. An endpoint comprising diabetes as indicated by any one of these indicators will also be considered.
8. Updating of information on collaborators and collaborating institutions (page 2 and 3)

Amendment 4; Protocol version 5.2 dated 29th January 2026

1. Cover page of protocol signed again to revise date of signature for Prof. Shabbar Jaffar and date updated to 29th January 2026. Version number updated to 5.2. Updating of information on the trial team.
2. Update of end date of clinical activity. It was outlined that clinical activity would end in February 2026, however we have determined that we are able to continue activity in the trial for slightly longer. The maximum duration of follow up in the trial for any individual will remain as 48 months, however the end of clinical activity in the trial will change to May 2026. The increased follow up time will allow us to have greater power in the trial, helping to address some of the loss of power due to us not recruiting the full number of participants.

3. An exploratory investigation of Vitamin B12 levels. The association between Vitamin B12 deficiency and long term use of metformin has been established. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. Recent updates to the safety information for Metformin which indicated that people who have been taking high dose metformin for at least 3 years should be investigated for Vitamin B12 deficiency, particularly in the case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), or should have B12 supplementation. Consultations with diabetologists familiar with the Tanzanian setting suggest that low levels of B12 are not common and that supplementation with long term metformin use does not generally occur. As trial subjects will have been taking high dose metformin for a period of up to 4 years, we seek to establish whether Vitamin B12 deficiency is common in the trial population. In the absence of baseline Vitamin B12 values for these participants, we will analyse the difference in Vitamin B12 levels between those in the placebo arm and those in the metformin arm.

To this end we will test Vitamin B12 levels in a selection of participants, randomly distributed between metformin and placebo groups, at trial exit. We will include participants who have anaemia based on their last full blood count results. No additional blood samples will be required as this test can be conducted on the samples that are already taken at the end of the trial. Samples will be analysed at the Muhimbili National Hospital Reference laboratory as with other trial samples, and the normal ranges as determined by the laboratory will be used. As these tests will be done at the trial end, participants identified with low Vitamin B12 levels will be contacted through the HIV Care clinics and offered Vitamin B12 supplementation. These actions will be taken together with the HIV care clinicians, who will be provided with all relevant information.

An addition has been made to the toxicity table (appendix table 4) to include the local serum Vitamin B12 values considered to be low.

4. Follow up appointments for participants who become pregnant or reach the endpoint at the end of the trial clinical activity. For some participants there will not be sufficient time at the end of trial activity to conduct the follow up visits to determine the outcome following pregnancy or referral to the diabetes clinic. In these cases, the referral will be noted but the follow up forms will be completed only so far as it is possible in the remaining time before the end of the trial activity. Routine clinical referrals will be made as appropriate based on findings from the last trial visit. Safety reporting obligations as per GCP remain unchanged.