Efficacy of *Tamarindus indica* fruit juice in optimizing cardiometabolic health of patients living with HIV and elevated triglycerides: A study protocol.

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1. Introduction

1.1 Background

Suboptimal cardiometabolic health is on a disproportional rise in Low- and Middle-Income Countries (LMICs). In sub-Saharan Africa (SSA), cardiometabolic dysfunction is being exacerbated by the ongoing nutrition transition, that has seen a change from traditional diets to fast and ultra processed foods rich in sugar, fats, and salt coupled by low physical activity (1). Similarly, chronic inflammatory diseases such as HIV can aggravate cardiometabolic risks (2). HIV aetiology and Antiretroviral Therapy (ART) have been shown to exacerbate metabolic syndrome. Although the pathophysiology remains rather elusive, HIV triggers glucose metabolism dysregulation and dyslipidaemia. In part, this is linked to the inflammation triggered by viral infection. The virus triggers chronic activation of the innate immune system with excessive production of inflammatory cytokines. These inflammatory mediators increase the risk of atherosclerosis and insulin resistance (2). Our recent study among people living with HIV (PLWH) under community-based HIV care model in Uganda revealed a high prevalence of metabolic syndrome (28%), central obesity (44.5%), raised fasting blood glucose (49.6%), hypertriglyceridemia (26.4%), low HDL-c (56.7%), and high blood pressure (31.5%). This cardiometabolic dysfunction is compounded by low quality carbohydrate-based diets devoid of fruits and vegetables (3). Fruits and vegetables are the bedrock of a healthy diet (4, 5). However, although WHO recommends a daily intake of at least 5 servings a day (6), in our

study the average intake of fruits and vegetables was just 1.5 servings and a low polyphenol intake (212 mg) (3).

Beyond conventional nutrients, fruits and vegetables have ubiquitous amounts of bioactive components including polyphenols, alkaloids, saponins, and terpenes and terpenoids, with polyphenols being the most ubiquitous of all. Dietary polyphenols are a diverse category of secondary plant metabolites that represent the largest group of naturally occurring antioxidants with cardioprotective benefits (7-9). A daily 5 servings intake of fruits and vegetables coincides with 500-1000 mg of total polyphenols, a threshold that is considered beneficial for cardiometabolic homeostasis (10). Our recent meta-analysis demonstrated that an average intake of 780 mg/d of total polyphenols significantly reduced blood pressure, total cholesterol, triglycerides, and improved vascular function (11). The (poly)phenolic composition of fruits and vegetables can vary considerably according to the region of growth among other factors (9, 12). For example, Africa's Indigenous Fruits and Vegetables (IFV) have been shown to contain high concentrations of polyphenols (13, 14). Our recent inventory study of Uganda's IFV with purported cardiometabolic benefits, highlighted the popularity of *Tamarindus indica* as a local adjuvant therapy for cardiometabolic risks among Ugandan communities (15). The study also revealed that the polyphenol composition of *T. indica* is superior in 4755mg/100g FW in relation to other IFV identified.

T. indica, is a leguminous tree belonging to the family Fabaceae with a wide range of bioactive constituents in varying levels- the highest being polyphenols followed by alkaloids, saponins, and terpenoids in that order (16). The principal flavonoids in *T. indica* fruit pulp are composed of flavanols especially the oligomeric procyanidins and their monomers- epicatechins and catechins (17, 18). Recent dietary guidelines for bioactives recommend a daily intake of 400-600 mg of flavanols for cardiometabolic protection (19) while the European Food Safety Authority (EFSA) recommends that 200 mg/d intake of cocoa flavanols is important for vascular homeostasis (20). Elsewhere, the COSMOS study showed that an intake of 500 mg/d of flavanols averts 27% of CVD mortality with significant reduction in CVD events (21). Flavanol increases the endothelial production and bioavailability of nitric oxide, a signalling molecule for endothelial function (20) .

A potential mechanism of action by which polyphenols confer hypotensive effects is by increasing the bioavailability of nitric oxide (NO) and upregulating endothelial NO-synthase activity. NO is a potent vasodilator that reduces blood pressure. Additionally, flavonoids

especially flavanols may block angiotensin converting enzyme (ACE) activity, reducing blood pressure. In fact, flavanols, anthocyanins, phenolic acids, tannins, and resveratrol have been identified as green ACE inhibitors (11).

Although the benefits of the community-based HIV care model in the resource limited HIV management settings are well documented, in Uganda, the lack of dietary interventions promoting cardiometabolic health could obscure such benefits (22-24). Lifestyle modifications such as programmed physical activity, weight loss, and dietary adjustments are indispensable to optimal cardiometabolic health (25, 26). However, the existence of a health-beauty paradox in SSA could thwart such interventions premised on maintaining a healthy body weight. The health-beauty paradox is a socio-cultural positive perception where a large body size is construed as a sign of prosperity and freedom from HIV (27). Moreover, dietary approaches that aim to add a healthy food portion on to one's habitual diet rather than completely changing their menu are by far more culturally diffusible (28). Therefore, we aim to evaluate the efficacy of *T. indica* fruit juice (added to patients' usual diets) on selected cardiometabolic risk markers of PLWH under the community-based HIV care model in Uganda in a proof-of-concept clinical trial. Evidence could lead to the concomitant use of such food products as adjuvant therapies in the secondary prevention of cardiometabolic risks.

1.2. Hypotheses

The hypotheses are:

H_1: Consumption of *T. indica* fruit juice will result into an overall improvement in cardiometabolic (vascular function, blood pressure, glycaemic, and lipidemic) response.

H_2: There will be differences in the dose-response relationship in cardiometabolic control following the intake of increasing doses of polyphenols in *T. indica* fruit juice.

2. Materials and Methods

2.1.1 Intervention food materials

Two blinded juice prototypes of 10% and 30% fruit pulp packaged in amber bottles each consisting of 300mls will be supplied by the Uganda Natural Chemotherapeutics Research Institute. The chemical and phytochemical characteristics of the test juice are presented in table 1.

Table 1: Chemical and phytochemical characteristics of *Tamarindus indica* fruits juice

Fruit juice prototypes (pulp %)	TPC (GAE, mg/100ml)	TFC (RE, mg/100ml)	TT (GAE, mg/100ml)	Alkaloids (%)	Brix	Ph	TTA (g of tartaric acid/100ml)	Antioxidant potential, IC50, µL
10%	8.30	6.75	8.30	0.34	6.80	3.28	0.35	36.71
30%	26.36	12.29	10.17	0.44	6.80	2.89	0.95	37.46

TPC, Total Polyphenols Content; TFC, Total Flavonoids Content; TT, Total Tannins; TTA, Titratable acidity

2.2 Study design and participants

This is a single centre, 2-arm, 4 weeks randomised, double-blinded parallel trial with equal allocation ratios (1:1). We will follow the Consolidated Standards of Reporting Trials (CONSORT) recommendations for randomized trials (32). Participants will be PLWH (30-60 years) managed under the community-based model (Community Drug Distribution Points-CDDPs) in Wakiso district, central Uganda. The district encircles Kampala, Uganda's capital city with an estimated population of over 2.9 million people. The district has the highest prevalence (10%) of HIV in Uganda. Over 3,801 PLWH are currently receiving the HIV care from CDDPs in Wakiso District (33). The study inclusion and exclusion criteria are presented in Table 2. The study will be announced during the drug refill days and interested patients will be provided with more information about the study before obtaining their consent to participate. Demographic and medical information will be collected from all consented patients,

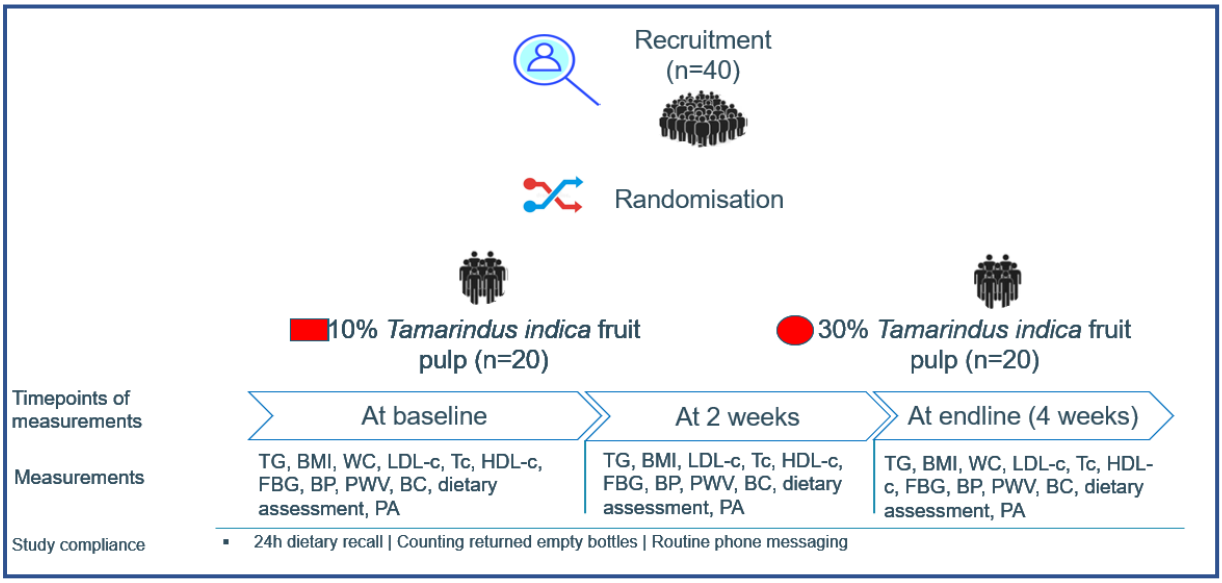
The study participants will be randomly allocated to consume twice-daily 300 mL of either 10% or 30% pulp of *T. indica* fruit juice, **figure 1**. Both participants and the study team will be blinded to the intervention materials. Measurements will be performed at three different timelines: 1) Baseline, 2) Week two of the study, and 3) Endline (week four of the study).

Compliance to the study protocol will be confirmed by weekly telephone inquiries, and by counting the returned empty juice bottles or unused study products at each follow-up visit. Participants will be asked to maintain their habitual dietary regimen.

Any reported unusual gastrointestinal side effects, including abdominal pain/cramps, heartburn, stomach acid/reflux, nausea, vomiting, abdominal rumbling, bloating, belching, excess gas/wind, stool type, etc, during the study will be recorded. Patients will be encouraged to contact a study staff by phone or e-mail if they experience any adverse health-related impacts of the interventions. In the case of *T. indica* fruit juice intolerance, patients will be excluded.

Randomisation and blinding

A biostatistician of Mildmay hospital will develop computer-generated sequence to randomly allocate participants to each of the two study arms, as shown in figure 1. The biostatistician responsible for generating the allocation sequences will not have any study-related tasks, for example, inclusion or examination of participants. The two juice prototypes will be blinded by assigning a secret code to each of the intervention products. As such, blinding of the investigators and participants will be undertaken to ensure a double-blind intervention. Moreover, the statistical analyses of the main endpoints will be done before breaking the intervention product concealment.



BP, Blood Pressure; BC, Body composition; FBG, Fasting Blood Glucose; TG, Triglycerides; Tc, Total cholesterol; PA, Physical Activity; PWV, Pulse Wave Velocity; WC, waist circumference.

Figure 1: Schematic overview of the study protocol.

Table 2: Eligibility criteria for study participants

Inclusion criteria	Exclusion criteria
Triglycerides ≥150 mg/dL	Taking dietary supplements
TLD regimen (ART) for ≥12 months	TB co-infection, renal failure disease, liver cirrhosis, chronic pancreatitis
95% ART adherence in last 6 months[1]	Pregnancy and Lactation or regular sport activity
Virally suppressed (most recent results viral load suppressed within the last 12 months)[1]	Parallel participation in another clinical trial
PLWH aged ≥30≤60 years.	On treatment for; dyslipidaemia, hypertension or diabetes and oral hypoglycaemic drugs
No plans to change location in the next 6 months	Very low blood pressure (< 90/50 mmHg)
	Not willing to consent or unable to consent

ART, Antiretroviral Therapy; DBP, Diastolic blood pressure; FGD, Focus group discussion; SBP, systolic blood pressure; TLD, Tenofovir Lamivudine Dolutegravir; WC, waist circumference.
[1]In line with the national guidelines for community drug distribution points (Community care model for HIV), WHO stages 1 or 2 (34).

2.3.1 Study outcomes

The primary endpoint will be changes in Triglycerides (TG). Secondary outcomes will include changes in fasting blood glucose and plasma levels of lipids, and parameters of vascular function, **Table 3**.

Table 3: Study outcome measures

Primary outcome measures	Secondary outcome measures	Exploratory outcomes
Triglycerides [mg/dL]	PWV [m/s], Blood pressure [mmHg]	BMI [kg/m^2]
	Fasting Blood glucose [mg/dL]	Fat mass composition
	HDL-c, LDL-c, Total cholesterol [mg/dL]	Waist circumference [cm]
	AIx (%), MAP	

BMI, Body Mass Index; PWV, Pulse Wave Velocity; HDL-c, High Density Lipoproteins; LDL-c, Low Density Lipoproteins; AIx, Augmentation Index; MAP, Mean Arterial Pressure

2.4 Protocols for measuring study outcomes.

2.4.1 Biochemical Measurements

CardioChek Plus will be used to assess fasting blood glucose and lipid profile (total cholesterol, HDL-c, LDL-c, and triglycerides). It is an on-site test which gives results in as little as 90 seconds. The CardioChek plus is patient friendly in that it requires a fingerstick blood sampling

of 15 to 40 µL. Participant safety is guaranteed; the trained laboratory technician handling the testing will sanitize and wear cloves while doing the test, the participants finger (middle or ring finger) will be cleansed with an alcohol wipe for at least 30 seconds and the stick will always be on the side of the finger rather than the tip. The testing will be performed by trained laboratory technician. Participants will be requested to fast overnight and not to indulge in exercise in the morning. To ensure this, tests will be carried out early morning before breakfast.

2.4.2 Parameters of vascular function

2.4.2.1 Pulse wave velocity, Mean arterial Pressure, and Augmentation Index

Increased arterial stiffness, measured non-invasively by aortic pulse wave velocity (PWV), is one of the earliest detectable manifestations of adverse structural and functional changes of the vessel wall (35). Aortic PWV will be estimated twice in the supine position on the right upper arm, using the validated Arteriograph device (TensioMed, Budapest, Hungary) (36). The Arteriograph is an operator-independent, non-invasive device that uses an oscillometric occlusive technique to estimate the aortic PWV and AIx. In short, after two conventional BP measurements, the Arteriograph produces a cuff pressure over the brachial artery that is 35 mmHg in excess of the systolic blood pressure measured. This suprasystolic pressure is used to analyse the pulse wave. To calculate the PWV, the distance from the jugulum to the symphysis is measured in a straight line using a tape measure, as a surrogate measure of the aortic length, and multiplied by two. The result is then divided by the difference in time between the beginning of the first wave and the beginning of the second (reflected) wave, resulting in the PWV in meters per second (m/s) (36, 37). The two conventional BP measurements of the Arteriograph will be used to calculate the mean arterial pressure (MAP). The AIx corresponds to the pressure difference (amplitude difference; P1-P2) between the first and second wave in relation to the pulse pressure (PP). The Arteriograph calculates the AIx on the basis of the formula, AIx% = [(P2-P1)/PP] *100 and thus provides the brachial AIx without applying a transfer function (37). In order to standardize the measurement, we will use the protocol provided by the manufacturer. At the end of every examination day, data will be directly exported from the Arteriograph output into SPSS, preventing data-entry errors.

2.4.2.2 Blood pressure

Blood pressure will be measured using blood pressure monitor – Seca b12. Blood pressure measurements will be taken on the left arm with the participant in a sitting position (after a five-minute rest in sitting position). Two readings will be taken at least one minute apart and the mean of the last two readings will be taken as the final blood pressure. In case of there's

more than a 5-mm Hg difference between the first and second readings, additional readings will be obtained and then the mean value of these multiple readings will be used (38).

2.4.3 Anthropometrics

Height will be taken to the nearest 0.1 cm using a portable stadiometer. Weight will be measured to the nearest 0.1 kg using the Seca 874 dr weighing scale. Participants will remove shoes and heavy clothing (jackets) and pocket items before measurements. Weight and height measurements will be used to calculate BMI (kg/m^2). Waist circumference (to the nearest 0.5 cm) will be measured using a non-stretchable standard tape measure (gulick measuring tape). The waist measurement will be taken at the level of the iliac crest with the participant standing, at the end of gentle expiration (39).

2.4.4 Body composition measurement

Body composition will be measured using Bodystat 1500 lite touch. This equipment uses the scientifically validated principle of bio-electrical impedance analysis, to measure body composition parameters namely, fat, lean weight, optimal total body weight range and body water levels, is instantly displayed on the screen of the Bodystat 1500 lite touch. The measurement is not recommended after strenuous exercise. The body would have lost excessive fluid through sweat, and an abnormally low fluid level would increase the impedance measurement resulting in an artificially higher percent fat than would normally be the case. Therefore, participants will be advised to avoid strenuous activities on the day of measurement. To ensure this, tests will be carried out early morning before breakfast.

5. Other measurements

5.1 Dietary intake

Data on dietary intake will be collected by a non-consecutive two day 24-hour dietary recall method (40). The recall will be interactive to allow for estimation of food quantities and sizes. The participants will be thoroughly probed to ensure that no foods consumed are forgotten. The time of food consumption will also be recorded. Participants will estimate their food portion sizes using a photographic atlas. The atlas utilizes photos of estimated food portions and their corresponding weight in grams.

5.2 Physical activity

Physical activity will be measured using the validated short form of the international physical activity questionnaire (41).

6. Statistical analysis

This is a proof-of-concept (no power calculation). The study will use a pragmatic sample size. Intention to treat analysis will be conducted. Continuous variables will be presented as mean and standard deviation. Student t-test will be applied to compare means of endpoints between patient groups. Outcome variables will be checked for normality and transformed where necessary. To account for any missing data, analyses will be conducted using linear mixed models. Analysis will be performed using the Statistical Package for the Social Science (SPSS) software version 22 (IBM Corp, Armonk, NY, USA). A p-value of <0.05 will be used for statistical significance.

7. Ethics and regulatory approvals

All study procedures will be conducted in accordance with the Helsinki Declaration and the study protocol will be registered in a public database (ClinicalTrials.gov). Research approval and permit has been sought and granted by the research ethics committee of Clarke International University and Uganda National Council of Science and Technology. All willing participants will be asked to voluntarily sign an informed consent form at the point of recruitment. The research team will protect the data from disclosure outside the research according to the terms of the research protocol and the informed consent document. The investigator will treat all information and data of participants as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the study. The subject's name or other identifiers will be stored separately from their research data and replaced with a unique code to create a new identity for the participant. It is anticipated that the results of the study will be presented at national and international conference or published in an international peer reviewed journal. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal. Each participant will be offered a healthy snack and also compensated USD 8 each visit to cater for transport.

8. Direct access to source data and documents

The investigator(s) will permit study related monitoring, ethical committee review and regulatory inspections (where appropriate) by providing direct access to source data and other documents.

9. Individual Participant Data (IPD) Sharing Statement

Plan to Share IPD:	Yes
Plan Description:	For all the data generated during the course of this study, we will follow the prevailing standards and guidelines in documenting and depositing data sets. The research team will disseminate results from this research through presentations at public lectures, scientific institutions and meetings, and/or publication in major journals. Regarding data sharing, International Committee of Medical Journal Editors recommendations will be followed. Individual deidentified participant data will be shared. In particular, individual participant data that underlie the results reported in our articles, after deindentification (text, tables, figures and appendices).
Supporting Materials:	Study Protocol Informed Consent Form (ICF) Analytic Code
Time Frame:	Data will become available from 9-36 months after the publication of the study-results by the research team.
Access Criteria:	Data will only be shared with investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. Proposals should be directed to Prof. Christophe Matthys (Christophe.matthys@uzleuven.be). To gain access, data requestors will need to sign a data access agreement.

10. Withdrawal of participants

Participants can withdraw from the study at any time for any reason if they wish to do so.

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