OPTIMAL MANAGEMENT OF HIV-INFECTED ADULTS AT RISK FOR KIDNEY DISEASE IN NIGERIA

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Optimal Management of HIV Positive Adults at Risk for Kidney Disease in Nigeria

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Table of Contents:

Background

HIV and non-communicable diseases (NCDs) are increasing in Africa. Effective antiretroviral therapy (ART) has promoted immunologic recovery, but at the cost of adverse metabolic complications and negative health outcomes, most commonly referred to as non-communicable diseases (NCDs), that have emerged as a major health concern among long-term ART-treated adults.[1-5] We are faced with a new challenge: namely, addressing morbidity and mortality from NCDs—specifically kidney disease plus heart disease, stroke, diabetes, and metabolic complications, and non-AIDS associated cancers—that increase with age and may be related to HIV, its treatment, host genetic factors, and/or modifiable risk factors.[6-11] Deaths due to NCDs are rapidly trending to occupy a larger share of deaths and disability-adjusted life years (DALYs) in resource-constrained settings. More than 38 million persons die each year from NCDs, with the vast majority (82%) residing in low- and middle-income countries (LMICs).[12] Current projections show that by 2020, 73% of all deaths worldwide will be due to NCDs and that the burden of NCDs will rise by more than 60% in LMICs, with the largest increases in NCD deaths in Africa. HIV infection and ART interact with NCD risk factors in complex ways, and research into this important area has so far been largely based on data from high income countries.[13] **Figure 1** (below) displays the share of age-standardized disability-adjusted life years (DALYs) among reproductive-aged adults for NCDs (**blue**), communicable diseases (**red**), and external causes (**green**) for Western sub-Saharan Africa (SSA) and North America, from the Global Burden of Disease project.[13] Darker color shades represent diseases that are increasing more rapidly.

Figure 1: Distribution of DALYs by region of the world (North America vs. Western SSA), ages 15-49 years, 2016.

North America **Western SSA**

The burden of *HIV-associated kidney disease in Africa is substantial*. Although ART has substantially reduced the impact of HIV-associated kidney disease in the U.S., the HIV epidemic continues globally in kidney disease-susceptible African-descent populations.[14,15] Chronic kidney disease (CKD), defined as the presence of proteinuria (defined as urine albumin/creatinine ratio >300 mg/g) and/or reduced eGFR (defined as. <60 mL/min/1.73m^2), is at least 3–4 times more frequent in Africa than in developed countries.[16-18] The reported prevalence of CKD in HIV positive ART-naive patients varies across SSA, ranging from 6 to 48%, with the highest prevalence reported in Nigeria, the most populous nation in Africa.[17-22] Stanifer et al [23], in their recent meta-analysis of 90 studies in SSA, found that the overall prevalence of CKD from 21 medium- and high-quality studies was 13.9% [95% CI: 12.2-15.7], and that among people with HIV, the prevalence of CKD was highest in Nigeria, Zimbabwe, and Uganda. In studies conducted by Mulenga et al.[19], the prevalence of kidney dysfunction (defined as eGFR of < 90 mL/min/1.73m^2), was 33.5% among HIV positive ART-naïve adults presenting for care at a large urban clinic in Lusaka, Zambia. Mulenga et al.[19] also showed that ART-naïve patients with kidney dysfunction in Zambia had a 4-fold higher mortality rate compared to those with normal renal function. CKD affects an estimated 14% of adults in SSA, but very little research has been done on the cause, progression, and prevention of CKD in this region.[21] As part of the Human Heredity and Health in Africa (H3Africa) Initiative, the H3Africa Kidney Disease Research Network [24] was established to study prevalent forms of kidney disease in SSA and increase the capacity for genetics and

genomics research. Dr(s) Winkler and Kopp are involved with the H3Africa initiative. Our proposed work does not overlap with any ongoing/planned work in this consortium, and we will share all study findings with them.

Host genetics play an important role in CKD risk. Because certain HIV-related kidney diseases (HIV-associated nephropathy [HIVAN] and focal segmental glomerulosclerosis [FSGS]) emerge exclusively (HIVAN) or largely (FSGS) in persons of African descent (~20-fold greater risk than non-African descent counterparts), several studies have sought associations between genetics and a predisposition to CKD in these patients.[25-37] Genovese et al.[37] described two risk alleles in the *APOL1* gene, a 2-allele haplotype (G1) that consists of the 2 derived non-synonymous coding variants rs73885319 (S342G) and rs60910145 (I384M), and a G2 allele that consists of a 6-base pair deletion (rs71785313) that removes 2 amino acids (NYK388K).[37] Kopp, Winkler, Pollak et al.[30,36-38] have shown that the *APOL1* high-risk genotype (defined by the carriage of two *APOL1* risk alleles) confers sizeable odds ratios (OR) for FSGS (OR = 17), HIVAN (OR = 29 in the US; 89 in South Africa), and hypertension-attributed end stage kidney disease (ESKD) (OR = 7). These variants are present only on African-origin chromosomes. The frequency of the risk alleles is highest in West Africa, specifically in Nigeria among persons of Yoruba (>50%) and Igbo (>50%) descent.[39,40] As the *APOL1* effect is largely recessive (2 risk variants), ~25% of the population is at substantially increased risk of kidney disease. In the setting of untreated HIV infection, we have estimated that ~50% of individuals carrying high-risk genotypes will develop CKD.[41,42] Even when HIV replication is suppressed, *APOL1* high-risk individuals remain at greatly increased risk for FSGS and hypertension-attributed ESKD, similar to HIV-negative *APOL1* risk individuals.[25]

Microalbuminuria is an important early marker of kidney disease, including in HIV positive adults. There is a continuum of kidney disease, typically defined by increasing stages of CKD. In some forms of kidney disease, such as diabetic nephropathy, the earliest detectable abnormality is microalbuminuria, which may progress to macroalbuminuria and finally to nephrotic range proteinuria. Albuminuria is an independent risk factor for cardiovascular and renal disease and a predictor of end organ damage.[43] Microalbuminuria (urine albumin/creatinine ratio (uACR) = 30-300 mg/g) can signify either glomerulosclerosis or glomerular microvascular dysfunction (often associated with systemic microvascular dysfunction) has been used in the early detection of several disease states, i.e. preeclampsia, diabetic nephropathy, and medication-induced nephrotoxicity.[43] As a result, various guidelines have recommended assessment of urinary protein in adults with hypertension or diabetes, and even in the general population to identify at-risk persons. Proteinuria has also been associated with decreased CD4+ cell counts and higher plasma viral loads among HIV-positive individuals, as well as increased systemic T-cell activation and more rapid progression to AIDS.[44-46] Microalbuminuria and macroalbuminuria are also important risk factors for mortality in ART-treated HIV-positive individuals, probably due to their role as a marker for inflammation and endothelial activation.[47-49] Even very low levels of albuminuria (uACR = 10-30 mg/g) have been associated with adverse cardiovascular and renal events.[44,50] Gerstein et al., [44] evaluating older patients with at least one risk factor for cardiovascular disease, found that routine screening for albuminuria identifies people at high risk for cardiovascular events.[44] Current guidelines recommend that all HIV positive adults with significant proteinuria of grade ≥ 1+ (by dipstick analysis) and/or reduced kidney function (eGFR < 60 ml/min per 1.73m^2) be referred to a nephrologist for additional quantification of urinary protein excretion and/or a kidney biopsy. While

therapy for HIV-associated kidney disease needs to be individualized, waiting for overt proteinuria may miss a potential earlier window for intervention to more effectively forestall progression to the more advanced stages of CKD. Microalbuminuria is an established screening test to detect early diabetic nephropathy, and there is growing interest to screen for microalbuminuria to identify early HIV-associated kidney disease in patients. Hadigan et al.[51] found the period prevalence of microalbuminuria in their U.S.-based HIV cohort to be 14%, and patients with microalbuminuria were more likely to have hypertension, metabolic syndrome, and immunosuppression (CD4+ cell count < 200 cells/mm).[32,51] Lastly, they determined that a single normal uACR determination effectively excluded microalbuminuria, whereas an elevated uACR required confirmation.[51] The UK National Institute of Health and Clinical Excellence (NICE) guidelines for CKD suggest defining pathologic albuminuria by a random urine albumin/creatinine ratio (uACR) > 30 mg/mmol (~300 mg/d).[52] Gansevoort et al.[53] demonstrated that progressively higher levels of ACR were predictive of worse renal outcomes across a range of eGFR values. In particular, detection of an increase in protein excretion had diagnostic and prognostic value in the initial identification and confirmation of kidney disease, and the quantification of protein excretion could be of considerable value in assessing disease progression, as well as treatment efficacy.[43,45,49,54] 24-hour urine collection has been considered the "gold standard" for urinary protein collection, but this technique is cumbersome.[54] Furthermore, Heerspink et al.[55] recently showed that in diabetic patients, first morning void uACR was superior to 24-hour urine protein or albumin in predicting renal outcomes. This suggests that 24-hour urine protein collections are no longer the gold standard. Easier alternatives include first morning voided or spot (random) samples, with data supporting the use of random uACR to accurately characterize protein and albumin excretion in adults with renal disease.[56-65] However, uACR measurements are not standard practice when screening HIV-positive patients for underlying kidney abnormalities, although their routine use is gaining popularity.

***HIV-associated kidney disease is common in Africa*.** HIV-positive adults are at risk for several chronic kidney diseases, including glomerular disease (collapsing glomerulopathy; commonly referred to as HIVAN, immune complex glomerulonephritis, FSGS, thrombotic microangiopathy, etc.), and tubulointerstitial disease associated with infections and specific medications (i.e. tenofovir). [34,66-73] The most severe of these, HIVAN, is a direct result of HIV replication in the kidney and occurs almost exclusively in persons of African descent.[71-73] Other hallmarks include proteinuria and normal/increased kidney size with increased echogenicity.[74-76] Renal disease, especially glomerular disease, is more prevalent in Africa and seems to be of a more severe form than that found in Western countries.[76] The true prevalence of HIVAN worldwide is not known- earlier studies suggested that approximately 10% of HIV positive, untreated persons with recent African ancestry develop HIVAN at some point in their HIV disease course;[77-80] however, a paucity of African data exists describing the prevalence of HIVAN.[80] We will not be performing renal biopsies in this study and therefore will examine HIV-associated kidney disease (not HIVAN specifically). Of relevance to our proposed study as we aim to intervene aggressively and early in the course of our Nigerian patients' kidney disease continuum, Han et al.[80] found 6 of 7 (86%) patients in their cohort with persistent microalbuminuria, when biopsied, to have structural kidney disease (HIVAN). Given the lack of dialysis and renal transplant options for the majority of Nigerians with HIV infection, our pharmacological research approach to halt or slow progression of CKD is especially urgent for SSA and may also be relevant for higher resource settings.

***Renin angiotensin aldosterone system (RAAS) inhibition can be used to reduce kidney complications*.** The renin-angiotensin aldosterone system (RAAS) is recognized as a central driver of the pathophysiology of CKD, based on numerous clinical trials in individuals with diabetes.[81,82] Renal dysfunction can be regarded as a continuum that extends from endothelial dysfunction to microalbuminuria, macroalbuminuria, ESKD, and ultimately death. All stages of this continuum are associated with progressively increasing cardiovascular risk.[83] Preventing the development and progression of kidney disease does require tight blood pressure control, but due to the important role of the RAAS in the pathogenesis of diabetic kidney disease, agents that inhibit this system (angiotensin converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARB's) are recognized first line therapy,[83] offering both effective blood pressure lowering and direct actions on the kidney. Numerous studies have documented the efficacy of RAAS inhibition as a means to slow the progression to CKD among at-risk diabetics.[81,82,84-90] Maione et al.,[91] in their systematic review of ACEi's and ARBs in patients with microalbuminuria, found a significant reduction in the risk of all kidney outcomes with ACEi's compared to placebo or no treatment (ESKD: 9 RCTs, 7988 patients, RR 0.67 [0.54–0.84]; doubling of serum creatinine: 9 RCTs, 8460 patients, RR 0.62 [0.46–0.84] and progression from micro- to macroalbuminuria: 18 RCTs, 2888 patients, RR 0.49, [0.36–0.65]. There was also a significant increase in the likelihood of regression from micro- to normoalbuminuria (15 RCTs, 1860 patients, RR 2.99 [1.82–4.91] (see **Section D.2** Sample size justifications). The end-organ protective effects of ACEis appear strongly related to their reactive oxygen species (ROS) lowering effects, and it has been hypothesized that high levels of ROS contribute to the pathogenesis of NCDs, including end-organ kidney complications.[85,92-97]

1.0 Rationale and Specific Aims

Nigeria is home to the fourth largest HIV-positive population in the world, having an estimated ~ 1,900,000 people living with HIV and 53,000 AIDS-related deaths annually.[98] Non-communicable diseases (NCDs), including kidney disease, among HIV-positive and HIV-negative adults in sub-Saharan Africa (SSA) represent a burgeoning epidemic. This study will be the first of its kind providing randomized controlled trial (RCT) evidence informing the optimal strategy to manage HIV-positive adults with albuminuria, particularly those with *APOL1* risk alleles who are genetically susceptible to kidney disease and potentially other life-threatening (i.e. cardiovascular) end-organ complications. Confirmation of the highest rates of adult HIV-positive populations globally carrying *APOL1* high-risk genotypes (~ 25%) would have significant implications for clinical care (including monitoring strategy) of persons in Nigeria and the West African region as a whole.

This study of HIV kidney disease is innovative for the following reasons:

1) Microalbuminuria among HIV-positive adults in Nigeria most likely represents underlying early structural kidney disease. This was the case in a small kidney biopsy series performed among HIV-positive adults presenting with persistent microalbuminuria in South Africa, of whom 6 of 7 were found to have HIV-associated nephropathy.[80] The present study will be the first to evaluate therapy to treat microalbuminuria in this population with the goal of preventing the progression of kidney disease.

2) *APOL1* variants are a major driver of kidney disease in HIV-positive persons. Most existing data on APOL1 risk variant prevalence are based on DNA from studies with very small sample sizes among specific African ethnic groups. This will be the largest genetic risk variant survey to date among individuals in West Africa, the region of the world with the highest documented carriage rates of the *APOL1* high-risk (HR) genotype.

3) If early therapy can reduce albuminuria, it could also reduce the burden of HIV-associated CKD and associated morbidity and premature mortality. Such findings would make a strong case for the adoption of population-based screening for albuminuria using uACR measurements (compared to less accurate urine dipstick and cumbersome 24-hour urine protein measurements). This testing would also greatly assist in the identification of persons in need of early intervention. In resource-poor settings, where access to therapies for ESKD (dialysis and kidney transplantation) are not widely available, prevention of CKD may prolong life.

4) Determining if the presence of an *APOL1* risk genotype correlates with ESKD risk (microalbuminuria, reduced eGFR, and/or early CKD), as well as determining whether it influences longitudinal renal outcomes among patients with prevalent albuminuria, is novel and will inform treatment guidelines and result in significant public health benefits, particularly if our results show that affordable and readily available treatment can be instituted early in the disease continuum; AND

5) Various interventional studies involving small numbers of subjects have been performed showing that the provision of RAAS inhibition is safe and may be beneficial when given to HIV-positive adults with HIV-associated nephropathy manifesting with varying levels of proteinuria.[99-106] Despite strong rationale and encouraging preliminary data, the role of RAAS inhibition in HIV-positive subjects with or at-risk for HIV-associated kidney disease remains to be confirmed by well-designed and adequately powered randomized controlled trials. The R3 study as designed is well poised to be the first RCT to provide definitive evidence regarding the role RAAS inhibition as adjunctive therapy to standard ART could play in the large numbers of HIV-positive adults at risk for long-term kidney complications. Such guidance is especially relevant in West Africa where the prevalence of the *APOL1* high risk genotype is highest globally. In addition, the promising pharmaceutical approach of the R3 study is particularly important in sub-Saharan Africa, where treatment options for ESKD (i.e. dialysis and transplantation) are extremely limited.

To accomplish our goals, we will pursue the following Specific Aims:

1.1 Specific Aim 1

Specific Aim 1: To determine the prevalence of *APOL1* renal risk variants among 2,600 HIV-positive individuals in Nigeria and assess whether *APOL1* HR status correlates with prevalent albuminuria, eGFR, and/or prevalent CKD (defined as macroalbuminuria or eGFR <60 ml/min/1.73 m^2) in this population.

***Hypothesis*:** ~25% of those screened will carry the *APOL1* HR genotype, which will be associated with albuminuria, lower baseline eGFR, higher uACR, and higher rates of prevalent CKD.

Definitions: Microalbuminuria will be defined as having a mean uACR of 30-300 mg/g. CKD will be defined by the presence of proteinuria or an eGFR of < 60 ml/min/1.73m^2.

Study Population: We will determine the prevalence of *APOL1* risk variants in a large group of HIV-positive adults (n = 2,600) in Nigeria and correlate them with early markers of kidney disease; namely microalbuminuria, reduced eGFR, and CKD. All consecutively seen HIV-positive ART-experienced (6+ months) adults (≥18-70 years of age) presenting for care at AKTH will be approached for enrolment into this study. **NOTE**: We will be enrolling ART-experienced adults (on ART for 6+ months). Specifically, if on ART for 6-12 months, then subjects need to have a plasma viral load value < 20 copies/mL from their 6-month blood draw, and if on ART for > 12 months, then enrolled participants need to have a suppressed viral load result (i.e. < 20 copies/mL) on their most recent viral load blood draw---which needs to be within the past 6 months). Routine viral load monitoring has only recently been implemented at our study site in north-central Nigeria, and by enrolling only patients with recent evidence of viral suppression, we will do our best to eliminate ongoing HIV-associated viral replication in non-adherent persons as a potential contributing cause to immune activation and therefore NCD end-organ complications, including kidney disease.

1.2 Specific Aim 2

Specific Aim 2: To assess whether RAAS inhibition with an ACEi compared to placebo, significantly reduces incidence of albuminuria or reduced eGFR among 280 HIV-positive individuals with microalbuminuria who are receiving ART.

Hypothesis: After two years,

- A significantly higher proportion of participants in the intervention vs. SOC arm will regress from microalbuminuria to normoalbuminuria (uACR<30 mg/g); anticipated hazard ratio = 2.5.
- Significantly higher proportions of participants in the SOC arm (60% vs. 25% in the intervention arm) will progress from microalbuminuria to macroalbuminuria (uACR>300 mg/g).
- Albuminuria will fall by an average of 40% in the intervention arm and increase by an average of 10% in the SOC arm.

Study population*:* All HIV-positive ART-experienced (6+ months) screened individuals (n = 2,600) found to have i) confirmed microalbuminuria (mean uACR between 30-300 mg/d obtained at 2 separate measurements at least 4 and no more than 8 weeks apart), (NOTE: based on variability of individual uACR measurements, we also plan to call back Aim 1 participants having normoalbuminuria (especially those with an average uACR value in the 20-29 mg/g range) as well as Aim 1 participants having macroalbuminuria), and ii) fairly well-preserved renal function, namely an eGFR > 60 ml/min/1.73m^2; will be approached for enrollment into this study. Based on recent studies at AKTH among HIV positive adults, we anticipate that a minimum of 18% of screened patients (n~460) will be eligible. Therefore, with a target sample size equal to

280 (see Section 10.0), 59% of eligible patients would need to consent for this Aim 2 study.

Primary Endpoints:

i) Regression from microalbuminuria (uACR=30-300 mg/g) to normoalbuminuria (uACR < 30 mg/g)
ii) Progression from microalbuminuria (uACR=30-300 mg/g) to macroalbuminuria (uACR > 300 mg/g) by study arm
iii) Mean change in uACR

Secondary Endpoints:

i) Doubling of serum creatinine from baseline; ii) All-cause mortality (**NOTE**: Planned follow-up is two years for all participants), iii) Proportion experiencing a 40% decline in eGFR (using CKD-EPI-Cr-CyC equation), iv) Mean change in eGFR over time (using CKD-EPI-Cr-CyC equation), and v) change in clinical/performance status (as ascertained via two measures, specifically the WHO quality of life (WHOQOL-HIV) tool (31 questions)[107,108] and the Karnofsky performance score)[109].

1.3 Specific Aim 3

Specific Aim 3: To determine whether the *APOL1* HR genotype is associated with worse longitudinal kidney outcomes among HIV-positive Nigerians with prevalent albuminuria, with regard to progression of albuminuria and eGFR decline.

Hypothesis: After two years of follow-up, independent of baseline uACR, eGFR, and/or treatment assignment:

- Study participants with the HR genotype will have a more rapid kidney function decline (median eGFR change) compared to those with the LR genotype.
- Study participants with the LR genotype will have 30% lower mean uACR values (compared to baseline) compared to study participants with the HR genotype.

Study population*:* All enrolled Aim 2 study participants who completed the study, namely, two years of study follow-up. However, to improve our power to evaluate the influence of *APOL1* risk allele status on key renal outcomes, we will include all enrolled Aim 2 study participants that completed a minimum of one year of clinical follow-up, meaning that if they were lost to follow-up after completing their one-year study visit, we will include them in our Aim 3 genetics outcome analyses.

2.0 Preliminary data

NCD incidence is high in SSA. We previously compared NCD incidence between a large urban U.S. setting (Nashville, TN) and a large urban African setting (Gaborone, Botswana). Standardized to an older, predominantly male U.S population, the overall NCD incidence rates were higher in Botswana (18.7 per 1000 PY).[11] Standardized rates differed most for cardiovascular events (8.4 vs. 5.0 per 1000 person-years) and non-AIDS-defining malignancies (8.0 vs. 0.5 per 1000 PY) - both higher in Botswana. This was one of the initial publications indicating that NCDs appeared to be a significant problem in our SSA setting and that monitoring, prevention, and treatment of NCDs should be a critical component of care in resource-limited settings.[11]

Angiotensin receptor blocker (ARB) and ACEi exposure is associated with decreased all-cause mortality in HIV positive adults.[88] Adults (≥18 years of age) who achieved virologic suppression within 180 days of ART initiation and were from one of four North American AIDS Cohort Collaboration on Research and Design (NA ACCORD) sites were included. Primary analysis assessed the effect of time-varying ACEi/ARB exposure on all-cause mortality, using a marginal structural model to control for time-dependent confounders. Among 5252 participants, ACEi or ARB use was associated with significantly lower odds of death among HIV positive adults receiving suppressive ART when properly accounting for time-dependent confounding.[88]

Kidney disease is common among HIV positive adults presenting for care at AKTH.[110] 400 consecutive treatment-naïve HIV-positive patients with no other condition known to cause kidney disease were screened for proteinuria and eGFR. Kidney disease was found in 227 patients (56.8%), and proteinuria, including persistent microalbuminuria, was found in 211 (52.8%), with reduced eGFR (<60 mL/min/1.73m^2) being identified in 64 persons (16.0%). Of note, the investigators biopsied a small series of patients (n = 20); among those with microalbuminuria, 2 of 5 (40%) had structural kidney disease in the form of collapsing FSGS (HIVAN). These findings confirmed that renal disease in HIV positive patients is high in Kano, Nigeria, and that microalbuminuria appears to be an important manifestation of collapsing FSGS.[110]

***APOL1 influences albuminuria in young African American adults*:** Kopp and Winkler have published data from the CARDIA study [111] (n=3,031) showing that the onset of *APOL1* kidney disease manifests as incident albuminuria and declining eGFR using serum cystatin C. Having *APOL1* HR genotypes was associated with a decline in eGFR only among those with albuminuria, compared to white adults (p=0.001).There were no differences in eGFR slopes for *APOL1* high-risk black adults without albuminuria or other blacks without albuminuria compared to the white adult reference group (**Figure 2**).[111]

Table 1. *APOL1* high-risk (HR) genotype and the risk for glomerular disease among African Americans and black Africans in South Africa

	Percent *APOL1* risk genotypes in black patients from U.S. and South Africa (SA)						
US published case/control studies					S. Africa published studies (Kasembeli JASN 2015[30])		
	No.	OR [95% CI]	*APOL1* HR	Ref	No.	OR [95% CI]	*APOL1* HR
HIVAN	54	29 [13-68.5]	72%	Kopp[36]	38	89 [18-911]	78.9%
Primary FSGS	217	17 [11-26]	72%	Kopp[36]	18	3.1 [0.04-249]	5.6%
HIV POSITIVEFSGS	-			-	19	3.6 [0.2-42]	10.5%
HIVICK	-			-	28	6.2 [0.4-97]	20.0%
	US published biopsy studies				**LEGEND:** HIVICK (HIV-associated immune complex disease); HIVAN (HIV-associated nephropathy) FSGS (focal segmental glomerulosclerosis). Population frequencies for carriage of *APOL1* high-risk genotype: US ~ 14%, SA ~ 2-3%, Nigeria ~ 25%.		
HIVAN	60	-	62%	Atta[35]			
HIV POSITIVEFSGS	35	-	63%	Fine[112]			
HIVICK	31	-	3%	Fine[112]			

While the CARDIA population was largely HIV-negative, these data show that *APOL1* kidney disease presents early as albuminuria and supports our hypothesis that HIV interaction with *APOL1* high-risk status may be associated with worse outcomes in Nigerians with albuminuria (Aims 1 and 3).

APOL1 high-risk genotype is associated with glomerular disease among African Americans and black Africans in South Africa: In a series of published studies, Kopp and Winkler[1,7-9,12,13] have shown that carriage of the *APOL1* HR genotype is strongly associated with primary FSGS and with HIVAN, with greater than 70% of individuals having these diagnoses possessing the *APOL1* HR genotype in the U.S. (Table 1). Interestingly, while the association for HIVAN was similar in African Americans (AA) and South African (SA) blacks, the enrichment of *APOL1* HR with primary FSGS (72%) in AA is strikingly higher compared to FSGS in SA blacks (5-10%) (Table 1). In a case-only biopsy series, we showed that the pathology of renal biopsies of HIVAN patients did not differ by *APOL1* genotype.[6]

Table 2. Selected relevant preliminary studies and data sources published by the project team

Study/setting/country	Study Methodology	Key findings, lessons learned
Comprehensive HIV and ART outcomes		
Pregnancy rates & birth outcomes among women on efavirenz (EFV)-containing ART, Botswana (Wester[113])	Prospective cohort	High pregnancy rates in women on EFV (7.9/100 person-years), indicating unmet need for family spacing services.
Mortality with ART initiation in advanced HIV-1, Botswana (Wester[114])	Retrospective cohort	Significant clinical benefit with ART, even for advanced immunosuppression.
Non-nucleoside reverse transcriptase inhibitor outcomes in Botswana (Wester[115,116])	RCT	Higher rates of treatment-modifying toxicities with nevirapine (NVP) (vs. EFV). NVP-treated women trended towards higher virologic failure with resistance vs. women on EFV.
Risk factors for symptomatic hyperlactatemia and lactic acidosis among combination ART-treated adults in Botswana (Wester[117])	RCT	Higher rates of symptomatic hyperlactatemia/lactic acidosis in overweight (BMI>25) females
Non-communicable diseases		
End stage renal disease among HIV positive adults in North America (Wester[33])	Large, retrospective observational cohort	High rates of end stage renal disease among blacks
Incidence rates of NCDs in a large U.S. center (Vanderbilt) versus a large African setting, Botswana (Wester[11])	RCT (Botswana) vs. retrospective observational data (U.S.)	Higher rates of age-standardized NCDs in Botswana
Clinical Trials		
Determine the optimal means (intervention package) for prevention of mother-to-child HIV transmission (PMTCT) in Nigeria (Aliyu) (Aliyu[118])	Cluster RCT	An integrated PMTCT package significantly improved a) ART initiation (adjusted RR (aRR)=3.3 (1.4-7.8)] and b) 12 week maternal and infant retention in care (aRR = 9.1 [5.2-15.9] in rural Nigeria
Stroke prevention in Nigerian children with sickle cell disease (SCD) trial (SPIN trial)	First NIH-sponsored sickle cell disease RCT in SSA	A hydroxyurea trial for children with SCD is feasible in SSA, but requires extensive capacity building

3.0 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria to be used for participant enrollment into Study Aim 1 are shown below.

Inclusion criteria:

- 18-70 years of age
- HIV-positive (as documented by HIV-1 ELISA testing)
- On ART for a minimum of six (6) months

Exclusion criteria:

- Patients unwilling to consent to participate in this study
- On ART for < 6 months

Recruitment strategies:
NOTE: Although the eligible population of the HIV clinic at AKTH is 40% male, we anticipate that females will be more likely to enroll in this study, given our previous experience. Therefore, study staff will specifically target males for enrollment in order to achieve a gender balance in our study enrollment. Strategies that will be utilized by staff include use of male counselors in the clinic, utilization of male peer counselors for targeted recruitment, and extension of clinic hours to accommodate male participants who may not be able to attend otherwise due to work engagements. These strategies have all been utilized successfully by our team in previous studies and HIV scale-up efforts within Nigeria and Mozambique.[118-120] In addition, given preliminary Aim 1 data, with the mean duration of ART among enrolled aim 1 participants being > 8 years, strategies will be utilized by staff to prioritize the identification of persons more recently (within the past 6-24 months) in order to enroll a large cohort of HIV-positive adults with a more balanced duration of time on ART. Lastly, also given preliminary Aim 1 data review coupled with DSMB feedback (January 23, 2019), it was seen that ~ 75% of enrolled aim 1 participants (n = 380) had a self-reported ethnicity of Hausa/Fulani; with only ~ 4-5% self-reporting their ethnicity as Yoruba. Based on published literature to date[39,40], carriage of the *APOL1* high risk (HR) genotype has been shown to be highest among persons of Yoruba descent and other ethnic groups (i.e. Igbo) and more prevalent in the southern part of Nigeria. To address this in order to increase enrolment of persons of Yoruba descent, we will plan to open a second study site; namely the Infectious Disease Hospital that is also in Kano, as the demographics of the population this hospital serves is quite different when compared to AKTH in that they service significantly higher proportions of persons of Yoruba and other ethnicities from southern Nigeria; where proportions of the population possessing the *APOL1* HR genotype are highest[39,4039-40].

Inclusion and exclusion criteria to be used for participant enrollment into Study Aim 2 are shown below.

Inclusion criteria:

- Participated in Study Aim 1: prevalence of *APOL1* high risk status and clinical correlates
- Suppressed plasma viral load result (≤ 20 copies/mL) within the past 6 months, and no unsuppressed viral load during that time. Routine viral load monitoring has only recently been implemented at AKTH. By enrolling only patients with recent evidence of viral suppression, we will reduce the impact of ongoing HIV-associated viral replication in non-adherent persons as a contributing cause of immune activation and therefore end-organ complications, including kidney disease.
- Completing Aim 1 of the study **AND** having a repeat single uACR value between 30-300 mg/g (based on first morning voided specimen) at time of Aim 2 screening to confirm eligibility.
- ≤ 1+ hematuria on urine dipstick
- eGFR ≥ 60 ml/min/1.73m^2 based on serum creatinine value obtained during Aim 1 **AND** based on repeat serum creatinine value obtained at time of Aim 2 screening to confirm eligibility (**NOTE**: eGFR for Aim 1 and Aim 2 calculated using the CKD-EPI-Cr-CyC equation).

AND

- If female, non-pregnant (documentation of negative urine pregnancy test) and not breastfeeding/lactating. In addition, if female (with reproductive potential), needs to be reliably/consistently be receiving contraceptives (including documentation of being receiving reliable/consistent contraceptives; including enrolment in family planning/consultative services).

Exclusion criteria:

- eGFR of < 60 ml/min/1.73m^2
- uACR < 30 mg/g or > 300 mg/g (on Aim 2 screening)
- K+ > 5.0 mmol/L, or reasons to be concerned about hyperkalemia
- History of diabetes mellitus (would qualify for treatment with an ACEi/ARB) [**NOTE**: Standardized diabetes screening procedure (fasting or random glucose ≥ 6.1 mmol/L)]
- ≥ 2+ hematuria on urine dipstick (assuming they might have glomerulonephritis from chronic active hepatitis B and/or C as both conditions can also cause albuminuria/proteinuria)
- Poorly controlled hypertension (Mean BP readings > 160/110 mm Hg in past 6 months)
- Persistent symptomatic hypotension (BP < 90/60 mm Hg) (on 2 or more successive readings)
- Known history of chronic congestive heart failure
- Initial screening uACR value > 300 mg/g plus urine dipstick ≥ 2+ for protein
- Currently receiving an ACEi and/or ARB;

OR

- Lack of suitability as a study candidate (i.e. active substance use disorder, active use of potentially nephrotoxic medication(s) [e.g. traditional medicines, etc.] and/or history of poor compliance [e.g. multiple missed scheduled clinic appointments, etc.])

4.0 Enrollment/Randomization

Participants will be enrolled at Aminu Kano Teaching Hospital (AKTH), Kano, Nigeria. All HIV-positive ART-experienced (≥6 months on ART) individuals found to meet the inclusion criteria will be approached by a study coordinator for enrollment into this study. The study coordinator will describe the purpose of the study and the included activities and will review the informed consent with the potential participant. Those who provide written informed consent will be enrolled.

Aim 2 will be a randomized double-blind (both participants and study physicians involved in the conduct of this study), placebo-controlled study to minimize crossovers and bias in the classification of outcomes and potential adverse effects secondary to ACE-inhibitor therapy (lisinopril), which we anticipate will be minimal. We will apply block randomization to ensure balance of baseline uACR between randomization arms. Using this block randomization, stratifying patients at time of study enrollment, we plan to enroll equal numbers of patients in each stratum.

5.0 Study Procedures

Aim 1 Study Procedures

Each consenting patient will have a full medical evaluation and will provide two first-morning void urine specimens (5 mL) because of variability. We will measure urinary albumin and creatinine levels to calculate a mean (2 sample) uACR value. The second first-morning uACR will be obtained 4-8 weeks after the first specimen. Assays will be performed using the Roche Hitachi Cobas C 311 (Roche Diagnostics, Indianapolis, IN) system, using pyrogallol red urine creatinine by a kinetic Jaffe method and urine albumin by immunoturbidimetry.[121,122] Each consenting patient will also provide one blood sample for serum creatinine and cystatin C, from which we will calculate eGFR using the CKD epidemiology collaboration (CKD-EPI-Cr-CyC)[123,124] equation. **NOTE**: We will use both serum cystatin C[125] and CKD-EPI[123,124] to calculate eGFR. Although the CKD-EPI equation is preferred/more accurate, Shlipak et al.[125] have shown that the use of both serum cystatin C and serum creatinine for eGFR estimations strengthens the association between eGFR and the risk of ESKD and death across diverse populations. During their first AKTH clinic visit, all screened patients will have their confirmatory HIV-1 ELISA test result as well as the most recent CD4+ count and viral load results obtained from their medical records/charts, per existing standard-of-care. Each screened patient will be given a unique study ID number, which the study team will maintain. The study ID can be linked back to individual patients (and will therefore be kept in a locked cabinet— all information linking patients to ID numbers will be destroyed once study follow-up for Aims 1-3 is complete). Individual patient data that will be collected and maintained by de-identified study ID include: age, race/ethnicity, sex, weight, BMI, and comorbid medical conditions (prior/current opportunistic infections, syphilis, cancer, hypertension, other cardiovascular diseases).

Genetics specimen collection and analysis: From all consenting patients, peripheral blood will be collected in one 10 mL EDTA vacutainer tube. Blood will be processed for buffy coat and whole blood, and will be aliquoted into multiple separate 1.0- and 2.0-mL vials (following the SOP for processing DNA blood specimens in Dr. Cheryl Winkler's laboratory) for and stored at -80 C. DNA (buffy coat and whole blood) specimens will be stored and shipped in batches to Dr. Winkler's laboratory for DNA extraction using Qiagen extraction kits and genetic testing of *APOL1* risk variants. Genotyping will be performed to identify the genetic correlates of risk for kidney and potentially other end organ complications.[17,38,126]. Genotyping will be done using TaqMan assays (San Diego,

CA) targeting the 3 chromosome 22 *APOL1* variants (rs73885319 [G1], rs60910145 [G1], and rs 71785313 [G2]) associated with CKD and HIV-associated kidney disease. The *APOL1* risk alleles are defined by the G1 haplotypes (rs73885319-G/rs60910145-G and rs73885319-G/rs60910145-T) and by the G2 haplotype (rs71785313-deletion). We will infer the *APOL1* genotype from the number of risk alleles: individuals exhibiting two risk alleles (G1/G1, G1/G2, or G2/G2) will be assigned to the "high-risk (HR)" group, while individuals carrying no or one risk allele (G0/G0, G0/G1, and G0/G2) will be attributed to the "low-risk (LR)" group. We will also examine the risk allele groups in a categorical manner (0 vs. 1 vs. 2 alleles and 0 vs. 1 risk alleles) to determine whether presence of a single risk allele poses increased risk. We will then determine the overall prevalence of *APOL1* risk alleles, including odds ratios for baseline CKD and albuminuria, and the standard error for beta comparing levels of microalbuminuria and eGFR stratified by genotype (including testing for association between the *APOL1* genotype and longitudinal eGFR slope using linear regressions). In addition, we will perform crude and adjusted linear regression analyses (modified Poisson regression) to test for associations with mean uACR, eGFR, and CKD, adjusting for sex, blood pressure, and age. Based on previous genetic association work in HIVAN, we will test both additive and recessive genetic models to capture all potential risk alleles associated with microalbuminuria and CKD. Because of the strong associations reported for *APOL1* with HIVAN (OR=29, U.S. and OR 89, South African, recessive model), our cohort exhibits substantial power to detect the effects of *APOL1* in the recessive model. For *APOL1*, we anticipate that 12% of controls and 36% of cases will carry the *APOL1* HR genotype; this is a strong epidemiological association, but modest on the scale of known effects of *APOL1* risk alleles on kidney disease.

NOTE: We also plan to collect and store plasma, sera, and urine specimens from all screened / consenting aim 1 study participants for future analyses that we will perform by obtaining separate/additional grant funding; specifically storing specimens (-80ºC) for future biomarker association and other relevant translational studies, and as a backup DNA source for quality control. We will also seek ancillary/supplemental funding to conduct 12- and 24-month follow-up of consenting Aim 1 patients for Aim 3 outcomes.

Aim 2 Study Procedures

Study Medication: **Participants in the intervention arm will be given lisinopril at a starting dose of 5 mg/day at time of Aim 2 enrollment**. Participants in the control arm will receive a matched placebo. Participants who are found to have symptomatic hypotension and/or new onset /persistent grade 3 (or higher) hyperkalemia after taking study medication (as evaluated at day 3 (safety phone call), week 1, month 1, or during an unscheduled visit will be removed from the study.

Participants who tolerate the initial study dose **(5 mg/day or placebo) will be increased to 10 mg/day lisinopril** (or matched placebo) at their **one (1)-month study visit**. All study participants having a dose change/escalation from 5 to 10 mg active medication (or matched placebo), will also (as was done following study enrollment) undergo safety monitoring in the form of a 3-day post dose escalation safety phone call, a 1-week post dose escalation study visit for blood draw/safety evaluation, and 1-month post dose escalation study visit for blood draw/safety evaluation. Those who do not tolerate an increase to the 10 mg/day dose will be returned to the 5 mg/day dose, while those who are able to tolerate an increase to the 10 mg/d dose will be closely monitored for

adverse events and re-assessed (see below) at their 3-month study visit for a possible dose escalation to 20 mg/d of lisinopril.

Participants who tolerate the **10 mg/day lisinopril (or matched placebo) will be increased to 20 mg/day lisinopril** (or matched placebo) at their **three (3)-month study visit**. All study participants having a dose change/escalation from 10 to 20 mg active medication (or matched placebo), will also (as was done following study enrollment and following the 1 month lisinopril dose escalation (from 5 to 10 mg/day)) undergo safety monitoring in the form of a 3 day post dose escalation safety phone call, a 1 week post dose escalation study visit for blood draw/safety evaluation, and a 1 month post dose escalation study visit for blood draw/safety evaluation. Those who do not tolerate an increase to the 20 mg/day dose will be returned to the 10 mg/day dose, while those who are able to tolerate an increase to the 20 mg/day dose will be closely monitored for adverse events and re-assessed (see below) at their 5-month study visit for a possible dose escalation to 40 mg/d of lisinopril.

Participants who tolerate the **20 mg/day lisinopril (or matched placebo) will be increased to 40 mg/day lisinopril** (or matched placebo) at their **five (5)-month study visit**. All study participants having a dose change/escalation from 20 to 40 mg active medication (or matched placebo), will also (as was done following study enrollment and following the 1 month lisinopril dose escalation (from 10 to 20 mg/day)) undergo safety monitoring in the form of a 3 day post dose escalation safety phone call, a 1 week post dose escalation study visit for blood draw/safety evaluation, and a 1 month post dose escalation study visit for blood draw/safety evaluation. Those who do not tolerate an increase to the 40 mg/day dose will be returned to the 20 mg/day dose, while those who are able to tolerate an increase to the 40 mg/day dose will remain at 40 mg/day for the duration of the study. For specifics regarding criteria to be intensively monitored (i.e. blood pressure, serum K+ values, and changes in renal parameters (eGFR and serum creatinine) during all study medication (or matched placebo) dose titrations, please see "**Table 3: Aim 2 Study Medication (Matched Placebo) Dose Titration Algorithm"** on pages 25-26 for details.

Alternative medications: Patients who develop side effects to lisinopril (particularly refractory cough) will be transitioned to the equivalent dose of an angiotensin receptor blocker (ARB), losartan, at a dose of 25 or 50 mg/day (depending on the dose of lisinopril (or matched placebo) they were receiving at the time of their adverse event). Most patients that develop a refractory cough on lisinopril (which we believe will be few) if they need anti-hypertensive control will be switched from lisinopril to 50 mg/d of losartan. A few patients may develop a refractory cough very early on study medication (within first 1-2 months of enrollment), and such patients, if they still require anti-hypertensive medication control may be switched to 25 mg/d of losartan. Patients in need of anti-hypertensive treatment that developed a refractory cough while on study medication will all need to be unblinded due to the severity of this adverse event and most importantly so it can be listed on the patient's active list of medication side effects, so they will not be prescribed ACE inhibitors again in the future. Patients who do not tolerate either study medication (lisinopril or losartan) will be removed from the study and referred to care if needed (see **Figure 2** for details).

Figure 2. Flow diagram of study medication dosing. Endpoints are outlined in green. Symptomatic hypotension will be defined as a reading of lower than 90 mm Hg systolic

or 60 mm Hg diastolic with associated symptoms (i.e. feeling of lightheadedness, weakness) (**NOTE**: All low blood pressure readings will be confirmed, orthostatic blood pressure will be obtained (when clinically indicated/appropriate), and all readings will be put in context of the individual's normal BP readings). Patients removed from the study due to failure to tolerate either the primary (lisinopril) or alternative (losartan) study drug will be unblinded (outlined in **red**) so as to enable their physician to best treat any conditions. (**NOTE**: Hyperkalemia will be graded using established DAIDS Toxicity grading Scale (Version 2.1, July 2017); with grade 1 hyperkalemia = 5.6-5.99 mmol/L, grade 2 hyperkalemia = 6.0-6.49 mmol/L, grade 3 hyperkalemia = 6.5-6.99 mmol/L and grade 4 hyperkalemia (K+ values) being ≥ 7.0 mmol/L).

***Nigeria standard of care*:** The Nigeria HIV/AIDS adult treatment guidelines recommend a baseline assessment of all HIV-positive patients to include a complete history and physical examination, staging of disease with clinical and immunological classification of the patient, and review of laboratory results. In addition, an evaluation of nutritional and psychosocial status, assessment of readiness for therapy, and development of patient-specific adherence strategy is recommended for all patients. All HIV-positive patients, regardless of CD4+ cell count (commonly referred to as the "Test-and-Start" or "Treat All" strategy) are started on ART. First line regimens include: tenofovir (TDF) + lamivudine (3TC) + efavirenz (EFV); TDF + 3TC + nevirapine (NVP); zidovudine (AZT) +3TC (or emtricitabine [FTC]) + EFV and AZT +3TC (or FTC) + NVP. A boosted protease inhibitor plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) are recommended for second-line ART, and available protease inhibitors include ritonavir-boosted lopinavir and atazanavir. The government of Nigeria will be transitioning to TLD (tenofovir, lamivudine, plus the integrase strand inhibitor dolutegravir) during 2018-2019. As a result, all HIV positive persons (> 10 years of age and weighing > 30 kilograms) will be switched to TLD during this transition period in accordance with national guidelines/WHO recommendations. In patients with renal insufficiency, i.e. a documented increase in serum creatinine, the guidelines recommend ART regimen dosage modifications if the calculated creatinine clearance (CrCl) is reduced at baseline (i.e. not initiating tenofovir in adult patients having a calculated eGFR of < 50 ml/min/1.73m^2 or if at any time during follow-up their CrCl decreases significantly (i.e. confirmed to < 50 ml/min/1.73m^2 from their baseline values). Modifications include switching patients from tenofovir to abacavir as well as investigating potential causes of their worsening renal function (i.e. looking for pre-renal causes such as dehydration, post-renal causes (prostatic obstruction, nephrolithiasis, and/or intra-renal causes such as initiation of new potentially nephrotoxic medications (such as traditional medicines, etc.). Of note, patients switched to dolutegravir (from efavirenz or nevirapine) as part of the soon to commence TLD rollout may also experience a sustained increase in their serum creatinine coupled with a corresponding decrease in their calculated eGFR. In brief, for a period of up to 48 weeks following dolutegravir (DTG) initiation, it is anticipated that study participants may experience a modest (0.2 mg/dL) increase in serum creatinine[127-129] that will not lead to significant changes in uACR values but will be lead to aim 2 study participants having a "new baseline eGFR" that is unrelated to study medication and based on the literature using iohexol [130] will not represent a true change in eGFR; but nonetheless will still need to be accounted for in the analysis plan. **NOTE**: Given the known limitations of CysC-based equations for HIV-positive individuals, from an analysis standpoint, the team will utilize/rely on significant changes in serum creatinine (sCr) safety monitoring/reporting among DTG-treated study participants. Patients with reductions in CrCl should undergo an evaluation for potential causes of decreased renal function and have serum creatinine monitored more frequently until

resolution of renal insufficiency or failure. Adjustments to medication dosages should be based on recommendations by drug manufacturers. The national treatment guidelines recommend that routine follow-up assessment of HIV-positive patients should cover: signs/symptoms of HIV-related conditions and potential medication toxicities; adherence; response to therapy; weight; and laboratory monitoring. Every 3 months, the patient should undergo a physical exam and clinical screening for tuberculosis (TB). Every 6 months, the following tests should be performed: CD4+ cell count, hemoglobin (Hgb) and hematocrit (Hct), alanine aminotransferase (ALT), and calculated creatinine clearance (CrCl). Viral load testing is recommended every 6 months. Asparate aminotransferase (AST), alkaline phosphatase (alk phos), fasting blood glucose (FBG), glycosolated hemoglobin (Hgb A1C), amylase, urine pregnancy testing, lipid profiles (including total/LDL/HDL cholesterol and serum triglyceride levels), serum electrolytes (including sodium, potassium, chloride, bicarbonate, blood urea nitrogen, and creatinine), sputum for acid fast bacilli (AFB) (for TB screening using conventional microscopy and/or GeneXpert MTB/RIF technology), and chest radiography will be performed as clinically indicated.

Longitudinal Study Assessments*:* All enrolled patients will undergo the following tests at baseline and then every 3 months while on study, until completing 2 years of follow-up: serum cystatin C, blood pressure, serum electrolytes (creatinine, potassium, sodium, chloride, bicarbonate, and urea), and uACR. Clinical performance status (as measured via the WHOQOL-HIV tool and the Karnofsky performance score) will be evaluated at baseline and at 12 and 24 months. If participant is a female with reproductive potential, she will undergo urine pregnancy testing every 3 months (please see below in **NOTE**). All enrolled aim 2 study participants will have their *APOL1* genotype data (i.e. whether HR or LR genotype) available prior to completing study follow-up (see **Study Timeline**). All patients will undergo routine standard laboratory monitoring as per existing guidelines; specifically, CD4+ cell count and viral load testing (q 6 monthly), liver function test monitoring (at month 1, 3, and 6, and then q 6 monthly following ART initiation), etc., as per Nigeria standard of care (SOC). All enrolled patients will undergo a blood pressure check and have serum electrolytes tested at week 1 and month 1 following study initiation and any changes in dose as part of a brief safety check. All enrolled patients will undergo hepatitis B and C screening at baseline. Additional funds have been allocated for patients to undergo unscheduled safety monitoring (up to two additional times per year) as needed, while on study.

NOTE: Females with reproductive potential will receive extensive education regarding the risks of ACEi therapy; namely the potential risk of congenital abnormalities during the first trimester (one study[131]) as well as the documented increased risk of fetal renal damage in the 2nd and 3rd trimesters.[132] All reproductive-aged females will undergo pre-enrolment and q 3-monthly urine pregnancy testing and, if they test positive, they will be immediately unblinded and their study medication (if on active study medication; i.e. lisinopril) will be discontinued immediately and an appropriate substitution will be made if needed (i.e. anti-hypertensive).[131,132] We will also educate all enrolled women having reproductive potential to immediately report to the study staff if they suspect being pregnant. If they do suspect being pregnant, they will immediately report to the research team, their ACEi will be discontinued, and they will undergo the necessary evaluations (i.e. urine pregnancy testing) with alternative anti-hypertensive medications being prescribed as needed among women confirmed as being pregnant.

Study medication and adherence: The medication or placebo will be provided to each study participant at no cost to the participant. Study medications will be stored at the clinical site in a locked storage cabinet that will be accessible to the study pharmacist and site PI. The study pharmacist will ensure the medicine is stored properly and dispensed only when needed for study participants. The site investigators will assure the medicine is stored properly and dispensed only when need for study participants to by the clinical pharmacist designated at the clinical site. The following will be monitored and completed on a continuous basis to assure the medicine is within study guidelines, onsite pharmaceutical compliance, and manufacturer guidelines:

1. Delivery Log of Medication
2. Drug Accountability Record
3. Drug Safety and Handling Sheet

We will ascertain adherence to study medication via self-report, medication possession ratio (using pharmacy prescription/dispensing data),[133] and by measuring change in blood pressure (post hoc) among patients randomized to the intervention (ACEi) arm. We will also measure adherence using a modified version of the brief medication questionnaire (BMQ)[134] every six months, and the score will be shared with the patient during this visit (i.e., high, average, or poor adherence). Using evidence-based strategies,[22-24] we will implement educational and behavioral interventions that have proven successful in other studies for persons categorized as having poor adherence (≥1 points). For persons demonstrating average to high adherence (<1 point), we will implement positive reinforcement with the continuation of educational interventions throughout the study.[21,23]

Randomization procedures (including assignment of randomized participants into 6 (six) strata based on uACR and *APOL1* risk allele genotype:
The randomization process will be a stratified randomization with varied block sizes and random block sequences. The stratified randomization addresses the need to balance the baseline uACR values and high-risk genotypes among the intervention and control groups. Enrolled patients will be stratified into six groups by uACR values and number of high risk alleles of range 30-59 + 2 high risk alleles, 30-59 + 1 high risk allele, 30-59 + 0 high risk alleles, 60-300 + 2 high risk alleles, 60-300 + 1 high risk allele, and 60-300 + 0 high risk alleles, and the six groups will have approximately 35, 35, 70, 35, 35, and 70 patients respectively. These six strata are determined to make sure that the study arms are well-balanced and that we will have enough participants with high risk genotypes to be able to complete Aim 3 of the study. This decision tries to find a balance between recommendations to keep the number of strata as small as possible (3 to 4 strata is generally advisable with an average of 50-100 patients per stratum)[135] while ensuring that we have adequate numbers of persons with high risk genotypes. Relatively small block sizes of 2, 4, and 6 will be used in order to ensure balanced group sizes among the two arms over time. To make the allocation of participants unpredictable, the sequence of blocks will also be randomized. Three series of randomly ordered letters of “A” and “B” will be generated using R software. The blockrand package of R will be used to generate random treatment assignment using the block design described above. To ensure there are enough random assignments for each group, we will generate lists of size 50, 50, 100, 50, 50, and 100 for the 6 strata.

6.0 Study Safety Monitoring Plan

Study participants will be recruited and consented at AKTH, Kano, Nigeria. Adherence to human subject regulations will primarily be the responsibility of the Multiple PIs. The study team will adhere to all requirements by: (i) developing a study protocol that is able to meet its stated research objectives, and thus reflect adequate risk-benefit ratios for human subjects; (ii) specifying study procedures in the protocol that protect the rights and safety of human subjects; (iii) developing a recruitment script and informed consent forms that include all elements of consent required by Federal regulations and accurately represents study requirements, risks, and benefits in language that is understandable to study participants, including human subject considerations; and (iv) monitoring adherence to protocol specifications and human subject requirements. The consent forms, protocol, and any subsequent modifications will be reviewed and approved by the Institutional Review Boards (IRB) at Vanderbilt University (FWA00005756), and AKTH (FWA00010841).

A. Adverse Event (AE) Assessment

1. Anticipated risks

   Risks that are expected/anticipated as part of participation in the study are detailed in the study information and consent forms that will be distributed to and reviewed with patients by trained study team members. These risks are described below, along with steps that will be taken to minimize these risks:

   *Risks of blood draw*s: As described in Study Procedures (Section 6.0), blood specimens will be collected from each participant by routine venipuncture. The risks of venipuncture include discomfort at the site of puncture; possible bruising and swelling around the puncture site; and rarely an infection. We expect no additional psychological or social harms to occur. Other risks may include pain, bleeding, or bruising where the needle enters the skin; lightheadedness; and in rare cases, fainting or infection. These risks will be minimized by hiring study staff who are well trained in phlebotomy and other clinical procedures.

   Risks of study medication (lisinopril and losartan)
   The common side effects of lisinopril includes the following: cough, headache, dizziness, depressed mood, drowsiness, gastrointestinal symptoms such as nausea, upset stomach, vomiting or diarrhea, and skin symptoms such as mild itching or a rash. Any patients experiencing persistent/refractory cough that is deemed possibly related to their lisinopril therapy (as a refractory cough has been reported in as many as 6-8% of participants, with higher rates seen in person of African descent (up to 12% in some studies), will be switched to an equivalent dose of the ARB losartan, as described above. Patients switching from lisinopril to losartan will remain on study (Aim 2), as a switch from an ACEi to an ARB is an allowable study substitution. Common side effects of losartan include the following: cold or flu-like symptoms such as stuffy nose, sneezing, sore throat, fever; dry cough; muscle cramps; pain in legs or back; stomach pain or diarrhea; headache or dizziness; tired feeling or insomnia.

   Refractory Cough: Cough occurs in 5-15% of patients. It is not dose- or brand-related, is more frequent in women than men, and is more frequent in persons of African descent (blacks) than Caucasians (whites). It usually develops within 1

week to 6 months following ACEi initiation and typically resolves within 4 days of cessation. Study investigators need to be aware of a confounding congestive heart failure cough and remember that changing to another formulation sometimes helps. **NOTE**: Persons with a history of chronic h/o congestive heart failure are not eligible for aim 2. Cough is not a reason to discontinue treatment unless it persists (and or escalates in intensity/severity) and/or study participants feel that they cannot tolerate it. A few studies have looked at the use of nonsteroidal anti-inflammatory drugs (NSAIDs), nifedipine, cromolyn, or nebulized bupivacaine for managing cough, but further studies are needed. Any aim 2 participants developing a cough (that is deemed new and significant by the study participant; and/or is grade 2 or higher as per DAIDS toxicity grading criteria; needs to involve the SOC and SSC. Each case will be handled on a one-on-one basis and decisions to hold or discontinue study medication will be made depending on the severity, progression (or lack thereof) and response to holding/discontinuing study medication. (**NOTE**: Please refer to "**Table 3: Aim 2 Study Medication (Matched Placebo) Dose Titration Algorithm**" for specific details).

Teratogenicity (Pregnancy Considerations): Lisinopril has been found to be teratogenic in mice and therefore is classified as class D by the FDA. All women of childbearing age (and potential) in this study will be extensively counseled about these potential risks and will be linked to family planning/spacing services, if desired. They will also undergo urine pregnancy testing at the beginning of the study and every three months at no cost. Any participant found to be pregnant will be withdrawn from the study. In addition, all women of childbearing age (and potential) will be extensively counseled and told to come immediately to clinic if they suspect for any reason that they may have become pregnant; i.e. missed/delayed menses, unexpected weight gain, etc.

Hyperkalemia: Given the potential risk for hyperkalemia in this study population, all study team members will be trained to educate participants on the risk of hyperkalemia, as well as prevention measures (e.g. maintaining adequate hydration, avoiding potentially nephrotoxic substances such as traditional medicines, etc.). Study team members will also train participants to recognize signs and symptoms of hyperkalemia, and study clinicians will be specifically trained on the risk, diagnosis, and management of hyperkalemia. We will explain to all study participants that lisinopril may cause hyperkalemia, and we will explain this in detail in the consent also strongly encouraging all study participants to notify our study staff before initiating any new medications or over-the-counter remedies, as we want to be sure that none of the new medications they are planning to start are associated with the possible risk of precipitating hyperkalemia. To protect study subjects and monitor them for this possible side effect, we will be performing frequent serum electrolyte monitoring; scheduled at least every three months while on study (Aim 2), including one additional serum electrolyte safety check visit at one week and at one month for all Aim 2 participants. (**NOTE**: Please refer to "**Table 3: Aim 2 Study Medication (Matched Placebo) Dose Titration Algorithm**" below for specific details). Participants will be extensively educated and told to call or come into the clinic if they experience decreased urine output, fatigue, palpitations, dyspnea, lightheadedness, and/or generalized fatigue/malaise. Patients receiving concomitant medications that have also been known to potentially cause hyperkalemia (i.e. cotrimoxazole (Emtrim™), the ARV

medication dolutegravir (DTG), and other medications) will undergo more frequent serum electrolyte/safety monitoring.

Angioneurotic edema: Angioneurotic edema, which occurs in 0.1- 0.2% of patients, usually develops within the first week of therapy but can occur at any time. This life-threatening adverse effect also occurs with angiotensin II receptor blockers but to a lesser extent. Any patient with a history of angioneurotic edema, whether related to an ACE inhibitor, angiotensin receptor blockers (ARBs), or another cause, should not be given an ACE inhibitor. (**NOTE**: any allergic reaction that is "*definitely related*" or "*possibly related to study medication*" that involves generalized urticaria OR angioedema with intervention indicated OR symptoms of mild bronchospasm is classified as a grade 3 acute allergic reaction and an SAE is needed and the participant is immediately unblinded, and if on active study medication (ACEi or ARB) it is to be discontinued immediately, and this allergic reaction is to be documented in their medical record. If the participant has acute anaphylaxis OR life-threatening bronchospasm OR laryngeal edema; this is a grade 4 acute allergic reaction and an SAE is needed and the participant is immediately unblinded, and if on active study medication (ACEi or ARB) it is to be discontinued immediately, and this allergic reaction is to be documented in their medical record.

Changes in blood pressure (Hypotension): Lastly, lisinopril may also cause and/or exacerbate changes in blood pressure, specifically hypotension given its primary indication for use as an anti-hypertensive agent. Such changes can occur at any time (and at any dosage) while on lisinopril, but in most cases reductions in blood pressure +/- with the associated symptoms of hypotension (i.e. dizziness, lightheadedness, fatigue/malaise, new onset or worsening headache, etc.) occur within the first 1-4 weeks following lisinopril (ACEi) initiation. To protect study subjects and monitor them for this possible side effect, we will be performing frequent blood pressure (BP) monitoring; scheduled at least every three months while on study (Aim 2), including one additional blood pressure (BP) safety check visits at one week and at one month for all Aim 2 participants. (**NOTE**: Please refer to "**Table 3: Aim 2 Study Medication (Matched Placebo) Dose Titration Algorithm**" below for specific details). Participants will be extensively educated and told to call or come into the clinic if they experience lightheadedness, dizziness, fatigue/malaise, weakness, new onset or worsening headache, etc. Patients receiving concomitant medications that have also been known to potentially cause or exacerbate changes in blood pressure (i.e. other anti-hypertensive medications such as thiazide diuretics (i.e. hydrochlorothiazide (HCTZ), etc.), calcium channel blockers (i.e. nifedipine, amlodipine, diltiazem, etc.), ß (Beta) blockers (i.e. metoprolol, propranolol, atenolol, carvedilol, etc.) and other classes of/specific anti-hypertensive (i.e. hydralazine, clonidine, etc.) and/or anti-anginal/cardiac protective medications (i.e. nitroglycerin, isosorbide mono- and dinitrate, etc.) will undergo more frequent blood pressure/safety monitoring.

Table 3: Aim 2 Study Medication (Matched Placebo) Dose Titration Algorithm

Parameter / Guidelines to follow	**Systolic blood pressure** (SBP)	**Serum potassium** (K+)
Step 1 to 2 (5 mg/d ↑ to 10 mg/d)	**SBP > 110** (**ESCALATE**) **SBP 100-110** (Repeat BP and √ for symptoms/perform orthostatics) (Escalate only if repeat SBP > 110 or repeat SBP 100-110 without symptoms and based on record review—confirmed that patient's normal BP in this range) **SBP < 100** (Hold and repeat BP; if repeat SBP < 100 and/or patient with + symptoms (low BP) then do not escalate); have patient come back in 1 week (or sooner) for safety visit (BP √) and re-assess (**Involve SOC/SSC**) **NOTE**: Any hypotensive episode when associated symptoms are corrected with oral fluid replacement is a grade 2 hypotensive event; when symptoms AND IV fluids indicated it is grade 3; and when this hypotensive event is classified as shock requiring use of vasopressors or mechanical assistance to maintain blood pressure, this is a grade 4 event.	**K+ < 5.0** (**ESCALATE**) **K+ 5.0 – 5.5** (Repeat BMP and have patient come back in 1-2 days for safety √); if repeat K+ < 5.0 and creatinine stable—**ESCALATE;** If repeat K+ 5.0 – 5.5; Hold and repeat BMP in 1 week; and re-assess (if repeat still 5.0-5.5; **Involve SOC/SSC**) **NOTE**: If any repeat K+ between 5.5 – 6.0 and no other discernible cause (i.e. dehydration, etc.) then complete SAE and hold study medication and follow advice of SOC/SSC **If any K+ > 6.0, complete SAE**; and discontinue study medication
Step 2 to 3 (10 mg/d ↑ to 20 mg/d)	**Same as above for Step 1**	**K+ < 5.0** (**ESCALATE**) **K+ 5.0 – 5.5** (Repeat BMP and have patient come back in 1-2 days for safety √); if repeat K+ < 5.0 and creatinine stable—**ESCALATE;** If repeat K+ 5.0 – 5.5; Hold and repeat BMP in 1 week; and re-assess (if repeat still 5.0-5.5; **Involve SOC/SSC**) **If repeat K+ 5.0 – 5.5;** Hold and repeat BMP in 1 week; and consider re-initiating study medication at 50% of prior dose (monitoring K+ closely) **If any K+ > 6.0**, complete SAE and discontinue study medication
Step 3 to 4 (20 mg/d ↑ to 40 mg/d)	**Same as above for Step 1**	**Same as above for Step 1**
Parameter / Guidelines to follow	**Serum creatinine (sCr)**	**Estimated glomerular filtration rate (eGFR)**

Step 1 to 2 (5 mg/d ↑ to 10 mg/d)	**sCr < 90 µmol/L (or < 1.0 mg/dL) for FEMALES OR < 110 µmol/L (or < 1.2 mg/dL) for MALES (ESCALATE)** **sCr remains < 1.2x below baseline (ESCALATE)** **sCr increases between 1.2 - 1.3x from baseline** (Repeat ScR and monitor closely for signs of worsening kidney function; i.e. decreased urinary output, fatigue, palpitations, dyspnea, lightheadedness, and/or generalized fatigue/malaise). If repeat sCr normalizes (< 1.2x below baseline value) **(ESCALATE)** **NOTE: Any time sCr increase 1.3 -1.8x the upper limit of normal (ULN) OR sCr increases between 1.3 - 1.49x from baseline;** this constitutes a grade 2 event. **Any time sCr increase 1.8 – 3.49x the ULN OR sCr increases between 1.5 – 1.99x from baseline;** this constitutes a grade 3 event (and requires an SAE to be completed) **Anytime sCr increases by ≥ 1.3-fold; immediately HOLD study medication**; look for other possible etiologies/contributing factors; and monitor closely; repeating BMP within 1 week; **If repeat sCr normalizes (< 1.2-fold below baseline value) (ESCALATE)**; **but if sCr elevations persist by ≥ 1.3-fold from baseline; continue to HOLD study medication; involve the SOC/SSC**; as study medication may need to be discontinued and AE report done **NOTE:** All study participants receiving dolutegravir (DTG)-based ART may experience a sustained increase in serum creatinine (sCr) (up to 0.2 mg/dL) that may persist for up to 48 weeks (or possibly longer) so to account for these potential modest changes in renal function, all safety events involving kidney function deemed "possibly" or "definitely related" to study medication among DTG-treated study participants will be evaluated and graded using serum creatinine (sCr) measurements.	**eGFR remains stable (and if diminishes; does so by < 20%** (ml/min/1.73m^2 (using CKD-EPI-Cr-CyC equation)) **when compared to baseline eGFR**; **(ESCALATE)** **eGFR decreases by 10-20% when compared to baseline**; (Repeat eGFR within 1 week and monitor closely for signs of worsening kidney function **eGFR worsens by 20-29% when compared to baseline** (Repeat eGFR within 1 week and monitor closely for signs of worsening kidney function; i.e. decreased urinary output, fatigue, palpitations, dyspnea, lightheadedness, and/or generalized fatigue/malaise). If repeat eGFR improves/normalizes (i.e. is reduced < 20% when compared to baseline) **(ESCALATE)** **NOTE: A 10-20% decrease in eGFR in baseline constitutes a grade 2 event;** and when any patient experiences a > 10% decline in eGFR (from baseline), their renal function needs to be more intensively monitored. **A decrease in eGFR between 30-50% (from baseline) constitutes a grade 3 event (and requires an SAE to be completed)** **Anytime eGFR diminishes by > 30% from baseline; immediately HOLD study medication;** look for other possible etiologies/contributing factors; and monitor closely; repeating eGFR within 1 week; If repeat eGFR improves/normalizes (< 20% below baseline value) **(ESCALATE); but if eGFR reductions persist by ≥ 30% from baseline; continue to HOLD study medication; involve the SOC/SSC; as study medication may need to be discontinued and AE report done** **Any study participant experiencing a drop in eGFR (at any time) to < 50 ml/min/1.73m^2** (using CKD-EPI-Cr-CyC equation); **immediately HOLD study medication**; look for other possible etiologies/contributing factors; and monitor closely; repeating eGFR within 1 week; **involve the SOC/SSC**; as study medication may need to be discontinued and AE report done
Step 2 to 3 (10 mg/d ↑ to 20 mg/d)	**Same as above for Step 1**	**Same as above for Step 1**

Step 23to 4 (20 mg/d ↑ to 40 mg/d)	**Same as above for Step 1**	**Same as above for Step 1**

Risks of prescribed combination antiretroviral therapy (ART) (specifically tenofovir (TDF):
All eligible/enrolled aim 2 study participants will be receiving ART for 6+ months, and we anticipate that a significant proportion (i.e. > 80%) of them will be receiving tenofovir (TDF)-based regimens. We mention this because of the potential adverse events that have been attributed to the nucleotide reverse transcriptase inhibitor TDF, namely kidney toxicity which may manifest as a reduction in eGFR. These potential TDF-associated kidney manifestations that include reduced eGFR, Fanconi's syndrome, etc. are due to tubular (rather than glomerular) insults; and they often present within the first 1-2 years following TDF initiation and based on our preliminary analysis of enrolled aim 1 study participants (January 2019), the majority of aim 1 study participants (from which we will be screening/enrolling for aim 2) have been receiving ART for considerably longer periods of time (i.e. mean duration of ART > 8 years).

Management of Worsening Renal Function Among Study Participants receiving tenofovir (TDF)-based ART regimens:
At an eGFR of 30-49 ml/min/1.73m^2, patients receiving a TDF-based regimen should ideally have their dose modified to 300 mg q48 hours. If the eGFR falls further into the 10-29 ml/min/1.73m^2 range, the dose should be adjusted to 300 mg q72 hours. However, these recommended dose adjustments are difficult to implement as most of the ARV regimens are dispensed as fixed drug combinations (FDCs). In addition, adjusting the dose to alternate day dosing makes things very challenging logistically and may promote poor adherence due to the increased likelihood of patients missing/forgetting doses. Therefore, at an eGFR 30-49 ml/min/1.73m^2, the standard of care (SOC) is to switch tenofovir (TDF) to an alternative NRTI (i.e. abacavir (ABC)); realizing that if the person is receiving abacavir plus lamivudine (3TC), the 3TC will need to be renally adjusted given that it is renally excreted (and 3TC dosing will be adjusted/modified per established standards). The on-site study team is to notify/involve the SOC/SSC of any/all participants with worsening renal function (as outlined above) so they can assist in the management, tracking and development of AE/SAE forms (as needed).

Management of worsening renal function among persons receiving TDF plus study medication (lisinopril/matched placebo)
The study team needs to immediately investigate for a potential cause of declining eGFR (i.e. looking for pre-renal causes such as dehydration, post-renal causes (prostatic obstruction, nephrolithiasis, and/or intra-renal causes such as initiation of new potentially nephrotoxic medications (such as traditional medicines). We should not wait until the eGFR drops to <50 ml/min/1.73m^2 before we discontinue the study medication. Further clinical decisions RE: management is to be based on the cause of declining eGFR. Please refer to "**Table 3: Aim 2 Study Medication (Matched Placebo) Dose Titration Algorithm**" for specific management details. In addition, in terms of specific management, if a study

participant's calculated eGFR drops < 50 ml/min per 1.73m^2, the team will need to complete an AE report (send to the SOC/SSC) and update as needed. At this level of kidney function decline (< 50 ml/min per 1.73m^2), the study participant's study medication needs to be immediately held and the patients need to be thoroughly evaluated for other potentially contributing causes of worsening kidney function; i.e. volume contraction (dehydration, sepsis, GI bleeding, etc.), obstruction, nephrotoxin (any potentially nephrotoxic medication (i.e. aminoglycosides, etc.), IV contrast, traditional medicines, etc.), and/or other causes (rhabdomyolysis, etc.). During this time of study medication hold, the participant needs to be monitored closely and have their blood pressure, electrolytes (specifically their K+), and kidney function (serum creatinine and calculated eGFR) monitored as deemed necessary by the study team in consultation with the SOC/SSC. Patients will need to have their eGFR re-evaluated within 7 days (or sooner at the discretion of the treating clinician). If their eGFR has not stabilized/improved, with no other apparent etiology for worsening kidney function, consider holding tenofovir (TDF)(if on TDF-based ART) and/or dose reducing study medication (on a case-by-case basis; also in close collaboration/communication with the SOC/SSC). Depending on the kidney function/other parameters (i.e. K+, etc.), the study participant may need to be switched to an alternative ART regimen (i.e. switch TDF to ABC) and continue to monitor; and if their study medication was dose reduced, the on-site team will continue to monitor them closely to determine next steps; i.e. permanently discontinue study medication and/or other medications or attempt to resume study medication and titrate up the dose as deemed appropriate.

If the participants eGFR keeps on falling despite holding the study medication, and no other discernible causes for the kidney insult can be identified, we will discontinue tenofovir (TDF) and switch/substitute with abacavir (ABC). Please note that in Nigeria and other similar resource-constrained settings, the, initiation of abacavir (ABC) does not require genetic testing; specifically, HLA-B*5701 testing; the risk variant associated with risk for ABC-associated hypersensitivity reactions. To maintain integrity of the study, participants will be informed and consented about the chance of switching their ARV medications when the need arises. In addition, we have emphasized that in a significant proportion of cases, individual ARV medications will be substituted (only one medication in the ART regimen will be changed (i.e. TDF to ABC) and not the entire regimen, i.e. from first to second line ART regimens.

2. <u>Evaluation of subjects for adverse events</u>
   Subjects will be evaluated by a study physician at each visit for AEs. In addition, additional safety monitoring visits in the form of scheduled clinic visits and phone calls have been included and can be summarized as follows:

   a) Study enrollment/initiation of study medication (5 mg of lisinopril or matched placebo) (**study entry/enrollment**);

      - 3-day safety phone call (post initiation of study medication (or matched placebo) evaluating for possible adverse events (and if during phone safety check screening there is any suggestion of a possible adverse event, then the participant will be instructed to come

in to clinic for immediate evaluation including blood draw and blood pressure check)

- 7-day safety clinic visit (blood draw plus blood pressure check)
- 1-month safety clinic visit (blood draw plus blood pressure check)
- Unscheduled study visit (study participants to contact study personnel at any time and if have signs/symptoms at suggestive of an adverse event, they will come to clinic for immediate assessment)

b) b) Dose escalation of study medication (increase from 5 mg/d of lisinopril or matched placebo to 10 mg/d) (**scheduled to take place at the 1- month study visit**);

- 3-day safety phone call (post initiation of study medication (or matched placebo) evaluating for possible adverse events (and if during phone safety check screening there is any suggestion of a possible adverse event, then the participant will be instructed to come in to clinic for immediate evaluation including blood draw and blood pressure check)
- 7-day safety clinic visit (blood draw plus blood pressure check)
- 1-month safety clinic visit (blood draw plus blood pressure check)
- Unscheduled study visit (study participants to contact study personnel at any time and if have signs/symptoms at suggestive of an adverse event, they will come to clinic for immediate assessment)

c) Dose escalation of study medication (increase from 10 mg/d of lisinopril or matched placebo to 20 mg/d) (**scheduled to take place at the 3- month study visit**);

- 3-day safety phone call (post initiation of study medication (or matched placebo) evaluating for possible adverse events (and if during phone safety check screening there is any suggestion of a possible adverse event, then the participant will be instructed to come in to clinic for immediate evaluation including blood draw and blood pressure check)
- 7-day safety clinic visit (blood draw plus blood pressure check)
- 1-month safety clinic visit (blood draw plus blood pressure check)
- Unscheduled study visit (study participants to contact study personnel at any time and if have signs/symptoms at suggestive of an adverse event, they will come to clinic for immediate assessment)

d) Dose escalation of study medication (increase from 20 mg/d of lisinopril or matched placebo to 40 mg/d) (**scheduled to take place at the 5- month study visit**);

- 3-day safety phone call (post initiation of study medication (or matched placebo) evaluating for possible adverse events (and if during phone safety check screening there is any suggestion of a possible adverse event, then the participant will be instructed to come in to clinic for immediate evaluation including blood draw and blood pressure check)

- 7-day safety clinic visit (blood draw plus blood pressure check)

- 1-month safety clinic visit (blood draw plus blood pressure check)

- Unscheduled study visit (study participants to contact study personnel at any time and if have signs/symptoms at suggestive of an adverse event, they will come to clinic for immediate assessment

Once participants complete their 4-month study visit including having their study medication dose (or matched placebo) increased to 40 mg/d and undergo the additional safety visits as outlined in b) and c) above, all study participants will continue to undergo scheduled safety/tolerability assessments (study visits during which time blood draws and blood pressure evaluations will be performed at a minimum of every 3 months.

Additionally, all participants will be counseled to contact study staff or come in at any time (including unscheduled visits) if they feel ill, feel that their urine output may have diminished, and/or have questions about potential side effects or about the care and treatment they are receiving. An interval history of medical events and potential adverse events will be obtained at these visits. This information will continue to be collected for three (3) months after the participant has stopped the study medication. Monitoring for AEs (including unanticipated AEs) will be performed by reviewing patient laboratory and clinic data and querying patients at each follow-up visit about the occurrence of complications since the patient's previous visit. All AEs will be characterized in terms of "*relatedness*" to study intervention (i.e. study medication) as follows: "*definitely related*", "*possibly related*", "*unable to assess relatedness to study medication*", "*definitely unrelated to study medication*" or "*possibly related to study medication*." In terms of severity, all AEs will be graded on the basis of severity (standard 1-5 grading scale using the DAIDS Toxicity Grading Scale; version 2.1, July 2017).

B. Adverse Event Reporting

Definitions

Definitions are per the January 2007 Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Participants or Others and Adverse Events, Office on Human Research Protection (OHRP) Guidance.

https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html

Adverse Event

An *adverse event (AE)* is any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (for example, abnormal physical examination or laboratory finding), symptom, and/or disease, temporally associated with the participant's involvement in the research, whether or not this event is considered related to the participant's participation in the research.

Serious Adverse Event

A *serious adverse event* (SAE*)* is any AE that is:

- fatal or results in death
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- results in congenital anomalies or birth defects
- an important medical event*

*Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. Based on expert medical judgment, this important medical event may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above

"Unanticipated Event" Involving Risk to Participants or Others

An "Unanticipated Event" is any incident, experience, or outcome that meets **ALL** of the following criteria:

- it is unexpected (in terms of nature, severity, or frequency), given the research procedures that are described in the IRB-approved research protocol and informed consent document and the characteristics of the participant population being studied;
- it is "*definitely related*" or "*possibly related*" to study medication/participation in the research, where "*possibly related*" means that there is a reasonable possibility that the incident, experience and/or outcome may have been caused by the procedures involved in the research, and
- it suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, and/or social harm) related to the research than was previously known or recognized.

Pre-Existing Condition

A "pre-existing condition" is one that is present at the start of the study. A "pre-existing condition" will be recorded as an AE if the frequency, intensity, or character of the condition worsens during the study period.

Adverse Event (AE) Reporting Period
The study period during which AEs must be tracked and reported is defined as the period from the initiation of study procedures to study completion.

Post-Study AEs
All unresolved AEs will be followed by the investigator until the events are resolved, the participant is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator will instruct each participant to report any subsequent event(s) that the participant, or the participant's personal physician, believes might reasonably be related to participation in this study. The investigator will notify the R3 Study Oversight Committee (SOC) and the Study Safety Committee (SSC) of any death or AE occurring at any time after a participant has discontinued or terminated study participation that may reasonably be related to the study. (**NOTE**: All enrolled aim 2 participants will be monitored/tracked for any AEs for 3 months after they complete the study; and any/all AEs that occur up to 3 months post study completion will be recorded/captured).

NOTE: The R3 **Study Oversight Committee (SOC)** will consist of the MPIs (Drs. Wester and Aliyu), the Trial Coordinator, The Program Manager, and the in-country lead investigator (Dr. Musa). The **Study Safety Committee (SSC)** will function independently to maintain the integrity of investigations into AEs and will be overseen by two Clinical Trials Safety Specialists, namely Drs. Ahonkhai and Burgner.

Recording of AEs
At each contact with the participant, the Co-Investigators and/or Research Coordinators will seek information on AEs by specific questioning and, as appropriate, by examination. Information on AEs will be recorded in the source documents as well as on the AE log case report form (CRF). All signs, symptoms, and abnormal diagnostic procedure results relating to the same event will be recorded under one diagnosis name.

All adverse events (AE), regardless of severity, that is reported to any study team member and meets the criteria for an AE, will be documented. This documentation will include the date the event occurred or began, the duration of the event (including resolution date when applicable), and the date and way in which the event was reported. Any clinical or other documentation to corroborate the event will be included in the report, as well as any determination of relatedness. All study staff will have access to an electronic structured report form in REDCap for these purposes. The form will include common side effects of lisinopril, and losartan and classifications based on seriousness, expectedness, and relatedness (i.e. "*definitely related to study medication*", "*possibly related to study medication*", "*definitely not related to study medication*", or "*unable to assess if related to study medication*"). Unanticipated AEs will include adverse reactions that are not consistent (nature or severity) with the available information on lisinopril or losartan. The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.1, July 2017, will be used to

determine clinical and laboratory grades of any/all grade 1 or higher events (including signs and symptoms, laboratory abnormalities, and diagnoses).

Anticipated AEs

The following AEs are anticipated in HIV-positive adults that are initiated on combination antiretroviral therapy (ART) and are not considered Unanticipated Problems. As such, they would be considered Non-Reportable Events. Please note that most of these side effects are typically seen within the first 1-4 weeks following ART initiation. Given that we will be enrolling ART-experienced patients (on ART >6 months), we anticipate encountering very few (if any) such events in the context of our R3 study. Note that the designation "Non-reportable" does not imply that the event is not an SAE but relates to the regulatory definition of Unanticipated Problems as provided in previous section.

- **Gastrointestinal**: Nausea and diarrhea (mild/grade 1) related to antiretroviral (ARV) medications; as mild to even moderate GI symptoms are often seen in persons in the first 1-6 weeks (sometimes up to 8 weeks) following initiation of most ART regimens, but this diarrhea/nausea is typically self-limited and resolves on its own. On rare occasions, it can continue/progress to grade 2 or higher and any persistent GI symptoms seen in R3 patients (all need to be on ART for 6+ months) will be captured/tracked if grade 1 or higher.
- **Hepatic**: Mild (grade 1 or 2) elevations in total bilirubin among persons receiving the boosted protease inhibitor atazanavir/ritonavir (as atazanavir is also known to cause asymptomatic elevations in unconjugated hyperbilirubinemia [**NOTE**: We will report when grade 2 or higher or deemed "clinically significant" by study team personnel].
- **Neurologic**: Dizziness, lightheadedness, abnormal dreams (more vivid dreams, nightmares, etc.), and possibly hallucinations (rare) during the first 30 days following initiation of an ART regimen that contains the NNRTI efavirenz (EFV) [**NOTE**: We will report when grade 2 or higher or deemed "clinically significant" by study team personnel]. **Renal**: The integrase strand inhibitor dolutegravir (DTG) will be coming into wide use for first line ART regimens (and other subsequent ART regimen lines) in Nigeria during the study period (2019), pending final safety data, consistent with the WHO directive for wide-scale implementation of Tenofovir, Lamivudine, plus Dolutegravir (TLD) for first-line ART, given it considerably more favorable genotypic drug resistance profile (i.e. significantly higher genetic barrier for resistance to develop) and tolerability profile. Of note, DTG induces a noticeable increase in serum creatinine following initiation of therapy due to non-pathologic tubular blockade of creatinine secretion through the inhibition of OCT2.[130] DTG can block the tubular uptake of creatinine from the blood, leading to increases in serum creatinine and decreased eGFR or creatinine clearance (Cr Cl), without changing the true GFR.[130] Therefore, based on published literature, an anticipated change in renal parameters is expected in study participants shortly after switching to DTG-based therapy. Specifically, patients switched to dolutegravir (from efavirenz or nevirapine) may experience a sustained increase in their serum creatinine coupled with a corresponding decrease in their calculated eGFR. In brief, for a period of up to 48 weeks following dolutegravir (DTG)

initiation, it is anticipated that study participants may experience a modest (0.2 mg/dL) increase in serum creatinine[127-129] that will not lead to significant changes in uACR values but will lead to aim 2 study participants having a "new baseline eGFR" that is unrelated to study medication and based on the literature using iohexol [130] will not represent a true change in eGFR; but nonetheless will still need to be accounted for in the analysis plan. **NOTE**: Given the known limitations of CysC-based equations for HIV-positive individuals, from an analysis standpoint, the team will utilize/rely on significant changes in serum creatinine (sCr) for safety monitoring/reporting among DTG-treated study participants.

Non-Reportable Events

Please see above "Anticipated AEs" section as the R3 study does not have any non-reportable events, other than these mild potential side effects (grade 1 only).

Reporting of SAEs and Unanticipated Problems

Study sites are required to report SAEs in REDCap to the R3 SOC and SSC within 24 hours of first knowledge of the event. To report such events, an SAE form will be completed by the investigator and faxed or emailed to the SOC/SSC. The SOC/SSC will facilitate the timely medical review and reporting of the event and provide reports to the NIDDK and the Data and Safety Monitoring Board (DSMB) in accordance with DSMB-approved study policies and regulatory requirements. All AEs will be reviewed within 48 hours, and an appropriate course of action will be determined. All study staff will also be encouraged to report any SAEs directly to the SOC and SSC by phone or direct email, as it is essential that they are notified with 24 hours of the study team member learning of the event.

Any/all grade 3 (i.e. grade 3 = "severe"; grade 4 = "life-threatening" and grade 5 = "death"), grade 3 or higher events deemed "*definitely related to study medication*" or "*possibly related to study medication*", and/or unanticipated adverse events will be reported to both IRBs (VU and AKTH), NIDDK, and the DSMB within 48 hours of the site becoming aware of the event. Non-serious (grade 1 or 2) unanticipated AEs will be reported to both IRBs and NIDDK within as outlined on Table 3 below; namely internally reviewed/reported from the study site to the SOC/SSC on a monthly basis and submitted/reported to the involved IRBs and NIDDK on a quarterly basis. All unanticipated events will be reported to the chair of the DSMB and the NIDDK Program Officer within 48 hours. Any determination by either IRB that results in a temporary or permanent suspension of the study will be immediately reported to NIDDK and the DSMB (within 24 hours of receiving notice from the IRB). Please refer to "**Table 3: R3 Adverse Event Reporting Timeline**" for full/specific details).

The study leadership (i.e. the Vanderbilt-based SOC as well as on-site Co-Investigators and Research Coordinator) will keep a copy of the SAE form on file at the study site (AKTH). At the time of the initial report, the following information should be provided:

- Study identifier
- Participant ID number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason the event is classified as serious or unanticipated
- Investigator assessment of the "*relatedness*" between the event and study participation

Within the following 7 days, the investigator will provide the SOC and SSC further information on the SAE or the unanticipated problem in the form of a written narrative. This should include a copy of the completed SAE form, and any other diagnostic information that will assist in the understanding of the event. Significant new information on ongoing SAEs should be provided promptly to the SOC/SSC.

If a participant becomes pregnant while participating in R3 will be reported as an AE and will trigger the collection of additional documentation about the pregnancy including the immediate unblinding of the participant and discontinuation of study medication (lisinopril) if they were randomized to the active /intervention arm. Pregnancy outcomes will be collected, including the outcome of the infant and if the pregnancy was terminated. This information will be submitted to the Vanderbilt University IRB, the AKTH (study site) IRB, and NIDDK (study funder---who will forward this along to the DSMB), as required.

SAEs that are still ongoing at the end of the study period must be followed up to ascertain the definitive outcome. Any SAEs that occur after the study period (up to 3 months post-study completion) and is considered to be "possibly related" to study treatment or study participation should be recorded and reported immediately.

Investigator Reporting to the IRB

Site investigators will report SAEs and Unanticipated events to their IRB in accordance with the reporting requirements of the local IRB or with the Office of Human Research Protections (OHRP) guidelines, whichever is sooner. OHRP recommends that:

1) ALL unanticipated events (regardless of grade) that are "*definitely related*", "*possibly related*" or "*unable to assess relatedness to study medication*" should be reported to involved IRBs and NIDDK within 48 hours of the investigator becoming aware of the event;

2) ALL serious adverse events (SAEs) that are unanticipated (regardless of "*relatedness*" to study medication*"*) should be reported to involved IRBs and NIDDK within 48 hours of the investigator becoming aware of the event

Table 3: R3 Adverse Event Reporting Timeline

Type of Event / Body being reported to	Anticipated Events (Grades 3 & 4) ["definitely related" OR "possibly related" to study medication]	Unanticipated Events (Grades 1 & 2) ["definitely related", "possibly related" OR "unable to assess relatedness" to study medication]	Unanticipated Events (Grades 3 & 4) ["definitely related", "possibly related", OR "unable to assess relatedness" to study medication]	Other Reportable Events* [regardless of "relatedness"] [Grade of Event "Not Relevant"]	Any Grade 5 Event [regardless of "relatedness"]
Involved IRBs (VU and AKTH)	Aggregate reporting on a quarterly basis	Aggregate reporting on a quarterly basis	Within 48 hours of site becoming aware of event	Within 48 hours of site becoming aware of event	Within 48 hours of site becoming aware of event
NIDDK (DSMB)	Aggregate reporting on a quarterly basis	Aggregate reporting on a quarterly basis	Within 48 hours of site becoming aware of event	Within 48 hours of site becoming aware of event	Within 48 hours of site becoming aware of event
AKTH Study Team	Aggregate review/internal reporting (to SOC/SSC) on a monthly basis	Aggregate review/internal reporting (to SOC/SSC) on a monthly basis	Notify SOC and SSC within 24 hours	Notify SOC and SSC within 24 hours	Notify SOC and SSC within 24 hours

*** Other reportable events include the following:**

1. Any AE that causes SOC to modify protocol/informed consent or prompt other action by IRB to assure patient protection
2. Breach of confidentiality
3. Change to the protocol made without prior IRB review to eliminate apparent immediate hazard to a research participant
4. Complaint of a participant that indicates unanticipated risks, or the complaint cannot be resolved by the study team
5. Protocol violation

Reporting Process

Unanticipated problems posing risks to participants or others as noted above will be reported using the appropriate IRB-designated form or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be maintained in the AKTH Study Site Investigator's study file.

Other Reportable Events (please also refer to LEGEND/FOOTNOTE at the bottom of **Table 3**)**:**

- Any AE that would cause the R3 SOC to modify the protocol or informed consent form or would prompt other action by the IRB to assure protection of human participants. Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency.
- Breach of confidentiality.
- Change to the protocol made without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk or affects the rights or welfare of participants.

NOTE: Any/all study events meeting "**Other Reportable Events**" criteria as outlined above should be reported to involved IRBs and NIDDK within 48 hours of the investigator becoming aware of the event.

SSC Notification to Participating Study Investigators

The R3 SCC will notify all on-site (AKTH-based) senior study leadership and the SOC, in a written safety report, of any AE that meets the criteria of an "unanticipated event" and/or AE "*definitely related to study medication*" or "*possibly related to study medication*" as described previously. The SOC will be responsible for notifying relevant other parties, including the Data and Safety Monitoring Board (DSMB), NIDDK, and involved IRBs.

Medical Monitoring

AKTH-based Co-Investigators and Research Coordinator will be responsible for overseeing the safety of the study at their study site. This safety monitoring will include careful assessment and appropriate reporting of AEs as noted above, as well as the implementation of a site data and approved Data Safety Monitoring Plan. Medical monitoring will include a regular assessment of the number and type of serious and/or unanticipated AEs.

C. Safety Monitoring Plan

All AEs will initially be reviewed (after being sent from the on-site study team) and categorized by the study Program Manager and then by the SOC and SSC (when relevant; i.e. the SSC is involved), according to the timeline as outlined above in "**Table 3: R3 Adverse Event Reporting Timeline"**. Weekly meetings with the study team will also look at overall statistics for AEs. Reports that include AEs will also be sent to NIDDK and the Chair of the DSMB on a quarterly basis for review and dissemination to other DSMB members (as specified above in "**Table 3: R3 Adverse Event Reporting Timeline")**.

Study progress (including recruitment, consent procedures, retention, laboratory results, and protocol adherence measures) will be reviewed on a **weekly** basis by the study team leadership at VUMC and on-site at AKTH.

Quarterly reports sent to NIDDK and the DSMB will include a list and summary of AEs, determination of whether these AE rates are consistent with pre-study assumptions (i.e. anticipated or unanticipated, etc.), a summary of recruitment and retention, as well as a summary of reasons for loss-to-follow-up, and whether the study is on track with respect to the original timeline and proposed milestones.

Given the long recruitment period, the sample size, and the relatively short follow-up period, we will not have stopping rules for this trial. We will perform interim analyses at six months after enrollment into Aim 2 begins or after 50% enrollment into Aim 2 (n=70/arm, n=140 total) occurs to evaluate safety/toxicity and efficacy. These results will be shared with the DSMB and all relevant parties.

D. Informed Consent

Informed consent will be obtained from each participant at entry into Study Aim 1, and again for those who proceed to Aim 2 (a subset of the participants from Aim 1). Informed consent will be collected in REDCap by trained study coordinators, who will provide a study information form and review the study consent form with the participant in the participant's language of preference (form will be available in both English and Hausa). The consent form will include all potential study risks and will be approved by both IRBs (Vanderbilt and AKTH). Forms will be uploaded through the central secure study database, housed at Vanderbilt.

E. Data Quality and Management

Study data will be collected in REDCap. Form fields, where possible, have include restrictions on data input (numeric fields restricted to possible ranges, text fields prevented from allowing numeric entries, etc.) to make data entry less prone to errors and prevent false outliers. Data cleaning and preparation for analysis will be ongoing, with consent forms and study data reviewed monthly or more frequently. Data management and data quality will be regularly reviewed by the study team

leadership (Multiple-PIs, Study Manager, and on-site AKTH study leadership). The study leadership will also provide results to the DSMB in twice-yearly reports.

F. Confidentiality

Study participants will be assigned a coded identification number at the time of study registration. In order to maintain patient confidentiality, all laboratory specimens, study case report forms, and reports will be identified using that coded number. Only research staff will have access to the coded number. Key study personnel including Dr(s). Wester and Aliyu (MPIs), Nalado, Abdu, Sani, Musa, Muhammad, Abdussalam, and Atanda will store research data including medical and laboratory records in locked cabinets and all e-files will be password protected. Data will be stored in password-protected files within secure buildings at AKTH and VUMC. We have additional measures to enhance security when data are housed at Vanderbilt. Access to all data will be ID and password-protected, including data warehouse software and computers managing and analyzing survey data. Clinical information will not be released without the written permission of the participant. No data will be released with any information that may directly or indirectly identify participants, their clinical information, or laboratory results to outside agencies.

The data gathered will be entered into the research electronic data capture (REDCap) data system, with each ID having a unique identifier for each participant. REDCap is a secure, web-based application for building and managing online databases. All data will be de-identified and samples will only have a unique identifier that will link the unique identifier with the patient's name. REDCap is a free, secure, web-based application designed to support data capture for research studies. The system was developed by a multi-institutional consortium initiated at Vanderbilt University. Data collection is customized for each study or clinical trial by the research team with guidance from Harvard Catalyst EDC Support Staff. REDCap is designed to comply with Health Insurance Portability and Accountability Act (HIPAA) regulations. REDCap provides user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails, and the ability to set up a calendar to schedule and track critical study events such as blood-draws, participant visits, etc. Also, designated users can assign different levels of access for each member of the research team.

REDCap and REDCap Survey (RS), as hosted by Vanderbilt, are available only to investigators from Vanderbilt University but can be used by investigators at other institutions as long as they are part of a project/group from Vanderbilt that is utilizing REDCap. REDCap and RS as software applications can be used at other institutions, when installed by and hosted at those institutions, if they are willing to sign a technology transfer agreement and join the REDCap Consortium. Investigators and research staff at AKTH are very comfortable with using REDCap, as Dr. Aliyu's ongoing research studies there all utilize REDCap for data management.

The REDCap clinical database will be maintained by the Vanderbilt Institute for Global Health under the direction of the MPIs. The study team members are trained in HIPAA privacy regulations and other applicable site privacy policies. No

information will be released, nor will participation in the research be acknowledged, to any party except where compulsory according to law or intuitional policy.

G. **Data and Safety Monitoring Board (DSMB)**

The information provided in this section of the protocol is a general description of the DSMB responsibilities and processes.

A DSMB has been established by the NIDDK and provides input to the study team. The DSMB is comprised of individuals with expertise in clinical trials design and methodology, biostatistics, clinical nephrology and other relevant medical specialties. The DSMB members are not affiliated with the study and are appointed by the NIDDK. DSMB members will be free of conflicts of interest that could be affected by the outcomes of the study. During the study, DSMB members who develop real or perceived conflicts of interest that impact objectivity will disclose them to NIDDK project officers, who will arrange for replacement of the member, if indicated.

The DSMB will review the protocol before initiation of the study. After initial approval and during the course of the study, the primary responsibilities of the DSMB will be to:

- Review safety data and provide input to protect the safety of the study participants;
- Provide input on major changes to the research protocol and plans for data and safety monitoring;
- Provide input on the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the study sites, and other factors that may affect study outcomes;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the need for continuation of the study, safety of the participants or the ethics of the study;
- Provide input on modification of the study protocol or possible early termination of the study because of attainment of study objectives, safety concerns, or inadequate performance (such as enrollment and retention problems).

The DSMB will review study data reports, including primary endpoint analyses, at a minimum of every six months either in a meeting or on a conference call.

7.0 Study Withdrawal/Discontinuation

Participants may decide to discontinue participation at any time during the study. If a patient voluntarily requests withdrawal from the trial, we request that the site investigator

elicit the reason for the withdrawal and provide documentation in the clinic record and complete the respective case report form. We will have a dedicated patient navigator on staff as well to help trace and re-engage all participants lost to follow-up, realizing that some may die or transfer their care and must be appropriately categorized. Those who drop out due to AEs or perceived AEs will be counseled by study physicians regarding their options and any potential risks for continuation. The site must invest time in trying to meet the needs of the patient and their caregivers in order to make the patient's participation a success. The patient's caregiver should provide the withdrawal in writing for the clinic record. All voluntary withdrawals must be communicated to the SOC located at Vanderbilt University Medical Center by completion of the case report form in REDCap and should be recorded in the participant's study binder onsite.

Principal Investigator-initiated Withdrawal
Investigators may discontinue any participant at their discretion, if in their professional opinion the participant's health, safety, and/or well-being is being threatened or at all jeopardized by continued participation in the study. The following circumstances require discontinuation of participants:

1. Withdrawal of assent to participate;
2. Parental withdrawal of consent to participate;
3. Study physician determines that continuation in the study would not be in the best interest of the participant, e.g., pregnancy;
4. Participant has experienced a serious and/or unanticipated adverse event.

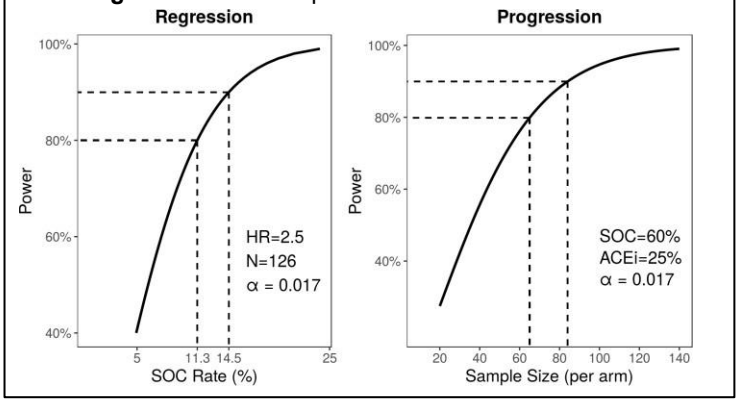
Adverse events caused by participation in the study may necessitate modifications to the level of participation of a subject or discontinuation of participation in the study. Participants who discontinue early from the study will not be replaced. They will continue to receive medical care at the AKTH HIV clinic as per standard care.

8.0 Statistical Considerations

Specific Aim 1
Sample size justification: A screening sample size of 2,600 participants will yield sufficient sample size for randomization in Specific Aim 2 detailed below. With 2,600 persons screened for Aim 1, the prevalence of *APOL1* renal risk variants may be estimated with precision (half-length of the 95% confidence interval) equal to 0.02 or better. Assuming a microalbuminuria prevalence of 17.5% based on recent data obtained from HIV-positive adults (n ~ 460) screened at AKTH,[110] where this study will take place, we will have 90% power to detect a relative risk of microalbuminuria of 1.37 or higher in participants with renal risk variants compared to participants without, and we anticipate that 1 in 4 participants will have renal risk variants. We estimate, based on our experience with our studies at this site, that enrollment for Aim 1 will take 12 months. In addition to analyzing *APOL1* risk as a binary high/low risk status, we will also examine relative risk of microalbuminuria with *APOL1* risk categorized based on the presence of 0, 1, or 2 alleles, as this will lead to an increased understanding of the risk associated with the presence of a single risk allele.

Statistical analysis plan: We will estimate the prevalence and associated 95% confidence interval of *APOL1* renal risk variants. We will test whether the presence of these variants is associated with log_{10}uACR or eGFR using Wilcoxon rank sum test. Multivariable linear regression for each of log_{10}uACR or eGFR will be used to adjust for potential confounders, including: sex, age, CD4+ cell count, viral load, and the presence/absence of specific comorbid medical conditions (hypertension, cardiovascular disease, diabetes mellitus, etc.). For linear regression, appropriate transformations of dependent variables will be used to satisfy modelling assumptions. To relax linearity assumptions, covariates will be modelled using restricted cubic splines.[135] Modified Poisson regression adjusted for similar variables, will be used to assess associations with prevalent CKD, microalbuminuria, and reduced eGFR (< 60 mL/min/1.73m^2), and 95% confidence intervals.

Figure 3: Aim 2 Sample Size and Power Justification



Specific Aim 2
***Sample size justification*:** We will enroll 280 eligible patients from Specific Aim 1 for 1:1 randomization in our RCT for Specific Aim 2. Based on our prior experience with ongoing RCTs in the study location, we anticipate that enrollment into Aim 2 will take 12 months and there will be 10% loss to follow up at end of year 2, yielding 252 patients on study (126 per arm). Aim 2A: At 2 years, we hypothesize that a higher proportion of intervention participants will regress from microalbuminuria to normoalbuminuria (uACR < 30 mg/g) with a hazard ratio (HR)= 2.50. Using the logrank test, we will have approximately 80% power if the rate of regression in the SOC arm is at least 12%, and 90% power if that rate is 16% or higher with a 1.7% type I error[136]. (The type I error rate was set at 5%/3=1.7% to account for multiple testing and the fact that we have 3 primary endpoints.) See Tables 3 and 4. Aim 2B: At 2 years, we hypothesize that a higher proportion of patients in the SOC arm, namely 60% vs. 25% in the intervention arm (HR≈0.42), will progress from microalbuminuria to macroalbuminuria (uACR > 300 mg/g). With 126 patients per arm (after removing 10% loss to follow-up), we will have >95% power for Aim 2B with a 1.7% type I error. See Tables 5 and 6. **Figure 3** shows changes in Aim 2A power for varying SOC regression rates and changes in Aim 2B power for varying sample size. The sample size for Aim 2C is such that we will have approximately 80% power to detect at the alpha=0.017 level a difference in the log-transformed mean uACR of 0.24, which is approximately 0.41 standard deviations. These power calculations are likely conservative, as they do not incorporate baseline covariates, which will be included in the actual analyses (see below) and should improve power; in addition, the uACR analysis will incorporate multiple longitudinal measures per person whereas these power calculations only assume a single final measurement per person.

The sample size was chosen to have sufficient power for all primary endpoints. Tables S1-S8, investigating power and detectable alternatives for the secondary endpoints with a total sample size of 280 are provided in Appendix B. In short, we anticipate low power to detect differences between intervention arms in the doubling of serum creatinine, all-

cause mortality, and tenofovir toxicity because the expected rates for these events in the placebo arm are anticipated to be small (i.e., 2-20%, <10%, and 2%, respectively). We should have sufficient power to detect meaningful differences in eGFR, quality of life scores, and blood pressure.

Table 3. Power calculation for regression

alpha	Events Needed	Approx Rate SOC	Approx Rate Exp	Patients per Arm	Power
0.010	38	0.12	0.3	100	0.595
0.010	50	0.16	0.4	100	0.751
0.010	45	0.12	0.3	120	0.695
0.010	60	0.16	0.4	120	0.838
0.010	53	0.12	0.3	140	0.775
0.010	71	0.16	0.4	140	0.898
0.010	60	0.12	0.3	160	0.838
0.010	81	0.16	0.4	160	0.938
0.010	68	0.12	0.3	180	0.886
0.010	91	0.16	0.4	180	0.963
0.017	38	0.12	0.3	100	0.666
0.017	50	0.16	0.4	100	0.807
0.017	45	0.12	0.3	120	0.758
0.017	60	0.16	0.4	120	0.880
0.017	53	0.12	0.3	140	0.828
0.017	71	0.16	0.4	140	0.928
0.017	60	0.12	0.3	160	0.880
0.017	81	0.16	0.4	160	0.958
0.017	68	0.12	0.3	180	0.918
0.017	91	0.16	0.4	180	0.976
0.025	38	0.12	0.3	100	0.717
0.025	50	0.16	0.4	100	0.844
0.025	45	0.12	0.3	120	0.801
0.025	60	0.16	0.4	120	0.907
0.025	53	0.12	0.3	140	0.862
0.025	71	0.16	0.4	140	0.946
0.025	60	0.12	0.3	160	0.907
0.025	81	0.16	0.4	160	0.969
0.025	68	0.12	0.3	180	0.938
0.025	91	0.16	0.4	180	0.983
0.050	38	0.12	0.3	100	0.804
0.050	50	0.16	0.4	100	0.902
0.050	45	0.12	0.3	120	0.870
0.050	60	0.16	0.4	120	0.946
0.050	53	0.12	0.3	140	0.915
0.050	71	0.16	0.4	140	0.971
0.050	60	0.12	0.3	160	0.946
0.050	81	0.16	0.4	160	0.984
0.050	68	0.12	0.3	180	0.966
0.050	91	0.16	0.4	180	0.992

For these calculations, an HR of 2.5 was assumed.

Table 4. Detectable hazard ratios (HR) for regression

alpha	Events Needed	Approx Rate SOC	Approx Rate Exp	Patients per Arm	Detectable HR
0.010	42	0.12	0.35	100	2.88
0.010	52	0.16	0.41	100	2.59
0.010	48	0.12	0.32	120	2.69
0.010	59	0.16	0.39	120	2.43
0.010	54	0.12	0.31	140	2.54
0.010	67	0.16	0.37	140	2.31
0.010	59	0.12	0.29	160	2.43
0.010	74	0.16	0.35	160	2.21
0.010	65	0.12	0.28	180	2.34
0.010	81	0.16	0.34	180	2.13
0.017	41	0.12	0.33	100	2.76
0.017	50	0.16	0.40	100	2.49
0.017	46	0.12	0.31	120	2.58
0.017	58	0.16	0.37	120	2.34
0.017	52	0.12	0.29	140	2.45
0.017	65	0.16	0.36	140	2.23
0.017	58	0.12	0.28	160	2.34
0.017	72	0.16	0.34	160	2.14
0.017	63	0.12	0.27	180	2.25
0.017	79	0.16	0.33	180	2.06
0.025	40	0.12	0.32	100	2.66
0.025	49	0.16	0.39	100	2.41
0.025	45	0.12	0.30	120	2.50
0.025	57	0.16	0.36	120	2.27
0.025	51	0.12	0.28	140	2.37
0.025	64	0.16	0.35	140	2.16
0.025	57	0.12	0.27	160	2.27
0.025	71	0.16	0.33	160	2.08
0.025	62	0.12	0.26	180	2.19
0.025	78	0.16	0.32	180	2.01
0.050	38	0.12	0.30	100	2.49
0.050	47	0.16	0.36	100	2.26
0.050	43	0.12	0.28	120	2.34
0.050	54	0.16	0.34	120	2.14
0.050	49	0.12	0.27	140	2.23
0.050	61	0.16	0.33	140	2.04
0.050	54	0.12	0.26	160	2.14
0.050	68	0.16	0.32	160	1.97
0.050	60	0.12	0.25	180	2.07
0.050	75	0.16	0.31	180	1.91

For these calculations, a power of 80% (0.80) was assumed.

Table 5. Power calculation for progression

alpha	HR	Progression events	Patients per arm	Power
0.010	0.42	76	100	0.895
0.010	0.42	92	120	0.947
0.010	0.42	107	140	0.975
0.010	0.42	122	160	0.988
0.010	0.42	138	180	0.995
0.017	0.42	76	100	0.925

0.017	0.42	92	120	0.965
0.017	0.42	107	140	0.984
0.017	0.42	122	160	0.993
0.017	0.42	138	180	0.997
0.025	0.42	76	100	0.944
0.025	0.42	92	120	0.975
0.025	0.42	107	140	0.989
0.025	0.42	122	160	0.995
0.025	0.42	138	180	0.998
0.050	0.42	76	100	0.969
0.050	0.42	92	120	0.987
0.050	0.42	107	140	0.995
0.050	0.42	122	160	0.998
0.050	0.42	138	180	0.999

For these calculations, we assumed HR=0.42, approximate rate of progression in the SOC arm=0.6, and approximate rate of progression among those on the experimental arm=0.25.

Table 6. Detectable hazard ratios for progression

alpha	Progression Events	Approx. Rate Exp	Patients per Arm	HR
0.010	79	0.28	100	0.46
0.010	97	0.30	120	0.50
0.010	116	0.32	140	0.53
0.010	134	0.33	160	0.55
0.010	153	0.35	180	0.58
0.017	80	0.29	100	0.49
0.017	99	0.31	120	0.52
0.017	117	0.33	140	0.55
0.017	136	0.34	160	0.57
0.017	155	0.36	180	0.60
0.025	81	0.30	100	0.50
0.025	100	0.32	120	0.54
0.025	119	0.34	140	0.57
0.025	137	0.35	160	0.59
0.025	157	0.37	180	0.61
0.050	83	0.32	100	0.54
0.050	102	0.34	120	0.57
0.050	121	0.36	140	0.60
0.050	140	0.37	160	0.62
0.050	160	0.39	180	0.64

For these calculations, we assumed a power of 80% (0.80) and an approximate rate of progression in the SOC arm of 60% (0.6).

***Statistical analysis plan*:** Our first approach will be to perform an intent-to-treat analysis, but we will also perform an on-treatment analysis to compare these data and present all available findings. *Primary analysis*: We will test the hypotheses that regression and progression rates are different across arms using multivariable Cox regression models with the intervention variable (randomization to RAAS [yes/no]) as the primary predictor variable, adjusting for baseline (pre-randomization) covariates including baseline uACR, *APOL1* renal risk variants, CD4+ cell count, blood pressure

ART regimen (DTG vs. other), and the presence/absence of comorbid medical conditions (hypertension, cardiovascular disease). To relax linearity assumptions, baseline uACR will be included in models using restricted cubic splines.[138] Primary analyses will be intention to treat, although we also plan to perform "per protocol" analysis. We will also test the impact of study arm on uACR using a linear mixed effects model to account for within patient correlation with the outcome of 3-monthly uACR values (with primary endpoints obtained by evaluating the uACR and other key renal outcomes at 18 and 30 months given that all enrolled study participants will not be placed or sustained on their maximum tolerated lisinopril dose or matched placebo until 6 months after study enrollment). The model will also adjust for the baseline covariates given above. For this analysis, we anticipate log-transforming uACR to meet modelling assumptions, although other transformations will be considered if needed.

Secondary analyses: Analyses for secondary endpoints will be similar to that described above. Time-to-event outcomes (doubling of serum creatinine from baseline, all-cause mortality, 40% decline in eGFR, and tenofovir toxicity) will be assessed using multivariable Cox regression models. Continuous outcomes (eGFR, quality of life metrics, and blood pressure) will be analyzed using mixed effects models after proper transformation of the outcome variable, if necessary. Baseline covariates listed above will be included in all secondary analyses.

In conversations with the DSMB, concerns were brought up regarding the nationwide switch to dolutegravir (DTG) and its potential impact on results. As sensitivity analyses, we will repeat the primary and secondary analyses listed above but also include any switch to a DTG-containing regimen post-randomization as a time-varying covariate. Our rationale for not including DTG-switch in the primary analysis, is that post-randomization variables (such as a switch to DTG) could be affected by treatment assignment and adjusting for it could therefore potentially bias results. However, we believe that the transition to DTG will not be affected by treatment assignment, in which case these analyses will be fine. If post-randomization DTG-uptake does differ by treatment arm (>5%), then we will investigate whether DTG-use is a mediator between treatment assignment and any of the primary or secondary outcomes listed above. Mediation analyses will follow the approaches outlined in VanderWeele TJ (2015) *Explanation in Causal Inference*. Finally, we will investigate whether the effect of assignment to ACEi could be modified by DTG-use. To do this, we will repeat the primary and secondary analyses but include an interaction between time-varying DTG-use and treatment assignment.

***Potential difficulty reaching desired sample size*:** Our microalbuminuria prevalence estimates among HIV positive adults engaged in care at AKTH are conservative, as they are based on published data from this same hospital among asymptomatic HIV positive adults, and we anticipate that only approximately 59% of those eligible for our aim 2 study will need to consent/enroll in order for us to reach our target sample sizes. Therefore, with a target sample size equal to 280, 59% of eligible patients would need to consent for Study Aim 2.

Retention Strategies: To increase the likelihood of retention in the trial, we plan to use several evidence-based methods that have been effective in clinical trials. The use of simple, clear, detailed written and verbal instructions regarding therapy, possible treatment side effects, and tests required for the study increases comprehension of the purpose and importance of the study, and yields better adherence to the trial.[137-140] In terms of specifics: i) We will develop a brochure outlining the study protocol in simple terms that will be translated into Hausa (native language of majority of individuals that live in Kano, Nigeria); ii) the key to successful follow-up and retention will be attention to detail, consistency of the research team, and trust between participants and study and clinic staff. The research staff will contact participants immediately and reschedule appointments when missed; iii) Close monitoring of participants' visits and need for return appointments with follow-up telephone calls are key elements for monitoring patient attendance and prevention of loss to follow-up. Every attempt will be made by the study team to contact participants prior to their scheduled visit based on the study schedule; and iv) identification of a trusted contact person who does not live with the study participant but always knows the participant's whereabouts will assist in tracking participants at risk of loss to follow-up and will decrease attrition. **NOTE**: The AKTH HIV clinic has historically had high retention rates. In a recent 10 year prospective cohort study conducted by our team (29,860 person-months of follow-up), 83% of our patients in the cohort were still in care after 10 years.[141] We will employ the same retention initiatives that have been shown to be effective in our study setting, including: active engagement of peer mentors in recruitment, counseling and monitoring activities, community involvement, supportive home-based care services, early case detection, and close tracking of at-risk persons with missed visits.

Specific Aim 3

***Statistical analysis and considerations*:** Analyses for Aim 3 will be the same as those outlined in Aim 2, except the predictor of interest will be *APOL1* haplotype (high risk vs. low risk) instead of intervention arm; analyses will adjust for intervention arm (similar to how analyses of Aim 1 adjusted for *APOL1* genotype). Assuming that ~30% (n = 84) of Aim 2 study participants have the high risk genotype, namely 2 copies of the risk variants (G1/G1, G1/G2, or G2/G2), with the remainder of Aim 2 study participants (n = 196) having the low risk genotype (carrying no or one risk allele [G0/G0, G0/G1, and G0/G2]), and that the rate of progression will be similar to that hypothesized in Aim 2, we anticipate having 80% power to detect hazard ratios on the order of 2.4 to 3.2. Specifically, if the rate of regression is 22% (e.g., 10% and 25% in the SOC and intervention arms, respectively), we will have 80% power to detect a hazard ratio of 3.2 between the low and high risk genotypes; if the rate of regression is 35% (e.g., 20% and 40% in the SOC and intervention arms, respectively), we will have 80% power to detect a hazard ratio of 2.4. With regards to progression, if the overall event rate is 42.5%, we anticipate having 80% power to detect a hazard ratio of 2.1 between the high and low risk genotypes; if the overall rate of progression is 28%, we anticipate approximately 80% power to detect a hazard ratio of 2.5. Analyses will be repeated treating number of risk alleles (0, 1, or 2) as a categorical variable to investigate differences in risks when having 0 vs. 1 risk allele.

9.0 Follow-up and Record Retention

In total, this study will last five years (2017-2022), with patients remaining in follow-up for two years within that time frame. Patient information and research results will be de-identified to maintain participants' privacy. Clinical records with identifiable information

will be destroyed at the conclusion of the study. De-identified information used for analysis purposes (those described here and potential subsequent analyses with de-identified information) may be retained for an indefinite period of time following conclusion of the study.

10.0 Foreign Justification

To be able to successfully answer the scientific questions posed by this study, the study setting must be one that has a high prevalence of three things: HIV, chronic kidney disease, and *APOL1* risk alleles. As aforementioned, Nigeria has a significant HIV/AIDS burden, and while the prevalence of CKD in HIV positive ART-naive patients varies from 6 to 48% across sub-Saharan Africa, the highest prevalence has been reported in Nigeria. The frequency of *APOL1* risk alleles is also highest in West Africa, specifically in Nigeria among persons of Yoruba and Igbo descent. Furthermore, the study team has long-established collaborations in Nigeria, including the completion of NIH-funded clinical research studies (including an RCT). Therefore, Nigeria provides the optimal setting to conduct this study.

Appendix A. Study Timeline

ACTIVITIES	MONTHS									
	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60
Introductory meeting										
Protocol development, including MOPs, CRFs										
IRB approvals										
DSMB review										
Hire and train study staff										
Pilot test surveys/forms, study kick-off										
Participant screening/enrollment-Aim 1										
Genotyping (*APOL1* SNPs) Aim 1										
Participant enrollment/randomization-Aim 2										
Follow-up visits with lab assessments-Aim 2										
Data collection										
Data management and QC										
Data analysis										
Dissemination of study findings, manuscript writing										

LEGEND: MOP = manual of operations, CRF = Case review forms, QC = quality control

Appendix B. Supplemental tables - Statistical calculations for secondary endpoints

Table S1. Detectable differences in means of log-transformed uACR values. The outcome is uACR measurement (units= mg/g) and a t-test will be used to compare the two means of log-transformed uACR for the two arms after follow-up. Given the inclusion criteria with the uACR range of 30-300 mg/g, we assume the log-transformed uACR has

a 95% probability interval from 3.4 to 5.7 and a standard deviation of 0.58. With 90 subjects at the end of study after adjustment for 10% loss to follow up (LTFU), we will have 80% power to detect a difference of 0.42 units of standard deviation (0.24 on log-transformed means assuming standard
deviation of 0.58).

alpha	Subjects per Arm	Detectable Difference
0.010	100	0.30
0.010	120	0.27
0.010	140	0.25
0.010	160	0.23
0.010	180	0.22
0.017	100	0.28
0.017	120	0.25
0.017	140	0.24
0.017	160	0.22
0.017	180	0.21
0.025	100	0.27
0.025	120	0.24
0.025	140	0.23
0.025	160	0.21
0.025	180	0.20
0.050	100	0.24
0.050	120	0.22
0.050	140	0.20
0.050	160	0.19
0.050	180	0.18

Table S2. Detectable differences in doubling of serum creatinine. Assuming 2% - 20% of subjects in the SOC arm will be doubling of serum creatinine, we will use an uncorrected chi-squared test to detect the difference between the two arms. In case of 10% of subjects on the SOC arm will have their serum creatinine doubled after follow up, we will have 80% power to detect a 9.3% decrease on the experimental arm to 0.7% (RR=0.07).

Alpha	Rate SOC arm	Detectable RR	Rate Exp arm
0.01	0.10	0.050	0.005
0.01	0.15	0.193	0.029
0.01	0.20	0.290	0.058
0.05	0.10	0.180	0.018
0.05	0.15	0.307	0.046
0.05	0.20	0.395	0.079

Table S3. All-cause mortality. With 140 patients on each arm, we will have 126 patients on each arm at the end of study assuming 10% LTFU. An uncorrected chi-square test will be used to test the difference of the all-cause mortality between the two arms. In case of the all-cause mortality is 10% on the SOC arm, we will have 80% power to detect an absolute 8.2% decrease on the treatment arm to 1.8%.

Rate of SOC	Power	Detectable Difference	RR	Detectable Rate Exp Arm
0.08	0.8	0.072	0.10	0.008
0.08	0.9	0.079	0.01	0.001
0.10	0.8	0.082	0.18	0.018
0.10	0.9	0.091	0.09	0.009
0.12	0.8	0.092	0.23	0.028
0.12	0.9	0.102	0.15	0.018
0.14	0.8	0.100	0.29	0.040
0.14	0.9	0.112	0.20	0.028
0.16	0.8	0.108	0.32	0.052
0.16	0.9	0.121	0.24	0.039
0.18	0.8	0.115	0.36	0.065
0.18	0.9	0.129	0.28	0.051
0.20	0.8	0.121	0.39	0.079
0.20	0.9	0.136	0.32	0.064

Table S4. Decline in eGFR. Proportion experiencing a 40% decline in eGFR (using CKD-EPI-Cr-CyC equation). With 140 patients per arm, assuming 10% LTFU, in case of 50% patients experienced a 40% decline in eGFR on the SOC arm, we will have 80% power to detect a relative 34% decrease on the treatment arm to 33% with 5% type I error.

Power	Rate SOC arm	RR	Rate Exp Arm
0.8	0.20	0.40	0.08
0.9	0.20	0.32	0.06
0.8	0.25	0.46	0.12
0.9	0.25	0.39	0.10
0.8	0.30	0.51	0.15
0.9	0.30	0.45	0.13
0.8	0.35	0.56	0.20
0.9	0.35	0.50	0.17
0.8	0.40	0.59	0.24
0.9	0.40	0.54	0.22
0.8	0.45	0.63	0.28
0.9	0.45	0.57	0.26
0.8	0.50	0.66	0.33
0.9	0.50	0.61	0.30
0.8	0.55	0.68	0.38
0.9	0.55	0.64	0.35
0.8	0.60	0.71	0.43
0.9	0.60	0.66	0.40

Table S5. Mean change in eGFR. Mean change in eGFR over time (using CKD-EPI-Cr-Cyc equation) with 126 patients per arm after LTFU. Detectable difference shown as unit of 1 SD.

Power	Detectable Difference
0.8	0.35
0.9	0.41

Table S6. Change in quality of life (QOL) score. The change in clinical/performance status (as ascertained via two measures, specifically the WHO quality of life (WHOQOL-HIV) tool (31 questions) and the Karnofsky performance score. WHOQOL-HIV evaluates quality of life based on six domains (physical, psychological, level of independence, social relationships, environment, and spiritual/beliefs) and includes questions specific to HIV/AIDS. The brief version contains 31 questions and each question is rated on a 5-point Likert scale. For the analysis of the data, the scores of the questions within each domain are averaged to get the domain score. The final score
will be the mean of domain scores multiplied by 4. The final score has a minimum value of 4 and maximum value of 20. Hence, we assume it has a standard deviation of 4. With 126 subjects on each arm after LTFU, we will have 80% power to detect a 1.4 points difference in means of WHOQOL-HIV scores, and 90% power to detect a 1.6 points difference in the overall WHOQOL-HIV scores between two arms. The Karnofsky Performance Score has a range of values from 100 to 0, where 100 is “perfect” health and 0 is death. We assume it has standard deviation of 25. With 126 subjects on each arm after LTFU, we will have 80% power to detect an 8.7-point difference in means of Karnofsky Performance Score, and 90% power to detect a 10-point difference in the means of Karnofsky Performance Score between two arms.

Power	Detectable Difference
0.8	0.35
0.9	0.41

Table S7. Change in TDF toxicity. Conservatively, we estimate 2% of patients will experience grade 3 or higher TDF toxicities. In this study, renal events are defined as i) a rise in serum creatinine to > 1.9 and ii) a drop in eGFR to < 50 ml/min. Given 126 patients on each arm after LTFU, assuming 2% TDF toxicity on the SOC arm, we will have 31% power to detect a relative 95% decrease from 2% to 0.1% with 5% type I error, or we have 83% power to detect an increase of toxicity from 2% on the SOC arm to 11% on the treatment arm.

Power	Detectable Difference	RR	Detectable Rate Exp Arm
0.07	0.01	1.5	0.03
0.15	0.02	2.0	0.04
0.25	0.03	2.5	0.05
0.37	0.04	3.0	0.06
0.48	0.05	3.5	0.07
0.59	0.06	4.0	0.08
0.69	0.07	4.5	0.09
0.77	0.08	5.0	0.10

0.83	0.09	5.5	0.11
0.88	0.10	6.0	0.12

Table S8. Change in blood pressure (BP). Recent research (Sakajiki, et al. Kidney disease in HIV/AIDS patients, Annals of Nigerian Medicine. Jul-Dec 2014. Vol 8. Issue 2) indicates SBP or DBP with standard deviation from 13.81 to 20.18 mmHg. We conservatively assume that BP will have a SD of 20 mmHg. With 126 subjects on each arm after LTFU, we will have 80% power to detect a 7-mmHg difference in means of BP, and 90% power to detect an 8.2 mmHg difference in the means of BP between two arms with 5% type I error.

Power	Detectable Difference
0.8	0.35
0.9	0.41

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