Remarkable advances in antiretroviral therapy (ART) for HIV infection have resulted in a medically manageable disease with an average life expectancy of 51 years from diagnosis.1 While the incidence of HIV-associated nephropathy has fallen, the prevalence of chronic kidney disease (CKD) remains high, affecting 16% of the 1.1 million with HIV in the U.S.2 Patients experience unique **HIV-specific CKD risk factors** (e.g., low CD4 count, lifelong, potentially nephrotoxic ART) and **traditional CKD risk factors** (e.g., age, black race). Tenofovir disoproxil fumarate (TDF) is recommended as a component of first-line combination ART even though it increases CKD risk up to 16% annually.3 Generic TDF is now available, making it an attractive option for some. Notably, we previously reported that 87% of patients in a large, U.S. cohort are receiving TDF-based ART.4This is likely becausethe optimal use of TDF in persons with normal renal function but with CKD risk factors remains unclear, especially when TDF is combined with two or more newly approved ARV drugs. It is known that some ART (e.g.,cobicistat, protease inhibitors) increase TDF concentration and potential for CKD. Many antiretrovirals (ARVs) recommended by guidelines and prescribed nationally were FDA-approved less than 4 years ago. One of these new ARVs, tenofovir alafenamide (TAF), provides a less nephrotoxic alternative to TDF, but there are virtually no data on its long-term safety. Furthermore,how TDF affects those with **genetic CKD risk factors** is uncertain.5 Both *APOL1* high-risk variants and 6 Sickle cell trait (SCT)5 are emerging genetic CKD risk factors that are more prevalent in African Americans (AA), a group disproportionately affected by HIV and CKD**. One genetic variant that affects oxidative stress,** Glutathione-S-transferase-μ1(GSTM1) null allele, is a genetic risk factor associated with accelerated CKD progression, especially in AA.7 Notably,HIV-positive blacks are 18 times more likely to develop end stage renal disease than Caucasians. **If genetic variants portend worse outcomes for AA after exposure to potentially nephrotoxic ART, then screening for them may inform safer ARV prescriptions**.

The **objective** of this proposal is to reduce the burden of CKD in AA HIV infected populations by more informed ART selection. The Center for AIDS Research Network of Integrated Clinical Systems (CNICS) is a rich database of > 33,000 HIV-infected persons from 8 U.S. sites and is representative of the current domestic HIV epidemic. By analyzing longitudinal data from CNICS to determine how demographic, clinical, and genetic traits affect kidney outcomes, the proposed research will elucidate optimal ART selection. *This proposal is in line with the priorities of Gilead’s HIV Program including HIV treatment and management and HIV complications in special populations including aging, women, and people of color*. In my preliminary research of CNICS participants starting ART from 2007 to 2012, I found that 7% of all patients experience treatment-limiting kidney dysfunction in the first few years of lifelong ART. My overarching **hypothesis** is that, for AA populations, *phenotypic and genetic risks contribute to clinically significant kidney dysfunction early in the course of ART.*

**AIM1. Characterize 5-year kidney outcomes in a contemporary, real world HIV cohort of African Americans receiving ART**

*Hypothesis: TDF associated CKD is reduced by avoiding combination with cobicistat and/or protease inhibitor*

Elucidate the incidence of CKD and CKD progression in a AA cohort initiating contemporary ART

**AIM2. Explore kidney outcomes of ART in 3 high-risk subgroups: *APOL1*, SCT, and GSTM1 risk variants**

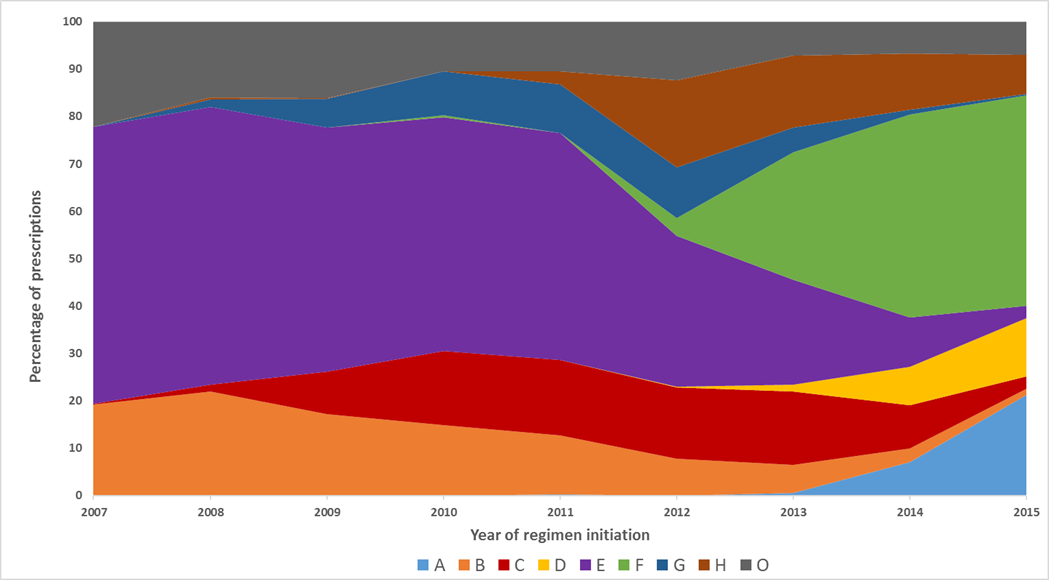
*Hypothesis: TDF is associated with greater risk of nephrotoxicity in high-risk genotypes*

Evaluate the incidence of CKD and CKD progression in patients with *APOL1* risk variants, GSTM1, and/or SCT

**Significance:** Current HIV treatment guidelines recommend a “one size fits most approach” and do not incorporate genotypic (e.g., *APOL1*) and phenotypic traits (e.g, race) that make patients more vulnerable to CKD, a condition that affects 16% or more of those with HIV.2 There is no race-specific guidance on ART prescribing despite the high incidence of CKD in AA with HIV, which could be due to *APOL1* risk variants, SCT, GSTM1 null allele or some combination of the three.6 Precision medicine for HIV treatment has never gained momentum. Almost 20 years ago, HLA-B\*5701 gene positivity was shown to predict “abacavir hypersensitivity,” a potentially fatal reaction to an otherwise safe ARV. Because HLA-B\*5701 screening reduced the incidence of hypersensitivity by 50%,8 HIV treatment guidelines now call for HLA testing prior to abacavir prescription. We expect that the contribution of the proposed research will be knowledge of the specific ART regimens that are associated with the best possible kidney outcomes for AA with CKD risk factors including genetic risks. This contribution will be significant because it **will minimize the burden of preventable ART-associated kidney dysfunction, allowing optimal prescribing patterns, for AA***.* A large body of high quality research has described the relationship between these genetic variants and CKD 5,6,9,10 but we are unaware of data analyzing the kidney outcomes of ART in APOL1 risk variants, SCT, and/or GSTM1 null allele. The **scientific premise** of this proposal is that both genetic traits and some ART are independently associated with CKD, yet there is little research into the relationship between these high-risk genotypes and CKD in ART-treated populations.

Although prior studies have evaluated real world ART outcomes,2,11 none incorporate the most recently approved ARV such as tenofovir alafenamide (TAF) and dolutegravir. There are additional concerns about protease inhibitors and the newest pharmacoenhancer (ie. booster), cobicistat, and their ability to increase tenofovir concentrations to potentially nephrotoxic levels.12 HIV treatment guidelines change annually as novel ART regimens replace older ones. This dynamic treatment landscape makes it challenging for researchers and providers to stay abreast of the safety and effectiveness of ART in real world cohorts. Because a majority of first-line ART has been prescribed for up to 4 years, now is the time to assess kidney outcomes associated with these regimens in a large observational database. This proposal will improve knowledge of ART outcomes by analyzing a large cohort of AAs with HIV with careful attention to relationships between age, sex, and high-risk genotypes, which individually and collectively influence kidney health and disease. By addressing HIV treatment and complications including kidney disease in AA patients who are aging and women, this proposal will advance the mission of the Gilead HIV Program.

**Innovation:** The only FDA-approved HIV prevention pill, also known as PrEP, contains TDF (combined with emtricitabine). Because generic TDF has recently become available, it is unlikely that TDF will be completely usurped by tenofovir alafenamide (TAF) for HIV prevention or treatment. Because AA and those of Caribbean background are at greater risk of HIV than Caucasians and carry *APOL1* and SCT risk genotypes, it is critical that we evaluate the combined contributions of TDF exposure and genetic risks to the development of CKD in this minority group.**5,6** Further, GSTM1 risk variants accelerate kidney disease, especially in combination with *APOL1* risk types. The results of the proposed research will have implications for the millions of racial/ethnically diverse HIV seronegative persons who are PrEP candidates both in the United States (US) and internationally.



**Figure 1. Prescribing Patterns for CNICS Participants initiating ART 2007-2015.**

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1. A. Not TDF based
2. B. TDF based
3. C. TDF based
4. D. TDF based
5. E. TDF based
6. F. TDF based
7. G. TDF based
8. H. TDF based
9. O. Not TDF based

**Introduction:** Because of recent changes in the HIV epidemic related to rapidly introduced ART and dynamic patient demographics, it is imperative to frequently assess the burden of kidney disease in real world settings to identify research priorities and patient care needs. HIV treatment options are changing and the population is aging: almost 20% are over age 50. *The* ***objective*** *of AIM 1 is to analyze the impact of trends in traditional (e.g., age), genetic (e.g., APOL1 risk variants), and contemporary HIV related factors (e.g., 3-drug ART composition) on kidney health and disease.* ART comes with inherent risks. For example, TDF may increase CKD risk by 16% each year.3 Yet, TDF is safe for many patients and is, therefore, included in a majority of first line ART regimens in HIV treatment guidelines.13 Our preliminary research in the large, multisite CNICS cohort, demonstrates that a majority (87%) of treatment naïve HIV infected persons were prescribed a TDF-based regimen between 2007 and 2015 (Figure 1).4 Some feel that the TDF nephrotoxicity issue has been resolved with the availability of tenofovir alafenamide (TAF), which reduces the incidence of significant GFR decline (GFR < 60mL/min) from 9 to 5% in small, select populations.14 But there are no long-term studies of TAF or other new ARV (e.g., integrase strand transfer inhibitors, protease inhibitors) individually or as part of 3-drug ART combinations in diverse settings. HIV disproportionately affects AA, who represent 45% of HIV infections in the U.S. AA are up to 18 times more likely to develop advanced CKD than Americans of European ancestry, 15 which highlights the role of genetic risk for kidney disease in AAs. **CKD disparities in AA with HIV require further analysis to insure that ART exposure is not contributing an additional kidney insult to those with vulnerable kidney function due to high-risk genotypes.**

*My overarching* ***hypothesis*** *is that, for AA populations, phenotypic and genetic risks contribute to clinically significant kidney dysfunction early in the course of ART.* We will test the hypothesis by identifying incident and progressive CKD, stratifying individuals by age, sex, genotypes and ART composition (Table 1). The rationale is that successful completion of the proposed research will contribute missing, fundamental knowledge, without which we cannot understand the safest use of contemporary ART in AA. The results will inform ART prescribing practices that preserve kidney function for diverse populations.

|  |  |
| --- | --- |
| **Table 1. Proposed Traditional and HIV-related Variables** | |
| **Traditional Independent Variables** | **Measurement** |
| Sociodemographic factors | Age, race, sex |
| Current or Prior AIDS diagnosis | CD4 cell count |
| HIV viral load | Viral Copies/mL |
| Baseline Kidney Function | eGFR |
| Diabetes | Diagnosis and/or prescription |
| Hypertension | SBP ≥140mmHg,  DBP≥90mmHg, diagnosis and/or prescription |
| **HIV-related Independent Variables** | **Measurement** |
| Hepatitis C Co-Infection (HCV) | HCV IgG |
| ART regimen | 3-drug composition |
| ART exposure time | Months |
| **Dependent Variable** | **Measurement** |
| Incident CKD | eGFR <60mL/min |
| CKD Progression | eGFR decline to more advanced stage |

**AIM 1. Characterize 5-year kidney outcomes in a contemporary, real world HIV cohort of African Americans receiving ART**

*Hypothesis: TDF is associated with incident CKD that is amplified with cobicistat and/or protease inhibitor usage*

***Research Design.*** This is a retrospective follow up study using the CNICS database, a research network capturing clinical, socio-demographic, and behavioral information on more than 33,000 persons with HIV at 8 treatment sites in the U.S, including the UAB 1917 Clinic (**R24 AI067039**). Over 170,000 patient-reported and clinical outcomes (e.g., creatinine) are collected from participants every 4 to 6 months along with biologic specimens (e.g., plasma). Creatinine values are standardized using isotope dilution mass spectrometry. This infrastructure is ideal for studying patient-oriented outcomes, like kidney disease, in a diverse population (45% White, 38% Black, 34% over 50) with a range of comorbidities.16

***Eligibility Criteria.*** *AA* CNICS enrollees who are ≥18 years old initiating ART on or after January 1, 2012 will be included if they have ≥2 measures of creatinine-based glomerular filtration rate (eGFR) obtained more than three months apart***.*** Self-reported AA race has been shown to correlate with genetically verified AA ancestry.20 Only treatment naïve patients (i.e., starting initial ART regimen) will be included to exclude eGFR changes associated with prior ART exposures. We will include those starting therapy in the last 5 years because we observed a noticeable shift in prescribing patterns in 2012 away from older ART in favor of newer ART (Fig 1).4We will exclude the following participants: those with a baseline eGFR <15 mL/min and/or on dialysis, those missing data for kidney function, and those not receiving ART.

***Measures/Procedures.*** Allcreatinine and eGFR values (calculated using Chronic Kidney Disease Epidemiology Collaboration equation, CKD-EPI) will be collected.17 Sociodemographic and clinical factors (Table 1) will be obtained from the initial visit (i.e., baseline). Baseline creatinine and eGFR will be defined as the measurements obtained at or up to 90 days before ART initiation. All patients receive this testing prior to ART initiation for appropriate ART selection and dosing. In the event of multiple creatinine measures obtained within a 30-day period, the median creatinine value will be used to represent the mean date of that time period. Diabetes will be defined by diagnosis and/or prescription for oral or injectable diabetes therapy at baseline. Hypertension will be defined by baseline systolic blood pressure ≥ 140mmHg and/or diastolic blood pressure ≥ 90 mmHg, diagnosis and/or prescription of antihypertensives (Table 1).

***Analytical Methods.*** We will use descriptive statistics to evaluate rescribing patterns in this contemporary cohort, updating the information in Figure 1. For those with baseline eGFR ≥60 mL/min, the primary outcome of interest will be incident CKD (eGFR <60 mL/min on 2 consecutive dates) while receiving the initial ART regimen. Initial exploration of the data will begin with descriptive statistics including calculation of incidence rates. We will conduct time-to-event (survival) analysis using Kaplan-Meier survival curves. Association of various factors with incident CKD will be evaluated using univariate and multivariable Cox proportional hazards analyses producing unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). For the multivariable analyses, we will include the following **key biological variables**: age, sex, viral load and CD4 cell count, diabetes, hypertension and Hepatitis C status (Table 1). Patients will be censored at death, loss to follow up, and modification of the initial ART regimen, whichever comes first. The statistical significance will be set at 0.05 level (two-tailed). As a secondary outcome of interest, for those with baseline eGFR <60 mL/min, we will analyze the progression to a more advanced CKD stage. CKD stages will be defined according to the KDIGO Clinical Practice Guidelines.18 Descriptive analyses will assess the prevalence of CKD (stages 3, 4, 5, 5D) at study start and end periods and ART exposures (3-drug composition). An estimated small sample size for this outcome (N=24) will limit our ability to conduct any regression analyses. *Anticipated timeline: data acquisition and management (3-4 mos), analysis (3-4 mos), abstract and manuscript preparation (3-4 mos). These activities will happen simultaneously with AIM 2 activities.*

***Size/Power Calculation***. Based on our prior work, we anticipate that 2,660 participants will meet inclusion criteria of which 99% (~N=2,633) will have baseline GFR ≥60 mL/min; of these, we estimate that 87% (N=2,291) will be on TDF-based regimen and 13% (N=298) on ‘other’ regimens. Based on the existing literature, we estimate incident CKD in 16% in those receiving TDF versus 3% in other regimens.19 Thus, approximately 366 and 9 events (incident CKD) are expected in the TDF and other groups, respectively. With an average median duration of 4 years of the first regimen, the estimated hazard rates (per 100 person-years) would be 4 and 0.75, respectively (HR=5.3). With the estimated sample size of 2633, the study will have >80% power to detect a HR of 2.3 or more at a significance level (alpha) of 0.05 (two-sided).4 This large, diverse sample is conducive to a **robust, unbiased study**.

***Expected Outcome.*** The results of this aim will provide clarity on the likelihood that AA persons initiating contemporary ART will experience CKD and/or CKD progression based on their initial ART regimen, sociodemographic, and clinical features. These research activities will allow me to test my hypothesis that, even in the current era of well-tolerated ART, specific ART combinations, namely TDF, cobicistat and/or protease inhibitors, contribute to eGFR decline. The results are a crucial next step to analyzing long-term kidney outcomes. This strategy will support my ***long-term objective*** to reduce the burden of CKD in AA by safer ART selection for AAs with HIV. The results will advance our knowledge of the burden of CKD in a rapidly evolving HIV treatment landscape and enable studies that analyze ART in HIV negative cohorts (i.e. PrEP). Through this mentored research, I will work with Dr. Mugavero, my primary mentor, and Drs. Christina Wyatt and Orlando Gutierrez (see Dr. Mugavero Letter of Support) to acquire knowledge in the epidemiology and disparities of CKD in HIV.

***Potential Problems & Alternative Approaches.*** The number of treatment naïve patients initiating TAF is not well-known but will be analyzed in this study. If TAF represents a small percentage of prescriptions, we will not have significant power to detect meaningful differences (e.g. TAF versus TDF-based ART). In CNICS, patient-reported race/ethnicity is recorded as according to black, white, Asian/pacific islander, multiracial and “other”, which may limit the ability to understand important populations with AA heritage such as Carribean participants. In observational cohorts, “channeling” may reduce the number of persons at risk of CKD receiving TDF prescriptions. Providers “channel” (i.e., prescribe) patients to or away from TDF based on one’s kidney function, not randomly. While this will limit the number of persons with baseline eGFR < 60mL/min receiving TDF-based ART, we do not anticipate that it will eliminate TDF prescriptions for those with CKD risk factors but normal eGFR based on current prescribing patterns.4 To reduce the impact of channeling bias, we will control for baseline eGFR and other covariates in our multivariable model **to reduce channeling bias**. We will consider analysis using propensity score matching. Another issue is that cobicistat, dolutegravir and other ARV may cause reversible inhibition of creatinine transporters and small eGFR elevations. These minimal, benign eGFR reductions are unlikely to lead to the outcomes of interest but are worth noting. We will exclude dialysis patients based on diagnostic codes due to unreliable creatinine and eGFR in the setting of dialysis.

**AIM 2. Explore kidney outcomes of ART in 3 high-risk subgroups: *APOL1*, SCT, and GSTM1 risk variants** *Hypothesis: TDF is associated with greater risk of nephrotoxicity in high-risk genotypes*

HIV now disproportionately affects AA who represent 45% of HIV infections in the U.S. AA are up to 18 times more likely to develop advanced CKD than Americans of European ancestry,15 which highlights the role of genetic risk for kidney disease in AAs. Both *APOL1*,6 SCT,5 and GSTM1 risk variants have been described as CKD risk factors in those of AA heritage. Those with HIV and two *APOL1* risk alleles are five times more likely to develop proteinuria6 and three times more likely to develop CKD.10 The risk of ESRD in AAs with SCT is similar to those with *APOL1* high-risk genotypes (HR of 2.03 and 1.77, respectively).5 GSTM1 null alleles have been associated with CKD and, in AAs, progressive hypertensive nephropathy. Furthermore, these genetic variants are common: *APOL1* high-risk genotypes, SCT, and GSTM1 occur in 11-13%, 8-9%, and 27% of AAs, respectively.5,9 Yet, there is little research into the relationship between specific ART exposures and kidney outcomes in individuals with thesehigh-risk genotypes independently or in combination. **CKD disparities in AA with HIV require further analysis to insure that ART exposure is not contributing an additional kidney insult to those with vulnerable kidney function due to high-risk genotypes.**

***Research Design.*** In this analysis, we will compare the outcome of interest (incident CKD defined in AIM 1A) for AA CNICS participants with and without high-risk genotypes (*APOL1*, SCT, and GSTM1 risk variants). We believe that these high risk genotypes are relevant **biologic variables** that are understudied particularly as they relate to health disparities in AA populations. Repositories at all CNICS sites collect specimens on targeted populations (e.g., treatment naïve individuals initiating therapy) and universally at specified sites on all consenting patients creating a broad sample for future studies. CNICS sites collect specimens that are most likely to address emerging translational and clinical questions, including plasma (e.g., for biomarkers) and peripheral blood mononuclear cells or PBMC (for genetic analyses).

***Eligibility Criteria***. Self-reportedAACNICS enrollees included in AIM 1 with an available PBMC sample will be included (n=1048)***.5,6*** Participants will be excluded if their initial eGFR is <60mL/min.

***Measures/Procedures.*** PBMC samples will be obtained from the CNICS biorepository on eligible participants. PBMC genotype analysis will be conducted by Dr. Cheryl Winkler, PhD, Senior Principal Scientist at the National Cancer Institute as part of research collaboration (see Collaborator Letter of Support). In addition to measures obtained in AIM 1A, we will obtain *APOL1* genotype, SCT, and GSTM1 status from PBMC genotyping. *APOL1* high-risk variants will be identified using genotype data from two alleles: **G1** [coding variants rs73885319 A>G (p.S342G) and rs60910145 G>T (p.I384M)] and **G2** (six base pair deletion, rs71785313). We will categorize participants as having two high-risk alleles (G1/G1, G1/G2, or G2/G2) or 0-1 risk allele (+/+, G1/+, or G2/+).20SCT will be defined as the presence of a single sickle mutation based on genotype data for rs334 encoding the sickle cell mutation (*HBB* p.GLU7Val).9 GSTM1 alleles will be analyzed usinga real–time PCR method. The *GSTM1* null group is defined by carrying the *GSTM1(-)* null allele [*GSTM1(+/-)* and *GSTM1(-/+)*]. The *GSTM1* active group, by definition, is homozygous for the active allele [*GSTM1(+/+)*].

***Analytical Methods.*** The outcome of interest will be incident CKD as defined above (see AIM 1) over the study period. This will be a sub-group analysis of AIM1including only AAs with a specimen available for genotyping (i.e., PBMC). Based on a feasibility assessment in the CNICS database, 1,048 individuals will meet inclusion criteria. We will stratify on the presence/absence of the risk variants (APOL1,SCT, GMST1). The stratified analysis will examine whether there is any effect measure modification of the association between the regimen (TDF vs. Other) and incident CKD. Additionally, we will examine the combined effect of the regimen and each genotype (exposures) by forming a 4-category variable as follows: 1. CKD+ and APOL1+, 2.CKD+ and APOL1-, 3. CKD- and APOL1+, and 4.CKD- and APOL1-. A similar 4-category variable will be examine for SCT and GMST1 genotype. As described in AIM1, time-to-event analyses using survival curves and Cox proportional hazard analyses will be conducted. *Anticipated timeline: data acquisition will take 6 months (including genotyping), analysis will take 4 months, and manuscript development will take 3-4 months. These activities will happen simultaneously with AIM 1.*

***Sample Size.*** Of the 2,660 patients (AIM 1), approximately 1,048 AAs meet the following criteria: have baseline GFR ≥60 mL/min, have creatinine and eGFR values as outlined in AIM1, and have PBMC specimen available for genotyping. We anticipate that 136 (13%), 94 (9%), and 283 (27%) will have high-risk *APOL1*, SCT, and GSTM1 variants respectively.5,6

***Expected Outcomes.*** The outcome of AIM 2 will be the demonstration of the relative safety and toxicities of specific 3-drug ART regimens in AA with a genetic predisposition to CKD relative to AA without these genetic traits. By identifying the ART regimens that are most likely to preserve kidney function, these findings will improve the clinical care of AA patients with HIV. If results reveal strong associations between genotype and kidney function following specific ART exposures (e.g., TDF-based regimens), *this research may be foundational to the use of genetic screening for AA populations prior to ART prescription. This is a critical step towards racial parity for kidney health in HIV and has significant implications for prevention (i.e., PrEP usage): the only FDA-approved PrEP contains TDF, and PrEP education and prescriptions are targeted to AA to curb racial disparities in HIV transmission.* As part of this activity, my co-mentor, Dr. Orlando Gutierrez will provide mentored training on disparities and genetic risks for CKD (See Dr. Mugavero Letter of Support)*.*

***Potential Problems & Alternative Approaches.*** Because this is a novel assessment, we cannot state with certainty that there will be an association between high risk variants and CKD. This specific aim is necessary to explore this relationship. Due to the moderate sample size (n=1,048), it may be difficult to identify the unique outcomes of specific 3-drug ART combinations, of which there are multiple first line options.4 Based on a feasibility assessment, we anticipate having power to categorize ART according to most frequently prescribed options (e.g., TDF-based, TAF-based, protease inhibitor based) to allow us to detect differences between ART regimens with known risk of nephrotoxicity. Due to the rapidly changing treatment landscape, it is impossible to predict the future use of TDF versus TAF over the study period. If a majority of participants receive one ART (e.g., TAF-based regimen), this will limit our ability to detect differences in the ART outcomes of those with high risk genotypes. Ideally, an assessment of proteinuria in addition to eGFR would be used to understand the potential nephrotoxicity of different ART in this proposal. Due to the scope of this funding mechanism (2 years) and budget, we believe that an analysis of proteinuria is not feasible. However, the research activities outlined in this proposal will be fundamental to a future R-series award wherein we will include prospective urinalysis assessment for both protein-to-creatinine and albumin-to-creatinine rations.

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