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Title

Assessing and Refining Myocardial Infarction Risk Estimation Among Patients With Human Immunodeficiency Virus: A Study by the Centers for AIDS Research Network of Integrated Clinical Systems.

Permalink

<https://escholarship.org/uc/item/7mk716zx>

Journal

JAMA cardiology, 2(2)

ISSN

2380-6583

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Publication Date

2017-02-01

DOI

10.1001/jamacardio.2016.4494

Peer reviewed



North American AIDS Cohorts Collaboration on Research & Design (NA-ACCORD)

Collaboration Concept Sheet Format & Guidelines

I. Format

Please review NA-ACCORD collaboration guidelines (located on page 3) before drafting your Concept Sheet (CS).

Use the following outline to present your study plan. Take whatever space is necessary to completely respond to each section. This form will not be accepted unless each lettered section listed below is included.

Email completed Concept Sheet in a Word, PDF or RTF file to Aimee Freeman (afreeman@jhsph.edu).

A. GENERAL INFORMATION

1. Study Title: The natural history of chronic kidney disease progression, cardiovascular events, and all-cause mortality in HIV-infected persons in North America
2. Date of submission: 08/26/16; Revised 10/20/2016
3. Lead Investigator(s): Michelle M. Estrella, Alison G. Abraham, Heidi Crane, Gregory M. Lucas, analyst
4. Institution: University of California, San Francisco
5. Address/Telephone/FAX/Email: 4150 Clement St., 111A1, San Francisco, CA 94121/ 415-221-4810 ext.24903/michelle.estrella@ucsf.edu
6. NA-ACCORD Liaison (if Lead Investigator is external to NA-ACCORD):
7. Will this project require the withdrawal of repository specimens? Yes* No
*If you select Yes, you must complete the Repository Specimens section located on page 2 of this document.

We are requesting assistance from Data Management Core to convert data on proteinuria into a format useable for analyses and assistance for analyses proposed in this project.

B. SPECIFIC AIMS AND HYPOTHESES

Aim 1: To describe rates of transition through stages of CKD and into cardiovascular disease (CVD) and death.

Goal: We will use estimated glomerular filtration rate (eGFR)-based CKD stages, CVD, and all-cause mortality in HIV-positive adults to estimate transition rates of CKD progression, CVD and all-cause mortality. Secondary analyses will also be

conducted in which proteinuria data are incorporated into the CKD stage definitions among the subset of studies with proteinuria data available.

Hypothesis 1a: Advancing severity of CKD is associated with stepwise increase in the rate of transition to CVD events, controlling for CVD risk factors.

Aim 2: To assess factors associated with transitions to higher CKD stages in HIV-positive adults and explore whether the propensity for CKD progression differs from HIV-negative adults

Hypothesis 2a: Non-suppressed HIV RNA is independently associated with CKD progression across both early and later CKD stages

Hypothesis 2b: Black race is more strongly associated with progression in later CKD stages than in the earliest stage (progression from $eGFR \geq 60$ to $eGFR < 60$ mL/min).

Aim 3: To assess factors associated with transitions from various CKD stages to CVD among HIV-positive individuals in the HAART era and to determine whether race and diabetes modify these associations, taking into account the competing risk of death

Hypothesis 3a: Black race and diabetes modify the risk of CVD events associated with CKD.

Hypothesis 3b: Rapid eGFR decline is associated with increased risk of MI events and all-cause mortality compared with stable eGFR trajectory, controlling for nadir eGFR.

C. BACKGROUND AND RATIONALE

CKD is common in HIV-positive adults,[1-3] although the risk of progression to end-stage renal disease has declined in the era of combination antiretroviral therapy (ART) compared with the pre-ART era. In the general population, CKD has important associations with CVD and with all-cause mortality. However, there have been few attempts to characterize the interrelated natural history of CKD and CVD in the HIV-positive population. We propose to use NA ACCORD data to provide a comprehensive model of CKD progression, CVD events, and all-cause mortality among HIV-infected persons followed in the modern ART era.

Several studies have shown that HIV-infected individuals are particularly at risk for cardiovascular disease.[4, 5] Using a large registry database, Triant and colleagues showed that the risk of acute myocardial infarction was nearly 3-fold greater in women and 1.4-fold greater in men infected with HIV compared with HIV-uninfected individuals independent of traditional risk factors[5]. In a recent study of the predominantly male Veterans Aging Cohort Study Virtual Cohort, HIV-infected veterans had nearly 1.5-fold higher risk of an acute myocardial infarction compared to HIV-uninfected veterans, even after adjustment for traditional CVD risk factors and substance use including smoking.[4]

In the general population, there has been a consistent link between CKD and CVD risk. In pooled analysis comprised of cohorts of the general population as well as individuals with CKD, lower levels of eGFR were associated with higher risk of CVD-

related mortality; this risk was augmented by the higher levels of albuminuria.[6] Similar associations between CKD and CVD have also been observed for acute myocardial infarction and CVD-related hospitalizations.[1] The association between CKD and CVD likely stems from their shared risk factors such as diabetes and hypertension, the two most common causes of CKD in the U.S.

Among HIV-infected individuals, however, the underlying causes of CKD differ from the general population. HIV-infected individuals present with ESRD at younger ages than the general population.[7] Moreover, CKD is primarily due to HIV effects on the kidneys, direct ART nephrotoxicity or related to the immune dysregulation associated with HIV infection while a smaller proportion of CKD in HIV-infected individuals has been attributed to traditional risk factors.[8] For example, TDF leads to tubular proteinuria and impaired kidney function[9,10]; however, tubular proteinuria (unlike albuminuria) is not associated with atherosclerotic CVD events in the older general population.[11] Moreover, TDF has been associated with less carotid intima-media thickness and may have lipid-lowering effects.[12, 13] Therefore, findings in the general population may not be generalizable to the HIV-infected population.

A limited number of studies have evaluated the link between CKD and CVD. In a single-center case-control study comprised primarily of African American HIV-positive persons, eGFR of <60 mL/min was associated with a 1.2-fold higher odds of a CVD event.[14] Similarly, Choi and colleagues found an independent graded association between baseline severity of CKD and coronary heart disease and heart failure in predominantly male HIV-negative veterans; this risk was augmented by the presence of albuminuria.[1] Our proposal will extend their work by evaluating the association between CKD and CVD using a study population representative of North America and by studying whether rapid declines in kidney function are also associated with CVD.

D. STUDY POPULATION / ELIGIBILITY CRITERIA

- HIV-positive adults
- Followed between 1995 and 2015
- Longitudinal serum creatinine data available
- No known history of CVD event at or within 6 months following cohort enrollment

For the proposed exploratory comparison of CKD progression between HIV-positive and –negative adults, HIV- adults followed between 1995 and 2015 will be included.

E. STUDY VARIABLES AND DEFINITIONS

The primary outcomes include: 1) CKD stage (Aims 1 and 2); and 2) CVD events (Aims 1 and 3). The outcome of CVD event will be comprised of acute MI, coronary artery bypass surgery, and percutaneous coronary interventions (i.e. stenting) as defined by discharge diagnoses. A more focused analysis on chart-validated acute MI (type 1) as the outcome will also be conducted using data from 1995-2010.

The primary independent variable of interest is CKD stage. GFR categories will be derived from GFR (ml/min/1.73 m²) estimated using the MDRD equation based on serum creatinine, sex, race, and age.[15] CKD will be defined based on the estimated GFR. As secondary analysis, we will also evaluate CKD based on the combination of estimated GFR and proteinuria level among the subset of cohorts within NA-ACCORD with available data on proteinuria. As proteinuria presence and level has been assessed in various ways (e.g. urine dipsticks, random urine protein (or albumin)-to-

creatinine ratios, and 24-hr urine samples) across these cohorts, we will work with the Data Management Core to standardize these proteinuria data for analyses. We envision that proteinuria will be necessarily be a binary variable, with its presence defined by urine dipstick >1+, urine albumin-to-creatinine ratio >30 mg/g, urine protein-to-creatinine ratio >200 mg/g or 24-hr urine protein level >300 mg/g.[16] We can further categorize individuals into those who have no proteinuria, possible proteinuria (presence of proteinuria on one occasion, without subsequent confirmatory assessment available), and confirmed proteinuria (presence of proteinuria on at least two occasions, 3 months apart).

CKD will be evaluated as a dichotomous outcome as well as an ordinal outcome as follows based on two occasions at least 3 months apart, consistent with the new KDIGO CKD Categories:[16]

- Dichotomous CKD: eGFR <60
- CKD categories without proteinuria data
 - No CKD: eGFR ≥60
 - CKD stage 3a: eGFR 45-59
 - CKD stage 3b: eGFR 30-44
 - CKD stage 4: eGFR 15-30
 - CKD stage 5: eGFR <15
- CKD categories *with* proteinuria data (secondary analysis)
 - No CKD: eGFR ≥60 and no proteinuria
 - CKD stage 1/2 : eGFR ≥60 with proteinuria
 - CKD stage 3a: eGFR 45-59 with or without proteinuria
 - CKD stage 3b: eGFR 30-44 with or without proteinuria
 - CKD stage 4: eGFR 15-30 with or without proteinuria
 - CKD stage 5: eGFR <15 with or without proteinuria

We will also evaluate the association of longitudinal changes in kidney function with risk of CVD through a couple of approaches. First, the absolute annual change in GFR will be calculated for each participant using the prior 3 years of eGFR data to characterize recent decline. Linear slopes will be estimated by regressing eGFR on time. The primary analysis will categorize participants into the following longitudinal GFR categories:

- Rapidly declining: annual change in GFR of <-5 mL/min/year. This is consistent with the definition of rapid kidney function decline put forth by the KDIGO CKD guidelines.[16]
- Stable: annual change in GFR of ≥-5 to ≤+5 mL/min/year
- Rapidly increasing: annual change in GFR of >+5 mL/min/year

An alternative approach will be used if the primary linear slope analysis proves infeasible (due to sparseness of data) or uninformative. We will use latent class trajectory analysis to determine GFR trajectory groups. The methods of Nagin (1999) can be implemented in SAS and will provide classifications of individuals based on their long term GFR trajectories, which will differentiate between those who experience periods of rapid decline and those who experience relatively stable kidney function over long time frames.

Covariate data as available will include:

- Sociodemographic factors: age, race, sex, injection drug use (where available),

smoking (where available)

- Co-morbid conditions: hepatitis C antibody status, diabetes, hypertension, obesity, hyperlipidemia, systolic blood pressure, use of ACEi/ARB. Hypertension will first be evaluated as a dichotomous variable (yes/no). As sensitivity analysis, we will also evaluate hypertension categorized into: 1) no hypertension; 2) controlled hypertension (history of hypertension with average BP <140/90 mm Hg); and 3) uncontrolled hypertension (history of hypertension with average BP >140/90 mm Hg) If sufficient data exists, we will adopt a similar approach for diabetes, utilizing hemoglobin A1c to gauge degree of diabetes control among diabetics.
- HIV-related factors: history of AIDS, CD4+ cell count, HIV-1 RNA, antiretroviral drug use. The primary analysis will evaluate CD4+ cell count and HIV-1 RNA levels as time-varying variables. We will also evaluate degree of HIV viral suppression as the cumulative number of days in which HIV-1 RNA levels remain below 400 copies/mL.

F. DATA ANALYSIS AND SAMPLE SIZE CALCULATIONS

A descriptive analysis of all covariates by baseline CKD status will be performed using t-tests or rank-sum tests for continuous variables and X^2 test for categorical variables. The incidence of the CVD outcome and each CVD event by baseline GFR category will be calculated per 1000 person-years. We will use longitudinal data to construct a transition model (see Figure as example). α , β and δ rates will be observed transition probabilities of CVD event, increasing CKD stage, or all-cause mortality, respectively (expressed as events per 1000 person-years). Defining transitions to stage 3 CKD (from no CKD) or to higher stage of CKD from a lower one (i.e., β_1 , β_2 , and β_3 in the Figure) will be operationalized as follows. An individual will be considered to move to a higher (more advanced) CKD stage if there is an index eGFR and a confirmatory eGFR (≥ 90 days after the index value) that are below the threshold in question, with no intervening eGFR values that exceed the threshold. Progression to higher (more severe) CKD stages will be assumed to be a monotonic process.

Cox proportional hazards models will then be constructed to estimate the relative hazard of an incident CVD event and the corresponding 95% confidence interval associated with baseline GFR categories. The no CKD group will serve as the reference group. Participants will be censored for last available follow-up or December 31, 2012. Adjustment for potential confounders will be staged as follows: 1) sociodemographic characteristics (age, gender, and race) and cohort; 2) traditional CVD risk factors (diabetes, hypertension, smoking, dyslipidemia, and obesity); 3) HIV-related factors (AIDs history, and time-varying CD4+ cell count, HIV-1 RNA level, and antiretroviral exposure) and 4)

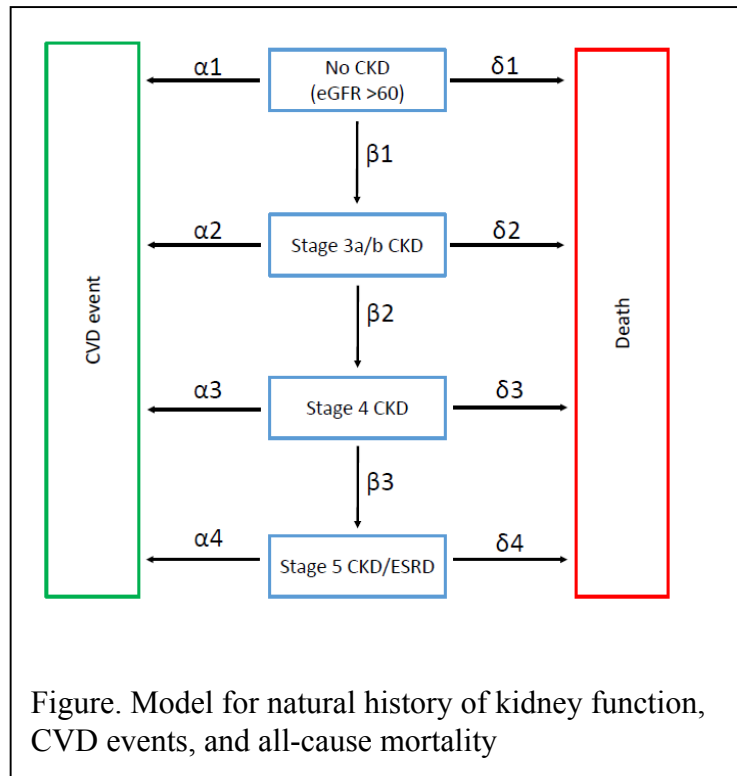


Figure. Model for natural history of kidney function, CVD events, and all-cause mortality

non-traditional CVD risk factors (injection drug use and hepatitis C serostatus). As noted above, CD4+ cell count and HIV-1 RNA level will be time-updated. In addition, we will evaluate the cumulative time with HIV-1 RNA levels below 400 copies/ mL. Effect modification by race and diabetes mellitus will be evaluated by the inclusion of a race*GFR category and race*diabetes interaction term in separate, parallel models and by race-/ diabetes-stratified analyses. The independent association between baseline proteinuria and CVD risk will also be evaluated using a similar approach among cohorts that have systematically collected data on proteinuria. Sensitivity analyses in which the outcome is restricted to validated acute MIs will also be conducted using a similar approach as described above. In addition, we will perform a competing risk analysis with CVD and **stage 5 CKD** as competing events to evaluate the influence of risk factors on each of these outcomes. The association of longitudinal GFR slope categories (and of piecewise linear splines) with CVD risk will be evaluated using a parallel approach, using the stable GFR group as the reference group.

Model assumptions of proportionality will be examined using log-log plots and Schoenfeld residuals. Missing data will be addressed in two ways: categorization of missing data a separate category for each variable and multiple imputation.

G. TIMEFRAME AND EXPECTED PUBLICATIONS

Analyses will be completed within 6 months of receipt of data with a conference abstract or manuscript draft available for circulation at that time.

H. REFERENCES

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15. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999,**130**:461-470.
16. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. *Am J Kidney Dis* 39:S1-S000, 2002 (suppl 1)

II. Repository Specimens

Complete this section if your proposal requires the withdrawal of repository specimens. Please note that not all NA-ACCORD collaborating cohorts have specimens available and those that do may elect not to contribute specimens for this project.

1. Will this project require the withdrawal of specimens? ___ Yes No
a. If *Yes*, date you will require specimens (MM/DD/YY):

2. Will this project require the withdrawal of host DNA? ___ Yes No
a. If *Yes*, please complete each section below:

18. Will this project require collection of new: No_ Data and/or _No_ Specimens

III. Guidelines

The NA-ACCORD Concept Sheet is intended for use for all collaborations initiated as part of the NA-ACCORD.

1. All investigators wishing to access NA-ACCORD resources are encouraged to review their proposed research with the NA-ACCORD Principal Investigator and NA-ACCORD Working Groups. For external investigators, a NA-ACCORD liaison will be assigned prior to formal submission.
2. Once submitted, the proposal will be reviewed by the Executive Committee for approval to post to the NA-ACCORD forum. Working Groups and Steering Committee members will have a 2 week opportunity to comment on the concept sheet. The investigator will then be notified whether the concept was approved, approved with comments, tabled for further clarification and resubmission, or rejected.
3. Once approved, the Data Management and Epidemiology/Biostatistics Cores will work with the investigator in constructing a protocol that provides further detail on study eligibility criteria and data elements to be requested by the cohorts.
4. Each participating cohort in NA-ACCORD will have the right to decide to participate or not participate in any scientific aim or sub-aim. By agreeing to participate, cohorts commit themselves to supplying the data elements as specified by the final study protocol. Data transmitted by an individual cohort will be used only to address the approved scientific aims. Additional analyses require the approval of the NA-ACCORD SC and participating cohorts.
5. Investigators agree to follow NA-ACCORD publication policy (posted on the web at <http://statepiaps.jhsph.edu/naaccord/admin>). Importantly, **all abstracts and manuscripts derived from this concept sheet MUST be submitted to the SC for review and approval before they are submitted to a journal or conference.** Forms required for this process are available on the web at <http://statepiaps.jhsph.edu/naaccord/forms>. Further, all manuscripts and presentations will acknowledge data collected through NA-ACCORD and credit all collaborating cohorts and institutions.

1. Please be specific as to the support you are requesting

We have specified the NA-ACCORD support we are seeking for this proposal under A7.

2. It needs to be clear as to what it can add to existing research and be careful of confounders that go along with viral suppression since there is no HIV-negative comparator group; if there is no difference by VL, then that would be publishable.

There are concerns about the novelty of these aims. Most of this is known in the general population, so it is not clear why this would be suspected to be different in an HIV infected population. How much additional information is going to be added to the field, particularly in light of the fact that there is no HIV- control group?

Aside from the early studies among HIV-negative diabetics, the rates of transition to CKD stages have not been well-delineated in the general population. Moreover, HIV-positive individuals have risk factors for CKD development and progression that are unique (e.g. ART-associated metabolic effects and direct nephrotoxicity) that render studies in the general population difficult to extrapolate to the HIV-positive population.

We acknowledge that the link between CKD and CVD risk in the general population has been well-delineated. However, HIV+ individuals generally develop CKD at younger ages and have underlying causes of CKD that differ from the general population. For example, TDF leads to tubular proteinuria and impaired kidney function; however, tubular proteinuria (unlike albuminuria) is not associated with CVD outcomes in the general population. Moreover, TDF has been associated with less cIMT and may have lipid-lowering effects. Therefore, we believe that an HIV-specific comprehensive analysis of the association between CKD transition and CVD would add novel information beyond the existing literature.

3. Suggest that methods of dealing with confounders be more detailed in the CS

In no analysis can one be assured that there will not be residual confounding despite best efforts. We will broadly seek expertise across the writing group as to potential confounders and will perform sensitivity analyses using different confounder specifications to determine if there is instability in our estimations.

4. If they find something, they are going to be limited as to how they can tease that apart whether it is truly a direct VL effect vs more common behavioral/comorbidity characteristics

The overall objective of this proposal is to understand the rates of transition to CVD or worse CKD and the relative sequence of these potential outcomes as they relate to one another. We have thoughtfully selected covariates based on biological plausibility of their association between kidney function and CVD to minimize potential confounding. These confounders include behavioral factors such as

injection drug use and smoking; however, we are limited in evaluating factors such as socioeconomic status given lack of data on these factors within NA-ACCORD. Moreover, as this analysis is based on observational data, we are limited in what could be inferred from the results, including causality. We will carefully interpret our results, keeping in mind the inherent limitations of observational studies and acknowledge the limitations of data included within NA-ACCORD.

5. Are they going to look at measures other than eGFR , such as urine labs, microalbumin or dialysis?

We have clarified the use of proteinuria as another assessment of CKD status in a proposed secondary analysis among the subset of NA-ACCORD cohorts with these data available. This addition has been detailed in section E.

6. Useful for lead investigators to work with Data Management Core to discuss what data they would like to use (especially for urine data); UW offered to help with biostat support

We appreciate this opportunity to work with the Data Management Core and will work with the Core to standardize the proteinuria data across cohorts. This will yield a valuable component of CKD assessment and a unique resource not readily available in other studies for future renal-focused research endeavors.

7. If you find no difference by HIV RNA, you may have trouble attributing to a direct viral effect vs. residual confounding. How would you handle this?

With the observational design, we are simply evaluating for factors associated with transition through stages of CKD, and do not intend on interpreting observed associations as causal in nature. Moreover, as with all observational studies, residual confounding is of concern. We will carefully interpret our findings with the constraints inherent in observational studies in mind.

8. Although you mention Stage 5 ESRD/CKD, this would limit the analysis to pre 2010. Please note how you would conduct these analyses on a subset.

We define stage 5 CKD based only on a persistent eGFR <15 ml/min as this would capture individuals with very advanced CKD who are not yet on dialysis as well as those who likely developed dialysis-dependent ESRD. Moreover, this approach allows us to utilize all available NA-ACCORD data when evaluating rates of transition through CKD stages and CVD outcomes based on discharge diagnoses. In the more focused analysis based on chart-validated acute MI (type 1) as the outcome, we would necessarily limit our data to pre-2010.

9. Microalbuminuria is only collected in a subset, and standardization is very challenging (dipstick vs. lab reported). More detail is needed to talk about how you would like to incorporate urine measures. In P2015, urine data is a focus, but it will need more work.

As noted above, we will work closely with the Data Management Core to carefully standardize the varying approaches by which proteinuria is captured into a format useable for statistical analyses. We envision that proteinuria will be a binary

variable, with its presence defined by urine dipstick >1+, urine albumin-to-creatinine ratio >30 mg/g, urine protein-to-creatinine ratio >200 mg/g or 24-hr urine protein level >300 mg/g. This approach is consistent with the Kidney Disease Improving Global Outcomes (KDIGO Guidelines on CKD Evaluation and Management). We can further categorize individuals into those who have no proteinuria, possible proteinuria (presence of proteinuria on one occasion, without subsequent confirmatory assessment available), and confirmed proteinuria (presence of proteinuria on at least two occasions, 3 months apart).