Rapid Progression of Kidney Dysfunction in Swiss People Living with HIV: Contribution of Polygenic Risk Score and D:A:D Clinical Risk Score.

Léna G. Dietrich,[1,13] Christian W. Thorball,[2,3] Lene Ryom[4], Felix Burkhalter,[5] Barbara Hasse,[6] Maria Christine Thurnheer,[7] Maja Weisser,[8] Patrick Schmid,[9] Enos Bernasconi,[10] Kathrine E.A. Darling,[11] Hélène Buvelot,[12] Jacques Fellay[2,3], Bruno Ledergerber[6], and Philip E. Tarr[1 *], for the Swiss HIV Cohort Study

[1] University Department of Medicine and Infectious Diseases Service, Kantonsspital Baselland, University of Basel, 4101 Bruderholz, Switzerland
[2] Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland
[3] School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, 1015 Lausanne, Switzerland
[4] Center of Excellence for Health, Immunity and Infections, CHIP, Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, 2100 Copenhagen, Denmark
[5] University Department of Medicine and Nephrology Service, Kantonsspital Baselland, University of Basel, 4101 Bruderholz, Switzerland
[6] Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, 8091 Zurich, Switzerland
[7] Department of Infectious Diseases, Bern University Hospital, University of Bern, 3010 Bern, Switzerland
[8] Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, 4031 Basel, Switzerland
[9] Division of Infectious Diseases, Kantonsspital St Gallen, 9007 St. Gallen, Switzerland
[10] Division of Infectious Diseases, Ospedale Regionale, 6900 Lugano, Switzerland
[11] Infectious Diseases Service, Lausanne University Hospital, University of Lausanne, 1011 Lausanne, Switzerland
[12] Division of Infectious Disease, Geneva University Hospital, 1205 Geneva, Switzerland
[13] Department of Surgery and Traumatology, Gesundheitszentrum Fricktal, 4310 Rheinfelden, Switzerland

*** Corresponding author**: Philip E. Tarr, MD, University Dept. of Medicine and Infectious Diseases Service, Kantonsspital Baselland, University of Basel, 4101 Bruderholz, Switzerland; Phone +41 (61) 436 2212, Fax +41 (61) 436 3670, philip.tarr@unibas.ch

** **Alternative corresponding author**: Léna G. Dietrich, MD, University Dept. of Medicine and Infectious Diseases Service, Kantonsspital Baselland, University of Basel, 4101 Bruderholz, Switzerland; Phone +41 (79) 383 21 35, lena.dietrich@unibas.ch

Brief, 40-word-or-less summary of the article's main point. We have previously associated genetic background with chronic kidney disease in people living with HIV (PWH). Here we show that an individual polygenic risk score is associated with rapid progression of kidney dysfunction in Swiss PWH.

ABSTRACT

Background. In people with HIV (PWH), it is unknown whether genetic background associates with rapid progression of kidney dysfunction; i.e. eGFR decrease of >5mL/min/1.73m^2 per year for ≥3 consecutive years.

Methods. We used time-to-event analyses to measure univariable and multivariable hazard ratios (HR) for rapid progression, based on the clinical D:A:D CKD risk score, antiretroviral exposures, and a polygenic risk score based on 14'769 genome-wide single nucleotide polymorphisms (SNPs) in white Swiss HIV Cohort Study participants.

Results. We included 225 participants with rapid progression (median age 42 years, 76% male, median baseline eGFR 101 mL/min/1.73m^2) and 3378 rapid progression-free participants. In multivariable analysis, compared to participants with a low risk D:A:D CKD risk score, participants with medium and high risk had rapid progression-HR=1.30 (0.99-1.71) and 1.82 (1.28-2.60), respectively. Compared to the first (most favorable) polygenic risk score quartile, participants in the second, third and fourth (most unfavorable) quartiles had rapid progression-HR=1.39 (0.94-2.06), 1.52 (1.04-2.24) and 2.04 (1.41-2.94), respectively. Recent exposure to tenofovir disoproxil fumarate was associated with rapid progression (HR=1.36 [1.06-1.76]).

Discussion. An individual polygenic risk score is associated with rapid progression in Swiss PWH, when analyzed in the context of clinical and antiretroviral risk factors.

Keywords. HIV infection, rapid progression of kidney disease, genetics, clinical risk factors, antiretroviral therapy.

INTRODUCTION

Chronic kidney disease (CKD) is a considerable concern in people with HIV (PWH). In addition to advancing age, risk factors for CKD in PWH include traditional risk factors such as pre-existing kidney disease, female gender, injection drug use, cardiovascular disease, hypertension, and diabetes[1]. Hypertension was defined as blood pressure ≥140/90mmHg or use of antihypertensive medication. Diabetes mellitus was diagnosed with confirmed plasma glucose >7.0mmol/L (fasting) or >11.1mmol/L (non-fasting) or receiving antidiabetic medication. HIV-related factors for CKD include the effects of immunosuppression and exposure to potentially nephrotoxic antiretroviral therapy (ART) including atazanavir/ritonavir (ATV/r), tenofovir disoproxil fumarate (TDF), and lopinavir/ritonavir (LPVr). The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D CKD risk score) study, the largest consortium of HIV observational studies with strict endpoint definition and validation, has summarized these risk factors in a well validated risk score for CKD, defined as confirmed (>3 months apart) eGFR<60 mL/min/1.73m^2 [1]. Another, more dynamic measure of kidney impairment in PWH is rapid progression of kidney dysfunction, variably defined as annual eGFR decline of ≥3 or ≥5mL/min/1.73m^2 in several consecutive years[2-4]. In comparison, the normal age-related rate of eGFR decline is approximately 1 mL/min/1.73m^2 per year[5,6]. Studying rapid progression is important because, in addition to potentially allowing early detection of kidney dysfunction and prediction of progression to CKD in PWH [4], rapid progression has been associated with CKD, all-cause and cardiovascular mortality in the general population[6-8].

Genome-wide association studies (GWAS) have shown that a significant proportion of CKD risk in the general population is genetically determined[9-11]. We have recently shown that a polygenic risk score that summarizes the effect of 86'613 single nucleotide polymorphisms (SNPs) independently predicts CKD in Swiss PWH with normal baseline kidney function[12]. The genetic effect remained robust after adjusting for D:A:D CKD risk score and exposure to potentially nephrotoxic ART[12]. The contribution of genetic background to rapid progression in PWH is currently unknown. Therefore, the aim of the present study was to assess and quantify the

contribution of genetic background, D:A:D CKD risk score, and relevant ART exposures to rapid progression. This is the first comprehensive study to apply GWAS genotyping and a longitudinal approach that includes validated clinical and antiretroviral risk factors for rapid progression in PWH.

METHODS

Study Population. Eligible participants were PWH enrolled in the Swiss HIV Cohort Study (SHCS; www.shcs.ch) after 1 January 2004[13]. We only considered eGFR values obtained per protocol at routine, 6-monthly SHCS visits, with creatinine values measured in local accredited hospital laboratories. We included participants who had 2 consecutive eGFR values ≥80 mL/min/1.73m^2 during follow-up, using the Chronic Kidney Disease Epidemiology Collaboration formula. The study was approved by the local ethics committees. Participants provided written informed consent for genetic testing. Because previous GWAS focusing on kidney insufficiency in the general population were performed in populations of predominantly European ancestry, we limited the study to participants of European ancestry, determined by principal component analysis of the genotyping data[9-11].

Nongenetic CKD Risk Factors. Only variables included in the D:A:D CKD risk score [1] were included (mode of HIV transmission, hepatitis C co-infection, age, baseline eGFR, gender, CD4 nadir, hypertension, prior cardiovascular disease, and diabetes mellitus). All ART agents are recorded in the SHCS database with start/stop dates. We adjusted only for those ART exposures that contributed to CKD in the D:A:D study[14], i.e. ATV/r, LPV/r, and TDF. As done previously [12], hypertension was defined as blood pressure ≥140/90 mmHg or use of antihypertensive medication; diabetes mellitus was diagnosed with confirmed plasma glucose >7.0 mmol/L (fasting) or >11.1 mmol/L (non-fasting) or receiving antidiabetic medication.

Genotyping. DNA samples were obtained from peripheral blood mononuclear cells and genotyped with the Infinium CoreExome-24 BeadChip, Global Screening Array v2.0+MD (Illumina, San Diego, CA), or in the setting of previous GWAS in the SHCS. Each genotyping batch underwent separate quality controls, filtering and imputation prior to merging of all batches and analyses (**Supplementary Methods**).

Genome-wide Polygenic Risk Score. Polygenic risk score for the filtered and imputed samples was calculated using the summary statistics and effect sizes from a previous large-scale genetic meta-analysis of baseline eGFR levels [11]. Specifically, the polygenic risk score was calculated with PRSice (v2.3.1e)[15], with clumping removing variants in linkage disequilibrium (LD) ($r^2 > 0.1$) within 1Mb windows and exclusion of ambiguous variants. Variants passing the initial filtering, but missing in some individuals were not counted in the score for these individuals.

Statistical Analyses. The baseline date was defined as the date of the 2nd of 2 consecutive eGFR values $\geq$80 mL/min/1.73m^2. Baseline eGFR was calculated as the average of these 2 eGFR values. Compared to our previous report[12], we lowered the eGFR entry criterion to the study from 90 to 80 mL/min/1.73m^2, in order to increase the size of the study population, and to make results more broadly applicable to aging PWH. Subsequent follow-up was split into yearly intervals and individual eGFR values were averaged for each year of follow-up. We interrupted follow-up when participants were switched to integrase inhibitor (INSTI)-containing ART, including raltegravir (RAL), dolutegravir (DTG), bictegravir (BIC), or cobicistat (COBI), because these agents can artefactually decrease eGFR without decreasing the actual GFR, due to inhibition of creatinine secretion [16,17]. Participants who started or switched to INSTI-containing ART could enter or re-enter the study for a second observation period with 2 consecutive eGFR $\geq$80 mL/min/1.73m^2 after starting INSTI; the date of the 2nd eGFR value, i.e. $\geq$6 months after the 1st eGFR value was taken as the new baseline eGFR, in order to account for the eGFR drop that typically occurs within few weeks of INSTI treatment[16,17].

The study endpoint was defined as the 3rd of 3 consecutive years with an eGFR drop of ≥5 mL/min/1.73m^2, each compared to the previous year. We subsequently refer to participants who reached this endpoint as having rapid progression of kidney dysfunction, as previously published by D:A:D investigators[4]; we refer to those who did not reach this endpoint as participants without rapid progression. We used time-to-event analyses with follow-up from baseline until the year of the event, last eGFR, death, or interruption due to switch to RAL, DTG, BIC, or COBI, whichever occurred first. Results were presented as Kaplan-Meier failure plots and Cox proportional hazard regressions. Cox models were calculated with robust standard errors, allowing for clustering of participants who entered the analyses both before and after switching to RAL, DTG, BIC, or COBI. The main exposures of interest were the D:A:D CKD risk score[1], stratified into low, medium and high risk, and the quartiles of the polygenic risk score. Interactions between D:A:D CDK risk score and polygenic risk score were analysed using the likelihood-ratio test. As additional co-variables we included time-updated exposure to potentially nephrotoxic ART agents until the rapid progression date in participants with rapid progression and until the date of last follow-up in the SHCS in participants without rapid progression. We considered both cumulative exposure to ART agents associated with increased CKD incidence in the D:A:D study[14], and recent exposure, defined as treatment in the 6 months before the rapid progression date. We also performed a Kaplan-Meier analysis to document how rapid progression translates into confirmed CKD, defined as the 2nd of 2 consecutive eGFR values <60 mL/min/1.73m^2 [12]. Analyses were done with Stata/SE 16.1 (StataCorp, College Station, Texas).

Sensitivity Analyses. To ascertain the applicability of results to PWH with a wider range of baseline eGFR, we performed 3 separate sensitivity analyses: First, we included tertiles of baseline eGFR as additional variable in the models; second, we expanded inclusion to participants with baseline eGFR >70 mL/min/1.73m^2; and third, we restricted participants to those with baseline eGFR >90 mL/min/1.73m^2.

Exploratory genome-wide association analysis. In an exploratory GWAS, we tested all SNPs on the genetic arrays for association with rapid progression (**Supplementary Methods**).

RESULTS

Participants. We analyzed 3603 SHCS participants, including 225 participants with rapid progression and 3378 participants without rapid progression. 26 participants with rapid progression and 716 participants without rapid progression contributed twice to the analyses, i.e. during a first observation period without INSTI/COBI and a second observation period during INSTI/COBI exposure. All subsequent analyses are therefore based on 4345 observation periods (251 periods with an rapid progression event and 4094 periods without rapid progression). The participants' baseline characteristics are shown in **Table 1**. Among the participants with rapid progression, compared to those without rapid progression, there were fewer men, CD4+ and CD4+ nadir counts were lower, there were slightly more participants with HCV co-infection, diabetes, injection drug use, and there were fewer participants in the low risk D:A:D category. Participants with rapid progression had higher genetic risk than those without rapid progression, as indicated by participants with rapid progression being overrepresented in the 4th (most unfavorable) polygenic risk score quartile (**Figure 1**). As expected, at the baseline date of potential second observation periods, participants were older, eGFR was lower, and the prevalence of "high risk" D:A:D CKD risk scores was higher than at the baseline date of the first period.

Polygenic Risk Score. Following p-value thresholding, the final model included 14,769 independent SNPs after clumping, explaining 3.3% of the rapid progression variance among the study participants.

Probability of rapid progression **According to Clinical D:A:D CKD Risk Score, Polygenic Risk Score, and ART: Univariable Analysis.** rapid progression probability was significantly associated with D:A:D CKD risk score (test for trend, p=0.003) and polygenic risk score (test for trend, p<0.001) (**Figure 2**). Compared to the low risk D:A:D CKD risk score, participants with medium and high D:A:D risk had a rapid progression hazard ratio (rapid progression -HR) of 1.26 (95% CI, 0.96-1.65) and 1.75 (1.23-2.48), respectively. Compared to the first (most favorable) polygenic risk score quartile, participants in the second, third and fourth (most unfavorable) quartiles had rapid progression -HR of 1.35 (0.91-1.99), 1.46 (0.99-2.15) and 1.96 (1.36-2.83), respectively. There was no evidence for an association of cumulative exposure to TDF, ATV/r and LPV/r with rapid progression, with HR=1.15 (0.96-1.39), 1.02 (0.79-1.31) and 0.97 (0.76-1.24), respectively. Recent exposure to TDF was associated with rapid progression (HR=1.37; 1.06-1.77), but there was no evidence for an association of recent exposure to ATV/r and LPV/r with rapid progression (rapid progression -HR=1.36; 0.99-1.87, and 1.06; 0.71-1.59, respectively).

Probability of Rapid Progression According to Clinical D:A:D CKD Risk Score, Polygenic Risk Score, and ART: Multivariable Analyses. Rapid progression was associated with the D:A:D CKD risk score, polygenic risk score, and recent TDF exposure (**Figure 3**). Compared to participants with a low risk D:A:D CKD risk score, participants with a medium and high risk D:A:D CKD risk score had rapid progression -HR of 1.30 (0.99-1.71) and 1.82 (1.28-2.60), respectively. Compared to the first (most favorable) polygenic risk score quartile, participants in the second, third and fourth (most unfavorable) quartiles had rapid progression -HR=1.39 (0.94-2.06), 1.52 (1.04-2.24) and 2.04 (1.41-2.94), respectively. Recent exposure to TDF was associated with rapid progression, with HR=1.36 (1.06-1.76). There was no evidence for an association of recent exposure to ATV/r or LPV/r, with rapid progression-HR=1.30 (0.95-1.79) and 1.11 (0.73-1.67), respectively), and no evidence for an association of cumulative exposure to TDF, ATV/r, and LPV/r with rapid progression, with HR=1.12 (0.93-1.35), 0.96 (0.74-1.25) and 0.93 (0.74-1.67), respectively.

Rapid progression **Probability, Interaction of D:A:D CKD Risk Score and** Polygenic Risk Score**.** When we applied an interaction term between the D:A:D CKD risk score and polygenic risk score, the model fit did not improve. (**Supplementary Tables 1 and 2)**

Rapid progression **predicts CKD.** Of all 4345 observation periods analyzed, 99/251 (39.5%) with rapid progression and 475/4094 (11.6%) without rapid progression progressed to CKD, defined as confirmed eGFR<60 mL/min/1.73m^2. The 5-year and 10-year probability of CKD was 14% (10-19%) and 34% (28-41%), respectively, in participants with rapid progression, and 3% (2-3%) and 9% (8-11%), respectively, in participants without rapid progression. The time until 10% of participants with and without rapid progression experienced CKD was 4.1 (2.8-4.8) and 10.3 (9.9-10.8) years, respectively (**Figure 4**).

Sensitivity Analyses with different baseline eGFR in the models. In order to evaluate whether the polygenic risk score association with rapid progression applies to various levels of baseline kidney function, we redefined the study population as participants with baseline eGFR $\geq$70 mL/min/1.73m^2 (n=4700) and as participants with baseline eGFR $\geq$90 mL/min/1.73m^2 (n=3423), with similar results (**Supplementary Table 3**). In an additional sensitivity analysis, we separated the study population into 3 tertiles according to baseline eGFR. This led only to modest effect modification (**Supplementary Table 4**). Median (IQR) eGFR at baseline was 89 (80-95), 100 (95-106), and 113 (106-181) mL/min/1.73m^2, in the 3 tertiles, respectively. In multivariable analysis including tertiles of baseline eGFR, results remained essentially unchanged; participants in the 2nd, 3rd, and 4th polygenic risk score quartiles had rapid progression -HR=1.42 (0.96-2.11), 1.54 (1.04-2.27), and 2.05 (1.42-2.96), compared to the 1st quartile.

Exploratory GWAS. In the exploratory GWAS, we did not observe any genome-wide significant association. However, we were able to nominally replicate ($p<0.05$) 2 of the genome-wide significant SNPs that were reported to be genome-wide significant in the general population, each with $p=0.03$ and the same direction of the effect in this dataset and in the reference paper[11]: rs56019566 (chromosome 2; BP 15788692; p=1.08E-10 in[11]) and rs1111571 (chromosome 16, BP 68363181; p=6.20E-09 in[11]) (**Supplementary Figures 1-3**). This low number of replicated SNPs is as expected: All the previous genome-wide significant individual SNPs have very low effect sizes[11], thus replication cohorts with very large sample sizes would be required to capture their effect well.

DISCUSSION

Here we describe, for the first time to our knowledge, that an unfavorable polygenic risk score increases the probability of rapid progression of kidney dysfunction in PWH approximately 2-fold. This extends our previous result that a GWAS-derived polygenic risk score is associated with CKD in PWH [12]. We found a robust association of unfavorable polygenic risk score with rapid progression: The polygenic risk score effect persisted after adjusting for multiple clinical risk factors that are summarized in the well validated D:A:D CKD risk score, and after considering the effect of antiretroviral agents with nephrotoxic potential[1,14,18]. Because eGFR>80 mL/min/1.73m^2 at baseline is ultimately an arbitrary threshold, we also used different baseline eGFR definitions in sensitivity analyses: polygenic risk score remained associated with rapid progression in participants in all 3 tertiles of baseline eGFR, and also when we variably defined baseline kidney function as eGFR $\geq$70, $\geq$80, and $\geq$90 mL/min/1.73m^2, respectively. Our finding of a significant association of genetic background with rapid progression in PWH is consistent with recently reported results of a GWAS meta-analysis in the general population[11,19].

We exploited prospectively collected clinical, laboratory and HIV-related data of 3603 HIV+ participants of the well-established Swiss HIV Cohort Study, in order to quantify the effect size of

polygenic risk score, D:A:D CKD risk score and ART. We applied the stringent rapid progression definition proposed by the D:A:D study [4], i.e. an eGFR drop of ≥5 mL/min/1.73m^2 per year for ≥3 consecutive years. We show that, rather than representing only a subtle degree of kidney impairment, rapid progression increases the probability more than 2-fold of progressing to CKD. This underlines the clinical importance of also considering a more dynamic measure of kidney impairment (i.e. declines in kidney function that are sustained over several years) in addition to the more static CKD endpoints to evaluate kidney dysfunction risk in PWH[12].

We identified an approximately 2-fold increased rapid progression hazard ratio, both for genetic background (polygenic risk score) and for clinical D:A:D CKD risk score, and a 36% increased rapid progression hazard ratio for recent TDF exposure in multivariable analysis. The effect size of genetic background on rapid progression risk therefore appears larger than the effect size of potentially nephrotoxic ART. Alternatively, the dynamics of the different risk factors on the development of kidney impairment may differ. Potentially nephrotoxic ART and clinical CKD risk factors such as diabetes mellitus may cause a gradual loss of nephrons and therefore a slow decline of eGFR, with the nephrotoxic effect typically becoming apparent only after accumulating years of exposure. This slow loss of kidney function may not fulfill rapid progression criteria and may explain why we did not identify an association of cumulative exposure to TDF, ATV/r, and LPV with rapid progression, whereas cumulative ART was associated with CKD in our previous report[12]. This also echoes the findings of the Veterans Health Study, where cumulative TDF exposure had a smaller effect on rapid progression risk than on CKD risk[2]. In contrast, an unfavorable genetic background may become clinically apparent as a rapid kidney dysfunction progression pattern, i.e. rapid progression.

It was beyond the scope of our study to assess the clinical value of genetic testing (this will require prospective trials), nonetheless, our findings suggest how determination of an individual polygenic risk score might be applied in clinical HIV practice. The knowledge that an unfavorable genetic

background significantly increases rapid progression risk approx. 1.5-fold (3rd polygenic risk score quartile) and 2-fold (4th polygenic risk score quartile), respectively, may suggest paying particular attention to optimal control of hypertension and diabetes, and to avoiding potentially nephrotoxic medication, including TDF and nonsteroidal anti-inflammatory agents. On the other hand, one might speculate that a favorable genetic background might argue against reflexive switching of all PWH from TDF to less nephrotoxic tenofovir alafenamide (TAF), providing an argument in addition to the emerging metabolic toxicities of TAF (obesity, dyslipidemia[20]), and in addition to the efficacy of dolutegravir-lamivudine-containing dual ART combinations that is now well recorded[21,22]. In addition to clinical kidney disease prediction, our results may inform future research. For example, detailed pathway analyses based on genetic information may provide additional pathogenic insights into rapid progression, and applying polygenic risk scores may inform the selection of PLW at increased risk for attaining appropriate endpoints in clinical trials.

In our previous CKD-GWAS study in Swiss PWH [12], we excluded INSTI-treated participants in the main analysis, in order to separate true longitudinal GFR decline from the well recorded INSTI effects on estimated GFR[16,17]. In the present study, we included episodes of INSTI-treatment by re-calculating a "new baseline" eGFR for each participant after starting INSTI therapy. This is important because rapid progression prediction by determination of an individual polygenic risk score appears broadly applicable also to modern INSTI-based ART. Longitudinal modeling through episodes of switching ART, as shown in our previous genetic-dyslipidemia studies [23-25], represents a powerful approach to quantifying the individual contribution of multiple intervening factors of relevance to eGFR. Other strengths of our study are that we restricted all analyses to gene variants based on GWAS, and that we restricted eGFR assessments to the per-protocol semi-annual measurements of kidney function at routine SHCS patient visits, in order to avoid confounding by intercurrent illness and its treatment. Our study also has limitations. We included only participants of European descent, because most GWAS of kidney disease have been conducted in populations of European

descent[9-11]. It is important to note, however, that previous genetic studies of CKD in PLW of African ancestry have solidly established *APOL1* gene variants as risk factors for HIV-associated nephropathy and other types of kidney disease[26,27]**.** Our population was 81% male and, with a median baseline age of 42 years, was relatively young. Thus, our results should only cautiously be extrapolated to elderly PWH. Also, we did not analyze any genetic associations with proteinuria, suggesting an important area of future research in PWH.

In conclusion, some PWH experience rapidly deteriorating kidney dysfunction and our analyses reveal an independent contribution of an individual polygenic risk score to explaining interindividual variation in rapid progression. We extend our previous observation that genetic background associates with CKD risk [12] and highlight the importance of longitudinal study design, in order to quantify the effect size of polygenic risk score on rapid progression, in the context of multiple shifting environmental risk factors, most notably clinical D:A:D CKD risk score and potentially nephrotoxic antiretroviral exposures.

NOTES

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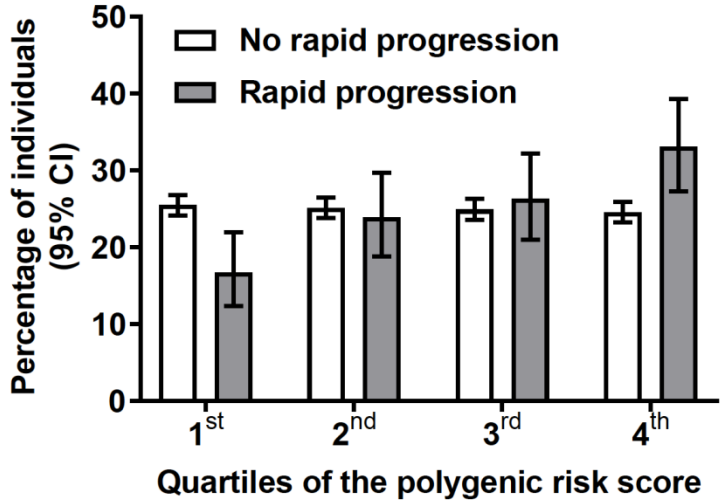
Table 1. Baseline Characteristics of 3603 Study Participants with and without Rapid Progression of Kidney Dysfunction.

Characteristic	Participants with rapid progression; first observation period (n=225)	Participants with rapid progression; second observation period (INSTI/ COBI) (n=26)	Participants without rapid progression; first observation period (n=3378)	Participants without rapid progression; second observation period (INSTI/ COBI) (n=716)
Male sex	171 (76)	16 (62)	2757 (82)	587 (82)
Age, years, median (IQR)	42 (37-50)	50 (45-53)	42 (37-48)	49 (44-54)
Baseline eGFR, mL/min/1.73m^2, median (IQR)	101 (93-111)	95 (88-102)	101 (93-110)	95 (88-102)
Baseline date, median (IQR)	26.5.2005 (20.10.2004-10.10.2007)	16.6.2013 (21.5.2012-25.6.2015)	30.7.2005 (28.10.2004-7.5.2008)	9.1.2016 (22.5.2013-21.3.2017)
Observation time, years, median (IQR)	10 (8-13)	6 (4-7)	10 (6-12)	4 (2.5-6)
Presumed mode of HIV transmission				
Heterosexual	75 (33)		928 (27)	
MSM	96 (43)		1676 (50)	
IDU	50 (22)		650 (19)	
other	4 (2)		124 (4)	
Duration of ATV/r treatment, years, median (IQR)				
All participants	0 (0-1.6)	0 (0-0.67)	0 (0-1.5)	0 (0-2.27)
Ever exposed	2.3 (0.9-4.3)	3.5 (1.4-6.8)	4.0 (1.4-7.4)	3.9 (1.4-7)
Duration of LPV/r treatment, years, median (IQR)				
All participants	0 (0-1.5)	0 (0-1.10)	0 (0-1.3)	0 (0-2)
Ever exposed	2.7 (1.1-4.8)	2.4 (0.7-4.1)	2.7 (0.9-6.3)	2.6 (1-6.2)
Duration of TDF treatment, years, median (IQR)				
All participants	3.5 (1.7-6.0)	5.8 (1.9-8.3)	5.5 (1.2-8.7)	6.2 (2.8-9)
Ever exposed	3.9 (2.4-6.4)	6.7 (3.9-8.8)	6.7 (3.7-9.4)	7 (4.7-9.7)
CD4+ count, cells/µL, median (IQR)	436 (291-580)	425 (320-1026)	429 (295-594)	654 (483-842)
CD4+ count nadir, cells/µL, median (IQR)	200 (89-327)	142 (54-233)	200 (70-333)	177 (60-278)
Hepatitis C co-infection	71 (32)	9 (35)	998 (30)	215 (30)
Current[a] smoking	126 (56)	16 (62)	1979 (59)	410 (57)
Hypertension	37 (16)	10 (38)	587 (17)	234 (33)
Prior cardiovascular disease	6 (3)	2 (8)	87 (3)	56 (8)

Diabetes mellitus	11 (5)	9 (35)	97 (3)	38 (5)
D:A:D CKD Risk Score				
Low risk	119 (53)	4 (15)	1926 (57)	242 (34)
Medium risk	74 (33)	12 (46)	1071 (32)	282 (39)
High risk	32 (14)	10 (38)	381 (11)	192 (27)

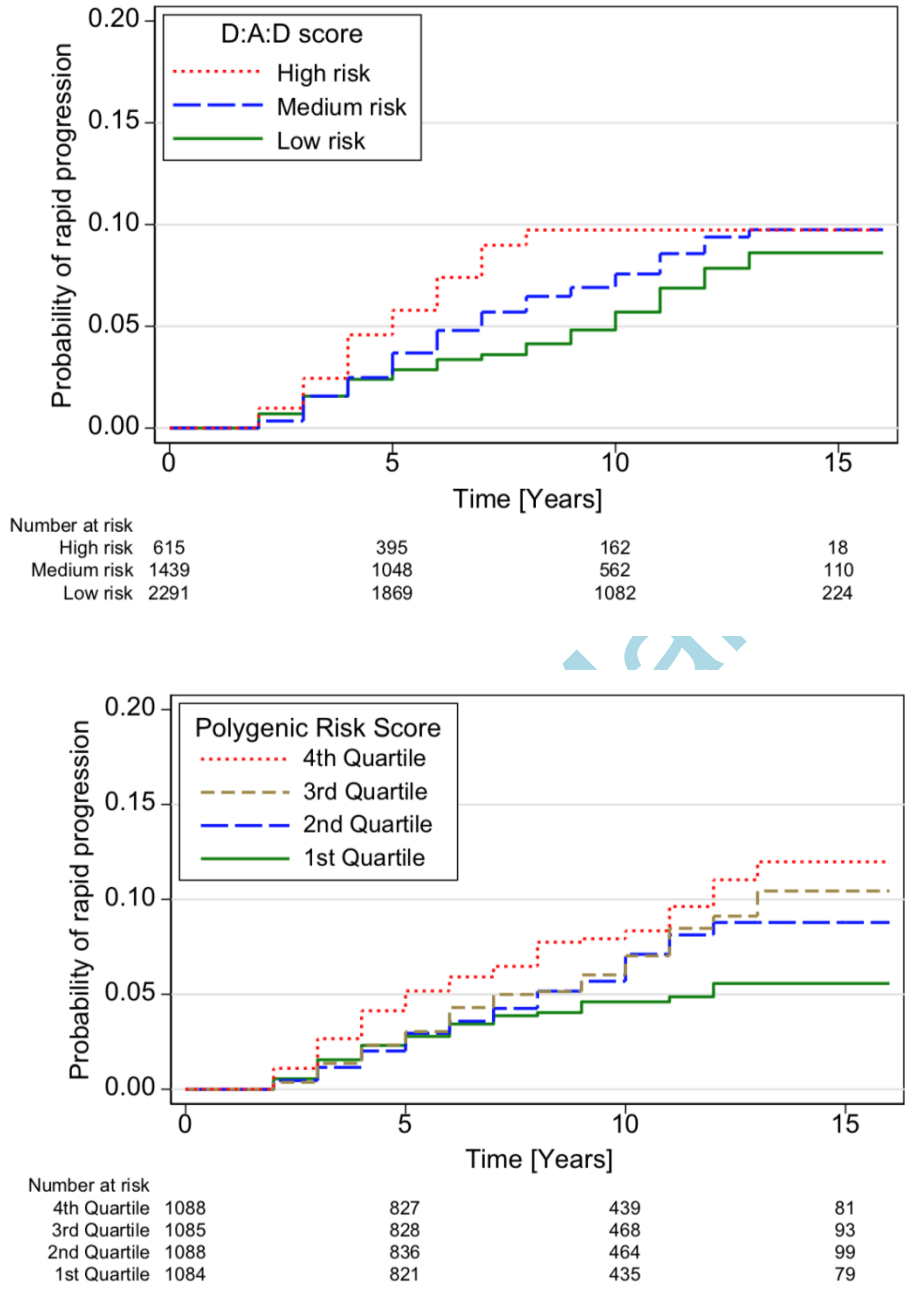
Note. Characteristics are shown at baseline dates of first and second observation period, respectively, unless otherwise indicated. Data are presented as no. (%) of participants unless otherwise indicated. [a] at baseline +/- 1 year. **Abbreviations**. ATV/r, atazanavir/ritonavir; CKD, chronic kidney disease; COBI, cobicistat; eGFR, estimated glomerular filtration rate; IDU, injection drug use; INSTI, integrase-inhibitor containing antiretroviral therapy; IQR, interquartile range; LPV/r, lopinavir/ritonavir; MSM, men who have sex with men; NA, not applicable; TDF, tenofovir disoproxil fumarate.

Figure 1. Distribution of Polygenic Risk Score in 3378 Participants without Rapid Progression (*white bars*) and in 225 Participants with Rapid Progression of Kidney Dysfunction (*black bars*)



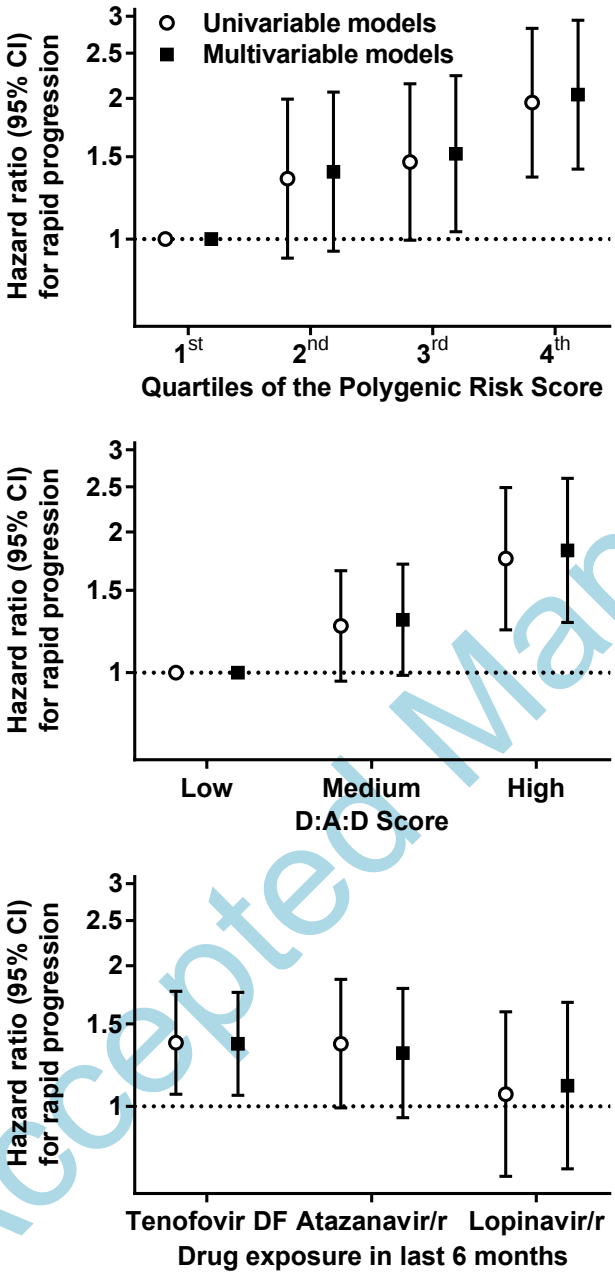
We divided study participants into 4 quartiles according to their individual polygenic risk score and show here the percentage and 95% confidence intervals of participants in each quartile. Among all 3603 participants, 898 (24.9%), 898 (24.9%), 901 (25%), and 906 (25.2%) were in the 1st (most favorable), 2nd, 3rd, and 4th (most unfavorable) polygenic risk score quartile, respectively. Among the 3378 participants without rapid progression, 859 (25.4%), 844 (25%), 842 (24.9%), and 833 (24.7%) were in the 1st, 2nd, 3rd, and 4th polygenic risk score quartile, respectively. Among the 225 participants with rapid progression, 39 (17.3%), 54 (24%), 59 (26.2%), and 73 (32.4%) were in the 1st, 2nd, 3rd, and 4th polygenic risk score quartile, respectively.

Figure 2. Kaplan-Meier Failure Curves showing the Probabilities of Rapid Progression of Kidney Dysfunction according to D:A:D CKD Risk Score (first panel) and Polygenic Risk Score (second panel).



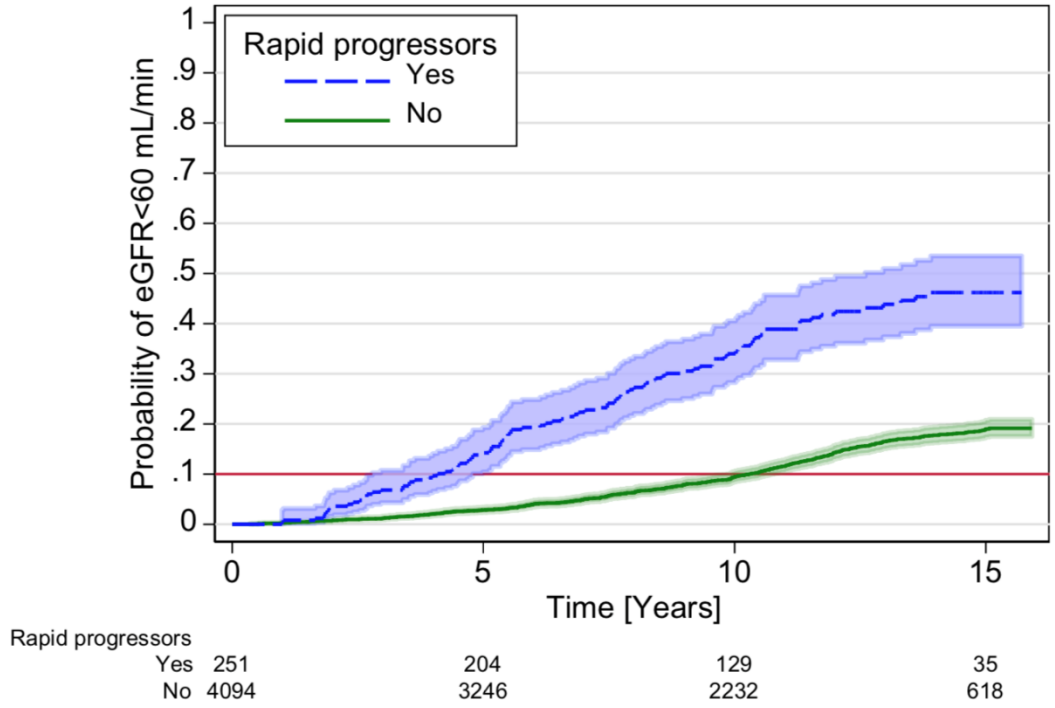
Kaplan-Meier Failure Curves showing the Probabilities of Rapid Progression of Kidney Dysfunction according to D:A:D CKD Risk Score (first panel) and Polygenic Risk Score (second panel). Test for trend for the D:A:D CKD risk score, p=0.003; test for trend across the quartiles of the Polygenic Risk Score, p<0.001.

Figure 3. Probability of Rapid Progression of Kidney Dysfunction According to Polygenic Risk Score, Clinical D:A:D CKD Risk Score, and ART.



Results are represented as the estimated effect and 95% confidence interval on the hazard ratio and 95% confidence interval for rapid progression of kidney dysfunction in univariable (white circles) and multivariable (black boxes) cox proportional hazard regression models, adjusted for all variables displayed, i.e. for polygenic risk score, D:A:D CKD risk score, and antiretroviral drug exposures, respectively.

Figure 4. Kaplan-Meier Failure Curve from Baseline to CKD or last eGFR Determination (whichever occurred first).



Kaplan-Meier Failure Curves from Baseline to CKD or last eGFR Determination (whichever occurred first), stratified by whether Participants had Rapid Progression or not. The shaded areas denote the 95% Confidence Intervals. The numbers below the x-axis represents the number of participants at risk.