Rigshospitalet

**Doctoral Dissertation**

# *Comorbidities And Adverse Drug Effects In People Living with HIV*

# *In A Modern Treatment Era: Risk Factors and Prognosis*

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**This dissertation is based on the following papers**

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4. **Use of Contemporary Protease Inhibitors and Risk of Incident Chronic Kidney Disease in Persons With Human Immunodeficiency Virus: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study**
   *Ryom L*, Lundgren JD, Reiss P, Kirk O, Law M, Ross M, Morlat P, Andreas Fux C, Fontas E, De Wit S, D' Arminio Monforte A, El-Sadr W, Phillips A, Hatleberg CI, Sabin C, Mocroft A; Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. J Infect Dis. 2019 Oct 8;220(10):1629-1634. PMID: 31504669
5. **Predictors of estimated glomerular filtration rate progression, stabilization or improvement after chronic renal impairment in HIV-positive individuals**
   *Ryom L*, Mocroft A, Kirk O, Reiss P, Ross M, Smith C, Moranne O, Morlat P, Fux CA, Sabin C, Phillips A, Law M, Lundgren JD; D:A:D study group.
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6. **Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D study**
   Mocroft A, Lundgren JD, Ross M, Law M, Reiss P, Kirk O, Smith C, Wentworth D, Neuhaus J, Fux CA, Moranne O, Morlat P, Johnson MA and *Ryom L;* D:A:D study group; Royal Free Hospital Clinic Cohort; INSIGHT study group; SMART study group; ESPRIT study group.
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7. **Serious clinical events in HIV-positive persons with chronic kidney disease**
   *Ryom L*, Lundgren JD, Law M, Kirk O, El-Sadr W, Bonnet F, Weber R, Fontas E, Monforte AD, Phillips A, Reiss P, de Wit S, Hatleberg CI, Sabin C, Mocroft A; D:A:D study group.
   AIDS. 2019 Nov 15;33(14):2173-2188. PMID: 31385862
8. **Renal Impairment and Cardiovascular Disease in HIV-Positive Individuals: The D:A:D Study**
   *Ryom L*, Lundgren JD, Ross M, Kirk O, Law M, Morlat P, Fontas E, Smit C, Fux CA, Hatleberg CI, de Wit S, Sabin CA, Mocroft A; D:A:D Study Group.
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9. **Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study**
   *Ryom L*, Lundgren JD, El-Sadr W, Reiss P, Kirk O, Law M, Phillips A, Weber R, Fontas E, D' Arminio Monforte A, De Wit S, Dabis F, Hatleberg CI, Sabin C, Mocroft A; D:A:D study group.
   Lancet HIV. 2018 Jun;5(6):e291-e300.Epub 2018 May 3. PMID: 29731407

10. **Use of antiretroviral therapy and risk of end-stage liver disease and hepatocellular carcinoma in HIV-positive persons**
    *Ryom L*, Lundgren JD, De Wit S, Kovari H, Reiss P, Law M, El-Sadr W, Monforte AD, Mocroft A, Smith C, Fontas E, Dabis F, Phillips A, Sabin C; D:A:D Study Group.
    AIDS. 2016 Jul 17;30(11):1731-43. PMID: 26752282

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**Abbreviations**

ABC: abacavir

ACTG: AIDS Clinical Trial Group

ADM: AIDS defining malignancy

AIDS: acquired Immunodeficiency syndrome

ART: antiretroviral treatment

ARV: antiretroviral agent

ATV: atazanavir

ATV/r: atazanavir boosted with ritonavir

CKD: chronic kidney disease

CG: Cockcroft-Gault

COBI: cobicistat

COBRA: COmorBidity in Relation to AIDS

COCOMO: The Copenhagen comorbidity in HIV-infection study

COHERE: Collaboration of Observational HIV Epidemiological Research Europe study

CVD: cardiovascular disease

D:A:D: Data collection on Adverse events of Anti-HIV Drugs

ddI: didanosine

d4t: stavudine

DRV: darunavir

DRV/r: darunavir boosted with ritonavir

EACS: European AIDS Clinical Society

EEA: European Economic Area

ECDC: European Center for Disease Control

EMA: European Medicines Agency

eGFR: estimated glomerular filtration rate

ESLD: end-stage liver disease

ESRD: end-stage renal disease

ESPRIT: Evaluation of Subcutaneous Proleukin® in a Randomised International Trial

EU: European Union

FDA: Food and Drug Administration

HIV: Human Immunodeficiency Virus

HBV: Viral hepatitis B

HCC: hepatocellular carcinoma

HCV: Viral hepatitis C

INSIGHT: International Network for Strategic Initiatives in Global HIV Trials

INSTI: integrase strand transfer inhibitor

IR: incidence rate

IRR: incidence rate ratio

IQR: interquartile range

KDOQI: Kidney Disease Outcomes Quality Initiative

KDIGO: Kidney Disease Improving Global Outcomes

KP: Kaiser Permanente

LPV: lopinavir

LPV/r: lopinavir boosted with ritonavir

MI: myocardial infarction

MSM: Men having sex with men

NADM: Non-AIDS defining malignancy

NNRTI: non-nucleoside reverse transcriptase inhibitor

NNTH: numbers needed to treat to harm

NRTIs: nucleos(t)ide reverse transcriptase inhibitor

OI: opportunistic infection

PLWH: people living with HIV

PI: protease inhibitor

PI/b: boosted protease inhibitor

PI/c: cobicistat boosted protease inhibitor

PI/r: ritonavir boosted protease inhibitor

POPPY: Pharmacokinetic and clinical Observation in PeoPle over fiftY

PYFU: person years of follow-up

RCT: randomized clinical trial

RFHCS: Royal Free HIV Cohort study

SHCS: Swiss HIV Cohort study

SILCAT: Subcutaneous Recombinant, Human Interleukin-2 in HIV-infected Patients with Low CD4+ Counts Under Active Antiretroviral Therapy

SMART: Strategies for Management of Antiretroviral Therapy

START: Strategic Timing of Antiretroviral Treatment

TAF: tenofovir alafenamide

TDF: Tenofovir disoproxil fumarate

US: United States

VA study: Veterans Affair Study

VL: viral load

WHO: World Health Organisation

ZDV: zidovudine

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**Introduction**

By 2019 the European Center for Disease Control (*ECDC*) and the European Regional Office of World Health Organization (*WHO*) estimated that more than 140.000 persons, corresponding to 16 per 100.000 persons, tested positive for HIV in the *WHO* European Region (53 countries) with an increasing incidence of 22% over the last decade [1]. Within the European Union (EU)/European Economic Area (*EEA*) (31 countries) the incidence is considerately lower with approximately 6 HIV-positive diagnoses per 100.000 persons, and a 17% decrease in incidence over the last decade [1]. The inter-regional diversity in Europe is also reflected in the reported HIV acquisition routes; in the Western and Central Europe almost half of those acquiring HIV were men-having-sex-with-men (MSM), while this was reported for only 5% of those in the Eastern Europe where the epidemic is driven by heterosexual contact and injecting drug use[1]. The male to female ratio of those diagnosed with HIV is 3 to 1, and more than half of those diagnosed were at a late disease stage (CD4 count <350 cells/µL) [1]. On the global scale almost 38 million persons are estimated to currently be living with HIV of which 79% are aware of their status, 62% are on antiretroviral treatment (ART) and 53% are virologically suppressed [2]. The clinical management of people living with HIV (PLWH) has undergone dramatic changes over the past four decades [3-6]. In the early years of the 1980's epidemic HIV care was centralised around symptomatic treatment with high rates of AIDS-related morbidity and mortality [7]. The nucleoside analogue azidothymidine (AZT) was, as the first antiretroviral agent (ARV) for HIV, fast-track approved in 1987 based on lower risk of mortality and opportunistic diseases among those using the drug vs. placebo [8]. Numerous ARVs from several different drug classes followed consecutively, but it soon became apparent that ARV monotherapy gave rise to resistance mutations and in turn virological failure [9-12]. By 1996 use of combination antiretroviral treatment (cART), which included three ARVs from two different drug classes, proved able to control HIV viremia and restore immune function on the longer term [12-15]. The early ARVs such as AZT, didanosine (ddI) and stavudine (d4t) carried a relatively high risk of adverse drug effects including severe anemia, hyperlactatemia, lipoatrophy and peripheral neuropathy, however the need for effective treatment and the limited number of alternatives greatly outweighed such detrimental effects [5]. Towards the end of the 1990'ties access to a broader palate of ARVs, more effective ARVs, implementation of cART and better means to monitor HIV viral load (VL) initiated a new era in HIV management where the improvement in survival led to increased focus on ART tolerability, but also revealed higher than expected rates of several non-AIDS events including renal, cardiovascular and liver diseases [16-20]. It was also in that era that the *Data collection on Adverse events of Anti-HIV Drugs* (*D:A:D*) study was founded, the study upon which all of the papers of this dissertation are based [21]. This large cohort collaboration was established in 1999 based on a request by the European Medicines Agency (*EMA*) to study potential associations between use of ARVs and cardiovascular disease (CVD) [21]. During the extent

of the prospective study follow-up (1999-2016) the focus expanded to include systematic pharmacovigilance of all ARVs and several organ diseases using both centrally validated clinical events and laboratory defined markers of specific organ impairment. The current wide range of available ARVs exceeds more than 30 options in high-income countries and has enabled a greater focus on adverse drug effects to better tailor ART to fit the individual risk profile and long term needs of PLWH as discussed in more detail in chapter 3 [6]. Systematic post-marketing studies of longer-term outcomes of ART using observational data have proven key for HIV care as the randomized clinical trials (RCT) have intrinsic imitations related to the often-limited study size, relatively short follow-up time and inclusion of highly selected study populations. As such, observational studies have reported drug associations that were not expected based on findings of the registrational RCTs, and have generated hypotheses for confirmation in other studies and for conducting of mechanistic studies to study biological plausibility [22, 23]. Despite large sizes, substantial heterogenicity and the ability to adjust for a large number of potential confounders observational studies including *D:A:D* hold major intrinsic limitations in terms of different types of bias, confounding by indication and unmeasured confounders. Great caution is therefore required when designing and interpreting the findings of any observational study in terms of causal inference. The Bradford Hill criteria for causality have been routinely considered in *D:A:D* when interpreting the study findings [24].

**Table 1, Bradford Hill Criteria, adapted from** [24]

| | |
|---|---|
| Strength | Strength of association and imprecision in effect estimate |
| Consistency | Consistency across studies, ie, across different situations (different researchers) |
| Temporality | Study design, specific study limitations; RCTs fulfil this criterion better than observational studies, properly designed and conducted observational studies |
| Biological gradient | Dose—response gradient |
| Specificity | Indirectness |
| Biological plausibility | Indirectness |
| Coherence | Indirectness |
| Experiment | Study design, randomisation, properly designed and conducted observational studies |
| Analogy | Existing association for critical outcomes will lead to not downgrading the quality, indirectness |

The comorbidities and adverse drug effects studied in this dissertation are some of the organ diseases associated with greatest morbidity and mortality in PLWH; chronic kidney disease (CKD), atherosclerotic CVD, end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC). The ten chapters of this dissertation include a description of the overall aims for the included work (chapter 1), an overview of the main applied methods (chapter 2), an introduction to the key principles of modern HIV care and adverse

effect of ART (chapter 3), a short introduction to comorbidities in PLWH (chapter 4) followed by an in depth discussion of the findings of the specific papers related to CKD, atherosclerotic CVD and ESLD/HCC (chapters 5-7). In chapter 8 management considerations for CKD, atherosclerotic CVD and terminal liver failure are discussed, while the final chapters discuss the limitations of the current data and analyses (chapter 9), conclude and provide perspectives (chapter 10) for the future-ART era in terms of HIV management and pending research questions.

**Chapter 1 Aims**

The overarching aim of all analysis of the *D:A:D* study, including all studies of this dissertation, is to improve insights into the pathogenesis and risk factors for non-AIDS morbidity and to systematically monitor drug safety of ART in order to ultimately improve clinical management of PLWH.

The studies of my 2013 Ph.D. thesis focused on renal impairment in PLWH exclusively (see details in chapter 5) [25]. As power in the *D:A:D* study increased, and our understanding of CKD improved we were able to expand our research agenda with studies investigating adverse renal outcomes related to more extended use of ART (papers 3-4) and impact of ART discontinuation (paper 5). We also developed a more detailed overview of the CKD risk profile in PLWH (papers 1,2 and 6) and of CKD related outcomes (papers 5, 7-8). We were further able to investigate the impact of use of more contemporary individual ARVs (papers 4 and 9) and to assess entirely new key organ diseases with pertinent and unmet reach needs such as predictors for atherosclerotic CVD in contemporary treated PLWH (papers 8 and 9) and for terminal liver impairment (paper 10). All questions that require a large and heterogenous dataset such as D:A:D.

More specifically the individual studies of this dissertation aimed to

- Explore associations between immune suppression and CKD in PLWH (papers 1 and 2)
- Determine if the association between use of individual ARVs with nephrotoxic potentials and incident CKD is cumulative in nature (paper 3)
- Assess if use of newer PIs is associated with increased incidence of CKD (paper 4)
- Investigate if the increased CKD risk related to use of ARVs with nephrotoxic potentials is reversable upon discontinuation (paper 5)
- Develop a clinical risk score for CKD prediction in PLWH (paper 6)
- Evaluate risks of serious clinical events following CKD in PLWH (paper 7)
- Investigate the relation between renal impairment and incident atherosclerotic CVD in PLWH (paper 8)
- Assess if use of newer PIs is associated with increased incidence of atherosclerotic CVD events similar to first generation PIs (paper 9)
- Establish the incidence, associated risk factors and prognosis of ESLD and HCC in PLWH (paper 10)

## Chapter 2 Main Applied Methods

This chapter will provide a brief overview of the study population included in the dissertation manuscripts and the considerations behind the applied analytical methods, further methodological details of the *D:A:D* study were summarised in my 2013 Ph.D. thesis [25].

*Study population and endpoints*

The *D:A:D* study was a prospective cohort collaboration following more than 49,000 HIV-1-positive persons in 212 clinics in Europe, the United States and Australia in the period 1999-2016 [21].

In many countries reporting on potential adverse drug effects are based on the volunteered reporting by the treating physicians- a system prone to underreporting and lack of systematism. The *D:A:D* study used rigorously defined clinical endpoints collected in real time during routine clinical care blind to the ART regimen used. These included end-stage renal (ESRD), ESLD, cancers (AIDS and Non-AIDS defining malignancies (ADM and DM), myocardial infarction (MI), stroke, invasive cardiovascular procedures (ICP), diabetes (DM) and death. All events were validated using study specific algorithms by a trained medical doctor, discussed with external experts blinded to the ART regimen provided and monitored for completeness and to limit risks of underreporting. A relatively conservative approach to the endpoint definitions were applied to ensure as clean clinical data as possible. This meant that milder cases of disease were not accepted e.g. for ischemic heart disease incidences of unstable angina were not accepted nor were type II MIs. Likewise, ascites was not accepted as part of the ESLD definition unless it could be verified that it was not caused be extra-hepatic causes and the patient had cirrhosis. As a consequence, the incidence rates reported in *D:A:D* have been considerately lower than in other studies [26].

In 2002 a prognostic staging for CKD was suggested from the US *National Kidney Foundation's Kidney disease outcomes quality initiative* (*KDOQI*) [27]. The definition has been widely implemented internationally and undergone several adaptions with the last classification being from 2012 from the *Kidney Disease Improving Global Outcomes* (*KDIGO*) describing five CKD stages based on confirmed, more than three months apart, eGFR levels under the threshold value, and three levels of proteinuria, Figure 1 [28, 29].

**Figure 1, CKD classification as per the 2012 KDIGO Guidelines [28]**

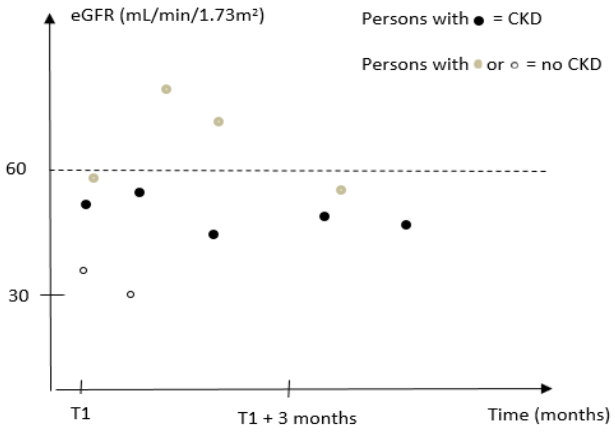
| GFR categories (ml/min/ 1.73 m²) Description and range | | | | Persistent albuminuria categories Description and range | | |
|---|---|---|---|---|---|---|
| | | | | A1 | A2 | A3 |
| | | | | Normal to mildly increased | Moderately increased | Severely increased |
| | | | | <30 mg/g <3 mg/mmol | 30–300 mg/g 3–30 mg/mmol | >300 mg/g >30 mg/mmol |
| | G1 | Normal or high | ≥90 | | Monitor | Refer* |
| | G2 | Mildly decreased | 60–89 | | Monitor | Refer* |
| | G3a | Mildly to moderately decreased | 45–59 | Monitor | Monitor | Refer |
| | G3b | Moderately to severely decreased | 30–44 | Monitor | Monitor | Refer |
| | G4 | Severely decreased | 15–29 | Refer* | Refer* | Refer |
| | G5 | Kidney failure | <15 | Refer | Refer | Refer |

A recent call have suggested to further subdivide these categories according to age, to better capture the normal related decline in renal function [30].

When using the term "CKD" in this dissertation it will generally refer to moderate CKD (CKD stage G3), unless anything else is stated. In some of our paper (SCE after CKD) we expanded the KDIGO definition according to the *International Network for Strategic Initiatives in Global HIV trials (INSIGHT*) CKD definition including a 25% decline confirmed (≥3 months apart) in eGFR if baseline eGFR ≤60 mL/min/1.73m$^2$ [31].

If an individual had more than one eGFR measurements within a given month, the median value of all measurements in that calendar month were used and assigned to the mean date of measurement. The confirmed definition required that individuals did not have any measurements >60 mL/min/1.73m$^2$ during the min. 3 months follow-up period (i.e. if someone had an eGFR ≤60 mL/min/1.73m$^2$ and then 1 month after eGFR >60 mL/min/1.73m$^2$ and one months later eGFR ≤60 mL/min/1.73m$^2$, the person would be not be considered to have CKD in that period, Figure 2, but could fulfill the criteria later if they then had a period of 3 months or more where all eGFRs ≤60 mL/min/1.73m$^2$). We used the *Cockcroft-Galt (CG)* equation as a surrogate for eGFR, as several cohorts in *D:A:D* are prohibited from reporting ethnic origin. The CG is recommended for calculating drug dosing, and the possible limitations of the equation were discussed extensively in my Ph.D. dissertation, but importantly sensitivity analyses in *D:A:D* and *EuroSIDA* have showed using the *CG* and *Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)* equations provides similar results [25, 32].

**Figure 2, Examples of Persons Fulfilling or not Fulling the CKD Definition Within a Given Time period**




In addition to the endpoint the study collected additional data electronically at enrolment and every six months. This included details on demographics, mode of HIV transmission, key HIV-related variables, viral hepatitis status, ART history, laboratory test results (including creatinine, transaminases, bilirubin and lipids), use of other drugs (i.e. antihypertensives and lipid lowering drugs), cardiovascular risk factors (such as family history, prior cardiovascular disease, body weight and hypertension), tobacco use, and AIDS events. For further details see the study manual of operations (https://www.chip.dk/Portals/0/files/Study%20documents/DAD_MOOP_revised2013.pdf). All data underwent extensive data quality assurance including external monitoring for completeness. The prospective data collection, large size and heterogeneity of the study are am unique feature of the study and ensured a high level of internal and external validity.

At the last data collection in 2016 the *D:A:D* study population was 74% male, 51% Caucasian with 44%, 33% and 15% reporting having acquired HIV by MSM, heterosexually or by injecting drug use (IDU) respectively. The median age at time of inclusion was 39 years (interquartile range, IQR, 33-46), 22% had an AIDS condition and 18% and 5% were HCV and HBV co-infected respectively. During >450.000 person-years of follow-up (PYFU) a total of 5,372 deaths, 1,191 MIs (of which 16% were fatal), and 432 ESLD/HCC accumulated. The incidence of CKD was close to 1%.

To validate a prediction model, it is recommended to use at least one external validation cohort. An alternative to external validation is to do bootstrap validation, in which the cohort data in split in two and use one part as the derivation cohorts and the other half as the validation cohort, this approach was done for the *D:A:D* CVD model [33]. In paper 6 we used data from the control arms of *the* Evaluation of

Subcutaneous Proleukin® in a Randomised International Trial *(ESPRIT)* and Strategies for Management of Antiretroviral Therapy (*SMART*) RCTs and the Royal Free HIV cohort study *(RFHCH)* to validate the *D:A:D* derived 5-years CKD prediction score [34].

*Statistical methods and responsibilities*

All statistical analyses included in this dissertation were approved by the D:A:D Steering Committee and performed by a team of extensively experienced statisticians/epidemiologists at University College London (*UCL*) based on pre-defined plans of analyses developed by the writing group and lead by the first and last author of the manuscript.

To account for the longitudinal data collection and that individuals in the study were not followed for the same periods of time we used predominately survival analyses and Poisson Regression models to assess associations between possible predictors including drug use and clinical outcomes, as this model deals well with rare outcomes in large studies.

In one analysis we compared three different eGFR outcomes (improvement, stabilisation and progression) at a specific point of time (24-36 months after CRI), and therefore used an ordinal logistic regression (paper 5) [35]. This model assumes that any change in odds comparing stable to progressive eGFR is the same as the change in odds comparing improved to stable eGFR (proportional odds assumption), and we confirmed in a sensitivity analysis that this assumption was reasonable.

*Fitting of ARV use*

ARV exposures were modelled based on the presumed mechanistics. More specifically all drug relations were evaluated based on existing literature and by evaluating incidence rates (IR) per 1000 PYFU stratified by time on the drug in raw unadjusted analyses. As such ARV exposure was fitted as a continuous variable (cumulative, per additional year of use) when it was considered plausible that a drug effect increased gradually (linearly) with longer exposures. If there was no evidence suggesting that a drug relation was gradually increasing, and instead mimicked a current (on/off) effect; depending on ongoing use of the drug without continuation of an increased IR after the exposure ends [22], ARV exposure was fitted categorically; never used, recently used (currently on or on <6 months), prior use (on >6 months ago) with time since cessation to allow for a wash out period. Further, if there was no indication that the drug effect would last after exposure ends only the follow-up time spend on the drugs was calculated as exposure. Alternatively, if there were indications than an effect would remain even after discontinuation the follow-up time on the drug would continue even after the use ended (with calculation of time since cessation, see below).

Follow-up time for each participant was divided into consecutive one-week periods with assessment of ART status at the beginning of each of these time periods. I.e. before starting a specific ARV, the exposure time and time since stopping the drug were zero. If a person then starts using the ARV, the follow-up time spend on that drug would start to accrue at the beginning of the following week and continue to accrue until the drug was discontinued. If the drug was later restarted the additional time spend on the drug would be added to the time that had already accrued earlier. In some of the analyses (i.e. papers 5 and 10) we were particularly interested in the reversibility potential of the shown ARV-associations, and investigated IRs with time since stopping the ARV, which accumulated each week the person remained off the drug, but was set back to zero if the ARV was subsequently restarted.
Further, all ARV exposures were considered, regardless of when they had accrued– thus, individuals may already have accrued several years of exposure to some of the ARVs prior to baseline (baseline differs according to the endpoints studied); but continued to accrue after baseline if the individuals continued to receive the drugs.

*Fitting of potential confounders and model building*
For all analyses it was a priori decided which key variables to consider.
Variables were generally fitted at baseline if they were unlikely to change during follow-up (i.e. gender and ethnicity) or if there were concerns about adjusting for factors on the potential causal pathway (i.e. CD4 count or dyslipidemia) between the exposure variable (i.e. ARV use) and the outcome variable (i.e. CKD or CVD). Variables subjected to change over time (i.e. age), and not considered to lie on the causal pathway between the exposure variable of interest and the outcome, were generally fitted as time-updated variables. For the prediction model (paper 6) we used baseline values to obtain a longer-term prediction model.
Model fit was assed comparing the Akaike information criterion (AIC) between models (with low values indicating a better fit), and by adding/removing possible confounders to determine how this impacted on the model fit.

In paper 7 we also calculated the population attributable risk fraction (PAF) for the key risk factors. PAF expresses the proportion of events that would not have occurred had that risk factor not been present and considers both the strengths of the associations and the incidence rate of the risk factor. Whilst we found this additional data gives a good impression of where to target future interventions calculating PAFs based on the effect sizes in multivariate analysis have; however, been criticised for not accounting for any potential correlations of the considered risk factors [45].

Due to the rigorous data collection process the annual loss to follow-up rates in *D:A:D* were less than 3%. Some data in *D:A:D* is missing non-randomly due to local restrictions (i.e. information on ethnicity) whilst others were missing randomly (i.e. incomplete records on hypertension, smoking and HCV status). Missing data was managed in several ways in the analyses including creation of unknown categories (i.e. for ethnicity) and by doing imputations (predominantly multiple imputations and in some instances last value carried forward if there were limited variability over time). In some analysis we also excluded those without key data available i.e. data on creatinine, VL or CD4 count but ensured a characterization of those excluded to assess the risk of selection bias.

The CKD risk prediction model (paper 6) was built in two steps; first step included development of a non-ARV prediction model and the second step addressed the added impact of starting ARVs with nephrotoxic potentials depending on the risk profile. We included prior identified demographic, traditional and HIV-related renal risk factors in a Poisson regression model with CKD as the outcome as tested several different model building strategies with similar results [31, 36, 37]. The effect estimate of each individual risk factor were then scaled to construct a point-based summed scoring model, in which points were calculated by dividing each incidence rate ratio with the lowest incidence rate ratio of the model. In addition to providing a continuous risk estimate, we defined low (score <0), medium (0-4) and high CKD risk ($\geq$5) strata, based on summed points divided in quantiles with three lowest combined into one based on low event numbers. We combined these findings with KM estimation to define the proportions developing CKD over 5 years in each of these risk strata. To ensure our model could be used widely we also constructed as short model without CVD risk factors (hypertension and prior CVD) as some cohorts (i.e. several British cohorts) do not collect such data systematically. In the prediction model it is assumed that the impact of each factor is additive (rather than multiplicative) in nature, which seems reasonable in this case as we did not find any interactions between key risk factors. To address the impact on the absolute CKD risk in each risk strata of starting nephrotoxic ARVs, use of TDF, LPV/r, ATV/r, ATV and other PI/r (predominantly older PIs) was then subsequently included as time-updated variables. While, at the time, there was growing evidence supporting a cumulative effect of TDF use with CKD risk, there were more ambiguity related to use of individual PI/r which was the reason for not including ARV use in the actual model. In addition to the change in CKD risk we also calculated the numbers-needed to treat to harm (NNTH) for starting each ARV, a methodology implemented in 2010 for CVD in PLWH, for each CKD risk stratum [38].
NNTH were also calculated in paper 9 for CVD risk associated with use of DRV/r in different risk strata.

*Sensitivity analyses*

To limit risks of misinterpretation of our data we routinely conducted extensive data checks to ensure the reported data was as accurate and complete as possible and undertook a meticulous analytical approach to the analysis in which several sub- and sensitivity analyses interrogate the robustness of our findings in different clinical scenarios. For instance, in the paper investigating use of contemporary PIs and CVD (paper 9) we investigated if the association between DRV/r and CVD differed according to the individual components (stroke and MI) of the composite CVD outcome and the impact of excluding everyone with prior CVD. In the same paper we also investigated the impact on fitting potential confounders, and in particular dyslipidemia, on the potential causal pathway as time updated as opposed to baseline variables and we investigated the effect of excluding everyone without any exposure to the two main drugs in question. To address potential confounding by indication we also tested for interactions with the *D:A:D* CVD risk score and assessed if the results differed according to having experienced virological failure. In the paper on ESLD/HCC (paper 10) a sensitivity analysis excluded those with HBV co-infection to test if the association between TDF and ESLD was confounded by HBV-coinfection not adequately captured by adjustment. In the paper on contemporary PIs and CKD (paper 4) we restricted the primarily analysis that included all individuals without prevalent CKD stage 3, to include only those with initial normal renal function (eGFR >90 mL/min/1.73m$^2$). Whilst in paper 3 on cumulative use of potentially nephrotoxic ARVs and CKD we censored any FU on other ARVs used concomitantly (in addition to adjustment hereof) to ensure the associations of TDF and PIs LPV/r and ATV/r were independent. In paper 7 to test for competing risks of death and ESRD in those with CKD, we conducted an analysis in which we removed all persons with more than one serious clinical event during follow-up with consistent results.

**Chapter 3 Principles of Modern HIV Care and Adverse Effects of ART**

During the past decade there has been a major shift in paradigm for HIV-treatment which has significantly impacted everyday clinical management of PLWH [3, 4, 39, 40]. This chapter contains a short overview of the latest European recommendations for HIV care including highlights of the studies defining modern ART strategies and main adverse drug effects with a focus on the most commonly used ARVs.

Concerns about ART-related toxicities and resistance lead to suggestions of a drug conservation or intermittent ART strategy as opposed to a continuous ART approach for managing HIV. In 2006 the randomised *SMART* study presented evidence that an intermittent ART strategy resulted in higher rates of progression to AIDS and death (hazard ratio, HR 2.6 [1.9-3.7]) and thereby a strong recommendation to treat continuously once ART is initiated [39]. As part of the secondary endpoints the study also suggested that risks of major CVD, renal and liver events were higher in those treated intermittently (HR 1.7 [1.1-2.5]) [39].

For years the best time for starting ART was discussed, some suggested an early start of ART (test and treat approach) would lower risks of conditions closely related to ongoing HIV-viremia and immunodeficiency and lower risks of onwards transmissions (treatment as prevention, TASP), whereas others were concerned about the potentials for accumulating drug toxicities and resistance, as well as the challenges with upscaling use by providing ART to everyone. Up to the years around publication of the Strategic Timing of ART *(START*) trial data the common practice was to defer initiation of ART until there was a specific need for it i.e. in the presence of an AIDS defining condition, co-infection with viral hepatitis, pregnancy or in asymptomatic persons with low CD4 count [41]. The definitive evidence came with the *START* trial showing that those starting ART immediately had lower risk of a combined endpoint of serious AIDS and non-AIDS events and all-cause mortality (HR 0.43 [0.30.0.62]) [40]. Treatment guidelines were immediately adapted to reflect these findings and now recommend initiation of ART as soon as possible [6]. There are still important data coming out on a number of *START* sub-studies to further investigate if there are added benefits on clinical outcomes on starting treatment with a high CD4 count [42, 43].

In 2016 the results of the *PARTNER* study further revolutionized HIV care by documenting no risk of HIV transmission in sero-discordant couples in case of fully suppressed HIV-VL by ART [44]. In addition to treating PLWH ARVs have since release of the first ARVs been used for Post-Exposure Prophylaxis (PEP) [45]. The 2016 *PROUD* and *IPERGAY* studies showed that ART was effective in reducing risk of HIV transmission in persons of high-risk of acquiring HIV and has since been incorporated as a primary prophylaxis measure (Pre-Exposure Prophylaxis, PrEP) in many European countries [6, 46, 47].

HIV care is organised differently across Europe, for instance in Denmark management is centralised in highly specialised university centres, whereas in Finland and United Kingdom specialised HIV nurses diagnose and manage most comorbidities, whilst doctors in general practises oversee care in many German states [48]. The European AIDS Clinical Society (*EACS*) is a non-profit organisation which aims to provide easy assessable recommendations on all key aspects of modern HIV management [3]. Originally the *EACS* Guidelines aimed at providing unifying guidelines for clinicians involved with HIV care throughout Europe, but due to the holistic approach to HIV management, which is unique to *EACS*, and a request from countries without national guidelines, or where guidelines are only updated infrequently, the EACS Guidelines are now more widely implemented including in parts of China, Russia and Japan. For the past nine years I have been involved with management of the *EACS* Guidelines; first assisting the chair of the comorbidity panel, later as the Guidelines Coordinator. As the studies of this thesis are all based on a primarily European population, the below discussed recommendations are primarily based on European recommendations from the *EACS* Guidelines.

There are four mainly used ART drugs classes; nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and integrase inhibitors (INSTIs). The basis for modern initial treatment for ART-naïve persons traditionally include a combination of a dual NRTI backbone plus one INSTI (preferred), one PI or one NNRTI [6]. Use of an unboosted INSTI with a high genetic barrier (dolutegravir, DTG or bictegravir, BIC) is currently the favored 3rd agent. In 2019 the possibility to treat ART-naïve persons with a two drug regimen (2DR) consisting of DTG and lamivudine (3TC) was added based on the *GEMINI* trials findings of non-inferiority to using a three drug regimen (3DR) of tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) and DTG [6, 49]. When deciding on which ART regimen to start in an individual there are several points to consider including pregnancy, risk of and prevalent comorbidities, use of other medications, addictions, swallowing difficulties, certain HLA types, co-infections and opportunistic infections. These considerations are all essential parts of modern HIV care to tailor ART to the needs of the individual PLWH to increase compliance and limit risks of drug-drug interaction and adverse effects. In addition, the presence of resistance mutations, drug availabilities and pricing may also impact choices. It may be necessary to adjust the treatment dosing in case of renal and/or liver impairment and to switch one or more ARVs in case of i.e. virological failure, pregnancy, serious drug-drug interactions or toxicities [6]. For INSTIs, the most modern 3rd agent, recent data suggest that approximately 10% discontinue use within six months, and most commonly due to toxicities [50].
ART may potentially impact organ function in different ways; neutral impact (no effect) which is most common, improvement of organ dysfunction (i.e. if related to viremia or immunodeficiency) or induction/further impair organ dysfunction (toxic effect) [37, 51]. Therefore, in addition to ensuring virological

and immunological control it is recommended to systematically monitor for development of toxicities after initiation of ART including asessment of renal, liver and bone marrow function, lipids, glucose and bilirubin as clinical symptoms may not arise until a late stage. Once the PLWH is stable on ART how frequently the person should be monitored for toxicity depends on several factors including the individual risk profile and the ART regimen used, for instance *EACS* recommends screening for renal impairment every 3-12 months for the general PLWH, but more frequently in those with impaired renal function, ongoing CKD risk factors and in those using drugs with nephrotoxic potentials [6]. Adverse effects related to ART use are a mixture of effects ranging from asymptomatic and mild laboratory abnormalities (i.e. hyperbilirubinemia related to use of atazanavir, ATV) to severe chronic or life threatening effects (i.e. lipodystrophy and lactic acidosis related to use of d4T) [4]. As discussed in the introduction there have been considerate advances in the adverse effect profile of individual ARVs over time moving towards options that have a high level of tolerability and where toxicities are most commonly seen only in a subset of those on the drug [6]. Identifying those that develop toxicities, may however be challenging, but *D:A:D* and other large studies have used the heterogenicity and extended follow-up time of study participants to develop prediction scores that may aid the clinical decision making, as will be discussed in more detail below [33, 34, 52]. Further, some toxicities are common for all ARVs within a class (class-effect) such as gastrointestinal adverse effects related to PIs, whereas other seem specific for only one or more of the ARVs within the class such as indinavir (IDV), and ritonavir boosted lopinavir (LPV/r) and darunavir (DRV/r) for CVD and IDV, LPV/r, ATV/r for CKD, as discussed in more detail in the below chapters [6, 53, 54]. Whilst some adverse effects appear reversible upon discontinuation of the offending ARV i.e. CNS toxicity related to DTG others are not i.e. lipodystrophy related to d4T use. For other ARVs, where the adverse effects are cumulative in nature the reversibility potentials are less clear, we examine some of these effects in more details in papers 5 and 10 for renal and liver outcomes [35, 55].

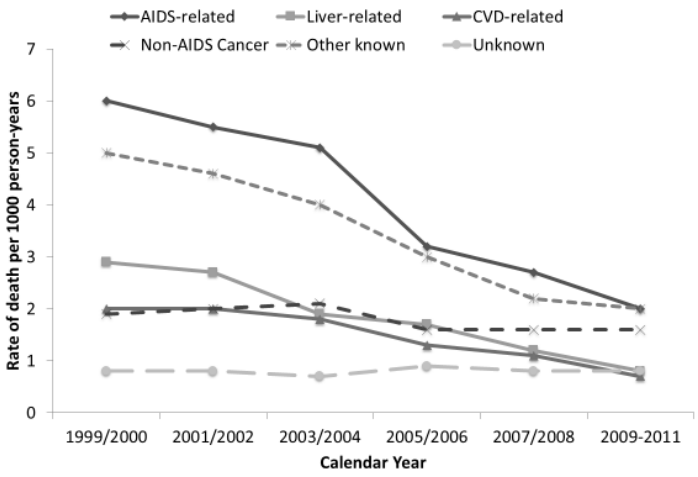
In addition to screening for adverse drug reactions and potential drug-drug interactions, modern HIV care include regular screening for a broad range of comorbidities seen at increased frequency in PLWH including several cancers, CVD, mental illness, metabolic syndrome and renal, liver and bone impairment [6]. Where risk estimations are available these are recommended [4, 33, 34, 52]. In addition to manifest organ diseases, use of more dynamic/earlier markers of organ dysfunction, have in recent years been adopted into the screening and management guidelines of PLWH i.e. rapid progression (RP) of renal function, for which we in *D:A:D* has developed a formalised definition [6, 56, 57]. Lifestyle factors including exercise, diet and all types of abuse should also be regularly assessed, as should social factors and issues related to sexual health. Additional regular screening focuses on diagnosing co-infections such as tuberculosis, viral hepatitis and sexually transmitted infections [6].

## Chapter 4 Comorbidities in PLWH

This chapter provides a short general introduction to comorbidities in PLWH and is followed by three chapters discussing the major disease entities of the kidneys, heart and liver and their relation to ART and other risk factors in more detail.

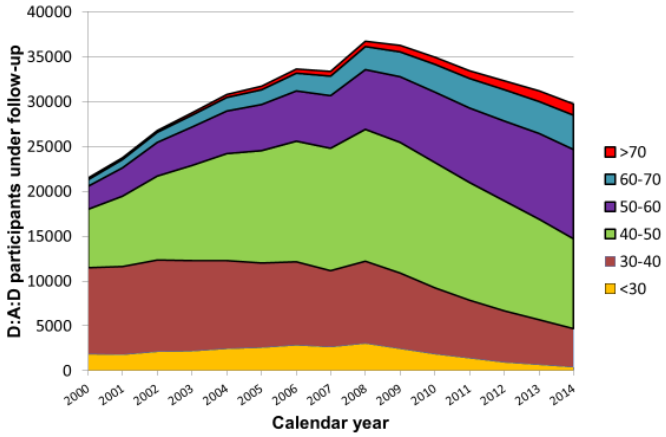
In 2014 the *D:A:D* study showed that mortality rates declined for most individual underlying causes of death over time from 18 per 1000 PYFU in 1999-2000 to 9 per 1000 PYFU in 2009-2011, Figure 3 [16].

**Figure 3, Temporal Changes in Mortality Rates in PLWH in D:A:D 1999-2011** [16]




AIDS was the most common individual cause contributing 29% of the death, followed by non-AIDS cancers (15%), liver related death (13%) and CVD (11%). Because of these significant improvement in survival due to ART the age distribution of PLWH also changed significantly, in 2014 10% of all individuals were older than 60 years, Figure 4.

**Figure 4, *D:A:D* Data Merger 16 Age Distribution of Study Participants, Unpublished data**



Several cohorts in England/Ireland (Pharmacokinetic and clinical Observation in PeoPle over fiftY, *POPPY*, and COmorBidity in Relation to AIDS, *COBRA*), the Netherlands (*AGEhIV* and *COBRA*), Italy (Geriatric patients living with HIV, *GEPPO*) and Denmark (COpenhagen COMObidity in HIV-infection, *COCOMO*)) are dedicated to compare rates and risk factors for non-AIDS comorbidities between PLWH and HIV-negative controls and to study the impact of ageing [58-62]. In 2014 the *AGEhIV* study described that PLWH had higher prevalence of several non-AIDS morbidities including hypertension, CKD and CVD compared to matched HIV-negative controls [60]. For all age-groups PLWH also had a higher burden of comorbidity i.e. for those older than 65 years more than 30% of PLWH had more than three comorbidities compared to 15% of the controls, and a mean of 1.3 (standard deviation, SD 1.14) non-AIDS conditions in PLWH vs 1.0 (SD 0.95; p <0.001) in controls [60]. Other studies in Europe and the US have reported similar findings of PLWH being disproportionally affected by a wide range of comorbidities [58, 63-66]. The reason for the discrepancy between persons with and without HIV is multifactorial, as will be discussed in detail in the following chapters for CVD, CKD and terminal liver failure. A collaboration between *AGEhIV* and *POPPY* described that many of these comorbidities in PLWH are seen in non-random disease clusters suggesting a common underlying pathogenesis [67]. With increasing age rates of several comorbidities in PLWH increase, although this is not specific for PLWH, this is key to acknowledge for the clinical managing [60, 68]. A 2015 study estimated that the proportion of PLWH with >1 comorbidity would increase form 29% in 2010 to 84% in 2030, similarly the proportion with >3 comorbidities would go from 0.3 to 28% [69]. The Swiss HIV Cohort Study (*SHCS*) found that on third of the cohort received at least one non-HIV co-medication, and 14% of those older than 65 years received more than four concomitant non-HIV co-medication most commonly a lipid-lowering agent, ACE-inhibitor, other antihypertensives and antiplatelets [68]. A recent study by *POPPY* also confirmed high rates of potential drug-drug interactions in older PLWH compared to younger PLWH and to HIV-negative controls [70]. The *EuroSIDA* study showed in 2018 an increase in the overall prevalence of several comorbidities including CVD (3.7% to 5.0%) and CKD (4.1% to 6.9%) in PLWH from 2006 to 2014 [71]. However, in fully adjusted models this increase could largely be attributed to increased age for CVD and to age and other CKD risk factors such as diabetes and hypertension for CKD [71]. The extent to which HIV may impact on the normal ageing process and increase risks of age-related comorbidities in PLWH remain conflicting with some studies suggesting PLWH develop these conditions at younger ages than HIV-negative controls, while others have not found support of an age-accelerated effect of HIV [64-66]. The *EACS* Guidelines have specialised in providing recommendations for a multifaceted approach to comorbidities and drug-drug interactions and provide HIV-specific age cut-offs for screening [6].

As will be discussed in detail in paper 7, investigating clinical outcomes after CKD, many of the comorbidities seen at higher rates in PLWH have closely related risk profiles, suggesting that effective

interventions focused against these common predictors such as smoking, diabetes, dyslipidaemia and hypertension may have a wide-ranging impact of HIV-related morbidity and mortality [6, 72, 73].

**Chapter 5 Renal disease in PLWH** *(papers 1-7)*

Over the past approximately 10-15 years several studies have documented that PLWH in diverse settings are at increased risk of developing CKD compared to the general HIV-negative population [58, 60, 74-78]. The risk factor profile for CKD in PLWH is complex with an interplay between multiple factors; HIV virus itself, immune suppression, genetic predisposition, nephrotoxic ART, viral hepatitis and traditional risk factors such as diabetes and hypertension [25, 31, 36, 37, 42, 57, 79-84]. In a recent analysis from the *COCOMO* study including only Caucasians without illicit drug use or viral hepatitis coinfection and fully virally suppressed on ART, we found that PLWH still had a higher CKD prevalence compared to matched HIV-negative controls (3.7% (IQR 2.3-5.5) vs 1.7% (1.2-2.2), p=0.001), and HIV status was independently associated with CKD 3.4 ([1.8-6.3]) especially in older persons (p for interaction 0.02) [58]. Renal function declines with age whilst the prevalence of several traditional renal risk factors increases with age, as a consequence of an increasing proportion of ageing PLWH the incidence of CKD is increasing making it imperative to optimise primary and secondary prophylaxis [85].

The most common HIV-related pathologies include classical HIV-associated nephropathy (HIVAN), non-collapsing focal segmental glomerulosclerosis and immune-complex kidney disease [86]. Classical HIVAN is associated with a high risk of progression to ESRD and mortality, and is predominantly (18-50 times more frequently) seen in PLWH of West-African origin due to a genetic predisposition related to high-risk variants of apolipoprotein L1 (APOL-1) on chromosome 22 [82, 87, 88]. These genetics variants are thought to be an evolutionary remain offering innate protection against Trypanosoma brucei brucei infections [88].The lack of such genetic risk alleles in PLWH of East-African origin, has been linked with a low overall susceptibility of HIVAN in Ethiopians, although other factors (genetic, viral, or environmental) also contribute to HIVAN [86, 89]. While the incidence of HIVAN has declined due to effective and early cART other renal pathologies in PLWH are increasing with a heterogenous presentation [86, 90-93]. HIVAN may further not be completely reversible despite effective treatment [90]. The APOL1 high-risk genetic variants also represent a particular fragile genotype for other types of CKD [89, 94]. The exact mechanisms by which APOL1 increases CKD risk in both HIV-positive and negative persons remain under investigation [88].

The papers of my 2013 Ph.D. thesis [25, 36, 37, 95, 96] focused on describing the incidence of various levels of CKD and disentangling the impact of individual traditional renal risk factors, ART and HIV related factors. While we found that in the predominantly white and male dominated cohorts of *D:A:D* and *EuroSIDA* CKD stage 3 (moderate CKD) had an incidence close to 1 per 100 person-years of follow-up (PYFU), more advanced levels of CKD (stages 4-5) and ESRD were much rarer with an incidence around 1 per 1000 PYFU [25, 37, 96]. We also showed that use of TDF, ATV and lopinavir (LPV) were independently of other factors

significantly associated with increased rates of renal impairment. This had already in part been shown in the *EuroSIDA* study a few years earlier, but with only 2 years of cumulative exposure rates, the *D:A:D* supplemented those findings by adding longer exposure time and showing an association in individuals with an initially normal renal function, suggesting these adverse drug effects were not depending on pre-existing renal impairment [37]. We also described that these ARV associations with renal function were independent of a combined use with each ARV contributing between 11-19% increased renal risk per additional year of use [37]. We were; however not able to show an association between use of these ARVs and development of more advanced levels of CKD and ESRD, most likely due to high rates of switches away from these ARVs as renal function declined [36, 37]. Instead we identified diabetes, hypertension, lower baseline renal function, smoking, CD4 count and increased CVD risk as main predictors for CKD stages 3-5, while female gender, substance abuse as risk of HIV acquisition, CD4 count and prior AIDS most strongly predicted progression from a normal renal function [36, 37]. We also described how progression to advanced CKD and ESRD was rare in those without prevalent traditional renal risk factors (2 per 10,000 PYFU)[36]. With an additional maturation of the *D:A:D* dataset (systematic creatinine collection was not initiated in *D:A:D* before 2004) we gained adequate power to assess other pertinent questions related to CKD in PLWH including impact of immune suppression, use of newer ARVs, reversibility potentials, 5-years prediction of CKD and CKD-related complications as described in detail in the following sections.

**CKD and HIV-related immune suppression** *(papers 1 and 2)*

Several studies, including our earlier renal studies from *D:A:D*, showed that immune suppression, expressed as a low CD4 count, is an important predictor for CKD in PLWH independently of AIDS events, HIV viremia and use of nephrotoxic ART [34, 36, 37, 52, 82, 84, 97]. Likewise, in the *START* renal sub-studies we described that the prevalence of CKD in PLWH with preserved immune function is relatively low [98], and that immediate ART initiation with two years median follow-up was associated with a slightly higher median eGFR and lower levels of proteinuria compared to deferring ART [42]. Obviously longer follow-up data in *START* is required to address if this observation will also translate into lower CKD risks on the longer term, or if the contribution of nephrotoxic ART will modify this relation over time.

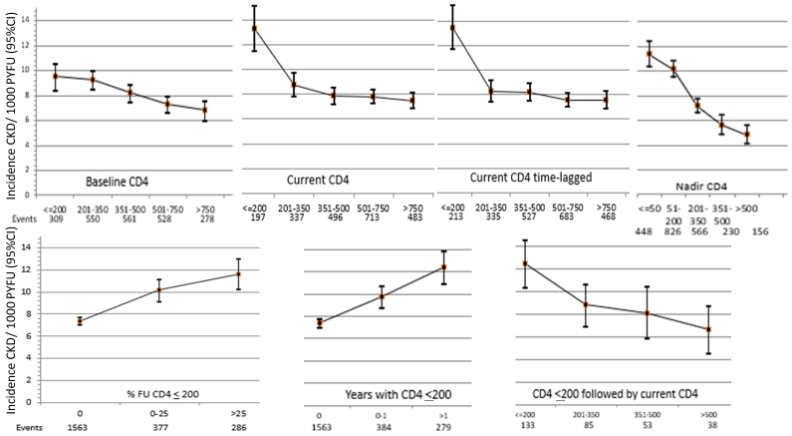
During a review in 2014 (paper 2) we found that data describing the exact nature of the negative association between various measures of immune suppression and CKD was incomplete and focused almost exclusive on severity of immune suppression [99]. A study from 2010 based on the control arms of the ESPRIT and Subcutaneous Recombinant, Human Interleukin-2 in HIV-infected Patients with Low CD4+ Counts Under Active Antiretroviral Therapy (*SILCAAT*) trails did however find that latest CD4 count over other CD4 metrics most strongly predicted serious non-AIDS events (including ESRD), but was limited by only 8 renal endpoints [97]. It also remained unclear if immune-related CKD changes had a potential to resolve if the immune function was restored. We therefore constructed the study of paper 1 to investigate the association between different measures of impaired immune function (severity, duration and recovery) and CKD incidence profiting from the large size and heterogeneous composition of the *D:A:D* study [100].

*Severity, duration and recovery of immune function*

During a median follow-up time exceeding eight years we found that all measures of immune suppression severity (CD4 count at baseline, current CD4 count, 6-months' time-lagged CD4 count and nadir CD4 count) and all measures of immune suppression duration (percentage of follow-up time, %FU, with CD4 count <200 cells/mm$^3$ and years with CD4 count <200 cells/mm$^3$) showed approximated linear relations with declining CD4 count levels and longer time of immune suppression, Figure 5 [100]. For the severity measures there were no additional differences in the CKD incidence rates as CD4 counts increased >500 cells/mm$^3$. Similarly, the CKD incidence declined linearly with increased levels of recovery (baseline CD4 count $\underline{<}$200 cells/mm$^3$ followed by current CD4 count >500 cells/mm$^3$ (5.3 [3.0-7.6]) compared to those without recovery (11.3 [9.1-13.6]), suggesting that immune reconstitution for CKD is around this level, and that the immunesupression related impact on CKD may at least in part be reversible. In comparison a 2013 study from Collaboration of Observational HIV Epidemiological Research Europe *(COHERE)* found that immune

reconstitution levels for AIDS events was at CD4 counts >750 cells/mm$^3$ [101]. For CKD it now appears this threshold is slightly lower [100].

**Figure 5, CKD Incidence Rates Stratified by Different Measures of Immune suppression** [100]




In unadjusted analysis we found that all the considered measures of immune suppression were significantly associated with increased rates of CKD (all p<0.01). The strongest association (judged by the magnitude of the association and the AIC, where a lower values indicates a better model fit) was seen for nadir CD4 count (>500 vs. ≤50 cells/mm$^3$, incidence rate ratio 0.43 [0.36-0.51], AIC 40814), %FU CD4 count ≤200 cells/mm$^3$ (0% vs. >25%, 0.63 [0.56-0.75], AIC 40921) and latest CD4 count (≥750 vs. <50 cells/mm$^3$, 0.56 [0.48-0.66], AIC 40943).

After we adjusted for the non-immunological variables included in the *D:A:D* CKD risk score (see paper 6), we found the strongest predictor of CKD was the relative duration of immune suppression expressed as the %FU CD4 count ≤200 cells/mm$^3$ (0% vs. >25%, 0.77 [0.68-0.88], AIC 36262) and immune suppression severity with nadir CD4 count (≥500 vs. ≤50 cells/mm$^3$, 0.77 [0.64-0.93], AIC 36304).

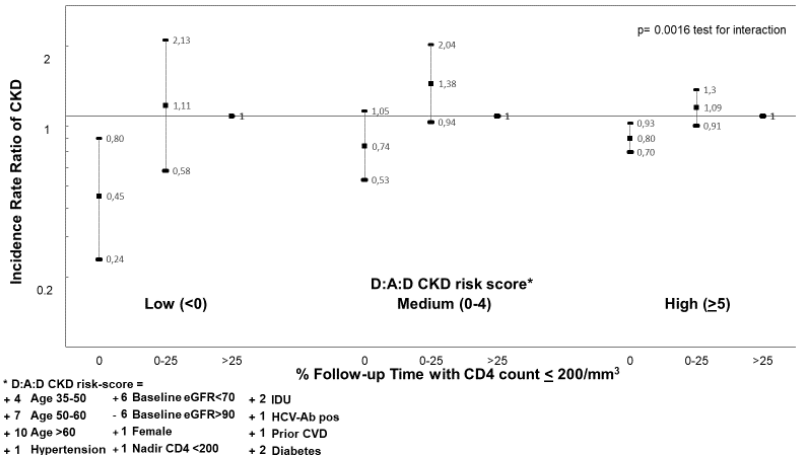
Whist this data suggest that immune suppression duration is statistically speaking the strongest CD4 count predictor of CKD, you could argue that severity of immune suppression, and nadir CD4 in particular, may be easier to use in every day clinical practice [34, 52]. In adjusted analysis, CD4 nadir was only very marginally inferior as a predictor of CKD compared to immune suppression duration and may be used as an alternative [100].

We further described a significant (p = 0.002) interaction between %FU CD4 count ≤200 cells/mm$^3$ and the *D:A:D* CKD risk score with those at the lowest estimated CKD risk had greater relative impact of a longer duration of immune suppression (0.45 [0.24-0.80]) compared to those at highest estimated CKD risk and longer duration of immune suppression (0.80 [0.70-0.93]), Figure 6. This finding suggest that immune

suppression has the greatest relative impact on renal function in persons at low estimated renal risk such as those without comorbid conditions such as diabetes, hypertension, viral hepatitis co-infection or advanced age [100].

**Figure 6, CKD Incidence Rate Ratio and % Follow-up Time with CD4 Count ≤200 cells/mm$^3$**

**Stratified By The *D:A:D* CKD Risk Score** [100]




*Mechanistics*

In terms of mechanistics, prior studies have suggested a close relation between CKD and several markers of HIV-related increased inflammation and coagulation activation [97, 102-107]. ART initiation has been shown to decrease both renal and inflammatory biomarkers, while ART disruption in SMART increased such markers suggesting that ART-related improvement in immune function, viremia, inflammation and coagulation activation is essential as renal protective measures in PLWH [104, 106, 108-110]. Even is the absence of HIV infection CKD and progression hereof is closely associated with increased inflammation, which has further been linked to the increased risk several CKD-related complications including CVD and mortality (see papers 7 and 8) [111-116] . Inflammation and increased coagulation activation may theoretically impact several of the renal structures including the vascular structure itself and the interstitial space in turn leading to diminished renal function [107, 116]. Several trails have investigated impact on use of different anti-inflammatory immune boosting interventions such as dipeptidyl peptidase-4 (DPP-4) inhibitors, statins and interleukin-2 (IL2) in PLWH with somewhat conflicting results, and those with potentially promising outcomes have been limited by relatively small size and short FU and require validation in larger settings [111, 117-122]. Such trials are pivotal in PLWH where inflammation is already increased and are likely to further worsen under progressive CKD [106, 107, 116].

*Conclusion, limitations and perspectives*

Both RCTs and observational studies have described a robust and independent risk of CKD due to HIV-related immunesupression. Recent data from *D:A:D* have extended this knowledge by showing that both severity and duration of HIV-related immune suppression adversely impacts renal function [100]. The *D:A:D* analysis was limited by the lack of systematic collection of CD8 count, data on proteinuria and genetic predisposition to CKD. In future analyses it would be relevant to test if the CD4 association we described here differ according to CKD stage, however this analysis was dominated by persons with moderate levels of CKD and only 46 ESRD cases. The immune suppression related CKD risk appears to be at least partly reversible if the immune function is restored. Early initiation of ART, and maintaining high levels of ART adherence therefore appear to be central in diminishing risks of immune-related CKD [40, 42, 102, 106, 109]. However, as immune suppression is not the only HIV-related parameter impacting the long-term renal prognosis in PLWH the gains of this aggressive treatment strategy on immune function, increased inflammation, coagulation activation, viral suppression and AIDS events will in future works be analysed against the potential risks of accumulating drug toxicities [42, 99].

**CKD and adverse effects of ARVs** *(papers 3 -5)*

A very high number of publications have reported findings on potentially nephrotoxic ARVs ranging from case reports, over small single center cross-sectional studies, to large prospective cohort studies with extended follow-up time and RCTs [57, 78, 123-131]. While initial RCTs reported good overall safety of TDF it soon became increasingly evident in real life experience that there was a potential renal safety concern, albeit only affecting a smaller proportion of all those exposed [127, 130-142]. In addition to having another primary aim, fairly small study sizes and relatively short follow-up time in most drug-discovery RCTs a likely reason for this apparent discrepancy is that ART-associated renal impairment is more frequent in individuals commonly excluded from such trials e.g. ageing individuals, those with co-morbidities and those using concomitant drugs with risk of drug-drug interactions (e.g. NSAID or PI/b) [125, 142-149]. The 2013 *SWITCH* trial supported this assumption by showing that co-morbid persons randomised to switch from ABC to TDF had a negative impact on eGFR already throughout the 48 weeks follow-up [150].

ART-associated renal impairment has been estimated to constitute 0.5–14% of all cases of renal impairment in PLWH, depending on the presence of other renal risk factors and the ARVs used, and therefore an important factor to consider in the prospects of early and life-long ART [86, 142, 143, 151, 152]. Depending on the initial renal function and the type and burden of renal risk factors CKD may take several years to develop [153] . As such studies investigating ARV-related nephrotoxicity without considerations of being adequately powered in terms of size and follow-up time must be interpreted with caution as the risk of type II errors are increased [142] .

As discussed in the renal introduction above in 2011 we showed that longer use of TDF, ATV/r and LPV/r were independently associated with development of chronic renal impairment, CRI (confirmed, >3 months apart, eGFR <70 mL/min/1.73m$^2$) in individuals with an initial normal renal function (eGFR >90 mL/min/1.73m$^2$) [99]. As a large proportion of individuals were; however, actively switched away from these ARVs as their renal function declined, we were at the time not able to fully determine if longer use of these drugs would be also be associated with progression to CKD (confirmed eGFR <60 mL/min/1.73m$^2$) from initial normal function. Furthermore, particularly RCTs with limited follow-up suggested that TDF-related decline in eGFR was limited to the first month's use (suggesting one-hit phenomenon seen only in those genetically predisposed), while several, primarily observational studies, suggested that TDF and PI-related renal effects were cumulative in nature [57, 130, 154-157]. However, it was not understood if this cumulative association would remain also after several years of use, or if levels would ultimately be reached upon which additional use would not cause further decline in renal function.

**Current and cumulative use of ART and risk of CKD** *(paper 3)*

To help clarify the nature of the relationship between longer treatment duration with nephrotoxic ARVs on risk of incident CKD in 2016 we reassessed our prior 2013 *D:A:D* analysis in which persons with an initial normal renal function progressed to chronic levels of renal impairment (CRI: eGFR<70 and CKD: eGFR<60 mL/min/1.73m$^2$, confirmed > 3 months apart) [37, 85]. In this updated analysis an additional 1,302 persons (23,905 vs. 22,603 persons in the original publication) were included with an increase in median follow-up from 4.5 (IQR 2.7-6.1) to 7.2 (IQR 5.1-8.9) years [37, 85]. The absolute number of incident CKD endpoints more than doubled from 131 (0,6%, Incidence rate 1.33/1000 PYFU [1.10-1.56]) in the initial publication to 285 (1%, 1.76/1000 PYFU [1.56–1.97]) in the updated analysis, wherefor CKD was made the primary outcome. With this additional power we were able to show that the association between more extended use of TDF, ATV/r and LPV/r and CKD was indeed cumulative in nature with a year-on-year steadily increase in incidence with longer follow-up time for all the ARVs, Figure 7. As such we found no indications that the drug-associated renal impairment levels off with more extended use, and confirmed a robust drug association compared to that originally shown for progression to the milder CRI endpoint (TDF-CKD 1.14 [1.10-1.19] vs TDF-CRI 1.18 [1.12-1.25], ATV/r-CKD 1.20 [1.13-1.26] vs ATV/r-CRI 1.19 [1.09-1.32] and LPV/r-CKD 1.11 [2.06-1.16]) vs LPV/r-CRI 1.11 [1.05-1.17] per additional year use). These associations further remained unchanged after censoring any exposure to the other nephrotoxic ARVs used (i.e. any follow-up time spend on ATV/r was censored for the TDF analysis and vice versa) confirming incident CKD is not co-dependent on exposure to both the PI and NRTI drug class.

The finding of a steadily increasing CKD incidence in individuals under prospective follow-up in *D:A:D* with an initial normal renal function from 0.11% [0·07–0·15] at 2 years to 1.46% [1.26-1.66] at 8 years underlines the importance of systematic screening [6]. Over a five-year period, risks of CKD will almost double (IRR 1.94) if individuals stay on TDF, increase 2.44 times if on ATV/r and 1.66 times if on LPV/r independently of any other factor. If an underlying absolute CKD risk is low (i.e. in a young persons without co-morbidities or co-infections) a doubling in CKD risk due to TDF may still be a low overall risk, but these data illustrate the importance of weighting potential risks and benefits of individual ARVs based on the individual risk profile, (see paper 6) [34]. The reported effect size of TDF on CKD risk in other large studies such as the *veterans affair (VA)* cohort was higher than in *D:A:D* (33% per years use), likely reflecting progression from different levels of initial renal function and including earlier time periods where TDF discontinuations were possibly somewhat lower due to less knowledge of the nephrotoxic properties [57]. In the same study the *VA* cohort also found increased risk of proteinuria (34% per years use) and RP of eGFR (11% per years use) in PLWH exposed to TDF [57].

**Figure 7, Crude Incidence Rate of CKD per Longer use of ARVs with Nephrotoxic Potentials** [85]

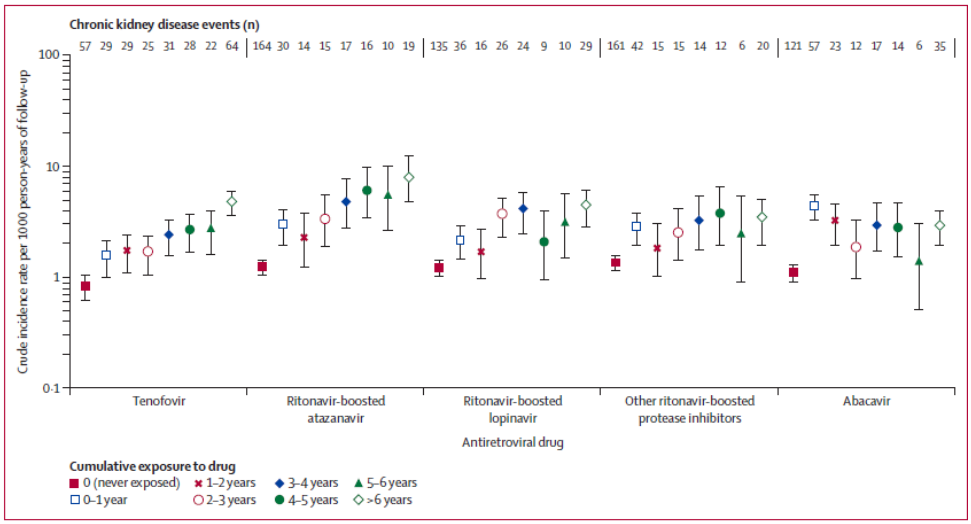



*Figure 2:* **Crude incidence rates of chronic kidney disease and cumulative exposure to potentially nephrotoxic antiretrovirals**
Error bars are 95% CIs. Chronic kidney disease is defined as confirmed (>3 months apart) estimated glomerular filtration rate <60 mL/min per 1·73 m².

We did not find an association between CKD and other PI/r after adjustment, suggesting there was no effect of the ritonavir (RTV) boosting itself on CKD risk. RTV has been shown to inhibit creatinine secretion and may artifactually decrease eGFR, but the renal function declines investigated in this analysis (per definition a delta of minimum 30 mL/min/1.73m$^2$ going from eGFR >90 to <60 mL/min/1.73m$^2$) were of a such a magnitude that minor artifactual increase related to RTV did not in itself impact CKD risk. Since, we have shown that use of RTV in boosting doses does not significantly impact use of creatinine based eGFR equations [158] .

The other PI/r group consisted of both older and newer PIs in whom follow-up was too limited to investigate CKD associations independently at the time.

In the 2013 analysis we saw trends of an association with ABC, which was possibly related to channeling reflecting those changing from TDF to ABC with declining eGFR levels. In the updated analysis there were no significant association with ABC.

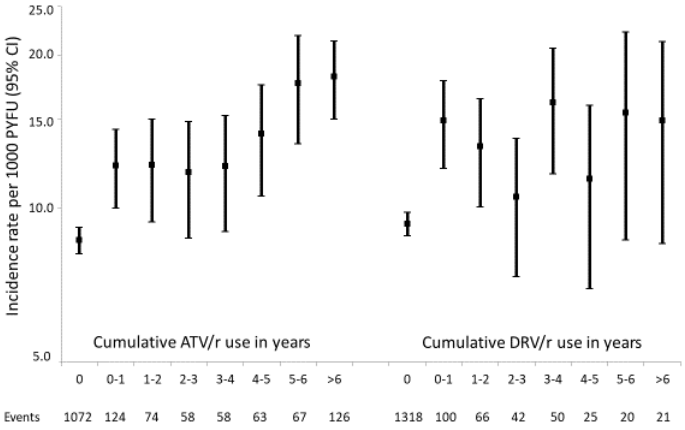
**Use of contemporary PIs and risk of CKD** *(paper 4)*

In 2017 we had accrued additional power to reliably investigate impact on ritonavir boosted darunavir/r (DRV/r) on CKD risk [54]. As DRV/r was not widely implemented as part of routine clinical care in Europe before 2009 there is considerately less data on potential nephrotoxic properties and only few case reports of DRV/r related urolithiasis compared to other PI/r [159-163]. A switch study did however suggested DRV/r effects on eGFR trajectories were better compared to other PIs [160]. Recent data comparing outcomes on 2 drug regimens (2DR) have also indicated favorable impact on renal outcomes on DRV-containing regimens, how much this effect is related to exclusion of the TDF component in a 3DR is however not clear[164].

We included 27,675 persons in the analysis of which 28.7% were at low, 35.6% at median and 35.7% at high estimated risk of CKD according to the 5 year *D:A:D* CKD risk score (see paper 6). Median follow-up was 6.8 years (IQR 5.4-7.1) during which 1,642 persons (5.9%) developed CKD (incidence rate 10.0 [9.5-10.4] per 1000 PYFU).

Whilst we found the raw CKD incidence increased gradually with longer exposure to ATV/r, the incidence with longer DRV/r exposure was more variable, and in adjusted models we saw no significant relation with longer DRV/r use (adjusted incidence rate ration 1.0 [0.8-1.3] after >4 years use vs. never exposed), Figure 8 [54]. In contrast, ATV/r remained associated with increased CKD despite increased rates of discontinuing ATV/r at declining eGFR levels and increased estimated CKD risks. Discontinuation of DRV/r use was in contrast largely unaffected by eGFR levels and CKD risks. This lack of a gradual or equally strong association between DRV/ and other PI/b after almost seven years median follow-up argues against a PI group effect on CKD risk. As DRV/r has a propensity to precipitate in urine (see below regarding potential mechanisms), it is however not possible to exclude the possibility that there is an association between DRV/r and CKD, but that this only emerges with very extended drug use, although our data did not indicate any gradual year on year relation [163].

**Figure 8, Use of ATV/r and DRV/r and crude incidence of CKD** [54]

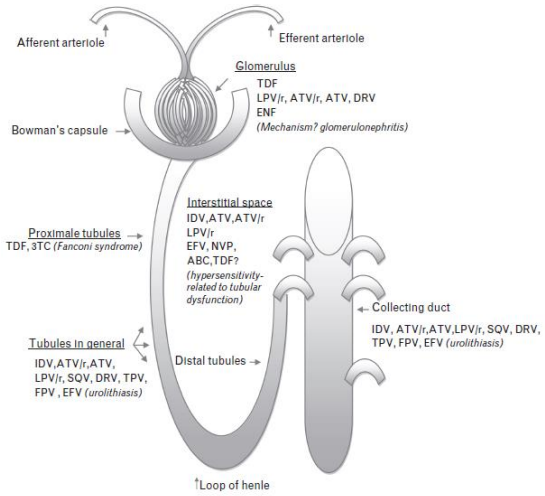



The strength of the ATV/r related CKD risk shown in 2017 was smaller than previously shown [37, 85]. This decrease is likely related to the greater awareness of the nephrotoxic potential of ATV/r in more recent years, which are highlighted in international guidelines, and supported by high rates of switching away from ATV/r in PLWH with high predicted CKD risks and/or declining eGFR levels [34, 85, 144, 160].

*Proposed mechanistics of ARV-related nephrotoxicity*

Adverse renal effects of ARVs may arise in a number of different ways as schematically illustrated in Figure 9 [99]

**Figure 9, Schematic drawing of a nephron with presumed points of attack for ARVs** [99]




Some PI/b may cause renal impairment by precipitation in urine and cause crystalluria, urolithiasis and interstitial nephritis [86, 99, 123, 124, 129, 153, 165]. Interstitial nephritis is a common finding in biopsies of PLWH and can be related to use of several different drugs [86, 166]. The proportion of a PI/b that is renally excreted differ

for the individual PIs, and may reflect some of the differences in the propensity to cause renal impairment [99, 163].

TDF may also directly impact renal function by accumulation in proximal tubular cells causing mitochondrial toxicity and tubular dysfunction [95, 99, 167-170]. Several studies have further suggested that certain single-nucleotide polymorphisms (SNPs) in the renal tubular drug efflux transporters are associated with increased risk of TDF tubulopathy [171-174]. While these findings still need external validation in other studies these findings may contribute to determining why only some individuals develop TDF-associated CKD. Investigations of the interplay between such genetic pre-dispositions and comorbid conditions such as diabetes, hypertension, immune suppression and viral hepatitis co-infection are starting to be undertaken, i.e. in a recent study based on the Swiss HIV cohort we found that the genetic profile seems to play a large role of CKD development in PLWH (see discussion on paper 6) [175]. In time if commercial test become available this may become an important contributor to help tailor ART also according to the genetic risk profile. In addition to an impact on genetic pre-disposition, an animal study suggested gradual accumulation of TDF within the renal cortex with longer use [155], which may explain the cumulative relations observed.

Several studies have shown that individuals exposed to a combinations of TDF and PI/b experience greater declines in renal function compared to those on a combinations with a NNRTI[145, 176, 177]. We and others have as described above; however, shown that concomitant PI/b and TDF use is not prerequisite for nephrotoxicity [85, 163, 178].

Some ARVs may also cause renal impairment more indirectly mediated by other adverse effect such as diabetes and dyslipidemia[179-181].

Several ARVs (DTG, rilpivirine, RTV and cobicistat) inhibits tubular creatinine secretion (acting via the OCT2 and MATE 1 +2 transporters) and can cause artifactual increases in plasma creatinine as also described for trimethoprim [144, 182]. As discussed above for RTV boosting doses this is less of a practical issue [158]. For the other drugs this may, however, be a challenge when co-administered with drugs with nephrotoxic properties. The artifactual eGFR increase is approximately 10-15 mL/min/$m^2$ and seen early after the drugs are started, wherefore a new renal baseline set-point is recommended after 1-2 months [144]. Changes in muscles mass (i.e. due to wasting or intense body building) or intake of creatinine may also artificially impact plasma creatinine and are important to consider as potential causes of measurement bias. If there are concerns about using a creatine-based eGFR estimation an alternative may be to use a cystatin C based eGFR estimation.

Whilst the majority of publications on ART-related nephrotoxicity is derived from Europe, North USA and Australia consistent and primarily observational data have in recent years also been reported from Asia and South America [136, 183-185]. Studies investigating ART-related nephrotoxicity in African and particularly sub-Saharan Africa setting, which is one of the epicenters of the infection, are generally more heterogenous than in many other regions [77, 178, 186-192]. While some of these African studies are well-designed and of an adequate size to allow for reliable conclusion, many suffer from considerate methodological issues [77, 178, 186-192]. In addition, there are considerate challenges related to use of standard creatinine based eGFR equations (e.g. CG, MDRD, CKD-EPI) in Africa settings as these, due to a significantly different body compositions of PLWH in Africa, are ill-fitted and underestimate CKD risks [193, 194]. In two large studies in Zambia and South Africa eGFR outcomes differed significantly according to baseline eGFR, in that those with pre-existing renal impairment improved on TDF based ART (by reverting HIV-related impairment) whereas those with normal to mild renal function experience an eGFR decline over time (toxicity, see figure 2 in chapter 3) [178, 186], but neither formally assessed interactions between TDF and baseline eGFR. Such competing pathologies may be particularly relevant in west-Africa due to the genetic pre-disposition to HIV-related CKD and may account for some of these inter-study differences [82]. A recent French study showed a significant interaction between TDF use and ethnicity ($p = 0.03$) for risk of proximal tubular dysfunction (PTD) in which TDF was only associated with PTD in those of non-Africans origin [195]. A large British study from 2017 also found white ethnicity to be major risk for TDF related tubulopathy. These findings are intriguing and needs further investigation in large studies of PLWH with diverse ethnic background. Further, it remains unclear if similar ethnic differences may apply to ATV/r and LPV/r.

**eGFR Outcomes After Chronic Renal Impairment and relation to nephrotoxic ARVs** *(paper 5)*

Having seen increasing CKD incidence over time with higher CKD incidence in PLWH, and having identified potential predictors hereof including use of several ARVs, the natural next pertinent step is to analyse what happens to renal function after chronic impairment has developed [58, 60, 85]. In particular, understanding the potential impact of discontinuation of the ARVs with nephrotoxic properties on subsequent renal prognosis is crucial for clinical management and monitoring recommendations [99].

Experience from studies of non-ARV nephrotoxicity including aminoglycosides have shown that drug-induced tubular or interstitial renal damage is reversible when recognised early, the causative drug is discontinued, low cumulative doses are administered and the exposed individual has no/few comorbidities [35, 196-201].

There are; however, several methodological challenges related to investigating potentials of "reversibility" of renal impairment. The lack of a unifying definition of reversibility is evident from the literature which is dominated by case reports and several different analytical approaches [152, 196, 202-208]. A small *FDA* study based on volunteer adverse event reporting found that everyone discontinuing ATV due to acute renal impairment and urolithiasis subsequently improved renal function [209]. A British study investigated eGFR slopes before initiation, under and six months after discontinuing TDF, and has the advantage of using all available eGFRs and not requiring a lot of power [210]. They found that discontinuation of TDF caused significant improving in mean changes in eGFR slope. However, in addition they reported that 39% did not experience full eGFR recovery at six months. An issue with analysing reversibility/recovery of renal function is that increasing age and declining renal function are closely related [211]. Further, several co-morbidities causing progressive renal impairment (i.e. diabetes and hypertension) are common in PLWH with chronic renal impairment. When analysing longitudinal data on renal function the effect of age and comorbidities needs to be taken into consideration, as it will be unlikely regardless of any drug discontinuation for the renal function to return to earlier pre-treatment levels. Despite this important limitation several studies have still concluded incomplete recovery after TDF discontinuation as only some subsequently reached their pre-exposure eGFR levels [152, 156, 204, 207, 210].

Additionally, many studies reporting on renal outcomes after ARV discontinuation have only been small in size, with limited follow-up and many have focused on acute and/or mild impairment [152, 196, 202-209].

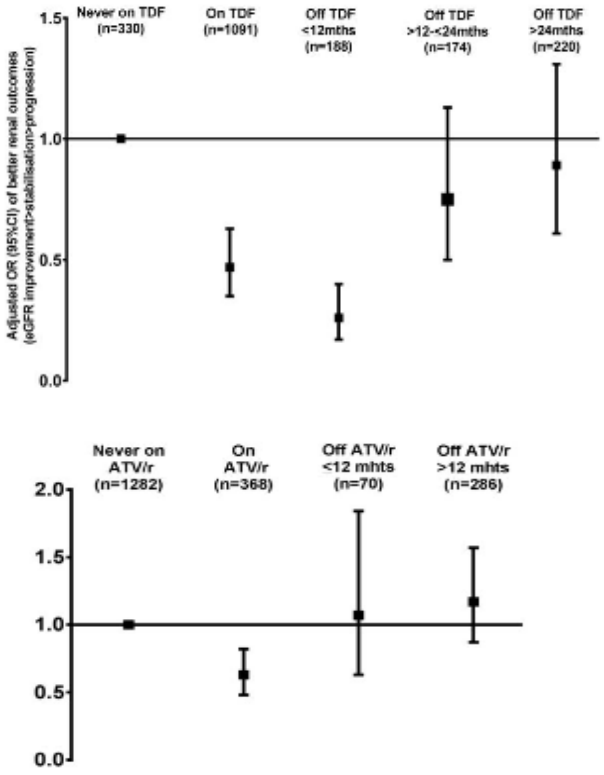
When looking at outcomes after chronic renal impairment another challenge is the duration of the impairment, as such longstanding chronic disease is less likely to improve (due to formation of nephrofibrosis) than those with a shorter disease course. In our 2017 analysis on renal outcomes (paper 7) we therefore only included individuals with initial progressive renal disease [37, 56, 152]. Related to the challenges of high ARV discontinuation rates already before eGFR declined below 70 mL/min/1.73m$^2$, we

further decided to re-use the CRI endpoint from our 2013 JID paper as the primary outcome, but ART status was estimated at 24 months after the CRI diagnosis to allow for assessment of drug switches at and around the time of CRI [35, 154]. We compared the median of all eGFRs measured 24-36 months post-CRI to the median eGFR defining CRI, and grouped eGFR outcomes into improvement (>+10 mL/min/1.73m$^2$), stabilisation (-10 to +10 mL/min/1.73m$^2$) and progression (<-10 mL/min/1.73m$^2$). Our study therefore has a clear advantage of being the only study to date with longer term renal outcomes and using confirmed renal measures of renal outcomes in a large diverse population.

Of those with CRI the majority (67%) stabilised renal function, a large proportion (21%) improved, and the smallest proportion (12%) progressed. Individuals remaining on TDF or ATV/r after a diagnosis of CRI had worse long term eGFR outcomes compared to those unexposed to these ARVs (TDF: 0.47 [0.35-0.63], ATV/r: 0.63 [0.48-0.82]). However, individuals who discontinued these ARVs, and had been off TDF for 12-24 months (0.75 [0.50-1.13]) or off ATV/r for more than 12 months (1.17 [0.87-1.57]) had similar eGFR outcomes as those unexposed to these ARVs, Figure 10. Results for LPV/r did not reach statistical significance.

This data suggests that the eGFR declines observed for TDF and ATV/r may not represent irreversible renal tissue damage as the ARV-related impairment may be halted or reversed after their cessation. As our data suggest the TDF related nephrotoxicity takes time (>12 months) a too short follow-up may therefore in addition to the methodological issues discussed above be some part of the explanation for the large proportion with incomplete eGFR recovery at 6 months in the British study [210]. Since our publication only a small single center Polish study has studied TDF reversibility. Using a less rigorous definition of reversibility after CKD they confirmed a large proportion subsequently improved renal function after TDF discontinuation [212]. While the bulk of data suggests that with appropriate monitoring and management at least some of the excess renal risk among PLWH can be modified [34, 52]. However, we did find a concerning interaction between TDF and age, suggesting that odds of a better eGFR outcomes associated with discontinuing TDF were decreased for individuals older than 50 years. This finding emphasises the need for focusing on declining renal function in particular in those on TDF older than 50 years due to a lower regenerative potential.

**Figure 10, Adjusted Odds of better renal outcomes after CRI according to use of TDF and ATV/r [35]**




We were, however, unfortunately not able to clarify if there is a threshold nadir eGFR level in PLWH, below which better renal outcomes after discontinuation of ARVs will no longer be possible. Evidence from the general population points to having lost a critical number of nephrons will initiate an irreversible progressive process with accelerated loss of nephrons resulting in needs of renal replacement therapy [213]. The British study in PLWH indicated that such a level may exist for ART-nephrotoxicity as lower eGFR levels after TDF discontinuation were associated with higher risks of incomplete renal function recovery at six months, but were also not able to specify any nadir value [210]. While this question is key, it will not be ethically to study impact of nadir eGFR levels in prospective studies, and with guidelines recommending to consider changing away from ARVs with nephrotoxic properties in case of increasing levels of urine protein to creatinine levels, rapidly decreasing eGFR levels, high CKD risk, low body weight and eGFR $\leq$60 mL/min/1.73m$^2$ it is unlikely to be addressed systematically in future studies [86, 144].

We were unable to reliably evaluate if the impact of longer cumulative duration of TDF and ATV/r exposure on the odds of better renal outcome, but a small Australian have suggest those with shorter TDF duration were more likely to improve median renal function [152]. Likewise the British study suggested more-prolonged exposure to TDF were associated with an increased risk of incomplete renal recovery 6 months

after discontinuation of TDF [210]. It will be relevant to reassess this question in adequately powered studies with long follow-up

As the *D:A:D* study does not collect data on proteinuria or other tubular markers we were unable to assess the reversibility potential related to tubulopathy, but a small US case-control study by Gupta and colleagues have suggested that TDF-related tubulopathy is easier to resolve than TDF associated eGFR decline [214].

The impact of the eGFR slope (fast vs slow) before CRI was not found to be associated with renal outcomes in our study, which contrasts findings from the small Australian study, were a faster eGFR decline had better (median) eGFR outcomes [152]. The requirement of an active progression to CRI in our analysis may have impacted the slope asessment.

As expected, we showed that progressive co-morbid condition like older age, diabetes and hypertension to be independently associated with a worse renal prognosis.

We did not find an association with CD4 count, which may be related to the relatively high CD4 count of those included (median 520 cells/mm$^3$), and the interaction between immune suppression and CKD, in which immunesupression has a greater impact in those at low CKD risk, and in this analysis everyone per definition had progressed to CRI [100].

It is a positive finding that more than 20% with CRI had a potential to subsequently improve in renal function, similar observations have been done in the general population where reports have suggested that up to 15% may improve renal function after CKD stage 3 [213].

While, based on current evidence, it seems plausible that better eGFR outcomes are possible after discontinuation of TDF and ATV/r, even after more chronic level of renal impairment have developed, additional studies are urgently needed to determine which renal interventions are the most effective for PLWH, and at which level of renal impairment they should be initiated (see paper 7).

*Conclusions, limitations and perspectives on use of ARVs with nephrotoxic properties and CKD in PLWH*

As observational data continue to dominate the literature of ART-related nephrotoxicity causality cannot be inferred. However, several of the Bradford Hill criteria are met supporting a likely causal relation. Firstly, the findings have been reproduced in several diverse study settings over more than a decade and in very different geographical regions [57, 136, 146, 160, 183, 185, 187].

Further, the drug signals have been confirmed using various different types of renal function measures [57, 160, 187, 195] and of different types of statistical modelling including marginal structural models [57, 146].

Furthermore studies have also showed an effect of TDF on renal function in other study populations than those living with HIV such as HBV mono-infected persons [215] and HIV-negative persons on PrEP [216].

We have further showed that the ART associations have a cumulative dose-response relationship of a significant effect size and that discontinuations of the suspected offending drugs have a positive impact on renal function [35, 85, 157, 160, 212, 217].

Additionally, we have showed specificity of these toxicities, as only use of some PIs and NRTIs were related to CKD, and the different ARVs considered have different risks of CKD and different NNTH [34, 54].

Finally, there are in part biological plausible mechanisms described for both the ATV/r, LPV/r and TDF associations, although a better understanding including the role of genetic variations in drug-efflux transporters, mitochondrial toxicity, interstitial inflammation and impact of ethnicity is warranted [86, 155, 161, 168, 218-221].

Our analyses were limited by not having systematic data available on proteinuria or other tubular markers (see chapter on limitations), which may likely have underestimated the true incidence of ARV-associated nephrotoxicity. Further, due to the observational nature of the analyses we are unable to capture the impact of unmeasured and unknown confounders such as concomitant use of other drugs with nephrotoxic potentials, impact of diet including intake of creatinine and of genetic predispositions, as discussed below (paper 6)

In currently years PI/b are becoming less frequently used due to a greater potential of drug-drug interactions and adverse drug effects, and several other effective treatment options [144]. Further DRV/r, which is currently the only recommended first line PI/b in *EACS* Guidelines, has not consistently or strongly been associations with CKD risks (see paper 4) [54, 144]. This may result in decreased PI-related renal impairment in PLWH. For TDF (as for ATV/r and LPV/r) clinicians are, in accordance with current recommendations from i.e. *EACS* and *KDIGO* switching away in case of emerging signs of renal impairment as there are often other viable options including switching to a NRTI-sparing regimen or use of more renal friendly options like TAF [86, 144, 222-226]. In addition guidelines provide recommendations how to reduce ARV dosing in individuals with different levels of renal impairment, which may theoretically better prognosis in those unable to change to other ARVs [86, 144].

As discussed in the renal introduction section an association between nephrotoxic ART and ESRD has never been established; either due to ART-related renal effects only being moderate in size, due to too limited follow-up for rare events and/or due to clinician driven active avoidance of ARVs with nephrotoxic properties and switching away from these as renal function declines [35-37, 227].

In resource limited settings, such as sub-Saharan Africa, the possibilities to monitor renal function are often none to limited [76]. The 2010 *DART* trial argued that routine laboratory monitoring did not have a net benefit on mortality, WHO stage 4 events and serious adverse effects in ART-naïve individuals starting treatment in Zimbabwe and Uganda [192]. The *WHO* further underlined that the ability to monitor for

markers of toxicity, although desirable, should not be a precondition to starting ART, as benefits are believed to greatly outweigh risks of adverse events with current ART regimens [228]. In 2009 The *WHO* recommended implementing TDF-containing regimens in resource limiting setting [229]. However, the higher costs of TDF at the time meant that wide uptake of TDF occurred years later, and as such we may to date still not have seen the full spectrum of potential long-term consequences related to lack of systemic monitoring in a population of increased CKD risks. The approximate median 5 years follow-up and little more than 3300 persons in *DART* may further not have been adequately long to assess such accumulating renal impact in a young population (median 36 years). Conversely, as will be discussed below there may, in resource limited settings be some rational in prioritising monitoring in those at high renal risks, as the NNTH on TDF is high in low-risk individuals- at least in western study settings [34].

To date longer term renal outcomes related to use of TAF, which has significantly lower plasma levels of tenofovir, and of INSTIs that are being used increasingly common in persons at high renal risks or with drug-toxicity are still pending. A recent pooled analysis of 26 RCTs suggested lower risk of proximal tubulopathy and lower rates of drug discontinuation related to TAF vs TDF use[222]. It is essential to continue to study real life drug safety related to more extended use of TAF, INSTIs and other new ARVs to ensure a fuller picture of renal safety in PLWH and to ensure rational treatment strategies.

**CKD prediction model in PLWH** *(paper 6)*

Having gained insights into the natural history of incident CKD in PLWH and associated risk factors we developed a model in 2014 to help predict risks of developing CKD over a five year period [34, 230]. The *D:A:D* study has previously engaged in developing risk scores for accurate CVD prediction in PLWH [33].
The increased risks of CKD in PLWH are of great concern as undiagnosed and untreated CKD may progress to ESRD, CVD and death (see paper 7) [72, 154, 213]. The prediction tool aims to assist clinicians in identifying those at highest risk of CKD with needs of intensified monitoring and targeted interventions, and to aid evidence-based and individualised decision-making balancing the pros and cons of starting ARVs with nephrotoxic potentials. Such personalised approaches to HIV-management is strongly advocated by international HIV societies including the *EACS* Guidelines and *WHO* [4, 231].

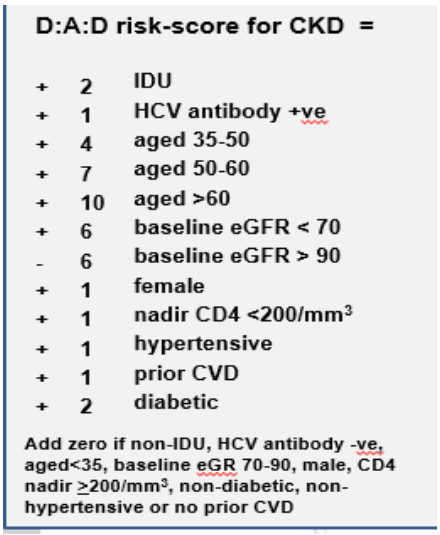
CKD is a concern worldwide and difficulties in identifying high risk individuals has led to development of numerous CKD prediction models in the general HIV-indeterminate population [232].
In 2007 the US *SCORED* study found age, female sex, diabetes, hypertension, peripheral vascular disease, history of CVD, congestive heart failure, proteinuria and anemia to be key predictors for CKD (stage 3) [233].
A 2010 Chinese study also identified age and diabetes as key predictors, but additionally included diastolic blood pressure, body mass index (BMI) and stroke in their model [234]. A 2011 Thai study similarly identified age, diabetes and hypertension as CKD stage 1-5 predictors but also identified kidney stones as a predictor [235], while the Dutch *PREVEND* study additionally included baseline eGFR, urinary albumin excretion and C-reactive protein [236]. A 2012 review concluded that most CKD prediction models in the general HIV-indeterminate population were poorly executed, of small size, cross-sectional, without external validation and without good discrimination of CKD risk (see below) [232]. While there are several overlapping key predictive factors in these studies, there are also several differences which may reflect genuine differences between study population and/or differences in the methodological approach [213]. In 2019 a large and geographically diverse collaboration with more than 5 million individuals from 34 cohorts and 28 countries contributed to development of a CKD scores in persons with and without diabetes [237]. The study follow-up ranged from 1990 to 2017 and the score was externally validated in nine additional cohorts. Over five years the main CKD predictors were age, sex, ethnicity, baseline eGFR, history of CVD, smoking, hypertension, BMI, albuminuria, diabetes treatment and, hemoglobin A1c with a discrimination of 0.85.
Nevertheless none of these prediction models have been widely implemented in PLWH as their utility is limited by the lack of data on key renal risk factors for PLWH [213, 233-236]. A 2011 Japanese study was the first to developed a CKD prediction score designated for PLWH [238]. The study included age, CD4 count, diabetes, proteinuria and baseline eGFR as the main score component with a discrimination of 0.84. The

study was, however significantly limited by only being able to predict short-term (within one-year) CKD risk, included a relatively limited number of persons and CKD events (620 persons with 18 CKD events) and was only partly externally validated.

In 2014 two large studies of PLWH with extended follow-up both published a 5-year CKD-prediction score. The US Veterans Affair *(VA)* study had a clear advantage of including data on proteinuria, and an ethnic diverse population, but was limited by only including men living with HIV, not being externally validated and focused on TDF use [52]. In addition to use of TDF the *VA* prediction model included age, glucose, systolic blood pressure, hypertension, triglycerides, proteinuria and CD4 count. The NNTH for persons on TDF depended on the risk profile with 108 for those at low risk (0 points) to 20 for persons at higher risk (≥9 points). The other CKD prediction model was based on the *D:A:D* study, dominated by European and Australian men and women living with HIV, and discussed below [34].

Over a long median follow-up (exceeding 6 years), with a high number of persons and CKD events (almost 18.000 persons and 641 events) we found that the best fitting CKD model included 9 key variables, Figure 11; age, female gender, IDU, HCV-coinfection, baseline eGFR, hypertension, diabetes, prior CVD and nadir CD4 count.

**Figure 11, Components of the D:A:D CKD Risk Score** [34]




Based on prior analyses and the literature these were all expected, and with good agreement with that of the US *VA* study [52]. Similarly, to the US CKD sore neither of the models found prior AIDS, HIV-VL or HBV as key CKD predictors.

We did exclude a substantial proportion of the cohort due to prevalent CKD, lack of adequate prospective follow-up, eGFR, CD4 count and VL measurements and due to prior expose to drugs with nephrotoxic potentials. This led to some concern about selection bias, as the incidence of CKD was higher in those excluded. To get an adequately clean study population these actions were; however, considered necessary and the external validation (see below) suggest this was not a major issue.
The median estimated CKD risk in the overall included *D:A:D* population was low (-2, IQR -4 to 2) as also reflected in the high median baseline eGFR (105 mL/min/1.73m$^2$, IQR 90-120, and 75% with eGFR >90 mL/min/1.73m$^2$). The proportion estimated to progress to CKD at low estimated CKD risk was 1 in 393 increasing to 1 in 6 at those at high estimated CKD risk. The median estimated CKD risk in those developing CKD was 10 (IQR 5-14).

The NNTH for ARVs with nephrotoxic potentials are shown in Figure 12. For TDF and ATV/r estimated CKD risk increased from 1 in 603 persons in those at low estimated CKD risk to 1 in 9 for high risk persons. This suggests TDF may be used as safe ART backbone for the large proportion of PLWH without renal risks and illustrates how using a prediction tool may aid in determining rational needs for monitoring and balancing risks and benefits for each individual.

**Figure 12, Number-Needed to Treat to Harm (NNTH) for Starting ARVs With Nephrotoxic Potentials in Different CKD Risk Strata** [34]

| CKD risk | Score | NNTH for LPV/r, ATV | NNTH for TDF, ATV/r, PI/r |
|---|---|---|---|
| **Low** | <0 | 1395 | 603 |
| **Medium** | 0-4 | 142 | 61 |
| **High** | ≥5 | 20 | 9 |

We assess the model's utility by calculating the discrimination (using Harrell's c statistics = area under the ROC curve), which expresses how well the model identifies those developing an event vs. those that do not. A value of 0.5 expresses a bad ability to discriminate between cases and non-cases (like flipping a coin), the closer the estimate is to 1.0 the better. In the *D:A:D* derivation cohort the discrimination was very good (0.92), which is substantially higher than in the CKD prediction models of the general population described

above. While the short CKD model also had good discrimination (0.91), it was significantly worse than the full model, and with a higher Akaike information criteria suggestion poorer model fit it should be reserved for the cases where CVD-related data cannot be assessed reliably.
To validate the model, we tested the performance in two very different independent cohorts, the British *RFHCH* (n=2500) and the control (non-interventional) arms of the *ESPRIT* and *SMART* studies (n= 2000). To assess the validity, we compared the IRRs for individual factors and the KM estimates for progression to CKD, which we found to be similar for each risk strata in-between derivation and validation cohorts. We further calculated the discrimination in the validation cohorts were also good (0.86 and 0.87), suggesting the model is appropriate and accurate also in other settings.

Our model has since also been validated by other independent research groups. An Australian study found the score to be well calibrated (good agreement between the predicted and observed rates of CKD), with superior discrimination to the *VA* CKD score [239]. A 2016 French study found the model classification useful for clinicians when making decisions on ART regimens depending on the risk profile [240]. Finally the US Observational Pharmaco-Epidemiology Research and Analysis *(OPERA)* study showed, in very recent analysis, that the adjusted IRRs were similar to those of the *D:A:D* cohort, the median score was -3, CKD rates increased by risk stratum and the model had good discrimination (0.87 to 0.92) [241]. This is an important observation given the large size and considerate difference of the study populations (*OPREA* population was younger, had more men, less co-infections and AIDS, but more with unsuppressed viremia) and shows the model can also be used by US clinicians.

A major aim related to developing the risk score in *D:A:D* was to produce an easy assessable risk score that could be used in everyday clinical practice as well as research settings. An online tool was therefore developed in which you simply enter the key patient characteristics, and based on the CKD probability equation the 5 years risk of progression to CKD is provided (https://www.chip.dk/Tools-Standards/Clinical-risk-scores).

*Conclusions, limitations and perspectives*

Currently there are at least two different CKD predictions models available for everyday clinical use for PLWH, one derived from European and Australian populations, but externally validated in several independent studies, and one US model. Each model has advantages and limitations. As recommended in the 2019 *EACS* Guidelines and the 2018 *KDIGO* HIV consensus report It is probably less essential which CKD model you use, the importance is to have a tool to allow for reliable identification of those at risk to

facilitate appropriate risk management and to have open, evidence-based and individualised discussions of pros- and cons of using specific ARVs depending on the underlying risk profile [86, 144].
All risk estimation tools have inherent limitations that should be acknowledged when interpreting the estimates. As such no CKD prediction tool will be equally appropriate for all PLWH. Whilst current data support reasonable agreement between the estimated and observed CKD rates (calibration) in several very diverse cohorts as described above, it is key to get insight into its accuracy (how well the model is calibrated in subgroups), i.e. particular relevant for our model will be to test the performance in women and in persons with proteinuria as these may both have been somewhat underrepresented in the derivation cohort. It is likely that the model will be less adequate in PLWH in sub-Saharan Africa as all current eGFR equations are based on western populations, and studies have found this leads to systematic overestimation of eGFR levels and underestimation of CKD risks [193]. As age and baseline eGFR are the main drivers of CKD in the model a commentary was published urging caution about the comparatively smaller impact of ARVs with nephrotoxic potentials and concerns about confounding by indication [242]. In a reply we stressed the importance of evaluating the potential impact of nephrotoxic ARVs in relation to the renal risk profile, as highlighted by the high NNTH for those a low CKD risk, and low number for those already at high renal risks and the cumulative nature of the association [242]. Further, while it is correct that in earlier years declining eGFR could be an independent indication for starting ART, i.e. in those with HIVAN, this indication was infrequent in the *D:A:D* population due to the low proportion of ART-naïve persons of African origin. Additionally, we only included specific ARVs previously described to be associated with increased CKD incidence, and any confounding due to this indication would actually work in the other direction as rates of discontinuing these ARVs increase as eGFR declines [154].

Whilst these data provide some evidence to suggest that regular monitoring of renal function for persons starting ARVs with nephrotoxic potentials is most cost-effective in those at high estimated renal risk (lowest NNTH), it should be underlined again that these data are derived in resource rich settings of primarily non-African men. Whilst the *DART* trial reached similar conclusions it should not be overlooked that the renal risk profile in PLWH changes over time, and hence future tools should also account for risk re-evaluation during ongoing ART [192].

Whether these equations over time will lead to the intended improvement in clinical outcomes with lower incidence of CKD and CKD-related outcomes should be the focus of future studies.
We aim to update the *D:A:D* CKD model to include more recent data, use of modern ARVs including TAF and INSTIs, cumulative use and discontinuation of individual nephrotoxic ARVs directly in the prediction model and to assess performance in key subgroups. A 2017 *D:A:D* study further suggested that risks of CVD

and CKD may advantageously be assessed concomitantly [243]. Further, the current *D:A:D* CKD model, as most prediction models of the general population, has risk variables fitted at baseline to obtain longer-term prediction. However, this approach has the disadvantage of not taking into account that risks may well change over the 5-year prediction period [33]. Therefore, when updating the model, we also intend to fit risks that may vary over time as time-updated rather than as time fixed variables.

In a recent study published in CID in 2020 based on the Swiss HIV cohort, we investigated the impact of more than 86,000 single nucleotide polymorphisms for a poly-genetic CKD risk score [175]. In models adjusted for the *D:A:D* CKD risk score and use of nephrotoxic ARVs an unfavorable genetic profile independently doubled the risk of progression from an initial normal renal function to CKD. The study further revealed an interaction between the genetic and clinical risk factor, suggesting that the most favorable genetic profile may protect against incident CKD even with several ongoing clinical risk factors (high *D:A:D* score), on the contrary those with the most unfavorable genetic profile will not develop CKD without clinical risk factors (low *D:A:D* score) [175]. The major limitation of this finding in modern management of PLWH is, however, that such genetic profiling is not broadly available as part for routine screening and therefore identifying those with a genetic vulnerable phenotype is currently only possible in research settings. The study, however, contributes with important information of a strong complementary effect of genetic predisposition for CKD in PLWH and future studies should investigate if clinical management stratified according to the genetic profile may improve long term renal outcomes.

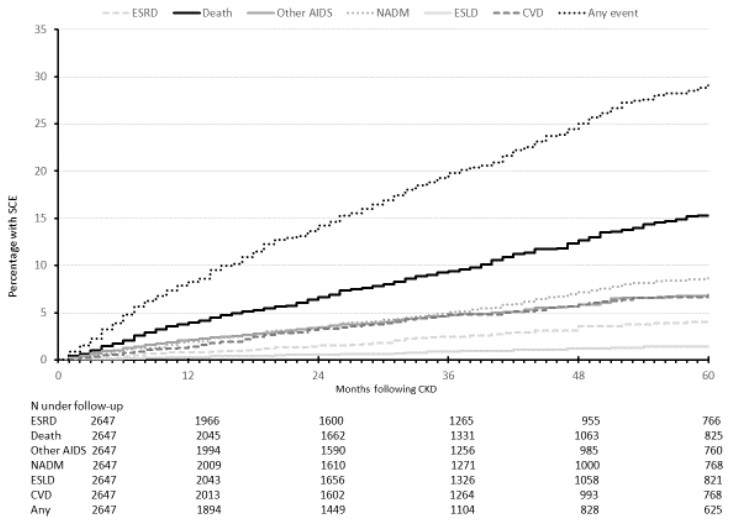
Having others studies build on the evidence on CKD prediction by adding additional predictive CKD data sources such as proteinuria, other (early) renal biomarkers and genetic profile will continue to be essential to limit the impact residual confound factors and to allow for as precise individual morbidity prediction as possible [175, 244].

**Serious clinical events (SCE) after CKD in PLWH** *(paper 7)*

Having spent considerable efforts on uncovering predictors of CKD in PLWH, we found that the insights into the morbidity burden after acquiring CKD, and the potential role of modifiable risk factors (i.e. diabetes and smoking), were relatively limited in PLWH. In the general population CKD has been associated with a wide range of complications including anemia, bone disorder, cancer, ESRD, CVD and death [245-251]. These heterogenous outcomes are believed to be related to the disequilibrium caused by disruption of the many endogen and exogen functions of the kidneys including derangement of fluid-, electrolyte- and pH balance, accumulation of toxins, impaired immune function, increased inflammation, oxidative stress, hormonal imbalance, hypertension and accelerated atherosclerosis [112, 213, 252]. In 2012 data from seven UK HIV-cohorts showed a U-shaped relation between eGFR and death over a median 5-year follow-up period [253]. Several other studies in PLWH have more formally investigated individual outcomes after CKD including ESRD, CVD and mortality, but many were carried out during an era where the prevalence of HIVAN was high, and lacked the broader overview of the spectrum of CKD-related outcomes as well as insights into possible preventive targets [36, 74, 154, 230, 253-257]

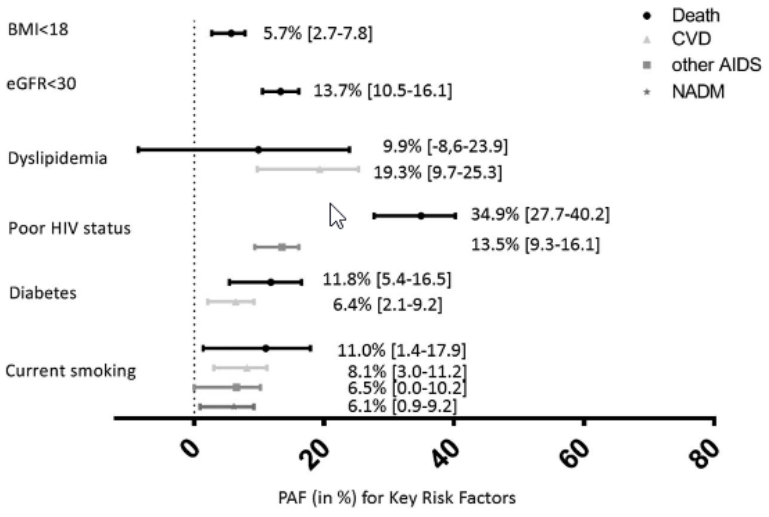
In our 2019 AIDS paper (paper 7) we included almost 2500 persons with CKD and found that those living with both HIV and CKD had a high burden of SCE, with almost one in three experiencing a SCE within five years of their CKD diagnosis [72]. The most common SCE was death (incidence 32.2/1,000 PYFU [28.6-35.8] and a five-year post-CKD mortality rate exceeding 15%), followed by NADM (15.2/1,000 PYFU [12.7-17.7]), CVD (14.6/1,000 PYFU [12.1-17.0]) and non-malignant AIDS events (13.0/1,000 PYFU [10.7-15.3]), Figure 13. With the relatively short median follow-up (less than three years) there were relatively few incident cases of ESRD, ESLD and ADM events after CKD. A large Canadian community cohort of HIV-indeterminate showed in 2010 that for a given eGFR level rates of MI, ESRD and death were independently increased in those with proteinuria, similarly data from the veteran's affair (*VA*) study showed higher ESRD risk in PLWH when combining eGFR with proteinuria, suggesting that the already high burden of disease described in *D:A:D* may be even higher due to lack of access to proteinuria data [84, 245].

**Figure 13, Kaplan Meier Estimation of Cumulative Incidence of SCE After CKD** [72]




Several modifiable risk factors strongly predict CKD-related SCE including smoking, poor HIV-status and diabetes. Each of the considered CKD-related SCE had a distinctive risk profile, as also shown for CVD, ESRD and mortality among HIV-indeterminant persons with CKD in the diverse US *CRIC* cohort [258], Figure 14.

**Figure 14, Population Attributable Fraction (PAF) of Risk Factors for Individual SCE after CKD** [72]




Smoking was; however, as the one factor consistently associated with all the CKD-related SCE, suggesting that had people not been current smokers between 6.1 and 11% of the complications may not have occurred. The small British *CRIB* study and several US studies have also identified smoking as a key risk factor for CKD-related death in the general HIV-negative population [246, 248]. In our study smoking was

somewhat more broadly associated with SCE after CKD, which may be related to both a higher proportion of smoking PLWH and the interaction between HIV-status and smoking in increasing inflammation and worsening immune impairment [259]. In the CKD-indeterminate *D:A:D* study population we've showed a major impact of smoking cessation on lowering incidence of several cancers [260] and CVD [261]. However, it remains to be explored if an effect of smoking cessation may be even more beneficial in those with CKD where even more pathological pathways may be activated concomitantly.

Of those with CKD a high proportion (47.9%) had experienced a prior SCE, most commonly a non-malignant AIDS event. Poor HIV-status further predicted non-malignant AIDS, as also described in a small Kenyan study [254], and death after CKD, underlying the close relation between HIV and both incident CKD [34, 100] and CKD disease burden [74, 253]. That non-malignant AIDS events were one of the most frequent SCEs after CKD may in addition to HIV-status be related to the exacerbated impairment of immune function in persons with CKD [262]. In 2007 Choi and colleges further described that people living with CKD and HIV in the US, regardless of ethnic origin, had higher risk of death than HIV-negative with CKD and diabetes, again emphasizing the strong potential impact of HIV, and the importance of timely and continuous ART to for a better renal prognosis (see section on immunesupression and CKD) [74, 98, 100, 102].

Diabetes is a very common and strong CKD predictors in PLWH and the general population [34, 74, 263, 264]. As in a large meta-analysis of the general population in 2018, we documented that in PLWH and CKD, diabetes independently predicts several SCE [248]. Hallan and colleagues also described how a high national diabetes prevalence increase the proportion of individuals with progression ESRD [263]. These findings are of great concern as the prevalence of diabetes continues to increase in PLWH, and efforts should therefor go into how to we can optimise DM management [71, 265].

Death was as the only SCE associated with all considered modifiable risk factors (apart from dyslipidemia) likely reflective of the heterogenous underlying causes of death. ESRD and death have consistently been described as competition outcomes in people with CKD, with ESRD being more common in younger individuals [248, 266, 267]. However, with the relatively short median follow-up and moderate levels of CKD we did not find indications that competing risks played a major role, although we were limited by only 72 ESRD events and a relatively high median age of those with CKD (60 years).

The relation between low eGFR and CVD will be discussed in more detail in the section below (paper 8) [154].

Cancers and CKD have a complex interplay; CKD may be an adverse outcome of cancer-treatment and paraneoplastic manifestations, Inversely, cancers may arise as a complication to CKD, perhaps due to shared risk factors (i.e. smoking and diabetes as shown in our analysis), accumulations of toxins and higher

occurrence infections [230, 249, 250]. The CKD-related cancer risk in the general population is particularly high in those with ESRD, but several observational studies have also described increased incidence of several cancers (including non-genitourethral cancers) in persons with more moderate levels of CKD [249, 268-270]

Our findings suggest that several of the factors which has previously been shown contribute to CKD development (initiators) are also instrumental in driving major CKD complications (perpetuators) [34, 52, 72, 213]. We did not consider the potential role of nephrotoxic ART on post-CKD SCE rates as such analyses would be highly confounded by indication due to frequent discontinuations of these drugs already before incident CKD [35, 37].To our knowledge no other study has undertaken such analyses for a wide range of non-renal SCE.

In our analysis SCE rates were significantly elevated already within a few years after the CKD diagnosis, which may suggest some level of reverse causality (especially relevant for cancers and ESLD), and renal function as a marker of general health deterioration. Importantly; however, time-lagging SCE and accounting for prior SCE did not impact the high complication rates after CKD [230].

We further described that those living with both CKD and HIV had an almost three-times higher disease burden than those without CKD (crude incidence of any SCE 23.0 per 1000 PYFU [22.4-23.6] vs 63.7/1000 PYFU [57.9-69.6]), despite median follow-up in those without CKD was four-times longer and without indication of surveillance bias in those with CKD. While we could compare SCE rates in those with and without CKD, in *D:A:D* we did not have a comparative HIV-negative cohort. However, judging by prior studies rates of several CKD-related complications in PLWH appear consistently higher [74, 246, 255]. Studies with access to renal biopsies in persons with CKD have described that a multifactorial genesis of CKD/CKD progression is in fact very common [247, 271]. The combination of ongoing CKD risk factors, the direct CKD-related disequilibrium and HIV will activate several different pathological pathways, but also have several pathways in in common such as impaired immune function and increased inflammation, which may explain why this group represents a particularly vulnerable group for developing SCE, although we and others have not formally been able to shown any interactions [112, 248, 262].

*Conclusion, limitations and perspectives*

This and other studies have shown that in an era where many PLWH require less monitoring due to effective and well-tolerated ART, those living with even moderate levels of CKD have a high morbidity and mortality burden[72, 74, 154, 253] . The *D:A:D* analysis was primarily limited by only having three years median follow-up after CKD, and by not having assess to proteinuria data or genetic predispositions. We identified several modifiable risk factors to be closely associated with the detrimental outcomes of CKD. In the

general population, and particularly amongst PLWH, there are; however, still substantial gaps in knowledge of optimal management of CKD [29, 86, 213, 272]. In *RxEACH trial* as mentioned above (paper 7) targeted intervention for dyslipidaemia, hypertension and smoking proved effective in reducing CKD-related CVD risks in the general population [273]. However, no study to date has adequately assessed impact of interventions on such factors on CKD prognosis in PLWH. As concluded during the 2018 *KDIGO* HIV/CKD consensus conference until more evidence becomes available it does seem rational to follow efficacy studies on interventions in the general population, despite these also remain incomplete [86]. The increasing CKD incidence in PLWH; however, makes it imperative to gain better understanding on were to focus interventions to guide development of a more personalised approach.

**Chapter 6 Atherosclerotic CVD in PLWH** *(papers 8 and 9)*

As described in the introduction excess risk of MI in young men living with HIV was one of the first non-AIDS events that came to the attention of both clinicians involved in HIV care and the authorities overlooking drug safety. In 2007 data from Triant and colleagues suggested US PLWH under care between 1996 and 2004 had up to 75% increased risk of MI compared to HIV-negative age-matched controls [274]. In more recent years ambiguity has been raised whether PLWH using modern and more CVD friendly ART, starting ART earlier, alongside increased awareness of potential adverse drug effects and increased use of primary prophylaxis had levelled out the differences in CVD among PLWH and the general HIV-negative population [60, 274-276]. A 2015 study by Klein and colleagues in the large (>24,000 PLWH) and well-described Californian *Kaiser-Permanente (KP)* cohorts found that rates of MI declined between 1999 and 2011 in PLWH, and in 2010-2011 reached similar levels compared to matched HIV-negative individuals (adjusted RR 1.0 [0.7-1.4]) [276]. In contrast, a recent large (>82,000 PLWH) US study by Rosenson and colleagues found that between 2011 and 2016 insured US PLWH remained at approximately 30% increased risk of atherosclerotic CVD when compared to the general HIV-negative background population [277]. The Roenson study was based on the *MarketScan* database, which contains data from different healthcare insurance sources. There are substantial differences in methodology and study population, the *KP* cohort i.e. is renowned for a highly reliable data capture and had a long average follow-up time (4.8 vs 1.6 years in the Roenson study). Given the increased focus and systematic approach applied to management of CVD risks in PLWH in the *KP* population the difference in findings may also represent difference in management in the *KP* and general US population living with HIV. The *KP* also showed that in the time period use of lipid lowering drugs, anti-hypertensives and other atherosclerotic preventive strategies increased in *KP*, whilst PLWH were also started on ART earlier and the use of PIs declined [277]. The *AGEhIV cohort* study also suggested increasing CVD rates in PLWH in recent years and related this to increased frequency and severity of common CVD risk factors such as hypertension and dyslipidemia in the aging population living with HIV [60].

*Mechanisms of atherosclerotic CVD and associated risk factors in PLWH*

Traditional major atherosclerotic CVD risk factors include diabetes, hypertension, dyslipidemia and smoking, all of which are highly prevalent in PLWH [60, 277, 278]. Applying standard atherosclerotic CVD preventional strategies in PLWH therefore remain essential [4, 279-281]. However, a higher prevalence of these CVD risk factors has proven inadequate to explain the increased MI incidence in PLWH [274, 282]. As such CVD prediction models developed in the general population i.e. *Framingham, QRISK* and *ASCVD* have been shown to systemically underestimate CVD risk in PLWH, whereas the *D:A:D* CVD risk equation which also includes HIV-relevant variables, generally has a better calibration in PLWH [33, 283-288].

The mechanisms of HIV-related atherosclerotic CVD involve multiple pathways with a complex interplay and are to date still not fully understood [281, 289, 290] .

There is substantial evidence suggesting that HIV itself induce a pro-atherogenic state with persistent inflammation, coagulation and immune activation, CMV reactivation, microbial translocation and changes in high-density lipoprotein (HDL) function **[289-296]**. Even in fully virally suppressed PLWH without CVD, ex vivo studies have shown an increase propensity to form lipid-laden foam cells known to promote atherosclerosis more than in HIV-negative controls [292, 297]. Data linking HIV-related immune suppression and CVD are conflicting; some studies have showed an association, while others have not, and misclassification i.e. type II MIs (see below) and space occupying diseases mimicking stroke have been suggested as concerns for those suggesting an association without using rigorously defined atherosclerotic CVD endpoints [275, 298, 299]. In the *START* study participants were relatively young, and the number of CVD events too limited to determine the impact of immediate vs. deferred ART start, but in a *START* sub-study using arterial elasticity as a proxy for CVD there were no indication that immediate vs. deferred start of ART impacted outcomes [300]. In the *SMART* study intermittent vs. continuous ART was associated with a 57% increased CVD risk, but the effect was only borderline significant (p=0.05), and potentially partly related to a poorer lipid profile, enhanced inflammation and coagulation activation [102, 295, 301]. In 2003 Friis-Moeller et al. in *D:A:D* showed that the risk of CVD was lowest in ART-naïve PLWH and increased linearly with longer duration of first generation ART [21]. A recent review and metanalysis suggested that the association between longer cumulative use of ARVs and CVD was simply a proxy for longer duration on the HIV infection [275]. However, if that was the case, you would expect to see a similar relation between use all ARVs and CVD risk, which is not the case. Several different studies have specifically for certain PI/b showed a gradually increasing CVD risk related to longer use hand with recent use of ABC [21-23, 53, 302-307]. CVD outcomes with specific ARVs have predominantly been examined in observational studies as drug discovery trials are not adequately powered to analyse such hard clinical outcomes [308]. In paper 9, discussed below, we explored impact of more contemporary PIs ATV/r and DRV/r on atherosclerotic CVD risk [53]. Recent data has suggested that use of INSTI with TAF may lead to weight gain and increased lipid levels, however it is unclear if such trends on the longer term may translate into increased risks of CVD, although a recent RCT with 96 weeks of follow-up did not suggest any changes in CVD risk [309-311]. To date there is no published data on CVD risks related to use of INSTIs, but such analyses are being undertaken by the new RESPOND cohort collaboration.

Relations between viral hepatitis, and HCV in particular, and atherosclerotic CVD are conflicting; some reporting increased inflammation related to untreated HCV causing accelerated atherosclerosis and

increased risk of stroke, whilst other report no association with type I MI, but doubling of risk of type II MIs [312-314].

*Characteristics of Atherosclerotic lesions in PLWH*

Several studies have reported higher rates of subclinical atherosclerotic CVD in PLWH compared to the general HIV-negative population [296, 315]. There is also evidence suggesting that the atherosclerotic lesions seen in PLWH differ from the lesion patterns seen in the general HIV-negative population with CVD, supporting a different atherosclerotic pathogenesis [316-318]. A recent US study found that PLWH experiencing MI more commonly have single-vessel disease than HIV-negative persons that more commonly present with multi-vessel disease [316]. A somewhat smaller Danish study did not find differences in the number of vessel involvement between PLWH and controls with MI, but observed less complex atherosclerotic lesions in PLWH [318]. A 2016 Australian study described a lower overall plaque burden in PLWH than HIV-negative controls and suggested that the higher MI rates in PLWH could be related to having more vulnerable plaques than a large burden of atherosclerotic changes [317]. Before the era of drug-eluding stents one study also reported a larger risk of restenosis in PLWH than in controls [289].

*CVD management and outcomes*

Outcomes after CVD and the current recommendations for screening and treating CVD in PLWH is described in more details in chapters 3 and 8.

In the sections below two key pending questions regarding relations between CKD and CVD, and on CVD risks related to use of contemporary PIs in PLWH are described.

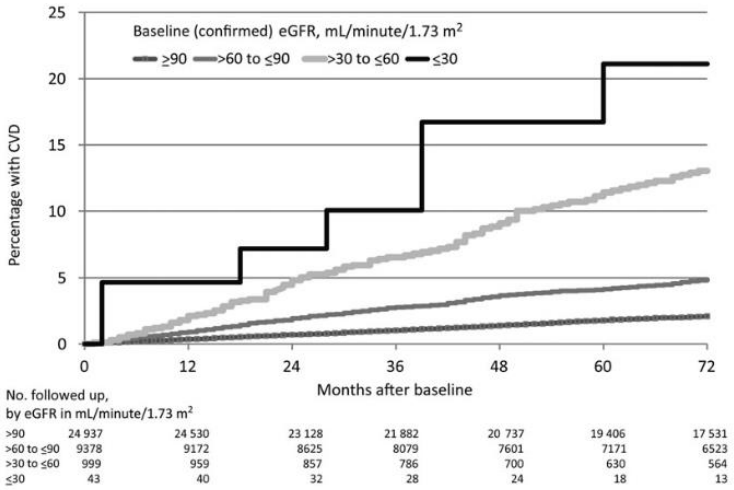
**Renal function & CVD** *(paper 8)*

While, CVD is among the leading causes of non-AIDS death in PLWH, CVD is the most common cause of death in persons with renal failure [16, 319]. Studying renal impairment and CVD in PLWH is therefore crucial to increase our understanding of the inter-disease relation. In the general population, there is solid data suggesting an association between renal impairment and CVD; a 2004 US study described that more than half of those admitted with an MI had CKD (stage 3), and those with CKD further experienced more post-MI morbidity and mortality than those without CKD [320].
We hypothesised that the generally higher burden of traditional shared CKD-CVD risk factors in PLWH and the contribution of HIV-related pro-atherogenic state the association between renal impairment and CVD may be even stronger. At the time of our 2015 analysis most studies in PLWH investigating this relation were limited by using single measures of renal impairment, very broad and sometimes less well-defined CVD endpoints, of relatively limited size or of cross-sectional design [154, 252, 256, 321-326].

The association between CKD and CVD is in the background population is especially strong for persons with ESRD, however we did not have adequate number of ESRD events to reliably assess this association in dept [324, 327-329]. Also, at the time we were limited by a limited number of persons with CKD with adequately long prospective follow-up, and hence required just that the eGFR measurements were confirmed, but not necessarily $\geq$ 3 months apart. However, by definition based on the *D:A:D* data collection, a confirmed measurement will be min 1 months apart. When we gained sufficient PYFU after CKD we reassess the association between CKD and CVD as part of the analysis on SCE after CKD, as discussed above with overall similar findings [72].

During 8.0 years median follow-up 1,357 individuals in *D:A:D* developed an incident CVD event (Incidence 5.2 /1000 PYFU (5.0–5.5]). Among those with normal baseline renal function (eGFR >90 mL/min/1.73m$^2$) less than 2% were estimated to develop CVD at 5 years, Figure 15. This proportion was ten times higher (20%) in those with severe renal impairment (eGFR ≤30 mL/min/1.73 m$^2$). Among those with confirmed eGFR <60 mL/min/1.73 m$^2$ the median time to CVD was 45 months (IQR, 21–76 months), without differences for the individual events of the composite endpoint. Whilst only 4% of those with a normal confirmed renal function experienced a fatal CVD event as many as 25% of those with confirmed current eGFR ≤30 mL/min/1.73 m$^2$ died (<28 days) from their CVD event. This finding may both reflect a more severe CVD event and less ability to recover after the CVD event in those with severely impaired renal function. Coronary by-pass was the only event more commonly observed at lower eGFR levels possible reflecting more advanced atherosclerotic disease.

**Figure 15, Kaplan-Meier Estimation of Progression to CVD by Confirmed Baseline eGFR Levels** [154]



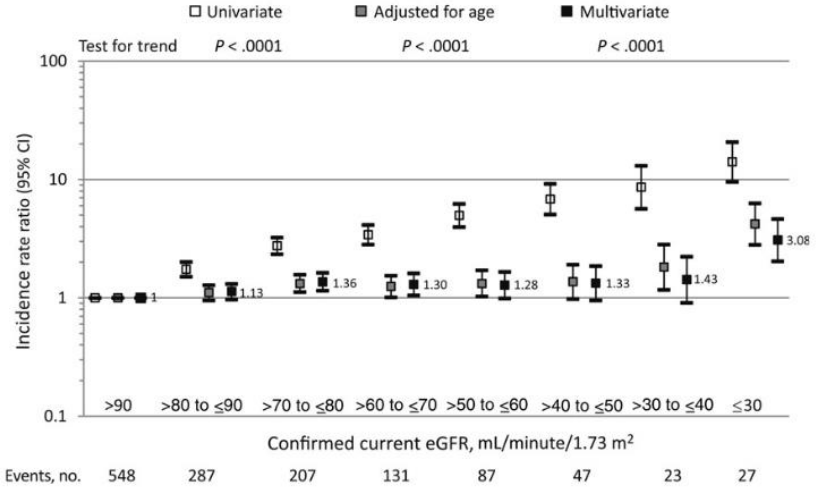

As also reported in the general HIV-negative population particularly high CVD rates (incidence rate ratio 3.08 [2.04–4.65]) were seen for those with severely impaired renal function [330]. The *VA* cohort reported similar findings of a gradual increase at low eGFR levels in PLWH in 2010, but also included cardiac failure and peripheral artery disease [256].

Increased age accounted for much of the inverse linearly increased risk between lower eGFR and CVD for eGFR levels >30mL/min/1.73m$^2$, although everyone with eGFR levels just below the normal range (eGFR <80 mL/min/1.73m$^2$) remained at 30%–40% increased CVD rates, Figure 16 [330]. In the literature some ambiguity does, however, still remain today about when the effect of renal impairment starts to significantly impact CVD risk. For PLWH a British study from 2012 using single eGFR measures, also described increased CVD rates in in PLWH with only mildly impaired renal function, after adjusting for age, with more than four-fold higher rates in individuals with eGFR <75 mL/min/1.73m$^2$ compared those without any eGFR impairment [326]. A small nested, matched, case-control in the US described that per 10 mL/min/1.73m$^2$ lower eGFR odds of CVD increased with 20% in PLWH [325] . Several studies in PLWH have also looked at CKD and subclinical or early stages of CVD. As such a small Spanish study in PLWH found that mild renal impairment predicted prevalent subclinical atherosclerosis by assessing carotid intima-medial thickness (cIMT) [331]. Using CT angiography a 2019 study also described than even mildly impaired eGFR, independently of other risk factors, predicted calcified coronary plaques and a higher Agatston score (indicating the extent of coronary artery calcification) in PLWH, but not in HIV-negative controls [332]. In contrast, a cross-section subanalysis of approximately 500 PLWH of the *FRAM* study did, in 2011, not find that lower eGFR or albuminuria predicted cIMT, using high-resolution B-mode ultrasound [252]. In the

general population the data on milder levels of renal impairment and CVD are also conflicting ranging from studies clearly demonstrating excess CVD risk while others fail to demonstrate a significant relation at eGFR levels above 60 mL/min/1.73m$^2$ [245, 321, 322, 330, 333]. Incorporating renal function in CVD prediction models are debated, and CKD is not formally included in the *Fragminham, 2019 ASCVD* nor the 2014 *D:A:D* CVD score, but is included in the *QRISK 2-3 scores* (in 2017 CKD stage 3 included), and is planned for the next update of the next *D:A:D* CVD score [33, 243, 284-286, 334]. It is however commonly noted that CKD status should be taking into consideration when evaluating CVD risk especially when evaluating benefits of different interventions [283, 284].

There are several methodological differences between the studies investigating renocardiac relations, including considerate heterogenicity in study sizes, study design, median renal function of those included and how broadly and rigorously CVD was defined. In our analysis we didn't see any strong evidence that the associations between renal impairment and CVD differed for the individual components of the composite CVD endpoint, so this inter-study difference does not appear to be an explanation for the different findings. Whilst the *D:A:D* study has the clear advantage of substantial geographical heterogenicity, large size and long prospective follow-up in addition to rigorously defined severe CVD endpoints we did not have access to proteinuria data which has been shown to provide important complementary prognostic information, and which may likely have further strengthen the associations seen also for milder levels of eGFR impairment [245, 256].

**Figure 16, Incidence Rate Ratio of CVD by Confirmed Current eGFR Levels** [154]




Interestingly we found that adjusting for other potential confounders than age, including hypertension, diabetes and ART use, did not greatly impact the association suggesting other underlying mechanisms may be driving the association.

The mechanistics linking CKD and CVD remain a hot topic and is sometimes referred to as the renocardiac or cardiorenal syndrome and may be driven by several distinct pathways [114, 213, 335-338]. CVD and CKD share common risk factors (i.e. diabetes and hypertension) and may drive both diseases concomitantly, and we have previously shown an inverse relation, in which CVD predicted CKD [34, 36, 319, 330]. However, there are also several more direct pathways leading from CKD to CVD [339]. Persons with CKD have higher levels of circulating uremic toxins, more oxidative stress, activated inflammation, impaired immune function, and hyperphosphatemia which may all accelerate atherosclerosis and increase CVD risk [114, 335-338, 340, 341]. Increased levels of renin release in CKD cause vasoconstriction and hypertension and in turn CVD [342]. In addition to these atherosclerotic pathways, persons with CKD more commonly have atrial fibrillation which predisposes to stroke, congestive heart failure and severe electrolyte derangements predisposing to malignant arrythmias [328, 333, 335, 343, 344].

While current literature doesn't indicate substantial differences in the renocardiac relation among PLWH and HIV-negative populations using hard clinical CVD endpoints, head-to-head comparisons across a wide range of renal levels are missing [245, 256, 321, 322, 325, 326, 333, 339]. Especially since a recent US study, as mentioned above, suggested higher prevalence of pre-clinical atherosclerotic coronary changes in PLWH with mildly impaired renal function this calls for exploration in larger settings, with a wider range of renal function and endpoints including harder clinical endpoints [332].

*Conclusion, limitations and perspectives*

The high rates of both fatal and non-fatal CVD events in older PLWH with continuously low eGFRs calls for increased monitoring and focus on potential modifying factors in this population. Whilst we were able to adjust for familiar disposition to CVD in this analysis, we did not have data on genetic factors nor proteinuria, which would likely have strengthened the association even further. As also discussed above interventions aimed at limiting progression of CKD and reducing the CKD-related CVD burden remain suboptimally explored especially in PLWH [273, 342]. In the general population a subanalysis of the randomised clinical *RxEACH* trial showed that already after three months an intensified approach on controlling hypertension, hypercholesterolemia and reducing smoking in persons with CKD reduced CVD risks [273]. However, given the several other pathways involved in CKD-related CVD development only addressing traditional risk factors will likely be insufficient in both PLWH and HIV-negative persons, and research efforts should therefore focus on the impact on disrupting various steps of these mechanisms [281, 289, 345].

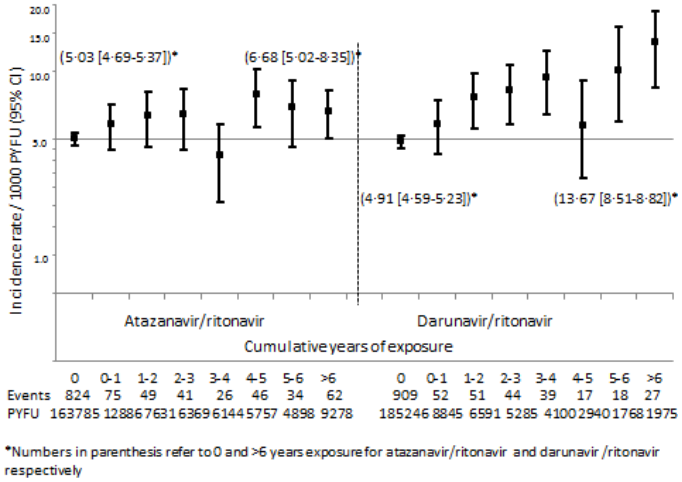
**Use of Contemporary PIs and risk of CVD** *(paper 9)*

As discussed above several earlier observational studies and some mechanistic studies have described an association between longer cumulative use of older first generation PIs including LPV/r (incidence rate ratio 1.54 per 5 years) and IDV (1.47 per 5 years) and CVD [23, 306, 307, 346, 347]. In 2016 our analysis on the *D:A:D* study population was the first to assess potential CVD risk with extended use of the two most frequently used contemporary PIs DRV/r and ATV/r [23, 306, 307, 346, 347].
ATV/r was first licensed in 2003 by the *FDA* and in 2004 by the *EMA*, and has been adversely associated with a benign increase in bilirubin levels causing jaundice, renal impairment and, as other PI/r, with gastrointestinal symptoms including nausea and diarrhea, and dyslipidemia [6]. DRV/r was licensed somewhat later (in 2006 by the *FDA* and in 2007 by the *EMA*) and initially, due to a high genetic barrier, predominantly used bid (twice daily) as salvage therapy for heavily treatment experienced PLWH. From 2008/2009 DRV/r qd (once daily) was more widely recommended for use in PLWH and remain today the only recommended first line PI/b in Europe [6]. DRV/r has as other PI/r rash, gastrointestinal symptoms and dyslipidemia a as most important adverse effects [6].

The underlying mechanism of the association between first-generation PIs and CVD is believed to be, at least partly, mediated by PI-induced dyslipidemia, and drugs within the PI drug class are have different metabolic profiles [43, 308, 348-350]. The *TITAN, ARTEMIS* and *ATADAR* trials have suggested that treatment-experienced individuals on DRV/r and ATV/r have fairly similar lipid profiles, but superior to first-generation LPV/r [180, 351, 352]. A *START* study analyses further found that immediate ART increased levels of total and LDL-cholesterol and use of lipid-lowering drugs[43]. Adjustment for lipids are therefor of particular interest in the analysis. To avoid adjusting for factors on the potential causal pathway from ATV/r and DRV/r use to CVD in our primary model we keep all such factors (dyslipidemia, CD4 count, BMI, diabetes and CKD) fixed at baseline. We did, however conduct, several sub-analyses to limit risk of bias and confounded data as much as the observational data allows (details below).

During seven years median follow-up 3.2% (n=1,157) of the study population developed CVD (Incidence 5.34 per 1000 PYFU [5.03-5.65]). The proportion exposed to ATV/r increased from 18.4% at baseline to 26.6% at end-of follow-up and from 4.0% to 22.7% for DRV/r. Among those exposed the median exposure at time of CVD was 3.1 years for ATV/r and 2.6 years for DRV/r. The crude incidence of CVD increased gradually from 4.91 [4.59-5.23] per 1000 PYFU in individuals unexposed to DRV/r to 13.67 [8.51-18.82] per 1000 PYFU in those exposed more than 6 years. The change in CVD incidence rate ratio over time while on ATV/r were less pronounced (5.03 [4.69-5.37] to 6.68 [5.02-8.35] per 1000 PYFU), Figure 17.

**Figure 17, Crude Incidence of CVD per 1000 PYFU Stratified by Cumulative Use of ATV/r and DRV/r** [53]

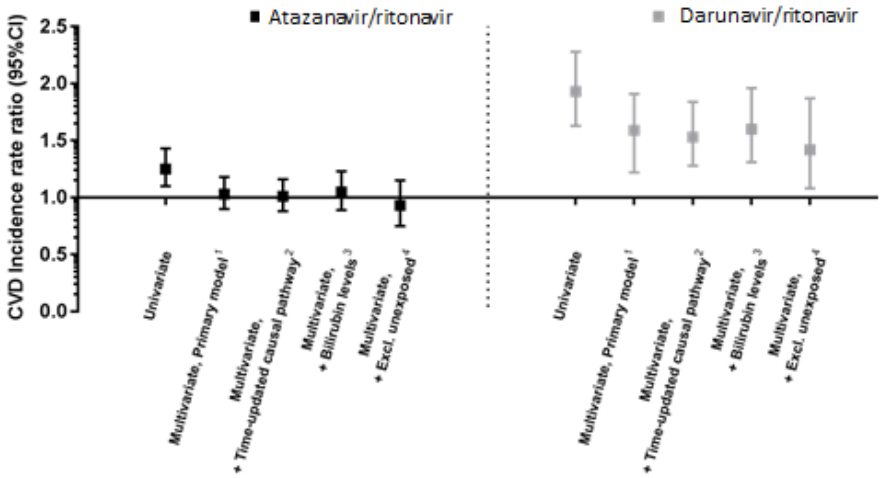



*Numbers in parenthesis refer to 0 and >6 years exposure for atazanavir/ritonavir and darunavir /ritonavir respectively

In adjusted models, longer use of DRV/r, but not ATV/r, was associated with increased risk of CVD (1.59 [1.33-1.91] and 1.03 [0.90-1.18] per 5 years use, respectively), Figure 18. We also conducted a sub-analysis in which we excluded PYFU in individuals without exposure to DRV/r or ATV/r (where the CVD IRR were lower) with entirely consistent findings. Age was one of the factors with greatest impact on the drug associations. The strengths of this association for DRV/r is of a comparable size and gradient compared to the first-generation PIs [23].

For individuals at high (>10%) estimated CVD risk, five years use of DRV would therefore increase the absolute CVD risk to 16%. The NNTH for DRV/r range from 533 in those at low CVD risk to 15 in those at high risk.

**Figure 18, Association Between Cumulative use of ATV/r and DRV/r and CVD** [53]




1. The primary multivariate model was adjusted for cumulative exposure to DRV/r, ATV/r, LPV/r, IDV, on ABC, prior AIDS, HIV VL, HBV and HCV status, family history of CVD, hypertension, smoking (all as time-updated covariates), gender, age, race, enrollment cohort, HIV risk of acquisition, CD4, CD4 nadir, prior CVD, BMI, diabetes, dyslipidemia (incl. lipid-lowering drugs), CKD and date of baseline (all as fixed covariates at baseline).

Subsequent multivariate models were additionally adjusted for:
2. Variables on the potential causal pathway (BMI, dyslipidaemia, CD4 count, diabetes and CKD) from ATV/r or DRV/r use to CVD were all time-updated
3.Time-updated bilirubin levels
4. Excluding PYFU with no exposure to ATV/r and DRV/r respectively

Adjustment for time-updated dyslipidemia and other time-updated variables on the potential causal pathway (BMI, CD4 count, diabetes and CKD) from ATV/r and DRV/r to CVD did not significantly impact the association. This suggests that the relation between DRV/r and CVD is not, in contrast to the first-generation PIs, mediated by simple changes in the lipid profile, nor by any of the other considered factors. However, we cannot rule out that the definitions of dyslipidemia used in this analysis may have been too simple to fully capture all the changes PIs may induce in lipid pathways leading to CVD such as increase of CD36-dependent cholesteryl ester accumulation in macrophages [43, 307, 349, 353, 354]. We also cannot rule out that DRV/r could activate other pro-atherogenic or thrombotic pathways, as described for ABC [303, 304, 346].

As ATV/r is known to increase plasma levels of bilirubin, and hyperbilirubinemia has been associated with a cardioprotective effect related to reduced oxidative stress, we investigated if adjustment for bilirubin levels could explain the lack of an association between ATV/r and CVD, but did not observe an impact hereof, neither did we find evidence of an interaction between ATV/r and bilirubin levels on CVD risk [355, 356].
The lack of an association between ATV/r and CVD confirmed a prior 2013 *D:A:D* analysis, where we were limited by less power [347]. LaFleur and colleagues based on the *VA* cohort also found that PLWH on ATV/r had between 36-41% lower risk of MI and stroke than those on non-ATV treatment (including other PIs, NNRTIs and INSTIs) [357]. In addition, Stein and colleagues based on the AIDS Clinical Trial Group Study (*ACTG*) A5260 found that ART-naïve PLWH randomised to an ATV/r containing regimen had slower progressing of cIMT than those randomised to DRV/r (or RAL) [358].

In secondary analyses we assessed MI and stroke outcomes separately rather than CVD as a composite endpoint and found no evidence of a differentiated association for each main component.
Appreciating DRV/r was used as salvage therapy in early years and use therefore likely confounded by indication we chose a 2009 baseline for our analyses where use of DRV/r was much broader. While *D:A:D* does not collect information on dosage and therefore unable to address if DRV/r was prescribed qd or bid, as a proxy we conducted a sensitivity analyses in which we investigated impact on DRV use in persons with an without persons with ongoing HIV viral control. In another analysis we restricted the study population to those using DRV/r as their first ever PI regimen (which to some extent would limit heavily treated experienced persons). All these sensitivity analyses provided entirely robust results and therefore did not provide strong arguments that the CVD association was confounded by DRV use as part of salvage therapy.

Results were also robust after excluding those with prior CVD (before baseline). Likewise, accounting for the estimated CVD risk in those starting DRV/r vs ATV/r, provided robust results suggesting that a higher CVD risk in those starting DRV/r was explaining the subsequent higher CVD rates compared to those starting ATV/r. Finally, adjustment for use of antiplatelets, which are indicted in individuals with prior CVD or at >10% estimated CVD risk, did not alter the association. Recent use of ABC has consistently in *D:A:D* been associated with increased CVD incidence, however in this analysis we did account for the backbone used with DRV/r and ATV/r, and adjusting for ABC use did not remove the seen association between DRV/r and CVD [359].

The association between use of PIs and CVD has only been described in observational and mechanistics studies, whereas no RCT has, or likely will be, adequately powered [308]. We did not find evidence to suggest PIs as a group increase CVD risk, but rather observed an association only related to use of DRV/r. Specificity is an important finding supporting potential causality. Importantly, as with the first-generation PIs, we also observed a small, but gradually increasing gradient in the association between DRV/r and CVD indicating a dose-response relation with longer use. The observed association was further of a magnitude, that make it relevant to consider in clinical practice, especially for those at high underlying CVD risks.
The association between PI use and CVD was somewhat stronger in earlier years, this may be related to more aggressive management of CVD risk factors and more selection in who are offered these ARVs based on their underlying risk profile as advocated in guidelines [6, 21, 23, 53, 276, 306, 308].

*Other studies assessing the association between DRV/r use and CVD risk, reproducibility?*
Whilst none of the DRV/r development trials reported increased CVD rates, the European, but not US product information does however mention both angina pectoris and MI as potential adverse effect (in up to 1 per 100 and 1 per 1000 respectively [351, 352, 360-362]. These original studies were however designed to assess virological efficacy and laboratory defined outcomes and not longer-term adverse effects in heterogenous populations of PLWH.

Janssen, the company behind DRV/r, were the first to respond to our findings by publishing merged post-marketing data that did not show an association between DRV/r and incident CVD [363]. However, none of those studies had CVD as their study primary aim, used un-validated endpoints and where considerately less powered in terms of follow-up time (1.9 vs 7.0 years) and number of included persons and CVD endpoints (5,721 persons with 66 CVD events vs 35,711 persons with 1,157 CVD events).

A recent French case-control study by Costagliola and colleagues did not find a significant association between use of DRV/r and CVD, but was also limited by less power (as indicated in the wide confidence intervals) with 408 CVD cases of whom only 10% (40 events) were in persons ever exposed to DRV/r (vs 249 events in D:A:D) **[364].** Whilst we included follow-up time between 2009 and 2016 in the *D:A:D* analysis, they included a somewhat earlier time period between 2006 and 2012, where DRV/r use, in particular in the earlier years, was highly selected.

Also an Italian study by Antinori and colleagues has assessed the association, but was even smaller with only 23 CVD events in total, and did therefore not surprisingly not find an association [365].

Triant and Siedner reviewed this data in a 2020 commentary published in JID, and also noted the differences in power [366]. They considered reproducing the finding in other large studies and a mechanistic explanation would support the *D:A:D* findings- and recommended a cautioned approach to DRV/r use in high risk individuals where possible until additional large studies have investigated the association.

*Conclusions, limitations and perspectives*

As the population living with HIV ages and with that follows an increased prevalence of several age-related complications it becomes increasingly important to tailor ART to fit the individual risk profile, as already discussed for CKD in the above, but certainly not any less relevant for CVD [33, 60].

For the first time we described that longer use of DRV/r but not ATV/r, is associated with higher incidence of CVD. The NNTH for DRV/r varied from 533 persons in those at low CVD risk to 15 persons in those at high risk suggesting that DRV/r is safe treatment option for a large group of PLWH without considerate CVD risks. It is key to appreciate the general limitations related to observational data including risks of unmeasured confounders and the lack of causal inference. However, as DRV/r remain among recommended first line therapies, and it is unlikely that adequately powered RCT of CVD risk with DRV/r will ever be carried out, considering safety signals from observational studies should play a role in every day clinical management, especially if the data comes from well-powered studies with extended follow-up, are based on rigorously defined hard clinical endpoints, and the association is specific to certain drugs, of a considerate size (almost 60% per 5 years use), with a biological gradient and is robust [6, 308, 366]. For this reason our data on DRV/r and CVD has since been included in the overview table of potential adverse effect table of individual ARVs in the *EACS* Guidelines [6] .

Few other studies have since we published our findings not been able to reproduce a significant association between DRV/r and CVD, however these were likely considerately underpowered, and hence investigation in other large well-powered studies with extended follow-up time on DRV/r remain essential. It also

pertinent to investigate possible mechanisms, as in contrast to the first-generation PIs, there is no satisfying explanation for the association seen. Assessing if the association between DRV/r and CVD declines once use of DRV/r is discontinued is another key analysis, which however, requires substantial follow-up time and power, and no study to date including *D:A:D*, have been sufficiently powered to do test this hypothesis reliably.

The perspectives for CVD prevention and management in PLWH seem increasingly bright. Whilst risks of CVD in PLWH remain plentiful and highly prevalent, the improved insights into key CVD predictors, mechanistics and effectiveness of interventions such as smoking cessation and treatment of dyslipidaemia have significantly improved both primary and secondary prophylaxis, and have in certain setting completely removed the excess risk of CVD in PLWH and in others lowered CVD-related mortality significantly [6, 33, 60, 261, 276, 279]. However, there are still substantial regional and gender inequalities in CVD care, and much more needs to be done to increase our understanding of systematic anti-inflammatory and anti-coagulant treatment on CVD risks in PLWH [280, 367]. Meanwhile, systematic screening and management of modifiable risk factors and tailored ART remain a cornerstone for CVD care in PLWH [6].

**Chapter 7 Terminal liver failure in PLWH** *(paper 10)*

In 2016 we published the first large, prospective and long-term analysis to investigate incidence, outcomes and impact of ART on clinically defined ESLD and HCC in HIV-mono and viral hepatitis co-infected persons [55].

ESLD is the terminal symptomatic stage of chronic liver disease in which the normal structure and function of the liver is disrupted, replaced by fibrosis and nodular architecture. The clinical symptoms of ESLD are closely related to these changes with reduced detoxification (hepatic encephalopathy), portal hypertension (variceal bleeding, ascites and hepatorenal syndrome) and impaired synthetic functions (hypoalbuminemia and ascites). In the general HIV-indeterminant population ESLD and HCC are most commonly seen in persons with viral hepatitis, alcohol abuse and obesity [368] with an 2% estimated prevalence in 2006 in the US population [368]. Towner and colleagues described in 2012 that PLWH from the *KP* cohort had a 3.5 times higher relative risk of hepatic dysfunction (defined as a combined endpoint of abnormal liver function markers, encephalopathy, varices and ICD10 codes of hepatic failure) compared to HIV-negative persons [369]. Further, HIV has been shown to accelerate liver disease related to viral hepatitis [370-373]. As with the other organ diseases investigated in this dissertation the increased risk of liver complications in PLWH has been related to a wide range of potential risk factors including HIV itself and HIV-related immunesupression, viral hepatitis co-infection, hepatotoxic ART, obesity, alcohol and diabetes [26, 60, 369, 371, 374-377].

As ESLD/HCC is rare, few studies have been sufficiently powered to investigated impact of use of individual ARVs with such hard clinical endpoints, and have therefore focused on ART use overall or on ART classes and milder liver outcomes such as liver function markers (i.e. transaminases and bilirubin), fibrosis markers (imaging and biochemically defined), imaging and histology[369, 378, 379]. Another limitation of the data investing liver safety outcomes is the relatively small study size and methodological challenges including cross-sectional assessments or only limited follow-up time [374, 379-385]

*ESLD/HCC Occurrence*

Between 2004 and 2014 we included 319 ESLD (209)/HCC (110) events with an overall incidence of 1.01 [0.90–1.12] per 1000 PYFU. The majority (83%) of all events were in persons with viral-hepatitis co-infection, and ESLD/HCC incidence in persons without HBV or HCV was low (0.12 [0.07-0.16] per 1000 PYFU). ESLD/HCC rates were similar in those co-infected with HBV vs. HCV, Table 2.

**Table 2, Incidence of ESLD/HCC per 1000 PYFU stratified by HBV and HCV status** [55]

| Factor | | No. of events | PYFU | Rate | 95% CI |
|---|---|---|---|---|---|
| Overall | | 319 | 315 368 | 1.01 | 0.90–1.12 |
| HCV status[a] | Negative | 72 | 229 434 | 0.31 | 0.24–0.39 |
| | Positive | 229 | 63 786 | 3.59 | 3.13–4.06 |
| | Unknown | 18 | 22 148 | 0.81 | 0.48–1.28 |
| HBV status[b] | Negative/Not active | 240 | 284917 | 0.84 | 0.74-0.95 |
| | Positive active | 59 | 12 907 | 4.57 | 3.40–5.74 |
| | Unknown | 20 | 17 545 | 1.14 | 0.64–1.64 |

CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus.
[a]HCV status (negative: seronegative, or seropositive but HCV-RNA negative; positive: seropositive and HCV-RNA positive or HCV-RNA unknown or not tested).
[b]HBV status positive: active infection (HBs antigen, HBe antigen, or HBV-DNA positive).

The most common ESLD symptom was hepatic encephalopathy grades III–IV (43.3%) and endoscopically verified variceal bleeding (27.4%), while hepatorenal syndrome (14.6%) and liver transplantation (5.1%) were less frequent. Almost 10% had several symptoms on the same event date.

In the *VA* cohort, Lo and colleagues described a considerately higher incidence of hepatic decompensation of 7.4 per 100 PYFU in HIV and HCV-coinfected persons, but also used a somewhat less strict case definition (unvalidated cases of ascites, spontaneous bacterial peritonitis and esophageal variceal bleeding)[26]. In *NA-ACCORD* Klein and colleagues described an ESLD incidence (per 1000 PYFU) of 1.2 in HIV-monoinfected persons, 6.1 in those with HIV/HCV and 8.7 in those with HIV/HBV respectively [386]. These higher rates may reflect both an earlier time period (1996 to 2010) than that of *D:A:D* (2004-2014), differences in the risk profile of the cohorts and a somewhat less strict case definition in *NA-ACCORD*, although cases were also validated and included laboratory, clinical diagnoses or procedures suggestive of ESLD. The incidence of ESLD in *NA-ACCORD* was further described as stable over the study period. In a slightly later time period (2001 to 2014) another HIV/HCV cohort collaboration reported that the incidence of HCC increased (+11%/year), while that of other liver-events declined (-4%/year) [387]. As liver events in that study were less strictly defined the incidence was also considerately higher (8.6 [7.8-9.5] per 1000 PYFU) than observed in *D:A:D.*

*Impact of ART on liver outcomes*

Assessing the impact of ART use on longer-term liver outcomes is complicated by several potential counteracting effects. Numerous studies in persons co-infected with HIV and viral hepatitis have documented that the ART-related improvements in immune function effectively decrease progression of liver impairment [369, 377, 387, 388]. In the *SMART* study those on continuous vs. intermittent ART had 30% lower risk of major hepatic events (decompensated cirrhosis) investigated as part as a composite endpoint with CVD and renal events[39]. In the *START* study there was a 40% lower risk of serious non-AIDS events

including decompensated cirrhosis in those starting ART immediately vs. those deferring treatment[40]. Further, certain ARVs (TDF, 3TC and FTC) have antiviral properties for both HIV and HBV and may therefore have an additional direct beneficial effect on liver-related outcomes. Conversely a 2006 *D:A:D* analysis found that 15% of all deaths in PLWH were liver-related, and after accounting for CD4 count and demographics longer use of ART was associated with an 11% increased risk of liver-death per additional year of use [377]. It was claimed that longer ART use was just a proxy for longer HIV duration, however if that was the only explanation then association should disappear after adjusting for HIV duration (which it did not) and you would not expect to see a differentiated association with individual ARVs. Risks of ART-related hepatotoxicity is described to increase in those co-infected with viral hepatitis [379], and D:A:D has also showed that liver-related death are relatively rare in persons without viral hepatitis co-infection [389]. Hepatotoxicity is a common adverse effect of ART, and seen in up to 30% of PLWH on ART, as many ARVs are metabolised hepatically [6, 380, 390]. Dosage adjustment are therefore also recommended in case of liver impairment for several ARVs [6]. Manifestations of drug-related hepatotoxicity are diverse and differ from i.e. mild, self-limiting and asymptomatic increase in transaminases to fulminant toxic hepatitis and liver failure [6, 380].

*Use of NRTIs and liver outcomes*

In a subanalysis of a RCT Bani-Sadr and colleagues described that in persons with HIV and HCV (n= 205) odds of histologically verified fibrosis were three-fold higher in those exposed to didanosine (ddI) compared to other drugs [391]. In a cross-sectional study of persons (n=671) with HIV and HCV Loko and colleagues further described that persons using ddI for more than a median of 5 months had a 70% increased odds of severe liver fibrosis [384]. Based on these findings and several other small studies suggesting that use of dideoxynucleoside analogues or 'd-drugs' including ddI and stavudine (d4T) may adversely impact liver function markers and lead to development of severe steatosis/fibrosis we focused our analysis on the potential longer term impact of these drugs on incident ESLD/HCC [381, 383, 385, 391-396].
In adjusted models we found that longer cumulative use of both ddI (1.32 [1.07-1.63] per 5 years) and d4T (1.46 [1.20-1.77] per 5 years) were strongly related to increased rates of ESLD/HCC, Figure 19. While most prior studies reporting adverse liver effect of d-drugs were in persons co-infected with HCV we found that the association was independent of viral hepatitis status (p for interactions 0.09-0.5)[383, 384, 391, 397]. Mitochondrial toxicity has been suggested as a potential underlying mechanism for the d-drug associated hepatotoxicity [380, 391, 398, 399]. When these results were first released into the public domain in 2016 some found these safety signals to be of limited interest as d-drugs, due to their adverse effects profile, were already infrequently used as part of modern ART [6, 228]. Importantly, however, in this analysis we also found

that the risk of ESLD/HCC among individuals exposed to ddI and/or d4T remained elevated even several years after the drugs had been discontinued, a finding that has also been described using less rigorously defined liver outcomes, Figure 20 [400]. These observations hence have potential clinical implications for modern management of individuals with a history of longer d-drug use, and in particularly in those with other ongoing liver risk factors such as HCV with the largest absolute risk of liver failure. It could therefore be advocated that persons with long cumulative d-drug history should also follow guidelines for regular assessment of liver function including use of liver function/damage biomarkers, evidence of fibrosis (i.e. by using transient elastography) and in cause of cirrhosis ultrasound for HCC asessment [6].

Somewhat more unexpectedly we also found an association between longer cumulative use of TDF, another more modern NRTI, and increased incidence of ESLD/HCC (1.46 [1.11-1.93] per five years), Figure 19. The magnitude of the TDF association with ESLD/HCC was strikingly similar to that observed for the older NRTIs. As TDF is the recommended backbone in PLWH and HBV, confounding due to viral hepatitis co-infection may immediately seem like a possible explanation for the observed association between TDF and ESLD/HCC [6]. However, we did not find the association between TDF use and ESLD/HCC to be affected by stratifying according to viral hepatitis status or by adjustment for viral hepatitis. Furthermore, we found that use of FTC and 3TC, the ARVs most commonly co-prescribed with TDF, did not follow the same pattern; FTC use was associated with a significantly lower risk of ESLD/HCC (0.51 [0.32– 0.83] per 5 years), while the 3TC association did not reach statistical significance. Another *D:A:D* study carried out almost simultaneously led by Kovari included only PLWH without HBV and confirmed an association between longer use of TDF and chronic liver enzyme elevation after adjustment for potential cofounders [401] with a relative rate of 1.18 ([1,05-1.32]) after more than two years use. These findings collectively therefore suggest that the observed relation between TDF and ELSD/HCC does not reflect a simple association confounded by HBV co-infection. It has however been suggested that the observed association with TDF may be related to unreported HBV infection, however if that was the case you would expect to find a similar association with 3TC and FTC, which was not the case. Having persons with liver impairment preferentially treated with TDF due to a perception of good liver safety has also been suggested as an explanation, but seeing similar effects using a chronic liver enzyme elevation in persons with initial normal liver function argues against this. While there is no well-described biological explanation for this association it has not been excluded that some level of mitochondrial toxicity, as also described for other NRTIs, and the suggested basis for TDF-related renal toxicity could be a possibility, although in vitro data report this at much lower levels for TDF than for the older NRTIs [402]. Relatively few case reports and small studies have reported on hepatotoxicity in persons on TDF, and mostly when co-prescribed with FTC and EFV as part of atripla [403-407]. In 2013 Fink and colleagues reported a case of acute liver failure in a young woman from

Zimbabwe with initial normal liver function who developed fulminant liver failure six months after initiating atripla, also in 2013 Echenique and colleagues reported on a 40-year old female without any other liver risk factors that developed increase in transaminases eight months after starting atripla, which disappeared upon discontinuation, and finally in 2008 Lattuada and colleagues described three cases that developed increase in liver enzymes after TDF was added to an EFV-containing regimen [403, 406, 407]. In these studies, it is, however not possible to determine the relative contribution of each of the individual drug components. The original registrational trails for TDF did not suggest increased risks of hepatotoxicity, but the limited size and constitution of those included in such trials may have prevented them to catch any such presumed relatively rare events [408-410]. The potential for TDF to cause liver steatosis and toxic hepatitis is however included in the drug package insert and acknowledged in international guidelines [6, 411]. As the TDF relation to ESLD/HCC was unexpected it is crucial for other large study to investigate if they can reproduce these findings in PLWH with/without viral hepatitis. In a European collaboration of HIV- and HBV co-infected persons (n= 3,625), TDF use did not impact the incidence of HCC over time [412], but as TDF was prescribed to 72% of the cohort, the number of events considerately smaller and focused on HCC (n=60 events) exclusively in HIV/HBV-coinfected persons, results are difficult to compare directly. Importantly, however our findings were consistent when analysing the HCC and ESLD events separately and excluding those with HBV co-infection (20%). If the risk of terminal liver failure decreases in persons that have discounted TDF use that would further support a causal relation, but no study to date have been adequately powered to assess such a relation. Equally it would be highly relevant to test if the association is also observed for persons using TAF, but to date to too limited follow-up date on TAF have accrued for such reliable analyses.

*Use of NNRTIs and liver outcomes*

Use of nevirapine (NVP), efavirenz (EFV) and rilpivirine (RPV) have all been described to adversely impact liver function by causing toxic hepatitis [390, 406, 413-416]. In this analysis, however, we only found that longer cumulative use of NVP, was significantly associated ESLD/HCC, but with a reduced IRR of 0.76 per 5 years use ([0.58 –0.98]). Use of NVP is contraindicated in persons with cirrhosis CHILD-Pugh class B and C, and awareness of NVP associated acute liver impairment could cause a greater likelihood of NVP discontinuation in case of liver enzyme increase potentially leading to an association confounded by indication [6]. An alternative explanation is that any adverse liver effect of NVP is only acute and does not cause terminal liver failure. Use of EFV is further recommended with caution in case of liver impairment, and could possibly also explain the lack of an association [6].

*Use of PIs and liver outcomes*

Whilst ATV may commonly cause hyperbilirubinemia and rarely cause cholecystolithiasis we did not find

evidence of a significant association with ESLD/HCC [6]. Likewise the other recent *D:A:D* analysis investigating impact of individual ARVs did not find use of ATV for more than two years lead to higher rates chronic liver enzyme elevations [401]. (Fos)amprenavir (APV) was the only PI associated with ESLD/HCC (1.47 [1.01– 2.15] per 5 years) in our analysis, Figure 19. APV is now rarely used, but has in the past commonly been associated with increased liver enzymes, but as also been used for calculating dose recommendations for various levels of liver impairment which may have led to confounding by indication [417, 418]. There are no described direct adverse liver effects of DRV, and at the time of this analysis we had inadequate power to investigate this association reliably for ESLD/HCC in *D:A:D*, however another *D:A:D* analysis on chronic liver enzyme elevation and a small Italian cohort did indicated good liver safety for DRV [6, 382, 401]. There have been speculations about PI induced dyslipidemia and risk of non-alcoholic fatty liver disease (NAFLD, see below), however findings have been inconclusive and to date recommendations for treatment of NAFLD does not include considerations of ART modifications [6, 419, 420]. The lack of a statistically significant associations for commonly used PIs during the extended follow-up time in *D:A:D* is an important finding as this suggested that longer cumulative use of this class can be safely administered in PLWH from a terminal liver perspective.

*Use of INSTIs and liver outcomes*

In 2016 we did not have adequate power in *D:A:D* to reliably analyse potential impacts of longer use of INSTIs on ESLD/HCC risk given the individual INSTIs were introduced into clinical care significantly later than the other ARVs investigated. An upcoming project in the RESPOND cohort, using a similar definition of ESLD/HCC is planned to investigate this question. Meanwhile only few smaller studies have suggested that individuals with NAFLD switching to an INSTI from a PI/r or EFV had less steatosis [420, 421].

The ARV-associated ESLD/HCC incidence estimations presented in the study are as in other D:A:D analyses of a conservative nature. As *D:A:D* is a pharmacovigilance study maintaining a very high degree of certainty for clinical event ascertainment is crucial. The observational nature of the study further means that despite our efforts when designing the analysis, we cannot completely rule out that the associations observed are confounded by indication. The current lack of a potential biological mechanism linking TDF use to incident ESLD/HCC is an important limitation for causal inference as per Bradford Hill. However, the robustness of the association in several sensitivity analyses, the reproducibility using an alternative endpoint of chronic liver enzyme elevation and the similar magnitude and biological gradient to that of other investigated NRTIs calls for further investigations. The *D:A:D* study does not systematically collect information on alcohol consumption. While alcohol is important for ESLD/HCC development, it is however unlikely to confound the choice of ART, and therefore not likely to have impacted the associations observed for individual ARVs.

**Figure 19, Association between ESLD/HCC and cumulative (per five years) use of ARVs** [55]

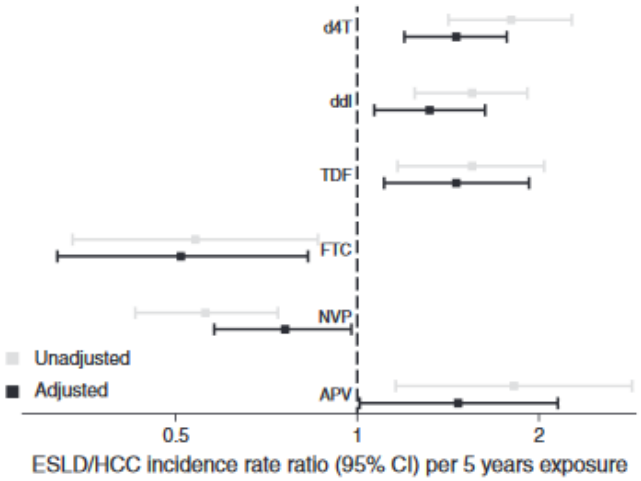



**Figure 20, Current, cumulative and past ddI and d4T use and rates of ESLD/HCC** [55]

| | | No other factor | Adjusted for exposure to other NRTIs, PIs and NNRTIs | Exposure to other NRTIs, PIs and NNRTIs and potential confounders[c] |
|---|---|---|---|---|
| | Rate of ESLD/HCC (per 1000 PYFU[a], 95% CI[a]) | Relative rate[b] (95% CI) | Relative rate (95% CI) | Relative rate (95% CI) |
| Never received d-drugs | 0.50 (0.40, 0.61) | 0.60 (0.37, 0.98) | 0.65 (0.40, 1.05) | 1.03 (0.60, 1.73) |
| Currently on d-drugs | 1.30 (0.87, 1.76) | Ref. | Ref. | Ref. |
| Stopped d-drugs and off for: | | | | |
| ≥0, <2 years | 1.89 (1.32, 2.45) | 1.70 (1.07, 2.69) | 1.72 (1.08, 2.72) | 1.64 (1.03, 2.60) |
| ≥2, <4 years | 1.85 (1.30, 2.41) | 1.60 (1.01, 2.52) | 1.65 (1.04, 2.61) | 1.59 (1.00, 2.52) |
| ≥4, <6 years | 1.93 (1.36, 2.50) | 1.63 (1.04, 2.56) | 1.72 (1.09, 2.73) | 1.63 (1.03, 2.59) |
| ≥6, <8 years | 1.56 (1.00, 2.12) | 1.34 (0.81, 2.20) | 1.48 (0.89, 2.46) | 1.48 (0.89, 2.47) |
| ≥8 years | 1.40 (0.95, 1.85) | 1.25 (0.78, 2.01) | 1.44 (0.88, 2.36) | 1.49 (0.90, 2.47) |
| Cumulative exposure (/year) to d-drugs | n/a | 1.07 (1.03, 1.11) | 1.07 (1.03, 1.12) | 1.06 (1.01, 1.10) |

[a]CI, confidence interval; d4T, stavudine; ddI, didanosine; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; PYFU, person-years of follow-up.
[b]Adjusted for time since stopping d-drug and cumulative exposure to d-drug.
[c]Age, sex, injection drug use as mode of HIV acquisition, previous AIDS diagnosis, HBV, HCV, calendar period, time since stopping d-drug and cumulative exposure to d-drugs.
AIDS

*Prognosis*

As expected from the general population the prognosis following an ESLD/HCC diagnosis was poor [368]. The 1-year estimated mortality rate was 63% and the median survival was 0.3 years vs 6-12 months in the general population. A total of 52 of the 319 cases (16%) were diagnosis on the date of death. Even after removal of those dying at the date of diagnosis the 1-year mortality rate remained high (55.0%) with a median survival of 0.7 years. A 2006 Spanish study by Mercante and colleagues described a 1-year mortality rate 40% of  for HIV/HCV co-infected persons with decompensated cirrhosis [422]. The worse prognosis in *D:A:D* is likely related to having a more severe ELSD case definition, as such ascites is often a first symptom of decompensated cirrhosis, which was excluded from this analysis. Encephalopathy, hepatorenal syndrome and HCC are commonly later occurring. The Child-Pugh score (based on bilirubin, albumin, international normalized ratio (INR), stage of ascites and encephalopathy) and Model for End-Stage Liver

Disease (MELD) score (bilirubin, INR and creatinine) are the most widely used tools internationally for ESLD prognostication, and are also recommended for PLWH with ESLD[6], Table 3. In *D:A:D*, unfortunately we did not have sufficient systematic data on all of these variables to calculate these prognostic scores. The impact of HIV-status on the prognosis after ESLD/HCC is unclear, and due to lack of a control group we were also unable to assess this question in *D:A:D*.

**Table 3, survival of HIV-indeterminate persons with ESLD stratified by CTP and MELD scores** [368]

SURVIVAL OF END-STAGE LIVER DISEASE PATIENTS BASED ON CHILD-TURCOTTE-PUGH/MODEL FOR END-STAGE LIVER DISEASE SCORES

| *CTP score* | *6 months* | *12 months* | *24 months* | *MELD score* | *6 months* | *12 months* | *24 months* |
|---|---|---|---|---|---|---|---|
| Class A | n/a | 95% | 90% | 0–9 | | | |
| Class B | n/a | 80% | 70% | 10–19 | 92% | 86% | 80% |
| | | | | 20–29 | 78% | 71% | 66% |
| Class C | n/a | 45% | 38% | 0–39 | 40% | 37% | 33% |

CTP, Child-Turcotte-Pugh; MELD, Model for End-Stage Liver Disease.

With the significant improvements in HCV management related to use of highly efficient direct acting agents (DAAs) in recent years the incidence of ESLD is declining in PWLH cured for HCV [423]. As a large percentage of the cases of ESLD/HCC in *D:A:D* had HCV (>70%), this will change the entire disease spectrum of ESLD and HCC in PLWH within a short period of time. In recent years, focus on alcoholic and non-alcoholic fatty liver disease has been increasing in PLWH and efforts are needed to improve insights into risk factors and impact of HIV, improvements in non-invasive diagnostics and management to avoid an evolving epidemic of fatty liver diseases related ESLD/HCC in ageing PLWH [396, 419] .

While it is generally recommended to screen regularly (every 6 months) for HCC in all cirrhotic individuals, a recent study by Willemse and colleagues from the *Collaboration of Observational HIV Epidemiological Research in Europe* (*COHERE*) demonstrated only 5.4% of HIV and viral hepatitis co-infected persons were screened according to guidelines in 2005 and 14.2% in 2014 [6, 424]. The 2016 study from *NA-ACOORD* further found that more than a third of the cohort with HIV/HBV co-infection did not have TDF included in the ART as generally recommended [6, 386]. With the bad prognosis related to an ESLD/HCC diagnosis it is crucial to optimise basic management in PLWH to prevent progression to terminal liver failure and death. The *EASL* Guidelines further recommend using the PAGE-B score for HCC risk prediction for Caucasians, but this has not been validated in HIV [425]. As for CVD and CKD, an ESLD/HCC prediction tool in PLWH would be important to help identify those at increased risk and facilities focused management of risk factors where possible. However, one of the challenges related to building such a score if the often-inadequate

information on alcohol consumption. Liver transplantation is the only treatment for ESLD, and considered safe in PLWH, and should be considered as in HIV-negative if the Milan criteria are fulfilled [6].

*Conclusions, limitations and perspectives*

For the first time we described a relatively low incidence of centrally validated ESLD/HCC in a large heterogeneous cohort of PLWH. ESLD/HCC was predominantly seen in individuals with viral hepatitis coinfection. The prognosis following a diagnosis of ESLD/HCC was very poor highlighting the need for improved care and preventional strategies. With the significant advances in treatment for especially HCV the spectrum of terminal liver disease is likely to change considerately in coming years in PLWH, especially in middle- and high-income countries with free access to treatment with direct acting antivirals (DAAs), and likely other causes such as NASH and alcohol will likely become the main determinant of ESLD/HCC in PLWH.

Cumulative use of ddI, d4T, TDF and APV was independently of other liver risk factors associated with increased rates of ESLD/HCC. Whilst we are unable to rule out confounding by indication and impact of unmeasured confounders our findings were confirmed in another *D:A:D* analysis focusing on chronic liver enzyme elevation in PLWH without viral hepatitis co-infection and in several sensitivity analyses. After cessation of d-drugs the risk of ESLD/HCC persisted even several years the drugs were discontinued, and therefore advice to consider avoidance of d-drugs whenever possible, but also to consider an intensified monitoring of liver function and avoidance of hepatotoxic compounds among those with longer-term expose to d-drug. This builds on evidence linking use of d-drugs to liver steatosis, non-portal hypertension and fibrosis. As discussed above the unexpected, and viral hepatitis independent, association with use of TDF calls for further investigation including assessment for reproduction in other large studies. Likewise, it will be important to assess the potential impact of TDF discontinuation on ESLD/HCC incidence. Furthermore, investigations of TAF use will be essential to investigate if there are intrinsic hepatotoxic effects related to tenofovir, or if the lower tenofovir plasma concentrations with TAF provide a differential impact on terminal liver impairment. Finally, there is a need to address the safety profile of newer ARVs incl DRV, DOR and all INSTIs on hard liver endpoints such as ESLD/HCC, and a study in the RESPOND collaboration is currently planning to address this question in 2021 when adequate power has accumulated.

**Chapter 8 Management of Comorbidities in PLWH**

As discussed in chapter 3 the clinical management of HIV extent far beyond that of ART [6], and findings that several non-AIDS comorbidities continue to be seen at higher rates in PLWH compared to the HIV-negative population and in common disease clusters underlines the need to ensure correct and timely management of these conditions [60, 67, 71, 281].

Joint care of PLWH with comorbidities with other specialties are highly recommended by *EACS* and others international guidelines i.e. referral to a nephrologist is relevant in case of RP of eGFR decline, low eGFR, substantial proteinuria or any level of hematuria [6, 29]. Referral to a cardiologist may be considered for asymptomatic persons with high risk of CVD [281]. Likewise, all cases of liver cirrhosis in PLWH should prompt joint care with a hepatologist to ensure regular screening for decompensation including varices and HCC [6]. In case of terminal organ failure transferal for transplantation should be considered in PLWH with the same criteria as for the general population. In addition, the PLWH should be fully virologically suppressed, have a CD4 count >200 cells/mm$^3$ (>100 cells/mm$^3$ for liver transplant), and no active opportunistic infection or HIV-associated malignancy [6].

Our analysis of SCE after CKD (paper 7) illustrated that PLWH with even moderate levels of CKD had substantially higher morbidity burden than those without CKD [72]. *EACS* Guidelines and *KDIGO* recommend a thorough work-up in those with signs of renal impairment to identify and treat possible offending modifiable risk factors such as uncontrolled HIV, diabetes, hypertension, viral hepatitis co-infection and use of nephrotoxic drugs including ARVs with nephrotoxic potentials [6, 86]. In case of proteinuria or hypertension it is further recommended to initiate treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist. Acknowledging the close relation between CKD and CVD optimisation of lifestyle factors including smoking, diet and dyslipidemia are also recommended [6, 281]. Several ARVs and other drugs further require dosage adjustment in case of CKD [6, 86]. Additionally, it is important to limit use of other nephrotoxic substances such as NSAID. With more advanced levels of CKD there is further often a need for symptomatic treatment of complications related to electrolyte derangement, low vitamin D levels, acidosis, anemia and fluid overload which follows recommendations in the general population [29].

Based on the 10-year predicted CVD risk *EACS* and other international guidelines recommend primary and secondary CVD prophylaxis concentrate on modifiable risk factors such as diet, exercise, smoking cessation, and management of hypertension, diabetes and dyslipidemia [6, 281]. In 2019 the threshold for considering ART modifications was further lowered from 20 to 10% 10 years risk by *EACS* [6]. In 2016 a *D:A:D* study

found that the one-month mortality rates after a centrally validated type I MI improved substantially over time in PLWH from 27% in 1999-2002 to 8% 2011-2014 [279]. The reason for this improvement was largely explained by an increased use of medical interventions such as lipid-lowering agents as secondary prophylaxis. Increased use of such interventions for primary prophylaxis has also led to lower incident MI in the *KP* cohort in recent years [276]. Despite this encouraging data, another *D:A:D* study highlighted great inequality in CVD management as women living with HIV were systematically undertreated for most CVD risk factors as opposed to men living with HIV [367]. Another study found that PLWH with HIV-related symptoms had lower chances of being treated with revascularization after a ST-elevation MI (STEMI) than were PLWH without HIV-related symptoms and HIV-negative controls [426]. PLWH, and in particularly those with symptomatic HIV are at increased risk of type II MIs (secondary MIs not related to underlying atherosclerosis) which can be a diagnostic challenge, but ensuring unlimited access to evaluation of revascularization regardless of HIV status is key [427]. The cross-sectional *AgehIV* study found that Dutch PLWH and HIV-negative controls were equally sub optimally managed for primary and secondary prophylaxis for CVD [428]. A 2016 *EuroSIDA* study further described that medical treatment of common CVD risk factors could be further improved across Europe in that only 33% of those with clinical indication for CVD risk modification stopped smoking, 20% improved cholesterol levels and 25% lowered increased BMI levels [278]. However, there were also indications that management has improved over time for certain factors (i.e. hypertension and smoking) in more recent calendar time.

In addition to the treating modifiable CVD risk factors and performing revascularization increased efforts are currently addressing impact of interventions directed to the increased levels of HIV-related ongoing inflammation and coagulation activation [4, 280, 290, 295]. A recent modelling analysis based on *D:A:D* data have suggested that use of pravastin (which in addition to lipid lowering properties also has anti-inflammatory effects), is cost-effective in lowering risks of CVD in PLWH aged 40-75 years, but RCTs are needed [429]. A small pilot study in 2013 suggested that one week of aspirin use had potentials to lower immune activation and increased levels of platelet activation, and a 2018 study further suggested that aspirin use reduced ABC induced platelet activation and hyperreactivity, but were unable to address subsequent impact on CVD risk, calls for studying longer term outcomes in prospective studies[430, 431].

As co-infection with viral hepatitis increases risks of ESLD in PLWH considerately effective treatment against HBV and HCV is key. All PLWH and HBV should have an ART regime containing a tenofovir backbone (as TDF or TAF), and if not tolerated treatment should include entecavir. 3TC is also active against HBV, but has a lower genetic barrier [6]. All PLWH and HCV should be considered for DAA treatment regardless of fibrosis stage. The decision on which DAA combination to use will depend on the HCV genotype, disease stage and prior treatment history (including testing for resistance) and potential drug-drug interactions with ART and

other ongoing treatment [6]. As discussed for paper 10 modern DAA treatment is highly effective in clearing HCV co-infection and thereby lowering incidence of ESLD/HCC, however recent study from the US suggest there are substantial racial inequality in access to care [432]. In addition to viral hepatitis, it is recommended to systematically assess modifiable factors including use of ARVs and other drugs with hepatotoxic potentials, alcohol use/overuse, metabolic syndrome and diabetes [6]. Like CKD, several drugs require dosage adjustment in case of hepatic impairment. In case of possible relation to alcohol, abstinence is recommended. In case of non-alcoholic fatty liver disease diet and exercise are central, other treatment modalities (including use of pioglitazone and vitamin E) have not been investigated in PLWH and should be discussed with hepatologists [6]. For persons with cirrhosis symptomatic treatment is directed to treatment of hypervolemic hyponatremia (i.e. fluid restriction), ascites (i.e. diuretics and drainage), encephalopathy (i.e. lactulose) and varices (i.e. propranolol).

Many of the common comorbidities in PLWH are closely related with considerate overlaps in their risk profiles as also discussed in paper 7, i.e. diabetes is a risk factor for both CKD, CVD and liver impairment, and CKD in turn increase CVD risks [67, 72]. In *NA-ACCORD* Althoff and colleagues estimated that prevention of hypertension would avoid 39% ([26- 51%]) of ESRD cases and 42% [28-56%] of all MIs. No smoking or increased cholesterol would further prevent 37% [7-66%] and 44% [30-58%] of MIs respectively. Avoidance of alcohol use and HCV infection would result in 35% ([9-60%]) and 33% ([17-48%]) lower risk of ESLD [73].

**Chapter 9 Limitations**

As highlighted in the introduction and discussed in the above chapters the primary limitation of the studies of this dissertation is the basic observational nature and hence the lack of causal inference for the observed findings. Risks of residual confounding should in particular be acknowledged and include both unmeasured and unknown confounders. In addition to the factors already discussed for the individual papers use of non-prescription drugs such as non-steroid anti-inflammatory drugs (NSAID) may work in different directions for different clinical outcomes i.e. aspirin, when taken continuously, may lower CVD risks, while ibuprofen may increase risks of CKD especially if co-administered with TDF [4]. In large study settings is not possible to reliably capture use of such over the counter drugs and therefore we are unable to address the impact of any such usage. Dosage information is also not systematically available in *D:A:D*, which was raised as a particular concern for paper 8 investigating associations between use of modern PI/r and CVD. However, we tried to account for this in several different ways by conducting sensitivity analyses looking specifically at the situations in which different dosages would be considered (i.e. virological failure) and did not find evidence of a differential association [53]. *D:A:D* also do not collect information on use of generic ARVs but is has been considered to conduct a survey amongst still active cohorts to obtain such data. Co-infection with CMV and the related immune response has both in PLWH and in the general HIV-indeterminate population been associated with increased risk of CVD. However, such data are not systematically collected in *D:A:D* and we were therefore unable to control for this effect directly [296, 433] . As discussed *D:A:D* also did not collect data on proteinuria or other urinary markers. The lack of proteinuria prevents us from providing a more detailed CKD subclassification, but more importantly may likely have underestimated associated outcomes including CVD and mortality after CKD. We also do not have data on use of non-pharmacological interventions such as physical activity and dietary advice to promote weight loss and treat dyslipidemia and hypertension. Intake of creatinine may further have artificially lowered eGFR.

Confounding by indication is another major intrinsic limitation of observational studies. When designing our analyses and we have tried to take as many potentially confounding factors into account, but we will never be able to control for this entirely as we are not able to fully control for all factors impacting choice of one ART regime over others. Use of propensity scores and marginal structural models have been suggested as alternative statistical approaches to overcome this limitation in observational studies, however in *D:A:D* such analyses have to date not provided robust results.

For the papers assessing renal function in PLWH we used confirmed eGFR measurements. Whilst this is in accordance with international guideline recommendations eGFR is only a surrogate measure of renal function. As systematic use of measured glomerular filtration rate is infrequent and continuous dialysis and

renal transplantation remain relatively rare events in PLWH this approach will likely continue in the years to come, although in more recent years more studies have started to collect data on proteinuria.

As discussed in the method section missing data was handled in several different ways to limit introduction of bias. None of the key variables or outcomes assessed were missing at rates that may have significantly impacted on the main study conclusion but may have underestimated some of the described associations i.e. for smoking and hypertension.

It can further be discussed what is the better way for a study to accumulate persons years of follow-up; a comparatively smaller study with extensive follow-up time or a larger study with comparatively shorter follow-up time. In *D:A:D* study was in a position of both having a very large size for any observational HIV study allowing for substantial heterogenicity and having extended follow-up time due to the longlivity of the study allowing for more detailed insights into temporal dynamics. However, even with the size and follow-up time in *D:A:D* for some of the analysis with a more recent baseline the exposure time on certain ARVS may be inadequate for rare clinical outcomes taking longer time to develop as discussed for paper 4. Conversely it can be argued that if the *D:A:D* study is unable to detect a significant association with an ARV the risk of any potential adverse effect is likely relatively small.

Whilst there is already considerate biological plausibility for several of the findings reported, others remain to be explored as part of evaluating Bradford Hill criteria for causality as discussed for each of the individual papers. However, as also underlined in the introduction section, the *D:A:D* study was a pharmacovigilance study designed to systematically assess ARV associations with clinical outcomes in large heterogenous settings - confirming those safety signals and hypotheses generated based on our data and finding biological mechanism is something that should be carried out by other groups with access to appropriate data sources.

**Chapter 10 Conclusion and Perspectives**

Over the last two decades substantial data on non-AIDS comorbidities and adverse drug effects in PLWH have accumulated. Some may even claim that by 2020 we know almost everything there is to know about non-AIDS morbidity. The studies included in this dissertation have brought us some steps closer to understanding the complexity of renal, liver and atherosclerotic cardiovascular disease in PLWH. Based on the large *D:A:D* study we have assessed the incidence of these non-AIDS conditions (papers 4,7-10), identified key predictors and quantified their relative importance (papers 1-4 and 8-10). We have also identified specific ARVs for which there are concerns about long-term cumulative adverse drug effects (papers 3,4, 6, 9-10) and equally important identified other ARVs for which there is no evidence for such adverse related risks (papers 4, 9-10). We have built and validated a CKD prediction model to aid identification of those at risk and to estimate consequences of using ARVs with nephrotoxic potentials to help improve and personalise HIV care (paper 6). Finally, we have documented a severe prognosis related to CKD and ESLD/HCC (papers 5,7, 8, 10).

In the early days of the HIV epidemic the risk of detrimental effects of ART were greatly outweighed by risks of opportunistic diseases and death in untreated individuals. In the current modern ART era improved insight into the HIV pathogenesis has led to development of ART that is considerately less toxic, but detrimental effects of ART may still contribute to significant morbidity and low quality of life in PLWH. Whilst the strength of the reported ARV-associations on clinical liver, renal and CVD outcomes can seem relatively small compared to other risk factors, the cumulative nature of these drug relations and the lifelong treatment duration should be taken into consideration. Further, it is key to appreciate that the risk estimates are relative risks and therefore will impact different PLWH differently according to their absolute risk of a given complication. In example if your underlying absolute risk is low then a doubling of that risk due to use of a specific ARV will still mean a low overall absolute risk. Conversely, if your underlying risk is moderate to high then a doubling of that risk may entail considerate likelihood of developing organ impairment and less toxic treatment options should be considered. This is also reflected in the differentiated NNTH across risk strata i.e. 1 in 603 persons for those at low CKD risk on TDF vs. 1 in 9 persons for those at high CKD risk on TDF.

Whilst the understanding of the type and distribution of comorbidities and adverse drug toxicities in PLWH has increased greatly, our knowledge remain incomplete on several essential points.
Real life data of several newer ARVs including INSTIs, TAF, doravirine, cabotegravir, ibalizumab and the pharmacological booster cobicistat, and the interplay with genetic factors are only now starting to be systematically undertaken [50, 434]. Based on the registrational RCTs, it was long believed that INSTIs had only

very limited toxicity profiles, however data from real life experience is starting to emerge suggesting considerately higher risks of CNS-toxicity for PLWH on DTG compared to other INSTIs and some evidence to suggest use of INSTIs increase body weight [6, 50]. Likewise, long-lasting ARVs are likely to soon become part of clinical care with additional considerations on optimal management and potential toxicities [435]. Insights into the reversibility potentials for several ARV-associated clinical outcomes including use of DRV/r for incident CVD and TDF for ESLD/HCC also remain limited.

Use of several NRTI-sparing regimens of only two active ARVs have proven effective in controlling HIV, and 3TC plus DTG was in 2019 included as a first line treatment option in *EACS* [6]. A 2DR may also be considered for those at high risk of or prevalent CKD or those with NRTI-related toxicity. A recent analysis for *RESPOND* did, however, not show a difference in shorter-term clinical outcomes in those on a 2DR vs a 3DR, but longer follow-up data is warranted to fully appreciated the impact of the this treatment strategy [436]. Continued large scale systematic pharmacovigilance studies like *RESPOND* using validated and hard clinical endpoint remain a crucial addition to RCTs to ensure reliable real-life capture of unexpected trends in morbidity and mortality, and assessment of how to best tailor ART to fit the individual needs of PLWH as part of a personalised medicine approach. Continued application of the Bradford Hill criteria in evaluating evidence of causality also remain key. We are further still some way from fully understanding who will develop adverse drug effects and who will not. Clinical prediction scores may, as discussed, contribute to identify those with increased risk of toxicities, but as recent data has illustrated there are unmeasured factors such as genetic predisposition that play an important role, and therefore efforts should be put into identifying such components to be included in every day clinical practice [175].

Moreover, whilst the work of this thesis has concentrated on renal, liver and atherosclerotic cardiovascular diseases, the range of comorbidities among PLWH reaches far beyond these three disease entities. Especially non-AIDS cancers remain an underdeveloped area in terms of risk profile, screening, management and outcomes in PLWH due to the vast heterogenicity of individual cancers. The *RESPOND* cohort is continuing the work from *D:A:D* in collecting and validating cancer events in a large cohort to ensure adequate number of individual cancer cases to allow for robust analyses.

Several groups of PLWH remain systematically underrepresented in studies of comorbidities and adverse drug effects. The lack of high-quality data on women living with HIV reflects such a major gap in knowledge [437, 438]. Further, some data suggest that women living with HIV are suboptimally managed i.e. for CVD [367]. The US Women's Interagency HIV study (*WIHS*) and the Women Against Viruses in Europe (*WAVE*) initiative in *EACS* aim to close these gaps and to promote equality in access to care (https://www.eacsociety.org/wave/about-wave/wave.html).

Persons of African origin, and particularly those living in the US, have disproportionally high rates of several comorbidities- an observation true for both those with and without HIV [316, 439, 440]. To disentangle the relative impact of genetic predisposition and lifestyle factors from HIV-related factors and ART toxicity studies focusing on comorbidities in PLWH of African ancestry in different geographical regions will be important. Whilst the *DART* trail, suggested ART can be safely delivered without regular screening for organ disease, the long-term impact of this strategy remains to be evaluated broadly amongst ageing and high risk Sub-Saharan populations of PLWH [192].

Studies investigating non-AIDS events in adults perinatally infected HIV will in the coming years have grown adequately to contribute additional insights into the pathogenesis of non-AIDS events. Difficulties in disentangling the effect of HIV itself to that of lifestyle and social factors closely related to acquiring HIV (i.e. use of recreational drugs and risk-taking behaviors), may be improved by investigating non-AIDS morbidity in perinatally infected persons [80]. Similarly risks of long-term adverse effects in HIV-negative persons using PrEP are unknown, but may also contribute to disentangle the impact of HIV status [441].

Irrespective of the reasons we are faced with an ageing population of PLWH experiencing disproportionally high rates of non-AIDS morbidity and multimorbidity [6, 279]. Concepts of frailty, polypharmacy, drug-drug interactions, drug-disease interactions and disease-disease interaction need to be carefully considered and managed. These concepts are already well-incorporated in geriatric medicine but remain a relatively new consideration for many of those carrying for PLWH and call for a close collaboration between specialties [6]. The *EACS* Guidelines were formed to ensure that scientific advances were communicated directly to those involved with everyday HIV care in a comprehensive and timely manner, and to help integrate these many different facets of HIV management. It is a great privilege to take part in that process. Whilst insights into ageing, comorbidities and HIV management is evolving, HIV guidelines have continued to expand in size, and screening recommendations have become extensive [5, 6]. In the coming years efforts should be made to prioritise these recommendations as they are not all necessarily equally important for all PLWH. Obtaining a better understanding of which interventions are most effective and at which disease stage is essential, as is clarifying the impact of moderating HIV-related systemic inflammation and coagulation activation [6, 102, 122, 272]. Multidisciplinary clinics to accommodate the complex needs of PLWH and multimorbidity. Whilst their longer-term utility has not yet been evaluated, the initiative is inspiring and may improve communication between specialties and ultimately help ensure a more coherent and effective HIV care. Prerequisite for a continued success of clinical management of PLWH is the conduct of high-quality and well-powered studies. If the society of HIV clinicians, researchers and policy makers collectively manage to move these activities forward, there is good reason to believe that PLWH will be facing a brighter future.

**English Summary**

The publications included in this dissertation consist of nine original papers and a review paper, published between 2013 and 2020. All papers are based on the large *D:A:D* study, upon which we utilised the substantial heterogenicity, systematic data collection and rigorous event classification. Whilst effective ART has significantly improved survival and lowered frequency of AIDS-related outcomes PLWH continue to experience disproportionally high rates of non-AIDS morbidities. All papers of this dissertation aim to improve management of PLWH by disentangling the complex relative contribution of individual risk factors for renal, liver and cardiovascular disease and describe occurrence and outcomes.

It was unclear if the relation between immune suppression and CKD was best characterised by severity or duration of immune suppression. Among almost 34,000 PLWH all measures of immune dysfunction predicted CKD, but most strongly for the relative duration of immune suppression with 23% increased CKD incidence. We also described an interaction with the CKD prediction score in which immune suppression impacted those at lowest estimated renal risk most strongly.

We have previously shown that use of TDF, LPV/r and ATV/r was independently associated with chronic renal impairment in PLWH also in persons with initial normal renal function. Additional power allowed us to expand this finding and conclude that the association between extended use of each of these ARVs and CKD is cumulative in nature with a steady year on year increased CKD risks and no indication that the association levels off over time.

DRV/r is currently one of the most commonly used PIs, however, as it is also one of the newest PIs no study had been adequately powered to address potential renal adverse effects reliably. Amongst almost 28,000 PLWH and almost seven years median follow-up we did not find evidence of a strong or gradually increasing risk of CKD with DRV/r. We did however confirm a cumulative association between CKD and ATV/r, another contemporary PI.

We assessed eGFR outcomes in PLWH progressing to chronic renal impairment to gain more insights into prognostics and related risk factors. We showed that 21% subsequently improved eGFR, whilst 67% stabilised and 12% progressed in eGFR. Those on TDF and ATV/r had lower odds of a more favorable renal outcomes, whilst those who discontinued these ARVs > 12 months had similar outcomes as those never exposed to the ARVs. This finding provides reassurance that the ARV-related renal effects may be haltered or reversed if use is discontinued in time.

To aid identification of PLWH in risk of CKD we developed a 5-year CKD prediction score including nine variables; age, gender, IDU, HCV, baseline eGFR, nadir CD4 count, diabetes, hypertension and prior CVD. The proportion estimated to progress to CKD at low CKD risk was 1 in 393, and 1 in 6 at those at high CKD risk. For use of TDF and ATV/r estimated CKD risk increased from 1 in 603 in those at low estimated CKD risk to 1 in 9 for high risk persons. The model was externally validated with good discrimination.

Having uncovered risk factors for incident CKD we investigated the burden of serious clinical events following CKD and predictive factors. PLWH and CKD had a poor prognosis with almost one in three experiencing a serious event within five years, and the five-year mortality rate exceeded 15%. The most common events were death, NADM, CVD and AIDS. Several modifiable risk factors acted as both CKD initiators and perpetrators for CKD-related events including poor HIV status, diabetes and smoking.

CVD and CKD share several risk factors, but the relation between different eGFR strata and CVD in PLWH was unclear. At 5 years <2% of PLWH with normal eGFR developed CVD compared to 20% of those with eGFR ≤30 mL/min/1.73 $m^2$. Increased age explained much of the association between eGFR and CVD for eGFR levels >30mL/min/1.73$m^2$, however even mildly impaired eGFR increased CVD rates with 30%-40%.

Whilst use of several older PIs are associated with increased CVD risk ambiguity existed for use of more contemporary PIs. During seven years median follow and including 1,157 CVD events we found that cumulative use of DRV/r, but not ATV/r, was associated with increased CVD rates of almost 60% per 5 years use. The NNTH for DRV/r was 533 in those at low CVD risk and 15 in those at high risk. This safety concern has led to recommendation of careful use of DRV in persons at increased CVD risks.

Insights into ESLD/HCC in PLWH were sparse. We found an ESLD/HCC incidence of 1 per 1000 PYFU with >80% of cases seen in PLWH with viral hepatitis. Use of d-drugs increased ESLD/HCC rates with 32-46% per 5 years use and persisted several years after discontinuation. TDF use (but not FTC or 3TC) was, independently of HBV co-infection, associated with 46% increased ESLD/HCC rates. This finding was confirmed in another *D:A:D* analysis using chronic liver enzyme elevation, but that calls for confirmation in other large studies. The prognosis after ESLD/HCC was poor with a 63% 1-year mortality rate.

Aims for future large studies should include assessment of long-term cardiovascular, renal, liver, bone and cancer outcomes of newer ARVs including TAF, doravirine and INSTIs, assessment of the reversibility potential of the shown adverse ARV associations i.e. for DRV and CVD, impact of current management strategies and test of interventions targeted to HIV-related inflammation and coagulation activation.

**Dansk Resume**

Publikationerne inkluderet i denne afhandling består af ni originale manuskripter og et review publiceret mellem 2013 og 2020. Alle manuskripter er baseret på *D:A:D* studiet, hvor vi benyttede os af den betydelige studie heterogenitet, systematiske dataindsamling and stringente event klassifikation. Effektiv ART har signifikant bedret overlevelsen og reduceret forekomsten af HIV-relateret sygdom, men PLWH oplever fortsat en disproportionalt høj forekomst af forskellige komorbiditeter. Alle manuskripter i denne afhandling som formål at forbedre den kliniske håndtering PLWH ved forsøg på af afklare det relative bidrag af individuelle risikofaktorer for udvikling af nyre, lever and kardiovaskulær sygdom og beskrivelse af såvel sygdomsforekomsten samt prognosen.

I litteraturen er det uklart, hvorvidt relationen mellem immunsuppression og CKD bedst kan forklares ved sværhedsgraden eller varighed af immunsuppression. Blandt næsten 34,000 PLWH prædikterede alle immunfunktions markører CKD, men stærkest var relation til den relative varighed of immunsuppression med en 23% øget CKD incidens. Vi beskrev også en interaktion med den estimerede CKD-risiko med en kraftigere effekt af immunsuppression hos de med lavest estimeret CKD-risiko.

Vi har tidligere vist at brugen af TDF, LPV/r og ATV/r uafhængigt af andre faktorer er associeret med kronisk nyresvigt også hos PLWH med initial normal nyrefunktion. Akkumulation af yderligere statistisk styrke muliggjorde en mere detaljeret analyse af de temporale associationer, og vi kunne vise at relationen mellem brugen af disse ARVs og udvikling af CKD er af kumulativ natur med en stabil øgning af CKD incidensen med hvert ekstra års yderligere eksponering, og uden evidens for at associationen flader ud over tid.

DRV/r er aktuelt en af de mest brugte PIs, men også en af de nyeste, hvorfor ingen studier har haft den nødvendige statistiske styrke til at kunne adressere mulige renale bivirkninger. Blandt næsten 28,000 PLWH og næsten syv års median opfølgning fandt vi ikke evidens for en stærk eller gradvis stigende incidens af CKD med længere tids brug af DRV/r. Til gengæld bekræftede vi tidligere fund med en fortsat kumulativ association mellem længere tids brug af ATV/r, en anden moderne PI, og CKD.

Med henblik på at øge indsigten i prognosen efter kronisk nyresvigt og relaterede risikofaktorer undersøgte vi den efterfølgende eGFR udviklingen blandt PLWH, der aktivt progredierede til kronisk nyresvigt. Vi fandt at 21% opleverede bedring i deres eGFR, mens hhv. 67% stabiliserede deres nyrefunktion og 12% progredierede yderligere med faldende eGFR. De, der forblev på TDF eller ATV/r, havde lavere odds for en mere favorabel nyre prognose, mens de, der ophørte brugen af disse ARVs > 12 måneder, havde samme prognose som de, der aldrig havde været eksponeret for disse ARVs. Dette studie viser således at ARV-

associerede renale bivirkninger kan bremses eller helt reverteres, hvis brugen af TDF og ATV/r stoppes i tide.

Med henblik på bedret identifikation af PLWH med øget risiko for udvikling af CKD udviklede vi en 5-års CKD-prædiktions model med ni variabler; alder, køn, IDU, HCV, eGFR på baseline, nadir CD4 tal, diabetes, hypertension og tidligere CVD. Andelen, der progredierer til CKD fra en lav estimeret CKD-risiko var 1 af 393, og 1 af 6 hos de med høj estimeret CKD-risiko. Brug af TDF og ATV/r første til en estimeret CKD-risiko på 1 af 603 for de med lav estimeret CKD-risiko og 1 af 9 for de med høj risiko. Prædiktionsmodellen blev eksternt valideret med en god diskriminations evne.

Efter at have undersøgt risikofaktorer for incident CKD undersøgte vi byrden af alvorlige kliniske diagnoser, efter en CKD-diagnose og relaterede prædiktorer. Vi fandt at personer, der lever med både HIV og CKD har en alvorlig prognose, hvor næsten 1 af 3 oplever en alvorlig diagnose indenfor fem år, og femårs mortalitet oversteg 15%. Den mest almindelige kliniske diagnose var centralt valideret død, NADM, CVD eller AIDS-definerende sygdom. Flere modificerbare risikofaktorer virkede som både CKD initiatorer og forværrende faktorer for CKD-relateret sygdom inklusiv dårlig HIV-status, diabetes og rygning.

CVD og CKD deler flere risikofaktorer, men relationen mellem forskellige eGFR strata and CVD hos PLWH var uafklaret. Vi fandt at efter 5 år udviklede <2% af PLWH med normal eGFR CVD, sammenlignet med 20% af de med eGFR ≤30 mL/min/1.73 $m^2$. Alder forklarede en stor del af variationen mellem eGFR and CVD for eGFR niveauer >30mL/min/1.73$m^2$, alligevel var selv milde grader af reduceret eGFR associeret med 30%-40% øget CVD incidens.

Mens brugen af flere ældre PIs er associeret med øget CVD-risiko, var det uklart om brugen af de mere moderne PIs ATV/r og DRV/r var associeret med same risiko. Over syv års median opfølgningstid og med 1,157 CVD-tilfælde fandt vi at kumulativ brug af DRV/r, men ikke ATV/r, var associeret med øget CVD incidens på næsten 60% per 5 års brug. NTHH for DRV/r var 533 blandt de med lav CVD-risiko og 15 blandt de med høj risiko. Dette sikkerhedssignal har ledt til anbefalinger om forsigtig brug af DRV/r hos personer med øget CVD-risiko.

Viden om ESLD/HCC hos PLWH var begrænset. Vi fandt en ESLD/HCC incidens på en promille og >80% af tilfældene var blandt PLWH med viral hepatitis. Brugen af d-drugs øgede ESLD/HCC incidensen med 32-46% per 5 års brug, og risikoen persisterede selv adskillige år efter brugen var ophørt. Brug af TDF (men ikke FTC eller 3TC) var, uafhængig af HBV co-infektion, associeret med 46% øget ESLD/HCC incidens Dette fund blev

konfirmeret I en anden *D:A:D* analyse med kronisk leverenzym forhøjelse, men kræver konfirmation i andre store studier. Prognosen efter ESLD/HCC var dårlig med en 1-års mortalitet på 63%.

Fremtidige studier bør fokusere på langtidsprognosen for organ sygdomme og cancer relateret til brugen af nyere ARVs inklusiv TAF, doravirine or INSTIs, undersøgelse af reversibilitetspotentialet for de viste ARV-associationer bl.a. for DRV og CVD, effekten af aktuelle kliniske behandlingsstrategier og test af nye interventioner rettet mod den HIV-relaterede inflammation and koagulation aktivering.

**References**


1. WHO **https://www.ecdc.europa.eu/en/publications-data/hivaids-surveillance-europe-2019-2018-data**. 2019. Assessed Dec 12th 2019
2. WHO. **MAINTAINING AND IMPROVING QUALITY OF CARE WITHIN HIV CLINICAL SERVICES**. In: *https://appswhoint/iris/bitstream/handle/10665/325857/WHO-CDS-HIV-1917-engpdf?ua=1*; 2019. Assessed Dec 12th 2019
3. Ryom L, Boesecke C, Bracchi M, Ambrosioni J, Pozniak A, Arribas J, et al. **Highlights of the 2017 European AIDS Clinical Society (EACS) Guidelines for the treatment of adult HIV-positive persons version 9.0**. *HIV medicine* 2018; 19(5):309-315.
4. **EACS Guidelines version 9.1**. 2018.
5. **European AIDS Clinical Society, eacs-guidelines version 6** October 2011.
6. **EACS. Guidelines v10.0** https://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html; 2019.
7. Centers for Disease C. **Mortality attributable to HIV infection/AIDS--United States, 1981-1990**. *MMWR Morbidity and mortality weekly report* 1991; 40(3):41-44.
8. Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, et al. **The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial**. *The New England journal of medicine* 1987; 317(4):185-191.
9. Larder BA, Darby G, Richman DD. **HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy**. *Science* 1989; 243(4899):1731-1734.
10. Bach MC. **Failure of zidovudine to maintain remission in patients with AIDS**. *The New England journal of medicine* 1989; 320(9):594-595.
11. Chow YK, Hirsch MS, Merrill DP, Bechtel LJ, Eron JJ, Kaplan JC, et al. **Use of evolutionary limitations of HIV-1 multidrug resistance to optimize therapy**. *Nature* 1993; 361(6413):650-654.
12. **Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. Delta Coordinating Committee**. *Lancet* 1996; 348(9023):283-291.
13. Hammer SM, Katzenstein DA, Hughes MD, Gundacker H, Schooley RT, Haubrich RH, et al. **A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. AIDS Clinical Trials Group Study 175 Study Team**. *The New England journal of medicine* 1996; 335(15):1081-1090.
14. **Randomised trial of addition of lamivudine or lamivudine plus loviride to zidovudine-containing regimens for patients with HIV-1 infection: the CAESAR trial**. *Lancet* 1997; 349(9063):1413-1421.
15. Saravolatz LD, Winslow DL, Collins G, Hodges JS, Pettinelli C, Stein DS, et al. **Zidovudine alone or in combination with didanosine or zalcitabine in HIV-infected patients with the acquired immunodeficiency syndrome or fewer than 200 CD4 cells per cubic millimeter. Investigators for the Terry Beirn Community Programs for Clinical Research on AIDS**. *The New England journal of medicine* 1996; 335(15):1099-1106.
16. Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, et al. **Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration**. *Lancet* 2014; 384(9939):241-248.
17. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, et al. **Decline in the AIDS and death rates in the EuroSIDA study: an observational study**. *Lancet* 2003; 362(9377):22-29.
18. Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al. **Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group**. *Lancet* 1998; 352(9142):1725-1730.
19. Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, et al. **Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study**. *Lancet* 2000; 356(9244):1800-1805.

20. Obel N, Omland LH, Kronborg G, Larsen CS, Pedersen C, Pedersen G, et al. **Impact of non-HIV and HIV risk factors on survival in HIV-infected patients on HAART: a population-based nationwide cohort study**. *PloS one* 2011; 6(7):e22698.
21. Friis-Moller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, et al. **Combination antiretroviral therapy and the risk of myocardial infarction**. *The New England journal of medicine* 2003; 349(21):1993-2003.
22. Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, Dabis F, et al. **Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration**. *Lancet* 2008; 371(9622):1417-1426.
23. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, et al. **Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study**. *The Journal of infectious diseases* 2010; 201(3):318-330.
24. Schunemann H, Hill S, Guyatt G, Akl EA, Ahmed F. **The GRADE approach and Bradford Hill's criteria for causation**. *J Epidemiol Community Health* 2011; 65(5):392-395.
25. L R. **CKD in HIV-Positive Persons; Contribution of Traditional Risk factors, HIV and Antiretroviral Agents** [PhD]; 2013.
26. Lo Re V, 3rd, Kallan MJ, Tate JP, Localio AR, Lim JK, Goetz MB, et al. **Hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus-monoinfected patients: a cohort study**. *Annals of internal medicine* 2014; 160(6):369-379.
27. Abra G, Tamura MK. **Timing of initiation of dialysis: time for a new direction?** *Current opinion in nephrology and hypertension* 2012.
28. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf. **KDIGO clinical practice guidelines**. 2012. Assessed Dec 12th 2019.
29. Chen TK, Knicely DH, Grams ME. **Chronic Kidney Disease Diagnosis and Management: A Review**. *JAMA : the journal of the American Medical Association* 2019; 322(13):1294-1304.
30. Delanaye P, Jager KJ, Bokenkamp A, Christensson A, Dubourg L, Eriksen BO, et al. **CKD: A Call for an Age-Adapted Definition**. *Journal of the American Society of Nephrology : JASN* 2019; 30(10):1785-1805.
31. Mocroft A, Neuhaus J, Peters L, Ryom L, Bickel M, Grint D, et al. **Hepatitis B and C co-infection are independent predictors of progressive kidney disease in HIV-positive, antiretroviral-treated adults**. *PloS one* 2012; 7(7):e40245.
32. Mocroft A, Ryom L, Reiss P, Furrer H, D'Arminio Monforte A, Gatell J, et al. **A comparison of estimated glomerular filtration rates using Cockcroft-Gault and the Chronic Kidney Disease Epidemiology Collaboration estimating equations in HIV infection**. *HIV medicine* 2014; 15(3):144-152.
33. Friis-Moller N, Ryom L, Smith C, Weber R, Reiss P, Dabis F, et al. **An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons: The Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study**. *Eur J Prev Cardiol* 2016; 23(2):214-223.
34. Mocroft A, Lundgren JD, Ross M, Law M, Reiss P, Kirk O, et al. **Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D study**. *PLoS medicine* 2015; 12(3):e1001809.
35. Ryom L, Mocroft A, Kirk O, Reiss P, Ross M, Smith C, et al. **Predictors of estimated glomerular filtration rate progression, stabilization or improvement after chronic renal impairment in HIV-positive individuals**. *AIDS* 2017; 31(9):1261-1270.
36. Ryom L, Mocroft A, Kirk O, Ross M, Reiss P, Fux CA, et al. **Predictors of advanced chronic kidney disease and end-stage renal disease in HIV-positive persons**. *AIDS* 2014; 28(2):187-199.
37. Ryom L, Mocroft A, Kirk O, Worm SW, Kamara DA, Reiss P, et al. **Association Between Antiretroviral Exposure and Renal Impairment Among HIV-Positive Persons With Normal Baseline Renal Function: the D:A:D Studya**. *The Journal of infectious diseases* 2013; 207(9):1359-1369.

38. Kowalska JD, Kirk O, Mocroft A, Hoj L, Friis-Moller N, Reiss P, et al. **Implementing the number needed to harm in clinical practice: risk of myocardial infarction in HIV-1-infected patients treated with abacavir**. *HIV medicine* 2010; 11(3):200-208.
39. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. **CD4+ count-guided interruption of antiretroviral treatment**. *The New England journal of medicine* 2006; 355(22):2283-2296.
40. Group ISS, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, et al. **Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection**. *The New England journal of medicine* 2015; 373(9):795-807.
41. commiitee EE. **European AIDS Clinical Society, eacs-guidelines version 7**. In; 2013
42. Achhra AC, Mocroft A, Ross M, Ryom-Nielson L, Avihingsanon A, Bakowska E, et al. **Impact of early versus deferred antiretroviral therapy on estimated glomerular filtration rate in HIV-positive individuals in the START trial**. *Int J Antimicrob Agents* 2017; 50(3):453-460.
43. Baker JV, Sharma S, Achhra AC, Bernardino JI, Bogner JR, Duprez D, et al. **Changes in Cardiovascular Disease Risk Factors With Immediate Versus Deferred Antiretroviral Therapy Initiation Among HIV-Positive Participants in the START (Strategic Timing of Antiretroviral Treatment) Trial**. *J Am Heart Assoc* 2017; 6(5).
44. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, van Lunzen J, et al. **Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy**. *JAMA : the journal of the American Medical Association* 2016; 316(2):171-181.
45. Ford N, Shubber Z, Calmy A, Irvine C, Rapparini C, Ajose O, et al. **Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: a systematic review**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2015; 60 Suppl 3:S170-176.
46. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. **On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection**. *The New England journal of medicine* 2015; 373(23):2237-2246.
47. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. **Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial**. *Lancet* 2016; 387(10013):53-60.
48. Boffito M, Ryom Nielsen L, Spinner C, Martinez E, Behrens G, Rockstroh J, et al. **Clinical management of ageing people living with HIV in Europe: the view of the care providers**. *Infection* 2020.
49. Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, et al. **Durable Efficacy of Dolutegravir Plus Lamivudine in Antiretroviral Treatment-Naive Adults With HIV-1 Infection: 96-Week Results From the GEMINI-1 and GEMINI-2 Randomized Clinical Trials**. *J Acquir Immune Defic Syndr* 2020; 83(3):310-318.
50. Greenberg L, Ryom L, Wandeler G, Grabmeier-Pfistershammer K, Ollinger A, Neesgaard B, et al. **Uptake and Discontinuation of Integrase Inhibitors (INSTIs) in a Large Cohort Setting**. *J Acquir Immune Defic Syndr* 2020; 83(3):240-250.
51. Choi AI, Shlipak MG, Hunt PW, Martin JN, Deeks SG. **HIV-infected persons continue to lose kidney function despite successful antiretroviral therapy**. *AIDS* 2009; 23(16):2143-2149.
52. Scherzer R, Gandhi M, Estrella MM, Tien PC, Deeks SG, Grunfeld C, et al. **A chronic kidney disease risk score to determine tenofovir safety in a prospective cohort of HIV-positive male veterans**. *AIDS* 2014; 28(9):1289-1295.
53. Ryom L, Lundgren JD, El-Sadr W, Reiss P, Kirk O, Law M, et al. **Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study**. *Lancet HIV* 2018; 5(6):e291-e300.
54. Ryom L, Dilling Lundgren J, Reiss P, Kirk O, Law M, Ross M, et al. **Use of Contemporary Protease Inhibitors and Risk of Incident Chronic Kidney Disease in Persons With Human Immunodeficiency Virus: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study**. *The Journal of infectious diseases* 2019; 220(10):1629-1634.

55. Ryom L, Lundgren JD, De Wit S, Kovari H, Reiss P, Law M, et al. **Use of antiretroviral therapy and risk of end-stage liver disease and hepatocellular carcinoma in HIV-positive persons**. *AIDS* 2016; 30(11):1731-1743.
56. Kamara DA, Ryom L, Ross M, Kirk O, Reiss P, Morlat P, et al. **Development of a definition for Rapid Progression (RP) of renal function in HIV-positive persons: the D:A:D study**. *BMC Nephrol* 2014; 15:51.
57. Scherzer R, Estrella M, Li Y, Choi AI, Deeks SG, Grunfeld C, et al. **Association of tenofovir exposure with kidney disease risk in HIV infection**. *AIDS* 2012; 26(7):867-875.
58. Petersen N, Knudsen AD, Mocroft A, Kirkegaard-Klitbo D, Arici E, Lundgren J, et al. **Prevalence of impaired renal function in virologically suppressed people living with HIV compared with controls: the Copenhagen Comorbidity in HIV Infection (COCOMO) study**. *HIV medicine* 2019; 20(10):639-647.
59. De Francesco D, Wit FW, Cole JH, Kootstra NA, Winston A, Sabin CA, et al. **The 'COmorBidity in Relation to AIDS' (COBRA) cohort: Design, methods and participant characteristics**. *PloS one* 2018; 13(3):e0191791.
60. Schouten J, Wit FW, Stolte IG, Kootstra NA, van der Valk M, Geerlings SE, et al. **Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014; 59(12):1787-1797.
61. Bagkeris E, Burgess L, Mallon PW, Post FA, Boffito M, Sachikonye M, et al. **Cohort profile: The Pharmacokinetic and clinical Observations in PeoPle over fiftY (POPPY) study**. *International journal of epidemiology* 2018; 47(5):1391-1392e.
62. Guaraldi G, Malagoli A, Calcagno A, Mussi C, Celesia BM, Carli F, et al. **The increasing burden and complexity of multi-morbidity and polypharmacy in geriatric HIV patients: a cross sectional study of people aged 65 - 74 years and more than 75 years**. *BMC Geriatr* 2018; 18(1):99.
63. Gallant J, Hsue PY, Shreay S, Meyer N. **Comorbidities Among US Patients With Prevalent HIV Infection-A Trend Analysis**. *The Journal of infectious diseases* 2017; 216(12):1525-1533.
64. Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, et al. **Premature age-related comorbidities among HIV-infected persons compared with the general population**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2011; 53(11):1120-1126.
65. Rasmussen LD, May MT, Kronborg G, Larsen CS, Pedersen C, Gerstoft J, et al. **Time trends for risk of severe age-related diseases in individuals with and without HIV infection in Denmark: a nationwide population-based cohort study**. *Lancet HIV* 2015; 2(7):e288-298.
66. Althoff KN, McGinnis KA, Wyatt CM, Freiberg MS, Gilbert C, Oursler KK, et al. **Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer in HIV-infected versus uninfected adults**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2015; 60(4):627-638.
67. De Francesco D, Verboeket SO, Underwood J, Bagkeris E, Wit FW, Mallon PWG, et al. **Patterns of Co-occurring Comorbidities in People Living With HIV**. *Open Forum Infect Dis* 2018; 5(11):ofy272.
68. Hasse B, Ledergerber B, Furrer H, Battegay M, Hirschel B, Cavassini M, et al. **Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2011; 53(11):1130-1139.
69. Smit M, Brinkman K, Geerlings S, Smit C, Thyagarajan K, Sighem A, et al. **Future challenges for clinical care of an ageing population infected with HIV: a modelling study**. *Lancet Infect Dis* 2015; 15(7):810-818.
70. Halloran MO, Boyle C, Kehoe B, Bagkeris E, Mallon P, Post FA, et al. **Polypharmacy and drug-drug interactions in older and younger people living with HIV: the POPPY study**. *Antiviral therapy* 2019; 24(3):193-201.
71. Pelchen-Matthews A, Ryom L, Borges AH, Edwards S, Duvivier C, Stephan C, et al. **Aging and the evolution of comorbidities among HIV-positive individuals in a European cohort**. *AIDS* 2018; 32(16):2405-2416.
72. Ryom L, Lundgren JD, Law M, Kirk O, El-Sadr W, Bonnet F, et al. **Serious clinical events in HIV-positive persons with chronic kidney disease**. *AIDS* 2019; 33(14):2173-2188.

73. Althoff KN, Gebo KA, Moore RD, Boyd CM, Justice AC, Wong C, et al. **Contributions of traditional and HIV-related risk factors on non-AIDS-defining cancer, myocardial infarction, and end-stage liver and renal diseases in adults with HIV in the USA and Canada: a collaboration of cohort studies**. *Lancet HIV* 2019; 6(2):e93-e104.
74. Choi AI, Rodriguez RA, Bacchetti P, Bertenthal D, Volberding PA, O'Hare AM. **The impact of HIV on chronic kidney disease outcomes**. *Kidney international* 2007; 72(11):1380-1387.
75. Althoff K, Wyatt C, Gibert C, Oursler KA, Rimland D, Rodriguez-Barradas M, et al. **HIV+ Adults Are at Greater Risk for Myocardial Infarction, Non-AIDS Cancer, and End-stage Renal Disease, but Events Occur at Similar Ages Compared to HIV– Adults #59**. In: *CROI* Atlanta, Geogia, USA; 2013.
76. Glaser N, Phiri S, Bruckner T, Nsona D, Tweya H, Ahrenshop N, et al. **The prevalence of renal impairment in individuals seeking HIV testing in Urban Malawi**. *BMC Nephrol* 2016; 17(1):186.
77. Banda J, Mweemba A, Siziya S, Mweene M, Andrews B, Lakhi S. **Prevalence and Factors Associated with Renal Dysfunction in HIV Positive and Negative Adults at the University Teaching Hospital, in Lusaka**. *Med J Zambia* 2010; 37(3):136-142.
78. Kooij KW, Vogt L, Wit F, van der Valk M, van Zoest RA, Goorhuis A, et al. **Higher Prevalence and Faster Progression of Chronic Kidney Disease in Human Immunodeficiency Virus-Infected Middle-Aged Individuals Compared With Human Immunodeficiency Virus-Uninfected Controls**. *The Journal of infectious diseases* 2017; 216(6):622-631.
79. Medapalli RK, Parikh CR, Gordon K, Brown ST, Butt AA, Gibert CL, et al. **Comorbid diabetes and the risk of progressive chronic kidney disease in HIV-infected adults: data from the Veterans Aging Cohort Study**. *J Acquir Immune Defic Syndr* 2012; 60(4):393-399.
80. Purswani MU, Chernoff MC, Mitchell CD, Seage GR, 3rd, Zilleruelo G, Abitbol C, et al. **Chronic kidney disease associated with perinatal HIV infection in children and adolescents**. *Pediatr Nephrol* 2012.
81. Szczech LA, Gupta SK, Habash R, Guasch A, Kalayjian R, Appel R, et al. **The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection**. *Kidney international* 2004; 66(3):1145-1152.
82. Jose S, Hamzah L, Jones R, Williams D, Winston A, Burns F, et al. **Chronic Kidney Disease Risk in African and Caribbean Populations With HIV**. *The Journal of infectious diseases* 2018; 218(11):1767-1772.
83. Dietrich LG, Barcelo C, Thorball CW, Ryom L, Burkhalter F, Hasse B, et al. **Contribution of genetic background and clinical D:A:D risk score to chronic kidney disease in Swiss HIV-positive persons with normal baseline estimated glomerular filtration rate**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2019.
84. Jotwani V, Li Y, Grunfeld C, Choi AI, Shlipak MG. **Risk Factors for ESRD in HIV-Infected Individuals: Traditional and HIV-Related Factors**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2011.
85. Mocroft A, Lundgren JD, Ross M, Fux CA, Reiss P, Moranne O, et al. **Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study**. *Lancet HIV* 2016; 3(1):e23-32.
86. Swanepoel CR, Atta MG, D'Agati VD, Estrella MM, Fogo AB, Naicker S, et al. **Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference**. *Kidney international* 2018; 93(3):545-559.
87. Bansi L, Hughes A, Bhagani S, Mackie NE, Leen C, Levy J, et al. **Clinical epidemiology of HIV-associated end-stage renal failure in the UK**. *AIDS* 2009; 23(18):2517-2521.
88. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. **Association of trypanolytic ApoL1 variants with kidney disease in African Americans**. *Science* 2010; 329(5993):841-845.
89. Behar DM, Kedem E, Rosset S, Haileselassie Y, Tzur S, Kra-Oz Z, et al. **Absence of APOL1 risk variants protects against HIV-associated nephropathy in the Ethiopian population**. *American journal of nephrology* 2011; 34(5):452-459.

90. Kudose S, Santoriello D, Bomback AS, Stokes MB, Batal I, Markowitz GS, et al. **The spectrum of kidney biopsy findings in HIV-infected patients in the modern era**. *Kidney international* 2020; 97(5):1006-1016.
91. Wyatt CM, Meliambro K, Klotman PE. **Recent progress in HIV-associated nephropathy**. *Annual review of medicine* 2012; 63:147-159.
92. Lescure FX, Flateau C, Pacanowski J, Brocheriou I, Rondeau E, Girard PM, et al. **HIV-associated kidney glomerular diseases: changes with time and HAART**. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2012.
93. Lucas GM, Eustace JA, Sozio S, Mentari EK, Appiah KA, Moore RD. **Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: a 12-year cohort study**. *AIDS* 2004; 18(3):541-546.
94. Fine DM, Wasser WG, Estrella MM, Atta MG, Kuperman M, Shemer R, et al. **APOL1 risk variants predict histopathology and progression to ESRD in HIV-related kidney disease**. *Journal of the American Society of Nephrology : JASN* 2012; 23(2):343-350.
95. Ryom L, Mocroft A, Lundgren J. **HIV Therapies and the Kidney: Some Good, Some Not So Good?** *Current HIV/AIDS reports* 2012; 9(2):111-120.
96. Ryom L, Kirk O, Lundgren J, Reiss P, Pedersen C, De Wit S, et al. **Advanced chronic kidney disease, end-stage renal disease and renal death among HIV-positive individuals in Europe**. *HIV medicine* 2013.
97. Achhra AC, Amin J, Law MG, Emery S, Gerstoft J, Gordin FM, et al. **Immunodeficiency and the risk of serious clinical endpoints in a well studied cohort of treated HIV-infected patients**. *AIDS* 2010; 24(12):1877-1886.
98. Achhra AC, Mocroft A, Ross MJ, Ryom L, Lucas GM, Furrer H, et al. **Kidney disease in antiretroviral-naive HIV-positive adults with high CD4 counts: prevalence and predictors of kidney disease at enrolment in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial**. *HIV medicine* 2015; 16 Suppl 1:55-63.
99. Ryom L, Mocroft A, Lundgren JD. **Antiretroviral therapy, immune suppression and renal impairment in HIV-positive persons**. *Current opinion in HIV and AIDS* 2014; 9(1):41-47.
100. Ryom L, Lundgren JD, Reiss P, Ross M, Kirk O, Fux CA, et al. **The impact of immunosuppression on chronic kidney disease in people living with HIV; the D:A:D study**. *The Journal of infectious diseases* 2020.
101. Mocroft A, Furrer HJ, Miro JM, Reiss P, Mussini C, Kirk O, et al. **The Incidence of AIDS-Defining Illnesses at a Current CD4 Count >=200 Cells/muL in the Post-Combination Antiretroviral Therapy Era**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2013.
102. Grund B, Baker JV, Deeks SG, Wolfson J, Wentworth D, Cozzi-Lepri A, et al. **Relevance of Interleukin-6 and D-Dimer for Serious Non-AIDS Morbidity and Death among HIV-Positive Adults on Suppressive Antiretroviral Therapy**. *PloS one* 2016; 11(5):e0155100.
103. Shinha T, Mi D, Liu Z, Orschell CM, Lederman MM, Gupta SK. **Relationships between renal parameters and serum and urine markers of inflammation in those with and without HIV infection**. *AIDS research and human retroviruses* 2015; 31(4):375-383.
104. Longenecker CT, Kitch D, Sax PE, Daar ES, Tierney C, Gupta SK, et al. **Reductions in Plasma Cystatin C After Initiation of Antiretroviral Therapy Are Associated With Reductions in Inflammation: ACTG A5224s**. *J Acquir Immune Defic Syndr* 2015; 69(2):168-177.
105. Kirkegaard-Klitbo DM, Mejer N, Knudsen TB, Moller HJ, Moestrup SK, Poulsen SD, et al. **Soluble CD163 predicts incident chronic lung, kidney and liver disease in HIV infection**. *AIDS* 2017; 31(7):981-988.
106. Neuhaus J, Jacobs DR, Jr., Baker JV, Calmy A, Duprez D, La Rosa A, et al. **Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection**. *The Journal of infectious diseases* 2010; 201(12):1788-1795.
107. Abraham AG, Darilay A, McKay H, Margolick JB, Estrella MM, Palella FJ, Jr., et al. **Kidney Dysfunction and Markers of Inflammation in the Multicenter AIDS Cohort Study**. *The Journal of infectious diseases* 2015; 212(7):1100-1110.
108. Wyatt CM, Kitch D, Gupta SK, Tierney C, Daar ES, Sax PE, et al. **Changes in proteinuria and albuminuria with initiation of antiretroviral therapy: data from a randomized trial comparing tenofovir disoproxil fumarate/emtricitabine versus abacavir/lamivudine**. *J Acquir Immune Defic Syndr* 2014; 67(1):36-44.

109. Mocroft A, Wyatt C, Szczech L, Neuhaus J, El-Sadr W, Tracy R, et al. **Interruption of antiretroviral therapy is associated with increased plasma cystatin C**. *AIDS* 2009; 23(1):71-82.
110. Emery S, Neuhaus JA, Phillips AN, Babiker A, Cohen CJ, Gatell JM, et al. **Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study**. *The Journal of infectious diseases* 2008; 197(8):1133-1144.
111. Rapa SF, Di Iorio BR, Campiglia P, Heidland A, Marzocco S. **Inflammation and Oxidative Stress in Chronic Kidney Disease-Potential Therapeutic Role of Minerals, Vitamins and Plant-Derived Metabolites**. *Int J Mol Sci* 2019; 21(1).
112. Amdur RL, Feldman HI, Gupta J, Yang W, Kanetsky P, Shlipak M, et al. **Inflammation and Progression of CKD: The CRIC Study**. *Clinical journal of the American Society of Nephrology : CJASN* 2016; 11(9):1546-1556.
113. Woziwodzka K, Dziewierz A, Pawica M, Panek A, Krzanowski M, Golasa P, et al. **Neutrophil-to-lymphocyte ratio predicts long-term all-cause mortality in patients with chronic kidney disease stage 5**. *Folia Med Cracov* 2019; 59(4):55-70.
114. Correa S, Pena-Esparragoza JK, Scovner KM, Waikar SS, Mc Causland FR. **Myeloperoxidase and the Risk of CKD Progression, Cardiovascular Disease, and Death in the Chronic Renal Insufficiency Cohort (CRIC) Study**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2019.
115. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, et al. **Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency**. *Circulation* 2003; 107(1):87-92.
116. Silverstein DM. **Inflammation in chronic kidney disease: role in the progression of renal and cardiovascular disease**. *Pediatr Nephrol* 2009; 24(8):1445-1452.
117. Dube MP, Chan ES, Lake JE, Williams B, Kinslow J, Landay A, et al. **A Randomized, Double-blinded, Placebo-controlled Trial of Sitagliptin for Reducing Inflammation and Immune Activation in Treated and Suppressed Human Immunodeficiency Virus Infection**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2019; 69(7):1165-1172.
118. Nixon DE, Bosch RJ, Chan ES, Funderburg NT, Hodder S, Lake JE, et al. **Effects of atorvastatin on biomarkers of immune activation, inflammation, and lipids in virologically suppressed, human immunodeficiency virus-1-infected individuals with low-density lipoprotein cholesterol <130 mg/dL (AIDS Clinical Trials Group Study A5275)**. *J Clin Lipidol* 2017; 11(1):61-69.
119. O'Brien MP, Hunt PW, Kitch DW, Klingman K, Stein JH, Funderburg NT, et al. **A Randomized Placebo Controlled Trial of Aspirin Effects on Immune Activation in Chronically Human Immunodeficiency Virus-Infected Adults on Virologically Suppressive Antiretroviral Therapy**. *Open Forum Infect Dis* 2017; 4(1):ofw278.
120. Funderburg NT, Jiang Y, Debanne SM, Storer N, Labbato D, Clagett B, et al. **Rosuvastatin treatment reduces markers of monocyte activation in HIV-infected subjects on antiretroviral therapy**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014; 58(4):588-595.
121. Ascher SB, Scherzer R, Nishtala A, Jotwani V, Grunfeld C, Parikh CR, et al. **Association of Statin Use With Kidney Damage and Function Among HIV-Infected Men**. *J Acquir Immune Defic Syndr* 2019; 82(2):202-210.
122. Group I-ES, Committee SS, Abrams D, Levy Y, Losso MH, Babiker A, et al. **Interleukin-2 therapy in patients with HIV infection**. *The New England journal of medicine* 2009; 361(16):1548-1559.
123. Doco-Lecompte T, Garrec A, Thomas L, Trechot P, May T, Rabaud C. **Lopinavir-ritonavir (Kaletra) and lithiasis: seven cases**. *AIDS* 2004; 18(4):705-706.
124. Tattevin P, Revest M, Chapplain JM, Ratajczak-Enselme M, Arvieux C, Michelet C. **Increased Risk of Renal Stones in Patients Treated With Atazanavir**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2013.
125. Zimmermann AE, Pizzoferrato T, Bedford J, Morris A, Hoffman R, Braden G. **Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2006; 42(2):283-290.

126. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. **Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2010; 51(5):496-505.
127. Izzedine H, Isnard-Bagnis C, Hulot JS, Vittecoq D, Cheng A, Jais CK, et al. **Renal safety of tenofovir in HIV treatment-experienced patients**. *AIDS* 2004; 18(7):1074-1076.
128. Calza L, Sachs M, Colangeli V, Borderi M, Granozzi B, Malosso P, et al. **Prevalence of chronic kidney disease among HIV-1-infected patients receiving a combination antiretroviral therapy**. *Clinical and experimental nephrology* 2019; 23(11):1272-1279.
129. Martinez F, Mommeja-Marin H, Estepa-Maurice L, Beaufils H, Bochet M, Daudon M, et al. **Indinavir crystal deposits associated with tubulointerstitial nephropathy**. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 1998; 13(3):750-753.
130. Arribas JR, Pozniak AL, Gallant JE, Dejesus E, Gazzard B, Campo RE, et al. **Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis**. *J Acquir Immune Defic Syndr* 2008; 47(1):74-78.
131. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, et al. **Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial**. *JAMA : the journal of the American Medical Association* 2004; 292(2):191-201.
132. Squires K, Pozniak AL, Pierone G, Jr., Steinhart CR, Berger D, Bellos NC, et al. **Tenofovir disoproxil fumarate in nucleoside-resistant HIV-1 infection: a randomized trial**. *Annals of internal medicine* 2003; 139(5 Pt 1):313-320.
133. Woodward CL, Hall AM, Williams IG, Madge S, Copas A, Nair D, et al. **Tenofovir-associated renal and bone toxicity**. *HIV medicine* 2009; 10(8):482-487.
134. Atta MG, Fine DM. **Editorial comment: tenofovir nephrotoxicity--the disconnect between clinical trials and real-world practice**. *The AIDS reader* d2009; 19(3):118-119.
135. Sax PE, Gallant JE, Klotman PE. **Renal safety of tenofovir disoproxil fumarate**. *The AIDS reader* 2007; 17(2):90-92, 99-104, C103.
136. Crum-Cianflone N, Ganesan A, Teneza-Mora N, Riddle M, Medina S, Barahona I, et al. **Prevalence and factors associated with renal dysfunction among HIV-infected patients**. *AIDS patient care and STDs* 2010; 24(6):353-360.
137. Gallant JE, Deresinski S. **Tenofovir disoproxil fumarate**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2003; 37(7):944-950.
138. Verhelst D, Monge M, Meynard JL, Fouqueray B, Mougenot B, Girard PM, et al. **Fanconi syndrome and renal failure induced by tenofovir: a first case report**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2002; 40(6):1331-1333.
139. Laprise C, Baril JG, Dufresne S, Trottier H. **Association Between Tenofovir Exposure and Reduced Kidney Function in a Cohort of HIV-Positive Patients: Results from 10 Years of Follow-up**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2012.
140. Post FA, Moyle GJ, Stellbrink HJ, Domingo P, Podzamczer D, Fisher M, et al. **Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study**. *J Acquir Immune Defic Syndr* 2010; 55(1):49-57.
141. Zolopa A, Sax PE, DeJesus E, Mills A, Cohen C, Wohl D, et al. **A randomized double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: analysis of week 96 results**. *J Acquir Immune Defic Syndr* 2013; 63(1):96-100.
142. Hamzah L, Jose S, Booth JW, Hegazi A, Rayment M, Bailey A, et al. **Treatment-limiting renal tubulopathy in patients treated with tenofovir disoproxil fumarate**. *The Journal of infection* 2017; 74(5):492-500.

143. Brennan A, Evans D, Maskew M, Naicker S, Ive P, Sanne I, et al. **Relationship between renal dysfunction, nephrotoxicity and death among HIV adults on tenofovir**. *AIDS* 2011; 25(13):1603-1609.
144. committee EE. **European AIDS Clinical Society Guidelines v10.0** In; 2019.
145. Young J, Schafer J, Fux CA, Furrer H, Bernasconi E, Vernazza P, et al. **Renal function in patients with HIV starting therapy with tenofovir and either efavirenz, lopinavir or atazanavir**. *AIDS* 2012; 26(5):567-575.
146. Cuzin L, Pugliese P, Allavena C, Rey D, Chirouze C, Bani-Sadr F, et al. **Antiretroviral therapy as a risk factor for chronic kidney disease: Results from traditional regression modeling and causal approach in a large observational study**. *PloS one* 2017; 12(12):e0187517.
147. Dieleman JP, Sturkenboom MC, Jambroes M, Gyssens IC, Weverling GJ, ten Veen JH, et al. **Risk factors for urological symptoms in a cohort of users of the HIV protease inhibitor indinavir sulfate: the ATHENA cohort**. *Archives of internal medicine* 2002; 162(13):1493-1501.
148. Gupta SK. **Tenofovir-associated Fanconi syndrome: review of the FDA adverse event reporting system**. *AIDS patient care and STDs* 2008; 22(2):99-103.
149. Perazella MA. **Renal vulnerability to drug toxicity**. *Clinical journal of the American Society of Nephrology : CJASN* 2009; 4(7):1275-1283.
150. Campo R, Dejesus E, Bredeek UF, Henry K, Khanlou H, Logue K, et al. **SWIFT: Prospective 48-Week Study to Evaluate Efficacy and Safety of Switching to Emtricitabine/Tenofovir From Lamivudine/Abacavir in Virologically Suppressed HIV-1 Infected Patients on a Boosted Protease Inhibitor Containing Antiretroviral Regimen**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2013; 56(11):1637-1645.
151. Alsauskas ZC, Medapalli RK, Ross MJ. **Expert opinion on pharmacotherapy of kidney disease in HIV-infected patients**. *Expert opinion on pharmacotherapy* 2011; 12(5):691-704.
152. Wever K, van Agtmael MA, Carr A. **Incomplete reversibility of tenofovir-related renal toxicity in HIV-infected men**. *J Acquir Immune Defic Syndr* 2010; 55(1):78-81.
153. Hamada Y, Nishijima T, Watanabe K, Komatsu H, Tsukada K, Teruya K, et al. **High Incidence of Renal Stones Among HIV-Infected Patients on Ritonavir-Boosted Atazanavir Than in Those Receiving Other Protease Inhibitor-Containing Antiretroviral Therapy**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2012.
154. Ryom L, Lundgren JD, Ross M, Kirk O, Law M, Morlat P, et al. **Renal Impairment and Cardiovascular Disease in HIV-Positive Individuals: The D:A:D Study**. *The Journal of infectious diseases* 2016; 214(8):1212-1220.
155. Di Mascio M, Srinivasula S, Bhattacharjee A, Cheng L, Martiniova L, Herscovitch P, et al. **Antiretroviral tissue kinetics: in vivo imaging using positron emission tomography**. *Antimicrobial agents and chemotherapy* 2009; 53(10):4086-4095.
156. Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, et al. **Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients**. *AIDS* 2010; 24(11):1667-1678.
157. Dauchy FA, Lawson-Ayayi S, de La Faille R, Bonnet F, Rigothier C, Mehsen N, et al. **Increased risk of abnormal proximal renal tubular function with HIV infection and antiretroviral therapy**. *Kidney international* 2011; 80(3):302-309.
158. Wyatt CM, Chaudhari J, Miao S, Krishnasami Z, Hellinger J, Levey AS, et al. **Ritonavir-Boosted Protease Inhibitors Do Not Significantly Affect the Performance of Creatinine-Based Estimates of GFR**. *Kidney Int Rep* 2020; 5(5):734-737.
159. de Lastours V, Ferrari Rafael De Silva E, Daudon M, Porcher R, Loze B, Sauvageon H, et al. **High levels of atazanavir and darunavir in urine and crystalluria in asymptomatic patients**. *The Journal of antimicrobial chemotherapy* 2013; 68(8):1850-1856.
160. Jose S, Nelson M, Phillips A, Chadwick D, Trevelion R, Jones R, et al. **Improved kidney function in patients who switch their protease inhibitor from atazanavir or lopinavir to darunavir**. *AIDS* 2017; 31(4):485-492.

161. Rockwood N, Mandalia S, Bower M, Gazzard B, Nelson M. **Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir**. *AIDS* 2011; 25(13):1671-1673.
162. Nishijima T, Hamada Y, Watanabe K, Komatsu H, Kinai E, Tsukada K, et al. **Ritonavir-boosted darunavir is rarely associated with nephrolithiasis compared with ritonavir-boosted atazanavir in HIV-infected patients**. *PloS one* 2013; 8(10):e77268.
163. Bonjoch A, Puig J, Perez-Alvarez N, Juega J, Echeverria P, Clotet B, et al. **Impact of protease inhibitors on the evolution of urinary markers: Subanalyses from an observational cross-sectional study**. *Medicine* 2016; 95(32):e4507.
164. Fontecha M, Monsalvo M, Rodriguez-Sagrado MA, Vivancos MJ, Moreno A, Casado JL. **Long-term improvement in renal, bone, lipid parameters, and CD4/CD8 ratio in HIV-infected patients switching to a dual therapy with lamivudine plus boosted darunavir**. *Infect Dis (Lond)* 2019; 51(4):293-298.
165. Harris M. **Nephrotoxicity associated with antiretroviral therapy in HIV-infected patients**. *Expert opinion on drug safety* 2008; 7(4):389-400.
166. Parkhie SM, Fine DM, Lucas GM, Atta MG. **Characteristics of patients with HIV and biopsy-proven acute interstitial nephritis**. *Clinical journal of the American Society of Nephrology : CJASN* 2010; 5(5):798-804.
167. Kohler JJ, Hosseini SH, Hoying-Brandt A, Green E, Johnson DM, Russ R, et al. **Tenofovir renal toxicity targets mitochondria of renal proximal tubules**. *Laboratory investigation; a journal of technical methods and pathology* 2009; 89(5):513-519.
168. Kohler JJ, Hosseini SH, Green E, Abuin A, Ludaway T, Russ R, et al. **Tenofovir renal proximal tubular toxicity is regulated by OAT1 and MRP4 transporters**. *Laboratory investigation; a journal of technical methods and pathology* 2011; 91(6):852-858.
169. Ray AS, Cihlar T, Robinson KL, Tong L, Vela JE, Fuller MD, et al. **Mechanism of active renal tubular efflux of tenofovir**. *Antimicrobial agents and chemotherapy* 2006; 50(10):3297-3304.
170. Saumoy M, Vidal F, Peraire J, Sauleda S, Vea AM, Vilades C, et al. **Proximal tubular kidney damage and tenofovir: a role for mitochondrial toxicity?** *AIDS* 2004; 18(12):1741-1742.
171. Likanonsakul S, Suntisuklappon B, Nitiyanontakij R, Prasithsirikul W, Nakayama EE, Shioda T, et al. **A Single-Nucleotide Polymorphism in ABCC4 Is Associated with Tenofovir-Related Beta2-Microglobulinuria in Thai Patients with HIV-1 Infection**. *PloS one* 2016; 11(1):e0147724.
172. Salvaggio SE, Giacomelli A, Falvella FS, Oreni ML, Meraviglia P, Atzori C, et al. **Clinical and genetic factors associated with kidney tubular dysfunction in a real-life single centre cohort of HIV-positive patients**. *BMC infectious diseases* 2017; 17(1):396.
173. Rodriguez-Novoa S, Labarga P, Soriano V, Egan D, Albalater M, Morello J, et al. **Predictors of kidney tubular dysfunction in HIV-infected patients treated with tenofovir: a pharmacogenetic study**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2009; 48(11):e108-116.
174. Nishijima T, Komatsu H, Higasa K, Takano M, Tsuchiya K, Hayashida T, et al. **Single nucleotide polymorphisms in ABCC2 associate with tenofovir-induced kidney tubular dysfunction in Japanese patients with HIV-1 infection: a pharmacogenetic study**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2012; 55(11):1558-1567.
175. Dietrich LG, Barcelo C, Thorball CW, Ryom L, Burkhalter F, Hasse B, et al. **Contribution of Genetic Background and Data Collection on Adverse Events of Anti-human Immunodeficiency Virus (HIV) Drugs (D:A:D) Clinical Risk Score to Chronic Kidney Disease in Swiss HIV-infected Persons With Normal Baseline Estimated Glomerular Filtration Rate**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2020; 70(5):890-897.
176. Albini L, Cesana BM, Motta D, Foca E, Gotti D, Calabresi A, et al. **A Randomized, Pilot Trial to Evaluate Glomerular Filtration Rate by Creatinine or Cystatin C in Naive HIV-Infected Patients After Tenofovir/Emtricitabine in Combination With Atazanavir/Ritonavir or Efavirenz**. *J Acquir Immune Defic Syndr* 2012; 59(1):18-30.

177. Goicoechea M, Liu S, Best B, Sun S, Jain S, Kemper C, et al. **Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy**. *The Journal of infectious diseases* 2008; 197(1):102-108.
178. Mulenga L, Musonda P, Mwango A, Vinikoor MJ, Davies MA, Mweemba A, et al. **Effect of baseline renal function on tenofovir-containing antiretroviral therapy outcomes in Zambia**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014; 58(10):1473-1480.
179. Friis-Moller N, Weber R, Reiss P, Thiebaut R, Kirk O, d'Arminio Monforte A, et al. **Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study**. *AIDS* 2003; 17(8):1179-1193.
180. Saumoy M, Ordonez-Llanos J, Martinez E, Ferrer E, Domingo P, Ribera E, et al. **Atherogenic properties of lipoproteins in HIV patients starting atazanavir/ritonavir or darunavir/ritonavir: a substudy of the ATADAR randomized study**. *The Journal of antimicrobial chemotherapy* 2015; 70(4):1130-1138.
181. Noubissi EC, Katte JC, Sobngwi E. **Diabetes and HIV**. *Curr Diab Rep* 2018; 18(11):125.
182. Casado JL, Monsalvo M, Vizcarra P, Fontecha M, Serrano-Villar S, Moreno S. **Evaluation of kidney function in HIV-infected patients receiving an antiretroviral regimen containing one or two inhibitors of the tubular secretion of creatinine**. *HIV medicine* 2019; 20(10):648-656.
183. Joshi K, Boettiger D, Kerr S, Nishijima T, Van Nguyen K, Ly PS, et al. **Changes in renal function with long-term exposure to antiretroviral therapy in HIV-infected adults in Asia**. *Pharmacoepidemiol Drug Saf* 2018; 27(11):1209-1216.
184. Suzuki S, Nishijima T, Kawasaki Y, Kurosawa T, Mutoh Y, Kikuchi Y, et al. **Effect of Tenofovir Disoproxil Fumarate on Incidence of Chronic Kidney Disease and Rate of Estimated Glomerular Filtration Rate Decrement in HIV-1-Infected Treatment-Naive Asian Patients: Results from 12-Year Observational Cohort**. *AIDS patient care and STDs* 2017; 31(3):105-112.
185. Cristelli MP, Trullas JC, Cofan F, Rico N, Manzardo C, Ambrosioni J, et al. **Prevalence and risk factors of mild chronic renal failure in HIV-infected patients: influence of female gender and antiretroviral therapy**. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases* 2018; 22(3):193-201.
186. De Waal R, Cohen K, Fox MP, Stinson K, Maartens G, Boulle A, et al. **Changes in estimated glomerular filtration rate over time in South African HIV-1-infected patients receiving tenofovir: a retrospective cohort study**. *Journal of the International AIDS Society* 2017; 20(1):21317.
187. Chadwick DR, Sarfo FS, Kirk ES, Owusu D, Bedu-Addo G, Parris V, et al. **Tenofovir is associated with increased tubular proteinuria and asymptomatic renal tubular dysfunction in Ghana**. *BMC Nephrol* 2015; 16:195.
188. Salome T, Kasamba I, Mayanja BN, Kazooba P, Were J, Kaleebu P, et al. **The effect of Tenofovir on renal function among Ugandan adults on long-term antiretroviral therapy: a cross-sectional enrolment analysis**. *AIDS Res Ther* 2016; 13(1):28.
189. Fritzsche C, Rudolph J, Huenten-Kirsch B, Hemmer CJ, Tekoh R, Kuwoh PB, et al. **Effect of Tenofovor Diproxil Fumarate on Renal Function and Urinalysis Abnormalities in HIV-Infected Cameroonian Adults**. *Am J Trop Med Hyg* 2017; 97(5):1445-1450.
190. Mulubwa M, Rheeders M, Fourie C, Viljoen M. **Associations between plasma tenofovir concentration and renal function markers in HIV-infected women**. *South Afr J HIV Med* 2016; 17(1):458.
191. Mtisi TJ, Ndhlovu CE, Maponga CC, Morse GD. **Tenofovir-associated kidney disease in Africans: a systematic review**. *AIDS Res Ther* 2019; 16(1):12.
192. Mugyenyi P, Walker AS, Hakim J, Munderi P, Gibb DM, Kityo C, et al. **Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial**. *Lancet* 2010; 375(9709):123-131.
193. Yilma D, Abdissa A, Kaestel P, Tesfaye M, Olsen MF, Girma T, et al. **Serum creatinine and estimated glomerular filtration rates in HIV positive and negative adults in Ethiopia**. *PloS one* 2019; 14(2):e0211630.

194. Wyatt CM, Schwartz GJ, Owino Ong'or W, Abuya J, Abraham AG, Mboku C, et al. **Estimating kidney function in HIV-infected adults in Kenya: comparison to a direct measure of glomerular filtration rate by iohexol clearance**. *PloS one* 2013; 8(8):e69601.
195. Lescure FX, Fellahi S, Pialoux G, Bastard JP, Eme AL, Esteve E, et al. **Prevalence of tubulopathy and association with renal function loss in HIV-infected patients**. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2019.
196. Kapitsinou PP, Ansari N. **Acute renal failure in an AIDS patient on tenofovir: a case report**. *Journal of medical case reports* 2008; 2:94.
197. Nolin TD, Himmelfarb J. **Mechanisms of drug-induced nephrotoxicity**. *Handbook of experimental pharmacology* 2010; (196):111-130.
198. Berdichevski RH, Luis LB, Crestana L, Manfro RC. **Amphotericin B-related nephrotoxicity in low-risk patients**. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases* 2006; 10(2):94-99.
199. Jao J, Wyatt CM. **Antiretroviral medications: adverse effects on the kidney**. *Advances in chronic kidney disease* 2010; 17(1):72-82.
200. Yao X, Panichpisal K, Kurtzman N, Nugent K. **Cisplatin nephrotoxicity: a review**. *The American journal of the medical sciences* 2007; 334(2):115-124.
201. Fabrizii V, Thalhammer F, Horl WH. **[Aminoglycoside-induced nephrotoxicity]**. *Wiener klinische Wochenschrift* 1997; 109(21):830-835.
202. Malik A, Abraham P, Malik N. **Acute renal failure and Fanconi syndrome in an AIDS patient on tenofovir treatment--case report and review of literature**. *The Journal of infection* 2005; 51(2):E61-65.
203. Yoshino M, Yagura H, Kushida H, Yonemoto H, Bando H, Ogawa Y, et al. **Assessing recovery of renal function after tenofovir disoproxil fumarate discontinuation**. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy* 2012; 18(2):169-174.
204. Bonjoch A. **Recovery after TDF nephrotoxicity**. In: *CROI*. Seattle; 2012.
205. Bredeek F GR, Yolo R and Schneider S. **A switch from TDF/FTC to raltegravir in patients on a boosted protease inhibitor is effective in reducing proteinuria and increasing GFR, Abstract H1-1399b**. In: *51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)*. Chicago, USA; 2011.
206. Izzedine H, Hulot JS, Vittecoq D, Gallant JE, Staszewski S, Launay-Vacher V, et al. **Long-term renal safety of tenofovir disoproxil fumarate in antiretroviral-naive HIV-1-infected patients. Data from a double-blind randomized active-controlled multicentre study**. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2005; 20(4):743-746.
207. Campbell LJ, Hamzah L, Post FA. **Is tenofovir-related renal toxicity incompletely reversible?** *J Acquir Immune Defic Syndr* 2011; 56(3):e95; author reply e95-96.
208. Nelson MR, Katlama C, Montaner JS, Cooper DA, Gazzard B, Clotet B, et al. **The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years**. *AIDS* 2007; 21(10):1273-1281.
209. Chan-Tack KM, Truffa MM, Struble KA, Birnkrant DB. **Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's Adverse Event Reporting System**. *AIDS* 2007; 21(9):1215-1218.
210. Jose S, Hamzah L, Campbell LJ, Hill T, Fisher M, Leen C, et al. **Incomplete Reversibility of Estimated Glomerular Filtration Rate Decline Following Tenofovir Disoproxil Fumarate Exposure**. *The Journal of infectious diseases* 2014.
211. Eriksen BO, Ingebretsen OC. **The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age**. *Kidney international* 2006; 69(2):375-382.
212. Matlosz B, Kowalska JD, Bakowska E, Firlag-Burkacka E, Vassilenko A, Horban A. **Discontinuation of tenofovir due to nephrotoxicity: insight into 12 years of clinical practice**. *Przegl Epidemiol* 2019; 73(2):249-255.

213. Taal MW, Brenner BM. **Predicting initiation and progression of chronic kidney disease: Developing renal risk scores**. *Kidney international* 2006; 70(10):1694-1705.
214. Gupta SK, Anderson AM, Ebrahimi R, Fralich T, Graham H, Scharen-Guivel V, et al. **Fanconi syndrome accompanied by renal function decline with tenofovir disoproxil fumarate: a prospective, case-control study of predictors and resolution in HIV-infected patients**. *PloS one* 2014; 9(3):e92717.
215. Tsai HJ, Chuang YW, Lee SW, Wu CY, Yeh HZ, Lee TY. **Using the chronic kidney disease guidelines to evaluate the renal safety of tenofovir disoproxil fumarate in hepatitis B patients**. *Aliment Pharmacol Ther* 2018; 47(12):1673-1681.
216. Tang EC, Vittinghoff E, Anderson PL, Cohen SE, Doblecki-Lewis S, Bacon O, et al. **Changes in Kidney Function Associated With Daily Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Preexposure Prophylaxis Use in the United States Demonstration Project**. *J Acquir Immune Defic Syndr* 2018; 77(2):193-198.
217. Young J, Wang Q, Fux CA, Bernasconi E, Furrer H, Vernazza P, et al. **The rate of recovery in renal function when patients with HIV infection discontinue treatment with tenofovir**. *HIV medicine* 2014; 15(8):505-510.
218. Couzigou C, Daudon M, Meynard JL, Borsa-Lebas F, Higueret D, Escaut L, et al. **Urolithiasis in HIV-positive patients treated with atazanavir**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2007; 45(8):e105-108.
219. Gitman MD, Hirschwerk D, Baskin CH, Singhal PC. **Tenofovir-induced kidney injury**. *Expert opinion on drug safety* 2007; 6(2):155-164.
220. Herlitz LC, Mohan S, Stokes MB, Radhakrishnan J, D'Agati VD, Markowitz GS. **Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities**. *Kidney international* 2010; 78(11):1171-1177.
221. Izzedine H, M'Rad M B, Bardier A, Daudon M, Salmon D. **Atazanavir crystal nephropathy**. *AIDS* 2007; 21(17):2357-2358.
222. Gupta SK, Post FA, Arribas JR, Eron JJ, Jr., Wohl DA, Clarke AE, et al. **Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials**. *AIDS* 2019; 33(9):1455-1465.
223. DeJesus E, Haas B, Segal-Maurer S, Ramgopal MN, Mills A, Margot N, et al. **Superior Efficacy and Improved Renal and Bone Safety After Switching from a Tenofovir Disoproxil Fumarate- to a Tenofovir Alafenamide-Based Regimen Through 96 Weeks of Treatment**. *AIDS research and human retroviruses* 2018; 34(4):337-342.
224. Hamzah L, Williams D, Bailey AC, Jones R, Ibrahim F, Musso CG, et al. **Early safety of tenofovir alafenamide in patients with a history of tubulopathy on tenofovir disoproxil fumarate: a randomized controlled clinical trial**. *HIV medicine* 2019.
225. Hagins D, Orkin C, Daar ES, Mills A, Brinson C, DeJesus E, et al. **Switching to coformulated rilpivirine (RPV), emtricitabine (FTC) and tenofovir alafenamide from either RPV, FTC and tenofovir disoproxil fumarate (TDF) or efavirenz, FTC and TDF: 96-week results from two randomized clinical trials**. *HIV medicine* 2018; 19(10):724-733.
226. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, et al. **Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials**. *Lancet* 2015; 385(9987):2606-2615.
227. Kalayjian RC, Lau B, Mechekano RN, Crane HM, Rodriguez B, Salata RA, et al. **Risk factors for chronic kidney disease in a large cohort of HIV-1 infected individuals initiating antiretroviral therapy in routine care**. *AIDS* 2012; 26(15):1907-1915.
228. WHO. **March 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach**. http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_march2014/en/; 2014. Assessed Dec 12th 2019

229. WHO. **Rapid advice Antiretroviral therapy for HIV infection in adults and adolescents** In. https://www.who.int/hiv/pub/arv/rapid_advice_art.pdf; 2009. Assessed Dec 12th 2019
230. Mocroft A, Ryom L, Begovac J, Monforte AD, Vassilenko A, Gatell J, et al. **Deteriorating renal function and clinical outcomes in HIV-positive persons**. *AIDS* 2014; 28(5):727-737.
231. WHO. **Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection**. In. https://www.who.int/hiv/pub/guidelines/arv2013/en/; 2013. Assessed Dec 12th 2019
232. Collins GS, Omar O, Shanyinde M, Yu LM. **A systematic review finds prediction models for chronic kidney were poorly reported and often developed using inappropriate methods**. *Journal of clinical epidemiology* 2012.
233. Bang H, Vupputuri S, Shoham DA, Klemmer PJ, Falk RJ, Mazumdar M, et al. **SCreening for Occult REnal Disease (SCORED): a simple prediction model for chronic kidney disease**. *Archives of internal medicine* 2007; 167(4):374-381.
234. Chien KL, Lin HJ, Lee BC, Hsu HC, Lee YT, Chen MF. **A prediction model for the risk of incident chronic kidney disease**. *The American journal of medicine* 2010; 123(9):836-846 e832.
235. Thakkinstian A, Ingsathit A, Chaiprasert A, Rattanasiri S, Sangthawan P, Gojaseni P, et al. **A simplified clinical prediction score of chronic kidney disease: a cross-sectional-survey study**. *BMC Nephrol* 2011; 12:45.
236. Halbesma N, Jansen DF, Heymans MW, Stolk RP, de Jong PE, Gansevoort RT, et al. **Development and validation of a general population renal risk score**. *Clinical journal of the American Society of Nephrology : CJASN* 2011; 6(7):1731-1738.
237. Nelson RG, Grams ME, Ballew SH, Sang Y, Azizi F, Chadban SJ, et al. **Development of Risk Prediction Equations for Incident Chronic Kidney Disease**. *JAMA : the journal of the American Medical Association* 2019.
238. Ando M, Yanagisawa N, Ajisawa A, Tsuchiya K, Nitta K. **A simple model for predicting incidence of chronic kidney disease in HIV-infected patients**. *Clinical and experimental nephrology* 2011; 15(2):242-247.
239. Woolnough EL, Hoy JF, Cheng AC, Walker RG, Chrysostomou A, Woolley I, et al. **Predictors of chronic kidney disease and utility of risk prediction scores in HIV-positive individuals**. *AIDS* 2018; 32(13):1829-1835.
240. Flandre P, Pugliese P, Allavena C, Isnard Bagnis C, Cuzin L, Dat AsG. **Does first-line antiretroviral regimen impact risk for chronic kidney disease whatever the risk group?** *AIDS* 2016; 30(9):1433-1438.
241. Mills AM, Schulman KL, Fusco JS, Brunet L, Hsu R, Beyer A, et al. **Validation of the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) chronic kidney disease risk score in HIV-infected patients in the USA**. *HIV medicine* 2020.
242. Tomlinson L. **https://journals.plos.org/plosmedicine/article/comment?id=10.1371/annotation/d35e8c5b-306a-4c21-8a28-588cab813ba4**. In; 2015. Assessed Dec 12th 2019
243. Boyd MA, Mocroft A, Ryom L, Monforte AD, Sabin C, El-Sadr WM, et al. **Cardiovascular disease (CVD) and chronic kidney disease (CKD) event rates in HIV-positive persons at high predicted CVD and CKD risk: A prospective analysis of the D:A:D observational study**. *PLoS medicine* 2017; 14(11):e1002424.
244. Scherzer R, Shlipak MG. **Risk factors: Individual assessment of CKD risk in HIV-positive patients**. *Nature reviews Nephrology* 2015; 11(7):392-393.
245. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, et al. **Relation between kidney function, proteinuria, and adverse outcomes**. *JAMA : the journal of the American Medical Association* 2010; 303(5):423-429.
246. Landray MJ, Emberson JR, Blackwell L, Dasgupta T, Zakeri R, Morgan MD, et al. **Prediction of ESRD and death among people with CKD: the Chronic Renal Impairment in Birmingham (CRIB) prospective cohort study**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2010; 56(6):1082-1094.
247. Titze S, Schmid M, Kottgen A, Busch M, Floege J, Wanner C, et al. **Disease burden and risk profile in referred patients with moderate chronic kidney disease: composition of the German Chronic Kidney**

**Disease (GCKD) cohort**. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2015; 30(3):441-451.
248. Evans M, Grams ME, Sang Y, Astor BC, Blankestijn PJ, Brunskill NJ, et al. **Risk Factors for Prognosis in Patients With Severely Decreased GFR**. *Kidney Int Rep* 2018; 3(3):625-637.
249. Stengel B. **Chronic kidney disease and cancer: a troubling connection**. *Journal of nephrology* 2010; 23(3):253-262.
250. Lowrance WT, Ordonez J, Udaltsova N, Russo P, Go AS. **CKD and the risk of incident cancer**. *Journal of the American Society of Nephrology : JASN* 2014; 25(10):2327-2334.
251. Arbel Y, Halkin A, Finkelstein A, Revivo M, Berliner S, Herz I, et al. **Impact of Estimated Glomerular Filtration Rate on Vascular Disease Extent and Adverse Cardiovascular Events in Patients Without Chronic Kidney Disease**. *The Canadian journal of cardiology* 2013.
252. Jotwani V, Scherzer R, Choi A, Szczech L, Polak JF, Kronmal RA, et al. **Reduced kidney function and preclinical atherosclerosis in HIV-infected individuals: the study of fat redistribution and metabolic change in HIV infection (FRAM)**. *American journal of nephrology* 2011; 33(5):453-460.
253. Ibrahim F, Hamzah L, Jones R, Nitsch D, Sabin C, Post FA. **Baseline Kidney Function as Predictor of Mortality and Kidney Disease Progression in HIV-Positive Patients**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2012; 60(4):539-547.
254. Gupta SK, Ong'or WO, Shen C, Musick B, Goldman M, Wools-Kaloustian K. **Reduced renal function is associated with progression to AIDS but not with overall mortality in HIV-infected Kenyan adults not initially requiring combination antiretroviral therapy**. *Journal of the International AIDS Society* 2011; 14:31.
255. Lucas GM, Mehta SH, Atta MG, Kirk GD, Galai N, Vlahov D, et al. **End-stage renal disease and chronic kidney disease in a cohort of African-American HIV-infected and at-risk HIV-seronegative participants followed between 1988 and 2004**. *AIDS* 2007; 21(18):2435-2443.
256. Choi AI, Li Y, Deeks SG, Grunfeld C, Volberding PA, Shlipak MG. **Association between kidney function and albuminuria with cardiovascular events in HIV-infected persons**. *Circulation* 2010; 121(5):651-658.
257. Lucas GM, Lau B, Atta MG, Fine DM, Keruly J, Moore RD. **Chronic kidney disease incidence, and progression to end-stage renal disease, in HIV-infected individuals: a tale of two races**. *The Journal of infectious diseases* 2008; 197(11):1548-1557.
258. Grams ME, Yang W, Rebholz CM, Wang X, Porter AC, Inker LA, et al. **Risks of Adverse Events in Advanced CKD: The Chronic Renal Insufficiency Cohort (CRIC) Study**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2017; 70(3):337-346.
259. Valiathan R, Miguez MJ, Patel B, Arheart KL, Asthana D. **Tobacco smoking increases immune activation and impairs T-cell function in HIV infected patients on antiretrovirals: a cross-sectional pilot study**. *PloS one* 2014; 9(5):e97698.
260. Shepherd L, Ryom L, Law M, Petoumenos K, Hatleberg CI, d'Arminio Monforte A, et al. **Cessation of Cigarette Smoking and the Impact on Cancer Incidence in HIV-positive Persons: The D:A:D Study**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2018.
261. Petoumenos K, Worm S, Reiss P, de Wit S, d'Arminio Monforte A, Sabin C, et al. **Rates of cardiovascular disease following smoking cessation in patients with HIV infection: results from the D:A:D study(*)**. *HIV medicine* 2011; 12(7):412-421.
262. Cohen G, Horl WH. **Immune dysfunction in uremia—an update**. *Toxins* 2012; 4(11):962-990.
263. Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, et al. **International comparison of the relationship of chronic kidney disease prevalence and ESRD risk**. *Journal of the American Society of Nephrology : JASN* 2006; 17(8):2275-2284.
264. Choi AI, Rodriguez RA, Bacchetti P, Volberding PA, Havlir D, Bertenthal D, et al. **Low rates of antiretroviral therapy among HIV-infected patients with chronic kidney disease**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2007; 45(12):1633-1639.
265. Duncan AD, Goff LM, Peters BS. **Type 2 diabetes prevalence and its risk factors in HIV: A cross-sectional study**. *PloS one* 2018; 13(3):e0194199.

266. O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS, et al. **Age affects outcomes in chronic kidney disease**. *Journal of the American Society of Nephrology : JASN* 2007; 18(10):2758-2765.
267. Agarwal R, Bunaye Z, Bekele DM, Light RP. **Competing risk factor analysis of end-stage renal disease and mortality in chronic kidney disease**. *American journal of nephrology* 2008; 28(4):569-575.
268. Fried LF, Katz R, Sarnak MJ, Shlipak MG, Chaves PH, Jenny NS, et al. **Kidney function as a predictor of noncardiovascular mortality**. *Journal of the American Society of Nephrology : JASN* 2005; 16(12):3728-3735.
269. Jorgensen L, Heuch I, Jenssen T, Jacobsen BK. **Association of albuminuria and cancer incidence**. *Journal of the American Society of Nephrology : JASN* 2008; 19(5):992-998.
270. Wong G, Hayen A, Chapman JR, Webster AC, Wang JJ, Mitchell P, et al. **Association of CKD and cancer risk in older people**. *Journal of the American Society of Nephrology : JASN* 2009; 20(6):1341-1350.
271. Berliner AR, Fine DM, Lucas GM, Rahman MH, Racusen LC, Scheel PJ, et al. **Observations on a cohort of HIV-infected patients undergoing native renal biopsy**. *American journal of nephrology* 2008; 28(3):478-486.
272. Black C, Sharma P, Scotland G, McCullough K, McGurn D, Robertson L, et al. **Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis**. *Health Technol Assess* 2010; 14(21):1-184.
273. Al Hamarneh YN, Tsuyuki RT, Jones CA, Manns B, Tonelli M, Scott-Douglass N, et al. **Effectiveness of Pharmacist Interventions on Cardiovascular Risk in Patients With CKD: A Subgroup Analysis of the Randomized Controlled RxEACH Trial**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2018; 71(1):42-51.
274. Triant VA, Lee H, Hadigan C, Grinspoon SK. **Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease**. *The Journal of clinical endocrinology and metabolism* 2007; 92(7):2506-2512.
275. Eyawo O, Brockman G, Goldsmith CH, Hull MW, Lear SA, Bennett M, et al. **Risk of myocardial infarction among people living with HIV: an updated systematic review and meta-analysis**. *BMJ open* 2019; 9(9):e025874.
276. Klein DB, Leyden WA, Xu L, Chao CR, Horberg MA, Towner WJ, et al. **Declining relative risk for myocardial infarction among HIV-positive compared with HIV-negative individuals with access to care**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2015; 60(8):1278-1280.
277. Rosenson RS, Hubbard D, Monda KL, Reading SR, Chen L, Dluzniewski PJ, et al. **Excess Risk for Atherosclerotic Cardiovascular Outcomes Among US Adults With HIV in the Current Era**. *J Am Heart Assoc* 2020; 9(1):e013744.
278. Shahmanesh M, Schultze A, Burns F, Kirk O, Lundgren J, Mussini C, et al. **The cardiovascular risk management for people living with HIV in Europe: how well are we doing?** *AIDS* 2016; 30(16):2505-2518.
279. Hatleberg CI, Ryom L, El-Sadr W, Smith C, Weber R, Reiss P, et al. **Improvements over time in short-term mortality following myocardial infarction in HIV-positive individuals**. *AIDS* 2016; 30(10):1583-1596.
280. Hatleberg CI, Lundgren JD, Ryom L. **Are we successfully managing cardiovascular disease in people living with HIV?** *Current opinion in HIV and AIDS* 2017; 12(6):594-603.
281. Feinstein MJ, Hsue PY, Benjamin LA, Bloomfield GS, Currier JS, Freiberg MS, et al. **Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV: A Scientific Statement From the American Heart Association**. *Circulation* 2019; 140(2):e98-e124.
282. Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, et al. **HIV Infection and the Risk of Acute Myocardial Infarction**. *JAMA internal medicine* 2013:1-9.
283. **CVD prediction models**. In. http://chd.bestsciencemedicine.com/calc2.html. Assessed Dec 12th 2019
284. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. **2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines**. *Circulation* 2019; 140(11):e596-e646.

285. Collins GS, Altman DG. **Predicting the 10 year risk of cardiovascular disease in the United Kingdom: independent and external validation of an updated version of QRISK2**. *BMJ* 2012; 344:e4181.
286. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. **General cardiovascular risk profile for use in primary care: the Framingham Heart Study**. *Circulation* 2008; 117(6):743-753.
287. Serrano-Villar S, Estrada V, Gomez-Garre D, Avila M, Fuentes-Ferrer M, San RJ, et al. **Diagnosis of subclinical atherosclerosis in HIV-infected patients: higher accuracy of the D:A:D risk equation over Framingham and SCORE algorithms**. *Eur J Prev Cardiol* 2014; 21(6):739-748.
288. Triant VA, Perez J, Regan S, Massaro JM, Meigs JB, Grinspoon SK, et al. **Cardiovascular Risk Prediction Functions Underestimate Risk in HIV Infection**. *Circulation* 2018; 137(21):2203-2214.
289. Hsue PY, Waters DD. **HIV infection and coronary heart disease: mechanisms and management**. *Nat Rev Cardiol* 2019; 16(12):745-759.
290. Baker JV, Lundgren JD. **Cardiovascular implications from untreated human immunodeficiency virus infection**. *European heart journal* 2011; 32(8):945-951.
291. Baker JV, Henry WK, Neaton JD. **The consequences of HIV infection and antiretroviral therapy use for cardiovascular disease risk: shifting paradigms**. *Current opinion in HIV and AIDS* 2009; 4(3):176-182.
292. Angelovich TA, Trevillyan JM, Hoy JF, Wong ME, Agius PA, Hearps AC, et al. **Monocytes from men living with HIV exhibit heightened atherogenic potential despite long term viral suppression with ART**. *AIDS* 2019.
293. Angelovich TA, Hearps AC, Oda MN, Borja MS, Huynh D, Homann S, et al. **Dysfunctional high-density lipoprotein from HIV+ individuals promotes monocyte-derived foam cell formation in vitro**. *AIDS* 2017; 31(17):2331-2336.
294. Parikh NI, Gerschenson M, Bennett K, Gangcuangco LM, Lopez MS, Mehta NN, et al. **Lipoprotein concentration, particle number, size and cholesterol efflux capacity are associated with mitochondrial oxidative stress and function in an HIV positive cohort**. *Atherosclerosis* 2015; 239(1):50-54.
295. Nordell AD, McKenna M, Borges AH, Duprez D, Neuhaus J, Neaton JD, et al. **Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation**. *J Am Heart Assoc* 2014; 3(3):e000844.
296. Hsue PY, Hunt PW, Sinclair E, Bredt B, Franklin A, Killian M, et al. **Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses**. *AIDS* 2006; 20(18):2275-2283.
297. Maisa A, Hearps AC, Angelovich TA, Pereira CF, Zhou J, Shi MD, et al. **Monocytes from HIV-infected individuals show impaired cholesterol efflux and increased foam cell formation after transendothelial migration**. *AIDS* 2015; 29(12):1445-1457.
298. Sabin CA, Ryom L, De Wit S, Mocroft A, Phillips AN, Worm SW, et al. **Associations between immune depression and cardiovascular events in HIV infection**. *AIDS* 2013; 27(17):2735-2748.
299. Helleberg M, Kronborg G, Larsen CS, Pedersen G, Pedersen C, Obel N, et al. **CD4 decline is associated with increased risk of cardiovascular disease, cancer, and death in virally suppressed patients with HIV**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2013; 57(2):314-321.
300. Baker JV, Hullsiek KH, Engen NW, Nelson R, Chetchotisakd P, Gerstoft J, et al. **Early Antiretroviral Therapy at High CD4 Counts Does Not Improve Arterial Elasticity: A Substudy of the Strategic Timing of AntiRetroviral Treatment (START) Trial**. *Open Forum Infect Dis* 2016; 3(4):ofw213.
301. Phillips AN, Carr A, Neuhaus J, Visnegarwala F, Prineas R, Burman WJ, et al. **Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial**. *Antiviral therapy* 2008; 13(2):177-187.
302. Sabin CA, Ryom L, d'Arminio Monforte A, Hatleberg CI, Pradier C, El-Sadr W, et al. **Abacavir use and risk of recurrent myocardial infarction**. *AIDS* 2018; 32(1):79-88.

303. De Pablo C, Orden S, Apostolova N, Blanquer A, Esplugues JV, Alvarez A. **Abacavir and didanosine induce the interaction between human leukocytes and endothelial cells through Mac-1 upregulation**. *AIDS* 2010; 24(9):1259-1266.
304. Esplugues JV, De Pablo C, Collado-Diaz V, Hernandez C, Orden S, Alvarez A. **Interference with purinergic signalling: an explanation for the cardiovascular effect of abacavir?** *AIDS* 2016; 30(9):1341-1351.
305. Elion RA, Althoff KN, Zhang J, Moore RD, Gange SJ, Kitahata MM, et al. **Recent Abacavir Use Increases Risk of Type 1 and Type 2 Myocardial Infarctions Among Adults With HIV**. *J Acquir Immune Defic Syndr* 2018; 78(1):62-72.
306. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D, Clinical Epidemiology Group from the French Hospital D. **Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men**. *AIDS* 2003; 17(17):2479-2486.
307. Stein JH, Klein MA, Bellehumeur JL, McBride PE, Wiebe DA, Otvos JD, et al. **Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction**. *Circulation* 2001; 104(3):257-262.
308. Lundgren J, Mocroft A, Ryom L. **Contemporary protease inhibitors and cardiovascular risk**. *Current opinion in infectious diseases* 2018; 31(1):8-13.
309. Huhn GD, Shamblaw DJ, Baril JG, Hsue PY, Mills BL, Nguyen-Cleary T, et al. **Atherosclerotic Cardiovascular Disease Risk Profile of Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate**. *Open Forum Infect Dis* 2020; 7(1):ofz472.
310. Kerchberger AM, Sheth AN, Angert CD, Mehta CC, Summers NA, Ofotokun I, et al. **Weight Gain Associated with Integrase Stand Transfer Inhibitor Use in Women**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2019.
311. Bourgi K, Rebeiro PF, Turner M, Castilho JL, Hulgan T, Raffanti SP, et al. **Greater Weight Gain in Treatment Naive Persons Starting Dolutegravir-Based Antiretroviral Therapy**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2019.
312. Williams-Nguyen J, Hawes SE, Nance RM, Lindstrom S, Heckbert SR, Kim HN, et al. **Association of Infection with Chronic Hepatitis C Virus and Myocardial Infarction in People Living with HIV in the United States**. *Am J Epidemiol* 2019.
313. Alvaro-Meca A, Berenguer J, Diaz A, Micheloud D, Aldamiz-Echevarria T, Fanciulli C, et al. **Stroke in HIV-infected individuals with and without HCV coinfection in Spain in the combination antiretroviral therapy era**. *PloS one* 2017; 12(6):e0179493.
314. McKibben RA, Haberlen SA, Post WS, Brown TT, Budoff M, Witt MD, et al. **A Cross-sectional Study of the Association Between Chronic Hepatitis C Virus Infection and Subclinical Coronary Atherosclerosis Among Participants in the Multicenter AIDS Cohort Study**. *The Journal of infectious diseases* 2016; 213(2):257-265.
315. Hanna DB, Post WS, Deal JA, Hodis HN, Jacobson LP, Mack WJ, et al. **HIV Infection Is Associated With Progression of Subclinical Carotid Atherosclerosis**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2015; 61(4):640-650.
316. Moran CA, Southmayd G, Devireddy CM, Quyyumi AA, Ofotokun I, Liberman HA, et al. **Clinical and procedural characteristics of persons living with HIV presenting with acute coronary syndrome**. *AIDS* 2020; 34(1):81-90.
317. O'Dwyer EJ, Bhamra-Ariza P, Rao S, Emmanuel S, Carr A, Holloway CJ. **Lower coronary plaque burden in patients with HIV presenting with acute coronary syndrome**. *Open Heart* 2016; 3(2):e000511.
318. Knudsen A, Mathiasen AB, Worck RH, Kastrup J, Gerstoft J, Katzenstein TL, et al. **Angiographic features and cardiovascular risk factors in human immunodeficiency virus-infected patients with first-time acute coronary syndrome**. *The American journal of cardiology* 2013; 111(1):63-67.
319. Kong X, Ma X, Cui M, Xu D. **Association of clustering of major cardiovascular risk factors with chronic kidney disease in the adult population**. *Clinical nephrology* 2014; 82(2):92-97.

320. McClellan WM, Langston RD, Presley R. **Medicare patients with cardiovascular disease have a high prevalence of chronic kidney disease and a high rate of progression to end-stage renal disease**. *Journal of the American Society of Nephrology : JASN* 2004; 15(7):1912-1919.
321. Arbel Y, Halkin A, Finkelstein A, Revivo M, Berliner S, Herz I, et al. **Impact of estimated glomerular filtration rate on vascular disease extent and adverse cardiovascular events in patients without chronic kidney disease**. *The Canadian journal of cardiology* 2013; 29(11):1374-1381.
322. Di Angelantonio E, Danesh J, Eiriksdottir G, Gudnason V. **Renal function and risk of coronary heart disease in general populations: new prospective study and systematic review**. *PLoS medicine* 2007; 4(9):e270.
323. Shara NM, Wang H, Mete M, Al-Balha YR, Azalddin N, Lee ET, et al. **Estimated GFR and incident cardiovascular disease events in American Indians: the Strong Heart Study**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2012; 60(5):795-803.
324. Collins AJ, Foley RN, Gilbertson DT, Chen SC. **The state of chronic kidney disease, ESRD, and morbidity and mortality in the first year of dialysis**. *Clinical journal of the American Society of Nephrology : CJASN* 2009; 4 Suppl 1:S5-11.
325. George E, Lucas GM, Nadkarni GN, Fine DM, Moore R, Atta MG. **Kidney function and the risk of cardiovascular events in HIV-1-infected patients**. *AIDS* 2010; 24(3):387-394.
326. Campbell LJ, Desai M, Hegazi A, Ibrahim F, Melikian N, Hay P, et al. **Renal impairment is associated with coronary heart disease in HIV-positive men**. *HIV clinical trials* 2012; 13(6):343-349.
327. Stenvinkel P, Barany P. **Dialysis in 2011: Can cardiovascular risk in dialysis patients be decreased?** *Nature reviews Nephrology* 2012; 8(2):72-74.
328. de Bie MK, Buiten MS, Rabelink TJ, Jukema JW. **How to reduce sudden cardiac death in patients with renal failure**. *Heart* 2012; 98(4):335-341.
329. Foley RN, Gilbertson DT, Murray T, Collins AJ. **Long interdialytic interval and mortality among patients receiving hemodialysis**. *The New England journal of medicine* 2011; 365(12):1099-1107.
330. Natali A, Boldrini B, Baldi S, Rossi M, Landi P, Severi S, et al. **Impact of mild to moderate reductions of glomerular filtration rate on coronary artery disease severity**. *Nutrition, metabolism, and cardiovascular diseases : NMCD* 2014; 24(6):681-688.
331. Serrano-Villar S, Estrada V, Gomez-Garre D, Avila M, Fuentes-Ferrer M, Sanchez-Parra C, et al. **Incipient renal impairment as a predictor of subclinical atherosclerosis in HIV-infected patients**. *J Acquir Immune Defic Syndr* 2012; 59(2):141-148.
332. Cheru LT, Fitch KV, Saylor CF, Lu M, Hoffmann U, Lo J, et al. **Mild renal impairment is associated with calcified plaque parameters assessed by computed tomography angiography in people living with HIV**. *AIDS* 2019; 33(2):219-227.
333. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. **Low glomerular filtration rate and risk of stroke: meta-analysis**. *BMJ* 2010; 341:c4249.
334. Hippisley-Cox J, Coupland C, Brindle P. **Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study**. *BMJ* 2017; 357:j2099.
335. Lekawanvijit S. **Cardiotoxicity of Uremic Toxins: A Driver of Cardiorenal Syndrome**. *Toxins* 2018; 10(9).
336. Uchida L, Tanaka T, Saito H, Sugahara M, Wakashima T, Fukui K, et al. **Effects of a prolyl hydroxylase inhibitor on kidney and cardiovascular complications in a rat model of chronic kidney disease**. *American journal of physiology Renal physiology* 2020; 318(2):F388-F401.
337. Rodrigues SD, Santos SS, Meireles T, Romero N, Glorieux G, Pecoits-Filho R, et al. **Uremic toxins promote accumulation of oxidized protein and increased sensitivity to hydrogen peroxide in endothelial cells by impairing the autophagic flux**. *Biochem Biophys Res Commun* 2019.
338. Fujii H, Kono K, Nishi S. **Characteristics of coronary artery disease in chronic kidney disease**. *Clinical and experimental nephrology* 2019; 23(6):725-732.

339. Matsushita K, Sang Y, Ballew SH, Astor BC, Hoogeveen RC, Solomon SD, et al. **Cardiac and kidney markers for cardiovascular prediction in individuals with chronic kidney disease: the Atherosclerosis Risk in Communities study**. *Arteriosclerosis, thrombosis, and vascular biology* 2014; 34(8):1770-1777.
340. Klawitter J, Reed-Gitomer BY, McFann K, Pennington A, Abebe KZ, Klepacki J, et al. **Endothelial dysfunction and oxidative stress in polycystic kidney disease**. *American journal of physiology Renal physiology* 2014; 307(11):F1198-1206.
341. Spoto B, Mattace-Raso F, Sijbrands E, Leonardis D, Testa A, Pisano A, et al. **Association of IL-6 and a functional polymorphism in the IL-6 gene with cardiovascular events in patients with CKD**. *Clinical journal of the American Society of Nephrology : CJASN* 2015; 10(2):232-240.
342. Formentini I, Bobadilla M, Haefliger C, Hartmann G, Loghman-Adham M, Mizrahi J, et al. **Current drug development challenges in chronic kidney disease (CKD)--identification of individualized determinants of renal progression and premature cardiovascular disease (CVD)**. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2012; 27 Suppl 3:iii81-88.
343. Baber U, Howard VJ, Halperin JL, Soliman EZ, Zhang X, McClellan W, et al. **Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study**. *Circulation Arrhythmia and electrophysiology* 2011; 4(1):26-32.
344. Wang AY, Lai KN. **Use of cardiac biomarkers in end-stage renal disease**. *Journal of the American Society of Nephrology : JASN* 2008; 19(9):1643-1652.
345. Bash LD, Astor BC, Coresh J. **Risk of incident ESRD: a comprehensive look at cardiovascular risk factors and 17 years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Study**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2010; 55(1):31-41.
346. Masia M, Padilla S, Bernal E, Almenar MV, Molina J, Hernandez I, et al. **Influence of antiretroviral therapy on oxidative stress and cardiovascular risk: a prospective cross-sectional study in HIV-infected patients**. *Clinical therapeutics* 2007; 29(7):1448-1455.
347. Monforte A, Reiss P, Ryom L, El-Sadr W, Dabis F, De Wit S, et al. **Atazanavir is not associated with an increased risk of cardio or cerebrovascular disease events**. *AIDS* 2013; 27(3):407-415.
348. Fontas E, van Leth F, Sabin CA, Friis-Moller N, Rickenbach M, d'Arminio Monforte A, et al. **Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles?** *The Journal of infectious diseases* 2004; 189(6):1056-1074.
349. Stein JH. **Dyslipidemia in the era of HIV protease inhibitors**. *Prog Cardiovasc Dis* 2003; 45(4):293-304.
350. Dragsted UB, Gerstoft J, Pedersen C, Peters B, Duran A, Obel N, et al. **Randomized trial to evaluate indinavir/ritonavir versus saquinavir/ritonavir in human immunodeficiency virus type 1-infected patients: the MaxCmin1 Trial**. *The Journal of infectious diseases* 2003; 188(5):635-642.
351. Banhegyi D, Katlama C, da Cunha CA, Schneider S, Rachlis A, Workman C, et al. **Week 96 efficacy, virology and safety of darunavir/r versus lopinavir/r in treatment-experienced patients in TITAN**. *Current HIV research* 2012; 10(2):171-181.
352. Orkin C, DeJesus E, Khanlou H, Stoehr A, Supparatpinyo K, Lathouwers E, et al. **Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial**. *HIV medicine* 2013; 14(1):49-59.
353. Masia M, Martinez E, Padilla S, Gatell JM, Gutierrez F. **Endothelial function in HIV-infected patients switching from a boosted protease inhibitor-based regimen to raltegravir: a substudy of the SPIRAL study**. *The Journal of antimicrobial chemotherapy* 2013; 68(2):409-413.
354. Dressman J, Kincer J, Matveev SV, Guo L, Greenberg RN, Guerin T, et al. **HIV protease inhibitors promote atherosclerotic lesion formation independent of dyslipidemia by increasing CD36-dependent cholesteryl ester accumulation in macrophages**. *The Journal of clinical investigation* 2003; 111(3):389-397.
355. Kunutsor SK, Bakker SJ, Gansevoort RT, Chowdhury R, Dullaart RP. **Circulating total bilirubin and risk of incident cardiovascular disease in the general population**. *Arteriosclerosis, thrombosis, and vascular biology* 2015; 35(3):716-724.

356. Marconi VC, Duncan MS, So-Armah K, Re VL, 3rd, Lim JK, Butt AA, et al. **Bilirubin Is Inversely Associated With Cardiovascular Disease Among HIV-Positive and HIV-Negative Individuals in VACS (Veterans Aging Cohort Study)**. *J Am Heart Assoc* 2018; 7(10).
357. LaFleur J, Bress AP, Rosenblatt L, Crook J, Sax PE, Myers J, et al. **Cardiovascular outcomes among HIV-infected veterans receiving atazanavir**. *AIDS* 2017; 31(15):2095-2106.
358. Stein JH, Ribaudo HJ, Hodis HN, Brown TT, Tran TT, Yan M, et al. **A prospective, randomized clinical trial of antiretroviral therapies on carotid wall thickness**. *AIDS* 2015; 29(14):1775-1783.
359. Sabin CA, Reiss P, Ryom L, Phillips AN, Weber R, Law M, et al. **Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration**. *BMC Med* 2016; 14:61.
360. Cahn P, Fourie J, Grinsztejn B, Hodder S, Molina JM, Ruxrungtham K, et al. **Week 48 analysis of once-daily vs. twice-daily darunavir/ritonavir in treatment-experienced HIV-1-infected patients**. *AIDS* 2011; 25(7):929-939.
361. Janssen Pharmaceuticals IabtUSFaDA. **http://www.prezista.com/sites/default/files/pdf/us_package_insert.pdf#zoom=100**; 2016. Assessed Dec 12th 2019
362. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000707/WC500041756.pdf. **ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS**. Assessed Dec 12th 2019
363. Opsomer M, Dimitrova D, Verspeelt J, Purrington A, Mehbob A, Chavers S, et al. **Evaluation of Cardiovascular Disease Risk in HIV-1-Infected Patients Treated with Darunavir**. *Drugs R D* 2018; 18(3):199-210.
364. Costagliola D, Potard V, Lang S, de Castro N, Cotte L, Duval X, et al. **Is the Risk of Myocardial Infarction in People With Human Immunodeficiency Virus (HIV) Associated With Atazanavir or Darunavir? A Nested Case-Control Study Within the French Hospital Database on HIV**. *The Journal of infectious diseases* 2020; 221(4):516-522.
365. Antinori A, Rusconi S, Gianotti N, Bini T, Mancusi D, Termini R. **Cardiovascular adverse events during treatment with darunavir-based regimens in an Italian observational study**. *Drug Des Devel Ther* 2019; 13:1667-1685.
366. Triant VA, Siedner MJ. **Darunavir and Cardiovascular Risk: Evaluating the Data to Inform Clinical Care**. *The Journal of infectious diseases* 2020; 221(4):498-500.
367. Hatleberg CI, Ryom L, El-Sadr W, Mocroft A, Reiss P, De Wit S, et al. **Gender differences in the use of cardiovascular interventions in HIV-positive persons; the D:A:D Study**. *Journal of the International AIDS Society* 2018; 21(3).
368. Potosek J, Curry M, Buss M, Chittenden E. **Integration of palliative care in end-stage liver disease and liver transplantation**. *J Palliat Med* 2014; 17(11):1271-1277.
369. Towner WJ, Xu L, Leyden WA, Horberg MA, Chao CR, Tang B, et al. **The effect of HIV infection, immunodeficiency, and antiretroviral therapy on the risk of hepatic dysfunction**. *J Acquir Immune Defic Syndr* 2012; 60(3):321-327.
370. Kirk GD, Mehta SH, Astemborski J, Galai N, Washington J, Higgins Y, et al. **HIV, age, and the severity of hepatitis C virus-related liver disease: a cohort study**. *Annals of internal medicine* 2013; 158(9):658-666.
371. Sherman KE, Peters MG, Thomas DL. **HIV and the liver**. *Topics in antiviral medicine* 2019; 27(3):101-110.
372. Thio CL, Seaberg EC, Skolasky R, Jr., Phair J, Visscher B, Munoz A, et al. **HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS)**. *Lancet* 2002; 360(9349):1921-1926.
373. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. **Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2001; 33(4):562-569.

374. Blanco F, Barreiro P, Ryan P, Vispo E, Martin-Carbonero L, Tuma P, et al. **Risk factors for advanced liver fibrosis in HIV-infected individuals: role of antiretroviral drugs and insulin resistance**. *Journal of viral hepatitis* 2011; 18(1):11-16.
375. den Brinker M, Wit FW, Wertheim-van Dillen PM, Jurriaans S, Weel J, van Leeuwen R, et al. **Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection**. *AIDS* 2000; 14(18):2895-2902.
376. Kovari H, Ledergerber B, Battegay M, Rauch A, Hirschel B, Foguena AK, et al. **Incidence and risk factors for chronic elevation of alanine aminotransferase levels in HIV-infected persons without hepatitis b or c virus co-infection**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2010; 50(4):502-511.
377. Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, et al. **Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study**. *Archives of internal medicine* 2006; 166(15):1632-1641.
378. Qin F, Jiang J, Qin C, Huang Y, Liang B, Xu Y, et al. **Liver damage in patients living with HIV on antiretroviral treatment with normal baseline liver function and without HBV/HCV infection: an 11-year retrospective cohort study in Guangxi, China**. *BMJ open* 2019; 9(4):e023140.
379. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. **Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection**. *JAMA : the journal of the American Medical Association* 2000; 283(1):74-80.
380. Abrescia N, D'Abbraccio M, Figoni M, Busto A, Maddaloni A, De Marco M. **Hepatotoxicity of antiretroviral drugs**. *Current pharmaceutical design* 2005; 11(28):3697-3710.
381. Maida I, Nunez M, Rios MJ, Martin-Carbonero L, Sotgiu G, Toro C, et al. **Severe liver disease associated with prolonged exposure to antiretroviral drugs**. *J Acquir Immune Defic Syndr* 2006; 42(2):177-182.
382. Lapadula G, Costarelli S, Chatenoud L, Castelli F, Astuti N, Di Giambenedetto S, et al. **Risk of Liver Enzyme Elevation during Treatment with Ritonavir-boosted Protease Inhibitors among HIV-monoinfected and HIV/HCV Coinfected Patients**. *J Acquir Immune Defic Syndr* 2015.
383. Suarez-Zarracina T, Valle-Garay E, Collazos J, Montes AH, Carcaba V, Carton JA, et al. **Didanosine (ddI) associates with increased liver fibrosis in adult HIV-HCV coinfected patients**. *Journal of viral hepatitis* 2012; 19(10):685-693.
384. Loko MA, Bani-Sadr F, Winnock M, Lacombe K, Carrieri P, Neau D, et al. **Impact of HAART exposure and associated lipodystrophy on advanced liver fibrosis in HIV/HCV-coinfected patients**. *Journal of viral hepatitis* 2011; 18(7):e307-314.
385. Merchante N, Perez-Camacho I, Mira JA, Rivero A, Macias J, Camacho A, et al. **Prevalence and risk factors for abnormal liver stiffness in HIV-infected patients without viral hepatitis coinfection: role of didanosine**. *Antiviral therapy* 2010; 15(5):753-763.
386. Klein MB, Althoff KN, Jing Y, Lau B, Kitahata M, Lo Re V, 3rd, et al. **Risk of End-Stage Liver Disease in HIV-Viral Hepatitis Coinfected Persons in North America From the Early to Modern Antiretroviral Therapy Eras**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2016; 63(9):1160-1167.
387. Gjaerde LI, Shepherd L, Jablonowska E, Lazzarin A, Rougemont M, Darling K, et al. **Trends in Incidences and Risk Factors for Hepatocellular Carcinoma and Other Liver Events in HIV and Hepatitis C Virus-coinfected Individuals From 2001 to 2014: A Multicohort Study**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2016; 63(6):821-829.
388. Marine-Barjoan E, Saint-Paul MC, Pradier C, Chaillou S, Anty R, Michiels JF, et al. **Impact of antiretroviral treatment on progression of hepatic fibrosis in HIV/hepatitis C virus co-infected patients**. *AIDS* 2004; 18(16):2163-2170.
389. Kovari H, Sabin CA, Ledergerber B, Ryom L, Worm SW, Smith C, et al. **Antiretroviral Drug-Related Liver Mortality Among HIV-Positive Persons in the Absence of Hepatitis B or C Virus Coinfection: The Data Collection on Adverse Events of Anti-HIV Drugs Study**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2013; 56(6):870-879.

390. Wit FW, Weverling GJ, Weel J, Jurriaans S, Lange JM. **Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy**. *The Journal of infectious diseases* 2002; 186(1):23-31.
391. Bani-Sadr F, Lapidus N, Bedossa P, De Boever CM, Perronne C, Halfon P, et al. **Progression of fibrosis in HIV and hepatitis C virus-coinfected patients treated with interferon plus ribavirin-based therapy: analysis of risk factors**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2008; 46(5):768-774.
392. Pinol V, Bessa X, Bruguera M, Rodes J. **[Steatosis and nonalcoholic steatohepatitis. A comparative analysis]**. *Gastroenterologia y hepatologia* 2000; 23(2):57-61.
393. McGovern BH, Ditelberg JS, Taylor LE, Gandhi RT, Christopoulos KA, Chapman S, et al. **Hepatic steatosis is associated with fibrosis, nucleoside analogue use, and hepatitis C virus genotype 3 infection in HIV-seropositive patients**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2006; 43(3):365-372.
394. Phan V, Thai S, Choun K, Lynen L, van Griensven J. **Incidence of treatment-limiting toxicity with stavudine-based antiretroviral therapy in Cambodia: a retrospective cohort study**. *PloS one* 2012; 7(1):e30647.
395. Miller KD, Cameron M, Wood LV, Dalakas MC, Kovacs JA. **Lactic acidosis and hepatic steatosis associated with use of stavudine: report of four cases**. *Annals of internal medicine* 2000; 133(3):192-196.
396. Perazzo H, Cardoso SW, Yanavich C, Nunes EP, Morata M, Gorni N, et al. **Predictive factors associated with liver fibrosis and steatosis by transient elastography in patients with HIV mono-infection under long-term combined antiretroviral therapy**. *Journal of the International AIDS Society* 2018; 21(11):e25201.
397. Bauerle J, Miquel R, Laguno M, Mallolas J, Murillas J, Gatell JM, et al. **Hepatic steatosis with stavudine in HIV/hepatitis C virus co-infection**. *AIDS* 2005; 19(13):1441-1442.
398. Moyle G. **Toxicity of antiretroviral nucleoside and nucleotide analogues: is mitochondrial toxicity the only mechanism?** *Drug safety : an international journal of medical toxicology and drug experience* 2000; 23(6):467-481.
399. Walker UA, Bauerle J, Laguno M, Murillas J, Mauss S, Schmutz G, et al. **Depletion of mitochondrial DNA in liver under antiretroviral therapy with didanosine, stavudine, or zalcitabine**. *Hepatology* 2004; 39(2):311-317.
400. Scourfield A, Jackson A, Waters L, Gazzard B, Nelson M. **The value of screening HIV-infected individuals for didanosine-related liver disease?** *Antiviral therapy* 2011; 16(6):941-942.
401. Kovari H, Sabin CA, Ledergerber B, Ryom L, Reiss P, Law M, et al. **Antiretroviral Drugs and Risk of Chronic Alanine Aminotransferase Elevation in Human Immunodeficiency Virus (HIV)-Monoinfected Persons: The Data Collection on Adverse Events of Anti-HIV Drugs Study**. *Open Forum Infect Dis* 2016; 3(1):ofw009.
402. Birkus G, Hitchcock MJ, Cihlar T. **Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors**. *Antimicrobial agents and chemotherapy* 2002; 46(3):716-723.
403. Lattuada E, Lanzafame M, Carolo G, Gottardi M, Concia E, Vento S. **Does tenofovir increase efavirenz hepatotoxicity?** *AIDS* 2008; 22(8):995.
404. Qayyum S, Dong H, Kovacic D, Sohail S, Waters B, Thornton C, et al. **Combination therapy efavirenz/emtricitabine/tenofovir disoproxil fumarate associated with hepatic failure**. *Current drug safety* 2012; 7(5):391-393.
405. Kosi L, Reiberger T, Payer BA, Grabmeier-Pfistershammer K, Strassl R, Rieger A, et al. **Five-year on-treatment efficacy of lamivudine-, tenofovir- and tenofovir + emtricitabine-based HAART in HBV-HIV-coinfected patients**. *Journal of viral hepatitis* 2012; 19(11):801-810.
406. Echenique IA, Rich JD. **EFV/FTC/TDF-associated hepatotoxicity: a case report and review**. *AIDS patient care and STDs* 2013; 27(9):493-497.
407. Fink DL, Bloch E. **Liver transplantation for acute liver failure due to efavirenz hepatotoxicity: the importance of routine monitoring**. *International journal of STD & AIDS* 2013; 24(10):831-833.

408. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, et al. **Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial**. *JAMA : the journal of the American Medical Association* 2004; 292(2):191-201.
409. Sax PE, Tierney C, Collier AC, Daar ES, Mollan K, Budhathoki C, et al. **Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results**. *The Journal of infectious diseases* 2011; 204(8):1191-1201.
410. Barditch-Crovo P, Deeks SG, Collier A, Safrin S, Coakley DF, Miller M, et al. **Phase i/ii trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in human immunodeficiency virus-infected adults**. *Antimicrobial agents and chemotherapy* 2001; 45(10):2733-2739.
411. FDA. **Drug Approval Package VIREAD (Tenofovir Disoproxil Fumarate) Tablets**. In. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-356_Viread.cfm; 2001. Assessed Dec 12th 2019
412. Wandeler G, Mauron E, Atkinson A, Dufour JF, Kraus D, Reiss P, et al. **Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients on tenofovir therapy: Relevance for screening strategies**. *J Hepatol* 2019; 71(2):274-280.
413. Shubber Z, Calmy A, Andrieux-Meyer I, Vitoria M, Renaud-Thery F, Shaffer N, et al. **Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis**. *AIDS* 2013.
414. Macias J, Berenguer J, M. J, al. E. **Cumulative exposure to ARV drugs leads to progressive hepatic steatosis among HIV/HCV-co-infected patients**. In: *CROI*. Seattle. ; 2012.
415. Chu KM, Boulle AM, Ford N, Goemaere E, Asselman V, Van Cutsem G. **Nevirapine-associated early hepatotoxicity: incidence, risk factors, and associated mortality in a primary care ART programme in South Africa**. *PloS one* 2010; 5(2):e9183.
416. Dieterich DT, Robinson PA, Love J, Stern JO. **Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2004; 38 Suppl 2:S80-89.
417. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000264/WC500022929.pdf. **Amprenavir package leaflet**. Assessed Dec 12th 2019
418. Seminari E, De Bona A, Gentilini G, Galli L, Schira G, Gianotti N, et al. **Amprenavir and ritonavir plasma concentrations in HIV-infected patients treated with fosamprenavir/ritonavir with various degrees of liver impairment**. *The Journal of antimicrobial chemotherapy* 2007; 60(4):831-836.
419. Crum-Cianflone N, Dilay A, Collins G, Asher D, Campin R, Medina S, et al. **Nonalcoholic fatty liver disease among HIV-infected persons**. *J Acquir Immune Defic Syndr* 2009; 50(5):464-473.
420. Calza L, Colangeli V, Borderi M, Coladonato S, Tazza B, Fornaro G, et al. **Improvement in liver steatosis after the switch from a ritonavir-boosted protease inhibitor to raltegravir in HIV-infected patients with non-alcoholic fatty liver disease**. *Infect Dis (Lond)* 2019; 51(8):593-601.
421. Macias J, Mancebo M, Merino D, Tellez F, Montes-Ramirez ML, Pulido F, et al. **Changes in Liver Steatosis After Switching From Efavirenz to Raltegravir Among Human Immunodeficiency Virus-Infected Patients With Nonalcoholic Fatty Liver Disease**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2017; 65(6):1012-1019.
422. Merchante N, Giron-Gonzalez JA, Gonzalez-Serrano M, Torre-Cisneros J, Garcia-Garcia JA, Arizcorreta A, et al. **Survival and prognostic factors of HIV-infected patients with HCV-related end-stage liver disease**. *AIDS* 2006; 20(1):49-57.
423. Mocroft A, Lundgren J, Gerstoft J, Rasmussen LD, Bhagani S, Aho I, et al. **Clinical Outcomes in Persons Coinfected With Human Immunodeficiency Virus and Hepatitis C Virus: Impact of Hepatitis C Virus Treatment**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2019.

424. Willemse S, Smit C, Sogni P, Sarcletti M, Uberti-Foppa C, Wittkop L, et al. **Low compliance with hepatocellular carcinoma screening guidelines in hepatitis B/C virus co-infected HIV patients with cirrhosis**. *Journal of viral hepatitis* 2019; 26(10):1224-1228.
425. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. **EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma**. *J Hepatol* 2018; 69(1):182-236.
426. Huang Lucas C, Wu L, Yue B, Bachoo N, Abed R, Berookhim J, et al. **Abstract 10613: Symptomatic Human Immunodeficiency Virus Infected Patients Receive Less Aggressive Revascularization Management After Acute Coronary Syndrome, a 5-year Nationwide Analysis**. *Circulation* 2019; 140(Suppl_1):A10613.
427. Nance RM, Crane HM, Ritchings C, Rosenblatt L, Budoff M, Heckbert SR, et al. **Differentiation of Type 1 and Type 2 Myocardial Infarctions Among HIV-Infected Patients Requires Adjudication Due to Overlap in Risk Factors**. *AIDS research and human retroviruses* 2018; 34(11):916-921.
428. van Zoest RA, van der Valk M, Wit FW, Vaartjes I, Kooij KW, Hovius JW, et al. **Suboptimal primary and secondary cardiovascular disease prevention in HIV-positive individuals on antiretroviral therapy**. *Eur J Prev Cardiol* 2017; 24(12):1297-1307.
429. Boettiger; Newall; Phillips AR, L.; Reiss, P.; Bendavid; Bonnet, F.; Weber, R.; El-Sadr, W.; Law, MG.; Kahn.; Lundgren, J.; Sabin, C.; Kazi. **COST-EFFECTIVENESS OF STATIN USE IN HIV-POSITIVE PERSONS IN THE USA**. In: *CROI*. Boston; 2020.
430. O'Brien M, Montenont E, Hu L, Nardi MA, Valdes V, Merolla M, et al. **Aspirin attenuates platelet activation and immune activation in HIV-1-infected subjects on antiretroviral therapy: a pilot study**. *J Acquir Immune Defic Syndr* 2013; 63(3):280-288.
431. Falcinelli E, Francisci D, Schiaroli E, Minuz P, Orsini S, Malincarne L, et al. **Effect of aspirin treatment on abacavir-associated platelet hyperreactivity in HIV-infected patients**. *Int J Cardiol* 2018; 263:118-124.
432. Levine RS, Mejia MC, Salemi JL, Gonzalez SJ, Aliyu MH, Husaini BA, et al. **A descriptive study of racial inequalities in mortality from hepatocellular cancer before and after licensure of lifesaving drugs for hepatitis C virus in the United States**. *EClinicalMedicine* 2020; 22:100350.
433. Wang H, Peng G, Bai J, He B, Huang K, Hu X, et al. **Cytomegalovirus Infection and Relative Risk of Cardiovascular Disease (Ischemic Heart Disease, Stroke, and Cardiovascular Death): A Meta-Analysis of Prospective Studies Up to 2016**. *J Am Heart Assoc* 2017; 6(7).
434. Neesgaard, Wandeler, Zangerle, Günthard, Smith, De Wit, Mussini, Castagna, Monforte, Vehreschild, Wasmuth, Pradier, Chkhartishvili, Wit, Law, Sönnerborg, Riera, Stephan, Vannappagari, Haubrich, Kowalska, Raben, Rockstroh, Larsen, Peters, Greenberg, Paredes, Grabmeier-Pfistershammer, Scherrer, Johnson, Necsoi, Borghi, Muccini, Tsertsvadze, Petoumenos, Lundgren and Ryom for RESPOND. **How to RESPOND to Modern Challenges for People Living with HIV: A New Cohort Collaboration**. *EACS 2019*. Zuric; 2019.
435. Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, Eron JJ, Yazdanpanah Y, Podzamczer D, et al. **Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial**. *Lancet* 2017; 390(10101):1499-1510.
436. Greenberg L; Ryom L.; Neesgaard, B.; Wandeler, G.; Staub, T.;Gisinger, M.; Skoll, M.; Günthard, H.; Scherrer, A.; Mussini, C.; Smith, C.; Johnson, M.; De Wit, S.; Necsoi, C.; Pradier, C.; Wit, F.; Lehmann, C.; d'Arminio Monforte, A.; Miró, J.M; Castagna, A.; Spagnuolo, V; Sönnerborg, A.; Law, M.; Hutchinson, j.; Chkhartishvili, J.; Bolokadze, J-C Wasmuth, N.; Stephan, C.; Vannappagari, V.; Rogatto, F.; Llibre, J.; Duvivier, C.; Hoy, J.; Bloch, M.; Bucher, H.C.; Calmy, A.; Volny Anne, A.; Pelchen-Matthews, A.; Lundgren, J.D.; Peters, L.; Bansi-Matharu L.; Mocroft, A.; on behalf of the RESPOND study group. **Clinical Outcomes of 2-Drug Regimens (2DRS) vs 3-Drug Regimens (3DRS) in HIV**. *CROI*. Boton; 2020.
437. Mekuria Y, Yilma D, Mekonnen Z, Kassa T, Gedefaw L. **Renal Function Impairment and Associated Factors among HAART Naive and Experienced Adult HIV Positive Individuals in Southwest Ethiopia: A Comparative Cross Sectional Study**. *PloS one* 2016; 11(8):e0161180.

438. Reid A, Stohr W, Walker AS, Williams IG, Kityo C, Hughes P, et al. **Severe renal dysfunction and risk factors associated with renal impairment in HIV-infected adults in Africa initiating antiretroviral therapy**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2008; 46(8):1271-1281.
439. Derose SF, Rutkowski MP, Crooks PW, Shi JM, Wang JQ, Kalantar-Zadeh K, et al. **Racial Differences in Estimated GFR Decline, ESRD, and Mortality in an Integrated Health System**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2013.
440. Choi AI, Rodriguez RA, Bacchetti P, Bertenthal D, Volberding PA, O'Hare AM. **Racial differences in end-stage renal disease rates in HIV infection versus diabetes**. *Journal of the American Society of Nephrology : JASN* 2007; 18(11):2968-2974.
441. Mocroft A, Ryom L. **The benefits and risks of PrEP and kidney function**. *Lancet HIV* 2016.

**Appendix (papers 1-10)**