CVD and CKD event rates in PLHIV at high predicted CVD and CKD risk: results from the D:A:D Study

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Combined CVD and CKD risk in D:A:D

Background

- ART has transformed the lives of people living with HIV (PLH)
- PLH experience greater and earlier onset of comorbidities compared with their HIV-negative peers
- In the general population, chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease (CVD); CVD in turn is associated with CKD
- The D:A:D study has developed predictive risk-scores for CVD and CKD events in PLH

Combined CVD and CKD risk in D:A:D

Hypothesis

That D:A:D participants at high risk for both CKD and CVD are at even greater risk for CVD and CKD events

Combined CVD and CKD risk in D:A:D

Methods

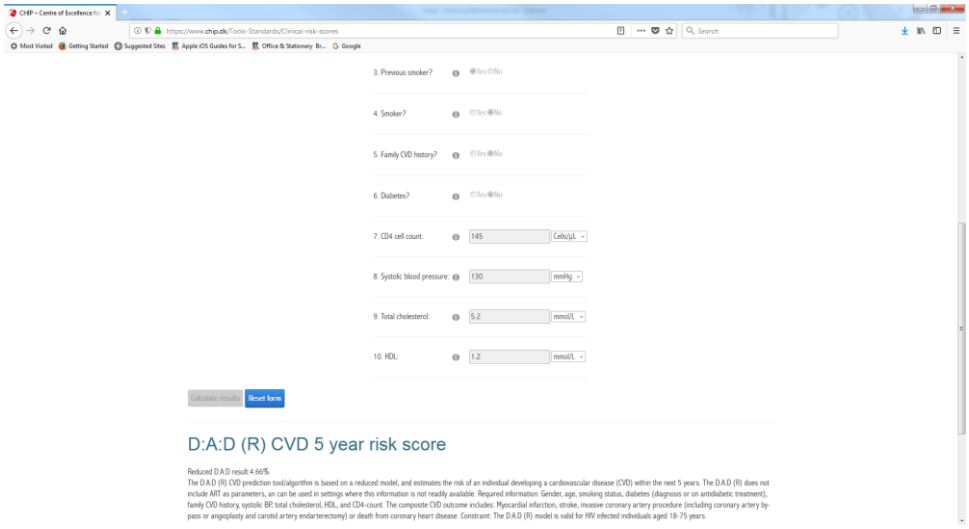
- PLH with a complete set of risk covariate data available
- PLH with a baseline eGFR >60 ml/min/1.72m^2 and ≥2 eGFRs thereafter >60 ml/min/1.72m^2 to calculate CVD and CKD scores
- CVD events were centrally validated clinical events
- CVD and CKD event rates calculated by predicted 5-year CVD and CKD risk strata (≤1%, 1-5% and >5%)
- Poisson models fitted to assess whether CKD and CVD risk strata effects were additive or multiplicative

Combined CVD and CKD risk in D:A:D

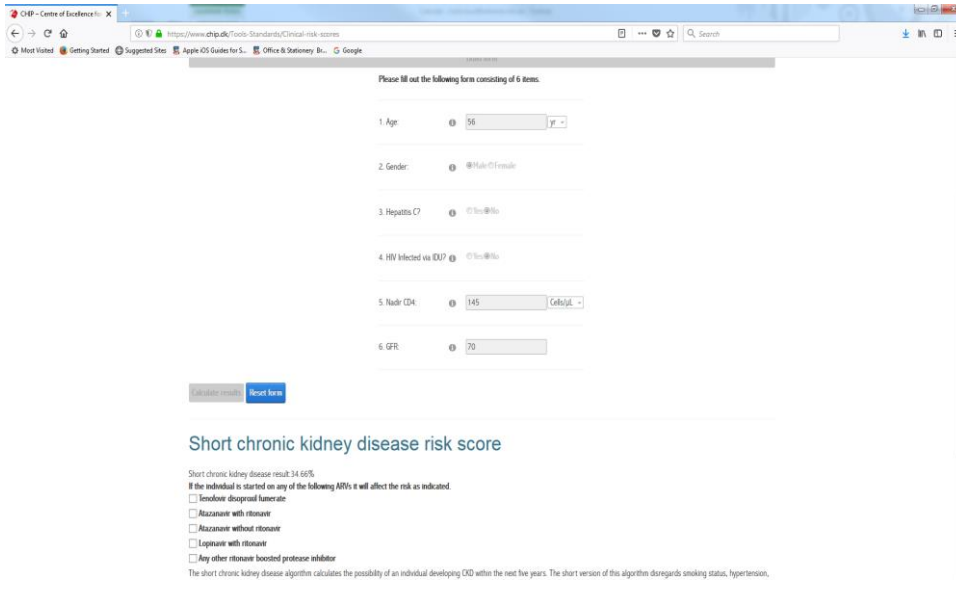
Results

- 49,717 participants enrolled in D:A:D
- 55% had the required complete covariate data (n=27,215) after January 2004 and were included in the analysis
  - 202,034 person years of follow-up

D:A:D CVD 5 year risk score



D:A:D CKD 5 year risk score



Baseline characteristics

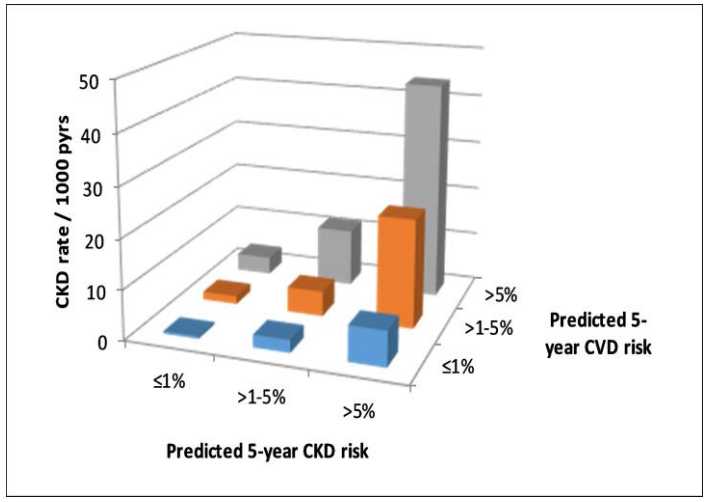
Characteristic	N (%) or median (IQR)
Overall study population	27,215 (100%)
Male	20,206 (74.3%)
Age (years)	42 (36, 49)
Current smoker	13,466 (49.5%)
Diabetes	1,031 (3.8%)
Family history of CVD	2,257 (8.3%)
Receiving abacavir	4,551 (16.7%)
Receiving tenofovir	8,212 (30.2%)
Receiving atazanavir	2,336 (8.6%)
Receiving lopinavir	4,522 (16.6%)
Receiving ritonavir	8,295 (30.5%)
eGFR (ml/min/1.73 m^2)	100 (86, 117)
Total cholesterol (mmol/l)	4.8 (4.1, 5.7)
HDL cholesterol (mmol/l)	1.2 (0.9, 1.5)
CD4 count (cells/mm^3)	464 (319, 650)
Systolic BP (mm Hg)	120 (113, 130)
Diastolic BP (mm Hg)	80 (70, 82)
Cumulative PI use (years)	0.9 (0, 4.0)
Cumulative N(t)RTI use (years)	3.9 (0, 4.0)
5-year predicted CKD risk	1.1% (0.6%, 3.7%)
5-year predicted CVD risk	1.6% (0.8%, 3.3%)
Year of baseline	2005 (2004, 2008)

Numbers of PLH in each predicted risk group combination

5-year CKD predicted risk	5-year CVD predicted risk		
	≤1%	>1%–5%	>5%
≤1%	6,225 (22.9%)	5,926 (21.9%)	383 (1.4%)
>1%–5%	2,047 (7.5%)	6,026 (22.1%)	1,592 (5.9%)
>5%	546 (2.0%)	2,865 (10.5%)	1,585 (5.8%)

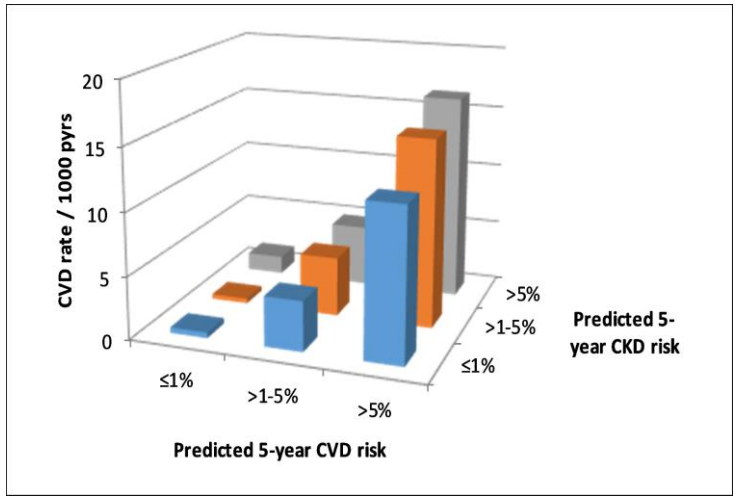
Combined CVD and CKD risk in D:A:D

CKD event rate by predicted CKD and CVD risk



Combined CVD and CKD risk in D:A:D

CVD event rate by predicted CKD and CVD risk



Combined effect of CKD and CVD risk groups in predicting CKD and CVD events

CKD and CVD risk group	*IRR (95% CI)	p-value	Interaction
Predicting CKD events			
CKD ≤1%	1.00		
CKD >1%–5%	3.46 (2.79, 4.30)	<0.001	
CKD >5%	13.81 (11.22, 17.01)	<0.001	
CVD ≤1%	1.00		
CVD >1%–5%	2.70 (2.16, 3.38)	<0.001	
CVD >5%	5.63 (4.47, 7.09)	<0.001	0.291
Predicting CVD events			
CVD ≤1%	1.00		
CVD >1%–5%	8.43 (5.91, 12.03)	<0.001	
CVD >5%	26.97 (18.68, 38.95)	<0.001	0.329
CKD ≤1%	1.00		
CKD >1%–5%	1.19 (1.01, 1.44)	0.041	
CKD >5%	1.31 (1.09, 1.56)	0.005	

*IRR – Incidence rate ratio

Covariates of CVD risk score as predictors for CKD events adjusted for CKD risk group

	Adjusted only for CKD risk group		Fully adjusted model	
	IRR (95% CI)	p-value	IRR (95% CI)	p-value
CKD ≤1%	1.00		1.0	
CKD >1%–5%	4.92 (3.98, 6.09)	<0.001	4.49 (3.63, 5.57)	<0.001
CKD >5%	23.56 (19.30, 28.77)	<0.001	20.53 (16.77, 25.14)	<0.001
Family history of CVD (yes)	0.95 (0.80, 1.14)	0.617		
Current smoker	0.91 (0.80, 1.03)	0.121		
Ex-smoker	1.01 (0.88, 1.17)	0.861		
Ln total cholesterol	1.48 (1.20, 1.83)	<0.001	1.49 (1.20, 1.84)	<0.001
Ln HDL cholesterol	0.89 (0.77, 1.03)	0.121		
Ln base 2 CD4 count	0.90 (0.86, 0.95)	<0.001	0.87 (0.83, 0.91)	<0.001
Receiving abacavir	0.93 (0.81, 1.06)	0.287		
Cumulative PI use	1.11 (1.06, 1.15)	<0.001	1.04 (0.99, 1.10)	0.149
Cumulative NRTI use	1.05 (1.03, 1.08)	<0.001	1.04 (1.02, 1.07)	0.002

*IRR – Incidence rate ratio

Covariates of CKD risk score as predictors for CVD events adjusted for CVD risk group

Risk group or covariate	Adjusted only for CVD risk group	
	IRR (95% CI)	p-Value
CVD ≤1%	1.00	
CVD >1%–5%	9.00 (6.33, 12.80)	<0.001
CVD >5%	30.89 (21.65, 44.08)	<0.001
HIV exposure through IDU	1.00 (0.82, 1.21)	0.979
HCV positive	1.04 (0.88, 1.22)	0.653
eGFR (per 10 units)	1.00 (0.98, 1.03)	0.772
Nadir CD4 count (per 100 cells)	0.94 (0.91, 0.98)	0.002

Diabetes prevalence at baseline by predicted CKD and CVD risk group

5-year CVD risk group	5-year CKD risk group	N	N with diabetes (%)
≤1%	≤1%	6,225	23 (0.4%)
≤1%	≥1%–5%	2,047	10 (0.5%)
≤1%	>5%	546	2 (0.4%)
>1%–5%	≤1%	5,946	61 (1.0%)
>1%–5%	≥1%–5%	6,026	192 (3.2%)
>1%–5%	>5%	2,865	104 (3.6%)
>5%	≤1%	383	39 (10.2%)
>5%	≥1%–5%	1,592	234 (14.7%)
>5%	>5%	1,585	366 (23.1%)
Overall		27,215	1,031 (3.8%)

Limitations

- Prediction models are limited by restrictions in the available data
- In this analysis the risk equations were applied to the same data that were largely used to develop them
- Bias toward male participants
- The CVD and CKD endpoints were established differently
  - CVD events were serious clinical events adjudicated according to specific criteria and subject to central validation
  - CKD events were based on the decline of a laboratory marker observed over 2 consecutive occasions ≥3 months apart

Conclusions

- PLH not uncommonly have CVD and/or CKD
- CKD and CVD interact to create substantial risks for future morbid events
  - particularly in those with both high CKD and CVD risk
- Combining the CVD and CKD risk-scores improved prediction of CVD and CKD events, in particular CKD. This suggests CVD and CKD risk in PLH should be assessed in tandem
- The results highlight the need to identify and treat risk factors that play a major role in HIV-associated comorbidity

Acknowledgements

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