



CRICOS PROVIDER 00123M

**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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## Disclosures

- Research grants: Gilead, MSD
- Advisory boards: Gilead, ViiV Healthcare
- Stock: none

## 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<sup>2</sup> and  $\geq 2$  eGFRs thereafter  $>60$  ml/min/1.72m<sup>2</sup> 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 ( $\leq 1\%$ , 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

3. Previous smoker?  Yes  No

4. Smoker?  Yes  No

5. Family CVD history?  Yes  No

6. Diabetes?  Yes  No

7. CD4 cell count  Cells/µL

8. Systolic blood pressure  mmHg

9. Total cholesterol  mmol/L

10. HDL  mmol/L

[Calculate result](#) [Reset form](#)

### D:A:D (R) CVD 5 year risk score

Reduced DAD result: 4.66%

The DAD (R) CVD prediction tool algorithm is based on a reduced model, and estimates the risk of an individual developing a cardiovascular disease (CVD) within the next 5 years. The DAD (R) does not include ART as parameters, as can be used in settings where this information is not readily available. Required information: Gender, age, smoking status, diabetes (diagnosis or on antidiabetic treatment), family CVD history, systolic BP, total cholesterol, HDL, and CD4-count. The composite CVD outcome includes: Myocardial infarction, stroke, invasive coronary artery procedure (including coronary artery bypass or angioplasty and carotid artery endarterectomy) or death from coronary heart disease. Constraint: The DAD (R) model is valid for HIV infected individuals aged 18-75 years.

## D:A:D CKD 5 year risk score

Please fill out the following form consisting of 6 items.

1. Age  yr

2. Gender  Male  Female

3. Hepatitis C?  Yes  No

4. HIV infected via IDU?  Yes  No

5. Nadir CD4  Cells/µL

6. GFR

[Calculate result](#) [Reset form](#)

### Short chronic kidney disease risk score

Short chronic kidney disease result: 34.85%

If the individual is started on any of the following ARVs it will affect the risk as indicated.

- Tenofovir disoproxil fumarate
- Atracurium with ritonavir
- Atracurium without ritonavir
- Legitimus with ritonavir
- Any other ritonavir boosted protease inhibitor

The short chronic kidney disease algorithm calculates the possibility of an individual developing CKD within the next five years. The short version of this algorithm disregards smoking status, hypertension,

## 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 <sup>2</sup> )	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 <sup>3</sup> )	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)

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## Numbers of PLH in each predicted risk group combination

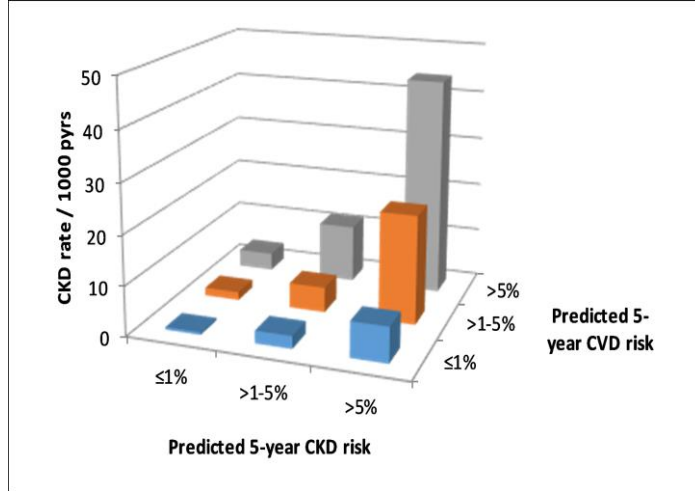
5-year CKD predicted risk	5-year CVD predicted risk		
	≤1%	>1%–5%	>5%
≤1%	6,225 (22.9%)	5,926 (21.9%)	383 (1.4%)
>1%–5%	2,047 (7.5%)	6,026 (22.1%)	1,592 (5.9%)
>5%	546 (2.0%)	2,865 (10.5%)	1,585 (5.8%)

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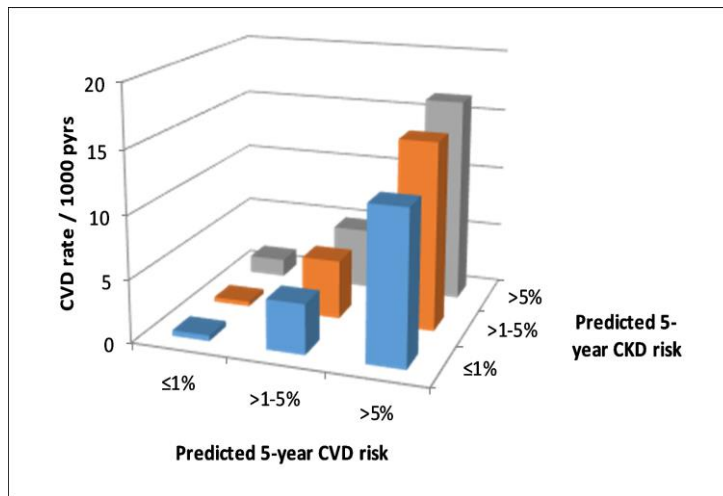
## Combined CVD and CKD risk in D:A:D

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
<b>Predicting CKD events</b>			
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
<b>Predicting CVD events</b>			
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	

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\*IRR – Incidence rate ratio

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## 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

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\*IRR – Incidence rate ratio

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## 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 $\leq$ 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 (%)
$\leq$ 1%	$\leq$ 1%	6,225	23 (0.4%)
$\leq$ 1%	$\geq$ 1%–5%	2,047	10 (0.5%)
$\leq$ 1%	>5%	546	2 (0.4%)
>1%–5%	$\leq$ 1%	5,946	61 (1.0%)
>1%–5%	$\geq$ 1%–5%	6,026	192 (3.2%)
>1%–5%	>5%	2,865	104 (3.6%)
>5%	$\leq$ 1%	383	39 (10.2%)
>5%	$\geq$ 1%–5%	1,592	234 (14.7%)
>5%	>5%	1,585	366 (23.1%)
<b>Overall</b>		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  $\geq 3$  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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