A clinically useful risk-score for chronic kidney disease (CKD) in HIV infection

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D:A:D

UCL

insight

chip

Background

- Deteriorating renal function is a major public health issue for both HIV+/HIV-, associated with both mortality and cardiovascular outcomes[1-2]
- As HIV-positive persons age, identifying those at greatest risk becomes increasingly important
- Risk prediction models (risk-scores) developed for CKD in both HIV+/HIV-[3-4]
- Use of risk-scores in routine care allows choice of safest drugs when initiating/switching ARVs and targeting of renal monitoring

(1) Ibrahim F et al. Am J Kidney Dis 2012;60(4):539-47. (2) Lee M,et al. BMJ 2010;341:c4249. (3) Chien KL et al. Am J Med 2010 (9):836-46. (4) Scherzer R et al. AIDS 2014;28(9):1289-95.

Objective

- To develop a simple, externally validated and widely applicable long-term risk-score model for CKD in HIV-positive persons that can guide decision making in clinical practice

Patients and Definitions

- Participants from the D:A:D study aged > 16 years
- eGFRs calculated using CG
- Baseline : first eGFR > 60 mL/min/1.73m^2 after 1/1/2004 or study enrolment
- Persons were censored at last eGFR, last visit plus 6 months, 1/1/2013
- Persons with <3 eGFRs were excluded
- Persons with exposure to TDF, ATV, ATV/r, LPV/r or other boosted PIs (PI/r) before baseline were excluded
- CKD was defined as a confirmed (>3 months apart) decrease in eGFR to <60 mL/min/1.73m^2

D:A:D : The Data Collection on Adverse events of Anti-HIV Drugs Study

Statistical Methods

- Poisson regression was used to develop a risk-score using baseline information; estimates were used to develop the risk-score
- Three risk groups;
  - low (risk-score <0)
  - medium (risk-score 0-4)
  - high (risk-score≥5)
- Initiation of TDF, ATV, ATV/r, LPV/r, PI/r was included in the final risk-score model as time-dependant covariates
- Number needed to treat to harm (NNTH) over 5 years for those at low, medium and high risk of CKD were calculated

External validation

- Risk-score validated using 2 external cohorts of HIV-positive persons
  - The Royal Free Hospital (RFH) clinic cohort
  - The control arms (i.e. non-intervention) of the SMART and ESPRIT trials from the INSIGHT network
- eGFRs calculated using CKD-EPI[1]
- Short version of score for settings where complete data unavailable; excludes CVD-associated risk factors (CVD/diabetes/hypertension status)

(1) Levey AS et al;. Ann Intern Med 2009;150(9):604-12.

Baseline characteristics of 18055 included HIV+ persons from D:A:D

		Did not develop CKD		Developed CKD	
		N	%	N	%
All		**17414**	**96.5**	**641**	**3.6**
Gender	Male	12741	73.2	459	71.6
Race	White	8087	46.4	321	50.1
HIV Risk	MSM / IDU	8086/2015	46.4/11.6	264/86	41.2/13.4
Hypertension[1]	Yes	1338	7.7	120	18.7
CVD[1]	Yes	251	1.4	44	6.9
HCV+	Yes	2192	12.6	89	13.9
AIDS	Yes	2490	14.3	159	24.8
Diabetes[1]	Yes	498	2.9	68	10.6
VL < 400	Yes	7552	43.4	398	62.1
		Median	IQR	Median	IQR
Age	Years	40	33 – 46	56	47 – 64
CD4	/mm^3	460	320 – 644	440	300 – 615
Nadir CD4	/mm^3	292	170 – 438	202	93 – 337
eGFR	mL/min/1.73m^2	105	91 – 121	73	65 - 84

[1]Defined previously in Ryom et al, JID 2013;207:1359-1369.
Baseline : first eGFR > 60 after latest of 1/1/2004 and enrolment to D:A:D. IQR; interquartile range.

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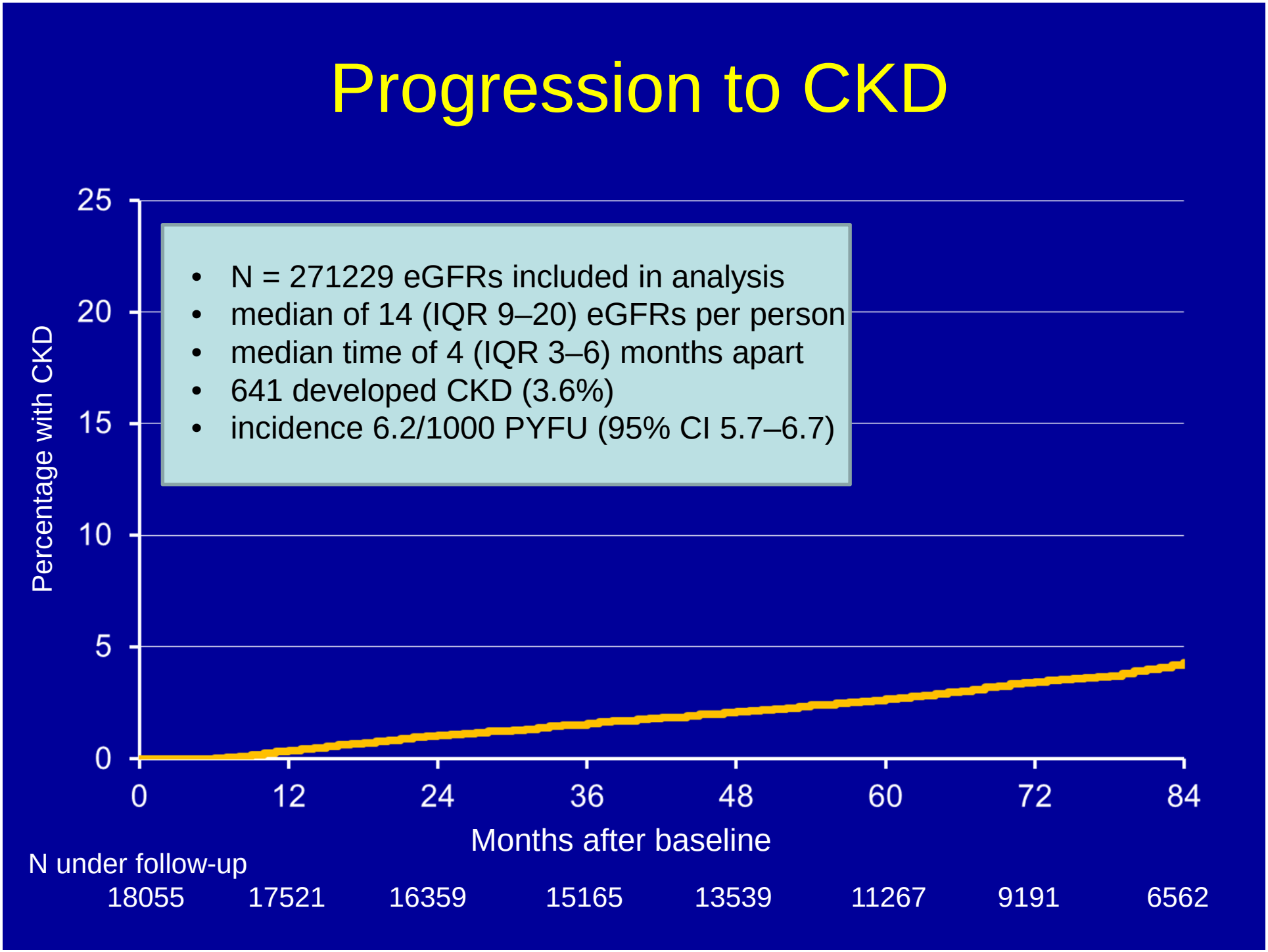
Progression to CKD



- N = 271229 eGFRs included in analysis
- median of 14 (IQR 9–20) eGFRs per person
- median time of 4 (IQR 3–6) months apart
- 641 developed CKD (3.6%)
- incidence 6.2/1000 PYFU (95% CI 5.7–6.7)

D:A:D risk score for CKD and example of how to calculate the score

D:A:D risk-score for CKD =

+	2	IDU
+	1	HCV antibody +ve
+	4	aged 35-50
+	7	aged 50-60
+	10	aged >60
+	6	baseline eGFR < 70
-	6	baseline eGFR > 90
+	1	female
+	1	nadir CD4 <200/mm^3
+	1	hypertensive
+	1	prior CVD
+	2	diabetic

Add zero if non-IDU, HCV antibody -ve, aged<35, baseline eGR 70-90, male, CD4 nadir ≥200/mm^3, non-diabetic, non-hypertensive or no prior CVD

IDU, HCV coinfected, aged 53, baseline eGFR 82, male, nadir CD4 276/mm^3, no hypertension, CVD or diabetes

Example

+	2	IDU
+	1	HCV antibody +ve
+	4	aged 35-50
+	7	aged 50-60
+	10	aged >60
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Example

+	2	IDU
+	1	HCV antibody +ve
+	4	aged 35-50

SCORE = 10

+	1	hypertensive
+	1	prior CVD
+	2	diabetic

External validation cohorts

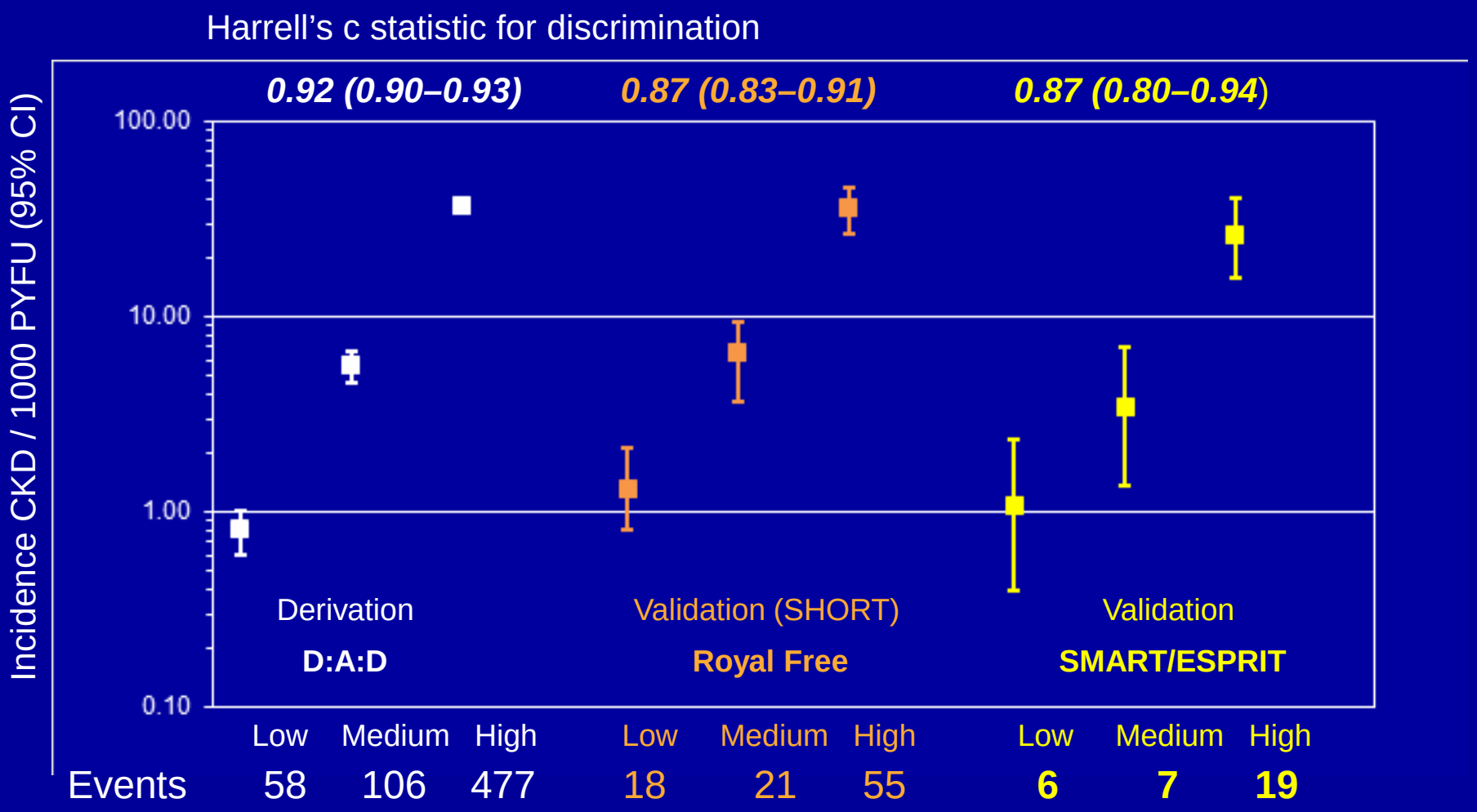
RFH : Royal Free Hospital Clinic Cohort

INSIGHT : control arms from SMART/ESPRIT

		RFH		INSIGHT	
		N	%	N	%
N		**2603**	**100**	**2013**	**100**
Gender	Male	1984	76.2	1523	75.7
HIV Risk	IDU	77	3.0	220	10.9
HCV+	Yes	147	5.7	270	13.4
Nadir CD4	$\leq$200/mm^3	884	34.0	840	41.7
Prior CVD				64	3.2
Prior diabetes				98	4.9
Prior hypertension				437	21.7
Baseline CD4	Median (IQR)	411	(248 – 591)	513	(405 – 685)
Age	Median (IQR)	36	(31 – 42)	42	(35 – 49)
eGFR	Median (IQR)	106	(95 – 115)	112	(101 – 122)
N eGFRs	*Median (IQR)*	*22*	*(10 – 33)*	*6*	*(4 – 7)*
Months bt eGFRs	*Median (IQR)*	*3.2*	*(2.2 – 4.4)*	*11.7*	*(9.6 – 12.6)*

Validation of D:A:D renal risk score in 2 independent cohorts

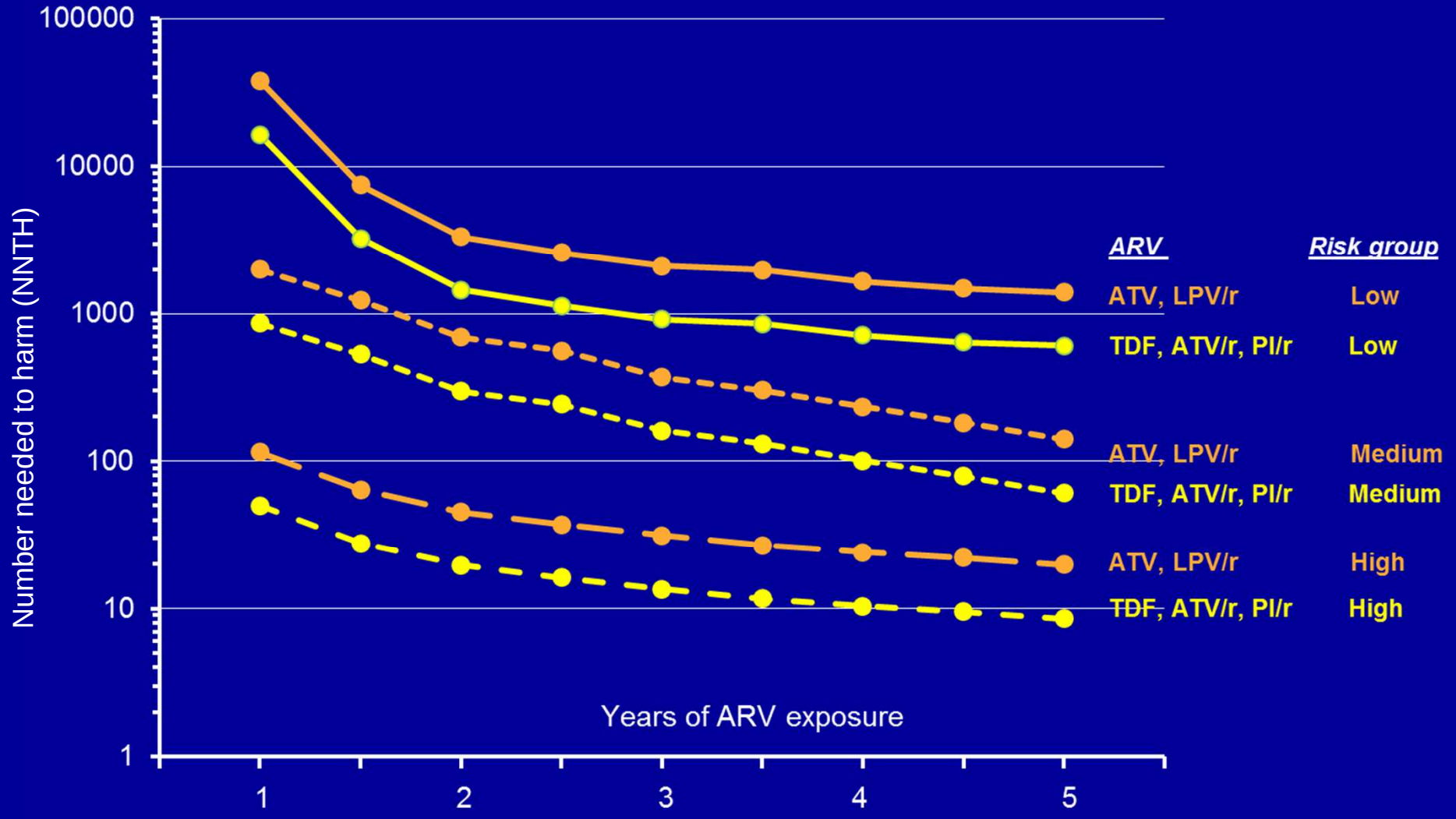
Low, medium and high risk of CKD



Score risk groups : Low score <0; Medium 0-4; High ≥5

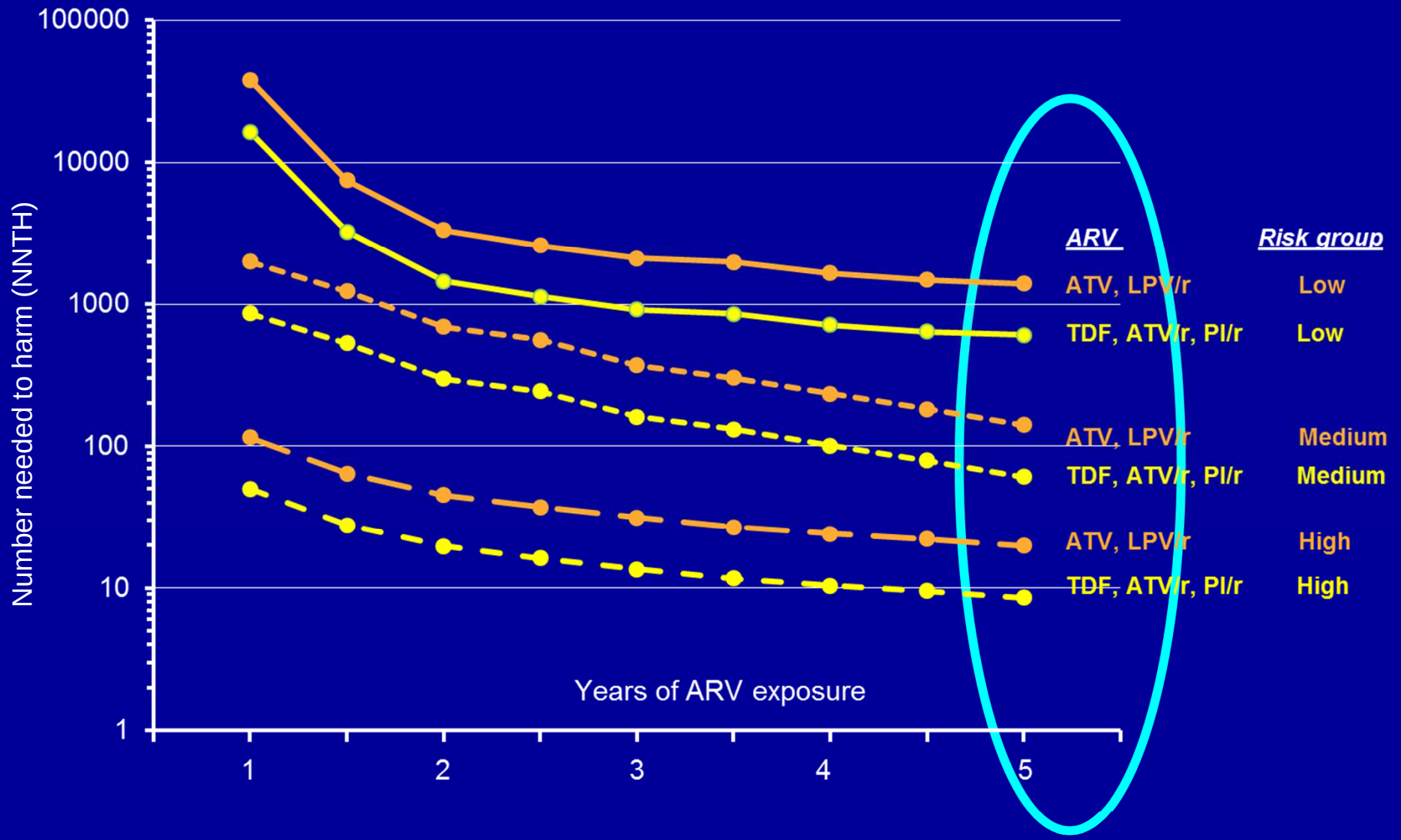
NNTH: Adding antiretrovirals in those at low, medium or high risk of CKD

Score: Low <0; Medium 0-4; High ≥5



NNTH: Adding antiretrovirals in those at low, medium or high risk of CKD

Score: Low <0; Medium 0-4; High ≥5



NNTH: At 5 years

D:A:D risk-score for CKD =

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+	1	HCV antibody +ve
+	4	aged 35-50
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Add zero if non-IDU, HCV antibody -ve, aged<35, baseline eGR 70-90, male, CD4 nadir ≥200/mm^3, non-diabetic, non-hypertensive or no prior CVD

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

Limitations

- Included only persons naïve to TDF, ATV, ATV/r, LPV/r and other PI/r
- Cannot fully adjust for race and used CG for eGFRs
  - Results highly consistent in validation cohorts
- Creatinine clearance used to measure renal function
- Data on proteinuria not available
  - Consistent with previous risk model[1], includes wider range of patients, all potentially nephrotoxic ARVs included and external validation

(1) Scherzer R et al;. AIDS 2014;28:1289-1295.

Conclusions

- Developed and externally validated a simple, clinically useful risk-score for predicting CKD at 5 years
- Risk score will be available at www.cphiv.dk
- NNTH associated with potentially nephrotoxic ARVs calculated for those at low, medium or high risk of CKD
- Allows clinicians and HIV+ to consider risk of CKD, given potential benefits of treatment regimen

Acknowledgements

The D:A:D Study group

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Laboratory: M Connell, G Clewley, S Martin, M Thomas

SMART/ESPRIT

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(1) Abrams D et al. N Engl J Med 2009;361:1548-59. (2) El-Sadr WM et al. N Engl J Med 2006;355:2283-96.