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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Ian Williams	None
Date	**22 September 2012**

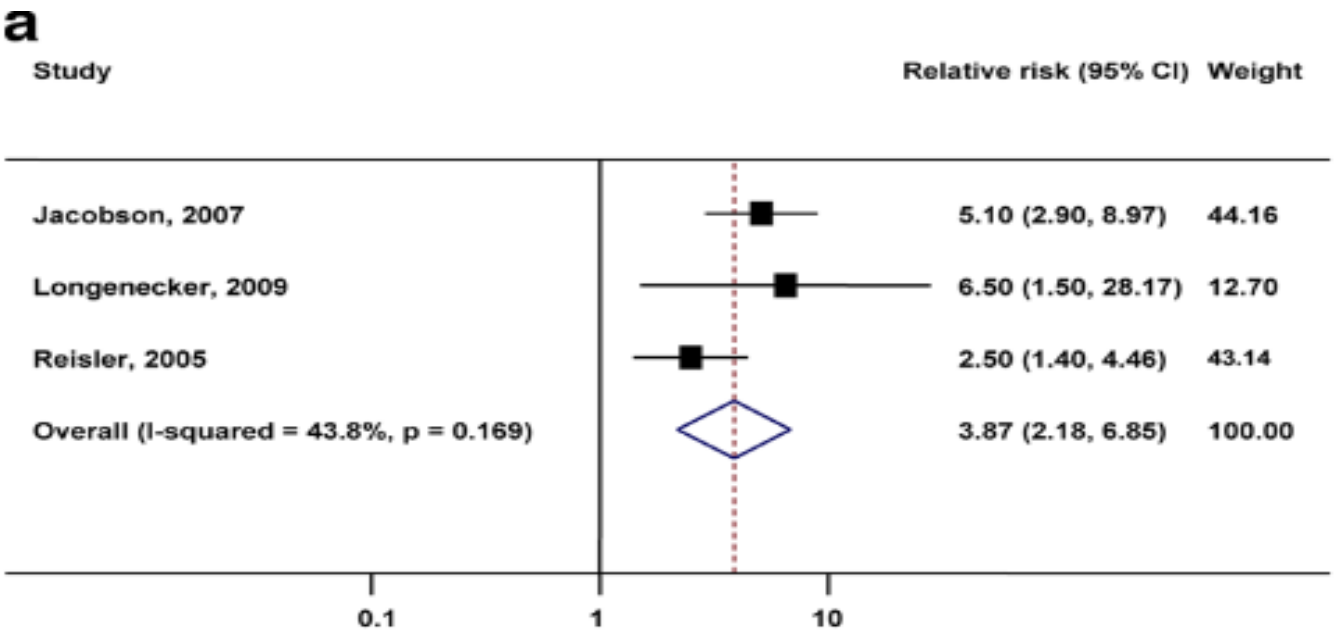
Antiretrovirals and the kidneys

Ian Williams

ARVs and the kidney

- Epidemiology of renal disease in HIV
- Impact of ART on CKD
- ARV associated renal toxicity
- Cases

Risk of renal disease in HIV

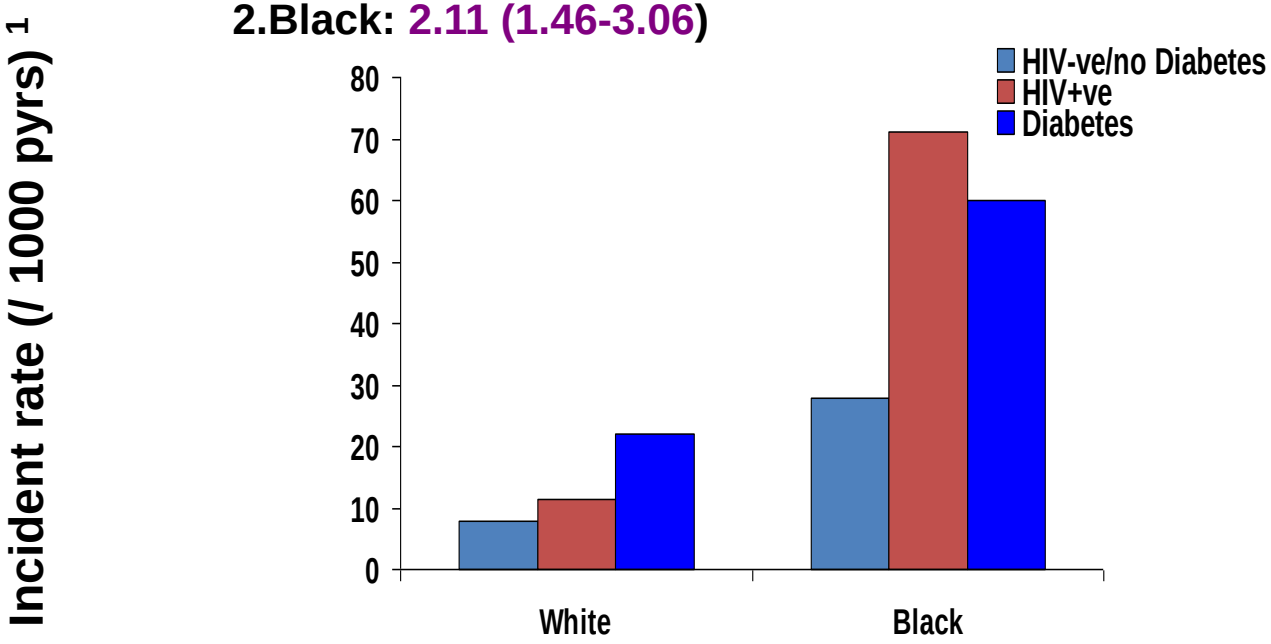


Relative risk of renal disease: HIV+ve v HIV-ve population

Islam et al BMC Public Health 2012

Incidence of ESRD in patients with CKD

Hazard Ratio (95%CI)[2]
HIV +ve v HIV –ve
1.White: 0.68 (0.26-1.76)
2.Black: 2.11 (1.46-3.06)

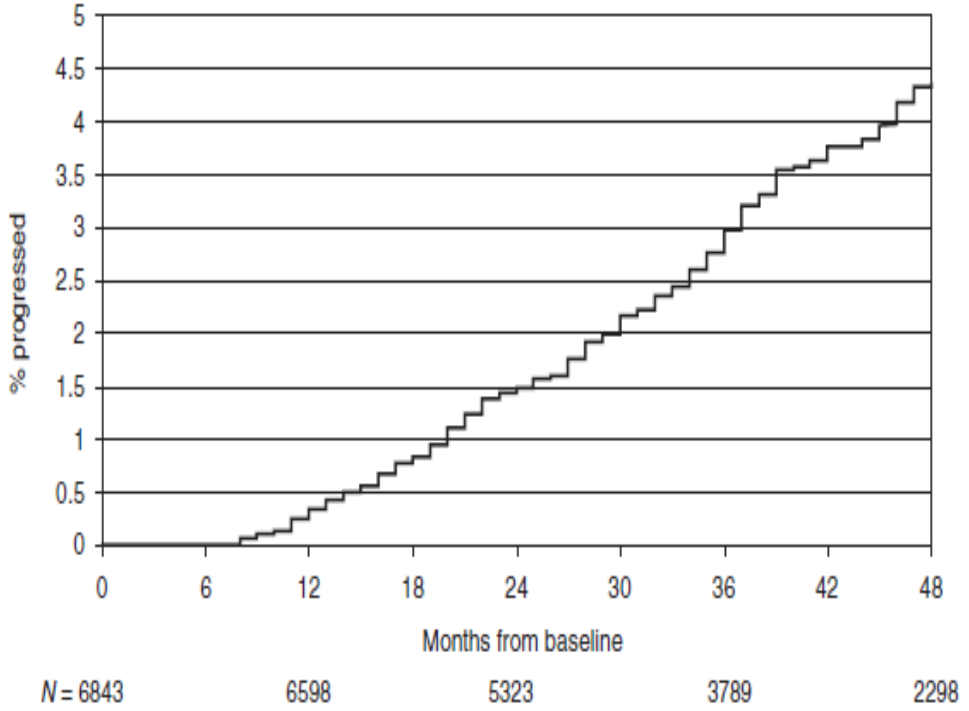


VA study, n: 202,927 with CKD stage 3 or greater (0.3% HIV)
Median follow up: 3.8 years (2000-2004)
HIV associated with 2 fold increase in risk of death in both black and white

1.Adjusted for age and sex-
2. Adjusted for age, sex, race, hypertension, Hep C, CVD, COPD, socio-economic status
Choi Ai, Kid Int, 2007, 72: 380-1387

Incident CKD in EuroSIDA

- CKD defined as:
  - Confirmed eGFR <60 if baseline eGFR >60
  - >25% decline if baseline eGFR <60
- 21,482 PYFU
  - median 3.7 years
- 225 (3.3%) progressed to CKD
  - Incidence 1.1 (0.9-1.2) per 100py



Mocroft A et al. AIDS 2010; 24: 1667-78

At risk population for CKD in HIV

- Demographic:
  - Black race
  - Older age
- Non-HIV:
  - Hypertension
  - Diabetes
  - HBV/HCV co-infection
  - Pre-existing renal disease/damage
- HIV:
  - CD4 count <200 x10^6/l, prior AIDS
- Drugs: treatment with potential nephrotoxic drugs

Practice point:

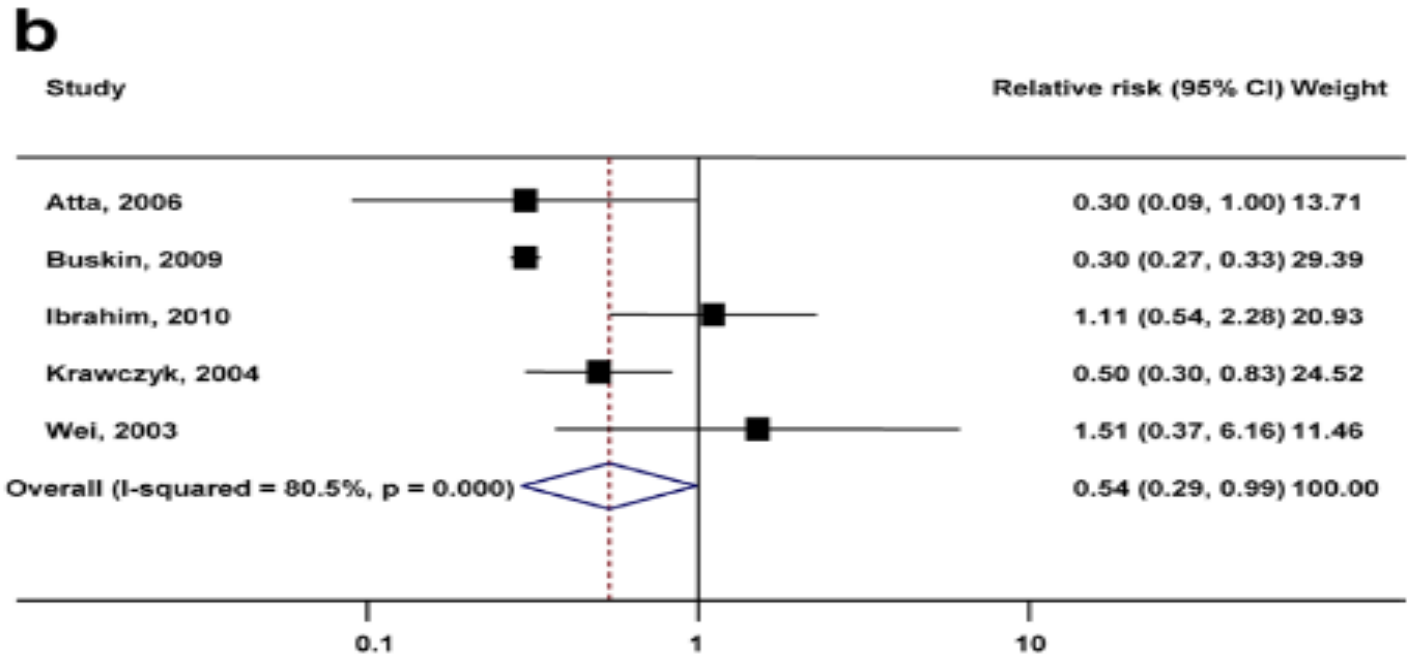
Patients with HIV should be assessed and screened for the presence and risk factors for CKD

Why is this important?

- Increased risk of drug toxcity
- Increased risk of cardiovascular disease
- Potential need for adjustment of drug doses
- Importance to prevent CKD progression

- What is the potential impact of ART on the kidney?

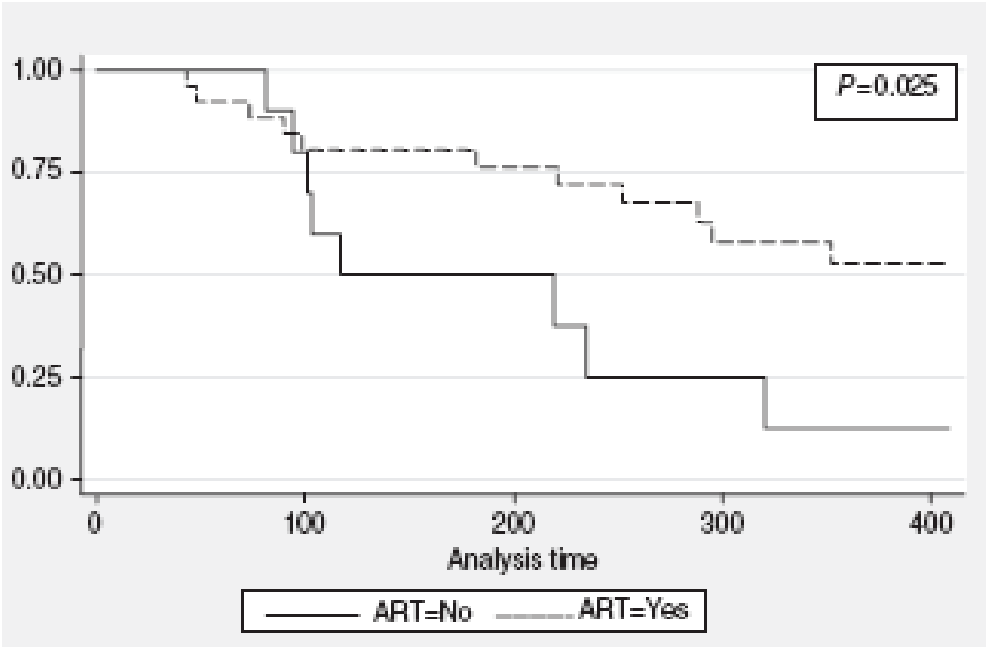
Antiretrovirals and the Kidney



Relative risk of renal disease in HIV+ve people:
ART treated v ART naive

Islam et al BMC Public Health 2012

HIVAN: impact of ART



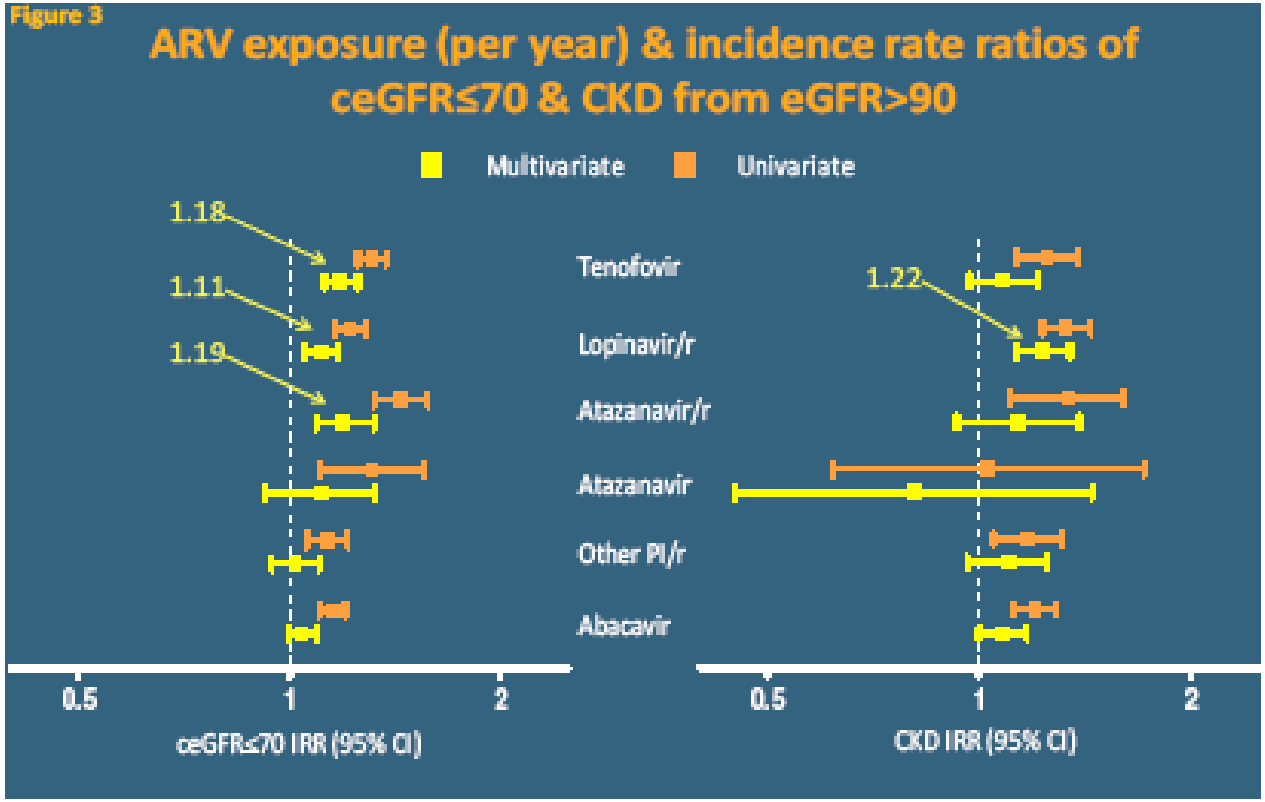
- **Kaplan-Meier estimate of renal survival**
- **N:36, 1995-2004**
- **Increased renal survival in patients who started ART with 3 months of diagnosis and who achieved VL suppression on ART**

Atta GM et al 2006, Nephrol Dial Transplant, 21: 2809-2813

Rate of decline in renal function: DAD study

N:22,603, eGFR>90 at baseline

Rate to eGFR <70: 4.78/1000 PY; to eGFR<60:1.33/1000 PY; 4.5 years FU



Adjusted for gender, race, HIV risk group, enrolment cohort, Prior AIDS, HBV/HCV status, smoking status, hypertension, diabetes, prior CV event, baseline eGFR, age (per 10 yrs), CD4 per doubling/nadir, VL and cumulative exposure (per year) tdf, ind, lpv/r, atv, atv/r, abc and other PI/r

Abs: 865 CROI 2012

Renal toxicity of ARVs

Anti-retroviral	Renal abnormality	Epidemiology
Tenofovir	1. Acute kidney injury/acute interstial nephritis 2. Proximal renal tubulopathy - proteinuria/glycosuria - renal impairment - ↓BMD, osteomalacia	1. Rare (≥1/10,000 - <1/1000) 1. 0.5-2.0% (1-2/100 pyrs)
Atazanavir	1. Nephrolithiasis - haematuria/flank pain - Obstructive nephropathy 2. Acute interstitial nephritis	1. 7.3 per 1000 pyrs[a] 2. Case report
Indinavir	1. Nephrolithiasis - Haematuria/flank pain - Obstructive nephropathy 2. Acute/Chronic interstitial nephritis	1. Common (≥ 1/100- <1/10)

a: Rockwood et al AIDS 2011

Renal toxicity of ARVs

Antiretroviral	Renal abnormality
Abacavir	Acute interstitial nephritis Fanconi Syndrome
Lamivudine	Renal tubular acidosis
Efavirenz	Nephrolithiasis
Ritonavir	Acute kidney injury
Didanosine	Acute kidney injury Fanconi syndrome

Izzedine et al Nature Reviews 2009

ART and renal disease

Case 1

34 year old, heterosexual black African man recently diagnosed with HIV and nephrotic syndrome secondary to HIVAN. CD4 count 80 cells/µL, viral load 60,000 copies/ml, no transmitted resistance, HLA B5701 negative, creatinine 135µmol/L, eGFR 67ml/min, albumen 20g/dl, UP/C 550 mg/mmol.

What ART regimen would you advise he starts on?

Question 1: which ART regimen?

1. Efavirenz + TDF/FTC
2. Efavirenz + ABC/3TC
3. Atazanavir/r + ABC/3TC
4. Darunavir/r + TDF/FTC
5. NRTI sparing regimen (eg: PI/r monotherapy, PI/r based dual therapy)
6. None of the above

ART and renal disease

Case 2:

34 year old, white gay man diagnosed with HIV for 5 years, Chronic HBV (eAg +ve, HBV DNA level 8 million), CD4 count 450 cells/µL, HIV VL 25,000 copies/ml. Recently diagnosed with Nephrotic syndrome secondary to membranous nephropathy, no transmitted resistance, HLA B5701 negative, creatinine 104µmol/L, eGFR 75ml/min, albumen 22g/dl, UP/C 903mg/mmol.

What ART regimen would you advise he starts on?

Question 2: which ART regimen?

1. Efavirenz + TDF/FTC
2. Efavirenz + ABC/3TC
3. Darunavir/r + TDF/FTC
4. Raltegravir +TDF/FTC
5. NRTI sparing regimen: (eg PI/r monotherapy, PI/r based dual therapy)
6. Does not need to start ART
7. None of the above

ART and renal disease

Case 3:

55 year old, white gay man diagnosed with HIV 5 years, CD4 count 370 cells/µL, HIV VL 65,000 copies/ml, ART naïve, no transmitted resistance, HLAB5701 negative. Hypertensive, cigarette smoker, CKD 3(a) secondary to chronic interstitial nephritis, creatinine 128µmol/L, eGFR 54ml/min, UP/C 45mg/mmol. Total cholesterol 5.8 mmol/l

What ART regimen would you advise he starts on?

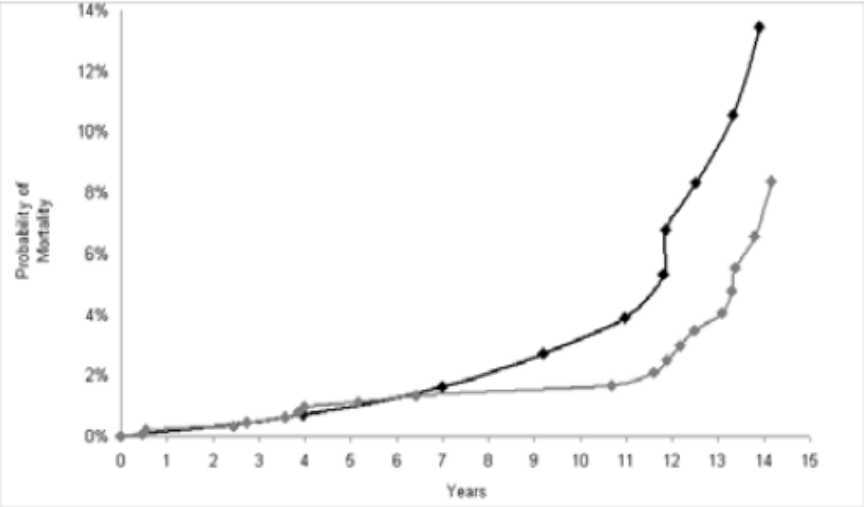
Question 3: which ART regimen?

1. Efavirenz + TDF/FTC
2. Efavirenz + ABC/3TC
3. Atazanavir/r + ABC/3TC
4. Darunavir/r + TDF/FTC
5. Raltegravir +TDF/FTC
6. NRTI sparing regimen (eg: PI/r monotherapy, PI/r based dual therapy)
7. None of the above

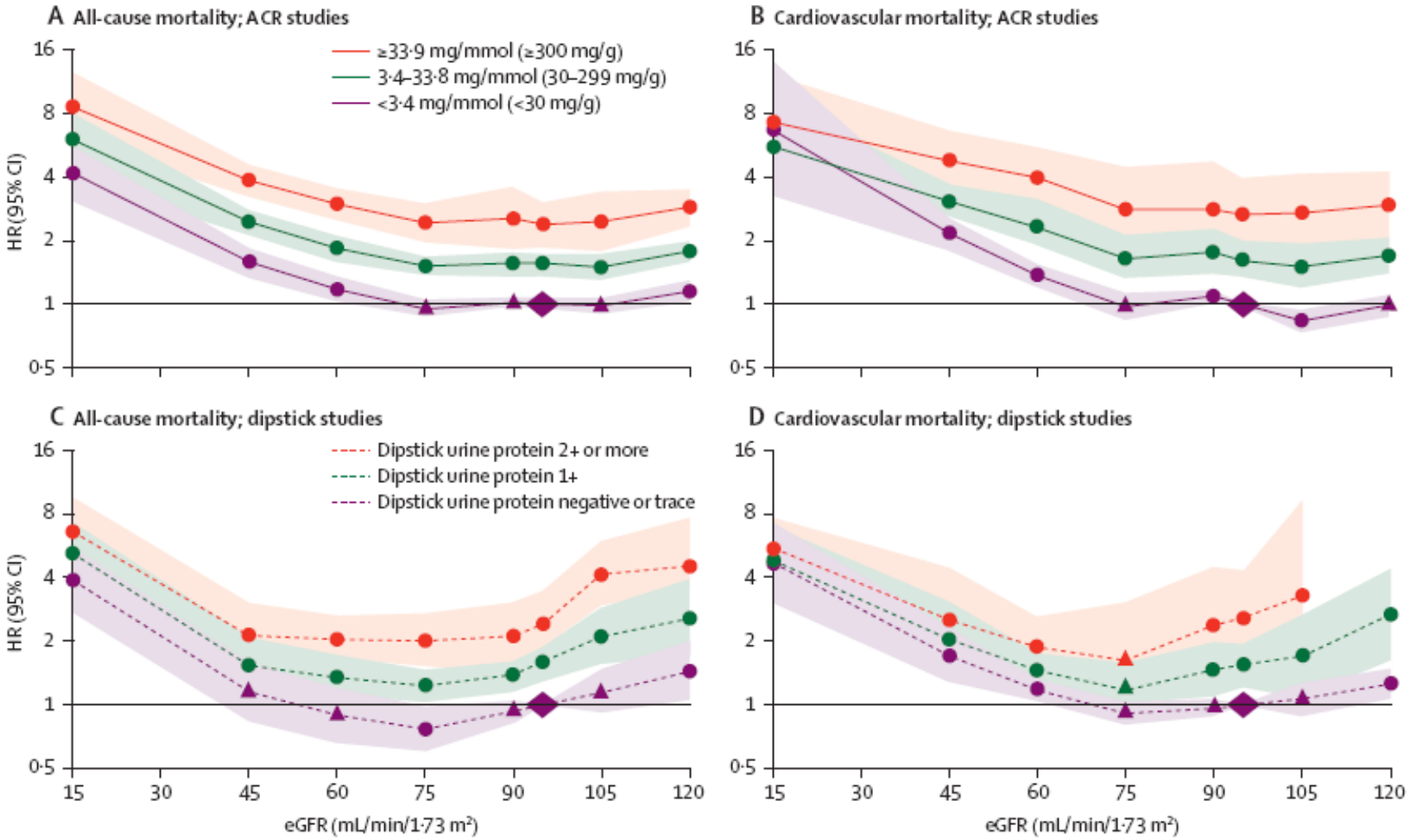
Renal impairment/disease associated with increased risk of clinical events

- CROI 2012: Abs 868: Italian cohort: n:2648
  - strong gradient between renal impairment and the risk of CVD independent of traditional risk factors. No association between eGFR and risk of AIDS events
- CROI 2012 Abs 869: British Columbia, n:1430. microalbuminuria (n:211) associated with increased risk of all cause mortality

Kaplan Meier curve stratified by microalbuminuria diagnosis: no versus confirmed microalbuminuria



Reduced eGFR, albuminuria, and (cardiovascular) mortality



Lancet 2010; 375: 2073

ART and renal disease

Case 4:

28 year old gay man started on efavirenz TDF/FTC 3 months ago. Symptomatically well

Baseline tests: creatinine 85 µmol/L, eGFR >90 ml/min, PO4 1.02 mmol/l, UP/C 8 mgs/mmol

At 3 months: creatinine 104 µmol/L, eGFR 79 ml/min, PO4 0.80 mmol/l, UP/C 10 mgs/mmol, urine dipstick negative for blood

Question 4: what is your initial management?

1. Stop tenofovir and switch to alternative NRTI
2. Check use of creatine and protein supplements
3. Check use of NSAIDs
4. Consider potential tenofovir renal toxicity and screen for proximal renal tubule dysfunction
5. Repeat tests in 3 months

Tenofovir renal toxicity

Screening tests for Tenofovir renal toxicity

- Serum creatinine
- e GFR
- Phosphate
- Urine Protein/creatinine ratio
- Fractional excretion/reabsorption phosphate (phosphaturia)
- Urinalysis: glycosuria
- Tubular proteinuria

Effect of UP/C when eGFR is ‘normal’

- Half of the patients who developed TDF-RT maintained normal eGFR levels throughout follow-up
- If Restrict cohort to the subpopulation of patients for whom eGFR is in the ‘cohort-specific’ normal range (eGFR >75)
- UP/C still predictive of TDF-RT

Effect of current UP/C on Risk of TDF-toxicity			
UP/C (mg/mmol)	**H.R.**	**95% C.I.**	**p-value**
<=13	1	-	-
13-30	6.15	(0.64, 59.3)	<0.001
>30	51.3	(6.3, 415)	

Estimated GFR v actual GFR

-Tenofovir associated with early and small decline in estimated GFR, but not actual GFR

-10-15% of creatinine clearance is secreted across the proximal tubule epithelium via several membrane transporters

-Tenofovir may competitively inhibit creatinine uptake by membrane transporter proteins (OAT)

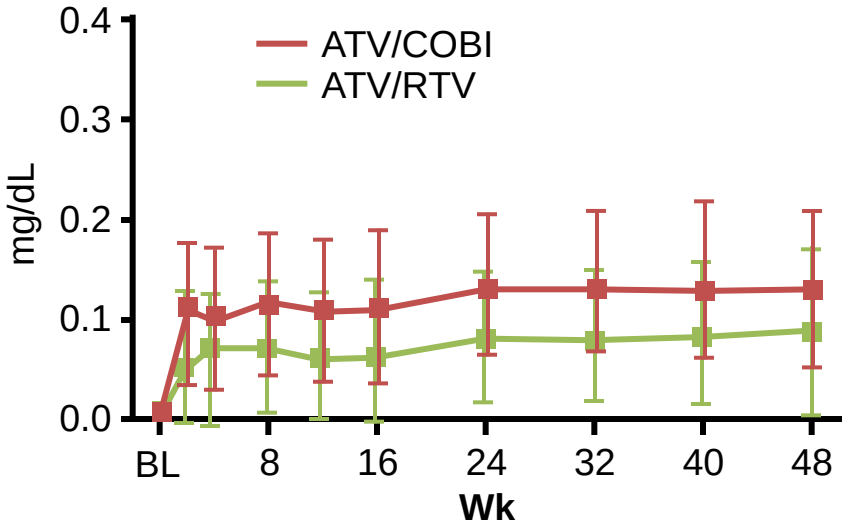
-Inhibition of tubular secretion of creatinine is seen with other drugs (eg cimetidine, trimethoprim)

-Increases in serum creatinine also seen with creatine and protein supplements and dietary changes.

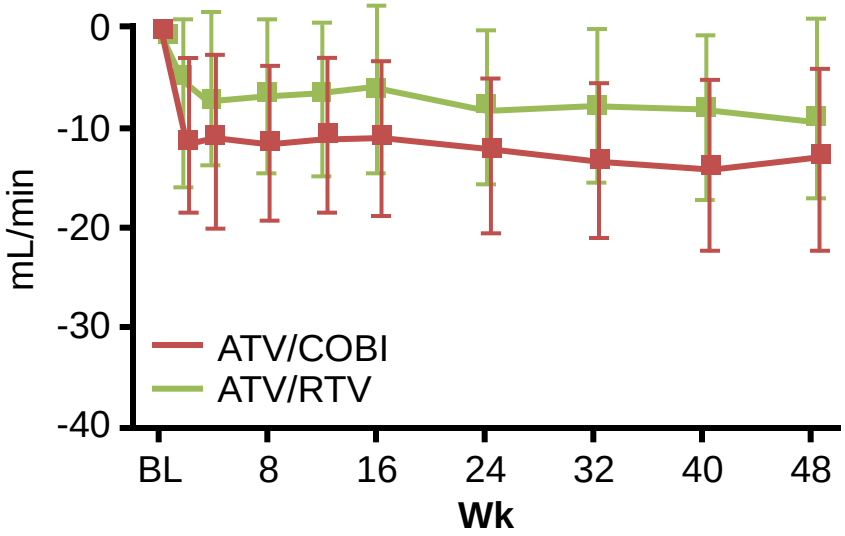
ATV/COBI vs ATV/RTV: Changes in Serum Creatinine and eGFR

- COBI ↑ serum creatinine and ↓ eGFR by inhibiting renal creatinine secretion[1]
- COBI does not affect actual glomerular filtration rate[2]

Change in Serum Creatinine, Median (IQR)



Change in eGFR, Median (IQR)



- 5 of 6 in COBI arm vs 2 of 5 in RTV arm with proximal tubulopathy discontinued therapy

1. Lepist EI, et al. ICAAC 2011. Abstract A1-1724. 2. German P, et al. J Acquir Immune Defic Syndr. 2012;[Epub ahead of print]. 3. Gallant J, et al. AIDS 2012. Abstract TUAB0103. Graphics reproduced with permission.

Dolutegravir

- Is associated with small and early changes in serum creatinine and eGFR

- Is an inhibitor of OCT2 membrane transporters

- OCT2 is the predominant transporter for creatinine secretion in the proximal tubule

- Studies in human volunteers have shown that dolutegravir causes modest decreases in Creatinine clearance (10-14%), but does not effect GFR

Summary 1

- HIV is associated with increased risk renal disease compared to a HIV negative population
- ART is associated with a reduction in risk of renal disease compared to ART naïve population
- Selected ARVs are associated specific renal toxicities and increased risk of decline in GFR and will affect choice of ART in patients with CKD
- It is important to regularly assess and screen for the presence and risk factors for CKD

Summary 2

- Routine monitoring should include serum creatinine, eGFR, UPCR, dipstick urinalysis
- Falls in eGFR and increases in serum creatinine may not always reflect actual decreases in GFR
- CKD and albuminuria is independently associated with increased risk of CVD and all cause mortality
- Adjustment of drug doses for selected ARVs is required in patients with CKD 3-5