TDF Renal Dysfunction

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Introduction

- Is TDF nephrotoxic?
  - In vitro evidence
  - Epidemiologic evidence
  - Case reports

In vitro studies

- in vitro study
  - TDF is a weak inhibitor of mammalian DNA polymerases
    - Has not decreased mtDNA levels
    - Shows low cytotoxicity

Epidemiology

- Phase I/II
  - Barditch-Crovo P et al, Antimicrob Agents Chemother. 2001
  - N = 49
  - Tenofovir: 75mg, 150 mg, 300 mg, or 600 mg
  - No renal abnormalities at 28 days

- Phase II
  - Schooley, et al, AIDS. 2002
  - RCT
  - N = 181
  - Tenofovir: 75mg, 150 mg, or 300 mg
  - No renal abnormalities after 48 weeks

Conclusion from Clinical Trials

- Double-blind, placebo-controlled studies
  - No difference in incidence of renal events between TDF and placebo groups

- No TDF-related toxic side effects were noted in the recommended drug combination regimes of TDF

But……

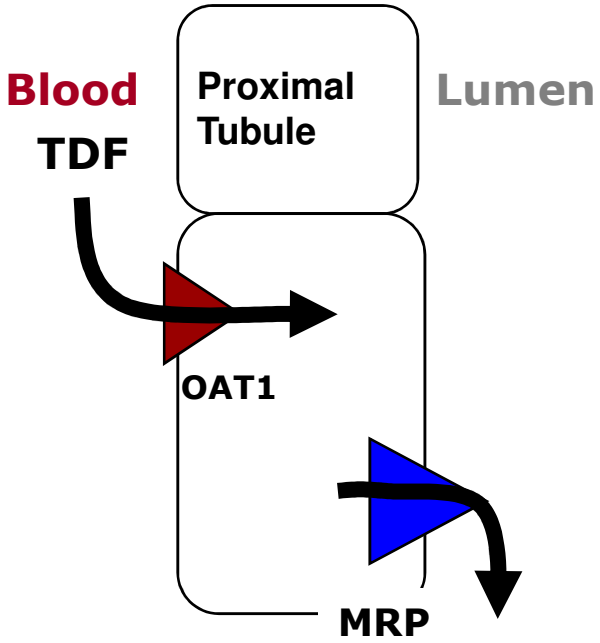
Post-marketing surveillance

- Post-marketing safety data 455,392 person-years of TDF exposure
  - Renal SAE in 0.5%
  - Incr serum creatinine in 2.2%

  [Nelson et al. AIDS 2007]

TDF nephrotoxicity

- Potential for nephrotoxicity
  - Similar structure to Adefovir and Cidofovir, known nephrotoxins
  - Accumulation in renal proximal tubule
    - Vd of 0.8 L/kg
    - Minimally protein bound (<8%)
    - Mainly excreted in urine, unchanged form
  - The Mitochondrial Cytopathy Hypothesis



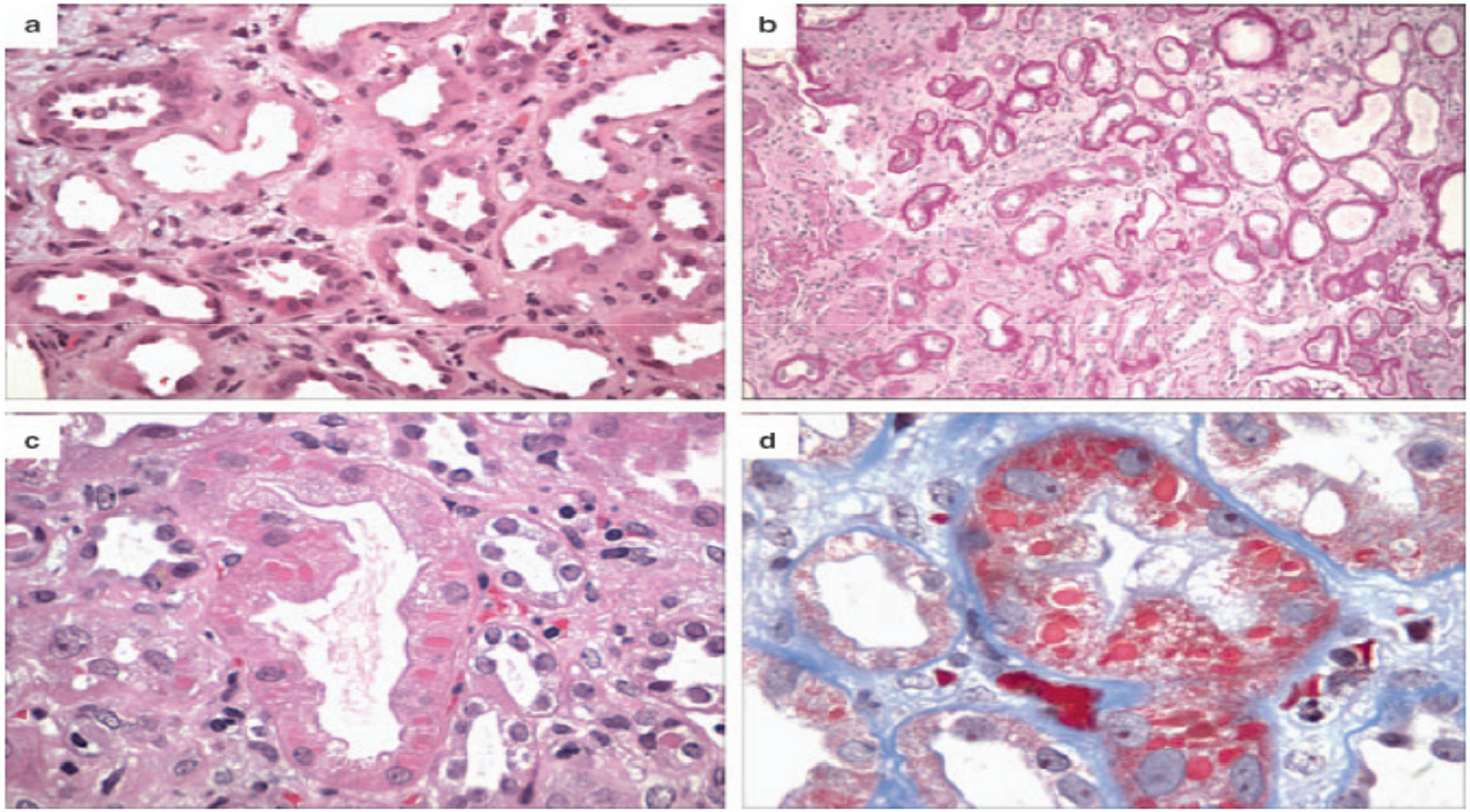
TDF renal toxicity

- Acute kidney injury
- Chronic kidney disease
- Proximal tubular injury, including
  - Fanconi syndrome
  - Isolated hypophosphataemia
  - Decreased bone mineral density

TDF Nephrotoxicity

- Herlitz et al, Kidney Int 2010
  - 13 patients with TDF nephrotoxicity
    - AKI in 9
    - Mild renal dysfunction and subnephrotic proteinuria in 4
    - Glycosuria in 7
  - Renal Histology
    - LM: toxic ATN; PT eosinophilic inclusions
    - EM: mitochondrial enlargement, depletion and dysmorphic changes
  - Outcomes: complete recovery 6; partial recovery 5

LM: TDF Nephrotoxicity



Herlitz et al. Kidney Int, 2010; 78: 1171-1177

EM: TDF Nephrotoxicity

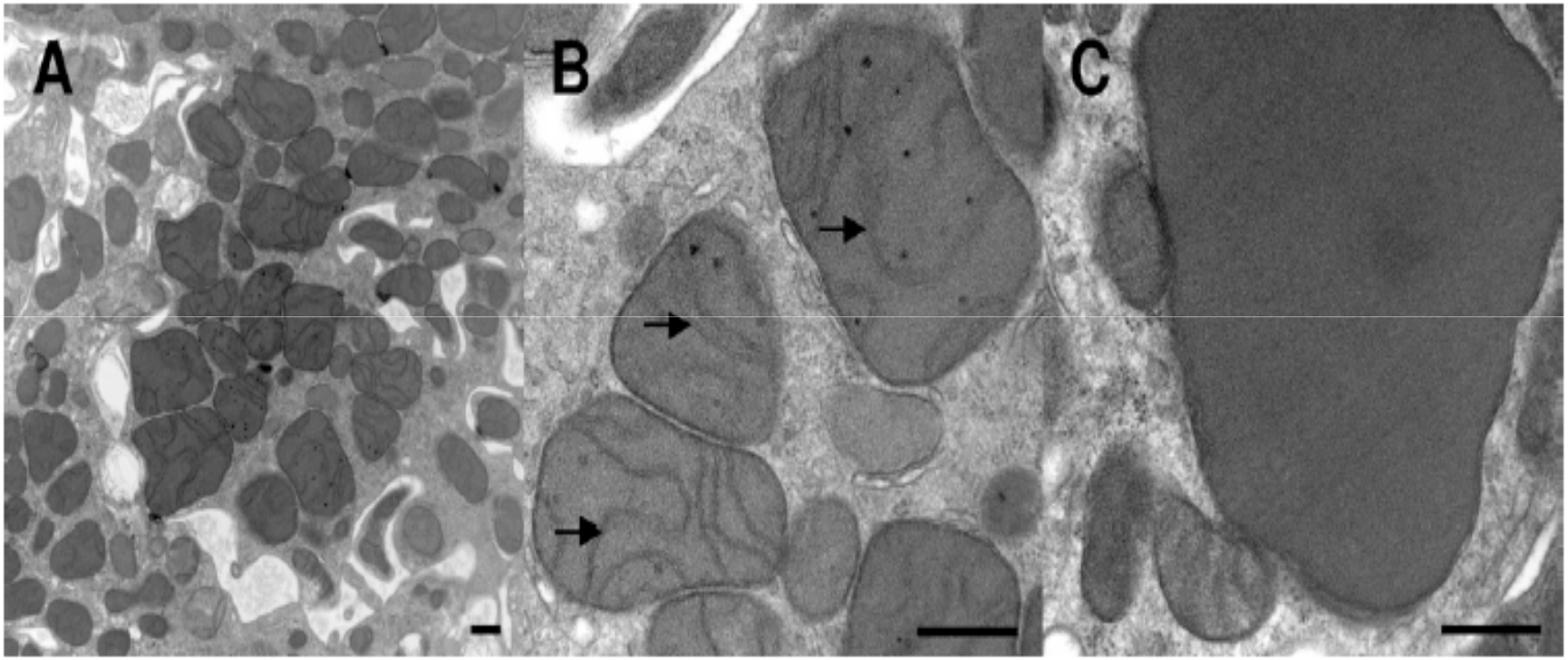


Figure 1. Electron micrographs of proximal tubule cells in a kidney biopsy specimen from a patient with Fanconi syndrome secondary to tenofovir toxicity. (A) Mitochondrial size and morphologic characteristics are highly irregular, with (B) disruption of the normal cristae (arrows) and (C) occasional giant mitochondria. (Scale bars = 500 nm.)

Clinical Studies

- Metanalysis: 17 studies
  - Small but significant loss of kidney function of 3.9ml/min [Cooper et al. Clin Infect Dis, 2010]
- Cohort study 10,000 pts: incr in serum creatinine
  - >0.5mg/dl in 2.2%
  - >2mg/dl in 0.6% [Nelson et al. AIDS. 2007]
- Case series 22 pts with TDF-renal tubular toxicity (1.6% of those on Rx): proteinuria, decr PO4, bone pain due to osteomalacia, incr UPCr, incr serum creatinine [Woodward et al. HIV Med. 2009]

TDF Nephrotoxicity

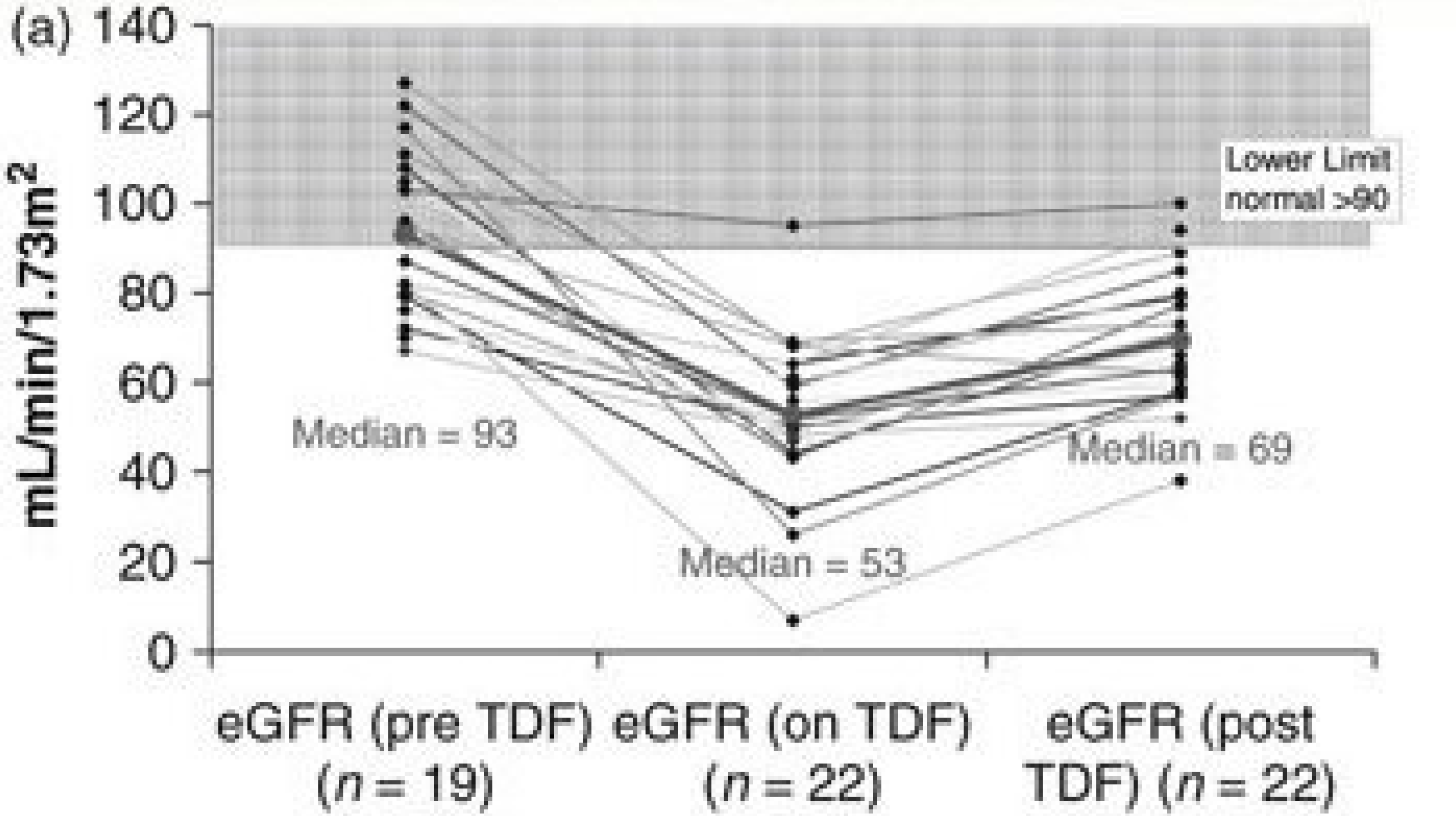
- Scherzer et al. AIDS 2012
  - 4303 of 10,4841 pts on TDF in VA program 1997-2007
  - 34% incr risk of proteinuria; median time 3.9 years
  - 11% incr risk of rapid decline in renal function
  - 33% incr risk of CKD

TDF- the Johannesburg Experience

- Renal function at ART initiation in 890 pts on TDF 2004-2009 at Themba Lethu Clinic, Helen Joseph Hospital, JHB
  - 64.4% normal renal function
  - 30.4% with eGFR 60-89ml/min
  - 5.2% with eGFR 30-59ml/min
- Outcomes at 48 months
  - Nephrotoxicity 2.4% at median of 3.6 months
  - Death 7.8%
  - Lost to follow up 9.7%
- Risk for nephrotoxicity
  - renal dysfunction
  - Age>40yrs; anaemia; low CD4 count; detectable viral load

Brennan et al. AIDS, 2011;25:1063-1069

Tenofovir & estimated GFR

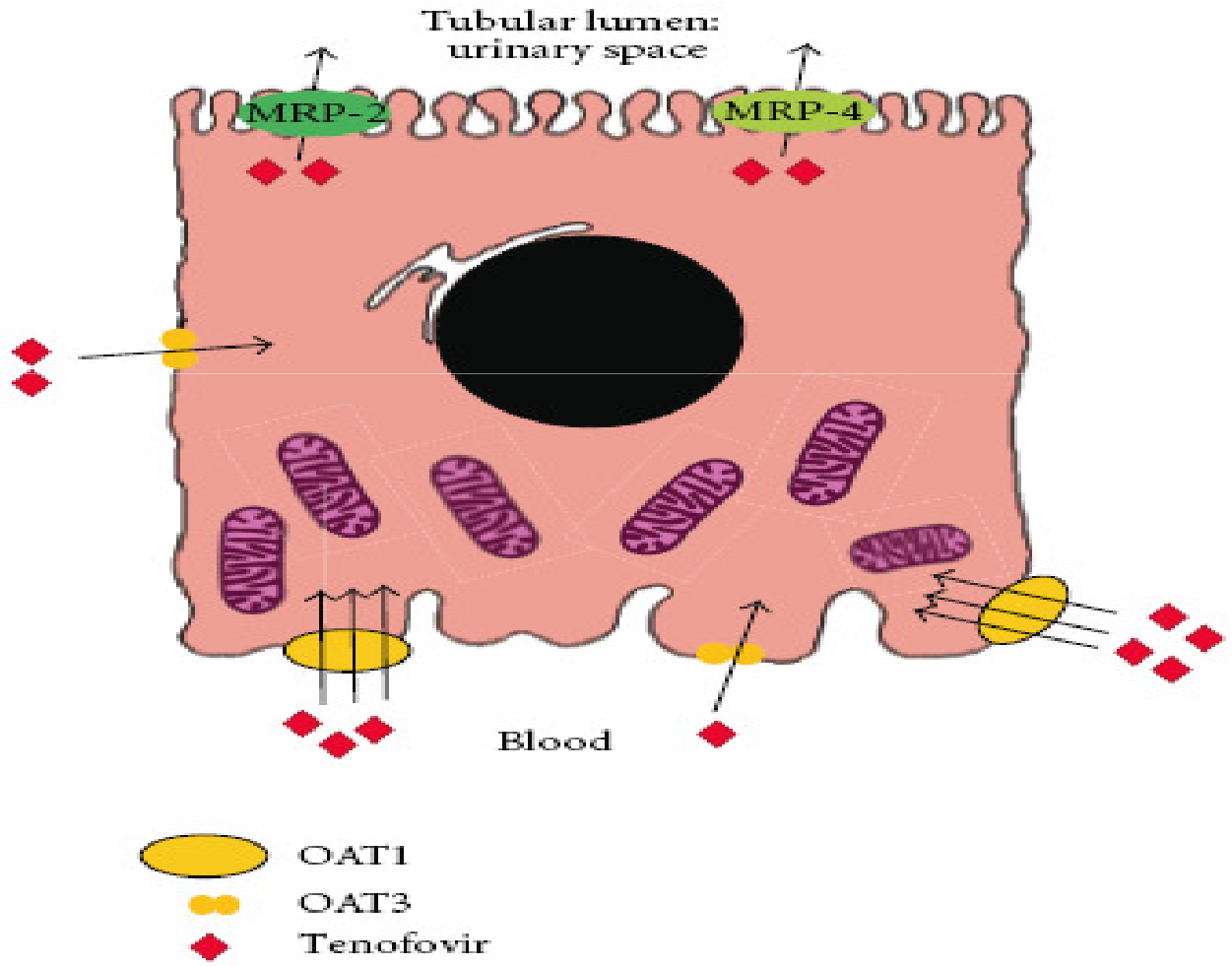


Woodward et al. HIV Medicine. 2009;10(8):482-487

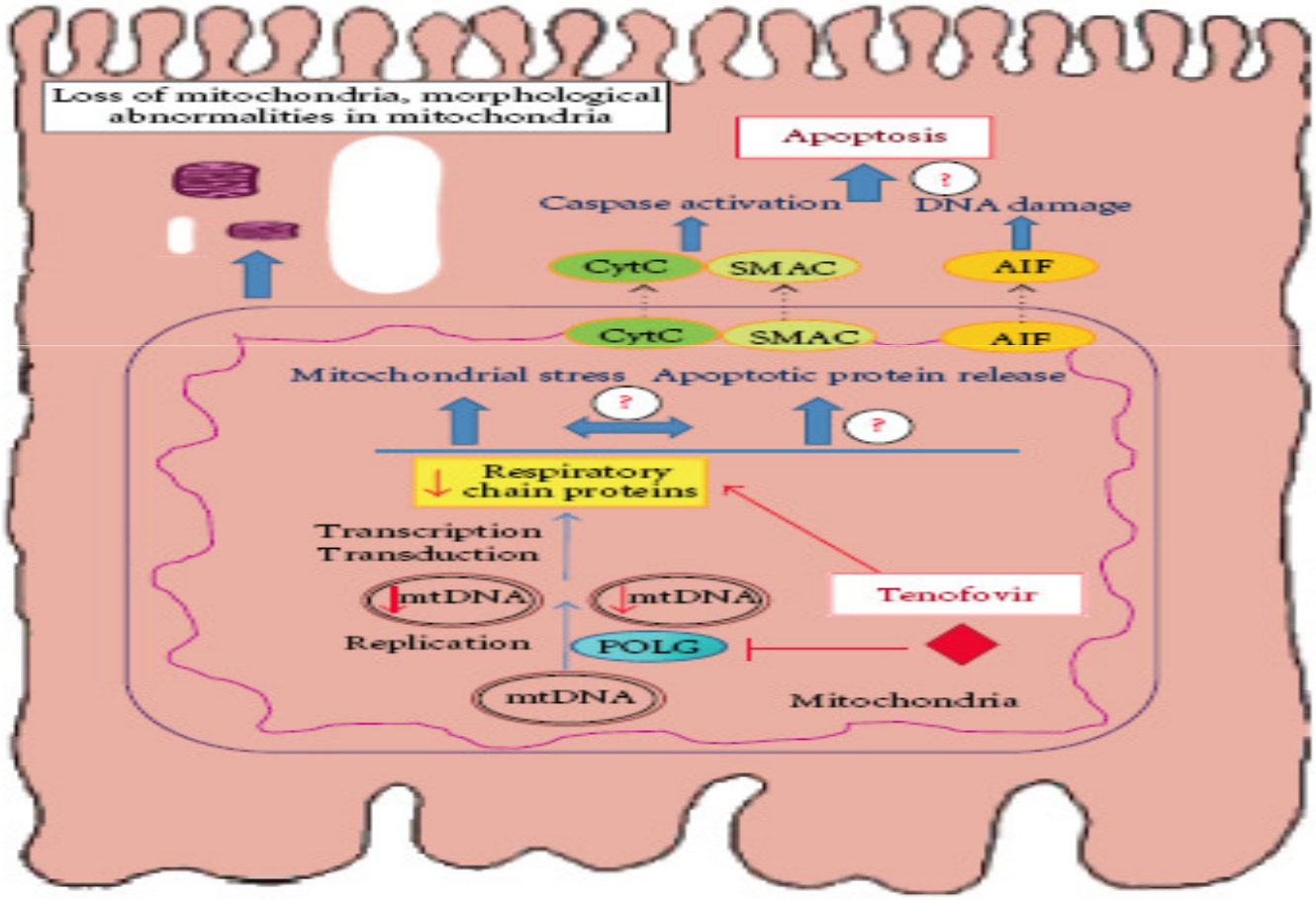
Subclinical Renal Tubular Toxicity

- Severe TDF-tubular toxicity relatively rare; Fanconi Syndrome in <0.1%
- 34/154 (22%) on TDF with normal eGFR had abnormal PT function:
  - Glycosuria
  - Phosphaturia
  - Amino aciduria [Labarga et al.AIDS. 2009]

TDF handling by PT cell



Molecular mechanisms and consequences of TDF nephrotoxicity



Fernandez et al. AIDS Research and Treatment, 2011

Mechanism of TDF nephrotoxicity

- Polymorphism in ABCC2 (gene encoding MRP2): partly responsible for efflux of TDF from PT, resulting in TDF accumulation intracellularly [Rodriguez-Novoa et al, Clin Infect Dis. 2009]

- TDF renal toxic may be decreased by co-adm of drugs inhibiting hOAT1 (transporter responsible for TDF entry into tubular cells)[Izzedine et al. Nat Rev Nephrol, 2009]

Mechanism of Nephrotoxicity

- NRTIs impair mt replication by inhibition of DNA polymerase-*y* [Brinkman et al. AIDS 1998]
- TDF-exposed rats show low mtDNA copy number and impaired expression of mt-encoded proteins(cytochrome *c* oxidase1; COX 1) [Lebrecht et al. J Acquir Immune Defic Syndr 2009]
- Murine HIV transgenic model: decr mtDNA in PT and mt ultrastructural abn [Kohler et al. Lab Invest. 2009]

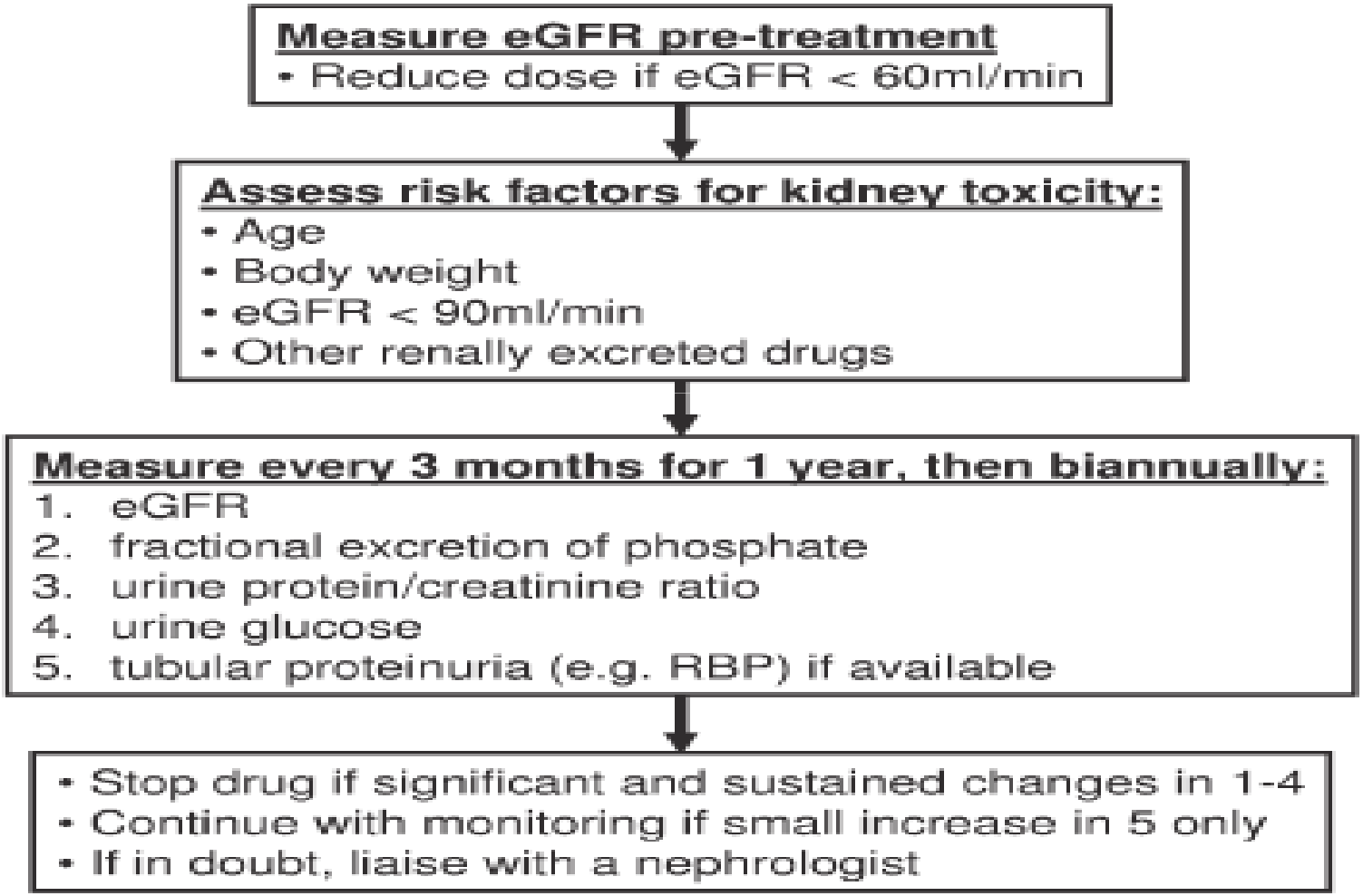
Mitochondrial injury by TDF

- Impairs
  - molecular transport
  - Vitamin D activation
  - Urinary acidification

Patients at risk

- older age
- low body wt
- incr serum creatinine before TDF
- lower CD4
- Co-morbid disease (DM/HPT/HCV infection)
- concurrent use of nephrotoxic drugs or PIs (lopinavir; ritonavir)
- ABCC2 gene polymorphisms

Algorithm for monitoring for TDF renal toxicity



Gupta et al. Clin Infect Dis. 2005

Proposal to decrease TDF nephrotoxicity

- Screening of patients for TDF toxicity
- Adjust TDF dose to GFR
- Consider adding EFV to TDF regimens
  - TDF/LAM/EFV <TDF/LAM/NEV renal toxicity
    - Higher GFR
    - lower rates of proteinuria [Manosuthi et al, AIDS Res Ther, 2010]

Dose Adjustments for ART in CKD and ESRD

Name	CKD (adjusted according to creatinine clearance or by eGFR)	Dialysis
Nucleoside or nucleotide analogues		
Abacavir	No adjustment	No adjustment HD: dosing independent of dialysis sessions
Azidothymidine (AZT), zidovudine[a]	CrCl ≥ 15 ml/min: no adjustment CrCl <15 ml/min: 100 mg PO q6-8h	HD:100 mg PO q6-8h[a] or 300 mg PO qd PD: no data
Didanosine (ddi)	Weight >60 kg / Weight <60 kg CrCl 30-59 ml/min: 200 mg PO qd / 150 mg PO qd CrCl 10-29 ml/min: 150 mg PO qd / 100 mg PO qd CrCl <10 ml/min: 125 mg PO qd / 75 mg PO qd	Dose for CrCl <10 ml/min[b] HD, PD: same dose
Emtricitabine[d]	CrCl >50 ml/min: no adjustment CrCl 30-49 ml/min: 200 mg PO q48h CrCl 15-29 ml/min: 200 mg PO q72h CrCl <15 ml/min: 200 mg PO q96h	HD:200 mg PO q96h[b] PD: no data
Lamivudine[a] (3TC)	CrCl >50 ml/min: no adjustment CrCl 30-49 ml/min: 150 mg PO qd CrCl 15-29 ml/min: 150 mg first dose, then 100 mg PO qd CrCl 5-14 ml/min: 150 mg first dose, then 50 mg PO qd CrCl <5 ml/min: 50 mg first dose, then 25 mg PO qd	HD:50 mg first dose, then 25 mg PO qd[b]
Stavudine (d4T)	CrCl >50 ml/min: no adjustment CrCl 26-50 ml/min: 15-20 mg PO bid CrCl ≤25 ml/min: 15-20 mg PO qd	20 mg PO qd[b] PD: has been used safely
Tenofovir[d]	CrCl >50 ml/min: no adjustment CrCl 30-49 ml/min: 300 mg q48h CrCl 10-29 ml/min: 300 mg q72h	300 mg PO every 7 days[b]
Zalcitabine	CrCl ≥40 ml/min: no adjustment CrCl 10-40 ml/min: 0.75 mg q12h CrCl <10 ml/min: 0.75 mg q24h	HD: dose for CrCl <10 ml/min[b] PD: no data
Non-nucleoside reverse transcriptase inhibitors[c]	No adjustment	
Protease inhibitors[c]	No adjustment	No adjustment
Entry or fusion inhibitor	CrCl ≥35 ml/min: no adjustment	Unknown, use with caution
Enfuvirtide	CrCl <35 ml/min: unknown, use with caution	
CCR5 antagonist	No dosage recommendations	No data
Maraviroc	Patients with CrCl <50 ml/min should receive maraviroc and CYP3A inhibitor only if potential benefit outweighs the risk	
Integrase inhibitor[c]	No adjustment	No adjustment
Raltegravir		

[a] Combination AZT/lamivudine tablets (300mg/150mg) should be administered separately when eGFR<50ml/min
[b] Defer daily dose/s after hemodialysis (extraction of drug occurs on dialysis)
[c] No dose adjustment necessary for any drug from this class in patients with renal dysfunction, hemodialysis or pertoneal dialysis
[d] Combination emtricitabine/tenofovir tablets (200 mg/300 mg): if CrCl 30–49 ml/min: 1 tablet po q48h; if CrCl <30 ml/min the combination tablet should not be prescribed

Fig. 56-4. **Dose adjustments for ART in CKD and ESRD.** FDA recommendations are based on CrCl or eGRF calculated as ml/min, but are likely valid for these expressed as ml/min per 1.73 m^2. Atripla (efavirenz, tenofovir, and emtricitabine is not recommended for CrCl < 5 ml/min. CrCl, creatinine clearance; HD, hemodialysis; PD, peritoneal dialysis.

Kopp, Fabian and Naicker. Clinical Comprehensive Nephrology, 2010

Deriving estimated glomerular filtration rate (eGFR) using Serum creatinine measurements

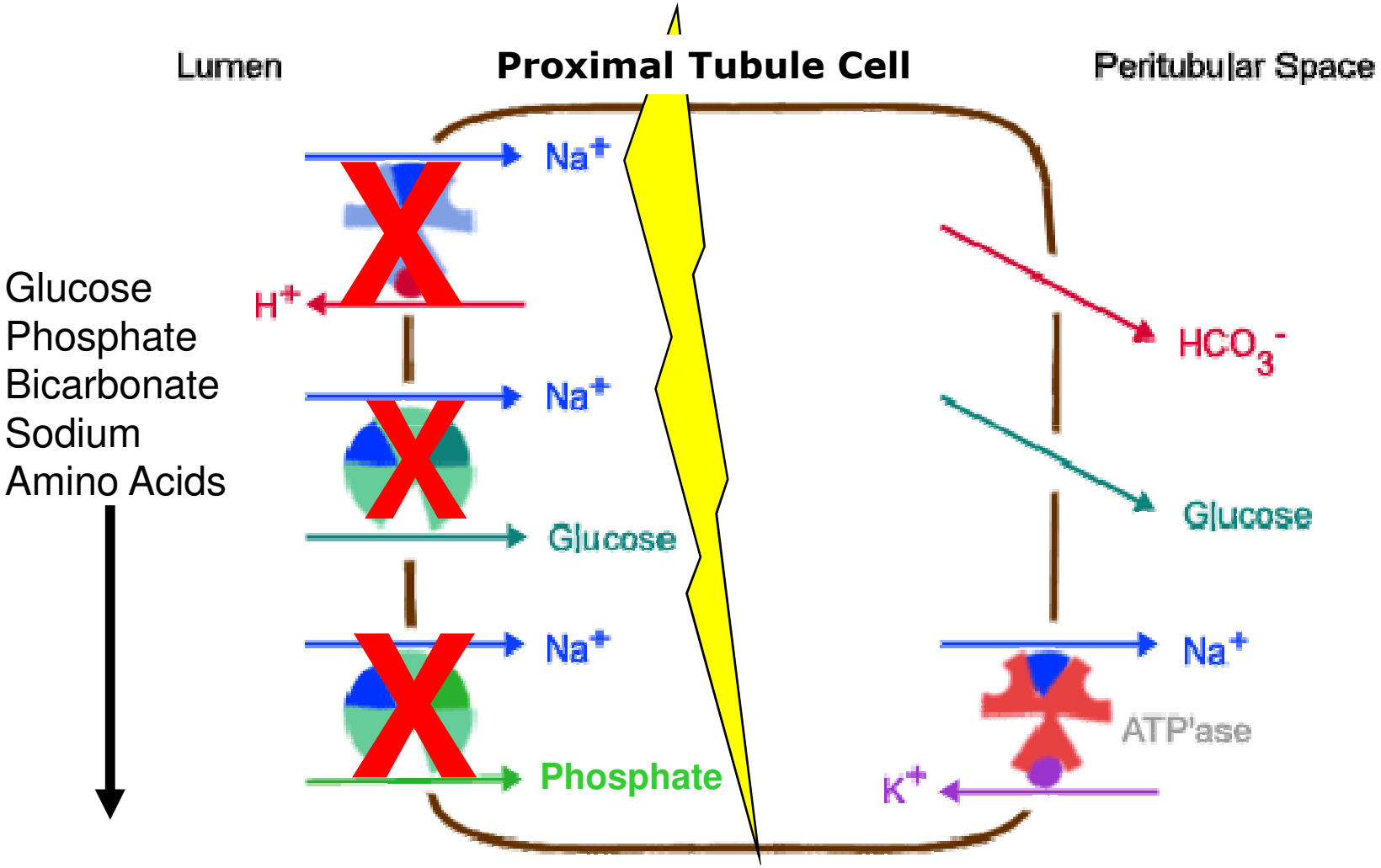
- Cockcroft-Gault (CG):

$$eGFR = \frac{(140 - age) \times weight\ (kg)}{Serum\ creatinine \times 72} \times 0.85\ (for\ women)$$

- Abbreviated MDRD study equation

$$eGRF = 186 \times S\text{-}creatinine^{-1,154} \times age^{-0,203} \times 0,742\ (if\ female) \times 1,21\ (if\ black)$$

Fanconi Syndrome



Hypophosphatemia, acidosis, glycosuria, aminoaciduria, hypokalemia = *FANCONI SYNDROME*

Tenofovir related renal toxicity

Dysfunction of proximal renal tubules - unclear mechanism

"wasting" of substances normally reabsorbed in PT

- small proteins
- glucose
- phosphates
- bicarbonates

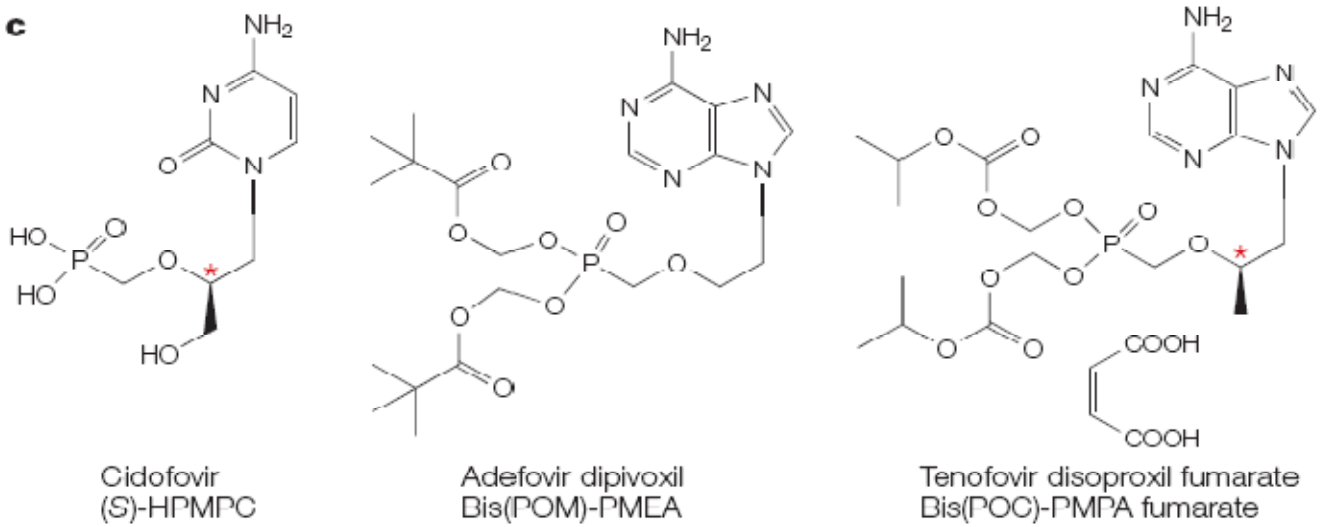
Proteinuria
Glycosuria
Phosphaturia
Metabolic acidosis

secondary glomerular dysfunction

Reduced Creatinine Clearance (CKD)

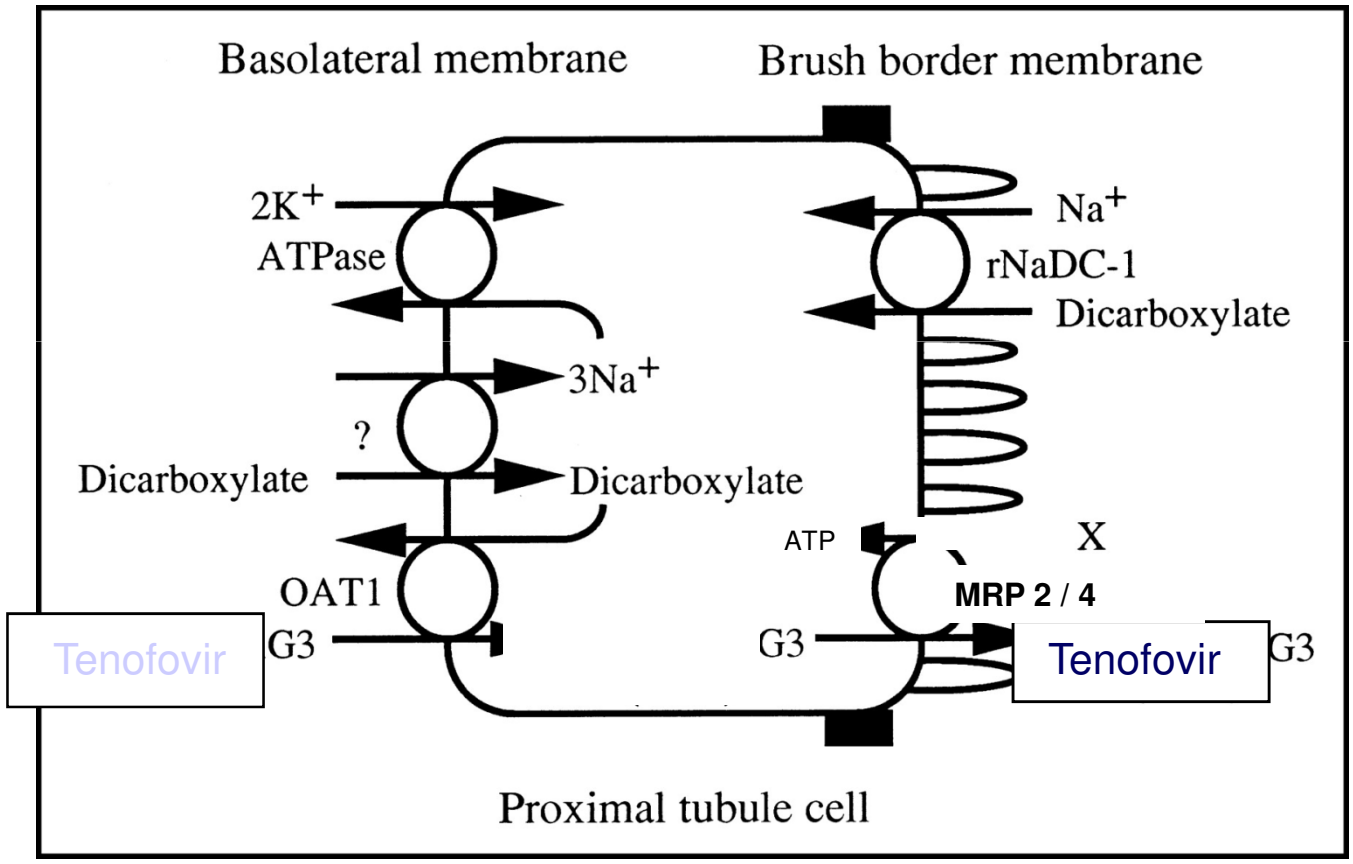
Disordered Bone Metabolism

What is tenofovir disoproxil fumarate (TDF)?



- Orally administered pro-drug of tenofovir
- Tenofovir is a nucleotide analogue inhibitor of reverse transcriptase (NtRTI)
  - Others in the family are Adefovir and Cidofovir, well described nephrotoxins
  - Tenofovir similar to Adefovir
  - The only NtRTI used for treatment of HIV

TDF is eliminated through the Kidney



Potential for accumulation of high concentration of TDF in proximal tubule cells

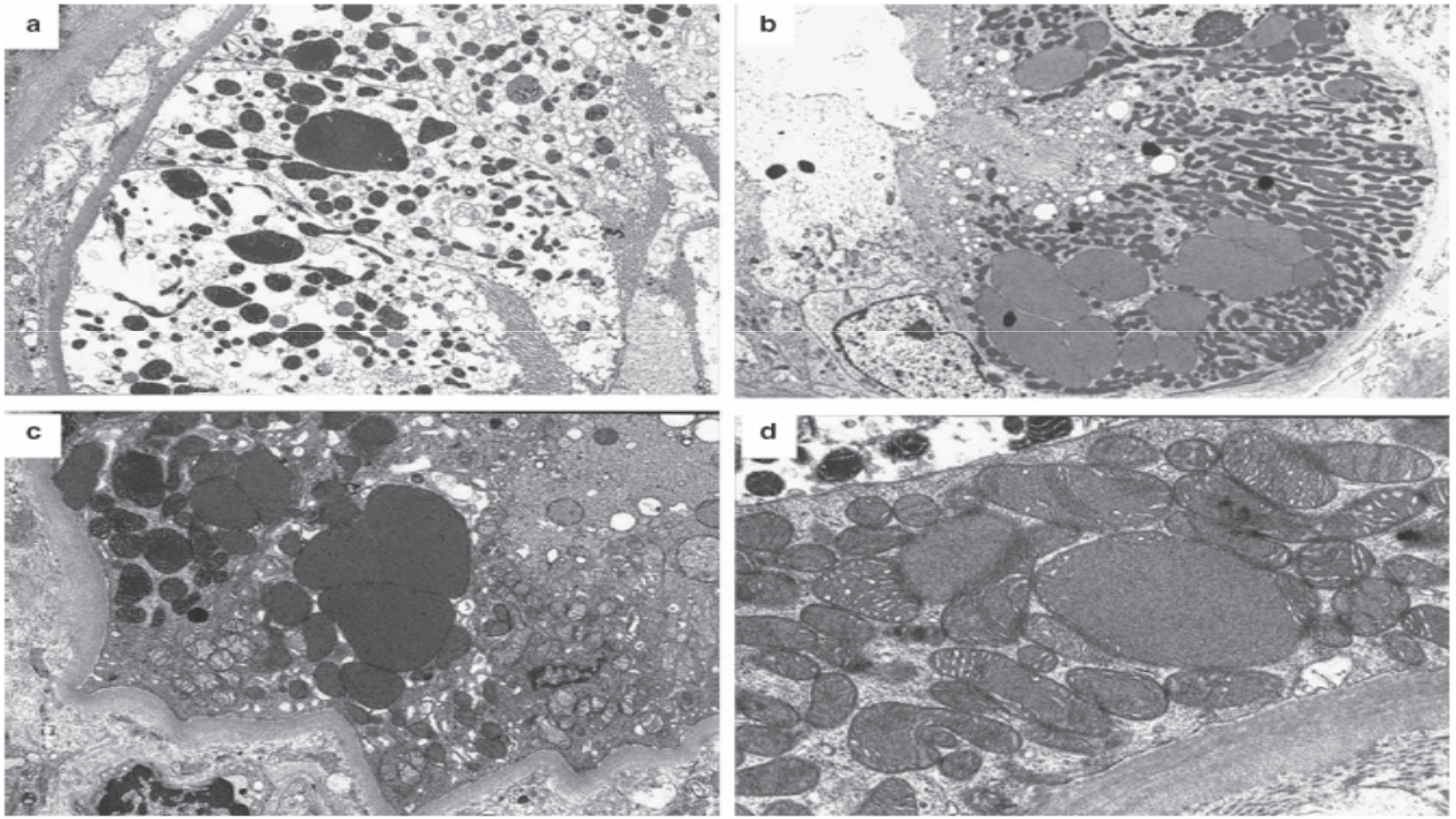
TDF

- Single Agent
  - Viread
    - marketed for the treatment of HIV since 2001
- Combination
  - Truvada
    - Fixed-dose combination
      - TDF and emtricitabine (NRTI), 2004
  - Atripla
    - Fixed-dose triple combination of
      - TDF, emtricitabine (NRTI) and efavirenz (NNRTI), 2006

Conclusion from case reports

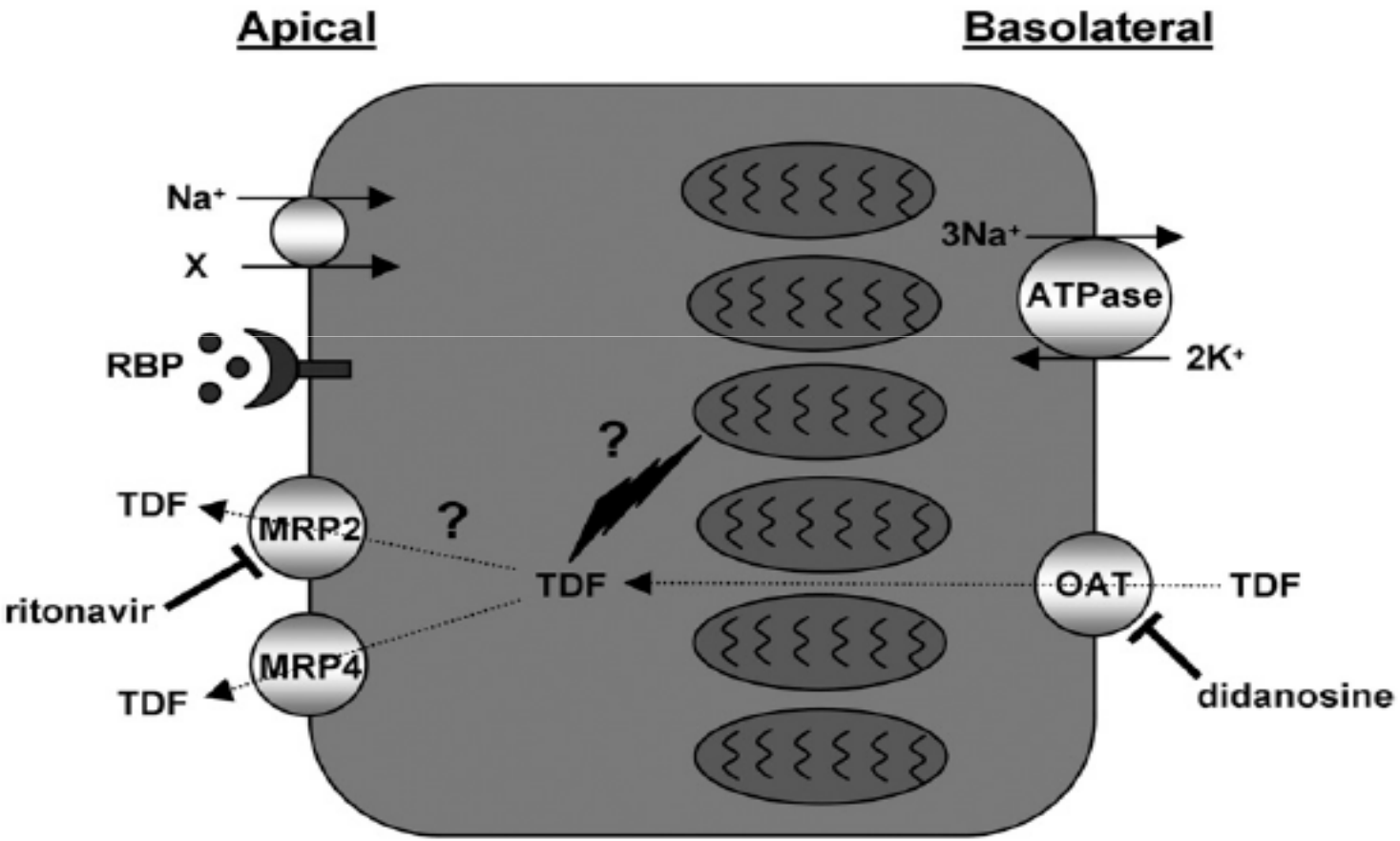
- Potential role of drug interactions
  - Ritonavir
    - has been shown to increase serum TDF by >30%
    - Inhibitor of MRP-2 -> increase proximal tubular concentration of TDF by decreasing secretion
  - Didanosine
    - Coadministration with TDF may increase serum concentration of didanosine -> proximal tubular dysunfction
- Polymorphism in the renal tubular drug transporter
  - variant MRP 2 or 4

EM: TDF Nephrotoxicity



Herlitz et al. Kidney Int, 2010

TDF transport in renal PT



Hall et al. Am J Kid Dis. 2011