Kidney Disease in HIV Patients

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Non-AIDS Complications in HIV

Contributing causes of death

SMART Trial
More serious non-AIDS events than serious OI
El Sadr et al. NEJM 2006

Selik et al. JAIDS 2002
Kidney Disease in HIV

Acute Kidney Injury

Nephrotoxicity

HIV-Associated

Comorbid Disease

End-stage Renal Disease (ESRD)
Acute Kidney Injury (AKI) in HIV

- More common in HIV patients
  - OR 2.8 in hospitalized patients*
- Associated with increased mortality
  - OR 5.8 in hospitalized patients*
- Risk factors: chronic kidney disease (CKD), advanced HIV, hepatitis C co-infection

Franceschini et al. KI 2005
Wyatt et al. AIDS 2006*
Roe et al. CID 2008
Common Causes of AKI in HIV

- Infection (52%)
  - 76% AIDS-defining
- Drugs (32%)
  - Antibiotics
  - ARV (indinavir & tenofovir)
  - NSAIDS, radiocontrast, lithium
- Liver Failure (10%)
  - 90% Hepatitis C

Franceschini et al. KI 2005
Antiretroviral Nephrotoxicity

- Tenofovir (Viread®, Truvada®, Atripla®)
- Indinavir (Crixivan®)
- Atazanavir (Reyataz®)
- Boosted PI
- Rare case reports with other agents

Kirk et al. for EuroSIDA, CROI 2010
Tenofovir Toxicity

- Classic presentation: proximal tubulopathy
  - Phosphate wasting
  - Metabolic acidosis
  - Euglycemic glycosuria
  - Elevated creatinine
- 1-2% of patients develop significant toxicity
  - More frequent sub-clinical abnormalities
Tenofovir Toxicity

- Risk factors remain controversial
  - Unrecognized low GFR
  - Genetic predisposition?
  - Concomitant medications (ddi, boosted PI)
Tenofovir Toxicity

Tenofovir

OAT1
OAT3

Na-K

OCT

C creatinine

Tenofovir

MRP4

Ritonavir

MRP2

(Urine)

(Blood)

Tenofovir Toxicity

Courtesy of Glen Markowitz & Vivette D’Agati
Indinavir Toxicity

- Classic presentation: crystalluria, obstruction, & interstitial nephritis
- Poorly soluble at physiologic urine pH
  - Crystalluria in up to 2/3 of patients
- Rarely used in the US
  - May inform toxicity of other agents
    - Atazanavir?
  - Still used in resource-poor settings
HIV-Associated Kidney Disease

- May present with either AKI or CKD
  - Glomerular disease excluded from AKI studies
- HIV-associated nephropathy (HIVAN)
- Immune complex kidney disease (“HIVICK”)
- Thrombotic microangiopathy
HIVAN: Classic Presentation

- Rapid progression to ESRD
- Large, echogenic kidneys
- Advanced HIV disease
- Almost exclusively in blacks

Rao et al. NEJM 1984
Pardo et al. Annals 1984
HIVAN: Pathology

Wyatt, Klotman, & D’Agati. Seminars in Nephrology 2008
HIVAN Pathogenesis: Mouse Model

- “Tg26” HIV-1 transgenic mouse
  - Gag/pol deleted HIV construct
  - Expressed in most tissues, including kidney
  - Kidney disease indistinguishable from human HIVAN

Dickie et al. Virology 1991
Ross et al. JASN 2001
HIVAN Pathogenesis: Mouse Model

- HIV gene expression in kidney → HIVAN
  - Reciprocal transplantation
  - Podocyte-specific expression
- HIV gene expression in lymphoid tissue → interstitial inflammation

Bruggeman et al. JCI 1997
Zhong et al. KI 2005
HIVAN Pathogenesis: Human Data

- HIV sequences detected
- Cluster separately from PBMC
- Mechanism of entry is unknown

Bruggeman et al. JASN 2000
Marras et al. Nat Med 2002
HIVAN Epidemiology: Impact of ART

- Decline in ESRD attributed to HIVAN
- Case reports of HIVAN regression

HIVAN is an indication for cART

Ross & Klotman JASN 2002
Winston et al. NEJM 2001
HIVAN Pathogenesis: Genetics

- Strong racial disparity in HIVAN & ESRD
  - ~90% of ESRD attributed to HIVAN
  - 4-30 fold increased risk of ESRD
- Genetic strain also influences mouse model

Lucas et al. JID 2008
Choi et al. JASN 2007
Gharavi et al. PNAS 2004
HIVAN Pathogenesis: Genetics

- Mapping by admixture linkage dysequilibrium (MALD) identified *MYH9* as a risk gene
- Mutations in *MYH9* cause kidney disease
- Polymorphisms in *MYH9* may account for racial disparity in HIVAN
  - Function is unknown
  - Cofactors are required for disease

Kopp et al. Nature Gen 2008
Changing Spectrum of CKD in HIV

- Decline in biopsies with classic HIVAN
- Recognition of other HIV-related diseases
- More comorbid kidney disease
  - Hepatitis co-infection
  - Diabetes & hypertension

Szczech et al. Kidney Int 2004
CKD & Hepatitis Co-infection

10 studies of CKD in HIV
Pooled RR associated with HCV 1.49 (1.08-2.06)

Wyatt et al. AIDS 2008
CKD Screening in HIV

- Screen all newly diagnosed individuals
  - Urinalysis
  - Creatinine-based GFR estimate
- Annual screening for “high risk” patients
  - Black race
  - Advanced HIV disease
  - Diabetes, hypertension, or hepatitis C

Gupta et al. CID 2005
CKD Management in HIV

- Consider nephrology referral
  - Diagnosis
  - ESRD preparation
- Aggressive management of comorbidities
  - DM
  - HTN
  - Hepatitis?
- Cardiovascular risk reduction*

Gupta et al. CID 2005
Choi et al. Circulation 2010
George et al. AIDS 2010
HIV & ESRD: Survival

Ahuja et al. JASN 2002
Atta et al. CID 2007
HIV & ESRD: Choice of Dialysis

Ahuja et al. AJKD 2003
HIV & Kidney Transplant

- Observational data
- Prospective studies
  - Good outcomes in selected patients
  - No increase in OI
  - High incidence of rejection
  - Drug interactions (especially PI, NNRTI)

Kumar et al. Transplantation 2005
Kidney Disease in HIV

- AKI & CKD are more common in HIV
  - Guidelines recommend screening for CKD
- Spectrum of disease has changed with ART
  - HIV-associated disease
  - Medication toxicity
  - Comorbid CKD
- Survival of HIV+ ESRD patients has improved
  - Transplant is an option in selected patients