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Special Challenges and Co-Morbidities

Renal Disease/ Hypertension/
Diabetes in African-Americans

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Learning Objectives

At the conclusion of this presentation, participants should be able to:

- Assess the impact of co-morbidities on HIV infected African Americans, including their impact on the risk of cardiovascular disease, in order to identify potential targets for clinical intervention
- Appraise the implications of delayed diagnosis and treatment of co-morbidities on this patient population in order to build a case for early intervention

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Background

- Kidney function is abnormal in up to 30% of HIV-infected patients¹
 - 'Abnormal' ranges from mild to severe
- The incidence of AIDS nephropathy in Blacks has remained constant since the mid-1990s²
- Antiretroviral therapy has decreased mortality due to HIV-associated nephropathy (HIVAN)², but patients with HIVAN on HAART have declines in kidney function similar to those seen with diabetic nephropathy³

¹Gupta SK, et al. *Clin Infect Dis*. 2005; 40:1559-1585.
²Schwartz EJ, et al. *J Am Soc Nephrol*. 2005; 16:2412-2420.
³Szczeczek LA, et al. *Clinical Nephrology*. 2002; 57:336-341.

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Role of HIV HCPs in Diagnosing and Managing Kidney Disease

- The HCP providing care for a patient's HIV infection usually manages all aspects of that person's medical care and treatment
- This presentation covers
 - Clinical manifestations of kidney disease
 - Risk factors for kidney disease, especially among HIV-infected people
 - Screening HIV-infected people for kidney dysfunction
 - When referral to a nephrologist may be appropriate

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A Little Nephrology

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Clinical Manifestations and Markers of Kidney Disease

- Clinical manifestations
 - Often asymptomatic
 - High blood pressure
 - Edema of hands and feet
- Markers
 - Protein and/or blood in the urine
 - Elevated serum creatinine and/or BUN
 - Decreased glomerular filtration rate (GFR)
 - Anemia

National Kidney Foundation. www.kidney.org.

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Measuring Proteinuria

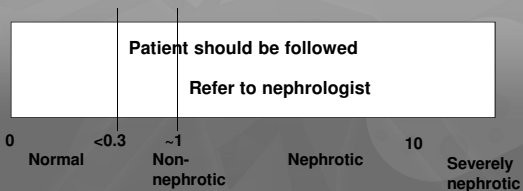
- Urinalysis gives a qualitative measure
 - Results are negative, trace, +1, +2
 - Easy, but cannot follow changes over time
- Spot urine protein:creatinine ratio gives a quantitative measure¹
 - Easy to collect sample in office
 - Reliable
 - Can use to follow changes over time
- 24-hour urine collection is also quantitative
 - Difficult to implement

¹Ginsberg JM, et al. *N Engl J Med*. 1983; 309:1543-1546.

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Urine Protein:Creatinine Ratio

- Calculate from lab results, making sure that both values are in g or mg



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Measurements or Estimations of Glomerular Filtration Rate (GFR) or Creatinine Clearance (CrCl)

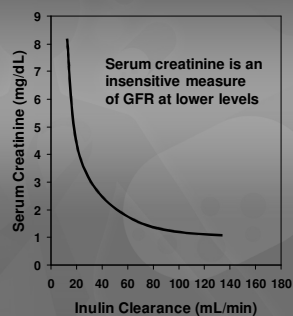
- CrCl vs. GFR
 - Technically different
 - Functionally similar
- Ways to measure
 - Inulin clearance
 - Nuclear imaging via radio-labeled markers
 - Creatinine clearance using 24-hour urine collection
 - Estimating formulas using serum creatinine
 - Serum creatinine

Johnson RJ and J Feehally. *Comprehensive Clinical Nephrology*. New York: Mosby, 2000.

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Is Serum Creatinine Enough?

- Abnormal kidney function may not be recognized in patients with lower relative muscle mass using serum creatinine alone
 - Females
 - Older patients
 - Wasted (decreased lean muscle mass)



Levey AS, et al. *Ann Int Med*. 1999; 130:461-470.

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Accuracy of Serum Creatinine Can Be Improved by Using an Estimating Equation

- Equations yield more accurate estimations of GFR because they adjust for surrogates of muscle mass
- Most common equations
 - Cockcroft-Gault: serum creatinine, age, sex, weight
 - MDRD: serum creatinine, age, sex, race

Levey AS, et al. *Ann Int Med*. 1999; 130:461-470.

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Estimating Equations

- Cockcroft-Gault
$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) * \text{weight} * (0.85 \text{ if F})}{\text{sCr} * 72}$$
- MDRD
$$\text{GFR (mL/min per 1.73 m}^2\text{)} = 186 * \text{sCr}^{-1.154} * \text{Age}^{-0.203} * (0.742 \text{ if female}) * (1.210 \text{ if black})$$
- See www.nephron.com for some easy online calculators

Cockcroft DW and Gault MH. *Nephron*. 1976; 16:31-41.
Levey AS, et al. *Ann Int Med*. 1999; 130:461-470.
Levey AS, et al. *J Am Soc Nephrol*. 2000; 11:A0928.

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Summary: Nephrology

- Kidney function is abnormal in up to 30% of HIV-infected patients
 - 'Abnormal' ranges from mild to severe
- Proteinuria is an early marker of kidney disease
- Monitoring kidney function requires more accurate measures than serum creatinine alone
- Estimating equations yield a more predictive measure of GFR without additional lab tests

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Causes of Kidney Disease

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Acute Renal Failure: Common Causes

- Non-HIV related
 - Pre-renal: hypovolemia, hypoperfusion
 - Renal: ischemia/toxins, interstitial nephritis due to drug allergies or infections, acute glomerulonephritis, and drugs (NSAIDs, aminoglycosides, statins)
 - Post-renal: obstruction (stones, cancers, etc.)
- HIV-related
 - ART or medication for opportunistic infections

Johnson RJ and J Feehally. *Comprehensive Clinical Nephrology*. New York: Mosby, 2000.

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Chronic Kidney Disease (CKD)

- Kidney damage for ≥ 3 months as defined by structural or functional abnormalities of the kidney, with or without decreased GFR
 - Damage manifests as pathological abnormalities; or markers of kidney damage, including abnormalities in the composition of the blood or urine; or abnormalities in imaging tests
- GFR < 60 mL/min per 1.73m^2 for ≥ 3 months, with or without kidney damage

<http://www.kidney.org/professionals/KLS/aboutCKD.cfm>

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Causes of CKD

- Non-HIV related
 - Hypertension
 - Diabetes mellitus
 - Non-diabetic glomerular disease
 - Cystic kidney disease
 - Tubulointerstitial disease
 - Co-infection with HBV, HCV, or syphilis
- HIV-related
 - HIV-Associated Nephropathy (HIVAN)
 - Glomerulopathies, e.g., immune complex glomerulonephritis, IgA glomerulonephritis, membranous glomerulopathy, etc.
 - ART or OI medications

<http://www.kidney.org/professionals/KLS/aboutCKD.cfm>
Kimmel P, et al. *Ann Int Med*. 2003; 139:214-226.
Gupta SK, et al. *Clin Infect Dis*. 2005; 40:1559-1585.

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HIV-Associated Nephropathy (HIVAN)

- Most common cause of HIV-related chronic renal disease
- Collapsing form of focal segmental glomerulosclerosis (FSGS)
 - Definitive diagnosis can only be made by biopsy
- Classic presentation (without ART)
 - Proteinuria (>3 grams)
 - Rapidly decreasing GFR (over weeks to months)

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Winston JA, et al. *Kidney International*. 1999; 55:1036-1040.

Who is at Risk for CKD

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Risk Factors for Kidney Disease

- General population^{1,2,3,4}
 - Hypertension
 - Diabetes mellitus
 - Race and other genetic factors
 - Family history
 - Hepatitis C infection
- In people with HIV
 - All of the above^{1,2,3,4}
 - Decreased CD4 cell count^{5,6}
 - Increased viral load⁶

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¹US Renal Data System Annual Data Report, 2005. www.usrds.gov
²Freedman BL, et al. *American Journal of Kidney Diseases*. 1999; 34:254-258.
³Laradi A, et al. *J Am Soc Nephrol*. 1998; 9:2327-2335.
⁴Kimmel P, et al. *Ann Int Med*. 2003; 139:214-226.
⁵Winston JA, et al. *Kidney International*. 1999; 55:1036-1040.
⁶Szczech LA, et al. *Kidney International*. 2002; 61:195-202.

Diabetes and Hypertension are the Most Common Causes of End-Stage Renal Disease (ESRD)

In general population, adjusted for age, gender, and race

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www.usrds.org/slides.htm

Black Americans Have Higher Rates of Risk Factors

- Black Americans are 1.8 times as likely to have diabetes mellitus than age-adjusted White Americans¹
- ~43% of Black Americans over age 20 have hypertension²
 - Compared with White Americans, hypertension develops earlier and blood pressures are higher
- Black Americans have the highest observed rate of Hepatitis C (3.2%)³

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¹www.diabetes.org/uedocuments/NationalDiabetesFactSheetRev.pdf
²www.americanheart.org/presenter.jhtml?identifier=3000927
³Alter MJ, et al. *N Eng J Med*. 1999; 341:556-562.

In US, AIDS Disproportionately Affects Black and Hispanic Populations

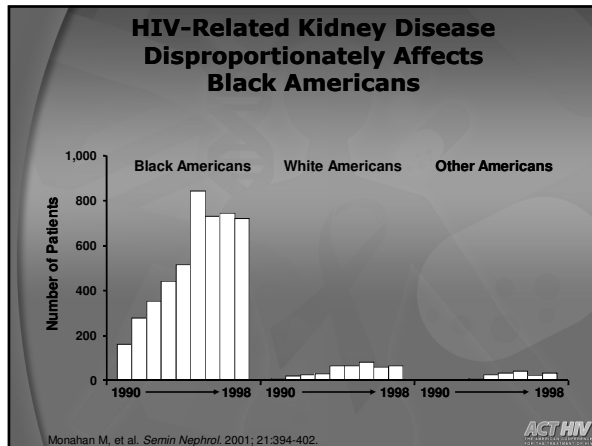
Proportion of Reported AIDS Cases and Population, by Race/Ethnicity, 2003—50 States and D.C.

■ White, not Hispanic ■ Asian/Pacific Islander
 ■ Black, not Hispanic ■ American Indian/Alaska Native
 ■ Hispanic

Note. Excludes persons from US dependencies, possessions, and associated nations.
 * Includes 225 persons of unknown race or multiple races.

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<http://www.cdc.gov/hiv/graphics/images/1178/1178-12.ppt>



- ### Summary: Risk Factors for Kidney Disease
- Black Americans are particularly at risk for kidney disease
 - Comorbidities such as hypertension, diabetes, and HCV are also risk factors for kidney disease
 - Black Americans have higher rates of these comorbidities than White Americans
 - HIV is an independent risk factor for kidney disease¹
- ¹Szozech LA, et al. *Kidney International*. 2002; 61:195-202.

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IDSA guidelines for screening and management of chronic kidney disease in people with HIV

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- ### Recommendations from IDSA Guidelines
- At time of HIV diagnosis, all patients should be screened for existing kidney disease
 - Screening should include a calculated estimate of kidney function and an assessment of proteinuria
 - An estimate of kidney function allows the HCP to properly prescribe those antiretrovirals and other commonly-used medications that require dosing adjustment
- Gupta SK, et al. *Clin Infect Dis*. 2005; 40:1559-1585.

Screening Algorithm for HIV-Related Kidney Diseases

Qualitative Assessment for Risk of Kidney Disease

- Family history of kidney disease
- CD4 lymphocyte count
- HIV RNA level
- History of use of nephrotoxic medication
- Race
- Comorbidities
 - Diabetes mellitus
 - Hypertension
 - Hepatitis C coinfection

↓

Screening Studies at Initial HIV Documentation

- Urine analysis (for proteinuria)
- Serum creatinine and estimation of CrCl (Cockcroft-Gault) or GFR (MDRD)

(Continued on next slide)

Gupta SK, et al. *Clin Infect Dis*. 2005; 40:1559-1585.

Screening Algorithm for HIV-Related Kidney Diseases, cont'd.

Screening Studies at Initial HIV Documentation

- Urine analysis (for proteinuria)
- Serum creatinine and estimation of CrCl (Cockcroft-Gault) or GFR (MDRD)

↓

<p>Abnormal Values (Continued on next slide)</p> <p>↓</p> <p>With Kidney Disease Risk Factors*</p> <ul style="list-style-type: none"> • Screen annually • Screen twice per year if taking certain ART agents 	<p>No Abnormal Values</p> <p>↓</p> <p>Without Kidney Disease Risk Factors</p> <ul style="list-style-type: none"> • Follow clinically • Reassess based on signs/symptoms • Reassess per clinical events
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*Risk factors: black race, diabetes, hypertension, HCV, CD4 cell count <200 cells/mm³, HIV RNA >4000 c/mL

Gupta SK, et al. *Clin Infect Dis*. 2005; 40:1559-1585.

Screening Algorithm for HIV-Related Kidney Diseases, cont'd.

Screening Studies at Initial HIV Documentation

- Urine analysis (for proteinuria)
- Serum creatinine and estimation of CrCl (Cockcroft-Gault) or GFR (MDRD)

Abnormal Values

- Grade $\geq 1+$ proteinuria by dipstick
- CrCl or GFR < 60 mL/min per 1.73 m²

- Evaluate proteinuria further with spot protein/creatinine ratio
- Perform renal ultrasound
- Consider referral to nephrologist for further evaluation and potential biopsy

No Abnormal Values

(See previous slide)

Gupta SK, et al. *Clin Infect Dis.* 2005; 40:1559-1585.



Management of CKD in HIV-Infected People: What You Can Do

- Control blood pressure ($< 125/75$)
- Patients should be given HAART immediately upon diagnosis of HIVAN
 - Consider adding ACE inhibitors, angiotensin receptor blockers, and/or corticosteroids if HAART alone does not improve renal function
- Assess impact of concomitant nephrotoxic agents on patient's kidney function and minimize use
- Refer to nephrologist

Gupta SK, et al. *Clin Infect Dis.* 2005; 40:1559-1585.



Management of CKD in HIV-Infected People: The Role of a Nephrologist

- Determine need for renal biopsy
- Monitor for complications of CKD
 - Anemia
 - Hyperparathyroidism
 - Cardiovascular disease
 - Acidosis/malnutrition
- Assess need for renal replacement therapy
 - Peritoneal and hemodialysis
 - Renal transplantation



Antiretroviral Dosing and Monitoring in HIV-Infected Patients with CKD

- Appropriately dose-reduce ART and drugs for opportunistic infections
 - Most NRTIs require dose adjustment
 - Most NNRTIs and PIs do not require dose adjustment
- Monitor patients at least twice per year for kidney function, serum phosphorus, and urinalysis for proteinuria and glycosuria if:
 - Receiving certain ART agents with GFR < 90 mL/min, boosted PIs, or other renally-excreted medications
 - Have diseases such as diabetes or hypertension

Gupta SK, et al. *Clin Infect Dis.* 2005; 40:1559-1585.



Summary

- Kidney disease is increasingly recognized as an important factor to consider when treating patients with HIV
- Comorbidities such as hypertension, diabetes, and HCV are also risk factors for kidney disease
 - Black Americans have higher rates of these comorbidities than White Americans
- Monitor kidney function using GFR estimates and urine protein excretion

Gupta SK, et al. *Clin Infect Dis.* 2005; 40:1559-1585.



Summary, cont'd.

- At least annual monitoring of renal function is necessary in people with these risk factors
 - CD4 cell count < 200 cells/mm³
 - HIV RNA > 4000 c/mL
 - Black race
 - Co-morbidities (diabetes, hypertension, HCV)
- Monitoring at least twice per year is recommended for patients receiving certain ART agents
- Discuss your patients with kidney disease with a nephrologist

Gupta SK, et al. *Clin Infect Dis.* 2005; 40:1559-1585.

