

Update on HIV-Related Kidney Diseases



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THE MEDICAL MANAGEMENT OF HIV/AIDS
DECEMBER 15, 2006

Agenda



- 1. EPIDEMIOLOGY:**
 - A) END STAGE RENAL DISEASE (ESRD)**
 - B) CHRONIC KIDNEY DISEASE (CKD)**
- 2. HIV-ASSOCIATED NEPHROPATHY (HIVAN)**
- 3. INSIGHTS INTO PATHOGENESIS**

What are the most common causes of ESRD among African Americans (age 20-64 years)?

Etiology of ESRD in Blacks age 20-64

ESRD Diagnosis	Number (%)
1. DM Type 1&2	4795 (46%)
2. HTN	4116 (39%)
3. AIDS nephropathy	935 (9%)
4. Focal GN	438 (3%)
5. Systemic Lupus	340 (3%)
6. Membranous GN	63 (1%)

From the USRDS Annual Data Report 2001

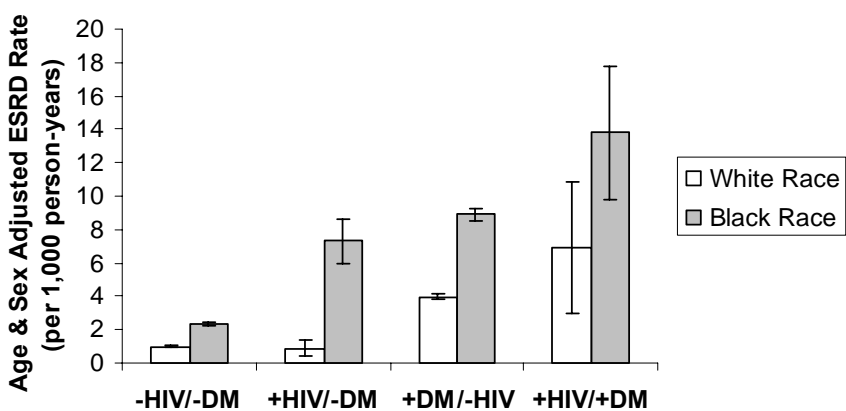
Racial Differences in End-Stage Renal Disease Rates in HIV Infection *versus* Diabetes

Andy I. Choi,^{*†‡} Rudolph A. Rodriguez,[§] Peter Bacchetti,^{||} Daniel Bertenthal,[¶]
Paul A. Volberding,[‡] and Ann M. O'Hare[§]

Setting: VA health care system

Subjects: 15,135 HIV-infected individuals and over 2 million HIV-negative controls

Age and Sex Adjusted Incidence of ESRD



Adjusted Risk for ESRD among Whites

	Persons (n)	ESRD events (n)	Person-years of Observation	Multivariate Hazard Ratio for ESRD [±] (95% CI)
White Race				
-HIV/-DM	1,201,870	3,991	4,238,246	Referent
+HIV/-DM	6,139	13	22,038	0.75 (0.42-1.36)
+DM/-HIV	495,211	6,749	1,712,545	2.16 (2.07-2.25)
+HIV/+DM	881	16	3,095	2.10 (1.06-4.16)

Adjusted Risk for ESRD among Blacks

	Persons (n)	ESRD events (n)	Person-years of Observation	Multivariate Hazard Ratio for ESRD (95% CI)
Black Race				
-HIV/-DM	206,636	1,425	730,909	Referent
+HIV/-DM	6,816	129	23,693	2.37 (1.88-2.99)
+DM/-HIV	97,039	2,775	337,344	2.09 (1.95-2.23)
+HIV/+DM	1,299	50	4,370	2.67 (1.75-4.06)

Summary

- Among **black individuals**, the risk of ESRD is similar between those with HIV and diabetes.
- Among **white individuals**, the risk of ESRD is no greater in those with HIV compared to the general population.

External Validation

- **National Data:** Rates of ESRD (for both HIV-infected and diabetic groups) are similar to estimated rates from USRDS and CDC data.
- **Quality of Care:** VA HIV care and population is similar to that found in other health care systems.

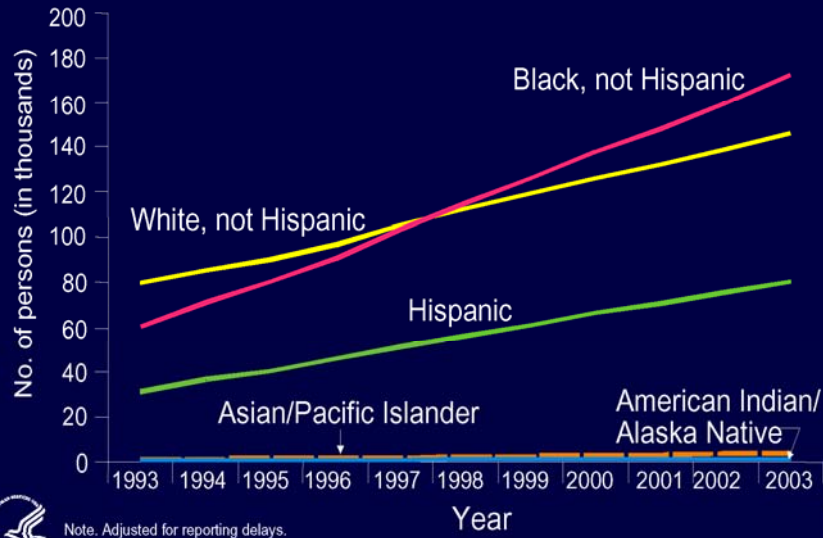
Racial Predilection of Kidney Disease

1. 90% of HIV-infected patients on dialysis are black in the US.
2. Kidney biopsy studies have revealed similar renal disease patterns among HIV-infected black patients in Africa, America, France, and Brazil.

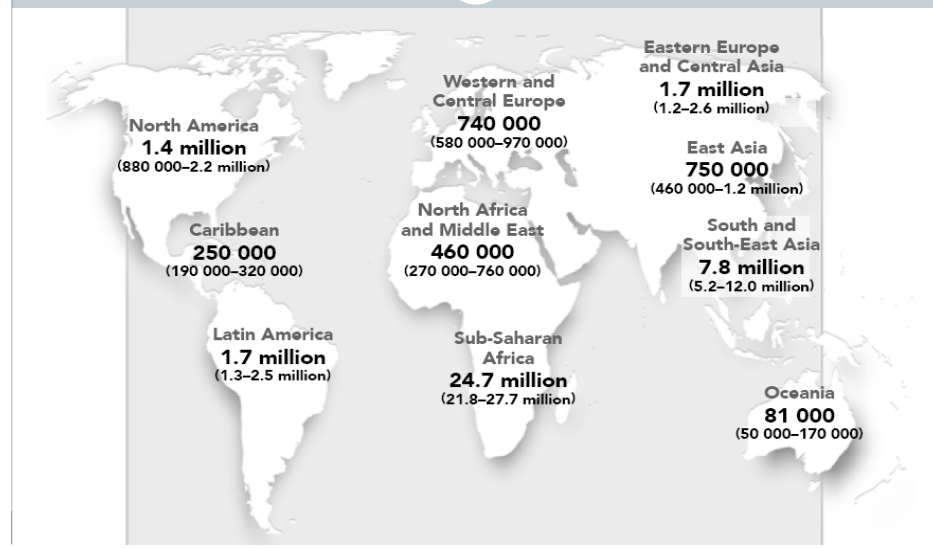
Table 7 | Renal biopsy series

Study	Country	Number of patients biopsied	HIVAN (%)	% African descent with HIVAN
Bourgoignie ²⁷ (1990)	Literature review of biopsies reported before 1990	176	146 (83%)	?
Nochy <i>et al.</i> ²⁵ (1993)	France	60 (29B+31C)	26 (43%)	79% (23/29)
Casanova <i>et al.</i> ²⁸ (1995)	Italy	26 (all white Italian)	0 (0%)	0%
Connolly <i>et al.</i> ²² (1995)	UK	19 (11B+7C+1A)	11 (58%)	73% (8/11)
Assounga <i>et al.</i> ²⁶ (1996)	Congo	32 (all black African)	6 (19%)	19% (6/32)
Praditpornsilpa <i>et al.</i> ²⁹ (1999)	Thailand	26 (all Asian)	0 (0%)	0%
Winston <i>et al.</i> ²³ (1999)	USA	20 (17AA+3H)	10 (50%)	53% (9/17)
Ahuja <i>et al.</i> ²⁴ 1999)	USA	14 (12AA+2C)	9 (64%)	75% (9/12)
Our study	South Africa	30 (29B+1mixed race)	25 (83%)	83% (25/30)

Estimated Number of Persons Living with AIDS by Race/Ethnicity, 1993–2003—United States



WHI: Worldwide HIV Infection 2006



Case: newly diagnosed HIV

You are seeing a 40 y/o black male with a history of unprotected heterosexual sex and newly diagnosed HIV. He does not have any family members with kidney disease.

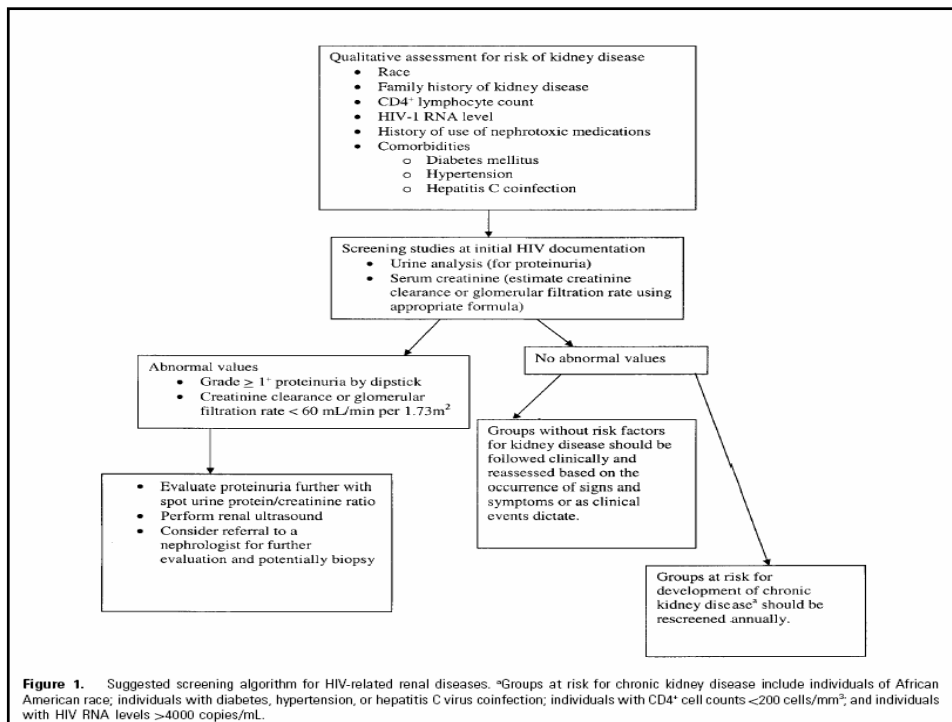
- Should you screen for CKD?
- If yes, what tests do you order?

Infectious Disease Society of America Guidelines

IDSA GUIDELINES

Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America

Samir K. Gupta,¹ Joseph A. Eustace,³ Jonathan A. Winston,⁴ Ivy I. Boydston,⁵ Tejinder S. Ahuja,⁷ Rudolph A. Rodriguez,⁸ Karen T. Tashima,¹⁰ Michelle Roland,⁹ Nora Franceschini,¹¹ Frank J. Palella,¹¹ Jeffrey L. Lennox,¹⁴ Paul E. Klotman,⁴ Sharon A. Nachman,⁶ Stephen D. Hall,² and Lynda A. Szczech¹²



When should you screen for CKD?

1. All patients **upon diagnosis** of HIV
2. **Annual screening** for high risk groups.

Patients at high risk for CKD include:

- blacks, patients with HCV, diabetes, hypertension, CD4 counts <200 cells/ μ L or HIV RNA levels >4000 copies/mL.

What is CKD?

Two aspects:

1. Kidney Damage

- Primarily manifested as proteinuria
- Also includes other pathologic or imaging abnormalities.

2. Decreased Function (Low GFR)

- Usually serum creatinine based measures

Creatinine Based Measures of GFR

- 24 Urine collection no longer recommended.

Prefer:

- MDRD equation (4 & 6 variable)
- Cockcroft-Gault formula for adults
- Schwartz formula for pediatrics

MDRD Equation

- Modification of Diet in Renal Disease
- Based on a gold standard measurement GFR using iothalamate clearance
- Predicts GFR, not CrCl

MDRD Equation

6 Variable

Estimated GFR = $170 \times \text{SCr}^{-0.999} \times \text{age}^{-0.176} \times \text{BUN}^{-0.17} \times \text{albumin}^{0.318} \times (1.18 \text{ if black}) \times (0.762 \text{ if female})$

4 Variable

Estimated GFR = $186 \times (\text{SCr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American})$

- PDA: MedCalc
- <http://www.kidney.org/professionals/kdoqi/index.cfm>

Measurement of Proteinuria

- Instead of a 24 hour collection just send a spot urine protein and urine creatinine for the **protein to creatinine ratio**

Example:

- 10 mg/dl of proteinuria (urine)
- 100 mg/dl of creatinine (urine)
- The ratio will provide an estimate in grams of proteinuria
- $10/100 = 0.1$ grams of proteinuria

Albuminuria

Normal	Microalbuminuria	Macroalbuminuria
Albumin to creatinine ratio <30 mg/g	Albumin to creatinine ratio 30-300 mg/g	Albumin to creatinine ratio >300 mg/g

National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification

Andrew S. Levey, MD; Josef Coresh, MD, PhD; Ethan Balk, MD, MPH; Annamaria T. Kausz, MD, MS; Adeera Levin, MD; Michael W. Steffes, MD, PhD; Ronald J. Hogg, MD; Ronald D. Perrone, MD; Joseph Lau, MD; and Garabed Eknoyan, MD

Ann Intern Med. 2003;139:137-147.

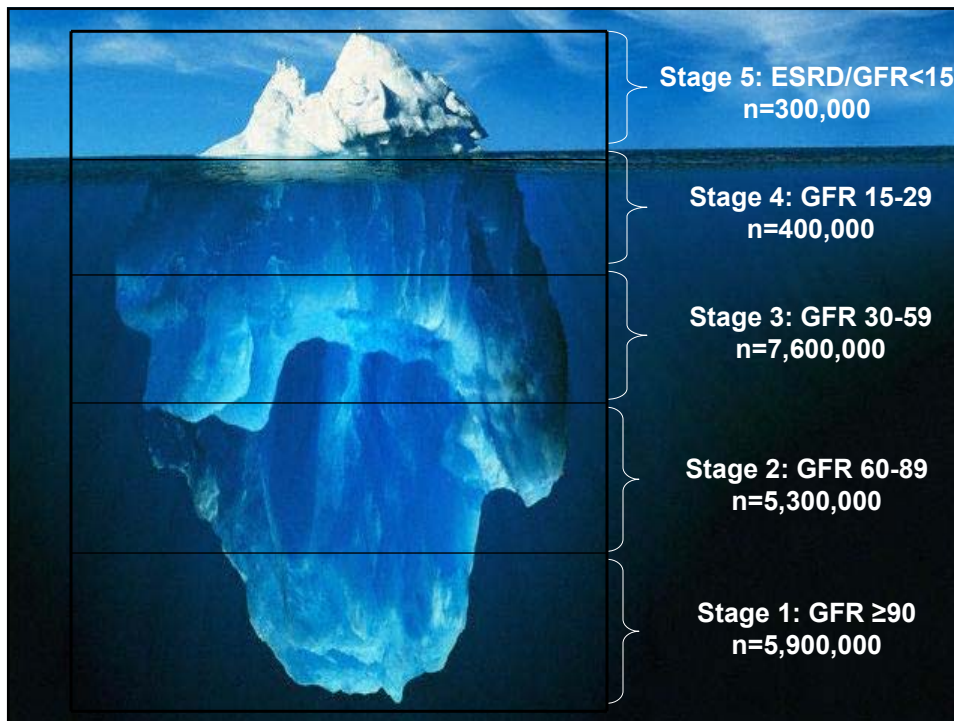
- **Kidney Disease Outcomes Quality Initiative (K/DOQI)**
- Can also be found at:
<http://www.kidney.org/professionals/kdoqi/index.cfm>

CKD Staging

Stage	Description	GFR	Action
1	Kidney damage <i>with</i> normal or increased GFR	≥90	Diagnosis and treatment Slowing progression CVD risk reduction
2	Kidney damage <i>with</i> mild decrease in GFR	60-89	Estimating progression
3	Moderate decrease in GFR	30-59	Evaluating and treating complications
4	Severe decrease in GFR	15-29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement therapy

CKD Staging

Stage	Description	GFR	ICD Code
1	Kidney damage with normal or increased GFR	≥ 90	585.1
2	Kidney damage with mild decrease in GFR	60-89	585.2
3	Moderate decrease in GFR	30-59	585.3
4	Severe decrease in GFR	15-29	585.4
5	Kidney failure	<15	585.5
5	ESRD	Dialysis	585.6



What is the GFR?

1. 40 y/o Black Male with **creatinine 1.1?**
 - >90 mL/min/1.73m²
 - 60-90 mL/min/1.73m²
 - 30-59 mL/min/1.73m²
2. 50 y/o White Female with **creatinine 1.1?**
 - >90 mL/min/1.73m²
 - 60-90 mL/min/1.73m²
 - 30-59 mL/min/1.73m²

What is the GFR?

1. 40 y/o Black Male with **creatinine 1.1?**
= **eGFR 95** mL/min/1.73m²
2. 50 y/o White Female with **creatinine 1.1?**
= **eGFR 56** mL/min/1.73m²
 - **Stage 3 CKD!**
 - **Needs drug dose adjustment, etc.**

Limitations of eGFR

- It is unknown whether these equations are accurate in the setting of HIV infection.
- May be inaccurate due to changes in lean body mass/wasting.
- Creatinine may be inaccurate because of medications and malnutrition.

Summary: CKD Case

- **Screening for CKD:**
 1. All patient upon diagnosis
 2. Annually for high risk patients: blacks, HCV, DM, HTN, CD4 counts <200, or VL >4000
 3. **Tests to Order:** serum creatinine + urinalysis or spot urine albumin/urine creatinine
- Must calculate GFR using MDRD or CG equation!**

The impact of HIV on chronic kidney disease outcomes

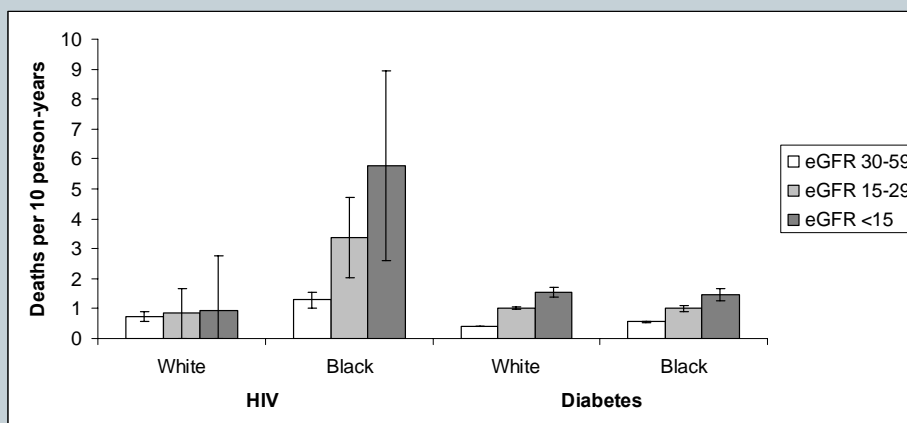
Al Choi^{1,2}, RA Rodriguez³, P Bacchetti⁴, D Bertenthal⁵, PA Volberding² and AM O'Hare³

Setting: VA health care system

Subjects: 202,927 patients with eGFR < 60 mL/min per 1.73m² confirmed over 3 months.

Outcomes: 1) Death, 2) Renal replacement therapy, 3) Rates of eGFR decline

CKD & Mortality Rates



CKD & ESRD Rates

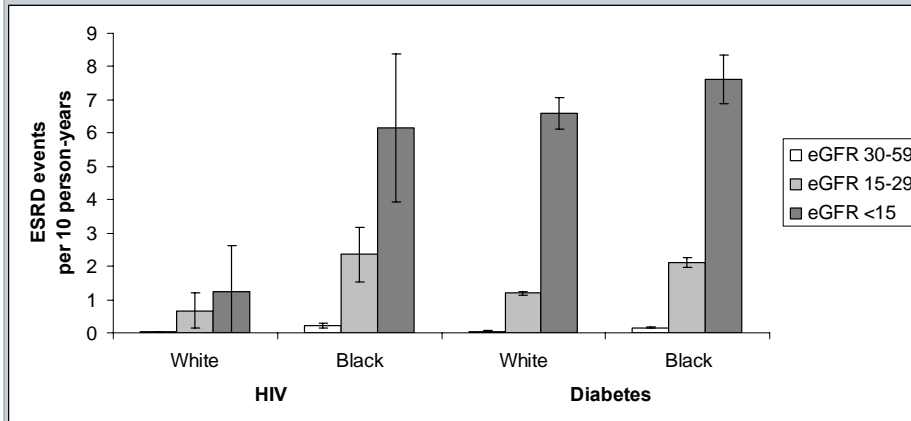


Table 2 | Incidence rates and adjusted risk of ESRD and death^a

	Persons (n)	Time at risk (person-years)	ESRD events (n)	Deaths (n)	Age and Sex adjusted rates of ESRD (per 1000 person-years)	Multivariate hazard ratio for ESRD ^b	Age and sex adjusted rates of death (per 1000 person-years)	Multivariate hazard ratio for death ^b
<i>White</i>								
No HIV or diabetes	103 692	338 985	2065	20 366	7.8 (7.5-8.3)	Referent	35.0 (34.2-35.7)	Referent
HIV	265	863	17	55	11.3 (5.9-16.6)	0.68 (0.26-1.76)	70.8 (52.0-90.0)	2.21 (1.57-3.13)
Diabetes	76 765	239 224	4183	19 313	22.0 (21.2-22.8)	1.97 (1.86-2.08)	50.3 (49.3-51.3)	1.23 (1.21-1.26)
<i>Black</i>								
No HIV or diabetes	10 531	32 434	808	2 354	27.9 (25.7-30.1)	Referent	49.7 (46.8-52.6)	Referent
HIV	269	674	85	66	71.1 (55.4-86.7)	2.11 (1.46-3.06)	120.5 (90.9-150.1)	2.32 (1.70-3.18)
Diabetes	11 575	33 623	1 808	2 781	59.9 (56.7-63.1)	1.78 (1.63-1.93)	60.4 (57.4-63.4)	1.06 (1.00-1.12)

ESRD, end stage renal disease; HIV, human immunodeficiency virus.

Numbers in parentheses indicate 95% confidence intervals.

^aThere were 170 patients who had both HIV and diabetes and contributed to event rates for both groups. The multivariate hazard ratio for ESRD and death utilize interaction terms to exclude the effect of overlap between diagnoses and isolate the individual effect of HIV and diabetes, respectively.

^bAdjusted for age, race, sex, baseline estimated glomerular filtration rate, hypertension, coronary artery disease, heart failure, chronic obstructive lung disease, peripheral vascular disease, hepatitis C infection, cerebrovascular disease, and socioeconomic status.

Table 3 | Age and sex-adjusted rates of mean eGFR change per year stratified by race, HIV or diabetes status, and starting eGFR category

	Overall	eGFR 45-59 ml/min/1.73 m ² at baseline	eGFR 30-44 ml/min/1.73 m ² at baseline	eGFR 15-29 ml/min/1.73 m ² at baseline
<i>White race</i>				
No HIV or diabetes	-0.1 (-0.1, -0.1)	-0.1 (-0.2, -0.1)	-0.1 (-0.1, 0.0)	-0.8 (-0.9, -0.7)
HIV	-0.4 (-1.3, 0.5)	-0.1 (-0.9, 0.8)	-0.6 (-2.0, 0.7)	-3.8 (-7.1, -0.5)
Diabetes	-1.4 (-1.4, -1.3)	-1.4 (-1.4, -1.3)	-1.5 (-1.6, -1.4)	-1.8 (-1.9, -1.7)
<i>Black race</i>				
No HIV or diabetes	-0.8 (-0.9, -0.7)	-0.4 (-0.5, -0.3)	-1.2 (-1.4, -1.0)	-2.0 (-2.4, -1.7)
HIV	-3.7 (-5.2, -2.1)	-2.9 (-4.5, -1.3)	-3.5 (-5.5, -1.6)	-4.0 (-6.8, -1.2)
Diabetes	-2.3 (-2.4, -2.1)	-2.0 (-2.1, -1.8)	-2.5 (-2.7, -2.3)	-3.2 (-3.4, -2.9)

eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus.
Rates are reported in ml/min/1.73 m² per year with 95% confidence intervals reported in parentheses.

Variable	Hazard ratio adjusted ^a	95% CI	p value
Age	1.2 per 10 years	(0.96, 1.45)	.11
Race			
White vs. black	1.3	(0.89, 1.81)	.19
Hispanic/other vs. black	1.3	(0.89, 1.84)	.18
CD4 cell count >500 vs. <200	0.3	(0.18, 0.48)	<.0001
CD4 cell count 200-500 vs. <200	0.4	(0.30, 0.57)	<.0001
Viral load from 500 to 10,000 vs. <500	1.8	(0.84, 3.70)	.13
Viral load above 10,000 vs. <500	3.5	(1.68, 7.44)	.002
Clinical AIDS	4.1	(2.99, 5.50)	<.0001
HAART use vs. other ART or no ART	0.7	(0.44, 1.03)	.07
Hepatitis C antibody positivity	1.5	(1.07, 2.01)	.02
Injection drug use at enrollment	1.1	(0.81, 1.49)	.53
Diabetes mellitus	2.2	(1.10, 4.35)	.03
Hypertension	1.9	(1.21, 2.84)	.004
Renal abnormalities	2.5	(1.90, 3.32)	<.0001

^a Adjusted for all other variables listed.

HAART, highly active antiretroviral therapy; ART, antiretroviral therapy (not HAART).

Gardner LI et al. J Acquir Immune Defic Syndr. 2003 Feb 1;32(2):203-9.

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 - A) **END STAGE RENAL DISEASE (ESRD)**
 - B) **CHRONIC KIDNEY DISEASE (CKD)**
2. **HIV-ASSOCIATED NEPHROPATHY (HIVAN)**
3. **INSIGHTS INTO PATHOGENESIS**

Differential Dx of Renal Failure in HIV

HIV-related:

1. HIV-associated nephropathy
2. HIV-related Immune Complex GN

Medication Related: indinavir, tenofovir, sulfadiazine, bactrim

Other: usual causes in the general population, HCV/HBV related, amyloid

HIV-Associated Nephropathy (HIVAN)

- Most common etiology of kidney disease in biopsy series (~60% of cases)
- Likely due to the direct pathogenic effect of HIV on the kidney
- Predilection for blacks
- Definitive diagnosis by renal biopsy

HIV Associated Nephropathy

Typical Presentation characterized by:

1. Nephrotic Syndrome
2. No Hypertension
3. Minimal Edema
4. Large, echogenic kidneys on U/S
5. Rapid Deterioration of Renal Function

A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa

TM Han¹, S Naicker², PK Ramdial³ and AG Assounga¹

¹Department of Nephrology, Division of Medicine, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa; ²Division of Nephrology, Department of Internal Medicine, University of the Witwatersrand, Johannesburg, South Africa and ³Department of Pathology, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa

615 patients without established risk factors for CKD were screened

- 38 (6.2%) had macroalbuminuria
- 90 (14.6%) had microalbuminuria, but confirmed in only 7 (1.1%)

Proteinuria in South Africa



***Kidney Biopsies* obtained in 6/7 with confirmed microalbuminuria and 19/38 with macroalbuminuria!**

“Ethical approval for the study was obtained from the Ethics Committee of the University of KwaZulu-Natal.”

Table 3 | Characteristics of patients with microalbuminuria

Patient no.	Age (year)	Sex	Serum creatinine		eGFR (ml/min/1.73 m ²) (MDRD equation)	Hepatitis serology		Urine protein (g/24h)	Renal biopsy	
			CD4	(μ mol/l)		Cr Cl (ml/min)	B			C
26	30	F	239	37	188	188	(-)	(-)	0.13	IN
3	26	F	204	65	63	123	(-)	NA	0.06	HIVAN
4	34	F	246	62	95	123	(-)	(-)	0.30	HIVAN
5	40	M	199	111	78	82	(-)	(-)	0.23	HIVAN
6	43	M	114	70	91	137	(-)	(-)	0.04	HIVAN+Mem GN
7	27	F	379	58	104	140	(-)	(-)	0.17	HIVAN
8	21	F	137	61	130	138	(-)	(-)	0.07	HIVAN

Cr Cl, creatinine clearance; eGFR, estimated glomerular filtration rate; HIVAN, HIV-associated nephropathy; IN, interstitial nephritis; MDRD, modification of diet in renal disease; Mem GN, membranous glomerulonephritis; NA, not available; (-), negative. All were black Africans.

Table 4 | Detailed morphologic changes of microalbuminuric patients

Patient no.	Total no. of glomeruli	No. of collapsing glomeruli (%)	No. of glomeruli with FSGS	Microcystic tubular dilatation (%)	Interstitial inflammation/fibrosis (%)	Diagnosis
26	28	0 (0)	0	0 ^a	60	IN
3	11	5 (45)	5	25	40	HIVAN
4	11	6 (55)	3	30	30	HIVAN
5	17	5 (29)	5	30	10	HIVAN
6	45	8 (18)	8	25	10	HIVAN+Mem GN ^b
7	23	6 (26)	6	25	10	HIVAN
8	11	5 (45)	5	30	40	HIVAN

FSGS, focal segmental glomerulosclerosis; HIVAN, HIV-associated nephropathy; IN, interstitial nephritis; Mem GN, membranous glomerulonephritis.

^a30% atrophic tubules present.

^bAlso has prominent glomerular basement membrane with spikes+electron-dense subepithelial deposits.

HIVAN: Management Recommendations

1. Patients with HIVAN should be **treated with HAART** at diagnosis.
2. HAART should not be withheld from patients simply because of the severity of their renal dysfunction.
3. Addition of **ACE inhibitors, ARBs, and/or prednisone** should be considered in patients with HIVAN if HAART alone does not result in improvement of renal function.

Treatment of HIVAN

1. **HAART**
 - No trials
 - Anecdotal data
2. **ACE-inhibitors**
 - Non-randomized studies
3. **Prednisone**
 - Small numbers, non-randomized studies
 - Works but effects are short-lived

Summary: HIVAN Treatment

1. HAART
2. ACEI/ARB: Goal BP < 125/75
3. Steroids
4. Dialysis with AVF
5. Kidney Transplant: <http://hivtransplant.com>

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CD4+ Count-Guided Interruption of Antiretroviral Treatment

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group*

Randomized, controlled trial:

Continuous versus episodic use of HAART

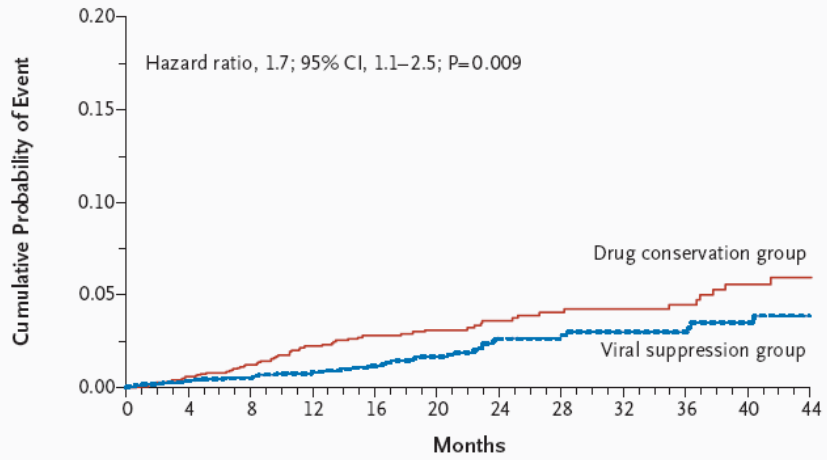
Patients:

**5,472 HIV-infected patients with a CD4 count
>350 cells per mm³**

ESRD Outcome Definition

For non-fatal renal disease either 1) dialysis or kidney transplant required to preserve life or 2) supporting documentation indicating the results of the procedure(s) giving rise to the diagnosis of end stage renal disease (ESRD) were counted.

C Major Cardiovascular, Renal, or Hepatic Disease



No. at Risk

	0	4	8	12	16	20	24	28	32	36	40	44
Drug conservation	2720	2070	1663	1292	1041	867	693	543	443	375	273	157
Viral suppression	2752	2077	1692	1307	1070	899	713	563	462	380	282	165

Table 2. Primary and Major Secondary End Points.^a

End Point	Drug Conservation Group (N=2720)		Viral Suppression Group (N=2752)		Hazard Ratio for Drug Conservation Group vs. Viral Suppression Group (95% CI)	P Value
	No. of Participants with Event	Event Rate (per 100 Person-Yr)	No. of Participants with Event	Event Rate (per 100 Person-Yr)		
Primary end point	120	3.3	47	1.3	2.6 (1.9-3.7)	<0.001
Death from any cause	55	1.5	30	0.8	1.8 (1.2-2.9)	0.007
Opportunistic disease						
Serious	13	0.4	2	0.1	6.6 (1.5-29.1)	0.01
Nonserious	63	1.7	18	0.5	3.6 (2.1-6.1)	<0.001
Major cardiovascular, renal, or hepatic disease	65	1.8	39	1.1	1.7 (1.1-2.5)	0.009
Fatal or nonfatal cardiovascular disease	48	1.3	31	0.8	1.6 (1.0-2.5)	0.05
Fatal or nonfatal renal disease	9	0.2	2	0.1	4.5 (1.0-20.9)	0.05
Fatal or nonfatal liver disease	10	0.3	7	0.2	1.4 (0.6-3.8)	0.46
Grade 4 event	173	5.0	148	4.2	1.2 (1.0-1.5)	0.13
Grade 4 event or death from any cause	205	5.9	164	4.7	1.3 (1.0-1.6)	0.03

Summary: SMART study

- ESRD increased in the antiretroviral treatment interruption arm of the trial.
- Adverse events associated with decrease in CD4 counts and increased viral loads.

Take Home Points

1. What is the risk of ESRD in HIV infection?
 - Comparable to diabetes among **black** individuals.
 - Comparable to the general population in **white** individuals.

Take Home Points

2. What is the impact of HIV on CKD outcomes?

When compared to the general population, **white** individuals have:

- Similar rates of **ESRD**
- Higher rates of **Death**
- Similar rates of **kidney function decline**

Take Home Points

3. What is the impact of HIV on CKD outcomes?

When compared to the general population, **black** individuals have:

- Higher rates of **ESRD**
- Higher rates of **Death**
- Higher rates of **kidney function loss**

Take Home Points

Screening:

1. All patients **upon diagnosis** of HIV
2. **Annual screening** for high risk groups.

Patients at high risk for CKD include:

- blacks, patients with HCV, diabetes, hypertension, CD4 counts <200 cells/ μ L or HIV RNA levels >4000 copies/mL.