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INTERVIEW WITH:

Christina M. Wyatt, MD

**CKD screening and referring,
plus insights on TDF and TAF 20**

Articles by **Mark Mascolini**

**Kidney disease with HIV:
not rare, not rarely fatal 5**

**Classic and HIV-specific risk factors
for kidney disease 26**

**Screening and monitoring
HIV-positive people for CKD 40**



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Table of Contents



INTERVIEW

Christina M. Wyatt, MD	20
CKD screening and referring, plus insights on TDF and TAF	
<i>with Mark Mascolini</i>	

PERSPECTIVES

Kidney disease with HIV: not rare, not rarely fatal	5
<i>By Mark Mascolini</i>	
Classic and HIV-specific risk factors for kidney disease	26
<i>By Mark Mascolini</i>	
Screening and monitoring HIV-positive people for CKD	40
<i>By Mark Mascolini</i>	

BOARD & STAFF

46



Kidney disease with HIV: not rare, not rarely fatal

By Mark Mascolini

Abstract: US clinicians described HIV-associated nephropathy (HIVAN) in the early days of the epidemic. Although combination antiretroviral therapy (cART) made HIVAN an increasingly rare complication, chronic kidney disease (CKD) persists in HIV populations, affecting 5% to 25% of HIV groups in the United States and Europe. Three studies in Europe and the United States estimate CKD incidence at 1 per 100 person-years in people with HIV. Incidence of acute kidney injury and end-stage renal disease ranges widely in recent US and European studies, depending on definitions of these conditions and cohort variables. Several studies link kidney disease to a higher chance of death in people with HIV, though the largest of these studies do not extend beyond 2008. Other research ties CKD to cardiovascular endpoints in people with HIV, findings that some experts believe call for cardiovascular risk modification in people with CKD.

In Shakespeare's day people sometimes called kidneys *reins*, derived from the Latin term for kidneys, *renes*, which also gave rise to our word renal. But whether calling kidneys reins implied a controlling

function may be a stretch. Biblically and through Shakespeare's time, kidneys seemed the seat of feelings, conscience, or temperament—not organs with a prosaic physiologic duty. In the Bible, Psalm 7 invokes a sheltering deity “who test the hearts and kidneys”—now usually translated as “hearts and minds”—of man. When Falstaff described his abduction in a humid laundry hamper, he meant “temperament” when he complained, “think of that,—a man of my kidney,—think of that,—that am as subject to heat as butter; a man of continual dissolution and thaw” (*Merry Wives of Windsor*, III, v).

In the second century an otherwise-sagacious Galen rejected the notion that kidneys filter urine from blood.¹ But in 1564, the year of Shakespeare's birth, Bartolomeo Eustachio, an anatomy professor at Collegio della Sapienza in Rome, described renal tubules (“furrows and small canals”) that transport urine from nephrons (**Figure 1**).¹ In 1662, at the age of 19, anatomist and physiologist Lorenzo Bellini determined that the kidneys separate urine from blood “by a distinct anatomical arrangement which would become known as the kidney glomeruli.”¹

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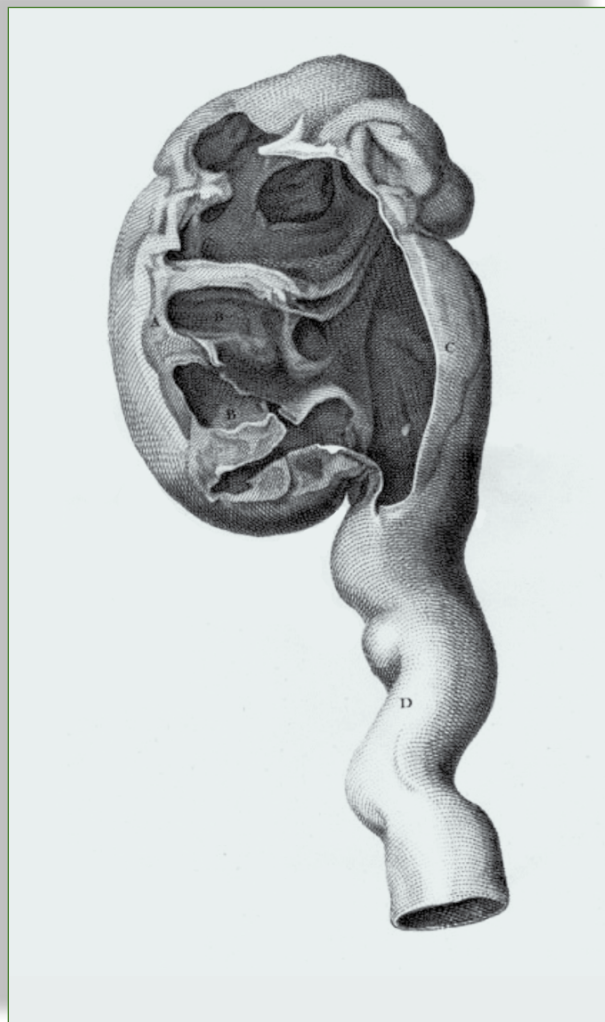


Figure 1. John Hunter, 18th-century Scottish surgeon and champion of the scientific method, drew this enlarged kidney.

(Source: Wikipedia Commons.

http://upload.wikimedia.org/wikipedia/commons/7/7a/Hunter_enlarged_kidney.jpg).

Today we know the kidneys—fist-sized organs toward the bottom of the ribcage—do much more than filter waste from the circulation. They also eliminate excess fluid, remove some drugs from the body, control blood pressure, help make red blood cells, and produce a form of vitamin D that promotes bone health.² When they're working well, the kidneys filter 200 quarts of fluid every day.³ When they're not working well, unfiltered wastes pile up and trouble ensues.

The National Kidney Foundation figures 26 million people in the United States have chronic kidney disease (CKD),⁴ usually defined as kidney damage or an estimated glomerular filtration rate (eGFR) below 60 mL/min per 1.73 m² for at least 3 months (**Figure 2**).⁵ The Centers for Disease Control and Prevention (CDC) reckons that more than 15% of the US population has CKD, including more than one third with diabetes.⁶ Rates are higher in women than in men and in blacks, Hispanics, Pacific Islanders, and American Indians than in whites. In 2011 more than 113,000 people in the United States began treatment for end-stage renal disease (ESRD).⁶ Kidney disease ranks as the ninth leading cause of death in the United States.⁶

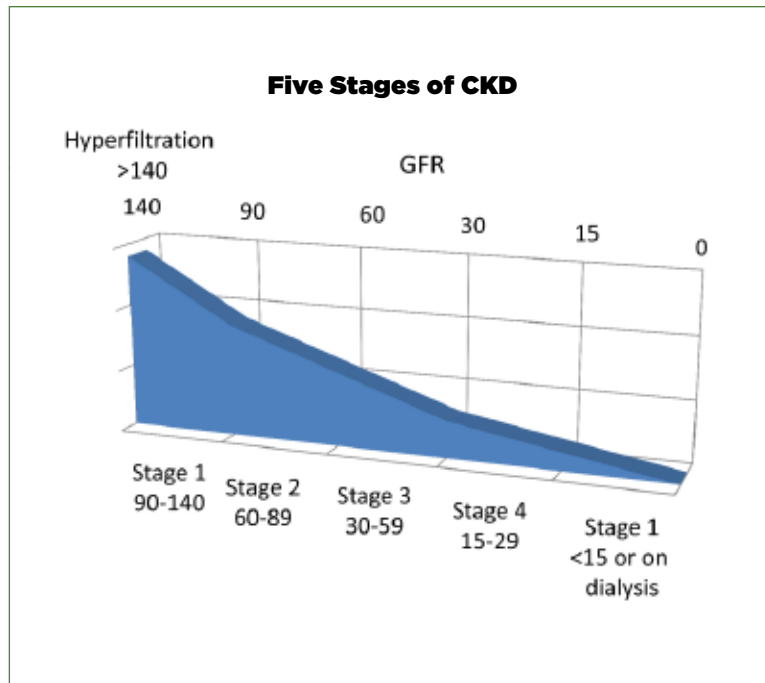


Figure 2. Chronic kidney disease (CKD) has five stages based on glomerular filtration rate (GFR). Stage 1 is normal, stage 2 indicates mildly reduced kidney function, stage 3 indicates moderately reduced kidney function, stage 4 indicates severely reduced kidney function calling for end-stage renal failure planning, and stage 5 indicates very severe or end-stage kidney failure. Hyperfiltration—a GFR above 140 mL/min in people over 40—may be an early signal of a subsequent drop in GFR and resulting CKD. (Source: The Renal Association. CKD stages.)

Early in the HIV epidemic, kidney disease emerged as HIV-associated nephropathy (HIVAN), first reported in African Americans and Haitian immigrants with AIDS in 1984 by a group at the State University of New York in Brooklyn.⁷ By the 1990s HIVAN had become a leading cause of ESRD in African Americans.⁸ Susceptibility of African Americans to HIVAN (and other forms of kidney disease) can be traced at least partly to single-nucleotide polymorphisms in the apolipoprotein L1 gene that are more prevalent in West Africans than in people from other regions.⁹

From 1985 (just after the dawn of the US HIV epidemic) until 2000 (early in the current antiretroviral era) the proportion of US centers providing dialysis to people with HIV jumped more than 3-fold from 11% to 37%.¹⁰ But midway through the 1990s, combination antiretroviral therapy (cART) profoundly altered the epidemiology of HIV-related kidney

disease in the United States and in countries with similar HIV epidemics and antiretroviral access.⁸ Clinicians learned that cART prevents or reverses HIVAN, developments consistent with a plateau in ESRD incidence after cART arrived¹¹ and with the observation that ongoing HIV replication directly injures the kidney.¹² Today US adult and adolescent antiretroviral guidelines say “regardless of CD4 count, ART should be started in all patients with HIVAN at the earliest sign of renal dysfunction.”¹³

But the arrival of cART did not banish kidney complications in people with HIV. Kidney experts at New York’s Icahn School of Medicine at Mount Sinai explain that “the spectrum of HIV-related kidney disease now reflects the growing burden of comorbid disease in an aging HIV population” as well as antiretroviral-induced toxicity.⁸ At Baltimore’s

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Johns Hopkins University clinic, dwindling HIVAN incidence paralleled emergence of noncollapsing focal segmental glomerulosclerosis, acute interstitial nephritis, and over a dozen other renal insults that can cause CKD,¹⁴ defined above.

CKD prevalence ranges from 5% to 25% in HIV groups

Prevalence of CKD among HIV-positive people in the United States and Western Europe ranges widely from 5% to 25%, depending on the CKD definition and the population studied. Among the earliest post-HIVAN cART-era studies, retrospective analysis of 417 HIV-positive people seen at a Connecticut center in 2004 determined that 100 (24%) had CKD as defined by the National Kidney Foundation, and 12 of these 100 had stage 4 or 5 CKD.¹⁵ In 2007 clinical researchers at New York's Mount Sinai Medical Center determined that 192 of 1239 adults seen over the course of 12 months (15.5%) had CKD (defined as proteinuria or eGFR below 60 mL/min) or ESRD.¹⁶ Fifty-one people (4.1%) had ESRD.

More recent multicenter studies in Europe chart lower CKD prevalence in HIV populations. Among 7378 people seen at seven large HIV referral centers in France from 1993 to 2006, 349 (4.7%) had CKD defined as eGFR at or below 60 mL/min for at least 3 months.¹⁷ A 2010 literature review charted CKD prevalence ranging from 3.5% to 4.7% in 31 European countries, Israel, and Argentina.¹⁸

But among 23,155 HIV-positive US veterans in care from 1998 to 2004, 12% had classically defined

CKD,¹⁹ a rate almost as high as that seen in the earlier New York study.¹⁶ This higher prevalence partly reflects the high proportions of blacks and Hispanics in the study group (52% and 8%) compared with whites (38%). In contrast, a Multicenter AIDS Cohort Study (MACS) of CKD involved 783 men who have sex with men (MSM) in care in 2006 and 2007, only 33% of whom were black.²⁰ Figuring CKD as eGFR below 60 mL/min based on serum creatinine or cystatin C, the MACS team calculated prevalence of 5% with the creatinine formula and 7% with the cystatin C formula. CKD prevalence was lower still in an analysis of 1415 women starting cART in the Women's Interagency HIV Study (WIHS), only 44 (3%) of whom had prevalent CKD—and 56% of these women were black.²¹

In a study of 448 children and adolescents, Pediatric HIV/AIDS Cohort Study investigators defined CKD as two or more sequential urine protein/creatinine ratios at or above 0.2, or a clinical diagnosis not contradicted by a normal ratio, or eGFR below 60 mL/min.²² Almost three quarters of these children were black and almost one quarter Hispanic. Twenty children (4.5%) had CKD during 3 years of study in the late 2000s, though 94 (21%) had proteinuria.

Race is hardly the only factor that explains differing CKD prevalence in these populations. Each study group comes with its complement of other CKD risk factors, prominently including older age, hypertension, diabetes, HCV infection, proportion responding to antiretroviral therapy, and type of antiretroviral therapy. The article starting on page 26 of this issue details research on key risk factors.

CKD incidence 1 per 100 person-years in 3 cohorts

Three big prospective cohort studies in the current cART era—one in Europe,²³ one in France,²⁴ and one in the United States²⁵—charted a CKD incidence of about 1 per 100 person-years, meaning CKD developed in 1 of every 100 HIV-positive people each year (**Table 1**). One US military study calculated a CKD incidence of 0.5 per 100 person-years,²⁶ while the largest study—in the European-US-Australian DAD Cohort—estimated an incidence of only 0.13

per 100 person-years.²⁷ (Incidence in the general US population lies below 0.5 per 100 person-years, although incidence rose substantially from 2000 to 2008.²⁸) Reasons for this wide incidence range in HIV populations are not hard to find.

Because the DAD study wanted to gauge CKD incidence in people with initially normal renal function, it began with people whose eGFR lay at or above 90 mL/min and so had low prevalence of renal risk factors such as diabetes, hypertension, and HCV coinfection.²⁷ And follow-up extended only 4 or 5

Table 1. CKD* incidence in 5 prospective cohorts in the current cART era

Author	Location	Years	Number	Incidence	Risk factors
Mocroft ^{23†}	Europe (EuroSIDA)	2004-2008, median 3.7 y follow-up	6843, median age 43, 75.1% men, 85.5% white, 4.9% DM, 21.7% HTN, 37.2% SM	1.05 per 100 p-y	Increasing cumulative exposure to tenofovir, indinavir, or lopinavir/ritonavir
Morlatt ²⁴	France (Aquitaine cohort)	2004-2012, median 5.8 y follow-up	4350, 65.3% <45 years old, 74.4% men, 3.9% DM, 9% HTN, 21.2% HCV	0.95 per 100 p-y	Women, older age, DM, HTN, hyperlipidemia, AIDS, low baseline eGFR, current CD4 <200, tenofovir
Kalayjian ²⁵	United States, 8 clinical sites in CNICS cohort	1996-2009, median 4.8 y follow-up	3329, median age 40, 81% men, 38.5% black, 3.2% DM, 16.1% HTN, 14.9% HCV	10.5 per 1000 p-y (1.05 per 100 p-y)	Black race, HCV, lower CD4, higher viral load, tenofovir, ritonavir-boosted PIs

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continued from **page 9**

Table 1. CKD* incidence in 5 prospective cohorts in the current cART era *continued...*

Author	Location	Years	Number	Incidence	Risk factors
Ganesan ²⁶	United States (US Military HIV Natural History Study)	1995-2010, median 7.5 y follow-up	3360, median age 29, 92% men, 44% black, 0.9% DM, 4% HTN, 1.2% HCV	5.0 per 1000 p-y (0.5 per 100 p-y)	Older age, lower CD4 at HIV diagnosis, lower nadir CD4, HIV diagnosis pre-cART, DM, HBV, HTN, less cART use
Ryom ^{27‡}	Europe, US, Australia (DAD cohort)	2004-2009, median 4.5 y follow-up	22,603, median age 39, 73% men, 47% white, 8% African, 43% unknown race, 3% DM, 8% HTN, 12% HCV, 42% SM	1.33 per 1000 p-y (0.13 per 100 p-y)	Increasing cumulative exposure to lopinavir/ritonavir

* Defined as eGFR \leq 60 mL/min unless otherwise noted.

† eGFR \leq 60 mL/min if eGFR higher at baseline or confirmed 25% decline in eGFR if \leq 60 mL/min at baseline.

‡ All cohort members \geq 90 mL/min at baseline.

DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HTN, hypertension; PIs, protease inhibitors; p-y, person-years; SM, smokers.

years. As a result, the DAD team observed, “the presented estimates of chronic renal impairment may be underestimated.” Even so, the nearly 7-mL/min yearly decline in eGFR among people with incident CKD far exceeded the expected age-related annual drop of 1-mL/min. In the French study, the yearly drop in people with incident CKD measured 9.0 mL/min.²⁴

In contrast, the US military study included anyone with an initial eGFR of 60 mL/min or higher, and follow-up was much longer (**Table 1**).²⁶ Thus, even though this 92% male group had even lower rates of renal

risk factors than the DAD cohort,²⁷ CKD incidence was almost 5 times higher, at 0.5 per 100 person-years. That incidence in the military study approximately halved the rate recorded in the other three cohorts,²³⁻²⁵ perhaps because the military group had the youngest median age, included almost no injection drug users, and had low background kidney risk rates. Also, US military members typically get diagnosed with HIV early in the course of the disease and thus receive ongoing early care. The link between lower CD4 count and CKD in the US military study suggested to the authors that “routine HIV screening to identify subjects early in infection and timely introduction of [cART] to preserve CD4 counts may reduce the burden of CKD.”²⁶

The remaining three cohort studies all recorded a CKD incidence around 1 per 100 person-years,²³⁻²⁵ more than twice the CKD incidence in the general US population.²⁸ All three studies considered people with an initial eGFR above 60 mL/min instead of the high 90-mL/min threshold used by DAD.²⁷ Two of these three studies^{24,25} echoed the US military analysis²⁶ in identifying independent ties between low CD4 counts and CKD development, and all three studies²³⁻²⁵ found links between CKD and tenofovir and/or ritonavir-boosted PIs.

In both EuroSIDA and the French cohort,^{23,24} people with a baseline eGFR below 90 mL/min proved most likely to end up with a sub-60 eGFR by the end of follow-up. The French team suggested many HIV clinicians do not appreciate this heightened risk, which should prompt them to monitor people with a sub-90 eGFR more closely.²⁴ These investigators also noted that CKD incidence remained fairly constant from year to year in this nearly 6-year study, a find-

ing suggesting a need for regular eGFR monitoring regardless of the initial measure.

Incidence of end-stage renal disease with HIV

Other studies assessed incidence of acute kidney injury (also called acute renal failure) or end-stage renal disease in people with HIV in the United States and Europe (**Table 2**).

US Veterans Affairs researchers analyzed incidence of acute kidney injury (AKI) and AKI requiring dialysis in 56,823 HIV-positive veterans—nearly all of them men—from 1986 through 2006.²⁹ They defined AKI as an acute in-hospital serum creatinine jump of at least 0.3 mg/dL, or a relative increase of 50% or more. AKI incidence rose inexorably from 10 per 1000 person-years in 1986 to a peak of 62 per 1000 person-years in 1995, the year before wide cART use. AKI incidence then fell to 30 per 1000 person-years in 1999 but remained around that mark through 2006. Dialysis-requiring AKI rose from 2 per 1000 person-years in 1986 to more than 7 per 1000 in 1989, then fell back to 2 per 1000 in 1999. From that point, dialysis-requiring AKI climbed to 3.5 per 1000 person-years in 2006.

Analysis of 4509 HIV-positive and 1746 HIV-negative African Americans in Baltimore calculated standardized incidence ratios (SIRs) to compare rates of renal replacement therapy (dialysis or kidney transplant) with rates in people the same age and race in the general population.³⁰ Follow-up from 1998 through 2004 spanned the dawn of the cART era.

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continued from **page 11****Table 2.** CKD* incidence in 5 prospective cohorts in the current cART era

Author	Location	Years	Number	Incidence*	Risk factors
Li ²⁹	US veterans	1984-2007	56,823; in those with AKI: mean age 42.7, 98.6% men, 20% white, 38% black, 42% other, 6.6% HCV, 11.8% HTN, 4.5% DM	AKI peak 62 per 1000 p-y in 1985, decline to 25 per 1000 p-y in 2006	Black race, HTN, diabetes, dyslipidemia, cardiovascular disease, HCV, CD4 count below 350 vs above 500, viral load above 30,000 vs below 500, body mass index below 18.5 vs 18.5 to 25.0, albumin below 3 mg/dL, eGFR below 60 mL/min†
Lucas ³⁰	Baltimore	1998-2004	4509 with HIV, 1746 without HIV, median age 37, 68% men, all black, 70% IDU, 54% HCV	5.8 per 1000 p-y before cART, 9.7 per 1000 p-y with cART	AIDS
Roe ³¹	London	1998-2005	2274, mean age 34.6, 62% men, 58% black, 9.6% HCV, 6% IDU	19.3 per 100 p-y in first 3 m of HIV care, 1.1 per 100 p-y in later HIV care	<i>For acute renal failure in first 3 m of HIV care:</i> Nadir CD4s <100, AIDS <i>For acute renal failure in later HIV care:</i> Nadir CD4s <100, IDU, HCV
Franceschini ³²	North Carolina	2000-2002	754, mean age 40, 68% men, 61% black, 21% HCV, 17% HTN, 6% diabetes	5.9 per 100 p-y	CD4s <200, HIV RNA >10,000 copies/mL, AIDS, cART use, male gender, HCV, drug toxicity

Author	Location	Years	Number	Incidence*	Risk factors
Bickel ³³	Frankfurt	1989-2010	9198, mean age 36.5 to 42.7 across 3 study periods, 78% men, 89% white, HCV 9.3% to 14.4% across 3 study periods, IDU 23.1% to 11.9% across 3 study periods	<i>Whites:</i> 29.9, 41.0, 43.4 per 100,000 p-y in 1989-1996, 1997-2003, 2004-2010 <i>Blacks:</i> 788.8, 130.5, 164.1 per 100,000 p-y in same 3 periods	Black race, IDU

* Calculated for acute kidney injury (AKI) by Li,²⁹ for renal replacement therapy by Lucas,³⁰ for acute renal failure by Roe,³¹ for acute renal failure by Franceschini,³² and for ESRD and dialysis by Bickel.³³ See text for further details.

† Calculated for AKI, not for AKI requiring dialysis.

aIRR, adjusted incidence rate ratio; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HTN, hypertension; IDU, injection drug use.

SIRs were 2.3 for HIV-negative people, 6.9 for HIV-positive people without AIDS, and 16.1 for people with AIDS. Incidence of renal replacement therapy measured 5.8 per 1000 person-years before cART and 9.7 per 1000 person-years with cART. The higher rate in the cART era—meaning 1 of 100 people in this cohort needed renal replacement therapy every year—did not differ significantly from the pre-cART rate. CKD prevalence in the cohort rose over time, reflecting longer survival after cART arrived.

A London study covering a similar period, 1998 through 2005, charted more than a 10-fold lower acute renal failure incidence among HIV-positive people in care for at least 3 months compared with those in the first 3 months of HIV care.³¹ Defining acute renal failure as a rapid but usually reversible drop in eGFR, a King's College Hospital team ana-

lyzed 2274 people receiving HIV care. Age averaged only 34.6 years, 58% were black, 6% had injected drugs, and 67% took cART. During the study period acute renal failure developed in 130 people (5.7%).

Incidence measured 19.3 per 100 person-years in people in the first 3 months of HIV care and 1.1 per 100 in people seen longer than 3 months—nearly the same incidence measured in the all-black Baltimore group in the cART era.³⁰ Multivariate analysis identified two independent risk factors for acute renal failure in the under-3-month group (nadir CD4 count below 100 cells/mm³ and AIDS) and three risk factors in the over-3-month group (nadir CD4 count below 100 cells/mm³, injection drug use, and HCV coinfection.)

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continued from **page 13**

A 2000-2002 study of 754 HIV-positive adults in care at the University of North Carolina HIV clinic identified acute renal failure (defined by rising creatinine or chart review) in 71 people (9.4%).³² The group was young, averaging 40 years in age, 68% were men, and 61% were black. Acute renal failure incidence measured 5.9 per 100 person-years, much higher than rates of renal replacement therapy seen before and after cART arrived in the Baltimore study,³⁰ and much higher than acute renal failure incidence after 3 months of HIV care in London.³¹

As in the Baltimore³⁰ and London³¹ cohorts, poor HIV control raised chances of acute renal failure in the North Carolina group³²—specifically a CD4 count below 200 cells/mm³ and a viral load above 10,000 copies/mL. Acute renal failure was more common in men, people with AIDS or HCV infection, and people taking cART (probably indicating more advanced HIV disease). Half of the cases could be attributed to systemic infections, and three quarters of those infections were AIDS-related. Drugs caused one third of acute kidney injuries, and those drugs included indinavir or tenofovir, antibiotics (beta-lactams and aminoglycosides), radiocontrast agents, nonsteroidal antiinflammatory drugs, and lithium.

The largest and longest single-center study of end-stage renal disease involved 9198 people with HIV seen at Goethe University in Frankfurt from 1989 through 2010.³³ Three quarters (78%) of these people were men and 89% were Caucasian. The researchers considered ESRD incidence and prevalence in three periods: 1989-1996 (pre-cART), 1997-2003 (early cART), and 2004-2010 (late cART).

ESRD incidence rose across the three periods in Caucasian patients, from 29.9 to 41.0 to 43.4 per

100,000 person-years. Incidence was much higher in black patients but fell from the pre-cART era (788.8 per 100,000 person-years) to the two cART periods (130.5 and 164.1 per 100,000 person-years). All of these rates, when refigured per 100 person-years, are much lower than in the VA, Baltimore, London, and North Carolina studies.²⁹⁻³² ESRD prevalence rose over time as more people survived longer, but people with ESRD had 10-fold higher mortality than people without ESRD (relative risk 9.9, 95% CI 6.3 to 14.5, $P < 0.0001$).

Widely differing incidence of ESRD or acute renal failure in the five studies defies easy explanation. Incidence was higher in the VA cohort than in the other groups, a finding perhaps partly explained by older age in the VA patients.²⁹ The VA groups with and without AKI averaged 42.7 and 43.5 years in age, slightly older than the North Carolina group and much older than the Baltimore, London, and Frankfurt groups; and older age certainly heightens renal disease risk. Only 20% in the VA cohort were white, a much lower proportion than in London, North Carolina, or Hamburg. But everyone in the Baltimore group was black.

Yet other classical risk factors were not highly prevalent in the VA cohort (**Table 2**), and even after cART arrived in 1996, AKI incidence remained much higher than in the other cohorts. These investigators stressed that their findings conform to results of the other studies showing that AKI incidence has not continued to drop in the cART era. They speculate that this intransigence “might indicate possible increasing severity of underlying CKD, and may also reflect the lowered threshold for dialysis in the general population.”²⁹

The single-center study cohorts³⁰⁻³³ were largely similar in age, but the US and London studies included much higher proportions of blacks than the Frankfurt study—100% in Baltimore, about 60% in London and North Carolina, and 11% in Frankfurt. The Frankfurt group had a much lower proportion of IDUs than the Baltimore group but not the London group (**Table 2**). The North Carolina researchers did not report IDU status. HCV rates were similar in Frankfurt and London at about 9%, higher in North Carolina at 21%, and highest in Baltimore at 54%.

Despite the lower ESRD incidence in Frankfurt than in the other cohorts, the Frankfurt researchers noted that ESRD incidence among people with HIV in the late-cART period (2004-2010) remained twice higher than in HIV-negative people in Germany. And HIV-positive people were more than 25 years younger at ESRD diagnosis than people in the general German population (42.3 versus 70 years).

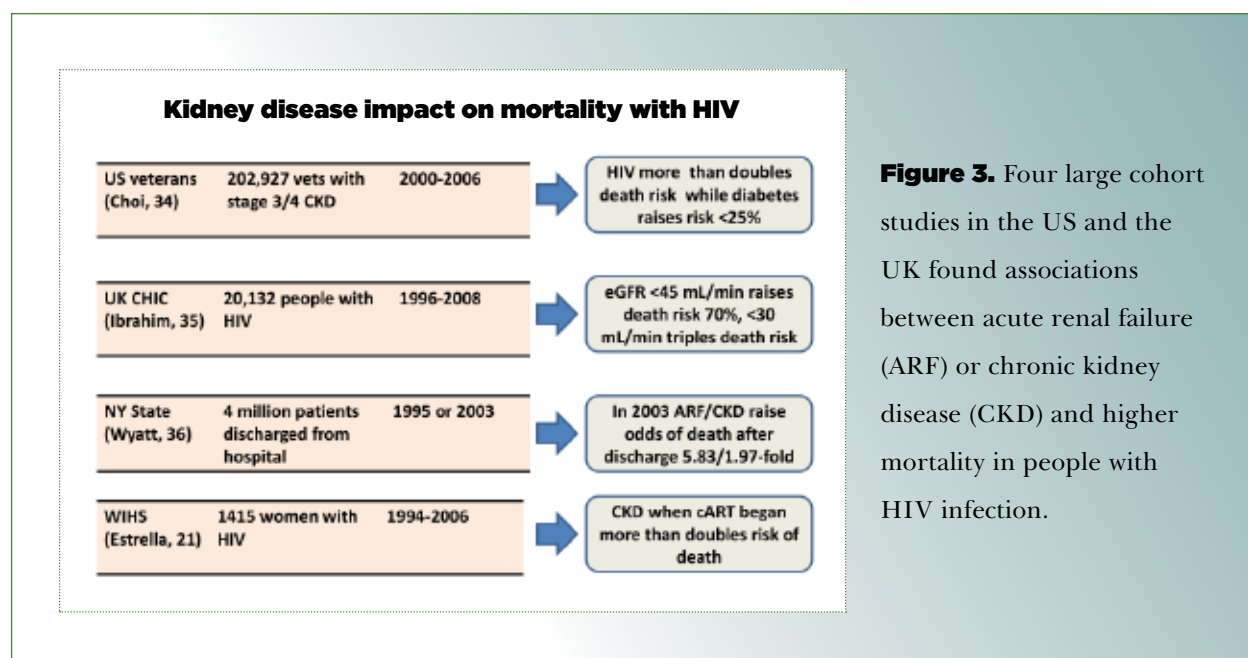
If an exercise in teasing out reasons for differing kidney failure incidence fails to yield clear answers,

the studies are more concordant in pinpointing risk factors. The two US studies and the London study all identified more advanced HIV infection—defined various ways—as an independent risk factor. The Frankfurt study did not identify AIDS as an independent ESRD risk factor, though a marginally higher proportion of people with than without ESRD had AIDS (43.6% versus 30.1%, $P = 0.095$). Both the Frankfurt and London studies identified injection drug use as an independent predictor of kidney failure.

CKD impact on mortality in HIV populations

Strong evidence—though not unanimous evidence—from the United States and the United Kingdom indicates that CKD boosts the risk of death among people with HIV in analyses adjusted for other risks.

The largest mortality study, published in 2007, involved a national sample of 202,927 US veterans with stage 3 or 4 CKD, including 534 (0.3%) with HIV and 88,340 (43.5%) with diabetes (**Figure 3**).³⁴ Through



continued from **page 15**

a median follow-up of 3.8 years between 2000 and 2006, HIV infection conferred more than a doubled risk of death in both white veterans (adjusted hazard ratio [aHR] 2.21, 95% confidence interval [CI] 1.57 to 3.13) and black veterans (aHR 2.32, 95% CI 1.70 to 3.18) in an analysis adjusted for age, baseline eGFR, hypertension, and other risk factors. These heightened death risks easily surpassed the greater death risk conferred by diabetes for whites (aHR 1.23, 95% CI 1.21 to 1.26) or blacks (aHR 1.06, 95% CI 1.00 to 1.12). Only about 20% of these people started cART before they entered the cohort.

A UK CHIC cohort analysis of 20,132 HIV-positive people found that 1820 of them died during a median follow-up of 5.3 years through December 2008.³⁵ About 80% of these people had started cART. Compared with people whose baseline eGFR lay between 90 and 104 mL/min, those with a baseline eGFR from 45 to 59 mL/min had a one third higher risk of death from any cause in an association that stopped short of statistical significance (aHR 1.34, 95% CI 0.95 to 1.89, $P = 0.09$). People with a baseline eGFR between 30 and 44 mL/min had a 70% higher death risk (aHR 1.70, 95% CI 1.06 to 2.72, $P = 0.03$). And those with a baseline eGFR below 30 mL/min had a tripled risk of death (aHR 3.08, 95% CI 1.94 to 4.88, $P < 0.001$). The UK CHIC team recommended that HIV-positive people with an eGFR between 30 and 59 mL/min “should be investigated, monitored carefully, and considered for targeted interventions to slow the decrease in kidney function.”³⁵

A 4-million patient study of adults discharged from New York State acute care hospitals in 1995 (before cART) or 2003 (during cART era) charted a higher incidence of acute renal failure among HIV-positive

people both pre-cART (adjusted odds ratio [aOR] 4.62, 95% CI 4.30 to 4.95) and during cART (aOR 2.82, 95% CI 2.66 to 2.99).³⁶ During the cART era, acute renal failure more than quintupled odds of death in people with HIV (aOR 5.83, 95% CI 5.11 to 6.65). CKD doubled chances of death in this analysis (aOR 1.97, 95% CI 2.45).

A US Women’s Interagency HIV Study (WIHS) analysis of 1415 women starting cART up to the end of 2006 found that those with CKD when starting treatment had more than a doubled risk of death (aHR 2.23, 95% CI 1.45 to 3.43) in an analysis adjusted for age, race, HCV status, AIDS, and CD4 count.²¹ When the analysis also adjusted for hypertension and diabetes, CKD no longer independently predicted death (aHR 1.89, 95% CI 0.94 to 3.80). Among women without AIDS when they started cART, every 20% lower eGFR when treatment began boosted the death risk almost 10% in a borderline-significant association (aHR 1.09, 95% CI 1.00 to 1.19).

Not every study confirms an association between kidney disease and death in people with HIV. A US single-center observational study involved 2127 HIV-positive people with or without CKD seen in 1998-2005.³⁷ More than a third of this Nashville group (38%) was taking cART, and 3% had CKD at their baseline visit. During a median follow-up of 2.1 years, AIDS developed in 227 people (11%) and 80 (4%) died. Statistical analysis adjusted for sex, race, age, kidney function level, and several HIV variables found no link between CKD and AIDS or death (aHR 1.3, 95% CI 0.5 to 3.2), AIDS alone (aHR 1.0, 95% CI 0.4 to 3.1), or death alone (aHR 1.6, 95% CI 0.4 to 3.1).

Why did this analysis find no link between CKD and death when several others did? The study is smaller, took place at a single center, and has shorter follow-up than the others, and the researchers adjusted the analysis for a great many variables (besides those already listed, anemia, cART use, HCV, cardiovascular disease, ACEI/ARB use, diabetes, injection drug use, HIV risk, and albumin at baseline).³⁷ Clinically relevant associations may sometimes be “adjusted away” by analyses awash in variables. Or perhaps CKD management or overall care was better at this center than for patients in the other cohorts studied.

CKD and cardiovascular disease risk

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Given the profound impact of kidney disease on mortality in people with HIV, it is no surprise that poor kidney function also bolsters the risk of major killers—like cardiovascular disease. A study of 17,325 HIV-positive US veterans discharged from their first hospital stay in 1986-2006 analyzed associations between acute kidney injury and cardiovascular endpoints, ESRD, and death starting 90 days after discharge.³⁸

Researchers typically define acute kidney injury, sometimes called acute renal failure, as a rapid drop in kidney function coupled with increased creatinine or dropping urine output. In this national sample, 2453 veterans had stage 1 acute kidney injury, 273 had stage 2 or 3, and 334 had dialysis-requiring acute kidney injury. All told, 1 in 6 of these hospitalized veterans had acute kidney injury. Follow-up averaged 5.7 years.

Multivariable analysis adjusted for age, sex, race, comorbid conditions, HIV variables, eGFR, and other factors determined that stage 2 or 3 acute kidney injury and dialysis-requiring injury each independently raised the risk of heart failure and ESRD (for

heart failure: HR 2.11, 95% CI 1.07 to 4.16 for stage 2-3; HR 4.20, 95% CI 2.24 to 7.88 for dialysis). Dialysis-requiring kidney injury independently doubled chances of cardiovascular disease (aHR 1.96, 95% CI 1.14 to 3.38). Stage 1 acute kidney injury, stage 2 or 3 injury, and dialysis-requiring injury each independently raised the risk of death (HRs 1.20, 95% CI 1.13 to 1.28; 1.18, 95% CI 1.00 to 1.41; 1.73, 95% CI 1.49 to 2.01).

A study of 7828 HIV-positive men seen at three London clinics between January 2004 and December 2009 recorded 32 coronary heart disease (CHD) diagnoses in 28 people for an incidence of 1.2 per 1000 person-years.³⁹ Adjusted analysis linked eGFR below 75 mL/min to more than a quadrupled risk of CHD (aIRR 4.30, 95% CI 1.33 to 14.5). Older age and HCV infection also boosted CHD risk.

A case-control study at Baltimore's Johns Hopkins HIV Clinic involved 63 people with a cardiovascular diagnosis between 1998 and 2008 and 252 controls without heart disease matched for sex, race, and age.⁴⁰ People with a cardiovascular diagnosis had a significantly lower eGFR than controls (68.4 versus 103.2 mL/min, $P < 0.001$). Multivariate analysis determined that every 10-mL/min lower eGFR hoisted chances of a cardiovascular event 20% (aOR 1.20, 95% CI 1.1 to 1.4). Depending on the formula used to calculate eGFR, a level below 60 mL/min was independently associated with 5 to 6 times higher odds of a cardiovascular diagnosis compared with an eGFR above 90 mL/min. Proteinuria also independently predicted a cardiovascular event. The Hopkins team believes their findings “suggest the potential value of early screening and treatment of CKD in HIV-1-infected patients, particularly those with other cardiovascular risk factors.”⁴⁰ Another re-

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continued from **page 17**

view article in this issue outlines current thinking on CKD screening in people with HIV.

Because of heightened cardiovascular disease risk with CKD and HIV, Icahn/Mount Sinai HIV/kidney

experts advise that “diagnosis of CKD [in people with HIV] should prompt consideration of cardiovascular risk modification, with the caveat that no studies have been performed to evaluate the impact of risk modification in this population.”⁴¹

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CKD screening and referring, plus insights on TDF and TAF

An interview with **Christina M. Wyatt, MD**

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CKD screening and referring pointers

Mascolini: What are the chronic kidney disease (CKD) screening basics clinicians should know for people with HIV?

Wyatt: I think what most clinicians do in routine practice in terms of creatinine and eGFR [estimated glomerular filtration rate] screening probably exceeds what the 2014 HIV/kidney guidelines recommend.¹ The guidelines advise screening HIV-positive

patients for chronic kidney disease at least annually. But most HIV patients engaged in care are probably getting quarterly chemistries.

The additional screening measure probably not routinely done in practice is some form of testing for urine protein. I suspect that for most diabetics clinicians are following the ADA [American Diabetes Association] guidelines, screening for microalbumin² at least once a year. For the remaining patients with HIV, current HIV guidelines recommend screening

at least once for proteinuria, at the time of HIV diagnosis.¹ Any patient with a CKD risk factor besides HIV—such as diabetes, hypertension, lupus, or black race—should have some form of screening for urine protein at least annually.

What should that screening be? The HIVMA panel did not reach a firm consensus on that question.¹ Although data clearly show more precise and sensitive results with urine protein-to-creatinine ratio screening rather than dipstick urine protein, for cost-benefit reasons a dipstick is probably a reasonable screening test for now.

Mascolini: Which CKD patients can HIV clinicians manage on their own, and which should they refer to a nephrologist?

Wyatt: Any patient in whom there's not a clear diagnosis—and you could make a case that that's *anybody*—should be referred. Certainly patients who've got proteinuria and an unclear diagnosis should see a nephrologist. With a diabetic patient who has proteinuria and retinopathy, the primary care physician can decide whether to refer.

But for a nondiabetic patient with HIV and proteinuria, I think the differential in patients with protein in their urine is broad enough that it's reasonable to consider referring that patient early for diagnostic purposes. That patient might have hepatitis C-related disease that might respond to less toxic new therapies; or that patient could have primary kidney disease that has nothing to do with their HIV status; or a patient of African descent who is not completely virologically suppressed could have HIV-related kidney disease. So I think most HIV patients with proteinuria should probably be referred.

Patients who have rapidly progressing kidney dysfunction—someone with rising creatinine at every quarterly visit—to me that's another patient who should be sent to a nephrologist because the nephrologist may identify some treatable disease. Certainly there is a spectrum of treatable diseases that can be managed if you diagnose them.

If patients were not seen by a nephrologist early for diagnosis—or if they were seen and a diagnosis was made—sometimes it's not essential to continue seeing a nephrologist. For example, if that patient has stage 3 kidney disease with a little proteinuria, and if that patient is taking an ACE inhibitor or an angiotensin-receptor blocker and the HIV clinician feels comfortable managing high blood pressure, diabetes, or other risk factors—that patient may not need to return to a nephrologist as long as kidney function is stable.

When should an HIV patient with kidney disease return to a nephrologist? Certainly any patient who's got stage 4 kidney disease—somebody with a GFR below 30 mL/min—should see a nephrologist to start talking about end-stage renal disease (ESRD) planning. Not all those patients will reach ESRD. We know from the general population that patients with stage 4 kidney disease are more likely to die of cardiovascular disease than they are to reach ESRD; but certainly a considerable proportion of them will reach ESRD. We get much better outcomes if they know what they want to do before progressing to ESRD, and if they're going to need hemodialysis it's better to have a fistula in place when they're ready to start.

Mascolini: In your experience talking to HIV clinicians, what are the main gaps in their understanding of diagnosing and managing CKD?

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Wyatt: I recently spoke to a group of HIV clinicians who were given a pretest before my talk. I was surprised by the proportion of clinicians in active practice who misdiagnosed HIVAN [HIV-associated nephropathy] or were under the impression that it is still very common.³ I think HIVAN is a disease we all need to be aware of because we still see it, and when we see HIVAN it is usually treatable. But at this point the treatment is probably not different from what you should be doing in that patient anyway. I think there may be a misconception that more kidney disease in HIV patients is from HIV itself or from its treatment rather than from comorbidities that develop as patients get older.

Mascolini: When you say the care that HIVAN patients should be getting anyway, you mean . . .

Wyatt: . . . putting them on antiretroviral therapy. Even if there were no trend toward treating everyone with HIV, these are the patients who would have firm indications to start therapy apart from HIVAN.

Prescribing and monitoring TDF and TAF

Mascolini: Are there kidney markers or other variables that should make clinicians steer clear of tenofovir?

Wyatt: So far the data have not suggested that a patient with established chronic kidney disease—say someone with diabetic nephropathy—is necessarily at higher risk of tenofovir toxicity than someone who has normal kidney function, as long as the drug is dosed appropriately.

I think the challenge in those patients is not so much that we think they're at increased risk, but that it becomes a little harder to monitor them. If you have a patient who's got diabetic nephropathy, a little proteinuria, and occasionally some glucosuria⁴ because of intermittently uncontrolled diabetes, that might be a patient whose monitoring is going to be challenging, although their risk of tenofovir toxicity is not increased. A clinician caring for that patient should know what they're going to do if this patient's proteinuria increases or they suddenly have glucosuria all the time. In those cases you have to plan management on a case-by-case basis.

In general, I think it's almost always reasonable to start tenofovir in someone who hasn't already had an adverse reaction to tenofovir or related drugs. If someone was in an adefovir trial before and they had Fanconi syndrome,⁵ I would avoid giving tenofovir to that patient. If they were treated with tenofovir before and had classic evidence of tenofovir toxicity, I would hesitate to rechallenge that patient.

But in the average patient, the most important thing is to know the renal baseline. Get a baseline urinalysis so you know if that patient has underlying proteinuria or glucosuria or any other evidence of renal impairment. You have to be careful dosing tenofovir and other renally excreted drugs in anyone with reduced kidney function (**Table 1**). And you have to think hard about risks and benefits, particularly for patients who are close to dose-reduction thresholds. They can be challenging.

Table 1. Renal dose adjustments for tenofovir and Truvada (tenofovir/emtricitabine)

	Tenofovir (TDF)	Truvada (TDF/FTC)
Usual dose	300 mg daily	300/200 mg daily
Creatinine clearance		
≥50 mL/min	No adjustment	No adjustment
30 to 49 mL/min	300 mg every 2 days	300/200 mg every 2 days
<30 mL/min		Do not use combination tablet
10 to 29 mL/min	300 mg every 3 to 4 days	
With hemodialysis	300 mg every 7 days*	
With peritoneal hemodialysis	Unknown, use with caution, reduce dose	

* Additional dose may be needed if more than 12 h hemodialysis weekly.

Source: Lucas GM, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 Update by the HIV Medicine Association of the Infectious Diseases Society of America.¹

See Tables 6 and 7 of 2014 HIVMA guidelines for other antiretroviral and nonantiretroviral dose adjustments.¹

Mascolini: Do you monitor people taking tenofovir differently for renal function than people not taking tenofovir?

Wyatt: The guidelines suggest that you monitor them more often, but the guidelines assume a bare minimum of monitoring for patients who are not on tenofovir.¹ If clinicians are doing quarterly renal monitoring, that's certainly adequate. I don't think you need to get a urinalysis at every visit, although some nephrologists in the HIV community might believe you do. I think it's not totally straightforward. I certainly would follow up any abnormal creatinine with a confirmatory test and urine testing as well.

Mascolini: Have you seen enough data on TAF (tenofovir alafenamide fumarate) to decide whether it poses a lower kidney risk than TDF (tenofovir disoproxil fumarate)?

Wyatt: Based on what we think we know about why tenofovir causes kidney injury, it makes sense that TAF might pose a lower risk. We think the mechanism of tenofovir kidney toxicity involves accumulation of higher levels of the active metabolite of tenofovir inside proximal renal tubular cells. As a result they become sensitive to injury, potentially mitochondrial injury. Presumably that accumulation is a result of high plasma levels of the active drug, and we know

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that TAF results in much lower levels of active drug in the blood than TDF does.^{6,7} On that basis it makes sense that TAF would have less renal toxicity. Certainly the phase 2 studies⁸ and what we know so far about the phase 3 trials would be consistent with that. There may be a small differential effect in favor of TAF over TDF for both kidney and bone toxicity.

I think the proof is in the pudding in terms of whether what we see in randomized trials turns out to be true in clinical practice. We know that TDF did not have a renal safety signal at all in clinical trials. So at least for now I would consider TAF the same as TDF in terms of monitoring. And if I was going to consider not starting a patient on TDF, I would consider TAF with the same level of vigilance, with the expectation that it's going to be safer. But I think that until we know for sure we should consider TAF use and monitoring carefully.

Consulting a pharmacologist on renally excreted drugs

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Mascolini: Many antiretrovirals and other drugs are eliminated via the kidney. Should HIV clinicians consult a pharmacologist to review possible dose adjustments in people with declining kidney function?

Wyatt: I think that depends on the clinician's comfort with GFR estimates and with the medications they're using. If a patient is on a group of drugs that are not cleared by the kidney or if the clinician is familiar and comfortable with the HIV drugs prescribed, then I don't think it's necessary to consult a pharmacologist.

At the same time, I can certainly think of a lot of cases where consultation would be helpful, particularly for patients who are very close to dose-adjustment thresholds, with a Cockcroft-Gault creatinine clearance of 55 mL/min, for example, and who are taking multiple drugs that are renally eliminated. In a case like that consulting a pharmacologist might be worthwhile. We know that GFR estimates are not perfect.

In a case like the one I just described, prescribers need to consider the therapeutic window of the drug—the range between the minimum effective concentration and maximum tolerated concentration. If the drug has a wide therapeutic window, then you can probably give it at the higher dose. If the drug has a narrow therapeutic window and you're worried about toxicity, then the question becomes whether you should recalculate creatinine clearance and recalculate GFR by another method. If there's evidence of an overestimate or underestimate of kidney function, you can adjust the dose accordingly. So I think the need to consult a pharmacologist varies from patient to patient, but there certainly are cases where it would be valuable.

Mascolini: Are there any other points you would like to make that you think HIV clinicians should consider concerning kidney disease in people with HIV?

Wyatt: One thing I like to mention when I'm talking about tenofovir is that, until we know how safe it is in healthy people, when healthy HIV-negative people take tenofovir as PrEP, the same monitoring guidelines should apply.

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Classic and HIV-specific risk factors for kidney disease

By Mark Mascolini

Abstract: Several variables that heighten kidney disease risk in the general population are highly prevalent in HIV populations, including diabetes, hypertension, HCV infection, and smoking. Blacks run a higher risk of kidney disease than whites. As people with HIV live longer thanks to antiretroviral therapy, older age confers an ever-increasing kidney disease risk. Tenofovir and the obsolete protease inhibitor indinavir threaten the kidney. To lesser extents, ritonavir, atazanavir, and lopinavir/ritonavir have been tied to kidney disease risk. There is no question, though, that the higher CD4 counts and lower viral loads that come with successful antiretroviral therapy ease the risk of kidney trouble.

Risk factors for kidney disease in people with HIV mirror those in the general population: black race, diabetes, hypertension, HCV infection, and smoking. HIV clinicians will immediately recognize that all these risk factors are more common in people with than without HIV in the United States. Further complicating the renal risk picture, people with HIV typically take more drugs than HIV-negative people—and several key antiretrovirals and drugs for comorbidities buffet the kidney. HIV infection itself threatens the kidneys, and poorly controlled HIV

infection compounds the threat. Finally, older age weakens the kidneys, an important concern as people with HIV survive into their 60s and beyond.

A 2012 systematic review and meta-analysis of 23 studies confirm the impact of the higher kidney disease prevalence and incidence in HIV populations cataloged in the first article in this issue of RITA!¹ Compared with HIV-negative populations, people with HIV have almost a quadrupled risk of renal disease (relative risk [RR] 3.87, 95% confidence interval [CI] 2.85 to 6.85). This article reviews classic and HIV-related risk factors that drive the higher kidney disease risk in people with HIV. Except for age, race, and family history of kidney disease, all these risk factors can be prevented or modified.

Older age: the risk factor everyone wants

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In the general population, people over 60 years old have a 20% to 30% lower glomerular filtration rate (GFR) than people younger than 50.² HIV/kidney experts at New York's Icahn School of Medicine at Mount Sinai note that as HIV populations age thanks to combination antiretroviral therapy (cART), risk of acute and chronic kidney disease (CKD) grows apace, and they offer a practical review of the interactions between HIV infection, age, and renal impairment.³

Cohort studies in France and the United States found a similar impact of age on CKD despite a great difference in the racial composition of these two HIV cohorts—fewer than 10% black in the French Aquitaine cohort⁴ and 78% black in Baltimore’s Johns Hopkins cohort.⁵ In France 45- to 60-year-olds with HIV had a 70% higher CKD incidence than people under 45, and people older than 60 had more than a doubled CKD incidence (**Figure 1**). In Baltimore 45- to 55-year-olds had a 45% higher CKD incidence than people under 45, and those older than 55 had more than a tripled risk (**Figure 1**).

Other notable age-related findings on renal disease emerged from a large meta-analysis and big prospective cohorts in Italy and Germany:

— In a 23-study meta-analysis of people with HIV, every 10 years of age raised renal disease risk by half (RR 1.54, 95% CI 1.16 to 2.05).¹

— In a case-control comparison of 2854 HIV-positive people in Italy and 8562 HIV-negative controls, HIV-positive people 51 to 60 years old had a significantly higher CKD prevalence than age-, sex-, and race-matched controls (5.2% versus 0.29%, $P < 0.001$), as did HIV-positive people older than 60 (24.3% versus 0.49%, $P < 0.001$).⁶

— In a study of 9198 people in the Frankfurt HIV Cohort, incidence of end-stage renal disease (ESRD)

remained twice higher than in the general population in the most recent study period (2004-2010).⁷ People with HIV were more than 25 years younger when diagnosed with ESRD than were people in the general German population (42.3 versus 70 years).

But a Veterans Aging Cohort Study comparison of 31,139 people with HIV and 68,113 without HIV found that ESRD did not develop at an earlier age in the HIV group, although ESRD incidence was higher with than without HIV (adjusted incidence rate ratio [aIRR] 1.43, 95% CI 1.22 to 1.65).⁸ And HIV-positive

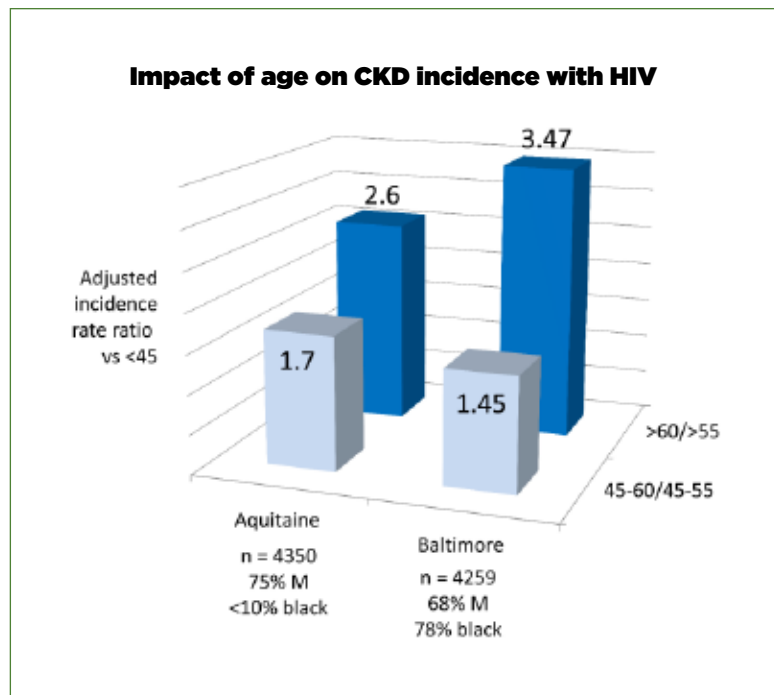


Figure 1. Despite a difference in racial make-up in two large HIV cohorts, older age had a similar impact on CKD incidence in France⁴ (45 to 60 and over 60 versus under 45) and the United States⁵ (45 to 55 and over 55 versus under 45).

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people 60 or older in the CDC Medical Monitoring Project cohort did not have higher CDK prevalence than age-matched HIV-negative controls in the National Health and Nutrition Examination Survey.⁹ The CDC team cautioned that this lack of difference in CKD prevalence among older adults with and without HIV could reflect premature death among HIV-positive people with CKD.

Black race: high risk outlives HIVAN

In 2010 blacks made up 12% of the US population but accounted for 44% of all new HIV infections.¹⁰ Black women contribute to this disparity. The CDC estimates that 5300 black heterosexual women got HIV infection in 2010, 4 times the rate in white heterosexual women.¹⁰

In 1984 emergence of HIV-associated nephropathy (HIVAN) in African Americans and Haitians with AIDS made it clear that this immunodeficiency syndrome did not spare the kidneys.¹¹ Although cART profoundly minimized the HIVAN threat, blacks continue to run a higher risk of kidney disease than whites, partly because of single-nucleotide polymorphisms in the apolipoprotein L1 gene that arise in West Africans more than in people from other regions.¹² In the mid-2000s, for example, the US Renal Data System figured that HIV-positive blacks ran about a 50% higher risk of ESRD than HIV-positive whites.¹³ This same analysis determined that African-American men between 25 and 44 account for 40% of HIV-positive people receiving renal replacement therapy (dialysis or transplant) yet make up only 2% of the US population.

Why HIV-positive African Americans in the cART era reach ESRD so much more often than whites with HIV remained poorly understood until a comparison of 3332 blacks and 927 whites with HIV at

Johns Hopkins University in Baltimore.⁵ The Hopkins team asked whether CDK incidence is greater among HIV-positive blacks than whites, whether progression rates are faster in blacks, or whether both factors play a role.

Through an average follow-up of 4.5 years from 1990 through 2004, CKD developed in 284 people—253 blacks (7.6%) and 31 whites (3.3%).⁵ Kaplan-Meier analysis determined that blacks had almost a twice higher CKD incidence than whites (hazard ratio [HR] 1.9, 95% CI 1.2 to 2.8). After statistical adjustment for age, sex, AIDS status, injection drug use, and calendar period, the higher CKD rate in blacks diminished to a marginally significant 1.65 (95% CI 1.00 to 2.71). But progression from CKD proved almost 18 times more frequent in blacks than whites (HR 17.7, 95% CI 2.5 to 127.0). This accelerated progression in blacks reflected a 6 times more rapid fall in GFR after CKD diagnosis in blacks than whites.

The Hopkins team proposed that “African American-white disparities in HIV-related ESRD are explained predominantly by a more aggressive natural disease history in African Americans and less by racial differences in CKD incidence.”⁵ The authors noted that HIVAN accounted for a portion of the excess progression risk in blacks, but progression risk also proved higher in blacks with non-HIVAN histopathology than in whites. They cited evidence of faster progression from CKD to ESRD in blacks versus whites in the general US population¹⁴ and suggested that “genetic susceptibility to kidney failure has been hypothesized on the basis of familial clustering of ESRD, in several settings.”¹⁵⁻¹⁷

A 2000-2001 study of more than 2 million US veterans with a median 3.7 years of follow-up confirmed faster progression to ESRD in blacks than whites with HIV.¹⁸ The cohort included 15,135 veterans with HIV

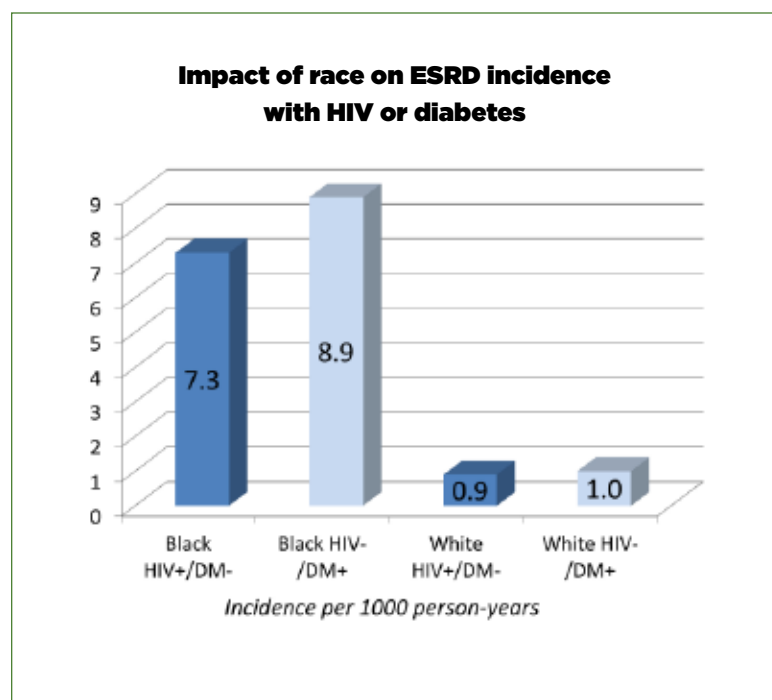


Figure 2. In a study 2,015,891 US veterans with or without HIV and with or without diabetes mellitus (**DM**), black veterans with HIV and without diabetes had a 7 times higher age- and sex-adjusted incidence of end-stage renal disease (**ESRD**) than whites with HIV and without diabetes or whites with diabetes and without HIV.¹⁸

(0.8%) and 594,430 with diabetes (29.5%). Age- and sex-adjusted ESRD incidence was similar in blacks with HIV and without diabetes and in blacks without HIV and with diabetes (**Figure 2**). ESRD incidence among blacks with HIV and without diabetes was more than 7 times higher than incidence in whites with HIV and without diabetes or in whites without HIV but with diabetes (**Figure 2**). HIV did not boost ESRD incidence among whites, but HIV more than quadrupled ESRD risk in blacks (HR 4.56, 95% CI 3.44 to 6.05).

Other cohort studies in the United States and Europe largely support findings in the Baltimore and veterans studies:^{5,18}

— A prospective study of 56,823 HIV-positive veterans determined that black race raises risk of acute kidney injury 20% compared with white race (HR 1.22, 95% CI 1.14 to 1.29)¹⁹

— A single-center study of 2468 HIV-positive people in Nashville determined that blacks did not have a statistically significant difference in risk of estimated glomerular filtration rate (eGFR) decline than non-blacks.²⁰ But blacks had a significantly higher risk of ESRD and tended to have a higher risk of death.

— A study of 21,951 HIV-positive people in the UK CHIC cohort found that prevalence of ESRD rose among blacks from 0.26% in 1998-1999 to 0.92% in 2006-2007 ($P = 0.001$).²¹ Black race boosted the risk of ESRD 7 times (HR 6.93, 95% CI 3.56 to 13.48)—a risk similar to that found in the US veterans study.¹⁸

— A more recent UK CHIC analysis of 20,132 people with HIV figured that blacks had almost a tripled risk of progression to stage 4 or 5 CKD compared with whites and others (rate ratio 2.8, 95% CI 1.6 to 4.8).²²

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Troublesome triad: diabetes, hypertension, HCV

Among comorbid diseases, diabetes, hypertension, and HCV infection all pose a substantial threat to the kidneys. And all three diseases disproportionately affect people with HIV. US Health Resources and Services Administration (HRSA) HIV care guidelines note that people with HIV run a 4-fold higher risk of diabetes and a 3-fold higher risk of hypertension than HIV-negative individuals.²³ Chronic HCV infection affects 30% to 40% of HIV-positive people in the

United States,²³ and HCV rates among HIV-positive injection drug users range from 50% to 90%.²⁴

In the United States in 2011, diabetes accounted for 44% of new kidney failures and hypertension for 28%.²⁵ In other words nearly three quarters of kidney failures in 2011 could be traced to diabetes or hypertension. A 2008 systematic review and meta-analysis determined that HCV infection heightened the risk of CKD about 50% (relative risk 1.49, 95% CI 1.08 to 2.06).²⁶ **Tables 1** and **2** outline key findings on how diabetes and hypertension affect kidney disease risk.

Table 1. Impact of diabetes on kidney disease risk in people with HIV

Author	Location	Years	Number	Key findings*
Choi ¹⁸	US, veterans	2000-2001, median 3.7 y follow-up	2 million veterans, 0.8% with HIV, 29.5% with diabetes	<i>In blacks:</i> ESRD risk 4.56-fold higher with HIV alone, 4.15-fold higher with DM alone, 5.28-fold higher with HIV and DM† <i>In whites:</i> ESRD risk similar with and without HIV, 2.18-fold higher with DM alone,† 2.27-fold higher with HIV and DM†
Mcroft ²⁷	Europe, EuroSIDA	2004-2008, median 3.7 y follow-up	6843 with HIV	Progression to CKD 1.5-fold more likely with DM
Medapalli ²⁸	US, Veterans Aging Cohort Study	NR, median 5 y follow-up	31,072 with eGFR >45 mL/min, 34% with HIV alone, 16% with diabetes alone, 6% with both	Progression to eGFR <45 mL/min 2.48-fold higher with DM alone, 2.8-fold higher with HIV alone, 4.47-fold higher with HIV and DM
Li ¹⁹	US, veterans	1984-2007, median 5.1 y follow-up	56,823 with HIV	Risk of AKI‡ 1.22-fold higher with DM; risk of dialysis-requiring AKI 1.38-fold higher with DM in 1996-2006

* Only independent associations reported.

† Compared with whites without HIV or diabetes.

‡ In-hospital serum creatinine increase ≥ 0.3 mg/dL or a relative increase $\geq 50\%$.

AKI; acute kidney injury; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; NR, not reported.

Table 2. Impact of hypertension on kidney disease risk in people with HIV*

Author	Location	Years	Number	Key findings*
Mocroft ²⁷	Europe, EuroSIDA	2004-2008, median 3.7 y follow-up	6843 with HIV	Progression to CKD 1.69-fold more likely with HTN
Medapalli ²⁸	US, Veterans Aging Cohort Study	NR, median 5 y follow-up	31,072 with eGFR ≥ 45 mL/min, 34% with HIV alone, 16% with DM alone, 6% with both	Progression to eGFR < 45 mL/min 1.39-fold greater with HTN in HIV+, 1.59-fold higher with DM
Li ¹⁹	US, veterans	1984-2007, median 5.1 y follow-up	56,823 with HIV	Risk of AKI [†] 1.08-fold higher with HTN; risk of dialysis-requiring AKI 1.8-fold higher with HTN in 1996-2006

* Only independent associations reported.

[†] In-hospital serum creatinine increase ≥ 0.3 mg/dL or a relative increase $\geq 50\%$.

AKI, acute kidney injury; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension.

HCV infection ranks prominently in many analyses of kidney disease risk, but its impact on renal impairment remains a bit tougher to pin down than the impact of diabetes or hypertension. The strong associations between diabetes or hypertension and acute or chronic kidney disease can overwhelm potential associations between HCV and kidney disease if all factors are considered in the same analysis. Also, IDUs account for a high proportion of people with HCV/HIV coinfection, and IDUs shoulder an array of other comorbidities and risk behaviors that can muddy the specific impact of HCV on kidney disease.

For example, a 1994-2004 retrospective cross-sectional analysis of 13,139 people in care in Indianapolis (11% with HIV and 30% positive for HCV) determined that testing positive for HCV decreased risk

of CKD (adjusted odds ratio [aOR] 0.69, 95% CI 0.62 to 0.77) in an analysis controlling for diabetes, hypertension, age, aspartate aminotransferase, and HIV status.²⁹ Longitudinal analysis of 7038 people without CKD at their initial visit found no association between HCV positivity and incident CKD (adjusted hazard ratio [aHR] 0.896, 95% CI 0.79 to 1.015) in an analysis adjusted for age, baseline eGFR, diabetes, hypertension, aspartate aminotransferase, and HIV status. The authors noted that reasons for their findings are unclear “but may include decreased creatinine production from muscle wasting or altered creatinine metabolism due to liver disease such that the eGFR is artificially low in patients with hepatitis C.”²⁹

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On the other hand, numerous other large cohort studies and randomized trial analyses in North America, Europe, and Australia (outlined below) document strong and consistent associations between HCV and chronic or acute kidney disease. Notably, though, cleared HCV infection—indicated by undetectable HCV RNA—did not bolster kidney disease risk in some of these studies.

A 2008 meta-analysis of 27 randomized controlled trials and observational studies linked HCV to a significantly increased risk of incident CKD (RR 1.49, 95% CI 1.08 to 2.06) in people with HIV.²⁶ Risk of acute renal failure was about two thirds higher in people with than without HCV (RR 1.64, 95% CI 1.21 to 2.23).

Large cohort studies also confirm a link between HCV and kidney disease:

— A 2684-woman analysis of the Women's Interagency HIV Study identified an independent association between HCV positivity and a 5% annual drop in eGFR in women who already had CKD, defined as an eGFR below 60 mL/min.³⁰ But the analysis did not link HCV to eGFR decline in women with a baseline reading above 60 mL/min.

— A 7.6-year study of 25,155 HIV-positive veterans found that those with HCV coinfection had significantly higher rates of CKD (14% versus 11%, $P < 0.001$) and significantly greater mortality (IRR 1.23, 95% CI 1.17 to 1.29).³¹

— An 8235-person EuroSIDA analysis determined that, compared with HCV-negative people, those with chronic HCV infection had a higher incidence of CKD (aIRR 1.85, 95% CI 1.49 to 2.30, $P < 0.0001$), but those with cleared HCV infection did not, find-

ings suggesting that active HCV infection contributes to CKD pathogenesis.³²

— An NA-ACCORD analysis of 52,602 HIV-positive North Americans without HCV, 9508 with HCV viremia, and 913 positive for HCV but with undetectable HCV RNA figured that, compared with HCV-negative individuals, HCV viremic people had a higher risk of stage 3 CKD (aHR 1.36, 95% CI 1.26 to 1.46), stage 5 CKD (aHR 1.95, 95% CI 1.64 to 2.31), and progressive CKD (aHR 1.31, 95% CI 1.19 to 1.44).³³ And compared with HCV-negative people, HCV-positive but aviremic individuals had an increased risk for stage 3 CKD (aHR 1.19, 95% CI 0.98 to 1.45), stage 5 CKD (aHR 1.69, 95% CI 1.07 to 2.65), and progressive CKD (aHR 1.31, 95% CI 1.02 to 1.68).

— A study of 3441 antiretroviral-treated people enrolled in the SMART trial or ESPRIT trial found that HCV positivity raised chances of progressive CKD, defined as ESRD, renal death, or significant eGFR decline (aOR 1.72, 95% CI 1.07 to 2.76).³⁴ But chances of progressive CKD were similar in HCV-positive people with low or undetectable HCV RNA and in HCV-negative people.

— Analysis of 56,823 HIV-positive veterans followed for a median 5.1 years determined that HCV infection boosted the risk of acute kidney injury 33% (aHR 1.33, 95% CI 1.26 to 1.40).¹⁹

Other kidney disease risk factors listed by the CDC and the American Kidney Fund—abnormal lipids, cardiovascular disease, and obesity—are part of the same pathologic web that involves diabetes and hypertension. Out-of-line lipids and heart disease are highly prevalent comorbid conditions in many HIV populations. Obesity affects a lower proportion of people with than without HIV—according to a 2013

CDC analysis of a nationally representative sample.³⁵ Still, the CDC estimates that 25% of HIV-positive people in care in the United States are obese.

Smoking, hyperfiltration, non-HIV drugs

Smoking, hyperfiltration (GFR above 140 mL/min over age 40), and a lengthy list of non-HIV drugs threaten the kidneys in people with and without HIV infection.

A higher proportion of people with than without HIV smoke, but surprisingly little research addresses the impact of smoking on kidney disease in people with HIV. Calling smoking “the obvious missing piece” of the CKD risk puzzle, Miami-based researchers conducted a case-control study comparing 75 HIV-positive in-hospital patients with CKD and 461 HIV-positive inpatients without CKD.³⁶ Logistic regression analysis indicated that smoking triples the odds of CKD (aOR 3.0, 95% CI 1.4 to 5.6, $P = 0.005$). CKD odds climbed from about 1.5 among people who smoked 1 pack a day to more than 3.0 among those who smoked 2 or 3 packs daily. Former smokers had essentially the same chance of CKD as people who never smoked.

The lower the eGFR, the worse the CKD. But a stratospheric glomerular filtration rate—above 140 mL/min in people over 40—also betokens declining kidney function as albuminuria climbs and GFR subsequently nosedives. Multicenter AIDS Cohort Study (MACS) investigators noted that both diabetes and hypertension, the leading comorbid predictors of kidney disease, are linked to hyperfiltration.³⁷

To analyze rates and risk factors of hyperfiltration (GFR measured by iohexol plasma clearance), MACS researchers studied 367 gay/bisexual men with HIV and 241 without HIV.³⁷ A significantly higher proportion of HIV-positive men had hyperfiltration

(25% versus 17%, $P = 0.01$). And after adjustment for other risk factors, HIV raised chances of hyperfiltration 70% (aOR 1.70, 95% CI 1.11 to 2.61). The MACS team stressed that hyperfiltration is a modifiable predictor of kidney disease progression.

Besides certain antiretrovirals, a rich pharmacopoeia of medications can harm the kidneys (**Table 3**). Nonsteroidal antiinflammatories (NSAIDs) deserve special mention because of their wide use and over-the-counter availability. New York States guidelines on care for HIV patients with renal impairment advise clinicians to assess NSAID use in people with declining renal function, to individualize NSAID use, and to educate patients about possible kidney toxicity with NSAIDs.³⁸

Impact of antiretroviral therapy: mostly good news

HRSA guidelines for HIV care list tenofovir, abacavir, atazanavir, and the obsolete protease inhibitor indinavir as antiretrovirals that may cause acute or chronic kidney injury.²³ Some would add lopinavir/ritonavir. Certain antiretrovirals may need a higher or lower dose in people with CKD or on dialysis. Tables 6 and 7 in the 2014 HIVMA guidelines on CKD list dose adjustments for antiretrovirals and other agents (click on link at reference 43).

As tricky as antiretroviral prescribing may sound for patients with a sinking eGFR, finding the right regimen pays huge kidney-protecting dividends. Mountains of data confirm that more advanced HIV infection imperils kidney health, while taking antiretrovirals slashes kidney disease risk. The 2012 meta-analysis of 23 studies¹ and the 56,823-veteran study¹⁹ made six key findings on cART’s kidney-friendly prowess (**Figure 3**).¹

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Table 3. Nonantiretroviral drugs that can cause acute or chronic kidney injury

Antibiotics

Aminoglycoside antibiotics (streptomycin, gentamycin, amikacin)
Beta-lactam antibiotics
Fluoroquinolone antibiotics
Sulfonamide antibiotics
TMP-SMX (trimethoprim-sulfamethoxazole, cotrimoxazole, Bactrim, Septra)
Dapsone (prevention of *Pneumocystis* pneumonia, treatment of acne, malaria, leprosy)

Antivirals

Acyclovir (herpes virus infections)
Cidofovir (cytomegalovirus)
Ganciclovir (cytomegalovirus)
Foscarnet (cytomegalovirus, herpes simplex virus)

Anti-TB drugs

Rifampin
Isoniazid

Antifungals

Amphotericin B (cryptococcal meningitis, thrush)
Pentamidine (prevention of *Pneumocystis* pneumonia)

Other agents

Nonsteroidal antiinflammatories
Phosphate-containing enemas

Based largely on: US Department of Health and Human Services. Health Resources and Services Administration. Guide for HIV/AIDS clinical care. January 2011.²³ Renal disease. Table 2.

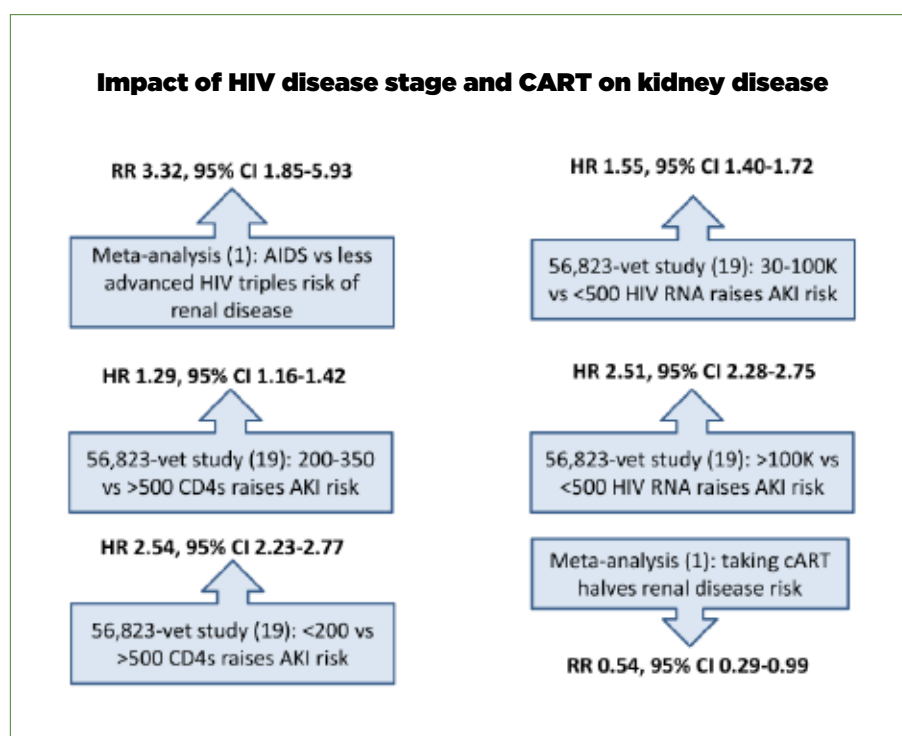


Figure 3. A 2012 meta-analysis of renal disease in HIV-positive people¹ and a 2012 study of 56,823 HIV-positive veterans¹⁹ yielded strong evidence that more advanced HIV infection or untreated HIV infection independently raise the risk of renal disease or acute kidney injury (**AKI**). **HR**, hazard ratio; **RR**, relative risk.

The SMART trial found a lower risk of CKD and a lower risk of progressive CKD in people randomized to continuous cART versus CD4-guided interrupted therapy.³⁹ A case-control comparison in the HIV Outpatient Study determined that cART for at least 56 days halved chances of newly diagnosed CKD (OR 0.5, 95% CI 0.3 to 1.0).⁴⁰ Among HIV-positive participants in the Fat Redistribution and Metabolic Change in HIV (FRAM) study, every 10-fold higher baseline viral load raised chances of declining kidney function (annual eGFR decline more than 3 mL/min), as did every 10-fold increase in viral load during follow-up (OR 1.35, 95% CI 1.00 to 1.83; OR 1.38, 95% CI 1.07 to 1.77).⁴¹ In contrast, every 10-fold gain in viral load during follow-up halved chances of improving kidney function (an-

nual eGFR increase more than 3 mL/min) (OR 0.53, 95% CI 0.37 to 0.75). The FRAM team believes their results “suggest that HIV viral replication is a primary pathogenic factor in the development of kidney disease in HIV-infected persons and a potential therapeutic target for HIV-related kidney disease.”⁴¹

For reasons like these, HRSA HIV care guidelines stress that “ART should be given to HIV-infected individuals with renal disease, according to usual criteria for ART initiation.”²³

Research dissecting the renal ramifications of individual antiretrovirals has reached vast proportions.

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Three researchers who focus on kidney issues in the EuroSIDA and DAD cohorts offer a cogent analysis of this sprawling data horde in a recent review.⁴² They stress two points: First, “most commonly used cART regimens are well tolerated by the kidneys in the majority of HIV-positive individuals.” Second, relative risk is not absolute risk. If a person has an underlying CKD risk of 4% over 4 years, a relative doubling of the risk attributable to an antiretroviral will raise the absolute risk to 8%. But if the underlying risk is 0.4% over 4 years, a relative doubling will raise the absolute risk to only 0.8%. With these ideas in mind, the EuroSIDA/DAD experts propose the following conclusions about the renal impact of frequently used antiretrovirals (annotated below with findings from individual studies):

- **Tenofovir.** Research shows that “tenofovir exposure adversely affects kidney function,” but further data are needed on pathologic mechanisms and possible interactions with other risk factors.⁴² New York State HIV/kidney guidelines counsel that, “as an initial regimen, tenofovir is relatively contraindicated in patients with preexisting kidney disease and GFR levels near 50 to 60 mL/min.”³⁸ HIV Medicine Association (HIVMA) 2014 guidelines advise avoiding tenofovir (and other nephrotoxic drugs) in people with a GFR below 60 mL/min.⁴³ HIVMA recommends replacing tenofovir with another antiretroviral in people with a confirmed GFR drop greater than 25% to below 60 mL/min.
- **Abacavir.** One cohort study linked abacavir use to a 37% higher CKD risk,⁴⁴ but this study did not address the possibility that more patients with higher renal risk tend to take abacavir because of tenofovir’s nephrotoxic notoriety.⁴²
- **Atazanavir.** Prospective analysis of 6843 EuroSIDA cohort members linked atazanavir to inci-

dent CKD.⁴⁵ But “the mechanism for atazanavir-induced kidney dysfunction is . . . unclear” and “larger studies are needed to determine the extent and type of renal adverse manifestations associated with atazanavir use.”⁴²

- **Ritonavir.** Case reports link boosting doses of ritonavir to kidney failure. But it remains unclear whether case reports of boosted protease inhibitor nephrotoxicity are misleading because clinicians often favored boosted protease inhibitors for patients with advanced immunosuppression (and hence a higher risk of CKD).⁴²
- **Lopinavir/ritonavir.** A prospective 6843-person EuroSIDA study identified lopinavir/ritonavir as an independent predictor of progression to CKD.⁴⁵ But, overall, “the role of boosted lopinavir for development of kidney impairment remains uncertain.”⁴²

A different form of tenofovir now in development, tenofovir alafenamide fumarate (TAF), may have a better renal safety profile,^{46,47} a boon that would moot concerns over kidney toxicity with tenofovir disoproxil fumarate (TDF). But it will take time to confirm the efficacy and safety of TAF and to replace TDF with TAF in the many antiretroviral coformulations. See the interview with Christina Wyatt (page 20) for more on prescribing and monitoring TDF and TAF.

Is antiretroviral-induced renal impairment reversible when someone stops taking an offending drug? The EuroSIDA/DAD team cites studies finding that only some people return to baseline levels of proteinuria and eGFR—and a similar number of studies demonstrating “faster and more complete resolution.”⁴² In the EuroSIDA study of CKD incidence, elevated CKD risk with atazanavir or lopinavir/ritonavir returned to the level seen in people not taking those

protease inhibitors immediately after atazanavir or lopinavir/ritonavir stopped, but it took 12 months for complete reversion of tenofovir-associated CKD risk.⁴⁴ After 6 years of follow-up in the largely white DAD cohort, people who took but stopped tenofovir had advanced CKD/ESRD rate ratios similar to people who never took tenofovir.⁴⁸ One 13,007-person UK study of tenofovir-related drops in renal function found that more than one third of patients did not fully reverse declines in a median 2.2 years of follow-up.⁴⁹ But a 1049-person Swiss study of people taking tenofovir for at least 1 year then followed for a median 26 months found that tenofovir-related renal

function recovered more rapidly than it dropped.⁵⁰ The EuroSIDA/DAD kidney experts believe studies with diverse HIV populations and longer follow-up are needed to answer questions on CKD reversion when antiretrovirals stop.⁴²

Table 4 in HIVMA 2014 CKD guidelines offers a concise summary of relative risks for CKD and ESRD conferred by several antiretrovirals, as well as CD4 count, viral load, African descent, female sex, family history of ESRD, age, diabetes, hypertension, and HCV coinfection.⁴³

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Screening and monitoring HIV-positive people for CKD

By Mark Mascolini

Abstract: Late in 2014 the HIV Medicine Association (HIVMA) updated its guidelines on screening for and managing chronic kidney disease in adults and children with HIV. These HIV kidney experts recommend monitoring creatinine-based estimated glomerular filtration rate (eGFR) when antiretroviral therapy begins or changes and at least twice yearly in people with stable HIV infection. These guidelines, plus advice from the New York State Department of Health AIDS Institute and other authorities, also offer straightforward guidance on managing CKD in adults and children with HIV, how to evaluate people with borderline GFR, when to refer HIV CKD patients to a nephrologist, which GFR estimating equations to use, which antiretrovirals and other medications need dose adjustments in people with declining kidney function, and an array of other clinical topics.

Updated guidelines on screening for and managing chronic kidney disease (CKD) in people with HIV appeared in the fall of 2014.¹ This RITA! article offers a concise summary of CKD screening in the new guidelines, supplemented with insights from published research, recent reviews by kidney experts, and 2012

New York State Department of AIDS Institute Advice on kidney disease in HIV-positive people.²

Early CKD causes no symptoms or only nonspecific symptoms that may hint at an array of illnesses. Only targeted blood and urine tests can identify people with early CKD.³ When the HIV Medicine Association of the Infectious Diseases Society of American (HIVMA/IDSA) last issued kidney guidelines for HIV providers in 2005,⁴ clinicians at the University of Mississippi started screening HIV-positive people by measuring serum creatinine, proteinuria, and estimated glomerular filtration rate (eGFR) by the abbreviated Modification of Diet in Renal Disease (MDRD) equation.⁵ Among 941 people without previously recorded CKD, screening identified CKD in 96 (10%).

With 43 pages of text and references, the 2014 HIVMA guidelines¹ almost double the length of the 2005 guidelines.⁴ But the 2014 version is helpfully succinct in its advice on screening HIV-positive people for CKD:

1. "We recommend monitoring creatinine-based estimated glomerular filtration rate (GFR)

when antiretroviral therapy (ART) is initiated or changed, and at least twice yearly in stable HIV-infected patients, using the same estimation method to track trends over time. More frequent monitoring may be appropriate for patients with additional kidney disease risk factors . . .¹

2. "We suggest monitoring kidney damage with urinalysis or a quantitative measure of albuminuria/proteinuria at baseline, when ART is initiated or changed, and at least annually in stable HIV-infected patients. More frequent monitoring may be appropriate for patients with additional kidney disease risk factors . . ."¹

What about kids? HIVMA recommends the same screening and monitoring advice summarized in points 1 and 2 above for children and adolescents but adds that GFR should be estimated with an equation developed for children. These experts suggest avoiding tenofovir in first-line regimens for prepubertal children (Tanner stages 1 to 3) "because tenofovir use is associated with increased renal tubular abnormalities and bone mineral density loss in this age group."¹

HIVMA experts recommend a thorough workup for people with new-onset kidney disease or newly diagnosed kidney disease (**Table 1**). The HIVMA team and New York State experts advise referring certain HIV-positive people with kidney disease to a nephrologist for diagnostic evaluation (**Table 2**).

Table 1. Workup for new-onset or newly diagnosed kidney disease

1. Serum chemistry panel
2. Complete urinalysis
3. Quantitation of albuminuria (albumin-to-creatinine ratio from spot sample or total albumin from 24-hour collection)
4. Assessment of temporal trends in eGFR, blood pressure, and blood glucose control (in patients with diabetes)
5. Markers of proximal tubular dysfunction (particularly if treated with tenofovir)
6. Renal sonogram
7. Review of prescription and over-the-counter medications for agents that may cause kidney injury or require dose modification for decreased kidney function

Source: HIVMA/IDSA CKD guidelines.¹

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continued from **page 41**

Table 2. Refer HIV-positive person with CKD to a nephrologist if . . .

1. GFR drops more than 25% to a level below 60 mL/min and does not resolve after nephrotoxic drugs* stop (HIVMA)
2. Albuminuria exceeds 300 mg/day (HIVMA)
3. Hematuria is accompanied by albuminuria/proteinuria or increasing blood pressure (HIVMA)
4. Patient has advanced CKD (GFR < 50 mL/min) (HIVMA)
5. Diagnosis is uncertain (NY State)
6. Kidney disease is progressing rapidly (NY State)
7. Kidney biopsy is being considered (NY State)

Source: HIVMA/IDSA CKD guidelines¹ and New York State HIV CKD guidelines.²

*See Table 3 on page 34 of this issue.

New York State HIV CKD guidelines differ somewhat from HIVMA/IDSA guidance in calling for assessment of kidney function by eGFR at the initial visit then every 6 months² (not when antiretroviral therapy begins then every 6 months). New York also endorses (1) blood urea nitrogen (baseline and at least every 6 months), (2) urinalysis (baseline and at least annually), and (3) in people with diabetes and no known proteinuria, urine albumin-to-creatinine ratio to detect microalbuminuria (baseline and at least annually).² New York State guidelines also suggest evaluations when GFR is borderline (**Table 3**).

Table 3. Diagnostic evaluation for people with borderline GFR

1. Urinalysis to screen for cells and cellular casts
2. Quantitation of urinary protein excretion
3. Renal sonogram
4. Careful physical examination

Source: New York State HIV CKD guidelines.²

HIVMA 2014 primary care guidelines offer specific advice for blacks and people starting tenofovir:

- Baseline urinalysis and calculated creatinine clearance or eGFR are especially important in blacks with HIV and people with advanced HIV infection or comorbid conditions because these groups run a higher risk of nephropathy.⁶
- People starting tenofovir or other potentially nephrotoxic drugs (see Table 3 on page 34 of this issue) should first undergo urinalysis and calculated creatinine clearance so that these parameters can be tracked after treatment begins.⁶
- What's the best way to calculate eGFR? Both HIVMA and New York State lean toward the Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) equation, which may be more accurate than MDRD for people with HIV. New York State summarizes CKD-EPI, MDRD, and the Cockcroft-Gault formula and provides links to online calculators:²
 - CKD-EPI estimates GFR based on age, race, and serum creatinine. Calculator at <http://mdrd.com>
 - MDRD estimates GFR based on age, race, sex, and serum creatinine. Calculator at <http://mdrd.com>
 - Cockcroft-Gault estimates creatinine clearance based on serum creatinine, age, weight, and sex. Calculator at <http://nephron.com/cgi-bin/CGSI.cgi>
 - With any of these formulas, rising creatinine will result in falling GFR and stable creatinine will result in a stable GFR (**Figure 1**).

New York State also lists “Important Limitations to Calculating GFR” and notes that CKD-EPI is used by clinical labs when reporting eGFR from serum creatinine, but drug makers recommend dose adjustment based on Cockcroft-Gault.² CKD-EPI, but not the other two formulas, has been validated in people with normal kidney function.

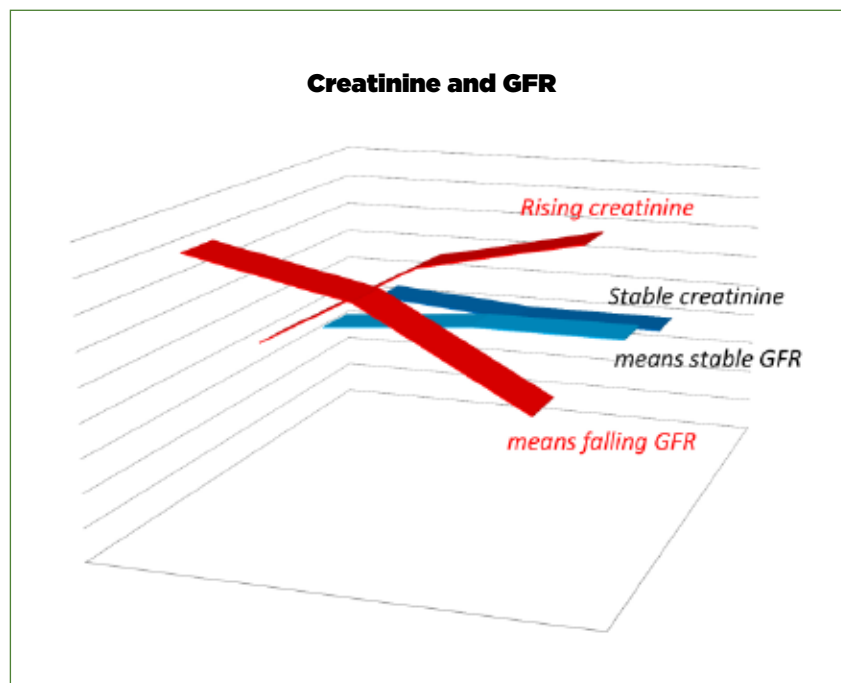


Figure 1. With any formula to estimate glomerular filtration rate (GFR), rising creatine results in falling GFR and stable creatinine results in stable GFR.

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continued from **page 43**

In a recent review of “HIV and the aging kidney,” noted HIV nephrologist Christina Wyatt and colleagues from New York’s Icahn School of Medicine at Mount Sinai cite recent evidence that the CKD-EPI equation “provide[s] a reasonable estimate of GFR in HIV-infected adults, when compared with a direct measurement of GFR.”⁷

The Icahn/Mount Sinai team reminds colleagues that drugs affecting tubular secretion of creatinine also sway creatinine-based kidney function estimates.⁷ Those drugs include the booster cobicistat (a constituent of Stribild), the integrase inhibitor dolutegravir, and the nonnucleoside rilpivirine. Because these drugs do not affect cystatin C, they note, measuring serum cystatin C “may be useful as an adjunct measure to exclude deterioration of kidney function in patients with marginal eGFR who are starting therapy with one of these agents.”⁷ But they caution that

cystatin C should not be used by itself to estimate GFR in people with HIV.

Most antiretrovirals—and many other drugs—require dose adjustment or even discontinuation in the face of declining kidney function. Notably, fixed-dose combination antiretrovirals must often be shelved when kidney function drops because doses of individual components must be adjusted separately.¹ Table 6 of the 2014 HIVMA CKD guidelines spells out antiretroviral dose adjustments according to creatinine clearance levels.¹ Table 7 of those guidelines details dose adjustments for other medications commonly taken by people with HIV. **Table 4** in this article lists nonantiretroviral drugs that require dose adjustments with declining kidney function. See the interview with Christina Wyatt for more dose-adjustment advice.

Table 4. Nonantiretrovirals requiring dose adjustment with declining kidney function*

- | | | |
|------------------|-------------------------|---------------------------------|
| • Acyclovir | • Flucytosine | • Ribavirin |
| • Adefovir | • Foscarnet | • Rifabutin |
| • Amphotericin B | • Ganciclovir | • Rifampin |
| • Cidofovir | • Isoniazid | • Sulfadiazine |
| • Ciprofloxacin | • Levofloxacin | • Trimethoprim/sulfamethoxazole |
| • Clarithromycin | • Pentamidine | • Valacyclovir |
| • Ethambutol | • Pyrazinamide | • Valganciclovir |
| • Famciclovir | • Peginterferon alfa-2a | |
| • Fluconazole | • Peginterferon alfa-2b | |

*Source: HIVMA/IDSA CKD guidelines.¹ See guidelines for individual dose adjustments.

HIV clinicians should download and save the 2014 HIVMA/IDSA guidelines at the link provided in reference 1. Besides screening and referral advice, the guidelines include advice on (1) evaluating HIV-positive people with kidney disease, (2) managing antiretroviral therapy in people with CKD or end-stage renal disease (ESRD), (3) roles of ACE inhibi-

tors, angiotensin II receptor blockers, statins, and aspirin in HIV-positive people with CKD, (4) the optimal blood pressure goal for HIV-positive people with CKD, (5) corticosteroid use to prevent ESRD, (6) kidney transplantation, and (7) treating HIV-related kidney disease in children and adolescents with HIV versus adults.

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