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## In this issue:

### **Kidney disease in people with HIV: a clinical review (part one); *by Theo Smart* **page 2****

- Key points
- An epidemic of HIV-related kidney disease?
- Background on the kidneys and measures of kidney function
- Glomerular filtration rate
- Measures of glomerular filtration rate
- Estimating GFR in African populations and people living with HIV
- More sensitive biomeasures of tubule damage

# Kidney disease in people with HIV: a clinical review (part one)

By Theo Smart

## Key points

- Kidney disease is an often unrecognised problem in people with HIV.
- Loss of kidney function may lead to high blood pressure, bone thinning and anaemia, and eventually to severe kidney damage that requires replacement of kidney function either through dialysis or transplantation. Both forms of treatment are difficult to obtain in resource-constrained settings.
- Loss of kidney function will also require adjustment of doses of some HIV medications and drugs used to treat opportunistic infections.
- A number of factors place people at greater risk of kidney disease including high blood pressure, malaria, older age, tuberculosis and cancers.
- HIV itself can cause damage to the kidneys, as can some medications used to treat HIV or opportunistic infections.
- There is some evidence that people of African descent are at higher risk of developing kidney disease, including HIV-related kidney disease, but more study of this question is needed throughout the African continent to determine whether this applies to all Africans, or only to people of a particular genetic make-up.
- Most people with kidney disease do not know they have it. Laboratory tests are needed to diagnose it.
- The most basic test to monitor kidney function is the measurement of creatinine clearance. Kidney function can be measured by looking at how well the kidneys filter creatinine from the blood and calculating the glomerular filtration rate (GFR) – the speed at which the millions of tiny tubes in the kidney can filter out waste products from the blood.
- If GFR is below 90, this is a sign of damage to the kidneys. GFR below 50 is a sign of moderate to severe damage.
- This article discusses in detail some of the problems with interpreting kidney function tests in people with HIV and in black Africans. This information is particularly intended for researchers and clinicians studying these problems, and summarises some of the problems with current testing methods.
- The next edition in this series of three articles will look at acute and chronic kidney disease in people with HIV.

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This series of articles seeks to describe some of the more common kidney disorders observed in people living with HIV. Subsequent articles will discuss some of the issues around their diagnosis and management, including palliative care for people with CKD and ESKD, and to provide dosage adjustment charts for people with renal deficiency.

## An epidemic of HIV-related kidney disease?

In Europe and North America, since the widespread use of antiretroviral therapy, chronic diseases have bypassed opportunistic infections as the cause of death in HIV-positive people. In those settings, kidney disease has emerged as an important cause of morbidity and mortality among people living with HIV,<sup>1</sup> though it still ranks relatively low in the order of individual causes of death, partly because clinicians and facilities in that part of the world are well-equipped to diagnose and support patients with kidney problems.<sup>2</sup>

In Africa, developing a kidney disorder that would be manageable in industrialised countries often means death.

Even a middle-income country such as South Africa has trouble supporting the growing population that is being diagnosed with severe kidney disease. For instance, access to haemodialysis – artificial filtration of the blood that is necessary in some patients with severe loss of kidney function – is extremely limited here and in most of the continent. A [recent BBC article reported that four out of five people who need dialysis for end-stage renal disease at the big public hospitals in Cape Town are turned down, and described the difficult life and death decisions hospitals must make regarding who gets dialysis](#). The article stressed that only patients who were good candidates for having a kidney transplant – and there are very few kidneys available for transplanting – could qualify for dialysis.

One dialysis candidate, Karen MacPherson, who was interviewed in the article, “desperately wanted to live. ‘My daughter needs me,’ the 43-year-old widow with three children said.” Unfortunately, she was considered overweight, which is associated with a poorer prognosis after transplantation, so her case was turned down. Within two weeks of the committee meeting hearing her case, Ms MacPherson had already been buried.

That is the fate of almost everyone with end-stage kidney disease (ESKD) in most of sub-Saharan Africa, especially those living with HIV, who are actively excluded from renal replacement therapy (dialysis and kidney transplant) programmes in most countries.<sup>3</sup> Even though these policies are being reviewed or revised in some countries in light of growing access to antiretroviral drugs, there is too little capacity for kidney transplantation for these policies to change in most of Africa. One possible solution, at least for middle-income countries, will be discussed in a later part of this clinical review series. Is it possible to form an organ donor pool among HIV-positive people, [as recent work at Groote Schuur Hospital in Cape Town, has shown that kidneys from other people living with HIV can safely be transplanted into people living with HIV who need them](#).<sup>4</sup>

But in most other resource-constrained countries, the huge cost of managing chronic kidney disease (CKD) with long-term dialysis and kidney transplantation puts such care beyond the reach of all but a few. In many places, where there is little or no access to intensive care or dialysis, many people who develop what should be a treatable and reversible case of acute kidney injury face the same fate. Making matters worse, kidney disease often goes unnoticed, with few symptoms until it is advanced, and patients present with end-stage kidney disease when they have few other options.

Notably, there are few, if any, kidney disease specialists (nephrologists) in some African countries – most have less than ten.<sup>5</sup> Even South Africa has only about 50 nephrologists for a population of almost 50 million people. Likewise, there are few surgeons to do kidney transplants, or nurses trained to attend to people with kidney disease.

Kidney disease has simply not made it onto health agenda in Africa, despite the fact that it usually strikes Africans in their prime (20-50 years of age) rather than late in life and despite the fact that severe kidney disease is three to four times more common in people of African descent in developed countries.<sup>6, 7</sup> The epidemiological data in Africa are actually rather mixed, however. The incidence of some types of kidney disease appears to be many times greater than in other parts of the world while other forms are either not as common, or are significantly under-reported.<sup>8</sup> As for acute kidney injuries in Africa, there are no reliable statistics according to one recent review, though many of the factors associated with acute kidney damage are abundant on the continent, including a huge burden of diseases that can cause kidney failure such as malaria.<sup>9</sup> Likewise, it is difficult to know the burden of chronic kidney disease in Africa because of poor diagnostic capacity, inadequate research and the fact that health systems have not established programs and registries to monitor it.<sup>10</sup>

But there are reasons to worry that Africa may have a large unrecognised and growing problem with CKD in particular. It has often been observed that African-Americans (especially those with HIV) in the US have a much higher risk of kidney disease than other populations – to such an extent that ‘black’ race is considered a risk factor for kidney disease and end-stage renal disease in that country.<sup>11</sup> It is not known whether the drivers of kidney disease in high-income countries will have the same impact in other settings, or whether the epidemiology of kidney disease will prove to be shaped by distinct regional forces. Furthermore, it is inadvisable to make assumptions about what the epidemiology of kidney disease in people of African descent in other parts of the world means for black Africans.

However, there is now evidence suggesting that a genetic adaptation that may have conferred a survival benefit in Africa, which was passed down in many African populations as well as among people of African descent, may increase susceptibility to specific types of kidney injury.<sup>12</sup> Some studies suggest one of these mutations is fairly widespread, though it is not found in every population.<sup>13</sup> Already, there is evidence that glomerular kidney disease (explained later in this series) is more prevalent in Africa, and according to Dr Saraladevi Naicker of the University of Witwatersrand, it “seems to be of a more severe form than that found in western countries, and is characterized by poor response to treatment and progression to renal failure.”<sup>14</sup> Hypertension is already one of the most common causes of kidney disease among Africans, and it appears likely that CKD could become even more common as Africans are increasingly exposed to a more urban westernised lifestyle and diet, with its attendant vascular risk factors, diabetes and hypertension which commonly lead to kidney problems in industrialised countries.<sup>15</sup>

On top of this, there is sub-Saharan Africa’s burden of HIV disease (and associated infections/conditions), which plainly increases the risk of kidney disorders. HIV can cause severe kidney disease directly – including acute kidney injuries, (possibly) thrombotic microangiopathies, HIV-associated nephropathy (HIVAN), and HIV immune complex kidney disease (HIVICK). Likewise, tuberculosis (TB), sexually transmitted infections, opportunistic infections, hepatitis B & C, bacterial infections, and neoplasms that are more common in the context of HIV infection can cause a variety of kidney disorders. Kidney damage may also be the result of some of the medications used to treat these infections.

Concern about one medication, tenofovir, a cause of kidney injury in some individuals, which is now entering into much more widespread use, finally has more HIV clinicians thinking about

kidney disease, and ART programmes are beginning to consider whether they need, can afford or have the capacity to begin monitoring their patients’ kidney function. However, the scope of this concern is at present rather narrow, centred primarily on the safety of this drug, or to make appropriate dosage adjustments on other drugs the patient is taking.

HIV programmes may have a much greater problem lying in wait as people living with HIV on ART begin aging – especially as other chronic health problems such as diabetes and cardiovascular disease become more common in people living with HIV. How this will play out in populations that may be more susceptible to kidney injury from the start and where there is a huge burden of illnesses that can cause kidney injury, is anyone’s guess. However, if measures of kidney function are reliable across populations – and this is not yet clear (see below) – a number of cross-sectional surveys have already identified very high rates of renal impairment in people living with HIV in a variety of sub-Saharan African settings. For instance, an analysis of more than 25,000 Zambians starting ART suggests that approximately 8500 (33%) had mild to severe renal impairment (though other ways of measuring suggest kidney impairment was not as common).<sup>16</sup>

But findings such as these have led one international kidney journal to ask whether sub-Saharan Africa might be on the cusp of an epidemic of HIV-related chronic kidney disease.<sup>17</sup>

“We believe that the epidemic of HIV renal disease in Africa has arrived but has not been widely announced due to lack of documentation,” said Dr Nicola Wearne, Senior Registrar of Groote Schuur Hospital last year at a meeting of the South African Congress of Nephrology.<sup>18</sup> “The extent of the HIV epidemic and its associated burden of kidney disease, makes management of these patients extremely difficult given limited resources – especially for renal replacement.”

Indeed, before effective ART regimens became available, renal impairment was shown to be associated with faster progression to AIDS and death in HIV-positive US women.<sup>19</sup>

In the current treatment era, kidney disease at the time of ART initiation was associated with a higher risk of death in a cohort of 1415 US women during 8148 person-years of follow-up.<sup>20</sup> A similar finding emerged from the Zambian study – those who had renal impairment when they initiated treatment were found to be more likely than their counterparts to die during a two-year follow-up period.<sup>21</sup>

Other consequences of kidney disease have important implications in HIV-positive populations as well. A US study comparing HIV-positive people who had experienced either a heart attack or stroke with those who had not done so found a below-normal kidney function to be a significant risk factor for those events. The association persisted after controlling for confounding factors such as diabetes and high blood pressure.<sup>22</sup> Other recent research that appears to confirm that renal impairment is strongly associated with the risk of cardiovascular disease and heart failure in people living with HIV is discussed later in this article. These and other findings raise the prospect of kidney disease greatly complicating HIV clinical care. For instance, aside from high blood pressure, kidney disease can lead to bone thinning and anaemia – both of which are already considerable problems in some HIV-positive populations – as well as a variety of other conditions that are difficult to diagnose or which may complicate the diagnosis of other HIV-related illness.

Unfortunately, such complex clinical problems don’t always seem to fit into streamlined target-driven ART programmes. [But data are beginning to show that a ‘get the patient in and out’ by the numbers](#)

[approach is leading to more and more losses to follow-up, possibly because people feel their needs are going unmet.](#) <sup>23</sup>

"We like saying that we're going to be looking after our patients on ART into old age," Dr Kevin Rebe of Health4Men in Cape Town told HATIP, "but our ART programmes aren't actually prepared to deal with the illnesses such as CKD affecting ageing patients."

However, adopting a palliative care approach, which aims both to address the causes of illness and to treat the symptoms to alleviate suffering, could better help families living with kidney disease and its related complication, and may help those with advanced CKD cope with progressive loss of kidney functions, and perhaps even slow down that loss over time. It is also important to remember that, in resource-constrained settings where there is little or no screening for kidney disease, people may only present once their condition is terminal. They will need end-of-life care and their families, support, beyond what the health services alone can offer. This goes beyond what any already overburdened health provider can do by themselves — and will require a multidisciplinary approach that employs the strengths of civil society, different community-based and faith-based organisations.

Nevertheless, many potentially serious kidney problems are reversible or can be slowed if recognised in time. In light of this, and the high costs of managing chronic or end-stage disease, prevention and early detection and treatment of kidney disease are especially critical for people living with HIV in Africa.

## Background on the kidneys and measures of kidney function

The kidneys are a pair of bean-shaped, fist-sized organs that filter waste from the bloodstream, produce urine and perform a number of other essential regulatory functions in the body. In a healthy kidney, there are up to one million tiny structures called nephrons. Each nephron contains a glomerulus, small loops of capillaries packaged inside a cup-like sac called a Bowman's capsule, and a connected tubule.

The glomeruli filter the blood, leaving in blood cells and large proteins, such as albumin, while other materials, including small proteins, water and waste products are passed into the Bowman's capsule and then into the tubule.

Different parts of the tubule perform different functions. The proximal convoluted tubule (the part closest to the glomerulus), processes and reabsorbs substances that the body can still use (water, electrolytes, glucose, amino acids and minerals) passing them back into the bloodstream. Note that while this occurs, other substances such as hydrogen ions, ammonia, creatinine and the metabolic products of medications are secreted from the bloodstream directly into the tubule.

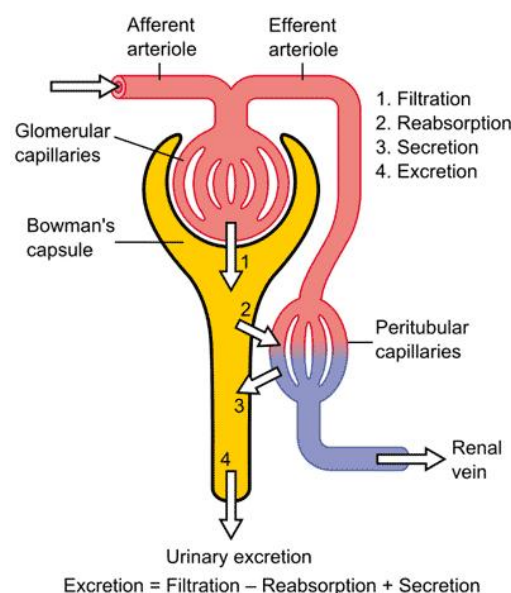
More water is reabsorbed in the distal tubule, which passes the excess water and waste into the collecting tubule, as they are concentrated into urine, which travels on through the ureter, and then into the urinary bladder until it is discharged.

Proper kidney functioning is necessary for the body to maintain the optimal hydration and the proper balance of electrolytes (sodium, phosphorus, and potassium) and acid-base content of the blood.

The kidneys also release hormones, such as renin, which helps regulate blood pressure, erythropoietin, which stimulates the creation of red blood cells, and calcitriol, which helps the body absorb the calcium that is required to keep bones strong.

While the kidneys are resilient organs, they can be damaged in a number of ways that can, in turn, upset the rather complex activities they orchestrate.

Toxins or infections can cause acute kidney injury (sudden and often severe decrease in kidney function) or damage may develop chronically (over more than three months). Kidney disorders may primarily be either glomerular, affecting the glomeruli and essentially causing 'filtering' problems, or tubulointerstitial, affecting the tubules and the area surrounding them, often associated with electrolyte imbalances and problems concentrating urine—though severe problems can overlap.



## Physiology of the nephron

(image reproduced from Wikimedia Commons)

## Consequences of changes in kidney function

Changes in kidney function can lead to changes in hormone secretion with consequences upon other organ systems, causing high blood pressure, for instance, which then can lead to further kidney damage.

However, with the exception of the rather dramatic clinical presentations seen with a severe or complete loss of kidney function, many kidney disorders are asymptomatic or the symptoms are non-specific, such as fatigue, loss of appetite, nausea, headaches etc. Again, this is part of the reason why many people with kidney problems present so late for care.

For this reason, many kidney disorders can only be recognised with laboratory tests. Although a variety of screening tools exist, the most important ones for making the initial diagnosis of kidney disease look for the presence of two biomarkers: protein in the urine and a high creatinine level in the blood.

However, to identify some kidney problems, especially acute kidney injuries, it can also be important to look for blood and white cells in the urine, urinary output, and to check the blood for blood urea nitrogen (BUN) and electrolyte imbalances.

The kidneys are supposed to leave large proteins in the blood as they filter out the waste products. Thus, if a urine sample contains



these proteins, a condition known as proteinuria, this means something is wrong.

The presence of a specific protein, albumin in the urine, a condition known as albuminuria, indicates that the kidney's filtering mechanisms are failing. Some kidney injuries may also allow blood cells to flow into the urine – a condition known as haematuria (though urinary tract infections (UTI) are more commonly the cause of haematuria).

At the same time, build up in the blood of creatinine, a waste product of muscle metabolism, indicates that the kidneys are failing to do their job of eliminating waste from the body. Another consequence of this may be the accumulation of nitrogenous waste products in the blood (azotemia), which is called uraemia once levels become harmful and the condition becomes symptomatic.

On their own, these measurements provide only a general picture of whether there is serious kidney deficiency – though they can play very important diagnostic roles.

However, by the time the measurements described here are outside normal ranges, a significant amount of kidney function may have already been lost.<sup>24</sup> Research is ongoing into biomarkers that might provide an earlier indication of kidney damage.

## Glomerular filtration rate

Stage	Description	GFR (mL/min/1.73 m <sup>2</sup> )
1	Kidney damage with normal or ↑GFR	≥90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	<15 (or dialysis)

Currently, the best overall measure of how well the kidney is functioning is the glomerular filtration rate (GFR) – the rate at which blood is being filtered through the kidney over a unit of time. There are several methods to measure GFR, but the gold standard, involves administering a foreign substance that the glomeruli will filter completely as waste, without reabsorption by the tubules, and measuring its clearance over time. These include a substance called inulin and various radioisotopes. But these methods are complex and/or too expensive to use outside a research setting.

Another method that is considered relatively representative of GFR involves measuring the amount of creatinine cleared in urine specimens collected over 24 hours, but this is also awkward and laborious. So researchers have come up with equations to calculate an estimated GFR (eGFR) based upon the creatinine levels in the blood serum taking into account variables relating to age, sex and (in some cases) race. However, there is some controversy surrounding the best way to estimate eGFR in different races and settings.

A person's eGFR is expressed in terms of milliliters filtered per minute x 1.73 m<sup>2</sup> (henceforth in this article mL/min). Someone with healthy kidneys can be expected to have an eGFR of 90 mL/min or greater, while lower levels are used to stage the severity of CKD (see table).

## Topic for research: Biomarkers for kidney injury and function

**The biomarkers currently used to detect kidney injury or monitor kidney function have limited sensitivity or dubious accuracy and have not been well studied in people living with HIV, according to a recent review by Post et al. in *Current Opinion in HIV and AIDS*.<sup>25</sup> The review's findings suggest that the kidney-related conclusions of some studies (including some major ones) using these markers need to be taken with a grain of salt. At the same time, other markers are being investigated which may provide a better or earlier indication of specific forms of kidney damage, including tenofovir-related proximal tubule damage.**

## Measures of glomerular filtration rate

The measurement of creatinine clearance in urine (or its estimation based upon serum levels) is a biomarker for GFR, but it is an imperfect one at best. The best biomarker for GFR would be something produced in the body at a constant rate, which is filtered freely by the glomeruli and then not reabsorbed or secreted as it passes through the tubules.

Creatinine is filtered, but small amounts are secreted directly from the bloodstream into the tubules. Furthermore, it is produced at a variable rate since it is a by-product of muscle metabolism, and levels also vary depending upon how much animal protein a person ingests.

There are three commonly used equations used to calculate estimated GFR (eGFR). The first and most widely used is the Cockcroft-Gault equation which was based upon data derived from over two hundred hospitalised Canadians (96% of whom were male), using 24-hour urine creatinine clearance as the gold standard.

This equation does not correct for major differences in muscle mass. The Modification of Diet in Renal Disease (MDRD) equation (sometimes called MDRD-4 or 4-v-MDRD, since it contains adjustments for four variables – age, gender, serum creatinine and ethnicity) was based on measurements of clearance of a radioisotope in 1600 people.

The CKD Epidemiology Collaboration (CKD-EPI) developed a formula by combining data from 8254 people with measured GFR from several clinical and observational studies. Each equation is supposed to correct for age and gender. The MDRD and CKD-EPI also attempt to correct by race since metabolism and body composition can differ in different racial groups – at least in some settings (see estimating GFR in resource-limited settings below).

Although a number of studies in people living with HIV have used these equations for eGFR, and they are used in clinical practice, none of the equations have really been validated in people living with HIV. Only a handful of studies with fairly small numbers of participants, mostly HIV-positive white men, have been conducted – and they reached different conclusions about the agreement between and relative accuracy of GFR based on 24-hour urine creatinine clearance measurements, and the eGFR based on Cockcroft-Gault and MDRD equations.

Serum measurement of an alternative marker, cystatin C (a cysteine proteinase inhibitor produced by all nucleated cells), has been proposed as a better way to assess GFR since it is not affected by tubule secretion and less dependent on body composition and other factors. Use of cystatin C to measure kidney function in the general public appeared to be validated in 825 participants from the MDRD study – and cystatin C was a better predictor of mortality than other measures.

It has been suggested that cystatin C may be more sensitive to early kidney dysfunction in people living with HIV, even though in the one published study that compared cystatin C to directly measured GFR in 27 HIV-positive people, it was not as accurate as serum creatinine-based estimates.

For instance, in [a US study](#) looking at body fat and metabolic changes in HIV-positive patients (the FRAM – Fat Redistribution and Metabolic Change in HIV Infection – cohort), investigators conducted a cross sectional sub-study where they compared kidney function, as measured by cystatin C and creatinine levels in 1008 HIV-positive subjects and 208 HIV-negative controls.<sup>26</sup>

Cystatin C measurements were consistently higher in the HIV-positive participants (at levels that would be indicative of poor outcomes in the general population) but creatinine-based eGFR levels were similar in HIV-infected individuals and controls. In [a subsequent analysis of the FRAM cohort](#), kidney function as measured by cystatin C appeared to correspond with the extent to which HIV viraemia was controlled.<sup>27</sup> Later, an analysis of the SMART (treatment interruption) study suggested that treatment interruptions were associated with an increase in cystatin C levels but not eGFR as calculated with the MDRD equation.<sup>28</sup>

[Another study using data from participants from the SMART study](#) found that cystatin C and other biomarkers of serious health problems were elevated in people living with HIV as compared to the general population (based on data from two large studies monitoring the development of heart disease), even while people were taking antiretroviral therapy.<sup>29</sup> “In summary”, write the investigators, “we found that markers of inflammation, coagulation, and renal function were elevated in HIV-infected study participants receiving or not receiving antiretroviral therapy, compared with patients in two large population-based studies.”

All of this would tend to support some of the key points of this clinical review – that HIV causes kidney disorders and these increase the risk of poor outcomes in people living with HIV. However, Post et al. quite correctly point out that “although changes in virologic control could plausibly influence kidney function, it is also possible that changes in cystatin C reflect the influence of viral replication on systemic inflammation.”

Indeed, a number of other illnesses and factors appear to influence cystatin C levels.<sup>30</sup> It may be premature to conclude that cystatin C could be used as an ‘early’ marker for kidney disease in people living with HIV until prospective studies show that cystatin C can be used to predict which individuals will experience declines in directly measured GFR, or other measures of clinical kidney disease.

“Until the results of larger studies comparing creatinine and cystatin C-based GFR estimates to a gold standard in HIV-infected individuals become available, the optimal GFR estimate for use in clinical practice remains unclear,” wrote Post et al.

## Estimating GFR in African populations and people living with HIV

This may be doubly true of people living with HIV in Africa. According to recent studies in Ghana and South Africa, the existing formulas to estimate GFR may not be very accurate in non-Caucasian populations in resource-limited settings – and adjustments made to the equations to account for race, actually made the estimations less reliable.

The most recent study compared 24-hour urinary creatinine clearance to eGFR as determined by MDRD, CKD-EPI and Cockcroft–Gault equations in rural Ghana.<sup>31</sup> The study included 944 people from 12 Ashanti communities in Ghana, excluding those who were pregnant, lactating or suffering from any severe mental or physical illness, though people with hypertension, diabetes or known kidney disease could participate. HIV status was not reported.

In this mostly healthy population, the mean GFR by urinary creatinine clearance (Ccr) was 84.1 mL/min. However, the mean eGFR by Cockcroft–Gault was 9.4 mL/min lower, which suggests that estimates using the equation have the potential to significantly overestimate kidney damage in this population.

The Cockcroft–Gault equation has been much criticized for not correcting estimates on the basis of race. The MDRD and CKD-EPI equations both have factors to correct for race, based on “racial” differences in body composition. However, in this African population, the mean eGFRs by both these equations were much (18.2–19 mL/min) higher than the Ccr GFR when using the factor for race. When the factor for race was omitted, the mean results were much closer to the Ccr GFR. Eastwood et al. note that the factors correcting for race were based upon data derived from African-Americans, which may not be appropriate for lean rural African populations (the mean body weight of the participants in the Ghanaian study was 54.4 kg with mean BMI 21.1 kg/m<sup>2</sup>). It is probably safe to say that creatinine-based equations should be used with caution in people with abnormally high or low muscle mass.<sup>32</sup>

The South African study reached similar conclusions about factors correcting for race in the MDRD equation.<sup>33</sup> The study included 100 patients with various health complaints from Chris Hani Baragwanath Hospital in Johannesburg, South Africa, and compared MDRD, and Cockcroft–Gault eGFR estimates to a gold standard direct GFR measurement using an administered radioisotope.

Because of the mixed health status of this cohort (20 were HIV-positive), there was a significant number of subjects with moderate to severe kidney disease. In this study, when compared to the gold standard, *both* Cockcroft–Gault and MDRD underestimated kidney disease. Without the racial correction factor however, there was very little difference between the direct GFR measurement and the MDRD. In addition, with a slight correction (Cockcroft–Gault x 0.82) based upon the gold standard GFR measurement, the Cockcroft–Gault equation became fairly accurate as well.

The authors had several theories for the difference between eGFR in black South Africans and African-Americans. One was that there could be a difference between body composition in this population and the West African population where African-Americans originated, but the results of the Eastwood et al. paper would tend not to support this. Another possibility was diet. “Differences in dietary intake are difficult to quantify,” they wrote, “but it is likely that black South Africans consume less

creatinine-generating food than African-Americans owing to poorer socioeconomic circumstances.”

The question remains which equation to use. Deventer et al. concluded that both the MDRD equation, without (what should now probably be called) the ‘ethnicity’ rather than racial adjustment factor, and the Cockcroft-Gault  $\times 0.82$  equation could be used in black South Africans. At least in that part of South Africa (the country includes many different tribes, races and ethnicities).

However, in the study in Ghana, the researchers noted that MDRD did not appear to account for age as well as the other equations in this cohort. They concluded that, in their setting, the CKD-EPI without the ethnicity factor was ‘the most useful’, the most reliable in different age groups and close enough to the Ccr.

However, this becomes troubling when looking at how few people in the cohort were categorized as having CKD stages 3-5 — who are important to identify in a clinical setting. With MDRD, it was 1.6% and 7.2 % without factor for black race; CKD-EPI 1.7% and only 4.7% without factor for black race, Ccr however was 13.2% and Cockcroft–Gault 21.0%.

For clinical purposes, the more sensitive measure may be important to identify (or at least not miss) people with kidney disease. On the other hand, mis-staging CKD based upon inaccurate GFRs could have serious consequences when making dosage adjustment for medications (including antiretrovirals).

It also makes it difficult interpreting epidemiological data based on eGFR on CKD in other countries. Another cause for concern is that, as noted in the Deventer et al. study, it is critically important to making absolutely certain that the serum creatinine measurements are perfectly calibrated to match international standards because of variability in creatinine measurement assays. Unfortunately, it is not clear that every study, or every laboratory in resource-limited settings has or are doing this.

A better biomarker that is not as susceptible to differences in diet, muscle metabolism, body composition or renal tubule secretion would be ideal, but for the time being, creatinine measurements are cheaper than anything on the horizon and more widely available. In the meantime, more research is needed on how to adapt the equations for eGFR to make them more reliable in other populations, especially those with HIV, in different resource-limited settings.

## More sensitive biomeasures of tubule damage

The review paper by Post et al. also looks at a number of tests for other biomarkers that could serve as more specific indicators of kidney injury.

### Traditional urine biomarkers:

Widely available, urine tests that screen for proteinuria and albuminuria, have been shown to identify people at higher risk of kidney disease and other adverse outcomes in the general population and in people living with HIV. However, [a recent study has found that the sensitivity of the cheapest, simplest method of screening for proteinuria, the dipstick test, may be affected by urinary concentration](#).<sup>34</sup>

Researchers compared dipstick results to an analysis of spot urine collections over the same 48-hour time period. For the urinalysis, the amount of protein and creatinine was measured, with a ratio of more than 0.3 grams of protein to grams of creatinine (gp/gc) indicating abnormal proteinuria. They found that 13 out of 64 patients (21%) with lower levels of abnormal protein-to-creatinine ratios (0.3-0.99 gp/gc) — which are nonetheless indicative of

clinically relevant kidney disease — had normal urine dipstick results. Meanwhile, eight of the patients had false positive results on the dipstick test.

So dipstick tests may miss about one out of five people with kidney disease, and positive dipstick test results for proteinuria may have to be confirmed by other lab tests.

Another short-coming of the dipstick test for proteinuria, that the study’s authors pointed out, was that dipstick tests only measure albumin, which is a more specific indication of glomerular injury, such as is seen in HIVAN. People with kidney disease localized in the renal tubule may have mild proteinuria composed of other proteins but rarely of albumin. Thus, dipstick tests are an unreliable way to screen for renal tubular injuries such as the Fanconi-like syndrome (see section on tenofovir) that tenofovir can cause.

Conversely, however, Post et al. suggest researching whether urinalysis of the ratio of albumin to creatinine to proteinuria to creatinine could be used to screen for tubular proteinuria and detect tenofovir-associated proximal tubular dysfunction.

### Experimental markers:

There are a number of other biomarkers that could potentially be more specific for tubular inflammation or damage and that may serve as earlier and better indications of which patients are likely to experience tenofovir-associated toxicity. Post et al. note that since the proximal tubule is supposed to reabsorb substances such as phosphate, and small proteins (low molecular weight proteins — LMWPs), increased excretion of these in the urine could indicate tubular dysfunction. LMWPs being studied as potential biomarkers for urinalysis include retinol-binding protein (RBP), cystatin C, b2-microglobulin (B2M), and neutrophil gelatinase-associated lipocalin (NGAL). Another possible biomarker is N-acetyl-beta-D-glucosaminidase (NAG), which is a large protein present within tubule epithelial cells that would only be found in urine if there is tubular cell necrosis.

Tests for these markers are not yet affordable or widely available, and research into the use of these substances as biomarkers for renal tubule disorders is still in its infancy. While promising, some markers may turn out to be influenced by other factors, such as diet or systemic inflammation. Furthermore, there need to be studies demonstrating the clinical relevance of changes to these markers. In the meantime, studies that use these markers as evidence of kidney damage should be interpreted with caution.

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