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# Acute and chronic kidney disease

By Theo Smart

## Key points

- This article is intended for HIV physicians and for kidney specialists who wish to learn more about the complex presentations of acute and chronic kidney disease in people with HIV in low and middle-income settings, particularly sub-Saharan Africa. This is the second in a series of three clinical review articles on kidney disease.
- Acute kidney injury (AKI) refers to a rapid decline in kidney function which develops over 48 hours, and which may be life-threatening. Damage to other organ systems is common. Full recovery is unlikely unless the cause can be addressed.
- Acute kidney injury may be a result of oxygen deprivation, drug exposure or poisoning (acute tubular necrosis, ATN). If the cause is identified and treated, the kidneys will repair themselves. Kidney damage can also be caused by severe allergic reaction to drugs (Acute interstitial nephritis, AIN).
- Crystals of drugs such as the HIV protease inhibitors indinavir and atazanavir can cause kidney damage. Crystalluria is usually characterised by sharp flank pain, blood in the urine and/or difficulty in urinating. The condition can be avoided by drinking a lot of water, and treated by stopping the drug and raising fluid intake.
- The microscopic tubes in the kidneys can also become inflamed due to infections or the immune system's response to them (glomerulonephritis).
- Blood clots may also form in the microscopic tubes for reasons that are poorly understood (thrombotic microangiopathy, TMA). Diagnosis of TMA is challenging, but it is important to investigate as a cause of acute kidney injury, because the mortality rate in people left untreated is very high.
- Common symptoms of acute kidney injury tend to include decreased appetite, fatigue, nausea, vomiting, fluid retention, swollen ankles, wrists and feet, and changes in urination. Glomerulonephritis is often accompanied by fluid retention and swelling in the face and eyelids, and haematuria. Very severe cases are likely to present with delirium, confusion, severe lethargy, seizure or coma.
- Chronic kidney disease (CKD) is kidney damage or reduced kidney function that has lasted more than three months. In people with HIV the most likely cause is a glomerular form of kidney disease. It is unusual for people to notice on their own that kidney function is declining because the symptoms are non-specific and resemble other conditions common in people with HIV.
- The symptoms of chronic kidney disease are similar to those of acute kidney disease, and often accompanied by darkening of the skin, muscle cramps, itching and numbness, and difficulty in concentrating.
- Studies in Africa have found varying rates of chronic kidney disease in people with HIV; around 5-7% seem to have severe kidney disease, but the proportion with milder kidney dysfunction has ranged from 12% to 45%.
- Chronic kidney disease places people at high risk for cardiovascular disease, and is itself caused by diabetes and/or

hypertension. Patients with one or both of these conditions require careful kidney function monitoring.

- Several forms of chronic kidney disease are seen in people with HIV. HIV-associated nephropathy (HIVAN) is seen almost exclusively in people of African descent, and is caused by HIV infection of kidney cells. It is difficult to diagnose as a cause of renal dysfunction. Antiretroviral therapy greatly improves kidney function in most patients who suffer this condition.
- Complexes of antibodies and HIV antigens can become lodged in the kidneys, leading to a loss of function. This is called HIV immune complex disease (HIVICK).
- Hepatitis co-infection can also cause chronic kidney disease. People with HIV and hepatitis C have a higher risk of death as a result of kidney disease than people with HIV who have kidney disease.
- The antiretroviral drug tenofovir might also play a role in damaging kidney function. In a small proportion of people who take it, the drug causes damage to a small group of tubes within the kidney, leading to a disorder called Fanconi syndrome.
- In the United States monitoring of kidney function is recommended twice a year for people taking tenofovir if they have any sign of reduced kidney function. This may not be possible in all resource-limited settings, although monitoring has been introduced successfully in Zambia alongside the use of tenofovir.
- The World Health Organization says that lack of kidney function monitoring (creatinine clearance) should not be a barrier to using tenofovir, but recommends monitoring in those with pre-existing kidney disease, older people and those with diabetes or high blood pressure. Monitoring is also advised in people taking tenofovir with a ritonavir-boosted protease inhibitor.

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## Forms of kidney disease in HIV-positive people

HIV-positive people are vulnerable to renal disorders caused both indirectly and directly by HIV. Additionally, it is important to remember that people living with HIV are also susceptible to non-HIV-specific kidney disorders — in fact, their risk of developing some non-HIV-specific kidney disorders may be elevated as a direct or indirect consequence of having HIV or being on treatment for HIV.

The various forms of kidney disease are categorised according to whether they are acute and potentially reversible versus chronic and generally irreversible; whether the source of the condition is 'pre-renal, renal or post-renal' as well as whether the site of the damage is *glomerular* versus *non glomerular* (tubulo-interstitial).

A differential diagnostic approach to HIV-related kidney disease (from: McCullough MI. Nephrology, In: South African Handbook of HIV Medicine, 2008)			
	Glomerular	Tubulointerstitial	Differential diagnosis: acute or chronic?
<b>ACUTE</b>	<ul style="list-style-type: none"> <li>● Crescentic</li> <li>● Glomerulonephritis</li> </ul>	<ul style="list-style-type: none"> <li>● ATN</li> <li>● AIN</li> <li>● Obstruction</li> </ul>	Haemoglobin >11g/dl = acute
<b>CHRONIC</b>	<ul style="list-style-type: none"> <li>● HIVAN</li> </ul>	<ul style="list-style-type: none"> <li>● ATN/AIN obstruction</li> </ul>	Ultrasound: <9cm = chronic

	● HIVICK ● Other GNs	● Reflux	(normal or big kidneys = chronic)
<b>Differential diagnosis: Glomerular or tubular</b>	Urine dipstick > 2 = glomerular, usually chronic (minimal / no proteinuria = glomerular or tubular)		

## Acute kidney injury (AKI)

What was once broadly referred to as acute kidney failure is now referred to as acute kidney injury (AKI). AKI is currently defined as an abrupt decline in renal function, manifested by an acute decrease in GFR or serum creatinine, or oliguria (urinary output of less than 400/ml per day) occurring within 48 hours.<sup>1</sup> However, although the initial decrease in renal function can happen quickly, the injury may worsen for days or weeks before someone presents for care. While not as common as CKD, AKI can be rapidly fatal.

AKI can be divided into reversible stages depending on severity of insult, starting from increased risk to damage, followed by drop in GFR, and, with further progression, to kidney failure and death.<sup>2</sup> A consensus staging system for AKI that has been validated in over 200,000 people (in industrialised settings) called the RIFLE system, which is an acronym based upon three levels of severity—Risk, Injury, and Failure—and two outcomes—persistent acute renal failure which is called ‘Loss’ and End-stage kidney disease.<sup>3,4</sup> See Table. Note, some kidney specialists have recommended using a numbering system (1-3) rather than RIFLE and to refine the risk criteria to be somewhat more sensitive, but the differences between the systems are relatively modest.<sup>5</sup>

RIFLE Classification System for Acute Kidney Injury	
	Definition
<b>RISK</b>	Serum creatinine increased 1.5 times, or GFR decreased by 25% or urine production of <0.5 ml/kg for 6 hours
<b>INJURY</b>	Doubling of serum creatinine or GFR decreased by 50% or urine production <0.5 ml/kg for 12 hours
<b>FAILURE</b>	Tripling of serum creatinine or creatinine >4 mg/dl; acute rise of 0.5 mg/dl, or GFR decreased by 75% or urine output below 0.3 ml/kg for 24 hours
<b>LOSS</b>	Persistent AKI or complete loss of kidney function for more than 4 weeks
<b>END-STAGE RENAL DISEASE</b>	Loss of kidney function for more than 3 months

The staging system can help guide emergency care, but a person with AKI is unlikely to recover unless the cause is addressed. Many nephrologists categorise the causes of injury based upon whether they are ‘pre-renal’ (primarily due to volume depletion or a drop in blood supply to the kidneys), ‘intrinsic/renal’ when there is inflammation, damage or death of cells within the kidneys (glomerular or tubulo-interstitial damage), or ‘post-renal,’ generally due to an obstruction of the urinary tract. However, there can be some overlap because kidney functions can be interdependent. For instance, cutting off the blood and oxygen supply to the kidney can result in tubule death, or casts of dead tubules may even cause a

urinary obstruction, while inability to excrete urine can cause a backflow that affects other kidney functions.

The symptoms of AKI vary depending on the part of the kidney that has been injured, the cause and the severity of the case at presentation — and the predominant symptoms may be due to the underlying infection or condition to which the kidney injury is secondary. (AKI may be detected incidentally during routine laboratory studies in people under care for other conditions before there are noticeable symptoms of kidney dysfunction).<sup>6</sup>

However, common symptoms tend to include decreased appetite, fatigue, nausea or vomiting that may last for days, high blood pressure, fluid retention, with swelling in the ankles, wrists and feet, and changes in urination (either increased urination at night or a decrease in or complete halt to urination).

In cases with uraemia, chest pain due to pericarditis or shortness of breath as a result of pulmonary oedema may develop. Very severe cases may present with danger signs, delirium or confusion, severe lethargy, seizure or coma.

Damage to other organ systems commonly occur as a consequence of AKI. For instance, fluid and electrolyte disturbances could lead to long-term hypertension and heart problems, while severe uraemia can result in neurological impairment and platelet dysfunction.<sup>7</sup> Thus, even though patients can recover their kidney function, their long-term prognosis may be poor.

There are no reliable data on how often AKI occurs in Africa, and the incidence no doubt varies by region. One estimate, based upon some cases reported in regional publications is only 150 per one million population,<sup>8</sup> but AKI may be underreported as it is not the primary illness, but rather a secondary (and potentially fatal) complication observed in patients already in care. Another reason cases go undocumented is that many people never make it to a facility where they can be diagnosed. So this figure is dubious at best.

The incidence of AKI can be expected to be higher in people living with HIV who are not yet on or who are just beginning ART, due to their increased susceptibility to bacterial infections and opportunistic infections, and increased likelihood of initiating a medication that can trigger AKI. In settings where ART is not so widespread, low CD4 cell counts and concurrent opportunistic infections are common risk factors for AKI.<sup>9</sup>

According to one large study of hospitalised patients in the US, AKI was almost 4.6 times more common among people living with HIV than in HIV-negative patients in the pre-ART era, and was still 2.8 times as common in the era of widespread access to ART.<sup>10</sup> AKI in people living with HIV “was associated with traditional predictors such as age, diabetes mellitus, and chronic kidney disease, as well as acute or chronic liver failure or hepatitis coinfection ( $P < 0.001$  for all comparisons).” The study also found that the risk of mortality in HIV-positive people was six times higher if they had an AKI.

Another more recent study evaluated the long term consequences of AKI in people living with HIV in the VA Study.<sup>11</sup> The records of over 17,000 patients were reviewed for hospitalisations due to AKI and for the association of AKI with risk for heart failure, cardiovascular events, ESKD, and mortality more than 90 days after being discharged. Using the AKIN 1-3 staging system, 2453 subjects had stage 1 AKI; 273 had stage 2 or 3; and 334 had AKI that required dialysis. In multivariate-adjusted analyses, AKI stage 1 was associated with death and ESKD, but not heart failure or other CVD, although more severe AKI had much stronger associations with each negative outcome. Even after recovery, people who had had AKI were more likely to die than other patients in the VA study. “In this national sample of HIV-infected persons, we found the

clinical repercussions of AKI appear to extend beyond the hospital setting contributing to excess cardiovascular risks, ESRD, and mortality,” the authors wrote.

Most of the reports on the prognosis for people with AKI in Africa come from hospitals with nephrology departments where dialysis is available and where outcomes are not so much worse than in industrialised countries. In more resource-constrained settings, however, the outcomes can be extremely poor. In one report on people living with HIV and AKI at a hospital in Kinshasa, Democratic Republic of Congo, (DRC), renal replacement therapy was not available and 91.6% of the patients died very shortly after admission.<sup>12</sup>

But if the cause of AKI is diagnosed and treated promptly, recovery is possible even in low-resourced settings.

“In our experience in South Africa, hospitalised patients are at advanced stages of immunosuppression” Dr Saraladevi Naicker of Johannesburg Hospital and colleagues wrote in a recent review, but “with aggressive and appropriate management, the AKI is potentially reversible, even if there is an underlying chronic component. This concept is critical for those managing patients in circumstances where there is limited/no access to intensive or high levels of care and/or acute dialysis.”

The following conditions can lead to severe losses of kidney function.

## Forms of acute kidney injury

### Acute Tubular Necrosis (ATN)

is tubular cell destruction that can occur when tubular cells are oxygen-deprived (due to a drop in the blood pressure or supply) and when they have been exposed to a toxin including certain drugs and traditional remedies.

The reabsorption process that occurs in the tubules is metabolically demanding and a pre-renal problem that reduces the oxygen supply to the kidneys can result in abrupt tubular cell damage or dysfunction; if blood pressure/supply drops suddenly for even a relatively short period of time (around 30 minutes), it can cause tubule death. The most common reasons for this are severely low blood pressure, vasoconstriction following septicaemia or other forms of shock, blood loss due to injuries or surgery, obstetric complications and severe dehydration associated with diarrhoea or vomiting.<sup>13</sup> ATN may be more common in people living with HIV, particularly with advanced disease, due to susceptibility to different diarrhoeal pathogens, vasoconstriction associated with some opportunistic infections, and some of the medications used to treat HIV-related infections, such as amphotericin B, and the aminoglycosides.

In Africa, many of the people who present with ATN have been ‘treated’ by traditional healers. A number of the plants used, such as *Impila* (*Callilepis laureola*) found throughout southern Africa, can cause ATN. Another traditional ‘remedy’ involves enemas containing potassium dichromate (which is used by the leather industry as a tanning agent). This causes both severe, bloody diarrhoea and is a direct tubular cell toxin.

ATN is one of the most common causes of AKI, but tubules can grow back, restoring kidney function if the cause of ATN is identified and treated.

### Acute Interstitial Nephritis

(AIN) involves inflammation of the tubules and surrounding tissue. The vast majority of AIN are due to severe allergic reactions to medications, generally within days of exposure (with the exception

of reactions to NSAIDs that may only develop after months). Auto-immune disorders, such as lupus and Sjögren syndrome, may also trigger similar acute inflammatory responses in the kidneys, though these often become chronic.<sup>14</sup>

Although person may have an allergic response to ANY drug, however, reactions are due to antibiotics (penicillins, cephalosporins, sulfa drugs, quinolones), followed by other drugs including NSAIDs, diuretics, thiazides and furosemide. Herbal remedies and recreational drugs may also be to blame.<sup>15</sup>

In people who have been treated for TB more than once, kidney injury may rarely occur as a result of an allergic reaction to rifampicin. Rifampicin-related AIN presents with flu-like symptoms, flank pain, hypertension, and decreased urine output.<sup>16</sup>

With the exception of the reactions to NSAIDs and rifampicin, most people with AIN present with symptoms of allergy such as rash and fever as well as signs of a systemic inflammatory immune response.

### Crystalluria:

A number of the medications used by people living with HIV are poorly soluble, and crystals from the drug may act directly as irritants, causing nephritis, or may precipitate as stones in the kidneys causing urinary obstructions, flank pain and haematuria.

There is ample evidence that the protease inhibitor indinavir (*Crixivan*) causes kidney stones in a sizeable number of people, although less use of indinavir in settings where better options are available has limited the scope of this problem.

Of more concern are case reports of kidney stones associated with the protease inhibitor atazanavir (*Reyataz*). They appear to occur much more rarely than with indinavir, but atazanavir may soon become more widely available as part of the second-line combinations in some resource-limited settings. A French cohort study found that about one in 100 patients developed atazanavir-related kidney stones after an average of two years on the drug,<sup>17</sup> thirty cases were reported to the US Food and Drug Administration in the first three years of its use,<sup>18</sup> and one patient out of 121 in a trial comparing maraviroc with tenofovir/FTC, both combined with atazanavir, withdrew because of kidney stones.<sup>19</sup>

In the industrialised world, the kidney stones associated with both these drugs, though painful, may be avoidable by drinking plenty of water, and gradually resolve if the drugs are withdrawn. However, crystalluria may occur more frequently in hot and/or arid settings, and recommendations to ‘just drink more fluids’ may be difficult to those with less access to clean drinking water.

In rare cases, crystalluria has also been attributed to the use of acyclovir and some sulfonamides.<sup>20,21</sup>

### Glomerulonephritis (acute):

The glomeruli can also become acutely inflamed leading to sudden appearance of haematuria, hypertension, water retention and swelling, especially in the face and eyelids.<sup>22</sup> Urine volume may be normal or low, but the colour of the urine may be tea-coloured or brown. Resulting uraemia and hypertension can lead to congestive heart failure, seizures and coma. Although the presentation may be acute, many of the problems described below are persistent, and scarring and fibrosis is possible, so these cases may progress to CKD even when the cause is identified and treated.

There are a variety of forms and aetiologies, but acute glomerulonephritis is generally due to certain infections, cancers and/or, more commonly, the immune system’s response to them, while some cases may be autoimmune (especially lupus), congenital or idiopathic. The mechanisms are complex, but in most



cases appear to involve the trapping of either viral antigens, antibodies, immune complexes (antibody-bound antigens) or immunoglobulins within the glomerular pores or membrane, leading to inflammation and/or in some cases morphological changes and/or destruction and collapse of parts of the glomerulus with a massive loss of large proteins into the urine.

When there are infiltrates (due to inflammation) in the glomeruli (observable on histology) it is called proliferative glomerulonephritis. Sometimes the damage to the glomeruli may be caused by direct infection, for instance, in some individuals, HIV appears to directly infect the podocytes (supportive cells in the glomerulus). How the virus enters the cell is unclear — podocytes have no CCR5 and CXCR4 co-receptors (more on this in the section on HIV-associated nephropathy).

Immunoglobulin A (IgA) glomerulonephritis appears to be triggered by respiratory or gastrointestinal infections and may have a mild or rapid course. Some acute glomerulonephritides are post-infectious, only appearing after infections subside. This is usually associated with certain strains of streptococcus that infect the throat or the skin, or other skin infections such as staphylococcus, with nephritis generally appearing a week or several weeks after the infection resolves. This is most often seen in children and is more common when those infections were left untreated.<sup>23</sup>

Parasitic (malaria), fungal and viral infections have also been known to trigger acute glomerulonephritis, particularly after acute infection or during convalescence (Mozart is believed to have died due to kidney failure after recovering from Scarlet Fever).<sup>24</sup> However, with chronic infections, such as viral hepatitis and HIV, kidney damage may occur at any time over the course of the disease and generally becomes chronic (see under *Chronic Kidney Disease*).

Crescentic glomerulonephritis is a rapidly progressing form of glomerulonephritis that can be caused by any of the above aetiologies. It often presents with flu-like symptoms: weakness, fatigue, and fever, and sometimes loss of appetite and nausea. The name refers to the histological appearance of the glomeruli.

#### **More on infections or neoplasms associated with AKI:**

According to the recent survey of nephrologists in Africa, infections, including malaria, HIV and diarrhoeal pathogens, are the most common causes of AKI on the continent.<sup>25</sup> It has already been noted that sepsis and infections that cause severe dehydration or vasoconstriction can trigger ATN, and that infections or immune responses to them can cause glomerulonephritis. In other cases, infections in or near the kidney can also cause inflammation both in the tubules and glomeruli or form obstructions, particularly when scar tissue develops in the urinary tract — though urinary tract infections are the most common cause of urinary obstructions.

AKI is an uncommon complication of malaria, only seen in less than 1% of cases (mostly in adults), but it has a mortality rate of up to 45%.<sup>26</sup> Malaria can cause either ATN or glomerulonephritis leading to AKI. A recent retrospective review from a kidney disease and research centre in Gujarat, India, found that 100 (10.43%) out of 958 cases of AKI were associated with malaria.<sup>27</sup> According to the survey of nephrologists in Africa, malaria was the leading cause of AKI in Cameroon, Côte D'Ivoire, Burundi, Ethiopia, Mozambique and Zambia, and a common cause in a number of others.<sup>28</sup>

HIV increases the risk of malaria — in studies in Uganda, HIV infection was associated with a greater than 6-fold increased risk of new malarial infections — and according to some reports, the interplay between the two infections is associated with a high risk of AKI.<sup>29</sup> In the Democratic Republic of Congo, a study of 43 pre and

post-mortem renal specimens from patients with HIV found evidence of acute malarial infection in 28%.<sup>30</sup> In a prospective study of 210 HIV-positive patients, the same facility found AKI in 24 (11.4%), 16% of which were associated with malaria.<sup>31</sup> A subsequent study found 36.8% of AKI cases were associated with acute malaria.<sup>32</sup>

In addition, in people with low CD4 cell counts, there can be unusual aetiologies if opportunistic infections, or neoplasms such as lymphoma or Kaposi's sarcoma spread to the kidneys or surrounding tissue.<sup>33</sup> For instance, the gastrointestinal tract, including the kidneys and bladder, is the second-most common site of mycobacterial TB infection outside of the respiratory system. Infection can lead to granulomas, with fibrosis and scarring that form an obstruction in the urinary tract. However, as with other forms of extrapulmonary TB, a person with urological tract tuberculosis may or may not have respiratory symptoms of TB, which, of course, makes diagnosis more challenging.<sup>34</sup>

Hepatitis B can cause either a nephritis and/or a nephrotic syndrome leading to AKI and/or CKD (sometimes called membranous glomerulonephritis), especially in children.<sup>36</sup> As already noted, HIV infection may cause AKI in a number of ways, either by provoking an immune response or by directly infecting renal epithelial cells, however, it is more common for chronic kidney disease to develop.

#### **Thrombotic microangiopathy**

is another less common cause of AKI that HIV might cause or perhaps trigger, which bears mentioning because it often leads to death, especially in Africa, since a high level of care is required to treat it.<sup>37</sup> Thrombotic microangiopathy (TMA) literally means the formation of blood clots in small blood vessels (such as the glomeruli), and the term refers to a spectrum of syndromes where this occurs. These conditions have a poorly understood pathogenesis and many of the cases reported in the literature do not seem to share a common pathology.<sup>38,39</sup> The diagnostic criteria and clinical definitions for TMA aren't entirely agreed upon, either, or are non-specific, so it is not clear exactly how common TMA is since there is controversy about whether it is being diagnosed appropriately in all of the published reports.<sup>40</sup>

One form of TMA is thrombotic thrombocytopenic purpura (TTP), in which platelets aggregate to form clots in blood vessels, which then leads to thrombocytopenia (an abnormal drop in the number of platelets), microangiopathic haemolytic anaemia (a breakdown of blood cells leading to anaemia), fever, neurological and renal abnormalities.<sup>41</sup> Purpura, a rash caused by small blood vessels leaking into the skin is a common symptom. A similar condition, haemolytic-uraemic syndrome (HUS) is more of a renal disorder, also characterised by microangiopathic haemolytic anaemia, thrombocytopenia, fever, and severe AKI.<sup>42</sup>

Studies in South Africa have reported a higher frequency of TMA among people living with HIV than other settings. A study at Groote Schuur Hospital reported that HIV-related TTP was found predominantly among black women with CD4 cell counts below 100.

In people without HIV, many cases of TMA are autoimmune-related or idiopathic, while others seem to be related to certain infections or even medications. A variety of pathogenic mechanisms have been proposed for the related syndromes, mostly focused on an immunological component, with antibodies or immune complexes causing damage to endothelial cells (which line the interior of blood vessels) which then causes platelet activation (possibly through altered expression of von Willebrand's factor, a

platelet binding receptor) and localised coagulation, with clots being deposited in the microvasculature.<sup>43</sup>

However, identifying the cause of TMA and responding correctly raises some complex issues. Some studies have shown that many people with TTP have a deficit of a particular enzyme, ADAMTS13, which is involved in keeping platelets from clumping together and forming blood clots.<sup>44</sup> One theory is that, after certain infections, the body produces antibodies that are cross-reactive with this enzyme, and that measuring levels of it could be diagnostic of TTP.<sup>45</sup>

However, other studies found that 1) measurements of ADAMTS13 are not specific or sensitive enough to distinguish TTP from other severe conditions<sup>46</sup> and/or 2) that enzymatic activity and the presence of ADAMTS13 and its inhibitors appears to be heterogeneous in people living with HIV-related TTP — in fact, a substantial proportion of cases have normal levels of the enzyme.<sup>47</sup> Meanwhile, other reports suggest ADAMTS13 levels are often normal in cases of HUS.<sup>48</sup> This would tend to suggest that other factors are important in the pathogenesis of HIV-related TMA, such as direct viral pathogenic activity due to toxic viral proteins<sup>49</sup> (p24 antigen has been found inside endothelial cells)<sup>50</sup> and/or the effects of inflammatory cytokines, such as TNFα or IL-1B.<sup>51</sup>

Another possibility is that some cases are simply being misclassified as TMA. In one paper, Benjamin et al tried to analyse the reports of TTP in people living with HIV in the literature and found diagnostic details wanting, and then did a chart review of one registry of TTP (HIV and non-HIV related) and found many alternative diagnoses were possible in people living with HIV. “The diagnostic criteria for TTP, requiring only the presence of microangiopathic haemolytic anaemia and thrombocytopenia with no alternative cause are not specific, and because AIDS-related disorders may cause these abnormalities, the diagnosis of TTP is often uncertain in patients with HIV infection,” they wrote.

In other words, these conditions may be found together in people living with HIV, especially in advanced disease, but may have unrelated causes such as opportunistic infections, bone marrow suppression and so on.

So, different pathologies and diagnoses could have important prognostic and therapeutic implications, particularly if the diagnosis proves to be wrong. Biopsy-proven TMA has a mortality rate in excess of 95% if left untreated.<sup>52</sup> Treatment usually requires plasma exchange therapy (plasmapheresis) a process in which the blood plasma is removed, filtered and returned to the body. But this requires skilled operators, expensive equipment that isn't available in every hospital in resource limited settings, and it can also lead to a number of complications.<sup>53</sup>

Researchers from Groote Schuur have published encouraging results treating HIV-related TTP with plasma infusions (which could be performed at institutions where plasmapheresis is not readily available, particularly in isolated communities and in developing countries).<sup>54</sup> In fact, HIV-positive patients with TTP had much better responses than HIV-negative people with TTP, which, again, raises the question of whether this is indeed the same syndrome or whether it has a different pathology. On the plus side, the research suggests that TMA in people living with HIV might be more easily and inexpensively treated than many think. However, the authors noted that plasma infusion might not be tolerated as well by patients with HUS-related AKI who have developed fluid overload or oliguria.

#### Immune reconstitution inflammatory syndrome (IRIS):

Since a number of infections, such as tuberculosis, can involve the kidneys, it is not surprising that IRIS-like reactions to these

infections might occur shortly after the initiation of ART. Naicker et al note that AKI still seems quite frequent in the era of ART, particularly in the first year on treatment — which would seem to suggest IRIS. A case report in CID described a case of IRIS leading to AKI in a person with miliary TB, eight weeks after starting TB treatment, and six weeks after starting ART.<sup>55</sup> After treatment with prednisone, the patient recovered.

#### Obstetric complications

are a significant cause of AKI in Africa secondary to pre-eclampsia and eclampsia, septic conditions, obstetric haemorrhage and herbal toxins (traditional medicine).<sup>56</sup>

#### AKI in children:

Children with HIV are susceptible to many of the same types of kidney injury as adults with HIV, though they may be particularly vulnerable to AKI resulting from dehydration (due to diarrhoeal diseases), HUS, and due to reactions to drugs such as cotrimoxazole.<sup>57</sup> Obviously, however, creatinine levels and GFR calculations are different in young children. Also, although dipstick tests for proteinuria can be used in children, fever, intercurrent infections and and/or nappy rash can lead to false positives.

#### Schwartz formula and age related normal value of creatinine and glomerular filtration rate

Normal age related serum Creatinine (μmol/L)	
Infant	1835
Child	2762
Adolescent	4488
Schwartz Formula: GFR (μmol/L) = k x height (cm) x Creatinine (μmol/L)	
Preterm Infants	k=29
Infants less than one year old	k=40
Children 1 to 13 years old	k=49

#### Chronic kidney disease

Kidney disease is defined as being chronic when there is evidence of either kidney damage or reduced kidney functioning for three months or longer. Most of the pathologies seen in AKI can become chronic decreasing kidney function gradually over time, and possibly causing a cascade of chronic hormonal or electrolyte imbalances. But in people with HIV, chronic disease is much more likely to be glomerular, presenting with syndromes such as HIVAN, HIVICK (see below) and other disorders.

As already noted, eGFR is used to describe the severity of CKD, in accordance with a staging system established by the United States' National Kidney Foundation. Stage 1 is defined as a normal eGFR alongside some evidence of kidney damage such as protein in the urine. At Stage 5, the most severe stage, an eGFR value of less than 15 mL/min indicates kidney failure, at which point a person cannot be expected to survive for long without dialysis or a kidney transplant. The five stages are summarised in the table below.

### Glomerular filtration rate (GFR) staging

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)

This staging system has also come under some criticism, for a variety of reasons. Some have to do with the use of the MDRD equation, which the staging system is based on. There are some questions about whether stage 1 and even stage 2 should really be seen as CKD, and whether the thresholds for stage 1 and 2 really signify a clinically relevant difference.

There is also controversy about Stage 3 disease. Some investigators are concerned that the prognosis of stage 3 individuals may vary widely. Some have recommended dividing stage 3 into stage 3A (with GFRs between 45-59 mL/min) and 3B (with GFRs 30-44 mL/min), while guidelines in the UK recommend further subdivisions based upon the presence or absence of proteinuria (denoted as a 'p').<sup>58</sup> For instance, staging someone with 31 eGFR and proteinuria as CKD stage 3Bp would better indicate a greater risk of rapid progression and a greater need for specialised care than CKD stage 3.

Generally, as people age, renal function declines, but once significant CKD has been established, it can accelerate other illness that in turn causes further injuries to the kidneys. CKD thus becomes increasingly severe, in some cases rapidly, in others more gradually. While the decline may be slowed with treatment – in fact, a number of studies in people living with HIV experience improvement in eGFR on ART (see below) – severe CKD is seldom reversible.

As already noted, it is typical for people with CKD not to notice symptoms until the disease has progressed considerably. Even when people are aware of problems, these are often the same generalised complaints common to a number of illnesses in people living with advanced HIV. Common symptoms of chronic renal impairment include tiredness, loss of appetite, nausea and vomiting, headaches, a more frequent or less frequent need to urinate or reduced urine flow, difficulty concentrating, darkening of the skin, muscle cramps, itching and numbness, swelling in the hands and feet, puffiness around the eyes.

CKD can interfere with the kidney's regulatory functions, causing sometimes very subtle but chronic imbalances in electrolytes and minerals and renal hormone production. This leads to a wide array of complications and damage to other organ systems, with haematological abnormalities such as anaemia and TTP, weakening bones, hypertension and heart problems. CKD has been linked with dyslipidaemia, an excess of cholesterol and fats in the blood, which leads to atherosclerosis.<sup>59</sup> It has also been associated with a dramatically increased risk of all-cause mortality, particularly from cardiovascular disease.<sup>60</sup>

The association between CKD and cardiovascular disease (CVD) goes beyond shared risk factors. They form something like a feedback loop, with problems in the cardiovascular system putting strain on the kidneys, while injured kidneys contribute to CVD in a variety of ways. In fact, in the US, scientific and professional bodies concerned with heart and kidney disease now recommend that everyone presenting with CVD should be screened for evidence of kidney disease, while people with CKD should be regarded as being at very high risk of coronary heart disease.<sup>61,62</sup>

In the general population, study after study has shown that CKD is a significant risk factor for heart attack, stroke and other poor health outcomes.<sup>63,64,65,66</sup> One of the most recent was a prospective population-based cohort study in Iceland that included almost 17,000 people aged 33-81 who were followed for a median of 24 years, which found that even the earliest stages of CKD were associated with excess risk of subsequent coronary heart disease.<sup>67</sup> After adjustments for traditional CVD risk factors (age, sex, smoking, history of diabetes, systolic blood pressure, and total cholesterol), the hazard ratios for coronary heart disease were 1.55 (95% confidence interval 1.02 to 2.35) for stage 1, 1.72 (1.30 to 2.24) for stage 2, 1.39 (1.22 to 1.58) for stage 3A, 1.90 (1.22 to 2.96) for stage 3B, and 4.29 (1.78 to 10.32) for stage 4. Similarly, a just published study in 10,181 men found that moderate to severe CKD increased the risk of heart failure or CVD death by two and a half times, and in a subset without hypertension or diabetes, these risks were still 2.2 fold higher.<sup>68</sup>

Finally, a recent meta-analysis of studies containing over 1.2 million participants whose kidney function was measured either by urine dipstick (~1.1 million people) or albumin to creatinine ratios (~100,000) followed for a median of 7.9 years (range 2.1–11.6) was recently published in *The Lancet*.<sup>69</sup> Qualitative positive urine dipstick values were used as a surrogate for albuminuria, while eGFRs were calculated using the MDRD equation for those studies that reported creatinine levels. After adjustments for age, ethnic origin (meaning, generally, African-American), gender, history of cardiovascular disease, systolic blood pressure, diabetes, smoking, and total cholesterol concentration, the study did not find a significantly greater risk of mortality at higher eGFRs. However, an eGFR of less than 60 mL/min and ACRs 1.1 mg/mmol (10 mg/g) or more are independent predictors of all-cause mortality and cardiovascular mortality in the general population.

So it should really come as no surprise that similar poor outcomes are seen in people living with HIV and CKD.

In the first part of this series, we noted one study demonstrating that renal impairment was a significant risk factor for heart attack and strokes in people living with HIV. A number of other studies have now been published that support these findings.

The largest analysed the association of CKD and CVD in 17,264 participants from the Veterans' Health Administration Study (VA Study) for whom they could find data on kidney function (creatinine/eGFRs and ACRs).<sup>70</sup> Then patient records were reviewed for the incidence of CVD, defined as coronary, cerebrovascular, or peripheral arterial disease, and incident heart failure, between the years 1999 and 2008.

They found that rates of CVD and heart failure were at least 6-fold greater in people living with HIV and an eGFR <30 mL/min and albuminuria > or =300 mg/dL compared to those with an eGFR of 60 mL/min or higher and no albuminuria. After multivariable adjustment, eGFR levels 45 to 59, 30 to 44, and <30 mL/min were associated with hazard ratios for incident CVD of 1.46 (95% CI, 1.15 to 1.86), 2.03 (1.47 to 2.82), and 1.99 (1.46 to 2.70) compared with eGFR > or =60 mL/min. Similarly, albuminuria levels 30, 100,



and  $> \text{or} = 300 \text{ mg/dL}$  had hazard ratios for CVD of 1.28 (1.09 to 1.51), 1.48 (1.15 to 1.90), and 1.71 (1.30 to 2.27) compared without albuminuria. Both markers eGFR and albuminuria levels were strongly associated with risk of CVD and heart failure. Kidney function and albuminuria provide complementary prognostic information that may aid CVD risk stratification in HIV-infected persons.

The question is, whether the association between CKD and CVD, with or without HIV disease, is applicable to Africa and other resource-limited settings. This is not yet clear, because factors such as diet could play a significant role in the continuum between CKD and CVD. However, as noted in the first part of this series, one programme in Zambia has already found that its clients who had renal impairment when they initiated treatment were more likely than their counterparts to die during a two-year follow-up period.<sup>71</sup> Other factors will increase the outcome of all-cause mortality in Africa as well, because, as pointed out in the series introduction, resource-constrained settings are poorly equipped to detect and manage people with CKD and particularly ESKD. Where there is virtually no renal replacement therapy available, people with ESKD simply die of kidney disease.

And at least in the US, there is yet another reason why CKD could lead to poor outcomes among people living with HIV — they may not be taking ART.<sup>72</sup> People living with HIV and stage 3 CKD or higher need dosage adjustment for several drugs, including antiretrovirals, otherwise they may experience more side effects which could lead them to quit treatment. So in another analysis of patients in the VA study, Choi et al examined the available pharmacy records to see whether people with CKD (eGFR  $< 60 \text{ mL/min}$  by the MDRD equation) were less likely than the population without kidney disease to receive ART and/or be prescribed appropriate doses of the renally excreted antiretrovirals. They found that people with CKD were less likely to be taking ART, and of those who were, many received prescriptions with inadequate dose adjustments. Collectively, this was associated with 22.2%–35.5% of excess mortality risk among patients with CKD, depending on the level of renal function. (There will be more on dosage adjustments in the next part of this series).

Since, as we describe below, HIV can directly cause severe CKD, there will be a higher percentage of people with CKD in the population not yet on ART — and despite the rapid scale up of treatment in resource constrained settings, we still have a long way to go to getting everyone on treatment.

## Risk factors for chronic kidney disease in people with HIV

A large body of research provides insight into which HIV-positive people in high-income countries are most likely to be vulnerable to kidney disease. Although it is not known how much can be extrapolated to resource-limited settings, the available evidence may at least offer a starting point for assessing risk factors in those settings.

In its guidelines on managing chronic kidney disease in HIV-positive people, the HIV Medical Association (HIVMA) of the Infectious Diseases Society of America (IDSA) considers the following groups to be at elevated risk for kidney disease: African-Americans; people with diabetes, high blood pressure and Hepatitis C; people whose CD4 cell counts are under 200 cells/mm<sup>3</sup>; and people whose viral loads exceed 4000 copies/mL. The IDSA/HIVMA guidelines also identify the following as risk factors for

HIVAN specifically: African-American ethnicity, decreased CD4 cell count and a family history of renal disease.<sup>73</sup>

Since the guidelines were published in 2005, recent research has confirmed the predictive value of those and closely related risk factors. A 2007 analysis of approximately 4500 members of the EuroSIDA study cohort, including HIV-positive people from all regions of Europe, found that having chronic kidney disease was associated with older age, lower CD4 cell count nadirs and diagnoses of AIDS, diabetes and hypertension.<sup>74</sup> Two studies of urban US HIV-positive populations found similar associations, and also found African-American ethnicity to be an independent predictor of chronic kidney disease.<sup>75,76</sup> At least one study addressing this issue in HIV-positive people outside of Europe and North America has been published. In a Chinese cohort, older age and lower CD4 cell count were independent predictors of CKD.<sup>77</sup>

In sub-Saharan Africa, high blood pressure is responsible for much of the CKD that is reported. But risk factors for CKD in the black sub-Saharan African population could be quite different. For instance, data show that CKD strikes black Africans at a much younger age (between 20-50 years old) and glomerular diseases appear much more common.<sup>78</sup>

But the question of ethnicity is for obvious reasons of particular importance in sub-Saharan Africa, given the rates of CKD, ESKD and CKD-associated mortality in African-Americans, especially those living with HIV compared to non-black Americans.<sup>79</sup> To cite one study by Lucas et al, who monitored the development of CKD and ESKD in 3,332 HIV-infected African-Americans and 927 HIV-infected white Americans over a follow-up period of 4.5 years, African-Americans had only a slightly higher risk of developing CKD (as staged by eGFRs), but were 18 times more likely to progress to ESKD, with a decline that was six times more rapid than white Americans.<sup>80</sup>

Much of the literature in this realm is based on studies of African-Americans, whose greater vulnerability to HIVAN (a glomerular condition) is strongly linked to genetic factors. However, African-Americans and other descendants of the African diaspora are unlikely to represent the vast genetic diversity of the continent. Even African populations that have historically lived in close proximity to each other may exhibit considerably different health-related vulnerabilities. The ethnic diversity in South Africa alone is noteworthy, with 11 black African tribes, the Khoisan/Bushmen (who come from a entirely separate mitochondrial lineage), white Europeans, Indians, Cape Malay and mixed race individuals.

A 2009 review article on kidney disease among HIV-positive people in sub-Saharan Africa calls attention to the very different outcomes of three South African studies that utilised biopsies to determine the causes of kidney impairment in HIV-positive people. While HIVAN was by far the most common kidney disease diagnosed in one South African study, participants in another South African study were found to have only 5% prevalence of HIVAN and 40% prevalence of HIV immune complex-mediated kidney disease (HIVICK).<sup>81,82</sup> Biopsy results in a third study from South Africa indicated that 27% of cases of kidney disease were attributable to HIVAN; 21% to HIVICK; and the remainder to other conditions.<sup>83</sup> (All participants in the first two studies were ART-naïve, and 92% of participants in the third study were ART-naïve.) The review authors conclude, “Evidently the histological patterns of renal disease in patients with HIV are variable, even within the same region. This observation might reflect the high degree of genetic variability among black South Africans from different ethnic groups.”<sup>84</sup>



However, using diagnoses of HIVAN and HIVICK at different facilities may be somewhat misleading for several reasons—one is that HIVICK can be found in people of black African descent as well. But, more importantly, the diagnostic definitions of these disorders are in a state of flux (see below).

“There’s much confusion over the terminology,” Dr Nicola Wearne said during her talk last year at the Nephrology conference in Cape Town. “There is *no* clearly defined definition of HIVICK.” The diagnosis of HIVICK is often made after finding evidence on biopsy of immune complex disease, but this is also common in people who also have features of HIVAN—the histological picture is often mixed. Furthermore, she said that the classification of HIVAN needs to be expanded because they are seeing presentations that were previously not described in the literature (based primarily what had been observed in African-Americans).

So differences in the diagnoses of one condition versus the other may have less to do with differences in genetic susceptibility and more to do with a lack of standardisation in diagnostic definitions.

Another recent study has found that HIVAN appears to be entirely absent in a population of Semitic Ethiopians living with HIV.<sup>85</sup> The study was conducted in Israel, and the researcher compared measures of kidney disease between Ethiopian and non-Ethiopian Israelis, and found no evidence whatsoever of HIVAN in either population. The incidence of HIVAN among the Ethiopian Israelis is “strikingly less than that reported for other populations for recent African ancestry. This does not appear to be attributable to differences in HIV infection control or viral subtype and most likely represents population-based differences in host genetic factors. This finding emphasizes the importance of avoiding generalizations with respect to phylogeographic ancestry in disease-susceptibility studies,” the investigators wrote.

However, recent genetic advances suggest that mutation or mutations associated with increased susceptibility in African-Americans do appear to be fairly widespread on the continent—with the notable exception of the Northeast. Initially, it was thought that the genetic factor was a variation in the MYH9 locus of chromosome 22, which was found to be highly associated with glomerular kidney diseases including idiopathic focal segmental glomerulosclerosis, hypertensive nephrosclerosis and HIVAN.<sup>86</sup> This haplotype was found to be present in 60% of African-Americans and in less than 4% of Europeans. A subsequent analysis of the Human Genome Diversity Panel found the frequency of this risk haplotype followed a gradient, or cline, being most frequent within sub-Saharan African populations (range 50–80%), less frequent in populations from the Middle East (9–27%) and Europe (0–9%), and rare or absent in Asia, the Americas, and Oceania.<sup>87</sup> Other evidence gathered by this study suggested that natural selection was perpetuating this mutation because it conferred protection from disease, or some other environmental factor.

However, the researchers noted that the MYH9 gene was sitting almost immediately next to the APOL1 gene that encodes apolipoprotein L-I, which is involved in the resistance to infection by *Trypanosoma brucei*, the cause of African trypanosomiasis or sleeping sickness in sub-Saharan Africa. They suggested that the MYH9 might have been dragged along by its neighboring gene, rather than conferring a population benefit in itself.

As that paper was published, two papers came out showing that there are in fact two mutations in the APOL1 gene that are even more significantly associated with ESKD than all previously reported genetic variations in MYH9 that are common in African chromosomes but absent from European, Chinese or Japanese

chromosomes.<sup>88,89</sup> Then the researchers examined the frequencies of these mutations in a sample set of 676 individuals from 12 African populations, including 304 individuals from four Ethiopian populations.<sup>90</sup> This was coupled with the corresponding distributions for the African ancestry MYH9 risk mutations. They found a pattern of reduced frequency of the APOL1 mutations as well as the MYH9 variants in northeastern Africa, in contrast to most of the central, western, and southern African populations examined. “Especially striking was the complete absence of the APOL1 missense mutations in Ethiopia,” the authors wrote.

Exactly how these mutations may increase susceptibility to glomerular kidney disease has yet to be determined, but even if there is an increased genetic risk for certain forms of kidney disease in a large part of Africa, it may not lead immediately to an epidemic of CKD. There are great differences in diet, and body composition between African-Americans and many black Africans that no doubt play a role in the evolution of kidney disease. Certainly the prevalence of some chronic diseases such as diabetes is lower in Africa than in the United States. So in the absence of the Western urban lifestyle, increased genetic susceptibility may not become manifest as CKD. However, that risk may be changing with increased development and globalisation.

“Recent hospital morbidity and intensive care unit statistics in South Africa indicate that the prevalence of coronary heart disease (CAD) in urban blacks is increasing,” Dr Saraladevi Naicker wrote in a recent review.<sup>91</sup> “Hypertension, diabetes, coronary heart disease and ESRD are on the verge of becoming an epidemic in Africa with urbanization.”

Nevertheless, if an inherited trait makes sub-Saharan black Africans more susceptible to HIV-related glomerular nephropathies, there is an immediate cause for concern. Proper (and standardised) surveillance for CKD in people living with HIV are needed to better characterise how great this risk is.

## Prevalence of CKD in people living with HIV

Unfortunately, current knowledge about renal disease in HIV-positive people in low- and middle-income countries is based on a fairly small number of studies that have assessed renal health in a variety of ways, often relying on non-resource-intensive screening and diagnostic tools. Thus, it is difficult to characterize the incidence, prevalence and severity of kidney impairment.

“Very little data are available on the worldwide prevalence of CKD in people with HIV. This is also true regarding the prevalence and impact of HIV-related renal disease in sub-Saharan Africa,” Dr Wearne said during her talk in Cape Town.<sup>92</sup> However, she cited recent research published in *The Lancet* showing an increase in deaths due to chronic disease in South Africa from 1999–2006.<sup>93</sup> “Although there has been an increase in death due to diabetes and hypertension.... this cannot account for the 67% increase in mortality [related to kidney disease]. Kidney disease in HIV must be contributing to this rise,” she said.

One of the few large cohort studies of renal functioning in the context of HIV in the developing world utilised serum creatinine measurements and the Cockcroft-Gault equation to calculate eGFR levels of more than 25,000 Zambians taking ART. By this measure, at the time they initiated treatment, one-third of all cohort members had eGFR values below 90 mL/min, indicating some degree of renal impairment. While most cases of renal impairment were mild, almost a quarter of cases were of moderate severity, and 3% were severe.<sup>94</sup> However, when GFR was calculated by the MDRD equation, only 3,209 individuals (12.4%) appeared to have a renal

insufficiency: about three quarters of these cases were classified as mild, 20.0% were moderate, and 5.3% were severe.

The Development of Antiretroviral Therapy in Africa (DART) study group, which has the primary purpose of assessing ART clinical management strategies in resource-limited settings, published research on kidney functioning in 3316 Ugandans and Zimbabweans at the time of ART initiation. An analysis of eGFR values, again using Cockcroft-Gault, indicated that as many as 45% of study participants had mild renal impairment, and that 7% of study participants had stage 3 CKD.<sup>95</sup>

Isolated screening studies suggest that many sub-Saharan African countries have high prevalences of kidney disease. Small studies in Kenya (11.5% had stage 3 or higher CKD) and Uganda also found high prevalence of reduced eGFR in HIV-positive people. The Kenyan cohort was ART-naïve, and the ART status of the Ugandan cohort was not specified.<sup>96, 97</sup>

Notably, the investigators in the Kenyan study explored using both the Cockcroft-Gault and MDRD equations and found that the Cockcroft-Gault equation suggested a prevalence of renal insufficiency two to four times higher than that estimated by the MDRD equations and question the validity of its use in a population so different from which it is based upon. "It is important to understand that neither of these tests has been validated in HIV-infected persons or East African populations," the investigators wrote. "Furthermore, the MDRD equation has not been validated in patients without chronic kidney disease and thus may underestimate GFR in such patients. In order to address these issues a study using more direct measurements of renal function in a cohort of HIV-infected Kenyans is under development."

Other studies have simply reported proteinuria, albuminuria and serum creatinine. For instance, a Nigerian study that defined renal disease in terms of the presence of proteinuria or abnormal serum creatinine found the prevalence of renal disease to be 38% in a cohort of 400 HIV-positive people, most of whom were ART-naïve.<sup>98</sup> HIV-positive study cohorts in Cote d'Ivoire (both ART-naïve and ART-experienced) and Tanzania (unspecified ART status) respectively had 26% and 28% prevalence of albuminuria.<sup>99, 100</sup>

ART has the potential to change the dynamics of kidney disease in complex ways. Over the short-term, studies have suggested that ART regimens that successfully suppress viral load can, temporarily at least improve renal function – and may interrupt the course of severe conditions such as HIVAN. At the same time however, it should be noted ART may not, on its own, be adequate to interrupt the continuum of gradually worsening kidney disease once it has become established. For instance, a review of death certificates found that the percentage of deaths in HIV-infected people attributed to kidney disease actually increased from 6.3% to 9.1% in the US between the years 1995 and 2000 (after the ART era had begun).<sup>101</sup>

Furthermore, now that ART can suppress viral activity on a long-term basis, more people are living long enough to experience ageing-associated health problems such as diabetes and cardiovascular disease – and in many cases are at elevated risk for these problems because of metabolic side-effects of ART. Other ART-related toxicity may directly increase the risk of CKD (see below).

Other types of treatment may benefit people living with HIV and CKD. Since the prognosis and management of CKD differs by cause, it is important to distinguishing between the various causes of chronic kidney disease in people living with HIV.

## Causes of chronic disease in people with HIV: diabetes and hypertension

Just as with AKI, people living with HIV are at risk of CKD caused directly by HIV, indirectly due to HIV treatment and coinfections. People living with HIV may also have increased susceptibility to non-HIV related conditions that cause renal disease in the general public. Important causes of CKD in HIV-positive populations worldwide include non-inflammatory glomerular diseases caused by diabetes and high blood pressure, HIV-associated nephropathy (HIVAN), HIV immune complex disease and other immune glomerulonephropathies, chronic Hepatitis B and Hepatitis C, as well as exposure to nephrotoxins – including heroin. Less commonly, tubulointerstitial injuries can become chronic, as with some autoimmune diseases, or when there is persistent exposure to toxins and certain medications. This is true of some antiretrovirals, in particular, tenofovir.

### Diabetes

is the leading cause of kidney disease in the general population globally. In Europe and the US, the prevalence of stage 3 CKD is 4.6% among the general population, but is 26.4% among people with diabetes.<sup>102</sup>

Like other chronic diseases, diabetes has not been prioritised in sub-Saharan Africa. There is again a paucity of good epidemiological data on both the disease burden and on the rate of major complications such as diabetic nephropathy. Most diabetes cases reported are type 2, but the low prevalence of type 1 diabetes may simply be a reflection of poor survival of those who have it.<sup>103</sup> While it is certainly under-diagnosed, the prevalence of diabetes is generally much lower than in the industrialised world, with estimates of an overall 2-3% prevalence, but with wide variations between rural and urban/periurban settings.<sup>104</sup> Diabetes is much more common in urban settings, because of increased access to less healthy foods, alcohol, cigarettes, which is usually coupled with less physical activity than in rural settings and increasing levels of obesity (more on this below).

The International Diabetes Federation estimates that sub-Saharan Africa's burden of diabetes was 12.1 million in 2010. However, due to increased urbanisation, this is expected to increase by 98% to 23.9 million by 2030 – more than twice the predicted global increase.<sup>105</sup> Furthermore, as Mbanya et al wrote recently in *The Lancet*, "the rate of undiagnosed diabetes is high in most countries of sub-Saharan Africa, and individuals who are unaware they have the disorder are at very high risk of chronic complications."

Notably, estimates of the prevalence of diabetic glomerulopathy in sub-Saharan Africa also vary greatly from study to study, ranging from 6% to 30%.<sup>106, 107</sup>

Diabetes is increasingly recognised as a major challenge in HIV clinical management. A growing epidemic of diabetes among HIV-positive people in many high-income countries appears to be partially attributable to metabolic changes associated with ART use. While it is important to bear in mind that genetic, lifestyle and environmental factors contribute much of the variation in diabetes incidence across different populations, studies of HIV-positive people taking ART in industrialised settings have consistently called attention to this problem.

One large multicentre study, for example, found that ART use was associated with a fourfold increase in diabetes.<sup>108</sup> According to most papers, the drugs most strongly associated with diabetes are the “first generation” NRTI drugs AZT, ddI and especially d4T.<sup>109</sup> However, one of the largest studies, which found that longer cumulative exposure to NRTI in general was associated with an increased diabetes incidence, could find no association between use of some of the individual NRTIs such as AZT, abacavir, or d4T with the development of diabetes.<sup>110</sup> Perhaps surprisingly, though, it did find that cumulative exposure of more than one year to 3TC was associated with a nearly three-fold increase in the rate of diabetes incidence after adjustment for covariates including cumulative use of protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

Notably, a cross-sectional study at Kenyatta National Hospital of 295 people living with HIV, 45% of whom were on ART, could find no significant association between use of ART and increased dysglycaemia (the presence of impaired fasting glucose or impaired glucose tolerance, or diabetes mellitus).<sup>111</sup> Although, it is possible that differences in lifestyle-related risk factors may affect the development of diabetes in people taking ART, the survey was conducted in early 2006, not that long after the ART roll-out, possibly before there was enough exposure to the NRTI's to trigger the metabolic changes leading to diabetes.

If ART does eventually lead to an increase in diabetes in Africa, there may be a subsequent increase in diabetic nephropathy, but it may take a while to become apparent as the complication generally develops or evolves over several years. The pathogenesis of diabetic neuropathy is complex and perhaps not fully resolved. In the condition's early stages, hyperglycaemia, oxidative stress and possibly altered insulin signalling appear to trigger renal vasodilation, leading to a dramatic increase in glomerular filtration with rates as much as 25-50% higher than normal.<sup>112</sup> Although seen as a primarily glomerular disease, early changes in the proximal renal tubule can result in increased sodium reabsorption, prompting the kidney's sodium regulatory functions to send out signals to boost the GFR, which in turn causes an increase in blood pressure and the blood volume flowing into the glomeruli, resulting in glomerular capillary distention. On imaging studies, the kidneys become significantly larger.<sup>113</sup>

The increased strain and inflammation begins to cause changes to the renal parenchyma, with glomerular and tubular basement membrane thickening (sclerosis) as well as the proliferation of mesangial and interstitial cells, within 3-5 years of an individual's developing diabetes.<sup>114</sup> The hypertrophy in turn compresses the glomerular capillaries leading to decreased glomerular filtration with microalbuminuria and hypertension. Over time, there is increased cellular damage, including renal podocyte apoptosis, which leads to a further breakdown of GFR and the appearance of overt proteinuria (> 3g/day). Without any intervention, the patient will progress to ESKD.

On the plus side, however, severe diabetic nephropathy can take years to develop, and should be preventable provided diabetes is detected soon enough.

### Hypertension

(high blood pressure) is another leading cause of kidney disease — and of course CVD — in the general population, particularly in sub-Saharan Africa. “People of African origin may be particularly vulnerable to hypertension,” wrote the investigators of one recent study, noting that numerous other studies have found a higher prevalence of hypertension among people of African origin than

people of white European descent, independent of body mass index, and the age of onset is younger in Africa, and among people of black African descent.<sup>115</sup>

According to several recent studies, hypertension is becoming an epidemic in Africa's urban and periurban areas. For instance, one just-published study of 5368 suspected heart disease patients at Chris Hani Baragwanath Hospital in Soweto, found very high levels of uncomplicated hypertension (in 988 patients) and hypertensive heart failure (1146 patient), as well as other forms of heart disease related to a changing lifestyle.<sup>116</sup> The authors wrote: “As a likely barometer for other Sub-Saharan communities in epidemiological transition, the mostly African residents of Soweto are subject to dynamic and complex factors. This includes economic development, erosion of traditional lifestyles, rural migration, and global influences likely to adversely impact the health of vulnerable communities. A growing local appetite for products historically absent from the region (e.g. processed foods) will almost inevitably ‘feed’ new forms of disease. As a consequence of high levels of risk but poor awareness of healthy lifestyle choices, it appears that Soweto already stands at the crossroads between historically prevalent and newer forms of heart disease due to epidemiological transition.”

Another recent study, with over one thousand participants from randomly selected households in Soweto, found approximately 46% of participants had systolic/diastolic BP values  $\geq 140/90$  mmHg and about half of these were not on high blood pressure medication — including 6.7% who were at very high CVD risk.<sup>117</sup> Notably around 40% of these participants were obese — which is also a risk factor for CKD and CKD.<sup>118</sup>

In a recent cross-sectional population-based survey of 4396 Kenyans, there was a high prevalence of hypertension (50.1%, 47.5-52.6%), obesity (13.0%, 11.7-14.5%), diabetes (6.6%, 5.6-7.7%) and high cholesterol (21.1%, 18.6-23.9). Hypertension, diabetes and obesity were generally more common in participants from urban areas, even after adjustment for socio-demographic, lifestyle, obesity and cardiovascular risk markers.<sup>119</sup> However, the authors attributed most of this effect to urbanisation, with its changes in diet and physical activity, citing an earlier study in Kenya that found that members of the Luo ethnic group who moved to urban areas experienced a rise in systolic and diastolic blood pressure after only one month of migration.<sup>120</sup> But even among participants surveyed in rural areas, the prevalence of hypertension was over 40%.

What may be critically important to note is that, in contrast to the household survey in Soweto, the vast majority of people with hypertension were untreated (76% in rural areas, 90% in urban). Another study from Ghana found that the overall detection rate [of hypertension] was 22%, and rates of treatment and control were 11.3% and 2.8%, respectively. “In much of sub-Saharan Africa, due to scarce resources and inadequate healthcare provision, detection, treatment, and control [of hypertension] are very poor.”

Given the high and increasing prevalence and poor control of hypertension in sub-Saharan Africa, one can expect the prevalence of hypertension-related CKD to grow. Already, hypertension accounts for a much of the continent's burden of CKD ranging from 25% in Senegal, 29.8% in Nigeria, 45.6% in South Africa and 48.7% in Ghana, and it is the cause of ESKD in around 21% of the people receiving renal replacement therapy in South Africa.<sup>121,122</sup>

The association of HIV, and/or the potential of ART-induced metabolic changes to affect an increase in hypertension are less clear. A 2005 study of HIV and hypertension among participants in the Multicenter AIDS Cohort Study in the United States found that



HIV-positive men who had been taking ART for two to five years were significantly more likely to have systolic hypertension than HIV-negative men (odds ratio [OR]: 1.51, 95% confidence interval [CI]: 1.25 – 1.82).<sup>123</sup> However, other studies have failed to confirm this. One study compared 542 men with HIV to almost 25,000 age, sex and BMI-matched members of the general population and found no significant difference in the rate of hypertension.<sup>124</sup> However, the study did note that people on ART for more than five years had the highest risk of hypertension.

In a small German study looking at the effects of hypertension on renal and cardiovascular health, HIV-positive people who developed hypertension had far higher prevalence of elevated urine protein levels, signaling the presence of kidney disease, than those who did not.<sup>125</sup> Those findings are somewhat difficult to interpret because the investigators were not certain whether kidney disease caused the hypertension or the hypertension caused the kidney disease. The investigators concluded that ART appeared to have no clear effect upon hypertension. Likewise, a recent review concluded that ART had only a modest effect on blood pressure.<sup>126</sup> Nonetheless, since high blood pressure causes so much kidney disease in the general population, any link between ART and high blood pressure has worrisome implications for renal health in HIV-positive people.

What is perhaps more worrisome is the likelihood that HIV disease and hypertension could work together to increase the prevalence of CKD and/or the rate of CKD progression.

High blood pressure can cause kidney disease in a variety of ways – perhaps the most important of which is the increased blood volume pumped through the glomeruli, which puts stress on the glomerular cells, including mesangial and epithelial cells and podocytes.<sup>127</sup> This stimulates the production of vasoactive substances that, in turn, activate the production of inflammatory cytokines and growth factors that contribute to cell damage and fibrosis, reducing glomerular filtration.<sup>128</sup> People with this nephrotic syndrome typically present with severe proteinuria (> 3 g/day), oedema and uremia, which can lead rapidly to death, frequently from cerebral hemorrhage.<sup>129</sup>

## HIV-related causes of chronic kidney disease

### **HIV-associated nephropathy (HIVAN)**

is a form of glomerular nephropathy that is almost exclusively observed in people of African descent for reasons already discussed. It was first observed at the very start of the epidemic in African-Americans and Haitian immigrants living in New York, and described as a unique form of ‘collapsing’ focal and segmental glomerulosclerosis (FSGS) associated with AIDS.<sup>130</sup> Subsequent reports found evidence of HIV infecting renal epithelial cells, and the condition was named HIVAN. Although it is usually seen in advanced AIDS, people living with HIV may present with HIVAN before developing other symptoms of AIDS, or even during acute seroconversion illness.<sup>131</sup> Before the discovery of ART in the mid-1990s, HIVAN often led rapidly to renal failure and death within months or weeks.

Due to the government’s policies until just a few years ago, researchers in South Africa observed the same rapid progression.

“The AIDS denialists unfortunately allowed us to study the natural history of untreated HIVAN,” said Dr Wearne during her talk last year in Cape Town.<sup>132</sup> She described an analysis of survival over time in 140 biopsy-proven cases of HIVAN at Groote Schuur Hospital. For untreated patients with HIVAN alone, the median survival was 16 weeks, and when there was a mixed picture with HIVAN and features of HIVICK (see below) the median survival was

only 13 weeks. Although other illnesses may have contributed somewhat to the high mortality, 86% of these patients had renal disease listed as the primary or secondary cause of death.

In the US, HIVAN became the third leading cause of ESKD in African American men between the ages of 20–64 years.<sup>133</sup> Also in the US, a study in the primary care setting found a prevalence of 3.5% among people living with HIV,<sup>134</sup> while an autopsy series found it in 12% of renal biopsies.<sup>135</sup> Given the regional burden of HIV disease, “If these statistics were to be extrapolated to sub-Saharan Africa, between 770,000 and 2.6 million HIVAN cases would be predicted,” Naicker and Fabian wrote in their review.

One would expect such large numbers would be noticed, however, there are few data to suggest a similar prevalence of HIVAN in Africa. One possibility is that HIVAN indeed may not be as common in Africa, for the same reasons other late-stage HIV-related conditions that were common in Europe and the US were rarely seen in Africa – people usually died of other illnesses first. Another possibility is that progression of HIVAN is so rapid that many people die before they can be diagnosed. As already noted, some African populations may not be susceptible to HIVAN but existing reports can be hard to interpret because of the lack of biopsy evidence and because cases don’t always match the ‘classical’ clinical definitions.

The “classical” clinical features of HIVAN, according to Dr Wearne, are as follows:

- Rapidly rising creatinine and progressive renal failure, proteinuria – frequently in the nephrotic range and almost invariably, a detectable viral load
- Large, echogenic kidneys may aid in the diagnosis of HIVAN
- Oedema and hypertension are thought to be uncommon
- Urinalysis often bland.

In addition, people with HIVAN usually have relatively normal blood pressure. But according to Dr Wearne, there can be exceptions to each of these rules.

“It is often difficult to distinguish HIVAN from other kidney lesions on clinical grounds alone,” said Dr Wearne. “There should be no presumptive diagnosis of HIVAN made on clinical grounds.”

At Groote Schuur Hospital, Dr Wearne and colleagues performed a prospective and retrospective study including 180 kidney biopsies from people living with HIV.<sup>136</sup> Of these, 168 individuals were black, 11 were mixed race and one was white European. Evidence of HIVAN (alone) was found in 51% of the biopsies, a mixed picture of HIVAN with features of different immune complex glomerulonephropathies was found in 22%, immune complex diseases (including one due to hepatitis C) were found in 6%, and a variety of other conditions were diagnosed in 16%.

HIVAN is believed to be triggered by viral infection of renal epithelial cells, in particular the podocyte.<sup>137</sup> However, HIV has now been shown to directly infect all the epithelial cells of the kidney, including parietal epithelial cells, tubular epithelial cells, as well as the interstitium, which appears to lead to their proliferation and hypertrophy.<sup>138</sup> But many of the details of HIVAN’s pathogenesis have yet to be worked out.

“Podocytes are terminally differentiated, highly specialised renal cells that do not normally proliferate,” said Dr. Wearne. However, it has been suggested that expression of viral genes such as *nef* could change the infected cell’s behaviour.

“We postulate that the epithelial cells undergo proliferation and then fall off into Bowman’s space,” said Dr Wearne. “Ultimately, abnormal proliferative response with loss of the podocyte into



Bowman's space disrupts the glomerular architecture critical for structural integrity, which leads to collapse of the glomerulus."

But she noted there is also evidence of concurrent tubulointerstitial disease, with proliferation of tubular epithelial cells leading to the formation of microcysts, as well as inflammation, lymphocytic infiltration and fibrosis in the interstitium.

"Although evidence supports the idea that direct infection of renal parenchymal cells is pathogenic for HIVAN, systemic and local immune responses might precipitate or exacerbate renal disease," said Dr Wearne. She also noted that she and her colleagues have identified variants of HIVAN, such as where the glomerulus does not always collapse, that have not been previously described in the literature. They are working to expand and refine a classification system for HIVAN based on clinical and histological features.

ART has been found to greatly slow HIVAN-related kidney decline, and so HIVAN is less likely to be observed in cohorts recently placed onto treatment. But even if HIVAN seems less threatening in the context of ART, it is difficult to know how much this disease will continue to contribute to the HIV-related burden of disease at the population level. Confirming widespread clinical observations, a US cohort study showed a significant drop in HIVAN incidence from 1995-1997 to 1998-2001, and also determined that ART use reduced HIVAN risk by 60% in cohort members.<sup>139</sup> A more recent study looking at kidney biopsy results in 86 HIV-positive US residents with symptoms of renal impairment found greater incidence of hypertensive vascular disease than HIVAN.<sup>140</sup>

However, if ART, by reducing mortality, increases the sheer number of people at risk for HIVAN, then HIVAN incidence and prevalence could conceivably increase over time.

In 2005, a US research team proposed that as the number of African-Americans living with HIV increased, such a scenario was likely to develop in the United States. Since HIVAN itself is not systematically monitored on a national level, the researchers used proxy data on end-stage renal disease (ESRD) among HIV-positive African-Americans to predict how ART use was likely to affect HIVAN prevalence between 2002 and 2020. Their mathematical model suggested that even with ART considerably slowing the rate at which people progressed to ESRD, there would still be a steady increase in the absolute number of HIV-positive African-Americans with ESRD over time.<sup>141</sup> According to the most recent report from the United States Renal Data System, which was the source of data for the 2005 study, overall HIV-associated ESRD incidence decreased 2% from 1996-1998 to 2006-2008, while prevalence more than doubled.<sup>142</sup>

In addition, for unclear reasons, ART does not always prevent HIVAN from emerging or progressing, possibly because infected kidney cells may be a protected reservoir for the virus in individuals with HIVAN, or due to poor adherence to treatment. Finally, another factor to consider in resource-constrained settings where ART failure is more likely to be determined on clinical or immunological grounds, is that a much larger proportion of people on ART may have detectable viral loads for longer periods of time than in industrialised settings, which could increase the risk of HIVAN developing or progressing.

### **HIV Immune Complex Disease (HIVICK)**

and a variety of other immune complex-mediated glomerulonephritides are also significant causes of CKD. (Their pathogenesis is briefly explained in the acute kidney section). These conditions can occur in any population, including black Africans – in fact, the prevalence of non-HIV related glomerulonephritides is many times higher in Africa than in other settings.<sup>143</sup>

HIVICK appears to be triggered by the deposition of HIV-related immune complexes in the renal tissue. It can have a virtually identical clinical presentation as HIVAN with heavy proteinuria, hypoalbuminaemia, varying cholesterol levels and degrees of renal dysfunction.<sup>144</sup>

According to one review, the prevalence of HIV-associated, immune complex-mediated glomerulonephritides among the causes of CKD in people living with HIV may be anywhere between 15%–80%, depending upon the population.<sup>145</sup> It accounts for a higher percentage of CKD in HIV-infected individuals of non-African descent. However, Dr Wearne believes there is much confusion over terminology.

"There is no clearly defined definition of HIVICK," said Dr Wearne. One issue is that features of immune complex disease are often seen in conjunction with HIVAN, and the outcomes depend upon whether HIVAN is also present. So the diagnosis must be based on biopsy. She and her colleagues have proposed a definition based upon the histological features of the condition that will be discussed in the next issue of HATIP.

### **Hepatitis-related nephropathies:**

Both HBV (see section on acute kidney injury) and HCV infection have been associated with CKD, though the relationship between hepatitis C (HCV) and kidney disease in HIV-positive people is unclear. The EuroSIDA study, which reported 20% HCV prevalence among the approximately 4500 cohort members, did not detect an association between HCV and renal impairment, defined by researchers as an eGFR of less than 60 ml/min.<sup>146</sup> Similarly, a 2008 US study involving 422 HIV-positive people, 100 of whom had chronic kidney disease, did not find HCV status to be predictive of chronic kidney disease.<sup>147</sup> Several other studies, however, have contradicted these findings, and a 2008 meta-analysis of ten studies representing more than 14,000 people found higher CKD incidence among HIV/HCV co-infected people than among those who only had HIV (6.2% versus 4.0%; relative risk 1.49; 95% CI: 1.08-2.06).<sup>148</sup>

As for the health impact of HIV/HCV co-infection, French researchers comparing three groups of people who had diagnostic kidney biopsies performed as a result of renal disorders – 40 people with HIV, 30 people with HCV and 30 people with HIV/HCV co-infection – found that mortality was highest in the HIV/HCV group over an eight-year period. HIV/HCV co-infected study participants had a 2.1 times greater relative risk of death than those who only had hepatitis C, and a 7.5 times greater relative risk of death than those who only had HIV.<sup>149</sup>

A 2010 analysis of the medical records of more than 23,000 HIV-positive military veterans found that HIV/HCV co-infected veterans with renal decline had a higher mortality rate over a median of 7.6 years of follow-up than those who had HIV monoinfection and renal decline. HIV/HCV co-infected people with eGFR rates between 30 and 59 mL/min had a mortality rate of 13.3 per 100 person-years, while HIV monoinfected people with eGFR rates in that range had a mortality rate of 10.8 per 100 person-years. For co-infected and monoinfected people with eGFR rates below 15 ml/min (end-stage kidney disease), mortality rates were 20.4 per 100 person-years and 16.6 per 100 person-years, respectively. Having HCV was independently associated with a 23% higher risk of death (95% CI, 1.17-1.29).<sup>150</sup>

## Tenofovir and chronic kidney disease

The impact of tenofovir (*Viread*, also in *Truvada* and *Atripla*) on the kidneys has been difficult to gauge. Since this drug's approval almost ten years ago, a number of studies have suggested that tenofovir may negatively affect renal functioning in sometimes subtle ways. In some people, it damages the upper portion of the tubules (the proximal tubule), resulting in symptoms similar to an already-known but rare, usually inherited condition called Fanconi syndrome.

In Fanconi syndrome, the reabsorption process in the proximal tubular is reduced and electrolytes (eg. phosphate) glucose, amino acids and low weight molecular proteins are passed into the urine. This can lead to mild to moderate proteinuria, inadequate levels of calcium and uric acid in the blood, and sometimes low blood pH (metabolic acidosis).<sup>151</sup> There can also be problems in urinary concentration and in some cases renal failure. Even some of the more subtle electrolyte imbalances could eventually lead to clinical problems. Already bone pain, osteomalacia, or pathological fractures have also been reported in people with tenofovir-associated Fanconi syndrome.<sup>152</sup>

There is no clear consensus about the importance of the findings – but they suggest that HIV programmes need to keep an eye on the long-term side effects of this drug.

An Australian study published in early 2000 called into question the belief that kidney functioning soon returns to normal in people who stop taking tenofovir because of renal toxicity. Researchers using a sensitive screening tool found that almost half of 24 men with tenofovir-induced renal toxicity still had impaired kidney functioning more than a year after discontinuing the drug.<sup>153</sup>

In a EuroSIDA cohort of nearly 7000 patients, cumulative exposure to tenofovir or atazanavir was associated with a 16% and 21% increased risk, respectively, of chronic kidney disease, though the actual proportion of people who developed CKD for any reason was relatively low, at one case per 105 patients a year.<sup>154</sup> On the other hand, a recent meta-analysis of 17 studies involving 11,000 HIV-positive people concluded that from a statistical standpoint, taking tenofovir was indeed associated with higher risk of impaired kidney functioning, but that “the clinical magnitude of this effect was modest.”<sup>155</sup>

Nonetheless, it may be too early to dismiss the association between tenofovir and kidney impairment, since more deleterious effects could conceivably be observed with longer-term tenofovir usage. The median follow-up time in the meta-analysis was 48 weeks, and only four of the 17 studies had a follow-up time of longer than 96 weeks (Campbell et al, 2009, n = 3439, follow-up = 104-520 weeks; Arribas et al, 2008, n = 517, follow-up = 144 weeks; Winston et al, 2006, n = 948, follow-up = 121 weeks; Gallant et al, 2004, n = 600, follow-up = 144 weeks).

<sup>156,157,158,159,160</sup> Reflecting on the significance of the follow-up time, the authors of the meta-analysis point out that tenofovir-related kidney problems may be most likely to occur within a few months of the initiation of tenofovir, according to some research. Still, they conclude, “Whether the risk for TDF-associated nephrotoxicity increases with prolonged use or is cumulative is of critical importance and would be an important area of future study; especially given recent clinical practice recommendations to start ART earlier in the course of HIV infection.”

Weighing the risks and benefits of prescribing tenofovir involves different considerations in different settings. In high-income countries, renal impairment is not thought to preclude use of

tenofovir, since it is generally feasible to implement kidney disease screening protocols such as those recommended by IDSA/HIVMA. According to that group's guidelines, someone who has an eGFR below 90 mL/min and is taking tenofovir “should be monitored at least biannually for measurements of renal function, serum phosphorus and urine analysis for proteinuria and glycosuria.”<sup>161</sup> In poorer countries, health care providers' capacity to monitor kidney functioning in tenofovir recipients is often more limited.

This is not to say that all forms of monitoring are out of reach. For instance, in the Zambian study, researchers ultimately had access to eGFR rates for 70% of the full cohort of 36,289 Zambians taking ART.<sup>162</sup> The same study calls attention to the Zambian Ministry of Health's 2007 decision to include tenofovir in its recommended first-line ART regimen, observing that routinely prescribing tenofovir to HIV-positive people whose renal health is unknown might have consequences of considerable magnitude. The authors note that if tenofovir had been in use at the time that members of their study cohort of approximately 25,000 initiated ART, 5% of people would have benefited from tenofovir dose adjustments and almost 30% of people would have benefited from ongoing monitoring because of their mild-to-moderate renal impairment (as indicated by eGFR rates of 50 to 89 mL/min).<sup>163</sup>

The authors conclude, “These considerations should probably be included in future cost-benefit analyses of tenofovir use in resource-limited settings. Although a strategy of routine screening will increase costs in resource-constrained settings, this must be balanced against the risk of iatrogenic renal failure. Similar concerns should be raised for other routinely used drugs with known renal toxicities.”<sup>164</sup>

As for the World Health Organization's position on tenofovir and kidney monitoring, the recently released 2010 treatment guidelines state: “Creatinine clearance is not a barrier to TDF use. Creatinine clearance monitoring is recommended in those with underlying renal disease, of older age groups, and with low body weight or other renal risk factors such as diabetes or hypertension. There is evidence that individuals taking TDF and a PI/r may experience greater median decline in creatinine clearance than those taking TDF and an NNRTI-based regimen. Creatinine clearance should be monitored more closely when TDF is used with a ritonavir-boosted protease inhibitor.”<sup>165</sup>

However, in their review on biomarkers. Post et al note that “Fanconi syndrome may occur without changes in GFR and may affect those with previously normal renal function. Although guidelines for the management of HIV-infected patients recommend monitoring of renal function, the optimal strategy for early detection of Fanconi syndrome remains to be defined.”<sup>166</sup>

Any balanced discussion of the impact of antiretroviral therapy on the kidneys needs to also take into account the fact that the initiation of ART – including tenofovir-containing regimens – also has the potential to *improve* kidney functioning. The effectiveness of ART as treatment for HIVAN is the most dramatic example of this point. Some studies indicate that the course of other forms of kidney disease not directly caused by HIV may be affected by ART use as well. A review article on HIV and the kidneys calls attention to three such studies, but cautions that “the clinical significance of these generally small or modest changes in renal function remains unclear.”<sup>167</sup>

One study investigated the effects of ART on eGFR rates in a group of 1776 US residents. It found that viral suppression as a result of ART usage was associated with increases in eGFR scores among a subset of 59 people who had CD4 cell counts below 200

cells/mm<sup>3</sup> and stage 2 CKD or worse at the time they initiated treatment. Subset members who achieved viral suppression experienced an average eGFR increase of 9.2 mL/min during a median follow-up time of 160 weeks (95% CI, 1.6–16.8,  $p=0.02$ ). People who had greater baseline renal impairment experienced greater improvements.<sup>168</sup>

The other two highlighted studies were conducted in African cohorts. One looked at renal functioning in a cohort of 508 Ugandans starting ART, 20% of whom had eGFR 25–50 mL/min at the time they initiated treatment. In the full cohort, there was a statistically significant 21% increase in the median eGFR rate after two years of ART ( $p<0.0001$ ), while in people whose eGFR rate had been in the 25–50 mL/min range, there was a 53% increase in the median eGFR rate ( $p<0.0001$ ). Notably, however, the first-line ART regimen given to study participants did not include tenofovir or indinavir.<sup>169</sup> In the other study, researchers looked at eGFR changes in the 96 weeks after ART initiation in a subset of 3316 members of the DART cohort. The mean ( $\pm$ SD) eGFR was  $94 \pm 32$  mL/min at baseline and ranged between 91 and 95 mL/min (median, 89–91 mL/min) during the follow-up period. Lower baseline eGFR was associated with a greater eGFR increase, although this change was not dramatic. Seventy-four percent of study participants were taking tenofovir.<sup>170</sup>

Several countries, including South Africa, have recently adopted tenofovir as part of their first line regimen, and their experience should help clarify tenofovir's kidney related toxicity in sub-Saharan Africa.

"Clinically, we are just not seeing a significant increase in kidney toxicity in our patients since introducing tenofovir," Dr Kevin Rebe in Cape Town told HATIP.

However, given the poor sensitivity of eGFR or urine dipstick tests for tenofovir-related renal tubule damage, it may take some time before clinically significant kidney damage becomes evident. Moreover, it will be important to watch whether, over time, there will be an increase in clinical conditions that may related to subtle defects in tubule reabsorption or renal hormone imbalances, potentially including bone thinning and anaemia.

## References

- [1] Mehta RL et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Critical Care* 11 (2): R31, 2007.
- [2] Lameire N, Van Biesen W, Vanholder R. Acute kidney injury. *Lancet* 372:1863–1865, 2008.
- [3] Bellomo R et al. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 8 (4): R204–12, 2004.
- [4] Kellum JA. Defining and classifying AKI: one set of criteria. *Nephrol Dial Transplant* 23: 1471–1472, 2008.
- [5] Murray PT. A framework and key research questions in AKI diagnosis and staging in different environments. *Clin J Am Soc Nephrol* 3: 864–868, 2008.
- [6] The Merck Manual.
- [7] Ibid.
- [8] Naicker S et al. Epidemiology of acute kidney injury in Africa. *Seminars in Nephrology*, 28(4):348–353, 2008.
- [9] Ibid.
- [10] Wyatt CM, Arons RR, Klotman PE, Klotman ME. Acute renal failure in hospitalized patients with HIV: risk factors and impact on in-hospital mortality. *AIDS*. 20:561–5, 2006.
- [11] Choi AI et al. Long-term clinical consequences of acute kidney injury in the HIV-infected. *Kidney Int*. 78(5):478–85, 2010.
- [12] Pakasa NM. Acute tubular necrosis, acute renal failure and unusual histologic stigmata of acute malaria in HIV/AIDS patients from the democratic Republic of Congo. *Saudi J Kidney Dis Transpl*; 21:153–4, 2010. Available from: <http://www.sjkd.org/text.asp?2010/21/1/153/58793>
- [13] Naicker, S et al. op cit.
- [14] McCullough CE. "Nephrology" in Handbook of HIV Medicine, 2<sup>nd</sup> Edition. D Wilson et al. Oxford University Press, 2008
- [15] Foley RJ et al. Amphetamine-induced acute renal failure. *Southern Medical Journal*, 77(2):258–261, 1984.
- [16] De Vriese AS et al. Rifampicin-associated acute renal failure: pathophysiologic, immunologic, and clinical features. *Am J Kidney Dis*. 31(1):108–15, 1998.
- [17] Couzigou C et al. Urolithiasis in HIV-positive patients treated with atazanavir. *Clin Infect Dis* 45(8):e105–8, 2007.
- [18] Chan-Tack KM et al. Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's adverse event reporting system. *AIDS* 21: 1215–1218, 2007.
- [19] Mills A et al. Safety and immunovirological activity of once daily maraviroc (MVC) in combination with ritonavir-boosted atazanavir (ATV/r) compared to emtricitabine 200mg/tenofovir 300mg QD (TDF/FTC) + ATV/r in treatment-naïve patients infected with CCR5-tropic HIV-1 (Study A4001078): a week 24 planned interim analysis. Eighteenth International AIDS Conference, Vienna, abstract THLB203, 2010.
- [20] Diaz F et al. Sulfadiazine-induced multiple urolithiasis and acute renal failure in a patient with AIDS and Toxoplasma encephalitis. *Ann Pharmacother* 30:41, 1996.
- [21] Brigden D, Whiteman P. The clinical pharmacology of acyclovir and its prodrugs. *Scand J Infect Dis Suppl*. 47:33–9, 1985.
- [22] The Merck Manual.
- [23] Rodriguez-Iturbe B, Musser JM. The current state of poststreptococcal glomerulonephritis. *J Am Soc Nephrol*; 19(10):1855–64, 2008.
- [24] Zegers RH, Weigl A, Steptoe A. The death of Wolfgang Amadeus Mozart: an epidemiologic perspective. *Ann Intern Med* 151(4):274–8, W96–7, 2009.
- [25] Naicker S et al. 2008, op cit.
- [26] Mishra SK, Das BS. Malaria and acute kidney injury. *Seminars in Nephrology*, 28(4):395–408, 2008.
- [27] Kanodia KV, Shah PR, Vanikar AV, Kasat P, Gumber M, Trivedi HL. Malaria induced acute renal failure: A single center experience. *Saudi J Kidney Dis Transpl* 21:1088–91, 2010. Available online at <http://www.sjkd.org/text.asp?2010/21/6/1088/72296>.
- [28] Naicker S et al. 2008, op cit.
- [29] Kanya MR et al. Effect of HIV-1 infection on malaria treatment outcome in Uganda: a population-based study. *J Infect Dis* 193:9–15, 2005.
- [30] Pakasa NM, op cit.
- [31] Nyimi ML, Lepira FB, Sumaili KE, Ebengo BC, Nseka MN, Longo-Mbenza B. Acute renal failure associated with HIV infection. A report of 24 cases. *Louvain Medical* 120:167–72, 2001.
- [32] Pakasa NM, op cit.
- [33] Al-Salam S et al. Acute kidney injury secondary to renal large B-cell lymphoma: role of early renal biopsy. *International Urology and Nephrology*, 2010.
- [34] McCullough, 2008, op cit.
- [35] Ozdamar SO, Gucer S, Tinaztepe K. Hepatitis-B virus associated nephropathies: a clinicopathological study in 14 children. *Pediatr Nephrol* 18(1):23–8, 2003.
- [36] Naicker, op cit.
- [37] Fine DM, Fogo AB, Alpers CE. Thrombotic microangiopathy and other glomerular disorders in the HIV-infected patient. *Seminars in Nephrology* 28(6):556–562, 2008.
- [38] Brecher ME, Hay SN, Park YA. Is it HIV TTP or HIV-associated thrombotic microangiopathy? *J Clin Apher* 23(6):186–90, 2008.
- [39] Benjamin M et al. Frequency and significance of HIV infection among patients diagnosed with thrombotic thrombocytopenic purpura. *Clin Infect Dis*. 48(8):1129–37, 2009.
- [40] Becker S et al. HIV-associated thrombotic microangiopathy in the era of highly active antiretroviral therapy: an observational study. *Clin Infect Dis* 39 Suppl 5:S267–75, 2004.
- [41] Ibid.
- [42] Ahmed S et al. HIV associated thrombotic microangiopathy. *Postgrad Med J* 2002;78:520–524



- [43] Furlan M, et al. Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *N Engl J Med* 1998;339:1578-84.
- [44] Tsai HM, Lian ECY. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med* 339:1585-94, 1998.
- [45] George JN. Thrombotic thrombocytopenic purpura. *N Engl J Med* 354:1927-35, 2006.
- [46] Gunther K, Garizio D, Nesara P. ADAMTS13 activity and the presence of acquired inhibitors in human immunodeficiency virus-related thrombotic thrombocytopenic purpura. *Transfusion* 47(9):1710-1716, 2007.
- [47] Moake JL. Thrombotic microangiopathies. *N Engl J Med* 347: 589–600, 2002.
- [48] Alpers CE. Light at the end of the TUNEL: HIV-associated thrombotic microangiopathy. *Kidney Int* 63:385-96, 2003.
- [49] del Arco A et al. Thrombotic thrombocytopenic purpura associated with human immunodeficiency virus infection: demonstration of p24 antigen in endothelial cells. *Clin Infect Dis* 17:360-3, 1993.
- [50] Hymes KB, Karpatskin S. Human immunodeficiency virus infection and thrombotic microangiopathy. *Semin Hematol* 34:117-25, 1997.
- [51] Becker, op cit.
- [52] Novitzky N et al. Thrombotic thrombocytopenic purpura in patients with retroviral infection is highly responsive to plasma infusion therapy. *British Journal of Haematology*. 128(3):373–379, 2005. Online: <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2004.05325.x/full>
- [53] Ibid.
- [54] Jehle AW et al. Acute renal failure on immune reconstitution in an HIV-positive patient with miliary tuberculosis. *Clinical Infectious Diseases* 38:e32-e35, 2004
- [55] Naicker et al, op cit.
- [56] Rabie H et al. Important HIV-associated conditions in HIV-infected infants and children. *SA Fam Pract* 49(4) 22, 2007.
- [57] Kirsztajn GM, Suassuna JHR, Bastos MG. Dividing stage 3 of chronic kidney disease (CKD): 3A and 3B. *Kidney Int* 76:462-463, 2009.
- [58] National Collaborating Centre for Chronic Conditions. Chronic kidney disease: national clinical guideline for early identification and management in adults in primary and secondary care. London: Royal College of Physicians, 2008.
- [59] Schiffrin EL, Lipman, ML, Mann JFE. Chronic kidney disease. Effects on the cardiovascular system. *Circulation* 116:85-97, 2007.
- [60] Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. *Lancet* 356:147-52, 2000.
- [61] Sarnak MJ et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 108:2154-69, 2003.
- [62] Brosius FC III et al. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: a science advisory from the American Heart Association Kidney and Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: developed in collaboration with the National Kidney Foundation. *Circulation* 114:1083-7, 2006.
- [63] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351:1296-305, 2004.
- [64] Brugs JJ, Knetsch AM, Mattace-Raso FUS, Hofman A, Witteman JCM. Renal function and risk of myocardial infarction in an elderly population: the Rotterdam study. *Arch Intern Med* 165:2659-65, 2005.
- [65] Meisinger C, Doring A, Lowel H, for the KORA Study Group. Chronic kidney disease and risk of incident myocardial infarction and all-cause and cardiovascular disease mortality in middle-aged men and women from the general population. *Eur Heart J*; 27:1245-50.
- [66] an Biesen W, De Bacquer D, Verbeke F, Delanghe J, Lameire N, Vanholder R. The glomerular filtration rate in an apparently healthy population and its relation with cardiovascular mortality during 10 years. *Eur Heart J* 28:478-83, 2007.
- [67] Di Angelantonio E et al. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. *BMJ* 341:c4986, 2010. Online: <http://www.bmj.com/content/341/bmj.c4986.full>.
- [68] Dhingra R, Gaziano JM, Djoussé L. Chronic kidney disease and the risk of heart failure in men. *Circ Heart Fail*. 2011 [Epub ahead of print].
- [69] Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 375: 2073–81, 2010.
- [70] Choi AI et al. Association between kidney function and albuminuria with cardiovascular events in HIV-infected persons. *Circulation*. 121(5):651-8, 2010.
- [71] Mulenga LB et al. Baseline renal insufficiency and risk of death among HIV-infected adults on antiretroviral therapy in Lusaka, Zambia. *AIDS* 22: 1821-1827, 2008.
- [72] Choi AI et al. Low rates of antiretroviral therapy among HIV-infected patients with chronic kidney disease. *Clinical Infectious Diseases* 45:1633–9, 2007.
- [73] Gupta SK et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 40: 1559-1585, 2005.
- [74] Mocroft A et al. Chronic renal failure among HIV-1-infected patients. *AIDS* 21: 1119-1127, 2007.
- [75] Fernando SK et al. Prevalence of chronic kidney disease in an urban HIV infected population. *Am J Med Sci* 335: 89-94, 2008.
- [76] Wyatt CM et al. Chronic kidney disease in HIV infection: an urban epidemic. *AIDS* 21: 2101-2103, 2007.
- [77] Cheung CY et al. Prevalence of chronic kidney disease in Chinese HIV-infected patients. *Nephrol Dial Transplant* 22: 3186-3190, 2007.
- [78] Naicker S, op cit.
- [79] Ibid.
- [80] Lucas GM et al. Chronic kidney disease incidence and progression of ESRD in HIV-infected individuals: a tale of 2 races. *J Infect Dis*. 197: 1548-1557, 2008.
- [81] Han TM et al. A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa. *Kidney Int* 69: 2243-2250, 2006.
- [82] Fabian J et al. Urinary screening abnormalities in antiretroviral-naïve HIV-infected outpatients and implications for management: a single-center study in South Africa. *Ethn Dis* 19: S1-80-5. 2009.
- [83] Gerntholtz TE et al. HIV-related nephropathy: a South African perspective. *Kidney Int*. 69: 1885-1891, 2006.
- [84] Fabian J, Naicker S. HIV and kidney disease in sub-Saharan Africa. *Nat Rev Nephrol* 5: 591-598, 2009.
- [85] Behar DM et al. Absence of HIV-Associated nephropathy in Ethiopians. *American Journal of Kidney Diseases* 47(1):88-94, 2006.
- [86] Kopp JB et al. MYH9 is a major-eVect risk gene for focal segmental glomerulosclerosis. *Nat Genet* 40:1175–1184, 2008
- [87] Oleksyk TK et al. Worldwide distribution of the MYH9 kidney disease susceptibility alleles and haplotypes: evidence of historical selection in Africa. *PLoS ONE* 5(7): e11474, 2010.
- [88] Tzur S, Rosset S et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. *Hum Genet* 128:345–350, 2010.
- [89] Genovese G et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science*. 329(5993):841-5, 2010.
- [90] Tzur S, Rosset S et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. *Hum Genet* 128:345–350, 2010.
- [91] Naicker, S. Burden of end-stage renal disease in sub-Saharan Africa, op cit.
- [92] Wearne, op cit.
- [93] Mayosi BM et al. The burden of non-communicable diseases in South Africa, *The Lancet* 374(9693): 934 - 947, 2009.
- [94] Mulenga LB et al. Baseline renal insufficiency and risk of death among HIV-infected adults on antiretroviral therapy in Lusaka, Zambia. *AIDS* 22: 1821-1827, 2008.



- [95] Reid A et al. Severe renal dysfunction and risk factors associated with renal impairment in HIV-infected adults in Africa initiating antiretroviral therapy. *Clin Infect Dis* 46: 1271-1281, 2008.
- [96] Wools-Kaloustian K et al. Renal disease in an antiretroviral-naïve HIV-infected outpatient population in Western Kenya. *Nephrol Dial Transplant* 22: 2208-2212, 2007.
- [97] Andia I et al. Prevalence Of renal disease In patients attending the HIV/AIDS clinic, at Mbarara University Teaching Hospital. Third International AIDS Society Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, Abstract TuPe15.3C02, 2005.
- [98] Emem CP et al. Renal disease in HIV-seropositive patients in Nigeria: an assessment of prevalence, clinical features and risk factors. *Nephrol Dial Transplant* 23: 741-746, 2008.
- [99] Mortier E et al. Urinary pH in HIV-infected adults in Ivory Coast and in France. *AIDS* 17: 2003-2005, 2003.
- [100] Janabi MY. Renal abnormalities associated with human immunodeficiency virus infection among police officers in Dar-es-Salaam, Tanzania. Fourteenth International AIDS Conference, Barcelona, Abstract ThPeB7197, 2002.
- [101] Selik RM, Byers RH Jr, Dworkin MS. Trends in diseases reported on U.S. death certificates that mentioned HIV infection, 1987–1999. *J Acquir Immune Defic Syndr* 29:378–87, 2002.
- [102] National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002 Feb;39(2 Suppl 1):S1-266.
- [103] Gill G.V. A sub-Saharan African perspective of diabetes. *Diabetologia*. 52(1):8-16, 2009.
- [104] *ibid*.
- [105] Mbanya JCN et al. Diabetes in sub-Saharan Africa. *Lancet* 375(9733):2254–2266, 2010.
- [106] Choudhury D, Tuncel M, Levi M. Diabetic nephropathy – a multifaceted target of new therapies. *Discovery Medicine*, 2010.  
<http://www.discoverymedicine.com/Devasmita-Choudhury/2010/11/12/diabetic-nephropathy-a-multifaceted-target-of-new-therapies/>
- [107] Dalla Vestra M, Saller A, Bortoloso E, Maurer M, Fioretto P. Structural involvement in type 1 and type 2 diabetic nephropathy. *Diabetes Metabol* 26(Suppl)4:8-14, 2000.
- [108] Brown TT et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch Intern Med* 165: 1179-1184, 2005.
- [109] De Wit S et al. Relationship between use of stavudine and diabetes mellitus. Eighth International Congress on Drug Therapy in HIV Infection, Glasgow. Abstract PL9.5. 2006.
- [110] Tien PC et al. Antiretroviral therapy exposure and incidence of diabetes mellitus in the Women's Interagency HIV Study. *AIDS* 21(13): 1739-1745, 2007.
- [111] Manuthu EM et al. Prevalence of dyslipidemia and dysglycaemia in HIV infected patients. *East Afr Med J*. 85(1):10-7, 2008.
- [112] Choudhury D (2010), *op cit*.
- [113] Saito A et al. Proximal tubule cell hypothesis for cardiorenal syndrome in diabetes. *Int J Nephrol*. 2011. Online:  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3005801/?tool=pubmed>
- [114] Choudhury D (2010), *op cit*.
- [115] Mathenge W, Foster A, Kuper H. Urbanization, ethnicity and cardiovascular risk in a population in transition in Nakuru, Kenya: a population-based survey. *BMC Public Health* 10:569, 2010.  
<http://www.biomedcentral.com/1471-2458/10/569>
- [116] Stewart S et al. Standing at the crossroads between new and historically prevalent heart disease: effects of migration and socio-economic factors in the Heart of Soweto cohort study. *European Heart Journal*, 2010. Online at:  
<http://eurheartj.oxfordjournals.org/content/early/2010/12/15/eurheartj.ahq439.long>
- [117] Maseko MJ Global cardiovascular risk profiles of untreated hypertensives in an urban, developing community in Africa. *Cardiovasc J Afr* 21, 2010.
- [118] Kopple JD. Obesity and chronic kidney disease. *J Ren Nutr* 20(5 Suppl):S29-30, 2010
- [119] Mathenge W, Foster A, Kuper H. Urbanization, ethnicity and cardiovascular risk in a population in transition in Nakuru, Kenya: a population-based survey. *BMC Public Health* 10:569, 2010.  
<http://www.biomedcentral.com/1471-2458/10/569>
- [120] Poulter NR et al: The Kenyan Luo migration study: observations on the initiation of a rise in blood pressure. *BMJ* 300(6730):967-972, 1990.
- [121] Naicker S (2008), *op cit*.
- [122] Arogundade FA, Barsoum RS. CKD prevention in Sub-Saharan Africa: a call for governmental, nongovernmental, and community support. *Am J Kidney Dis*. 2008; 51: 515-523.
- [123] Seaberg EC et al. Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003. *AIDS* 19: 953-960, 2005.
- [124] Baekken M, Os I, Sandvik L, Oektedalen O. Hypertension in an urban HIV-positive population compared with the general population: influence of combination antiretroviral therapy. *J Hypertens*. 26(11):2126-33, 2008.
- [125] Jung O et al. Hypertension in HIV-1-infected patients and its impact on renal and cardiovascular integrity. *Nephrol Dial Transplant* 19: 2250-2258, 2004.
- [126] Bernardino de la Serna JI et al. Hypertension, HIV infection, and highly active antiretroviral therapy. [Article in Spanish] *Enferm Infecc Microbiol Clin*. 28(1):32-7, 2010.
- [127] Johnston CI et al. Mechanism of progression of renal disease: current hemodynamic concepts. *J Hypertens Suppl*. 16(4):S3-7, 1998.
- [128] Lopez-Novoa. Etiopathology of chronic tubular, glomerular and renovascular nephropathies: clinical implications. *Journal of Translational Medicine* 9:13, 2011.
- [129] Naicker S (2008), *op cit*.
- [130] Rao TK et al. Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome. *N Engl J Med* 310: 669-673, 1984.
- [131] Carbone L et al. Course and prognosis of human immunodeficiency virus-associated nephropathy. *Am J Med* 1989, 87:389–395.
- [132] Wearne, *op cit*.
- [133] USRDS. US Renal Data System 1999 Annual Data Report. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1999.
- [134] Ahuja TS et al. Is the prevalence of HIV-associated nephropathy decreasing? *Am J Nephrol*. 19: 655-659, 1999.
- [135] Shaninian V et al. Prevalence of HIV-associated nephropathy in autopsies of HIV-infected patients. *Am J Kid Dis*. 35:884-888, 2000.
- [136] Wearne, *op cit*.
- [137] Röling J et al. HIV-Associated renal diseases and Highly Active Antiretroviral Therapy-induced nephropathy. *Clinical Infectious Diseases* 42:1488–95, 2006.
- [138] Wearne, *op cit*.
- [139] Lucas GM et al. Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: a 12-year cohort study. *AIDS* 18: 541-546, 2004.
- [140] Estrella M et al. HIV type 1 RNA level as a clinical indicator of renal pathology in HIV-infected patients. *Clin Infect Dis* 43: 377-380, 2006.
- [141] Schwartz EJ et al. Highly active antiretroviral therapy and the epidemic of HIV+ end-stage renal disease. *J Am Soc Nephrol* 16: 2412-2420, 2005.
- [142] U.S. Renal Data System. USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010.
- [143] Naicker S (2008), *op cit*.
- [144] McCullough CE (2008), *op cit*.
- [145] Röling, *op cit*.
- [146] Mocroft A et al. Chronic renal failure among HIV-1-infected patients. *AIDS* 21: 1119-1127, 2007.
- [147] Fernando SK et al. Prevalence of chronic kidney disease in an urban HIV infected population. *Am J Med Sci* 335: 89-94, 2008.
- [148] Wyatt CM et al. The impact of hepatitis C virus coinfection on HIV-related kidney disease: a systematic review and meta-analysis. *AIDS* 22: 1799-1807, 2008.
- [149] Izzedine H et al. Kidney diseases in HIV/HCV-co-infected patients. *AIDS* 23: 1219-1226, 2009.

- [150] Fischer MJ et al. Hepatitis C and the risk of kidney disease and mortality in veterans with HIV. *J Acquir Immune Defic Syndr* 53: 222-226, 2010.
- [151] Post FA, Wyatt CM, Mocroft A. Biomarkers of impaired renal function. *Nephrol Dial Transplant* 25: 2178-2187, 2010.
- [152] Woodward CL et al. Tenofovir-associated renal and bone toxicity. *HIV Med* 10:482-487, 2009.
- [153] Wever K et al. Incomplete reversibility of tenofovir-related renal toxicity in HIV-infected men. *J Acquir Immune Defic Syndr* 55(1):78-81, 2010.
- [154] Mocroft A et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. *AIDS* 24: 1667-1678, 2010.
- [155] Cooper RD et al. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis* 51: 496-505, 2010.
- [156] Cooper RD et al. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis* 51: 496-505, 2010.
- [157] Campbell LJ et al. Spectrum of chronic kidney disease in HIV-infected patients. *HIV Med* 10: 329-336, 2009.
- [158] Arribas JR et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naïve patients: 144-week analysis. *J Acquir Immune Defic Syndr* 47: 74-78, 2008.
- [159] Winston A et al. Minor changes in calculated creatinine clearance and anion-gap are associated with tenofovir disoproxil fumarate-containing highly active antiretroviral therapy. *HIV Med* 7: 105-111, 2006.
- [160] Gallant JE et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA* 292: 191-201, 2004.
- [161] Gupta SK et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 40: 1559-1585, 2005.
- [162] Mulenga LB et al. Baseline renal insufficiency and risk of death among HIV-infected adults on antiretroviral therapy in Lusaka, Zambia. *AIDS* 22(14): 1821-1827, 2008.
- [163] Ibid.
- [164] Ibid.
- [165] World Health Organization. *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach, 2010 revision*. Geneva, 2010.
- [166] Post, op cit.
- [167] Post, op cit.
- [168] Kalayjian RC et al. Suppression of HIV-1 replication by antiretroviral therapy improves renal function in persons with low CD4 cell counts and chronic kidney disease. *AIDS* 22: 481-487, 2008.
- [169] Peters JP et al. Antiretroviral therapy improves renal function among HIV-infected Ugandans. *Kidney Int* 74: 925-929, 2008.
- [170] Reid A. Severe renal dysfunction and risk factors associated with renal impairment in HIV-infected adults in Africa initiating antiretroviral therapy. *Clin Infect Dis* 46: 1271-1281, 2008.

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A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

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