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Managing kidney disease in people living with HIV

By Theo Smart

Key points

- A general principle of palliative care is to first take care of the most pressing needs of the patient, to quickly address reversible conditions to improve clinical outcomes when possible and to reduce the patient's suffering.
- Once this has been done, it should be possible to pursue other aspects of the diagnostic process, and to assess the patient's other physical needs providing curative care and pain relief, and to assess and attend to whatever psychological, social, spiritual, and cultural needs the patient and family may have. In resource-limited settings without access to expensive and complicated treatments, these needs more often include end of life care and bereavement care for their families.
- In the case of kidney disease, clinical presentations may be quite varied and complicated by other concurrent illnesses to which the kidney injury is often secondary, especially in people living with HIV.
- The previous HATIP described how common symptoms associated with acute and chronic kidney disease (CKD) can vary significantly depending upon which part of the kidney is injured.
- Symptoms such as decreased appetite, fatigue, rash, nausea, vomiting, oedema, high blood pressure, and decreased consciousness are non-specific. Kidney disease is often only detected by laboratory investigations.
- The most severe cases of kidney disease can present with emergency signs denoting the presence of a life-threatening condition, and stabilising the patient as quickly as possible could be a matter of life or death.
- The first step in managing people with kidney disease (although it is yet to be diagnosed as such), and who come in unscheduled for emergency care should involve a quick check for emergency signs and priority signs of severe illness that need to be managed urgently.
- It is important for healthcare workers to know that initiating urgent management at this stage, which is sometimes as basic as restoring proper hydration, may prevent some of the most serious complications of kidney disease and can save the patient's life.
- Once a patient has been stabilised, and when a patient presents to care without emergency signs, a more thorough assessment and diagnosis process can begin, to guide care that can improve quality of life and may reverse some conditions.
- It is important to recognise that asymptomatic people with kidney disease can have life-threatening conditions that can only be detected by laboratory tests.
- Although not as immediately life-threatening, if CKD is detected early enough, it may also be possible to take action to preserve remaining kidney function – and the quality of life it allows – as long as possible, and to watch for other chronic conditions that usually appear in people with chronic kidney disease (CKD) such as anaemia.

- Detecting renal impairment is also important for the best possible management and care of HIV disease as dosage adjustments of various medications may be necessary.
- Some cases of AKI may rather easily be managed by simply correcting appropriate hydration and treating or removing the cause of the injury.
- Even chronically developing conditions such as HIVAN may respond to antiretroviral therapy (ART).
- However, complicated cases that don't respond to these basic measures may require emergency dialysis, which may be virtually impossible for patients to access. Peritoneal dialysis should be considered.
- Renal replacement therapies, including long-term dialysis and kidney transplantation are simply out of reach for most people with end-stage kidney disease (ESKD) in Africa, there is now a discussion about the potential to perform kidney transplants for people living with HIV using kidneys from other people with HIV.
- This article stresses that the principles of palliative care – addressing the patient's symptoms and pain, providing treatment for reversible conditions, acknowledging the non-physical consequences of illness, and consulting with the family about important treatment decisions – should be employed from the first presentation into care.
- Kidney disease can evolve slowly, but it can also be rapidly fatal, so it is especially important that family be consulted about decisions regarding invasive interventions and referrals, and where the patient prefers to receive care.
- In the case of relatively stable CKD, most people will benefit from support to deal with a gradual decline in their kidney function, with good palliative care and nutritional support to preserve quality of life. As people with CKD approach ESKD they will need end of life care and and their families bereavement care.
- Given the high cost and risks associated with renal replacement therapy, the best way to manage kidney disease is to prevent it from happening in the first place, with early screening and management of renal impairment and its risk factors, such as hypertension and advanced HIV disease.
- Unfortunately, such programmes are rarely put into place in sub-Saharan Africa. However, HIV programmes – which intend to treat patients into old age, have an opportunity to lead in this regard.

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Emergency and priority care for suspected severe kidney disease

The kidney plays such a key role in regulating so many essential body functions and blood chemistry that people with acute kidney injury (AKI) and severe chronic kidney disease (CKD) may present to

care as medical emergencies, or with signs of very severe illness, some of which healthcare workers and people living with HIV may not immediately associate with kidney disease. Conversely, people presenting with emergency signs, trauma or signs of severe illness (with septic shock or malaria for example) are often at great risk of AKI. In either case, triage and appropriate emergency care can prevent the loss of kidney function, and in some cases of severe acute kidney injury, leading to recovery of lost kidney function.

For healthcare workers and people who are unfamiliar with performing a quick check for emergency signs requiring urgent care, [WHO's Integrated Management of Adolescent and Adult Illness \(IMAI\) Guidelines on Acute Care](#)¹ provide a basic overview for first-level healthcare workers. A flowchart in the guidelines walks the healthcare worker through a rapid assessment for emergency signs of serious life threatening problems for people who make unscheduled visits to a health facility for an acute illness. This begins with an assessment of the patient's airway passages and breathing (for example checking for obstructions, severe respiratory distress or whether the patient or their gums are turning blue from lack of oxygen). Then, the healthcare worker should check for circulation problems (especially looking for signs of shock or heavy bleeding), lack of or altered consciousness (delirium, convulsions, coma), pain (in the chest, abdomen, neck or head) or fever due to a potentially life-threatening cause. Should any of these signs be present, the guidelines recommend that first-tier healthcare workers should call for assistance, organise access to an IV and begin providing emergency treatment to stabilise the patient.

Primary care providers or a nurse at a higher tier facility should be trained and empowered to ask about the patient's history and symptoms, look for key signs, measure blood pressure, and draw blood for emergency lab investigations in order to help distinguish between the potential causes of an emergency sign, and initiate emergency care. The capacity for laboratory investigations is limited at the primary care setting. If the patient requires investigations and care that are beyond the capacity of the facility to manage, it may be necessary to try to arrange referral to a hospital that can offer a higher level of care.

Note that even though the emphasis of this section is on managing emergencies and providing urgent care, it may be important to stop, take a breath, and consider the patient and their loved ones in front of you. Is this patient someone who already is in chronically poor health or someone with a new and sudden onset of illness? It is important to let the family know that some of the urgent care might seem aggressive or invasive, reassuring them if there is a good chance of recovery, but being honest if the prognosis seems poor. In particular, any referral to another facility is a decision that should be made together with the patient and/or their family, taking into consideration the costs of transport and care, the invasiveness of the interventions the patient will face and how likely they are to improve prognosis.

Emergency signs and symptoms

The following list is not complete but addresses several of the emergency signs and priority signs of severe illness that may need urgent symptom management that are associated with kidney disease (or which put the patient at risk of severe kidney injury). When some of these signs occur together, particularly in the context of recent reduction in urine production, they may point toward kidney disease. However, other aetiologies for the conditions may be more likely and will also need to be considered in the diagnostic process. The following section is primarily concerned with urgent

care that is more likely to stabilise and reduce the patient's suffering in lower resource settings, long enough to refer the patient when necessary, and/or to start the diagnostic process. However, in some cases, a clinician may be needed to make some of the following management decisions, considering other symptoms and referring to emergency laboratory test results (which again may require referral). Except where otherwise noted, the material is drawn from the IMAI Acute Care Guidelines² (which focus on primary care), and from a section on emergency and priority care from an IMAI resource on Care at District Hospitals that is in press (and frequently referencing the Merck Manual and Tabor's Cyclopedic Medical Dictionary).

Severe respiratory distress due to pulmonary oedema (fluid accumulation in the lung tissue)

: In some cases of kidney failure, fluid retention may result in pulmonary oedema and severe respiratory distress (although it may also be due to a cardiac problem or other causes). It is usually possible to hear bilateral crackles (crackles or rattles in both lungs) with a stethoscope. Hypoxia (low oxygen saturation, <90% on room air) is also characteristic of the condition. Raised jugular pressure, rapid heartbeat, peripheral oedema (such as around the ankles) and in some cases, sweatiness could also be present. Without immediate treatment, the patient can slip into a coma or die due to lack of oxygen.

Emergency (and palliative) management: the patient should be assisted to patient sit in an upright position to make breathing easier, and they should be given supplemental oxygen, if available.

A diuretic such as furosemide is often administered when there is suspected heart disease but studies suggest that it does not always improve outcomes in the case of severe renal injury. In such cases, it may be urgent to perform, or refer for, emergency dialysis (see section on dialysis later in the article).

If dialysis is not possible, administering a morphine sulphate solution (titrated at 1mg/ml - giving 1-2mg bolus hourly IVI) may reduce the patient's discomfort. Note that morphine is metabolised by the kidneys, and renal impairment can lead to accumulation of the drug's metabolites and toxicity. While some experts suggest that morphine should not be administered to people with significant renal impairment, others suggest the drug may be titrated with caution gradually escalating the dose until achieving a therapeutic effect (see section on dose adjustments).

Hyperventilation

: People with **metabolic acidosis** (low blood pH that can be a complication of severe kidney disease) may present to care with very rapid, deep and laboured breathing — the symptom is a physiological response, where the body is trying to reduce acidity of the blood. The lungs are generally clear on auscultation. However, the severe metabolic acidosis causing this symptom is an emergency that can rapidly lead to potentially fatal ventricular arrhythmias, hypotension and congestive heart failure.

There can be other causes of hyperventilation (such as anxiety), and there are several possible causes of metabolic acidosis besides kidney disease, including diabetic ketoacidosis, severe sepsis, and lactic acidosis in people taking antiretroviral therapy (these are typically associated with a high anion gap, see footnote)³ In addition, management of metabolic acidosis caused by kidney disease may vary depending upon whether there is a loss of kidney function versus renal proximal tubular dysfunction.

Management is guided by emergency laboratory results. If the blood pH is below 7.2 or plasma bicarbonate is above 15mmol/L,

the case is quite severe and administration of sodium bicarbonate (bolus one ampoule (50 mEq) NaHCO₃, and a constant infusion - 150 mEq NaHCO₃ in 1 liter of D5W over 24 hours) should help raise blood pH and may be life-saving. Serum chemistry should be monitored routinely (at least every 24 hours) to see if blood pH or bicarbonate levels have normalised.

Outside of severe cases, bicarbonate administration should be used with caution as it can have some complications, such as the potential for fluid overload and hypokalemia. In some cases of metabolic acidosis with a high anion gap (see below), it may also be unwarranted since simply treating the cause (as in the case of sepsis) may stabilise the patient. For instance, bicarbonate replacement is counter-indicated in cases of diabetic ketoacidosis.

Again, if the patient does not stabilise, they may require emergency dialysis.

Shock

: Severe illnesses or trauma to the body can lead to shock — when the oxygen supply to the body's cells, tissues and organs is insufficient to meet metabolic needs, usually as the result of a marked decrease in blood pressure. Shock may be caused by dehydration secondary to diarrhoeal illnesses, sepsis, haemorrhage, poisoning, myocardial infarction and other heart problems — and can result in rapid failure of multiple organ systems, often starting with the kidneys.

Quick recognition and treatment of shock is essential to preserve and/or restore kidney function and prevent death.

People presenting with shock may be pale and have cold and clammy skin, with a weak but fast pulse, and capillary refill longer than two or three seconds. (Capillary refill is assessed by holding the patient's hand up above their heart, squeezing their fingertip until it grows pale, and measuring the time it takes to go back to its natural colour). Dizziness and fatigue are also common, and there may be other symptoms related to the cause of shock.

According to the IMAI Guidelines on Acute Care, the healthcare worker should measure blood pressure and pulse and check for bleeding (remembering that this may be internal as a result of trauma). He or she should also ask whether the patient has had diarrhoea (or severe vomiting) as both can lead to dehydration leading to shock and AKI.

The patient may be in shock if systolic blood pressure is less than 90 mmHg or pulse is over 110 per minute. In this case, it is essential to insert an IV and give fluids rapidly (initially as much as 2 or more litres per hour) until systolic BP rises. If this is not possible in the facility where the patient presents, the patient should be positioned with their legs higher than their chest, kept warm (covered), and given appropriate broad spectrum IV/IM antibiotics if sepsis appears likely — and then referred urgently to a hospital.

If diarrhoea: assess for dehydration and follow plan C for rehydration (see *Rehydration* box).

After urgent care is initiated, whatever has triggered shock will still require diagnosis and treatment but that goes beyond the scope of this article. Note also that some forms of shock also may require different urgent care. For instance, anaphylactic shock, which usually presents a very sudden onset with oedema and other signs of hypersensitivity after ingestion of a new medication or substance, requires emergency treatment with epinephrine and hydrocortisone.

Treat severe dehydration quickly — at any age: a decision tree

The IMAI Guidelines on Acute Care provides a 'decision tree' to guide healthcare workers treatment of dehydration, which is adapted in text form below:

Can you give intravenous (IV) fluid immediately?

If yes:

Start IV fluid immediately. If the patient can drink, give ORS by mouth while the drip is set up. Give 100 ml/kg Ringer's Lactate Solution (or, if not available, normal saline), divided as follows:

Age	First give: 30 ml/kg in:	Then give 70 ml/kg:
Infants (under 12 months)	1 hour*	5 hours
Older (12 months or older, including adults)	30 minutes*	2 1/2 hours

* Repeat once if radial pulse is very weak or not detectable.

- Reassess the patient every 1-2 hours. If hydration status is not improving, give the IV drip more rapidly

- Also give ORS (about 5 ml/kg/hour) as soon as the patient can drink: usually after 3-4 hours (infants) or 1-2 hours for children, adolescents, and adults

- Reassess an infant after 6 hours and older patients after 3 hours. Classify dehydration. Then choose the appropriate plan (A, B which are based on oral rehydration, please see the IMAI Guidelines or plan C) to continue treatment.

If you cannot give IV fluid immediately,

is IV treatment available nearby (within 30 minutes)? If yes:

- Refer URGENTLY to hospital for IV treatment

- If the patient can drink, provide the mother or family/friend with ORS solution and show how to give frequent sips during the trip

If IV treatment is not available nearby, are you trained to use a naso-gastric (NG) tube for rehydration, and/or, can the patient drink? If yes:

Start rehydration by tube (or mouth) with ORS solution: give 20 ml/kg/hour for 6 hours (total of 120 ml/kg)

- Reassess the patient every 1-2 hours:

- If there is repeated vomiting or increasing abdominal distension, give the fluid more slowly

- If hydration status is not improving after 3 hours, send the patient for IV therapy

- After 6 hours, reassess the patient. Classify dehydration. Then choose the appropriate plan (A, B, or C) to continue treatment

If no, refer URGENTLY to hospital for IV or NG treatment.

Note: When the patient is a child, if possible, observe the child at least 6 hours after rehydration to be sure the mother can maintain hydration giving the child ORS solution by mouth.

Decreased consciousness including confusion, seizures, unconsciousness or coma

may occur in severe cases of AKI, due to uraemia and/or metabolic acidosis, shock or a number of non-renal causes such as meningitis, severe malaria, head or neck trauma, drug overdose etc. A patient in a coma (who can not be roused and does not react to pain) is in particular need of urgent care. The acute care guidelines

recommend that healthcare workers ask about recent convulsions (asking the relative or caregiver if the patient is unconscious) and measure blood pressure and temperature.

Important emergency and palliative care includes protecting the patient from a fall or injury — the healthcare worker may need to get help to do this — and placing the patient into the recovery position on their side. The patient should not be left alone lest they should choke.

Acute care to stabilise the patient involves inserting an IV and giving fluids slowly, along with appropriate broad spectrum IV/IM antibiotics, antimalarials where indicated, and glucose, unless the patient has high glucose levels. Patients who are having seizures may need to be given diazepam and again, watched closely to make sure their airways remain clear.

When possible, patients with severe delirium should be referred to and/or managed until they improve in a hospital setting, in order to accurately determine and treat the cause of the condition. To help reduce the patient's suffering and avoid exacerbating their confusion while in the health facility, care should be given to lighting and noise levels (so that the patient can have normal sleep patterns). Access to their glasses or hearing aids, if they use them, and to a window, clock, and calendar may help reduce disorientation.

Chest pain due to pericarditis (inflammation of the membrane surrounding the heart)

may occur when kidney dysfunction leads to severe uraemia. Typically the chest pain is worse when air is drawn into the lungs or when the patient lies down, there may be pericardial friction rub (which is an abnormal raspy heart sound). There may be signs of pericardial tamponade, a life-threatening condition when intrapericardial pressure interferes with the heartbeat, limiting diastole (the expansion of the heart that allows blood to fill the heart). This results in low blood pressure, which in turn may aggravate kidney dysfunction.

Emergency management consists of treatment with non-steroidal anti-inflammatories and if the patient has presented at a primary care facility, they should be urgently referred to a facility that can diagnose and care for the patient since a wide range of illnesses can cause pericarditis. Furthermore, uraemia severe enough to cause pericarditis will probably not resolve without acute dialysis (see below).

Other signs of life-threatening illness

possibly related to kidney disease (or posing a risk of kidney injury) may become apparent during the initial assessments and may need urgent management. Some, such as a variety of electrolyte abnormalities are discussed later in the diagnosis section, since they are generally only detected with laboratory tests. However, every facility should be able to detect high blood pressure

Extremely high blood pressure

may be either the result of kidney disease or the cause of it, but needs to be managed lest it causes stroke, myocardial infarction, heart failure or aneurisms. A blood pressure measurement above 180/110 mmHg may indicate that some heart disease is already present as a result of longstanding idiopathic hypertension. However, the body may have become accustomed to such high blood pressure over time, and reducing it too quickly could lead to inadequate blood circulating to the brain and other organs. Therefore, treatment should aim to lower blood pressure gradually.

In cases of suspected kidney injury, with hypertension levels above 160/110, blood pressure should be reduced according to the local protocol, with an IV medication if possible. If these are not available, a long-acting oral calcium channel blocker or ACE inhibitor should be used together with a diuretic such as furosemide. Note, if creatinine levels are above > 200 µmol/L or 2.5 mg/dL, ACE inhibitors should be avoided due to the risk of hyperkalaemia.

Hyperkalaemia,

high serum potassium, can alter the electrical responsiveness of cells, nerves and membranes in a number of organ systems, and may be associated with symptoms such as lethargy and muscle weakness. However, if laboratory tests detect potassium levels above 6.5mEq/L, urgent correction is needed since it can pose a high risk of life-threatening fatal arrhythmias and sudden death. Hyperkalaemia is often found in people with severe CKD, but it may also develop when certain medications (including ACE inhibitors, ibuprofen, naproxen, Bactrim, and pentamidine and other drugs) cause a renal distal tubule dysfunction that interferes with urinary potassium excretion. Electrocardiogram measurements may further help define cardiac status and monitor response to treatment.

Management involves provision of calcium chloride, 5 mL of 10% sol IV over 2 minutes, or calcium gluconate, 10 mL of 10% sol IV over 2 minutes, to restore the responsiveness of the cardiac membrane (to prevent arrhythmias).⁴ As a stop gap measure, treatment with insulin (10-15U rapid-acting insulin with 50ml of 50% glucose IV bolus — with regular blood glucose monitoring) can shift potassium ions from the bloodstream into cellular compartments, reducing the risk of complications. If there is metabolic acidosis, sodium bicarbonate administration, as mentioned above, may also be indicated. Aerosolised salbutamol may also provide temporary reduction of serum blood levels. Longer-acting medications, such as kayexalate (15g hourly x 4), a potassium-binding resin may also then be administered, although some studies question the evidence base supporting the efficacy and safety of the drug.⁵

If no reversible cause of hyperkalaemia can be identified and managed, dialysis may be necessary. However, such cases are often due to CKD and may be difficult to correct.

The assessment of kidney disease and its complications in people living with HIV

As described in the previous HATIP, serious kidney disease is much more common in people living with HIV — especially those who have not yet started treatment, with high viral loads and CD4 cell counts below 200.

Even when there are no symptoms, the possibility of kidney disease should be assessed in every HIV positive patient during their initial clinical visit. Clinical history taking should include asking about previously known kidney disease, or diseases known to cause kidney failure (such as diabetes, hypertension, heart disease), or a family history of kidney disease. Blood pressure should be measured. While laboratory capacity varies depending upon where a person receives care, some resources recommend at a bare minimum, that a urine dipstick test for proteinuria, and drawing blood for serum urea and creatinine should be performed at the initial clinic visit (and at the very least annually thereafter, and biannually for people with evidence of renal impairment, such as CKD).⁶ Other investigations may be necessary according to the symptoms at presentation (see investigations below). If initial investigations suggest kidney disease or impairment, a more

detailed history should be taken, including history of opportunistic infections and a detailed drug history (including traditional medicines — see sections on AKI in the previous HATIP) — note: if the patient shows signs of AKI, any medication suspected of causing it should be discontinued until the diagnosis shows otherwise.

If initial investigations suggest kidney disease, the HIV Medicine Association of the Infectious Diseases Society of America (HMA-IDSA) recommend referral to a nephrologist.⁷ Clearly, this is not possible in many settings in sub-Saharan Africa where there are very few nephrologists, and clinicians may have to consult by phone or email.

A prompt assessment (and ongoing monitoring) of the patient's hydration status is critical in people with or at risk of kidney injury. According to the South African Handbook of HIV Medicine, during the initial assessment “no one sign is sufficient and instead this is a composite ‘guesstimate’ using skin turgor, blood pressure with or without postural drop (>10mm Hg), heart rate, jugular venous pressure (both at 45% and with the patient flat when underhydrated) and oedema.” For patients already in care, it is extremely important to keep monitoring hydration status as well, particularly if they are receiving IV fluids for rehydration, or conversely, diuretics for fluid overload.

Key kidney disease investigations

The following laboratory tests may be indicated for differential diagnoses, to identify serious complications or to help distinguish one form of kidney injury or disease from another.

Proteinuria/Urine dipstick testing:

The early and accurate assessment of proteinuria is a critical aspect in the detection and management of kidney disease in people living with HIV.⁸ Urinary dipstick tests yield qualitative results. “Usually, if there is more than 2g/day (~ 2+ on a dipstick) of proteinuria, the kidney disease is glomerular. Anything less can come from tubulointerstitial or glomerular disease” according to the South African Handbook of HIV Medicine.

However, as noted in the first HATIP in this series, urine dipstick tests for proteinuria aren't perfect. They primarily measure albumin and their accuracy is somewhat affected by urine concentration, hydration and other factors, but they are inexpensive and relatively easy to perform even at the primary care clinic level.

Urine spot protein creatinine ratios

are the ratio of grams of protein to creatinine measured in a urine specimen. These ratios are a more accurate and sensitive measurement of proteinuria, especially people with low levels of abnormal proteinuria (0.3 to 0.99 gp/gc).⁹ This investigation may also prove more useful in detecting proteinuria due to renal proximal tubular disorders (such as that due to tenofovir).

Haematuria:

There are also dipstick tests to detect red blood cells in the urine, haematuria. Whenever there is evidence of haematuria, urine should be sent off for microscopy (including bilharzia ova) bacterial culture and sensitivity and, importantly, TB culture.¹⁰

Urine microscopy:

should look for red blood cells, white blood cells, casts (dead cells from damaged kidney tissue) and crystals (drug precipitates).

Albumin

: Albuminuria, in the urine may be a marker of glomerular kidney disease, (however, the measurement is not specific since it may also be elevated as a result of fever, malignant hypertension or even vigorous exercise.

Urinary volume:

Asking about or monitoring changes in urine output may prove both helpful for isolating the cause (or site) of acute kidney injury, and for staging AKI (see previous HATIP) after excluding for urinary tract infections. Although some people with serious kidney disease may experience no change in urine output, urine output is often reduced (oliguria) or virtually absent (anuria). Oliguria is defined as a urinary output of less than 400/mL per day, and sometimes occurs as a result of a reversible cause of acute tubular necrosis, such as septic shock or dehydration due to diarrhoea. When oliguria occurs in the context of other types of kidney injury, it suggests a poorer prognosis. Anuria is output of less than 50-100 mL of urine per day. If the onset has been sudden, it is generally due to a bilateral obstruction (check for a palpable bladder), but it could also be associated with a rapidly progressive acute glomerulonephritis leading to loss of kidney function.

Malaria smears

for microscopy should also be done in endemic regions, as malaria can cause AKI, and should also be considered in the differential diagnosis of some symptoms.

Serum urea/blood urea nitrogen:

Azotemia (high levels of urea in the blood) is generally asymptomatic but very high levels (eg, two times normal) generally indicate kidney injury and may help identify uraemia.

Serum electrolyte

assessments of sodium (Na⁺), potassium (K⁺), chloride (Cl⁻), and bicarbonate, reveal fluid and electrolyte disturbances that are quite common in people living with HIV. These imbalances are sometimes due to kidney damage, but may be due to other serious illness as well. Regardless, electrolyte imbalances can have important clinical consequences. These include **hyponatraemia**, low concentrations of sodium can result in fluid overload, and if the onset is severe or abrupt, it may be associated with symptoms including nausea, vomiting, fatigue, seizures and coma.

Hypokalemia, abnormally low potassium levels, is usually asymptomatic, although severely low potassium levels can cause cardiac complications. **Hyperkalaemia**, high serum potassium, can alter the electrical responsiveness of cells, nerves and membranes in a number of organ systems, and may be associated with symptoms such as lethargy and muscle weakness. If potassium levels are above 6.5mEq/L, urgent correction is needed since it can pose a high risk of life-threatening fatal arrhythmias and sudden death. Bicarbonate helps moderate blood pH, and high plasma bicarbonate levels > 15mmol/L indicate metabolic acidosis.

FeNa is the Fractional Excretion of Sodium

(Na⁺), which can provide an indication of whether there is an altered excretion of sodium (perhaps due to tubular dysfunction):

$$\text{FeNa} = (\text{Urine sodium} \div \text{Serum sodium}) / (\text{Urine Cr} \div \text{Serum Cr})$$

Serum calcium:

High levels are generally asymptomatic, but severe cases of **hypercalcaemia**, can be life-threatening and require urgent management, presenting with confusion, coma or cardiac

arrhythmias. Hypercalcaemia can have a number of causes, including hyperparathyroidism secondary to renal failure, and is sometimes seen in severe CKD. It can also lead to pre-renal kidney failure and kidney stones.

Serum phosphate:

Hyperphosphataemia is sometimes seen in severe CKD. Hypophosphataemia may be an indicator of tenofovir-related renal proximal tubule dysfunction.¹¹ Note, dysregulation of calcium and phosphate levels have been associated with alternations in bone metabolism.¹²

Fasting glucose levels

are useful for the diagnosis of diabetes, and a host of other conditions

Full blood count:

Special attention should be given to haemoglobin levels. According to the South African HIV Handbook, “A normal haemoglobin (>11g/dl) points towards an *acute* kidney illness, while a low haemoglobin, in the setting of HIV infection could be due to a number of causes including chronic renal failure.”

Serum creatinine

levels can be used to estimate **glomerular filtration rates (GFR)** in patients whose levels are in a steady state, and serve as the best marker of kidney dysfunction, used both for staging CKD and recognising AKI. As noted in the first HATIP in this series, none of the three equations to calculate the estimated GFR have been adequately validated in people living with HIV or in different sub-Saharan African populations — and in the two studies, factors to adjust for African-American ethnicity did not appear to be appropriate in Ghanaian or South African populations.

The HMA-IDSa guidelines recommend the simplified MDRD equation for monitoring people living with HIV. However, the Cockcroft-Gault equation was what was used to determine whether medication dosage adjustments are necessary. It is unclear, to this author at least, how reliable the recommended dose adjustments are in sub-Saharan African populations, until the equation determining renal impairment is validated here. If Cockcroft-Gault over-estimates kidney impairment here, the recommendations could lead to underdosing a potentially significant number of people.

The simplified MDRD GFR (mL/min/1.73m²) = 186 x [serum creatinine (mg/dL)] x [age (yr) x 0.742 if female] (with the ethnicity factor omitted).

CrCl (mL/min) = [140 – Age (yr)] x weight (kg) [0.85 in female] / (72 x serum creatinine (mg/dL))

Serum anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, complement levels, hepatitis B and C virus antibodies, syphilis serology

(if a biopsy is contemplated) can be useful in identifying when kidney disease may be auto-immune related or potentially due to HBV, HCV or syphilis.

Lactate:

increased lactate levels may occur as a result of nucleoside analogue-associated lactic acidosis. Levels five times the upper limit of normal are life-threatening.

Ultrasound scans

can show whether a kidney is normally sized (normal 10-12cm), large, or shrunken or whether there are obstructions in the urinary track. According to the South African Handbook, small kidneys (<9cm) may point towards CKD, “whilst with normal or big kidneys it is difficult to be sure as many HIV related nephropathies cause increased size initially.”

Renal biopsy:

The definitive diagnosis of some types of kidney disease cannot be made on clinical grounds alone, but requires a biopsy. The South African HIV Handbook suggests considering a biopsy when there is heavy proteinuria or in cases of acute kidney failure where the cause is not immediately apparent (such as ATN).

But what does a kidney biopsy really involve? It may be interesting to refer to patient directed educational materials from the industrialised world and try to picture how what they describe would play out in resource limited settings.

According to materials published by the National Kidney Federation in the United Kingdom [see here], many doctors in the UK are cautious about recommending a kidney biopsy because it is a somewhat invasive procedure and there is a small risk of bleeding afterwards. This risk may be minimised by telling the patient to discontinue any drugs — including aspirin — that thin the blood a couple of days before the procedure, and then by assessing whether the patient's blood clots properly (which it doesn't always do in people living with HIV and some forms of kidney disease) before the procedure is performed.

The procedure is done under local anaesthetic and, when guided by ultrasound or CT imaging, should take less than a half hour to perform. Afterwards the patient needs to rest in a bed at the facility for at least six hours and have their blood pressure and pulse monitored. Their urine should be repeatedly tested for blood and they should be given pain killers when the anaesthesia wears off. If there is no bleeding, they may be sent home that same day, or possibly the next day. They should also be told not to exercise for the next couple of days and to contact the facility if there is any blood in their urine or if they develop severe pain.

The educational materials state that after the procedure, about one out of ten cases have visible bleeding that resolves by itself. One out of 50 have bleeding that requires a blood transfusion. Complications that lead to surgery to stop the bleeding or in removal of the kidney only occur in one out of 1500, and one out of 3000 respectively. The risk of death is small.

It's not clear that these safety statistics would be matched in many resource-limited settings outside of a good kidney unit, such as at Groote Schuur Hospital in Cape Town — which incidentally performs baseline biopsies on all of its patients with ESKD. But elsewhere, getting a kidney biopsy may be easier said than done — even at tertiary hospitals in Africa. Even in South Africa, doctors on our advisory panel told HATIP that kidney biopsies can be a bit difficult to arrange within the public health system. Therefore, there needs to be a compelling reason to believe that the biopsy findings will truly affect the course of treatment and affect a patient's clinical outcome. For many of the conditions below, that does not appear to always be the case.

Diagnosis and management of kidney disease and major complications

The approach to HIV related kidney disease table below, from the South African HIV Handbook is a good basic to recognising some of the most common kidney disease in people living with HIV. The

reader is advised to refer to the last issue of HATIP for definitions, descriptions and symptoms of the following kidney disorders. In addition, we should note that the diagnosis of some conditions and their management, such as thrombotic microangiopathy, was already discussed in that issue or in emergency management and will not be revisited here.

A differential diagnostic approach to HIV-related kidney disease (from: McCullough ML. Nephrology, In: South African Handbook of HIV Medicine, 2008)			
	Glomerular	Tubulointerstitial	Differential diagnosis: acute or chronic?
ACUTE	<ul style="list-style-type: none"> ● Crescentic ● Glomerulonephritis 	<ul style="list-style-type: none"> ● ATN ● AIN ● Obstruction 	Haemoglobin >11g/dl = acute
CHRONIC	<ul style="list-style-type: none"> ● HIVAN ● HIVICK ● Other GNs 	<ul style="list-style-type: none"> ● ATN/AIN obstruction ● Reflux 	Ultrasound: <9cm = chronic (normal or big kidneys = chronic)
Differential diagnosis: Glomerular or tubular	Urine dipstick > 2 = glomerular, usually chronic (minimal / no proteinuria = glom)		

Acute kidney injury (AKI):

Marked abrupt increases in serum creatinine, reductions in eGFR and changes in urine output are the key markers for acute kidney injury, see **Rifle Classification System for Acute Kidney Injury**. In people living with HIV, particularly those with low CD4 cell counts, there should be a higher index of suspicion of obstructions and other kidney injuries due to coinfections such as TB and opportunistic infections. When history, signs or other symptoms suggest, the clinician should send out for urine cultures and other laboratory tests.

Acute tubular necrosis:

AKI following soon after shock, sepsis or other illness associated with severe dehydration or hypotension, or after exposure to a known nephrotoxin (such as amphotericin B), muscle necrosis, surgery or trauma is suggestive of ATN. In most cases, urine microscopy should reveal cellular debris, and muddy coloured casts of tubule epithelial cells. Should the patient be biopsied, histology reveals tubular damage.

In the previous HATIP, we did not make a distinction between cases of AKI that are entirely pre-renal and ATN, where there is much more intrinsic damage to the kidney, largely because they often overlap. Some resources indicate that there is less evidence of tubule damage on microscopy/histopathology, and FeNa is below 1%. The most significant distinction, however, appears to be that when pre-renal AKI is much more responsive to the administration of IV fluids to re-establish renal perfusion.

Management

:

- Correct fluid losses: see section on *Shock* for IMAI guidelines on IV fluid administration. The *South African HIV Handbook* also

notes that heart rate, jugular venous pressure and skin turgor can help guide clinical monitoring, but more precise measurements of venous pressure may be required using an indwelling central venous catheter

- Once normal hydration is achieved, blood pressure should be restored with [inotropes](#) such as [norepinephrine](#) and [dobutamine](#)
- The cause of shock, dehydration or hypotension triggering AKI must also be treated
- Any drug or medication that may have triggered toxic ATN should be discontinued
- Additionally, stop other medications that may interfere with renal perfusion, including ACE-inhibitors and non-steroidal anti-inflammatory drugs

Cases that do not stabilise may require acute dialysis (see section on *Dialysis* below).

Acute Interstitial Nephritis (AIN):

AIN is commonly found with other signs of an allergic reaction (fever, rash, eosinophilia and transaminitis) to a medication. The urine findings include eosinophiluria, sterile pyuria (white bloods cells with no bacteria), blood, and granular casts. However, definitive diagnosis can only be made with biopsy findings, which shows inflammatory (with oedema) infiltration with lymphocytes, eosinophils and plasma cells in the interstitium.

However, it is unclear whether a biopsy is warranted — AIN usually resolves completely once the offending drug is stopped (any drug or medication that might be responsible should be discontinued). Some studies suggest that the administration of corticosteroids may speed recovery.¹³

Crystalluria:

Crystalluria may be diagnosed upon finding drug crystals on urinary microscopy, particularly when found in a person taking a medication known to cause the condition (such as indinavir). In the case of indinavir, imaging studies have revealed signs of obstruction from calculi (essentially kidney stones made of precipitated drug), while tubular crystals, tubule necrosis and dilation, with diffuse eosinophilic interstitial infiltrates and scarring may be observed on histology.¹⁴

After initial management of nephrolithiasis, the literature suggests that the offending drug may be restarted with improved hydration. However, most of those recommendations came from a period when there were fewer treatment options available.

Post-renal injuries due to obstructions:

Other obstructions in the urinary tract may also cause post-renal kidney injury, or altered urine output (for example, anuria or polyuria) or abnormal findings on urinalysis. For instance, infections may cause inflammation and fibrosis — balls of fungal growths have even been reported to cause bilateral blockage and renal failure. Urine cultures may show evidence of an infection. However, ultrasound is the best way to identify obstructions and can guide management.

Surgical interventions may be curative. However, if this is not feasible, if the patient's medical condition makes this impossible or the patient and their family refuse surgery, less invasive options such as urethral stints or percutaneous nephrostomies may provide relief. A good resource for facilities or clinicians with little experience performing such procedures is offered online by an NGO, [International Humanitarian Surgery](#), which has a number of surgery

texts available for download, including, for example, instructions [on how to pass a catheter](#).

Diagnosis and management of glomerular diseases

As described in the previous HATIP, there are a wide range of glomerular diseases, which can present acutely, and sometimes leads very rapidly to loss of kidney function, or which may become chronic. The aetiology of many of these conditions is poorly understood.

In glomerulonephritic diseases, such as IgA nephropathy, a misdirected immune response, often autoimmune or in response to a recent but cleared infection, is a common feature, leading to the deposition of antibodies or immune complexes in the glomeruli, causing inflammatory infiltration and disruption of their structure. This results in haematuria and proteinuria, reduced glomerular filtration, oliguria and hypertension due to fluid retention.

At the other end of the spectrum, diabetes, hypertension and other conditions cause either chemical or mechanical damage to the glomeruli, leading to a nephrotic syndrome that presents with severe proteinuria (> 3 g/day), hypoalbuminaemia, oedema and altered lipids and cholesterol but without haematuria. HIV-associated nephropathy (HIVAN) can be placed in this latter group, although cholesterol levels may not be high. HIV-Immune Complex Kidney disease (HIVICK) seems similar, although it appears to have a somewhat different pathology.

However, none of the above features can reliably distinguish between glomerular diseases. Unfortunately, to make a definitive diagnosis, a biopsy is needed to look for hallmark features on histology.

HIV-associated nephropathy (HIVAN):

In her talk to the South African Nephrology Society, Dr Nicola Wearne of Groote Schuur Hospital in Cape Town stressed that clinical features could not be used to make a diagnosis, because HIVAN can often mimic other glomerulopathies. However, she also said that in most cases, blood pressure is normal, pedal oedema is minimal, renal ultrasound shows that kidneys are NOT small (in contrast to other chronic kidney conditions), and proteinuria is in the nephritic range (3+).

The classical histology features include the following:

- Focal segmental glomerular sclerosis (FSGS) which may be collapsing in nature
- Hypertrophy of epithelial cells
- Cystic-like tubular dilatation with atrophy. "Microcyst formation"
- Interstitial lymphocytic infiltrate with a plasma cell predominance and fibrosis.

However, she noted that there appear to be variants that don't match these features exactly, for instance where FSGS does not lead to collapse. In addition, she noted that many cases of HIVAN had features associated with immune complex glomerulopathies. [For those with an interest in histology, we would urge you to download [Dr Wearne's powerpoint presentation for its images](#)].

Management:

Although most people who develop HIVAN tend to have advanced HIV disease, it can occur at any stage of HIV disease – and can be very rapidly progressive, leading to ESKD and death within 8 to 16 weeks of diagnosis. While there have been no prospective controlled clinical trials of treatment for HIVAN, in light of the natural

course of the illness without ART, the anecdotal and retrospective data showing that ART has a profound impact slowing the progression of HIVAN cannot be ignored.

For instance, in Dr Wearne's cohort, for people with any biopsy evidence of HIVAN, ART reduced mortality by 78%.

"ART appears to be **very effective** but not completely effective," she said, possibly because of incomplete adherence, and the location of the renal reservoir, ie, the epithelial cell, may impede treatment with ART."

The *South African HIV Handbook* offers a few other suggestions:

Angiotensin converting enzyme inhibitors (ACE inhibitors) "diminish the degree of proteinuria in a non specific fashion and have proven benefits in many other forms of kidney disease. Maximum doses should be used, blood pressure and potassium permitting. If the patient develops side effects such as angioneurotic oedema or a persistent cough, substitute angiotensin receptor blockers."

Dr Wearne also suggested trying ACE-I, noting that even though the evidence was mainly extrapolated from benefit in other proteinuric kidney diseases and there are limited data in HIVAN, some small studies do support that they may be of benefit.

Additionally, although many people living with HIVAN are hypotensive, or have normal or low cholesterol, those who do have elevated blood pressure should add standard anti-hypertensive drugs to achieve a systolic pressure of ≤ 130 mmHg, while those with high cholesterol should add standard statin therapy to achieve a cholesterol of < 5.5 mmol/l. Finally, even though HIVAN is believed to be directly caused by HIV's toxic effects, some small trials have suggested corticosteroids may have some benefit.

Dr Wearne noted that there are significant amounts of tubulointerstitial inflammation in HIVAN, so there may be a rationale for steroid use. Of course, corticosteroid use is always saddled with concerns that it may increase opportunistic infections or TB. Dr Wearne is currently commencing a randomised clinical trial of steroids for HIVAN.

HIV Immune Complex Kidney Disease (HIVICK):

As noted in the previous HATIP, there is some debate over how to define HIVICK. A pivotal paper on kidney biopsies in Johannesburg, South Africa, by Gerntholtz et al has helped to better characterise HIVICK.¹⁵ (Note, the paper also provides histological descriptions of the various other glomerulopathies that were seen in the cohort).

The cases Gerntholtz et al defined as HIVICK had the following features:

- Immune complex deposition in the glomeruli in varying patterns: (1) diffuse mesangial (lupus like); (2) subendothelial; (3) subepithelial "ball in cup" pattern
- Interstitial infiltration, often accompanied by some of the features seen typically in HIVAN (e.g. glomerular collapse and interstitial microcyst formation).

Dr Wearne questioned whether the cases with mixed features should be considered as HIVICK, and suggested that HIVICK refer to the disease with the following histological features:

- Ball and Cup phenomena
- Large subepithelial deposits – larger than the humps of postinfectious' diffuse proliferative glomerulonephritis
- Basement membrane-encasing the deposits
- Appears to be specific for HIV

Dr Wearne suggested the distinction is significant for treatment and prognosis, pointing out observations by Szezech et al that the initiation of ART does not improve renal function among people living with HIV and renal disease other than HIVAN.¹⁶ However, in the cohort at Groote Schuur, people with classical HIVAN and those signs of immune complex disease mixed with evidence of HIVAN had a similar response to ART.

"It really does appear to depend on whether there is any evidence of HIVAN on the renal biopsy," she said. "Hence the need for an accurate classification system."

In those with HIVICK without signs of HIVAN, there is virtually no evidence-based guidance on management. ART is probably worth trying anyway, as may be treatment with ACE-inhibitors, blood pressure control and statins, and possibly steroids and/or cyclophosphamide.

Management of other glomerulonephritides:

Non-HIV related glomerulopathies should be managed just as they are in people without HIV, while watching closely for the development of HIVAN since these individuals may be at greater risk. An exception to this rule is **HBV membranous or proliferative-membranous nephropathy**, which should be treated with lamivudine — not as a monotherapy — but as part of ART.

Diagnosis and management in children

Children living with HIV are also developing CKD, and the numbers may increase in resource-constrained settings as survival improves on ART, according to a review by McCullough and Ray.¹⁷

This appears to be the case in the US, where prior to the introduction of ART, roughly 40% of all HIV-infected children experienced renal complications that led to poor growth and sped progression to AIDS and/or premature death.¹⁸ But even prior to ART, survival in children with HIV in the US was higher than in Africa, where young children frequently die of diarrhoeal or respiratory diseases before kidney disorders can develop or are recognised. This is now changing however.

In their review, McCullough and Ray noted that in the earliest days of the HIV epidemic in the US, tubulointerstitial lesions were detected during autopsy studies in HIV-positive children who died of other causes.

Shortly after HIVAN was recognised in adults living with HIV, it was identified in children as well, usually around the age of 2 or 3 years old. However, while kidney disease reduced the quality of life in HIV-positive children, they usually died from other HIV-related conditions before they developed end-stage renal disease. Once ART became available in the US, survival improved dramatically — and this allowed more opportunities for CKD to develop.

HIVAN is still being diagnosed, however, but at an older age; and the numbers of children living with HIV and CKD is increasing, with a growing number of children now requiring renal replacement therapy.

"It is anticipated that as ART becomes available to more children in resource-limited settings, a similar epidemiologic and clinical pattern will be seen in Africa," McCullough and Ray wrote.

Indeed, this appears to be the case according to Dr Elaene Naicker, who is a paediatric nephrologist working at Inkosi Albert Luthuli Central Hospital in KwaZulu Natal, South Africa.

"Our unit at Inkosi Albert Luthuli Central Hospital is the only paediatric renal service in the province and the following stats, although reflecting trends in Kwazulu Natal only, also mimics the national data.

Prior to the HIV pandemic the commonest causes of chronic kidney diseases in children were congenital abnormalities like obstructive uropathies, reflux disease; glomerulonephritides like focal segmental glomerulosclerosis or were secondary to multisystemic diseases.

Over the past few years HIV nephropathy has fast become the commonest indication for renal biopsies in our unit and patients are being referred for various renal manifestations including persistent proteinuria, renal impairment: both acute and chronic, overt nephrotic syndrome, tubulopathies and HIV-related haemolytic uraemic syndrome."

She said that only four patients were biopsied with HIV nephropathy in 2006, but this went up to 29 patients in 2008, and has stayed steady at 18 patients in 2009 and 2010.

"Of the total cohort approximately 50% of these patients presented with some renal impairment: the aetiologies ranged from pre-renal disease to intrinsic and chronic insufficiency," she said adding, "at present our resources do not allow enrolment of these patients onto chronic dialysis programmes."

These numbers may just represent the tip of the iceberg, since a large proportion of children may never make it to a facility where their condition can be diagnosed.

McCullough and Ray discuss a number of renal conditions that merit special attention in children. In one study with 60 children with HIV and renal impairment in Johannesburg, 23% had severe urinary tract infections leading to pyelonephritis.¹⁹

There are also tubular disorders resulting in insufficient reabsorption of sodium, potassium, and phosphate that may lead to metabolic complications that may be in part responsible for growth impairment, and in more severe cases metabolic acidosis.

Metabolic acidosis is a change in blood pH can lead to a constellation of worsening symptoms ranging from nausea or headaches and eventually to severe neurologic complications and death. "Renal tubular disorders often are identified when electrolyte abnormalities do not improve after diarrhea or other gastrointestinal complications have resolved," McCullough and Ray wrote.

HIV-related haemolytic uraemia syndrome is another condition clinicians need to diagnose quickly because it often leads to death. In South Africa, it is typically seen in children under 2 years of age, "who usually present in critical condition, often too sick to undergo renal biopsy, but with the classic clinical symptoms of HUS. These children are treated with supportive therapy and peritoneal dialysis, but often die from overwhelming sepsis without the growth of any specific organism."

And growing numbers are being diagnosed with HIVAN, and/or HIVICK. McCullough and Ray note that there is more than one pattern of HIVAN, one of which may be more commonly seen than in adults, which (on histology) involves hyperplasia of mesangial cells rather than classic FSGS. This appears to have a somewhat less aggressive course, although it may just represent an earlier stage of HIVAN.

ART may resolve or reduce the progression of these conditions. However, it is possible that the ongoing subclinical kidney injury in children on ART may simply lead to CKD with an insidious onset.

When to consider dialysis

Dialysis is a technique that removes toxic materials from the blood across a semi-permeable membrane, and which can restore fluid, electrolyte and acid base balance and save the life of an individual with a severe kidney injury.

In well-resourced settings, the conservative clinical management described above would be unheard of when managing the more life-threatening complications of kidney disease or cases of AKI. Most patients with a severe reversible condition would be put on acute haemodialysis as soon as possible, since it would provide the best chance of stabilising the patient quickly and offer the best chance of recovery.

Clearly, this is not a widely accessible option in most resource-limited settings, where the cost of haemodialysis is around US \$100 per session. In sub-Saharan Africa, haemodialysis equipment is generally only available at larger hospitals and in only some countries. For instance, according to a recent review by Katz et al, in South Africa, there are roughly 4000 people on haemodialysis; in Rwanda, not one of the poorest country in sub-Saharan Africa, there did not appear to be anyone on haemodialysis (although it was not clear from the paper when the data were gathered).

However there is another modality for dialysis. Peritoneal dialysis is a process, often used in children, which uses the lining of the patient's peritoneal cavity as the dialysing membrane, across which fluids, electrolytes, nitrogenous wastes and other small molecules are exchanged from the blood by osmosis — though somewhat less efficiently than haemodialysis. Fluid is introduced through an indwelling catheter in the peritoneum and flushed out via regular exchanges throughout the day (continuous ambulatory peritoneal dialysis).

An advantage of the technique is that it could theoretically be performed outside of hospital settings. In fact, it has been used in combat settings and disaster relief areas. Great care must be taken to use antiseptic technique to minimise the risk of infections in the dialysate and peritoneum.

While peritoneal dialysis is not used as commonly, it has been used successfully in people living with HIV in industrialised countries.²⁰ In the era before ART, there was an increased risk of serious infections, though since ART, some people living with HIV and CKD have used it for up to 12.5 years according to one study — though there was a significantly higher risk of hospitalisation and peritonitis among people living with HIV.^{21, 22} Notably, a report on managing kidney disease in West Africa described a fair amount of success using peritoneal dialysis.²³ Out of 64 people with severe kidney disease put on dialysis, only 15 died.

"Perhaps the most striking and significant observation was that of a total of 256 peritoneal dialyses done on an open medical ward, there were no cases of peritonitis. The most impressive results were with patients who presented with pre-renal causes, and nephrotoxins. Most of these patients responded to rehydration and peritoneal dialysis, respectively, and regained normal or near normal renal function," the author wrote.

McCullough and Ray also note the importance of this modality for children. "Peritoneal dialysis may be associated with increased infections, but is more readily available than haemodialysis in resource-poor countries, and may present less risk for health care professionals." (There is some risk of exposure to bodily fluids containing HIV in both forms of dialysis, so healthcare workers must follow universal precautions).

Despite these reports, there is even less access to pericardial dialysis than haemodialysis in sub-Saharan Africa — due to the high cost of the dialysis fluids, and the continuing perception of a high risk of peritonitis. Nevertheless, there are a handful of people on it in countries without access to haemodialysis, and in South Africa, one out of four people on dialysis are on peritoneal dialysis.

One final reason that it is not being used more widely could be that healthcare workers have not been trained in how to perform the technique. It is worth noting however, that international nephrology agencies have begun providing more training to doctors in resource-limited settings — and according to another recent paper by Naicker et al, one of these agencies now includes the International Society of Peritoneal Dialysis.

However, even though some of the cases described above involved people with CKD, the most critical application for expanding access to dialysis is for acute care.

While emergency care such as correcting fluid status may indeed save lives, some cases are simply more complicated, and will need acute dialysis.

The South African HIV Handbook suggests the following indications for dialysis.

- Fluid overload and pulmonary oedema that does not respond to diuretics
- Potassium overload (hyperkalaemia) that does not respond to insulin, intravenous dextrose and/or bicarbonate and gastrointestinal transfer gels such as calcium resonium (kayexelate)
- Uraemia syndrome defined by encephalopathy, bleeding, serositis (usually pericardial effusion) and acidosis. This is not dependent on a set biochemical "cut off" point.

In addition, severe metabolic acidosis that does not respond appropriately to sodium bicarbonate management indicates a life-threatening condition that can be extremely difficult to manage without dialysis. Such cases could also benefit from acute dialysis, if it is available.

However, given the limited access to dialysis at present, and the possibility that both transport and the cost of care may represent out of pocket costs for people and their families, healthcare providers should be prepared to discuss the prognosis and care options with the patient and or their family.

Kidney transplants for people living with HIV?

As mentioned in the first HATIP in this series, in sub-Saharan Africa, dialysis for people with CKD is only available for a fraction of the population at risk of ESKD — and only for those cases who are considered good candidates for kidney transplants. Kidney transplantation works out to be much more cost-effective for the health system than dialysis and studies have also shown that it greatly improves patients' quality of life and survival as compared to dialysis.^{24, 25} But until recently, people living with HIV did not qualify for kidney transplantation because of the perception that they would have poor outcomes.

Several studies showing similar benefits to kidney transplantation for HIV negative and HIV positive individuals led the South African government to change its policy to allow HIV-infected patients access to dialysis and kidney transplantation, provided that they have a CD4 count >200 cells, an undetectable viral load and are adherent to a stable ART regimen. In practice, this changed little as there were few kidneys available for transplantation.

However, last year, researchers from Groote Schuur Hospital in Cape Town [published their experience transplanting kidneys](#) from HIV-positive donors to patients with end-stage renal disease who have HIV infection.²⁶ This raises the possibility (in South Africa at least) that kidney transplantation could become a possibility for people living with HIV — an option Dr Elmi Müller, the surgeon who performed the kidney transplants, thinks is clearly needed.

"We are seeing an increasing amount of stable HIV positive patients with ESKD," Dr Müller told HATIP. "In the last 12 months our clinic numbers have more than doubled. So we have a large amount of potential patients with HIV who are developing end-stage renal failure and progressing towards dialysis. It is as a result of this that we started the HIV positive to positive transplant programme at GSH. Now, the waiting list for transplantation is increasing as well. This could be the result of increased awareness among referring physicians or alternatively just simply increasing numbers of patients."

On the basis of the work at Groote Schuur and similar work with a larger cohort conducted by the US National Institutes of Health (NIH) and [published in the New England Journal of Medicine last November](#),²⁷ there are now discussions in South Africa about establishing an HIV-positive organ donor pool. Of course, the procedure is not without its risks — there is a theoretical possibility that re-infection with a different strain of HIV from the donor organ might hasten HIV progression. Similarly, it is possible that drug resistance could be transmitted. However, the researchers at Groot Schuur took precautions to prevent this.

"Our donors were mostly naive to antiretroviral therapy," she said. "They should not have viral resistance, but [just in case] there is a safety measure in using second-line treatment in the recipient who receives a new viral strain."

But there are other risks as well. For instance, this is a very invasive procedure, and there is always the possibility of going through the whole ordeal of surgery only to face graft-versus host disease.

"They need careful monitoring as these patients have acute rejection rates as high as 30% in some studies," Dr Müller said.

Also it is quite possible that whatever processes caused injury to the recipient's original kidneys could cause the same disease in their new ones.

In fact, Dr Müller told HATIP that the vast majority of the patients in their transplant list had HIVAN as the cause for end-stage renal failure — and it may remain a problem. "We also see some suggestion of HIVAN in our post-transplant population. In the recent NIH trial, they reported some recurrent HIVAN in the transplanted patients as well," she said.

In light of these risks, it is worth asking whether this is treatment that people living with HIV and CKD want.

That is precisely what researchers in Johannesburg recently did, by conducting a survey to assess the attitudes of South African patients and healthcare workers to the prospect of HIV positive-to-positive kidney transplants.²⁸ The response was very positive with 90% of health care workers and 80% of patients, (N=20 and 80, respectively) in favour of it.

But another question is whether this is really the best way to spend limited health resources. However, the South African public health system is one of the few that does pay for kidney transplantation for HIV-positive people. Until recently it was limited to HIV-negative individuals.

Ironically, though, "transplanting an HIV-positive patient is much cheaper than a HIV-negative patient, if the patient is put on protease inhibitors (PIs)," Dr Müller told HATIP. (Protease inhibitors slow the metabolism of calcineurin inhibitors, allowing a lower dose to be used).

"The boosted PI regimen is partly [to protect against resistance] and partly to save cost. It is true that the PIs react with the calcineurin inhibitors, but the NRTIs and NNRTIs do as well. For us it made a significant impact on cost. With the NNRTIs, the patients need a little more calcineurin inhibitor which pushes up cost. The

PIs save pots of money. Patients on PIs need 1mg or sometimes only 0.5mg of Tacrolimus per week. HIV-negative patients need 14-16mg/day and pts on NNRTIs need 20-25mg/day," she said.

Indeed, the difference in cost is profound. Tacrolimus is an extremely expensive drug, costing almost 100,000 Rand per year, or 272 Rand per day in HIV-negative people. However, because of the drug interaction with the PI-based ART regimen, it only costs 1.39 Rand per day in HIV-positive organ transplant recipients, roughly 500 Rand per year.

At that price, in South Africa, it might *only* be cost-effective to perform kidney transplants for people living with HIV.

Dr Müller conceded that there are dangers with this drug interaction though.

"It needs very careful monitoring and some overseas centres prefer not to take the risk of calcineurin toxicity with the PIs," she said.

What now remains to be done is to get people living with HIV to become organ donors — once they pass away.

"We feel that utilising kidneys from living donors carries too high a risk for them. We regard HIV as a similar situation to diabetes and hypertension. The donor with these diseases carries a significant risk for end-stage renal failure in the future and therefore we do not want to reduce their renal mass. So all the donors we have used so far have been deceased donors. We would be happy to do a living donor transplant for an HIV-positive patient, but then he/she [the donor] must be HIV-negative," she said.

Palliative care for best quality of life for people living with HIV and CKD

The vast majority of people with chronic kidney disease in sub-Saharan Africa are unaware of their condition. However, as a result of expanding HIV programmes with expanding screening for kidney disease, a growing number of HIV-positive people with chronic CKD may be finding themselves living with two terminal illnesses.

But people should not be made to feel helpless in the face of steadily declining kidney function and related conditions — there are a number of actions that can be taken to preserve their quality of life, as well as a number of steps to take to get the most out of the life they have left.

For instance, the HIVMA-IDSA guidelines emphasize the importance of controlling hypertension, and aggressive management of cardiovascular risk factors as an increasingly important aspect of both HIV care and the management of CKD.

Studied avoidance of the Western life-style — with its high salt, high fat, processed food, lack of physical exercise, smoking, high stress levels and lack of connectedness to one's community — could go a long way towards slowing progression of CKD. In fact, a number of studies are evaluating how changes to these lifestyle factors affect cardiovascular disease.²⁹

It is interesting to note that the large MDRD study (that validated the MDRD equation of estimating GFR — at least in a Western population) actually stood for the Modification of Diet in Renal Disease study, which showed that the adoption of a low protein diet could slow the progression of CKD modestly.

In fact, a subsequent Cochrane Analysis confirmed this, concluding that a low protein diet significantly reduced the risk of progression to ESKD and death.³⁰ This was despite poor adherence for study participants to a diet which had to be strictly weighed and was considered unpalatable. Ironically, many people in the world already eat a low protein diet without trying.

However, a diet with too little protein carries other risks, such as fatigue, low iron levels, malnutrition and potentially, frailty. So if possible, people with HIV and CKD should be referred to a nutritionist who has been trained in specialised diets.

Anaemia is already a significant problem in many parts of sub-Saharan Africa, and anaemia can become quite marked with advancing CKD. Iron, folate, vitamin B12, and a multivitamin supplements may be helpful. If the patient is ambulant and symptomatic, haemoglobin levels < 7 g/dl may be treated with a transfusion — however the patient should be warned of risks such as blood-borne infections and iron overload.

As kidney and cardiovascular function decrease, the patient may become less active, and may need assistance with daily activities such as bathing, dressing, cooking and feeding. The family may also need support, especially considering that with CKD, these symptoms of advancing age may be seen in relatively young patients. They should also be prepared for a greater risk of AKI and sudden cardiac problems — and have a strategy about whether to accept further emergency care should the need arise.

In other parts of the world, hospitalised and high level care might be able to extend their lives further. But treatment for all who may be affected with CKD is beyond the reach of most countries in Africa. The only cost effective and sustainable means is prevention.

“Prevention and early detection [of kidney disease] is of paramount importance. And this needs to be implemented at the primary health care level—currently this is NOT done optimally,” said Dr Nicola Wearne in Cape Town.

Antiretroviral dosage adjustments for people with impaired renal functioning

Making antiretroviral dosage adjustments in HIV-positive people under certain circumstances is an essential aspect of HIV clinical care. The need to use lower doses of antiretroviral drugs in people with chronic kidney disease is well established, and yet there may not be sufficient awareness of this issue in many clinical settings, even in high-income countries.

The nucleoside reverse transcriptase inhibitor (NRTI) class of drugs presents the most issues, with dosage adjustments being advised for all NRTIs other than abacavir in the presence of kidney impairment.

In HIV-positive people whose kidney functioning is being sustained by dialysis, NRTIs and some other antiretrovirals should be administered after dialysis.

Appropriately treating HIV-positive people with impaired renal functioning often requires a switch from fixed-dose combination antiretrovirals (e.g., *Atripla*, which contains tenofovir, FTC and efavirenz) to regimens that allow for individual drug adjustments.

The following table, adapted from the 2005 IDSA/HIVMA guidelines on managing chronic kidney disease in HIV-positive people, summarizes treatment recommendations for all antiretrovirals that should be administered differently in HIV-positive people with impaired kidney functioning. An updated version of these guidelines is anticipated in 2012.

A mid-2010 article posted on the HIV InSite website provides similar guidelines, while also summarising treatment recommendations for newer antiretrovirals.

Chronic kidney disease does not appear to warrant adjustments in the usage of enfuvirtide (a fusion inhibitor) or raltegravir (an integrase inhibitor). For maraviroc (a chemokine coreceptor antagonist), the article reports that dosage adjustments are not necessary in cases of mild or moderate chronic kidney disease, but

that “maraviroc should not be used in patients with severe renal impairment or end-stage renal disease (CrCl <30 mL/min) who are taking a potent CYP3A inhibitor or inducer.”³¹

One of the most important reasons to screen for renal impairment in people living with HIV is to make certain that other care being providing is not harmful to them.

Many medications are metabolised or eliminated by the kidney, and failure to adjust the dosages of the medications in people with renal impairment could lead to increased side effects or even dangerous toxicity. However, even when laboratory data on kidney function are available for the patient, numerous studies have found that healthcare workers generally fail to make appropriate dosage adjustments.

A recent example comes from Decloedt and colleagues at Groote Schuur Hospital (again), who reviewed the medical records of people admitted to the wards between January to March 2008.³²

They found renal impairment, defined as an eGFR ≤50 ml per minute, in found 32% (97/301) of the medical admissions. 615 prescription entries made for the 97 patients with renal impairment, *after* their renal impairment was detected, and 19% (117/615) of these prescription entries should have been had dosage adjustments.

Only 32% (37/117) of these prescription entries were correctly dose adjusted. Of 97 patients, 69 received one or more drugs that required dose adjustment but only 8 (12%) of the patients had all of their drugs appropriately dosed. The majority of people with renal impairment who were given renally metabolized medications (59% (41/69)), did not have appropriate dose adjustments appropriately.

The researchers postulated that some of the people could have had AKI, in which case eGFRs can change quickly, and it wasn't necessarily clear from a chart review whether a dose adjustment was indeed necessary.

However, they felt that lack of awareness about the need for dose adjustment was very likely and wrote that “increasing availability of reference texts in medical wards, providing clinicians with an eGFR with all creatinine results, and electronic aids to identify drugs requiring dose adjustment, should be considered.”

HATIP had difficulty finding a concise, *open source*, reference text for dosage adjustments for drugs commonly used in people living with HIV and for palliative care, although we have included a table for antiretroviral drug dose adjustments. See below.

In their review Decloedt et al used *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*.³³ Also, the African Palliative Care Association and the [Hospice Palliative Care Association of SA](#) offer a [Clinical Guide to Supportive and Palliative Care for HIV/AIDS in Sub-Saharan Africa](#), contains an [appendix on Essential Medications](#), which includes recommendations for dose adjustments on drugs that were on the Essential Medications list when that resource went to press. That was several years ago however, so the appendix isn't entirely up to date.

Decloedt et al also noted that it is unclear which equation to use to assess eGFR in black African populations. The South African Renal Society recommends using the MDRD with the ‘black race’ adjustment factor, but as mentioned in the first HATIP in this series, this factor was based on African-Americans who may have substantially different body composition and diets. Researchers from the only two significant studies we were able to find assessing eGFR estimations in black African populations *did not support* using the racial adjustment factor.

Now that it is clear that chronic renal impairment is going to increasingly be a problem in black African populations, the time is long overdue for local institutions to carefully validate the eGFR

equations against a gold standard measure of creatinine clearance, in adequately sized studies in different African populations, including, separately, those with HIV.

Dose adjustment table

Table: antiretroviral adjustments for people with impaired renal functioning

Nucleoside reverse transcriptase inhibitors	
Zidovudine^a	
<i>Usual dosage</i>	300 mg po b.i.d.
Dosage for patients with CKD or ESRD	
Creatinine clearance ≥15 mL/min	No adjustment
Creatinine clearance <15 mL/min	100 mg po q6–8h
Receiving hemodialysis	100 mg po q6–8h ^b
Receiving peritoneal dialysis	100 mg po q6–8h
Lamivudine^a	
<i>Usual dosage</i>	150 mg po b.i.d./300 mg po q.d.
Dosage for patients with CKD or ESRD	
Creatinine clearance ≥50 mL/min	No adjustment
Creatinine clearance 30–49 mL/min	150 mg po q.d.
Creatinine clearance 15–29 mL/min	150 mg po first dose, then 100 mg po q.d.
Creatinine clearance 5–14 mL/min	150 mg po first dose, then 50 mg po q.d.
Creatinine clearance <5 mL/min	50 mg po first dose, then 25 mg po q.d.
Receiving hemodialysis	50 mg po first dose, then 25 mg po q.d. ^b
Receiving peritoneal dialysis	50 mg po first dose, then 25 mg po q.d.
Abacavir^c	
<i>Usual dosage</i>	300 mg po b.i.d./600 mg po q.d.
Dosage for patients with CKD or ESRD	
All creatinine clearances	No adjustment
Receiving hemodialysis	No adjustment ^b
Receiving peritoneal dialysis	Unknown, use with caution
Stavudine immediate release (IR)	
<i>Body weight ≥ 60 kg, usual dosage</i>	40 mg po b.i.d.
Body weight ≥60 kg, dosage for patients with CKD or ESRD	
Creatinine clearance 150 mL/min	No adjustment
Creatinine clearance 26–50 mL/min	20 mg po b.i.d.
Creatinine clearance <25 mL/min	20 mg po q.d.

Receiving hemodialysis	20 mg po q.d. ^b
Receiving peritoneal dialysis	Unknown, use with caution
Didanosine buffered tablets	
<i>Body weight <60 kg, usual dosage</i>	30 mg po b.i.d.
Body weight <60 kg, dosage for patients with CKD or ESRD	
Creatinine clearance 150 mL/min	No adjustment
Creatinine clearance 26–50 mL/min	15 mg po b.i.d.
Creatinine clearance <25 mL/min	15 mg po b.i.d.
Receiving hemodialysis	15 mg po q.d. ^b
Receiving peritoneal dialysis	Unknown, use with caution
Didanosine EC	
<i>Body weight ≥ 60 kg, usual dosage</i>	200 mg po b.i.d.
Body weight ≥60 kg, dosage for patients with CKD or ESRD	
Creatinine clearance >60 mL/min	No adjustment
Creatinine clearance 30–59 mL/min	200 mg po q.d.
Creatinine clearance 10–29 mL/min	150 mg po q.d.
Creatinine clearance ≤10 mL/min	100 mg po q.d.
Receiving hemodialysis	100 mg po q.d. ^b
Receiving peritoneal dialysis	100 mg po q.d.
Didanosine EC	
<i>Body weight <60 kg, usual dosage</i>	125 mg po b.i.d.
Body weight <60 kg, dosage for patients with CKD or ESRD	
Creatinine clearance >60 mL/min	No adjustment
Creatinine clearance 30–59 mL/min	150 mg po q.d.
Creatinine clearance 10–29 mL/min	100 mg po q.d.
Creatinine clearance ≤10 mL/min	75 mg po q.d.
Receiving hemodialysis	75 mg po q.d. ^b
Receiving peritoneal dialysis	75 mg po q.d.
Didanosine EC	
<i>Body weight ≥ 60 kg, usual dosage</i>	400 mg po q.d.
Body weight ≥60 kg, dosage for patients with CKD or ESRD	
Creatinine clearance >60 mL/min	No adjustment
Creatinine clearance 30–59 mL/min	200 mg po q.d.
Creatinine clearance 10–29 mL/min	125 mg po q.d.
Creatinine clearance ≤10 mL/min	125 mg po q.d.
Receiving hemodialysis	125 mg po q.d. ^b
Receiving peritoneal dialysis	125 mg po q.d.
Didanosine EC	
<i>Body weight <60 kg, usual dosage</i>	250 mg po q.d.
Body weight <60 kg, dosage for patients with CKD or ESRD	
Creatinine clearance >60 mL/min	No adjustment

Creatinine clearance 30–59 mL/min	125 mg po q.d.
Creatinine clearance 10–29 mL/min	125 mg po q.d.
Creatinine clearance ≤10 mL/min	Do not use; use buffered tablets instead
Receiving hemodialysis	Do not use; use buffered tablets instead
Emtricitabine (FTC)	
Usual dosage	200 mg po q.d.
Dosage for patients with CKD or ESRD	
Creatinine clearance ≥50 mL/min	No adjustment
Creatinine clearance 30–49 mL/min	200 mg po q48h
Creatinine clearance 15–29 mL/min	200 mg po q72h
Creatinine clearance <15 mL/min	200 mg po q96h
Receiving hemodialysis	200 mg po q96h ^b
Receiving peritoneal dialysis	Unknown, use with caution
Tenofovir	
Usual dosage	300 mg po q.d.
Dosage for patients with CKD or ESRD	
Creatinine clearance ≥50 mL/min	No adjustment
Creatinine clearance 30–49 mL/min	300 mg po q48h
Creatinine clearance 10–29 mL/min	300 mg po q72h
Receiving hemodialysis	300 mg po every 7 days ^b
Receiving peritoneal dialysis	Unknown, use with caution
Emtricitabine/tenofovir	
Usual dosage	200 mg/300 mg po q.d.
Dosage for patients with CKD or ESRD	
Creatinine clearance ≥50 mL/min	No adjustment
Creatinine clearance 30–49 mL/min	One tab po q48h
Creatinine clearance <30 mL/min	Unknown, should not use combination tablet
Non-nucleoside reverse transcriptase inhibitors	
Nevirapine	
Usual dosage	200 mg po b.i.d.
Dosage for patients with CKD or ESRD	
Creatinine clearance >20 mL/min	No adjustment
Receiving hemodialysis	No adjustment ^b
Receiving peritoneal dialysis	Unknown, use with caution

a) Zidovudine/lamivudine should be administered as separate component medications in patients with creatinine clearance ≤50 mL/min.

b) Administer either the daily dose or one of the daily doses after hemodialysis.

c) Zidovudine/lamivudine/abacavir and lamivudine/abacavir should be administered as separate component medications in patients with creatinine clearance ≤50 mL/min.

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