Clinicians often lack confidence in dealing with both the diagnosis and management of renal disease. There is good reason for this:

- It presents in non-specific ways so is not easily identified.
- Urine dipsticks are not routinely performed as part of pre-ART work-up so some renal disease is missed.

What clinicians generally do correctly:

- When an elevated serum creatinine is encountered clinicians are good at remembering not to use tenofovir in the ARV regimen.
- Remembering to adjust the doses of some of the ARVs.

Where clinicians often struggle:

- To identify renal disease in the first place.
- When identified, TDF is avoided, the ARV doses are often adjusted but the further evaluation of the renal disease is often overlooked.

The purpose of this booklet is to try and increase clinician confidence with renal disease by:

- Improving understanding of renal disease.
- Increasing detection of renal disease in primary care.
- Providing feasible, practical steps for diagnosing and managing renal disease.

This booklet is designed primarily to assist primary care clinicians (doctors, clinical officers and nurses) in the management of kidney disease in out-patient HIV clinics and district hospitals.

Acknowledgements

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AN OVERVIEW OF RENAL DISEASE IN HIV POSITIVE PATIENTS

Symptoms of renal disease are non-specific so, unless it is actively looked for, it is often missed.

How renal disease presents:
- The commonest presentation is an **incidental finding of elevated serum creatinine**
- Symptoms are rarely helpful. If there are any, they are just tiredness or nausea and as these are so frequent in our HIV/TB patients, renal disease is often overlooked
- Oedema is a poor marker as it is a feature of advanced renal disease and is also not seen with HIVAN. Its absence therefore does not exclude significant renal disease.
- Chronic renal disease may present with anaemia – due to reduced production of erythropoietin. It is occasionally detected by an astute clinician acting on the detection of proteinuria and/or haematuria discovered on urine dipstick testing
- It needs to be strongly suspected and actively looked for in all patients with dehydration, sepsis and on nephrotoxic drugs

Common renal diseases seen in primary care OPD and IPD settings

There is a fairly narrow range of renal conditions that clinicians need to be aware of. They can be divided into three broad categories:

1. CHRONIC KIDNEY DISEASE (CKD)
2. HIV-ASSOCIATED NEPHROPATHY (HIVAN)
3. ACUTE KIDNEY INSULT (AKI)

The next few pages provide an overview of the key features of the common conditions in the above classification. This is followed by a summary of the tests used in the evaluation of renal disease and then a practical approach to the diagnosis and management of the patient presenting with possible renal disease in both OPD and IPD settings.
ACUTE KIDNEY INSULT (AKI)

Overview
This the commonest presentation of renal disease in both OPD and IPD settings. It can be reversed if treated promptly. These patients usually require admission for intra-venous fluids and close monitoring.

- Dehydration and sepsis affect the kidney by dropping the perfusion pressure in the glomerulus. The solution is rapid rehydration and management of the sepsis.
- If a patient presents with dehydration or sepsis, either do an urgent creatinine or rehydrate (see page 7) and refer urgently for closer monitoring.
- The commonly encountered drugs that can damage the kidney are tenofovir, co-trimoxazole and rifampicin. Treatment is of course to stop the offending drug.

The causes of an acute kidney insult can be categorized as:
- Pre-renal
- Intrinsic
- Post-renal

All AKI are associated with increased morbidity and mortality.

A. Pre-renal causes

1. Acute tubular necrosis
   - Hypovolaemia, sepsis. Untreated, can progress to acute tubular necrosis
   - TDF toxicity
   - Other toxins: e.g. contrast media and other drug side-effects

2. Interstitial nephritis
   - Rifampicin
   - Cotrimoxazole

3. Acute glomerulonephritis

B. Intrinsic causes

C. Post-renal causes

a. Pre-renal causes

Main precipitants which act by decreasing blood pressure in glomerulus:
- Sepsis
- Hypovolaemia – especially in setting of diarrhoea
- Hypotension

An elevated serum creatinine in the setting of dehydration is a common presentation in sicker patients presenting to clinics or hospitals. If the cause of the pre-renal failure is rapidly corrected, renal function can soon improve. But, be aware of a delayed or inadequate intervention. The kidney is highly sensitive to hypoperfusion so, if blood flow is sufficiently compromised, ischemia-induced ATN develops. Several days to weeks are then necessary to recover and the patient may need dialysis.

Treatment
- Stop all potentially nephrotoxic drugs.
- Essentially raise the perfusion pressure in the glomerulus by rehydrating, treating the sepsis, treating the diarrhoea.
- Because of the sensitivity of the kidney to hypo-perfusion the patient will need IV fluids and preferably in-patient management till renal function has normalised.

(Usual management is to pre-load with a 500ml bolus of normal saline, followed by 3 more litres over 24 hours with pushup of oral fluids as well.)
b. Intrinsic causes

There are two conditions that are more commonly seen in the setting of HIV:

- Acute tubular necrosis (ATN)
- Acute interstitial nephritis (AIN)

The third, acute glomerulonephritis (AGN), is less common but clinicians must be aware of how it presents so that it is not missed.

1. Acute tubular necrosis

- The commonest cause is ischaemia due to dehydration and/or sepsis that has not been managed early enough. These patients will have a high creatinine and need to be managed in hospital.
- The other cause seen fairly commonly is tenofovir, which is known for its potential nephrotoxicity.
- Other nephrotoxins causing ATN are rhabdomyolysis and contrast media.

**Tenofovir toxicity**

**Pharmacology and pathology**

Tenofovir may be directly cytotoxic to the tubular cell or cause damage via mitochondrial injury. The prevalence of TDF toxicity is about 1-2%.

**Clinical manifestations:** Tenofovir can cause AKI and CKD. Can present with elevated creatinine, oedema or hypertension.

**AKI**
- Early: Most common manifestation is Fanconi syndrome. Often presents with normal eGFR and variable loss of bicarb, glucose, amino acids, uric acid and phosphate in the urine.
- Late: Acute Tubular Necrosis - usually non-oliguric renal failure.

**CKD**
- ATN-associated ARF may not resolve with tenofovir withdrawal. The reversibility of renal impairment is usually a function of baseline renal function as well as the length of exposure to the tenofovir insult. This will usually manifest as an elevated creatinine.

**Those at risk of TDF toxicity:** pre-existing renal impairment; older age; advanced HIV disease; use of other nephrotoxic drugs and low BMI.

**TDF usage and monitoring**

Consult local government guidelines. General principles are, where possible:

- Baseline creatinine and calculation of creatinine clearance with Cockroft-Gault.
- Creatinine is repeated at 6 months then annually in patients with normal baseline creatinine clearance. (If baseline clearance is 50 – 60, monitor more closely).
- Tenofovir should be avoided with Cr Cl < 50 ml/min.

**Treatment**

Stop drug if TDF toxicity is suspected and monitor the return to normal renal function. First choice replacement for TDF is abacavir.

2. Acute interstitial nephritis (AIN)

- An immunologically mediated hypersensitivity reaction to an antigen
  - Classically drug or infectious antigen
  - Not dose dependent
  - May occur with extrarenal manifestations of hypersensitivity
  - Rash, fever, joint pain, eosinophilia
  - Recurs on re-exposure
  - Usually raised creatinine, mild haematuria and mild or absent proteinuria

**Causes**

The commonest causes in the HIV/TB setting are cotrimoxazole and rifampicin.

**2.1 Drugs – any drug can potentially do it**

- Antibiotics (penicillins, cephalosporins, quinolones, sulfa drugs (Cotrimoxazole))
- Rifampicin
- Herbal remedies / traditional medications
- NSAIDs
- Diuretics (thiazides and furosemide)
- Allopurinol
- Phenytoin

**2.2 Infections:**
- TB
- Leptospirosis

**2.3 Systemic disease**
- Sarcoid
- DILS- diffuse inflammatory lymphocytic syndrome
- Lymphoma

**Bactrim**

A frequently encountered cause of severe acute interstitial nephritis; not, however, dose-dependent. Frequently no fever or rash present. Can happen any time from weeks to months after starting cotrimoxazole. Also causes crystal nephropathy. Bactrim can also inhibit tubular secretion of creatinine and lead to increased levels (there may be a transient benign elevation of creatinine in the first month of starting cotrimoxazole).

**Rifampicin**

AIN due to rifampicin generally occurs when the antibiotic is re-introduced after an interval. Usually occurs within one to two weeks. Flu-like symptoms, flank pain, oliguria, fever and ARF are common. Not normally associated with eosinophilia. Can also cause acute tubular necrosis. Rifampicin may be associated with low platelets and haemolytic anaemia.
Treatment of drug-induced AIN

Cessation of the drug normally results in recovery of renal function (may take time)
If no improvement within a few days:
- High dose prednisone: Eg – stat dose of 500mg of methylprednisone IV or prednisone 200 mg orally.
  This is followed by 1mg/kg of prednisone and tapered over 1 month. Promptly starting steroids after diagnosis of AIN lessens subsequent interstitial fibrosis and incomplete recovery of renal function.
- Consider referral for renal biopsy if available.
- After causing an AIN, rifampicin and cotrimoxazole must never be given again.

3. Acute glomerulonephritis (AGN)

Usually presents with a combination of several of the following: haematuria, proteinuria, hypertension, oedema and sometimes a rash.

There are several causes. The full diagnostic work-up and management are beyond the scope of this booklet. However, awareness of the possibility of an AGN is important so that the diagnosis is not missed. In reports from secondary or tertiary institutions the following may be seen as the work-up for a diagnosis:
- ASOT for post-streptococcal GN
- Anti-dsDNA and ANA for lupus
- ANCA for Wegener’s granulomatosis
- Complement – low levels are associated with some AGNs
- RPR as syphilis can cause an AGN
- HepBsAg & Hep C – both can cause an AGN.

C. Post-renal causes

In the HIV clinic the commonest cause is bilateral ureteric obstruction due to large TB nodes. Occasionally the nodes can be from a malignancy such as CA cervix or lymphoma. The clinical setting of a wasted patient with probable other large nodes will alert the clinician and the diagnosis will have to be confirmed with an ultrasound showing hydronephrosis. Consult with a urologist where possible as an urgent nephrostomy may be required.

Treatment

Treat the underlying condition, whilst monitoring the renal function to ensure it returns to normal. May need specialist advice.

CHRONIC KIDNEY DISEASE (CKD)

CKD is at least 3 times more frequent in Africa than in developed countries. Common presentations seen in an ARV clinic are chronic hypertensive and diabetic nephropathy. Also seen are chronic HIVAN or other Acute Glomerulonephritis (AGN), missed previously. By the time they present with elevated creatinine or proteinuria there is already significant renal disease. However, careful management from this point onwards may slow the progression to end stage renal disease (ESRD).

Diagnosis

- Usually elevated creatinine with proteinuria and/or haematuria. The patient is often a known diabetic or hypertensive with poor control. Can also be chronic GN or chronic HIVAN
- A few similarly elevated creatinines a few months apart supports a chronic disease process
- An FBC often shows a normochromic, normocytic anaemia
- An ultrasound, if obtainable, usually shows small kidneys (<9cm). Diabetic nephropathy can show enlarged kidneys.

Management

a. The following have been shown to slow the progression to ESRD:
- Stop smoking
- Treat blood pressure effectively
- Tighten diabetic control
- Avoid NSAIDs
- Start ARVs. Avoid TDF, replace it preferably with abacavir

b. Adjust renally excreted drug doses as needed (see dosing charts at the back)

c. Monitor creatinine and urine six-monthly and re-stage (renal staging - see page 15)

d. Consider referral to specialist clinics when creatinine rises above 250 or CrCl/eGFR < 30. This allows time to prepare for dialysis or transplant. Acceptance criteria for replacement programmes vary.

The stark reality in South Africa and many developing countries is that most people with ESRD and HIV face a very high risk of mortality and many of them have limited access to dialysis.
INVESTIGATIONS IN RENAL DISEASE

Having reviewed the common renal conditions seen in the primary care setting, it will have been noted that the diagnosis of certain conditions will be assisted by specific investigations. These tests:

- Evaluate the degree of renal impairment
- Gather additional information towards finding the cause

They have been grouped according to likely availability in OPD or IPD settings.

OUT-PATIENTS

Much information can be gained from two simple tests, almost universally available in primary care HIV/TB clinics. All patients with suspected renal disease should have BOTH tests performed.

Creatinine

This is now done routinely in most settings before starting TDF

- The definition of normal varies considerably according to age, weight and gender. Creatinine clearance is more accurate but is time-consuming to calculate. A time-saving tip is as follows:

If creatinine < 100, weight > 50kg, and age < 50 years and the patient is not pregnant, the creatinine will be within normal range so there is no need to calculate it. If the calculation is needed, use the Cockcroft-Gault formula:

\[
\text{Cockcroft-Gault formula: } \frac{(140 \text{ – age in years}) \times \text{weight (kg)}}{72} \times (0.85 \text{ for women})
\]

Creatinine clearance is:

\[
\text{Serum creatinine in (µmol/L)} \times (0.85 \text{ for women})
\]

HIV ASSOCIATED NEPHROPATHY (HIVAN)

Summary points

- The histological appearance is of collapsing glomeruli, hence the pathology term for it, collapsing focal sclerosing glomerulosclerosis – FSGS
- Can have rapidly rising creatinine that can progress to end stage renal disease (ESRD) in a few months
- Variable CD4 count, but is a stage 4 disease requiring fast-tracking for ARVs
- Usually nephrotic range proteinuria (2+ protein on dip stick and, if urine prot/creat ratio available, a level of at least more than 0.1. It is often much higher)
- There is rarely hypertension and oedema
- There are frequently enlarged echogenic kidneys on ultrasound but they can be normal size

Diagnosis

- Prevention and early detection is important. This needs to be implemented at the primary care level with routine dipstick screening and serum creatinine measurement.
- Biopsy is the only way to confirm the diagnosis but, as this is rarely available the diagnosis needs to be made using a combination of findings. A presumptive diagnosis can be made if there is:
  - proteinuria (> 2+ and or a pr/cr ratio > 1)
  - no hypertension and oedema

Treatment

- Start ARVs as soon as possible as there is clear evidence of the benefit. In one study ART reduced mortality from HIVAN by 57%. Avoid TDF, preferably replacing it with abacavir
- Protein damages the kidney so treat proteinuria with and ACE inhibitor such as enalapril. Start with 2.5 mg bd and watch the blood pressure (can drop) and potassium (can rise, so check at one month)
- Continue to monitor the proteinuria and serum creatinine

Note:

HIV can present with proteinuria only and a normal serum creatinine

Missing the early diagnosis and treatment of HIVAN can result in increased, long-term renal morbidity and mortality

HIV is the 2nd commonest cause of nephrotic syndrome at a large academic hospital in South Africa after lupus. It is the commonest renal lesion in HIV positive patients.

HIVAN is the 2nd commonest cause of nephrotic syndrome at a large academic hospital in South Africa after lupus. It is the commonest renal lesion in HIV positive patients.

HIVAN can present with proteinuria only and a normal serum creatinine

Missing the early diagnosis and treatment of HIVAN can result in increased, long-term renal morbidity and mortality
IMPLEMENTING ROUTINE URINE DIPSTICK TESTING IN A PRIMARY CARE HIV CLINIC

Some renal diseases can have abnormal dipsticks but normal renal function, and other renal diseases can have normal dipsticks with abnormal renal function.

In order not to miss potentially damaging renal disease it is important to be doing both screening dipsticks and serum creatinine in all our patients as soon as possible after HIV diagnosis, ideally in the wellness clinics. Ongoing monitoring is recommended.

A. Dipstick tests in the clinic:
An enrolment room for doing routine vital signs, including urine dipsticks, on all new HIV positive patients would be ideal as this has benefits for many other aspects in the enrolment of a new patient to an HIV clinic.

Routine observations usually done in this prep room are:
- Pulse
- Blood pressure
- Temperature
- Respiratory rate
- Urine dipstick
- Blood glucose.

Ideally a register is kept of all patients with proteinuria ≥2+. The result is documented in the clinical records and the responsibility passed on to the managing clinician. (A urine register can be kept to document total dipsticks performed as well as proteinuria ≥2+.)

B. Serum creatinine is now routinely performed prior to starting tenofovir. This provides a useful compulsory renal pathology screen.

URINE DIPSTICK
- Protein and blood indicate renal disease. They can also be present in a urinary tract infection (UTI) but findings usually include cloudy urine with white blood cells and/or nitrites.
- *Always* follow up with another dipstick after treatment of a UTI to ensure resolution. Kidney disease is often missed because abnormal dipstick findings are not followed up.
- Urine dipsticks are not often performed in clinics and hospitals. Based on the success of this in a few primary care settings, with benefits wider than just kidney care, a suggestion is made in the following section regarding the setting up of a small observation room for new patients enrolling into HIV care.

IN-PATIENTS

Creatinine
All patients needing hospital admission should have creatinine checked.

Urine dipstick
As with patients in clinics, the evaluation of renal disease in hospitalized patients needs a urine dipstick test.

Sodium and Potassium
- Look for associated electrolyte changes: abnormal sodium and potassium are common in acute kidney injury and may be life-threatening.
- Potassium and sodium can be very low in severe acute or chronic diarrhoea.
- Potassium may be very high in chronic kidney disease.

Urine microscopy
- WBC with or without bacteria suggest a urinary tract infection.

Renal ultrasound
- Shows general anatomy.
- Large or normal size echogenic kidneys suggests HIVAN.
- Small kidneys suggest chronic kidney disease.
- Cannot give further information about the underlying cause.
- Urine protein/creatinine ratio. Often abbreviated to u pr/cr ratio. Reported in g/mmol.

Urine protein/creatinine ratio. (u pr/cr ratio) (Reported as g/mmol)
This is a test done on a routine urine sample sent to a laboratory. It is a more accurate measurement of the amount of protein in the urine. Multiply the value by 10 to give an approximate value of grams of protein excreted per 24 hours. A protein/creatinine ratio of 0.03 g/mmol is approximately 0.3 g/24 hours and correlates approximately to 1+ protein on dipstick, 0.06 to 2+ and 0.1 to 3+ to 4+. This is not an accurate measurement but gives a guideline.
RENAL EVALUATION SUMMARY

Whether we have come to this place by one of two routes:

- We have incidentally noted that a patient has an elevated creatinine or protein and/or blood on urine dipstick.
- We have actively looked for renal disease in patients presenting with diarrhoea, dehydration, sepsis or taking nephrotoxic drugs.

Either way we have a patient with either an elevated creatinine or abnormal urine dipstick findings. Our task now is to evaluate this further, using the limited range of diagnostic tests available in primary care settings, so that we can make our way to a diagnosis of one of the conditions noted earlier.

The next series of pages contains three different algorithms that lead the clinician from the point of either an elevated creatinine or abnormal dipstick findings. They are designed for use by less experienced clinicians in primary care settings but may also be useful for a wider range of clinicians.

For those who prefer to use the facts and work out their own diagnostic approach, the key points of each algorithm are summarized below.

Algorithm 1 tracks the management of an abnormal dipstick findings

Summary of content

- Whenever there is proteinuria, check the serum creatinine
- If a UTI is considered as the cause of proteinuria follow up after treatment to ensure resolution
- Take seriously any proteinuria of 2+ or more
- Proteinuria is common in acute toxic illnesses. Ensure follow-up when patient has recovered
- Proteinuria with a normal creatinine can still be due to HIVAN. Don’t ignore it
- Proteinuria and haematuria, especially associated with oedema and/or hypertension and/or a vasculitic rash could indicate an acute glomerulonephritis and requires urgent referral to a specialist.

Algorithm 2 tracks the evaluation of a serum creatinine result.

Summary creatinine algorithm

- If the creatinine is elevated always do a urine dipstick
- Evaluate the creatinine clearance for every patient. Use the “50, 50, 100, pregnant rule”. If the patient is < 50 years old, weighs > 50 kg and the creatinine < 100 the creatinine clearance will be more than 50 so it is not necessary to calculate it. Always calculate the cr.cl if the patient is pregnant.
- HIVAN does not always present with an elevated creatinine. It can be normal.

Algorithm 3A and 3B

Guides the gathering of information and the processing towards a diagnosis and management

- They guide clinicians through the approach to an elevated creatinine or persisting proteinuria
- They help clinicians gather the relevant information and direct them towards a likely disease scenario
- Alternatively they provide the clinician with the information the specialist will need if contacted
- Significant proteinuria or an abnormal creatinine clearance will direct you here
- Almost all the history, examination, side-room and lab results are completed by the time the patient presents to you.
- Ultrasound is a luxury often not available. Fortunately most of the time it is not critical to the diagnostic process.

"Renal disease pattern recognition” (3b)

- Using the information gained from algorithm 3A you now categorise the patient into one of the three main listed groups and head for a diagnosis
- The notes on the overview of renal disease on pages 7 –12 can be referenced for support.

The US National Kidney Foundation describes five stages in the progression of kidney disease according to creatinine clearance or eGFR:

1. > 90
2. 60-90
3. 30-60
4. 15-30
5. <15

A creatinine clearance of 55 is considered acceptable for the use of tenofovir but does not mean that there is no renal impairment. It is stage 3 renal disease so continued monitoring of renal function is important especially if using tenofovir.
ALGORITHM 1 FOR EVALUATING A URINE DIPSTICK RESULT

No abnormality

- Check creatinine

2+ or more on dipstick

- Check creatinine and pr/cr ratio* if available

≥ 2+ protein or pr/cr ratio* > 0.06: go to algorithm 3a and gather info

Refer to creatinine algorithm

Protein ≥ 2+ and blood ≥ 1+

- CAUTION ? acute GN

- Protein ≥ 2+ and blood ≥ 1+ and protein and blood only

- If urine cloudy and leucocytes/nitrites present, treat as UTI and follow up after treatment

1. Check creatinine and calculate CrCl or eGFR
2. Look for high bp, oedema and vasculitic rash

No abnormalities but eGFR/cr cl <50

Look for other causes: menses, discharge, UTI...

- Treat and/or follow up. If persisting proteinuria, go to algorithm 3a

Other combinations are beyond the scope of this booklet

NOTE: if glycosuria is present, investigate for diabetes, as it may be a cause of renal disease

Caution:

- If Creatinine clearance (cc) or eGFR
  - Use either eGFR from lab report or calculate creatinine clearance using formula below
  - (140 – age) x wt / creatinine
  - x 0.85 for females
  - If:
    - weight > 50
    - Age < 50
    - Creatinine < 100
    - non-pregnant, the clearance will be within normal range so no need to calculate it

- pr/cr ratio – see details on pages 20, 26

The nurses need to understand the dipstick algorithm clearly and know when to refer patients with abnormal creatinines.
**ALGORITHM 2**

FOR EVALUATING A CREATININE RESULT

Creatinine clearance (CrCl) or eGFR. Use either eGFR from lab report or calculate creatinine clearance using formula below:

\[
\frac{(140 - \text{age}) \times \text{wt}}{\text{creatinine}} \times 0.85 \text{ for females}
\]

If weight > 50 / Age < 50 / Creatinine < 100 / non-pregnant, the clearance will be within normal range so no need to calculate it.

**Test serum creatinine and urine dipstick on all patients**

(NB: HIVAN can have normal creatinine)

Measure eGFR or creatinine clearance (CrCl) if indicated (see box top left)

- **CrCl > 50 with protein only on dipstick (2+ or more)**
  - Send urine for protein/creatinine ratio if available
  - See algorithm 3
  - Treat accordingly

- **CrCl > 50 with normal dipstick**
  - No significant renal disease
  - pr/cr ratio < 0.1 or < 2+ proteinuria
  - Follow-up monthly
  - Settles - nil more

- **CrCl > 50 with protein and blood. Could be severe renal disease e.g. Acute GN. Check for high bp, oedema and vasculitic rash**
  - pr/cr ratio > 0.1 or ≥ 2+ proteinuria
  - Look for other causes - menses, discharge, UTI
  - See algorithm 3
  - Treat accordingly

- **No abnormality**
  - Any positive finding
  - Seek specialist advice

- **CrCl > 50 regardless of dipstick**
  - Renal problem
  - pr/cr ratio > 0.1 or > 2+ proteinuria
  - Persists – See algorithm 3
Persisting proteinuria

Gather information as follows:

**History**
- PH of renal disease
- Hypertension or diabetes
- Fever
- Rash
- Meds history - recent start of:
  - Co-trimoxazole
  - Aminoglycosides
  - Tenofovir
  - Amphotericin B
  - NSAIDs
  - Rifampicin
  - Penicillins
  - Cephalosporins
- Recent significant diarrhoea and vomiting.
- Is patient passing urine? Anuria? Oliguria?
- Recent significant strep infection

**Examination**
- Hydration
- Elevated temp
- Blood pressure
- Oedema
- Rash – allergic or vasculitic

**Side room**
- Urine dipstick for infection, protein or blood
- Finger prick glucose

**Laboratory**
- Urine: protein/creatinine ratio* – request only if protein ≥ 2+ on dipstick or unexplained oedema
- Blood: RPR – can cause an acute GN
  - Urea, electrolytes, creatinine
  - HBV – can cause an acute GN
  - FBC – low Hb can be chronic renal disease
  - CD4 (VL if indicated)

**Ultrasound** – if available
- Small kidneys suggest chronic renal disease
- Normal or large, echogenic kidneys suggest acute renal disease including HIVAN

Using above information follow guidelines in 38 opposite

**CrCl or eGFR**
- 30-50: Stage 3 renal disease
- 15-30: Stage 4 renal disease
- < 15: Stage 5 renal disease

**Seek immediate specialist advice.**
Gather as much information as possible from the list opposite as it will help the consultant you are discussing the problem with.

1. Could this be an acute kidney insult? (see AKI diagram in section 1, renal review notes)
   Look for this first as it is the most reversible and treatment is urgent.
   Actively look for the common causes: Dehydration, Sepsis, Drugs especially tenofovir, cotrimoxazole and rifampicin.

   **A. Could this be pre-renal?**
   Usually associated with hypovolaemia and low bp. Look for dehydration (often due to diarrhoea) or sepsis. Will need admission, IV fluids, investigation and management of the sepsis and in-patient monitoring.

   **B. Could this be an intrinsic nephropathy?**
   1. Tubular necrosis – usually follows an episode of severe dehydration or sepsis (pre-renal)
      Will need hospitalisation, IV fluids and monitoring

    **TDF toxicity** involves the tubules by direct damage or via mitochondrial damage
    Can occur in weeks to months
    Can present as rising creatinine, glycosuria or even oedema. (See page 6)

   2. Acute interstitial nephritis
      - Has there been recent commencement of nephrotoxic drugs? Commonest causes in HIV/TB setting are cotrimoxazole and rifampicin.
      - May occur with extra-renal manifestations of hypersensitivity; rash, fever and joint pain.
      - Can look like pyelonephritis with fever and flank pain.
      - Recurs on re-exposure to the drug.
      - Treatment is to stop offending drug and sometimes give steroids.
      (See pages 11 and 12 for more detail)

   3. Acute glomerulonephritis (AGN)
      - Usually presents with haematuria, proteinuria, hypertension, oedema and sometimes a rash.
      - Needs fuller work-up in a more specialized hospital setting. Refer soon to establish diagnosis and prevent long-term damage
      (See page 12 for more detail)

   Intrinsic nephropathy can result in long-term renal damage. If unsure seek experienced advice soon to establish diagnosis and prevent long-term damage.
KIDNEY DISEASE EVALUATION (contd)

C. Could this be an obstructive nephropathy?
- Are there large lymph nodes due to TB or a malignancy?
  If so, will need an ultrasound to confirm diagnosis. Arrange within the week and manage with specialist advice.

D. Could this be acute-on-chronic kidney disease?
- Are there features of an acute kidney insult but also features to suggest chronicity?
  - Does the patient have evidence of chronic kidney disease such as poorly controlled diabetes or hypertension, or perhaps other known CKD?
  - Is there high level proteinuria but with long-term renal impairment? This could be HIVAN that was missed earlier in the patient’s HIV illness and is now chronic.
  If so, manage the acute problem as above and at the same time take appropriate care with CKD management as outlined above.

2. Could this be HIVAN?
- Proteinuria – usually ≥ 2+ on dipstick, urine pr/cr ratio > 0.1 and no haematuria
- Usually normal bp, no oedema and no rash
- CD4 not necessarily low. Can be > 500
- Usually normal to enlarged kidneys on ultrasound
No definitive diagnosis without biopsy but a presumptive diagnosis can be made if bullets 1 and 2 present and other conditions are excluded by the acute kidney insult screening process below.

If so: Start ARVs as soon as possible (stage 4 condition)
Start enalapril, initially 2.5 mg bd, and watch the bp and potassium
Monitor the creatinine and proteinuria
(see details in section 1, the renal disease overview)

3. Does this look like chronic kidney disease (CKD)?
- Commonly poorly controlled diabetes and/or hypertension
- Other known CKD (e.g. chronic GN)
- Some evidence of chronicity (a few similarly elevated creatinines a few months apart)

If so, refer to the appropriate clinic for improved management of the chronic condition
Commence CKD management principles to prevent further damage (see page 7)
  - Stop smoking
  - Treat bp
  - Treat diabetes (remember that serum glucose can drop with worsening CKD)
  - Avoid TDF, preferably replacing it with abacavir
  - Avoid NSAIDs
  - Adjust drug doses as needed
  - Highlight condition in the file
Contact or refer to a specialist clinic when the CrCl / eGFR drops below 30.

DRUG DOSING CHARTS IN RENAL IMPAIRMENT

<table>
<thead>
<tr>
<th>Drug</th>
<th>ARVs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clearance &gt; 50</td>
</tr>
<tr>
<td>3TC</td>
<td>150 bd or 300 daily</td>
</tr>
<tr>
<td>D4T</td>
<td>30 mg bd</td>
</tr>
<tr>
<td>AZT</td>
<td>300 mg bd</td>
</tr>
<tr>
<td>TDF</td>
<td>300 mg nocte</td>
</tr>
<tr>
<td>abacavir</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>nevirapine</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>efavirenz</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>PIs</td>
<td>No adjustment needed</td>
</tr>
</tbody>
</table>

Anti-hypertensives

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clearance &gt; 50</th>
<th>Clearance 10-50</th>
<th>Clearance &lt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>enalapril</td>
<td>2.5-10 mg bd</td>
<td>75-100%</td>
<td>50%</td>
</tr>
<tr>
<td>atenolol</td>
<td>25-50 mg daily</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>HCTZ</td>
<td>12.5-25mg daily</td>
<td>100%</td>
<td>avoid</td>
</tr>
<tr>
<td>amlodipine</td>
<td>5-10 mg daily</td>
<td>No adjustment needed</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>doxazosin</td>
<td>2-4 mg daily</td>
<td>No adjustment needed</td>
<td>No adjustment needed</td>
</tr>
</tbody>
</table>

Diabetic meds

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clearance &gt; 50</th>
<th>Clearance 10-50</th>
<th>Clearance &lt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>gliclazide</td>
<td>40-80 mg bd</td>
<td>AVOID</td>
<td>AVOID</td>
</tr>
<tr>
<td>glibenclamide</td>
<td>2.5-5 mg bd</td>
<td>AVOID</td>
<td>AVOID</td>
</tr>
<tr>
<td>metformin</td>
<td>500-1000 mg bd</td>
<td>25%</td>
<td>AVOID</td>
</tr>
</tbody>
</table>

Anti-fungals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clearance &gt; 50</th>
<th>Clearance 10-50</th>
<th>Clearance &lt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluconazole</td>
<td>200-400 daily</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>itraconazole</td>
<td>100-200 bd</td>
<td>100%</td>
<td>50%, IV form contra-indicated</td>
</tr>
</tbody>
</table>

Anti-virals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clearance &gt; 50</th>
<th>Clearance 10-50</th>
<th>Clearance &lt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>acyclovir</td>
<td>200-800mg 4-12 hourly</td>
<td>100%</td>
<td>200 mg bd</td>
</tr>
</tbody>
</table>
Monitor creatinine clearance regularly for all DR TB patients, especially for those at high risk of renal impairment (diabetic, patient >60 years of age)

If patient has renal impairment with creatinine clearance < 30ml/min they will need some of their DR TB meds to be adjusted as follows:

### TABLE 9: DOSING OF SELECTED ANTITUBERCULOSIS DRUGS IN RENAL FAILURE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adjusted doses according to creatinine clearance or eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clearance &gt; 30</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>600 mg daily</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>300 mg daily</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>30-40 mg/kg daily</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>25 mg/kg daily</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15-20 mg/kg daily</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>15-20 mg/kg daily</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15-20 mg/kg daily</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg daily</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>15-20 mg/kg daily</td>
</tr>
<tr>
<td>PAS</td>
<td>150 mg/kg daily</td>
</tr>
<tr>
<td>Ethionamide/prothionamide</td>
<td>15-20 mg/kg daily</td>
</tr>
<tr>
<td>Terizidone/Cycloserine</td>
<td>15-20 mg/kg daily</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg daily</td>
</tr>
<tr>
<td>Delamanid</td>
<td>100 mg bd for 24 weeks</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>400 mg daily for 2 weeks, then 200 mg 3x a week for 22 weeks</td>
</tr>
</tbody>
</table>

### DRUG DOSING CHARTS IN RENAL IMPAIRMENT contd

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adjusted doses according to creatinine clearance or eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 50</td>
</tr>
<tr>
<td>amoxycillin</td>
<td>250-1000 mg tds</td>
</tr>
<tr>
<td>azithromycin</td>
<td>500 mg daily</td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>1-2 g daily</td>
</tr>
<tr>
<td>clarithromycin</td>
<td>250-500 mg bd</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>250-750 mg bd</td>
</tr>
<tr>
<td>clindamycin</td>
<td></td>
</tr>
<tr>
<td>co-trimoxazole prophylaxis</td>
<td>2 tabs daily</td>
</tr>
<tr>
<td>co-trimoxazole treatment</td>
<td>2 bd – 4 qid</td>
</tr>
<tr>
<td>erythromycin</td>
<td></td>
</tr>
<tr>
<td>linezolid</td>
<td></td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400 mg daily</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>200-400 mg bd</td>
</tr>
<tr>
<td>penicillin g</td>
<td>0.5-4 MU 4-6 hourly</td>
</tr>
</tbody>
</table>

### TB drugs

#### NSAIDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adjusted doses according to creatinine clearance or eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>metoclopramide</td>
<td>AVOID</td>
</tr>
<tr>
<td>omeprazole</td>
<td>10 mg tds</td>
</tr>
<tr>
<td>ranitidine</td>
<td>150-300 mg nocte</td>
</tr>
</tbody>
</table>

### Miscellaneous

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adjusted doses according to creatinine clearance or eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delamanid</td>
<td>100 mg bd for 24 weeks</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>400 mg daily for 2 weeks, then 200 mg 3x a week for 22 weeks</td>
</tr>
</tbody>
</table>

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### Glossary of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>Abacavir</td>
</tr>
<tr>
<td>AGN</td>
<td>Acute glomerulonephritis</td>
</tr>
<tr>
<td>AKI</td>
<td>Acute kidney insult</td>
</tr>
<tr>
<td>ARF</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td>ATN</td>
<td>Acute tubular necrosis</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>ESRD</td>
<td>End stage renal disease</td>
</tr>
<tr>
<td>HIVAN</td>
<td>HIV-associated nephropathy</td>
</tr>
<tr>
<td>IPD</td>
<td>In-patient department</td>
</tr>
<tr>
<td>OPD</td>
<td>Out-patient department</td>
</tr>
<tr>
<td>TDF</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>U pr/cr ratio</td>
<td>Urine protein/creatinine ratio</td>
</tr>
<tr>
<td>VDRL</td>
<td>Venereal Disease Research Laboratory – a serological test for syphilis</td>
</tr>
</tbody>
</table>

As new research and clinical experience broaden our knowledge in the field of HIV/AIDS-related kidney disease, changes in approach and management will be required. At the time of publication the authors have attempted to provide information that is as complete and up to date as possible. This information however will not always remain complete and accurate so clinicians are urged constantly to update themselves with new product information.
Education for capability must focus on supporting learners to construct their learning goals, receive feedback, reflect and consolidate their learning experience.

BMJ: Education for Capability