RENAL MANAGEMENT AND DOSE ADJUSTMENT ADVICE FOR HEALTHCARE PROFESSIONALS WITH ADULT PATIENTS RECEIVING TENOFOVIR DISOPROXIL FUMARATE

HIV-positive patients are at increased risk of renal impairment, requiring baseline and subsequent renal monitoring.¹ For those adult patients on tenofovir disoproxil fumarate (TDF)-based regimens specific recommendations are detailed below.

Important Points to Consider

- ✓ Check all patients' creatinine clearance before starting TDF therapy
- During TDF therapy, renal function (creatinine clearance and serum phosphate should be assessed regularly (every 4 weeks during the 1st year and then every 3 months) (see Table 1 below)
- ✓ Consider more frequent monitoring of renal function in patients at risk for renal impairment
- ✓ In patients with renal impairment, TDF should only be used if the potential benefits of treatment outweigh the potential risks, and the dosing interval of TDF may need to be prolonged (see Table 2 overleaf)
- ✓ Consider interrupting treatment with TDF in patients with creatinine clearance decreased to <50 mL/min or decreases in serum phosphate to <1.0 mg/dL (0.32 mmol/L)</p>
- ✓ Avoid concurrent or recent use of nephrotoxic medicinal products

TDF renal safety profile

In TDF clinical studies and post-marketing safety surveillance, rare events of renal failure, renal impairment, and proximal tubulopathy (including Fanconi syndrome) have been reported. In some patients proximal renal tubulopathy has been associated with myopathy, osteomalacia (manifested as bone pain and infrequently contributing to fractures), rhabdomyolysis, muscle weakness, hypokalaemia and hypophosphataemia.^{2–5}

Monitoring of renal function

The recommendations for monitoring renal function in all patients prior to and during TDF therapy are provided in Table 1 below.

Use of TDF should be avoided with concurrent or recent use of a nephrotoxic medicinal product and drugs secreted by the same pathway; if concomitant use is unavoidable, renal function must be monitored weekly.^{2–5} Higher tenofovir concentrations, associated with co-administration with lopinavir/ritonavir, atazanavir/ritonavir or darunavir/ritonavir, could potentiate tenofovir-associated adverse events, including renal disorders.

Table 1: Monitoring of renal function^{2–5}

	Prior to TDF	During 1st year on TDF*	>1 year on TDF*
Frequency	At baseline	Every 4 weeks	Every 3 months
Parameter	Creatinine clearance	Creatinine clearance and serum phosphate	Creatinine clearance and serum phosphate

^{*} In patients at risk for renal impairment, consideration should be given to more frequent monitoring of renal function.

If serum phosphate is <1.5 mg/dL (0.48 mmol/L) or creatinine clearance is decreased to <50 mL/min in any patient receiving TDF, renal function should be re-evaluated within 1 week, including measurements of blood glucose, blood potassium and urine glucose concentrations. Consideration should also be given to interrupting treatment with TDF in patients with creatinine clearance decreased to <50 mL/min or decreases in serum phosphate to <1.0 mg/dL (0.32 mmol/L). $^{2-5}$

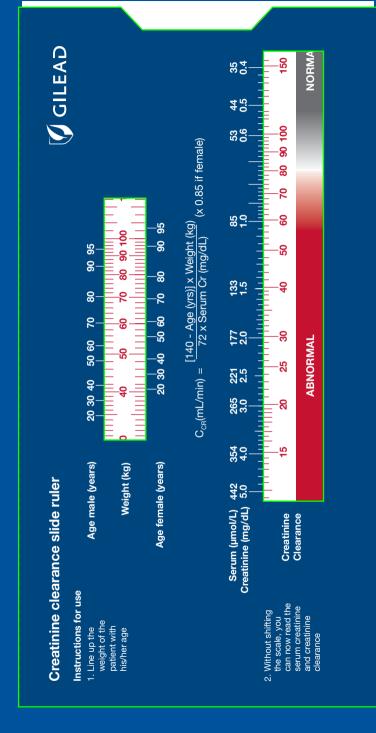
Use in Renal Impairment

In patients with renal impairment, TDF should only be used if the potential benefits of treatment outweigh the potential risks, and close monitoring of renal function is recommended. TDF is principally eliminated via the kidney and exposure to tenofovir increases in patients with renal dysfunction. Limited data from clinical studies support once daily dosing of TDF in patients with mild renal impairment (creatinine clearance 50–80 mL/min). The dosing interval adjustment guidelines for patients with creatinine clearance <50 mL/min are shown in Table 2 below.

Table 2: Dosing interval adjustments for patients with renal impairment²⁻⁵

	Creatinine clearance (mL/min)			Haemodialysis
	50-80	30–49	10-29	patients
Atripla	Every 24 hours (no adjustment required)	Not recommended for use in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min)		
Eviplera	Every 24 hours (no adjustment required)	Not recommended for use in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min)		
Truvada	Every 24 hours (no adjustment required)	Every 48 hours*	Not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) or in haemodialysis patients	
Viread	Every 24 hours (no adjustment required)	Every 48 hours*	Not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) or in haemodialysis patients. If no alternative treatment is available, prolonged dose intervals may be used: Severe renal impairment – every 72–96 hours (dosing twice a week). Haemodialysis patients – every 7 days following completion of a haemodialysis session.**	

Dose interval adjustment of Viread and Truvada is recommended for patients with creatinine clearance between 30 and 49 mL/min. This dose interval adjustment has not been confirmed in clinical studies and the clinical response to treatment should be closely monitored in these patients. Limited clinical study data suggest that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response.



^{**} Assuming 3 haemodialysis sessions per week, each of approximately 4 hours duration or after 12 hours cumulative haemodialysis. No dosing recommendations can be given for non-haemodialysis patients receiving Viread with creatinine clearance <10 mL/min.⁵



Renal monitoring tool

References

- 1. Gupta SK et al. Clin Infect Dis 2005;40:1559-1585
- 2. Atripla Summary of Product Characteristics
- 3. Eviplera Summary of Product Characteristics
- Truvada Summary of Product Characteristics
 Viread Summary of Product Characteristics

Date of Preparation: October 2012 HIV/IHQ/12-07//1507

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Presentation: Viread film-coated tablet containing 245mg of tenofovir disoproxil (as furnarate), equivalent to 300mg of tenofovir disoproxil furnarate, or 136mg of tenofovir.

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Use in pregnancy and lactation: The use of viread may be considered during pregnancy, viread should not be dised undiperast feeding.

Side effects: Very commonly reported adverse events (≥1/10): hypophosphataemia*, dizziness, diarrhoea, vomitting, nausea, rash, asthenia. Common (≥1/100): http://distruction.py.com/p

Frantaceutical Precautions: No special precautions for storage or narioling.

Legal Category: Prescription only medicine

Package Quantities: Bottle of 30 film coated tablets

Marketing Authorisation numbers: EU/101/200/001

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Overdosage: If overdose occurs, monitor for evidence of toxicity. Apply standard supportive treatment if necessary. Tenofovir

aceutical Precautions: No special precautions for storage or handling Legal Category: Prescription only medicine
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associated with proximal rene* to bulge the total patents between Miscinordial dysfunction. Immune Reactivation Syndrome. Osteonerosis. Avoid in entiretive the standard patents berbouring K65R mutation.

Interaetions: Low potential for Malther interactions was other medicinal products. Viread should not be administered concomitantly with other medicinal products containing tendovir disoproxil furniarate or adefovir diplovali, nephrotoxic agents or medicinal products that reduce renef function of compete for active tubular secretion. Monitor renal function if tendovir disoproxil furniarate administered with accuranus. Co-administration with didanosine is not recommended as it may result in a 40-60% increase in systemic exposure to didanosine which may increase the risk of didanosine-related adverse events. Co-administration with 100 mg daily didanosine has been associated with significant decreases in C04 cell counts. A reduced dose of 250 mg didanosine administered with tenofovir disoproxil furniarate has been associated with reports of high rates of virological failure. Co-administration with lopinaviritionavirity coresistings could note related advanced to the proposition of the propositio atzazinavir concentrations, but increased exposure to tendrovir. Higher tendrovir concentrations could potentiate tendrovir associated adverse events including renal disorders. Food has been shown to enhance the bloavailability of Viread. Refer to SPC for drug interaction details for protease inhibitors, NRTIs, NNRTIs.

tion: The use of Side effects: Very commonly reported adverse events (>1/10): hypophosphataemia* dizziness diarrhoea yomiting nausea

Side effects: very commonly reported adverse events: [21/10]: hypoprosphataemia*, dczlness, diarmoea, vomining, hailayer rash, asthenia. Common [21/10.00 to <1/10; fatulence, headache, abdominal pain, abdominal distension, fatigue, increased transaminases. Uncommon (≥ 1/1,000 to < 1/100): hypokalaemia*, pancreatitis, rhabdomyolysis*, muscular weakness, increased creatinine. Bare [≥1/10,000, ≤1/1,000]: lactic acidosis, hepatic steatosis, hepatitis, anglicedema, osteomalacia*, myopathy*, renal failure, poutre enal failure, poutre cuaceres inspirus. The side effects marked "may occur as a consequence of proximal renal tubulopathy. In patients with generally exhowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART), cases of osteonecrosis have been reported. Inflammatory reaction to asymptomatic or residual opportunistic infections may arise in patients with severe immunodeficiency at the time of initiation of CART. CART has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholestroleamia, insulin resistance, hyperglycaemia, hyperacticatemia and lipodystyph, in patients with CHB, exacerbations of hepatitis during treatment may arise. Refer to SPC for full information on adverse events.

Overdosage: If overdose occurs, monitor for evidence of toxicity. Apply standard supportive treatment if necessary. Tenofovir can be removed by haemodialviss.

ed by haemodialysis

ceutical Precautions: No special precautions for storage or handling Legal Category: Prescription only medicine Package Quantities: Bottle of 30 film coated tablets

Marketing Authorisation numbers: EU/1/01/200/001 nation is available from the marketing authorisation holder: Gilead Sciences International Ltd, Granta Park, Abington,

Cambridge CB21 6GT + 44 (0) 208 587 2394. Email: intlmed.info@qi

CONSULT THE SUMMARY OF PRODUCT CHARACTERISTICS REFORE PRESCRIRING PARTICULARLY IN RELATION TO SIDE EFFECTS. PRECAUTIONS AND CONTRAINDICATIONS.

Date of PI preparation: August 2011.

Suspected adverse drug reactions (ADRs) should be reported to the Medicines Authority Post-LicensingDirectorate, 203, Level 3, Rue D'Argens, Gzira GZR 1368, MALTA or at http:/www.medicinesauthority.gov.mt/pub/adr.doc

ispected adverse drug reactions may also be reported to GILEAD SCIENCES INTERNATIONAL LTD via email to csafety@gilead.com or tel: +44 (0) 1223 897500 or to AM MANGION Ltd via email to pv@ammangion.com.mt or tel: (+356) 2397 6333

Prescribing information can be found within	