



Title: Management of Renal Dysfunction in HIV-Infected Patients Receiving Tenofovir: A Review of Markers for Renal Dysfunction and Guidelines

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Context and policy issues:

Tenofovir disoproxil fumarate (Viread®) is a nucleotide reverse transcriptase inhibitor that was approved by Health Canada in 2003.¹ It is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in patients 18 years of age and older. Tenofovir is often favored over other antiretrovirals in its class due to the convenience of once daily dosing.² Co-formulation with other antiretrovirals (Truvada® and Atripla™) in a single pill has increased its popularity even further.³

In large randomized controlled trials (RCTs), tenofovir-related adverse effects including nephrotoxicity did not differ significantly from placebo⁴⁻⁶ or other antiretrovirals including stavudine^{7,8}. These results were supported by several cohort and case control studies that found the risk of developing clinically significant nephrotoxicity to be rare.⁹⁻¹⁵ However, as clinical use increases, case reports of tenofovir-associated renal adverse effects including acute renal failure, proximal renal tubular dysfunction, and Fanconi's syndrome (a disorder in which proximal tubular function of the kidney is impaired, resulting in increased urinary excretion of filtered proteins, potassium, glucose, phosphate, uric acid, amino acids, bicarbonate, and calcium) are growing in number.^{3,16} The majority of these patients had identifiable risk factors including pre-existing renal dysfunction, co-morbidities (including diabetes and hypertension), low body weight, advanced HIV disease, longer duration of tenofovir use, combination with ritonavir-boosted protease inhibitor regimens, and concomitant use of nephrotoxic medications.^{3,17-20} In the majority of cases, kidney damage was reversed upon discontinuation of tenofovir.

In clinical practice, estimation of the glomerular filtration rate (GFR) is used to assess the degree of renal impairment and follow the course of disease.²¹ The most common methods used to estimate the GFR are the serum creatinine concentration, the creatinine clearance, or

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estimation equations based on serum creatinine [such as the Cockcroft-Gault (CG) equation or the Modification of Diet in Renal Disease (MDRD) Study equations].²¹ Although the GFR estimation equations incorporate known demographic and clinical variables, the accuracy of these equations has not yet been evaluated in HIV-infected individuals.²² Available studies used varying methods to estimate GFR and definitions for nephrotoxicity differed widely.

There are several limitations to using creatinine as a marker to screen for tenofovir-related nephrotoxicity. Firstly, during tenofovir-induced acute renal failure or rapidly changing kidney function, estimation of GFR based on serum creatinine may be less accurate.²¹ Secondly, subtle changes in renal function may be under-appreciated when using creatinine alone to estimate renal function as it only rises above the upper limit of normal when over half of the nephrons have become nonfunctional.²¹ Hence, serum creatinine alone is not a sensitive indicator of early kidney dysfunction in patients receiving tenofovir. Furthermore, serum creatinine is influenced by sex, muscle mass, and age and hence may not be accurate in HIV-infected patients with low body weight.³ There is also speculation that creatinine may not be a sensitive marker for tenofovir-associated proximal tubular dysfunction. This report will review studies that evaluated the possibility for more sensitive markers of tenofovir-related nephrotoxicity. Guidelines for the management of tenofovir-induced renal dysfunction will also be presented.

Research questions:

1. What markers should be used to assess renal function in HIV-infected patients receiving tenofovir?
2. What are the guidelines for management of renal dysfunction in HIV-infected patients receiving tenofovir?

Methods:

A limited literature search was conducted on key health technology assessment resources, including Pre-Medline, Medline, Embase, Biosis, Pubmed, the Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and the February 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, guidelines, randomized controlled trial (RCT) studies, and observational studies. This search was supplemented by hand searching the bibliographies of selected papers.

Summary of findings:

No relevant health technology assessments, systematic reviews, or meta-analyses were identified. Randomized controlled trials (RCTs) and observational studies examining the use of markers for nephrotoxicity in patients receiving tenofovir are discussed below.

Serum phosphate:

Hypophosphatemia caused by reduced phosphate reabsorption and excessive loss of phosphates into the urine may be a marker of renal tubular dysfunction in patients receiving tenofovir.²³

Two RCTs of HIV-infected patients with normal baseline renal function found a comparable incidence of hypophosphatemia when tenofovir was compared with stavudine⁸ or placebo⁴. In a phase 3 trial, antiretroviral-naïve patients were randomized to receive either tenofovir (n=299) or stavudine (n=301) in addition to lamivudine and efavirenz.⁸ The incidences of grades 1 (2.0-2.2 mg/dL), 2 (1.5-1.9 mg/dL), and 3 (1.0-1.4 m/dL) hypophosphatemia at week 144 did not differ significantly between the two groups (4%, 3%, and <1%, respectively in the tenofovir group versus 4%, 2%, and <1%, respectively in the stavudine group) (p>0.05).⁸ No patients experienced grade 4 (<1.0 mg/dL) hypophosphatemia or developed Fanconi's syndrome during the study. A second RCT (n=189) evaluated the rate of hypophosphatemia in treatment-experienced patients randomized to receive 75mg, 150 mg, or 300 mg of tenofovir or placebo in addition to an existing antiretroviral regimen.⁴ The incidence of treatment emergent grade 2 (1.5-1.9 mg/dL) hypophosphatemia at 24 weeks was similar between the placebo (4%) and tenofovir groups (2%-7%) (p value not reported). These results remained consistent at 48 weeks. No patients developed treatment emergent grade 3 or grade 4 hypophosphatemia. These trials are limited by the fact that patients with existing renal dysfunction and significant co-morbidities (including diabetes and hypertension) were excluded. Therefore, these results may not be generalizable to HIV-infected patients with underlying renal impairment.

Several observational trials have also indicated comparable rates of hypophosphatemia when patients receiving tenofovir are compared with patients who have never been treated with tenofovir. A prospective cohort study, assessed the development of hypophosphatemia among patients initiating treatment with tenofovir-containing (n=165) or tenofovir-sparing (n=90) antiretroviral regimens during a 24 month period.²³ A higher percentage of patients receiving tenofovir developed grade 2 (2.0-2.4 mg/dL) and 3 (1.0-1.9 mg/dL) hypophosphatemia versus non-tenofovir recipients (12.7% versus 6.7% and 2.4% versus 0%, respectively). However, these differences were not statistically significant (p values not reported). The median time to development of hypophosphatemia was approximately 2.5 months and was not significantly different between the two groups (p=0.27). No patients developed grade 4 (<1.0 mg/dL) hypophosphatemia. The incidence rates of hypophosphatemia did not vary by gender, age, baseline CD4 cell count, baseline HIV viral load, type of regimen, or duration of antiretroviral therapy. Hypophosphatemia resolved in all patients who developed incident grade 2 or higher hypophosphatemia and who had phosphate measurements during the 24 month study period. A cross-sectional study of HIV-infected patients in routine care (n=174) also did not find statistically significant differences in the excretion rate of phosphate (measured after a mean of 9 months on tenofovir) when patients receiving tenofovir were compared to non-tenofovir recipients.²⁴ These results were consistent with another cross-sectional trial (n=252) where no significant differences in the prevalence of hypophosphatemia were detected when measured after a median of 5 months on tenofovir when compared with patients on tenofovir-sparing regimens.²⁵ Multivariate analysis revealed that only cumulative time on antiretroviral therapy and use of ritonavir-boosted lopinavir were independently associated with hypophosphatemia. Elevated creatinine and urea, or use of tenofovir were not independently associated with hypophosphatemia. These trials are limited by trial design that did not control for confounding variables in patient groups. Larger long-term studies are needed to confirm which risk factors (including use of tenofovir) are significantly associated with hypophosphatemia and address if persistent reduction in phosphate levels may lead to clinically significant outcomes such as changes in bone mineral density.

Overall, these results question the utility of routine phosphate testing to detect rare cases of proximal tubular dysfunction associated with tenofovir use.

Serum cystatin C:

Serum cystatin C, a protein that is ubiquitously produced by nucleated cells, may provide an alternative renal clearance marker in patients being treated with tenofovir.²¹ A potential advantage of cystatin C over creatinine is reference values for the assessment of GFR are believed not to be dependent on diet, sex, muscle mass, or age, although this has not yet been confirmed.²¹ There is also evidence that serum cystatin C is more sensitive in identifying mild renal impairment than serum creatinine.²¹

One cross-sectional study assessed the sensitivity of cystatin C in 82 patients receiving tenofovir (for a mean duration of 9.2 ± 7.3 months) and 92 patients who had never been treated with tenofovir.²⁴ GFR was estimated using creatinine in serum and in urine collected over 24 hours to calculate the creatinine clearance, serum cystatin C, or the modified MDRD equation (which is based on serum creatinine only). Creatinine, urea, uric acid, cystatin C, sodium, potassium, calcium, phosphate and chloride were measured in the serum. In urine collected over 24 hours, the excretion rate of total protein, creatinine, urea, uric acid, sodium, potassium, calcium, phosphate, and chloride were analyzed. Patients on tenofovir showed a significantly lower mean GFR estimated by creatinine clearance compared with patients never treated with tenofovir (97 ± 49 mL/min/1.73m² versus 107 ± 39 mL/min/1.73m²; $p=0.03$). A similar result was obtained using cystatin C with a significantly lower mean GFR in patients receiving tenofovir when compared to those who were not (86 ± 21 mL/min/1.73m² versus 97 ± 20 mL/min/1.73m²; $p=0.001$). An impaired GFR as estimated by creatinine clearance (normal range >90 mL/min/1.73m²) or cystatin C (normal range >80 mL/min/1.73m²) was observed in 46% or 34% of patients on tenofovir compared with 32% or 21% of control patients ($p=0.04$ for creatinine, $p=0.06$ for cystatin C). Results for GFR estimated using the MDRD formula were not statistically significant ($p=0.375$) for patients receiving tenofovir (106 ± 54 mL/min/1.73m²) versus those who were never treated with tenofovir (104 ± 22 mL/min/1.73m²). A significantly higher number of patients receiving tenofovir had proteinuria greater than 130 mg/d when compared with the control group (30% versus 5%; $p<0.001$). In the majority of patients, the proteinuria was of tubular origin. Electrolyte excretion (urea, uric acid, sodium, potassium, calcium, phosphate, and chloride) were in the normal range and did not differ significantly between groups. No patient developed Fanconi's syndrome.

These results indicate that tenofovir is associated with mild renal dysfunction in a higher proportion of patients when compared to patients not receiving tenofovir. These results also suggest that GFR estimated by using creatinine clearance or serum cystatin C appears to be more sensitive for tenofovir-related renal dysfunction than using the MDRD equation. The authors concluded that cystatin C levels may be a more sensitive marker for tenofovir-associated changes in kidney function than serum creatinine and could be used in the future to help to detect subtle renal impairment in patients using tenofovir. This study is limited by its cross-sectional design. Prospective studies using a larger cohort are needed to confirm whether cystatin C correlates better with GFR than serum creatinine in HIV-infected patients using tenofovir. However, although reference ranges have been reported, there is no current standard for serum cystatin C measurements.²¹ In addition, testing for cystatin C is only available in a limited number of laboratories.

Urinary β_2 -microglobulin:

An increase in urinary β_2 -microglobulin (BMG) may be a sensitive marker of proximal tubule damage associated with tenofovir use. In a prospective cohort trial, serum creatinine, serum

phosphate, serum uric acid, urine BMG and percentage tubular reabsorption of phosphate (%TRP) were monitored every 3 months in 17 patients initiating treatment with tenofovir-containing regimens for a total of 24 weeks.²⁶ As a control group, 12 patients treated with zidovudine or stavudine-containing regimens excluding tenofovir were monitored using the same markers. The mean urine-BMG for the tenofovir group was significantly higher at 12 weeks than in the control group (174 µg/L; $p=0.003$). Low %TRP (<90%) was observed in 19% of tenofovir-treated patients at 12 weeks versus 0% in the control group. In the tenofovir group, two cases of tubular toxicity were reported, one of which presented as Fanconi's syndrome. No significant changes from baseline were noted for serum creatinine, phosphate, or uric acid during the 24 week follow-up. These results suggest that Fanconi's syndrome may not be detected by monitoring serum creatinine alone. Based on these findings, the authors recommended more intensive screening for proximal tubular dysfunction by measuring urine β_2 -microglobulin and calculating the fractional reabsorption of phosphate.²⁶ A cross-sectional study compared creatinine clearance estimated by using the CG equation with urinary BMG in 70 patients treated with tenofovir and 90 control patients on other antiretroviral therapy who had never been exposed to tenofovir.²⁷ Results showed that the mean urinary BMG was significantly higher in patients receiving tenofovir when compared with control patients (2.79 ± 0.85 µg/L versus 2.09 ± 0.43 µg/L; $p<0.0001$), though no statistical difference was detected in their serum creatinine (0.76 ± 0.18 versus 0.76 ± 0.15 mg/dL), or estimated creatinine clearance (114.2 ± 34.3 mL/min versus 120.0 ± 29.8 mL/min). Multivariate analysis revealed that co-administration of boosted lopinavir-containing treatment and patients with low body weight were associated with high urinary BMG levels in tenofovir-treated patients. These studies are limited by trial designs that do not control for confounding variables and small sample sizes.

Overall, these results suggest that relative to serum creatinine, urinary BMG could be a more sensitive marker of renal tubular injury associated with tenofovir therapy. However, urinary β_2 -microglobulin is elevated in many forms of renal disease and is also elevated in non-tenofovir treated patients.²⁸⁻³⁰ Longitudinal analyses of urinary BMG in association with tenofovir therapy in a larger cohort are required.

Guidelines:

Two guidelines providing recommendations for dosing adjustments (see Table 1) and monitoring parameters for renal dysfunction associated with tenofovir use were identified.^{17,22}

Guidelines published in 2005 from the HIV Medicine Association of the Infectious Diseases Society of America recommend that all patients at the time of HIV diagnosis should be assessed for existing kidney disease.²² This includes a screening urinalysis for glycosuria and proteinuria and a calculated estimate of GFR using either the CG or MDRD method. For CKD staging purposes, the simplified MDRD equation is generally preferred. However, because studies of medications in renal failure have traditionally used the CG equation, it would be appropriate to use this formula for dosage adjustments. If there is no evidence of proteinuria at the initial evaluation, patients at high risk for the development of proteinuric renal disease (e.g. African Americans, those with advanced HIV disease, diabetes mellitus, hypertension, or hepatitis C coinfection) should be screened annually. The guidelines recommend that patients who are receiving tenofovir with a GFR of less than 90 mL/min/1.73 m², are receiving other medications that are eliminated by renal secretion (e.g. adefovir, acyclovir, ganciclovir, or cidofovir), have comorbid conditions likely to affect renal function (e.g. diabetes or hypertension), or are receiving ritonavir-boosted protease inhibitor regimens, should have their renal function, serum phosphate, and urine protein and glucose monitored at least twice a year.²² Dosage adjustment

is recommended for patients with a creatinine clearance of less than 50 mL/min (Table 1). These dosing recommendations are intended for patients with stable chronic kidney disease and not for those whose renal function deteriorates as a result of tenofovir-related nephrotoxicity. However, no long-term safety data are available in patients with renal dysfunction who have received tenofovir using these dosing guidelines. Furthermore, the pharmacokinetics of tenofovir have not been evaluated in patients receiving peritoneal dialysis with creatinine clearance <10 mL/min. Hence tenofovir should be used with caution in these patients.

Guidelines from the Department of Health and Human Services also recommended that renal function, urinalysis, and electrolytes be monitored in patients while on tenofovir.¹⁷ The guidelines indicate that calculated creatinine clearance using either the CG equation or the MDRD equation, is a more sensitive indicator of impaired or declining renal function than serum creatinine. The guidelines also recommended dosage adjustment for creatinine clearance less than 50 mL/min but indicate that due to lack of safety and efficacy data using these dosage adjustments, the use of alternative nucleoside reverse transcriptase inhibitors (especially abacavir) may be preferred.

Table 1: Dosing Recommendations for Tenofovir^{17,22,31}

Creatinine Clearance (mL/min)*	Dose
≥ 50	300 mg once daily
30-49	300 mg every 48 hours
10-29	300 mg twice weekly
<10 (patients with end stage renal disease requiring hemodialysis)	300 mg every 7 days or after a total of approximately 12 hours of dialysis**

* Calculated using ideal (lean) body weight with the CG equation

**Once weekly dosing assumes 3 hemodialysis sessions a week lasting approximately 4 hours each; tenofovir should be administered following completion of dialysis.

Conclusions and implications for decision or policy making:

Currently, no consensus exists as to the frequency of monitoring for renal function in patients receiving tenofovir or when the medication should be discontinued. This is a reflection of the paucity of data regarding clinically relevant markers for tenofovir-associated nephrotoxicity. Due to the fact that clinically significant tenofovir-related nephrotoxicity is rare, it is difficult to design studies powered to assess for appropriate markers. Most of the existing evidence stems from observational studies with small numbers of patients. Evidence from cross-sectional and prospective cohort trials indicate that cystatin C or β_2 -microglobulin may be useful as alternative markers to serum creatinine for renal dysfunction in patients receiving tenofovir. Long-term studies are needed to confirm if these or other markers specific for renal tubular injury will be useful to help guide therapy with tenofovir. Available evidence from RCTs and observational studies does not indicate that tenofovir increases the risk for hypophosphatemia in HIV-infected patients. Larger long-term studies are needed to confirm this finding. Given the often transient

nature of hypophosphatemia in this group²³, patients with asymptomatic changes in serum phosphate should have these levels periodically assessed before discontinuation of therapy with tenofovir. This is especially important because patients taking tenofovir are often highly treatment experienced with few alternative options. In the absence of clinical findings, continuing tenofovir with or without phosphate supplementation may be a viable option.

Current guidelines recommend checking serum creatinine and phosphate, as well as performing a urinalysis for glucosuria and proteinuria at least biannually in patients receiving tenofovir. Further studies are needed to determine the best method for estimating GFR among HIV-infected patients given the significant weight and body morphology changes observed in this group. In patients with renal impairment (creatinine clearance of less than 50 mL/min), the potential benefit of tenofovir therapy should be weighed against the potential risk for renal toxicity given the lack of safety and effectiveness data for dose interval adjustment recommendations.

In the future, drug level monitoring³² may also be a valuable preventative strategy for tenofovir-related nephrotoxicity, but its use has not yet been validated in a well-designed trial. Overall, tenofovir is a well-tolerated effective treatment option for HIV-infected patients² but further long-term studies are required to help guide the management of drug-related nephrotoxicity.

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