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Tenofovir Renal Toxicity: Evaluation of Cohorts and Clinical Studies—Part One

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ABSTRACT

Tenofovir is one of the most commonly used antiretrovirals in adolescents and adults because of its potency and favorable pharmacokinetic and relative safety toxicological profile. It has been combined successfully with antiretroviral drugs from classes such as protease inhibitors, non-nucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors to achieve virologic suppression in a high percentage of recipients. Despite its therapeutic success, quite a number of cohorts and clinical studies have associated tenofovir with the development of renal toxicity with few studies on the opposing end. This stimulated us to review reported cohorts and clinical studies on tenofovir renal toxicity. In this study it was observed that literature reported incidence of tenofovir renal toxicity falls within the range of 0.7% - 17%. Available studies gave different appellations to tenofovir renaltoxicity, which include fanconis syndrome, proximal tubule dysfunction, acute renal failure, chronic renal failure, chronic kidney disease and nephrogenic diabetes insipidus. Markers of renal toxicity (tubulopathy) which include glycosuria, hyperaminoaciduria, proteinuria, hyperphosphaturia, hyperuricosuria, retinol-binding protein, beta2-microglobulinuria, decreased creatinine clearance and decreased glomerular filtration rate were also reported. In some studies renal biopsy demonstrated cytoplasmic vacuolization, apical localization of nuclei and reduction of the brush border on proximal tubule epithelial cells. This study observed that tenofovir renal toxicity could be reversible on discontinuation of tenofovir therapy despite contrary views by some studies. Regardless of tenofovir reported renal toxicity, it is well tolerated with a relative safety profile but it is advised that renal profile of patients should be evaluated before and routinely during tenofovir therapy.

Keywords: Tenofovir; Pharmacology; Renal; Toxicity; Cohorts

1. Introduction

The human immunodeficiency virus (HIV-1) is a retrovirus of the lentivirus genus that primarily infects cells of the host immune system. Once an individual is infected, HIV-1 replication takes place in several steps. In the first step, the virion attaches itself and fuses with the host cell membrane using co-receptors and releases two single-stranded RNA molecules and three different viral enzymes into the host cell cytoplasm. The introduced viral RNA is transcribed by viral reverse transcriptase enzyme into DNA and the viral DNA is transported into the nucleus. The viral DNA is processed and incorporated by the viral integrase enzyme into the host genome. The integrated viral DNA (aprovirus) is transcribed and translated by the host system to produce viral proteins and single-stranded RNA for new virions. After assemblage, the new virions bud off and mature using the viral protease, completing the HIV-1 lifecycle [1].

One of the key principles of antiretroviral therapy is the inhibition of the above mentioned HIV replication stages. These have led to the combination of at least three antiviral drugs, preferably from at least two different classes as the standard practice and are known as highly active antiretroviral therapy (HAART) which is currently the therapy of choice for HIV infected patients [2]. Different types of antiretroviral combination therapies are available and use of a particular therapy depends on the tolerability, the cost, and the therapeutic objectives [3]. However, despite remarkable viral replication suppression, immune response restoration and decreased mortality, long-term HAART appears to be associated with the development of some toxicological effects like cardiotoxicity, hepatotoxicity and nephrotoxicity [4,5]. These

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have impaired therapeutic success via poor adherence, loss of serum HIV suppression, development of drug-resistant HIV strains, and increased probability of illness progression [6]. Among these HAART associated toxicological effects is renal toxicity which was reported to be pronounced in tenofovir (TDF) containing antiretroviral regimen [7].

Tenofovir is one of the most commonly used antiretrovirals (ARVs) in adolescents and adults because of its potency and a favorable pharmacokinetic (PK) profile that allows it to be dosed once daily [8,9]. Tenofovir has been found to be effective in many combination regimens for the treatment of HIV infection, both in previously untreated and in treated individuals. It has been combined successfully with antiretroviral drugs from classes like protease inhibitors. Non-nucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors to achieve virologic suppression in a high percentage of recipients, but researches have associated tenofovir with renal toxicity and decreased mineral bone density [10]. Due to increased reports on tenofovir induced renal toxicity and its place in the management of HIV, this work which is the first part (Part 1) of two parts investigated reported cohorts and clinical studies on the renal profile of tenofovir.

2. Pharmadynamics and Pharmacokinetics of Tenofovir

Tenofovir was approved by the US Food and Drug Administration (FDA) on October, 29, 2001 as a once-daily 300 mg tablet for individuals aged 18 years and above for the treatment of HIV-1 infection in combination with other ARVs [11]. It is a 9-*R*-2-phosphonomethoxypropyl adenine (PMPA) that belonging to the acyclic nucleoside phosphonate family [12]. It is an ester prodrug and is orally administered. Due to the presence of a phosphonate group, tenofovir is negatively charged at neutral pH, which limits its oral bioavailability [13]. When administered, it is first hydrolyzed by carboxylesterase and phosphodiesterase during its first passage through the liver to producedtenofovir [14,15]. Tenofovir is later phosphorylated in the cell by adenylate kinase to produce tenofovir monophosphate (TFV-MP). TF-MP undergoes conversion by nucleotide diphosphate kinase to produce tenofovir diphosphate (TFV-DP). TFV-DP has antiviral property and it competes with the naturally nucleotide counterpart deoxyadenosine 5'-triphosphate to inhibit viral reverse transcriptase. The incorporation of TFV-DP into the viral DNA chain terminates DNA elongation and stops further DNA synthesis [16].

Tenofovir has a relatively long half-life of 12 - 18 hours [17]. The oral bioavailability in fasted patients is approximately 25%. Administration of food (high fat meal) increases the oral bioavailability, with an increase in the AUC of approximately 40%. The binding of tenofovir to human plasma or serum proteins is less than 7.2%. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg respectively [18]. Tenofovir is not metabolized by liver enzymes but is extensively and rapidly eliminated as unchanged drug in the urine TDF is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition with other compounds that are also excreted through the kidney [19]. TDF associated toxicities include a decline in mineral density of bone, renal increase in parathyroid hormone (PTH) secretion, phosphaturia and hypophosphataemia while fatal lactic acidosis has been reported when TDF was added to a regimen containing didanosine due to TDF induced increase indidanosine concentration [20].

The use of TDF is associated with proximal tubular dysfunction with or without decreased renal function. Renal impairments, including cases of acute renal failure and Fanconi's syndrome, have been reported with the use of TDF in clinical practice [21]. The pharmacokinetics of tenofovir are altered in patients with renal impairment and patients with creatinine clearance <50 mL/min or with end-stage renal disease (ESRD) requiring dialysis. It is recommended that the dosing interval for tenofovir be modified in patients with creatinine clearance <50 mL/min or in patients with ESRD who require dialysis [22]. Renal tubular dysfunction and tubular toxicity have been associated with increased TDF plasma concentration. TDF-associated elevations of PTH have been found independent of vitamin D deficiency and have also been linked to vitamin D deficiency in studies of adults with HIV [23,24].

Tenofovir is recommended as one of the preferred nucleotide reverse transcriptase inhibitors (NRTIs) for first-line ART in adults. It is available as a co-formulation with other ARVs to make dual or triple fixed-dose combinations. Tenofovir exhibited synergistic and additive activity when combined with certain antiretrovirals and demonstrates no antagonistic interactions in their presence. Strong synergism has been seen with zidovudine and nevirapine. Additive inhibition has been reported when co-administered with abacavir, lamivudine and emteicitabine [25,26]. There are reports of HIV-1 isolates with reduced susceptibility to tenofovir in vitro. These viruses expressed a K65R mutation in reverse transcriptase and showed a 3 - 4 fold reduction in susceptibility to tenofovir [27].

3. HIV Associated Renal Disease

Renal functions abnormalities are present in a large percentage of patients with HIV infection especially those with very high viral load and comobidities. HIV-associ-

ated renal disease has become a relatively frequent cause of end-stage renal disease (ESRD) requiring dialysis and seems to be associated with progression to AIDS and death. Kidney disease associated with HIV is a significant challenge to patients and clinicians by increasing the risk for AIDS-defining illness, hospitalization, and death [28,29]. Due to morbidity and mortality as a result of HIV associated renal disease, in this section we critically examine reported cases of renal disease attributed to HIV. One of the first cases of kidney disease associated with HIV as reported in 1984 by Rao *et al*. [30] was characterized by nephrotic syndrome with focal and segmental glomerulosclerosis in nine cases of acquired immunodeficiency syndrome (AIDS). Naicker and colleagues in their work also attested to the fact that the association between HIV and renal disease was first reported in 1984 in New York City and Miami. These groups showed that HIV-positive individuals have proteinuria and progression to end-stage renal disease which occurs within 8 - 16 weeks; death rate approached 100% within 6 months of diagnosis [31].

Subsequently, various glomerular and renal syndromes were described in histology or autopsy studies [32]. Different types of renal diseases associated with HIV have been reported this include classic Human immunodeficiency virus associated nephropathy (HIVAN), HIV-associated thrombotic microangiopathy, and immune-mediated glomerulonephritis which were discussed in the second part of this work. A survey conducted during the period 1995 through 1999 showed an increasing prevalence of HIV associated renal disease from 6.3% to 9.1% in HIV patients [33]. Another report revealed that prevalence of chronic kidney disease in HIV patients may be between 5% to 15% depending on the series. However, some studies revealed that the prevalence of renal histological involvement ranged from 1% - 15% depending on the different autopsy series [34,35].

Similar increase in prevalence was also reported by Deti and colleagues who showed that incidence rate of chronic renal failure were 1.27 cases per 100 person-years. This tends to rise with time: 1.9% at one year, 3.3% at two years, 4% at three years, and 4.4% at four years [36]. Rates of ARF in HIV outpatients were reported at 2.9% in 1995 and 6.0% in 2003 in a study of 25,114 patients which shows an increase in trend [37]. Data from the US Renal Database System (USRDS) showed that every year, approximately 800 - 900 new cases of end-stage renal disease (ESRD) attributed to HIVAN are recorded in the US and nearly 90% are reported in African-Americans [38]. Szczech in her study also reported CKD correlated with proteinuria and elevated creatinine level in 7% to 32% of HIV-seropositive patients and were associated with an increased rate of death in a study of 2038 female HIV-infected patients [39]. Another study that showed the prevalence of HIV infection in renal disease is the report from the Veterans Affairs Medical System. This report showed that the overall incidence of end-stage renal disease was 3.9 cases/1000 person-years among HIV-infected veterans. In this report a higher incidence of end-stage renal disease was observed among HIV-infected African-Americans which may suggests genetic predisposition in HIV associated renal disease [40].

A similar incidence of higher end-stage renal disease in blacks was also reported in a single-center study from Johns Hopkins, with an 18-fold higher risk for progression to ESRD among HIV infected African-Americans compared with HIV-infected Caucasians [41]. Hailemariam *et al*. (2001) [42] reported series of 239 autopsies performed on patients with AIDS in Switzerland from 1981 to 1989 (before the introduction of HAART). Various renal abnormalities were reported among the 228 white patients. However, the only case of HIVAN in this series was detected in one of six African patients included in the study. The prevalence of higher HIV associated kidney disease in black population is supported by a study which employed varying criteria for diagnosis of kidney disease. This study reported a variable prevalence of these diseases in patients with HIV in sub-Saharan Africa: 6% in South Africa, 38% in Nigeria, 26% in Côte d'Ivoire, 28% in Tanzania, 25% in Kenya, 20% - 48.5% in Uganda and 33.5% in Zambia. Results from these studies also suggested that a broader spectrum of histopathological lesions in HIV-associated kidney disease exists in African populations than previously thought [43].

A study conducted on an urban US HIV population found evidence of CKD in 24% of the patients. Forty patients which represents (10%) had CKD stage 1, 19 patients which represents (4%) had stage 2, 29 patients (7%) stage 3, four patients (1%) stage 4, and eight patients (2%) stage 5 [44].

Another study carried out in Baltimore, Maryland supported the involvement of HIV in renal disease. In their work they measured CKD incidence, GFR slope, and progression to ESRD in 3332 African American and 927 white HIV-infected subjects. A total of 284 subjects developed CKD, 35% of whom subsequently developed ESRD [45]. In a cross-sectional study of another urban HIV-infected population in New York City, 22% of African-American patients (versus 11.4% of whites) had either CKD or ESRD; 4.1% of the studied population including Caucasians and Hispanics had ESRD [46]. Rollins *et al*., 2006 [47] reported that HIV-associated nephropathy is caused by focal sclerosing glomerulopathy with is characterized by proteinuria, renal failure, and rapid progression to ESRD. It is said to have a genetic predisposition because it is very common in Africans

infected with HIV. It occurs late in the course of HIV-1 infection and includes a CD4 cell count 200 cells/mm^3 and a high viral burden. But with the advent of HAART in the treatment of HIV, the incidence of HIV associated renal disease must have decreased due to decline in morbidity and mortality rate.

4. Tenofovir Renal Toxicity

Tenofovir is one of the widely prescribed antiretroviral drugs and is an essential part of all the regimen (HAART) use in the treatment of HIV-1 adults. TDF has achieved very wide acceptability because it is easy to be administered, efficacious, and relatively favorable toxicological profile. These qualities have increase the choice and use of TDF as one of the widely prescribed antiretroviral drugs for the treatment of HIV-1. Despite its therapeutic success some reports have associated TDF with development of renal toxicity which include proximal tubular dysfunction, Fanconi syndrome, acute kidney injury, acute renal failure and chronic renal failure. Reports of renal toxicity attributed to TDF have been published as case reports, cohorts and clinical studies. This section analyzed "with all degree of clarity" these reported cohorts and clinical studies taking into cognizance, the incidence, reversibility of tenofovir renal toxicity and discrepancy in reports.

4.1. Epidemiology

The incidence of a disease could be fundamentally correlated with its morbidity and mortality rate hence the incidence of tenofovir associated renal toxicity can't be overemphasized. Studies have reported different incidence. This portion evaluated reported incidence of tenofovir associated renal toxicity. We will start by looking at a retrospective review of the Food and Drug Administration Adverse Events Reporting System from 2001 through 2006 which registered 164 subjects who had Fanconi's syndrome. Report showed that 83% of subject with Fanconi syndrome received tenofovir with protease inhibitors [48]. Evaluation of 754 HIV infected subject treated with tenofovir by SCOLTA reported 2.5% incidence of creatinine elevations over 1.5-fold the upper limit of normal in a mean followup of 19.5 months [49,50]. Similar observation was reported when a total of 172 patients receiving tenofovir disoproxil fumarate (TDF) for a median of 16 months were evaluated. Seven (4%) patients developed grade 1 increases in serum creatinine (SCr). Fifteen (8.7%) patients had an increase in SCr of greater than 1.5 times baseline values. Four (2.3%) patients discontinued TDF due to increase in SCr and/or abnormal urinalysis. Of 62 patients with urinalysis, twenty-eight which represents (16%) and 11 which represents (6%) of the patients developed grade 1 and grade 2 hypophosphataemia respectively [51].

Some studies have identified rising incidence of hypophosphatemia in patients treated with tenofovir a prevalence of 9.8% among tenofovir-treated patients, 6.7% among non tenofovir, HAART-treated patients and 2.6% among treatment-naive, HIV-infected individuals were reported. This observed hypophosphatamia which is a biomaker of renal toxicity may be associated with some comorbidities [52,53]. An outstanding incidence was reported by retrospective cohort analysis of HIV-infected adults who received tenofovir at the Themba Lethu in South Africa. Of 890 patients initiated on tenofovir, 573 (64.4%) had normal renal function had mild renal dysfunction and 46 (5.2%) had moderate renal dysfunction. 2.4% experienced nephrotoxicity, 7.8% died and 9.7% were lost during 48-months of follow-up. Incidence of tenofovir associated renal toxicity can be seen from an evaluation of 10,343 tenofovir-treated patients [54].

Another study showed 8.4% of patients attained a greater than 1.5-fold increase in SCr within 6 months of starting tenofovir therapy [55]. One of the studies that could have correlated incidence of tenofovir renal toxicity, risk and exposure was the evaluation of association of cumulative and ever exposure to tenofovir on kidney outcomes in 10,841 HIV-infected patients. After multivariable adjustment, each year of exposure to tenofovir was associated with 34% increased risk of proteinuria 11% increased risk of rapid decline and 33% increased risk of CKD [56]. In a cohort Of 4183 HIV-positive patients, 1058 patients were exposed to tenofovir DF, Only 84 (8%) patients experienced a creatinine value >120 μmol/L [57]. Some incidence as reported by some authors include 0.7% by Cooper *et al*., (2010) [58] 1.65% by Padilla *et al*., (2005) [59] 0.78% and 2% by Gupta *et al*., (2012) [60].

4.2. Cohorts and Clinical Studies

Tenofovir has been associated with development of renal toxicity in humans and animals. Quite a number of cohorts, case reports and clinical studies have reported different forms of tenofovir associated renal toxicity. In this section, we critically looked at various cohorts andclinical studies to evaluate the profile of tenofovir on the renal system. Verhelst *et al.* (2002) [61] was the first to describe a patient who was treated with tenofovir and developed reversible Fanconi syndrome, nephrogenic diabetes insipidus, and acute renal failure. Renal biopsy demonstrated cytoplasmic vacuolization, apical localization of nuclei, and reduction of the brush border on proximal tubule epithelial cells. Subsequently more reports on tenofovir associated renal toxicity were rolled out from various studies. One of these reports is a retrospective cohort analysis of 1647 patients enrolled in the

Kaiser Permanente Health Maintenance Organization during 2002 to 2005. In this study tenofovir exposure was found to be significantly associated with a decline in GFR and proximal tubular dysfunction [62].

Another cohort that showed the nephrotoxic effect of tenofovir was performed by Milinkovic and colleagues. They evaluated 1293 patients and reported that 103 patients stopped tenofovir therapy in which 29 discontinued due to renal toxicity [63]. In the ANRS CO_3 Aquitaine Cohort, 2613 HIV-infected patients were followed-up between 2004 and 2008 to estimate the incidence of chronic renal failure and related risk factors. The incidence rate of chronic renal failure was much higher (12.7 cases for 1000 person-years) which is said to be associated with factors like immunodeficiency and tenofovir exposure [64]. The above reports are in agreement with the work of Wood ward and friends who evaluated the renal profile of 5687 patients in a clinical centre providing HIV care services. They identified 22 patients with TDF associated renal toxicity of which 21 were males and one female [65]. Also a similar Swiss HIV Cohort Study found a consistent evidence for a significant reduction in GFR associated with tenofovir use [66].

The incidence of CKD was also investigated in the Euro-SIDA Cohort Study, which included 6843 HIV-infected persons that were followed-up from 2004 onwards. Progression to chronic nephropathy was observed in 225 patients among 21,482 person-years which represents an incidence of 1.05/100 person-years. After adjustment for traditional risk factors, exposure to tenofovir was significantly associated with a higher incidence of CKD [67]. This is consistent with a study that evaluated 281 HIV infected patients receiving TDF followed up for 4 - 6 weeks, 3, 6, 9 and 12 months, result showed association between TDF and renal toxicity [68]. It is outstanding to know that in a retrospective cohort study conducted by Manosuthi *et al*. one hundred and thirty patients were evaluated. Report showed that the overall incidence of renal failure was 0.26 per 100 persons/ month [69]. Also a cross-sectional study involving 845 HIV-infected outpatients showed a prevalence of chronic renal failure higher than that of the general population, and significant predictors of lower GFR in multivariate analyses were found to be associated with the use of tenofovir or stavudine [70].

Cao and others investigated the impact of tenofovir containing regiment in 75 HIV-positive patients. Their results showed that tenofovir containing regimen resulted in greater renal function decline over 48 weeks [71]. This may agree with an observational cohort of renal evaluation of patients on TDF performed by Patel and coresearchers. In this cohort, 1271 patients were evaluated, 83 developed renal dysfunction of which 79 had impaired serum creatinine and 5 had faconis syndrome. Renal dysfunction was higher in tenofovir and PI containing regimen [72]. Soler-Palacin and co researchers in their study also showed the capability of tenofovir to induced renal toxicity. The evaluated 40 patients on TDF for a median duration of 77 months and reported significant association between TDF and renal tubular dysfunction in HIV infected children [73].

In a cross-sectional study of 99 HIV-infected patients who used tenofovir had increased urine retinol-binding protein/creatinine ratio and protein/creatinine ratio, showing a subclinical renal tubulopathy [74]. This can be correlated with a cross-sectional study of plasma and 24-hour urine markers of tubulopathy (glycosuria, hyperaminoaciduria, hyperphosphaturia, hyperuricosuria, and beta2-microglobulinuria) in 284 HIV-positive patients who demonstrated a significant relationship between exposure to tenofovir and tubular dysfunction in the absence of impaired glomerular function [75]. Similar findings were reported in the ASSERT study, a multicenter, randomized, open-label trial comparing the safety profiles of tenofovir/emtricitabine and abacavir/ lamivudine in association with efavirenz in 385 HIV-infected subjects. After a 48-week follow-up, no difference in eGFR was observed between the arms, but markers of tubular damage (urinary excretion of retinol-binding protein and beta2-microglobulin) increased significantly in the tenofovir/emtricitabine group [76].

Compel *et al*., also added their voices to affirm the renal toxicity of tenofovir by evaluating 843 patients on TDF containing ART. They discovered that 26 patients developed chronic kidney disease. Those who developed CKD were older and 85% of participants had other risk factor for progression [77]. Decrease in renal function via was also reported in a study involving 40 patients starting a TDF-containing regimen and 388 patients starting regimen not containing TDF, and followed during 42 months. Between baseline and 12 months, the eGFR decreased significantly in patients receiving TDF (−10.40 ml/min), After 12 months, patients receiving TDF experienced a higher rate of transition from mild renal impairment (60 - 90 ml/min/1.73 m^2) to moderate renal impairment (30 - 60 ml/min/1.73 m^2) when compared with patients not receiving TDF [78].

Cohorts studies performed in African countries are consistent with reports from other countries on renal toxicity associated with tenofovir and this can be correlated with report of higher incidence of tenofovir nephrotoxicity in blacks [79]. In a cohort that took place in Zambia involving 10485 patients on ART in which 6900 were on TDF containing regimens available result showed that exposure to TDF was associated with a mean decrease of −14.7 ml/min in crcl from baseline of 6 months [80]. Another study of 324 ARVnaıve patients found a greater incidence of proximal tubular dysfunction and greater

decline in eGFR over 24 months in tenofovir-treated patients [81].

In a cohort analysis of 512 patients on tenofovir containing antiretroviral regimen for 26 months it was observed that TDF induced AKI developed in 25 patients. On stopping TDF 15 patients had complete recovery of renal function, 5 had partial recovery while 5 patients died [82]. This is in agreement with a study involving 324 patients in which 201 TDF exposed patients were compared with 123 tenofovir un-exposed subjects. Results showed that tenofovir exposed patients had a significant greater decline in glomerular filtration rate and a significant higher incidence of proximal tubular dysfunction through 24 months [83]. Similarly, both current and past tenofovir use were associated with increased risk of proximal renal tubular dysfunction in a cross-sectional study of 399 HIV infected persons [84].

A single-centre cohort study of 503 Japanese patients administered either tenofovir or abacavir base ART was performed by Nishijima *et al.* and incidence of renal function was defined as more than 25% fall in estimated glomerular filtration rate from the base line. Result showed that incidence of renal dysfunction in tenofovir arm was higher than the abacavir arm per 100 persons-year [85]. This report is consistent with an evaluation of 226 patients on TDF containing regimen in which 18 patients had a decline in renal function [86]. This can be correlated with a European multicenter cohort study involving 78 HBV infected patients exposed to TDF for 76 weeks and reported significant renal damage [87]. Johns Hopkins cohort data showed significant reductions in creatinine clearance at 180 days, 270 days, and 360 days over a 360-day follow-up in 344 patients receiving tenofovir compared with 314 patients who received nRTIs other than tenofovir [88].

4.3. Is It Reversible?

Still on tenofovir associated renal toxicity, there are discrepancies in reports on the reversibility of tenofovir renal toxicity. Some studies have reported the reversibility of tenofovir associated renal toxicity. These studies include a research that evaluated the association between tenofovir use and renal abnormality in HIV-1-infected children on antiretroviral therapy; the biochemistry results for 456 ART-exposed children were evaluated. Results showed that twenty out of 456 (4.4%) had hypophosphataemia, and one had eGFR less than 60 ml/min per 1.73 m^2. The hypophosphataemia incidence rate was 4.3/100 person-years in the TDF group versus 0.9/100 person-years in those not exposed to TDF. They concluded that hypophosphataemia was uncommon (4%), but was associated with prolonged TDF use, and was generally reversible following TDF withdrawal [89].

Another study in which patients received tenofovir therapy for a mean of 19.6 months show that nine patients presented with acute kidney injury, and four had mild renal insufficiency with subnephrotic proteinuria,. 11 of 13 patients who discontinued tenofovir showed significant recovery of renal function including four who required transient hemodialysis [90]. The progress of renal damage after discontinuation of tenofovir (TDF) in patients who started therapy with normal renal parameters was also assessed by Bonjoch and colleagues. They evaluated 183 patients who were exposed to TDF for 39 (22 - 63) months. After 22 (13 - 49.5) months of TDF discontinuation, renal parameters returned to normal values in 59% of patients [91]. Kelly and colleagues also reported that proteinuria was reversible in 11 of 12 patients who discontinued tenofovir because of proteinuria without altering other medications [92].

Other cases of reversible tubular dysfunction, including Fanconi syndrome, nephrogenic diabetes insipidus, and/or ARF, have also been reported, with onset usually within 5 to 12 months after starting therapy and recovery usually occurring within a few months after tenofovir discontinuation [93,94]. Another study that supports the reversibility of tenofovir nephrotoxicity is a cohort of 1286 HIV patients treated with tenofovir containing regimens and followed up for 48 weeks results showed an incidence of 0.39 per 100/year which was reversed on cessation of therapy [95].

Some studies gave contrary views on the reversibility of tenofovir renal toxicity. One of these studies was performed by McKelvey who evaluated the renal function of 24 HIV positive patients treated with tenofovir for greater than 3 months and reported that the use of TDF is associated with impairment of renal function. This impairment was not fully reversible in the majority of patients following cessation of TDF [96]. This is consistent with a study by Wever and colleagues which evaluated the reversibility of TDF-related nephrotoxicity in 24 HIV-infected male outpatients who ceased TDF due to renal impairment and observed that TDF-related renal toxicity was not always fully reversible [97]. Zimmerman and co researchers in their work reported that tenofovir-associated ARF manifests as acute tubular necrosis that may not resolve with tenofovir withdrawal [98]. Comparatively more studies gave credence to the reversibility of tenofovir associated nephrotoxicity.

4.4. Discrepancy in Reports

Despite reported cases of tenofovir associated renal toxicity some few studies have attested to the safety of tenofovir on the renal system. One of the studies that showed the safety profile of tenofovir on the renal system is a long time follow up of 542 tenofovir exposed patients in which no significant renal impairment was observed [99]. Another report is a 3-year study that com-

pared 602 therapy-naive patients with a backbone of lamivudine and efavirenz treatment with either tenofovir or stavudine, no difference in the incidence of renal dysfunction was found [100]. In a HIV Outpatient Study (HOPS), use of tenofovir-containing HAART was associated with modest decreases in GFR during the first year of therapy, but clinically significant renal toxicity was very uncommon [101] and decline in GFR in subjects with preexisting renal dysfunction was also very limited [102]. Similar observation was reported in an analysis involving a total of 514 patients receiving tenofovir which report showed that TDF containing ART was associated with less renal impairment than ART without tenofovir [103].

Clinical trials and post-marketing data reported excellent safety profile of tenofoviron HIV + subjects including the absence of significant renal injury. This finding is supported by an in vitro experimental study [104]. A long-term analysis of renal safety in patients receiving TDF compared with d4T for 144 weeks; mean serum creatinine did not change in the TDF group compared with a 0.1 mg/dl decrease from baseline in the d4T group. No patient experienced grade 4 (1.0 mg/dl) hypophosphatemia and no patient developed Fanconi's syndrome or proximal renal tubular dysfunction [105]. Gallant, *et al*., 2009 [106] evaluated 432 antiretroviral-naive patients who initiated either tenofovir or any alternative NRTI. Patients taking both tenofovir and NRTI experienced an initial decline in GFR during the first six months of therapy, but renal function stabilized between six and 24 months. A comparative randomized study of ABC/3TC versus TDF/FTC in 333 persons found no statistically significant differences in eGFR over 48 weeks [107].

Furthermore, tenofovir did not appear to be associated with worsening kidney function in the multicenter, observational FRAM study, despite widespread use at the follow-up visit [108]. A 1-year prospective study of 424 HIV-infected persons also reported no association between tenofovir use and tubular damage [109]. This is consistent with an investigation on the safety and efficacy of once daily doses of tenofovir administered in combination with other antiretroviral therapy in treatment-experienced HIV-1-infected patients. One-hundred and eighty-nine subjects were exposed to various doses of TDF for 48-weeks; no significant changes in renal function were observed [110].

Observation from a STACCATO trial where Thai patients were treated with tenofovir containing antiretroviral drug showed lack of renal toxicity [111]. Vigano and co researcher evaluated the renal safety of tenofovir in HIV-infected children treated with tenofovir for 96 weeks. They reported no evidence of renal toxicity in tenofovir treated HIV infected children [112]. In a cohort of 933 HIV patients treated with tenofovir containing antiretroviral regimen, followed through for 6 and 12 months showed that TDF associated renal toxicity is rare [113]. Another cohort of 53 HIV patients exposed to TDF containing antiretroviral regimens for 48 weeks performed by Gerard and co-researchers reported that TDF related severe nephrotoxicity is an uncommon event [114]. The safety and efficacy of TDF compared with placebo in 235 patients was evaluated in addition to other observations TDF had a similar safety profile with placebo [115]. On the other hand, large observational studies and clinical trials have shown no evidence of glomerular or tubular damage when tenofovir is employed as a component of an initial antiretroviral regimen [116,117].

5. Conclusion

Cohorts and clinical studies have attested to the fact that tenofovir may have renal toxicity which could be reversible on discontinuation of therapy. The incidence of tenofovir renal toxicity may be low due to reports and with respect to therapeutic success achieved with the clinical use of tenofovir in combination with other antiretroviral agents. Due to reports, it is recommended that patients' renal status should be evaluated before and in the course of tenofovir therapy.

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