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A concise and informative title:

The renal and bone adverse effects of tenofovir based regimen in the treatment of HIV-infected children: A systematic review

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ABSTRACT

Introduction

Tenofovir disoproxil fumarate (TDF)-containing regimens in the treatment of HIV-infected children have safety concerns with respect to renal and bone toxicity.

Objective

The aim of the study was to systematically review and critically appraise the literature relating to the reported renal and bone adverse effects of TDF-based regimens in the treatment of HIV-infected children from 2 to 19 years old.

Methods

Searches were performed using the Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, OvidSP, ScienceDirect and Web of Science databases and platforms. All primary studies involving tenofovir use in HIV-infected children were sought. Studies that involved use of TDF for pre- and post-exposure prophylaxis, and treatment of chronic hepatitis B virus infection were excluded. Data on study characteristics, participant's characteristics, therapeutic intervention and adverse effects were extracted using a piloted tool. In addition, pharmacovigilance data from the WHO Adverse Reaction database was included.

Results

We identified 19 studies that reported presence of renal and bone adverse effects of TDF and these included a total of 1100 study participants. The reports were in distinctly heterogeneous participant groups. A total of 287 renal and bone adverse effects were reported (250 renal and 37 bone adverse effects). Approximately 238 (21.6%) participants were affected by these adverse effects. Of these, 15 participants stopped their TDF-containing regimen due to these adverse effects. In addition, the pharmacovigilance data from the WHO Adverse Reaction database reported 101 renal and bone adverse effects for patients whose indication was HIV/AIDS.

Conclusion

This systematic review summarises the reports of renal and bone adverse effects of TDF-containing regimen in the treatment of HIV-infected children. Our findings suggest that the benefits of using TDF in children need to be balanced against the potential risk of toxicity.

Key Points

- The magnitude of the renal and bone adverse effects of Tenofovir disoproxil fumarate (TDF)-containing regimens in HIV-infected children is of clinical relevance, particularly for the reported effects on renal toxicity.
- A multidisciplinary approach with monitoring of renal and bone adverse effects (including the decision to withdraw treatment and vitamin D supplementation for bone health) are recommended to address the benefit-risk balance of TDF-containing regimens in children aged 2-19 years.
- There is a need for continued vigilance in this age group, more rigorous monitoring for and reporting of potential long-term renal and bone adverse effects/toxicities, particularly in resource-limited setting.

1. Introduction

Globally, the estimated number of children younger than 15 years of age living with HIV in 2013 was 3.2 million, and an estimated 240,000 children were newly infected with HIV [1]. The introduction of highly active antiretroviral therapy (HAART) has resulted in a dramatic reduction in the morbidity and mortality rate in HIV-infected children [2]. In the USA and UK, a significant decline in mortality (81%–93%) has been reported in HIV-infected children between 1994 and 2006, while a significant decline in HIV-related morbidity and hospitalisations in children has been observed in the USA and Europe over the same time period [3]. Combined antiretroviral therapy (ART) or HAART regimens include at least three drugs from at least two drug classes of ART and have been associated with enhanced survival, reduction in opportunistic infections and other complications of HIV infection such as tuberculosis, cytomegalovirus infection, Kaposi's Sarcoma and candidiasis among others. They have also been shown to improve growth and neurocognitive function in children resulting in an improved quality of life [3].

Tenofovir disoproxil fumarate (TDF) is an orally bioavailable prodrug of tenofovir (also called 9-(R)-(2-(phosphonomethoxy)propyl}adenine or PMPA), which is principally eliminated by the kidney [4]. It is a nucleotide reverse transcriptase inhibitor (NRTI) approved by the US Food and Drug Administration (FDA) in 2001. It is licensed as a once-daily 300 mg tablet for individuals aged 18 years and over for the treatment of HIV-1 infection in combination with other antiretrovirals [5]. TDF is recommended by the World Health Organisation (WHO) as one of the preferred NRTIs for first-line ART in individuals over 18 years of age and is available as a co-formulation with other antiretrovirals [6]. In March 2010, the FDA approved the 300mg dose of TDF for use in adolescents ages 12–17 years [5,7]. The safety profile observed from a phase III study of a TDF-containing antiretroviral regimen compared to an antiretroviral regimen containing zidovudine or stavudine in HIV-infected treatment-experienced children ages 2-12 years was consistent with that observed in clinical trials in adults. This provided evidence for use of TDF in children aged 2 to <12 years [5]. In January 2012, the FDA approved the use of TDF in combination with other antiretroviral agents for the treatment of HIV-1 infections in pediatric patients ages 2–12 years at a recommended dose of 8 mg/kg of body weight (up to a maximum of 300 mg) once daily, administered as oral powder or tablets, based on the patient's age and weight [5].

The efficacy of TDF in HIV-infected children has been demonstrated in some studies. Some small studies suggest that TDF was well tolerated and effective in children [8,9]. A retrospective cohort study of 159 treatment-experienced HIV-infected children in the UK and Ireland showed good efficacy with 38% attaining virological

suppression at 12 months. The age range at first prescription of TDF was 9.3–13.7 years [10]. The safety and efficacy of TDF has not been established in children less than two years of age.

Preclinical studies have shown that the principal target organs of TDF toxicity are the gastrointestinal tract, kidneys and bone, but effects on the gastrointestinal system are mild [5]. HIV-associated abnormalities in growth factors and cytokines in HIV-infected children increases concerns about toxicities of HAART in the treatment of HIV. Limited studies of TDF in HIV-infected children have been performed and little is known about TDF toxicity in paediatric patients. The majority of TDF toxicities have been investigated in individuals over 18 years of age, but there are some recent data from studies in children and adolescents. Two studies in children receiving TDF as part of their HAART regimens showed a favourable safety profile for the drug [9,11], whereas renal toxicity mainly affecting the renal tubules has been described in some paediatric cohort studies [10,12-14]. A further safety concern for TDF use in children is the potential for adverse effects on bone metabolism. Tenofovir-containing HAART is associated with >6% loss in bone mineral density (BMD) in one-third of children. This tends to occur in heavily treatment-experienced prepubertal children or those in early puberty, and seems to recover partially with discontinuation of TDF [14,15].

This systematic review is aimed at identifying and summarising the reports of renal and bone adverse effects of tenofovir based regimen in HIV-infected children from 2 to 19 years of age.

2. Methods

A protocol for conducting the review was prepared using standard guidelines [16,17].

2.1 Eligibility Criteria

All primary studies that involved use, safety, efficacy, adverse effects and toxicity of tenofovir in combination with other recommended antiretrovirals in treatment of HIV infection in children from 2 to 19 years old were eligible. These included randomised controlled trials (RCTs), observational studies such as controlled and uncontrolled cohort studies, case control studies, retrospective studies, case reports and pharmacovigilance data. This age group was considered based on the WHO definition of a child as a person 19 years or younger unless national law defines a person to be an adult at an earlier age; however, those aged 10–19 years are referred to as adolescents [6]. Studies with children younger than 2 years old were excluded because the safety and efficacy of tenofovir has not been

established in children younger than 2 years of age [5]. Studies that involved the use of tenofovir for pre- and post-exposure prophylaxis, and treatment of chronic hepatitis B were also excluded.

2.2 Database Search and Study Selection

The following databases were searched by Rose I Okonkwo (RIO) from 1 May, 2014 to 18 July 2014: Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, OvidSP, ScienceDirect and Web of Science databases and platforms. Search terms included MeSH and free text [19]; no language, publication date, or publication status restrictions were imposed. The ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform were searched for additional published and unpublished research. A list of the terms used to search the databases and platforms are shown in a tabular form in Electronic Supplementary Material Table 1. We contacted Gilead Sciences (Foster City, CA, USA), a pharmaceutical company that developed a brand of TDF (Viread®) for information about any unpublished or ongoing studies and pharmacovigilance data. In addition, pharmacovigilance data was requested from the WHO Adverse Reaction Database, which is maintained by the Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre for International Drug Monitoring. The UMC collects reports of suspected adverse drug reactions from participating countries [20]. Once all databases searches had been conducted, duplicate citations were identified and excluded using reference management software (RefWorks 2.0 [<http://www.refworks.com/>]). Following the removal of duplicate entries by RefWorks 2.0, the selection process was trialled by RIO by applying the inclusion criteria to ten of the identified papers in order to check that they can be reliably interpreted. Eligibility assessment and selection of included studies were performed independently by RIO and Emmanuel E. Effa (EEE). Study selection was carried out by an initial screening of titles and then abstracts against the pre-specified eligibility criteria based on the review aim and the inclusion and exclusion criteria. Studies that were not relevant were excluded without reasons being recorded; those that addressed the topic of interest but failed on one or more criteria such as population were noted and reasons recorded. For studies that reported same cohort, it was agreed that the earlier study or publication be considered and the others excluded. Studies that reported absence of renal and bone adverse effects of TDF were excluded with documented reasons. For studies that appeared to meet the inclusion criteria, or in cases when a definite decision could not be made based on the title and/or abstract alone, the full papers were obtained for detailed assessment against the inclusion criteria. Instances where the full papers were

unable to be retrieved were documented. Reference lists were scrutinised and any additional relevant titles included.

The researchers RIO and EEE met to resolve any differences in their results.

2.3 Data Extraction

Data extraction tools were developed based on the Cochrane data collection form for intervention reviews for randomised controlled trials (RCTs) and non-randomised controlled trials (non-RCTs), and these included information pertinent to the review aim. The data extraction sheet developed for this review was trialled by RIO on five randomly selected included studies (RCTs, non-RCTs and observational studies) and refined accordingly [17].

The relevant information extracted from the included studies (RCTs, non-RCTs and observational studies) were study characteristics (country of research, study design, sample size and duration of therapy), characteristics of participants (age, sex, viral load and CD4 cell count), therapeutic interventions and control regimen. Outcomes measures extracted included reports of renal and bone related adverse effects, side effects, adverse events and/or adverse drug reactions of TDF-containing regimen. Relevant data extracted from case reports and case series included age, therapeutic intervention and outcome measures. Also, the data extracted from the WHO Adverse Reaction Database were adverse drug reactions related to renal and bone adverse effects and the number of reports. Additional details on whether the drug reaction was suspected, caused by an interaction or as a result of concomitant use were also extracted. Data were extracted by RIO and validated by EEE.

2.4 Quality Assessment

The assessment of methodological quality of the included studies was performed using the Cochrane Collaboration's tool for assessing risk of bias for RCTs [16] and the Newcastle Ottawa Scale (NOS) for non-randomised studies [21]. To ascertain the validity of eligible RCTs, the adequacy of randomisation and concealment of allocation, blinding of patients, healthcare providers, data collectors, and outcome assessors, and extent of loss to follow-up were determined. To assess the quality of non-randomised studies using the NOS, studies were judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for cohort studies. The quality of case reports and case series were not assessed as there is no generally acceptable tool for such studies.

2.5 Data Analysis

Due to differences in the study design, participants, background antiretroviral regimens and time of reporting of adverse effects, a meta-analysis was considered inappropriate. A narrative approach was used to highlight study findings [18,22].

Data analysis was categorised by study designs as data derived from divergent sources cannot be combined because of different study designs, different populations and different data collection methods [18]. These include analysis of:

- (a) RCTs;
- (b) Non-randomised and observational studies; and
- (c) Case reports and case series

In addition, the results retrieved from the search of the WHO Adverse Reaction database received were analysed.

3. Results

3.1 Preliminary Synthesis of Findings

Nineteen studies (two RCTs [23,24], nine non-randomised and observational studies [9,10,14,15,25-29], four case reports [12,30-32] and four case series [13,33-35]) that reported the presence of renal and bone adverse effects of TDF-containing regimen were identified, including a total of 1100 study participants. The various study designs for the non-randomised and observational studies included, three single arm open label trials [9,14,15], two retrospective cohorts studies [10,25], one cross-sectional evaluation study [26] and three prospective cohort studies [27-29], of which one involved retrospective and prospective data collections in a two-phase design. The total number of reported renal and bone adverse effects were 287 reports (250 renal and 37 bone adverse effects). Approximately 238 (21.6%) participants were affected by these adverse effects. Of these, 15 stopped TDF-containing regimen due to these adverse effects. The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flow chart [36] is given in Fig. 1. The results of the quality assessment of the RCTs, the non-randomised studies and observational studies are shown in a tabular form in Electronic Supplementary Material Tables 2 and 3, respectively. Reporting of losses to follow-up and adverse events was adequate in all these studies. For the RCTs, non-randomised and observational studies, the median study duration was 96 weeks (range, 48–308 weeks) and, for this analysis, it was considered equivalent to time receiving treatment. The sample size ranged from 6 to 448 participants (median 70 participants). The studies varied greatly with respect to the specific antiretroviral

drug used as comparator and antiretroviral co-interventions. In all of the studies reviewed that had comparators, TDF was not the only antiretroviral drug that differed between the treatment and control groups. However, despite the variations in ART combinations, each study allowed for comparison of an ART regimen containing TDF with a regimen not containing TDF. In addition, there were single arm studies with no comparison. Seven studies [9,10,14,15,24,25,28] recruited only participants who were ART-experienced, one study [28] included both ART-naive and ART-experienced participants and for three studies [25,26,29] this was unclear. The detailed characteristics of these studies are shown in a tabular form in Electronic Supplementary Material Table 4. The mean age of participants across the included studies ranged from 7 to 16 years, and the proportion of participants who were male ranged from 42.9% to 66.7% (median 47.5%). The proportion of black participants ranged from 10 to 76.1% (median 28.7%). The baseline viral load, CD4 cell count and CD4 cell percent were not available for some studies. The characteristics of participants included in these studies and the baseline parameters for the RCTs, non-randomised and cohort studies can be seen in Electronic Supplementary Material Table 5.

For the case reports and case series, relevant data on age, treatment and outcomes (renal and bone adverse effects) were extracted (see Electronic Supplementary Material Table 6).

3.2 Analysis of Results

In this review, analysis of results of adverse effects data were categorised by study designs and summarised in a descriptive approach as the study designs and data varied markedly. Analysis of the results described the studies, the number and specific types of renal and bone adverse effects of TDF-containing regimen; and the number of affected participants [17]. The analysis of the reported renal and bone adverse effects and the number of affected participants for the RCTs, non-randomised and observational studies, case report and case series is shown in Table 1.

Table 1 Analysis of the reported renal and bone adverse effects and the number of affected participants for the randomised controlled trials, non-randomised and observational studies; case report and case series

RANDOMISED CONTROLLED TRIALS		
Adverse Effects	Number of reports	Number of patients
Renal Adverse Effects		
Proximal renal tubulopathy	4	4
Bone Adverse Effects		
Decreased spine bone mineral density (BMD) > 4%	6	6
Decreased total body BMD > 4%	1	1
Fractures	1	1 (1 patient with spine BMD)
Total	12	11

NON-RANDOMISED AND OBSERVATIONAL STUDIES		
Adverse effects	Number of reports	Number of patients
Renal Adverse Effects		
Nephrolithiasis	1	1
Proximal renal tubular dysfunction (PRTD)	3	3
Renal toxicity	1	1
Fanconi syndrome	1	1 (1 patient with PRTD)
Haematuria and nephrocalcinosis	1	1
Acute renal failure	1	1
Proximal renal tubulopathy	2	2
Elevated β_2 -microglobulinuria >350 $\mu\text{g/L}$	12	12
Mild reduction in glomerular filtration rate	3	3
Asymptomatic renal tubule dysfunction	7	7
Hypophosphatemia	8	8 (3 patients with asymptomatic renal tubule dysfunction)
Proteinuria	127	127
Chronic kidney disease (CKD)	20	20 (20 patients with proteinuria)
Nephropathy	7	7 (7 patients with CKD)
Nephrotic syndrome	1	1 (1 patient with CKD)
Abnormal urine osmolality	8	8
Decreased tubular phosphate absorption	28	28
Hypokalaemia	1	1 (1 patient with asymptomatic renal tubule dysfunction)
Bone Adverse Effects		
Decreased BMD	16	16
Increased serum osteocalcin levels	5	5 (5 patients with decreased BMD)
Increased bone-specific alkaline phosphatase levels	4	4 (4 patients with decreased BMD)
Total	257	215
CASE SERIES AND CASE REPORTS		
Adverse effects	Number of reports	Number of people
Renal Adverse Effects		
Nephrogenic diabetes insipidus	2	2
Fanconi syndrome	4	4 (1 patient with nephrogenic diabetes insipidus)
Renal insufficiency	1	1 (1 patient with nephrogenic diabetes insipidus)
Increased alkaline phosphatase (ALP) level	1	1
Irreversible renal failure	1	1
Acute renal tubulopathy	3	3
Hypophosphataemia	2	2 (1 increased ALP patient and another with rickets)
Bone Adverse Effects		
Rickets	2	2 (1 patient with rickets)
Osteopenia	1	1 (1 patient with rickets)
Osteomalacia	1	1 (1 patient with fanconi syndrome)
Total	18	12

3.2.1 Analysis of Randomised Controlled Trials

The data on renal and bone adverse effects of TDF-containing regimen were identified and extracted from two RCTs [23,24] which had a total of 187 study participants. There were twelve reported renal and bone adverse effects due to TDF-based regimen in these studies (four renal and eight bone adverse effects) and a total of 11 participants were affected by these adverse effects. One RCT was aimed at the efficacy and safety of TDF in combination with an optimized background regimen (OBR) in treatment-experienced HIV-1 infected adolescents (12 to <18 years) with viremia despite antiretroviral treatment [23] and the other assessed the efficacy and safety of TDF in virologically suppressed, treatment-experienced HIV-infected children ages 2 to <16 years [24]. The study of Negra et al. [23], reported that one subject in the TDF group had acute renal failure not considered related to the study drug by the investigator, after receiving amphotericin B for cryptococcosis, but none had clinically relevant increase in serum creatinine related to TDF and no subject discontinued TDF due to renal events. However, in the placebo group, two subjects were reported to have nephrolithiasis and haematuria, both considered related to the study drug. The study only enrolled those with normal renal function, and therefore, the renal safety in adolescents with abnormal renal function was not assessed. Two subjects in the TDF group had fractures reported, both of which were trauma-related and not considered related to the study drug by the investigator. Six subjects in the TDF group had significant decrease of spine BMD (>4.0%) at week 48. Of the six subjects with significant spine BMD decrease in the TDF group, one subject had an ankle fracture. One subject from the TDF group had significant decrease of total body BMD (>4.0%) at week 48. However, in the placebo group, one subject had decreased total body BMD (>4.0%). In the study by Saez-Llorens et al. [24], no subjects discontinued the study drug due to an adverse event in the 48 weeks of the randomised phase. Four subjects discontinued due to either hypophosphatemia or glycosuria (considered to be clinically consistent with proximal renal tubulopathy) in the extension phase. All four subjects were taking lopinavir/ritonavir concomitantly with TDF at the time of discontinuation; however, no subject in the stavudine- or zidovudine-containing regimen group experience any adverse effects. In the TDF group, three subjects experienced fractures during the extension phase, all of which were considered to be related to high impact trauma.

3.2.2 Analysis of Non-Randomised and Observational Studies

The data of renal and bone adverse effects of TDF-containing regimen were identified and extracted from nine non-randomised and observational studies [9,10,14,15,25-29] that had a total of 901 study participants. Not all the non-randomised and observational studies reported the presence of renal and bone adverse effects of TDF-containing

regimen. There were 257 reported renal and bone adverse effects (232 renal and 25 bone adverse effects) and about 215 participants were affected by these adverse effects.

3.2.2.1 Renal Adverse Effects Seven studies [10,14,25-29] reported renal adverse effects of TDF-containing regimen (a total of 877 study participants). There were 232 reported renal adverse effects due to TDF-based regimen in these studies, affecting 199 participants. These included 40 reports of proximal/renal tubular abnormalities, one report of renal failure, one report of Fanconi syndrome and one report of renal toxicity. There were 127 reports of proteinuria, eight reports of hypophosphatemia, one report of hypokalaemia and one report of haematuria and nephrocalcinosis (variably defined in each study). Twelve children had abnormally elevated β_2 -microglobulinuria ($>350 \mu\text{g/L}$), suggesting proximal renal tubular damage [26]. Chronic kidney disease was identified in 20 participants (the clinical diagnoses were nephropathy in seven subjects and nephrotic syndrome in one subject) [28] and one patient developed nephrolithiasis [14]. However, in one study [26], the TDF-sparing group had two reports of abnormally elevated β_2 -microglobulinuria ($>350 \mu\text{g/L}$).

3.2.2.2 Bone Adverse Effects Three studies (the single arm open label trials) reported bone adverse effects of TDF-containing regimen [9,14,15] (a total of 43 study participants). There were 25 reported bone adverse effects due to TDF-based regimen in these studies affecting 16 participants. Sixteen participants were reported to have absolute decreases in BMD. Of these, 12 participants had $> 6\%$ decrease in BMD. Increased levels of bone-specific alkaline phosphatase were reported in four subjects and increased serum osteocalcin levels in five subjects. There were no reports of fracture in these studies.

3.2.3 Analysis of Case Reports and Case Series

There were four case reports [12,30-32] and four case series [13,33-35] in which participants were treated with TDF-containing regimen. A total of 12 children were identified in the case reports and case series that specifically reported adverse effects. There were 18 reported renal and bone adverse effects due to TDF-based regimen in these studies (14 renal and 4 bone adverse effects).

3.2.4 Analysis of Pharmacovigilance Data

The results of the search of WHO Adverse Reaction database were divided into three groups based on the WHO Adverse Reaction Terminology, System-organ classes (SOC) body organ groups. The results were stratified according to Adverse Drug Reaction–Preferred Term, reports indicated for HIV infection/AIDS and those whose indications are unclear. There were 101 reported adverse effects indicated for HIV/AIDS treatment and 48 reported

renal and bone adverse effects of a TDF-based regimen for which the indication was unclear or not mentioned. Of the 101 reports indicated for HIV/AIDS, 88 were renal and 13 bone adverse effects. For additional details on whether the drug reaction was suspected, caused by an interaction or as a result of concomitant use, see Electronic Supplementary Material Table 7

3.2.4.1 Renal Adverse Effects There were 17 reports of renal tubular disorder, which was the most reported renal adverse effect. The second most reported renal adverse effects were hypophosphatemia and abnormal renal function, which had seven reported cases each. There were also cases of nephropathic toxicity (six reports), acute renal failure (two reports), chronic renal failure (three reports) and nephrogenic diabetes insipidus (two cases).

3.2.4.2 Bone Adverse Effects Of the 13 reports of bone adverse effects of TDF, there were three cases of fractures, three cases osteoporosis and one report of abnormal bone development.

4. Discussion

The most reported renal adverse effect was proximal renal tubulopathy, sometimes with Fanconi syndrome, occurring together with reduced glomerular filtration rate and reduced creatinine clearance. It is possible that detection of early or mild cases of TDF-associated nephrotoxicity would require testing for proximal tubule injury (for example, urinalysis for proteinuria or glycosuria, measurement of bone density, serum phosphate level, or bone fracture rate) [37]. Most of these cases involved the concomitant use of didanosine and/or a ritonavir-boosted protease inhibitor [10,12,13,15, 24,25,27,30-33,35]. Of the studies that reported these cases, some reported cases of higher than recommended doses of didanosine and/or a ritonavir-boosted protease inhibitor used [10,15]. Diabetes insipidus have been reported in children receiving tenofovir-containing regimen including ritonavir-boosted lopinavir and didanosine [12,30]. Irreversible renal failure has been reported in an adolescent with an underlying kidney disease and who was treated with a tenofovir regimen including ritonavir-boosted lopinavir but without didanosine [35]. It is important to note that the RCTs [23,24] included in this review typically combined TDF with non-NRTI-based ART (rather than a ritonavir-boosted regimen and/ or didanosine). The most commonly reported TDF-associated bone adverse effects was low BMD, which was seen in over 60% of studies. The clinical implication of this remains unclear given the often short duration of many studies. Studies with a longer duration may be needed to evaluate clinically important complications [39].

In some of the studies, accurate dosing was an important issue. This was a challenge as TDF was previously only available as a once-daily adult dose of 300 mg, but the children's formulation has now been made available by the manufacturer. Several studies [11,14,23,24,26-28,38] have examined the effect of TDF on kidney function in HIV-infected children, including the two RCTs, with variable reports of evidence of renal impairment (including a decrease in glomerular filtration rate, hypophosphatemia, and proximal tubule dysfunction). In general, most of the studies have small sample sizes and are non-comparative, suggesting the need for adequately powered RCTs. Caution should therefore be exercised in interpreting results and larger studies are needed, ideally incorporating measures of both glomerular and tubular function [40].

Toxicity affecting proximal tubular renal function and reduced bone mineralization are serious concerns. Proximal tubular dysfunction causes a partial or complete Fanconi syndrome with metabolic acidosis and increased phosphate loss, both of which contribute to bone demineralisation. Tenofovir also reduces calcitriol synthesis in proximal tubular mitochondria, contributing to bone demineralisation [41]. BMD decline begins after 12–24 weeks and has been noted after up to 144 weeks on therapy. Children and young adolescents grow rapidly and bone mineralisation should peak with the pubertal growth spurt. Young children, especially Tanner Stage 1 and 2, are at higher risk for decreased BMD [42,43]. Cumulative exposure to tenofovir has been associated with an increased risk of fractures in adults [44], which may explain cases of fractures reported in children. However, not all studies of tenofovir in children have identified a decline in BMD [23,45,46]. No effect of tenofovir on BMD was found in a study in paediatric patients on stable therapy who had an undetectable viral load and who were switched from stavudine and protease inhibitor-containing regimens to tenofovir/lamivudine/efavirenz [45]. All patients in this study remained clinically stable and virologically suppressed after switching to the new regimen [47]. However, as with kidney function, studies on the effects of TDF exposure on bone health in HIV-infected children have generally involved small numbers of participants [14,15,48-50], and have reported conflicting results. It is noteworthy that TDF is not unique in its ability to cause a reduction in BMD. HIV infection itself and many other antiretroviral drugs also cause a decline in BMD [51-55]. Vitamin D deficiency is common in children with HIV infection, and this may be an additional factor in the development of bone disease; supplementation may be required in some cases [40].

The reported adverse effects underscore the need to monitor children closely with renal function tests at appropriate intervals. The availability of such facilities for frequent monitoring and the inherent tendency towards escalation of the cost of care in resource-constrained settings needs to be considered. As ART is often paid for by donor agencies,

it is likely that such tests are not routinely performed for every child. Given that children will be on these medications for life, an extended period of monitoring for renal and bone adverse events will be necessary during the studies.

4.1 Limitations

Like all systematic reviews, the strength of our conclusions is limited by the available evidence. This review does not perform a causality assessment of the renal and bone adverse effects of TDF containing-regimen in HIV-infected children but only documents the adverse effects that have been reported during its use. The information is subject to many potential sources of error, including the methods used to collect the adverse effects information. However, the method adopted for this review has helped ensure this is a complete and thorough summary of published and unpublished literature on this topic. There was incomplete retrieval of studies identified during our search as five studies screened for titles and abstracts could not be accessed. In addition, the identified studies were of varied study designs and comparative studies were few and inadequately powered. When considering case reports and case series, it is important to note that these types of studies are only published when something happens and not when something does not happen, subjecting them to extreme publication bias.

5. Conclusion

There are uncertainties associated with the long-term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. A multidisciplinary approach is recommended to address the risk/benefit balance of any TDF-containing treatment regimen on a case by case basis. This should include appropriate monitoring of renal and bone adverse effects during treatment (including decision for treatment withdrawal) and the need for supplementation with vitamin D for bone health. Further research is needed, especially long-term studies that monitor clinically relevant markers of proximal tubulopathy and the impact of low BMD on the long-term risk of fragility fractures. In addition, future trials should focus on patients treated in resource-limited settings.

The importance of toxicity studies in HIV-infected children cannot be over-emphasised particularly for children who may be adversely affected during growth and development and are likely to take ART for longer than adults. The magnitude of the renal and bone adverse effects is of clinical relevance, particularly for the renal adverse effects. This suggests the need for continued vigilance and efficient strategies for dissemination of the renal and bone

adverse effects. The systematic review findings suggest that the benefits of using TDF in children need to be balanced against the potential risk of toxicity.

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Compliance with Ethical Standards

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Table 1: SEARCH STRATEGIES

Database and Platform		Search Strategies	Date and Coverage
Medline	S1	TX tenofovir OR viread OR truvada OR atripla OR aproovir OR 9 2 Phosphonomethoxypropyl Adenine OR Pmpa	1998 - 2014
	S2	TX children OR paediatric OR pediatric OR adolescent OR teen*	
	S3	TX (HIV or AIDS) NOT TX Hepatitis	
	S4	S2 AND S3	
	S5	TX safety or toxicit* OR "side effect" OR "adverse effect" OR renal OR nephro* OR kidney OR bone OR osteo* or "fanconi syndrome" OR anuria	
	S6	S1 AND S4 AND S5	
ScienceDirect	expert search	(tenofovir OR viread OR truvada OR atripla OR aproovir OR "9 2 Phosphonomethoxypropyl Adenine" OR Pmpa) AND (children OR paediatric OR pediatric OR adolescent OR teen*) AND (safety or toxicit* OR "side effect" OR "adverse effect" OR renal OR nephro* OR kidney OR bone OR osteo* or "fanconi syndrome" OR anuria) AND (HIV or AIDS) AND NOT hepatitis.	1991 - 2014
*Ovid SP	1	(tenofovir or viread or truvada or atripla or aproovir or 9 2 Phosphonomethoxypropyl Adenine or Pmpa).mp. [mp=tx, bt, ti, ab, ct, hw]	1991 - 2014
	2	(children or paediatric or pediatric or adolescent or teen*).mp. [mp=tx, bt, ti, ab, ct, hw]	
	3	((HIV or AIDS) not hepatitis).mp. [mp=tx, bt, ti, ab, ct, hw]	
	4	2 and 3	
	5	(safety or toxicit* or "side effect" or "adverse effect" or renal or nephro* or kidney or bone or osteo* or "fanconi syndrome" or anuria).mp. [mp=tx, bt, ti, ab, ct, hw]	
	6	1 and 4 and 5	

Database and Platform		Search Strategies	Date and Coverage
CINAHL (EBSCOhost)	S1	TX tenofovir OR viread OR truvada OR atripla OR aproovir OR 9 2 Phosphonomethoxypropyl Adenine OR Pmpa	2002 - 2012
	S2	TX children OR paediatric OR pediatric OR adolescent OR teen*	
	S3	TX (HIV or AIDS) NOT TX Hepatitis	
	S4	S2 AND S3	
	S5	TX safety or toxicit* OR "side effect" OR "adverse effect" OR renal OR nephro* OR kidney OR bone OR osteo* or "fanconi syndrome" OR anuria	
	S6	S1 AND S4 AND S5	
Cochrane Central Register of Controlled Trials (CENTRAL)		<i>tenofovir OR viread OR truvada OR atripla OR aproovir OR "9 2 Phosphonomethoxypropyl Adenine" OR Pmpa in Title, Abstract, Keywords) and HIV or AIDS in Title, Abstract, Keywords not hepatitis in Title, Abstract, Keywords and children OR paediatric OR pediatric OR adolescent OR teen* in Title, Abstract, Keywords and safety or toxicit* OR "side effect" OR "adverse effect" OR renal OR nephro* OR kidney OR bone OR osteo* or "fanconi syndrome" OR anuria in Title, Abstract, Keywords</i>	1998 - 2013
Web of Science	1	TOPIC: (tenofovir OR viread OR truvada OR atripla OR aproovir OR "9 2 Phosphonomethoxypropyl Adenine" OR Pmpa)	1998 - 2014
	2	TOPIC: (children OR paediatric OR pediatric OR adolescent OR teen*)	
	3	TOPIC: (HIV OR AIDS) <i>NOT</i> TOPIC: (Hepatitis)	
	4	#3 AND #2	
	5	TOPIC: (safety or toxicit* OR "side effect" OR "adverse effect" OR renal OR nephro* OR kidney OR bone OR osteo* or "fanconi syndrome" OR anuria)	
	6	#5 AND #4 AND #1	

*OvidSP interface provides access to the following biomedical and health-related databases:

AMED, EMBASE , Health and Psychosocial Instruments, HMIC, Maternity and Infant Care, MEDLINE, PsycEXTRA, PsycINFO, PsycCRITIQUES, Psyc BOOKS, Social Policy and Practice, Transplant Library, International Pharmaceutical Abstracts and access to a range of electronic journals and electronic books.

Note: This search was carried out from 1st May, 2014 to 18th of July 2014.

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Table 2 Assessment of risk of bias for randomized controlled trials

Domains in the Cochrane Collaboration's risk of bias tool; (type of bias)	Negra 2012 [23]	Saez-Llorens 2014 [24]
Random sequence generation (Selection bias)	Low risk of bias	Low risk of bias
Allocation concealment (Selection bias)	Unclear risk	High risk of bias
Blinding of participants and personnel (Performance bias)	Low risk of bias	Low risk of bias
Blinding of outcome assessment (Detection bias)	Low risk of bias	Low risk of bias
Incomplete outcome data (Attrition bias)	Low risk of bias	Low risk of bias
Selective reporting (Reporting bias)	Low risk of bias	Low risk of bias
Other bias	Unclear risk; insufficient information to assess whether an important risk of bias exists	Unclear risk; insufficient information to assess whether an important risk of bias exists

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Table 4 Characteristics of included studies

First author Year [reference]	Design	ART-naive participants	Treatment	Tenofovir dose	Comparator	Sample size	Duration of follow up	Country	Outcome ^a
Randomised Controlled Trials									
Negra 2012 [23]	randomised, double-blinded, placebo- controlled study	No	TDF- containing regimen	mean 216.8mg/m2	placebo in addition to an OBR	90	48 weeks	US, Brazil and Panama	6 subjects had significant decrease of spine BMD >4.0%, of these 1 subject had an ankle fracture. One subject had significant decrease of total body BMD >4.0%.
Saez-Llorens 2014 [24]	randomised, open label, active-controlled study	No	TDF- containing regimen (included a ritonavir- boosted protease inhibitor)		d4T or ZDV containing regimen	97	144 weeks	US, UK and Panama	4 subjects discontinued due to either hypophosphatemia or glycosuria (clinically consistent with proximal renal tubulopathy).
Non-randomised studies and observational studies									
Hazra 2005 [9]	open-label, phase I trial	No	TDF monotherapy for 6 days was followed by TDF- containing regimen	mean 237mg/m2	None	18	48 weeks	US	5 subjects had >6% decrease in BMD , necessitating the discontinuation of TDF therapy for 2
Pontrelli 2012 [27]	prospective observational study	No	TDF- containing regimen		TDF-sparing regimen	49	104weeks	Italy	Three patients presented a mild eGFR reduction, Five patients developed hypophosphatemia

First author Year [reference]	Design	ART-naive participants	Treatment	Tenofovir dose	Comparator	Sample size	Duration of follow up	Country	Outcome ^a
Gafni 2006 [14]	single-arm, open-label, phase 1b/2a trial	No	TDF monotherapy for 6 days was followed by TDF-containing regimen	median 208 mg/m2	None	19	96 weeks	US	One patient developed nephrolithiasis. Absolute decreases in BMD were observed in 6 children.
Riordan 2009 [10]	Retrospective cohort analysis	No	TDF-containing regimen (included a ritonavir-boosted protease inhibitor)	median of first doses for those not taking the maximum once-daily adult dose of 300 mg was 7.1 mg/kg		159	median of 81.4 weeks	UK and Ireland	3 subjects had of Proximal renal tubular dysfunction, of which 1 subject also had Fanconi syndrome. 1 subject had renal toxicity, 1 subject had haematuria and nephrocalcinosis, 1 subject had acute renal failure
Purdy 2008 [15]	open-label trial, before-and-after study	No	TDF-containing regimen (included a ritonavir-boosted protease inhibitor)	median 268mg/m2	None	6	48 weeks	US	Five children had BMD, of these 2 subjects experienced > 6% BMD decreases. 1 subject was the smallest child and experienced a 27% decrease, necessitating withdrawal of TDF. Serum levels of osteocalcin increased between baseline and week 48 in 5 subjects, and bone-specific levels of alkaline phosphatase increased in 4 subjects
Papaleo 2007 [26]	cross sectional evaluation, observational analysis	unclear	TDF-containing regimen	median dose of 6 mg/kg per day	TDF-sparing regimen	92	60 weeks	France	Eleven children interrupted tenofovir, of these 2 children presented clinical and biologic symptoms of proximal tubulopathy. Twelve children had abnormally elevated beta 2-microglobulinuria (>350 microg/L)

First author Year [reference]	Design	ART-naive participants	Treatment	Tenofovir dose	Comparator	Sample size	Duration of follow up	Country	Outcome ^a
Purswani 2013 [28]	prospective cohort study	Both	TDF- containing regimen		None	448	156 weeks	US	94 met the criterion for proteinuria. CKD was identified in 20 subjects. The clinical diagnoses were nephropathy in seven subjects and nephrotic syndrome in one subject
Soler-Palacín 2011 [29]	prospective cohort study with retrospective and prospective data collection in a two-phase design	unclear	TDF- containing regimen		None	40	median of 308 weeks	Spain	Urine osmolality was abnormal in 8 patients, a decrease in tubular phosphate absorption was documented in 28 patients, and 33 patients had proteinuria
Lim 2014 [25]	retrospective study	unclear	TDF- containing regimen		None	70	median of 280 weeks	UK	7 children had asymptomatic renal tubular dysfunction (3 developed hypophosphataemia, 1 developed hypokalaemia).

NOTE: OBR, Optimised Background Regimen; ART, Antiretroviral therapy; BMD, Bone mineral Density; TDF, Tenofovir; d4T, Stavudine;

ZDV, Zidovdine; UK, United Kingdom; US, United States

^a Renal and bone adverse effects of TDF containing regimen

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Table 5 Characteristics of participants included in the studies

First author, Year [reference]	Age (years)	Male participants (%)	Ethnicity and/ race (%)	Viral Load (log10 copies/ml)	CD4 cell count (cells/ μ L)	CD4 cell percentage (%)
Randomised controlled trials						
Negra 2012 [23]	mean 14	43.60%	28.70%	4.7	mean 323.5	17.70%
Saez-Llorens 2014 [24]	mean 7	51.30%	19.70%		mean 1167	mean 33.9
Non-randomised studies and observational studies						
Hazra 2005 [9]	mean 12	61.10%	55.50%	median 5.4	median 206
Gafni 2006 [14]	mean 12	66.70%	median 5.4	median 206
Riordan 2009 [10]	median age at first prescription of TDF was 11.8	49.70%	76.10%	In the 3 months before starting TDF, 38% children had a viral load median 2.0
Purdy 2008 [15]	median 12.8	66.70%

First author, Year [reference]	Age (years)	Male participants (%)	Ethnicity and/ race (%)	Viral Load (log10 copies/ml)	CD4 cell count (cells/μL)	CD4 cell percentage (%)
Papaleo 2007 [26]	median 12.3 (No TDF), 16.0 (Continuing TDF) 15 (Stopped TDF)	46.60%	Viral load copies/mL, median 50 (No TDF); 50 (Continuing TDF); 790 (Stopped TDF)	CD4% median 28.5 (No TDF); 23.0 (Continuing TDF); 20.0 (Stopped TDF)
Pontrelli 2012 [27]	13.6 mean	42.90%	16%		mean 27.1 %
Purswani 2013 [28]	mean 11.5	46.70%	72%	78% had CD4 counts >500 cells/ μ L.
Soler-Palacín 2011 [29]	Median age was 12.5 years at the start of TDF-containing regimen	47.50%	10%
Lim 2014 [25]	median 12	44%

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Table 6 Data from case reports and/ case series

First author, Year [reference]	Age	Treatment	Outcome ^a
Costa 2012 [30]	12 years	TDF, FTC, ddI and LPV/r	Nephrogenic diabetes insipidus
Giacomet 2013 [34]	7 years	TDF, 3TC, EFV	Fanconi syndrome
Gracey 2012 [31]	17 years	TDF, FTC and LPV/r	Fanconi syndrome
Hussain 2006[12]	12 years	TDF, ddI and LPV/r	nephrogenic diabetes insipidus, renal insufficiency and Fanconi-like syndrome
Lucey 2013 [32]	17 years	TDF, FTC and LPV/r	Fanconi syndrome; osteomalacia
Bengleil 2008 [33]	12 years	TDF, FTC and LPV/r	increased alkaline phosphatase level and hypophosphataemia
	10 years	ABC, TDF, FTC and LPV/r	Osteopenia and ricketic changes
Wood 2009 [35]	16 years	TDF, FTC and LPV/r	irreversible renal failure (had underlying kidney disease)
	16 years	TDF, FTC and LPV/r	rickets with hypophosphatemia
Hawkins 2007 [13]	12 years 2 months	TDF and ddI together as part of their triple combination antiretroviral therapy	acute renal tubulopathy
	5 years 1 month	TDF and ddI together as part of their triple combination antiretroviral therapy	acute renal tubulopathy
	2 years	TDF and ddI together as part of their triple combination antiretroviral therapy	acute renal tubulopathy

NOTE: TDF, Tenofovir disoproxil fumarate; FTC, Emtricitabine; ddI, Didanosine; LPV/r, ritonavir-boosted lopinavir; 3TC, Lamivudine; EFV, Efavirenz; ABC, Abacavir.

^a Renal and bone adverse effects of TDF containing regimen

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Table 7 Analysis of pharmacovigilance data

Urinary System Disorders – SOC						
Adverse Drug Reaction-Preferred Term	Number of reports indicated for HIV infection/ AIDS			Number of reports with unclear indication		
	S	I	C	S	I	C
Nephropathy Toxic	6	0	0	0	0	0
Renal Function Abnormal	7	0	0	2	0	0
Renal Tubular Disorder	16	1	0	5	0	0
Renal Calculus	1	0	0	0	0	0
Renal Failure Chronic	3	0	1	1	0	0
Renal Failure Acute	2	0	0	2	0	0
Nocturia	1	0	0	0	0	0
Albuminuria	4	0	0	2	0	0
Diabetes Insipidus Nephrogenic	2	0	0	1	0	0
Nephritis	1	0	0	0	0	0
Creatinine Clearance Decreased	2	0	0	1	0	0
Haematuria	3	0	0	0	0	0
Polyuria	1	0	0	0	0	0
Azotemia	5	0	0	0	0	4
Urethritis	1	0	0	0	0	0
Dysuria	0	0	0	1	0	0
Micturition Frequency	0	0	0	1	1	0
Musculo-Skeletal System Disorders – SOC						
Adverse Drug Reaction-Preferred Term	Number of reports indicated for HIV infection/ AIDS			Number of reports with unclear indication		
	S	I	C	S	I	C
Bone Development Abnormal	1	0	0	0	0	0
Fracture	3	0	0	0	0	0
Osteomyelitis	0	0	2	0	0	0
Osteoporosis	3	0	0	1	0	1
Skeletal pain	3	0	0	1	0	0
Metabolic and Nutrition Disorders – SOC (Metabolic parameters related to renal and bone adverse effects)						
Adverse Drug Reaction-Preferred Term	Number of reports indicated for HIV infection/ AIDS			Number of reports with unclear indication		
	S	I	C	S	I	C
Acidosis	3	0	0	0	0	0
Acidosis Lactic	2	0	0	0	0	0
Glycosuria	4	0	0	0	0	0
Hyperkalaemia	1	0	0	0	0	1
Hypocalcaemia	2	0	0	1	0	1
Hypokalaemia	4	1	1	2	0	2
Lactate Dehydrogenase Increased	1	0	1	1	0	0
Hypophosphataemia	7	0	0	2	0	0
Osteomalacia	1	0	0	0	0	0
Phosphatase Alkaline Increased	3	0	0	0	0	0

NOTE: S, Suspect; I, Interacting; C, Concomitant

Fig. 1 PRISMA flow chart describing study selection, inclusion and exclusion processes

