HIV/AIDS Programme

TECHNICAL UPDATE ON TREATMENT OPTIMIZATION

USE OF TENOFOVIR IN HIV-INFECTED CHILDREN AND ADOLESCENTS: A PUBLIC HEALTH PERSPECTIVE

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SUMMARY

The aim of this update is to provide information and guidance to countries on how best to use tenofovir (TDF) for the treatment of children with HIV. It is intended to complement the World Health Organization (WHO) normative guidelines on antiretroviral therapy (ART) and also support the goal of increasing access to simpler paediatric antiretroviral (ARV) formulations, in line with Treatment 2.0.

TDF is recommended by WHO for use in adults and adolescents as a preferred first-line drug for the treatment of HIV infection, in combination with other ARVs. TDF is well tolerated and is available as a co-formulation with other ARVs to make dual or triple once-daily fixed-dose combinations. In this technical update, WHO has reviewed the currently available published and unpublished data on the safety, efficacy and dosing of TDF in children and adolescents.

The US Food and Drug Administration (FDA) has approved TDF for use in adolescents and children above the age of two years. The recommended dose is 8 mg/kg body weight (up to a maximum of 300 mg), administered once daily using either an oral powder formulation or low-strength tablets.

There are many potential benefits to using TDF in children – especially the ability to harmonize TDF-containing paediatric regimens with adult treatment recommendations, and the possibility of developing a once-daily paediatric fixed-dose combination. However, TDF also has potential risks. TDF toxicities have been investigated better in adults but there are some recent data from studies in children and adolescents. The main toxicities are decreases in bone mineral density (BMD), and glomerular and renal tubular dysfunction resulting in phosphaturia, hypophosphataemia and increased levels of parathyroid hormone.

The TDF product label calls for patients with a history of pathological fracture and those at risk for osteoporosis to undergo BMD testing. It also recommends assessment of creatinine clearance before treatment initiation with TDF. In resource-limited settings, routine monitoring of creatinine clearance is frequently not possible. However, long-term data suggest that routine biochemistry testing does not improve patient outcome compared with clinical monitoring alone.

When compared with population norms, HIV-infected children have lower-than-expected bone mass for their age and gender. This may be due to delays in growth, sexual maturity, time with HIV infection and disease severity. Bone turnover is higher in young children than in adults and adolescents because of skeletal growth. TDF-associated decreases in BMD correlate with young age, but also with a decline in viral load, suggesting that young virological responders may be at greater risk for loss of BMD if taking TDF. In addition, use of other ARVs, such as stavudine and protease inhibitors, especially ritonavir, is also associated with lower bone mass measurements. It is important to note that the clinical consequences of low BMD – related to either HIV or ART – remain unclear. Although bone fracture has not been observed in children treated with TDF, the impact of lower BMD on the long-term risk of osteoporosis and fracture is unknown.

A decrease in renal function, phosphaturia and hypophosphataemia occur over time in HIV-infected children and adolescents on ART. Hypophosphataemia has been identified at higher rates in children treated with TDF as compared to those treated with other ARVs. Several studies from the United Kingdom, United States and Spain have suggested significant glomerular and renal tubular toxicity attributable to TDF, but the influence of other ARVs, such as didanosine and ritonavir-boosted lopinavir, could not be eliminated. The relationship between renal dysfunction, increased levels of parathyroid hormone, hypophosphataemia and BMD decline in persons treated with TDF is complex; however, it is possible that renal phosphate loss drives an increase in parathyroid hormone levels which, in turn, may be responsible for the loss of BMD. The precise mechanism by which this occurs remains unclear and should be the topic of more research.

In summary, based on the available paediatric data and extrapolating from data in adults, TDF seems to be efficacious in children and adolescents aged 2 years to less than 18 years at the current US FDA-approved doses. The benefits of using TDF in children need to be balanced against the potential risk of toxicity. Extensive clinical experience with TDF shows that it is well tolerated in adults. Data in children are much more limited but suggest that the toxicities are similar to those seen in adult populations. Further research and long-term pharmacovigilance are warranted as TDF is rolled out in treatment programmes for children and adolescents.

INTRODUCTION

This technical update reviews the current published and unpublished data on the safety and efficacy of tenofovir disoproxil fumarate (TDF) in children and adolescents, and seeks to provide guidance to national programmes that are considering the use of TDF in paediatric patients. It is intended to complement the World Health Organization (WHO) normative guidelines on antiretroviral therapy (ART) and also support the goal of increasing access to simpler paediatric antiretroviral (ARV) formulations, in line with Treatment 2.0.[1]

TDF is an orally bioavailable prodrug of tenofovir and an acyclic nucleotide analogue. TDF was approved by the US Food and Drug Administration (FDA) in 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. TDF is recommended by WHO as one of the preferred nucleotide reverse transcriptase inhibitors (NRTIs) for first-line ART in adults as it is well tolerated, requires once-daily administration and is available as a co-formulation with other ARVs to make dual or triple fixed-dose combinations (FDCs).[2]

In March 2010, the US FDA approved TDF for use in adolescents aged 12–17 years and, in January 2012, this approval was extended to children aged 2 to less than 12 years. The FDA approved supplemental new drug applications (NDAs) for three lower-strength tablets of TDF, in doses of 150 mg, 200 mg and 250 mg, for children aged 6–12 years, and for an oral powder formulation of TDF for children aged 2–5 years.[3,4] The safety and efficacy of TDF has not been established in children less than two years of age. The FDA-recommended dose of TDF in children aged 2 to less than 12 years is 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. Currently, TDF is approved by the European Medicines Agency (EMA) for the treatment of HIV-1 infection in combination with other ARVs in persons aged 18 years and older.[5]

EFFICACY IN ADULTS

TDF is one of the most commonly used ARVs in adolescents and adults because of its potency and a favourable pharmacokinetic (PK) profile that allows it to be dosed once daily.[6,7] Early studies showed that in HIV-1 infected adults with detectable plasma HIV RNA viral load while on ART, the addition of TDF resulted in a significant decrease in viral load at week 24 compared with placebo.[8] In a double-blind study, TDF was compared to stavudine (d4T) in combination with lamivudine (3TC) and efavirenz (EFV) in 600 ARV-naive patients through 48 weeks of therapy. The results showed non-inferiority of TDF, with 76% in the TDF group and 79% in the d4T group maintaining a viral load less than 50 copies/ml.[9] In an open-label study of TDF plus emtricitabine (FTC) plus EFV versus zidovudine (AZT) plus 3TC plus EFV in 517 ARV-naive patients, the TDF arm was comparable to the AZT arm in terms of tolerability and effectiveness.[10] TDF/FTC-based regimens have comparable efficacy to abacavir (ABC)/3TC-based regimens in switch studies,[11,12] and in studies enrolling ART-naive patients.[13–15]

Dual and triple FDC tablets containing TDF combined with FTC or 3TC and EFV are commercially available, and have been approved by the US FDA and WHO. Recently, TDF-containing FDCs with rilpivirine and boosted elvitegravir have also been approved by the US FDA. Use of FDCs has been

shown to improve adherence to medication.[16] FDCs are preferred by WHO and should be prioritized by programmes to optimize and scale up ART services. Generic formulations of TDF are widely available under voluntary licensing from the originator.

RESISTANCE

Although resistance to TDF is conferred by the single-point mutation *K65R*, TDF remains active against clones of HIV which are resistant to didanosine (ddI) and AZT as well as against the multinucleoside resistance mutation *Q151M*.[17] Moreover, TDF has increased activity against HIV with the 3TC resistance mutation *M184V*.[8,18] The *K65R* mutation occurs in only 2%–3% of patients treated with TDF in combination with other ARVs, and is rare in patients not previously treated with TDF.[17]

TOXICITY

Preclinical studies have shown that the principal target organs of TDF toxicity are the gastrointestinal tract, kidneys and bone. In general, gastrointestinal side-effects are mild and transient.[7] The important clinical toxicities of TDF in adults and children include a decline in bone mineral density (BMD), renal tubular and glomerular dysfunction, increased parathyroid hormone (PTH) secretion, phosphaturia and hypophosphataemia. While fatal lactic acidosis has been reported when TDF was added to a regimen that also contained ddI, that effect was because TDF increases ddI concentrations and ddI causes significant mitochondrial toxicity. TDF itself has less effect on mitochondrial DNA than ddI or the thymidine NRTI analogues AZT and d4T.[17,19]

BONE TOXICITY

Initiation of combination ART (cART) containing TDF has been consistently associated with larger decreases in BMD than initiation of non-TDF-containing cART regimens.[6,9] In adults, BMD decreases are reported to occur relatively early during therapy, and then appear to plateau.[6,9,20] Markers of increased bone turnover, such as raised levels of bone alkaline phosphatase and C-telopeptide, have been reported in patients taking TDF.[17,21]

Although the clinical significance of these losses in BMD has not been established, a recent preliminary analysis of data from the US Veterans' Affairs clinical registry suggests that the risk of fracture is higher in those exposed to TDF. Furthermore, this risk may be increased in those using TDF and a ritonavir (RTV)-boosted protease inhibitor (PI), a combination that is known to increase TDF exposure.[22]

BONE TOXICITY IN CHILDREN

TDF-related bone toxicity has not been as well studied in children as in adults. Since children have increasing BMD over time, and BMD stays constant or declines with age in adults, a direct comparison of BMD response to TDF use is difficult across age groups.

Complicating factors include HIV infection itself and the concomitant use of other ARVs. Children and adolescents with HIV infection may have lower BMD than those without HIV infection, even when not treated with TDF.[23–25] Other NRTIs have also been implicated as potential causes of low BMD in children with HIV.[23,26,27]

Two small studies in children reported BMD decreases following TDF use. One noted an age-dependent reduction of BMD in younger participants.[28] In the second study of six children who received the 300 mg formulation of TDF, two prepubertal children experienced more than a 6% BMD decrease; the smallest child experienced a 27% decrease.[29]

In contrast, no effect of TDF on BMD was found in an Italian study of paediatric patients who were switched from d4T- and PI-containing regimens to TDF/3TC/EFV. The lack of effect on BMD seen in this study may have been because the children enrolled were older, receiving lower doses of TDF and were not taking concomitant PIs.[30,31]

While the pattern of TDF-associated changes in BMD is similar in adults and children, an industry-sponsored study of TDF in children 12 to less than 18 years of age suggested that the decline in BMD may be more prolonged in adolescents,[32] rather than reaching a plateau after 6–12 months as it does in adults.[9,21] Unpublished findings from an industry-sponsored randomized trial in younger children (aged 2 to less than 12 years) also showed a decline in BMD following initiation of TDF, but longer-term follow up till 96 weeks suggested that, as with adults, this gradually improves.[a] Increased levels of bone markers and calcium excretion imply that TDF stimulates bone reabsorption. Bone turnover is higher in young children than in older children and adolescents because of faster skeletal growth and this makes direct comparison of BMD changes in adults and children difficult. Increased bone turnover in children could possibly explain why TDF-related changes in BMD may be more marked in children than in adults.[33]

At the same time, it is important to note that data are sparse and the clinical impact of this bone toxicity is not clear. An increased fracture risk has been reported in adults treated with TDF[22] but, to date, clinical adverse events related to decreases in BMD have not been seen in children. However, it is reasonable to hypothesize that a high bone remodelling rate can decrease bone strength.[34] If disturbance of normal bone physiology during childhood or adolescence leads to low peak bone mass, there could be an increased lifetime risk of osteoporosis and fractures.[35]

a The data from this unpublished study are on file with FDA and accessed from the sponsor by WHO for the purpose of this review. This study, entitled "Safety and efficacy of switching from stavudine or zidovudine to tenofovir DF in HIV-1 infected children" is estimated to be completed in August 2014. The findings were last updated on 15 February 2012. Details available at: http://www.clinicaltrials.gov/ct2/show/NCT00528957?term=Gilead+HIV+in+children&rank=1 and http://www.gilead.com/pdf/viread_pi.pdf (Study 352, page 20).

RENAL TOXICITIES

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.[17] The TDF product label recommends assessment of creatinine clearance before initiating treatment with TDF.[36] In resource-limited settings, routine creatinine monitoring is frequently not possible. Long-term data from the DART clinical trial suggest that significant changes in the estimated glomerular filtration rate (eGFR) rarely occur in adults taking TDF and that routine biochemistry testing does not improve patient outcome compared with clinical monitoring alone.[37]

The use of TDF is associated with proximal tubular dysfunction with or without decreased renal function.[38] Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported with the use of TDF in clinical practice.[17] From case studies in France, Peyriere et al. reported proximal tubulopathy as a rare adverse effect of long-term TDF therapy, occurring more often in patients with low weight or mild, pre-existing renal impairment.[39]

Renal tubular dysfunction and tubular toxicity have been associated with increased TDF plasma concentration.[40] In patients taking TDF in addition to boosted PIs, TDF levels are increased and renal toxicity is more common. Although renal impairment is a well-described toxicity of TDF, only in a small minority of patients does it become severe enough to warrant a change in therapy. A meta-analysis of 17 studies showed that TDF use was associated with a statistically significant loss of renal function; however, the clinical magnitude of this effect was modest.[41]

RENAL TOXICITY IN CHILDREN

A decrease in renal function and hypophosphataemia occur over time in HIV-infected children and adolescents on ART.[42] Higher rates of hypophosphataemia have been identified in children treated with TDF compared to those treated with other ARVs.

In a retrospective analysis of 1253 HIV-infected children in the national cohort of HIV-infected children in the United Kingdom and Ireland, 159 children had taken TDF. TDF was effective despite the fact that under- or over-dosing occurred in more half of all cases. A small number of children (12/159) experienced serious adverse events while taking TDF; half had renal toxicity, and in all but one child this occurred in association with concurrent treatment with lopinavir–ritonavir and/or ddI.[43] Hypophosphataemia was significantly more common with recent TDF exposure, but was generally reversible if TDF was stopped.[44] Of 2102 children enrolled in the Pediatric AIDS Clinical Trials Group (PACTG) 219/219C cohort, 22% had a persistent renal abnormality and TDF use was associated with a twofold increase in the risk of renal toxicity.[45] A prospective study of 40 children less than 18 years who had received at least six months of TDF found no change in creatinine clearance, but serum phosphate levels showed a significant decrease over the duration of follow up.[46] By contrast, another study in 27 Italian children who had had two years of TDF treatment found no evidence of impaired glomerular or tubular renal function.[31,47]

The industry-sponsored trial of TDF in 2 to 12-year-olds randomized children who were well controlled on AZT or d4T to either continue that drug or switch to TDF. Their findings confirmed that TDF-associated glomerular toxicity was mild and that patterns of renal tubular dysfunction were similar to those seen in adults.[a]

TDF is associated with both renal dysfunction and increased levels of PTH;[17,48] however, the relationship between renal toxicity, PTH elevation and decreased BMD in persons treated with TDF is unclear.[49] It is possible that hypophosphataemia secondary to low tubular reabsorption of phosphate may be related to the high PTH levels associated with TDF use.[50–52]

VITAMIN D DEFICIENCY

Vitamin D deficiency is common in children and adolescents with HIV infection,[53,54] and can itself lead to low BMD and high PTH. 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.[48, 51,55,56] A randomized, double-blind, placebo-controlled trial in young adults aged 18–24 years confirmed the association of TDF use with higher PTH concentrations, and also identified vitamin D deficiency as an important covariate in baseline elevations of PTH. The authors concluded that in adolescents and young adults taking TDF, vitamin D3 supplementation decreased PTH.[51] Further studies are needed before vitamin D supplementation can be recommended as a safe and/or effective intervention for children treated with TDF.

DRUG–DRUG INTERACTIONS

Co-administration of TDF with ddI significantly increases the levels of ddI, leading to a concomitant increase in the risk of ddI-related toxicities, including pancreatitis, neuropathy, enhanced nephrotoxicity and falling CD4 cell count [19,57–60] While a reduced dose of ddI may be used, there are no data to support this strategy in children or adolescents less than 18 years of age and this combination is best avoided if possible.[7,57]

PHARMACOKINETICS AND DOSE IN CHILDREN AND ADOLESCENTS

The standard adult dose of TDF is 300 mg daily, which corresponds to 175 mg/m^2 body surface area. Children, especially younger children, may need a higher dose because of higher renal clearance than adults.[61] In a PK study by Hazra et al., the median dose used was 208 mg/m^2 body surface area, and smaller children were treated with doses of up to 300 mg/m^2 body surface area once daily.[61] Despite this, values of TDF area under the curve[b] (AUC) and C_{max} [c] were lower in children than in adult studies.

A dose of 208 mg/m^2 body surface area results in an administered milligram amount of TDF within 5% of the dose of 8 mg/kg body weight, which was used in the industry-sponsored study in children aged 2 to less than 12 years. In this study, TDF-containing cART showed non-inferiority to AZT- or d4T-containing cART over 48 weeks using a snapshot analysis.[a]

b AUC is the area under the plot of plasma concentration of drug against time after drug administration, and is useful in estimating the bioavailability of drugs, and in estimating the total clearance of drugs.

c C_{max} refers to the maximum (or peak) concentration that a drug achieves after it has been administrated and prior to the administration of a second dose.

In a previous PK study of TDF, a dose of 8 mg/kg body weight (oral powder) or 208 mg/m^2 body surface area (reduced strength tablets) elicited good virological response, with control of viral load linked to both drug exposure and baseline resistance. In addition, there was wide inter-individual variation in drug exposure for the same administered dose.[61] Confirmation of alternatives to the currently suggested doses (8 mg/kg or 208 mg/m^2) cannot be made in the absence of more data linking virological outcome to specific drug exposures. Appropriate weight-band dosing choices might best be made with the availability of more PK data from formulations that will be used in paediatric clinical practice (e.g. FDC tablets).

PHARMACODYNAMICS IN CHILDREN AND ADOLESCENTS

Pharmacodynamics (PD) links PK parameters[d] to outcomes. In this context, the outcomes of interest are therapeutic benefit (such as control of viral load) and toxicity (such as renal tubular dysfunction or change in BMD).

A study by the National Institutes of Health (NIH) enrolled 18 highly pre-treated children with a mean age of 10 years who were failing therapy after a median 9.7 years of ART. They had taken a median of 10 prior ARVs, and harboured viruses that carried multiple reverse transcriptase and protease mutations.[28] This study was able to link single-dose AUC, steady-state AUC and decrease in BMD at 24 and 48 weeks to virological outcome. These data suggest that virological response is associated with higher TDF exposure (both following a single dose and in steady state) and a decrease in BMD. Virological response can be used as a proxy variable for drug exposure and to inform the relationship between exposure and response.[33] It is possible that the decrease in BMD is due to changes in the inflammatory state associated with better control of HIV (immune reconstitution inflammatory syndrome), but the effect of differences in drug exposure on outcome remains unclear and more research is needed.

Virological response is also related to ARV resistance. In the industry-sponsored study of TDF in 12 to 18-year-olds, there was a high rate of resistance to TDF and to drugs in the optimized background regimen.[32] Even though participants in that study had a TDF AUC similar to that found in adults, only 41% had a viral load less than 400 copies/ml at week 24. In a similar heavily pre-treated study population, six of 18 participants had a viral load less than 400 copies/ml at study week 48.[28]

Adherence is another factor that may obscure PD relationships. In the same industry-sponsored trial, only 39% of the study participants maintained more than 95% adherence.[32] The NIH study, which required long-distance travel for most of its participants, may have had better adherence, perhaps adding to the ability of that study to show evidence of a PK–PD relationship even in a heavily pre-treated study group.[61] The industry-sponsored trial in children aged 2 to less than 12 years noted that adherence to the TDF powder was especially challenging.[a]

d C_{max}, AUC, C_{min}

Further PK studies in children from 2 to less than 18 years of age would be useful to confirm the most appropriate dosing and the suitability of weight-band dosing choices. Such studies would be best performed with and without boosted PIs in the background regimen, since RTV increases TDF exposure.

WHO PAEDIATRIC ARV WORKING GROUP GUIDANCE ON FUTURE DOSAGE FORMS

Based on the approval of TDF in the paediatric population, the WHO Paediatric ARV Working Group (PAWG) has developed guidance on appropriate future dosage forms for TDF-containing paediatric FDCs and a simplified weight band-based dosing schedule.[62]

Four TDF-containing formulations were suggested for development, in descending order of priority:

1. Dual TDF/3TC FDC for paediatric use – either scored adult tablet if feasible or a child-specific tablet containing TDF 75 mg and 3TC 75 mg (a 1/4 scale down of the adult tablet)

2. Triple TDF/3TC/EFV FDC for paediatric use – either scored adult tablet or a child-specific tablet containing TDF 75 mg, 3TC 75 mg and EFV 150 mg (a 1/4 scale down of the adult tablet)

3. Dual TDF/FTC FDC child-specific tablet containing TDF 75 mg and FTC 60 mg

4. Triple TDF/FTC/EFV child-specific tablet containing TDF 75 mg, FTC 60 mg and EFV 150 mg.

The content of these proposed FDCs in terms of dosage and ratios of the individual drugs were modelled using a tool to determine the appropriate dose delivered against the target dose for each component of the FDC.[63] This generic tool uses WHO weight bands in order to harmonize with current dosing recommendations.[64] The models assume an optimal target range between the target dose described for each drug and up to 25% above this dose.

All the proposed TDF- and 3TC-containing formulations (scored adult tablets and child-specific tablets) could be administered to effectively deliver target doses to children. These would also be easier and quicker for manufacturers to bring to market since the ratio of each of the drugs would remain the same as in the adult preparation.

The PAWG discussed the feasibility of scoring adult FDC tablets on both sides of the tablet in order to be able to divide them into halves and thirds. The doses delivered by third and half split tablets would be acceptable, but there was concern that in practice it may be difficult to manufacture, score and split large, multilayered FDC tablets in this way. If such tablets are manufactured, it would be important to establish feasibility, PK and bioavailability data to support this dosing strategy.

The PAWG also reviewed the efficacy and safety data from the industry-sponsored (unpublished) trial on TDF in children aged 2 to less than 12 years, in particular, information on the dose recommended and the reported renal and bone toxicities.[a] The PAWG noted that bone and renal toxicity was observed in children and stressed the importance of ongoing studies and programme surveillance of cohorts of children being treated with TDF.

CONCLUSION AND FUTURE DIRECTIONS

This technical update reviews the current published and unpublished data relating to the use of TDF in children and adolescents following the recent approval by the US FDA of TDF[3] in combination with other ARV agents for the treatment of HIV-1 infection in paediatric patients aged 2 to less than 12 years.

Based on the available data, TDF is efficacious in children and adolescents aged 2 to less than 18 years at current US FDA-approved doses. Further studies are needed to confirm the dose and investigate the side-effects of TDF in combination with EFV in children. Programme managers need to balance the benefits of using TDF in children and adolescents (such as the ability to harmonize with adult treatment, better sequencing of NRTIs in first- and second-line regimens, and the convenience of a potential once-daily FDC) against the risks of bone and renal toxicity, especially the impact of low BMD on the long-term risk of fragility fractures. At the same time, it is noteworthy that TDF is not unique in its ability to cause a reduction in BMD. HIV infection itself and many other ARV drugs also cause a decline in BMD. Furthermore, TDF is active against both HIV and the hepatitis B virus (HBV) and, for some children, including those for whom a one-pill-once-daily regimen could improve adherence, and those coinfected with HIV and HBV, the benefits of TDF outweigh the risks.

REFERENCES

1 WHO, UNAIDS. *The Treatment 2.0 framework for action: catalysing the next phase of treatment, care and support.* Geneva, WHO, 2011. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20110824_JC2208_outlook_treatment2.0_en.pdf (accessed on 10 June 2012).

2 WHO. *Antiretroviral therapy for HIV infection in adolescents and adults: recommendations for a public health approach.* Geneva, World Health Organization, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf (accessed on 02 June 2012).

3 US Food and Drug Administration. *Drugs@FDA. Viread.* Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails (accessed on 03 June 2012).

4 Gilead Sciences, Inc. *U.S. Food and Drug Administration approves new formulations of Viread® for use by children living with HIV.* Foster City, CA, Gilead Sciences, Inc., 18 January 2012. Available at: http://www.gilead.com/pr_1650180 (accessed on 03 June 2012).

5 European Medicines Agency. *Truvada (emtricitabine/tenofovir disoproxil).* Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000594/human_med_001113.jsp&mid=WC0b01ac058001d124 (accessed on 03 June 2012).

6 Lyseng-Williamson KA, Reynolds NA, Plosker GL. Tenofovir disoproxil fumarate: a review of its use in the management of HIV infection. *Drugs*, 2005, 65(3):413–432. Epub 2005/01/27.

7 Chapman TM, McGavin JK, Noble S. Tenofovir disoproxil fumarate. *Drugs*, 2003, 63(15):1597–1608.

8 Squires K et al. Tenofovir disoproxil fumarate in nucleoside-resistant HIV-1 infection: a randomized trial. [summary for patients in *Annals of Internal Medicine*, 2003, 139(5 Pt 1):I22; PMID: 12965954]. *Annals of Internal Medicine*, 2003, 139(5 Pt 1):313–320.

9 Gallant JE et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. [see comment]. *Journal of the American Medical Association*, 2004, 292(2):191–201.

10 Gallant JE et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *New England Journal of Medicine*, 2006, 354(3):251–260.

11 Martinez E et al. A simplification trial switching from nucleoside reverse transcriptase inhibitors to once-daily fixed-dose abacavir/lamivudine or tenofovir/emtricitabine in HIV-1-infected patients with virological suppression. *Journal of Acquired Immune Deficiency Syndromes*, 2009, 51(3):290–297.

12 Martin A et al. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine: a randomized, 96-week trial. *Clinical Infectious Diseases*, 2009, 49(10):1591–1601.

13 Smith KY et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS*, 2009, 23(12):1547–1556.

14 Post FA et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. *Journal of Acquired Immune Deficiency Syndromes*, 2010, 55(1):49–57.

15 Sax PE et al. Abacavir–lamivudine versus tenofovir–emtricitabine for initial HIV-1 therapy. *New England Journal of Medicine*, 2009, 361(23):2230–2240.

16 Deeks ED, Perry CM. Efavirenz/emtricitabine/tenofovir disoproxil fumarate single-tablet regimen (Atripla): a review of its use in the management of HIV infection. *Drugs*, 2010, 70(17):2315–2338.

17 Gilead. *Product monograph tenofovir disoproxil fumarate tablets 300 mg.* Foster City, CA2012, Gilead Sciences, Inc., 2012. Available at: http://www.gilead.ca/pdf/ca/viread_pm_english.pdf (accessed on 02 June 2012).

18 Miller MD et al. Antiviral activity of tenofovir (PMPA) against nucleoside-resistant clinical HIV samples. *Nucleosides Nucleotides Nucleic Acids*, 2001, 20(4–7):1025–1028.

19 Murphy MD, O'Hearn M, Chou S. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. *Clinical Infectious Diseases*, 2003, 36(8):1082–1085. Epub 2003/04/10.

20 Cassetti I et al. The safety and efficacy of tenofovir DF in combination with lamivudine and efavirenz through 6 years in antiretroviral-naive HIV-1-infected patients. *HIV Clinical Trials*, 2007, 8(3):164–167.

21 Stellbrink H-J et al. Comparison of changes in bone density and turnover with abacavir – lamivudine versus tenofovir – emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clinical Infectious Diseases*, 2010, 51(8):963–972.

22 Bedimo R et al. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. *AIDS*, 2012, 26(7):825–831.

23 Jacobson DL et al. Total body and spinal bone mineral density across Tanner stage in perinatally HIV-infected and uninfected children and youth in PACTG 1045. *AIDS*, 2010, 24(5):687–696.

24 Arpadi SM et al. Bone mineral content is lower in prepubertal HIV-infected children. *Journal of Acquired Immune Deficiency Syndromes*, 2002, 29(5):450–454.

25 Jacobson DL et al. Predictors of bone mineral density in human immunodeficiency virus-1 infected children. *Journal of Pediatric Gastroenterology and Nutrition*, 2005, 41(3):339–346.

26 Zuccotti G et al. Antiretroviral therapy and bone mineral measurements in HIV-infected adolescents. *Bone*, 2010, 46(6):1633–1638.

27 Mora S et al. Longitudinal changes of bone mineral density and metabolism in antiretroviral-treated human immunodeficiency virus-infected children. [see comment]. *Journal of Clinical Endocrinology and Metabolism*, 2004, 89(1):24–28.

28 Hazra R et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. *Pediatrics*, 2005, 116(6):e846; DOI: 10.1542/peds.2005-0975.

29 Purdy JB et al. Decreased bone mineral density with off-label use of tenofovir in children and adolescents infected with human immunodeficiency virus. *Journal of Pediatrics*, 2008, 152(4):582–584.

30 Giacomet V et al. A 12-month treatment with tenofovir does not impair bone mineral accrual in HIV-infected children. *Journal of Acquired Immune Deficiency Syndromes*, 2005, 40(4):448–450. Epub 2005/11/11.

31 Vigano A et al. Long-term renal safety of tenofovir disoproxil fumarate in vertically HIV-infected children, adolescents and young adults: a 60-month follow-up study. *Clinical Drug Investigation*, 2011, 31(6):407–415.

32 Negra MD et al. A randomized study of tenofovir disoproxil fumarate in treatment-experienced human immunodeficiency virus-1 infected adolescents. *Pediatric Infectious Disease Journal*, 2012, 31(5):469–473.

33 Gafni RI et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics*, 2006, 118(3):e711–718. Epub 2006/08/23.

34 Chavassieux P, Seeman E, Delmas PD. Insights into material and structural basis of bone fragility from diseases associated with fractures: how determinants of the biomechanical properties of bone are compromised by disease. *Endocrine Reviews*, 2007, 28(2):151–164.

35 Heaney RP et al. Peak bone mass. *Osteoporosis International*, 2000, 11(12):985–1009.

36 *Tenofovir product label*. Available at: http://www.gilead.com/pdf/viread_pi.pdf (accessed on 12 June 2012).

37 Stöhr W et al., DART Trial Team. Glomerular dysfunction and associated risk factors over 4–5 years following antiretroviral therapy initiation in Africa. *Antiviral Therapy*, 2011, 16(7):1011–1020.

38 Fernandez-Fernandez B et al. Tenofovir nephrotoxicity: 2011 update. *AIDS Research and Treatment*, 2011, (2011):354908. Epub 2011/07/01, doi:10.1155/2011/354908..

39 Peyriere H et al. Renal tubular dysfunction associated with tenofovir therapy: report of 7 cases. *Journal of Acquired Immune Deficiency Syndromes*, 2004, 35(3):269–273. Epub 2004/04/13.

40 Rodriguez-Novoa S et al. Impairment in kidney tubular function in patients receiving tenofovir is associated with higher tenofovir plasma concentrations. *AIDS*, 2010, 24(7):1064–1066. Epub 2010/03/20.

41 Cooper RD et al. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clinical Infectious Diseases*, 2010, 51(5):496–505.

42 Pontrelli G et al. Renal function in HIV-infected children and adolescents treated with tenofovir disoproxil fumarate and protease inhibitors. *BMC Infectious Diseases*, 2012, 12:18. Epub 2012/01/25, doi:10.1186/1471-2334-12-18.

43 Riordan A et al. Tenofovir use in human immunodeficiency virus-1-infected children in the United kingdom and Ireland. *Pediatric Infectious Disease Journal*, 2009, 28(3):204–209. Epub 2009/02/12.

44 Judd A et al. Effect of tenofovir disoproxil fumarate on risk of renal abnormality in HIV-1-infected children on antiretroviral therapy: a nested case–control study. *AIDS*, 2010, 24(4):525–534.

45 Andiman WAMD et al. Incidence of persistent renal dysfunction in human immunodeficiency virus-infected children: associations with the use of antiretrovirals, and other nephrotoxic medications and risk factors. *Pediatric Infectious Disease Journal,* 2009, 28(7):619–625.

46 Soler-Palacin P et al. Prospective study of renal function in HIV-infected pediatric patients receiving tenofovir-containing HAART regimens. *AIDS*, 2011, 25(2):171–176. Epub 2010/11/16.

47 Vigano A et al. Renal safety of tenofovir in HIV-infected children: a prospective, 96-week longitudinal study. *Clinical Drug Investigation*, 2007, 27(8):573–581.

48 Masiá M et al. Early changes in parathyroid hormone concentrations in patients initiating antiretroviral therapy with tenofovir. *AIDS Research and Human Retroviruses*, 2012, 28:242–246.

49 Peacock M. Primary hyperparathyroidism and the kidney: biochemical and clinical spectrum. *Journal of Bone and Mineral Research*, 2002, 17 (Suppl 2):N87–N94.

50 Domrongkitchaiporn S et al. Oral phosphate supplementation corrects hypophosphatemia and normalizes plasma FGF23 and 25-hydroxyvitamin D3 levels in women with chronic metabolic acidosis. *Experimental and Clinical Endocrinology and Diabetes*, 2010, 118(2):105–112. Epub 2009/05/19.

51 Havens PL et al. Vitamin D3 decreases parathyroid hormone in HIV-infected youth being treated with tenofovir: a randomized, placebo-controlled trial. *Clinical Infectious Diseases*, 2012, 54(7):1013–1025. Epub 2012/01/24.

52 Marks KH, Kilav R, Naveh-Many T, Silver J. Calcium, phosphate, vitamin D, and the parathyroid. *Pediatric Nephrology*, 1996, 10(3):364–367. Epub 1996/06/01.

53 Arpadi SM et al. Effect of bimonthly supplementation with oral cholecalciferol on serum 25-hydroxyvitamin D concentrations in HIV-infected children and adolescents. *Pediatrics*, 2009, 123(1):e121–e126. Epub 2009/01/02.

54 Stephensen CB et al. Vitamin D status in adolescents and young adults with HIV infection. *American Journal of Clinical Nutrition*, 2006, 83(5):1135–1141. Epub 2006/05/11.

55 Rosenvinge MM et al. Tenofovir-linked hyperparathyroidism is independently associated with the presence of vitamin D deficiency. *Journal of Acquired Immune Deficiency Syndromes*, 2010, 54(5):496–499.

56 Childs KE et al. Short communication: inadequate vitamin D exacerbates parathyroid hormone elevations in tenofovir users. *AIDS Research and Human Retroviruses*, 2010, 26(8):855–859.

57 Pecora Fulco P, Kirian MA. Effect of tenofovir on didanosine absorption in patients with HIV. *Annals of Pharmacotherapy*, 2003, 37(9):1325–1328.

58 Martinez E et al. Pancreatic toxic effects associated with co-administration of didanosine and tenofovir in HIV-infected adults. [see comment]. *Lancet*, 2004, 364(9428):65–67.

59 Rollot F et al. Tenofovir-related Fanconi syndrome with nephrogenic diabetes insipidus in a patient with acquired immunodeficiency syndrome: the role of lopinavir – ritonavir – didanosine. *Clinical Infectious Diseases*, 2003, 37(12):e174–176.

60 Negredo E et al. Unexpected CD4 cell count decline in patients receiving didanosine and tenofovir-based regimens despite undetectable viral load. *AIDS*, 2004, 18(3):459–463. Epub 2004/04/20.

61 Hazra R et al. Single-dose and steady-state pharmacokinetics of tenofovir disoproxil fumarate in human immunodeficiency virus-infected children. *Antimicrobial Agents and Chemotherapy*, 2004, 48(1):124–129.

62 WHO Paediatric Antiretroviral Working Group. *Developing dosing guidance for new and upcoming formulations of paediatric antiretrovirals in line with Treatment 2.0 priorities: meeting report.* Geneva, Switzerland, WHO, 25–26 October 2011 (in press).

63 WHO. *WHO generic tool for assessing paediatric ARV dosing*. Available at: http://www.who.int/hiv/paediatric/genericTool/en/ (accessed on 10 June 2012).

64 WHO. *Prescribing information and weight-based dosing of available ARV formulations for infants and children*. Available at: www.who.int/hiv/pub/paediatric/paediatric_arv_dosing.pdf (accessed on 10 June 2012).

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