HIV/AIDS Programme

TECHNICAL UPDATE ON TREATMENT OPTIMIZATION

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

JUNE 2012

World Health Organization

WHO Library Cataloguing-in-Publication Data

Technical update on treatment optimization: use of tenofovir disoproxil fumarate in HIV-infected children and adolescents aged 2–18 years: a public health perspective.

1.HIV infections – drug therapy. 2.Anti-HIV agents – administration and dosage. 3.Anti-HIV agents – adverse effects. 4.HIV Protease Inhibitors. 5.Child. 6.Child, Preschool. 7.Adolescent I.World Health Organization.

ISBN 978 92 4 150382 2 (NLM classification: WC 503.2)

Printed in France

Acknowledgement: This technical update was prepared by Peter Havens and Shaffiq Essajee.

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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 In this technical update, WHO has reviewed the currently available published and unpublished data on the safety, efficacy and dosing of TDF in children and adolescents.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