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Review

Tenofovir alafenamide: A novel prodrug of tenofovir for the treatment of Human Immunodeficiency Virus

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ABSTRACT

Despite substantial progress in the development of antiretroviral regimens that durably suppress Human Immunodeficiency Virus (HIV) infection, new agents that maintain high efficacy while further optimizing the safety of lifelong, chronic therapy are needed. Tenofovir alafenamide (TAF; formerly known as GS-7340) is a novel prodrug of the antiviral acyclic nucleoside phosphonate tenofovir (TFV) with improved properties relative to tenofovir disoproxil fumarate (TDF). Although potent and generally well tolerated, TDF therapy has been associated with changes in markers of renal function, decreases in bone mineral density and a rare occurrence of serious renal adverse events, including Fanconi's Syndrome. The renal and bone toxicity observed with TDF is associated with high circulating plasma levels of TFV. TAF was discovered to be a more efficient prodrug able to further refine HIV therapy and better address life-long therapy in an older and increasingly comorbid HIV infected population. By enhancing stability in biological matrices while being rapidly activated in cells, TAF produces higher levels of intracellular TFV diphosphate, the pharmacologically active metabolite, in HIV-target cells at substantially reduced oral doses of TFV equivalents. All TFV released in the body is eventually eliminated renally; therefore, lowering the TFV equivalents administered reduces off-target kidney exposure. Effective therapy is thus achieved at approximately 90% lower systemic exposure to TFV, translating to statistically and clinically significant improvement in safety parameters associated with bone mineral density and markers of renal function.

Contents

1. Introduction 64
   1.1. Frontiers in HIV therapy 64
   1.2. Tenofovir 64
   1.3. Tenofovir disoproxil fumarate 64
   1.4. Goal of this review 64
2. Tenofovir disoproxil fumarate associated toxicity 65
   2.1. Effects on bone and kidney 65
   2.2. Mechanism for tenofovir renal accumulation 65
3. Mechanism of action 65
   3.1. *In vitro* studies 65
   3.2. Nonclinical pharmacokinetics and distribution 66
4. Proof of concept 66
   4.1. Antiviral potency 66
   4.2. Efficacy 67
   4.3. Safety 67
5. Conclusion 68

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Conflicts of interest . . . 68
Acknowledgments . . . 68
References . . . 68

1. Introduction

1.1. Frontiers in HIV therapy

Highly active antiretroviral therapy (HAART) has greatly reduced morbidity and mortality in patients living with HIV (The Antiretroviral Therapy Cohort Collaboration, 2008; Kitahata et al., 2009; Mocroft et al., 1998; Palella et al., 1998). Despite the impact of HAART, mortality in successfully treated HIV infected patients remains higher than in the general uninfected population (Bhaskaran et al., 2008; Losina et al., 2009; Nakagawa et al., 2012). The effects of persistent inflammation and drug toxicity on comorbidities that are considered non-HIV related, including metabolic, cardiovascular and renal disease, contribute to these differences in the health of infected individuals. Even in the face of successful viral suppression, markers of inflammation (e.g., interleukin 6, C-reactive protein) are elevated in HIV infected patients and have been linked to an increase in type-2 diabetes and hyperlipidemia resulting in a higher prevalence of cardiovascular and kidney disease (De Wit et al., 2008; El-Sadr et al., 2006; Gupta et al., 2015a; McComsey et al., 2014; Samaras, 2012). Further, a number of the drugs used as part of HAART, particularly those associated with dyslipidemia and mitochondrial toxicity, have been found to increase the risk of non-HIV related disease (De Wit et al., 2008; Friis-Moller et al., 2003). In order to further advance therapy, new agents are needed that have minimal impact on comorbidities and maximize long-term tolerability in the context of earlier diagnosis, earlier initiation and longer duration of treatment, and older age.

1.2. Tenofovir

The anti-HIV activity of the acyclic nucleoside phosphonate tenofovir (TFV; structures of TFV and its prodrugs are presented in Fig. 1) was reported in 1993 (Balzarini et al., 1993). Subsequent studies showed that the pharmacologically active diphosphate metabolite (TFV-DP; an analog of 2′-deoxyadenosine-triphosphate) is a potent inhibitor of HIV reverse transcriptase with an inhibition constant (K_i) in biochemical assays with an RNA template of 0.022 μM (Cherrington et al., 1995), and remained active against drug resistant variants including the observation of hypersensitivity by the methionine to valine mutation at 184 (M184V) that is resistant to lamivudine and emtricitabine (Wainberg et al., 1999). Moreover, TFV-DP is an exceedingly poor substrate and inhibitor of the mitochondrial DNA polymerase γ with an incorporation efficiency 11,400-fold less than the natural substrate 2′-deoxyadenosine triphosphate and a K_i of 59.5 μM (Cherrington et al., 1995; Johnson et al., 2001). Consistent with biochemical results, TFV did not selectively deplete mitochondrial DNA when incubated with cells at up to 300 μM for up to 3 weeks *in vitro* (Birkus et al., 2002; Venhoff et al., 2007). TFV-DP also has a long intracellular half-life measured to be 150 h in peripheral blood mononuclear cells (PBMC) isolated from patients (Hawkins et al., 2005; Pruvost et al., 2005). Despite these favorable properties, TFV in parent form could never be an orally administered drug. TFV is a dianion at physiological pH and suffers from poor membrane permeability, as reflected in its poor *in vitro* anti-HIV activity in cell-based assays, and low oral bioavailability (Shaw et al., 1997).

1.3. Tenofovir disoproxil fumarate

The disoproxil prodrug was found to have substantially improved cell permeability and anti-HIV activity *in vitro* (Robbins et al., 1998), increased oral bioavailability in animals (Shaw et al., 1997), and more efficient loading of PBMC relative to parenteral TFV observed *in vivo* (Durand-Gasselin et al., 2009; Lee and Martin, 2006). Based on its improved properties, TFV disoproxil formulated as the fumarate salt (TDF) was the first selected for clinical development and was ultimately approved by the US Food and Drug Administration in 2001, the European Medicines Evaluation Agency in 2002, and was subsequently approved in other countries around the world. TDF administered at a dose of 300 mg has been used extensively (over 9 million patient years) as the preferred backbone of HIV combination therapy. Integral to the clinical success of TDF has been the low rates of discontinuations due to TFV-related viral resistance or toxicity. However, while TDF therapy is generally well tolerated it has been associated with effects on renal function and bone mineral density.

1.4. Goal of this review

Other prodrugs of TFV have been assessed in the interest of further refining long-term therapy and to allow for use in the broadest population of those infected with HIV to determine if more efficient delivery of TFV to HIV-target tissues could be achieved while reducing off-target exposure, particularly to the kidney. One of these prodrugs, tenofovir alafenamide (TAF) was selected for further study based on its favorable properties and will be the

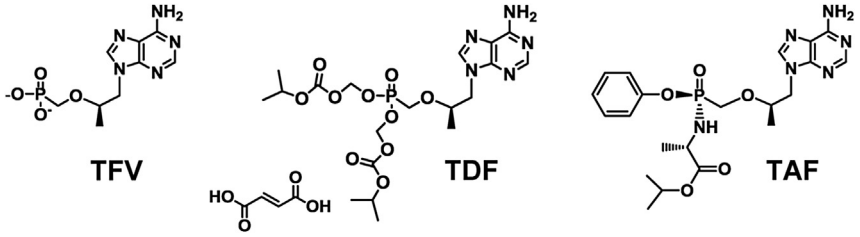

Fig. 1. Structures of acyclic nucleoside phosphonate tenofovir (TFV) and its lipophilic prodrugs tenofovir disoproxil administered as its fumarate salt (TDF) and tenofovir alafenamide (TAF).