

Tenofovir and its potential in the treatment of hepatitis B virus

Laura Reynaud
Maria Aurora Carleo
Maria Talamo
Guglielmo Borgia

Department of Public Medicine
and Social Security – Section
of Infectious Disease University
of Naples “Federico II”, Italy

Abstract: Recent literature is reviewed about treatment of chronic hepatitis B virus (CHB), focusing on tenofovir disoproxil fumarate (TDF; Viread®), among the nucleotide and nucleoside analogs. TDF pharmacokinetics and pharmacodynamics, activity in respect of hepatitis B virus (HBV) multi-drug-resistant mutations, efficacy in treatment-naïve and treatment-experienced patients, and side effects are described. The most predictive response factors to TDF therapy are discussed and all available combination therapies to optimize clinical outcome in the various patient profiles are analyzed, such as compensated and/or decompensated cirrhotic patients. The use of TDF in pregnancy, and prophylaxis after exposure to HBV and post-liver transplantation are also evaluated.

Keywords: HBV, chronic hepatitis B, tenofovir, antiviral therapy

Introduction

Hepatitis B virus (HBV) is a hepadnavirus (DNA virus) transmitted percutaneously, sexually and perinatally; despite the impressive impact of vaccination it remains a global health problem that affects 350 to 400 million persons worldwide.^{1,2}

It is estimated that hepatitis B ranks third among the causes of liver-related death annually in Italy. The burden of HBV infection in Italy has recently been further increased by a massive influx of immigrants from Europe, Africa and Asia.³

HBV integrates into the host cell genome, with the primary targets being hepatic cells; although HBV is not a retrovirus, it relies on a retroviral strategy of reverse transcription from pregenomic RNA to negative-strand DNA. It establishes covalently closed circular DNA (cccDNA) as a durable and stable miniature chromosome in the host nucleus. Like retroviruses, it is susceptible to nucleoside reverse transcriptase inhibitors (nRTIs) and nucleotide reverse transcriptase inhibitors (nRTIs). HBV can develop mutations that confer resistance.^{1,4}

Genotypic resistance is universally defined by the detection of viral populations bearing amino acid substitutions in the reverse transcriptase region of the HBV genome that confer resistance to antiviral drugs.⁵

HBV infection is a complex and heterogeneous disease that can evolve in a variety of ways, including severe liver disease: cirrhosis with portal hypertension, liver failure and hepatocellular carcinoma (HCC).²

The end points of therapy in chronic hepatitis B virus (CHB) are:

- serologic: hepatitis B e antigen (HBeAg) loss or seroconversion, usually reflecting a transition to inactive HBV carriage and, more rarely, hepatitis B surface antigen (HBsAg) loss or seroconversion, representing serologic recovery;
- virological: suppression of HBV DNA to an undetectable level or reduction in the HBV DNA level (at least 1–2 log₁₀);
- biochemical: normalization of the serum alanine aminotransferase (ALT) level;
- histological: improvement in the necroinflammatory grade and stage of fibrosis.^{1,6}

Correspondence: Laura Reynaud
Department of Public Medicine and Social
Security – Section of Infectious Disease,
University of Naples “Federico II”, Via
Sergio Pansini, 5, 80131 Naples, Italy
Tel +39 08174 63086
Fax +39 08174 63094
Email reynaud@unina.it

The HBeAg status distinguishes two categories of chronic HBV infection. HBeAg-reactive chronic HBV infection is accompanied by high-level HBV replication, and spontaneous seroconversion from HBeAg-positive to hepatitis B e antibody (HBeAb)-positive infection coincides with a reduction in HBV replication and clinical improvement. HBeAg-negative chronic HBV infection, in which precore or core-promoter gene mutations preclude or reduce the synthesis of HBeAg, accounts for an increasing proportion of cases. Patients with HBeAg-negative chronic HBV infection tend to have progressive liver injury, fluctuating ALT activity, and lower levels of HBV DNA than patients with HBeAg-reactive HBV infection; however, they cannot have treatment-induced HBeAg seroconversion, a durable response that may permit the discontinuation of antiviral therapy.

Eight HBV genotypes and differences in clinical outcomes to genotype are recognized. These differences, however, are not sufficiently established to guide management.

Successful antiviral therapy retards hepatic fibrosis, and even reverses cirrhosis and improves survival.¹

The number of medications to treat CHB continues to increase. Since 1990 many treatment options have been available: interferon (IFN) α 2a and α 2b, lamivudine (3TC/LAM), adefovir dipivoxil (ADV), entecavir, pegylated IFN α 2a (PEG-IFN), telbivudine, and more recently tenofovir disoproxil fumarate (TDF; Viread®, Gilead Sciences, Foster City, California, USA), which was licensed by the Food and Drug Administration in August 2008.^{2,5}

IFN- α therapy for 3 to 6 months is associated with loss of HBV DNA and HBeAg in 37% and 33% of patients, respectively. However, IFN- α is expensive and may be accompanied by frequent and unpleasant side effects.⁷ In HBeAg-negative patients, HBV DNA suppression is sustained after IFN therapy in a minority of patients and degrades gradually over time.¹

Treatment of HBV with LAM for HBeAg-positive chronic hepatitis shows similar results. This treatment may not completely suppress viral replication and often fails as a result of LAM resistance associated with the appearance of the substitution of methionine within the tyrosine-methionine-aspartate-aspartate (YMDD) and other mutations at the domain C of reverse transcriptase.^{1,7,8}

LAM treatment may be successful but resistance develops at the rate of 10% a year (20% a year for HIV-positive patients). LAM resistance is also successful for a while in HBeAg-positive patients.^{5,6}

Nucleotide and nucleoside analogs are effective in patients who previously did not respond to IFN, with

contra-indications to PEG-IFN and/or non-responders to this therapy; they can be used safely and effectively as salvage therapy in patients with hepatic decompensation (delaying or averting liver transplantation), and may prevent hepatic decompensation in patients with advanced fibrosis and cirrhosis. Often this kind of strategy is used for a long period, even indefinitely, which is justified because of the possibility of flares after treatment withdrawal, the better histological response associated with longer suppression of HBV DNA, and the low chance of a sustained, post-treatment response.^{1,9}

The aim of this review is to define the role of TDF in CHB therapy, with a focus on recent guidelines.

Methodology

Literature on TDF and CHB treatment was reviewed. The pertinent literature was obtained by research including the most recent articles and PubMed of the last 8 years. The following keywords were used: hepatitis B virus, chronic hepatitis B, tenofovir, antiviral therapy, interferon, liver disease. Abstracts presented at major international congresses on viral hepatitis were also reviewed.

Tenofovir and its activity against HBV

TDF is an acyclic nucleotide analog, reverse transcriptase inhibitor. As ADV, its congener, it possess a phosphonate group attached to an acyclic nucleotide moiety through a stable P-C bond.¹⁰

With this configuration it bypasses the first phosphorylation kinase step that is needed to activate various nucleoside analogs²: it needs just two, instead of three, phosphorylation steps to reach the active metabolite stage. Therefore, it does not depend on the virus-induced kinase to exert its antiviral action and may be expected to have selective activity against a broad range of DNA virus, including hepadnaviruses (as HBV) and retroviruses (as human immunodeficiency virus, HIV).¹⁰

TDF, diphosphorylated, competes with natural triphosphate deoxynucleosides for binding to the active site of HBV polymerase, and its incorporation at the end of the growing DNA terminates chain elongation. Furthermore TDF has a higher affinity for the viral DNA polymerases than for human cellular DNA polymerases α , β , γ , δ and ϵ .

According to this mechanism, TDF minimally interferes with human nuclear DNA synthesis, and this may at least partially explain its low cytotoxicity and favorable safety profile.¹⁰

TDF is currently approved for therapeutic use as the bis-alkoxyester prodrug tenofovir disoproxil fumarate. TDF is orally bioavailable, and the promoieties are cleaved during absorption to release it into systemic circulation.¹¹

In 2001, TDF was licensed for HIV therapy because it is a potent inhibitor of HIV replication, but also it has proved a potent and selective anti-HBV agent *in vitro*.²

Clinical studies then confirmed the efficacy of TDF in suppressing HBV replication. Most of the studies, based on retrospective analysis of small subsets of HIV/HBV coinfecting patients who received TDF primarily for HIV infection, demonstrated its excellent activity against HBV in both LAM-naïve and LAM-resistant patients.^{12–15}

Activity of TDF has also been observed in different series of patients with HBV mono-infection.¹²

In several studies on HBV-infected patients, the vast majority with LAM-resistant virus, TDF 300 mg once daily resulted in a reduction of 4 to 6 log₁₀ copies/mL in serum HBV DNA level from baseline over 48 weeks and in reduction of 5 log₁₀ copies/mL compared with placebo; also HBV DNA was undetectable by PCR assay in 30% to 100% of patients after more than 24 weeks treatment.^{4,6,12}

TDF, at a dose of 300 mg, is tolerated and more potent than ADV in achieving viral suppression defined as <400 copies/mL (76% vs 13%), histological improvement (67% vs 12%), and higher rates of HBsAg loss (3.2% vs 0%) at 48 weeks in patients with HBeAg-positive and HBeAg-negative CHB.^{5,16,17}

In the study of Heathcote et al all eligible HBeAg-positive subjects were randomized to receive TDF (N = 176) or ADV (N = 90) for the first 48 weeks; after 48 weeks they were either continued on TDF or switched from ADV to TDF for an additional 4 years.¹⁸ Recent 72-week data demonstrate that 79% of patients who were originally randomized to receive TDF (vs 76% of switched patients) had <400 copies/mL HBV DNA, 26% (vs 21% of switched patients) had HBeAg seroconversion and 5% (vs 0% of switched patients) had HBsAg loss. Additionally, the switch to TDF after 48 weeks of ADV therapy produced significant additional viral suppression in 78% of patients with HBV DNA levels above 400 copies/mL.^{5,18}

The same study with HBeAg-negative patients obtained similar results: 91% of patients who were originally randomized to receive TDF (vs 88% of switched patients) had HBV DNA < 400 copies/mL. Similarly the switch to TDF after 48 weeks of ADV therapy produced significant additional viral suppression in 94% of patients with HBV DNA levels above 400 copies/mL.^{5,19}

Both ADV and TDF were well tolerated, with no evidence of significant renal toxicity. Resistance surveillance through week 72 did not detect any TDF-associated mutation.^{5,18,19}

van Bömmel et al described 20 patients with chronic HBV infection who suffered a virological breakthrough (defined as a ≥ 1 log₁₀ increase in serum HBV DNA above nadir on 2 or more occasions after 1 month of therapy) during LAM therapy. This therapy was followed by an incomplete virological response (defined as a reduction in HBV DNA of less than 1 log copies/mL, a persistently high level of HBV replication, greater than 10⁶ copies/mL after 4 months, or a HBV DNA level still greater than 10⁵ copies/mL after 12 months of ADV treatment) to ADV with persistently high viral replication. These patients showed a rapid virological response with TDF dosage of 300 mg/day. The presence of YMDD had no influence on TDF efficacy.^{20,21}

Differences between TDF and ADV in intracellular phosphorylation kinetics and possibly immunoregulatory mechanisms should also be considered as responsible for the observed differences in the antiviral effects of the two drugs.

These results raise questions about the role of TDF in clearing both the replicating forms in the hepatocyte cytoplasm and the HBV cccDNA inside the nucleus, and also the possible correlation between HBV cccDNA levels and changes in aminotransferase levels or histology.

Further studies are necessary to assess the superiority of TDF over ADV in suppressing HBV replication in patients with LAM-resistant mutations.²¹

Tan et al described 5 patients with a virological breakthrough during ADV treatment in the absence of known ADV-resistant mutations, and 4 patients with a suboptimal virological response to ADV. Of these 9 patients, who were switched to TDF monotherapy, 2 had a suboptimal response while 7 had rapid virological response with undetectable serum HBV DNA within 3 to 15 months.^{20,22}

Lada et al showed, *in vitro*, the excellent efficacy of TDF on LAM-resistant virus independently of the resistance mutation profile.^{22,23}

In the study of van Bömmel et al limited to 3 patients with ADV-resistant HBV infection, although TDF monotherapy had significant antiviral efficacy in patients with ADV resistance, it could not induce complete suppression of HBV DNA in any of the three patients studied or prevent further selection of ADV-associated resistance mutations.^{22,24}

These *in vivo* observations confirm *in vitro* data that TDF has decreased antiviral activity against ADV-resistant

HBV compared to wild type virus, indicating the potential for cross-resistance.^{11,22}

In terms of antiviral activity against multi-drug-resistance mutations, *in vitro* analysis indicates that TDF is far superior to the combination of LAM and ADV, and has a marginal benefit over entecavir.²⁵

The dose of 300 mg was chosen because first studies were conducted in HBV/HIV coinfecting patients with a dosage active against HIV; ADV is approved for the treatment of CHB at the dosage of 10 mg/day.

Many authors consider this difference in the dosage between TDF and ADV as primarily responsible for the failure of ADV to confer a sustained virological response.

Published data report the possible susceptibility of HBV to lower dosage of TDF (75 mg/day). In a 2007 study 11 patients were treated with TDF 75 mg/day for a median period of 80 weeks and then 7 cases were shifted to an ADV 10 mg/day treatment group. All patients had been pre-treated with LAM: 5 had YMDD-resistant mutants and 6 wild-type virus. When TDF was started 4 patients had low-level viremia and 6 were PCR-negative. During TDF treatment, PCR remained negative in 10 patients. When TDF 75 mg was substituted with ADV 10 mg, 3 of 7 patients had a persistent viral rebound. The use of a reduced dose of TDF could have several practical implications, such as a lower cost of therapy, treatment of patients suffering from advanced stage CHB with a borderline renal function. Further studies are necessary.²⁶

In terms of liver disease status, the rapid and strong antiviral efficacy of TDF makes it an attractive rescue therapy for patients with liver cirrhosis.²⁷

Choe et al studied a group of 6 patients afflicted with HBV-related cirrhosis with resistance or non-response to ADV. These patients underwent TDF/LAM combination therapy for at least 6 months: HBV DNA levels became undetectable in all patients, ALT levels were normalized in 4 patients and the Child-Pugh scores improved in 2 of 3 patients with decompensation. The authors suggested that TDF plus LAM may be a promising rescue therapy in this kind of subject.²⁸

Two reports of 6 and 7 HIV/HBV LAM-resistant coinfecting decompensated cirrhotic patients, respectively, have also been published, supporting evidence for the role of TDF in the management of these cases. Marked clinical and laboratory improvement was shown in liver function (HBV viral suppression, HBeAg seroconversion, significant changes in albumin, prothrombin, ALT and bilirubin levels).^{29,30}

Furthermore, a recently published study by Buti et al demonstrated that TDF has good efficacy and tolerability

compared with ADV in subjects with compensated cirrhosis due to HBV.³¹

Predictors of response: genotype, ALT level and fibrosis

As a possible predicting factor for TDF therapy, HBV genotype may be considered. Different studies confirmed that genotype A has better response to therapy. Genotype A would favor HBeAg seroconversion independent of type of therapy. Stephan et al showed a 50% response rate in HBV/HIV patients coinfecting with HBV genotype A vs a 19% response rate in patients with non-A genotypes, who received a year of TDF-based antiretroviral therapy regimen. Also Jain et al demonstrate that infection with genotypes G, A/G, F and D is significantly associated with non-response.^{1,32,33}

In contrast, Lacombe et al concluded in their study that baseline HBV genomics such as genotype did not influence HBV decay; similar results had been reported previously with LAM and ADV.^{14,34,35}

Stephan et al showed that patients with high-replicative virus may benefit from TDF therapy with a reduction in replicative status while subjects with low-level HBV replication who become undetectable HBV DNA and HBsAg carriers remain DNA negative.³³

Elevated ALT levels at baseline were also associated with a more rapid HBV decay, whereas a METAVIR fibrosis score above 2 was associated with slower HBV decay. This result suggests that TDF is more efficient in patients with active inflammatory disease.¹⁴

Clearance of HBV by TDF

van der Eijk et al studied viral dynamics in the course of TDF therapy in patients with LAM-resistant HBV mutants.

The effect of antiviral therapy was evaluated by mathematical modeling: a biphasic clearance of HBV DNA has been demonstrated with an initial fast phase of viral load decline reflecting the clearance of HBV particles from plasma with a half-life of approximately 24 hours, followed by a second slower phase of viral load decline, mirroring the rate-limiting process of the loss of infected cells.^{36,37}

The duration of the first phase is <7 days, which means that the transition from the first to the second phase occurs in the first week.³⁷

The death of these cells requires a cellular immune response by the host. In HBV monoinfection a possible marker of the strength of host immune response is the level of ALT, which is an indicator of the level of cell damage and death.^{37,38}

van der Eijk et al concluded in their 2005 study that analysis of these viral kinetics can be used to calculate both the effectiveness of therapy in inhibiting viral production as well as the clearance of cells infected with HBV. They also described that after 4 weeks, treatment response was less predictable and a variety of patterns of viral decay was observed.

The authors also showed that TDF is capable of blocking viral replication with an efficacy of 0.99 in both HBV and HBV/HIV coinfecting patients with LAM-induced drug-resistant mutants, so that some low-grade viral replication remains and may present a risk for development of mutation resistance during TDF therapy.³⁷

Although the majority of patients experience a significant reduction in HBV DNA levels and a normalization of serum ALT levels, an even smaller percentage of patients seroconverts to HBeAb, and thus far seroconversion of HBsAg to hepatitis B surface antibody (HBsAb) is rare. The use of combination chemotherapy, or especially immunomodulators, which shape cytotoxic or regulatory cells of the innate and adaptive immune system during the initial period of virus infection, should accelerate the loss of HBV DNA.³⁹

HIV/HBV coinfection and TDF

The *in vivo* antiviral activity of TDF appears to be similar among patients with and without HIV coinfection.¹²

TDF is an ideal drug to treat HBV/HIV coinfecting patients.

Also, the anti-HIV activity of TDF, which ADV lacks, and its excellent tolerability in patients with advanced HIV infection, make it more attractive for patients with limited therapeutic options in which the goal of antiretroviral therapy is not necessarily to reach HIV undetectability, but to try to lower the RNA load as much as possible.^{7,8}

In coinfecting HBV/HIV patients indicated for antiretroviral therapy, regimens should include TDF in association with LAM or emtricitabine (FTC); in patients who have developed LAM- or FTC-resistant HBV, addition of TDF to antiretroviral regimen including maintenance of LAM or FTC is the preferred choice.⁴⁰

Tenofovir resistance

Typically, genotypic resistance is followed after some variable time interval by virological breakthrough, followed later by biochemical breakthrough (defined as a rise in ALT levels after achieving normalization while continuing to receive therapy) and possible clinical symptoms (significant changes in prothrombin, ALT and bilirubin levels), sometimes called clinical breakthrough.

Recently published data suggest that monotherapy, long duration of therapy and inappropriate use of antiviral drug are the most important risk factors for emergence of viral resistance.⁵

The nucleotide analogs (ADV and TDF) are associated with mutations in polymerase domains B and D.¹

Although LAM resistance is sufficiently high to limit its clinical impact, resistance to entecavir and TDF remains low.¹

Despite advances in HBV genotypic resistance testing, not all mutations can be detected at present. Therefore, genotypic testing cannot be recommended prior to initiation of therapy. Instead, patients receiving monotherapy need frequent monitoring (every 3–6 months) for emergence of resistance by checking serum HBV DNA.⁵

Once a patient develops virological breakthrough, resistance testing is paramount in identifying mutations and guiding the choice of a different agent.⁵

Patients with LAM resistance can be successfully treated by adding or switching to ADV, or by switching to entecavir, resulting in viral suppression, normalization of ALT levels and histological improvement. The current guidelines recommend adding a second drug rather than switching to a nucleotide agent to minimize the subsequent development of resistance to the new agent. Furthermore, a second drug added should be not cross-resistant with the first drug.⁵

Combination therapy is not recommended except for patients in whom drug resistance can precipitate or aggravate hepatic failure, as in decompensated cirrhosis or after liver transplantation.¹

Combination therapy with agents with differing resistance profiles should limit the emergence of resistance; however, resistance is so negligible during early treatment with entecavir or TDF that demonstrating the superiority of pre-emptive combination therapy over initial monotherapy will be challenging.¹

TDF represents an optimal choice for treatment-experienced patients, especially those with LAM resistance; however, patients with previous therapy with ADV and the presence of ADV-resistance mutations have an inferior response to TDF.⁵

van Bömmel et al reported the results of a retrospective analysis of a cohort of 127 patients (all HBV mono-infected) from 15 centers in Germany and the Netherlands. They had been treated with TDF between 2002 and 2006: 6 were treatment naïve and 121 were treatment experienced (16 LAM, 9 ADV, 72 sequential LAM and ADV, 21 add-on combination LAM and ADV, 2 entecavir and 1 sequential LAM and entecavir).

At month 12, 85% of patients had undetectable HBV DNA. Virological breakthrough was not observed. Baseline characteristics such as age, sex, liver cirrhosis, as well as HBeAg status or LAM resistance, showed no influence on response to TDF. The rates of undetectable serum HBV DNA after 12 months of TDF were 100% in those with no mutations, 92% in those with YMDD mutations and only 30% in those with ADV-resistance mutations.^{5,41}

A previous study by van Bömmel on 10 HBV monoinfected patients concluded that although TDF shows significant antiviral efficacy in patients with genotypic ADV resistance, undetectable HBV DNA is only achieved in a minority of the patients. Furthermore, ADV-resistance-associated mutations persisted during TDF treatment and required combination therapy with TDF or ADV plus LAM or entecavir.⁴²

TDF had previously demonstrated full activity against LAM-resistant HBV (YMDD, rtL180M, rtM204V) *in vitro* and clinically.^{11,25}

Since 2005 many authors have shown *in vitro* that ADV-resistance mutations (rtN236T, rtA194T, rtA181V) did not cause a significant change in TDF susceptibility, supporting its development for the treatment of CHB.^{11,18,20,25,43,44}

These data were confirmed in the reports of two patients with rtN236T, who had serum HBV DNA reductions of ≥ 4 log₁₀ copies/mL when switched from ADV to TDF therapy. TDF induces a rapid response also in patients with resistance or suboptimal response to ADV.^{11,45,46}

Until now TDF resistance has been described in only two HIV/HBV coinfecting patients, demonstrating the rtA194T mutation in addition to LAM resistance.²⁰

In vitro studies on TDF susceptibility to the rtA194T mutation demonstrate conflicting results, so its clinical significance needs to be determined. Also the two cases reported above do not represent the typical clinical pattern (CD4 count cells, HBV DNA levels, aminotransferase levels) seen in patients who develop antiviral-resistance mutations, and the surveillance for other TDF-resistance mutations should be continued.^{12,20}

The most recent literature reports sporadic observations about rtI233V mutation and rtV214A and rtQ215S variants associated with suboptimal response to TDF monotherapy: further studies are needed to clarify the clinical significance of these data.^{22,47}

Overall, HBV resistance to TDF is infrequently found during the first years on therapy, making it an attractive candidate for treatment of CHB. In a matched-controlled study no marked difference was found in antiviral efficacy of treatment with TDF after the development of LAM resistance compared

with the first-line combination therapy of TDF plus LAM during a median follow-up of about 2 years: inhibition of HBV DNA, loss of HBeAg and loss of HBsAg did not differ between the two study groups. However, differences might be seen beyond a treatment period longer than 2 years.⁴⁸

Although the authors matched for HBV DNA level at TDF initiation, this study was performed at non-comparative time-points, ie, pretreatment in the combination group and after the development of LAM resistance in the monotherapy group. To compare the efficacy of the two strategies on HBV DNA suppression over time appropriately, matching should have been performed at baseline (pre-HBV therapy) in all patients.

Therefore Matthews and Dore suggest the importance of a new randomized clinical trial analyzing pre-therapy HBV DNA levels in the two groups.⁴⁹

It has been observed *in vitro* that the use of antiviral drugs induces changes in antigenic sites of HBsAg; YMDD mutation may also provide a means for escape of HBV vaccine. Circulation of HBV encoding envelope mutations with diminished HBsAg–HBsAb binding, as a result of selection of drug-resistance mutations, may occur particularly in patients infected with HBV genotype A, the most prevalent genotype among HBV/HIV coinfecting patients. Such mutations might represent a public health concern because of the potential risk of transmission of HBV drug- and vaccine-resistant strains.^{50–52}

Thus, TDF could potentially reduce transmission of resistant HBV to both vaccinated and unvaccinated contacts.⁵⁰

TDF and entecavir represent currently the only drugs that have demonstrated a very low rate of resistance and thus are preferred for monotherapy.⁵

Nevertheless the first case of entecavir resistance in a LAM-resistant patient has already been described: entecavir was discontinued and treatment was switched to TDF, which resulted in a decline of HBV DNA below 1000 copies/mL. On the basis of therapy outcomes, TDF has proven to be a good treatment option for entecavir-resistant patients.⁵³

The future management of CHB appears to be more promising than ever before, with many therapeutic options currently available, new drugs in development, and different on-treatment strategies for optimizing the use of current agents undergoing investigation.⁵

Unfortunately, in the management of CHB, combination therapy with nucleos(t)ide analogs may be limited because they have essentially similar sites of actions, the HBV polymerase, which may make it difficult to enhance antiviral efficacy through additive or synergic effects.²⁸

Treatment strategies should, however, be focused on preventing development of resistance by suppressing viral replication as quickly and completely as possible, rather than adjustment of therapy after the emergence of resistance, thereby limiting treatment options due to cross-resistance, and allowing for development of multi-resistant HBV variants.²⁰

Adverse events

TDF is both safe and well tolerated. The most frequent adverse reactions in patients receiving TDF in clinical trials, which were not dose-related, were mild to moderate gastrointestinal events, as nausea, diarrhea, vomiting, and flatulence.^{54,55}

Laboratory abnormalities observed in these studies occurred with similar frequency in the TDF and placebo or active control groups, with the exception of lipid abnormalities, which were reported at higher frequencies in the control groups. In one study reduction in bone mineral density, but not incidence of bone fractures, was greater in the TDF group compared with the active control.⁵⁵

In terms of nephrotoxicity, several case reports have been published on the occurrence of renal insufficiency, tubular dysfunction, Fanconi's syndrome, and diabetes insipidus in HBV/HIV coinfecting patients treated with TDF. In most instances, the renal problems resolved after TDF was discontinued and were observed in patients who were receiving multiple medications, some of which may be nephrotoxic or compete for renal tubular secretion of TDF.^{6,12,56}

Nelson et al reported the results of a study on 10,343 HIV-positive patients after 4 years of treatment with TDF to analyze its possible adverse effects. The incidence of any type of serious renal adverse events was 0.5%, similar to other data reported in smaller cohorts: elevations in serum creatinine at or above grade 1 or grade 2 were observed in 2.2% and 0.6% of patients, respectively; renal failure (acute and chronic) was reported in 0.3%. Other renal events, such as nephritis and proteinuria, occurred in <0.1%. As possible risk factors for renal adverse events, sepsis/serious infection (24%), history of renal disease/baseline renal impairment (24%), late stage HIV (22%), concurrent nephrotoxic drug (19%) and hypertension (16%) were observed.⁵⁵

Other serious adverse events observed in the study of Nelson et al with an incidence <1%, included pancreatitis (0.3%), fever (0.1%), pneumonia (0.1%), lactic acidosis (0.1%), bone abnormalities (<0.1%).⁵⁵

Toxicity, as shown by peripheral neuropathy, lipodystrophy, lactic acidosis and pancreatitis, appears associated with mitochondrial dysfunction.^{10,55}

Because TDF may cause nephrotoxic effects, periodic monitoring of renal function during nucleotide therapy is advisable,^{1,6,55} but we can conclude that this drug, alone, is characterized by a relative lack of nephrotoxicity and appears an optimal drug for post-transplantation HBV prophylaxis.⁵⁷

TDF also showed in vitro an hematopoietic toxicity, compared with other antiviral molecules, superior only to LAM.⁵⁸

TDF has been assessed for its safety and efficacy in pregnant typo Rhesus monkeys. Efficient placental transport of TDF and significant reduction of viral load in simian immunodeficiency virus (SIV)-infected fetuses were shown to result in healthy newborns, although the maternal dose used (30 mg/kg/day) throughout gestation transiently affected maternal bone biomarkers and altered some fetal parameters. Further studies are necessary to determine the long term effects.¹⁰

Conclusions

CHB is a largely diffuse infectious disease, so an efficient and safe arsenal of medications is very important.

Among the nucleoside and nucleotide agents TDF may be preferable for first-line therapy and also represents a milestone. However further studies are necessary to investigate the incidence of side effects, its efficacy in the long term and to prove its potential availability in other clinical challenges.

We consider that in the near future HBV genome sequencing and phenotypic analysis, rather than empirical treatment, will critically influence clinical approach such as treatment choice, dosage and duration therapy.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Dienstag JL. Hepatitis B. virus infection. *N Engl J Med*. 2008;359(14): 1486–1500.
2. Ying C, De Clercq E, Nicholson W, Furman P, Neyts J. Inhibition of the replication of the DNA polymerase M550V mutation variant of human hepatitis B virus by adefovir, tenofovir, L-FMAU, DAPD, penciclovir and lobucavir. *J Viral Hepat*. 2000;7:161–165.
3. Carosi G, Rizzetto M. Treatment of chronic hepatitis B: recommendations from an Italian workshop. *Dig Liv Dis*. 2008;40(8):603–617.
4. Dieterich DT. Perspective – HIV and Hepatitis B virus: options for managing coinfection. International AIDS Society-USA. Topics in HIV medicine. 2003;11(1):16–19.
5. Ayoub WS, Keeffe EB. Review article: current antiviral therapy of chronic hepatitis B. *Aliment Pharmacol Ther*. 2008;28:167–177.
6. Núñez M, Puoti M, Camino N, Soriano V. Treatment of chronic hepatitis B in the human immunodeficiency virus-infected patient: present and future. *Clin Infect Dis*. 2003;37:1678–1685.

7. Risting MB, Crippin J, Aberg JA, et al. Tenofovir disoproxil fumarate therapy for chronic hepatitis B in human immunodeficiency virus/hepatitis B virus-coinfected individuals for whom interferon- α and lamivudine therapy have failed. *J Infect Dis*. 2002;186:1844–1847.
8. Núñez M, Pérez-Olmeda M, Díaz B, Ríos P, González-Lahoz J, Soriano V. Activity of tenofovir on hepatitis B virus replication in HIV-co-infected patients failing or partially responding to lamivudine. *AIDS*. 2002;16(17):2352–2354.
9. Borgia G, Gentile I. Treating chronic hepatitis B: today and tomorrow. *Curr Med Chem*. 2006;13(23):2839–2855.
10. De Clercq E. Clinical potential of the acyclic nucleoside phosphonates cidofovir, adefovir, and tenofovir in treatment of DNA virus and retrovirus infections. *Clin Microbiol Rev*. 2003;16(4):569–596.
11. Delaney WE 4th, Ray AS, Yang H, et al. Intracellular metabolism and in vitro activity of tenofovir against hepatitis B virus. *Antimicrob Agents Chemother*. 2006;50(7):2471–2477.
12. Wong SN, Lok ASF. Tenofovir disoproxil fumarate: role in hepatitis B treatment. *Hepatology*. 2006;44(2):309–313.
13. Benhamou Y, Fleury H, Trimoulet P, et al. Anti-hepatitis B virus efficacy of tenofovir disoproxil fumarate in HIV-infected patients. *Hepatology*. 2006;43:548–555.
14. Lacombe K, Gozlan J, Boelle PY, et al. Long-term hepatitis B virus dynamics in HIV-hepatitis B virus-co-infected patients treated with tenofovir disoproxil fumarate. *AIDS*. 2005;19:907–915.
15. Peters MG, Andersen J, Lynch P, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. *Hepatology*. 2006;44:1110–1116.
16. Heathcote EJ, Gane E, De Man R, et al. A randomized, double-blind, comparison of tenofovir DF (TDF) versus adefovir dipivoxil (ADV) for the treatment of HBeAg positive chronic hepatitis B (CHB): study GS-US-174–0103 [abstract]. *Hepatology*. 2007;46(4 Suppl 1):861A.
17. Marcellin P, Buti M, Krastev Z, et al. A randomized, double-blind, comparison of tenofovir DF (TDF) versus adefovir dipivoxil (ADV) for the treatment of HBeAg-negative chronic hepatitis B (CHB): study GS-US-174–0102 [abstract]. *Hepatology*. 2007;46(4 Suppl 1):290A–291A.
18. Heathcote J, George J, Gordon S, et al. Tenofovir disoproxil fumarate (TDF) for the treatment of HBeAg-positive chronic hepatitis B: week 72 TDF data and week 24 adefovir dipivoxil switch data (study 103) [abstract]. *J Hepatol*. 2008;48:S32.
19. Marcellin P, Jacobson I, Habersetzer F, et al. Tenofovir disoproxil fumarate (TDF) for the treatment of HBeAg-negative chronic hepatitis B: week 72 TDF data and week 24 adefovir dipivoxil switch data (study 102) [abstract]. *J Hepatol*. 2008;48:S26.
20. Reijnders JGP, Janssen HLA. Potency of tenofovir in chronic hepatitis B: Mono or combination therapy? *J Hepatol*. 2008;48:383–386.
21. van Bömmel F, Zöllner B, Sarrazin C, et al. Tenofovir for patients with lamivudine-resistant hepatitis B virus (HBV) infection and high HBV DNA level during adefovir therapy. *Hepatology*. 2006;44:318–325.
22. Tan J, Degertekin B, Wong SN, Husain M, Oberhelman K, Lok ASF. Tenofovir monotherapy is effective in hepatitis B patients with antiviral treatment failure to adefovir in the absence of adefovir-resistant mutations. *J Hepatol*. 2008;48:391–398.
23. Lada O, Benhamou Y, Cahour A, Katlama C, Poynard T, Thibault V. In vitro susceptibility of lamivudine-resistant hepatitis B virus to adefovir and tenofovir [abstract]. *Antivir Ther*. 2004;9(3):353–363.
24. van Bömmel F, Zöllner B, Möller B, et al. Is tenofovir effective in treatment of adefovir resistant hepatitis B virus (HBV) infections? [abstract]. *Hepatology*. 2006;44(4 Suppl 1):567A–568A.
25. Brunelle MN, Jacquard AC, Pichoud C, et al. Susceptibility to antivirals of a human HBV strain with mutations conferring resistance to both lamivudine and adefovir. *Hepatology*. 2005;41:1391–1398.
26. Del Poggio P, Zaccanelli M, Oggionni M, Colombo S, Jamoletti C, Puhalo V. Low-dose tenofovir is more potent than adefovir and is effective in controlling HBV viremia in chronic HBeAg-negative hepatitis B. *World J Gastroenterol*. 2007;13(30):4096–4099.
27. Fung SK, Andreone P, Han SH, et al. Adefovir-resistant hepatitis B can be associated with viral rebound and hepatic decompensation. *J Hepatol*. 2005;43(6):937–943.
28. Choe WH, Kwon SY, Kim BK, et al. Tenofovir plus lamivudine as rescue therapy for adefovir-resistant chronic hepatitis B in hepatitis B e antigen-positive patients with liver cirrhosis. *Liver Int*. 2008;28(6):814–820.
29. Gutiérrez S, Guillemi S, Jahnke N, Montessori V, Harrigan PR, Montaner JSG. Tenofovir-based rescue therapy for advanced liver disease in 6 patients coinfecting with HIV and Hepatitis B virus and receiving lamivudine. *Clin Infect Dis*. 2008;46:e28–e30.
30. Matthews GV, Cooper DA, Dore GJ. Improvements in parameters of end-stage liver disease in patients with HIV/HBV-related cirrhosis treated with tenofovir [abstract]. *Antivir Ther*. 2007;12(1):119–122.
31. Buti M, Hadziyannis S, Mthurin P, et al. Tenofovir disoproxil fumarate (TDF) is highly active for treatment of chronic hepatitis B in subjects with cirrhosis [abstract]. *Hepatology*. 2008;48:S33.
32. Jain MK, Comanor L, White C, et al. Treatment of hepatitis B with lamivudine and tenofovir in HIV/HBV-coinfected patients: factor associated with response. *J Viral Hepat*. 2007;14:176–182.
33. Stephan C, Berger A, Carlebach A, et al. Impact of tenofovir-containing antiretroviral therapy on chronic hepatitis B in a cohort co-infected with human immunodeficiency virus. *J Antimicrob Chemother*. 2005;56:1087–1093.
34. Nafa S, Ahmed S, Tavan D, et al. Early detection of viral resistance by determination of hepatitis B virus polymerase mutations in patients treated by lamivudine for chronic hepatitis B. *Hepatology*. 2000;32(5):1078–1088.
35. Westland C, Delaney W 4th, Yang H, et al. Hepatitis B virus genotypes and virologic response in 694 patients in phase III studies of adefovir dipivoxil. *Gastroenterology*. 2003;125(1):107–116.
36. Bruno R, Sacchi P, Zocchetti C, Ciappina V, Puoti M, Filice G. Rapid hepatitis B virus-DNA decay in co-infected HIV-hepatitis B virus “e-minus” patients with YMDD mutations after 4 weeks of tenofovir therapy. *AIDS*. 2003;17(5):783–784.
37. van der Eijk AA, Hansen BE, Niesters HGM, et al. Viral dynamics during tenofovir therapy in patients infected with lamivudine-resistant hepatitis B virus mutants. *J Clin Virol*. 2005;12:364–372.
38. de Vries-Sluijs TEMS, van der Eijk AA, Hansen BE, Osterhaus ADME, de Man RA, van der Ende ME. Wild type and YMDD variant of hepatitis B virus: No difference in viral kinetics on lamivudine/tenofovir therapy in HIV-HBV co-infected patients. *J Clin Virol*. 2006;36:60–63.
39. Blendis L. New therapies for lamivudine-resistant hepatitis B infection. *Gastroenterology*. 2005;128(5):1521–1522.
40. Massard J, Benhamou Y. Treatment of chronic hepatitis B in HIV co-infected patients [abstract]. *Gastroenterol Clin Biol*. 2008;32(1 Pt 2):S20–S24.
41. van Bömmel F, de Man RA, Stein K, et al. A multicenter analysis of antiviral response after one year of tenofovir mono-therapy in HBV-monoinfected patients with prior nucleos(t)ide analog experience [abstract]. *J Hepatol*. 2008;48:S32.
42. van Bömmel F, Trojan J, Feucht HH, et al. Tenofovir shows limited efficacy in treatment of HBV infections resistant against adefovir [abstract]. *Hepatology*. 2007;46(4 Suppl 1):664A.
43. Sheldon J, Camino N, Rodès B, et al. Selection of hepatitis B virus polymerase mutations in HIV-coinfected patients treated with tenofovir [abstract]. *Antivir Ther*. 2005;10(6):727–734.
44. Qi X, Xiong S, Yang H, Miller M, Delaney WE 4th. In vitro susceptibility of adefovir-associated hepatitis B virus polymerase mutations to other antiviral agents [abstract]. *Antivir Ther*. 2007;12(3):355–362.
45. Villeneuve JP, Willems B. Efficacy of tenofovir in patients with chronic hepatitis B and resistance or sub-optimal response to adefovir [abstract]. *Hepatology*. 2005;42:588A.
46. Ratzliff V, Thibault V, Benhamou Y, Poynard T. Successful rescue therapy with tenofovir in a patient with hepatic decompensation and adefovir resistant HBV mutant. *Comp Hepatol*. 2006;5:1–4.

47. Leemans WF, Janssen HLA, Niesters HGM, de Man RA. Switching patients with lamivudine resistant chronic hepatitis B virus from tenofovir to adefovir results in less potent HBV-DNA suppression. *J Viral Hepat*. 2008;15:108–114.
48. Schmutz G, Nelson M, Lutz T, et al. Combination of tenofovir and lamivudine versus tenofovir after lamivudine failure for therapy of hepatitis B in HIV-coinfection. *AIDS*. 2006;20:1951–1954.
49. Matthews GV, Dore GJ. Response to Schmutz et al. “Combination of tenofovir and lamivudine versus tenofovir after lamivudine failure for therapy of hepatitis B in HIV-coinfection”. *AIDS*. 2007;21(6):777–778.
50. Dore GJ, Cooper DA, Pozniak AL, et al. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naïve and -experienced patients coinfecting with HIV-1 and hepatitis B virus. *J Infect Dis*. 2004;189:1185–1192.
51. Sheldon J, Ramos B, Garcia-Samaniego J, et al. Selection of hepatitis B virus (HBV) vaccine escape mutants in HBV-infected and HBV-HIV-coinfected patients failing antiretroviral drugs with anti-HBV activity [abstract]. *J Acquir Immune Defic Syndr*. 2007;46(3):279–282.
52. Quiros-Roldan E, Calabresi A, Lapadula G, et al. Evidence of long-term suppression of hepatitis B virus DNA by tenofovir as rescue treatment in patients coinfecting with HIV [abstract]. *Antivir Ther*. 2008;13(3):341–348.
53. Leemans WF, Niesters HG, van der Eijk AA, Janssen HL, Schalm SW, de Man RA. Selection of an entecavir-resistant mutant despite prolonged hepatitis B virus DNA suppression, in a chronic hepatitis B patient with preexistent lamivudine resistance: successful rescue therapy with tenofovir [abstract]. *Eur J Gastroenterol Hepatol*. 2008;20(8):773–777.
54. van Bömmel F, Wünsche T, Schürmann D, Berg T. Tenofovir treatment in patients with lamivudine-resistant hepatitis B mutants strongly affects viral replication. *Hepatology*. 2002;36:507–508.
55. Nelson MR, Katlama C, Montaner JS, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. *AIDS*. 2007;21:1273–1281.
56. Gitman MD, Hirschwerk D, Baskin CH, Singhal PC. Tenofovir-induced kidney injury [abstract]. *Expert Opin Drug Saf*. 2007;6(2):155–164.
57. Taltavull TC, Chahri N, Verdura B, et al. Successful treatment with tenofovir in a child C cirrhotic patient with lamivudine-resistant hepatitis B virus awaiting liver transplantation. Post-transplant results. *Transpl Int*. 2005;18(7):879–883.
58. Cihlar T, Birkus G, Greenwalt DE, Hitchcock MJ. Tenofovir exhibits low cytotoxicity in various human cell types: comparison with other nucleoside reverse transcriptase inhibitors [abstract]. *Antiviral Res*. 2002;54(1):37–45.

