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PRODUCT MONOGRAPH



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A CLEAR CHOICE to help their mind be clear of Hep B

Tenfoclear™

Tenofovir Disoproxil Fumarate Tablets I.P. 300 mg

Abbreviated Prescribing Information: TENOFOVIR DISOPROXIL FUMARATE TABLETS IP 300 MG TENFOCLEAR™
COMPOSITION: Each film coated tablet contains Tenofovir Disoproxil Fumarate IP 300 mg eq. to Tenofovir Disoproxil 245 mg
INDICATION: Tenofovir Disoproxil Fumarate Tablets IP 300 mg is indicated for the treatment of chronic hepatitis B in adults and as an anti-HIV agent. **DOSAGE AND ADMINISTRATION:** Recommended Dose in Adults and Pediatric Patients 12 Years of Age and Older (35 kg or more): For the treatment of chronic hepatitis B, Tenofovir Disoproxil Fumarate should be administered orally once daily at a dose of Tenofovir Disoproxil Fumarate 300 mg (tablet) or 8 mg/kg of body weight (powder) up to a maximum dose of 300 mg was similar to exposures achieved in adults receiving once-daily doses of Tenofovir Disoproxil Fumarate 300 mg. Safety and effectiveness of Tenofovir Disoproxil Fumarate in pediatric patients younger than 12 years of age or less than 35 kg with chronic hepatitis B have not been established. Clinical trials of Tenofovir Disoproxil Fumarate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. No change in Tenofovir Disoproxil Fumarate dosing is required in patients with hepatic impairment. Dosage Adjustment for Patients with Altered Creatinine Clearance • Creatinine clearance > 50 mL/min: 300 mg every 24 hours. • Creatinine clearance 30-49 mL/min: 300 mg every 48 hours. • Creatinine clearance 10-29 mL/min: 300 mg every 72 to 96 hours. • Hemodialysis: 300 mg every 7 days or after approximately 12 hours of dialysis. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **WARNINGS AND PRECAUTION:** Lactic Acidosis/Severe Hepatomegaly with Steatosis: Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Exacerbation of Hepatitis after Discontinuation of Treatment: Patients infected with HBV who discontinue Tenofovir Disoproxil Fumarate should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. New Onset or Worsening Renal Impairment: Dosing interval adjustment of Tenofovir Disoproxil Fumarate Tablets and close monitoring of renal function are recommended in all patients with creatinine clearance below 50 mL/min. Tenofovir Disoproxil Fumarate should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)). Coadministration with Other Products: Tenofovir Disoproxil Fumarate should not be used in combination with the fixed-dose combination products where tenofovir disoproxil fumarate is a component of these products. Tenofovir Disoproxil Fumarate should not be administered in combination with adefovir dipivoxil. Patients Coinfected with HIV-1 and HBV: Due to the risk of development of HIV-1 resistance, Tenofovir Disoproxil Fumarate should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen. Mineralization Defects: Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF. Fat Redistribution, Immune Reconstitution Syndrome: During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections, which may necessitate further evaluation and treatment. Early Virologic Failure: Triple nucleoside regimens should be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification. **PREGNANCY AND LACTATION:** There are no adequate and well-controlled studies in pregnant women. It is recommended that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. **ADVERSE REACTIONS:** In HIV-infected adult subjects: Most common adverse reactions (incidence greater than or equal to 10%, Grades 2-4) are rash, diarrhea, headache, pain, depression, asthenia, and nausea. In HBV-infected subjects with compensated liver disease: most common adverse reaction (all grades) was nausea (9%). Issued on: 22nd December 2015. Source: Prepared based on full prescribing information, version 1, dated 7th December 2015. For full prescribing information, please contact: Abbott India Limited, 3-4 Corporate Park, Sion-Trombay Road, Mumbai - 400071, India.

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SECTION 1

Chronic hepatitis B

Understanding the disease and issues related to diagnosis and treatment

HEPATITIS B: CURRENT BURDEN

Hepatitis B infection is one of the leading causes of liver disease and contributes to significant morbidity and mortality. The infection is caused by a virus which belongs to the *Hepadnaviridae* family. Hepatitis B virus is a small DNA virus with unusual features similar to retroviruses. It has a spherical structure and consists of an outer lipid envelope containing the HBsAg which surrounds an inner nucleocapsid core composed of HBcAg complexed with virally encoded polymerase and the viral DNA genome.¹ Absence of proof reading ability of the hepatitis B virus along with high viral turnover rates account for its wide genetic diversity.² Hepatitis B infection has been recognized as a major public health problem globally which warrants aggressive intervention. It is the tenth leading cause of death.³ The World Health Organization (WHO) has estimated that there are more than 2 billion people infected with hepatitis B worldwide. Among them, about 360 million affected individuals have evidence of chronic liver infection and therefore are at a risk of its complications, including liver cirrhosis and hepatocellular carcinoma (Figure 1). More than 780,000 people die every year due to the acute or chronic consequences of hepatitis B.⁴

The burden of hepatitis B infection globally is estimated based on the prevalence of HBsAg. Therefore, regions across the world are categorized into those with high hepatitis B endemicity (HBsAg prevalence $\geq 8\%$), intermediate hepatitis B endemicity (HBsAg prevalence between 2–7%) or low hepatitis B endemicity (HBsAg prevalence $<2\%$). Most of South-East Asia, China, parts of the Pacific islands, the Middle East and the Amazon basin have high prevalence of hepatitis B (high endemicity regions). Parts of South Asia, including India, Central and South America, Russia, Eastern and Central Europe have intermediate prevalence of hepatitis B (intermediate

Figure 1: The burden of hepatitis B and chronic hepatitis B cases worldwide



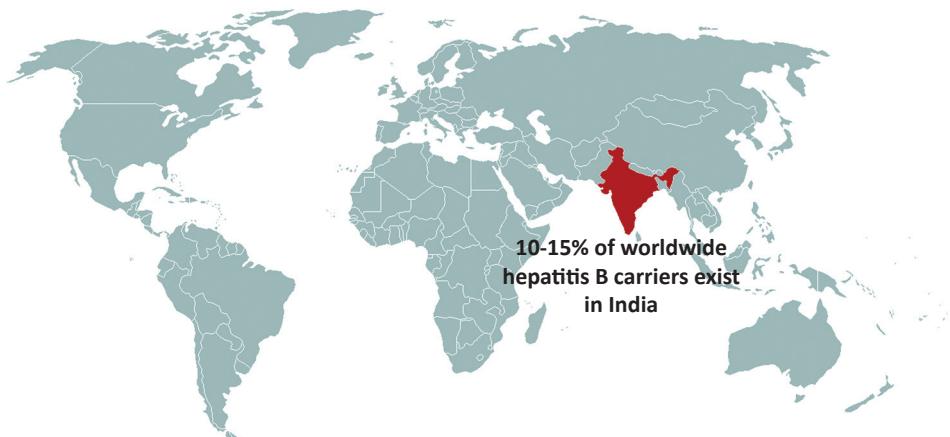
Based on information from: World Health Organization. Immunization, Vaccines and Biologicals. Available at: <http://www.who.int/immunization/topics/hepatitis/en/> [Accessed on 15/1/2016].

endemicity regions). The prevalence of hepatitis B in the United States, Australia and Western Europe is low (low endemicity regions).⁵

HEPATITIS B IN INDIA

India is an intermediate hepatitis B virus endemicity region with HBsAg prevalence between 2–10%. There are an estimated 40 million hepatitis B carriers in India alone, which constitutes 10–15% of the total pool of hepatitis B carriers globally (Figure 2). Among them, 15–25% are likely to develop liver cirrhosis and cancer and may die prematurely. Furthermore, from among the 26

Figure 2. Hepatitis B carriers in India as a percentage of worldwide carriers



Based on information from: Operational guidelines for Hepatitis B vaccine introduction in the universal immunization programme. Printed by World Health Organization on behalf of Ministry of health and family welfare, Govt of India 2011 [cited 2014 Dec 07]; Available from: http://www.searo.who.int/india/topics/routine_immunization/Operational_Guidelines_for_Hepatitis_B_vaccine_introduction_in_UIP_2011.pdf?ua=1.

million infants born in India every year, about 1 million carry life-time risk of developing chronic hepatitis B infection.⁶ The prevalence of hepatitis B is known to vary widely across the subcontinent owing to cultural and socioeconomic differences. The prevalence of hepatitis B infection appears to be significantly higher in the tribal compared to non-tribal population. Investigators from a hospital in Delhi reevaluated data from a published meta-analysis on prevalence of hepatitis B in India and showed its overall prevalence to be 3.7%. The prevalence of hepatitis B was 3.07% in non-tribal population vs. 11.85% in the tribal population.⁷ Several factors, including selected socioeconomic practices, close person-to-person contact, and compromised hygiene, are likely to be the primary underlying causes for this overwhelmingly higher occurrence of hepatitis B infection in tribal compared to non-tribal population.⁵

MODES OF TRANSMISSION AND NATURAL DISEASE PROGRESSION

Hepatitis B virus is contained in different body fluids, including blood. The infection is spread through contact with these infected body fluids. The risk of disease transmission is highest with blood; other body fluids may also transmit the disease, although less frequently. Three modes of hepatitis B transmission are recognized; perinatal (transplacental), sexual, and parenteral/percutaneous. Perinatal transmission is the transmission of hepatitis B

from an infected mother to her child during the perinatal period. It is the most important form of transmission of hepatitis B in high endemicity regions. Sexual transmission of hepatitis B is also known. Both homo- and heterosexual contact promote risk of hepatitis B infection. This is the most important mode of disease transmission in low endemicity regions. Parenteral route is also becoming an important mode of transmission of hepatitis B, especially among healthcare workers. Their most likely mode of contamination is through accidental needle stick injuries at their place of work when dealing with infected blood/fluid. Additionally, parenteral/subcutaneous route of transmission of hepatitis B is also important in injection drug users, and infection transmitted during tattooing, acupuncture, and transfusions.⁸ Initial (acute) hepatitis B infection in neonates and young children is invariably subclinical and is highly likely to progress to chronicity. In contrast to childhood infections, adult-acquired hepatitis B is usually symptomatic, although clearance of the HBsAg occurs in a large majority of the patients and therefore chronic infection only rarely develops.⁹

Chronic hepatitis B infection passes through three well-defined stages; immune-tolerant stage, immune-clearance stage, and carrier stage with or without reactivation (Table 1). Immune-tolerant stage is continuation of the acute stage of hepatitis B infection and is characterized by an essentially asymptomatic individual who is HBeAg+, has high levels of serum hepatitis B virus DNA, normal

**Table 1. Changes in serological markers in acute hepatitis B and different stages of chronic hepatitis B**

	Acute hepatitis B	Chronic hepatitis B			
		Immune-tolerant stage	Immune-clearance stage	Carrier stage	Reactivation
HBsAg	+	+	+	+	+
Anti-HBs	-	-	-	-	-
IgM anti-HBc	+	-			
HBeAg	+	+	+	-	±
Anti-HBe	-	-	±	+	+

Based on information from:

1. Liang TJ. Hepatitis B: The Virus and Disease. *Hepatology*. 2009 May; 49(5 Suppl): S13–S21.
2. Liaw Y. HBeAg seroconversion as an important end point in the treatment of chronic hepatitis B. *Hepatol Int*. 2009 September; 3(3): 425–433.

alanine aminotransferase (ALT) levels and minimal histological changes on liver biopsy. This stage may be followed by loss of immune tolerance and aggressive immune-mediated lysis of infected hepatocytes (immune-clearance stage); when this happens, patients become symptomatic, hepatitis B virus DNA level decreases and ALT level increases. The carrier stage is characterized by an essentially asymptomatic individual with seroconversion of HBeAg to anti-HBs antibody, non-detectable hepatitis B virus DNA, normal ALT and little or no evidence of hepatic injury. These patients may undergo spontaneous resolution or may have disease reactivation (either spontaneous or immunosuppression-induced) with increase in serum hepatitis B virus DNA titers, elevated ALT levels, histological evidence of liver injury with or without HBeAg seroreversion (HBeAg+ chronic hepatitis B and HBeAg- chronic hepatitis B).¹⁰

DIAGNOSIS OF HEPATITIS B

Early detection of hepatitis B infection and its appropriate management is critical to improved patient outcomes. Untreated, the disease may progress to liver cirrhosis; liver cancer may also develop. Diagnosis of the disease and its severity can be assessed by a wide range of serological, biochemical and histological markers. During acute hepatitis B infection, hepatitis B virus DNA is the first viral marker of infection to be detectable, followed shortly by gradually rising titers of HBsAg and HBeAg. Shortly after HBsAg and HBeAg become detectable and before the onset of clinical illness, anti-HBc antibodies also appear, initially IgM anti HBc appears followed by IgG anti HBc. Disappearance of HBeAg mid-way during clinical illness is followed by appearance of its corresponding antibody (anti-HBe). Anti-HBs antibodies appear late in the disease after disappearance of HBsAg. Acute hepatitis B infection is diagnosed based on the presence of IgM anti

HBc along with HBsAg. Persistence of HBsAg beyond 6 months indicates chronic infection, especially when IgM anti HBc is absent. Estimation of Hepatitis B virus DNA concentration indicates to the viral load and HBeAg assessment is a marker of infectivity.¹

Biochemical markers of liver injury, both ALT and aspartate aminotransferase (AST), are frequently assessed in patients with hepatitis B infection. Levels of AST are considered a good marker of disease activity in patients with chronic hepatitis B.¹¹ Similarly, both persistent elevation of ALT levels without flares and flares without normalization in patients with chronic hepatitis B indicates to increased risk of cirrhosis, hepatic decompensation and liver cancer compared to patients with normal ALT levels or flares in ALT concentration with intermittent normalization.¹² Patients with chronic hepatitis B having normal ALT levels have traditionally responded poorly to antiviral therapy and are therefore not considered candidates for treatment.¹³ Recent evidence, though scarce, however has emerged suggesting that normal ALT levels in patients with chronic hepatitis B may be associated with high hepatitis B virus DNA levels and significant hepatocellular injury, prompting researchers to reconsider treatment in them.¹⁴ Liver biopsy is the best method for directly visualizing hepatic inflammation and fibrosis. Although not used for securing the initial diagnosis of hepatitis B, liver biopsy is primarily indicated for grading and staging the extent of liver injury. It should be taken into consideration when deciding treatment.¹⁵

MANAGEMENT OF CHRONIC HEPATITIS B

Considerable advances have occurred in the management of chronic hepatitis B in the last few decades, although complete viral eradication continues to remain a distant goal. In light of the difficulties in completely eradicating the virus, currently available treatment options for

chronic hepatitis B aim to induce clinical, biochemical and histological improvement and prevent progression of the disease to cirrhosis, decompensation and hepatocellular carcinoma.¹⁶ Currently licensed antiviral treatment options for chronic hepatitis B virus infection include the immunomodulatory agent (interferons) and five orally administered nucleoside/nucleotide analogs. Nucleoside analogs which are being used for treating chronic hepatitis B virus infection include lamivudine, telbivudine, and entecavir; nucleotide analogs in clinical use include adefovir and tenofovir.^{16,17} Clevudine, a new nucleoside analogue, has been approved in South Korea and the Philippines for the treatment of chronic hepatitis B.¹⁶

Traditional interferons have currently been replaced with pegylated interferons. PEGylated interferon is a cytokine with a dual antiviral and immunomodulatory activity. It aims to provide an immune-mediated control of hepatitis B infection.¹⁸ Interferons have demonstrated efficacy in only a small proportion of patients with chronic hepatitis B. Moreover, their treatment is frequently associated with troublesome adverse effects which affects compliance and is a major hindrance to prolonged maintenance therapy which most patients with chronic hepatitis B require.¹⁹ Moreover, pegylated interferons are contraindicated in patients with decompensated cirrhosis secondary to chronic hepatitis B, in those with autoimmune disease, in patients on chemo- or immunosuppressive therapy, in those with uncontrolled severe depression or psychosis, and in pregnancy. Nucleoside/nucleotide analogs have a direct antiviral action and specifically inhibit the viral polymerase/reverse transcriptase enzyme, a critical enzyme in the life cycle of hepatitis B virus. These agents block the production of new virions and progressively reduce serum hepatitis B virus DNA to undetectable levels.¹⁸ Nucleoside/nucleotide analogues are more practically suitable for prolonged treatment as they are orally administered, are required to be given once-daily with good safety and efficacy potential.¹⁹ In contrast to interferons, there are no contraindications to the use of oral nucleoside/nucleotide analogs.¹⁸ Tenofovir has over the last few years emerged as one of the front-line antiviral agent for the treatment of chronic hepatitis B. Its high antiviral efficacy, favorable safety profile, and high barrier to the development of resistance renders it a treatment of choice in both treatment-naïve and treatment-experienced patients.^{20,21}

WHO SHOULD RECEIVE TREATMENT?

It is widely agreed that the decision to treat chronic hepatitis B should primarily be made keeping into consideration the levels of hepatitis B virus DNA and ALT.

In general, patients with chronic hepatitis B having high hepatitis B virus DNA and ALT levels are suitable candidates for receiving antiviral treatment.²² Several guidelines have focused on the treatment area of chronic hepatitis B; the optimal hepatitis B virus DNA and ALT cutoff values to initiate treatment, however, remain debatable in these patients.²³ The WHO in its recent 2015 guidelines for the prevention, care and treatment of persons with chronic hepatitis B²⁴ recommends the following category of patients to be suitable for receiving antiviral therapy:

1. As a priority, all adults, adolescent and children with chronic hepatitis B and clinical evidence of compensated or decompensated cirrhosis (or cirrhosis based on APRI* score > 2 in adults), irrespective of the hepatitis B virus DNA, ALT levels and HBeAg status
2. All adults (particularly those aged more than 30 years of age) with chronic hepatitis B, no clinical evidence of cirrhosis (or based on APRI* score ≤ 2 in adults), having persistently abnormal ALT levels and evidence of high-level hepatitis B virus replication (hepatitis B virus DNA >20 000 IU/mL), regardless of their HBeAg status
3. If hepatitis B virus DNA testing is not available, decision to initiate treatment may be based on persistently abnormal ALT levels alone, regardless of HBeAg status.

*APRI score - Aspartate aminotransferases-to-platelet ratio index score

The American Association for the Study of Liver Diseases (AASLD)²⁵ 2015 guidelines recommends the following category of patients with chronic hepatitis B should receive antiviral treatment:

- Chronic hepatitis B patients in the immune-active stage (HBeAg- or HBeAg+) to decrease the risk of liver-related complications
- Select group of adults > 40 years of age having normal ALT and elevated hepatitis B virus DNA ($\geq 1,000,000$ IU/mL) and liver biopsy showing significant necroinflammation or fibrosis
- Adults with compensated cirrhosis and low levels of viremia (<2,000 IU/mL) to reduce the risk of decompensation, regardless of ALT level
- HBeAg+ children (ages 2 to < 18 years) with both elevated ALT and measurable hepatitis B virus DNA levels, with the goal of achieving sustained HBeAg seroconversion
- HBsAg+ pregnant women with an hepatitis B virus DNA level >200,000 IU/mL to reduce risk of perinatal transmission of the disease.

REFERENCES

1. Liang TJ. Hepatitis B: The Virus and Disease. *Hepatology*. 2009; 49(5 Suppl): S13–S21.
2. Mohamadkhani A, Montazeri G, Poustchi H. The Importance of Hepatitis B Virus Genome Diversity in Basal Core Promoter Region. *Middle East J Dig Dis*. 2011 Mar; 3(1): 13–19.
3. Singhal V, Bora D, Singh S. Hepatitis B in Health Care Workers: Indian Scenario. *Lab Physicians*. 2009 Jul-Dec; 1(2): 41–48.
4. World Health Organization. Immunization, Vaccines and Biologicals. Available at: <http://www.who.int/immunization/topics/hepatitis/en/> [Accessed on 15/1/2016].
5. Puri P. Tackling the Hepatitis B Disease Burden in India. *Clin Exp Hepatol*. 2014 Dec; 4(4): 312–319.
6. Operational guidelines for Hepatitis B vaccine introduction in the universal immunization programme. Printed by World Health Organization on behalf of Ministry of health and family welfare, Govt of India 2011 [cited 2014 Dec 07]; Available from: http://www.searo.who.int/india/topics/routine_immunization/Operational_Guidelines_for_HepatitisB_vaccine_introduction_in UIP_2011.pdf?ua=1.
7. Batham A, Gupta MA, Rastogi P, Garg S, Sreenivas V, Puliyl JM. Calculating prevalence of hepatitis B in India: using population weights to look for publication bias in conventional meta-analysis. *Indian J Pediatr*. 2009 Dec;76(12):1247-57.
8. Hou J, Liu Z, Gu F. Epidemiology and Prevention of Hepatitis B Virus Infection. *Int J Med Sci*. 2005; 2(1): 50–57.
9. Tran TT. Immune Tolerant Hepatitis B: A Clinical Dilemma. *Gastroenterol Hepatol (N Y)*. 2011 Aug; 7(8): 511–516.
10. Pan CQ, Zhang JX. Natural History and Clinical Consequences of Hepatitis B Virus Infection. *Int J Med Sci*. 2005; 2(1): 36–40.
11. Cho SC, Lee SH, Shim JJ, Han SH, Roh BJ, Sohn JH, Lee DH, Kee CS. HBV DNA levels, aminotransferase and histological activity in young male patients with HBeAg positive chronic hepatitis B. *Taehan Kan Hakhoe Chi*. 2002 Mar;8(1):44-51.
12. Park BK, Park YN, Ahn SH, Lee KS, Chon CY, Moon YM, Park C, Han KH. Long-term outcome of chronic hepatitis B based on histological grade and stage. *J Gastroenterol Hepatol*. 2007 Mar;22(3):383–8.
13. Han K, Kim DY. Chronic HBV infection with persistently normal ALT b. not to treat. *Hepatol Int*. 2008 June; 2(2): 185–189.
14. Sarin SK, Kumar M. Should chronic HBV infected patients with normal ALT treated: debate. *Hepatol Int*. 2008 June; 2(2): 179–184.
15. Mani H, Kleiner DE. Liver biopsy findings in chronic hepatitis B. *Hepatology*. 2009 May;49(5 Suppl):S61-71.
16. Fung J, Lai CL, Seto WK, Yuen MF. Nucleoside/nucleotide analogues in the treatment of chronic hepatitis B. *J Antimicrob Chemother*. 2011 Dec;66(12):2715–25.
17. Buster EH, Schalm SW, Janssen HL. Peginterferon for the treatment of chronic hepatitis B in the era of nucleos(t)ide analogues. *Best Pract Res Clin Gastroenterol*. 2008;22(6):1093-108.
18. Santantonio TA, Fasano M. Chronic hepatitis B: Advances in treatment. *World J Hepatol*. 2014 May 27; 6(5): 284–292.
19. Dusheiko G. Treatment of HBeAg positive chronic hepatitis B: interferon or nucleoside analogues. *Liver Int*. 2013 Feb;33 Suppl 1:137-50.
20. Adusumilli S. Tenovir disoproxil fumarate for the treatment of hepatitis B infection. *Drugs Today (Barc)*. 2009 Sep;45(9):679-85.
21. Jenh AM, Thio CL, Pham PA. Tenovir for the treatment of hepatitis B virus. *Pharmacotherapy*. 2009 Oct;29(10):1212-27.
22. Morgan M, Park W, Keeffe EB. Diagnosis and treatment of chronic hepatitis B: an update. *Minerva Gastroenterol Dietol*. 2007 Mar;53(1):25-41.
23. Lau DT, Bleibl W. Current Status of Antiviral Therapy for Hepatitis B. *Therap Adv Gastroenterol*. 2008 Jul; 1(1): 61–75.
24. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. March 2015. Available at http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1.
25. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016 Jan;63(1):261-83.

SECTION 2

The solution

Tenofovir: An ‘ideal’ first-line treatment option for chronic hepatitis B

Tenofovir disoproxil fumarate (tenofovir DF) is a nucleotide analog reverse transcriptase inhibitor that has been available for the treatment of human immunodeficiency virus (HIV) since 2001. Nevertheless, as the drug effectively blocked replication of hepatitis B virus in liver cells, and also demonstrated superior efficacy than adefovir in randomized controlled trials in treatment of chronic hepatitis B virus infection, tenofovir was subsequently approved by the United States Food and Drug Administration (FDA) in 2008 for treatment of chronic hepatitis B virus infection in adults.^{1–5} Since then, tenofovir has potentially emerged as a first-line monotherapy option in treatment of hepatitis B virus in monoinfected patients, based on its potent antiviral activity, favorable safety profile, and higher barrier to development of resistance. Additionally, tenofovir monotherapy, or in combination with nucleoside analogs, is an effective option for patients who have developed resistance to other therapies for chronic hepatitis B virus, including adefovir and lamivudine. Besides, tenofovir is already a preferred agent in combination with other anti-hepatitis B virus agents (lamivudine or emtricitabine), which are cotreatments for HIV as well, in patients coinfecte

PHARMACOLOGICAL PROFILE OF TENOFOVIR

Tenofovir is available orally as tenofovir disoproxil fumarate (ester pro-drug of tenofovir), and inhibits replication of both HIV-1 and hepatitis B virus.^{2,6}

Pharmacodynamics

Mechanism of action

Tenofovir acts by inhibiting viral polymerases by direct binding, and after incorporation into DNA, by termination of the DNA chain because of absence of a requisite 3' hydroxyl on the drug molecule.⁷ In the gastrointestinal tract, tenofovir DF is hydrolyzed to tenofovir, which is phosphorylated to the active drug tenofovir diphosphate

after being taken up by the target cells. This active drug is utilized by hepatitis B virus polymerase and it competes with the nucleotide deoxyadenosine 5'-triphosphate for incorporation into the viral DNA, where it acts as a chain terminator, thereby inhibiting replication of the hepatitis B virus DNA. Of note, tenofovir diphosphate has been observed to exhibit selectivity for viral DNA polymerase over human DNA polymerase.⁶ Incidentally, incubation of the hepatic cells for 24 hours with a 10 µmol/L solution of tenofovir demonstrated that intracellular half-life ($t_{1/2}$) of tenofovir diphosphate in hepatic cells was 95 hours.⁶

Antiviral activity

Tenofovir DF has been shown to have potent activity against both HIV-1 and hepatitis B virus.⁶ In the latter cases, level of hepatitis B virus DNA at the time of switch to tenofovir is the most important factor for determining virologic response.⁵

Kinetics of virologic responses

Tenofovir treatment helps in achieving high virologic and biochemical response in both HBeAg+ and HBeAg- chronic hepatitis B virus infections. However, the rate of HBsAg loss with tenofovir could vary according to the patient's HBeAg status. Chan et al⁸ conducted an analysis to investigate HBsAg decline in different sub-populations of chronic hepatitis B initially treated with tenofovir in three late phase studies: HBeAg- chronic hepatitis B, HBeAg+ active chronic hepatitis B, and immune-tolerant chronic hepatitis B. HBsAg levels were determined (dynamic range 0.05–250 IU/mL) in 763 chronic hepatitis B patients across different sub-populations: HBeAg- [250 in tenofovir, 125 in adefovir (ADV)-tenofovir], active HBeAg+ (174 in tenofovir, 90 in ADV-tenofovir), immune-tolerant [64 and 60, respectively, in tenofovir and emtricitabine (FTC)/tenofovir]. Investigators evaluated absolute and categorical declines of HBsAg values every 24 weeks through 4 years of continuous treatment. Both univariate

and multivariate analyses were used to investigate factors predictive of HBsAg decline and ultimately of HBsAg loss. Results showed that significantly more patients with HBeAg+ active chronic hepatitis B had a ≥ 1 log IU/mL decline than patients with immune-tolerant chronic hepatitis B and HBeAg- chronic hepatitis B at week 192. In 488 subjects initially treated with tenofovir, HBsAg decline of ≥ 1 log at week 24 was the strongest predictor of HBsAg loss; overall, 6.3% (31/488) patients showed an HBsAg decline ≥ 1 log at week 24; 29/31 patients with active chronic hepatitis B were HBeAg+. A multivariate model identified ALT, HBeAg status (+ vs. -), and HBsAg level (≥ 50000 vs. < 50000 IU/mL) at baseline as the strongest factors associated with achieving the HBsAg decline ≥ 1 log at week 24. In conclusion, the results showed that different sub-populations of chronic hepatitis B demonstrate different kinetics of HBsAg reduction, with decline being highest in HBeAg+ patients and lowest in HBeAg- patients. Importantly, an HBsAg reduction of ≥ 1 log at week 24 was predictive of HBsAg loss in patients with HBeAg+ active chronic hepatitis B.

Likewise, Marcellin P et al⁹ also evaluated HBsAg kinetics in patients with and without HBsAg loss and predictors of HBsAg loss. Levels of HBsAg were quantified every 12 weeks, and a multivariable regression analysis, involving prespecified baseline characteristics and on-treatment response parameters, was performed. Results showed that among patients with HBsAg loss, 14 (61%), 1 (4%), 0 and 7 (30%) were genotypes A through D, respectively; 1 (4%) was genotype F. HBsAg loss was found to be preceded by viral suppression (hepatitis B virus DNA < 29 IU/ml; n=23) and HBeAg loss (n=19). Among treated patients, the strongest independent predictors of HBsAg loss were Caucasian race with genotype A/D and ≤ 4 years of infection and an HBsAg decline of ≥ 1 log₁₀ IU/ml at week 24. Among tenofovir-treated patients, a reduction in HBsAg level of ≥ 1 -log₁₀ by week 12 or 24 was found to have a positive predictive value (PPV) of 35%-45%, respectively, and a negative predictive value (NPV) of 94%-97%, respectively. The study thus suggested that the loss of HBsAg in HBeAg+ patients receiving tenofovir involves a chronology of virologic and serologic responses; HBsAg loss is more likely in patients with hepatitis B virus genotypes A or D and a rapid early decline in HBsAg.⁹

Pharmacokinetics

Tenofovir DF is the prodrug of tenofovir, the active moiety, which undergoes phosphorylation inside the cells. After oral administration, the prodrug is rapidly absorbed and converted to the active moiety. Data on pharmacokinetics of oral tenofovir DF in patients with chronic hepatitis B is limited, and it is mostly derived from information in

patients with HIV-1 infection.⁶ In this latter cohort, the oral bioavailability of tenofovir was found to be ~25% in fasted individuals or after a light meal and ~39% after a high-fat (40-50% fat) meal. It has been observed that the pharmacokinetics of tenofovir is dose proportional over the dose range 75-600mg; values remain unaffected after multiple doses of 300mg once daily in the fed state (mean Cmax 326 ng/mL, and minimum serum concentration 64.4 ng/mL).⁶

In-vitro plasma and serum protein binding of tenofovir was found to be <0.7% and <7.2% over a concentration range of 0.01-25 mg/L. Following intravenous (IV) administration, steady-state volume of distribution of tenofovir was 800mL/kg.⁶

Tenofovir is eliminated largely unchanged by kidneys; 70-80% of the dose is recovered unchanged in the urine up to 72 hours after administration. The terminal elimination half-life ($t_{1/2}$) of tenofovir has been reported to be about 12-18 hours (and ~17 hours).⁶

Dosage adjustment for tenofovir is required for patients with renal impairment, but not for those with impaired hepatic function.⁶ Drug interactions mediated via CYP450 enzymes are minimal with tenofovir.

Variations in pharmacokinetics of tenofovir can be seen in different populations. Lu C et al¹⁰ evaluated the pharmacokinetic properties and food interaction of tenofovir in healthy Chinese volunteers, and demonstrated that:

- After a single dose of 150, 300 and 600 mg, the main pharmacokinetic parameters for tenofovir were as follows: Cmax 209·6, 456·7, 989·8 ng/mL; AUClast 1744·9, 2663·5, 6010·2 ng h/mL, respectively.
- After multiple doses of 300 mg, the main pharmacokinetic parameters for tenofovir were Cmax 523·4 ng/mL, AUClast 4152·4 ng h/mL.
- After a single dose of 300 mg with a high-fat and high-energy standard breakfast, the main pharmacokinetic parameters for tenofovir were Cmax 448·5 ng/mL, AUClast 3286·8 ng h/mL.
- The plasma Cmax and AUC of tenofovir showed significant difference between a single dose of 300 mg and the accordingly multiple doses.
- A standard high-fat meal was found to enhance the mean AUClast values of tenofovir; however, food did not show any significance on Cmax.

The authors thus concluded that oral tenofovir DF produces predictable and dose-proportional plasma tenofovir pharmacokinetics. The accumulation ratio was 1·51, suggesting that the drug displayed accumulation after repeated administration. When taken with food, the bioavailability of tenofovir DF was increased by ~25%, as

measured by AUClast after a single dose, compared with fasting.¹⁰

Concurrently, another open-label, single- and multiple-dose study aimed to investigate the pharmacokinetic properties and tolerability of tenofovir in healthy Chinese subjects.¹¹ Subjects received tenofovir 300 mg once daily, administered as a single dose (day 1) and multiple doses (days 4-10), followed by collection of multiple plasma samples over time, and determination of tenofovir concentrations. The study enrolled 14 volunteers (7 men, 7 women; mean age, 24.6 years). Results showed that tenofovir was rapidly absorbed; median Tmax was 0.75 hour, and $t_{1/2}$ was ~21 hours with single dosing. The mean ratio of AUC0-t steady state/AUC0-24 single dose was 1.55. The pharmacokinetic properties of tenofovir were observed to be consistent between the single dose and multiple doses, and between men and women. The study thus showed that there was an accumulation of approximately 55% in tenofovir exposure in healthy Chinese between multiple dose and single dose. Importantly, tenofovir exhibited a pharmacokinetic profile similar to that of healthy Western subjects in a historical comparison.

DOSAGE AND ADMINISTRATION⁶

- Route of administration: Oral
- Recommended dosage: 300 mg once daily

Renal function (sodium phosphate and creatinine clearance) should be monitored every 4 weeks during the first year of treatment and every 3 months thereafter; more frequent renal function monitoring should be considered for patients at risk of renal impairment.⁶

CLINICAL PROFILE OF TENOFOVIR

With its potent anti-viral activity, favorable resistance profile, and demonstrated efficacy as rescue regimen, tenofovir indeed has the makings of an “ideal” first-line drug for the treatment of chronic hepatitis B.¹² The drug has repeatedly demonstrated sustained viral suppression, no resistance, and good safety in chronic hepatitis B patients.

EFFICACY OF TENOFOVIR IN DIFFERENT SUBPOPULATIONS AND SETTINGS

Tenofovir has shown excellent treatment efficacy in treatment-naïve as well as nucleos(t)ide analogues-experienced patients in various studies.⁵ In chronic hepatitis B, its efficacy against hepatitis B virus was evaluated in two large randomized, phase 3 clinical studies in HBeAg- or HBeAg+ adults, with compensated liver function. The trials (planned duration of eight years) were double-blind for the first 48 weeks; and then patients could

receive open-label tenofovir. Later, multiple subgroup analyses potentiated the clinical profile and use of tenofovir across diverse settings and outcomes. More importantly, evidence in real life setting also show that tenofovir can be used safely and successfully in those patients that were naïve, experienced with immune modulators and/or antivirals, HBeAg-, and HBeAg+ patients. The proposition has been validated in a recent retrospective analysis, which evaluated effectiveness of tenofovir in patients with chronic hepatitis B infection in a real life setting by analyzing data from 164 chronic hepatitis B patients who were treated with tenofovir. Among the 164 patients with chronic hepatitis B, 86 patients (52.4%) were naïve, 77 (46.9%) patients were previously treated with anti-viral drugs, including standard interferon (n=4), pegylated (PEG) interferon (n=14), standard interferon together with lamivudine (n=13), lamivudine alone (n=41), adefovir (n=2), lamivudine together with adefovir (n=1), and entecavir (n=2). Six patients (3.7%) had liver cirrhosis prior to treatment with tenofovir.¹³ Chronic hepatitis B patients who had hepatitis B virus DNA >104 copy/mL were included in the tenofovir treatment, with average follow up time of 30.31 ± 14.33 months. Results showed that hepatitis B virus DNA suppression gradually increased from 70.6%-89% with treatment of tenofovir from a period of 6 to 24 months; hepatitis B virus DNA negativity continued to plateau up to the 36th month and was 86.5% at the last visit (Table 1). Concurrent improvement in ALT levels was seen in patients. ALT levels, which were 103.52 ± 126.67 IU at baseline, were reduced to normal in 70.2% of patients after 6 months of treatment with tenofovir, and remained so until the last visit in 71.3% of the patients (Table 1). HBeAg seroconversion occurred in 11/164 (19.6%) patients. During follow-up, four (2.4%) patients developed liver

Table 1. Hepatitis B virus DNA negativity and ALT normalization from 6 months to final visit

Follow-up	Negativity of hepatitis B virus DNA	Normalization of ALT
6 months	70.6%	70.2%
12 months	78.9%	68%
24 months	88.9%	73.75%
36 months	89%	71.6%
Final visit (Average follow up time: 30.31 ± 14.33 months)	86.5%	71.3%

Based on information from: Örmeci N, Özbaş B, Güner R, Özkan H, Yalçın A, Çoban Ş, Dökmeci A, Kalkan Ç, Akinci H, Yüksel O, Başar Ö, Yüksel İ, Balık İ. Tenofovir-best hope for treatment of chronic hepatitis B infection? *Turk J Gastroenterol.* 2015 Jul;26(4):322-7.

cirrhosis and five (3%) patients developed hepatocellular carcinoma (HCC). HBsAg seroconversion was seen in one patient (0.6%). Based on study results, the authors thus inferred that tenofovir can be used safely and successfully in diverse subgroups of patients with chronic hepatitis B infection in actual life settings, including those who are naïve, experienced with immune modulators and/or antivirals, and both HBeAg+ and HBeAg- patients. There was no statistical difference between the two groups, naïve and treatment experienced with immune modulators and/or antivirals, in terms of sustained virological response and ALT normalization after treatment with tenofovir. Likewise, there was no statistical difference in terms of sustained virological response in patients with or without HBeAg seroconversion at 6 months; normalization of ALT levels and the negativity rate of hepatitis B virus DNA were however found to be higher in patients with seroconversion of HBeAg than in patients without HBeAg seroconversion.

Long-term efficacy in patients with high baseline viral load

Chronic hepatitis B patients with high pretreatment viral load represent a clinical challenge because higher levels of hepatitis B virus DNA are associated with an increased risk for cirrhosis and HCC, and could affect virologic response to treatment. Gordon et al³ evaluated the antiviral response of patients with chronic hepatitis B who had baseline high viral load (defined as having hepatitis B virus DNA $\geq 9 \log_{10}$ copies/mL), after 240 weeks (5 years) of tenofovir DF treatment. A total of 641 HBeAg- and HBeAg+ patients (129 with high viral load) received 48 weeks of tenofovir 300 mg (high viral load n=82) or adefovir dipivoxil

Table 2. Week 240 on-treatment clinical characteristics

Characteristics	HVL [†] (%)	Non-HVL [†] (%)
ALT normalization	69.5	83.5
HBsAg loss [§]	19.3	4.3
HBsAg seroconversion [§]	13.6	4.3
HBeAg loss [§]	48.9	57.7
HBeAg seroconversion [§]	38.3	47.9
Cirrhosis (Ishak 5/6)	2.1	9.5
Persistent viremia [#]	0	0

[†]Excludes patients who added emtricitabine.

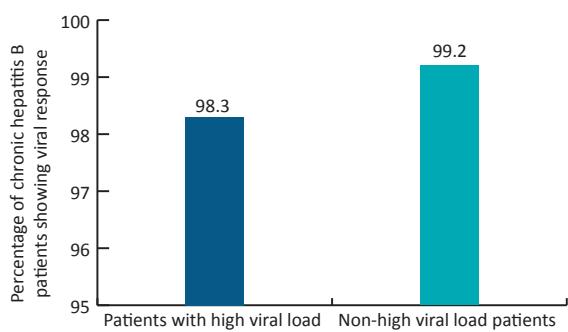
[‡]High viral load (HVL), pretreatment hepatitis B virus DNA $9 \log_{10}$ copies/mL. Non-HVL, pretreatment hepatitis B virus DNA $<9 \log_{10}$ copies/mL.

[§]For patients HBeAg+ at baseline.

[#]Persistent viremia defined as never having hepatitis B virus DNA <400 copies/mL.

Based on information from: Gordon SC, Krastev Z, Horban A, Petersen J, Sperl J, Dinh P, Martins EB, Yee LJ, Flaherty JF, Kittrinos KM, Rustgi VK, Marcellin P. Efficacy of Tenofovir Disoproxil Fumarate at 240 Weeks in Patients With Chronic Hepatitis B With High Baseline Viral Load. *Hepatology* 2013;58:505-513.

Figure 1. Percentage of chronic hepatitis B patients showing high viral response by week 240



Based on information from: Gordon SC, Krastev Z, Horban A, Petersen J, Sperl J, Dinh P, Martins EB, Yee LJ, Flaherty JF, Kittrinos KM, Rustgi VK, Marcellin P. Efficacy of Tenofovir Disoproxil Fumarate at 240 Weeks in Patients With Chronic Hepatitis B With High Baseline Viral Load. *Hepatology* 2013;58:505-513.

(ADV) 10 mg (high viral load n=47), followed by open-label tenofovir for an additional 192 weeks. Patients with confirmed hepatitis B virus DNA ≥ 400 copies/mL on or after week 72 were free to add emtricitabine (FTC). The results showed that by week 240, 98.3% of patients with high viral load and 99.2% of non-high viral load patients on treatment achieved hepatitis B virus DNA <400 copies/mL (Figure 1), thus showing high viral response. Between baseline and week 240, rates of histologic regression were similar in both the groups. Although patients with high viral load in general took longer to achieve hepatitis B virus DNA <400 copies/mL than non-high viral load patients, the percentages of patients with hepatitis B virus DNA <400 copies/mL were largely similar in both groups by week 96. Among patients HBeAg+ at baseline, HBsAg loss was higher among those with high viral load, compared with non-high viral load patients; 19.3% among those with high viral load and 4.3% in the non-high viral load group (Table 2). Anti-HBsAg seroconversion also demonstrated a similar pattern, being 13.6% among patients with high viral load and 4.3% among non-high viral load patients. Furthermore, among patients with high viral load, time to achieve hepatitis B virus DNA <400 copies/mL was shorter among those who initially received tenofovir, compared to ADV. No patient with baseline high viral load was found to have persistent viremia at week 240 or amino acid substitutions associated with resistance to tenofovir. The findings thus clearly showed that patients with high viral load could achieve hepatitis B virus DNA negativity with long-term treatment with tenofovir. Long-term tenofovir monotherapy can thus lead to virologic suppression in vast majority of chronic hepatitis B patients with high viral

load, irrespective of the HBeAg status. Time to hepatitis B virus DNA <400 copies/mL might be longer in patients with high viral load at baseline, compared to those with non-high viral load, but high viral load should not be a deterrent for treatment, seeing that tenofovir was highly efficacious in patients with high baseline hepatitis B virus load $\geq 9 \log_{10}$ copies/mL. The treatment resulted in >95% of patients achieving hepatitis B virus DNA <400 copies/mL, high rates of HBeAg and HBsAg loss, without any observable resistance to the drug.¹⁴

Tenofovir in treatment naïve cases

There are few studies in literature evaluating the long-term efficacy and tolerability of tenofovir in nucleosid(t)e -naïve HBeAg+ chronic hepatitis B patients, compared to studies reporting its effectiveness for treatment of patients with drug-resistant hepatitis B virus, and those with HIV-1 and hepatitis B virus coinfection. Recently, a multicenter study aimed to retrospectively provide 96 week long-term efficacy and safety data with tenofovir treatment in nucleosid(t)e-naïve HBeAg+ chronic hepatitis B patients.⁷ Thirty-one patients (20 males, 11 females; age range, 20-59 years; mean age, 37.6 ± 9.4 years), with initial serum hepatitis B virus DNA levels >2,000 IU/ml, and who had never taken nucleosid(t)e treatment, received 245 mg tenofovir DF per diem and were followed for 96 weeks. Evaluation of serum ALT levels, HBeAg, hepatitis B e antibodies (anti-HBe), HBsAg, hepatitis B surface antibodies (Anti-HBs), hepatitis B virus DNA, creatinine and urea levels was done at baseline, and then at weeks 12, 24, 48 and 96 of therapy. All patients completed 96 weeks of treatment. The findings revealed that the initial mean value of ALT was 79 ± 39.9 IU/L, and at baseline, mean of fibrosis (Ishak) of liver biopsies was 2.3 ± 0.7 . At 12 weeks of the treatment, two (5.9%) patients achieved hepatitis B virus DNA<300 copy, and this rate increased to 97.1% at week 96. HBeAg loss was observed in 6.7% of patients at week 96, though HBsAg loss was not observed in any of the patients. Mean ALT at week 48 was 32.7 IU/L, and was 32.6 IU/L at week 96. Furthermore, safety, including renal function, was good, with creatinine remaining stable through week 96. Thus, tenofovir DF produced potent, continuous viral suppression with increasing HBeAg loss and was well-tolerated in nucleosid(t)e-naïve HBeAg+ chronic hepatitis B patients.⁷

Tenofovir in cirrhotic vs. non-cirrhotic patients

It has been repeatedly shown that suppression of chronic hepatitis B with tenofovir improves transaminases, results in regression of liver fibrosis and increases rate of HBeAg seroconversion. In the current study, Sievert et al¹⁵ described long-term clinical outcomes for subset of cirrhotic patients enrolled in two pivotal trials of tenofovir in comparison

Table 3. Year 5 comparison: Cirrhotic vs. non-cirrhotic patients

Characteristics	Baseline cirrhosis (n = 152)	Baseline non-cirrhosis (n = 482)
Hepatitis B virus DNA <400 copies/mL	99%	98%
ALT < ULN	80%	82%
HBeAg loss	62%	45%
HBsAg loss	2%	3%
Mean increase in platelets ($\times 10^3$)	31	20
Mean increase in albumin (g/dL)	0.27	0.1
Fibrosis: regression	74%	42%
Fibrosis: no change	25%	54%
Fibrosis: worsening	1%	1%

Based on information from: Sievert W, Strasser S, Gane E, George J, Weilert F, Elsome AM, Flaherty JF, Martins E, Bekele N, Bornstein JB, Buti M, Marcellin P. Clinical, virological, serological and histological outcomes in cirrhotic patients with chronic hepatitis B (CHB) treated with tenofovir disoproxil fumarate (TDF) for up to 5 years. *Journal of Gastroenterology and Hepatology* 2012; 27(Suppl. 4): 161-182.

with non-cirrhotic patients. The authors performed a retrospective analysis of these trials of tenofovir to assess whether clinical outcomes differed between cirrhotic and non-cirrhotic patients. In these studies, efficacy and safety of tenofovir vs. adefovir was assessed for 48 weeks in HBeAg- and HBeAg+ patients, followed by open-label tenofovir treatment. Overall, the analysis included a total of 634 subjects. The results showed that despite variations in baseline characteristics, outcomes were comparable between patients with and without cirrhosis (Table 3). No cases of hepatic encephalopathy or variceal bleeding were detected in either group, while ascites occurred in one non-cirrhotic patient with HCC. The incidence of HCC was 3.3% in cirrhotics and 1.5% in non-cirrhotics. In conclusion, cirrhotic patients differed from non-cirrhotic subjects at baseline, but demonstrated significant treatment benefits, with 74% experiencing regression of cirrhosis. Cirrhotic patients treated with tenofovir were able to achieve similar rates of viral suppression and serological responses as non-cirrhotics, and derived comparable clinical benefit after 5 years of viral suppression. Furthermore, data seem to establish the link between long-term suppression of hepatitis B virus with tenofovir and regression of advanced fibrosis;¹⁶ tenofovir therapy results in reversal of fibrosis and cirrhosis in majority of the treated patients.¹⁷ In a retrospective analysis, Gane et al¹⁸ reported that persistence of cirrhosis is most likely when risk factors for a second disease, such as obesity induced liver disease, co-exist.



Tenofovir as rescue therapy

Kim et al¹⁹ conducted a study to evaluate the efficacy and safety of tenofovir DF for chronic hepatitis B patients after multiple failures in 29 patients with chronic hepatitis B who had a suboptimal response or developed resistance to ≥2 previous nucleoside/nucleotide analogue treatments. Patients were treated with tenofovir alone (n=13) or together with lamivudine (LAM, n=12) or entecavir (ETV, n=4) for ≥6 months. Complete virologic response was defined as an achievement of serum hepatitis B virus DNA level ≤60 IU/mL by real-time polymerase chain reaction (RT-PCR) method during the treatment, while safety assessment was based on serum levels of creatinine and phosphorus. Past history of the patients revealed that 11 patients were exposed to LAM and adefovir dipivoxil (ADV) treatment and 18 patients were exposed to LAM, ADV, and ETV. A total of 27 patients (93.1%) were HBeAg+ and the mean value of baseline serum hepatitis B virus DNA level was $5.5 \log \text{IU/mL} \pm 1.7 \log \text{IU/mL}$. The median duration of treatment was 16 months (range 7 to 29 months). Results showed that all patients had been treated with LAM and developed resistance to it, both genotypic and phenotypic. Resistance to ADV and ETV was present in 7 and 10 patients, respectively; 1 patient had resistance to both ETV and ADV. The cumulative probabilities of complete virologic response at 12 and 24 months of tenofovir containing treatment regimen were 86.2% and 96.6%, respectively. Although one patient failed to achieve complete virologic response, serum hepatitis B virus DNA level decreased by $3.9 \log \text{IU/mL}$ from the baseline and the last serum hepatitis B virus DNA level during treatment was 85 IU/mL, thereby depicting achievement of near complete virologic response. None of the study patients showed viral breakthrough or primary non-response during the follow-up period. The cumulative probability of HBeAg clearance in 27 HBeAg+ patients was 7.4%, 12%, and 27% at 6, 12, and 18 months of treatment, respectively. It was found that the treatment efficacy of tenofovir containing regimen was not statistically different according to presence of specific hepatitis B virus mutations. As well, the treatment outcome remained largely unaffected by history of prior exposure to specific antiviral agents. In addition, combination therapy with LAM or ETV also did not affect the treatment efficacy of tenofovir. No case of renal toxicity, or hypophosphatemia associated with tenofovir therapy was observed. Besides, no other adverse events related to tenofovir therapy were observed in the patients. Overall, the evidence thus demonstrated that tenofovir can be an effective and safe rescue therapy in chronic hepatitis B patients after multiple nucleoside/nucleotide analogue therapy failures.

In a recent retrospective study, Kim et al⁵ aimed to investigate the efficacy and safety of tenofovir rescue

therapy in a cohort of Asian patients with chronic hepatitis B after multiple nucleos(t)ide analogues treatment failure. The analysis was performed on data from 52 chronic hepatitis B patients who experienced failure with ≥ 2 nucleos(t)ide analogues and who were switched to regimens containing tenofovir. The efficacy and safety assessments included hepatitis B virus DNA undetectability, HBeAg seroclearance, ALT normalization, and changes in serum levels of creatinine and phosphorus. The results showed that the mean hepatitis B virus DNA level at baseline was $5.4 \pm 1.76 \log_{10} \text{IU/mL}$. At a median duration of 34.5 months of tenofovir treatment, the cumulative probabilities of achieving complete virological response were 25.0%, 51.8%, 74.2%, and 96.7% at 6, 12, 24, and 48 months, respectively. HBeAg seroclearance was seen in 7/48 patients (14.6%), whereas ALT levels normalization occurred in 27/31 patients (87.1%) with elevated ALT at baseline. Lower levels of hepatitis B virus DNA at baseline were found to be significantly associated with increased rates of complete virological response. Nonetheless, rates of complete virological response did not differ between tenofovir monotherapy or combination therapy with other nucleos(t)ide analogues, and remained unaffected by mutations associated with resistance to nucleos(t)ide analogues. There were no significant adverse events. The authors thus concluded that tenofovir is an efficient and safe rescue therapy for chronic hepatitis B patients after treatment failure with multiple nucleos(t)ide analogues.

Tenofovir in acute-on-chronic liver failure

Spontaneous reactivation of chronic hepatitis B constitutes an important cause of acute-on-chronic liver failure. Herein, use of antiviral drugs may help to reduce the high morbidity and mortality in such patients, especially in areas with non-availability of liver transplantation. In the current study, authors aimed to evaluate the efficacy of tenofovir and to determine predictors of mortality in patients with spontaneous reactivation of chronic hepatitis B with acute-on-chronic liver failure.²⁰ Per protocol, consecutive patients of acute-on-chronic liver failure because of spontaneous reactivation of chronic hepatitis B were randomized to receive either tenofovir or placebo, with primary endpoint being survival at 3 months. The findings revealed that amongst the 90 patients with acute-on-chronic liver failure of different etiologies, 27 (26%) cases due to reactivation of chronic hepatitis B were enrolled. The median baseline hepatitis B virus DNA level was $9 \times 10^5 \text{ IU/mL}$. A total of 14 patients received tenofovir and 13 received placebo. The results showed that the probability of survival at 3 months was higher in the patients receiving tenofovir compared to the placebo group [57% (8/14) vs. 15% (2/13), respectively]. In 15 patients, the cause of death

was progressive liver failure leading to multiorgan failure. Liver transplantation was not considered because of non-availability. In surviving patients, a significant improvement in Child-Turcotte Pugh (CTP) and model for endstage liver disease (MELD) scores was observed, together with significant decline in hepatitis B virus DNA levels in the tenofovir group; these parameters, however, did not change significantly in the placebo group. It was noted that >2 log reduction in hepatitis B virus DNA levels at 2 weeks was an independent predictor of survival. In conclusion, the study thus showed that tenofovir significantly reduces hepatitis B virus-DNA levels, improves both CTP and MELD scores, and also reduces mortality in patients with severe spontaneous reactivation of chronic hepatitis B presenting as acute-on-chronic liver failure. As follows, it emerges that reduction in hepatitis B virus DNA levels at 2 weeks should be a desirable goal, and represents a good predictor of survival.

Tenofovir in adolescents

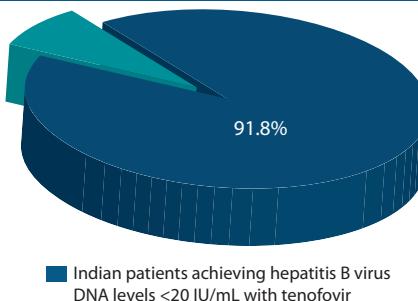
Tenofovir is highly effective for suppression of hepatitis B virus in chronically infected adults. In the current double-blind, placebo-controlled trial, Murray et al²¹ evaluated the efficacy and safety of tenofovir DF in adolescent patients with chronic hepatitis B. Adolescents 12 to <18 years of age with chronic hepatitis B were randomized to tenofovir DF 300 mg (n=52) or placebo (n=54) once daily for a period of 72 weeks. Virologic response (hepatitis B virus DNA <400 copies/mL) at week 72 was the primary endpoint. Overall, 106 patients were enrolled; and 101 patients completed 72 weeks of treatment. At baseline, 91% of patients were HbeAg+ and 85% had prior exposure to hepatitis B virus therapy. According to the study results, virologic response was observed in 89% (46/52) of patients who received tenofovir DF, compared to 0% (0/54) of patients receiving the placebo. Treatment response remained unaffected by prior hepatitis B virus treatment. As well, there was no resistance to tenofovir DF through week 72. Among patients with an ALT level more than the upper limit of normal at baseline, ALT normalized in 74% of patients receiving tenofovir DF and 31% of patients receiving placebo. The rate of grade 3/4 adverse events was found to be higher among patients treated with placebo (24%) compared to patients treated with tenofovir DF (10%). There was no patient who met the safety endpoint of a 6% decrease in spine bone mineral density (BMD) at week 72. In conclusion, tenofovir DF therapy in hepatitis B virus-infected adolescents was highly effective at suppressing hepatitis B virus DNA and normalizing ALT values in both treatment-naïve adolescents and those having prior exposure to hepatitis B virus therapy. In addition, the treatment was well-tolerated.

Tenofovir: Effects on incidence of hepatocellular carcinoma

As shown in efficacy trials, antiviral therapy improves outcomes of patients with chronic hepatitis B virus infection. However, there is limited prospective data on effect of antiviral therapy on incidence of HCC, especially among patients without cirrhosis. Recently, Kim et al²² used a validated prediction model to examine the impact of tenofovir DF on the incidence of HCC. The incidence of HCC in patients treated with tenofovir was obtained in the pivotal tenofovir registration studies after 384 weeks of follow-up. The Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) model was used to calculate the predicted risk of HCC in individual patients. The REACH-B model estimates HCC incidence for up to 10 years based on age, sex, ALT level, HBeAg status, and hepatitis B virus DNA. Standardized incidence ratios were calculated comparing the observed and predicted numbers of HCC cases in the study cohort. The results showed that among 634 patients with evaluable baseline biopsies, 152 had cirrhosis (Ishak fibrosis score of 5 or 6), and 482 did not. During 384 weeks of study, 14 cases of HCC were reported, of which 4 occurred within the 1st year. Overall, the incidence of HCC was 0.37% per year in the study (0.28% among patients without cirrhosis and 0.65% among patients with cirrhosis). The observed incidence of HCC was found to be significantly lower than predicted among patients without cirrhosis (standardized incidence ratio, 0.40). The last HCC case in a cirrhotic patient occurred around week 192, with a standardized incidence ratio of 0.51 reported at week 384. In conclusion, based on the REACH-B risk calculator, long-term antiviral therapy with tenofovir was found to be associated with a reduced incidence of HCC among patients without cirrhosis who met the treatment criteria.

In another recent large, multicentre, retrospective cohort study, Papatheodoridis et al²³ evaluated the incidence and predictors of HCC and the accuracy of existing HCC risk scores in chronic hepatitis B patients receiving entecavir (ETV)/tenofovir. The study included 1666 adult Caucasian chronic hepatitis B patients under ETV/tenofovir for 39 months. Chronic hepatitis B without cirrhosis, compensated and decompensated cirrhosis were present in 67%, 39%, and 3% of patients, respectively. Assessment was done for predictability of baseline parameters and three risk scores (CU-HCC, GAG-HCC, and REACH-B), developed for Asian patients. The results showed that cumulative probability of HCC was 1.3%, 3.4%, and 8.7% at year-1, year-3, and year-5 after ETV/tenofovir onset. Older age and lower platelets were found to be strong independent HCC predictors in the total population and in the subgroups of cirrhotic and non-cirrhotic patients,

Figure 2: Indian patients achieving hepatitis B virus DNA levels <20 IU/mL at 1 year of tenofovir therapy



Based on information from: Goyal SK, Dixit VK, Shukla SK, Ghosh J, Behera M, Tripathi M, Gupta N, Ranjan A, Jain AK. Prolonged use of tenofovir and entecavir in hepatitis B virus-related cirrhosis. *Indian J Gastroenterol* (July–August 2015) 34(4):286–291.

while severity of liver disease was an independent HCC predictor in the total population and in cirrhotics. The risk scores (CU-HCC, GAG-HCC, and REACH-B) were associated with HCC development only in univariable but not in the multivariable analyses, and had poor to modest predictability. The authors thus concluded that HCC can still develop, although at a lower rate, in chronic hepatitis B patients treated with ETV/tenofovir. It is more likely to develop in patients with cirrhosis, and especially in older patients. Furthermore, besides the well-known predictors of HCC, such as older age, male gender and more advanced liver disease, lower platelets is an independent risk factor for higher HCC risk.

TENOFOVIR EVIDENCE IN INDIAN POPULATION

There exists limited data from India on outcome and efficacy of antiviral drugs in hepatitis B virus-related cirrhosis when used for prolonged time, though studies have shown that long-term virologic and histologic efficacy and safety of tenofovir are comparable in Asian and non-Asian chronic hepatitis B patients.²⁴ In a recent retrospective study, Goyal et al²⁵ reported long-term efficacy and outcome of tenofovir and entecavir treatment in patients with chronic hepatitis B virus infection, with compensated or decompensated cirrhosis. The laboratory and clinical data of 400 patients with hepatitis B virus-related cirrhosis without access to liver transplantation, who were treated with tenofovir/entecavir therapy, from January 2007 to January 2014, were analyzed. Findings revealed that at baseline 52.5% (210/400) patients had at least one of the components of decompensation. Overall, 220 (55%) and 180 (45%) patients were initiated on treatment with tenofovir and entecavir, respectively, with follow-up period being 45 (12–68) and 36 (11–60) months. Results showed that at the end of 1 year, levels

of hepatitis B virus DNA <20 IU/mL were achieved in 91.8% (Figure 2) and 88.8% of patients, and ALT normalized in 54.5% and 55.5% of patients who received tenofovir and entecavir, respectively. The 5-year cumulative rate of liver decompensation, HCC, and cirrhosis-related complications were 3.1%, 1.9%, and 2.1% with an annual incidence of 0.8%, 0.3%, and 0.5% per person-year, respectively. Overall, the study thus showed that tenofovir was effective and potent for prolonged treatment of hepatitis B virus cirrhosis and improved the overall clinical course in Indian patients.

LONG-TERM SAFETY OF TENOFOVIR

The data so far confirm the efficacy and safety of long-term tenofovir for chronic hepatitis B.

At 3 years

Heathcote et al²⁶ evaluated the long-term efficacy and safety of tenofovir monotherapy in patients with chronic hepatitis B who were positive or negative for HBeAg (HBeAg+ or HBeAg-), and found that tenofovir was safe and effective in the long-term management of both HBeAg+ and HBeAg- patients with chronic hepatitis B. Per protocol, after double-blind comparison of tenofovir to adefovir dipivoxil over 48 weeks, patients who underwent liver biopsy were eligible to continue the study on open-label tenofovir for 7 additional years; data presented were collected up to 3 years (week 144) from 85% of participants. The primary efficacy end points at week 144 were levels of hepatitis B virus DNA and ALT, development of resistance mutations, and presence of HBeAg or HBsAg. Results showed that at week 144, 72% of HBeAg+ and 87% of HBeAg- patients treated with tenofovir had levels of hepatitis B virus DNA <400 copies/mL. Among patients who had previously received adefovir dipivoxil and then received tenofovir, 71% of the HBeAg+ and 88% of the HBeAg- patients had levels of hepatitis B virus DNA <400 copies/mL; overall, 74% and 81%, respectively, maintained normalized levels of ALT and 34% had lost HBeAg. Amino acid substitutions in hepatitis B virus DNA polymerase that are associated with resistance to tenofovir were not detected in any of the patient. Cumulatively, 8% of HBeAg+ patients lost HBsAg. Importantly, the drug maintained a favorable safety profile for up to 3 years.

At 5 years

In phase 3 clinical studies, long-term treatment with tenofovir was found to suppress hepatitis B viral load and promote significant fibrosis regression and cirrhosis reversal in a majority of patients with chronic hepatitis B. In a recent retrospective study,²⁷ representing the largest analyses to date of chronic hepatitis B patients with sequential liver biopsies, authors investigated the impact

of baseline cirrhosis status on virologic, serologic, and histologic outcomes in patients treated with tenofovir. Patients enrolled in two phase 3 studies who had baseline liver biopsy-diagnosed cirrhosis and entered the open-label phase of the studies were included in the virologic and serologic analyses. Both HBeAg+ and HBeAg- patients with paired liver biopsies at baseline and 5 years (n=348) were included in a histologic analysis.

After 5 years on study, comparing patients with and without baseline cirrhosis, respectively:

- 99.2% and 98.0% achieved virologic response (hepatitis B viral load <69 IU/ml)
- 79.7% and 81.9% had normal serum levels of ALT; 4.0 and 1.2% developed HCC.

In HBeAg+ patients with and without baseline cirrhosis, HBsAg loss occurred in 14.4% and 8.3% of patients, respectively; 1 HBeAg- patient also had HBsAg loss. This large retrospective analysis thus demonstrates that treatment with tenofovir for up to 5 years was associated with favorable virologic, serologic, and histologic outcomes, regardless of the baseline cirrhosis status. Especially, histologic improvement was observed in majority of cirrhotic and non-cirrhotic patients. No statistically significant differences were observed between the two cohorts in key safety parameters, and incidences of renal adverse events were low in the cohort with and without cirrhosis at baseline.

At >5 years

The data confirm the safety and efficacy of long-term tenofovir for chronic hepatitis B. Long-term tenofovir treatment for chronic hepatitis B has been found to be associated with sustained viral suppression and regression of fibrosis and cirrhosis at year 5 (240 weeks) and no resistance to tenofovir through 6 years (288 weeks). In the current study conducted recently, Buti et al²⁸ aimed to assess the efficacy, safety, and resistance of tenofovir for up to 7 years (336 weeks) in HBeAg+ and HBeAg- chronic hepatitis B patients, and confirmed the safety and efficacy of long-term tenofovir for chronic hepatitis B. In the study, patients who completed 1 year (48 weeks) of randomized treatment with tenofovir or adefovir dipivoxil were eligible to receive open-label tenofovir for a total duration of 8 years (384 weeks). Results revealed that of the 641 patients initially randomized, 91.3% (n=585) entered the open-label phase; 74.7% of them (437/585) remained on study at year 7. Of note, for patients on treatment at year 7, 99.3% were found to maintain viral suppression (hepatitis B virus DNA <69 IU/mL), 80.0% achieved normalization of serum ALT. Together, in HBeAg+ patients, 54.5% (84/154) and 11.8% (25/154) achieved HBeAg and HBsAg loss, respectively; 1/375 (0.3%) HBeAg- patients achieved

HBsAg loss. No resistance to tenofovir was detected through 7 years. During the open-label phase of the study, grade 3/4 drug-related adverse events were uncommon (1.0%); 10 (1.7%) patients were found to have elevation of serum creatinine ≥0.5 mg/dL above baseline. There was no significant change in bone mineral density (BMD) from week 192 to week 336 (year 4 to year 7). The authors thus concluded that long-term treatment with tenofovir was associated with sustained virologic, biochemical, and serologic responses, without demonstrating any resistance. Furthermore, the treatment was well-tolerated, with a low incidence of renal and bone events.

NO RESISTANCE TO TENOFOVIR IN LONG-TERM

Resistance to drugs in nucleoside/nucleotide analog therapy has always been a challenge in the management of chronic hepatitis B.¹² Nevertheless, emerging data suggest that tenofovir is largely devoid of this concern, and appears to have a favorable resistance profile in patients with chronic hepatitis B.⁶ The drug has been shown to achieve undetectable hepatitis B virus DNA (< 400 copies/mL) at 48 weeks in 76% HBeAg+ and 93% HBeAg- patients. As well, resistance to tenofovir is low in real world setting.²⁹

At 2 years

In the current study, authors reported findings from resistance analyses conducted for a recent study that compared the efficacy of tenofovir DF vs. combination of emtricitabine and tenofovir (FTC/tenofovir) in patients with lamivudine-resistant chronic hepatitis B who were treated for as long as 96 weeks.³⁰ A total of 280 patients with chronic hepatitis B virus infection and lamivudine resistance were randomly assigned (1:1) to groups treated with tenofovir or FTC/tenofovir. The hepatitis B virus reverse transcriptase domain from the polymerase gene was sequenced from all patients at baseline and from 18 viremic patients at week 96 or early discontinuation. Findings revealed that at screening for the efficacy study, 99% of patients had lamivudine resistance. Prior exposure to entecavir or entecavir resistance was observed in 12% of patients; 22% of patients had been previously exposed to adefovir, with 1.8% developing resistance to it. Eighteen patients (6.4%) qualified for sequence analysis, including one patient who experienced virologic breakthrough and 17 with persistent viremia. Six of these patients were found to have no sequence changes from baseline in hepatitis B virus reverse transcriptase (33%), while sequence analysis could not be performed for five patients (28%). In two patients who qualified for phenotypic analysis (1 given tenofovir and 1 given FTC/tenofovir), no resistance to tenofovir was observed. Viral kinetics remained unaffected by prior treatment exposure or resistance to entecavir or adefovir. Nevertheless, the mean baseline level of hepatitis

B virus DNA was found to be significantly higher in viremic patients than in patients with viral suppression by week 96 ($7.28 \log_{10}$ IU/mL vs. $5.62 \log_{10}$ IU/mL). Thus, no resistance to tenofovir was detected through 96 weeks of treatment in patients with lamivudine-resistant chronic hepatitis B. As well, prior treatment or resistance to adefovir or entecavir was found to have no impact on the viral kinetics through 96 weeks.

At 3 years

In two phase 3 studies, 375 HBeAg- patients and 266 HBeAg+ patients with chronic hepatitis B (some nucleoside-naïve and some lamivudine-experienced) were randomized 2:1 to receive tenofovir DF (n=426) or adefovir dipivoxil (ADV; n=215) for 48 weeks. After week 48, eligible patients received open-label tenofovir with no interruption. In the current work, Snow-Lampart et al³¹ presented the week 144 data. Per protocol, viremic patients (hepatitis B virus DNA level ≥ 400 copies/mL or 69 IU/mL) had the option to add emtricitabine (FTC) at or after week 72. The findings showed that most patients maintained tenofovir monotherapy treatment across both studies (607/641, 95%). A resistance analysis of hepatitis B virus pol/RT was performed at the baseline for all patients, for viremic patients at week 144 or at the last time when they were on tenofovir monotherapy (34 on tenofovir and 19 on ADV-tenofovir), and for patients who remained viremic after the addition of FTC (7/20 on tenofovir and 5/14 on ADV-tenofovir). The results showed that no patient developed amino acid substitutions associated with resistance to tenofovir. Virological breakthrough on tenofovir monotherapy was infrequent over 144 weeks (13/426, 3%) and in most cases (11/13, 85%), was attributable to documented non-adherence. Persistent viremia (≥ 400 copies/mL) through week 144 was rare (5/641, 0.8%) and was found to be not associated with virological resistance to tenofovir by population or clonal analyses. In conclusion, no nucleoside-naïve or nucleoside-experienced patient developed hepatitis B virus pol/RT mutations associated with tenofovir resistance after up to 144 weeks of exposure to tenofovir monotherapy.

At 6 years

Kitrinos et al³² analyzed data from 347 HBeAg- and 238 HBeAg+ patients receiving tenofovir DF in an open-label, long-term extension of two phase 3 studies, and presented resistance analyses for patients receiving up to 288 weeks (6 years) of tenofovir. Population sequencing of hepatitis B virus polymerase/reverse transcriptase (pol/RT) was attempted for all patients at baseline, and any patient who remained viremic [hepatitis B virus DNA 400 copies/mL (69 IU/mL)] at week 288 or at the end of treatment with tenofovir (n=52) or emtricitabine (FTC)/tenofovir (n=7).

About half of the patients on open-label treatment who qualified for genotyping had pol/RT sequence changes compared to baseline [23/52 (44%) on tenofovir, 4/7 (57%) on FTC/tenofovir]. Most of the changes were at polymorphic sites and none were associated with resistance to tenofovir. Virologic breakthrough was infrequent and in majority of cases (12/16, 75%), was associated with non-adherence to the study medication. Per protocol, 57 patients (10%) were eligible to switch to FTC/tenofovir; the majority had hepatitis B virus DNA < 400 copies/mL at their last study visit irrespective of whether they switched to FTC/tenofovir (n=34) or maintained tenofovir DF monotherapy (n=17). None of the patient was found to exhibit persistent viremia (hepatitis B virus DNA never < 400 copies/mL) after week 240. The authors thus concluded that tenofovir monotherapy maintains effective suppression of hepatitis B virus DNA through 288 weeks of treatment with no evidence of resistance to tenofovir.

At 8 years

After reporting sustained viral suppression through 5 years of treatment with tenofovir DF in mostly naïve patients, with regression of fibrosis, and cirrhosis reversal in 74% of patients, and no evidence of resistance to tenofovir through year 6, Marcellin³³ and colleagues presented year 8 results, the initially pre-specified end of study period, for two phase 3 studies in HBeAg+ and HBeAg- chronic hepatitis B patients, at American Association for the Study of Liver Diseases (AASLD) 2014 conference. Per protocol, patients were eligible to continue the open-label tenofovir after 48 weeks of double-blind comparison of tenofovir to adefovir dipivoxil. For evaluation, patients were assessed every three months for efficacy and safety, together performing annual surveillance for resistance; annual BMD assessments by dual-energy X-ray absorptiometry (DXA) were included starting at year 4. Overall, 641 patients were randomized and treated; 91% (n=585) patients entered the tenofovir extension phase at year 1, and 64% (n=412) remained on study at year 8. The investigators noted that durable viral suppression was maintained, and seven additional patients (5 HBeAg+ and 2 HBeAg-) experienced loss of HBsAg (5 patients demonstrated seroconversion to anti-HBs) between years 5-8. Of note, there was no resistance to tenofovir through year 8. At this timepoint, a confirmed renal event (either ≥ 0.5 mg/dL increase in serum creatinine, or serum phosphorus < 2 mg/dL, or creatinine clearance < 50 mL/min) was observed in 2.2% of patients; nevertheless, the BMD T scores of hip and spine were stable between years 4-8. Thus, based on these long-term observations from two studies, the authors concluded tenofovir to be safe and effective. Especially, there was no evidence of resistance to tenofovir through 8 years.

REFERENCES

- Jenh AM, Thio CL, Pham PA. Tenofovir for the treatment of hepatitis B virus. *Pharmacotherapy*. 2009 Oct;29(10):1212-27.
- Jenh AM, Pham PA. Tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. *Expert Rev Anti Infect Ther*. 2010 Oct;8(10):1079-92.
- Gordon SC, Krastev Z, Horban A, Petersen J, Sperl J, Dinh P, Martins EB, Yee LJ, Flaherty JF, Kitrinos KM, Rustgi VK, Marcellin P. Efficacy of Tenofovir Disoproxil Fumarate at 240 Weeks in Patients With Chronic Hepatitis B With High Baseline Viral Load. *Hepatology* 2013;58:505-513.
- Feld J, Janssen HLA, et al. World Gastroenterology Organisation Global Guideline. *Hepatitis B. Version 2.0*, February 2015:1-35.
- Kim HJ, Cho JY, Kim YJ, Gwak GY, Paik YH, Choi MS, Koh KC, Paik SW, Yoo BC, Lee JH. Long-term efficacy of tenofovir disoproxil fumarate therapy after multiple nucleos(t)ide analogue failure in chronic hepatitis B patients. *Korean J Intern Med* 2015;30:32-41.
- Perry CM, Simpson D. Tenofovir Disoproxil Fumarate. In *Chronic Hepatitis B. Drugs*. 2009;69(16):2245-2256.
- Ayaz C, Çelen MK, Dal T, Deveci Ö, Bayan K, Mert D, Oruç E, Özcan N, Kandemir I, Dal MS. Tenofovir disoproxil fumarate treatment in HBeAg-positive patients. *Infekz Med*. 2015 Mar;23(1):31-5.
- Chan HL, Buti M, Marcellin P, Lin L, Massetto B, Flaherty J, Subramanian M, McHutchison J, Foster G, Fung S, Thompson A, Lampertico P. 761 Comparison of serum HbsAg declines during tenofovir disoproxil fumarate (TDF) treatment in different chronic hepatitis B (CHB) sub-populations. *Journal of Hepatology*. 2013;58(Supplement 1):S309-S310.
- Marcellin P, Buti M, Krastev Z, de Man RA, Zeuzem S, Lou L, Gaggar A, Flaherty JF, Massetto B, Lin L, Dinh P, Subramanian GM, McHutchison JG, Flisiak R, Gurel S, Dusheiko GM, Heathcote EJ. Kinetics of hepatitis B surface antigen loss in patients with HBeAg-positive chronic hepatitis B treated with tenofovir disoproxil fumarate. *J Hepatol*. 2014 Dec;61(6):1228-37.
- Lu C, Jia Y, Chen L, Ding Y, Yang J, Chen M, Song Y, Sun X, Wen A. Pharmacokinetics and food interaction of a novel prodrug of tenofovir, tenofovir dipivoxil fumarate, in healthy volunteers. *J Clin Pharm Ther*. 2013 Apr;38(2):136-40.
- Hu CY, Liu YM, Liu Y, Chen Q, Wang W, Wu K, Dong J, Li J, Jia JY, Lu C, Sun SX, Yu C, Li X. Pharmacokinetics and tolerability of Tenofovir disoproxil fumarate 300 mg once daily: an open-label, single- and multiple-dose study in healthy Chinese subjects. *Clin Ther*. 2013 Dec;35(12):1884-9.
- Seto WK, Yuen MF, Fung J, Lai CL. Tenofovir disoproxil fumarate for the treatment of chronic hepatitis B mono-infection. *Hepatol Int*. 2013;7:327-334.
- Örmeci N, Özbaş B, Güner R, Özkan H, Yalçın A, Çoban Ş, Dökmeci A, Kalkan Ç, Akıncı H, Yüksel O, Başar Ö, Yüksel İ, Balkı İ. Tenofovir-best hope for treatment of chronic hepatitis B infection? *Turk J Gastroenterol*. 2015 Jul;26(4):322-7.
- Gordon SC, Marcellin P, Krastev Z, Horban A, Petersen J, Sperl J, Dinh P, Martins EB, Yee LJ, Flaherty JF, Kitrinos KM, Berger N, Rustgi VK, Heathcote EJ. Efficacy of 5 Years of Tenofovir Disoproxil Fumarate (TDF) in Chronic Hepatitis B Patients With High Viral Load (HBV DNA ≥9 Log10 Copies/mL). *Gastroenterology*. 2012;142(5)Supplement 1:S-954.
- Sievert W, Strasser S, Gane E, George J, Weilert F, Elsome AM, Flaherty JF, Martins E, Bekele N, Bornstein JB, Buti M, Marcellin P. Clinical, virological, serological and histological outcomes in cirrhotic patients with chronic hepatitis B (CHB) treated with tenofovir disoproxil fumarate (TDF) for up to 5 years. *Journal of Gastroenterology and Hepatology*. 2012; 27(Suppl. 4): 161-182.
- Elsome AM, Sievert W, Strasser S, Gane E, George J, Weilert F, Bornstein JD, Flaherty JF, McHutchison JG, Marcellin P. Five years of treatment with tenofovir disoproxil fumarate (TDF) for chronic hepatitis B (CHB) infection is associated with sustained viral suppression and significant regression of histological fibrosis and cirrhosis. *Journal of Gastroenterology and Hepatology*. 2012; 27(Suppl. 4):161-182.
- Marcellin P, Gane E, Buti M, Afshai N, Sievert W, Jacobson IM, Washington MK, Germanidis G, Flaherty JF, Schall RA, Bornstein JD, Kitrinos KM, Subramanian GM, McHutchison JG, Heathcote EJ. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet*. 2013;381:468-75.
- Gane ED, Afshai N, Buti M, Elsome AM, Flaherty JF, Martins E, Bekele N, Bornstein JD, Marcellin P. Factors associated with regression of cirrhosis in patients with chronic hepatitis B (CHB) infection treated with tenofovir disoproxil fumarate (TDF). *Journal of Gastroenterology and Hepatology*. 2012; 27 (Suppl. 4): 161-182.
- Kim YJ, Sinn DH, Gwak GY, Choi MS, Koh KC, Paik SW, Yoo BC, Lee JH. Tenofovir rescue therapy for chronic hepatitis B patients after multiple treatment failures. *World J Gastroenterol*. 2012;18(47):6996-7002.
- Garg H, Sarin SK, Kumar M, Garg V, Sharma BC, Kumar A. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. *Hepatology*. 2011 Mar;53(3):774-80.
- Murray KF, Szenborn L, Wysocki J, Rossi S, Corsa AC, Dinh P, McHutchison J, Pang PS, Luminis LM, Pawlowska M, Mizerski J. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. *Hepatology*. 2012 Dec;56(6):2018-26.
- Kim WR, Loomba R, Berg T, Aguilar Schall RE, Yee LJ, Dinh PV, Flaherty JF, Martins EB, Therneau TM, Jacobson I, Fung S, Gurel S, Buti M, Marcellin P. Impact of long-term tenofovir disoproxil fumarate on incidence of hepatocellular carcinoma in patients with chronic hepatitis B. *Cancer*. 2015 Oct 15;121(20):3631-8.
- Papatheodoridis GV, Dalekos GN, Yurdaydin C, Buti M, Gouli J, Arends P, Syspa V, Manolakopoulos S, Mangia G, Gatselis N, Keskin O, Savvidou S, Hansen BE, Papaioannou C, Galanis K, Idilman R, Colombo M, Esteban R, Janssen HL, Lampertico P. Incidence and predictors of hepatocellular carcinoma in Caucasian chronic hepatitis B patients receiving entecavir or tenofovir. *J Hepatol*. 2015 Feb;62(2):363-70.
- Tsai NC, Marcellin P, Buti M, Washington MK, Lee SS, Chan S, Trinh H, Flaherty JF, Kitrinos KM, Dinh P, Charuworn P, Subramanian GM, Gane E. Viral suppression and cirrhosis regression with tenofovir disoproxil fumarate in Asians with chronic hepatitis B. *Dig Dis Sci*. 2015 Jan;60(1):260-8.
- Goyal SK, Dixit VK, Shukla SK, Ghosh J, Behera M, Tripathi M, Gupta N, Ranjan A, Jain AK. Prolonged use of tenofovir and entecavir in hepatitis B virus-related cirrhosis. *Indian J Gastroenterol* July-August 2015;34(4):286-291.
- Heathcote EJ, Marcellin P, Buti M, Gane E, De man RA, Krastev Z, Germanidis G, Lee SS, Flisiak R, Kaita K, Manns M, Kotzev I, Tchernev K, Buggisch P, Weilert F, Kurdas OO, Schiffman ML, Trinh H, Gurel S, Snow-lampart A, Borroto-esoda K, Mondou E, Anderson J, Sorbel J, Rousseau F. Three-Year Efficacy and Safety of Tenofovir Disoproxil Fumarate Treatment for Chronic Hepatitis B. Three-Year Efficacy and Safety of Tenofovir Disoproxil Fumarate Treatment for Chronic Hepatitis B. *Gastroenterology*. 2011;140:132-143.
- Buti M, Fung S, Gane E, Afshai NH, Flisiak R, Gurel S, Flaherty JF, Martins EB, Yee LJ, Dinh P, Bornstein JD, Subramanian GM, Janssen HLA, George J, Marcellin P. Long-term clinical outcomes in cirrhotic chronic hepatitis B patients treated with tenofovir disoproxil fumarate for up to 5 years. *Hepatol Int*. 2015;9:243-250.
- Buti M, Tsai N, Petersen J, Flisiak R, Gurel S, Krastev Z, Schall RA, Flaherty JF, Martins EB, Charuworn P, Kitrinos KM, Subramanian GM, Gane E, Marcellin P. Seven-Year Efficacy and Safety of Treatment with Tenofovir Disoproxil Fumarate for Chronic Hepatitis B Virus Infection. *Dig Dis Sci*. 2015;60:1457-1464.
- Hun TC, Ponnuswamy SKK, Kontorinis N, Tarquinio L, Flexman JP, Cheng W, Cheng W. Evaluation of treatment of chronic hepatitis B with tenofovir in a major tertiary hospital in Western Australia – a real world perspective. *Journal of Gastroenterology and Hepatology*. 2012; 27 (Suppl. 4): 161-182.
- Corsa AC, Liu Y, Flaherty JF, Mitchell B, Fung SK, Gane E, Miller MD, Kitrinos KM. No Resistance to Tenofovir Disoproxil Fumarate Through 96 Weeks of Treatment in Patients With Lamivudine-Resistant Chronic Hepatitis B. *Clinical Gastroenterology and Hepatology*. 2014;12:2106-2112.
- Snow-Lampart A, Chappell B, Curtis M, Zhu Y, Myrick F, Schawalder J, Kitrinos K, Svarovskia ES, Miller MD, Sorbel J, Heathcote J, Marcellin P, Borroto-Esoda K. No resistance to tenofovir disoproxil fumarate detected after up to 144 weeks of therapy in patients monoinfected with chronic hepatitis B virus. *Hepatology*. 2011 Mar;53(3):763-73.
- Kitrinos KM, Corsa A, Liu Y, Flaherty J, Snow-Lampart A, Marcellin P, Borroto-Esoda K, Miller MD. No detectable resistance to tenofovir disoproxil fumarate after 6 years of therapy in patients with chronic hepatitis B. *Hepatology*. 2014 Feb;59(2):434-42.
- Marcellin P, Gane EJ, Flisiak R, Trinh HN, Petersen J, Gurel S, Kaita KD, Kotzev IA, Tsai N, Flaherty JF, Schall REA, Kitrinos KM, Subramanian M, McHutchison JG, George J, Janssen HL, Buti M. Long Term Treatment with Tenofovir Disoproxil Fumarate for Chronic Hepatitis B Infection is Safe and Well Tolerated and Associated with Durable Virologic Response with no Detectable Resistance: 8 Year Results from Two Phase 3 Trials. Available at: http://www.natap.org/2014/AASLD/AASLD_144.htm [Accessed on 31/12/2015].

SECTION 3

Tenofovir in contrast

Combined and comparative profile

Nucleoside/nucleotide analogues such as lamivudine, adefovir, entecavir and tenofovir disoproxil fumarate (DF) are important therapeutic avenues for treatment of hepatitis B virus infection. These agents are widely used due to their viral suppressive activity associated with single daily use and favorable tolerability profile. Development of drug resistance in nucleoside/nucleotide analogues is an emerging concern, hampering the treatment outcomes. Importantly, lamivudine, and adefovir have been associated with high resistance rates that compromise its use and lead to inadequate viral suppression, and biochemical flare. The resistance to tenofovir however is low, and supported with potent viral suppression. Additionally, studies have shown efficacy of tenofovir in patients exhibiting resistance to lamivudine and adefovir.^{1,2} On similar lines, several comparative studies on tenofovir have attested promising prospects of this drug for treatment of hepatitis B virus infection.

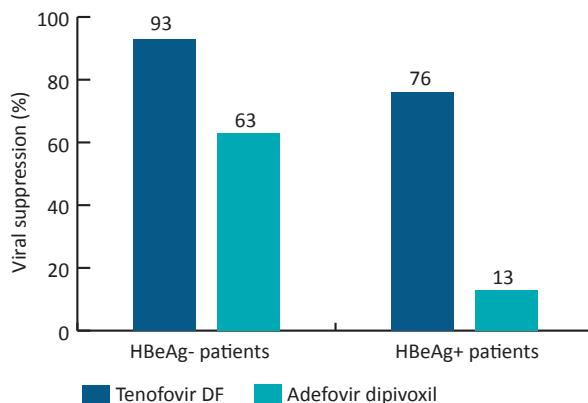
TENOFOVIR VS. ADEFOVIR

Tenofovir DF as monotherapy is considered as an important agent for virologic suppression in cases with inadequate response to adefovir antiretroviral therapy. Additionally, combination drug therapy is useful in cases with resistance to adefovir. Studies have been conducted to understand the nature of mutations imparting resistance and its association to treatment failure with adefovir, and to estimate virologic response to tenofovir DF monotherapy and tenofovir combination therapy in patients. For the study³, serum sample of 13 patients prior to and after changed treatment protocol with tenofovir and tenofovir with emtricitabine were derived and analyzed. Resistant mutations involved in adefovir resistance were rtA181V and rtN236T in 3 of 8 patients with virologic breakthrough. In the group of patients with suboptimal virologic response, rtA181T, rtI233V and rtN236T were present in 3 patients. Of the 10 patients administered tenofovir DF, 8 individuals exhibited virologic response. Baseline characteristics showed that one patient had adefovir resistance, and the resistance

mutation persisted during treatment with tenofovir; the addition of emtricitabine in the treatment regimen resulted in further reduction in hepatitis B virus DNA. One patient had no adefovir resistance at baseline and had selection adefovir-resistant mutation while on treatment with tenofovir. The patients who were administered combined tenofovir and emtricitabine regimen attained undetectable hepatitis B virus DNA within 3-12 months of treatment, including 2 individuals with resistance at baseline. The tenofovir monotherapy was considered effectual for individuals with virologic breakthrough or suboptimal response to adefovir therapy. Additionally, combination of tenofovir and nucleoside analogue was useful for treatment of patients with adefovir resistance.

A double-blind, phase 3 trial⁴ was conducted among patients with HBeAg- and HBeAg+ chronic hepatitis B virus infection. Patients were categorized in the ratio of 2:1 in order to receive either once daily tenofovir DF or adefovir dipivoxil for a period of 48 weeks. The primary efficacy outcomes were established as plasma hepatitis B virus DNA level <400 copies per millimeter (69 IU per millimeter) and histological improvement (denoted by decrease in the Knodell necroinflammation score of 2 or more points without worsening fibrosis) at 48 weeks. Secondary outcomes were viral suppression, histological improvement, serological response, normalization of alanine aminotransferase levels and occurrence of resistance mutation. The outcomes reflected that significantly higher proportion of patients in the tenofovir DF group achieved the primary efficacy end point as compared to adefovir dipivoxil group. Viral suppression at 48 weeks in HBeAg- individuals was observed in 93% patients on tenofovir DF as against 63% patients on adefovir dipivoxil, whereas in HBeAg+ individuals, 76% on tenofovir and 13% on adefovir dipivoxil attained viral suppression (Figure 1). Around three fourth patients showed histological improvement, which was similar in both the groups. Significant proportion of HBeAg+ individuals administered tenofovir DF (68%) had normalized alanine aminotransferase levels

Figure 1: Viral suppression with tenofovir DF and adefovir dipivoxil in HBeAg- and HBeAg+ patients at 48 weeks



Based on information from: Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, Germanidis G, Lee SS, Flisiak R, Kaita K, Manns M, Kotzov I, Tchernev K, Buggisch P, Weilert F, Kurdas OO, Schiffman ML, Trinh H, Washington MK, Sorbel J, Anderson J, Snow-Lampart A, Mondou E, Quinn J, Rousseau F. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med.* 2008 Dec 4;359(23):2442-55.

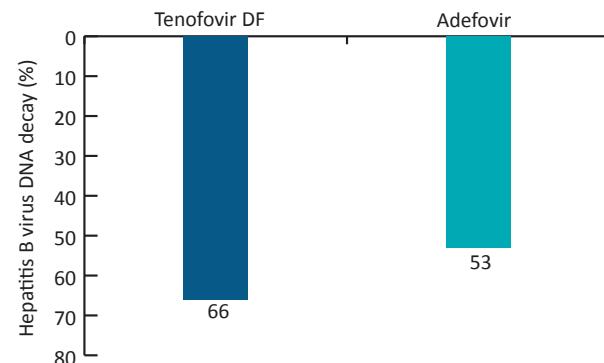
as compared to adefovir dipivoxil (54%). Loss of hepatitis B surface antigen was 3% in tenofovir DF group and 0% in adefovir dipivoxil group. None of the patients developed amino acid substitutions within hepatitis B virus DNA polymerase related with phenotypic resistance to tenofovir or any other agent used for the treatment of hepatitis B virus infection. The hepatitis B virus DNA response with tenofovir DF was similar in patients previously administered lamivudine as well as patients not given lamivudine. Importantly, HBsAg loss or seroconversion is considered as an important parameter that defines sustained immune control of the virus; the HBsAg loss was appreciable in tenofovir recipients. The trial thus attested that tenofovir DF at daily dose of 300 mg was superior to adefovir dipivoxil daily dose of 10 mg in patients with chronic hepatitis B virus infection.

Similarly, Hou and colleagues⁵ conducted a phase 3, randomized, double-blind, controlled study to compare the effectiveness of tenofovir DF and adefovir dipivoxil in a cohort of Chinese subjects with chronic hepatitis B virus infection. The treatment response was calculated over a period of 48 weeks. The main outcome was number of patients with hepatitis B virus DNA <400 copies/mL. This was calculated using pooled Z-test for superiority. Other outcomes observed were viral suppression, histological improvement, serologic response, normalization of alanine aminotransferase and development of resistance mutations. Patients were randomized into two groups,

each administered with daily dose of tenofovir DF 300 mg or adefovir dipivoxil 10 mg. It was observed that among 509 patients recruited in the study (202 HBeAg+ individuals and 307 HBeAg-), with hepatitis B virus DNA $\geq 10^5$ copies/mL, the viral suppression at 48 weeks was superior with tenofovir DF (76.7% and 96.8%; HBeAg+ and HBeAg-, respectively) compared to adefovir dipivoxil (18.2% and 71.2%; HBeAg+ and HBeAg-, respectively). Alanine aminotransferase normalization was achieved in more than 85% patients in both the groups. Patients did not develop resistance to tenofovir DF. Tenofovir DF was more effective than adefovir dipivoxil for viral suppression in patients with chronic hepatitis B infection at 48 weeks of treatment.

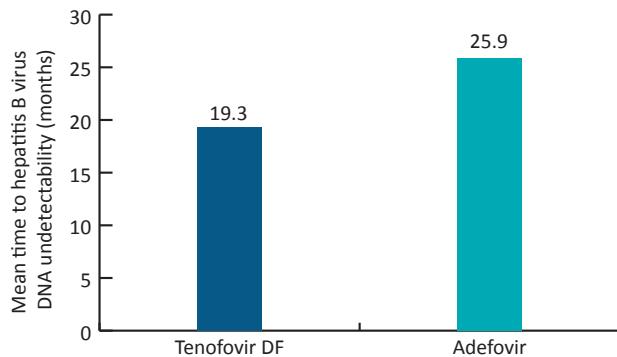
Of note, tenofovir DF shows profound activity against wild type and lamivudine resistant hepatitis B virus strains, in vitro as well as in vivo. It is believed that dual action of tenofovir DF may provide an optimal therapeutic response in patients coinfected with HIV and hepatitis B virus as compared to adefovir, which only has anti-hepatitis B virus activity at therapeutic dose used for management of chronic hepatitis B virus infection. The aspects of hepatitis B virus dynamics need to be evaluated as it might reflect biology of hepatitis B virus and provide important information on therapy used. In a study⁶ population including HIV-hepatitis B virus coinfecting patients, the characteristics and factors affecting viral decay with tenofovir DF and adefovir therapy were compared. A total of 85 patients with HIV-hepatitis B virus coinfection were included in the study. These patients were administered combined antiretroviral drugs along with tenofovir DF and adefovir. A mixed linear

Figure 2: Hepatitis B virus DNA decay, after adjusting for baseline viral load, with tenofovir DF and adefovir at 12 weeks in HIV-hepatitis B virus coinfecting patients



Based on information from: Lacombe K, Gozlan J, Boyd A, Boelle PY, Bonnard P, Molina JM, Mialhès P, Lascoux-Combe C, Serfaty L, Zoulim F, Girard PM. Comparison of the antiviral activity of adefovir and tenofovir on hepatitis B virus in HIV-HBV-coinfecting patients. *Antivir Ther.* 2008;13(5):705-13.

Figure 3: The mean time to hepatitis B virus DNA undetectability with tenofovir DF and adefovir

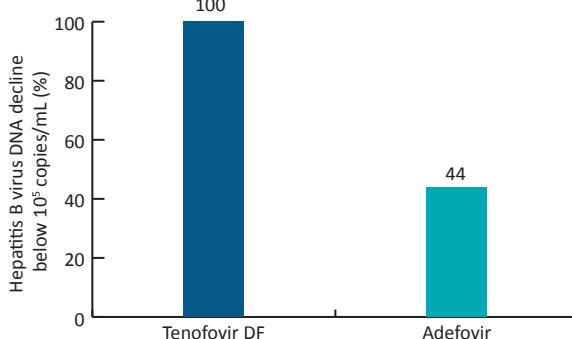


Based on information from: Lacombe K, Gozlan J, Boyd A, Boelle PY, Bonnard P, Molina JM, Mialhe P, Lascoix-Combe C, Serfaty L, Zoulim F, Girard PM. Comparison of the antiviral activity of adefovir and tenofovir on hepatitis B virus in HIV-HBV-coinfected patients. *Antivir Ther.* 2008;13(5):705-13.

model was used to evaluate the variations in viral load during first 6 months of the therapy. Additionally, hazards ratio that compared the rates of undetectable hepatitis B virus DNA between treatments was calculated. It was observed that after adjusting for baseline hepatitis B virus load, the hepatitis B virus DNA decay at 12 months was pronounced in patients treated with tenofovir DF (-66%) as compared to those treated with adefovir (-53%) (Figure 2). On assessing the hepatitis B virus DNA kinetics, individuals in the tenofovir DF group showed a steeper slope of decline at 1.1 compared with 0.8 in the adefovir group. Hepatitis B virus DNA undetectability was evaluated when there were <200 copies/mL. The hepatitis B virus DNA undetectability was achieved by 66% and 28% patients treated with tenofovir DF and adefovir, respectively. Success curves indicated that time-to-undetectability was favorable for patients receiving tenofovir DF as compared to adefovir. The mean time to hepatitis B virus DNA undetectability was 19.3 months in tenofovir DF recipients and 25.9 months in adefovir recipients (Figure 3). The results for time to undetectability remained consistent when adjusted for HBeAg, hepatitis B virus DNA and alanine aminotransferase levels. The early phase hepatitis B virus DNA kinetics was strongly affected by tenofovir DF in comparison to adefovir. This may be attributable to sustained antiviral activity in tenofovir recipients leading to threshold of hepatitis B virus undetectability at a rapid rate in large number of patients in comparison to adefovir.

Evidences reinforce the usefulness of tenofovir in treatment of lamivudine resistant hepatitis B virus infection. A study⁷ compared tenofovir with adefovir in

Figure 4: Hepatitis B virus DNA decline below 10^5 copies/mL with tenofovir DF and adefovir at 48 weeks in patients with lamivudine-resistant hepatitis B virus infection



Based on information from: van Bömmel F, Wünsche T, Mauss S, Reinke P, Bergk A, Schürmann D, Wiedenmann B, Berg T. Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection. *Hepatology*. 2004 Dec;40(6):1421-5.

a cohort of 53 patients with high hepatitis B virus DNA levels ($>6 \log_{10}$ copies/mL) and with lamivudine resistance. Patients were randomized into two groups. Group 1 consisted of 35 patients and received tenofovir therapy for 72 to 130 weeks. Group 2 consisted of 18 patients and received adefovir for 60 to 80 weeks. Variations in hepatitis B virus DNA levels were evaluated for 48 weeks. Early viral kinetics was evaluated in subgroups consisting of 5 patients each. Strong early suppression was observed in all tenofovir treated individuals. Significant individual variations were observed in hepatitis B virus DNA decline in adefovir treatment group. The assessment made at 48 weeks showed that hepatitis B virus DNA decline (below 10^5 copies/mL) was 44% in adefovir group and 100% in tenofovir group (Figure 4). Phenotypic viral resistance was not evident in tenofovir recipients even after long-term follow up of 130 weeks. Thus, tenofovir was considered as a potent agent for therapy in lamivudine resistant hepatitis B virus infection.

TENOFOVIR VS. ENTECAVIR

Tenofovir DF and entecavir are oral antiviral agents used for treatment of chronic hepatitis B virus infection. Both these agents have been compared in several clinical trials.

A meta-analysis⁸ was conducted to evaluate the efficacy and tolerability of entecavir and tenofovir. Relevant clinical trials through June 2014 were included in the study. A total of 1656 patients from 2 randomized controlled trials, 2 prospective cohort studies and 7 case-control studies were included in the study. The number of nucleos(t)ide

naïve chronic hepatitis B virus individuals was 842/992 in entecavir group and 481/664 in tenofovir group. The study observations showed that virological response with tenofovir was superior to entecavir, particularly in nucleos(t)ide naïve chronic hepatitis B virus individuals at 48 weeks. The virological response at 24 weeks was similar in entecavir and tenofovir group. The alanine aminotransferase normalization rate, serological response, and adverse event rate were not notably different between entecavir and tenofovir groups at 24 and 48 weeks. The outcomes thus reflected that tenofovir has higher ability to suppress hepatitis B virus load with similar tolerability as compared to entecavir.

Another study⁹ compared the viral kinetics and virological response of tenofovir and entecavir in patients with hepatitis B virus infection. Survey analysis was conducted to evaluate independent variables affecting virological response to treatment (entecavir or tenofovir). The decline in serum hepatitis B virus DNA was estimated at 3rd, 6th, 12th, 18th, and 24th month of the therapy in both the groups. The study recruited 117 patients; 66 patients received tenofovir and 51 patients received entecavir. The virological response was better with tenofovir and patients having high fibrosis score. The hepatitis B virus DNA decline rate was not different in both the groups except at 3rd month. Thus, virological response with tenofovir was considered to be better as compared to entecavir.

A trial by Hung et al¹⁰ compared the short-term effectiveness of tenofovir DF and entecavir in patients with chronic hepatitis B virus infection with severe acute exacerbation. The study was conducted by recruiting a group of 189 consecutive chronic hepatitis B virus patients with severe acute exacerbation from 2008 to 2013. The patients enrolled were treatment naïve and were randomized into two groups; tenofovir DF (n=41) and entecavir (n=148). The overall mortality and liver transplantation by week 24 constituted primary endpoint of the study. The baseline data was comparable for both the groups. The results at 24 weeks showed that 8 patients in tenofovir DF group and 26 patients in entecavir group died or underwent liver transplantation procedure. Liver related complications and biochemical and virological responses were similar in both the groups at 24 weeks. Few of the independent factors for mortality or liver transplantation were baseline viral DNA level, hypertension, model for end-stage liver disease (MELD) score, early development (within 4 weeks) of ascites, hepatic encephalopathy, platelet count and hepatorenal syndrome. The survivors in both the groups had no remarkable variations in the serum creatinine increase of ≥ 0.5 mg/dl from baseline; however, both the groups exhibited significant reduction in the estimated glomerular filtration rate. The treatment

response and clinical outcomes were similar with tenofovir DF and entecavir in chronic hepatitis B patients with severe acute exacerbation.

Jayakumar et al¹¹ performed a study in a group of chronic hepatitis B patients with hepatitis B virus DNA levels $>10^4$ copies/mL not accounting for their HBeAg status. The patients were administered study drugs as follows: 21 patients received lamivudine (100 mg/day) with adefovir (10 mg/day), 20 patients received entecavir (0.5 mg/day) monotherapy and 19 patients received tenofovir (300 mg/day) monotherapy. The study duration was 24 weeks and virological, serological and biochemical parameters were assessed at 12 and 24 weeks. All the study drugs showed no marked differences in lowering hepatitis B virus DNA levels to undetectable levels; however, median decrease from baseline was superior and statistically significant with tenofovir and entecavir monotherapies as compared to lamivudine and adefovir combination. Other parameters including HBsAg and HBeAg seroconversion and normalization of biochemical levels were similar in all the groups.

A study¹² compared the efficacy of two antiviral agents; tenofovir and entecavir in previously untreated patients with chronic hepatitis B virus infection. The study group included both HBeAg+ and HBeAg- patients. Patients were compared on the following parameters: baseline characteristics, reduction in alanine transaminase (ALT) levels, reduction in hepatitis B virus DNA to undetectable levels, HBeAg loss and anti-HBe development. In the study, 121 individuals were administered tenofovir and 130 individuals were administered entecavir. Patients were mainly males, and were followed up for 18 months in tenofovir group and 20 months in entecavir group. Tenofovir and entecavir lead to comparable rate of HBeAg loss, undetectable hepatitis B virus-DNA level, ALT normalization, ALT reduction and decrease in hepatitis B virus-DNA. Viral control with both tenofovir and entecavir was effective.

TENOFOVIR VS. EMTRICITABINE

Tenofovir DF and emtricitabine is a potent combination widely used for treatment of HIV infection. It has significant activity against hepatitis B virus infection as well. Several clinical trials have assessed the effectiveness of tenofovir DF in patients with chronic hepatitis B virus infection.

Literature is replete with studies that attest the efficacy of tenofovir DF in lamivudine-resistant hepatitis B virus infection. Fung et al¹³ conducted a prospective, double-blind study in patients with hepatitis B virus infection. Patients enrolled in the study were HBeAg+ and HBeAg- with hepatitis B virus DNA load

$\geq 3 \log_{10}$ IU/mL and had lamivudine resistant mutations (hepatitis B virus polymerase or reverse transcriptase amino acid substitutions rtM204I/V ± rtL180M). Patients were randomized into two groups of 141 and 139 patients; one group was administered 300 mg tenofovir DF and other group was administered combination of 200 mg emtricitabine and 300 mg tenofovir. The main outcome assessed was proportion with hepatitis B virus DNA < 69 IU/mL. All patients were well-matched for demographic variables and disease characteristics. A total of 45% patients had hepatitis D genotype, and 47% patients were HBeAg+. The mean duration with lamivudine was 3.8 years. The outcomes at 96 weeks showed that 89.4% and 86.3% patients in tenofovir and tenofovir plus emtricitabine group, respectively, attained hepatitis B virus DNA levels < 69 IU/mL. The HbeAg loss and seroconversion was similar in both the groups. The treatment was well-tolerated by the patients. Additionally, no resistance mutation developed in the tenofovir group. The efficacy of tenofovir alone was confirmed in patients with lamivudine resistant hepatitis B virus infection.

In a trial by Lavocat and collaborators,¹⁴ the viral kinetics, nucleoside analog resistance mutations and evolution of quasispecies with tenofovir DF or emtricitabine and tenofovir DF combination was compared in a patient population exhibiting inadequate response to adefovir therapy. The study population thus consisted of patients with chronic hepatitis B virus infection and inadequate response to adefovir therapy. Patients were randomized to receive either tenofovir or combination of tenofovir and emtricitabine. Evolution of quasispecies was extensively monitored in 17 patients throughout 48 weeks of therapy. The results at 24 weeks showed that 48% patients gained hepatitis B virus DNA undetectability (amounting to < 69 IU/mL) with no variations amongst the groups. Adefovir and lamivudine mutations were observed in all patients at baseline and 5/6 analyzable patients at 48 weeks. Clonal analysis was not suggestive of any significant variation at baseline in quasispecies complexity or diversity in the treatment groups. The quasispecies complexity increased at 12 weeks and subsequently decreased at 48 weeks. Individual analysis did not highlight any consistent selection/accumulation of specific viral resistance patterns during treatment; however, mutation rtA181 was seen in 4 patients at week 48. Tenofovir therapy alone and in combination with emtricitabine demonstrated excellent viral suppression in subgroup of patients with incomplete response to adefovir and no significant selective pressure on pre-existing adefovir and lamivudine resistant strains.

A study¹⁵ appraised long-term effectiveness of tenofovir and tenofovir plus emtricitabine combination in patients with inadequate virologic response to adefovir therapy.

Patients with HBeAg+ and HBeAg- serotypes and hepatitis B virus DNA levels ≥ 1000 copies/ml despite being on adefovir therapy for 96 weeks were categorized to receive tenofovir or emtricitabine plus tenofovir for 168 weeks. Patients having hepatitis B virus DNA ≥ 400 copies/mL at or beyond 26 weeks were then switched to emtricitabine plus tenofovir. The study period of 168 weeks was completed by 86% patients, including 70% patients who continued on initial treatment. Long-term viral suppression was observed in 84% patients in emtricitabine plus tenofovir group and 82% patients in tenofovir group. Factors such as baseline viral load and lamivudine resistance had no impact on treatment response. Additionally, no resistance mutations emerged in tenofovir group through 168 weeks of study. Tenofovir alone or in combination with emtricitabine was effective for long-term viral suppression in subgroup of patients with inadequate response to other antiretroviral agents.

HIV AND HEPATITIS B VIRUS COINFECTION: THE SPECIAL SUBPOPULATION AMENABLE TO TENOFOVIR COMBINATION

Hepatitis B virus infections often co-occur in patients with HIV infections due to shared mode of transmission. Prevalence estimates suggest that nearly 10% patients with HIV are coinfected with hepatitis B virus infections. It is noteworthy that in patients with this comorbidity, development of hepatitis B virus infection increases the immunological and clinical progression of HIV infection, with profound risk of hepatotoxicity when combined antiretroviral therapy is initiated. Conversely, HIV infection increases the risk of hepatitis, cirrhosis and end stage liver disease associated with chronic hepatitis B virus infection. Nevertheless, combined antiretroviral therapy is effective for long-term suppression and control of HIV and hepatitis B virus replication.¹⁶

A systematic review and meta-analysis¹⁷ was conducted to appraise the viral suppressive activity, duration and durability of viral suppression and impact of prior resistant therapies on efficacy of tenofovir. The study was conducted following PRISMA guidelines and with multilevel mixed effects logistic regression analysis characterized by previous or concurrent use of lamivudine and emtricitabine. The information from 23 studies with 550 hepatitis B virus/HIV coinfected individuals administered tenofovir was assessed. The follow up data of 3 years was considered for the study. The proportion of patients attaining suppression of hepatitis B virus replication was 57.4% at 1st year, 79.0% at 2nd year and 85.6% at 3rd year. No virological relapse was observed with tenofovir therapy. It was derived that tenofovir was useful in suppressing hepatitis B virus DNA to undetectable levels in large



number of hepatitis B virus/ HIV coinfecting individuals, with proportion of full suppression increasing with continuous treatment. Tenofovir alone was equipotent to tenofovir and emtricitabine therapy.

Moreover, tenofovir DF alone also appears to be a highly effective antiviral therapy for treatment of hepatitis B virus infection in HIV infected patients. The long-term influence of tenofovir DF on hepatitis B virus replication has been inadequately addressed in HIV-hepatitis B virus coinfecting patients. A prospective study¹⁸ was conducted by Lacombe and colleagues to understand the hepatitis B virus DNA decay kinetics in coinfecting individuals. Viral kinetics was understood with mixed linear models and by estimating the baseline characters affecting kinetics with Cox models. A decline in hepatitis B virus DNA load by means of 4.6 log copies/mL was observed during follow-up. These levels reduced below the detection limit (200 copies/ml) in 21 individuals. Inhibition of viral replication with tenofovir was associated with decrease in alanine aminotransferase levels. Biphasic pattern of viral DNA decay was observed; with rapid fall followed by gradual decline. Baseline factors affecting a steeper first slope in the hepatitis B virus-DNA reduction were high hepatitis B viral load, positive HBeAg and YMDD mutations. Baseline characteristics increasing the time to reach hepatitis B virus DNA level less than 200 copies/ml were high viral load and positive HBeAg. Previous use of lamivudine or tenofovir-lamivudine had no influence on hepatitis B virus DNA decrease under therapy in this subgroup of patients. Tenofovir therapy was effective in HIV-hepatitis B virus coinfecting cohort; not considering hepatitis B virus strain and replication.

The usefulness of tenofovir was assessed in a study¹⁹ group consisting of HIV and hepatitis B virus coinfecting patients. A total of 20 coinfecting individuals previously treated with 108 weeks of lamivudine were administered tenofovir in adjunct or as a part of combined antiretroviral therapy. Patients were monitored for immunological response, HIV-1 RNA and hepatitis B virus DNA viral load for 52 weeks. The frequency of YMDD mutation (associated with lamivudine resistance) was also assessed using hepatitis B virus DNA polymerase at baseline. The decrement in hepatitis B virus DNA viral load and alanine aminotransferase levels was substantial. No marked variations were observed in lamivudine experienced and naïve patients. A total of 25% patients exhibited HBeAg seroconversion. YMDD mutation was present in 10 of 15 lamivudine experienced patients. Tenofovir addition to antiretroviral therapy for 52 weeks was active against hepatitis B virus and it seemed to surmount lamivudine resistance.

A multicenter, prospective trial by de Vries-Sluijs et al²⁰ evaluated the long-term efficacy of tenofovir DF as a part of antiretroviral regimen in patients with HIV-hepatitis B virus coinfection. A total of 102 patients were included in the study. Patients were treated with tenofovir. Baseline assessment suggested that 80% patients had detectable viral load (hepatitis B virus DNA >20 IU/mL). Among group of HBeAg+ individuals, virological response (hepatitis B virus DNA < 20 IU/mL) was observed in 92% patients after 5 years of therapy. Virological response among HBeAg- individuals was 100% after 4 years of therapy. Patients with or without lamivudine resistance showed no variations in response. Rate of HBeAg and HBsAg loss was 46% and 12%, respectively, among HBeAg+ patients. Rate of HBsAg loss was 13% among HBeAg- individuals. Twenty patients (all HBeAg-) acquired undetectable hepatitis B virus DNA levels during a median follow-up period of 52 months. Among them, 19 (95%) patients maintained a virologic response and 2 (10%) lost HBsAg. Combined resistance mutation developed in only one patient. Tenofovir was thus considered to be effective option for treatment of coinfecting individuals.

REFERENCES

1. Fung J, Lai CL, Seto WK, Yuen MF. Nucleoside/nucleotide analogues in the treatment of chronic hepatitis B. *J Antimicrob Chemother.* 2011 Dec;66(12):2715-25.
2. Ke W, Liu L, Zhang C, et al. Comparison of Efficacy and Safety of Tenofovir and Entecavir in Chronic Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis. *Miao X, ed. PLoS ONE.* 2014;9(6):e98865.
3. Tan J, Degertekin B, Wong SN, Husain M, Oberhelman K, Lok AS. Tenofovir monotherapy is effective in hepatitis B patients with antiviral treatment failure to adefovir in the absence of adefovir-resistant mutations. *J Hepatol.* 2008 Mar;48(3):391-8.
4. Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, Germanidis G, Lee SS, Flisiak R, Kaita K, Manns M, Kotzev I, Tchernev K, Buggisch P, Weilert F, Kurdas OO, Schiffman ML, Trinh H, Washington MK, Sorbel J, Anderson J, Snow-Lampart A, Mondou E, Quinn J, Rousseau F. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med.* 2008 Dec 4;359(23):2442-55.
5. Hou JL, Gao ZL, Xie Q, Zhang JM, Sheng JF, Cheng J, Chen CW, Mao Q, Zhao W, Ren H, Tan DM, Niu JQ, Chen SJ, Pan C, Tang H, Wang H, Mao YM, Jia JD, Ning Q, Xu M, Wu SM, Li J, Zhang XX, Ji Y, Dong J, Li J. Tenofovir disoproxil fumarate vs adefovir dipivoxil in Chinese patients with chronic hepatitis B after 48 weeks: a randomized controlled trial. *J Viral Hepat.* 2015 Feb;22(2):85-93.
6. Lacombe K, Gozlan J, Boyd A, Boelle PY, Bonnard P, Molina JM, Mialhès P, Lascoix-Combe C, Serfaty L, Zoulim F, Girard PM. Comparison of the antiviral activity of adefovir and tenofovir on hepatitis B virus in HIV-HBV-coinfected patients. *Antivir Ther.* 2008;13(5):705-13.
7. van Bömmel F, Wünsche T, Mauss S, Reinke P, Bergk A, Schürmann D, Wiedenmann B, Berg T. Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection. *Hepatology.* 2004 Dec;40(6):1421-5.
8. Zuo S, Zuo X, Wang C, Ma Y, Zhang H, Li Z, Song L, Deng Z, Liu S. A meta-analysis comparing the efficacy of entecavir and tenofovir for the treatment of chronic hepatitis B infection. *The Journal of Clinical Pharmacology.* 2015;55(3):288-297.
9. Ceylan B, Yardimci C, Fincancı M, Eren G, Tozalgan U, Muderrisoglu C, Akkoyunlu Y. Comparison of tenofovir and entecavir in patients with chronic HBV infection. *Eur Rev Med Pharmacol Sci.* 2013 Sep;17(18):2467-73.

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10. Hung CH, Hu TH, Lu SN, Lee CM, Chen CH, Kee KM, Wang JH, Tsai MC, Kuo YH, Chang KC, Chiu YC, Chen CH. Tenofovir versus entecavir in treatment of chronic hepatitis B virus with severe acute exacerbation. *Antimicrob Agents Chemother*. 2015;59(6):3168-73.
 11. Jayakumar R, Joshi YK, Singh S. Laboratory evaluation of three regimens of treatment of chronic hepatitis B: tenofovir, entecavir and combination of lamivudine and adefovir. *J Lab Physicians*. 2012 Jan;4(1):10-6.
 12. Ozaras R, Mete B, Ceylan B, Ozgunes N, Gunduz A, Karaosmanoglu H, Cagatay A, Gokturk K, Erdem L, Kocak F, Senates E, Tabak F. First-line monotherapies of tenofovir and entecavir have comparable efficacies in hepatitis B treatment. *Eur J Gastroenterol Hepatol*. 2014 Jul;26(7):774-80.
 13. Fung S, Kwan P, Fabri M, Horban A, Pelemis M, Hann HW, Gurel S, Caruntu FA, Flaherty JF, Massetto B, Dinh P, Corsa A, Subramanian GM, McHutchison JG, Husa P, Gane E. Randomized comparison of tenofovir disoproxil fumarate vs emtricitabine and tenofovir disoproxil fumarate in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology*. 2014 Apr;146(4):980-8.
 14. Lavocat F, Dény P, Pichoud C, Al Hawajri N, Kitrinos K, Borroto-Esoda K, Zoulim F. Similar evolution of hepatitis B virus quasispecies in patients with incomplete adefovir response receiving tenofovir/emtricitabine combination or tenofovir monotherapy. *J Hepatol*. 2013 Oct;59(4):684-95.
 15. Berg T, Zoulim F, Moeller B, Trinh H, Marcellin P, Chan S, Kitrinos KM, Dinh P, Flaherty JF Jr, McHutchison JG, Manns M. Long-term efficacy and safety of emtricitabine plus tenofovir DF vs. tenofovir DF monotherapy in adefovir-experienced chronic hepatitis B patients. *J Hepatol*. 2014 Apr;60(4):715-22.
 16. Sun H-Y, Sheng W-H, Tsai M-S, Lee K-Y, Chang S-Y, Hung C-C. Hepatitis B virus coinfection in human immunodeficiency virus-infected patients: A review. *World Journal of Gastroenterology: WJG*. 2014;20(40):14598-14614.
 17. Price H, Dunn D, Pillay D, Bani-Sadr F, de Vries-Sluijs T, Jain MK, Kuzushita N, Mauss S, Núñez M, Nüesch R, Peters M, Reiberger T, Stephan C, Tan L, Gilson R. Suppression of HBV by tenofovir in HBV/HIV coinfected patients: a systematic review and meta-analysis. *PLoS One*. 2013 Jul 10;8(7):e68152.
 18. Lacombe K, Gozlan J, Boelle PY, Serfaty L, Zoulim F, Valleron AJ, Girard PM. Long-term hepatitis B virus dynamics in HIV-hepatitis B virus-co-infected patients treated with tenofovir disoproxil fumarate. *AIDS*. 2005 Jun 10;19(9):907-15.
 19. Nelson M, Portsmouth S, Stebbing J, Atkins M, Barr A, Matthews G, Pillay D, Fisher M, Bower M, Gazzard B. An open-label study of tenofovir in HIV-1 and Hepatitis B virus co-infected individuals. *AIDS*. 2003 Jan 3;17(1):F7-10.
 20. de Vries-Sluijs TE, Reijnders JG, Hansen BE, Zaaijer HL, Prins JM, Pas SD, Schutten M, Hoepelman AI, Richter C, Mulder JW, de Man RA, Janssen HL, van der Ende ME. Long-term therapy with tenofovir is effective for patients co-infected with human immunodeficiency virus and hepatitis B virus. *Gastroenterology*. 2010 Dec;139(6):1934-41.

SECTION 4

Supplementary data on tenofovir

Recommendations on tenofovir
from various guidelines

WHO 2015 Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection¹

World health organization (WHO) guidelines are first developed set of guidelines for prevention, care and treatment of persons living with chronic hepatitis B infection. These guidelines are consistent with similar recent publication by WHO on hepatitis C virus infection. The guidelines are directed towards country programme managers in all settings and healthcare providers to help in prevention and treatment of hepatitis B virus infection. The treatment guidelines at various instances recommend the use of tenofovir for management of chronic hepatitis B virus infection.

As first-line antiviral therapy for chronic hepatitis B virus infection

- As a priority, all adults, adolescents and children with chronic hepatitis B and clinical evidence of compensated or decompensated cirrhosis (or cirrhosis based on APRI score >2 in adults) should be treated, regardless of ALT levels, HBeAg status or hepatitis B virus DNA levels.
- Treatment is recommended for adults with chronic hepatitis B who do not have clinical evidence of cirrhosis (or based on APRI score ≤2 in adults), but are aged more than 30 years (in particular), and have persistently abnormal ALT levels and evidence of high-level hepatitis B virus replication (hepatitis B virus DNA >20 000 IU/mL), regardless of HBeAg status.
- Agents such as lamivudine, adefovir and telbivudine have low barrier to resistance and may lead to development of drug resistance; therefore, their use is not recommended.

In hepatitis B virus and HIV co-infected individuals

- In adults, adolescents, and children 3 years or more with hepatitis virus and HIV coinfection, fixed dose combination consisting of tenofovir + lamivudine (or emtricitabine) + efavirenz is recommended as treatment of choice for initiation of antiretroviral therapy.

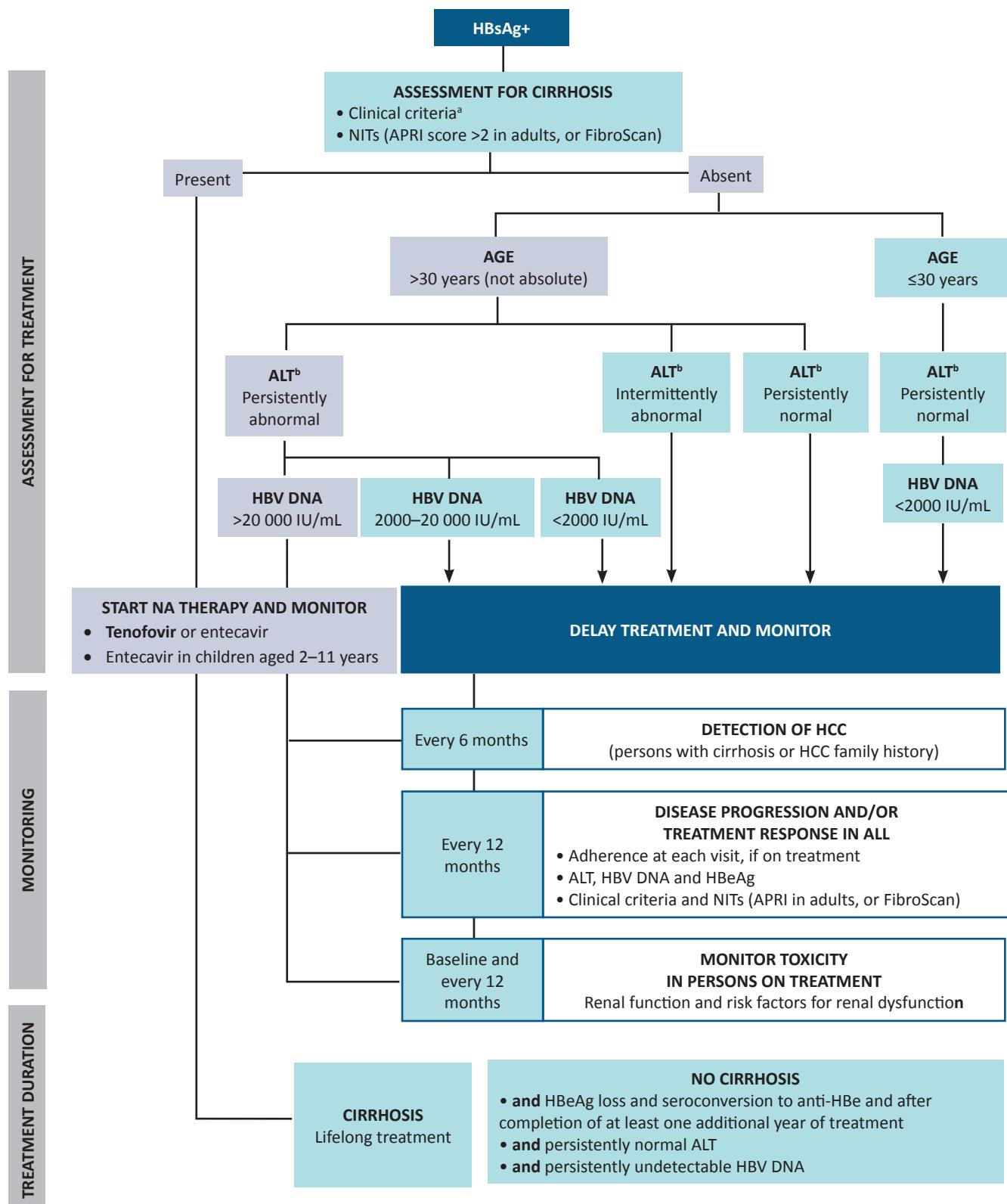
Second-line antiviral therapy for treatment failure

- A switch to tenofovir therapy is recommended in patients with confirmed or suspected antiviral resistance to lamivudine, entecavir, adefovir and telbivudine.

For prevention of mother-to-child hepatitis B transmission

- In pregnant females with hepatitis B virus monoinfection, indications for treatment are similar to that for adults, and tenofovir is recommended
- The treatment algorithm (Figure 1) shows that if cirrhosis is present then patient must be initiated with tenofovir or entecavir as a potent therapeutic option.

Figure 1: Treatment algorithm of WHO recommendations for individuals with chronic hepatitis B infection



Abbreviations:

NITs-non-invasive tests, HBV DNA-Hepatitis B virus DNA, NA Nucleos(t)ide analogue, ALT-alanine transaminase, APRI-aspartate aminotransferase-to-platelet ratio index, HCC-hepatocellular carcinoma

^aClinical features of decompensated cirrhosis include portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy, or liver insufficiency (jaundice). Features of advanced liver disease/cirrhosis may include hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema, and oedema.

^bUpper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women, the levels must be ascertained according to local laboratory normal ranges. Persistently normal/abnormal may be defined as three ALT determinations below or above the upper limit of normal, made at unspecified intervals during a 6–12-month period or predefined intervals during 12-month period. In case HBV DNA testing is not available, treatment may be considered based on persistently abnormal ALT levels, but other common causes of persistently high ALT levels such as impaired glucose tolerance, dyslipidaemia and fatty liver must be excluded.

Based on information from: Guidelines for the prevention, care and treatment of persons with chronic hepatitis b infection 2015. Available at: http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf. Accessed on: 4.1.2016.

WHAT OTHER GUIDELINES SAY ABOUT TENOFOVIR

World Gastroenterology Organization Global Guidelines on Hepatitis B, 2015²

- Therapy should be considered in HBeAg+ patients with persistent ALT levels $\geq 2 \times$ the upper limit of normal, and with hepatitis B virus DNA ≥ 2000 IU/mL. Any approved antiviral agent may be used based on efficacy, safety and genetic potential for resistance. However, tenofovir and entecavir are preferred nucleoside/nucleotide analogues
- In HBeAg- patients, oral nucleoside/nucleotide analogues with low resistance potential, such as tenofovir and entecavir are agents of choice, especially in patients with cirrhosis. Accounting for economic considerations, therapy can be started with lamivudine, with early adefovir add-on therapy or a change to tenofovir at instance of drug resistance or when hepatitis B virus DNA remains at ≥ 2000 IU/mL at week 24 of therapy
- In patients with hepatitis B virus and HIV coinfection, if therapy is indicated, a tenofovir-based regimen is preferred, in combination with other highly active agents for HIV.

American Association for the Study of Liver Diseases (AASLD) Guidelines for Treatment of Chronic Hepatitis B, 2015³

- The guidelines suggest pegylated-interferon, entecavir, or tenofovir as agents of choice for initial therapy in adults with immune-active chronic hepatitis B virus infection.
- For the management of patients with persistent low-level viremia on entecavir or tenofovir, therapy must be continued regardless of ALT levels
- For the management of adults with cirrhosis and low-level viremia, guidelines suggest antiviral therapy (entecavir and tenofovir as preferred agents) to reduce the risk of decompensation, regardless of ALT levels.

REFERENCES

- Guidelines for the prevention, care and treatment of persons with chronic hepatitis b infection 2015. Available at: http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf. Accessed on: 4.1.2016.
- World Gastroenterology Organisation Global Guideline hepatitis B 2015. Available at: <http://www.worldgastroenterology.org/guidelines/global-guidelines/hepatitis-b/hepatitis-b-english>. Accessed on: 4.1.2016.
- Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016 Jan;63(1):261-83.



TENFOCLEAR PRODUCT INFORMATION

For the Use of a Registered Medical Practitioner or a Hospital or a Laboratory Only

TENOFOVIR DISOPROXIL FUMARATE TABLETS

IP 300 MG

TENFOCLEAR™

COMPOSITION

Each film coated tablet contains:

Tenofovir Disoproxil Fumarate IP..... 300 mg
Eq. to Tenofovir Disoproxil 245 mg

INDICATIONS

Tenofovir Disoproxil Fumarate Tablets IP 300 mg is a nucleotide analog HIV-1 reverse transcriptase inhibitor and an HBV reverse transcriptase inhibitor.

Tenofovir Disoproxil Fumarate Tablets IP 300 mg is indicated for the treatment of chronic hepatitis B in adults and as an anti-HIV agent.

DOSAGE AND ADMINISTRATION

Recommended Dose in Adults and Pediatric Patients 12 Years of Age and Older (35 kg or more)

For the treatment of HIV-1 or chronic hepatitis B: The dose is one 300 mg "Tenofovir Disoproxil Fumarate Tablets IP 300 mg" tablet once daily taken orally, without regard to food.

Dose Adjustment for Renal Impairment in Adults

Significantly increased drug exposures occurred when Tenofovir Disoproxil Fumarate Tablets IP 300 mg was administered to subjects with moderate to severe renal impairment.

Dosage Adjustment for Patients with Altered Creatinine Clearance

- Creatinine clearance ≥ 50 mL/min: 300 mg every 24 hours.

- Creatinine clearance 30-49 mL/min: 300 mg every 48 hours.
- Creatinine clearance 10-29 mL/min: 300 mg every 72 to 96 hours.
- Hemodialysis: 300 mg every 7 days or after approximately 12 hours of dialysis.

No dose adjustment of Tenofovir Disoproxil Fumarate is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed in patients with mild renal impairment.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including Tenofovir Disoproxil Fumarate, in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Tenofovir Disoproxil Fumarate should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Exacerbation of Hepatitis after Discontinuation of Treatment

Discontinuation of anti-HBV therapy, including Tenofovir Disoproxil Fumarate, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue Tenofovir Disoproxil Fumarate should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

New Onset or Worsening Renal Impairment

Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of Tenofovir Disoproxil Fumarate.

It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with Tenofovir Disoproxil Fumarate. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving Adefovir Dipivoxil, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of Tenofovir Disoproxil Fumarate, and periodically during Tenofovir Disoproxil Fumarate therapy.

Dosing interval adjustment of Tenofovir Disoproxil Fumarate Tablets and close monitoring of renal function are recommended in all patients with creatinine clearance below 50 mL/min. No safety or efficacy data are available in patients with renal impairment who received Tenofovir Disoproxil Fumarate using these dosing guidelines, so the potential benefit of Tenofovir Disoproxil Fumarate tablets therapy should be assessed against the potential risk of renal toxicity.

Tenofovir Disoproxil Fumarate should be avoided with concurrent or recent use of a nephrotoxic agent [e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)]. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients.

Coadministration with Other Products

Tenofovir Disoproxil Fumarate should not be used in combination with the fixed-dose combination products – efavirenz/emtricitabine/tenofovir disoproxil fumarate, emtricitabine/rilpivirine/tenofovir disoproxil fumarate, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, or emtricitabine/tenofovir disoproxil fumarate – since Tenofovir Disoproxil Fumarate is a component of these products. Tenofovir Disoproxil Fumarate should not be administered in combination with adefovir dipivoxil.

Patients Coinfected with HIV-1 and HBV

Due to the risk of development of HIV-1 resistance, Tenofovir Disoproxil Fumarate should only be used in HIV-1 and HBV coinfecting patients as part of an appropriate antiretroviral combination regimen.

HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with Tenofovir Disoproxil Fumarate. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with Tenofovir Disoproxil Fumarate.

Bone Effects

Bone Mineral Density

In clinical trials in HIV-1 infected adults, Tenofovir Disoproxil Fumarate was associated with slightly greater decrease in bone mineral density (BMD) and increase in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving Tenofovir Disoproxil Fumarate.

Clinical trials evaluating Tenofovir Disoproxil Fumarate in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the Tenofovir Disoproxil Fumarate treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected.

The effects of Tenofovir Disoproxil Fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adults and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium

and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Mineralization Defects

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of Tenofovir Disoproxil Fumarate. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF.

Fat Redistribution

In HIV-infected patient's redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving combination antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including Tenofovir Disoproxil Fumarate. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, Cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

Early Virologic Failure

Clinical trials in HIV-infected subjects have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virologic failure and high

rates of resistance substitutions have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

Interaction with Other Medicinal Products and Other Forms of Interaction

This section describes clinically relevant drug interactions with Tenofovir Disoproxil Fumarate. Drug interactions trials are described elsewhere in the labeling.

Didanosine

Coadministration of Tenofovir Disoproxil Fumarate and didanosine should be undertaken with caution, and patients receiving this combination should be monitored closely for didanosine associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions.

When administered with Tenofovir Disoproxil Fumarate, Cmax and AUC of didanosine increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving Tenofovir Disoproxil Fumarate with didanosine 400 mg daily. In patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with Tenofovir Disoproxil Fumarate. In patients weighing less than 60 kg, the didanosine dose should be reduced to 200 mg once daily when it is coadministered with Tenofovir Disoproxil Fumarate. When coadministered, Tenofovir Disoproxil Fumarate and didanosine EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).

HIV-1 Protease Inhibitors

Tenofovir Disoproxil Fumarate decreases the AUC and Cmin of atazanavir. When coadministered with Tenofovir Disoproxil Fumarate, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Tenofovir Disoproxil Fumarate should not be coadministered with atazanavir without ritonavir.

Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations. Tenofovir Disoproxil Fumarate is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When Tenofovir Disoproxil Fumarate is coadministered with an inhibitor of these transporters, an increase in

absorption may be observed. Patients receiving Tenofovir Disoproxil Fumarate concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for Tenofovir Disoproxil Fumarate associated adverse reactions. Tenofovir Disoproxil Fumarate should be discontinued in patients who develop Tenofovir Disoproxil Fumarate associated adverse reactions.

Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys, coadministration of Tenofovir Disoproxil Fumarate with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to, cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs.

In the treatment of chronic hepatitis B, Tenofovir Disoproxil Fumarate should not be administered in combination with adefovir dipivoxil.

PREGNANCY AND LACTATION

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Tenofovir Disoproxil Fumarate should be used during pregnancy only if clearly needed.

Animal Data

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

Nursing Mothers

It is recommended that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is secreted in human milk. The impact of this exposure in breastfed infants is unknown. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving Tenofovir Disoproxil Fumarate.

Effects on Ability to Drive and use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with tenofovir disoproxil fumarate.

UNDESIRABLE EFFECTS

The following adverse reactions are discussed in other sections of the labeling. See special warnings and precautions for use:

- Lactic Acidosis/Severe Hepatomegaly with Steatosis
- Severe Acute Exacerbation of Hepatitis [See Warnings and Precautions]
- New Onset or Worsening Renal Impairment.
- Bone Effects [See Warnings and Precautions].
- Immune Reconstitution Syndrome.

ADVERSE REACTIONS FROM CLINICAL TRIALS EXPERIENCE

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In HIV-infected adult subjects: most common adverse reactions (incidence greater than or equal to 10%, Grades 2–4) are rash, diarrhea, headache, pain, depression, asthenia, and nausea.

In HBV-infected subjects with compensated liver disease: most common adverse reaction (all grades) was nausea (9%).

In pediatric subjects: adverse reactions subjects were consistent with those observed in adults.

In HBV-infected subjects with decompensated liver disease: most common adverse reactions (incidence greater than or equal to 10%, all grades) were abdominal pain, nausea, insomnia, pruritus, vomiting, dizziness, and pyrexia.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Tenofovir Disoproxil Fumarate. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders

Allergic reaction, including angioedema



Metabolism and Nutrition Disorders

Lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders

Dyspnea

Gastrointestinal Disorders

Pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders

Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, gamma GT)

Skin and Subcutaneous Tissue Disorders

Rash

Musculoskeletal and Connective Tissue Disorders

Rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders

Acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General Disorders and Administration Site Conditions

Asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use; nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF07

Mechanism of Action

Tenofovir Disoproxil Fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir Disoproxil Fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate

and, after incorporation into DNA, by DNA chain termination.

Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α , β , and mitochondrial DNA polymerase γ .

Activity Against HIV

Antiviral activity

The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC50 (50% effective concentration) values for tenofovir were in the range of $0.04 \times M$ to $8.5 \times M$. In drug combination studies, tenofovir was not antagonistic with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir). Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC50 values ranged from $0.5 \times M$ to $2.2 \times M$) and strain specific activity against HIV-2 (EC50 values ranged from $1.6 \times M$ to $5.5 \times M$).

Activity Against HBV

Antiviral activity

The antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC50 values for tenofovir ranged from 0.14 to $1.5 \times M$, with CC50 (50% cytotoxicity concentration) values greater than $100 \times M$. In cell culture combination antiviral activity studies of tenofovir with the nucleoside HBV reverse transcriptase inhibitors entecavir, lamivudine, and telbivudine, and with the nucleoside HIV-1 reverse transcriptase inhibitor emtricitabine, no antagonistic activity was observed.

Pharmacokinetic properties

The pharmacokinetics of Tenofovir Disoproxil Fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption

Tenofovir Disoproxil Fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from Tenofovir Disoproxil Fumarate in fasted subjects is approximately 25%. Following oral administration of a single dose of Tenofovir Disoproxil Fumarate 300 mg to HIV-1 infected subjects in the fasted state, maximum serum concentrations (Cmax) are achieved in 1.0 ± 0.4 hrs. Cmax and AUC values are 0.30

$\pm 0.09 \times g/mL$ and $2.29 \pm 0.69 \times g\cdot hr/mL$, respectively. The pharmacokinetics of tenofovir are dose proportional over a Tenofovir Disoproxil Fumarate dose range of 75 to 600 mg and are not affected by repeated dosing. In a single-dose bioequivalence study conducted under non-fasted conditions (dose administered with 4 oz. apple sauce) in healthy adult volunteers, the mean C_{max} of tenofovir was 26% lower for the oral powder relative to the tablet formulation. Mean AUC of tenofovir was similar between the oral powder and tablet formulations.

Distribution

In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 $\times g/mL$. The volume of distribution at steady-state is $1.3 \pm 0.6 L/kg$ and $1.2 \pm 0.4 L/kg$, following intravenous (IV) administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Metabolism and Elimination

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes.

Following IV administration of tenofovir, approximately 70-80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of Tenofovir Disoproxil Fumarate, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of Tenofovir Disoproxil Fumarate 300 mg once daily (under fed conditions), 32 \pm 10% of the administered dose is recovered in urine over 24 hours.

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Effects of Food on Oral Absorption

Administration of Tenofovir Disoproxil Fumarate 300 mg tablets following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir AUC_{0- ∞} of approximately

Table 1: Mean ($\pm SD$) Tenofovir Pharmacokinetic Parameters by Age Groups for HIV-1-infected Pediatric Patients

Dose and Formulation	300 mg Tablet	8 mg/kg Oral Powder
	12 to <18 Years (N=8)	2 to <12 Years (N=23)
Cmax ($\mu g/mL$)	0.38 ± 0.13	0.24 ± 0.13
AUCtau ($\mu g\cdot hr/mL$)	3.39 ± 1.22	2.59 ± 1.06

40% and an increase in C_{max} of approximately 14%. However, administration of Tenofovir Disoproxil Fumarate with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are $0.33 \pm 0.12 \times g/mL$ and $3.32 \pm 1.37 \times g\cdot hr/mL$ following multiple doses of Tenofovir Disoproxil Fumarate 300 mg once daily in the fed state, when meal content was not controlled.

Special Populations

Race: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Gender: Tenofovir pharmacokinetics are similar in male and female subjects.

Pediatric Patients 2 Years of Age and Older: Steady-state pharmacokinetics of tenofovir were evaluated in 31 HIV-1 infected pediatric subjects 2 to less than 18 years (Table 1). Tenofovir exposure achieved in these pediatric subjects receiving oral once daily doses of Tenofovir Disoproxil Fumarate 300 mg (tablet) or 8 mg/kg of body weight (powder) up to a maximum dose of 300 mg was similar to exposures achieved in adults receiving once-daily doses of Tenofovir Disoproxil Fumarate 300 mg.

Tenofovir exposures in 52 HBV-infected pediatric subjects (12 to less than 18 years of age) receiving oral once-daily doses of Tenofovir Disoproxil Fumarate 300

Table 2: Pharmacokinetic Parameters (Mean $\pm SD$) of Tenofovir^a in Subjects with Varying Degrees of Renal Function

Baseline Creatinine Clearance (mL/min)	>80 (N=3)	50-80 (N=10)	30-49 (N=8)	12-29 (N=11)
Cmax ($\mu g/mL$)	0.34 ± 0.03	0.33 ± 0.06	0.37 ± 0.16	0.60 ± 0.19
AUC _{0-∞} ($\mu g\cdot hr/mL$)	2.18 ± 0.26	3.06 ± 0.93	6.01 ± 2.50	15.98 ± 7.22
CL/F (mL/min)	1043.7 ± 115.4	807.7 ± 279.2	444.4 ± 209.8	177.0 ± 97.1
CLrenal (mL/min)	243.5 ± 33.3	168.6 ± 27.5	100.6 ± 27.5	43.0 ± 31.2

a. 300 mg, single dose of Tenofovir Disoproxil Fumarate

mg tablet were comparable to exposures achieved in HIV-1-infected adults and adolescents receiving once-daily doses of 300 mg.

Geriatric Patients: Pharmacokinetic trials have not been performed in the elderly (65 years and older).

Patients with Impaired Renal Function: The pharmacokinetics of tenofovir are altered in subjects with renal impairment. In subjects with creatinine clearance below 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, Cmax and AUC_{0-∞} of tenofovir were increased (Table 2). It is recommended that the dosing interval for Tenofovir Disoproxil Fumarate be modified in patients with estimated creatinine clearance below 50 mL/min or in patients with ESRD who require dialysis.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of Tenofovir Disoproxil Fumarate, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

Patients with Hepatic Impairment: The pharmacokinetics of tenofovir following a 300 mg single dose of Tenofovir Disoproxil Fumarate have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. No change in Tenofovir Disoproxil Fumarate dosing is required in patients with hepatic impairment.

Table 3: Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir^a in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters ^b (90% CI)		
			Cmax	AUC	Cmin
Abacavir	300 once	8	↔	↔	NC
Atazanavir ^c	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/Ritonavir ^c	300/100 once daily	12	↑ 34 (↑ 20 to ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/Ritonavir ^d	300/100 twice daily	12	↑ 24 (↑ 8 to ↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑ 37 (↑ 19 to ↑ 57)
Didanosine ^e	250 or 400 once daily × 7 days	14	↔	↔	↔
Emtricitabine	200 once daily × 7 days	17	↔	↔	↔
Entecavir	1 mg once daily × 10 days	28	↔	↔	↔
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	↔	↔
Lamivudine	150 twice daily × 7 days	15	↔	↔	↔
Lopinavir/Ritonavir	400/100 twice daily × 14 days	24	↔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Saquinavir/Ritonavir	1000/100 twice daily × 14 days	35	↔	↔	↑ 23 (↑ 16 to ↑ 30)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑ 13 (↑ 1 to ↑ 27)	↔	↔
Tipranavir/Ritonavir ^f	500/100 twice daily	22	↓ 23 (↓ 32 to ↓ 13)	↓ 2 (↓ 9 to ↑ 5)	↑ 7 (↓ 2 to ↑ 17)
	750/200 twice daily (23 doses)	20	↓ 38 (↓ 46 to ↓ 29)	↑ 2 (↓ 6 to ↑ 10)	↑ 14 (↑ 1 to ↑ 27)

a. Subjects received Tenofovir Disoproxil Fumarate 300 mg once daily. **b.** Increase = ↑; Decrease = ↓; No Effect = ↔; NC = Not Calculated. **c.** Reyataz Prescribing Information.

d. Prezista Prescribing Information. **e.** Subjects received didanosine buffered tablets. **f.** Aptivus Prescribing Information

Table 4: Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir Disoproxil Fumarate

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters ^a (90% CI)		
			Cmax	AUC	Cmin
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	↔	NA
Atazanavir ^b	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir ^b /Ritonavir	300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25 ^c (↓ 42 to ↓ 3)	↓ 23 ^c (↓ 46 to ↑ 10)
Darunavir ^d /Ritonavir	300/100 mg once daily	12	↑ 16 (↓ 6 to ↑ 42)	↑ 21 (↓ 5 to ↑ 54)	↑ 24 (↓ 10 to ↑ 69)
Didanosine ^e	250 once, simultaneously with Tenofovir Disoproxil Fumarate and a light meal ^f	33	↓ 20 ^g (↓ 32 to ↓ 7)	↔ ^g	NA
Emtricitabine	200 once daily × 7 days	17	↔	↔	↑ 20 (↑ 12 to ↑ 29)
Entecavir	1 mg once daily × 10 days	28	↔	↑ 13 (↑ 11 to ↑ 15)	↔
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	↔	↔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	↔	↔
Lopinavir/Ritonavir	400/100 twice daily × 14 days	24	↔ ↔	↔ ↔	↔ ↔
Saquinavir/Ritonavir	1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑ 41) ↔	↑ 29 ^h (↑ 12 to ↑ 48) ↔	↑ 47 ^h (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↔	↔	↔
Tipranavir ⁱ /Ritonavir	500/100 twice daily	22	↓ 17 (↓ 26 to ↓ 6)	↓ 18 (↓ 25 to ↓ 9)	↓ 21 (↓ 30 to ↓ 10)
	750/200 twice daily (23 doses)	20	↓ 11 (↓ 16 to ↓ 4)	↓ 9 (↓ 15 to ↓ 3)	↓ 12 (↓ 22 to 0)

a. Increase = ↑; Decrease = ↓; No Effect = ↔; NA = Not Applicable. **b.** Reyataz Prescribing Information. **c.** In HIV-infected subjects, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and Cmin values of atazanavir that were 2.3-and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone. **d.** Prezista Prescribing Information. **e.** Videx EC Prescribing Information. Subjects received didanosine enteric-coated capsules. **f.** 373 kcal, 8.2 g fat. **g.** Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions. **h.** Increases in AUC and Cmin are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered. **i.** Aptivus Prescribing Information.

Assessment of Drug Interactions

At concentrations substantially higher (~300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism mediated by any of the following human CYP isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP mediated interactions involving tenofovir with other medicinal products is low.

Tenofovir Disoproxil Fumarate has been evaluated in healthy volunteers in combination with other antiretroviral and potential concomitant drugs. Tables 3 and 4 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of Tenofovir Disoproxil Fumarate on the pharmacokinetics of coadministered drug. Coadministration of Tenofovir Disoproxil Fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Concomitant dosing of Tenofovir Disoproxil Fumarate with didanosine significantly increases the Cmax and AUC of didanosine. When didanosine 250 mg

enteric-coated capsules were administered with Tenofovir Disoproxil Fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown.

No clinically significant drug interactions have been observed between Tenofovir Disoproxil Fumarate and efavirenz, methadone, nelfinavir, oral contraceptives, or ribavirin.

OVERDOSE

Limited clinical experience at doses higher than the therapeutic dose of Tenofovir Disoproxil Fumarate 300 mg is available. In Study 901, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

If overdose occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Tenofovir is efficiently removed by hemodialysis with

an extraction coefficient of approximately 54%. Following a single 300 mg dose of Tenofovir Disoproxil Fumarate, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

STORAGE

Store protected from moisture at a temperature not exceeding 30°C.

MANUFACTURED BY:

Strides Arcolab Limited
No. 36/7, Suragjakanahalli, Indlavadi Cross,
Anekal Taluk, Bangalore-562106

MARKETED BY:

Abbott India Limited,
3-4, Corporate Park, Sion-Trombay Road,
Mumbai-400071.
India.

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Abbott

For the use of a registered medical practitioner, hospital or laboratory only

A CLEAR CHOICE to help their mind be clear of Hep B

Tenfo clearTM

Tenofovir Disoproxil Fumarate Tablets I.P. 300 mg

Abbreviated Prescribing Information: TENOFOVIR DISOPROXIL FUMARATE TABLETS IP 300 MG TENFOCLEAR™

COMPOSITION: Each film coated tablet contains Tenofovir Disoproxil Fumarate IP 300 mg eq. to Tenofovir Disoproxil 245 mg
INDICATION: Tenofovir Disoproxil Fumarate Tablets IP 300 mg is indicated for the treatment of chronic hepatitis B in adults and as an anti-HIV agent. **DOSAGE AND ADMINISTRATION:** Recommended Dose in Adults and Pediatric Patients 12 Years of Age and Older (35 kg or more): For the treatment of HIV-1 and hepatitis B. The dose is one 300mg tablet of Tenofovir Fumarate's tablet once daily taken orally, without regard to food. **Pediatric Patients 2 Years of Age and Older:** Tenofovir exposure achieved in pediatric subjects receiving oral once daily doses of Tenofovir Fumarate 300 mg (tablet) or 8 mg/kg of body weight (powder) up to a maximum dose of 300 mg was similar to exposures achieved in adults receiving once-daily doses of Tenofovir Disoproxil Fumarate 300 mg. Safety and effectiveness of Tenofovir Disoproxil Fumarate in pediatric patients younger than 12 years of age or less than 35 kg with chronic hepatitis B have not been established. Clinical trials of Tenofovir Disoproxil did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. No change in Tenofovir Disoproxil Fumarate dosing is required in patients with hepatic impairment. Dosage Adjustment for Patients with Altered Creatinine Clearance • Creatinine clearance > 50 mL/min: 300 mg every 24 hours. • Creatinine clearance 30-49 mL/min: 300 mg every 48 hours. • Creatinine clearance 10-29 mL/min: 300 mg every 72 to 96 hours. • Hemodialysis: 300 mg every 7 days or after approximately 12 hours of dialysis. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **WARNINGS AND PRECAUTION:** Lactic Acidosis/Severe Hepatomegaly with Steatosis: Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Exacerbation of Hepatitis after Discontinuation of Treatment: Patients infected with HBV who discontinue Tenofovir Disoproxil Fumarate should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. New Onset or Worsening Renal Impairment: Dosing interval adjustment of Tenofovir Disoproxil Fumarate Tablets and close monitoring of renal function are recommended in all patients with creatinine clearance below 50 mL/min. Tenofovir Disoproxil Fumarate should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)). Coadministration with Other Products: Tenofovir Disoproxil Fumarate should not be used in combination with the fixed-dose combination products where tenofovir disoproxil fumarate is a component of these products. Tenofovir Disoproxil Fumarate should not be administered in combination with adefovir dipivoxil. Patients Coinfected with HIV-1 and HBV: Due to the risk of development of HIV-1 resistance, Tenofovir Disoproxil Fumarate should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen. Mineralization Defects: Hypophosphatemia and osteomalacia secondary to proximal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF. Fat Redistribution, Immune Reconstitution Syndrome: During the initial phase of combination antiretroviral therapy, some individuals may develop an inflammatory response to latent or residual opportunistic infections, which may necessitate further evaluation and treatment. Early Virologic Failure: Triple nucleoside regimens should be used with caution. Patients on a therapy utilizing a triple nucleosides-only regimen should be carefully monitored and considered for treatment modification. **PREGNANCY AND LACTATION:** There are no adequate and well-controlled studies in pregnant women. It is recommended that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. **ADVERSE REACTIONS:** In HIV-infected adult subjects. Most common adverse reactions (incidence greater than or equal to 10%, Grades 2-4) are rash, diarrhea, headache, pain, depression, asthenia, and nausea. In HBV-infected subjects with compensated liver disease: most common adverse reaction (all grades) was nausea (9%). Issued on: 22nd December 2015. Source: Prepared based on full prescribing information, version 1, dated 7th December 2015. For full prescribing information, please contact: Abbott India Limited, 3-4 Corporate Park, Sion-Trombay Road, Mumbai - 400071, India.

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Tenfoclear™

Tenofovir Disoproxil Fumarate Tablets I.P. 300 mg



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