APPROXIMATELY
95% of new cases of chronic hepatitis B (CHB) in the United States originate from another country[2]

MORE THAN
50% of Americans living with CHB are Asian/Pacific Islanders[3]

#1 Prescribed oral antiviral according to US prescription data for treatment of CHB[1a]

TAKE A CLOSER LOOK AT VIREAD
IN THE TREATMENT OF CHINESE CHB PATIENTS WITH COMPENSATED LIVER DISEASE

RESULTS OF VIREAD CLINICAL STUDIES INCLUDING CHINA TRIAL

INDICATION AND USAGE

VIREAD® (tenofovir disoproxil fumarate) is indicated for the treatment of chronic hepatitis B in adults and pediatric patients 12 years of age and older.

The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- The indication in adults is based on data from treatment of subjects who were nucleoside–treatment-naïve and treatment-experienced with documented resistance to lamivudine. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease
- VIREAD was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease
- The numbers of subjects in clinical trials who had adefovir resistance-associated substitutions at baseline were too small to reach conclusions of efficacy

IMPORTANT SAFETY INFORMATION

BOXED WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals**
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted**

[a]Healthcare Analytics Monthly data, August 2014-December 2015.

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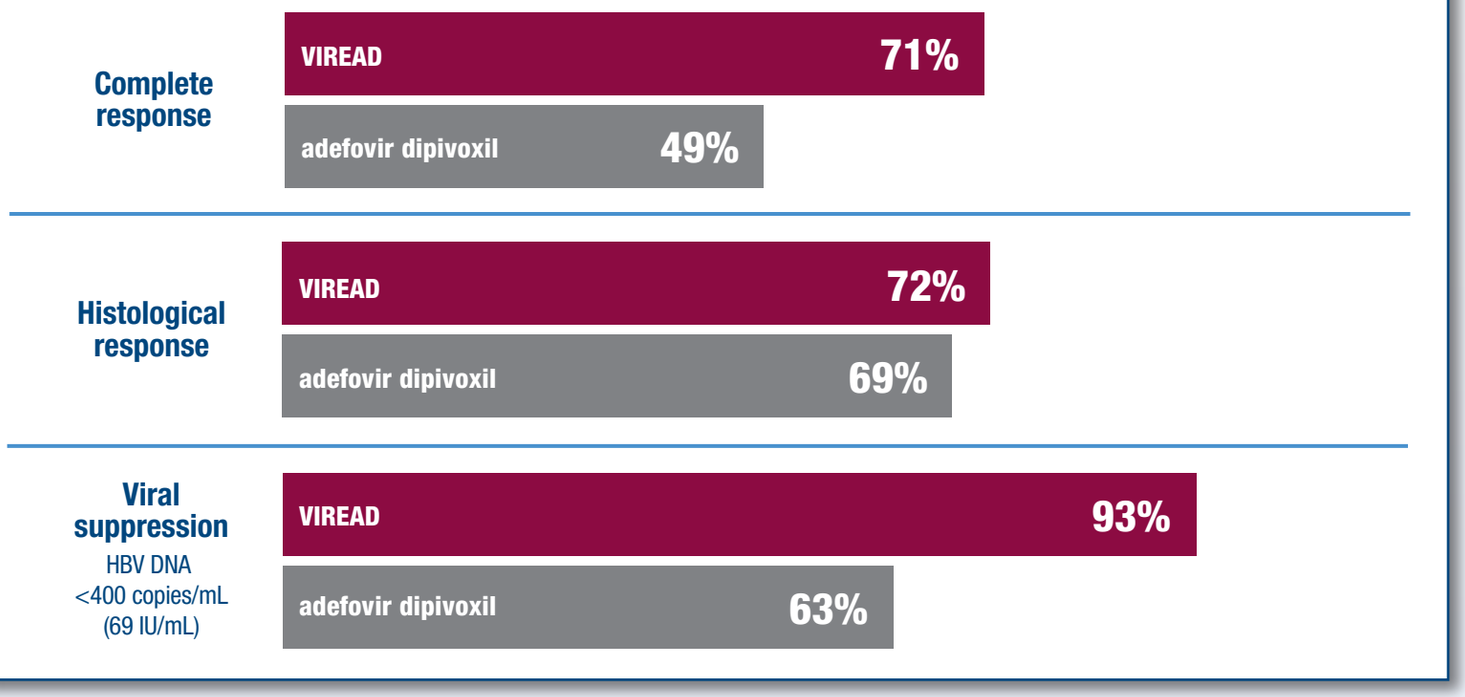
300 mg tablets® Viread® tenofovir disoproxil fumarate

VIREAD® (TENOFOVIR DISOPROXIL FUMARATE) CLINICAL TRIAL RESULTS...

Study design

In Studies 102 (HBeAg–, N=375) and 103 (HBeAg+, N=266), a combined total of 641 **adult patients with chronic hepatitis B (CHB) and compensated liver disease who were primarily nucleoside–treatment-naïve** entered a 48-week, randomized, double-blind, active-controlled treatment period comparing VIREAD 300 mg to adefovir dipivoxil 10 mg. Subjects who completed double-blind treatment at Week 48 were eligible to roll over with no interruption in treatment to open-label VIREAD. Of 641 patients enrolled in the initial trials, 412 (64%) completed 384 weeks of treatment.[4]

HBeAg– (Study 102) adult subjects from Week 0 to Week 48[4,5]
(VIREAD n=250, adefovir dipivoxil n=125)



IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

- **New onset or worsening renal impairment:** Cases of acute renal failure and Fanconi syndrome have been reported with the use of VIREAD. In all patients, assess estimated creatinine clearance (CrCl) prior to initiating and during therapy. In patients at risk for renal dysfunction, including those who previously experienced renal events while receiving adefovir dipivoxil, additionally monitor serum phosphorus, urine glucose, and urine protein. In patients with CrCl <50 mL/min, adjust dosing interval and closely monitor renal function. Avoid concurrent or recent use with a nephrotoxic agent. Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after initiation of high dose or multiple NSAIDs in HIV-infected patients with risk factors for renal dysfunction; consider alternatives to NSAIDs in these patients. 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

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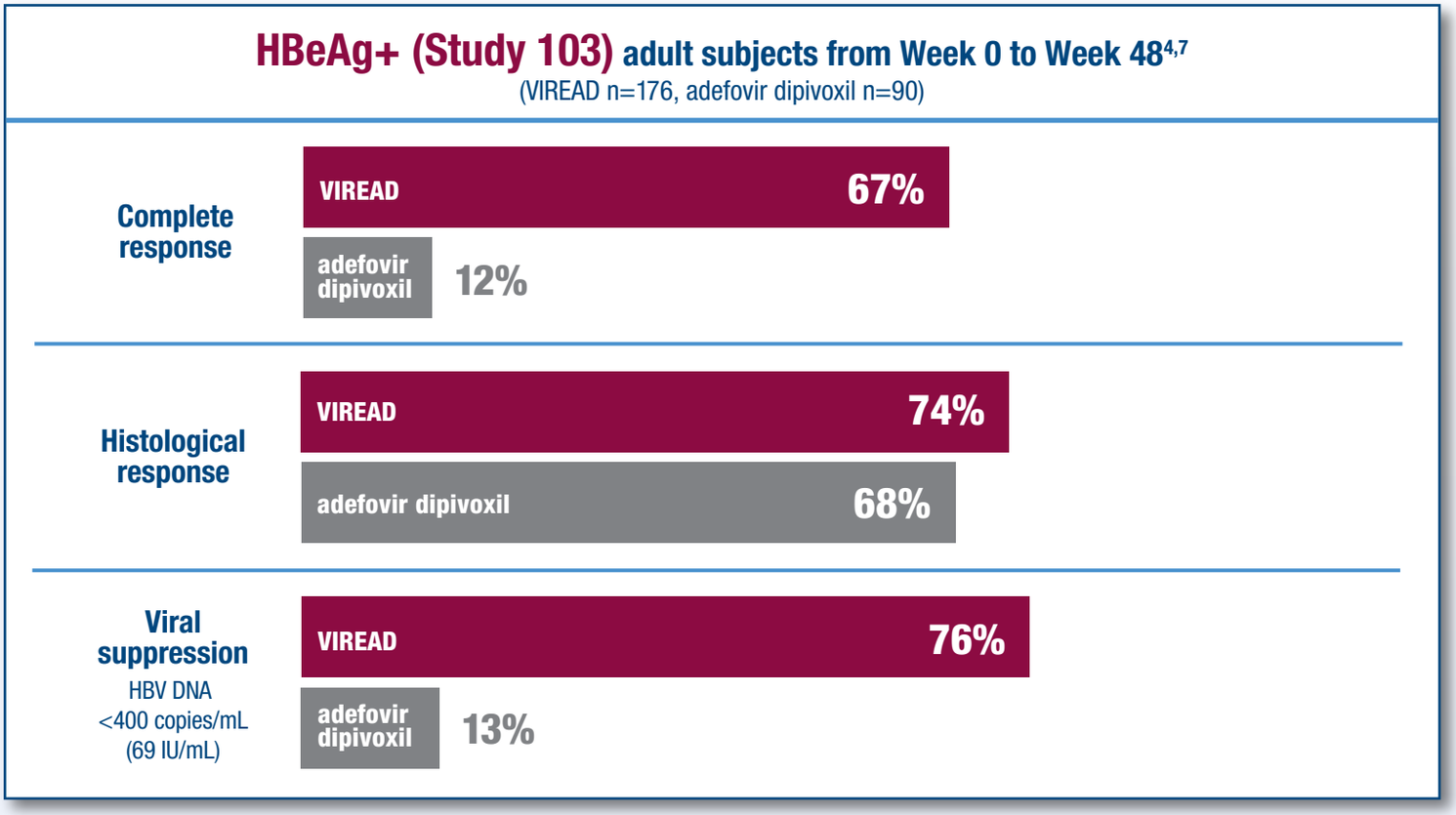
…STUDY 102 AND STUDY 103

Primary endpoint

The primary endpoint in Studies 102 and 103 (N=641) was complete response to treatment at 48 weeks as defined by HBV DNA <400 copies/mL (69 IU/mL) + histological response (Knodell necroinflammatory score improvement of ≥2 points without worsening in Knodell fibrosis score). **Evaluation of viral suppression was a prespecified secondary endpoint.**[4,6]



IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Coadministration with other products:**
  - — Do not use in combination with other products containing tenofovir disoproxil fumarate
  - — Do not administer in combination with adefovir dipivoxil
- **Patients coinfected with HIV-1 and HBV:** Due to the risk of development of HIV-1 resistance, VIREAD should only be used in HIV-1 and HBV coinfected 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 VIREAD
- **Bone effects:** Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia, have been seen in patients treated with VIREAD. Consider assessment of BMD in adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for bone loss. In a clinical trial conducted in pediatric subjects 12 to <18 years of age with chronic hepatitis B, total body BMD gain was less in VIREAD-treated subjects as compared to the control group. In patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms, hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered

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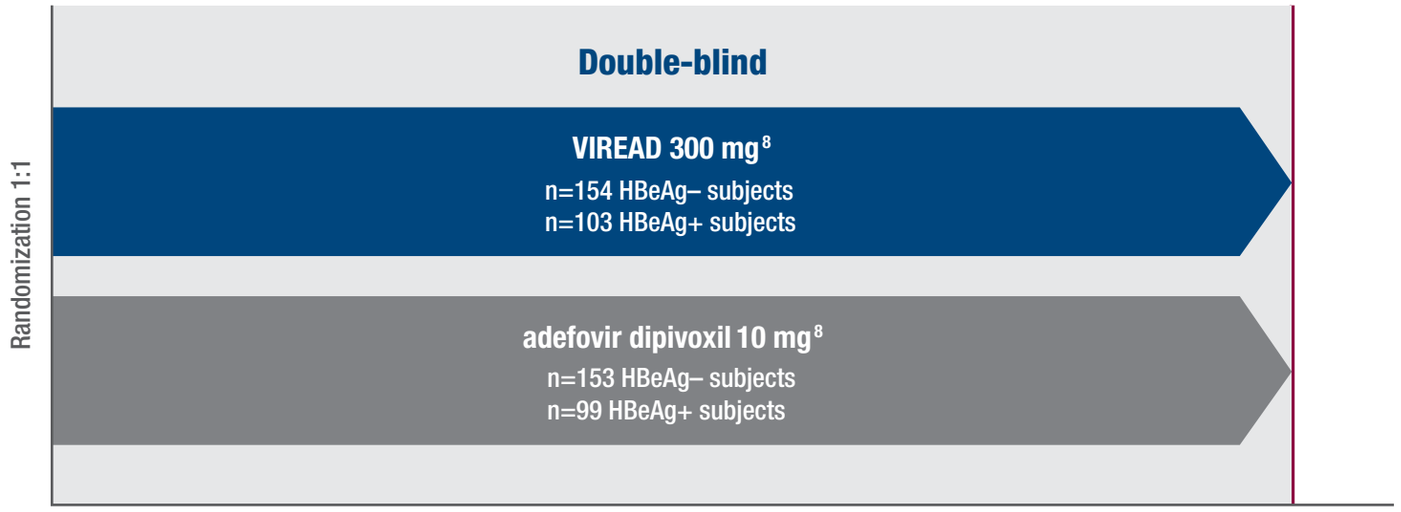
For more information, visit **www.viread.com/hcp**

48-WEEK STUDY OF VIREAD® (TENOFOVIR DISOPROXIL FUMARATE) IN CHINESE CHB PATIENTS

The primary endpoint in the Phase 3 study (N=509) was HBV DNA <400 copies/mL (69 IU/mL) at Week 48.[8]

PHASE 3 STUDY DESIGN: 48-week, double-blind, randomized, controlled study of 509 HBeAg+ and HBeAg– Chinese subjects with CHB. Subjects who completed 48 weeks of study treatment were permitted to roll over to open-label VIREAD[8]*



*Liver biopsy was performed at selected sites at Weeks 0 and 48 in 60 subjects in each treatment arm.[8,9]

97% (498/509) **retention rate** at Week 48

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

- **In HBV-infected subjects with compensated liver disease:** Most common adverse reaction (all grades) was nausea (9%). Other treatment-emergent adverse reactions reported in >5% of patients treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash
- **In HBV-infected subjects with decompensated liver disease:** Most common adverse reactions (all grades) reported in ≥10% of patients treated with VIREAD were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%)

DRUG INTERACTIONS

- **Didanosine:** Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy). Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. In patients weighing >60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with VIREAD and in patients weighing <60kg, the didanosine dose should be reduced to 200 mg once daily when coadministered with VIREAD

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VIREAD CHINA TRIAL DATA

Baseline characteristics in adult Chinese subjects with CHB[8] (VIREAD n=257, adefovir dipivoxil n=252)				
Mean age (years)*	36			
Male/Female*	83%/17%			
Asian—East Asian Heritage*	100%			
HBeAg status	**HBeAg–** (VIREAD n=154)	**HBeAg–** (adefovir dipivoxil n=153)	**HBeAg+** (VIREAD n=103)	**HBeAg+** (adefovir dipivoxil n=99)
Mean HBV DNA (log_{10} copies/mL)	6.9	7.0	8.7	8.7
Mean ALT (U/L)	133.4	112.6	199.1	189.0
Previous lamivudine experience, n (%)†	(n=153) Yes 7 (5) No 146 (95)	(n=151) Yes 4 (3) No 147 (96)	(n=102) Yes 4 (4) No 98 (95)	(n=99) Yes 4 (4) No 95 (96)
HBV genotype, %‡	(n=153) B-46.4, B/C-0.7, C-52.9	(n=152) B-48.7, B/C-0, C-51.3	(n=103) B-47.6, B/C-2.9, C-49.5	(n=99) B-45.5, B/C-4.0, C-50.5
Mean duration of hepatitis in months (range)	153 (7-429)	151 (7-466)	110 (8-413)	119 (7-338)

*Combined data from 2 separate study arms (VIREAD and adefovir dipivoxil).

†Four subjects had missing data.

‡Two subjects had missing data.

No clinically relevant creatinine-related adverse events[8,9]

No VIREAD subjects had a confirmed (defined as 2 consecutive visits)

- increase of ≥0.5 mg/dL from baseline serum creatinine concentration
- serum creatinine concentration ≥2 mg/dL
- creatinine clearance rate <50 mL/min

The incidence of adverse events related to the study drug was similar in the VIREAD (3.9%) and adefovir dipivoxil (4.8%) groups.[8]

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS (cont'd)

- **HIV-1 protease inhibitors:** Coadministration decreases atazanavir concentrations and increases tenofovir concentrations; use atazanavir given with ritonavir. Coadministration of VIREAD with atazanavir and ritonavir, darunavir and ritonavir, or lopinavir/ritonavir increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity
- **Hepatitis C antivirals:** Coadministration of VIREAD with HARVONI increases VIREAD exposure; monitor for adverse reactions associated with VIREAD. Consider an alternative HCV or HIV-1 therapy in patients receiving VIREAD concomitantly with HARVONI and an HIV-1 protease inhibitor with ritonavir or cobicistat
- **Drugs affecting renal function:** Coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir

DOSAGE AND ADMINISTRATION

- Recommended dose, in adults and pediatric patients ≥12 years of age (≥35 kg), for the treatment of chronic hepatitis B: one 300-mg tablet, once daily, taken orally, without regard to food
- In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown
- Safety and efficacy in pediatric patients <12 years of age or weighing <35kg with chronic hepatitis B have not been established
- The dosing interval of VIREAD should be adjusted (using recommendations in the table below) and renal function closely monitored in patients with baseline creatinine clearance <50 mL/min

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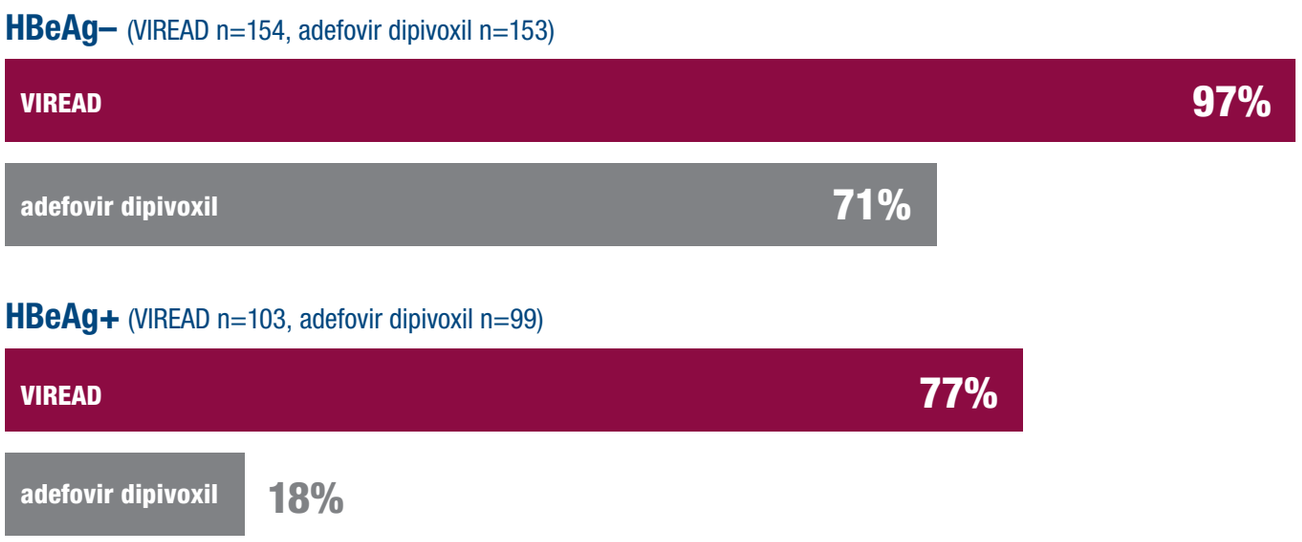
Viread® 300mg tablets
tenofovir disoproxil fumarate

VIREAD CHINA TRIAL: POTENT VIRAL SUPPRESSION

The trial in Chinese CHB patients had similar virologic suppression rates to Studies 102 and 103[5,7,8]

CHINA TRIAL (PHASE 3 STUDY)
subjects achieving viral suppression (HBV DNA <400 copies/mL [69 IU/mL]) at 48 weeks[8]



IMPORTANT SAFETY INFORMATION (cont'd)

DOSAGE ADJUSTMENT FOR PATIENTS WITH ALTERED CREATININE CLEARANCE

	Creatinine clearance (mL/min)[a]			Hemodialysis patients
	≥50	30-49	10-29	
Recommended 300 mg dosing interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis[b]

[a]Calculated using ideal (lean) body weight.

[b]Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

- The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients
- No dose adjustment 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 these patients
- No data are available to make dose recommendations in pediatric patients with renal impairment

References: 1. Data on file, Gilead Sciences, Inc. Healthcare Analytics. December 2015. **2.** Mitchell T, Armstrong GL, Hu DJ, Wasley A, Painter JA. The increasing burden of imported chronic hepatitis B–United States, 1974–2008. *PLoS One.* 2011;6(12):e27717. **3.** Centers for Disease Control and Prevention. Viral hepatitis populations: Asian and Pacific Islanders. CDC Web site. http://www.cdc.gov/hepatitis/Populations/api.htm. Accessed July 17, 2015. **4.** VIREAD [package insert]. Foster City, CA: Gilead Sciences, Inc.; February 2016. **5.** Data on file, Gilead Sciences, Inc. Study 102 CSR. **6.** Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med.* 2008;359(23):2442-2455. **7.** Data on file, Gilead Sciences, Inc. Study 103 CSR. **8.** Hou JL, Gao ZL, Xie Q, et al. Tenofovir disoproxil fumarate vs adefovir dipivoxil in Chinese patients with chronic hepatitis B after 48 weeks: a randomized controlled trial. *J Viral Hepat.* 2015;22(2):858-93. **9.** Data on file, Gilead Sciences, Inc. Study LOC114648 CSR.

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GILEAD IS COMMITTED TO THE EDUCATION AND TREATMENT OF CHRONIC HEPATITIS B.

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