

with active HBV replication. Moreover, in populations of patients with chronic hepatitis B who are at risk for HCC ([Chap. 82](#)), the risk is highest for those with continued, high-level HBV replication and lower for persons in whom initially high-level HBV DNA falls spontaneously over time. Therefore, management of chronic hepatitis B is directed at suppressing the level of virus replication. Although clinical trials tend to focus on clinical endpoints achieved over 1–2 years (e.g., suppression of HBV DNA to undetectable levels, loss of HBeAg/HBsAg, improvement in histology, normalization of ALT), these short-term gains translate into reductions in the risk of clinical progression, hepatic decompensation, HCC, liver transplantation, and death; regression of cirrhosis and of esophageal varices has been documented to follow long-term pharmacologic suppression of HBV replication. In addition, restoration of impaired HBV-specific T-cell function has been shown following successful suppression of HBV replication with antiviral therapy. To date, eight drugs have been approved for treatment of chronic hepatitis B: injectable interferon (IFN) α and pegylated interferon (long-acting IFN bound to polyethylene glycol, PEG [PEG IFN]) and the oral agents lamivudine, adefovir dipivoxil, entecavir, telbivudine, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF).

Antiviral therapy for hepatitis B has evolved rapidly since the mid-1990s, as has the sensitivity of tests for HBV DNA. When IFN and the first oral antiviral lamivudine were evaluated in clinical trials, HBV DNA was measured by insensitive hybridization assays with detection thresholds of 10^5 – 10^6 virions/mL; when subsequent treatments were studied in clinical trials, HBV DNA was measured by sensitive amplification assays (polymerase chain reaction [PCR]) with detection thresholds of 10^1 – 10^3 viral copies/mL or IU/mL. Recognition of these distinctions is helpful when comparing results of clinical trials that established the efficacy of these therapies (reviewed below in chronologic order of publication of these efficacy trials). Of the eight approved treatments, PEG IFN, entecavir, and the two tenofovir preparations (TDF and TAF) are recommended as first-line agents, and generally, the oral agents are favored over injectable PEG IFN.