with HBeAg-negative chronic hepatitis B, however, HBeAg seroconversion is not an option, and a sustained response (i.e., maintained even after cessation of treatment) is a less realistic goal; long-term suppressive therapy is usually necessary.[82] Chronic HBV infection is associated with the presence in hepatocytes of stable covalently closed circular HBV DNA (cccDNA). Although proponents of one type of therapy over another invoke relative efficacy of a drug in reducing cccDNA, no therapies have been shown to eradicate this stable form of HBV DNA, whereas all therapies that reduce HBV replication have also been shown to reduce cccDNA. Similarly, persons with spontaneous HBeAg seroconversion have a concomitant reduction in serum and liver HBV DNA and in hepatic cccDNA. Successful antiviral therapy with any agent is likely to have a beneficial impact on the long-term natural history of chronic hepatitis B.[98–100] Similarly, oral agents have been shown to retard the clinical progression of HBV-associated compensated cirrhosis and advanced fibrosis,[101,102] and an approximately 30% reduction in the number of patients with end-stage chronic hepatitis B listed per year for liver transplantation coincided with the introduction and wide use of oral antivirals between the years of 2000 and 2006.[103]

According to recommendations of the American Association for the Study of Liver Diseases (AASLD),[104] candidates for antiviral therapy have HBV DNA levels of more than 2×10^3 or $\times 10^4$ IU/mL (standardized IU/mL have replaced copies/mL [1 IU = 5.6 copies/mL] in contemporary usage), usually with elevated ALT levels and with histologic evidence of liver injury. Patients with HBeAg-reactive (with HBV DNA levels $>2 \times 10^4$ IU/mL) and HBeAg-negative (with HBV DNA levels $>2 \times 10^3$ IU/mL) chronic hepatitis B and with ALT two or more times the upper limit of normal (ULN) are candidates for therapy, according to the AASLD and, with slight modifications, guidelines from other societies.[105–107] Patients who meet HBV DNA criteria but have ALT less than two times the ULN constitute an indeterminate group in whom a liver biopsy or a noninvasive measure of liver fibrosis (e.g., liver elasticity) may be useful to guide treatment decisions (when moderate-to-severe inflammation, necrosis, fibrosis, or a combination of these are present). In the European Association for the Study of the Liver (EASL) guidelines, the threshold for treatment in both HBeAg-positive and HBeAg-negative chronic hepatitis B is HBV DNA $>2 \times 10^3$ IU/mL and an ALT level greater than the ULN. For patients who do not meet HBV DNA and ALT thresholds, included in factors to be considered that favor therapy are age above 40, family history of HCC, previous treatment history, or extrahepatic immune-complex manifestations. All patients with compensated cirrhosis with any detectable level of HBV DNA, regardless of ALT level, should be treated. Patients with decompensated chronic hepatitis B are not candidates for interferon (IFN) therapy, which is contraindicated because of ineffectiveness and intolerability, but are candidates for therapy with any level of HBV DNA or ALT and have been shown to derive therapeutic benefit from nucleoside or nucleotide analogues. Antiviral therapy is not indicated in inactive hepatitis B carriers (with persistently normal ALT, undetectable or very low HBV DNA [$<2 \times 10^3$ IU/mL], and normal to near-normal histologic findings).

Eight antiviral drugs have been approved in the United States by the FDA for treatment of chronic hepatitis B: injectable recombinant IFN-α,[108] pegylated (PEG) IFN-α,[109,110] and six oral agents—the nucleoside analogues lamivudine,[111–114] entecavir,[115,116] and telbivudine,[117,118] and the nucleotide analogues adefovir dipivoxil,[119,120] tenofovir disoproxil fumarate (TDF),[121] and tenofovir alafenamide[122,123] (also see Chapter 47). The relative antiviral potencies of the approved drugs are listed in Table 117.6. Of the eight, PEG IFN-α, entecavir, and the two tenofovir formulations are used as first-line agents.

TABLE 117.6 Relative Potencies of Approved Antiviral Drugs for Chronic Hepatitis B

	LOG_{10} REDUCTION OF HBV DNA IN HBeAg-REACTIVE DISEASE
Interferon-α	Not reported
Adefovir	3.5
Pegylated interferon	4.5
Lamivudine	5.5
Tenofovir	6.2
Telbivudine	6.5
Entecavir	6.9

HBeAg, hepatitis B e antigen; *HBV,* hepatitis B virus; *LOG,* logarithm.

Interferon-Based Therapy for Chronic Hepatitis B

Although reports that describe antiviral activity of IFNs in patients with chronic hepatitis B date back to the mid-1970s,[124] not until the late 1980s was the convincing efficacy of IFN-α in chronic hepatitis B shown in controlled clinical trials.[108,125] IFNs induce host antiviral gene expression and signal-transduction pathways and enhance cytolytic T-cell activity targeted at HBV-infected hepatocytes. A meta-analysis of 24 randomized controlled trials that involved 1299 patients showed that those with standard IFN-α treatment (5–10 million units subcutaneously for 16–24 weeks[126]) had a 25% advantage in normalization of ALT activity, a 25% advantage in HBeAg loss, a 23% advantage in clearance of HBV DNA as measured with hybridization assay (detection threshold of approximately $\geq 10^5$–10^6 virions/mL), and a 6% advantage in HBsAg loss.[127] Relapse is infrequent after a successful HBeAg response, and among patients with IFN-associated HBeAg responses, posttreatment HBsAg seroconversions occur in up to 80% over the decade after therapy in Western patients,[98,100,127–129] but not in Asian patients.[130,131] In addition, the natural history of chronic hepatitis B has been shown to be improved after successful IFN therapy; during the decade after successful IFN therapy, both long-term survival and freedom from hepatic decompensation have been reported,[99] as has a reduction in the frequency of HCC.[130,132] The first approved IFNs for hepatitis B were recombinant IFN-α preparations administered three times a week or every other day; however, long-acting once-weekly PEG IFN has supplanted standard IFN-α. A polyethylene glycol moiety is covalently linked to IFN through a reaction called pegylation, which renders the drug more stable and less immunogenic. Two forms are available: PEG IFN-α2a and PEG IFN-α2b. Although they differ in size (40 kD vs. 12 kD) and dosage regimen (180 μg vs. 1.5 μg/kg/wk), their efficacy appears similar; however, PEG IFN-α2a is the only PEG IFN approved for hepatitis B. IFN is administered via subcutaneous injection, and resistance does not emerge during therapy, as it does for some of the oral agents (see subsequent discussion).

Large-scale trials of 48 weeks of treatment with PEG IFN-α2a 180-μg injections weekly versus lamivudine 100 mg by mouth daily versus combination PEG IFN–lamivudine were conducted in HBeAg-positive and HBeAg-negative populations. In HBeAg-positive patients, at the end of the 48-week treatment period, HBV DNA was suppressed by 4.5 $\log_{10}$, 5.8 $\log_{10}$, and 7.2 $\log_{10}$ in the three groups, respectively. Although HBeAg seroconversions occurred during therapy in comparable proportions of all three groups (27%, 20%, and 24%, respectively), 24 weeks after cessation of therapy, HBeAg seroconversions were most common, 32%, in the PEG IFN monotherapy arm, compared with 27% in the combination arm and 19% in the lamivudine monotherapy arm.[109]

In HBeAg-negative patients, during 48 weeks of treatment, HBV DNA was suppressed by 4.1 $\log_{10}$, 4.2 $\log_{10}$, and 5.0 $\log_{10}$ in the PEG IFN monotherapy, lamivudine monotherapy, and combination therapy groups, respectively. Yet 24 weeks after completion of therapy, HBV DNA was suppressed to undetectable ($<10^2$ copies/mL [studies were done before adoption of international units per milliliter]) in only 19%, 20%, and 7% of the three groups, respectively.[110] The degree of HBV DNA suppression in the PEG IFN arms was durable 6 months later, at the end of 2 years (17%), at the end of 3 years (13%–18%), and at 5 years (12%)[133,134]; however, this is the only trial to demonstrate such short-term and long-term benefits of PEG IFN for HBeAg-negative chronic hepatitis B. In a randomized trial of 48 weeks of PEG IFN plus RBV versus PEG IFN in 138 patients with HBeAg-negative chronic hepatitis B, the addition of RBV conferred no benefit, but the more important outcome was the limited efficacy of PEG IFN–based therapy. Only 7.5% of the study population achieved suppression of HBV DNA

to less than 400 copies/mL at week 24 after treatment, and HBsAg loss did not occur in any trial participant.[135] In a study of patients with HBV genotype D, HBeAg-negative patients treated with PEG IFN for a median of 23 months,[136] *IL28B* genotype "CC" was associated with a higher rate of HBsAg loss (29%) than non-CC genotypes (13%); the beneficial impact of CC over non-CC genotypes has also been reported for HBeAg-reactive chronic hepatitis B.[137] Another predictor of PEG IFN responsiveness in chronic hepatitis B is the quantitative HBsAg level—a decline within the first 12 to 24 weeks and a reduction to less than 20,000 IU/mL at week 24. If these milestones are not achieved, therapy will be ineffective and can be stopped.[138,139]

These observations notwithstanding, in general, the value of PEG IFN in HBeAg-negative patients remains controversial because the benefits of therapy may not outweigh its side effects and intolerability.

Toxicities of IFN include systemic flulike symptoms; malaise; fatigue; marrow suppression (cytopenias); emotional liability (manifesting primarily as irritability, depression, or anxiety); hair loss or thinning; weight loss; and autoimmune events, most commonly thyroiditis. Side effects are usually manageable but limit therapy in those with marked hypersplenism and severe psychiatric disorders.

During IFN-based therapy, ALT flares that are typically well tolerated can occur, except in patients with advanced cirrhosis, in whom such flares can precipitate hepatic decompensation. Patients treated with IFN need frequent monitoring of blood counts and thyroid-stimulating hormone and close medical supervision. Because of its better efficacy and preferable once-weekly administration, PEG IFN has replaced standard IFN as first-line therapy. In practice, PEG IFN is discontinued after 1 year of therapy, whereas the oral agents are continued until treatment end points are met; the extension of therapy with oral agents can yield ultimate serologic response rates comparable with or exceeding those of PEG IFN (see subsequent discussion).

Direct Oral Antiviral Agents

Lamivudine. Although lamivudine has been superseded by newer, more effective oral agents, many important lessons gleaned from experiences with lamivudine apply to antiviral therapy with other nucleoside analogues. Lamivudine, the (−)enantiomer of β-L-2′,3′-dideoxy-3′-thiacytidine and an analogue of deoxycytidine, is a reverse transcriptase inhibitor that results in HBV and HIV RNA chain termination (see Chapter 128). The first nucleoside analogue, approved in 1998, for the treatment of chronic hepatitis B, lamivudine, 100 mg daily administered orally, reduces HBV DNA replication by a median of up to 5.5 logs.[115,117,140] In HBeAg-reactive chronic hepatitis B, 1 year of lamivudine treatment, whether in treatment-naïve or IFN-experienced patients, is associated with HBeAg loss in just under one-third, HBeAg seroconversion in 16% to 21%, histologic improvement in 50% to 60%, and a return to normal of aminotransferase activity in 40% to 75%.[111–117] Comparable results have been achieved in children.[141] Suppression of HBV DNA to levels undetectable with hybridization assays (with detectability thresholds of 10^5–10^6 virions/mL) is achieved in almost all patients[111–114] and to levels undetectable with PCR amplification assays (thresholds of 10^2–10^3 virions/mL) in 30% to 44%.[115,117] Unlike IFN, lamivudine is effective in patients with high-level HBV DNA, but like IFN, lamivudine is more likely to result in HBeAg loss and seroconversion among patients with high baseline aminotransferase levels.[112,142,143] In fact, for the subgroup of patients with ALT levels five or more times the ULN, whether Caucasian or Asian, lamivudine therapy achieves HBeAg seroconversion in approximately 55%. In contrast, for patients with normal aminotransferase activity, common in Asian populations, HBeAg responses are rarely achieved. HBeAg seroconversions are more likely if HBV DNA suppression is profound, confined to patients with HBV DNA suppressed to less than 10^4 virions/mL.[53] If HBeAg responses occur and therapy is stopped after 1 year, the response is durable in more than 80% of patients and (at least in Western cohorts, but not in Asians) may be followed by HBsAg seroconversion (>20% after 2–3 years).[95,96,144,145] Lamivudine responses are more durable among patients with more protracted treatment duration after HBeAg response[97,146,147] and among those with HBV genotype B than with C.[147] Lamivudine-associated HBV DNA suppression was found to be substantially more profound in patients with HBV subtype *ayw* (genotype D) than in those with subtype *adw* (genotype A).[148] If HBeAg remains detectable during therapy, cessation of therapy results in a return to baseline virologic and biochemical levels; long-term therapy, then, is indicated to maintain clinical benefit, and HBeAg seroconversions have been shown to increase over time with duration of therapy, approaching 50% after 5 years.[144,145,149]

During a year of lamivudine therapy, progression of fibrosis is retarded,[150] and with more protracted therapy, histologic benefit continues. Moreover, in patients with compensated cirrhosis treated for 3 years cumulatively, regression of cirrhosis has been documented histologically to occur in two-thirds of patients.[151,152]

In HBeAg-negative chronic hepatitis B, an HBeAg serologic response is not a goal; instead, responsiveness is measured with biochemical, virologic, and histologic end points. In this subgroup of patients treated for a year, biochemical responses are achieved in approximately 60% to 80% and histologic responses in two-thirds.[116,117,153] Undetectable HBV DNA as measured with PCR can be achieved in approximately 60% to 70% of patients, and HBV DNA can be suppressed by up to 4.7 $\log_{10}$ copies/mL.[116,117] When therapy is discontinued, a return to baseline is almost invariable; therefore, in order to maintain benefit in HBeAg-negative chronic hepatitis B, long-term therapy is necessary.[154,155]

During lamivudine treatment, flares in ALT activity accompany HBV DNA suppression in approximately 40% of patients, and in the absence of a sustained response (i.e., HBeAg response), posttreatment ALT flares occur in approximately 20% to 30% of patients.[112,156] Flares in biochemical activity may be no more common in patients with lamivudine treatment than in matched placebo recipients, but posttreatment flares are more common in treated patients.[145] Usually, posttreatment flares are mild and asymptomatic, but severe, even life-threatening, posttreatment flares have been reported, primarily in patients with cirrhosis with marginal hepatic compensation before treatment.[157] Therefore, whenever lamivudine is discontinued, patients should be monitored closely for several months.

Although patients with decompensated cirrhosis are not candidates for IFN therapy, they can respond to lamivudine, which can stabilize, retard, or even reverse clinical and laboratory markers of hepatic failure.[158–160] In one report of 23 patients referred to a liver transplantation center after the availability of lamivudine, the survival rate at 4 years was 60%. In contrast, among 23 patients referred to the same center in the period immediately before the availability of lamivudine, all patients for whom donor livers were not available died within just over a year.[159] In addition, a placebo-controlled trial of lamivudine in patients with compensated cirrhosis (or advanced hepatic fibrosis) showed a significantly higher frequency of disease progression (≥2-point elevation in Child-Turcotte-Pugh compensation score, life-threatening complications of cirrhosis, emergence of HCC) in the placebo group compared with the lamivudine group, which provided proof of principle that nucleoside-analogue maintenance therapy can prevent hepatic decompensation in patients with cirrhosis.[101] The observation that lamivudine treatment can retard the clinical progressions of cirrhosis adds to the evidence that drug treatment can improve the natural history of chronic hepatitis B, as has been shown in Western patients treated with IFN for chronic hepatitis B.[99]

Besides ALT flares that accompany treatment-related suppression of HBV DNA (similar to those seen during IFN therapy and to those that occur during spontaneous HBeAg seroconversion) and that accompany cessation of treatment (as viral replication resumes), no adverse effects of therapy were identified in registration trials of lamivudine compared with placebo, nor have adverse events been linked to lamivudine since its approval.[156] Unfortunately, when used as monotherapy, lamivudine is associated with viral resistance.[161] Mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) region of the HBV polymerase emerge in approximately a quarter of patients treated with lamivudine for a year.[53,111–114,153,161–163] The most common of these are methionine-to-valine or methionine-to-isoleucine mutations in polymerase domain C at amino acid 204 (M204V, M204I), often accompanied by upstream leucine-to-methionine mutations (L180M) in domain B.[164–166] With each successive year of lamivudine therapy, the frequency of YMDD mutations increases, reaching 70% at 5 years.[167] Initial observations suggested that YMDD-mutant hepatitis B was less "replicatively competent" in vitro,[162,168] which corresponded with the

biochemical, virologic, and histologic benefit (compared with pretreatment baseline) maintained after transient ALT and HBV DNA elevations accompanying the emergence of the mutations.[161] Although HBeAg seroconversions continue to occur after the emergence of YMDD mutations, the frequency of HBeAg responses is lower in YMDD-mutant chronic hepatitis B, and ultimately, clinical benefit is lost in some patients.[144,151,161,167,169] This clinical observation may be explained by the emergence of compensatory mutations in other polymerase domains.[165] In patients with immunologic compromise, such as those with HIV infection or those receiving immunosuppressive therapy after liver transplantation, the emergence of YMDD variants occurs earlier after the initiation of lamivudine therapy and is more likely to precipitate severe acute hepatitis-like flares and hepatic decompensation.[170] Severe flares can occur, as reported most frequently in Asian patients,[171] and are more common in patients with marginally compensated cirrhosis.[172] Moreover, in persons with HBV-HIV coinfection, treatment with lamivudine monotherapy results in universal rapid HIV resistance[173]; therefore, testing for HIV infection should be done before the initiation of lamivudine therapy for hepatitis B. When HBV-HIV coinfection is identified, lamivudine monotherapy is contraindicated; instead, combination drug therapy should be instituted, and if lamivudine is used, the 300-mg HIV dose should be given.

When lamivudine was introduced, no other nucleoside analogues were available (the value of lamivudine-IFN combination therapy was never established in YMDD-variant HBV infection). Because patients tended to do well clinically, certainly compared with baseline pretreatment status, for at least 1 or 2 years after the emergence of YMDD-mutant hepatitis B[144,151,161]; because cessation of lamivudine after YMDD mutations resulted in reversion to wild-type HBV and its attendant higher ALT and HBV DNA levels[163]; and because other antivirals were not available, the general approach was to continue lamivudine after the emergence of YMDD variants unless clinical benefit was lost. Now that other antivirals are available to which YMDD variants are responsive,[164,166,174,175] breakthrough resistance to lamivudine is managed with the addition of another antiviral drug (addition of adefovir or replacement by tenofovir; see later discussion).

The optimal duration of lamivudine or any oral therapy has not been determined. In HBeAg-reactive chronic hepatitis B, treatment may be stopped 6 months after HBeAg seroconversion, and the durability of the response is anticipated to be greater than 80%.[95,96] Data suggest that Asian patients should be treated even longer before stopping therapy.[97] For patients who have not achieved an HBeAg response, and for patients with HBeAg-negative chronic hepatitis B, lamivudine or any oral treatment may have to be extended indefinitely.

As the first oral antiviral introduced for hepatitis B, lamivudine has been studied extensively and has an excellent safety record. On the other hand, its poor resistance profile and the subsequent availability of newer, more potent, more effective, and less resistance-prone agents (see subsequent discussions) have reduced dramatically the current use of lamivudine and rendered it almost obsolete; it is no longer recommended as first-line therapy.

Adefovir dipivoxil. Adefovir dipivoxil, approved by the FDA in 2002, is the oral prodrug of adefovir, an acyclic phosphonate nucleotide analogue of adenosine monophosphate with antiviral activity against HBV and other hepadnaviruses, retroviruses such as HIV, and herpesviruses. Although doses of 30 mg or more daily are associated with nephrotoxicity, at a daily oral dose of 10 mg, adefovir dipivoxil suppresses HBV replication by medians of approximately 3.5 $\log_{10}$ in HBeAg-reactive hepatitis B and 3.9 $\log_{10}$ in HBeAg-negative hepatitis B, in both treatment-naïve and IFN-failed patients.[119,120] In a phase III clinical trial among HBeAg-reactive patients, adefovir treatment, 10 mg daily for 48 weeks, resulted in histologic improvement in 53%, return of ALT to normal in 48%, undetectable HBV DNA with PCR assay (<400 virions/mL) in 21%, loss of HBeAg in 24%, and HBeAg seroconversion in 12%.[120] A 30-mg group included in this study but abandoned because of nephrotoxicity achieved even better results: histologic response in 59%, biochemical response in 55%, undetectable HBV DNA with PCR assay in 29% (median 4.76 $\log_{10}$ reduction in copies/mL of HBV DNA), HBeAg loss in 27%, and HBeAg seroconversion in 14%.[120] As is the case for IFN and lamivudine, adefovir is more likely to result in HBeAg seroconversion in patients with elevated baseline ALT levels; for both the 10-mg and 30-mg doses of adefovir, the frequency of HBeAg seroconversion increased to 21% for the subset of patients with baseline ALT levels five or more times the ULN.[120] HBeAg seroconversion during adefovir therapy results in a durable response that allows treatment to be discontinued; in the absence of an HBeAg response, indefinite continuation of therapy is necessary.

In a phase III clinical trial among HBeAg-negative patients, adefovir treatment, 10 mg daily for 48 weeks, resulted in histologic improvement in 64%, return to normal of ALT in 72%, and undetectable HBV DNA with PCR assay (<400 virions/mL) in 51%.[119] Reactivation is the rule when treatment is discontinued, as observed after short-term IFN or lamivudine therapy. The histologic efficacy of adefovir is similar in patients with both mild and advanced fibrosis. In addition, adefovir reduces $\log_{10}$ HBV DNA levels comparably across all HBV genotypes.[176] Whether cross-genotype activity represents an advantage of adefovir over lamivudine is debatable; HBV genotyping was not available when lamivudine registration trials involving approximately 1000 patients were done, and the number of patients with lamivudine treatment in reports of variable responses across genotypes is too small to be conclusive.[147,148] In addition, HBeAg responses to adefovir did differ, ranging from 7% to 20%, among HBV genotypes A to D, but the numbers of HBeAg responses were too small for adequate statistical comparisons.[176] Like lamivudine, adefovir appears to retard progression of fibrosis in patients treated for a year.[119,120] Although reports have appeared in the literature to suggest that adefovir reduces cccDNA in treated patients, in fact, cccDNA is reduced (but not to undetectable levels) in patients who undergo HBeAg seroconversion spontaneously and in those who achieve seroconversion when treated with IFN, lamivudine, or adefovir.[177]

Adefovir, a flexible acyclic nucleotide that is similar to its natural substrate, is less likely to be sterically hindered by mutated amino acids in the HBV polymerase YMDD binding site pocket.[164] During courses of adefovir therapy that lasted 48 to 60 weeks in patients with immunocompetence, immunocompromise (e.g., persons with HIV coinfection or liver allograft recipients), HBeAg reactivity, and HBeAg negativity, no viral resistance was encountered.[178] Moreover, lamivudine-resistant, YMDD-mutant HBV responds to adefovir.[174,175] In clinical trials of adefovir for lamivudine-resistant YMDD-mutant hepatitis B, adefovir monotherapy (i.e., a switch from lamivudine monotherapy to adefovir monotherapy) reduced HBV DNA by a median of 4 $\log_{10}$ copies/mL and was just as effective as adefovir-lamivudine combination therapy (i.e., the addition of adefovir to lamivudine).[174,175] On the basis of this observation, some authorities had recommended switching to adefovir monotherapy in patients who become lamivudine resistant; however, when this is done, especially if any delay is introduced between the cessation of lamivudine and the addition of adefovir, ALT flares are encountered in approximately one-third of patients.[175] In addition, in vitro studies indicate that adefovir is actually more effective (half maximal inhibitory concentration [IC_{50}] is lower and resistance is reduced) in lamivudine-resistant than in wild-type HBV.[165,166] Finally, adefovir resistance (see subsequent discussion) occurs more frequently in patients who *switch* from lamivudine to adefovir compared with those in whom adefovir is *added* to lamivudine.[179,180] These observations argue for maintenance of lamivudine when adefovir is added because of lamivudine resistance. Although no resistance occurs during 48 or 60 weeks of adefovir therapy,[178] adefovir resistance does begin to emerge during the second year of treatment and can reach 30% at 5 years.[181] These mutations occur in polymerase domain D, usually an asparagine-to-threonine mutation at residue 236 (N236T),[182] but also in domain B, an alanine-to-valine mutation at residue 181 (A181V). These adefovir-associated mutations respond to lamivudine.

Safety of adefovir at a dose of 10 mg daily is similar to that of placebo.[119,120] Elevations of ALT occur during and after cessation of therapy, just as observed with lamivudine treatment. At doses of 30 mg or more a day of adefovir, however, nephrotoxicity is encountered.[120] A distal renal tubular acidosis occurs, with falling phosphorus and rising creatinine levels. At a dose of 10 mg, adefovir has a high therapeutic index, and creatinine elevations of 0.5 mg/100 mL or more were not observed in the registration trials of adefovir.[119,120] At doses of 30 mg or more, nephrotoxicity is not encountered before 6 to 8 months of

therapy, and when it occurs, it is reversible. Creatinine monitoring is recommended when adefovir is used, and reductions in dose frequency are mandated for patients with reduced creatinine clearance (CrCl; for CrCl 20 to 49 mL/min, every other day; for CrCl 10 to 19 mL/min, every third day; for patients undergoing hemodialysis, once a week after dialysis).

Although adefovir filled an important niche when it was introduced, providing effective therapy for lamivudine resistance, the drug has several limitations. Adefovir remains the least potent of all available oral agents in suppressing HBV DNA and in achieving HBeAg seroconversion, and it suppresses HBV DNA relatively slowly in most patients and hardly at all (by <2 $\log_{10}$) in a sizable proportion of treated patients.[183] Therefore, adefovir has been supplanted by its superior successor tenofovir (see subsequent discussion) and is no longer considered first-line therapy.

Entecavir. Entecavir (approved in 2005) is a cyclopentyl guanine nucleoside analogue that interferes with priming of the HBV polymerase, with reverse transcription of the minus strand of DNA and with DNA-dependent synthesis of the positive strand of HBV DNA. At a daily dose of 0.5 mg given for 48 weeks, entecavir was shown to be superior to lamivudine in preliminary and registration trials.[115,116] In patients with HBeAg reactivity, entecavir results in HBeAg seroconversion in 21%, reduces HBV DNA by a median of 6.9 $\log_{10}$ (5.0 $\log_{10}$ in patients with HBeAg negativity), suppresses HBV DNA to undetectable levels (<10^2 $\log_{10}$ copies/mL) with PCR assay in 67% (90% in HBeAg-negative patients), returns aminotransferase levels to normal in 68% (78% in HBeAg-negative patients), and improves histologic findings in 72% (70% in HBeAg-negative patients). Continuation of entecavir after the first year has been shown to result in increased HBeAg seroconversion rates (up to 39% at year 3) and HBsAg loss (5% at 2 years).[184,185] Data extending the duration of entecavir therapy for up to 5 years with a concomitant increase in dose from 0.5 mg to 1.0 mg daily in patients who did not seroconvert after 1 year are now available.[186] An additional 23% (33 of 141) achieved HBeAg seroconversion with treatment, although only 1.4% (2 of 145) lost HBsAg. A retrospective analysis of the 94 Asian patients enrolled in this extension study found that 95% of patients maintained an HBV DNA level of less than 300 copies/mL, and 76% had normalized levels of ALT at 5 years.[187] Important to note, long-term therapy was well tolerated, and resistance occurred in only 1 patient.

Although entecavir is cross-resistant with lamivudine, the blood levels achieved with daily doses of 0.5 or 1 mg exceed the increased IC_{50} for YMDD-variant hepatitis B in most patients.[165] At an increased dose of 1 mg daily, entecavir has also been proven effective in, and approved for use in, lamivudine-resistant chronic hepatitis B.[188] In previously treatment-naïve patients, entecavir resistance has not been encountered during the first year of therapy in phase II or phase III clinical trials; with its high barrier to resistance, entecavir has been observed to maintain its favorable resistance profile in cohorts followed for up to 5 years (1.2%).[184,189,190] On the other hand, resistance does occur at an unacceptable rate (from 7% at 1 year up to 43% at 4 years) among treatment-experienced patients with preexisting lamivudine resistance. In this setting, entecavir resistance requires the emergence of both YMDD-mutant HBV and a second mutation in domain B (T184A or I169T), C (S202G/I), or D (M250V).[191] Therefore, although approved for this indication, entecavir has not been embraced for the treatment of lamivudine-resistant HBV infection.

Although entecavir was found in preclinical toxicity testing to be associated with hepatic, pulmonary, and brain tumors in rodents, similar toxicity has not been detected in other animal species or in humans.[192,193] On the contrary, entecavir therapy has been associated with a reduction in HCC and in all-cause mortality.[194–196] Entecavir has a safety profile indistinguishable in clinical trials from that of lamivudine, but post-treatment ALT flares are much less frequent,[115,116] and the durability of HBeAg responses is comparable with that of the other oral agents. Initially believed to have no antiviral activity against HIV, entecavir does have low-level anti-HIV activity and cannot be used as monotherapy in patients with HBV-HIV coinfection who need treatment for HBV infection.[197] The entecavir dose should be reduced for patients with CrCl <50 mL/min.

Because of its high potency; high efficacy in achieving biochemical, serologic, virologic, and histologic endpoints; high barrier to resistance; beneficial impact on the natural history of chronic hepatitis B; and excellent short-term and long-term tolerability and safety profile, entecavir is recommended as first-line antiviral treatment for chronic hepatitis B.

Telbivudine. Telbivudine (approved in 2006) inhibits HBV polymerase, interfering with plus-strand synthesis of HBV DNA; in large-scale registration human trials, at an oral dose of 600 mg/day, it achieved a median 6.4 $\log_{10}$ (HBeAg-positive patients) and 5.2 $\log_{10}$ (HBeAg-negative patients) reduction in HBV DNA at 52 weeks.[117] In HBeAg-positive and HBeAg-negative patients, telbivudine suppressed HBV DNA to undetectable (<10^2 $\log_{10}$ copies/mL) in 60% and 88%, reduced ALT to normal in 77% and 74%, and improved histologic findings in 65% and 67%, respectively. HBeAg seroconversion occurred in 22% at the end of 1 year, with an increase to 30% at the end of year 2.[198] As an L-nucleoside, telbivudine is cross-resistant with lamivudine. Although telbivudine resistance at 1 year was less common (in 5% of HBeAg-positive and 2% of HBeAg-negative patients) than lamivudine resistance, by year 2[117] telbivudine resistance had increased to 22% and 9%, respectively.[198] The combination of telbivudine plus lamivudine is not additive and achieves no greater inhibition of HBV DNA than telbivudine alone.[118] In fact, none of the currently available nucleoside or nucleotide analogues provide more profound HBV suppression in combination with any others than the more potent one used alone.

Telbivudine has the same excellent tolerability profile as lamivudine (except for creatine kinase elevations), and durability of HBeAg responses after cessation of therapy is similar to that of the other antivirals (approximately 80%). Despite its high potency, telbivudine has not been widely embraced as therapy for hepatitis B because of its poor resistance profile and its inferiority to other available drugs; it is no longer recommended as a first-line agent for hepatitis B, and its production and distribution were discontinued after December 2016.

Tenofovir. Two formulations of tenofovir are available: TDF, approved for hepatitis B in 2008, and TAF, approved in 2016.

Tenofovir disoproxil fumarate (TDF), another acyclic nucleotide, approved as an inhibitor of HIV reverse transcriptase, has similar activity in vitro against wild-type and lamivudine-resistant hepatitis B. In trials among patients with immunocompetence and immunocompromise (e.g., with HIV-HBV coinfection and after liver allograft) and treatment-naïve or lamivudine-resistant patients, TDF, 300 mg daily, reduced HBV replication by more than 6 logs; achieved HBV DNA suppression much more rapidly and consistently, with negligible nephrotoxicity and resistance; and was superior to adefovir.[116,120,199,200] In a registration trial,[121] TDF (compared with adefovir; data shown for 48 weeks, except as noted) reduced HBV DNA by 6.2 $\log_{10}$ in HBeAg-reactive patients and by 4.6 $\log_{10}$ in HBeAg-negative patients and to levels undetectable with PCR in 76% and 93%; resulted in normal ALT in 68% and 76%; and improved histologic findings in 74% and 72%, respectively. HBeAg seroconversion was achieved in 21% at the end of 1 year, 27% at the end of 2 years, 34% at the end of 3 years, and 40% at the end of 5 years; HBsAg loss was recorded in 3% at 1 year, 6% at 2 years, and 8% at 3 and 5 years,[121,201,202] and no resistance was encountered through year 3[202] and year 5[90] and beyond to year 8. Among 348 patients who completed 5 years of therapy with TDF and who underwent liver biopsies at baseline and at the end of treatment, 87% had histologic improvement, 51% had a regression in fibrosis score, and 74% (71 of 96) no longer had cirrhosis (Ishak fibrosis score 5 or 6) as defined as a greater than or equal to 1-unit decrease in score.[102]

The safety profile of TDF continues to be reassuring in more than 5 years of patient experience on therapy. The rates of nephrotoxicity and renal tubular dysfunction are approximately 1%. In a 5-year, treatment-extension study, only 9 of 585 (2%) patients experienced a serious adverse event attributed to TDF. These side effects included an increase in ALT or AST, increase in lactate dehydrogenase (LDH), and three reports of a reduction in bone mineral density.[102] For patients with CrCl <50 mL/min, the TDF dose should be reduced.

TDF is effective and recommended for patients with resistance to lamivudine (common when this drug was in popular use) or entecavir (rare). In the past, in patients with lamivudine resistance, adefovir was added to lamivudine (to avoid ALT flares and adefovir resistance), but tenofovir preparations (TDF or TAF; see later) are so potent and have

such a high barrier to resistance that the current recommendation is to switch from lamivudine or entecavir and rely on tenofovir monotherapy. In clinical trials, such monotherapy is as effective as combination therapy, without the emergence of resistance during 3 to 5 years of observation.[203–205]

On the basis of potent suppression of HBV DNA, efficacy data, compelling evidence of histologic improvement, a high barrier to resistance, an excellent safety and tolerability profile, and a reduction in the long-term consequences of chronic hepatitis B (e.g., HCC),[196] TDF is recommended as first-line therapy for chronic hepatitis B; moreover, classified as pregnancy category B, tenofovir should be considered for women with chronic hepatitis B during their childbearing years and during pregnancy, when therapy is indicated.

Tenofovir alafenamide (TAF) is a prodrug of tenofovir that must be activated to tenofovir in hepatocytes, allowing for higher targeted delivery of the drug to the liver and a 90% reduction in systemic exposure, reducing significantly the risk of proximal renal tubular injury and loss of bone density (phosphate wasting as a result of proximal tubular injury). At an oral dose of 25 mg daily, TAF is as effective and well tolerated as 300 mg daily of TDF with a comparably high barrier to resistance. Two randomized, double-blind, phase III, noninferiority trials of TAF versus TDF were conducted, one in HBeAg-reactive and one in HBeAg-negative patients.[122,123] Primary end points for TAF versus TDF at week 48 were as follows, respectively. In *HBeAg-reactive* patients, HBV DNA was below 29 IU/mL in 64% and 67%; ALT was normal (in central laboratory) in 72% and 67%; HBeAg loss or seroconversion occurred in 14% and 10% and in 12% and 8%. HBsAg loss was negligible, occurring in 4 of 576 (1%) and 1 of 288 (0.3%). Mean reductions in bone density were lower for TAF (e.g., hip −0.10%) than for TDF (hip −1.72%), mean increases in serum creatinine were smaller for TAF (0.01 mg/dL) versus TDF (0.03 mg/dL), and median reductions in CrCl (estimated glomerular filtration rates) were lower for TAF (−0.6 mL/min) than for TDF (−5.4 mL/min). In *HBeAg-negative* patients, HBV DNA was below 29 IU/mL in 94% and 93%; ALT was normal (in central laboratory) in 83% and 75%. No study subjects lost HBsAg. Mean reductions in bone density were lower for TAF (e.g., hip −0.29%) versus TDF (hip −2.16%). Mean increases in serum creatinine were comparably small for TAF (0.01 mg/dL) and TDF (0.02 mg/dL), but median reductions in CrCl (estimated glomerular filtration rates) were lower for TAF (−1.8 mL/min) than for TDF (−4.8 mL/min). These findings were similar at week 96, the more substantial ALT reduction with TAF was sustained over 96 weeks, and no tenofovir resistance occurred in either group through 96 weeks. Between weeks 96 and 120, when initial TDF recipients were switched to TAF, earlier differences between TDF and TAF in ALT normalization, renal function, and bone density all resolved.

TAF is now one of the first-line antiviral drugs for chronic hepatitis B recommended for patients with impaired renal function (CrCl <50 mL/min), those with reduced bone density, anyone at risk for renal injury, and patients older than age 60, who are more prone to the potential nephrotoxicity of TDF.[106] The dose of TAF should be reduced for patients with CrCl below 15 mL/min.

Other Agents for Chronic Hepatitis B

Approved as therapy for HIV infection, but not approved officially for HBV infection, the cytosine analogue emtricitabine is similar in structure, activity, and resistance to lamivudine (see Chapter 128).[206] Although it has no advantage over lamivudine, emtricitabine is available (for HIV/AIDS) in a combination tablet with tenofovir, which some clinicians use when combination therapy is advisable (e.g., for patients with already established L-nucleoside resistance).

Clevudine, a pyrimidine nucleoside analogue that was approved for use in Korea, was being evaluated in clinical trials versus adefovir as comparator. Although clevudine has been purported to eradicate cccDNA, this clinical end point was not documented, and although HBV DNA is much slower to rebound after clevudine therapy, clinical trials showed no advantage of clevudine in potency or resistance profile over available agents.[207] In 2009, development of this drug was halted because of the emergence of severe myopathy after prolonged use.

Although the current armamentarium of antiviral drugs is effective in suppressing HBV replication profoundly and in achieving short-term and long-term improvements in clinical end points, most patients require therapy of indefinite duration; therefore efforts are underway to evaluate inhibitors that interfere with other components of the HBV life cycle and that enhance host immune responsiveness to HBV. Among the viral targeting strategies are inhibitors of viral entry, HBV core assembly, cccDNA, and HBV secretion; novel technologic approaches such as RNA interference and gene editing with CRISPR/Cas9 are being investigated. Immunomodulatory approaches being applied include reconstitution of innate and adaptive immune responsiveness, Toll-like receptor agonists, T-cell vaccines, checkpoint inhibitors, IFN gene agonists, and retinoic acid inducible gene-I (RIG-I) activation. These studies are in their early stages, and, to date, none has been successful in "curing" HBV infection—that is, in achieving HBsAg loss and seroconversion, the pattern of recovery from infection, and in eliminating the need for continued antiviral therapy.[208]

Optimal Use of Available Agents for Hepatitis B

The trend in drug development has been in the direction of agents with progressively more profound inhibition of HBV replication. Although the proportion of HBeAg-reactive patients who achieve HBeAg seroconversion after 1 year of therapy (approximately 20%) is no greater for the more potent oral agents than for the less potent,[115,117,121] patients treated with any drug who achieve the most robust inhibition of HBV DNA are the most likely to achieve HBeAg responses and to avoid drug resistance.[117,209] Thus, the more potent the antiviral in inhibiting HBV replication, the better the outcome is likely to be (see Table 117.6). Potentially, combination therapy with high-potency, low-resistance agents could achieve even more limited resistance and treatment synergies, such as improved antiviral kinetics.[210,211] To date, however, advantages of combination therapy have not been shown in clinical trials.[109,118] For example, in a trial of combination tenofovir and entecavir therapy, after 2 years the benefit of dual antiviral therapy compared with entecavir monotherapy was modest and restricted to a small subset of patients with HBeAg and very high baseline HBV DNA ($\geq 10^8$ IU/mL), in whom HBV DNA was reduced to less than 50 IU/mL in 79% versus 62% of patients, respectively; however, even in this subset, the difference in rates of HBeAg loss and HBeAg seroconversion were not statistically significant between the groups.[190] Therefore, currently, combination therapy is restricted to patients with established drug resistance,[174,175,180] and, as aforementioned, for the contemporary high-potency, low-resistance agents, monotherapy appears to be just as effective as combination therapy.[203–205]

Recommendations for Therapy

Recommendations or guidelines for the treatment of chronic hepatitis B have been issued by the AASLD,[105] the EASL,[106] the Asian Pacific Association for the Study of the Liver,[107] and several other official bodies (Table 117.7). PEG IFN, entecavir, or tenofovir is the preferred first-line therapy for chronic hepatitis B; however, the availability of entecavir and tenofovir in resource-limited settings across the world continues to be an issue.[212] Although an approved first-line treatment with an excellent frequency of 1-year HBeAg seroconversion, PEG IFN may not be as competitive as the first-line oral agents entecavir and tenofovir, the efficacy, simplicity of use, tolerability profile, and high barrier to resistance of which are appealing to physicians and patients. As discussed later, any advantage in achieving HBeAg seroconversion after a 1-year course of PEG IFN injection therapy is overcome by extending oral-agent therapy beyond a year, and HBeAg seroconversion frequencies increase with each year of additional oral-agent therapy, associated rarely, if at all, with the emergence of resistance variants. Moreover, therapy with entecavir or tenofovir has been shown to be associated with histologic evidence of regression of fibrosis and cirrhosis after 3 to 5 years of therapy.[102,213] Patients with hepatitis B genotype A have particularly favorable rates of HBeAg seroconversion and even HBsAg loss with PEG IFN compared with patients with non-A genotypes,[214] and some authorities favor PEG IFN in this subgroup of patients; however, patients with genotype A are also highly responsive to oral-agent therapy. Additional details for the antiviral drugs for hepatitis B are presented in Chapter 47.

A consensus from the AASLD recommendations[105] is that HBeAg-negative patients with normal ALT activity and HBV DNA levels below

TABLE 117.7 Recommendations and Guidelines of the American Association for the Study of Liver Diseases for the Treatment of Chronic Hepatitis B

HBeAg	HBV DNA (IU/mL)	ALT	TREATMENT	FIRST-LINE AGENTS
Chronic Hepatitis B Without Cirrhosis				
+	>2 × 10^4	>2 × ULN	Recommended	PEG IFN, ETV, TDF, TAF
+	>2 × 10^4	≤2 × ULN	Not recommended; consider assessment of fibrosis[a]; consider for age >40, family history of HCC, extrahepatic manifestations	
–	>2 × 10^3	>2 × ULN	Recommended	PEG IFN, ETV, TDF, TAF
–	>2 × 10^3	<2 × ULN	Not recommended; consider assessment of fibrosis[a]; consider for age >40, family history of HCC, extrahepatic manifestations	
–	≤2 × 10^3	Normal	Not recommended[b]	
Cirrhosis				
±	Detectable (Regardless of HBV DNA level)	Normal or ↑	Recommended	Compensated: treat with ETV or TDF, TAF for detectable HBV DNA (even <2 × 10^3 IU/mL, regardless of ALT level
±	Regardless of HBV DNA level	Normal or ↑	Recommended	Decompensated[c]: treat indefinitely with ETV or TDF, TAF
±	Undetectable (PCR[d])	Normal or ↑	Not recommended	[c]

Table is updated to reflect supplanting of the less effective drugs by the best available antiviral drugs.[104] Guidelines issued by the European Association for the Study of the Liver are similar, with the following exceptions: HBV DNA threshold of >2 × 10^3 IU/mL for HBeAg positive or HBeAg negative; ALT threshold greater than upper limit of normal.[218]

[a]If liver biopsy reveals advanced necroinflammatory activity or fibrosis, or if noninvasive assessment of fibrosis reveals advanced fibrosis, consider treatment.

[b]Inactive carrier.

[c]If decompensated, coordinate care with a liver transplantation center.

[d]<10^3 IU/mL.

ALT, Alanine aminotransferase; *ETV,* entecavir; *HBeAg,* hepatitis B e antigen; *HBV,* hepatitis B virus; *HCC,* hepatocellular carcinoma; *IU,* international units; *PCR,* polymerase chain reaction; *PEG IFN,* pegylated interferon; *TAF,* tenofovir alafenamide; *TDF,* tenofovir disoproxil fumarate; *ULN,* upper limit of normal.

the threshold associated with liver injury (≤2 × 10^3 IU/mL; i.e., inactive hepatitis B carriers) are not candidates for antiviral therapy. On the other hand, patients with HBV DNA levels greater than 2 × 10^4 IU/mL (for HBeAg-reactive patients) or greater than 2 × 10^3 IU/mL (for HBeAg-negative patients), and ALT levels greater than two times the ULN, are considered candidates for therapy. Recommendations issued by the EASL are similar, but the HBV DNA threshold for treatment is 2 × 103 IU/mL in both HBeAg-positive and HBeAg-negative patients, and the ALT threshold is above the ULN.[106] Such patients have been shown to benefit from antiviral therapy and are assumed to have at least moderate necroinflammatory activity and fibrosis at liver biopsy; therefore, liver biopsy is not necessarily needed. For HBeAg-reactive patients with HBV DNA greater than 2 × 10^4 IU/mL, but normal or minimally elevated ALT levels less than two times the ULN, common among those who acquire HBV infection at birth, sustained responses are not likely, and treatment is not recommended (except for patients aged ≥40, a family history of HCC, previous treatment history, or extrahepatic immune-complex manifestations). For patients who meet HBV DNA criteria for treatment but with normal to near-normal ALT (less than two times the ULN per AASLD; less than the ULN per EASL), a liver biopsy or a noninvasive assessment of liver fibrosis is recommended to assess the extent of liver injury and fibrosis, which, in turn, is helpful in the decision of whether or not to treat.[105,106] Some authorities suggest that therapy should be instituted earlier in life among those with high HBV replication but low ALT.[215,216] These thresholds and criteria, however, do not meet the most rigorous evidence-based standard, and adopting them has never been shown to result in clinical benefit.[105,217]

Treatment of patients with compensated cirrhosis has been shown to delay clinical progression.[101] All patients with cirrhosis and HBV DNA >2 × 10^3 IU/mL, independent of ALT level, should be treated according to the aforementioned AASLD guidelines; treatment is also indicated for compensated cirrhotic patients with HBV DNA <2 × 10^3 IU/mL. AASLD guidelines are essentially the same as EASL guidelines for patients with compensated cirrhosis, which include as candidates for therapy patients with any detectable level of HBV DNA, regardless of ALT level. For decompensated cirrhosis in the presence of any detectable HBV DNA, with any level of ALT, urgent therapy may be lifesaving, but care should be coordinated with a liver transplantation center. Patients with cirrhosis should be treated with oral agents, not PEG IFN.

Choice of Antiviral Agents

On the basis of demonstrated superiority, PEG IFN has supplanted standard IFN, entecavir has supplanted lamivudine, and tenofovir has supplanted adefovir; although better than lamivudine, telbivudine has a poor resistance profile, which limits its appeal. Therefore, for most patients with chronic hepatitis B who are candidates for therapy, either PEG IFN, entecavir, or tenofovir is a potential first-line treatment (see Tables 117.7 and 117.8).[104,218,219] Several authorities recommend IFN-based therapy as the first-line approach, focusing on its apparent immunomodulatory activity, the brief duration of treatment, the higher frequency of HBeAg seroconversion after a year of therapy, the potential for HBsAg seroconversion, and the absence of resistance.[109,110,219–223] In fact, ALT elevations attributed to the immunologic effects of IFN are seen just as commonly during nucleoside or nucleotide analogue therapy,[112,120] and restoration of endogenous cytolytic T-cell activity or function occurs during nucleoside or nucleotide analogue therapy, as the level of HBV DNA is reduced.[224–226] Some favor PEG IFN for the subgroups most likely to respond (i.e., those with high ALT, low HBV DNA levels, genotypes A and B, and early age)[222,223]; however, these are also the populations most likely to respond to nucleoside or nucleotide analogues. Moreover, HBsAg seroconversions were no more common in patients with IFN treatment than with lamivudine treatment in a head-to-head trial (although these HBsAg results were not included in the published report),[113] and the frequency of HBsAg loss during PEG IFN therapy can be accomplished with the newer oral agents after 1 to 2 years or longer. Similarly, rates of HBeAg seroconversion with oral agents extended beyond 1 year are comparable with those achieved with a year of PEG IFN[a] but without the need for injections, side effects, or intensive clinical and laboratory monitoring. Although PEG IFN requires

[a]References 131, 132, 168, 171, 172, 180, 204.

TABLE 117.8 Approved Antiviral Drugs for Chronic Hepatitis B

	IFN	PEG IFN	LAM	ADV	ETV	TBV	TDF	TAF
Dose	5 MU/day[a]	180 µg/wk	100 mg/day	10 mg/day	0.5 mg/day	600 mg/day	300 mg/day	25 mg/day
Route	Subcutaneous	Subcutaneous	Oral	Oral	Oral	Oral	Oral	Oral
Duration in trials	4 mo	48 wk	48–52 wk	48 wk	48 wk	52 wk	48 wk	48 wk
Tolerability	Poor	Poor	Excellent	Excellent[b]	Excellent	Excellent	Excellent[b]	Excellent
HBeAg seroconversion	18%–20%	27%[c]	16%–21%	12%	21%	22%	21%	10%
Log_{10} HBV DNA reduction								
HBeAg positive	?[d]	4.5	5.5	3.5	6.9	6.5	6.2	Not reported, likely same as TDF
HBeAg negative	?[d]	4.1	4.7	3.9	5.0	5.2	4.6	Not reported, likely same as TDF
HBV DNA PCR negative								
HBeAg positive	?	25%	44%	21%	67%	60%	76%	64%
HBeAg negative	?	63%	73%	64%	90%	88%	93%	94%
ALT normalization								
HBeAg positive	?[e]	39%	75%	61%	68%	77%	68%	72%
HBeAg negative	?[e]	38%	79%	77%	78%	74%	76%	83%
HBsAg loss during treatment	up to 8%	3%–4%	≤1%	0%	2%	<1%	3%	≤1%
Viral resistance	None	None	15%–30%	None	None	2%–5%	0%	0%
>1 yr	None	None	5 yr: 70%	5 yr: 29%	≤1%	2 yr: 9%–22%	0%	0%
Cost (US $)	5600[a]	18,500	2500	6600	8700	6000 (no longer available)	13,000	12,000

Data shown are maximum reported values for up to 1 year (48–52 weeks) of treatment in registration trials. These comparisons are head-to-head only for PEG IFN versus LAM, ETV versus LAM, TBV versus LMV, and TDF versus ADV.
[a]5 MU daily to 10 MU three times per week for 16 to 24 weeks; the cost is that of a complete course, not of a year of therapy.
[b]Creatinine monitoring recommended.
[c]At 32% 24 weeks after therapy.
[d]When these studies were conducted, HBV DNA was measured with insensitive hybridization assays.
[e]ALT is generally normal in those with adequate serologic/virologic response; reports rarely include ALT levels at the end of treatment. In HBeAg-reactive patients, a meta-analysis showed a 23% advantage in ALT normalization (after therapy) in treated versus untreated patients.[670]
ADV, Adefovir; *ALT,* alanine aminotransferase; *ETV,* entecavir; *HBeAg,* hepatitis B e antigen; *HBsAg,* hepatitis B virus surface antigen; *HBV,* hepatitis B virus; *IFN,* interferon; *LAM,* lamivudine; *MU,* million units; *PCR,* polymerase chain reaction; *PEG IFN,* pegylated interferon; *TAF,* tenofovir alafenamide; *TBV,* telbivudine; *TDF,* tenofovir disoproxil fumarate.

therapy of a brief finite duration and is not associated clinically with resistance, the need for subcutaneous injections and often intolerable systemic side effects reduce its appeal. In addition, resistance to the newest oral agents, entecavir and tenofovir, is absent to negligible even after several years of therapy.[184] Furthermore, oral agents are effective in a substantial proportion of patients with failure to respond to IFN,[114] including patients with immunocompromise[170,227,228] and patients with hepatic decompensation.[158–160]

For patients with lamivudine resistance, the *addition* of adefovir while continuing lamivudine has been recommended,[173,175,179,180,211] but tenofovir is a better choice. When resistance to lamivudine emerged, adefovir as a second drug that is not cross-resistant was added; however, because of its higher potency and barrier to resistance, tenofovir monotherapy ("switch" rather than "add") suffices. Although entecavir at double the regular dose is approved for treatment of lamivudine-resistant hepatitis B,[188] the frequency of emergent entecavir resistance in this population is unacceptably high.[184] Because the stakes are so high when resistance emerges in patients with decompensated cirrhosis and in organ allograft recipients, for these populations, initial therapy with two agents may be advisable,[104,218,229] although not proven to be superior to entecavir or tenofovir alone. Similarly, because of the risks of treatment failure in patients with cirrhosis, stopping antiviral therapy after HBeAg seroconversion may not be the best strategy.[104,218]

Special Patient Populations

Pregnancy

Experience with lamivudine and tenofovir in pregnant women with HIV infection suggests that both are safe during pregnancy. For pregnant women who meet routine criteria for antiviral treatment, guidelines are the same as for nonpregnant women. Although antiviral treatment during late pregnancy (weeks 28–32 of gestation) reduces levels of maternal HBV DNA, studies have not shown that such antiviral therapy reduces the frequency of maternal-fetal transmission of HBV infection below levels achieved with administration of HBIG and hepatitis B vaccine to newborns. The exception is in mothers with high-level viremia,[104,218,230] now defined as $>2 \times 10^5$ IU/mL. In HBeAg-positive pregnant women with HBV DNA $>2 \times 10^5$ IU/mL, treating mothers during the third trimester (gestational weeks 30–32) until postpartum week 28 with TDF was shown to reduce the rate of mother-to-child transmission to 0% from 7% (per-protocol analysis; to 5% from 18%, intention-to-treat analysis) in an untreated control group.[231] On the basis of preclinical teratogenicity studies, entecavir is classified as pregnancy category C, whereas tenofovir is classified as category B[218]; because of this theoretical advantage, the vast experience with tenofovir in HIV-infected pregnant women, and the demonstrated benefit of TDF in late trimester pregnancy, tenofovir is preferable to entecavir for treatment of pregnant women.[105]

Liver Transplantation

Antiviral therapy with any of the available antiviral agents in patients with decompensated chronic hepatitis B may delay the need for liver transplantation; however, once liver transplantation is undertaken, HBV reinfection of the new liver occurs universally unless preemptive antiviral measures are instituted.[232] Before the availability of such antiviral therapy, most patients undergoing liver transplantation could manage well clinically for several years, despite HBV reinfection; however, in an unpredictable proportion, severe allograft-compromising and life-threatening HBV-associated liver injury supervened. The most aggressive form of HBV reactivation, fibrosing cholestatic hepatitis, represents overwhelming expression of HBV in the hepatocyte.[233] Characterized histologically by fibrosis and cholestasis out of proportion to necroinflammatory activity, this dreaded form of hepatitis B is more reminiscent

of direct virus-induced cytopathic injury than indirect cell-mediated cytotoxicity characteristic of virus-associated liver injury in the immunocompetent host. The likelihood of recurrent hepatitis B (i.e., hepatitis associated with HBV infection) correlates with the level of HBV replication before transplantation; however, even patients with low-level HBV replication before liver transplantation can have recurrent hepatitis B because immunosuppression, especially with corticosteroids, enhances HBV replication.[234,235] In fact, even recipients of donor livers from anti-HBs–positive or anti-HBc–positive donors have had hepatitis B reactivation after liver transplantation.[236] Patients who undergo liver replacement for fulminant hepatitis B may be an exception to the rule of universal reinfection; in such cases, rapid and overwhelming elimination of HBV-infected hepatocytes depletes the substrate for new HBV replication.

All patients on the liver transplantation waiting list with HBV-related indications should receive antiviral therapy. Currently, centers that perform liver transplantation follow a protocol of preemptive prophylaxis with a combination of entecavir or tenofovir and intravenously administered, high-dose HBIG beginning during the anhepatic phase of the procedure and continuing daily for the first week, followed by periodic readministration indefinitely thereafter.[237,238] Rarely, however, HBV envelope (HBsAg) escape mutations emerge during HBIG therapy after liver transplantation.[239–241] The addition of a nucleoside or nucleotide analogue to this regimen has dramatically reduced the risk of recurrent hepatitis B after transplantation.[170,242] Moreover, availability of these potent nucleoside or nucleotide analogue antiviral agents—IFN is not effective—has permitted exploration of strategies to change the route of administration (intramuscular vs. intravenous) and to reduce the dose, frequency, and duration of HBIG treatment.[232,243,244] Although the success of posttransplantation lamivudine therapy was hampered by the emergence of resistance,[170] the addition of adefovir, either as rescue therapy or as primary therapy, overcame the problem of posttransplantation lamivudine resistance and its often dire clinical consequences. Therefore, currently, the outcome of liver transplantation for hepatitis B is comparable with that of the procedure for nonviral types of end-stage liver disease.[232,242] Now that newer, better oral agents are available, they have replaced lamivudine and adefovir, and in selected patients may even replace HBIG therapy.[245] Entecavir monotherapy without HBIG was shown in a report from a single center to be highly effective. At 8 years after transplantation, 92% of treated patients were HBsAg negative, and 100% had undetectable HBV DNA; the 9-year survival was 85%, and no deaths resulted from recurrent HBV infection.[246] In patients at high risk for posttransplantation hepatitis B, a combination of HBIG and an oral agent is recommended.[106]

HIV Coinfection (Also See Chapter 124)

Patients with HIV-HBV coinfection tend to have high levels of HBV DNA and more advanced histologic disease but with relatively limited elevations of aminotransferase activity.[247] Moreover, occasionally, immunologic reconstitution associated with successful antiretroviral therapy (ART) results in severe exacerbations of hepatitis B in patients with coinfection.[248] IFN is not effective in this subset of patients with immunocompromise.[54] Lamivudine, when administered as part of the ART drug cocktail used to treat patients with HIV infection, is given at a dose of 150 mg twice daily, three times the HBV dose, and is complicated frequently by lamivudine resistance,[249] which limits the value of lamivudine. When, in the past, adefovir was a first-line treatment for hepatitis B, it lowered HBV DNA levels by 4 to 5 $\log_{10}$ copies/mL and maintained this effect without resistance even after more than 2 years of treatment.[228,250] Eclipsing adefovir, tenofovir, which is effective against both HIV and HBV and now a popular component of ART, is the first-line agent to be used in this population.[250] Currently, combination therapy that includes the nucleotide analogue TDF and an L-nucleoside (e.g., with the combination tablet that includes tenofovir and emtricitabine) is recommended (monotherapy with anti-HIV agents is not advisable), and ideally, both HIV and HBV infections should be treated simultaneously.[104,218,219,251–253] If an HBV-HIV coinfected patient is a candidate for therapy for hepatitis B but not HIV, single agents that have activity against HIV (lamivudine, tenofovir, entecavir) are contraindicated because of the risk of HIV resistance to monotherapy. Currently, treating both HBV and HIV infections is the preferable strategy; all patients with HIV-HBV coinfection should receive tenofovir-based ART (containing TDF or TAF), independent of CD4 count.[106]

Immune-Complex Disease

Immune-complex glomerulonephritis and generalized vasculitis (polyarteritis nodosa) can occur in patients with chronic hepatitis B.[92] Because these extrahepatic manifestations occur in settings of viral antigen excess, reduction of hepatitis B replication can reverse the process. Early trials of IFN showed improvements in nephrotic syndrome and in clinical findings in generalized vasculitis,[254] but oral nucleoside or nucleotide analogues, especially now entecavir and tenofovir, have replaced IFN in the management of these cases. Patients with immune-complex extrahepatic manifestations should receive tenofovir or entecavir (PEG IFN, which can exacerbate immune-complex–mediated extrahepatic manifestation, is not recommended) regardless of whether or not they meet HBV DNA and ALT treatment thresholds in treatment guidelines.

Oncology Patients Who Need Cytotoxic Chemotherapy

When cytotoxic chemotherapy is administered to HBV-infected patients with malignant disease, levels of HBV replication are enhanced and cell-mediated immune injury of HBV-infected hepatocytes is suppressed. When cycles of chemotherapy are completed, however, restoration of cytolytic T-cell function occurs at a time of residual high-level HBV antigen expression on hepatocyte membranes, initiating a burst of hepatocytolysis and severe, often fatal, reactivation of hepatitis B.[30,32] Preemptive antiviral therapy with nucleoside or nucleotide analogues, initiated before chemotherapy (preemptive therapy), has been shown to prevent such reactivations of hepatitis B.[255] The risks of HBV reactivation and the advantages of preemptive antiviral therapy are similar for patients undergoing immunosuppressive or immunomodulatory (e.g., anti-TNF and other anticytokine) therapy. Current data do not support preemptive antiviral treatment for anti-HBs–reactive persons requiring immunomodulatory therapy; however, the risk is sufficiently high for antiviral therapy in anti-HBc–reactive patients treated with the most potent immunomodulators (e.g., rituximab).[59,60,582] The optimal duration of antiviral therapy after discontinuation of immunosuppressive chemotherapy remains to be defined.[105,106,256]

Chronic Hepatitis D

HDV is a defective agent that requires HBV (or hepadnaviruses of other species) to replicate and that depends absolutely on the persistence of HBV to establish chronic infection (see Chapter 146).[257–260] When acute coinfection with both agents occurs simultaneously, the duration of infection is determined by the duration of HBV infection; therefore, HDV does not increase the frequency of chronicity of acute HBV infection. When HDV superinfection occurs in a person already infected chronically with HBV, chronic hepatitis D follows almost invariably (with rare exceptions), maintained by chronic HBV infection. Clinically, hepatitis D superinfection may be recognized as a flare in aminotransferase activity in a person with chronic hepatitis B, and in general, chronic hepatitis B is converted to more severe chronic hepatitis after HDV superinfection; for example, severe, even fatal, chronic hepatitis can follow in an inactive hepatitis B carrier superinfected with HDV.

Clinical features of chronic hepatitis D are similar to those of chronic hepatitis B, except for the increased severity and more rapid progression to cirrhosis and end-stage liver disease; in addition, both early mortality and the risk of HCC are increased in patients with hepatitis D.[258] When hepatitis D was described originally, the more severe cases attracted clinical attention, and hepatitis D was believed to be invariably severe; however, mild hepatitis, even quiescent liver disease (inactive carriage), has been recognized, and the disease can become indolent after an early period of severe hepatitis lasting several years.[261] In addition, three genotypes have been identified, with distinct geographic distribution, and genotype 2 has been associated with milder disease.[258] Although focal outbreaks of hepatitis D continue to emerge throughout the world, in Mediterranean countries, where hepatitis D was first recognized, the frequency of hepatitis D declined dramatically during the 1990s, attributed

to changes in migration patterns, improvements in socioeconomic conditions, adoption of HIV-avoidance behavior among injection drug users, and hepatitis B vaccination programs (immunity to hepatitis B protects against infection with hepatitis D).[262] Still, HDV superinfection of persons with chronic hepatitis B continues to be observed, even in low-prevalence countries, among active injection drug users.[263]

Although chronic hepatitis D tends to be more severe than chronic hepatitis B, and to require concomitant chronic hepatitis B, these generalizations do not prevail in one clinical situation. After liver transplantation for chronic hepatitis D, hepatitis D reinfection can occur without high levels of HBV replication and without liver injury. Even in the absence of maneuvers to prevent the reestablishment of HBV infection (HBIG plus antiviral agents), the outcome of hepatitis D after liver transplantation is comparable with that after nonviral liver disease.[237,264,265] On the other hand, if after liver transplantation for hepatitis D, high-level HBV infection emerges, severe hepatitis D may follow. Although hepatitis D, like other viral hepatitides, is likely to injure hepatocytes indirectly via cytolytic T-cell activation, and although autoimmune markers (anti-LKM3) are common in hepatitis D,[266] the mechanism of HDV-associated liver disease has not been defined definitively.

Serologically, the diagnosis of hepatitis D is established by the presence of circulating antibody to HDV (anti-HDV). Unlike anti-HBc in HBV infection, the distinction between IgM and immunoglobulin G (IgG) anti-HDV is not useful clinically. Although not widely used clinically, testing is available in a limited number of specialized and research laboratories to detect HDV RNA with PCR.[267] Curiously, patients with chronic hepatitis D may harbor liver-kidney microsomal antibodies type 3 (anti-LKM3) that recognize uridine diphosphate glucuronosyltransferase and that are distinct from similar LKM antibodies observed in type 2 autoimmune hepatitis and chronic hepatitis C (anti-LKM1) and certain types of drug-induced hepatitis.[266]

Treatment

None of the currently available nucleoside or nucleotide analogues active against hepatitis B has been shown to be effective in patients with hepatitis D.[258] IFN-α at doses and durations recommended for hepatitis B are ineffective for chronic hepatitis D; however, IFN therapy extended to 12 months and at a dose of 9 million units three times a week can result in clinical improvement (return to normal of aminotransferase activity and an improvement in liver histologic findings) in more than two-thirds of treated patients, despite the fact that therapy has limited impact on HDV replication and that clearance of HDV RNA is unusual.[268] Although aminotransferase activity remained normal for 6 months after therapy in half of patients treated this way, ultimately, clinical reactivation followed after cessation of therapy in many patients. On the other hand, biochemical remission was maintained in a proportion of treated patients, even 14 years after completion of therapy, and in some, clearance of HDV RNA and regression of fibrosis were documented.[258,269] An anecdotal report of a sustained biochemical, virologic, and histologic response after 12 years of IFN therapy (5 million units daily) in one patient[270] raises the possibility that protracted treatment may be the best approach for patients with chronic hepatitis D. Therefore, some investigators have advocated chronic therapy until eradication of HDV RNA is achieved. PEG IFN has also been shown to have efficacy in chronic hepatitis D[271]; 48 weeks of PEG IFN resulted in sustained clearance of HDV RNA (as of 24 weeks after therapy) in a quarter of patients.[272] Ultimately, novel antiviral approaches for the treatment of chronic hepatitis D (clevudine, now abandoned, was shown to be active in woodchucks with HDV infection[273]) are necessary.[274]

As noted previously, liver transplantation for end-stage chronic hepatitis D has an excellent prognosis; still, the same protocol of HBIG plus a nucleoside or nucleotide analogue used after transplantation for chronic hepatitis B is recommended for patients with chronic hepatitis D to minimize the likelihood of recurrent hepatitis B and its deleterious impact on posttransplantation HDV infection.

Chronic Hepatitis C

In adults with clinically apparent acute hepatitis B, the likelihood of chronic infection is less than 1%.[70,72] In marked contrast, acute hepatitis C is followed by chronic HCV infection in at least 85% of cases.[5,275] Contributing to this high frequency of chronic HCV infection are its high replication rate (10^{11}–10^{12} virions per day with a virion half-life of 2 to 3 hours)[276] without polymerase error proofreading, molecular heterogeneity driven by a high mutation rate (1 mutation per synthesized genome), and, consequently, the virus's ability to change sufficiently and rapidly enough in the face of the evolutionary pressure of host immunity to circumvent neutralizing antibodies.[277] In addition to viral genotypes 1 to 6, the nucleotide sequences of which can differ by as much as 30% to 50%, HCV exists as multiple genetically distinct quasispecies, differing in nucleotide sequence by up to 5% (see Chapter 154).[278,279] Believed to have diverged phylogenetically from related viral agents more than 10,000 years ago and to have evolved in humans for this extended period, HCV has established itself firmly among humans, infecting as many as 175 to 185 million worldwide according to previous estimates; however, when reassessed in 2015, modeling of global prevalence of hepatitis C viremia was more consistent with a prevalence of 71 million worldwide. In developed nations, antibody to HCV is prevalent in 1% to 2% of the population.[18] In the United States alone, as many as 1.6% to 1.8% of the population have been infected (approximately 4 million in the 1990s; by 2010, 1% were estimated to be viremic, corresponding to approximately 3 million people, a reduction proposed to have been associated with deaths in the infected population), and the Public Health Service has estimated an annual death toll of 8000 to 10,000.[5,280–282]

The impact of hepatitis C is difficult to minimize. Chronic hepatitis C contributes to approximately 25% to 40% of all chronic liver disease[283] and accounts for up to 40% of all patients undergoing liver transplantation.[284–286] As of 2007, annual mortality associated with hepatitis C surpassed mortality associated with HIV/AIDS in the United States,[287] and, as of 2012, mortality associated with hepatitis C surpassed mortality of all 60 other nationally reportable infectious diseases.[288] Economic estimates of the annual hepatitis C–related direct medical care costs incurred in the United States exceed $1 billion.[285] These statistics may seem surprising in light of the documented decline of acute hepatitis C cases reported over the past several decades. Initially, hepatitis C was recognized in recipients of transfused blood and blood products, but the frequency among transfused persons declined from more than 30% in the 1960s, to more than 10% in the 1970s (exclusion of "commercial" blood donors),[289] to approximately 5% in the 1980s (adoption of "surrogate" screening tests that identified blood donors with an increased risk of bloodborne viral infections),[290–292] to less than 4% in the early 1990s (adoption of HCV-specific screening tests of donor blood).[293–295] During the 1990s, with progressively increasing sensitivity of donor screening tests for anti-HCV, the frequency of transfusion-associated hepatitis C fell to almost undetectable, effectively imperceptible levels, estimated now to be 1 in 103,000 units transfused.[296] This remarkable reduction in transfusion-associated hepatitis C, however, hardly made a dent in the overall frequency of reported cases, most of which occurred in groups other than blood recipients. In the 1990s, however, the overall frequency of reported cases of acute hepatitis C fell by more than 80% (to approximately 35,000), mirroring a similar decline among injection drug users, who adopted behavioral changes designed to minimize acquisition of HIV infection.[297]

Despite the fact that the annual incidence of new HCV infections declined substantially during the last decade of the 20th century, the burden of long-established chronic infections continues to grow and is expected to triple or quadruple over the next generation.[284,285,298] The relatively recent decline in new cases has had limited impact on the large reservoir of chronic infections established, in most instances, 4 to 5 decades ago.[281] Of the 3 to 4 million people estimated on the basis of serologic surveys to have chronic hepatitis C in the United States, less than one-third to one-half have come to clinical attention, mostly as a result of serendipitous discovery (e.g., when donating blood or during routine laboratory testing for other reasons).[299,300] In serologic surveys of the US population, three-quarters of persons found to harbor HCV infection were in the baby boomer age cohort (born from 1945 through 1965); whereas the prevalence in other birth cohorts was only 0.8%, in baby boomers, the prevalence was 3.2%, and 73% of HCV-related mortality occurs in this cohort. Therefore the US Public Health Service

has recommended birth-cohort screening in all persons born between 1945 and 1965.[301–303] This recommendation acknowledges the fact that in many cases an obvious epidemiologic source is not apparent and that most of the pool of currently infected persons was exposed during the 1960s and 1970s in adolescence and early adulthood; now that they are in their 50s to 70s many have moderate-to-advanced liver disease. Implementation of this one-time age-cohort screening policy has been predicted to identify approximately 800,000 cases of hepatitis C; to prevent 200,000 cases of cirrhosis, 47,000 cases of HCC, and 120,000 HCV-related deaths; and to be cost-effective.[303] In North America, although the several-decades-old pool in baby boomers has been the predominant source of HCV-infected persons, a new epidemic of acute hepatitis C has emerged during the first two decades of the 21st century among a new generation of young injection drug users (who have not adopted the precautions that led to a reduction in reported cases in the 1990s); furthermore, the spike in the number of new cases continues to be amplified by the opioid epidemic plaguing adolescents and young adults.[304–307]

Pathophysiology and Natural History

Long refractory to in vitro cultivation, HCV can now be replicated in cell culture, which has facilitated understanding of the viral life cycle.[308,309] One of the envelope proteins of HCV, E2, contains a binding site for a surface protein on hepatocytes and lymphocytes, CD81, which may represent a cellular receptor for the virus.[310] HCV also binds to the tight-junction protein claudin 1 and to other liver-surface proteins. Because HCV and lipids rely on the same low-density lipoprotein (LDL) assembly and secretion pathway, HCV appears to be able to "hijack" the LDL assembly and secretion pathway, which allows the virus to "masquerade," invisible to the adaptive immune response, as a lipoprotein; this ability to evade the immune system may contribute to the success of HCV as a chronic passenger in its human host.[311] Like the other hepatitis viruses, HCV is not cytopathic; instead, the presence of virus-infected hepatocytes initiates a cascade of host cellular immunologic events that culminate in clearance of HCV-infected hepatocytes. Early insight has been gleaned from studies of cell-mediated immunity to HCV polypeptides, and the host, genetic, and viral factors that distinguish between the small minority who recover and the large majority who proceed to harbor chronic infection after acute HCV infection are now beginning to be understood. From studies of cell-mediated immunity, a general consensus has emerged that attributes recovery to a more robust, broadly targeted $CD4^+$ and $CD8^+$ T-cell response to HCV proteins, and chronic infection or disease to an absent or minimal and narrowly directed HCV-specific T-cell response.[5,312–315] For spontaneous resolution of hepatitis C, $CD4^+$ T cells, specifically, have been found to be essential for viral clearance.[316] In addition, intrahepatic $CD4^+$ and $CD8^+$ responses against a wide spectrum of HCV epitopes have been shown to correlate with viral clearance and recovery from HCV infection, as has the presence of intrahepatic HCV-specific IFN-γ–producing T cells.[317] Moreover, genomic analysis of the progression of HCV infection in chimpanzees has revealed transcriptional changes in the IFN-α response that correlate with the duration of infection; and genomic signals for antigen-processing and presentation and for the adaptive immune response are expressed in association with viral clearance.[318] Also contributing to chronic HCV infection are mutations in $CD8^+$ T cell–targeted viral epitopes that allow HCV to escape immune-mediated clearance, and upregulation of inhibitory receptors on exhausted (functionally impaired) T cells.[319] For HCV infection to be established chronically, as noted previously, the host immune response to HCV is usually too limited in impact to contain the infection; in addition, this feeble immunologic response allows superinfection with a different genotype or viral isolate (absence of heterologous immunity) or even, under experimental conditions in chimpanzees, reinfection with the same viral isolate (absence of homologous immunity).[320–324] Accordingly, prospects for an effective hepatitis C vaccine to prevent infection are challenging.[325] On the other hand, neutralizing antibodies have been identified against broadly conserved HCV epitopes[326]; potentially, this advance in understanding the humoral immune response to HCV could be exploited to pursue passive immunoprophylaxis with globulin preparations or active immunization with vaccines.

Host factors that have been suggested to correlate with a higher frequency of chronicity after acute infection include male gender; older age (adults more than children); ethnicity (blacks more than whites); clinically mild, inapparent, or anicteric acute infection; certain extended human leukocyte antigen (HLA) haplotypes; and immunologic compromise.[327] From genome-wide association studies (GWASs) among patients treated with IFN-based antiviral therapy emerged the recognition that *IL28B*-related haplotypes coding for IFN lambda 3 (IFN-λ3) correlate strongly with response to antiviral therapy; the favorable CC genotype was associated with sustained virologic responsiveness (approximately 80%), whereas the unfavorable genotype TT reflected refractoriness to responsiveness (approximately 30%).[328] The same genotypes have also been shown to be associated with relative likelihood of HCV clearance after acute infection: CC is associated with a greater than 50% chance of resolution, TT with an approximately 25% chance of resolution, and heterozygous CT with an approximately 30% chance of resolution.[16] Resolution after acute hepatitis C is even more strongly linked to the combination of the *IL28B* CC genotype and an HLA class II allele near *DQB1*03:01*.[329] Further functional analysis of the link between resolution of acute HCV infection and *IL28B* has revealed a frameshift variant upstream of *IL28B* encoding IFN-λ3 on chromosome 19q13.13 that creates a novel IFN gene, *IFN-λ4,* associated with impaired HCV clearance.[330] Further GWAS results have permitted mapping of the mixed histocompatibility complex variant most closely associated with spontaneous HCV clearance to a 50-kilobase region on chromosome 19, rs8099917, approximately 7000 base pairs upstream of *IL28B*.[331]

The natural history of hepatitis C is variable.[327–330,332–339] As noted previously, up to 85% to 90% of acutely infected persons acquire chronic infection. Progression to cirrhosis among those with chronic hepatitis C has been observed even in patients with asymptomatic and otherwise clinically, biochemically, and histologically mild disease. An analysis of 57 adequately sized and documented published studies showed that, among adults (mean age of infection, 42 years) with transfusion-acquired chronic hepatitis C, progression to cirrhosis occurred in approximately 25% over the course of 20 years.[336] A similarly high 20-year, 22% rate of progression to cirrhosis, probably magnified by selection bias, was recorded in cohorts of patients (mean age of infection, 29 years) referred to liver clinics; however, recorded 20-year rates of progression were lower in community-acquired hepatitis C (mean age of infection, 26 years) at 7% and in blood donors (mean age, 22 years) at 4%.[336] In a systematic review of 111 studies (of 33,121 patients) of prognosis of chronic hepatitis C, Thein and colleagues[340] found that rates of progression from histologic fibrosis stage to stage varied (nonlinear progression), in that the overall progression to cirrhosis after 20 years was 16%, but that the 20-year rate of progression to cirrhosis varied according to study type: 18% for cross-sectional retrospective studies (attempt to time the duration of infection retrospectively, based on history of potential exposure, in patients presenting for clinical care), 7% for retrospective-prospective studies (i.e., prospective follow-up studies of subjects identified retrospectively after outbreaks of apparently acute hepatitis C), 18% for studies in clinical settings, and 7% for studies in nonclinical settings (e.g., blood donation center).

Histologic features are perhaps the best predictors of disease progression.[341,342] Among a cohort of Japanese patients who underwent serial liver biopsies over a 20-year period, progression to cirrhosis was limited in those with histologically mild necroinflammatory activity and fibrosis.[343] In contrast, those with moderate and severe hepatitis or fibrosis had progression to cirrhosis almost invariably over 20 to 10 years, respectively.[343] Therefore, baseline liver biopsy is helpful not only to define the degree of liver injury that transpired in the decades before clinical presentation but also to predict the pace of histologic progression over the ensuing 1 to 2 decades.[344,345] In a US cohort of 123 untreated patients who underwent paired biopsies a median of almost 4 years apart, histologic progression of fibrosis occurred in 39%, histologic stability in 37%, and improvement in 24%.[346] Although some investigators have devised models to assess linear progression of fibrosis in chronic hepatitis C,[341] others have emphasized that the rate of progression is variable, not linear.[340,346,347] In this US cohort, the best predictors of histologic progression of fibrosis were advanced age, grade of histologic necroinflammatory activity (especially periportal necrosis), and level

of aminotransferase activity.[346] Although a number of anecdotal reports have documented the presence of severe hepatitis and even, rarely, cirrhosis in patients with normal aminotransferase activity,[348] such severe histologic changes could have derived from an earlier period of biochemical activity, and in large groups of patients with normal aminotransferase levels, histologic studies have shown that the overwhelming majority of patients, with few exceptions, have mild histologic features.[300,349,350] In addition, in several longitudinal studies of patients with chronic hepatitis C and persistently normal aminotransferase activity, the absence of histologic progression over 5 years or more has been documented.[346,351,352] Therefore the rationale exists for monitoring patients with persistently normal aminotransferase activity without therapeutic intervention.[353] Still, because as many as a quarter of patients with normal aminotransferase activity followed for several years ultimately have aminotransferase elevations,[351] even patients with normal aminotransferase levels should be monitored regularly. In addition, patients with normal aminotransferase activity respond as well as those with elevated aminotransferase activity to antiviral therapy and are not excluded as treatment candidates (see subsequent discussion).

Variability in progression of chronic hepatitis C remains a confounding clinical feature of the disease. Yet to be explained are extreme differences in outcome between cohorts of young women who acquired hepatitis C from contaminated anti-D Rh immunoglobulin at the time of childbirth in 1977–79 (17- to 20-year progression to cirrhosis of only 0% to 2%[332,335]; 35-year progression to cirrhosis, in 2013, 19%[354]) and cohorts of recipients of HCV-contaminated intravenous globulin (<11-year progression to cirrhosis in 30%).[334] Similarly, the limited progression of transfusion-related chronic hepatitis C in young children compared with that in adults has been described but not explained.[355] For patients who acquired hepatitis C after transfusion in the 1970s, long-duration follow-up studies lasting 20 years (the Transfusion Transmitted Viruses Study) showed progression to cirrhosis in approximately 20% but no increase in overall mortality (and only a slight, almost negligible, increase in liver-related mortality) compared with a matched, transfused control group in whom hepatitis did not develop.[327,338] Therefore, for someone whose perspective is molded by experiences in a blood bank—where asymptomatic healthy persons with hepatitis C are identified during blood-donor screening and where disease progression in transfusion-related hepatitis C is slow and clinically inapparent—hepatitis C appears to be a slowly progressive and mild disease. In contrast, in a tertiary-care hospital with a liver-transplantation program, referrals that funnel in primarily the sickest patients along the spectrum of disease activity[333] bias hepatologists and transplant surgeons to the view that hepatitis C is an invariably progressive and fatal disease. A more balanced reality exists between these two extremes. In most patients, chronic hepatitis C is a slowly progressive liver disease that may have few clinical consequences over the first 2 decades; progression to cirrhosis occurs in 2% to 4% of young children and young women and in less than 10% of community-based young adult (<40 years) patient cohorts but in about 20% to 25% of referral center–based cohorts of older adults.[327,336] What is not known but is likely is whether, given a sufficiently long time (e.g., 3–5 decades or more), hepatitis C is progressive in most patients.

Neither level of HCV RNA, HCV genotype, nor HCV quasispecies diversity correlates with the degree and rapidity of progression of chronic hepatitis C, but more advanced liver disease is found in patients with higher liver iron levels, almost certainly an indirect reflection of duration of infection.[327] Several factors have been shown to accelerate or to be associated with accelerated progression of fibrosis in chronic hepatitis C, including advanced age at the time of infection; male gender; excessive alcohol use; coinfection with HBV or, as is common in hemophiliacs with multiple transfusions and in injection drug users, HIV; persistently elevated aminotransferase activity[346]; certain extended HLA haplotypes[356]; and concomitant other type of liver disease (e.g., hemochromatosis, steatohepatitis).[300,327,357] Fibrosis associated with steatosis has been recognized to be more common in patients with HCV genotype 3,[358] but hepatic steatosis associated with obesity and insulin resistance may also be associated with a higher frequency of cirrhosis in patients with chronic hepatitis C.[359,360] The intimate relation between HCV replication and the LDL assembly and secretion pathway contributes to the observed association between hepatic steatosis and progression of fibrosis.[311] Blacks, in whom acute hepatitis C is more likely to be followed by chronic hepatitis C, are actually less likely to have progression to cirrhosis than whites,[361] although in one report, the estimated risk of fibrosis progression in blacks was statistically indistinguishable from (albeit 10% lower than) that in whites.[362] Severity of chronic hepatitis C is thought to be increased in patients with acute hepatitis A, based primarily on a report of fulminant hepatitis in a group of patients with chronic hepatitis C superinfected with HAV.[363] This report, however, documented a unique experience not replicated by other observers.

Among patients with compensated cirrhosis resulting from chronic hepatitis C, long-term studies of the natural history of the disease have shown a very good prognosis, a 10-year survival rate of 80%.[364] Other investigators, however, have reported more rapidly progressive decompensation and mortality.[365] Once evidence for hepatic decompensation appears, the survival rate falls dramatically to 50%.[364] In most experiences, in patients with cirrhosis, decompensation occurs at an incidence rate of 4% to 5% per year, a mortality rate of 2% to 6% per year, and an HCC rate of 1% to 4% (up to 7% in some reports) per year.[364,366,367] In a study cohort of 1050 patients selected because of failed previous IFN-based therapy and advanced fibrosis (Ishak stage 3 or 4) or cirrhosis (Ishak stage 5 or 6; see Table 117.3), the rate of clinical decompensation was 18% over 3.5 years,[368] and the 5-year incidence of HCC was 5%, higher in the cirrhotic group at 7% than in the advanced fibrosis group at 4.1%.[369] In this cohort, the 5-year risk of HCC could be stratified into low (0.4% observed), medium (4.8% observed), and high (17.8% observed) risk based on a model in which risk increased with age, black race, alkaline phosphatase, presence of esophageal varices, smoking history, and lower platelet count.[369]

HCC, however, rarely occurs until HCV infection has been established for approximately 20, but more often 30, years, and almost all such patients are already cirrhotic or at least have advanced fibrosis.[369,370] HCV does not integrate into the human host genome, as does HBV. In vitro studies suggest that HCV core protein and nonstructural protein NS3 can transform mammalian cells in culture,[371] and HCV core protein has been shown to induce HCC in transgenic mice,[372] but the mechanism of hepatocarcinogenesis in chronic hepatitis C is unknown. Like other chronic liver diseases associated with cirrhosis and HCC (e.g., hemochromatosis, autoimmune liver disease, α_1-antitrypsin deficiency, nonalcoholic steatohepatitis, alcoholic cirrhosis), chronic hepatitis C may lead to liver cancer by promoting endlessly repetitive cycles of hepatocyte regeneration and repair, resulting ultimately in the emergence of malignant clones. Among patients with cirrhosis and hepatitis C, excessive alcohol intake, hepatic iron overload, and concomitant HBV infection appear to increase the risk of HCC. Currently, chronic hepatitis C accounts for approximately one-third of all cases of HCC in the United States, where the incidence and mortality of all causes of HCC have doubled over the past 25 years and of HCV-associated HCC tripled during the 1990s.[373,374] In Japan, where currently HCV infection accounts for 90% of all cases of HCC, the frequency of HCV-associated HCC tripled over 4 decades.[275] As the US cohort of those who acquired HCV infection in young adulthood matures to middle-aged adults, now predominantly otherwise healthy and in the prime of their careers, predictions made in the years 2000–03 were that, discounting the potential impact of antiviral therapy on the natural history of chronic hepatitis C, over the ensuing decades of the 21st century the frequency of cirrhosis would increase by more than 500%, of HCC by more than 250%, of liver-related deaths by more than 200%, and of both hepatic decompensation and liver transplantation by more than 60%.[285,298,375]

Clinical Manifestations

The most typical patient with recently discovered hepatitis C is asymptomatic, but fatigue is one of the more common clinical features in symptomatic persons. Overall, clinical features of chronic hepatitis C, and of decompensated cirrhosis associated with hepatitis C, are similar to those of chronic hepatitis B. Laboratory test abnormalities in chronic hepatitis B and C are similar; the principal abnormality is an elevation of serum aminotransferase activity, usually ALT exceeding AST, until cirrhosis supervenes, when, in general, AST exceeds ALT.[376] More characteristic of chronic hepatitis C than other forms of chronic liver

disease are episodic fluctuations in aminotransferase activity, postulated to result from bursts of hepatic necroinflammatory activity accompanying the emergence of new quasispecies that overcome host immunologic containment of HCV.[322,323] With progressive chronic hepatitis C and evolving fibrosis, hypersplenism occurs and platelet and white blood cell counts fall. In patients with compensated cirrhosis associated with hepatitis C, laboratory indicators of hepatic synthetic function—prothrombin time and serum albumin—remain normal, but these markers become abnormal in decompensated cirrhosis. Impaired hepatic excretory function tends to be maintained before the emergence of severe, end-stage cirrhosis, when bilirubin increases.

Chronic hepatitis C can be accompanied by circulating autoantibodies, including nuclear antibodies, especially liver-kidney microsomal antibody (anti-LKM1), similar to that seen in autoimmune hepatitis type 2.[46] Assays for circulating immune complexes (such as those that detect aggregated immunoglobulins or cold-precipitable globulins [cryoprecipitates]) can be detected in up to half of all patients with chronic hepatitis C,[377] but only a small fraction of patients have immune-complex disorders (see subsequent discussion).

Histologic features of chronic hepatitis C are similar to those observed in chronic hepatitis B (see previous discussion).[378,379] Fibrosis stage 3 in the 6-point Ishak scale (or F2 in the F0–F4 METAVIR staging system; see Table 117.3) represents septal fibrosis (i.e., scar tissue extending beyond the portal tract and bridging portal to portal or portal to central zones of the liver lobule).[40,42] Fibrosis stages higher than 3 (>F2) are usually progressive and are accepted as histologic criteria for timely treatment.[343]

Disease manifestations unrelated to the liver have been described in patients with chronic hepatitis C, and HCV RNA has been detected in extrahepatic sites, such as lymphocytes and the spleen.[380,381] Among the extrahepatic diseases linked with HCV infection are autoimmune disorders such as Sjögren (sicca) syndrome and immune-complex disorders such as EMC (with a spectrum from mild leukocytoclastic cutaneous vasculitis [palpable purpura, arthralgias] to membranoproliferative glomerulonephritis).[5,382] In patients with immune-complex disease, HCV RNA and anti-HCV have been found to be concentrated in circulating immune complexes.[383] EMC is associated not only with immune-complex diseases but also with lymphoproliferative disorders, such as monoclonal gammopathy of unknown source and B-cell non-Hodgkin lymphoma, also reported to be more prevalent in patients with hepatitis C (with or without EMC).[377,384–386] Lichen planus and porphyria cutanea tarda have also been linked with chronic hepatitis C; whether hepatitis C can cause neurologic disorders and impaired cognition is controversial. Hepatitis C has also been linked with insulin resistance and hepatic steatosis (metabolic syndrome), and type 2 diabetes mellitus.[360,387,388]

Hepatitis C Virus–HIV Coinfection (Also See Chapter 124)

Because of the common, bloodborne routes of acquisition of these two viral agents, approximately one-third of patients with HIV infection (three-quarters in the subset with injection drug use) are coinfected with HCV.[389] As the introduction of ART reduced dramatically the frequency of life-threatening opportunistic infections and malignant diseases and improved survival, hepatitis C emerged as an important cause of morbidity and mortality in persons with HIV. The level of viremia is amplified, the rate of hepatic fibrosis is higher, the course of chronic hepatitis C is accelerated, and the frequency of liver failure is more pronounced in patients with HIV-HCV coinfection.[390–392] Since the introduction of ART for HIV infection, mortality from end-stage liver disease caused by HCV infection in this patient population has increased fivefold.[393] Occasionally, an acute hepatitis-like biochemical flare follows the initiation of ART therapy in patients with HIV-HCV coinfection; ART-related immune recovery resulting in cytolytic T-cell injury of HCV-infected hepatocytes has been invoked to explain this observation.[394]

Treatment

When recombinant IFN-α was first approved and introduced in the early 1980s, the duration of therapy (at a dose of 3 million units administered subcutaneously three times a week) was 6 months. The therapeutic end point in early clinical trials was a return to normal of ALT activity (end-treatment response), which occurred in approximately half of all treated patients during therapy but that was sustained 6 months after therapy in fewer than a quarter.[395,396] When assays were introduced to detect the presence of HCV RNA with reverse-transcription PCR, application of these assays showed that SVRs (defined during most of the IFN-based–therapy era as undetectable HCV RNA for at least 24 weeks after the cessation of therapy), a more stringent end point than biochemical outcome, occurred in fewer than 10% of patients treated for 6 months.[396] Higher doses, more frequent administration, and different preparations (e.g., α2b, α2a, consensus, leukocyte) of IFN failed to increase the frequency of SVRs, as did induction therapy with higher doses and more frequent administration during the early months of therapy.[353,396–402] Doubling the duration of therapy to 12 months, however, doubled the frequency of SVR to approximately 20%.[396,398,399] The efficacy of therapy was doubled again to approximately 40% when the oral guanine nucleoside RBV was added to IFN treatment.[403,404] RBV has a minimal impact on HCV replication and is ineffective when used alone[405,406]; however, this nucleoside analogue could potentially result in immunologic modulation (shift from Th2 response to Th1 response), inhibition of host inosine monophosphate dehydrogenase (IMPDH) activity, depletion of intracellular guanosine triphosphate pools,[407] induction of viral mutational catastrophe,[408] enhancement of the effect of IFN through an increase in IFN-stimulated gene expression (which is suppressed by HCV NS5A), and a direct, albeit subtle, antiviral effect.[409–412] Although the mechanism of RBV activity in HCV infection is not known, the addition of RBV to IFN, with dose based on patient weight, reduces the frequency of virologic relapse at the end of therapy, increasing substantially the efficacy (SVR) of therapy.[402–404] Moreover, achievement of SVR after the completion of therapy has been shown to translate into a durable response characterized by maintenance of virologic, biochemical, clinical, survival, and histologic benefit (including regression of cirrhosis), equivalent to a "cure" in almost all cases.[413–416] As discussed later in this chapter, the IFN era has been surpassed (IFN-based therapy is no longer recommended for hepatitis C), and the current generation of orally administered, highly effective, well-tolerated, high-barrier-to-resistance DAAs achieves cure in almost all treated patients, across all genotypes, and across all patient populations, including those that had been less responsive to IFN-based therapy—a remarkable success story!

Pegylated Interferon and Ribavirin: Standard of Care 2001 to 2011—Treatment Principles Established

The efficacy of antiviral therapy was improved again by the introduction of PEG IFNs, long-acting IFNs bound to polyethylene glycol, α2b in 2001 and α2a in 2002. In patients with chronic hepatitis C, PEG IFN and RBV are no longer the standard of care, but important principles of antiviral therapy were established during the PEG IFN decade. Moreover, even after the introduction of first-generation protease inhibitors (PIs) for genotype 1 in 2011, PEG IFN–RBV remained the standard of care for genotypes 2 and 3, and, for genotype 1, PEG IFN–RBV remained the backbone of therapy to which direct antiviral agents were added when PIs and then polymerase inhibitors were introduced. Therefore, an appreciation of the role of PEG IFN and RBV remains relevant in the era of early-generation direct antivirals.

Limiting degradation of circulating IFNs, pegylation prolongs the half-life of IFNs substantially, permitting once, instead of thrice, weekly injections; PEG IFN monotherapy doubles the frequency of SVR relative to monotherapy with its non-PEG IFN counterpart.[417–420] Moreover, the addition of daily oral RBV to PEG IFN increases the frequency of SVR to approximately 55%.[421–423] Two PEG IFNs were approved: (1) the smaller, linear, 12-kDa, partially renally excreted PEG IFN-α2b,[418,421] and (2) the larger, branched, 40-kDa, non–renally excreted PEG IFN-α2a.[417,419,420,422,423] The two are comparable in efficacy when administered with RBV,[422,423] although the 40-kDa molecule has a longer half-life and, because of its large size, a more restricted (8-L) volume of distribution, allowing a common dose (180 μg) to be used over a wide range of patient weights. The smaller, 12-kDa molecule has a much larger (20-L) volume of distribution and is administered on the basis of weight (1.5 μg/

kg). At standard doses, neither PEG IFN–RBV combination has a higher efficacy than non-PEG IFN–RBV combination therapy for patients who weigh more than 85 kg.

The side effects of PEG IFN and RBV are similar to those of standard IFN (primarily flulike symptoms, marrow suppression, irritability or depression, and thyroiditis [the most common of potential autoimmune reactions]) plus those of RBV (hemolytic anemia [mean, 2–3 g/dL reduction in hemoglobin], nasal or chest congestion, pruritus, drug rashes, and gout); however, neutropenia is more profound, resulting in dose reductions more frequently, in patients treated with PEG (18%–20%) than with non-PEG (5%–8%) IFNs.[423] Because of the risk of anemia in patients with ischemic cardiovascular or cerebrovascular disease, RBV should be avoided in such patients and in patients with marked anemia. In addition, because it is teratogenic in animals, RBV should not be used in pregnant women or their sexual partners, and contraceptive use should be practiced by women of childbearing age and their sexual partners during and for several months after RBV therapy. Excreted by the kidneys, RBV is contraindicated in persons with renal insufficiency. The side effects of PEG IFN plus RBV are not inconsequential and require substantial support from those supervising therapy. In the registration trials of combination PEG IFN–RBV therapy, side effects or laboratory abnormalities led to dose reductions in 36% to 45% and drug discontinuation in 10% to 14%.[421,422] Although neutropenia is common, infections are not,[424] even when absolute neutrophil counts fall below 500/mm^3; therefore, white blood cell growth factors are almost never required. For patients with RBV-associated anemia, options included dose reduction or the addition of erythropoietin injections, which were shown to minimize RBV dose reductions and to improve symptoms of anemia (quality of life) but not to increase the frequency of SVR.[425–427]

For patients with genotypes 2 and 3, PEG IFN and RBV dose reductions had no impact on SVR rates.[428,429] In contrast, patients with genotype 1 did have reductions in SVR when they were not fully adherent to planned doses and durations of therapy.[428–430] An analysis to determine which of the two drugs was more important to maintain at full or near-full doses was undertaken in 936 patients with genotype 1 in whom treatment with standard IFN had failed and who were then retreated with PEG IFN and RBV.[430] Maintenance of PEG IFN to more than 60% of the prescribed dose during the first 20 weeks of therapy was found to be crucial to achieving SVR; however, reducing the RBV dose during the first 20 weeks had no negative impact on SVR if the PEG IFN dose was not reduced and RBV was not discontinued before completion.[431] These observations in re-treated prior nonresponders—that maintaining the PEG IFN dose during therapy is more important than maintaining the RBV dose—appeared to apply also to treatment-naïve patients being treated for the first time, as long as the cumulative RBV dose did not fall below 60% of anticipated therapy.[432] Although completing the full duration of planned RBV therapy was usually necessary, patients with suppression of HCV RNA to undetectable levels within 2 weeks of initiation of therapy were an exception.[433] The observation that reduction of RBV doses had little impact on SVR does raised doubt about the need for or value of maintenance of RBV doses with erythropoietin.[427]

In registration trials of PEG IFN-α2a and PEG IFN-α2b with RBV, RBV doses, definitions of response and of adverse effects (e.g., differences in objectivity of recording depression), and baseline characteristics (e.g., average weight, percent male, percent with bridging fibrosis or cirrhosis) of the study populations were not entirely equivalent,[421–423] and comparisons between the trials of the two PEG IFNs should be interpreted cautiously. In these registration trials, both PEG IFNs with RBV were tested versus a comparator arm of standard IFN-α2b with RBV. In these combination therapy trials, PEG IFN-α2b plus RBV was comparable in tolerability with standard IFN-α2b plus RBV, and PEG IFN-α2a plus RBV was somewhat better tolerated.[421,422] Nevertheless, in these trials, among patients with genotype 1, SVR was achieved in 42% of those in the trial of PEG IFN-α2b (albeit with a suboptimal RBV dose)[421] and in 46% to 51% of those in the trials of PEG IFN-α2a.[422,423] Further suggesting that PEG IFN-α2a is more effective against genotype 1 is the observation that among patients with genotype 1 and a high level of HCV RNA (>2 × 10^6 copies/mL), PEG IFN-α2a, but not PEG IFN-α2b, plus RBV achieved SVR more frequently than non-PEG IFN-α2b plus RBV.

In the only head-to-head trial of PEG IFN-α2b and PEG IFN-α2a (the IDEAL trial, supported by the manufacturer of PEG IFN-α2b) for 48 weeks in 3070 patients with HCV genotype 1, two doses of PEG IFN-α2b (standard 1.5 μg/kg and lower 1 μg/kg, with weight-based RBV doses ranging from 800 to 1400 mg and with RBV dose reductions for side effects at 200-mg decrements) were compared with PEG IFN-α2a (at the standard 180-μg dose, with weight-based RBV doses limited to the standard 1000 and 1200 mg and with RBV dose reductions by half, per package insert).[434] Because of potentially higher RBV doses and smaller RBV dose reductions for anemia in the PEG IFN-α2b groups, this trial might have been predicted to favor PEG IFN-α2b; however, patients randomized to the PEG IFN-α2a arm actually received higher median weight-based RBV doses (13.4 mg/kg) than those in the two PEG IFN-α2b arms (12.4–12.6 mg/kg). Whether the odds were weighted to favor one type of PEG IFN over the other, however, SVRs occurred in comparable proportions of all three groups: 39.8% and 38% in the two PEG IFN-α2b groups, 1.5 and 1.0 μg/kg, respectively, and 40.9% in the PEG IFN-α2a group. Adverse events, drug discontinuations for adverse events, serious psychiatric side effects, hematologic adverse effects, erythropoietin use, and cumulative RBV doses administered were indistinguishable across the three groups.[435] Although the two PEG IFNs were found to be of equivalent efficacy in this head-to-head trial, several meta-analyses have supported higher efficacy for PEG IFN-α2a than for PEG IFN-α2b.[436–438]

In patients with chronic hepatitis C, aminotransferase levels fall during IFN therapy, without the transient ALT flare characteristic of IFN treatment for chronic hepatitis B; however, in a small proportion of patients, ALT levels remain elevated during successful PEG IFN therapy, even after suppression of HCV RNA, returning to normal only after completion of therapy. A two-phase kinetic reduction in HCV RNA follows IFN-based therapy, with the first, steep-sloped phase lasting 2 to 3 days and representing inhibition of virus replication or release and with the second, less steep-sloped phase lasting weeks to months and believed to represent turnover of infected hepatocytes.[275,439] Studies of standard IFN-RBV combination therapy and of PEG IFN–RBV therapy showed convincingly that a 6-month course of therapy sufficed for patients with HCV genotypes 2 and 3, and a full year was necessary for optimal benefit in patients with genotype 1.[403,404,423] The duration of therapy and RBV dose were not assessed equally in registration trials of the two PEG IFNs with RBV; however, regardless of which PEG IFN was chosen, all treatment guidelines included a recommendation for treatment of patients who had the more refractory genotype 1 with a full year of combination therapy and daily doses of RBV—for PEG IFN-α2a, 1000 mg (for patients weighing <75 kg) or 1200 mg (for patients weighing 75 kg or more); for PEG IFN-α2b, a range of weight-based daily RBV doses from 800 mg for weight <65 kg, 1000 mg for weight 65 to 85 kg, 1200 mg for weight 85 to 105 kg, and 1400 mg for weight >105 kg. For patients with the more favorable genotypes 2 and 3, 6 months of therapy and a daily RBV dose of only 800 mg sufficed.[345,440–444] The likelihood of SVR was approximately 80% in patients with genotypes 2 and 3[421–423]; although comparable results could be achieved in patients with genotypes 2 and 3 when treated with non-PEG IFN plus RBV,[421,422] improved convenience and tolerability favored PEG IFN in these patients.

Hepatitis C genotype was an important predictor of PEG IFN–RBV response (2 and 3 more responsive than 1 and 4), as noted previously. On the basis of a GWAS of patients in the IDEAL trial, investigators found that the IFN-λ3-associated *IL28B* genotype of the host was a strong determinant of treatment responsiveness. As noted earlier, approximately 80% of patients with the favorable CC genotype achieved SVR, whereas only approximately 30% of patients with the unfavorable TT genotype achieved SVR.[328] The same genotypes have also been shown to be associated with relative likelihood of HCV clearance after acute infection, with CC favoring clearance and TT favoring chronicity.[16]

Other variables that correlated with reduced responsiveness to PEG IFN–RBV therapy included high-level HCV RNA; advanced histologic grade (necrosis and inflammation) and stage (fibrosis); higher HCV quasispecies diversity; higher hepatic iron levels; age >40 years; obesity; insulin resistance; hepatic steatosis; male gender; black ethnicity[361,435,445–447]; Latino ethnicity[448]; limited adherence (<80% of prescribed IFN, <80%

of prescribed RBV, <80% of prescribed duration of therapy)[429]; and immunologic compromise.[401,421,422,449–454] *IL28B* genotype contributes to the lower responsiveness of black patients, who are more likely to harbor non-CC genotypes, but race-associated differences in virus-specific CD4-positive T-cell responses at baseline (lower in blacks) and upregulated expression on cytolytic T cells and on natural killer cells of "programmed cell death-1" receptors (associated with functional CD8-positive T-cell impairment and exhaustion) also contributed to the reduced antiviral responsiveness in black patients.[455,456] Patients who did not achieve a ≥2-$\log_{10}$ reduction in HCV RNA during the first 12 weeks of therapy had a ≤3% likelihood of achieving an SVR. That is, absence of an early virologic response (EVR) was a strong predictor of nonresponsiveness; in contrast, among patients who achieved an EVR, approximately two-thirds had an ultimate SVR.[422,428] Therefore the absence of an EVR at 12 weeks was adopted widely as an important milestone, after which treatment was discontinued.[345,428]

Rapid virologic responses (RVRs) were defined as reductions of HCV RNA to undetectable levels within 4 weeks of initiation of antiviral therapy. Among patients with genotype 1 who achieved an RVR, 24 weeks of PEG IFN–RBV therapy was just as effective as 48 weeks of therapy, especially in those with low-level HCV RNA at baseline (<800,000 IU/mL), who could achieve SVR rates of approximately 90%.[457–460] Abbreviation of therapy to 24 weeks for RVR was shown to be effective also for patients with genotype 4.[461] Early analyses suggested that for patients with genotypes 2 and 3, the duration of PEG IFN–RBV therapy could be truncated from 24 to 12 or 16 weeks.[462,463] In the largest trial to test this strategy,[464] 24 weeks of therapy was superior to 16 weeks and, as shown in another trial,[465] even with daily RBV doses as high as 1400 mg. Although a full 24 weeks appeared to be the best regimen in patients with genotypes 2 and 3, patients with low-level viremia and an RVR were candidates for shortening of therapy, especially if tolerability of therapy was poor.

Tailored pegylated interferon and ribavirin therapy. As noted previously, the duration of therapy could be shortened for patients with genotype 1 (less securely shown for genotypes 2 and 3) who achieved rapid reductions in HCV RNA (RVRs), especially those with a low baseline HCV RNA. This observation supported the trend to improve outcomes by tailoring antiviral therapy based on patient characteristics (e.g., weight), viral factors (e.g., genotype and baseline level of HCV RNA), and initial drug response (e.g., presence or absence of RVR). Although shortening of therapy was helpful in patients with RVR, patients with genotype 1 who did not achieve RVR (slow responders) and who took longer to suppress HCV RNA to undetectable levels (including those with a ≥2 $\log_{10}$ reduction but with HCV RNA still detectable at 12 weeks; i.e., with an EVR) were shown to benefit from the extension of therapy to 72 weeks.[459,460,466–468] Therefore, the longer the time necessary to suppress HCV RNA to undetectable levels, the longer therapy was to be continued thereafter.[458,459]

For patients with genotype 3, but not 2, treated for 24 weeks with PEG IFN-α2a and RBV, a reduced daily RBV dose of 400 mg was found to be just as effective in yielding SVR as the full 800-mg dose.[469] In general, however, in most clinical trials, patients with genotype 3 did not respond quite as well as those with genotype 2,[459,463,465] and consideration tended to be given to lowering the threshold for extending therapy to 48 weeks in patients with genotype 3. In addition, many authorities preferred to treat patients with cirrhosis who had genotypes 2 and 3 for a full 48 weeks.

For patients with genotype 1 who are relatively refractory to treatment because of a high baseline HCV RNA level (>800,000 IU/mL) and because they are overweight (>85 kg), increasing the weekly PEG IFN-α2a dose to 270 μg and the daily RBV dose to a fixed 1600 mg was shown in a prospective randomized controlled trial of 188 patients to improve the rate of SVR (47%) compared with standard PEG IFN-α2a and RBV doses (SVR, 28%) or with an increase over the standard regimen in the dose of one drug but not the other (32% for increased RBV only; 36% for increased PEG IFN only). As might be anticipated, tolerability was lower in the group receiving higher doses of both drugs.[470] For patients treated with PEG IFN-α2b and RBV, a large (>5000 participants), community-based trial of weight-based RBV therapy (the WIN-R trial) showed that for patients with genotype 1 (but not 2 and 3), increasing the range of daily RBV doses from 800 to 1400 mg (including the 1400-mg dose for patients weighing >105 kg) was more effective, especially in overweight patients, than the standard 1000- to 1200-mg range without increased intolerability.[471] Similarly, another trial of 150 patients with genotype 1 treated with PEG IFN-α2b and RBV showed the benefit of increasing starting RBV doses from 13.3 mg/kg (800–1400 mg daily; SVR up to 29%) to 15.2 mg/kg (1000–1600 mg daily; SVR up to 49%), an SVR benefit that was not enhanced by the use of erythropoietin.[427] Finally, the IDEAL trial[435] showed that a higher, 1400-mg, daily RBV dose combined with PEG IFN-α2b achieved excellent rates of SVR, among the highest in the trial (42%–45%), in patients weighing >105 kg. Moreover, reduced-dose PEG IFN-α2b (1 μg/kg) was just as effective as full-dose PEG IFN-α2b (1.5 μg/kg)[435]; this reduced dose was considered potentially for patients in whom side effects of full-dose PEG IFN-α2b were intolerable. In short, tailoring PEG IFN or RBV doses and treatment duration to individual patients was found to improve the outcome of PEG IFN–RBV therapy. In contrast to the value of tailoring IFN-based therapy, the new generation of pangenotypic DAAs is so effective that the need for tailoring therapy has been largely surpassed (with the minor exception of patients undergoing initial therapy when resistance-associated substitutions [RASs] are present at baseline for one of the recommended regimens, but mostly for retreatment of patients when RASs emerge during failed initial therapy; see later).

Clinical benefits of interferon-based therapy. Successful treatment with IFN-based regimens has been associated with improved survival and with a reduction in complications of chronic hepatitis C in most analyses,[414,415,472–474] although not all.[402] Similarly, antiviral therapy has been calculated to be cost-effective,[475,476] even in patients with mild chronic hepatitis C.[477] In addition, therapy can retard the progression of, and even reverse, fibrosis and cirrhosis.[413,414,416,478,479] Many reports have appeared in the literature purporting to show that IFN treatment of patients with cirrhosis and hepatitis C, even in the absence of an SVR, can reduce the frequency of HCC.[480–484] These predominantly retrospective studies, however, were potentially flawed by a lead-time bias; treated patients may have had less advanced disease than untreated patients in these trials. Therefore, less advanced disease, not IFN treatment, may have accounted for the reduced frequency of this late neoplastic complication of chronic hepatitis C. Confidence in the conclusions of these studies is also minimized by other subject selection biases; incomparability of subjects, treatment, and monitoring among trials; inadequately addressed confounding variables (such as alcohol use); and lower publication frequency of studies with negative results.[485] In fact, in other retrospective and prospective studies, IFN treatment had no beneficial impact on the risk of HCC in patients with cirrhosis caused by chronic hepatitis C.[364,486,487] In addition, in a large, lengthy, prospective, randomized controlled trial (the HALT-C Trial) of maintenance PEG IFN therapy for 3.5 years in 1050 patients with chronic hepatitis C, advanced fibrosis, and prior failure to respond to IFN-based therapy (i.e., in the absence of an SVR), PEG IFN therapy had no impact on the incidence of HCC, even out to 5 years,[368,369] although a beneficial impact on late-emerging HCC after 5 years was suggested in patients with baseline cirrhosis (Ishak fibrosis score 5 or 6) but not advanced fibrosis (Ishak fibrosis score 3 or 4).[488] On the other hand, among patients of any stage of fibrosis who achieved an SVR following IFN-based therapy, the risk of HCC was reduced.[489] Similar benefits follow SVRs achieved after DAA therapy (see later).

First-Generation NS3-4A Protease Inhibitors for Chronic Hepatitis C: Boceprevir and Telaprevir—Standard of Care for Genotype 1, 2011–13

The first DAAs—telaprevir (TVR) and boceprevir (BOC)—gained FDA approval in May 2011 specifically for the treatment of genotype-1 chronic hepatitis C. BOC and TVR are linear ketoamide compounds that cause reversible covalent inhibition at the protease catalytic site. The NS3-4a viral protease is required for cleavage of the HCV polyprotein into mature proteins. Neither of these PIs could be used as monotherapy because of the rapid emergence of resistant variants; however, when these PIs were added to PEG IFN–RBV, the percentage of patients with genotype 1 who achieved SVR improved dramatically, both for treatment-naïve patients and treatment-experienced patients (i.e., who in whom

prior IFN-based treatment had failed). In the pivotal registration trials of TVR (ADVANCE)[490] and BOC (SPRINT 2)[491] in treatment-naïve patients, study patients were randomized to standard-of-care PEG IFN–RBV therapy versus triple therapy with PEG IFN–RBV plus a PI. In the ADVANCE trial, patients received PEG IFN-α2a–RBV–TVR for 8 or 12 weeks followed by PEG IFN–RBV for up to another 40 or 36 weeks, respectively. This trial included response-guided therapy (RGT); patients who achieved an undetectable HCV RNA level at weeks 4 and 12 (an extended rapid virologic response [eRVR]) could truncate PEG IFN–RBV therapy to a total of 24 weeks, whereas patients who did not achieve an eRVR but cleared virus by week 24 continued PEG IFN–RBV therapy for 40 to 36 more weeks. In the 12-week triple-drug therapy arm, 75% of patients achieved an SVR, compared with 44% of patients receiving PEG IFN–RBV therapy alone, and, even in the 8-week triple-therapy arm, SVRs occurred in 69%. (Of note, since the trials of the first of the DAAs, an SVR has been defined as undetectable HCV RNA through posttreatment week 12 (SVR_{12}), which was shown to be the equivalent of the former 24-week milestone.) On the basis of RGT rules, 58% of TVR-treated study patients met eligibility criteria to discontinue therapy at 24 weeks and had SVR rates of 83% to 89%, respectively, for the 8-week triple-therapy group and for the 12-week triple-therapy group; the likelihood of an SVR in patients who did not meet shortened-therapy criteria was lower—50% and 54%, respectively—but still better than in patients treated for 48 weeks in the PEG IFN–RBV control group who did not achieve an eRVR (39%). A follow-up study in 540 treatment-naïve participants (ILLUMINATE) confirmed the value of RGT with TVR; among the 65% of study patients who achieved an eRVR, 92% went on to an SVR.[492]

In the SPRINT 2 trial of BOC in treatment-naïve subjects, patients were randomized to 48 weeks of PEG IFN–RBV versus PEG IFN–RBV–BOC triple therapy; this trial included 4 weeks of lead-in therapy with PEG IFN–RBV for all subjects and both an RGT arm (BOC–PEG IFN–RBV for 24 weeks if HCV RNA was undetectable at weeks 8 and 24 or a full 48 weeks of triple therapy if RGT criteria were not met) and a fixed-duration arm (PEG IFN–RBV–BOC for 44 weeks following the 4-week PEG IFN–RBV lead-in). Rates of SVR rates were 63% in the RGT arm (44% meeting criteria for shortened, 28-week, therapy), 66% in the full 48-week-therapy arm, and 38% in the PEG IFN–RBV control arm. The rate of SVR was 67% to 69% in nonblack patients, but only 42% to 53% in blacks. Among subjects in the RGT arm who did not meet criteria for shortened therapy, SVRs were no more common than in the PEG IFN–RBV control arm.

REALIZE (TVR)[493] and RESPOND-2 (BOC)[494] were the registration trials in treatment-experienced patients with genotype-1 chronic hepatitis C who had not achieved SVRs during prior courses of IFN-based therapy: relapsers who had an end-of-treatment response (undetectable HCV RNA) but whose HCV RNA reemerged after therapy; partial responders who had a greater than or equal to 2-$\log_{10}$ IU/mL reduction in HCV RNA but never cleared viremia during previous IFN-based therapy; and null responders, in whom levels of HCV RNA fell by less than 2 $\log_{10}$ during previous therapy. The registration trial of TVR in prior nonresponders, REALIZE, involved all three categories of nonresponders, did not include RGT, but did have a lead-in arm. Subjects in the PEG IFN–RBV–TVR treatment arms (12 weeks of triple therapy with or without a 4-week lead-in phase followed by PEG IFN–RBV for the remainder of 48 weeks) had indistinguishable SVRs of 66% and 64%, respectively, compared with the control group, which received PEG IFN–RBV for 48 weeks and had a 17% rate of SVR. The likelihood of an SVR was inversely proportional to the relative level of treatment refractoriness during previous IFN-based therapy—31% in prior null responders, 57% in prior partial responders, and 86% in prior relapsers.

The registration trial of BOC in prior nonresponders, RESPOND-2, involved former relapsers and partial responders but not null responders and included both a 4-week PEG IFN–RBV lead-in period and RGT. Patients were randomized to 4 weeks of lead-in PEG IFN–RBV therapy followed by either triple-drug RGT (PEG IFN–RBV–BOC through week 36 for an eRVR [defined as undetectable HCV RNA at week 8 and at all subsequent time points through week 36] but for a full 44 weeks of triple-drug therapy if eRVR was not achieved) or fixed-duration triple-drug therapy (triple-drug therapy for 44 weeks after lead-in) or to a 48-week PEG IFN–RBV control group. An SVR was achieved in up to 52% of prior partial responders and in up to 75% in prior relapsers (differences between the RGT and fixed-duration triple-drug arms were small and related to unexplained slightly lower on-treatment responses in the RGT group that occurred during the initial 36 treatment weeks, when regimens were identical). In a subsequent open-label trial among 42 prior null responders, an SVR was achieved in 38% after 48 weeks of therapy (44 weeks of PEG IFN–RBV–BOC following 4 weeks of PEG IFN–RBV lead-in therapy).

Essential conclusions from trials of both PIs in treatment-experienced patients are that prior relapsers attained an SVR at rates exceeding those of treatment-naïve patients (69% for BOC and 86% for TVR); prior partial responders had intermediate SVR rates of 52% (48-week BOC arm) to 57% (48-week TVR arm); and prior null responders had the lowest SVR rates, in the 30% range. Pretreatment bridging fibrosis or cirrhosis at biopsy had no effect on SVR rates in prior relapsers but was associated with a poorer outcome in prior partial and, especially, in prior null responders. For example, among TVR-treated null responders, SVRs occurred in 41% of TVR-treated subjects with minimal fibrosis, in 39% with bridging fibrosis, but in only 14% with cirrhosis (for comparison, 10% of PEG IFN–RBV–treated prior null responders with cirrhosis had SVRs). For both PIs, responsiveness correlates with *IL28B* genotype (CC better than non-CC), ethnicity (white better than black), fibrosis stage (low stage better than high stage), HCV genotype subtype (1b more responsive than 1a), and, when available, level of HCV RNA reduction during lead-in PEG IFN–RBV therapy (≥1 $\log_{10}$ reduction better than <1 $\log_{10}$ reduction). Unlike the case for PEG IFN–RBV therapy, for PI-based triple-drug therapy, age, baseline HCV RNA level, and insulin resistance have little or no influence on treatment responsiveness.

Recommendations based on randomized controlled trials and on data extrapolated by FDA analysis from the body of data generated in treatment-naïve and treatment-experienced patients[495,496] were issued in 2011 for TVR and BOC, as follows. For treatment-naïve patients with chronic hepatitis C, genotype 1, treatment consisted of TVR or BOC along with PEG IFN–RBV. For TVR, 750 mg three times a day with a fatty diet, along with weekly PEG IFN and twice-daily, weight-based RBV, was administered for 12 weeks, followed by an additional 12 weeks of PEG IFN–RBV for patients with an eRVR (HCV RNA undetectable, but ≤1000 IU/mL, at weeks 4 and 12) and for an additional 36 weeks for patients without an eRVR (but with HCV RNA undetectable at week 24). For BOC, after 4 weeks of PEG IFN–RBV lead-in therapy, patients received BOC 800 mg three times daily with food along with weekly PEG IFN and twice-daily, weight-based RBV for 24 weeks (total duration of therapy, 28 weeks), if HCV RNA was undetectable at weeks 8 and 24. If HCV RNA was detectable at week 8, less than 100 IU/mL at week 12, but undetectable at week 24, triple-drug PEG IFN–RBV–BOC was continued for another 12 weeks (through week 36), followed by an additional 12 weeks of PEG IFN–RBV (total duration of therapy 48 weeks). Patients with cirrhosis treated with either TVR or BOC were treated for a full 48 weeks, without response-guided shortening of therapy.

For treatment-experienced patients who had relapsed after prior IFN-based therapy, the treatment regimen was the same as that for treatment-naïve patients. Data in relapsers with cirrhosis were too limited for a definitive recommendation about the duration of therapy.

For treatment-experienced patients who were prior partial responders and noncirrhotic, RGT with BOC (4 weeks of lead-in therapy with PEG IFN–RBV, followed by BOC along with PEG IFN and RBV through week 36 if HCV RNA was undetectable at weeks 8 and 24, but, if HCV RNA is detectable at week 8 but undetectable at week 24, followed by an additional 12 weeks of PEG IFN–RBV, through week 48) or full 48-week TVR-based therapy (12 weeks of triple-drug therapy followed by 36 weeks of PEG IFN–RBV therapy) was recommended. In BOC-treated patients, if HCV RNA did not fall by at least 1 $\log_{10}$ IU/mL during lead-in with PEG IFN–RBV, a full 44 weeks of triple-drug therapy was considered.

If a decision was made to treat null responders, a full 48 weeks of therapy was recommended (for TVR, 12 weeks of triple therapy followed by 36 weeks of PEG IFN–RBV; for BOC, 4 weeks of lead-in PEG IFN–RBV, followed by 44 weeks of triple-drug treatment, ending at week 48).

For these regimens, failure to achieve HCV RNA reductions at critical treatment milestones was shown to be invariably predictive of nonresponse, justifying absolute stopping rules for futility—for TVR, if HCV RNA was greater than 1000 IU/mL at weeks 4 or 12, or if HCV RNA remained detectable at week 24; for BOC, if HCV RNA was greater than or equal to 100 IU/mL at week 12, or if HCV RNA remained detectable at week 24. If PEG IFN–RBV was to be discontinued for any reason, the PI also had to be discontinued in order to protect the patient from being treated with PI monotherapy, which would engender the emergence of resistance.

Triple therapy did not avert the toxicities of PEG IFN–RBV, and both TVR and BOC could worsen the anemia induced by PEG IFN–RBV, mandating close laboratory monitoring for anemia and requiring red blood cell transfusions in some cases, especially in prior null responders with cirrhosis. Rectal burning occurred in approximately one-third of TVR-treated patients, and dysgeusia (altered sense of taste) was common to both PIs (approximately one-third of BOC-treated patients and approximately 10% of TVR-treated patients). Moreover, in TVR trials, 6% of patients withdrew because of the development of a severe, confluent, maculopapular, pruritic rash of the trunk and extremities, which in some cases necessitated systemic corticosteroid therapy; careful monitoring was necessary to identify rashes when they were early, mild, and easily reversible. Both drugs were administered every 8 hours with food, which, for TVR, had to be a 20-g fat meal. Lastly, both drugs are metabolized via the P-450 (CYP3A4) system, accounting for multiple drug-drug interactions, including with many medications (e.g., statins) taken in the middle-aged population in which hepatitis C is most prevalent. Careful review of coadministered medications was paramount before initiation of treatment. The rigors of triple-drug PI therapy—multiplied intolerability, complexity of RGT and stopping rules, thrice-daily dosing and high pill burden, multiple drug-drug interactions, and so on—and the imminent availability of next-generation and all-oral direct antiviral therapy (see later) tempered initial enthusiasm for this generation of direct antivirals. Although first-generation PI-based triple-drug therapy was the recommended standard of care from 2011 to 2013 for patients with genotype-1 chronic hepatitis C, in practice, the treating community became progressively more conservative as time elapsed, in anticipation of simpler, more effective DAA regimens to come. For patients with mild disease and low-stage fibrosis, treatment was postponed, whereas initiation of first-generation therapy was more selective, limited to specific populations of patients who warranted immediate therapy, such as prior relapsers who have bridging fibrosis or cirrhosis on biopsy or other subgroups in whom mitigating the risk of progressive liver disease and its complications commanded a high priority.

The most frequently described mutation in NS3/4A was R155K, which occurred at the catalytic site where BOC and TVR bind. This mutation is found more commonly in genotype 1a–infected patients because one nucleotide change creates the amino-acid substitution in 1a, whereas two nucleotide changes are required for the same substitution in genotype 1b. This common variant may explain the consistently higher SVR rates observed in genotype 1b patients on triple therapy. Although most nonresponders to PI-based triple-drug therapy acquired resistance variants, these variants were not archived and were supplanted by wild-type HCV within 2 years of stopping therapy in almost all patients.

Once IFN-free regimens consisting of NS5A inhibitors and improved PIs were introduced in 2016–17 (see later), TVR and BOC were discontinued; they are no longer recommended as treatment for hepatitis C. PEG IFN–based treatments have now been supplanted by combinations of orally administered, small-molecule HCV inhibitors with few side effects, simple dosing, treatment courses as brief as 8 to 12 weeks, pangenotypic efficacy, and negligible resistance.

Second-Generation NS3-4A Protease Inhibitor and First-Generation Nucleoside Polymerase Inhibitor for Chronic Hepatitis C: Simeprevir and Sofosbuvir—Standard of Care, 2014–15

Simeprevir (SMV), a second-generation PI for HCV genotype 1, was approved in November 2013; the pangenotypic nucleoside polymerase inhibitor SOF was approved in December 2013.

SMV, with antiviral activity against HCV genotype 1 (1b > 1a), had improved pharmacokinetic properties compared with those of first-generation PIs and, therefore could be taken once a day. Like first-generation PIs, SMV had to be taken with PEG IFN–RBV and with food. Approximately a third of patients with HCV genotype 1a harbor an NS3 polymorphism, Q80K, which renders them refractory to the antiviral activity of SMV; if SMV therapy was being considered, Q80K testing was advisable, and, if results were positive, discouraged the use of SMV.

In two phase III clinical trials among treatment-naïve participants with chronic hepatitis C (QUEST-1 and QUEST-2), SMV 150 mg daily plus PEG IFN–RBV for 12 weeks, followed by another 12 weeks of PEG IFN–RBV, yielded an SVR in 80% (compared with 50% of control subjects treated with PEG IFN–RBV). In participants with genotype 1a and a Q80K variant, SMV triple-drug therapy was no more effective than PEG IFN–RBV, and the efficacy of SMV-based triple-drug therapy was reduced to 58% in participants with cirrhosis. Phase III trials included RGT (if HCV RNA was <25 IU/mL at week 4 and undetectable at week 12, the treatment course could end at week 24; if these milestones were not met [but stopping rules not violated], treatment was extended to 48 weeks); however, in the 8% of study participants who did not meet RGT milestones for shortened therapy, only 25% experienced an SVR. Therefore, RGT was not recommended for SMV. The efficacy of SMV-based triple-drug therapy was similar in prior relapsers to IFN-based therapy, achieving (in the phase III PROMISE trial) an SVR in 79% (compared with 37% in a PEG IFN–RBV–treated control group). Phase III trials did not include treatment-experienced nonresponders, but, based on phase II trials, SMV-based triple-drug therapy was approved for partial responders and null responders, for all of whom a full 48 weeks of therapy (12 weeks of SMV with PEG IFN–RBV, followed by 36 weeks of PEG IFN–RBV) was recommended; in these phase II trials, an SVR was achieved in 85% of prior relapsers, 70% of prior partial responders, and 45% of prior null responders. These treatment approaches applied to patients with any stage of fibrosis, including those with cirrhosis. If an HCV RNA suppression milestone of ≤25 IU/mL was not met by week 4, further treatment was futile, and therapy was to be stopped; if HCV RNA was not suppressed to ≤25 IU/mL at week 12 or 24 (by which time SMV had been completed), PEG IFN–RBV was to be stopped for futility. In black patients, SMV therapy was approximately 10% less effective in achieving an SVR than in white patients. SMV is metabolized in the liver by cytochrome P-450 3A (CYP3A); therefore, concomitant administration of SMV along with CYP3A inducers or inhibitors could amplify or reduce SMV exposure, and it was important that prescribers consult prescribing information and/or the website www.hep-druginteractions.org before prescribing SMV. In addition to the side effects of PEG IFN–RBV, SMV-based therapy was associated with photosensitivity, rash, and mild hyperbilirubinemia (Janssen Therapeutics, Titusville, NJ, November 2013).[497–501] Fourth-generation PIs and second-generation NS5A inhibitors became standard of care in 2017 (see later) and reduced the appeal of SMV; it is no longer recommended as first-line treatment for hepatitis C (www.hcvguidelines.org).

SOF was the first non-PI DAA to be approved. SOF is a uridine nucleoside polymerase inhibitor with one of the best profiles among the new oral hepatitis C antiviral agents. It is very potent, has a high barrier to resistance and pangenotypic activity, is very well tolerated with few adverse events, requires only once-daily oral administration, and appears to be relatively free from major drug-drug interactions.[502,503] In clinical trials, SOF has been studied in all genotypes (1–6); in treatment-naïve patients and prior null-responders to PEG IFN–based therapy; in prior TVR and BOC nonresponders, with PEG IFN–RBV or in IFN-free regimens; in combination with RBV or with NS5A inhibitors; and for treatment periods as brief as 8 to 12 weeks to as long as 24 weeks.[504–506]

In a phase III, IFN-free trial of SOF plus RBV—in patients with genotypes 2 and 3 who were IFN intolerant, ineligible, or unwilling (55% *IL28B* non-CC; 16% cirrhotic)—78% achieved SVR (93% genotype 2, 61% genotype 3) versus 0% in placebo recipients.[506] Similarly, among prior PEG IFN–RBV nonresponders with genotypes 2 and 3 treated with open-label SOF-RBV (IFN free) for 12 or 16 weeks, 50% (86% genotype 2, 30% genotype 3) and 73% (94% genotype 2, 62% genotype

3), respectively, experienced SVRs.[506] In phase III trials, among patients with genotypes 1 and 4 to 6, open-label SOF plus PEG IFN–RBV for 12 weeks yielded SVRs of 90% (compared with 60% in historical control subjects); 89% in genotype 1; and 97% in genotypes 4 to 6 (NEUTRINO trial).[505] In treatment-naïve participants with genotypes 2 and 3, SVRs occurred in 67% of patients treated with either SOF and RBV for 12 weeks or PEG IFN–RBV for 24 weeks; again, SVR was more frequent in SOF-RBV recipients with genotype 2 (97%) than those with genotype 3 (56%) (FISSION trial).[505] IFN-free combinations of SOF plus NS5A inhibitors yielded near-100% SVRs in both treatment-naïve participants and prior null responders with genotypes 1, 2, and 3 after treatment durations as brief as 12 weeks (ledipasvir [LDV]) and 24 weeks (daclatasvir) (see later). A combination fixed-dose pill containing 400 mg of SOF plus 90 mg of LDV to be used with or without RBV for 8 weeks (treatment-naïve, noncirrhotic patients) to 12 weeks (treatment-experienced, cirrhotic patients) (LONESTAR, ION-1, ION-2, ION-3 trials) was approved in October 2014 (see later).[507–510] The combination of SOF and SMV was also found to be very effective in patients with genotype 1 and was a recommended first-line regimen until superseded by later-generation DAAs (see later).[511]

SOF may cause significant bradycardia when administered with amiodarone, particularly if a β-blocker is also being administered. Therefore, administration of amiodarone along with SOF-containing regimens should be avoided. SOF was approved for combination therapy of chronic hepatitis C with genotypes 1, 2, 3, and 4, including in patients with HCC awaiting liver transplantation and those with HCV and HIV-1 coinfection, in whom efficacy is comparable to that in patients with HCV monoinfection. SOF can be used in patients with mild-to-moderate renal impairment but is not recommended for patients with severe renal failure (CrCl <30 mL/min). Therapeutic acid suppression (e.g., proton pump inhibitors [PPIs]) raise gastric pH, which reduces the solubility of SOF; therefore, if a PPI is to be used, both the PPI (equivalent to ≤20 mg of omeprazole) and SOF should be taken together under fasted conditions. The dosage of SOF is 400 mg orally every day, and combination regimens are listed in Table 117.9, which reflect the September 2017 recommendations of the AASLD and the Infectious Diseases Society of America (IDSA), which have collaborated to update consensus treatment recommendations (www.hcvguidelines.org). Those specific recommendations are further discussed later.

First-Generation NS5A Inhibitors, Second-Generation Nucleoside Polymerase Inhibitors, and Third-Generation NS3-4A Protease Inhibitors—Standard of Care, 2015 to September 2017

The AASLD and IDSA have been formulating and updating recommendations for treatment of HCV-infected patients (www.hcvguidelines.org). The recommendations issued in January 2015 and February 2016 were

TABLE 117.9 AASLD and IDSA Recommendations for Treatment of Hepatitis C: September 2017

FIRST-LINE TREATMENT RECOMMENDATIONS IN DAA-NAÏVE PATIENTS*		
GENOTYPE	**NO CIRRHOSIS**	**COMPENSATED CIRRHOSIS**
1	GLE-PIB × 8 wk SOF-LDV × 8-12 wk (8 wk for noncirrhotic, nonblack patients with HCV RNA <6 × 10^6 IU/mL without HIV infection or PEG IFN–RBV experience) SOF-VEL × 12 wk GRZ-ELB × 12 wk	GLE-PIB × 12 wk GRZ-ELB × 12 wk SOF-LDV × 12 wk SOF-VEL × 12 wk
2	GLE-PIB × 8 wk SOF-VEL × 12 wk	GLE-PIB × 12 wk SOF-VEL × 12 wk
3	GLE-PIB × 8 wk SOF-VEL × 12 wk	GLE-PIB × 12 wk SOF-VEL × 12 wk GRZ-ELB + SOF × 12 wk SOF-VEL-VOX × 12 wk
4	GLE-PIB × 8 wk GRZ-ELB × 12 wk SOF-VEL × 12 wk SOF-LDV × 12 wk	GLE-PIB × 12 wk GRZ-ELB × 12 wk SOF-LDV × 12 wk SOF-VEL × 12 wk
5 or 6	GLE-PIB × 8 wk SOF-LDV × 12 wk SOF-VEL × 12 w	GLE-PIB × 12 wk SOF-LDV × 12 wk SOF-VEL × 12 w

GENOTYPE	**FIRST-LINE TREATMENT RECOMMENDATIONS IN DAA-EXPERIENCED PATIENTS (DURATION 12 WK FOR ALL CHOICES)***		
Experience with	PI + PEG IFN–RBV	SOF-containing DAA, no NS5A	NS5A
1	GLE-PIB SOF-LDV SOF-VEL	GLE-PIB SOF-VEL SOF-VEL-VOX	SOF-VEL-VOX
2	Not relevant	GLE-PIB SOF-VEL	No recommendation
3	SOF-VEL-VOX	SOF-VEL-VOX	SOF-VEL-VOX
4	SOF-VEL-VOX	SOF-VEL-VOX	SOF-VEL-VOX
5 or 6	SOF-VEL-VOX	SOF-VEL-VOX	SOF-VEL-VOX

AASLD, American Association for the Study of Liver Diseases; *DAA,* direct-acting antiviral; *ELB,* elbasvir 50 mg[a,b]; *GLE,* glecaprevir 300 mg[b,c]; *GRZ,* grazoprevir 100 mg[b,c]; *HCV,* hepatitis C virus; *IDSA,* Infectious Diseases Society of America; *LDV,* ledipasvir 90 mg; *PEG IFN,* pegylated interferon; *PI,* protease inhibitor; *PIB,* pibrentasvir 120 mg[b]; *RBV,* ribavirin; *SOF,* sofosbuvir 400 mg[d]; *VEL,* velpatasvir 100 mg; *VOX,* voxilapervir 100 mg[c]. (Note: drugs with endings "-buvir" are polymerase inhibitors, "-asvir" are NS5A inhibitors, and "-previr" are protease inhibitors.)

*Order of listing does not convey preference for one regimen over another. See www.hcvguidelines.org for caveats/minor exceptions, alternative treatments, treatment in special populations, situations that merit baseline resistance testing, and information on drug-drug interactions.

[a]Baseline high-fold NS5A resistance-associated substitutions for ELB should not be present in patients with genotype 1a.

[b]DAA regimens GLE/PIB and GRZ/ELB are recommended for patients with stage 4–5 kidney disease (creatinine clearance <30 mil/min).

[c]US Food and Drug Administration warning letter issued in October 2015 that hepatic decompensation and failure have been reported with protease inhibitor-containing DAAs, which are not recommended for patient with decompensated cirrhosis (Child-Pugh class B and C, see text).

[d]SOF-containing DAA combinations are not recommended for stage 4–5 chronic kidney disease (creatinine clearance <30 mil/min).

based on the approval of the fixed combination of LDV and SOF (Harvoni; Gilead Sciences, Foster City, CA); the fixed combination of paritaprevir, ritonavir, and ombitasvir, plus dasabuvir (Viekira Pak; AbbVie, North Chicago, IL) plus or minus RBV; the fixed combination of grazoprevir and elbasvir (Zepatier; Merck, Whitehouse Station, NJ); the NS5A inhibitor declatasvir (Daklinza; Bristol-Myers Squibb, Princeton, NJ); and the fixed combination of paritaprevir, ritonavir, and ombitasvir (Technivie; AbbVie). These and subsequently approved treatments are IFN-free regimens that rely on DAAs, such as next-generation NS3/4 PIs (names ending in *-previr*), nucleoside and nonnucleoside NS5B polymerase inhibitors (names ending in *-buvir*), and inhibitors of NS5A (a membrane-associated phosphoprotein that is part of the HCV RNA replication complex; names ending in *-asvir*).[503,512] (These drugs are discussed further in Chapter 47.) As a class, first-generation PIs had good efficacy in treatment-naïve patients and prior relapsers but only fair efficacy in prior nonresponders, a low barrier to resistance, a narrow genotype specificity, challenging tolerability, and multiple drug-drug interactions.[503]

Second-generation PIs—SMV, as discussed earlier, and ritonavir-boosted paritaprevir[513]—have improved pharmacokinetics (once-daily instead of thrice-daily administration), reduced regimen complexity, efficacy across genotypes, a higher barrier to resistance, improved tolerability, and fewer drug-drug interactions. SMV when combined with PEG IFN–RBV (as reviewed earlier) or with SOF and ritonavir-boosted paritaprevir in the absence of PEG IFN, with one or more other direct oral antivirals (polymerase inhibitors, NS5A inhibitors, RBV, or a combination of these), has been shown to achieve SVR rates greater than 90% in both treatment-naïve patients and prior null responders with genotype-1 HCV infection, including those with the more refractory *IL28B* non-CC host genotypes and viral genotype 1a.

The NS5A inhibitors suppress HCV replication rapidly and profoundly but tend to have less-than-ideal resistance profiles[503]; however, some in this class have been reported to have excellent resistance profiles and broad genotype specificity. Drug class combinations that have been approved are described here.

Ledipasvir-sofosbuvir (Harvoni). LDV-SOF was approved in October 2014 for treatment of hepatitis C, genotypes 1a, 1b, 4, and 6 (see Table 117.9). LDV, 90 mg, an NS5A inhibitor, is combined with SOF, 400 mg, an NS5B inhibitor, reviewed earlier. Based on the results of phase III trials in treatment-naïve noncirrhotic patients (ION-3),[509] treatment-naïve cirrhotic and noncirrhotic patients (ION-1),[508] and treatment-experienced cirrhotic and noncirrhotic patients (ION-2)[510] with genotype-1 chronic hepatitis C, the duration of therapy is 12 weeks for treatment-naïve patients and for treatment-experienced patients without cirrhosis. For treatment-naïve nonblack patients without cirrhosis who have HCV RNA levels of <6 million IU/mL, 8 weeks of therapy has been shown to be sufficient. For treatment-experienced patients with cirrhosis, 24 weeks of therapy is required. Clinical trials in both treatment-naïve and treatment-experienced patients have demonstrated SVR rates of 91% to 100%.[507–510] Moreover, studies with and without RBV have indicated that addition of RBV does not improve efficacy of LDV-SOF. Moreover, this combination therapy has been shown to be effective[514] and is now indicated for patients with decompensated cirrhosis; however, it has not been shown to be effective in patients with advanced renal failure. The combination of LDV-SOF is given once daily and is generally well tolerated. The most common side effects are fatigue, insomnia, headache, and nausea and are generally mild in intensity. As noted earlier, SOF may cause severe bradycardia when administered with amiodarone, particularly if a β-blocker is also being administered. Therefore, administration of amiodarone along with SOF-containing regimens should be avoided. As with other SOF-containing regimens, LDV-SOF is not recommended for patients with severe renal impairment (CrCl <30 mL/min).

Drugs that induce P-gp, such as St. John's wort and rifampin, may reduce the concentration of both LDV and SOF. Gastric acid inhibitors can also reduce LDV concentrations and should be used at low doses if possible. Ideally, PPIs and LDV-SOF should not be used together; however, if PPI treatment is necessary, LDV-SOF should be taken with food 4 hours prior to 20 mg of omeprazole. LDV and SOF are further discussed in Chapter 47.

Ritonavir-booster paritaprevir, ombitasvir, and dasabuvir (Viekira Pak). Paritaprevir is an NS3/4A PI boosted by ritonavir, ombitasvir is an NS5A inhibitor, and dasabuvir is a nonnucleoside NS5B inhibitor. Initially, the regimen was formulated as ritonavir-boosted paritaprevir and ombitasvir in a single tablet (taken once daily) plus dasabuvir in a separate tablet taken twice daily. Later, an extended-release version (Viekira XR) was approved, consisting of three individual tablets (ritonavir-boosted paritaprevir, ombitasvir, and long-acting dasabuvir) taken once daily (with or without twice daily RBV). The combination of ritonavir-boosted paritaprevir, ombitasvir, dasabuvir, and RBV (i.e., up to five drugs) was shown to be an effective all-oral, IFN-free regimen and was approved in December 2014 (the extended-release version approved in July 2016) for treatment of genotypes 1a and 1b (see Table 117.9). The combination without dasabuvir (Technivie) was approved for genotype 4 in July 2015. Clinical trials have demonstrated that this regimen is highly effective in treatment-naïve patients with and without cirrhosis and in those in whom therapy with PEG IFN and RBV has failed.[515–519] High rates of SVRs have been noted, ranging from 93% to 100%, with the highest efficacy seen in genotype-1b infection. In 473 noncirrhotic, treatment-naïve patients, the combination of ritonavir (100 mg)-boosted paritaprevir (150 mg once daily), ombitasvir (25 mg once daily), dasabuvir (250 mg twice daily), and weight-based RBV for 12 weeks achieved an SVR_{12} in 96.2% (SAPPHIRE-I).[515] For genotype 1a, efficacy was approximately 7% lower without RBV (90%) than with RBV (97%), whereas for genotype 1b, SVRs were achieved in 99% with or without RBV (PEARL-III and PEARL-IV).[516] In 297 noncirrhotic, treatment-experienced participants, this five-drug combination was associated with an SVR_{12} in 96.3%: 95.3% in relapsers, 100% in partial responders, and 95.2% in null responders (SAPPHIRE-II).[517] In a group of 380 treatment-naïve and treatment-experienced participants with well-compensated cirrhosis, the same five-drug treatment regimen for 12 weeks or 24 weeks yielded an SVR_{12} in 91.8% and 95.9%, respectively. In the treatment-naïve subgroup, 12- and 24-week SVR_{12} rates were 94.2% and 94.6%, respectively. In the treatment-experienced subgroup, 12- and 24-week SVR_{12} rates were 96.6% and 100%, respectively, in relapsers; 94.4% and 100%, respectively, in partial responders; and 86.7% and 95.2%, respectively, in null responders (TURQUOISE-II).[518] The rate of SVR_{12} after treatment with this drug combination was indistinguishable between study participants with genotypes 1a and 1b.[515,517,518] Null-responder cirrhotic patients with genotype 1a treated for 12 weeks responded less well (SVR_{12} 80%) than those treated for 24 weeks (SVR_{12} 92.9%).[518]

For genotype 1a, the combination is given with weight-based RBV (in two divided doses taken twice daily) for 12 weeks (no cirrhosis) or 24 weeks (compensated cirrhosis). For genotype 1b, this drug combination is given for 12 weeks, without RBV (no cirrhosis) or with RBV (compensated cirrhosis). For genotype 4, the regimen is given for 12 weeks with weight-based RBV but without dasabuvir. As noted earlier and reviewed later, this three-component fixed-dose regimen is available as Technivie.

In October 2015, the FDA issued a warning letter, which is added to prescribing information for both Viekira Pak and Technivie, noting that hepatic decompensation and failure have been reported with these medications. Patients who receive these drugs should be monitored closely for hepatic decompensation, and administration of medications should be stopped if hepatic decompensation is noted. Currently, all PI-containing DAAs for hepatitis C, although recommended in compensated cirrhosis (Child-Pugh class A), are contraindicated in patients with decompensated cirrhosis (Child-Pugh classes B and C).

The regimen has been generally well tolerated, with a variety of common, usually mild side effects. These include fatigue, asthenia, insomnia, headache, and pruritus. Hyperbilirubinemia (primarily unconjugated) and elevations in ALT were seen, which resolved during treatment or immediately thereafter. Components of the regimen are substrates and inhibitors of important metabolic enzymes, and drug interactions can occur, such as with rifampin, St. John's wort, anticonvulsants, salmeterol, and ethinyl estradiol–containing products. These drugs are discussed further in Chapter 47.

Now that more effective, simpler regimens are available, paritaprevir-ombitasvir-dasabuvir combinations are no longer recommended as first-line therapy (www.hcvguidelines.org).

Elbasvir-Grazoprevir (Zepatier). Elbasvir-grazoprevir is an oral fixed-dose combination that consists of an NS5A replication complex inhibitor, elbasvir (50 mg), and an NS3/4A PI, grazoprevir (100 mg). The elbasvir-grazoprevir combination was approved in January 2016 for treatment of HCV genotypes 1a, 1b, and 4 (see Table 117.9). Approval was based on the results of clinical trials in patients with HCV genotypes 1, 4, and 6, both in treatment-naïve and treatment-experienced patients, without cirrhosis or with compensated cirrhosis. A regimen of one tablet taken daily for 12 weeks resulted in high rates of SVR_{12} in treatment-naïve patients (95%–100%).[520] An SVR_{12} of 92% to 97% was found in treatment-experienced patients who received elbasvir-grazoprevir for 12 to 16 weeks with or without concomitant RBV.[521] Patients coinfected with HIV and HCV also had high SVR_{12} responses (92%).[522]

Resistance to elbasvir-grazoprevir in HCV 1a infections is conferred by baseline polymorphisms to HCV NS5A at positions M28, Q30, L31, or Y93. These result in apparent decreased efficacy of the 12-week regimen, and if present, extension of therapy to 16 weeks and addition of RBV are recommended.[523,524]

Elbasvir-grazoprevir is generally well tolerated. In pooled data from phase II and III clinical trials, the most common adverse events were fatigue (11%), headache (10%), and nausea (5%), similar to rates in placebo recipients.[523–525] ALT elevations greater than five times the ULN occurred in 1% of participants, usually at or after 8 weeks of therapy, and mostly resolved at or after completion of therapy. Anemia was observed when RBV was included in therapy.

For patients with compensated cirrhosis (Child-Pugh class A), dose adjustment is not necessary, but elbasvir-grazoprevir, like any PI-containing DAA combination, should not be used in patients with moderate or severe hepatic impairment[523,524] (Child-Pugh class B or C). Dose reduction is not necessary in patients with renal insufficiency, including those on hemodialysis; unlike SOF-containing regimens, which have not been shown in clinical trials to be effective in patients with renal failure (CrCl <30 mL/min), elbasvir-grazoprevir is effective in this population subset.

Potential drug-drug interactions are important considerations in the use of elbasvir-grazoprevir.[524,525] Both are substrates of cytochrome P3A (CYP3A) and should not be used with strong CYP3A inducers such as efavirenz and rifampin. CYP3A inhibitors, such as ketoconazole, and inhibitors of organic anion transporting polypeptide 1B1 (OATP1B1), such as cyclosporine, may raise levels of elbasvir-grazoprevir and should not be used concomitantly.

Daclatasvir (Daklinza). Daclatasvir is an oral medication that is an inhibitor of HCV phosphoprotein 5A (NS5A) and may also inhibit phosphorylation of NS4A. It was approved by the FDA in July 2015 for treatment of patients with HCV genotype 3 and in February 2016 for patients with genotypes 1a and 1b in combination with SOF, with and without RBV. Before, declatasvir was superseded by more effective pangenotypic drug combinations, the AASLD/IDSA guidelines also included a recommendation for its use in treatment of genotype-2 infections. The recommended dose of daclatasvir is one 60-mg tablet per day, along with one tablet of SOF (400 mg) per day.

Clinical trials of daclatasvir plus SOF have shown high rates of SVR_{12} in genotypes 1, 2, and 3 infections. In a study of 334 patients, an SVR_{12} was 98% for genotype-1 treatment-naïve or treatment-experienced patients, 92% for genotype 2–infected patients, and 89% for genotype 3–infected patients.[526] In patients with cirrhosis and Child-Pugh class A (compensated) and Child-Pugh class B or C (decompensated), treatment with daclatasvir plus SOF and RBV resulted in SVR_{12} of 94% to 56%.[527] Patients with HIV-HCV coinfection also responded well to daclatasvir and SOF (SVR_{12} of 97% to 98%).[528] Dose adjustments are not necessary for renal or hepatic impairment. Resistance to daclatasvir plus SOF in genotype-1a infection was associated with polymorphisms of amino acids at NS5A positions M28, Q30, L31, and Y93.[529,530]

Daclatasvir was generally well tolerated in reported studies. When administered along with SOF, the most commonly reported adverse events were fatigue (14%), headache (14%), nausea (8%), and diarrhea (5%). Because SOF can cause serious bradycardia when administered with amiodarone, particularly if a β-blocker is also being administered, administration of amiodarone along with the combination of daclatasvir and SOF should be avoided.

Daclatasvir is a substrate of CYP3A, and drug levels will be reduced when this agent is administered with strong inducers of CYP3As. Administration with strong CYP3A inducers such as rifampin, phenytoin, or St. John's wort should be avoided. If a moderate inducer of CYP3A, such as efavirenz, needs to be given, the daclatasvir dose may be increased to 90 mg/day. If a strong inhibitor of CYP3A is given, the dose of daclatasvir may be reduced to 30 mg/day.

Daclatasvir is an inhibitor of P-glycoprotein transporter (P-gp), OATP1B1 and OATP1B3, and breast cancer resistance protein (BCP). Daclatasvir may increase the levels of drugs that are substrates of these transporters, such as digoxin, rosuvastatin, and dabigatran. Because of the availability of more effective, pangenotypic drug combinations, declatasvir is no longer recommended as first-line therapy for hepatitis C (www.hcvguidelines.org).

Paritaprevir-ritonavir-ombitasvir (Technivie). Technivie is an oral fixed-dose combination that consists of three of the four components in Viekira Pak (paritaprevir-ritonavir-ombitasvir [discussed previously]) but does not include the fourth component, dasabuvir, which does not have activity against genotype 4. The regimen consists of two tablets taken daily, each containing paritaprevir (75 mg; two-tablet total dose 150 mg), ritonavir (50 mg; total dose 100 mg), and ombitasvir (12.5 mg; total dose 25 mg) along with meals. Technivie plus RBV received FDA approval in July 2015 for treatment of HCV genotype 4 in patients without cirrhosis but was recommended in the February 2016 AASLD/IDSA guidelines for patients with genotype 4 who have compensated cirrhosis. In October 2015, the FDA issued a warning letter that is added to prescribing information for both Technivie[531,532] and Viekira Pak, stating that hepatic decompensation and failure have been reported with these medications. Patients who receive these medications should be monitored closely for hepatic decompensation, and, if noted, administration of Technivie and Viekira Pak should be stopped.

The clinical trial on which approval of Technivie was based consisted of 135 participants with HCV genotype-4 infections without cirrhosis who were treated with Technivie with or without RBV for 12 weeks. SVR_{12} was achieved in 91% (40 of 44) of treatment-naïve patients treated without RBV, in 100% (42 of 42) of treatment-naïve patients treated with RBV, and in 100% (49 of 49) of treatment-experienced patients treated with the RBV-containing regimen.[533,534] Overall, the regimen was generally well tolerated, and the most common side effects consisted of fatigue, weakness, insomnia, and pruritus, most commonly in the RBV-containing regimen. Further discussion of adverse effects and drug-drug interactions of paritaprevir-ritonavir-ombitasvir can be found in the Viekira Pak section presented earlier.

Second-Generation NS5A Inhibitors and Fourth-Generation NS3-4A Protease Inhibitors—Standard of Care, September 2017

The AASLD/IDSA hepatitis C treatment guidelines (www.hcvguidelines.org) were updated in September 2017, as summarized in Table 117.9, to reflect approval of new drug combinations SOF-velpatasvir (VEL), SOF-VEL-voxilaprevir (VOX), and glecaprevir (GLE)-pibrentasvir (PIB). From among the other previously approved DAAs described earlier, only LDV-SOF and grazoprevir-elbasvir (see earlier) were retained as first-line agents.

Sofosbuvir-velpatasvir (Epclusa). With the introduction of the aforementioned combination DAAs, near-complete efficacy was achieved for genotypes 1, 2, 4, 5, and 6, but genotype 3 remained the most refractory and challenging, especially for patients with cirrhosis in whom PEG IFN–RBV therapy had failed. This last "frontier" was addressed with the development of a pangenotypic DAA regimen containing a single-pill, daily combination of the nucleoside polymerase inhibitor SOF, 400 mg, and the second-generation, low picomolar EC_{50} (in vitro drug concentration that achieves 50% of virus replication), high-barrier-to-resistance NS5A inhibitor VEL, 100 mg. SOF-VEL was approved in June 2016 for genotypes 1 to 6, and the approval was extended in August 2017 for patients with HIV infection. Efficacy of this pangenotypic combination was demonstrated in a series of trials, ASTRAL-1 to ASTRAL-4.[535–537]

In 626 patients (including treatment-naïve patients, treatment-experienced patients, noncirrhotics, and compensated cirrhotics) with

genotypes 1, 2, 4, 5, and 6, treatment with SOF-VEL achieved SVR_{12} in 97% to 100% (ASTRAL-1). In ASTRAL-1, among patients receiving SOF-VEL, treatment was well tolerated; adverse events occurred in indistinguishable percentages of SOF-VEL recipients (78%) and 116 placebo recipients (77%).[535] In 134 patients with genotypes 2 (ASTRAL-2) and 277 patients with genotype 3 (ASTRAL-3), of whom 26% to 29%, respectively, had failed prior antiviral treatment, and of whom 29% to 30%, respectively, had compensated cirrhosis, SOF-VEL for 12 weeks achieved SVR_{12} rates of 99% and 95%, respectively, superior to outcomes in control groups receiving the previous standard of care, SOF with weight-based RBV for 12 weeks in genotype 2 (n = 132, SVR_{12} 94%) and 24 weeks in genotype 3 (n = 275, SVR_{12} 80%).[536] Moreover, SOF-VEL was highly effective and superior to SOF-RBV in the most refractory patient subsets, those with genotype 3 who had cirrhosis and/or had failed prior IFN-based therapy. Among treatment-naïve participants, the rate of SVR_{12} for SOF-VEL versus SOF-RBV was 98% versus 90% in noncirrhotics and 93% versus 74% in compensated cirrhotics. The differences were even more pronounced in treatment-experienced participants: 91% versus 71% in noncirrhotics and 89% versus 58% in compensated cirrhotics.

In 267 patients with Child-Pugh class B decompensated cirrhosis (78% genotype 1, 4% genotype 2, 15% genotype 3, 3% genotype 4, <1% genotype 6; 55% treatment-experienced [44% with PEG IFN–RBV, 11% with a PI regimen], 75%–83% with ascites), SOF-VEL achieved SVR_{12} in 83% treated for 12 weeks and in 86% treated for 24 weeks; a third group treated with SOF-VEL-RBV for 12 weeks had a slightly higher SVR_{12} of 94%. Efficacy was comparable across genotypes, except for patients with genotype 3, in whom the SVR_{12} rate for the 12-week and 24-week SOF-VEL regimens were both only 50%, but 85% in the 12-week SOF-VEL-RBV regimen.[537] Baseline NS5A RASs did not affect responsiveness, except in cirrhotic patients with baseline Y93H, who had a slightly reduced SVR_{12} of 84% and in whom the addition of RBV has been recommended. Based on these data, SOF-VEL for 12 weeks is recommended as initial treatment for all genotypes, for noncirrhotics and compensated cirrhotics, and for retreatment in subgroups of treatment-experienced patients with genotype 1 and 2. For retreatment of patients with genotypes 3 to 6, the more effective triple combination of SOF-VEL-VOX (see later) is recommended (see Table 117.9). Like other SOF-containing DAA combinations, SOF-VEL is not recommended in patients with CrCl <30 mL/min or in patients taking amiodarone, especially with β-blockers. For all DAA treatment, before one initiates therapy, checking for drug-drug interactions is advisable (www.hcvguidelines.org).

Sofosbuvir-velpatasvir-voxilaprevir (Vosevi). First-line DAA regimens for chronic hepatitis C are so effective that the "cure" rate approaches 100%; however, a small subset of patients do not achieve SVR_{12}—up to 6% for genotype 1 and up to 12% for genotype 3. One of the latest-generation combination DAAs, the polymerase inhibitor SOF (400 mg), the NS5A inhibitor VEL (100 mg), and the high-potency, high-barrier-to-resistance pangenotypic PI VOX (100 mg), addresses this efficacy gap. In a randomized, double-blind, placebo-controlled, phase III trial involving 263 patients with genotype 1 in whom a course of an NS5A-containing DAA treatment had failed (114 patients with other genotypes were also included but were all assigned to the triple-combination group), 96% of SOF-VEL-VOX–treated participants (12-week course of daily treatment) versus 0% of placebo recipients achieved SVR_{12} (POLARIS-1).[538] The SVR_{12} was 91% for genotype 4, 95% for genotype 3, 97% for genotype 1 (1a and 1b indistinguishable), and 100% for the small numbers with genotypes 5 and 6. Noncirrhotics had higher SVR_{12} than compensated cirrhotics (99% vs. 93%), but the presence of baseline NS5A RASs did not influence efficacy (SVR_{12} in 98% without and in 97% with baseline RASs). In a complementary randomized, double-blind, positive-controlled trial among prior nonresponders to DAA regimens that did not contain an NS5A inhibitor (POLARIS-4), patients with genotypes 1 to 3 were randomized to receive 12 weeks of SOF-VEL-VOX (n = 163) versus SOF-VEL (n = 151); 19 additional patients with genotype 4 were treated with SOF-VEL-VOX without randomization, for a total SOF-VEL-VOX cohort of 182. SVR_{12} occurred in 98% of the triple combination group versus in 90% of the double-combination group.[538] SVR_{12} rates were higher for SOF-VEL-VOX than for SOF-VEL for all genotypes except for 1b (and, in genotype 4, none received SOF-VEL): genotype 1a, 98% versus 89%; genotype 1b, 96% versus 95%; genotype 2, 100% versus 97%; genotype 3, 94% versus 85%; genotype 4 100%. SOF-VEL-VOX responsiveness was indistinguishable between noncirrhotics (98%) and compensated cirrhotics (96%); as described earlier for SOF-VEL, responsiveness to SOF-VEL in this trial was reduced in compensated cirrhotics (86%) compared with noncirrhotics (94%). The presence of baseline NS5A or NS3 RASs did not influence efficacy (SVR_{12} in 99% without and in 100% with baseline RASs) in SOF-VEL-VOX recipients; similarly, in the SOF-VEL arm of POLARIS-4, SVR_{12} rates were the same in those with and without baseline NS5A or NS3 RASs (90% vs. 89%), consistent with the roughly 10% inferiority of SOF-VEL to SOF-VEL-VOX. Between POLARIS-1 and POLARIS-4, the number of baseline RASs (of any kind, NS3 and/or NS5A) had no influence on SVR_{12}—97% with one RAS, 98% with two, and 100% with three or more than four. In these trials, side effects in the SOF-VOL-VOX group were mild and uncommon; the four most common (in 12%–27%) were headache, fatigue, nausea, and diarrhea; the SOF-VEL-VOX side-effect profile was similar to that in placebo recipients and SOF-VEL recipients—for these four adverse events, 8% to 20% and 5% to 28%, respectively.

The potential for an 8-week course of SOF-VEL-VOX was pursued in treatment-naïve patients. Two SOF-VEL-VOX phase III trials in which an 8-week versus a 12-week course were compared showed that 8 weeks was inferior, yielding SVR_{12} rates of 95% versus 98% for all genotypes and for both compensated cirrhotics and cirrhotics (with the exclusion of cirrhotic patients with genotype 3), primarily because of the lower 8-week-course response in genotype 1a (92%) (POLARIS-2). An 8- versus 12-week regimen of SOF-VEL-VOX was evaluated separately in patients with genotype 3 and cirrhosis; 96% in both duration groups achieved SVR_{12}. (POLARIS-3).[539]

Based on these trials, the triple combination of SOF-VEL-VOX is recommended for patients with genotype 1 in whom a prior non-NS5A, SOF-containing regimen or an NS5A-containing regimen has failed, and for patients with genotypes 3 to 6 in whom any DAA regimen has failed. For cirrhotics with genotype 3 in whom a prior NS5A regimen had failed, SOF-VEL-VOX efficacy was slightly lower, leading to the recommendation that RBV be added. This triple-drug DAA combination is not recommended for treatment-naïve patients, except for patients with genotype 3 and cirrhosis (see Table 117.9). Like all other SOF-containing DAA combinations, SOF-VEL-VOX is not recommended along with concomitant amiodarone and in patients with creatinine clearance <30 mL/min; like all other PI-containing DAA combinations, SOF-VEL-VOX is not recommended in patients with decompensated cirrhosis. SOF-VEL-VOX can be taken with 20 mg of omeprazole (but the safety of other PPIs has not been evaluated). For all DAA treatment, before one initiates therapy, checking for drug-drug interactions is advisable (www.hcvguidelines.org).

Glecaprevir-pibrentasvir (Mavyret). The fixed-dose combination of two pangenotypic, high-potency, high-barrier-to-resistance DAAs, the PI GLE (300 mg) and the NS5A inhibitor PIB (120 mg) (total doses of GLE and PIB achieved with three fixed-combination pills taken once a day with food), has proven to be highly effective across all genotypes; in treatment-naïve noncirrhotic patients, an 8-week course suffices. In phase II and III trials of >2300 treatment-naïve and treatment-experienced noncirrhotic patients, this DAA achieved SVR_{12} in 99.0% to 99.7% of patients with genotypes 1, 2, and 4 to 6 and 95% with genotype 3; across all genotypes in noncirrhotic patients, 8 weeks of therapy was equivalent in efficacy to 12 weeks (phase III trials ENDURANCE-1 to ENDURANCE-4 and phase II trials SURVEYOR-1 and SURVEYOR-2).[540–543] In patients with compensated cirrhosis, both treatment-naïve and treatment-experienced (IFN-RBV–based or SOF-RBV ± PEG IFN), 12 weeks of GLE-PIB achieved SVR_{12} in 99% across genotypes 1, 2, and 4 to 6 (phase III EXPEDITION-1) and in up to 98% of patients with treatment-naïve genotype 3 (phase II SURVEYOR-2). In DAA-treatment–experienced patients (approximately a third each with PI experience only, NS5A inhibitor only, and both PI and NS5A experience) with genotypes 1 and 4, with or without compensated cirrhosis, GLE-PIB achieved SVR_{12} just as frequently after 12 weeks of treatment (89%) as after 16 weeks of treatment (91%) (phase II MAGELLAN-1). In this trial, both the number of previous DAA treatments and the number of baseline RASs

were associated with degradation of GLE-PIB treatment. For example, in the cohort treated for 12 weeks, the GLE-PIB–associated SVR_{12} fell from 100% for prior PI only, to 88% for prior NS5A inhibitor only, to 79% for prior PI and NS5A inhibitor; SVR_{12} rates were 100% for patients with no baseline RASs and baseline RASs limited to NS3 (PI) only but 83% for patients with NS5A baseline RASs[544]

Like all DAAs that include a PI, GLE-PIB should not be used in decompensated cirrhotics, but the combination is effective and recommended for patients with severe renal impairment. In a phase III trial among 104 patients with stage 4 or 5 renal disease (CrCl <30 mL/min), with or without cirrhosis, whether treatment naïve or treatment experienced, the SVR_{12} rate across all genotypes was 98%.[545] GLE-PIB should be taken with food. Drug-drug interactions should be considered prior to therapy (www.hcvguidelines.org).

Considerations in Direct-Acting Antiviral Therapy of Chronic Hepatitis C

The role of resistance testing. Because first-line DAA treatments are so highly effective, including in patients with baseline RASs, baseline testing for RASs is not recommended routinely. The exceptions are (1) elbasvir-grazoprevir—patients with genotype 1a (not genotype 1b) should be tested for elbasvir resistance, which, if present, justifies extending therapy to 16 weeks and adding RBV or selecting an alternative regimen; and (2) VEL-SOF—in treatment-naïve cirrhotic patients with genotype 3 who are to be treated with VEL-SOF, resistance testing is recommended, and, if a Y93H RAS is detected, RBV should be added.

For patients in whom an initial DAA course (or courses) has failed, pretreatment resistance testing is not recommended when treating with GLE-PIB or SOF-VEL-VOX, because these combinations are so effective against all RASs. For prior nonresponders to DAA regimens who are to be treated with elbasvir-grazoprevir, LDV-SOF, or VEL-SOF, however, resistance testing can help guide therapy. As was the case for treatment-naïve patients to be treated with elbasvir-grazoprevir, treatment-experienced patients with genotype 1a (not genotype 1b) should be tested for elbasvir resistance, which, if present, justifies extending therapy to 16 weeks and adding RBV or selecting an alternative regimen. For patients with genotype 1a (not 1b) who are to be treated with LDV-SOF, resistance testing should be considered, and if resistance is present, LDV-SOF treatment should be extended to 24 weeks for cirrhotics, and, in both noncirrhotic and cirrhotic patients, RBV should be added, or a different DAA regimen should be selected. For treatment-experienced patients with genotype 3 who are to be treated with VEL-SOF, resistance testing is recommended, and, if a Y93H RAS is detected, RBV should be added. A detailed primer on resistance testing, including a summary of the most common RASs for each DAA combination, appears in the AASLD/IDSA hepatitis C treatment guidelines (www.hcvguidelines.org).

Reactivation of hepatitis B. Cases of hepatitis B reactivation in DAA-treated patients with HBV-HCV coinfection began to appear in the medical literature in 2015[546,547]; by 2017, 29 such patient reports had been compiled, 28 from the FDA Adverse Event Reporting System and one case from the literature, over a 3-year period (2013–2016).[548] In a meta-analysis of 770 patients (from 36 studies) with chronic hepatitis C who were HBsAg reactive, HBV reactivation (a virologic outcome defined as an increase in HBV DNA by >2–4 $\log_{10}$ or to $>2 \times 10^3$ IU/mL) occurred in comparable proportions of patients managed with IFN-based therapy (14.5%) and those managed with DAA therapy (12.2%). The differences between the two groups were that for patients receiving IFN-based treatment, HBV reactivation occurred later, usually at the end of therapy or in the posttreatment period, whereas for DAA-treated patients HBV reactivation occurred earlier, within the first 4 to 12 weeks, always during therapy. In addition, HBV reactivation associated with "hepatitis," defined as an ALT elevation greater than 2 to 3 times the lowest level achieved during therapy or more than 10 times the ULN, and severe hepatitis cases (with liver failure or jaundice or necessitating liver transplantation) occurred in the DAA group (12.2%) but not in the IFN-based group (0%).[549]

In October 2016, for all DAAs, the FDA issued a black box warning about the risk of HBV reactivation (including severe cases of fulminant hepatitis, liver failure, and death) in HBV-HCV coinfected patients. All patients with chronic hepatitis C who are to be treated with DAAs should be screened for HBV infection. Therefore, before beginning DAA therapy for hepatitis C, all patients should be tested for HBV infection; preemptive hepatitis B antiviral therapy should be instituted in HBsAg-reactive patients, and close monitoring for HBV reactivation should be done in anti-HBc–reactive or anti-HBs–reactive/anti-HBc–reactive patients (www.hcvguidelines.org).

Does DAA cure increase the risk of HCC? The risk of HCC in patients with chronic hepatitis C and advanced fibrosis/cirrhosis is 1% to 4% per year,[369,550] especially after ≥3 decades of HCV infection. During the IFN-treatment era, the rate of HCC after treatment-associated SVR was shown to be reduced.[415,473,551] For example, over a 10-year posttreatment observation, HCC occurred in 5.1% of patients with SVR but in 21.8% of patients without SVR—that is, achievement of SVR was associated with a greater than fourfold reduction in HCC.[473] What these studies drove home was the fact that, among patients with established advanced fibrosis, cure of HCV infection reduces but does not eliminate the risk of HCC entirely. This important observation (and similar observations in the reduction but not elimination of liver failure and liver-related death) suggested that, ideally, patients with chronic hepatitis C should be treated before advanced fibrosis is established, allowing virologic cure to be accompanied by prevention of late-disease clinical complications.

The risk of HCC after IFN-associated SVR has been well documented.[552–554] In 2016, reports from Spain and Italy appeared to suggest that the risk of HCC recurrence after treatment and initial HCC occurrence were higher than expected in DAA-treated patients with SVR.[555,556] In contrast, and consistent with the data cited earlier about the reduction in HCC after SVR, a series of subsequent reports, including meta-analyses of multiple experiences—almost 14,000 patients involved in 41 studies, and data from Australia, North America (e.g., the Veterans Administration database), France, Italy, and the United Kingdom)—demonstrated that the risk of HCC after DAA-induced SVR was reduced compared with that in untreated patients and comparable to that after IFN-induced SVR.[557–563] A consensus emerged from these studies to indicate that the higher risk of HCC in DAA-treated patients reflected a cohort bias, in that DAA treatment was applied to an older, sicker population, more heavily weighted to advanced fibrosis or cirrhosis and including decompensated liver disease. In effect, the reason for the increased risk of HCC after DAA treatment was not the DAA treatment but more advanced liver disease in the DAA-treated patients. Thus, successful DAA treatment and cure (SVR) reduces the risk of HCC but does not eliminate it, and the fact that more patients with advanced liver disease are being treated with DAA means that, as was the case after IFN-induced SVR, continued HCC surveillance is necessary after SVR in patients with advanced fibrosis, a treatment recommendation that has been adopted widely (www.hcvguidelines.org).[564,565]

Candidates for Therapy

Evidence-based, authoritative treatment recommendations are issued and updated by a joint panel of the AASLD and IDSA[566] and the EASL.[567] The AASLD/IDSA guidelines are updated online whenever new DAA treatments are introduced (www.hcvguidelines.org). Patients with chronic hepatitis C, with detectable HCV RNA, with or without elevated aminotransferase activity, and with all grades of hepatitis and stages of fibrosis are candidates for antiviral therapy. The goal of therapy is to achieve SVR, which has been shown to reduce all-cause mortality and the health consequences of hepatitis C, including decompensated (end-stage) liver disease and HCC. The only exception are patients with a brief life expectancy, which is unlikely to be extended by eradication of HCV infection. Treating patients with advanced fibrosis (METAVIR stage F3) and cirrhosis (METAVIR stage F4) merits a high priority; however, treatment early in the natural history of chronic hepatitis C is the only way to prevent all the dire consequences of HCV-associated liver disease. In patients with histologically milder hepatitis C, progression was shown to be slow[345]; however, patients with histologically mild hepatitis respond as well as or better than patients with more severe hepatitis. Because histologic grade (absence vs. presence of cirrhosis) influences the choice and duration of DAA therapy (see Table 117.9), because fibrosis stage is predictive of future progression of chronic hepatitis C, and because the presence of cirrhosis determines the need for recommended surveillance screening for HCC and esophageal varices,

a baseline assessment of disease stage is recommended as a prelude to antiviral therapy.[344,345,440,441,443] Given how progressively simple and effective antiviral therapy has become with DAAs, and given advances in noninvasive measures of fibrosis (e.g., liver elasticity), a baseline liver biopsy before therapy is no longer necessary for most patients with chronic hepatitis C[568,569]; however, all patients should undergo an assessment of fibrosis stage. Whether antiviral therapy with IFN-based therapy prolongs survival in treatment-naïve persons and in prior nonresponders with cirrhosis was the subject of debate in the past,[b] but many definitive studies have shown that achieving SVR in cirrhotics, either with IFN-based therapy or DAA therapy, improves survival.[473,570–572] Therapy with DAAs has also been shown to reduce both liver and nonliver complications (cardiovascular events, bacterial infections), portal hypertension, and hepatic fibrosis.[571,573–575]

In patients with decompensated cirrhosis, PEG IFN–based antiviral therapy regimens, ineffective and poorly tolerated, are not recommended,[353] several reports to the contrary notwithstanding.[576] Instead, current DAA regimens containing combinations of nucleoside inhibitors (e.g., SOF) and NS5A inhibitors (e.g., LDV, VEL, daclatasvir) are treatment options, usually with RBV, that result in high rates of SVR_{12} (albeit not quite as effective as these DAAs in patients with compensated liver disease) and improvements in hepatic compensation (e.g., increased albumin, reduced Model for End-Stage Liver Disease [MELD] score, and reduced need for liver transplantation).[514,537,577,578] On the other hand, DAA combinations that include a PI (grazoprevir, VOX, ombitasvir) are not recommended in decompensated cirrhosis, because of either hepatic complications (including liver failure and death) or absence of data.

For patients who did not respond to the best available IFN-based antiviral regimen, potentially, maintenance therapy with PEG IFN could have retarded histologic and clinical progression. Supporting this hypothesis was the demonstration of a histologic benefit in three-quarters of patients with IFN treatment, including a sizable proportion without virologic response.[396] In addition, in prior nonvirologic responders to IFN monotherapy, a preliminary controlled trial of additional treatment versus no treatment for 2 years showed histologic benefit in the treated group.[579] Definitive clinical trials undertaken to determine whether maintenance therapy with PEG IFN can prevent histologic progression in virologic nonresponders, however, showed no benefit, and such maintenance therapy is not recommended.[368,580–582] Fortunately, now that more potent oral DAAs are available, the proportion of patients who remain nonresponders is growing vanishingly small.

As described earlier for the first-line DAA combinations, prior nonresponders to IFN-based therapy and prior nonresponders to DAA therapy have high SVR_{12} rates when re-treated with DAAs. A summary of current recommendations appears in Table 117.9 and www.hcvguidelines.org.

In the pivotal registration clinical trials of antiviral therapy for chronic hepatitis C, restrictive entry and exclusion criteria confined the treated population to a narrow subset without comorbid medical conditions, active alcoholism or other substance use, uncontrolled neuropsychiatric disorders, and so on.[583] Patients with these other conditions can be treated, however, if the other medical conditions can be managed effectively.[345,440] In most clinical trials, persons with advanced age were not included, and for many elderly patients with chronic hepatitis C, longevity is not affected by the disease or its treatment. In elderly persons, however, DAA therapy is as effective as in younger patients.[584–586]

In children, progression of chronic hepatitis C tends to be slow, and the disease follows a relatively benign course in most cases.[355] Unfortunately, progression to cirrhosis has been reported in a small proportion of those with childhood-acquired hepatitis C. In clinical trials of antiviral therapy in this population, efficacy is similar to that achieved in adult populations.[345,587] Data on safety and efficacy of the new DAA agents in children younger than age 18 are limited, but adolescents aged 12 to 17 have been treated effectively (SVR_{12} ≥87%) with LDV-SOF (genotype 1) and SOF-FRBV (genotypes 2 and 3).[588,589] Data on other DAAs and in children aged 3 to 11 are anticipated (www.hcvguidelines.org).

When they were first released, DAAs were very expensive; the most costly was $94,500 for a 12-week course of LDV-SOF. Fortunately, these exorbitant costs have come down, and the initial cost of the most recent of the new DAA regimens (GLE-PIB) is $26,400. Despite the high costs of DAAs, they have been shown to be cost-effective (e.g., for the most expensive, LDV-SOF).[590] Based on the known prevalence of chronic hepatitis C in the United States, the known rate of progression to cirrhosis and its complications, and the efficacy of DAA therapy, modeling has predicted that the hepatitis C–associated disease burden (liver-related death, HCC, decompensated cirrhosis, and liver transplantation) will fall by 50% to 70% between 2015 and 2030.[591]

Challenge to Benefits of Direct-Acting Antiviral Therapy

In a 2017 Cochrane review of the benefits and potential harms of DAA therapy, the authors challenged the validity of SVR_{12} as a meaningful end point, impugned the large body of clinical trials as being subject to bias in favor of benefit and against harms, and concluded that data were insufficient to demonstrate that such therapy reduced HCV-associated morbidity (including cirrhosis, decompensated liver disease, and HCC) and mortality.[592] This conclusion was rejected vociferously in responses by the AASLD and EASL,[593,594] among other organizations. In fact, the Cochrane reviewers included only studies that had placebo or untreated control groups, which eliminated many contemporary DAA-treatment trials for which an untreated control group would have been unethical. In addition, the rejection by the Cochrane reviewers of SVR as a meaningful end point had already been considered carefully and accepted by the FDA and regulatory agencies of other countries, which recognized SVR as a meaningful treatment end point for hepatitis C. For a disease such as hepatitis C that progresses slowly and insidiously in most patients, the long-term effects of DAA treatment on late clinical outcomes (progression to cirrhosis, hepatic decompensation, HCC, and death) take decades to measure. Moreover, the relation between immediate posttreatment SVR and improvements in these late outcomes already had been demonstrated definitively for IFN-based therapy; DAA treatment had already been shown to lower fibrosis stage, to improve MELD scores (and result in "delisting" patients on the liver transplantation waiting list) and reduce portal hypertension in patients with decompensated disease, to eliminate the deleterious impact of HCV reinfection after organ transplantation, to reverse extrahepatic manifestations of hepatitis C (e.g., renal disease, vasculitis, B-cell lymphoproliferative disorders including lymphoma), and to improved health-related quality of life. As stated bluntly in the EASL rebuttal, "The inability of the authors of the Cochrane review to determine a clinical benefit of DAA-based treatment of hepatitis C unfortunately reflects their flawed methodological approach and their ignorance of the natural history of HCV infection and associated systemic diseases."[594]

Similar imbroglios followed (1) the 2012 US Preventive Services Task Force (USPSTF) conclusion that data supporting screening for hepatitis C were inadequate,[595,596] followed subsequently by a retraction, and (2) the conclusion of a National Institutes of Health (NIH) Consensus Development Conference on management of hepatitis B in 2008 that data were insufficient to recommend antiviral therapy for hepatitis B[597] (for very similar reasons to the Cochrane reviewers' denial of clinical benefit of DAA therapy in hepatitis C). The notion that eliminating HCV does not translate to improving clinical outcomes of chronic hepatitis C is patently absurd, unsupportable, and well refuted by a robust body of clinical trial data and peer-reviewed literature. Not surprisingly, a strong consensus has emerged rejecting the validity and clinical relevance of the conclusions of the Cochrane review and bemoaning the deleterious effect this misguided analysis might have on efforts that are underway and supported by public health leadership (e.g., US Public Health Service, WHO, National Academy of Medicine) to reduce the global impact of hepatitis C (and B) on morbidity and mortality.

Special Patient Populations

Liver Transplantation

End-stage chronic hepatitis C is the most frequent indication for liver transplantation.[286,598] Recurrent HCV infection is reestablished invariably in the new liver and may be associated with an increase in the frequency of acute rejection episodes,[599,600] but clinical progression during the early years after transplantation may be limited, and overall early survival

[b]References 364, 366, 368, 414, 415, 487.

unaffected. In contrast, even during the first 5 years after liver transplantation, histologic progression appears to be accelerated; more than half of patients have moderate-to-severe hepatitis and approximately 10% have advanced fibrosis or cirrhosis,[601,602] and eventually, survival is impaired.[603,604] A small proportion of patients with chronic hepatitis C have early reactivation of hepatitis, and in those with early and difficult-to-manage rejection, added immunosuppression enhances HCV replication and may amplify HCV-associated liver injury.[600] Furthermore, management is confounded by difficulty in distinguishing between rejection and viral liver injury on the basis of often overlapping clinical and histologic features. The most aggressive form of recurrent hepatitis C after liver transplantation is fibrosing cholestatic hepatitis, a rapidly progressive form of liver injury, described previously in patients with hepatitis B undergoing liver transplantation, and characterized by progressive fibrosis, cholestasis, and severe jaundice out of proportion to necroinflammatory activity.[605] PEG IFN–RBV–based antiviral therapy for hepatitis C, whether begun preemptively immediately after transplantation or introduced after the emergence of recurrent HCV-associated liver injury, was disappointingly ineffective after liver transplantation, sometimes suppressing HCV replication but resulting only rarely in an SVR.[451,606] What is more, PEG IFN and RBV are poorly tolerated after liver transplantation, necessitating dose reductions.[606] Because immunosuppression enhances HCV replication,[607] attempts are made to minimize the use of immunosuppressive drugs after liver transplantation for chronic hepatitis C.[608] With all its limitations, however, PEG IFN–RBV–based antiviral therapy did appear to slow disease progression after liver transplantation, as reported in a study of 81 patients monitored histologically and hemodynamically.[609]

Trials of DAAs have shown that these regimens are effective in achieving SVR in patients with HCV infection after liver transplantation. Before transplantation, use of SOF with RBV in patients with hepatitis C and decompensated cirrhosis who were on the waiting list and who were treated for up to 48 weeks showed that more than 90% could experience complete suppression of HCV RNA before transplantation; if HCV RNA had been undetectable for at least 30 days before transplantation, recurrent HCV infection in the allograft could be prevented in almost all.[610] Moreover, approximately a third to a fifth of patients with decompensated cirrhosis on the liver transplantation waiting list improve sufficiently to be "delisted" for transplantation.[611] After transplantation, DAA treatments shown to be effective include SOF-RBV, which achieved a 70% SVR_{12} in patients with compensated liver disease but only 59% in patients with decompensated liver disease after transplantation.[612,613] The largest body of data involve LDV-SOF, which is nearly completely effective with or without RBV after liver transplantation in patients with compensated liver disease, again less so in patients with decompensated cirrhosis (Child-Pugh class B and C).[514,614–616]

Other DAA regimens that have been observed to be effective after liver transplantation include daclatasvir-SOF and SMV-SOF; although data are limited, GLE-PIB and SOF-VEL-VOX are likely to find a place in treatment of HCV infection after liver transplantation (www.hcvguidelines.org). In all patients treated after liver transplantation, consideration of drug-drug interactions is important, especially with calcineurin inhibitors. Based on available data, the AASLD/IDSA guidelines include the following as first-line regimens after liver transplantation: GLE-PIB, LDV-SOF, daclatasvir-SOF, and VEL-SOF (see www.hcvguidelines.org for details and for alternative-choice DAA regimens).

The timing of DAA treatment before liver transplantation in patients who are potential transplantation recipient candidates remains unsettled. If patients are treated before transplantation and are cured of hepatitis C, they may be denied the availability of donor organs from HCV-infected donors, potentially lowering their MELD scores, increasing their waiting time, and reducing their chances for obtaining a timely allograft—a situation labeled as MELD "purgatory" or "limbo."[617] Although policies vary across liver transplantation centers, the trend is to treat before transplantation patients with low-to-intermediate MELD scores (e.g., <20) who are sufficiently stable and not in imminent need of organ replacement, but to postpone DAA treatment until after transplantation (likely to be nearly completely effective) in patients with high MELD scores and advanced stages of liver decompensation (e.g., ≥20, in whom the efficacy of DAA treatment is reduced.[618,619]

HIV Coinfection (Also See Chapter 124)

Patients with HIV-HCV coinfection could respond to antiviral therapy with standard or PEG IFN plus RBV, but the likelihood of an SVR was approximately one-half to two-thirds that expected in immunocompetent patients with HCV infections alone,[345,620–625] PEG IFN–RBV treatment had to be administered for a full 48 weeks for all genotypes, and the target daily dose of RBV had to be reduced often to 600 to 800 mg,[622,623,625] although full doses had been recommended.[254,626] PEG IFN–RBV antiviral therapy of patients with HIV-HCV coinfection was shown to result in reduced antiretroviral drug hepatoxicity[627,628] and did not appear to have a deleterious effect on progression of HIV disease, but patients with coinfection tolerated PEG IFN and RBV less well than patients with HCV infection alone. Moreover, because RBV is an IMPDH inhibitor, its use had the capability to potentiate the activity and toxicity of the purine analogue didanosine; therefore, these two drugs could not be used together.[629] Similarly, zidovudine may exacerbate RBV-associated anemia, and stavudine-associated lipoatrophy may be enhanced by RBV.[626] Whether abacavir reduces PEG IFN–RBV efficacy is controversial.[630] Application of first-generation PI-based therapy (TVR–PEG IFN–RBV) in HIV-HCV coinfected patients was more effective (71% SVR_{24}) than PEG IFN–RBV therapy (41% SVR_{24}). No significant drug-drug interactions were apparent between TVR and ART, no HIV breakthroughs occurred in patients being treated with ART during PI-based therapy for hepatitis C, and safety and tolerability were similar to those in HCV monoinfected patients.[631]

The old standard-of-care PEG IFN–RBV and first-generation PIs have been supplanted in HIV coinfected patients by all-oral DAA regimens. High response rates in HIV-HCV coinfected patients are indistinguishable from those in HCV-monoinfected patients,[632–635] and treatment recommendations are the same for both groups. The importance of drug-drug interactions between DAAs for HCV infection and ART for HIV infection necessitates close attention, however (see www.hcvguidelines.org).

Immune-Complex Disease

The response to IFN-based antiviral therapy was variable and often disappointing in patients with cutaneous vasculitis or glomerulonephritis resulting from HCV-associated EMC. Although some patients responded during IFN-based therapy, SVR was unlikely, and many such patients needed indefinite maintenance of antiviral therapy.[353,636–639] Experience with current-generation DAAs has been encouraging. In patients with cryoglobulinemic vasculitis, the DAA combinations SOF-daclatasvir, SOF-RBV, SOF-SMV, LDV-SOF, and others have achieved SVR_{12} in 82% to 100% and clinical remission of vasculitis in 71% to 90%.[640–644] In refractory HCV-associated immune-complex syndromes, options include plasmapheresis, cytotoxic therapy, and B-cell blockade with monoclonal anti-CD20 (rituximab).[440,645]

B-Cell Lymphoma

In patients with B-cell, non-Hodgkin lymphoma associated with chronic HCV infection, antiviral therapy has been reported to achieve disease remission, initially with IFN-based therapy[646–648] and more recently with DAA therapy.[649,650]

Other Special Populations

The efficacy of DAA therapy is high in patients with renal failure. Although SOF-containing combinations are effective and can be used in patients with low-stage chronic kidney disease, SOF-based DAAs have not been shown to be effective in patients with CrCl <30 mL/min (stage 4 or 5 chronic kidney disease). In contrast, elbasvir-grazoprevir and GLE-PIB have been shown to be effective and are recommended in patients with stage 4 or 5 chronic kidney disease (see www.hcvguidelines.org). Treatment with DAAs is also effective in persons who inject drugs, but such patients benefit from concomitant addiction treatment, needle-exchange programs, and opioid agonist therapy delivered by multispecialty experts in addiction medicine; after cure in this population, reinfection rates of approximately 25% have been observed, but treating patients who inject drugs comes with an added benefit of reducing the spread of HCV infection in the population at

large. Reinfection with HCV has been noted as well in HIV-infected men who have sex with men, who also respond well to DAA therapy (see www.hcvguidelines.org).

Chronic Hepatitis E

Initially, HEV had been considered to cause acute hepatitis exclusively, albeit on occasion severe, particularly in pregnant women,[30,651] but HEV has been recognized as a cause of protracted and chronic hepatitis in immunocompromised patients. These have primarily involved solid organ transplant recipients, including liver, kidney, and kidney-pancreas transplants.[652] Chronic hepatitis E has also been reported in HIV-infected patients,[653] in a patient with lymphoma taking rituximab,[654] and in patients with hematologic disorders on chemotherapy.[655,656] In the largest series of reported patients with organ transplants, HEV infection led to chronic hepatitis in two-thirds of patients and cirrhosis in 10%.[657]

Chronic infection is associated with HEV genotype 3. The clinical manifestations of chronic HEV are similar to those of other chronic viral hepatitides.[30] Infected organ-transplant patients have relatively few symptoms, and most do not present with jaundice. Liver test results are usually only modestly abnormal (e.g., ALT levels are approximately 300 IU/L). Liver histopathologic findings in patients with chronic HEV infection are similar to those seen in chronic hepatitis C. Sequential liver biopsies may reveal rapid progression to liver fibrosis.[658]

In addition to liver involvement, extrahepatic complications are also seen. These include neurologic manifestations, such as Guillain-Barré syndrome, Bell palsy, peripheral neuropathy, muscle wasting, acute transverse myelitis, and acute meningoencephalitis.[659,660] Chronic glomerulonephritis and cryoglobulinemia can also be seen. HEV-associated neurologic and kidney manifestations may completely or partially resolve if HEV is cleared.

Treatment

Chronic HEV infection will clear, and associated chronic hepatitis will resolve in approximately one-third of organ transplant patients whose immunosuppression is diminished, particularly if drugs that target T-cell function are reduced.[657] For the remaining 70% whose hepatitis E cannot be resolved by reduction of immunosuppression, specific antiviral therapy has been used. PEG IFN and RBV, either individually or in combination, have been used in a small case series with encouraging results.[661–664] A retrospective case series was reported of 59 solid organ transplant patients with chronic hepatitis E who were treated with RBV monotherapy. The median time between diagnosis of HEV infection and beginning therapy was 9 months (range, 1–82 months). The median dose of RBV was 600 mg/day (range, 29–1200 mg) with a median treatment of 3 months (range, 1–18 months). At the end of therapy, HEV clearance was observed in 95% of patients. A relapse of HEV replication occurred in 10 patients when RBV was stopped. An SVR was observed in 78% (46 of 59) of patients and in 4 relapsers who were re-treated for longer periods of time. Anemia was the main side effect, which necessitated reductions in RBV dose, erythropoietin use, and blood transfusions.[29]

On the basis of this retrospective case series, the authors recommend therapy of chronic hepatitis E with RBV for 3 months and additional courses for those in whom relapse occurs. Determination of optimal dose and duration of therapy will require prospective, controlled studies. Resistance to RBV has been observed in patients with hepatitis E in whom RBV treatment failed.[665]

The hepatitis C antiviral agent SOF has activity against HEV in vitro, and anecdotal reports suggest that SOF at a daily dose of 400 mg reduces, but does not eliminate, HEV RNA in patients with HEV infection after immunosuppression. Further study of higher SOF doses has been suggested.[666–669]

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The complete reference list is available online at Expert Consult.

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O Acquired Immunodeficiency Syndrome

118 Global Perspectives on Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome

Peter Piot

SIZE OF THE PROBLEM

By the end of 2016, the estimated number of people infected with human immunodeficiency virus (HIV) worldwide was 36.7 million (range, 30.8 million–42.9 million), from a cumulative total of approximately 76.1 million persons infected since the beginning of the epidemic. Table 118.1 shows global estimates of the HIV epidemic.[1–3] On a global scale, the HIV epidemic is slowing down, although with unacceptably high levels of new HIV infections and acquired immunodeficiency syndrome (AIDS) deaths. In every day of 2016 alone, about 5000 persons became infected with HIV, and 1.0 million persons died of AIDS-related illnesses in 2016, mostly because of inadequate access to prevention and treatment of the infection.[4] In a growing number of communities, HIV infection has become endemic, with a fairly constant or slowly declining level of new infections over a long period of time.

Fig. 118.1 shows a world map with HIV prevalence rates by country. Eastern and southern Africa continues to bear a disproportionate share of the global burden of HIV, with around half of all people living with HIV infection and around 42% of AIDS deaths in 2016 occurring in that subregion. Altogether, sub-Saharan Africa is home to more than 70% of all people infected with HIV.[5] Most new HIV infections occur in sub-Saharan Africa, Asia, and Eastern Europe and Central Asia.[6] Young people aged 15 to 24 are thought to account for around 40% of all new HIV infections among adults.[7]

Women account for just over half (51%) of all people infected with HIV worldwide; in most affected regions, such as Africa and the Caribbean, nearly 60% of people who have HIV infection are women. HIV infection rates in young women (15–24 years) are twice as high as those in young men, with substantial increases in sub-Saharan Africa, where HIV infections among young women aged 15 to 24 made up 66% of new infections among young people.[6] From 2001 to 2016, the proportion of women infected with HIV increased in many regions (Fig. 118.2).

In 2016, around 2 million adolescents aged 10 to 19 years were living with HIV, nearly 85% of whom lived in sub-Saharan Africa. An estimated 260,000 adolescents were newly infected with HIV globally in 2016. In sub-Saharan Africa, three in four new HIV infections among 15- to 19-year-olds were among girls, and HIV-related illnesses remain the second leading cause of death for young women aged 15 to 24 years in Africa.[8] In 2016, 37% of global new HIV infections in adults were among young people aged 15 to 24.[9] At current HIV incidence rates, the significant increase in the youth population in many countries with high HIV burden will lead to a growing proportion of the young adult population living with HIV, infected perinatally or sexually. Programs need to increase their meaningful engagement with young people, because treatment adherence among adolescents is generally lower and treatment failure rates are comparatively higher than in other age groups.[10]

Trends suggest that HIV prevention efforts are having an impact in several of the most affected countries. East and West African countries, Côte d'Ivoire, several Caribbean countries, most Southeast Asian countries, and southern India have all seen downward trends in national HIV prevalence percentages. There were more than 1,200,000 fewer new HIV infections globally in 2016 than at the peak of the epidemic in the late 1990s.[11] Global goals to expand access to treatment to 30 million people by 2030 are on track, but the goal to reduce new global HIV infections to 500,000 or fewer by 2020 is off target. The steepest declines in HIV incidence have been seen in eastern and southern Africa, the region of the world most affected by the epidemic, with a 29% decline in infections between 2010 and 2016. In contrast, over the same period, new HIV infections rose by 60% in Eastern Europe and Central Asia.[10]

To monitor country-level progress, the Joint United Nations Programme on HIV and AIDS (UNAIDS) developed the 90-90-90 indicators, aiming for a world by 2020 in which 90% of people know their HIV status, 90% of all people diagnosed with HIV are on treatment, and 90% of all people receiving treatment will be virally suppressed. At the global level in 2016, 70% of people living with HIV know their status (range, 51%–84%), 77% of those diagnosed with HIV are on treatment (range, 57%–89%), and 82% of people on treatment are virally suppressed (range, 60%–89%). When the gaps across this "treatment cascade" are combined, this means that 44% of all people living with HIV were virally suppressed in 2016, short of the 73% required for achievement of the 90-90-90 targets. However, certain countries—both high-income areas such as Sweden and the United Kingdom, and low- and middle-income countries (LMICs) such as Cambodia and Botswana—are on track to achieve the targets by 2020.[10] In addition, there are major discrepancies among and within countries in terms of achieving these targets.

Surveillance for HIV infection worldwide is probably the most complete and consistent among global health issues since the mid-1990s. The selection of surveillance populations depends on the type of epidemics and the local context. In epidemics with at least 1% prevalence rates in the adult population and in which transmission is mostly heterosexual, the recommended surveillance population is pregnant women who attend antenatal clinics. In epidemics in which HIV has not spread into the general population, the primary focus of the surveillance system is among groups at higher risk for infection with HIV, such as sex workers, men who have sex with men (MSM), and injection drug users. In addition, more than 50 countries, mostly in Africa where heterosexual transmission of HIV is predominant, have conducted national population-based household surveys with HIV and syphilis testing.[12] These surveys give a more precise picture of HIV prevalence rates in men and women in rural areas, populations previously not well covered by figures from

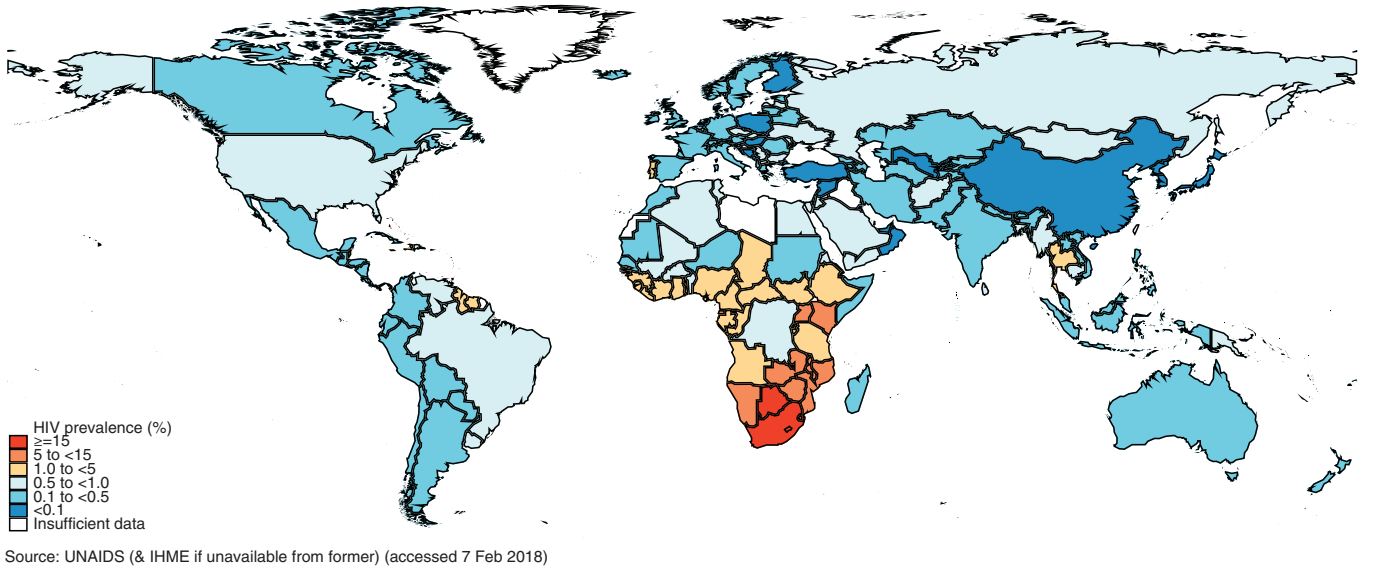

FIG. 118.1 Human immunodeficiency virus prevalence by country, 2016. *(Data from UNAIDS. http://aidsinfo.unaids.org; and Institute for Health Metrics and Evaluation. Global Burden of Disease Study 2015 [GBD 2015]. HIV incidence, prevalence, and mortality 1980–2015. http://ghdx.healthdata.org/record/global-burden-disease-study-2015-gbd-2015-hiv-incidence-prevalence-and-mortality-1980-2015. Accessed February 7, 2018.)*

TABLE 118.1 Global Summary of the Human Immunodeficiency Virus (HIV) Epidemic as of December 2016

Number of People With HIV in 2016	
Total	36.7 million
Adults	34.5 million
Women	17.8 million
Children <15 yr	2.1 million
People Newly Infected With HIV in 2016	
Total	1.8 million
Adults	1.7 million
Children <15 yr	160,000
AIDS Deaths in 2016	
Total	1.0 million
Adults	890,000
Children <15 yr	120,000

AIDS, Acquired immunodeficiency syndrome.
Data from UNAIDS.[3]

antenatal clinic attendees, but may also underestimate the extent of HIV infection among mobile populations and some of the most affected or vulnerable populations. Therefore several surveillance approaches are needed to achieve the most accurate estimates of HIV infection.[13]

Western Europe

The epidemiology of HIV infection in North America is extensively discussed in Chapter 119. Except for this section, this chapter deals mainly with the situation in the developing world. Western Europe had an estimated 651,380 persons living with HIV in 2015.[14] The number of annual reported new diagnoses of HIV infection almost tripled between 1999 and 2005 to reach nearly 20,000.[15] In 2011, the figure rose again to 30,000.[16] In 2016, the highest proportion of HIV transmission in European Union/European Economic Area (EU/EEA) countries was reported to be from sex between men (40%), followed by heterosexual transmission (32%); in 23% of the cases, the transmission mode remained unknown.[17] HIV infection diagnoses among MSM in the EU/EEA region increased from 8493 cases in 2007 and peaked at 10,079 cases in 2014, and are now declining slightly (9274 in 2016), whereas the number of cases among injection drug users decreased from 1450 cases in 2007 to 860 cases in 2016, although increases were observed in 2011 owing to outbreaks in Greece, Lithuania, and Romania.[18] More than half of the heterosexually transmitted HIV cases originated in migrants from countries with high HIV prevalence rates, although there has been a decline in foreign-born cases of HIV owing to sharp decreases among migrants originating from countries with generalized HIV epidemics (from 5873 in 2007 to 3388 in 2016). The highest rates of new HIV diagnoses in 2016 in the EU/EEA were reported in Latvia (18.5 per 100,000 population; 365 cases), Estonia (17.4; 229 cases), and Malta (14.5; 63 cases). The lowest rates were reported in Slovakia (1.6; 87 cases) and Hungary (2.3; 228 cases).[17]

The annual number of newly diagnosed HIV infections has declined from a peak of nearly 8000 to 5164 in 2016.[19] The decline in new infections may be linked to reduced HIV transmission among MSM; and among heterosexual men and women, the decline is potentially linked to a fall in migration from high HIV-prevalence countries. In Central Europe (as defined by the World Health Organization [WHO]), 5772 new HIV cases were diagnosed in 2016, with 1269 cases diagnosed in Poland and 625 in Romania.[17]

Eastern Europe and Central Asia

New HIV infections in Eastern Europe and Central Asia rose by 60% between 2010 and 2016, with 190,000 new infections in 2016, a rise more pronounced than in any other world region. Treatment coverage is only 28% (22%–32%) in the region; between 2010 and 2016, AIDS–related deaths had increased by 27%.[2] The most HIV infections in this region were from the two countries with the largest populations: the Russian Federation, with 1.16 million cumulative reported diagnoses in mid-2017,[20] and Ukraine, with around 247,000 cumulative reported diagnoses.[17] In the Russian Federation, the annual number of new infections dramatically increased from less than 40,000 in 2006 to more than 60,000 in 2011[16] and to 103,438 in 2016.[10] Ukraine has an adult HIV prevalence rate of 0.9% as of 2016.[3]

Of the new HIV cases reported in Eastern Europe and Central Asia, 42% were among people who inject drugs.[10] In Russia, the European Centre for Disease Prevention and Control (ECDC) estimates that for cases in which the transmission route is known, 49% of the diagnoses were among people who use drugs and 49% were ascribed to heterosexual transmission.[17] Large numbers of young and unemployed men inject and share drugs. Syringe exchange programs have recently increased,

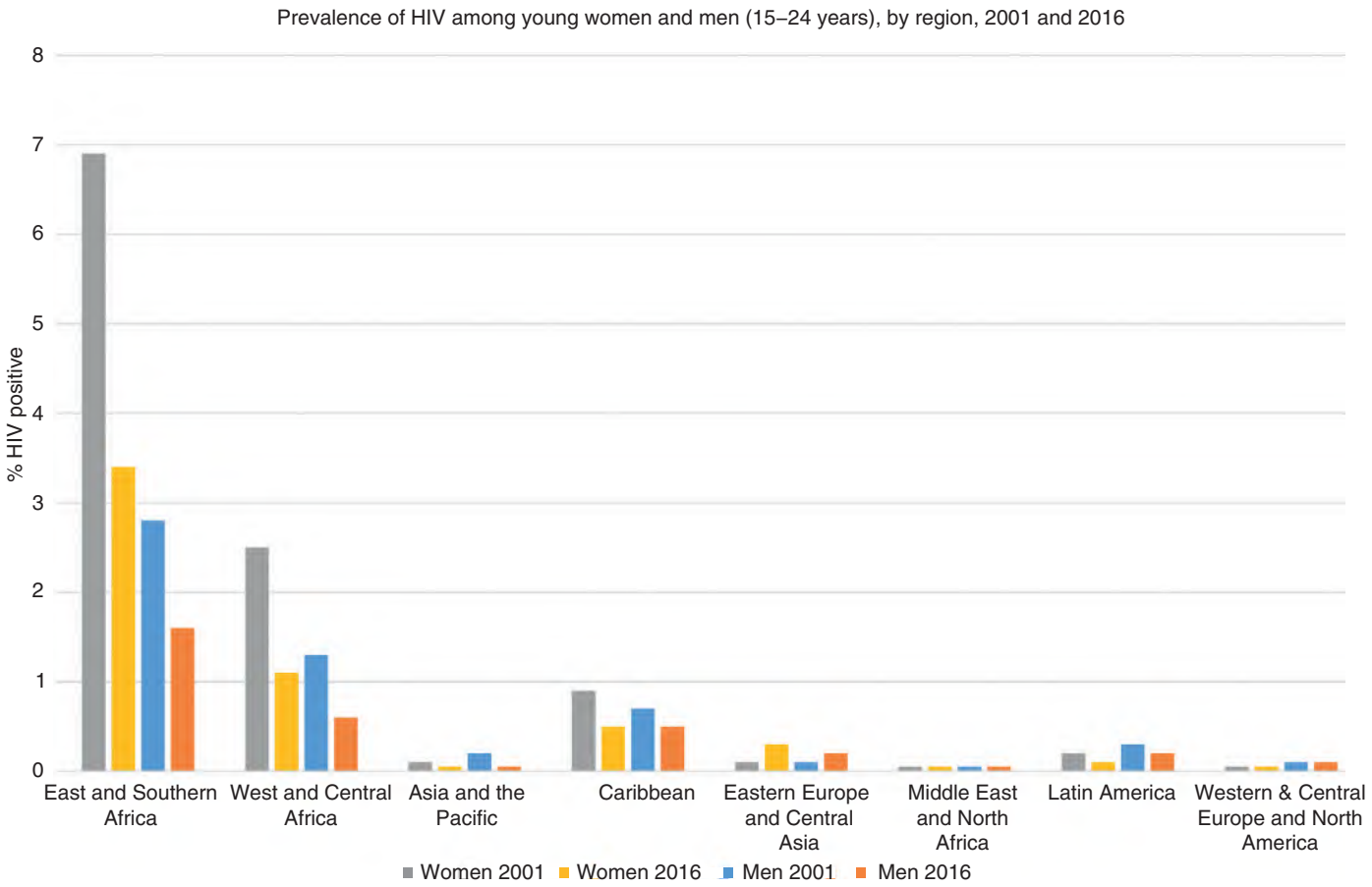

FIG. 118.2 Prevalence of human immunodeficiency virus *(HIV)* among young women and men (15–24 years old), by region, 2001 and 2016. *(Data from UNAIDS.* http://aidsinfo.unaids.org. *Accessed February 6, 2018.)*

but coverage is too limited to make an impact on the HIV epidemic curve; and in Russia, substitution therapy with methadone is still against the law. As Russia's epidemic matures, AIDS mortality rates will contribute significantly to the demographic decline of the country.

Elsewhere, the epidemics are comparatively small. In Eastern Europe between 2007 and 2016, the overall increase in HIV cases was driven by an increase in sexual transmission of HIV, which doubled for heterosexual transmission and rose ninefold for transmission through sex between men. Transmission through injection drug use decreased by 39% during this period.

In addition to that of HIV infection, major epidemics of tuberculosis and syphilis have occurred in Central Asia against a background of political and economic instability, increased mobility, drug use, and degradation of public health infrastructure.

Sub-Saharan Africa

AIDS more heavily affects sub-Saharan Africa than any other region of the world. In 2015, 29.4 million people in the region were estimated in the Global Burden of Disease (GBD) Study to be infected with HIV.[14]

Africa and the Caribbean are the only regions in which cases in women exceed cases in men.[21] Epidemics in sub-Saharan Africa vary significantly in scale. National adult HIV prevalence rates range from around a very low prevalence of 0.5% in some countries of West Africa (i.e., Senegal, Niger, Mauritania), to around 15% to 25% in southern Africa, to around 27% in Swaziland.[3] GBD estimates suggest that around 1.8 million people in sub-Saharan Africa became infected with HIV in 2015,[14] which was a decline from 2.2 million new infections in 2001.[16] Although AIDS was previously (in 2005) the single largest cause of mortality in the region, AIDS is now the second major cause of mortality, behind diarrhea, lower respiratory infections, and other common infectious diseases.[22] An estimated 10.9 million children have been orphaned by AIDS in this region.[8]

National adult HIV prevalence rates in 2016 exceeded 12% in eight countries,[3] all in southern Africa. Sub-Saharan Africa bears a disproportionate share of the global burden of HIV, with 85% of the world's HIV-positive pregnant women living in that region in 2014.[23] Of the children living with HIV in 2014, 91% lived in sub-Saharan Africa, although new infections in children in eastern and southern Africa decreased by 56% from 170,000 in 2010 to 77,000 in 2016; in West and Central Africa in the same period, new infections among children decreased by 33% from 90,000 in 2010 to 60,000 in 2016.[10] In South Africa, Tanzania, Uganda, Mozambique, Ethiopia, Namibia, and Swaziland, the number of children newly infected with HIV decreased by over 60% from 2009 to 2014.[24]

HIV prevalence and incidence in a growing number of African countries have declined significantly. The number of people acquiring HIV was reduced substantially in sub-Saharan Africa between 2001 and 2016. For example, the rate of new HIV infections dropped by 90% in both Senegal and Côte d'Ivoire and by 87% in Niger. In South Africa and Swaziland, with the largest number of HIV infections and the highest rate of infection respectively, reductions amounted to 55% in both countries. In West and Central Africa, Burundi's rates dropped 85%, and those in the Democratic Republic of the Congo (DR Congo), 84%. Other countries with declines included Guinea-Bissau, Cameroon, and Mali, with reductions of more than 60%. However, even when there has been a 46% reduction overall in the number of people acquiring HIV in sub-Saharan Africa, the region represented 64% of all new HIV infections in 2016.[3] A modeling study conducted in urban Kenya, Zimbabwe, and urban Haiti suggested that changes in patterns of HIV prevalence are consistent with behavior change.[25]

In Uganda, urban antenatal HIV seroprevalence rates peaked around 1992 (15%–30%), followed by a steady decline by 2002, most markedly among women aged 15 to 24 years.[26] This decline was associated with an increase in median age of sexual debut and a decline in multiple

partnerships among men, although no significant changes were found in extramarital sex among men. Between 1995 and 2000, condom use at last sex with a nonregular partner increased from 35% to 59% in men and 20% to 39% in women, respectively. In 2005, the national HIV prevalence rate was estimated to be 6.7%, with large regional variations. In particular, in the conflict-affected region of northern Uganda with 1.7 million internally displaced persons, the HIV prevalence rate was estimated to be close to 10%, which is very high for a rural population.[27] The national HIV prevalence rate fell slightly to 6.0% in 2016, and new infections were reduced by 47% from 2001 to 52,000 in 2016.[3,28]

There is significant heterogeneity in progress in reducing HIV incidence across eastern and southern Africa. For example, Swaziland is close to achieving the 90-90-90 targets (of 73% of all people living with HIV being virally suppressed), with 68% of all people living with HIV being virally suppressed. In 5 years from 2011 to 2016, incidence among adults fell by nearly half (44%).[29] This situation contrasts with Botswana, where 78% of people living with HIV are virally suppressed, but in this case treatment scale-up has not been associated with a meaningful decline in new HIV infections.[30] Young women are still disproportionally infected by HIV as compared with young men. A national household survey undertaken in South Africa in 2012 showed sustained high levels of HIV infection among young females. For example, among 15- to 24-year-olds, female prevalence (11.4%) was 3.9 times higher than that of males (2.9%).[31] Young women with older partners were also at increased risk for HIV infection. Among men and women, increasing partner numbers and inconsistent condom use were significantly associated with HIV infection. In a survey in 2005, young people who reported participation in at least one program for behavioral change were less likely to be infected with HIV.[32]

An understanding of sexual networks is crucial to understanding the rapid heterosexual spread of HIV, particularly in southern Africa. Why is southern Africa HIV hyperendemic? A multiplicity of risk factors, such as the lack of male circumcision, male sexual violence, concurrent and multiple partnerships, and migratory patterns, operates to create a "perfect storm"; no single factor in itself can explain such HIV levels, because all of them individually exist elsewhere. The practice of multiple sexual partnerships has been shown to be the most important risk factor in the transmission of HIV,[33] but the characteristics of each sexual partnership (e.g., whether it is transactional or whether payment is involved, older age of the male partner,[34] earlier age of the female partner, existence of concurrent partnerships) have been associated with HIV transmission.

The comparative impact on the spread of HIV of concurrent multiple relationships, defined as sexual relationships that overlap in time as opposed to serial multiple relationships, is less clear. Early modeling work concluded that, for the same number of partners per person, sexual partner networks that include concurrent partnerships lead to larger HIV epidemics than do networks without concurrent partnerships, especially at the beginning of the HIV epidemic curve.[35] However, empirical evidence so far has not confirmed such mathematical modeling. A study in five cities in sub-Saharan Africa and one in KwaZulu-Natal found no association between concurrency and HIV prevalence level.[36–38]

In the countries in southern Africa in which HIV prevalence rates are extremely high, the probability that one's partner is infected with HIV is around 1 in 3 to 1 in 6. This probability results in much higher levels of heterosexual exposure to HIV than occur anywhere else in the world and makes any new partnership, whether concurrent or not, a critical risk factor. Multiple and concurrent partnerships are often linked to mobility (including labor-related mobility), in that people may have different partners at different residences; also, those who stay behind may themselves have other partners, and living near major transport roads or locations with migrant labor generates "hot spots" for HIV transmission as demonstrated in KwaZulu-Natal.[39,40]

The disease burden of HIV infection in sub-Saharan Africa is high and will probably grow considerably higher. In 2016 alone, despite major progress in antiretroviral therapy (ART) coverage, around 730,000 sub-Saharan Africans died of AIDS, which constituted 73% of the global total.[2] The HIV adult prevalence rate in West and Central Africa is 2%. Guinea-Bissau has the highest HIV prevalence in West Africa, at 3.1%. In Central Africa, the estimated prevalence rates in all countries are 4% or lower, with the exception of Equatorial Guinea at 6.2%. HIV-2 is primarily found in West Africa but has also been confirmed in other African countries. The highest prevalence of HIV-2 infection is found in Guinea-Bissau, with prevalence rates as high as 8.0% in 1987 to 1988 and a decline to 2.5% in 2011. In contrast to the increasing spread of HIV-1, the prevalence rate of HIV-2 has remained rather stable in West Africa and has declined in Guinea-Bissau and in the Gambia,[41] probably the result of the higher transmissibility of HIV-1 compared with that of HIV-2. A mathematical modeling study predicts HIV-2 infection to fall below 0.1% in rural Guinea-Bissau by 2050.[42]

Middle East and North Africa

The number of HIV infections in Middle Eastern and North African countries is very low.[2] The number of people newly infected in the Middle East and North Africa continued to decline from its peak at 21,000 in 2005 to 18,000 in 2016. So far, the spread of the virus appears to be limited to those who pay for sex, MSM, and injection drug users in large cities. Most of the AIDS cases have been reported from Djibouti, Somalia, and Sudan, with only Djibouti having an estimated HIV prevalence rate higher than 1% (1.3%). Morocco, Egypt, Iran, Lebanon, Yemen, and Tunisia are at 0.1% HIV seroprevalence levels, or below, among the general population.[3] Iran has made needles and syringes available in pharmacies in an effort to cut the spread of HIV infection among an estimated 200,000 drug injectors, with half of them sharing injection equipment.[16] Libya's epidemic has been growing, with almost 90% of the 6000 to 10,000 HIV infections in Tripoli attributed to injection drug use. Transmission through contaminated injection equipment has also been reported in Bahrain and Oman. Because of the illegality of homosexuality in this region, concern exists that HIV may spread undetected among MSM.[43]

Asia and the Pacific

Overall, in Asia and the Pacific, an estimated 5.1 million people had HIV in 2016, including 270,000 people who were newly infected during the previous year. Approximately 170,000 died of AIDS-related illnesses in 2016.[2] The national HIV prevalence rate is highest in Southeast Asia (0.3%), with wide variations in epidemic trends among different countries.[44] Approximately 2.1 million people in India were estimated to have HIV in 2016, with a national adult HIV prevalence rate of around 0.3%.[3] The epidemic is extremely heterogeneous; for example, in Mumbai and Pune and in Karnataka, Andhra Pradesh, and Tamil Nadu states, HIV prevalence rates of 2% to 4% have been reported in pregnant women, in contrast to Calcutta and Delhi, in which prevalence rates have remained at less than 1%. A report suggests that the prevalence rate in pregnant women in Mumbai had fallen to 0.6% by 2012.[45] Injection drug use is the predominant mode of transmission in the northeastern states near Myanmar, where prevalence rates among drug users exceed 70%. In Manipur state, many of the women with positive HIV test results are sex partners of male injection drug users. HIV prevalence levels among injection drug users usually far exceed levels among sex workers. HIV among injection drug users is now also appearing in other parts of India, such as Punjab.[46,47] Over 90% of HIV-positive injection drug users in Manipur and its neighboring state of Mizoram are reported to be coinfected with the hepatitis C virus (HCV) which presents a challenge to ART treatment because coinfected patients were found to be less tolerant to several ARTs.[48]

In China, HIV infection was first noted in Yunnan province, which borders the Golden Triangle where Myanmar, Thailand, and Laos meet. The prevalence rate of HIV infection in injection drug users there climbed rapidly to 70% or more in the early 1990s, and HIV infection first emerged in sex workers in this region. Prevalence of HIV among injection drug users declined from 12.3% in 2008 to around 6% in 2014.[49] Around 115,000 persons in China were infected with HIV in 2015 according to data from China's Centre for Disease Control and Prevention,[50] with sexual transmission now the primary mode of HIV transmission. Although overall HIV prevalence remains low, with 0.037% of the population living with HIV, the provinces of Yunnan, Sichuan, and Guangxi each have over 50,000 people living with HIV; among MSM, HIV prevalence is 7.7%.[49] In cities and among young MSM, incidence may be particularly high; a 2014 study suggested that

HIV incidence among young MSM was 18.9 per 100 person-years in Guiyang, 10.6 per 100 person-years in Beijing, and 5.6 per 100 person-years in Shanghai.[51] Since 2005, China has established more than 1500 methadone clinics and needle exchange sites.[49] Examples in Sichuan show that these programs can reduce the reuse of nonsterile needles by almost half.

China's HIV prevalence rate remains low (estimated at <0.1% of the total population), but the epidemic continues to grow in several parts of the country, and among groups such as young MSM and individuals older than 60, with figures from China's Centre for Disease Control and Prevention suggesting that 15% of new infections in 2015 were among this latter age group.[50] The AIDS epidemic remains a potential challenge, particularly with regard to improving coverage of prevention of mother-to-child transmission and reducing AIDS-related deaths, which stood at 21,000 in 2014.[49] Several factors in China fuel it, including rapid economic growth and higher disposable income for men, commercial sex, injection drug use, high mobility of workers, and stigma and discrimination experienced by MSM and people living with HIV. China has dramatically improved its AIDS response since an initial phase of denial. This commitment has been translated into laws and policies, growing HIV prevention efforts, and increased access to treatment. China increased the number of people receiving HIV treatment by nearly 50% in 2011 alone,[16] and in 2014 59.0% of all adults and children living with HIV were receiving ART and over 90% of people on treatment were virally suppressed.[49]

The most heavily affected countries of Southeast Asia are Cambodia, Thailand, and Myanmar, with injection drug use and commercial sex driving HIV transmission. In Thailand, the epidemic has spread in overlapping waves through injection drug users and sex workers, their clients, and the female partners of clients, including female spouses. The prevalence rate among sex workers rose from 3% in 1989 to 30% in 1996, and the rate among sexually transmitted disease (STD) clinic attendees rose from nearly zero to 9% over the same period, before declining in the late 1990s. Convincing evidence shows a fall in risky behaviors after extensive programs to promote condom use in brothels and to discourage men from visiting them. The number of new annual HIV infections in Thailand continues to decline, from 21,000 in 2005 to 6400 in 2016, although the decline in HIV prevalence has been slowing in recent years as more people receive ART. The HIV prevalence rate among injection drug users has declined over the past 20 years but remains high, with an HIV prevalence of 19.02% among people who inject drugs in 2016.[52] Similarly, infection rates remain high among key populations such as transgender people and MSM, with HIV prevalence of 9.15% among this latter group. Programs for injection drug users and MSM are still inadequate. The percentage of sex workers reached with HIV prevention programs amounted to 57%, whereas the percentage of sex workers reporting the use of a condom with their most recent client was reported at 95% in 2011.[21] Estimates from UNAIDS suggest that 91% of people living with HIV knew their status in 2016, with 69% treatment coverage for adults living with HIV.[52]

The epidemic in Myanmar also shows signs of a decline, with a decrease in new infections from 24,000 in 2005 to 11,000 in 2016. The male-to-female ratio has changed significantly over time from almost 8 to 1 in 1994 to a steady increase in the proportion of women infected by 2008. However, the elevated prevalence rate of HIV among key populations at higher risk is of concern, with HIV prevalence of 26.3% among people who inject drugs in Myanmar, 6.4% among MSM, and 4.7% among prisoners.[52] The epidemic in Cambodia has shown a steep drop in HIV, with a prevalence of 0.6% in 2016 and fewer than 1000 new infections. The epidemic in Vietnam declined from 24,000 new infections in 2005 to 11,000 new infections in 2016. Commercial sex and injection drug use remain the most common risk factors for HIV infection in Vietnam. However, the HIV prevalence rates among pregnant women increased from 0.03% in 1994 to 0.5% in 2011. In 2007, the number of men living with HIV infection was 3.0 times higher than the number of women, with this ratio gradually decreasing to 2.6 by 2012. Although frequently ignored because of prevailing social attitudes, MSM are an emerging risk group, with 8.2% of MSM in Vietnam living with HIV in 2016. However, the epidemic is now present across the general population, with the growth in HIV infections among clients of sex workers and women at low risk.

An HIV prevalence rate of 0.9% has been documented in Papua New Guinea, fueled mainly through heterosexual transmission. Risky behavior is widespread, with research showing high rates of unsafe sex with multiple partners, sexual violence, and the frequent failure to use condoms.[53]

Injection drug use currently is the major mode of HIV transmission in several countries in Asia (Fig. 118.3). In China, with the largest estimated population of injection drug users (2.3 million–2.9 million) and an HIV prevalence rate of 6.4%[54] in users, HIV infection rates have been rising. In Vietnam, HIV prevalence among injection drug users was 30% in 2011, and it stabilized through to 2012. However, in certain areas HIV prevalence remains at high levels in well-established epidemics (Quang Ninh, 56%; Ho Chi Minh City, 55%; Can Tho, 45%), and prevalence is increasing in newer epidemics in northwestern provinces of Vietnam. In Malaysia, among injection drug users there is an HIV prevalence rate of over 26%. The first HIV outbreak in China occurred among injection drug users in Yunnan province in the late 1980s, with the epidemic rapidly expanding to its neighboring provinces. Despite large investments in prevention services for drug users, less than 25% of injection drug users in Yunnan obtain their own injecting equipment and have rates of sharing injecting equipment below 50%.[40,55]

New HIV epidemics in MSM are now firmly established across Asia. These data represent an alarming trend because male-male sexual activity in the region is diverse, often completely hidden, and beyond the reach of current HIV prevention efforts. Similarly, recent studies show increasing HIV prevalence rates among MSM in Bangkok, which rose from 17% in 2003 to 28% in 2007. The increasing sex industry in parts of Asia is of concern, and sex workers and male clients of sex workers are likely to be the most important groups to target for prevention programs.[39]

Latin America and the Caribbean

With an estimated 115,000 people newly infected with HIV in 2015, the HIV prevalence rate in Latin America and the Caribbean remains generally stable, but the epidemic is growing. The total number of people estimated to be infected with the virus is 2.1 million; annual new infections increased by 3% in Latin America between 2010 and 2015, and regional declines in new infections have been greater for children then adults. There are significant disparities among countries, with more than 20% decline in new infections in countries such as El Salvador, Colombia, Nicaragua, and Uruguay since 2010; in contrast, there were significant increases in new infections between 2010 and 2016 in Chile (34%), Guatemala (23%), Costa Rica (16%), Honduras (11%), and Panama (9%). In the Caribbean, new infections have remained relatively static; in Cuba, HIV infections more than doubled between 2010 and 2016, whereas in the same period new infections declined by nearly a quarter in Haiti and Trinidad and Tobago.[10] HIV transmission continues to occur among populations at higher risk for exposure, including sex workers, their clients, injection drug users, and particularly MSM.[16,56] The epidemic in Latin America was similar initially to that in North America and Europe, with most cases occurring among MSM and injection drug users. Systematic surveillance in the region is limited, and the picture is complex, with male-to-male transmission predominating in major cities. Pooled prevalence estimates suggest an HIV prevalence of 14.9% for MSM in Central and South America, and 25.4% for MSM in the Caribbean.[20] Reliable data on HIV rates among injecting drug users are limited, but there are indications of a decline in HIV infections among this population; for example, in Argentina, HIV prevalence among people who inject drugs declined from 7.6% in 2005 to 0.4% in 2013.[57] In Latin America, HIV prevalence decreased by nearly 20% among young people in 2011, with higher decreases among young men (33%), the group in which the majority of HIV infections occur in Latin America. In 2012, it was estimated that 43% of adolescents living with HIV (aged 10–19) in Latin America and the Caribbean were female, the lowest proportion of any region.[58] A large proportion of MSM often also have sex with women, which leads to an increased number of HIV infections among women. Bisexual behavior of male partners is an important source of HIV infection for women in several Latin American

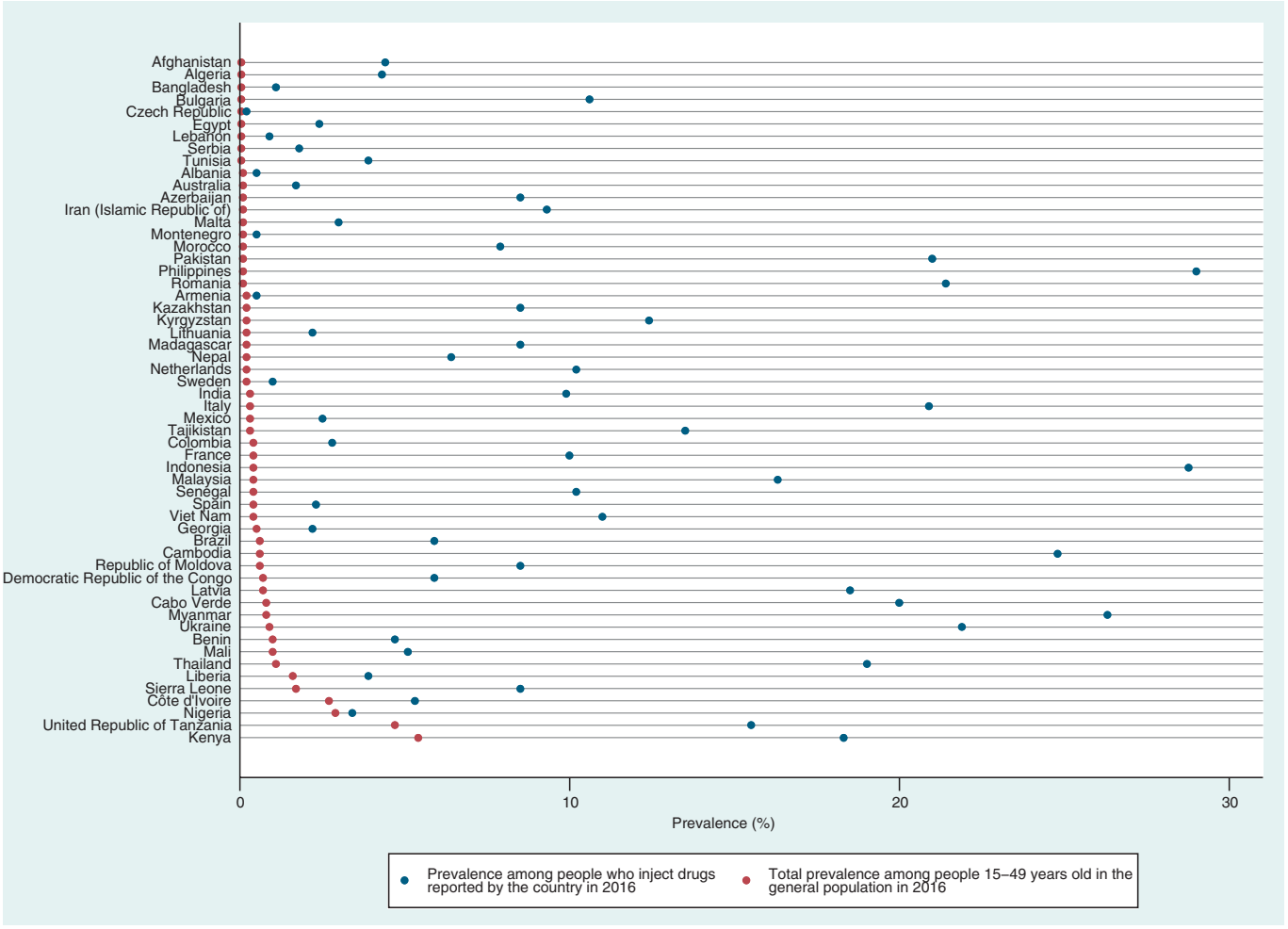

FIG. 118.3 Human immunodeficiency virus trends among injection drug users in selected countries, 2016. *(Data from UNAIDS.* http://aidsinfo.unaids.org. *Accessed February 6, 2018.)*

countries. HIV rates in pregnant women are generally low (around 0.5% or less), although estimates of prevalence rates are higher in countries of the Caribbean such as Haiti, where prevalence as high as 2.5% among pregnant women has been reported.[59]

Over one-third of all people with HIV in Latin America and the Caribbean region reside in Brazil, where in 2016 an estimated 830,000 people were living with HIV, which corresponds to 0.6% of the adult population. Although initially concentrated primarily among MSM, the epidemic subsequently spread to injection drug users and eventually into the general population, with increasing numbers of women becoming infected. A large proportion of infections among women may be attributed to the behavior of male sexual partners. However, unprotected sex between men remains an important factor. In 2014, the HIV prevalence rate among MSM was 10.5%.[60] Transgender women across the region, and particularly in Brazil, are at high risk of HIV infection and violence. In a 2017 respondent-driven sampling study, almost one-third of transgender women were estimated to be living with HIV; among this sample, new HIV diagnoses were associated with black race, and history of sex work and cocaine use.[61] HIV prevalence among injection drug users in Brazil has declined in some cities, as a result of harm-reduction programs and changes from injected to inhaled drugs, and mortality rates among drug users have also declined.[62] A 2015 study using data from eight Brazilian cities found that an estimated 9.9% of people who inject drugs were living with HIV.[63]

Brazil remains one of the world's first success stories in its political determination to secure antiretroviral drugs while also sustaining resources for prevention and care. More than 60% of the 830,000 living with HIV in need of treatment are receiving antiretroviral drug therapy in Brazil.[52]

Of the Central American countries, Honduras has been especially broadly affected by heterosexual transmission. However, overall, HIV infections are highest among female sex workers and their clients (there is a prevalence of 5.3% among sex workers overall in Honduras), among MSM (prevalence of 11.7%), and among transgender people (prevalence of 11.9%). Since 2010, new HIV infections have declined by 29%; however, in the same period, AIDS-related deaths have increased by 11%.[64]

In the Caribbean, the adult HIV prevalence rate is estimated to be 1.3%.[3] HIV prevalence is highest in the Dominican Republic and Haiti, which together account for around 70% of the 310,000 people infected with HIV in the Caribbean.[16,56] The HIV prevalence rates show clear signs of decline in these two countries, but AIDS remains one of the leading causes of death among adults. Declining HIV rates are also documented in Barbados and in Trinidad and Tobago. Although new infections are increasing in Cuba (from 1600 annual new infections in 2010 to 3300 new infections in 2016), 70% of people living with HIV have access to treatment, and Cuba was the first country validated by WHO to have eliminated mother-to-child transmission of HIV and syphilis. HIV infection in the Caribbean is a true mosaic of different epidemiologic patterns determined by the local interaction of various risk determinants for HIV transmission.

In 2016, HIV prevalence rates among MSM were 31.6 % in Trinidad and Tobago, 4.9% in Guyana, and 18.2% in Haiti.[21] Drug use and sex for drugs (mainly cocaine and crack) are major risk factors in the Bahamas, Bermuda, Puerto Rico, and Trinidad. Finally, heterosexual transmission is predominant in Haiti and in the neighboring Dominican Republic.[16,56] Among sex workers, an HIV prevalence rate of 8.4% has been found in Haiti, with 2.8% in Jamaica and 6.1% in Guyana.[52]

DYNAMICS OF THE SPREAD OF HUMAN IMMUNODEFICIENCY VIRUS

Basically, no difference exists among the various modes of transmission of HIV in the developing world and industrialized countries. Selected aspects of HIV transmission in the LMICs and other determinants of HIV spread are reviewed briefly in this section.

Modes of Transmission

Worldwide, HIV infection is predominantly sexually transmitted. Unprotected heterosexual intercourse accounts for most cases of HIV infection in sub-Saharan Africa and some countries in the Caribbean and Asia, but the situation is somewhat different in the rest of the world.

The low average efficiency of penile-vaginal intercourse for transmission of HIV in the absence of amplifying factors has now been well documented, especially for transmission from women to men.[65] A sustained and fulminant heterosexual epidemic can be explained only by a common occurrence of factors that amplify heterosexual transmission, probably in addition to high-risk sexual behavior patterns.[66]

Factors that enhance the efficiency of heterosexual transmission of HIV include higher viremia or more advanced immunodeficiency in the infecting partner, acute primary infection, receptive anal intercourse, sex during menses, lack of male circumcision, and the presence of other STDs. Viral load of HIV-1 has been shown to be the primary determinant of transmission risk in HIV-discordant couples,[67,68] and suppressing viral load through ART reduced HIV transmission in discordant couples by 96%.[69] Indeed, 5-year follow-up of the landmark treatment-as-prevention trial HIV Prevention Trials Network (HPTN) 052 observed no genetically linked infections in discordant heterosexual couples when HIV-1 infection was stably suppressed by ART in the index participant.[70] This is the foundation for the current strategy of ART as prevention.

Other factors that may increase the risk for heterosexual transmission but are less well documented include the use of various desiccating vaginal agents, traumatic sexual intercourse, hormonal contraception, and cervical ectopy.[71,72]

Data from three randomized controlled trials undertaken in South Africa, Kenya, and Uganda show that male circumcision reduces the risk for heterosexually acquired HIV infection in men by approximately 60%.[73–75] This evidence strongly supports the findings of numerous observational studies.[76] At this stage, what, if any, protective effect male circumcision may have on a woman's risk for acquiring HIV during sexual intercourse is unclear. A study in Uganda and Zimbabwe found that it neither increased nor decreased a woman's risk for infection.[77] A more recent mathematical modeling analysis conducted in Zimbabwe and Kenya suggested a 46% reduction in the rate of male-to-female HIV transmission, suggesting that women also benefit greatly from male circumcision.

Conventional STDs have attracted much attention as a risk factor because many are treatable with relatively inexpensive antibiotics and antiviral agents.[78] Evidence from prospective studies showed that genital ulcers (e.g., chancroid, syphilis, genital herpes) particularly enhance the sexual transmission of HIV by a factor of 3 to 8.[79,80] Early diagnosis and treatment of STDs reduced the spread of HIV infection in two randomized trials in Tanzania[81] and Uganda,[82] where a 38% to 42% decline in the rate of newly acquired HIV infections was observed in the interventions communities. However, later studies found no effect.[83] Perhaps STD treatment as a form of HIV prevention is more effective early in an epidemic. Since the first description of AIDS in the early 1980s, severe mucocutaneous herpes simplex virus (HSV) infections have been associated with the immunodeficiency syndrome. HSV type 2 (HSV-2) is also the most common cause of genital ulcer disease, with prevalence levels above 80% in Africa.[84] HSV-2 infection may facilitate HIV acquisition and potentially increase HIV genital shedding and infectiousness. A meta-analysis of prospective observational cohort studies showed that male and female patients with seropositive results for HSV-2 had a threefold higher risk for acquiring HIV compared with individuals with HSV-2–seronegative results.[85] More recently, in two cohort studies in Uganda and Zimbabwe, hazard ratios for HIV acquisition were 2.8 and 4.4 for prevalent HSV-2 infection, respectively, and 4.6 and 8.6 for incident HSV-2 infection, respectively.[86]

Several trials have been conducted to measure the effect of acyclovir suppressive therapy in reduction of HIV acquisition with HIV seronegativity, reduction of HIV transmission from persons with dual HIV and HSV-2 infections, and reduction of HIV disease progression. Two controlled trials reported no efficacy of HSV-2 suppressive therapy on reduction of HIV acquisition,[87,88] undermining the extensive evidence from epidemiologic studies.[89]

The relative risks of gonorrhea, chlamydial infection, and bacterial vaginosis for HIV acquisition in women are smaller than those of genital ulcers. However, because these STDs are far more common in most populations than are genital ulcers, their contribution to the heterosexual spread of HIV may also be greater. Several studies have found that genital shedding of HIV is greatly enhanced in the presence of urethral, cervical, or vaginal inflammation.[90,91] For example a recent cohort study in Uganda showed an association between recurrent bacterial vaginosis and risk of HIV; bacterial vaginosis may trigger an innate immune response that upregulates cytokines associated with HIV acquisition.[92] Overall, the case for STD control to reduce HIV transmission has been considerably weakened; and with the appearance of antiretroviral-based prevention interventions, STD treatment may no longer be a core HIV prevention strategy.

Mother-to-child transmission during pregnancy, delivery, or breast-feeding is a major mode of spread of HIV. The prevention of HIV transmission from mother to child is a success story in many countries, with a few such as Cuba, Thailand, Belarus, and Armenia having declared elimination of such transmission.[93,94] In Botswana, Mozambique, Namibia, South Africa, Swaziland and Uganda—designated "priority countries" in the Global Plan to eliminate new HIV infections in children—90% or more of pregnant women living with HIV were accessing treatment in 2015. During the five years of the Global Plan, four Africa countries reduced new infections by 80% or more: Uganda (86%), Burundi (84%), South Africa (84%) and Swaziland (80%).[95] In 2016, globally, an estimated 160,000 children became infected with HIV; this is a 47% reduction since 2010, when about 300,000 children were newly infected with HIV most of whom live in sub-Saharan Africa.[2] Mother-to-child transmission of HIV can occur during pregnancy, at the time of delivery, or postnatally via breast-feeding. Breast-feeding by mothers who are HIV positive (in the absence of ART for either mother or infant) can account for up to one-third of HIV infections among infants in sub-Saharan Africa. HIV transmission risk through breast-feeding is enhanced during primary maternal HIV infection acquired after the infant has been put to the breast.[96] The additional risk for postnatal transmission attributable to breast-feeding is estimated at about 14% (range, 5%–20%). Duration of breast-feeding, maternal plasma and breast milk viral load, cracked nipples, mastitis, breast abscess, and infant thrush increase the risk for transmission of HIV. Exclusive breast-feeding is associated with a reduced risk for HIV transmission as compared with mixed feeding.[97]

The situation has greatly improved in numerous countries, from 10% of pregnant women with HIV having access to medicines that prevent HIV transmission to their children in 2004 to more than 30% at the end of 2007, to 61% in 2011, and to 77% in 2015.[98]

Injection drug use is estimated to account for about 30% of new infections outside Africa.[99] HIV has spread considerably among injection drug users in parts of Asia, Eastern Europe, and Central Asia (where an estimated 51% of new infections are among injection drug users), the Middle East and North Africa (where an estimated 28% of new infections are among injection drug users), Latin America, and the Caribbean; this spread has sometimes occurred where injection has replaced smoking and inhaling as a more cost-effective way of drug administration.

Estimates from 2015 suggest that around 15.6 million people inject drugs worldwide.[100] The largest numbers of injectors are found in China, the United States, and Russia, where estimates of HIV prevalence rates among injectors were 12.4%, 8.7%, and 30.4%, respectively.[100] Worldwide, 2.8 million people who inject drugs are estimated to be HIV positive.[101] Injection drug–associated HIV epidemics are characterized by a high degree of regional and local heterogeneity. Explosive epidemics have occurred in both developing and developed countries, with documented HIV incidence rates reaching as high as 20% to 30% per year. Several interventions have been developed to reduce the spread of HIV among

injection drug users, including programs that promote sterile syringe acquisition, drug use treatment, and community outreach—jointly referred to as "harm reduction." Substitution treatment, and methadone maintenance in particular, has been associated with reduced injection frequency and declines in needle sharing, sexual risk behaviors, and HIV seroconversion. In cities in which cocaine and methamphetamine are the main drugs of use, little is available in terms of drug abuse treatment.[102]

A systematic review on coverage of HIV prevention, treatment, and care services in injection drug user populations concluded that coverage is still very low worldwide. The study concluded that although the number of countries with HIV prevention services for injection drug users is growing, the level of coverage remains poor. The study identified 82 countries implementing needle and syringe programs and 70 countries providing opioid substitution therapy, an increase of 5 and 8 countries, respectively, since the last audit had been published in 2008.[103] A systematic review drawing on 106 studies suggested that where drug use is criminalized, this has a negative impact on HIV prevention and treatment.[99]

Transfusion with HIV-contaminated blood continues to be a source of HIV infection in some parts of the developing world as a result of the recruitment of voluntary and unpaid donors and the absence of implementation of national policies for transfusion, proper screening of collected blood, and a strategy for its rational use.[104] Clinical indications for appropriate blood transfusions are often not met outside of large cities in the low-income countries.

Nosocomial transmission of HIV through injection with nonsterile syringes and needles occurs, but its relative contribution to the spread of HIV in the developing world is not well documented, although it is probably no more than 5%, with women and children at greater risk because of frequent anemia. The mean probability of HIV infection from puncture with a contaminated needle was estimated to be 0.23% (range, 0.00%–2.38%).[105] The potential for HIV transmission with unsterilized needles in medical settings is probably weak, but localized outbreaks in Romania and Libya among infants and young children through intravenous contamination have shown that it can occur when basic hospital hygiene is not applied. In 2001, it became widely known that in a number of Chinese provinces, but mostly in Henan in Central China, paid blood donation for plasmapheresis did not respect basic practices of infection control. This resulted in HIV infections, with estimates ranging from less than 100,000 to several hundreds of thousands. Those criminal practices seem to have ceased, but it is unclear whether those responsible for them were ever punished.

Reducing the Spread of Human Immunodeficiency Virus

Historically, the HIV epidemic is still in an early phase in most parts of the world, with continuing geographic spread and changing epidemiologic patterns. It is the complex mix and interaction of direct (behavioral) and indirect risk and vulnerability factors that determine how and when HIV spreads in the population.[106,107]

Safer Sexual Behavior

Sexual behavior is the most important determinant of HIV spread in most parts of the world; about 85% of HIV transmission is sexual, whether via penile-vaginal or anal sex.[56] Such behavior is heterogeneous among and within populations. Sexual behavior surveys around the world have documented this heterogeneity in terms of sexual orientation, marriage patterns, age of sexual debut, number of partners, and rates of casual, transactional, and commercial sex.[108–111] In addition, these studies found that men have generally more casual partners than women; that their female partners are often much younger, with age differences of 10 years or more; that in many societies, women before or within marriage also disclose several partners; and that in some societies, higher socioeconomic status and urban settings are associated with a higher number of partners. However, according to mathematical models, sexual mixing patterns are equally important in determining the spread of HIV, particularly in early stages of the epidemic.[112,113] The "core group" concept postulates that a relatively small proportion of the population contributes to maintenance of the epidemic; this pattern was first described in the 1970s with respect to the epidemiology of gonorrhea in the United States.[114] However, for a chronic viral infection such as HIV, this concept may be more relevant during the emerging phase of the epidemic than for epidemics with very high levels of HIV infection that already occur among persons at a very young age and with relatively low-risk behavior, such as in southern Africa.

The behavior of one's partner is as relevant for the risk for HIV infection as one's own behavior. In parts of sub-Saharan Africa, in discordant couples, as many couples have women with HIV as have men with HIV. However, outside of Africa, in most settings, up to 80% of women with HIV in long-term stable relationships have been infected by their partner. Data suggest that an increasing proportion of women with HIV infection in Latin America and most of Asia have their husbands as their only sexual contact.[16]

The rate of condom use in high-risk behaviors plays a major role in the control of HIV transmission. Despite much early skepticism and moral concerns, condoms are increasingly being used in many parts of the developing world, particularly in high-risk populations and where social marketing programs are dynamic.[115–117] In these groups, both increases in condom use and high rates of consistent condom use have been documented and have resulted in fewer HIV infections. Numerous studies have also shown moderate-to-high rates of condom use in the general population of many developing countries (Fig. 118.4).[117] For example, data collected by the Brazilian Ministry of Health in 2006 showed that 51% of men and 32% of women reported having used a condom during their last sexual encounter with a casual partner.[118] In Zimbabwe, where a decline in HIV prevalence has been documented, more than 70% of men reported using a condom the last time they had high-risk sex.[119] However optimistic the trends in condom use are in the world, the rise in condom use generally applies only to a suboptimal fraction of all sexual encounters. Condom use is much lower in rural areas, and condom promotion has had little impact in the context of steady sexual relationships.[120] Across the world, promotional efforts to encourage consistent condom use are poor, particularly within regular partnerships, in which condom use can be a very sensitive issue.[56,121] Globally, in 2005, estimates were that a condom was used in less than 10% of sex acts involving a nonregular partner. In most high-prevalence (>2%) countries between 2000 and 2016, male condom use increased significantly; for example, condom use at last high-risk sex (with a nonmarital, noncohabiting partner) was highest in Botswana (94%, 2013), Zimbabwe (85%, 2015), Namibia (80%, 2013), and Malawi (76%, 2015). However among 41 countries with data available for young people (aged 15–24 years) for the period 2011 to 2016, condom use at last high-risk sex in the previous year was less than 50% among young women in 31 countries and among young men in 18 countries.[10]

Country data available on the percentage of adults aged 15 to 49 who had more than one sexual partner in the past 12 months who reported use of a condom during last intercourse vary greatly worldwide. Females aged 15 to 49 reported condom use during their last intercourse at a rate of 12% in India, 35% in DR Congo, 48% in Ukraine, 55% in Swaziland, and 66% in Namibia, illustrating the variation worldwide.[21]

The use of condoms has played a role in the significant reduction of HIV incidence rate in MSM in the high-income countries; among intensively counseled discordant couples[122,123]; in large populations of men and women in Thailand, Uganda, and Senegal; and among sex workers in Kenya, DR Congo, India, and Bolivia. These best practices show that effective HIV prevention is possible, particularly when HIV prevention is comprehensive and sustained.

Male Circumcision

Studies in Kenya, South Africa, and Uganda indicated that male circumcision reduced the risk of female-to-male sexual HIV transmission by roughly 60%.[73–75,124] Since then, medically performed voluntary male circumcision is part of combination prevention programs in populations in which male circumcision is not the rule. By 2014, 3.2 million voluntary male medical circumcisions were taking place, in 14 priority countries in eastern and southern Africa; this declined to an estimated 2.6 million in 2016, presenting a challenge to global targets to reach 25 million voluntary circumcisions between 2016 and 2020.[10]

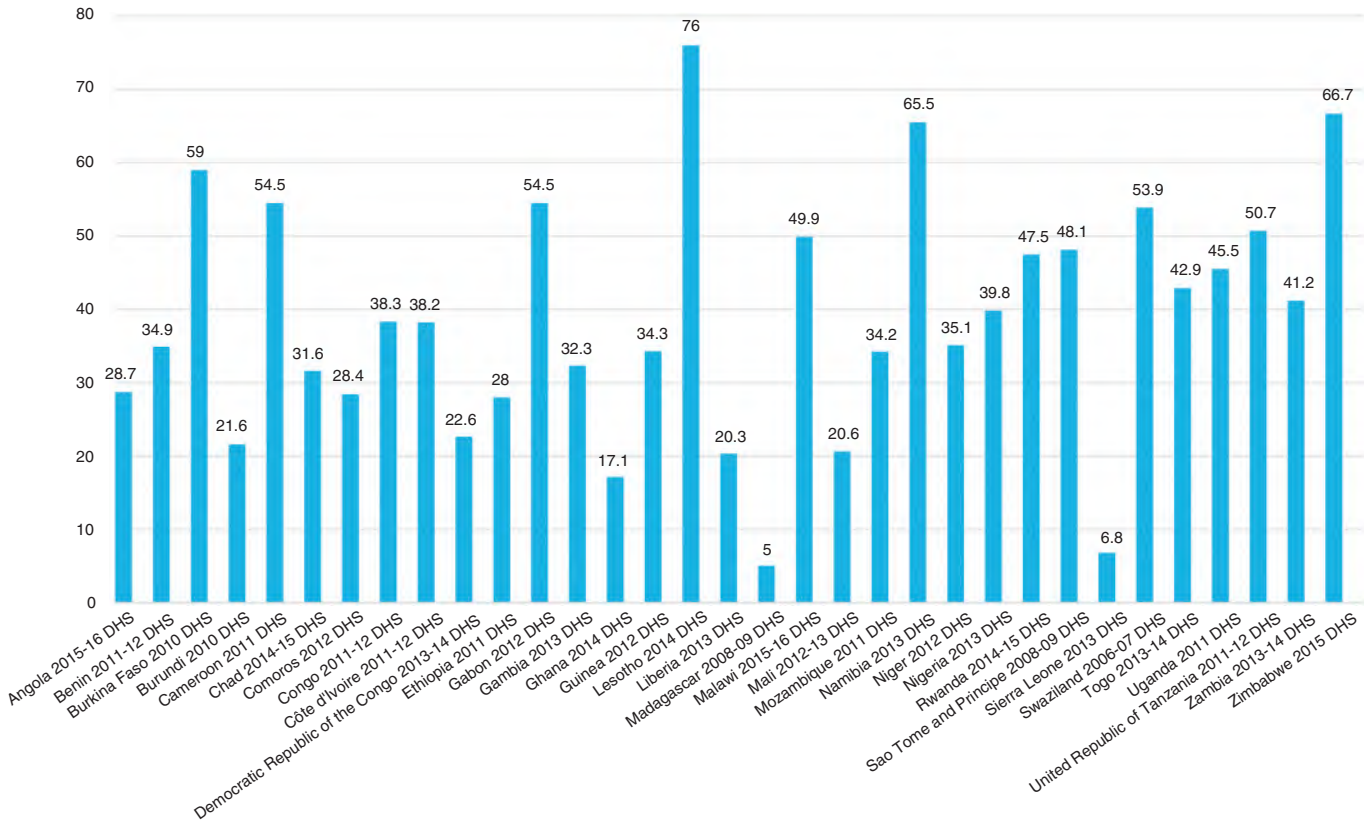

FIG. 118.4 Percentage of condom use at last high-risk sex among female adults (15–49 years old) in Africa, 2016. "High-risk" sex is defined as sex with a nonmarital, noncohabiting partner. *(Data from UNAIDS.* http://aidsinfo.unaids.org. *Accessed February 6, 2018.)*

However, circumcision of boys at birth is still not widely recommended or practiced in sub-Saharan Africa and would be the longer-term and less costly solution. In sub-Saharan Africa, rates of circumcision vary throughout the region, with important implications for HIV prevention efforts. In southern Africa, where one in three adults is infected in some countries, the rate of circumcision among men is lower than 30% in countries such as Botswana, Malawi, Namibia, Rwanda, Swaziland, Uganda, Zambia, and Zimbabwe.[10] Recent data from Uganda show that 5 years after the male circumcision intervention trial was performed, high effectiveness among the men who were circumcised still remained, with a 73% protective effect against HIV infection.[125]

Preexposure Prophylaxis

Recent advances in pharmaceutical-based HIV prevention have opened new and important approaches to combination prevention. Whereas a trial of a microbicide gel with tenofovir in South Africa found a 39% protection among women,[126] another large trial did not find effectiveness of a tenofovir gel.[127] More recently, the ASPIRE trial, which tested a vaginal ring containing dapivirine, showed that HIV incidence was 37% lower in the dapivirine group versus the placebo group. Researchers found that use of the ring was associated with protection against HIV in women older than 21, but not in women younger than 21, whose adherence was lower.[128] More research with various products is being conducted, but, as with oral preexposure prophylaxis (PrEP), adherence to the use of the microbicide is a key factor for effectiveness.

PrEP with an antiretroviral drug that is used before sex among HIV-negative individuals has been a major addition to the prevention armamentarium. Randomized controlled trials testing precoital use of different preexposure prophylactic products resulted in significant reductions in infection for various groups, such as women (39% reduction), MSM (44% reduction), uninfected partners in HIV serodiscordant partnerships (~70%), and young heterosexuals.[129] However, two other studies produced conflicting results, finding no efficacy. The main reason for the difference in these results seems related to low adherence to prophylaxis. In 2012, the US Food and Drug Administration approved one of the PrEP products (i.e., Truvada gel). Since then, trials of oral on-demand PrEP among MSM in the United Kingdom (the PROUD study) and France (ANRS IPERGAY) have shown significant reductions in new HIV infections relative to placebo.[130,131] Research is growing into long-acting injectable forms of PrEP, such as injectable cabotegravir, which could be a useful alternative for those who struggle to adhere to daily oral PrEP. Although PrEP may have a crucial role to play in prevention and is highly acceptable to many high-risk groups, access needs to be expanded together with support to promote adherence. National regulatory approval for PrEP has been granted in high-income countries such as the United States, France, Australia, Canada, Belgium, Norway, Israel, Portugal, Scotland, and Luxembourg. Among LMICs, approval for PrEP as been granted in Brazil, South Africa, Kenya, Zimbabwe, Namibia, and Thailand. PrEP coverage in LMICs is still thought to be low; the number of people who started on PrEP between 2012 and early 2017 has been estimated at nearly 250,000, of whom the vast majority (220,000) lived in the United States. Thus, scaling up PrEP rollout and increasing accessibility remain challenges.[10]

Treatment as Prevention

Five-year follow up of the landmark treatment-as-prevention trial HPTN 052 observed no genetically linked infections in discordant heterosexual couples when HIV-1 infection was stably suppressed with ART in the index participant.[70] However, evidence for the efficacy of treatment as prevention is still somewhat uncertain at the population level. The ANRS Treatment as Prevention trial, a cluster RCT in KwaZulu-Natal, found no reduction in HIV incidence in the 11 communities where HIV-positive participants received ART regardless of CD4 count, compared with the control arm, in which ART was offered in line with national guidelines. This may have been due to difficulties linking people to testing and treatment services, certain participants' choice not to access treatment, and the complex geography of sexual networks that extend beyond individual communities.[132] Early findings from the PopART universal test-and-treat intervention in Zambia show that after just 1 year, 87% of women and 78% of men living with HIV knew their status, although

linkage to care and ART initiation remains a challenge to reaching 90-90-90 targets.[133] Encouragingly, evidence from the Opposites Attract study in Australia, Thailand, and Brazil showed no linked HIV transmissions between discordant homosexual male couples, across 16,889 acts of condomless anal intercourse, when the HIV-positive partner had an undetectable viral load.[134]

Combination Prevention

There is wide agreement that a combination prevention strategy is the best approach to prevent new infections.[135] Biomedical interventions need to be introduced together with behavioral and structural approaches for the first to be successful. There is also a need to test in community trials what the optimum program design and content of a combination prevention strategy might be. Issues to consider are what key populations should be targeted and the need to provide a better understanding of the existent cultural barriers to the provision of such services.

The range of available prevention tools may continue to expand in coming years. For example, a safe and even moderately efficacious HIV vaccine could prove transformative for HIV prevention. A phase IIb proof-of-concept study, Imbokodo, is underway in South Africa, aiming to enroll 2600 HIV-negative women in sub-Saharan Africa and evaluate the safety and efficacy of a vaccine. The regimen is based on "mosaic" immunogens, which can stimulate immune responses against a wide variety of global HIV subtypes, and is drawing on results from early-stage clinical trials such as APPROACH, which evaluated seven different prime-boost vaccines.[136] In tandem, the HVTN 702 study, a phase IIb/III trial, is evaluating a new regimen in South Africa based on the regimen used in the RV144 trial in Thailand, the only candidate vaccine ever found to show some protection against HIV.[137]

Advances in bioinformatics may allow for improved phylodynamic analysis, to better understand patterns of HIV transmission and resistance in specific social networks and thus help target prevention efforts. For example, analysis of sequence data in the United States in 2017 demonstrated recent and disproportionately rapid transmission among young Hispanic/Latino MSM, allowing public health resources and campaigns to be tailored to this high-risk group.[138]

Demography and Social Context

Investigators took a long time to recognize that the determinants of the HIV epidemic involve more than multiple sexual and drug-using partners. There is increasing awareness that personal behavior is critically influenced and conditioned by the sociodemographic, cultural, and legal contexts within a society.[106,107,139,140] Some factors have an indirect effect; for example, the inconsistencies in harm-reduction policies and practices are obstacles to the prevention of the transmission of HIV through injection drug use.[102]

In developing countries, with demographic growth rates of more than 3% in some African countries and age pyramids that reflect the slow decline in mortality rates in the age group of those younger than 5 years, adolescents and the more sexually active age groups account for a high proportion of the population. This demographic by itself often results in higher incidence rates of STDs such as HIV infection.[141,142] In sub-Saharan Africa, the population will increase from 0.8 billion to over 2 billion by 2050, with around 605 million young people between 10 and 24 expected to live in sub-Saharan Africa by 2050.[143]

In 2008, the world reached an invisible but momentous milestone: for the first time in history, more than half the human population, 3.3 billion people, were living in urban areas.[144] Furthermore, the total urban population in sub-Saharan Africa is expected to increase from 298 million in 2010 to about 1.1 billion in 2050.[145] Urban population growth is driven partly by rural-to-urban migration of young adults seeking jobs and other livelihood opportunities. Estimates from UN-Habitat show that about 70% of all urban residents in sub-Saharan Africa live in slums.[144] The experiences of the urban poor are characterized by reliance on a cash economy, overcrowding, poor environmental sanitation, lack of security, lack of social and health services, and high levels of mobility and riskier sexual practices. These experiences have often led to the growth of marginalized conditions that have been associated with higher rates of STDs.[146] In many sub-Saharan African countries, the HIV prevalence rate is significantly higher in urban than in rural areas and is also higher in slums than in nonslum urban areas. Moreover, women who live in slums are particularly at risk, with higher HIV prevalence rates than those of both men and rural women.[56]

With globalization of the economy and increased inequalities, rural-to-urban movement migrations occur all over the developing world and have played a major role in the spread of HIV in some parts of the world, such as in Central and southern Africa[147] and also in the Mekong, Nepal, and China.[148] The Greater Mekong subregion includes a vast number of migrants and mobile people.[149] Border-crossing points are meeting places for many transport workers, workers without families, traders, tourists, border police, and military personnel; and the use of alcohol and drugs and commercial or casual sex are common.

With the insight that social, political, and economic contexts often contribute to health risk and HIV vulnerability, some HIV prevention programs have begun to include structural interventions. Structural interventions have been used extensively in public health policy for a broad range of issues, including injury prevention, smoking cessation, obesity control, and motor vehicle safety. These interventions address the determinants of health and seek to change the health environment of individuals, communities, and organizations. In HIV prevention, examples of such interventions include income-generating activities for women infected with HIV, conditional cash transfers, empowerment of women, enactment of laws to prevent HIV infection discrimination in the workplace, sex education programs in schools, antialcohol campaigns, and decriminalization of homosexuality Hard evidence that "structural interventions"[150] can be effective is still limited but was demonstrated for cash transfer in adolescent schoolgirls in Malawi and for a program to reduce violence against women in South Africa.[151,152] The effects of structural interventions on prevention outcomes may be complex and indirect; for example, a conditional cash transfer program was found not to reduce HIV incidence among young women in South Africa.[153] However, conditional cash transfers reduced these young women's risk of intimate partner violence by 34%, by reducing women's engagement in sexual partnerships and delaying sexual debut. These behaviors can in the longer term protect against HIV acquisition.[154]

The simplistic assumptions that "poverty causes AIDS" or that "AIDS is a disease of poverty" have been overturned. Higher-income groups and people who are better educated usually live in urban settings and may have higher-risk sex than those who live in rural areas. However, the HIV prevalence rate is not necessarily higher because more educated persons use condoms more often and have different sexual networks.[12] Economic inequality or disparities in wealth have been shown to be an important factor underlying HIV vulnerability. Poverty clearly makes it more difficult for individuals and communities to cope with the consequences of HIV infection and AIDS.[150]

At the microlevel, the evidence is more mixed. In some contexts, disposable income drives people into transactional sex.[149] Especially among women and girls, lack of income can impede access to HIV and other health information and services and can increase food insecurity.[155,156] Food insecurity in southern Africa was associated with increased transactional sex or multiple sexual partners. Among women who attended antenatal clinics in Soweto, South Africa, 21% said they had exchanged sex for goods or money; these women were considerably more likely to be HIV positive compared with the other women in the study.[157]

Gender

Gender inequalities are now widely recognized to drive HIV epidemics. In diverse regions, a greater percentage of women are HIV positive or face disproportionate risk for infection. In 2017, more than half (17.8 million) of the 34.5 million adults (15 years of age or older) living with HIV infection are women[6]; this figure is higher than the estimated 15.4 million in 2007 and the 13.8 million in 2001. In sub-Saharan Africa, 56% of adults infected with HIV in 2017 were women. The Caribbean region has experienced an increase in the number of HIV-infected women, with women representing 35% of newly infected adults, and women are more affected than men are by HIV.[6] Young women (aged 15–24) in the Caribbean may be especially vulnerable to HIV infection; for example in Haiti, women aged 20 to 24 are three times more likely

to be HIV positive than men of the same age.[158] Survey data show that 9% to 24% of women aged 15 to 24 reported having had sex with a man at least 10 years older than themselves in the previous 12 months. These age-disparate partnerships, especially when compounded by other risk factors such as concurrent sexual partners and infrequent condom use, can increase HIV risk.[159] The gender discrepancy in HIV infections is especially glaring among young people in sub-Saharan Africa, where women aged 15 to 24 years accounted for 23% of new HIV infections. Boys and young men in the same age group accounted for 11% of new infections in sub-Saharan Africa. In certain southern African localities, young women account for as much as 91% of infections among 15- to 19-year-olds[160] (Table 118.2).[161,162] This vulnerability does not match sexual risk behaviors; indeed, demographic and health surveys in 14 countries have shown that the proportion of young men aged 15 to 19 years who reported having had more than one sexual partner in the previous 12 months varied from 12% to 46%, with a median of 21%. For young women, the results were much lower, varying from 2% to 15%, with a median of 4%.[12] Studies suggest that in settings where young women have limited access to education, employment, and economic resources, age-disparate sexual relationships often involve potential economic benefits.[163] Wide age disparities between young women and older men play an important role in the high HIV infection levels found among young women because of power imbalances and economic dependence in such relationships.[164] In a Botswana study among 8000 men, the odds of unprotected sex rose by 28% for every year's increase in age difference between men and their female partners. Furthermore, phylogenetic data from recent research in KwaZulu-Natal, South Africa, shows that age-disparate sex (sex between women younger than 25 and men on average 8.7 years older) drives the HIV transmission cycle in this high-prevalence region.[34]

Condom use was shown to be least likely in relationships with the widest age disparities.[165] In rural Zimbabwe, for example, the HIV prevalence rate was approximately 16% among teenage girls whose last partner was younger than 5 years older than themselves, but among girls with partners 10 or more years older, the prevalence rate was twice as high.[166] Similarly, among South African women aged 15 to 24 years, the HIV prevalence rate was found to be 30% in those with partners at least 5 years older, compared with 19% in those with partners younger than 5 years older.[167]

Numerous studies in many parts of the world have linked sexual violence and intimate partner violence with heightened HIV infection risks for women.[168] Lifetime prevalence rate estimates of forced sex by an intimate partner varied from 4% in Serbia and Montenegro to 46% in Bangladesh and Ethiopia provinces.[169] Exposure to intimate partner violence can increase women's risk for HIV infection through forced sex with an infected partner, through limited or compromised negotiation of safer sex practices,[170] and through increased sexual risk-taking behaviors. Studies in Kenya and Tanzania show that women who have been subjected to violence by their partners are up to three times more likely to acquire HIV than women who have not experienced violence.[171,172]

Economic and social empowerment can help reduce some forms of violence against women. In South Africa, for example, a microfinance project targeting rural women was combined with training on HIV, gender norms, and domestic violence. Within 2 years, women's risks for intimate partner violence were reduced by more than half.[173] In South Africa, Stepping Stones is an HIV prevention program that aims to improve sexual health through building stronger, more gender-equitable relationships with better communication and less violence between partners.[174] A randomized controlled trial of the program found, in addition to a reduction in HIV infection, that the men in the program disclosed lower rates of perpetrating severe intimate partner violence at 12 and 24 months after intervention.[175]

Stigma and Discrimination

The spread of HIV is disproportionately high among many groups that experience discrimination and a lack of human rights protection. Since the beginning of the pandemic, reports of harassment and violence against sex workers, AIDS widows, bisexuals, transgender people, MSM, street children, and drug users have been widespread, occurring on all continents. In 2012, UNAIDS reported that 61% of countries now have

TABLE 118.2 Percentage of People Identified as Living With HIV and Incident Tuberculosis Who Received Treatment for Both HIV and Tuberculosis, 2016

<25%	25%–50%	51%–75%	76%–100%
	Argentina Bhutan Bolivia (Plurinational State of) Bosnia and Herzegovina Botswana Brazil Burkina Faso Cabo Verde Cameroon Central African Republic China Colombia Democratic Republic of the Congo Dominican Republic Ethiopia Gambia Guinea India Iran (Islamic Republic of) Jamaica Kenya Lao People's Democratic Republic Latvia Lebanon Lesotho	Azerbaijan Bahamas Belarus Benin Burundi Côte d'Ivoire Cambodia Djibouti Ecuador Egypt El Salvador Eritrea Georgia	
Afghanistan	Malaysia	Guatemala	
Bahrain	Mali	Guyana	
Bangladesh	Mauritius	Haiti	
Barbados	Mongolia	Honduras	
Bulgaria	Morocco	Kyrgyzstan	
Chad	Mozambique	Malawi	
Comoros	Myanmar	Malta	
Congo (Brazzaville)	Netherlands	Mexico	Albania
Equatorial Guinea	Niger	Nicaragua	Armenia
Gabon	Peru	Norway	Belize
Ghana	Serbia	Oman	Brunei Darussalam
Guinea-Bissau	Sierra Leone	Paraguay	Costa Rica
Indonesia	South Africa	Republic of Moldova	Cuba
Iraq	South Sudan	Romania	Dominica
Ireland	Sir Lanka	Russian Federation	Estonia
Kiribati	Suriname	Rwanda	Israel
Kuwait	Syrian Arab Republic	Saudi Arabia	Jordan
Liberia	Thailand	Senegal	Kazakhstan
Madagascar	Timor-Leste	Swaziland	Namibia
Nepal	Uganda	Tajikistan	Panama
Nigeria	Ukraine	Togo	Saint Lucia
Pakistan	United Republic of Tanzania	Trinidad and Tobago	Sao Tome and Principe
Papua New Guinea	Uruguay	Turkey	Slovenia
Philippines	Venezuela (Bolivarian Republic of)	Viet Nam	Tunisia
Somalia	Zambia	Zimbabwe	United Arab Emirates

Data from UNAIDS. http://aidsinfo.unaids.org. Accessed February 6, 2018.

some form of antidiscrimination law in place to protect people infected with HIV, although in many instances such laws are not enforced.[21] For example, in 2016, 93 countries reported the existence of accountability mechanisms to challenge discrimination in health care settings, but in almost one-third (30 of 93) of these countries, civil society and non-governmental partners reported that the mechanisms were not functioning.[10]

Factors that contribute to AIDS-related stigma include misconceptions about modes of transmission, the fatality of AIDS, widespread taboos about the sexual and drug use behaviors that are risk factors for infection, homophobia, and blaming of individuals for infection.

Stigma within health care systems is also common and can result in the transfer of HIV-positive patients to facilities with inferior care or in the disregard for patients' rights and confidentiality. However, research in rural Haiti suggests that the introduction of high-quality HIV care can lead to a reduction in stigma, with the result of increased uptake of HIV testing. Rather than stigma, logistic and economic barriers determine who will access such services.[176] A study in Botswana found that stigmatizing attitudes had lessened 3 years after the national program for universal access to ART was introduced. ART access was a factor in reducing stigma but did not eliminate stigma altogether and did not lessen the fear of stigma among people infected with HIV.[177]

Stigmatizing processes also play an important role in HIV risk, transmission, and the quality of life for people with AIDS. In China, a study with mobile populations found an association between increased levels of stigmatizing attitudes toward people infected with HIV and a reported unwillingness to engage in harm-reduction activities.[178] Comparative studies from Uganda and India show that individuals are more reluctant to seek HIV testing or care for fear of ostracism, humiliation, and unemployment and rejection from family members, colleagues, and the community as a whole.[179]

On a global scale, stigma has discouraged policy makers, political leaders, and also civil society leaders from prioritizing or even acknowledging AIDS as an urgent national issue.[180]

Interventions that have in part succeeded in reducing stigma related to HIV infection have integrated skill building (e.g., for caregivers and health care workers) with health information and communication activities, including media campaigns with opinion leaders and role models. Some stigma reduction interventions appear to work, at least on a small scale and in the short term, but many gaps remain, especially in relation to scale and duration of impact.[181]

IMPACT OF PREVENTION AND CARE PROGRAMS

The most important lesson from the past decades is that the spread of HIV can be reversed or prevented on a large scale, including in some of the poorest countries of the world. For example, the latest data suggest that between 2010 and 2016, the annual number of new HIV infections (all ages) declined by 16% to 1.8 million.[10] The debate over the relative priority of HIV prevention versus treatment and care should be viewed with skepticism.[182] The most successful responses to the epidemic combine prevention and care strategies to prevent future infections and improve the quality of life for both infected and uninfected individuals. One particular example is the case of Kenya, where the government's National AIDS Control Council has developed a strategic framework, spanning 2014–15 to 2018–19, to address structural drivers of the epidemic and provide comprehensive access to HIV prevention, treatment, and care services. It supports tailor-made prevention programs in each county, devised according to the local epidemiology and state of the AIDS response. The strategy has the flexibility to include innovation. Thus in 2017, the government launched self-test kits as part of its "Be Self Sure" campaign, and rollout of PrEP through public health facilities for groups at risk, including young people, serodiscordant couples, sex workers, and people who use injection drugs.[183]

Despite repeated claims of a single or simple intervention to stop the transmission of HIV, all real-world evidence points to the need for a combination of approaches to HIV prevention. Only when communities and decision makers come to terms with the complexity of HIV prevention and responses will programs succeed.[106] Whereas the precise mix of elements of "combination prevention" needs to be tailored to the local epidemiology and resources, in general it includes condom use, behavioral interventions, medical male circumcision, and expanded use of ART for infected persons and PrEP for uninfected persons at risk for infection. In addition, for maximal impact, resources should be directed to areas where transmission risk in a country is highest.

The effectiveness of national responses to the AIDS pandemic ultimately will determine how extensively HIV will spread. This effectiveness requires, in the first place, political and financial commitment to HIV prevention, which is still insufficient. Many countries need two to three times more financial resources than presently available to control the AIDS epidemic.

In 2016, investment in HIV programs in LMICs reached $19.1 billion, up from $16.8 billion in 2011, $10 billion in 2007, $8.3 billion in 2005, and $250 million in 1996, when UNAIDS was founded. Extraordinary efforts resulted in over 20.9 million people receiving ART as of June 2017.[2] International funding for the AIDS response in LMICs peaked at almost $10 billion (constant 2016 US dollars) in 2013, before declining to around $8.1 billion in 2016. Domestic spending became the majority of HIV expenditures in LMICs for the first time in 2011; whereas domestic spending in LMICs rose by an average of 11% each year from 2006 to 2016, the rate of that increase slowed to 5% in 2015 to 2016.

Access to antiretroviral drugs that prevent mother-to-child transmission of HIV has also greatly improved. Worldwide, 76% of pregnant women living with HIV had access to antiretroviral medicines to prevent transmission of HIV to their infants in 2016.[2] There is substantial interregional variation; in sub-Saharan Africa, antiretroviral coverage for pregnant women in 2016 was 77%, in Latin America it was 74%, but coverage was only 40% in the Middle East and North Africa.[184] However, the data demonstrate a substantial scale-up, given that antiretroviral coverage for pregnant women was only 45% in LMICs in 2008,[185] 33% of women in 2007, and 14% in 2005. Cuba, Thailand, Belarus, and Armenia have been certified as having eliminated vertical transmission through the expansion of access to services for prevention of mother-to-child transmission.[93,94] In Botswana, South Africa, Namibia, and Swaziland, the percentage of ART coverage for prevention of mother-to-child transmission is 95%; in the Central African Republic, it is 81%, in Ethiopia, 69%; and in Ghana, 56%. A few countries in sub-Saharan Africa still have to make progress, with less than 50% coverage (i.e., Nigeria, Republic of Congo, Guinea, and Somalia, among others).[21] The increased availability of point-of-care rapid tests for diagnosis of HIV infection has the potential to expand the already crucial role of voluntary counseling and testing in prevention and care. Health care centers with adequate resources can provide immediate prevention education or referral to treatment and care services, thus drastically reducing loss to follow-up among patients.

There is still a gap in expanding access to HIV testing services so that people can know their status; in 2016 an estimated 30% of people living with HIV infection did not know their HIV status, with particular gaps among young people and men.[10] Increasingly, couples testing and provider-initiated approaches in clinical settings are being promoted (i.e., health care providers routinely initiate an offer of HIV testing in a context in which the provision of, or referral to, effective prevention and treatment services is assured).[186] Self-testing (also known as home testing) holds significant promise. It may help reach people living with HIV who do not use facility-based testing and is a potential means of addressing testing disparities among groups tested less frequently, such as men and people from key populations.[187] Self-testing may be particularly acceptable to MSM, although common concerns about self-testing among MSM include the lack of counseling, possible user error, and accuracy.[188] Research carried out through the HIV Self-Testing Africa (STAR) project in Malawi suggests that self-testing is highly accepted by young people, if costs are kept low and their autonomy and confidentiality are respected.[189] A study in Zambia found that peer educators providing self-testing kits to female sex workers could improve testing uptake and rapid linkage to care.[190] WHO issued guidance for World AIDS Day 2016 to help encourage scale-up of self-testing rollout as an approach to be offered in addition to conventional testing.

Assisted partner notification, tracing sexual or drug-injecting partners of people diagnosed with HIV, may be another promising approach to improving testing uptake and rapidly linking HIV-positive individuals

to care. A recent meta-analysis of three randomized trials demonstrated that assisted partner notification services resulted in a 1.5-fold increase in adoption of HIV testing services among partners compared with passive referral, with few instances of violence or harm recorded.[191] This supports the rationale for scaling up the implementation of assisted partner notification services, together with HIV self-testing services, in line with 2016 WHO guidelines.[192]

Although there has been major progress in access to ART, there are several barriers to the provision of ART, resulting in a declining cascade of treatment access, adherence, and reduction in viral load. The percentage of people living with HIV who are virally suppressed was as low as 30% in the United States,[193] 17% in Lithuania, 7% in Venezuela, and 19% in Cameroon.[52] Most often reported reasons are related to inconsistent pattern of diagnosis, linkage to care, differences in levels of CD4 cell count for initiation, and retention in care.[194]

Considerably increased resources have been brought into countries for AIDS programs by major global health initiatives, particularly the Global Fund to Fight AIDS, Tuberculosis and Malaria and the President's Emergency Plan for AIDS Relief (PEPFAR). As a result, services to people with HIV have rapidly expanded. In many countries, infrastructure and laboratories have been strengthened; in some, primary health care services have been improved. The negative effect of AIDS on the health workforce has been lessened by the provision of ART to HIV-infected health care workers, by training, and, to an extent, by task shifting.[195] Of ongoing concern is the long-term sustainability of efforts in terms of the future burden of HIV and availability of the necessary funding.[196] In 2016, $19.1 billion of funding was available to support HIV efforts in LMICs, which will need to rise by one-third to $26.2 billion by 2020 to meet global targets to reduce the burden of HIV/AIDS.[197] The impact of reduced resources for AIDS is still unclear, but it should negatively affect some optimistic scenarios predicting the end of AIDS and an HIV-free generation. What is now needed is a long-term strategy to reduce the epidemic to low endemic levels—something that is realistic with the existing prevention and treatment tools.[198]

IMPACT OF THE AIDS EPIDEMIC

AIDS has been shown to affect not only individual patients and their relatives but also, in the worst affected countries, communities at large, with a long-term impact on households, the health sector, demography, and economic and social systems. With an estimated 19.4 million HIV infections and with an adult HIV prevalence rate of 7%, at least 10 times higher than in most other parts of the world, the magnitude of the impact in southern and eastern Africa on the population and economies is bound to be of a different scale.[158] In addition, within Africa, huge and widening differences in the spread of HIV are seen, which implies that the consequences of the epidemic differ substantially. The HIV prevalence rate among pregnant women in southern Africa is as much as five times higher than in western Africa and three times higher than in eastern Africa.[56]

Perhaps the most visible aspect of the burden of AIDS used to be the large number of men and women with AIDS in the hospitals of many African countries, where they may make up at least 50% of all adult patients in the absence of access to ART. However, as a result of the widespread access to ART, there are fewer and fewer patients with HIV in the hospitals of the continent, even if AIDS remains the second major cause of death in Africa.[22] Among people with HIV, tuberculosis is the most common and deadly opportunistic infection; it accounts for 40% of all adult deaths, although the cause of death in patients infected with HIV in the developing world is not well studied.[199] Recent data suggest that 57% of tuberculosis cases among people living with HIV were not diagnosed or treated, leading to 390,000 deaths from tuberculosis among people living with HIV in 2015.[200]

The impact of HIV infection on mortality, burden of disease, and the health system in major parts of Africa was enormous before the current wider access to ART. In a large study of a representative sample of patients who died during hospitalization in Abidjan, Côte d'Ivoire, tuberculosis, bacteremia with gram-negative rods, and cerebral toxoplasmosis caused 53% of the deaths.[201] Tuberculosis was found in half of the cadavers with an AIDS-defining pathologic process, compared with only 4% for *Pneumocystis jiroveci* pneumonia. In 2001, in the city of Pointe-Noire, Republic of the Congo, where by law all bodies should be registered at the morgue before they can be legally buried, a clinical examination of all bodies registered at the morgue was performed. Overall, 1309 adult deaths were investigated and the bodies tested for HIV. Forty-five percent of the deaths were from AIDS. The AIDS mortality rate among adults was 6.3 per 1000 for women and 4.9 per 1000 for men. In the most productive age group, 25 to 44 years, mortality was tripled by AIDS.[202]

In rural South Africa, since 1992, deaths have been rigorously monitored with a validated verbal autopsy instrument to establish probable cause. The dynamics of the mortality transition were investigated with comparison of the periods 2002 to 2005 and 1992 to 1994. Since 1994, all-cause mortality increased substantially because of a sixfold rise in deaths from infectious disease that affected most age and gender groups and a modest increase in deaths from noncommunicable diseases. The change in female risk for death from HIV infection and tuberculosis was almost double the change in male risk. The burden of disorders requiring chronic care increased disproportionately compared with those requiring acute care. The implications for primary health care systems are substantial, with integrated chronic care based on scaled-up delivery of ART needed to address this expanding burden.[203]

In countries of southern and eastern Africa, the direct effects of AIDS on the health sector have been dramatic, with greatly increased service needs associated with caring for people with HIV. Before the availability of ART, in Zambia, Malawi, and South Africa, for example, the availability of health workers was affected by morbidity and mortality, absenteeism due to personal or family illness, and attrition due to employment changes or family illness.[204] A study in four South African provinces found that an estimated 16% of health workers employed in the public and private health facilities had HIV in 2002.[205] In addition, in some African countries, 35% to 45% of physician posts and up to 15% of nurse posts are vacant.[206]

A growing number of persons with HIV infection and the 19.5 million people on chronic ART, 95% of whom live in LMICs,[207] put additional pressure on health services that are already under great strain. Absorbing this growing burden is a major challenge for health care systems in the worst affected countries.[208] A report in Tanzania concluded that the services of half the current health workforce are necessary to deliver ART to everyone in need.[209] The impact of AIDS on health services also applies to countries with much lower HIV prevalence rates. For example, in Vietnam in 2007, AIDS absorbed nearly 5% of all public health spending. Vietnam, with an adult HIV prevalence rate of 0.4%, has 250,000 people infected with HIV; a similar number of people are living with HIV in Swaziland, where adult prevalence is more than 27% but the population is about 1.3 million.[52]

The long-term demographic impact of AIDS is becoming clearer. The estimates from the GBD Study of 2017 confirmed that HIV/AIDS remains one of the leading causes of disease burden and death, although it is now the second highest cause of death in sub-Saharan Africa thanks to ART, and no longer the highest.[22,210] Since 2001, annual incidence of HIV infection has fallen in 38 countries, most of them in sub-Saharan Africa.[210] Research by Walker and Ghys[211] estimated that 10% of child mortality in sub-Saharan Africa as a whole was the result of HIV infection, but this proportion has decreased substantially as a result of successful prevention programs for mother-to-child transmission.[212]

In addition, the number of orphans—children and adolescents (0–17 years) with parents who died of AIDS—reached about 13.4 million worldwide as of 2015, down from a peak of 15 million in 2009.[8] In countries with a generalized epidemic, a significant proportion of orphaned children are orphaned because of AIDS; for example, 74% of orphaned children in Zimbabwe are orphaned owing to AIDS, and 63% in South Africa.[213] Orphans are less likely than other children to have basic material needs met and are more likely to be underweight.[56,214]

GLOBAL RESPONSES TO AIDS

Nearly 4 decades of response to AIDS are finally beginning to deliver results. In 2017, on a global basis, fewer people were infected with HIV, primarily because of scaling up of HIV prevention efforts, and fewer died of AIDS, partly because of increased access to treatment. Globally,

there were almost 1 million fewer deaths in 2016 than at the peak of AIDS-related deaths in 2005 (a fall of 48%, from 1.9 million AIDS-related deaths in 2005 to 1 million in 2016).[2] The decline in AIDS-related deaths has been particularly significant in eastern and southern Africa, with a 62% decrease from 1.1 million deaths in 2004 to 420,000 in 2016, attributable to the rollout of ART in the region.[10] This progress has been achieved through political leadership at the levels of both government and civil society, programs on the ground, and a spectacular increase in financing for the national response.

In June 2001, the United Nations General Assembly held a Special Session on HIV/AIDS at which the Declaration of Commitment on HIV/AIDS was adopted; this declaration has since served as a blueprint for action against the worsening pandemic, and has been updated as part of the Sustainable Development Goals, with a commitment to end AIDS as a public health problem by 2030 (reference on SDG Declaration).[214a] AIDS is inextricably linked to the other Sustainable Development Goals; education, gender equality, and poverty eradication are all vital in fighting it.[106]

After the General Assembly Special Session, the Global Fund to Fight AIDS, Tuberculosis and Malaria was established as a public-private financing mechanism among governments, civil society, and the private sector to raise and dispense resources worldwide to combat these three diseases. By May 2017 a total of $33.8 billion had been disbursed, over 50% of which was spent on HIV/AIDS activities.[215] In 2003, President George W. Bush launched PEPFAR, which is the largest funder of AIDS efforts in the developing world and the major financier of the Global Fund. From the financial years of 2004 to 2017, PEPFAR disbursed $72.7 billion to combat HIV/AIDS and tuberculosis.[216] Combined, these mechanisms have saved millions of lives, and are undoubtedly major achievements in international development (Fig. 118.5). Globally, $19.1 billion was available from all sources for the HIV/AIDS response in LMICs in 2016, although the estimated annual need by 2020 is $26.2 billion. International donor funding decreased in 2016 to $8.1 billion (from a peak of nearly $10 billion in 2013). Furthermore, although domestic spending in LMICs rose by an average of 11% each year from 2006 to 2016, the rate of that increase slowed to 5% between 2015 and 2016.[10]

Despite the progress accomplished in access in recent years, and although the number of new HIV infections has fallen in many countries and regions, the AIDS epidemic is not over in any part of the world. Current efforts to slow the AIDS pandemic are still inadequate (Fig. 118.6).

More progress has been accomplished in recent years on HIV treatment than on prevention. Globally, 76% of pregnant women living with HIV had access to antiretroviral therapies to prevent mother-to-child transmission in 2016, from 9% in 2004.[2] Antiretroviral drugs have succeeded in delaying the onset of illness, reducing mortality from AIDS, improving the quality of life for people infected with HIV, and probably limiting the spread of HIV. In rural Malawi, for example, deaths from AIDS were averted by the rapid scale-up of free ART, which led to a decline in adult mortality.[217] After years of debate, the dramatic drops in the prices of antiretroviral drugs because of generic manufacturing and differential pricing, combined with specific financing mechanisms, have made ART a reality in low-income nations (Fig. 118.7), but in 2017 approximately 15.8 million people who need ART still do not have access to it.

The nearly 2 million new HIV infections that continue to occur each year worldwide stresses the need for scaling up of prevention programs while broadening access to antiretroviral treatment.[123]

The future of the response to HIV requires continuous advocacy to remind policy makers that the AIDS pandemic is one of the defining issues of our time and that AIDS remains one of the most severe epidemics in modern history.[218,219] Rising rates of infections in certain regions such as Eastern Europe and Central Asia, and continuing high rates especially among young people and key populations, should serve as a wake-up call from complacency. There is an emerging gap between

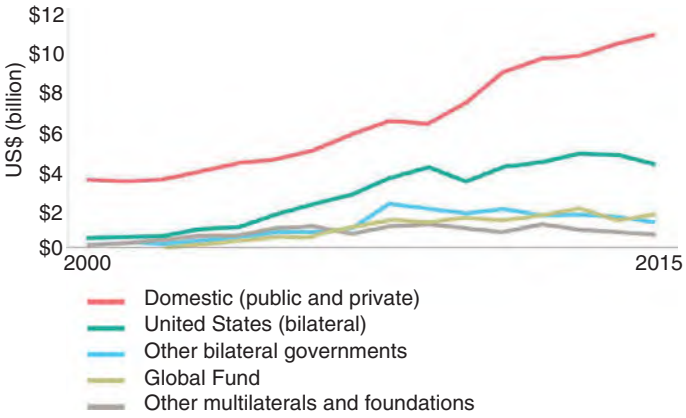

FIG. 118.5 UNAIDS estimates for resources available for human immunodeficiency virus in low- and middle-income countries, 2000 to 2015. *(Data from Kates J, Wexler A, Lief E. Financing the Response to HIV in Low- and Middle-Income Countries: International Assistance from Donor Governments in 2015; July 15, 2016. https://www.kff.org/global-health-policy/report/financing-the-response-to-hiv-in-low-and-middle-income-countries-international-assistance-from-donor-governments-in-2015/. Accessed June 2016.)*

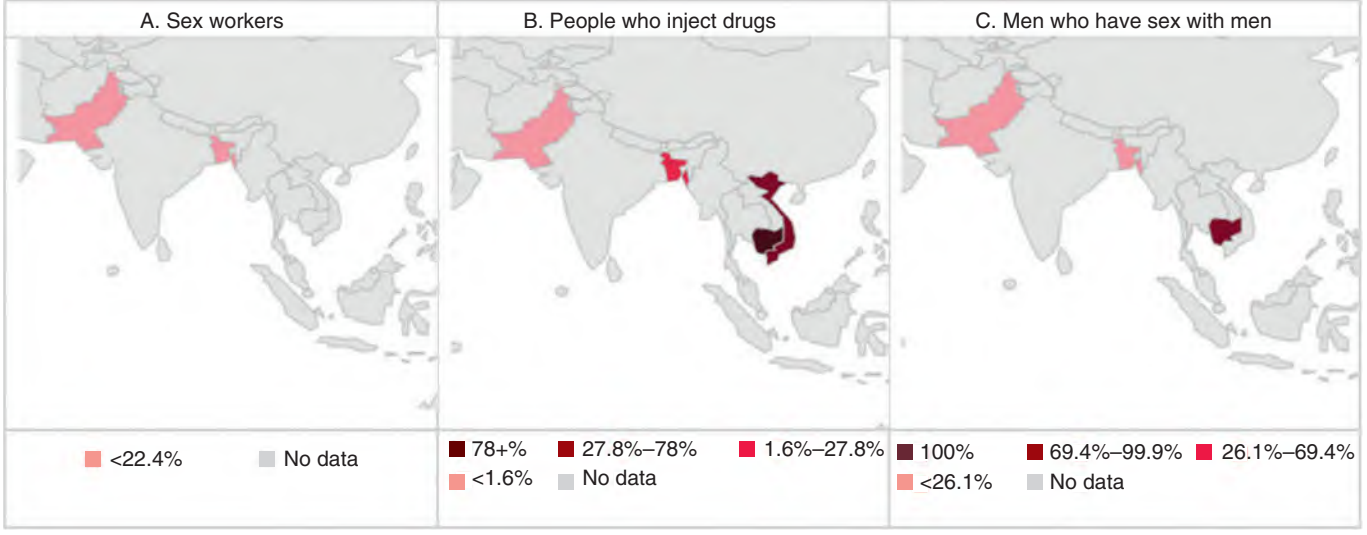

FIG. 118.6 Percentage of most at-risk populations in selected Asian countries reached by human immunodeficiency virus prevention programs, 2016. (A) Sex workers. (B) People who inject drugs. (C) Men who have sex with men. *(Data from UNAIDS. http://aidsinfo.unaids.org. Accessed February 6, 2018. Most recent data as of 2016.)*

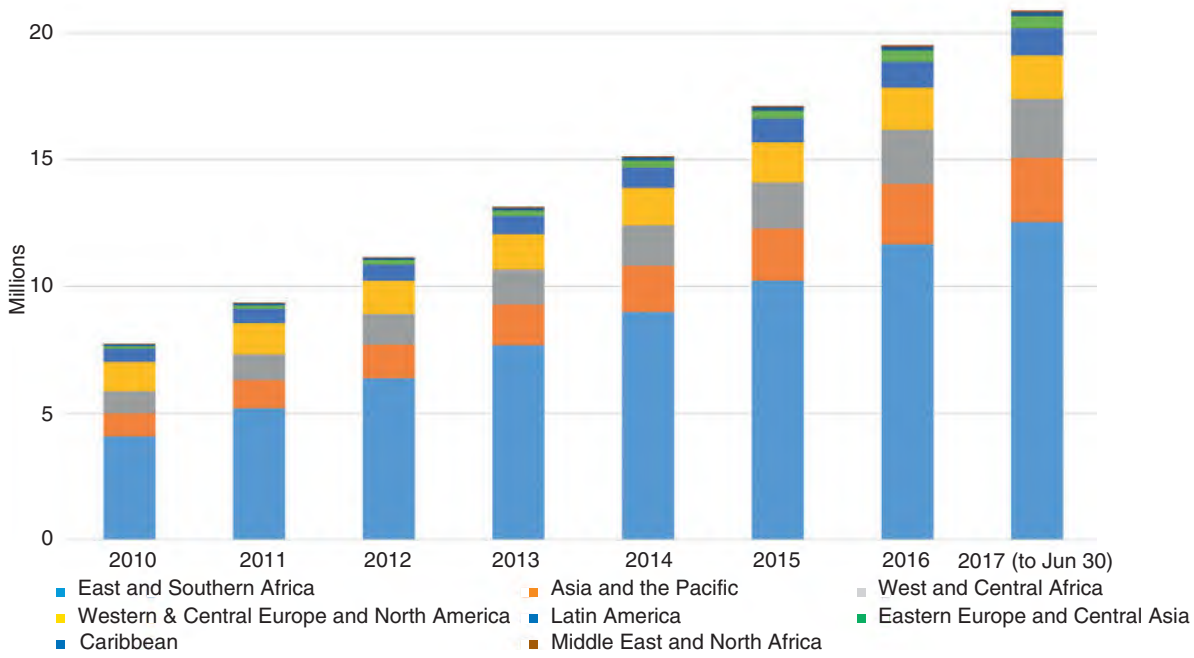

FIG. 118.7 Trends in the number of people identified as living with human immunodeficiency virus who are receiving antiretroviral therapy by region, 2010 through June 30, 2017. *(Data from UNAIDS. http://aidsinfo.unaids.org. Accessed February 26, 2018.)*

available resources and needs, and arguably the momentum to integrate human rights and social justice into the HIV/AIDS response is stalling in the context of a "shrinking civil society space."[220] Stigma, criminalization, and discrimination remain key nonmedical barriers that continue to drive new infections and hinder prompt testing and linkage to treatment.[221] Long-term strong leadership is needed to keep HIV prevention and treatment at the forefront of social policy and action, with scientific evidence and human rights as the basis for the response. This requires a broad-based coalition of people from civil society, business, faith-based organizations, and community groups and activists, and a stronger connection with other global health issues. Research and development for new prevention tools, including PrEP, and vaccines that can be made available and affordable across the world, need to be strengthened.

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