enzymatic activity of viral enzymes in the presence or absence of different concentrations of different drugs and have also been used to determine co-receptor tropism. These assays will generally detect quasispecies present at a frequency of ≥10%. NextGen sequencing may allow detection of quasispecies at frequencies down to 1%. It is generally recommended that resistance testing be used in selecting initial therapy in settings where the risk of transmission of resistant virus is high (such as the United States and Europe) and in determining new regimens for patients experiencing virologic failure while on therapy. Resistance testing may be of particular value in distinguishing drug-resistant virus from poor patient compliance. Due to the rapid rate at which drug-resistant viruses revert to wild-type, it is recommended that resistance testing performed in the setting of drug failure be carried out while the patient is still on the failing regimen. Measurement of plasma drug levels can also be used to tailor an individual treatment. The inhibitory quotient, defined as the trough blood level/IC_{50} of the patient's virus, is used by some to determine the adequacy of dosing of a given treatment regimen. Despite the best of efforts there will still be patients with ongoing high levels of HIV replication while receiving the best available therapy. These patients will receive benefit from remaining on antiretroviral therapy even though it is not fully suppressive.

In addition to the licensed medications discussed above, a large number of experimental agents are being evaluated as possible therapies for HIV infection. Therapeutic strategies are being developed to interfere with virtually every step of the replication cycle of the virus (Fig. 226-3). In addition, as more is discovered about the role of the immune system in controlling viral replication, additional strategies, generically referred to as "immune-based therapies," are being developed as a complement to antiviral therapy. Among the antiviral agents in early clinical trials are additional nucleoside and nucleotide analogues, protease inhibitors, fusion inhibitors, receptor and co-receptor antagonists, and integrase inhibitors as well as new antiviral strategies including antisense nucleic acids and maturation inhibitors. Among the immune-based therapies being evaluated are IFN-α, bone marrow transplantation, adoptive transfer of lymphocytes genetically modified to resist infection or enhance HIV-specific immunity, active immunotherapy with inactivated HIV or its components, IL-7, and IL-15.

HIV AND THE HEALTH CARE WORKER

Health care workers, especially those who deal with large numbers of HIV-infected patients, have a small but definite risk of becoming infected with HIV as a result of professional activities (see "Occupational Transmission of HIV: Health Care Workers, Laboratory Workers, and the Health Care Setting," above). The first case of HIV transmission from a patient to health care worker was reported in 1984. Occupational transmission of HIV has been reported in most countries; as noted above, the global number of HIV infections among health care workers attributable to punctures/cuts has been estimated to be 1000 cases (range, 200–5000) per year.

In the United States 57 health care workers for whom case investigations were completed as of 2010 had documented seroconversions to HIV following occupational exposures. The routes of exposure resulting in infection were as follows: 48 percutaneous (puncture/cut injury); 5 mucocutaneous (mucous membrane and/or skin); 2 both percutaneous and mucocutaneous; and 2 of unknown route. Of the 57 health care personnel, 49 were exposed to HIV-infected blood; 3 to concentrated virus in a laboratory; 1 to visibly bloody fluid; and 4 to an unspecified fluid. The individuals with documented seroconversions included 19 laboratory workers (16 of whom were clinical laboratory workers), 24 nurses, 6 physicians, 2 surgical technicians, 1 dialysis technician, 1 respiratory therapist, 1 health aide, 1 embalmer/morgue technician, and 2 housekeeper/maintenance workers. In addition, more than 140 possible cases of occupationally acquired HIV infection have been reported among health care personnel in the United States. The number of these workers who actually acquired their infection through occupational exposures is not known. Taken together, data from several large studies suggest that the risk of HIV infection following a percutaneous exposure to HIV-contaminated blood is ~0.3%, and after a mucous membrane exposure, ~0.09%. Although episodes of HIV transmission after nonintact skin exposure have been documented, the average risk for transmission by this route has not been precisely quantified but is estimated to be less than the risk for mucous membrane exposures. The risk for transmission after exposure to fluids or tissues other than HIV-infected blood also has not been quantified but is probably considerably lower than for blood exposures. A seroprevalence survey of 3420 orthopedic surgeons, 75% of whom practiced in an area with a relatively high prevalence of HIV infection and 39% of whom reported percutaneous exposure to patient blood, usually through an accident involving a suture needle, failed to reveal any cases of possible occupational infection, suggesting that the risk of infection with a suture needle may be considerably less than that with a blood-drawing (hollow-bore) needle.

Most cases of health care worker seroconversion occur as a result of needle-stick injuries. When one considers the circumstances that result in needle-stick injuries, it is immediately obvious that adhering to the standard guidelines for dealing with sharp objects would result in a significant decrease in this type of accident. In one study, 27% of needle-stick injuries resulted from improper disposal of the needle (over half of these were due to recapping the needle), 23% occurred during attempts to start an IV line, 22% occurred during blood drawing, 16% were associated with an IM or SC injection, and 12% were associated with giving an IV infusion.

Clinicians should consider potential occupational exposures to HIV as urgent medical concerns to ensure timely postexposure management and possible administration of postexposure antiretroviral prophylaxis (PEP). Recommendations regarding PEP must take into account that a variety of circumstances determine the risk of transmission of HIV following occupational exposure. In this regard, several factors have been associated with an increased risk for occupational transmission of HIV infection, including deep injury, the presence of visible blood on the instrument causing the exposure, injury with a device that had been placed in the vein or artery of the source patient, terminal illness in the source patient, and lack of postexposure cART in the exposed health care worker. Other important considerations when considering PEP in the health care worker include known or suspected pregnancy or breast-feeding, the possibility of exposure to drug-resistant virus, and toxicities of PEP regimens. Regardless of the decision to use PEP, the wound should be cleansed immediately and antiseptic applied. If a decision is made to offer PEP, U.S. Public Health Service guidelines recommend (1) a combination of two nucleoside analogue reverse transcriptase inhibitors given for 4 weeks for less severe exposures, or (2) a combination of two nucleoside analogue reverse transcriptase inhibitors plus a third drug given for 4 weeks for more severe exposures. Most clinicians administer the latter regimen in all cases in which a decision is made to treat. Detailed guidelines are available from the *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis* (CDC, 2005). The report emphasizes the importance of adherence to PEP when it is indicated, follow-up of exposed workers to improve PEP adherences, monitoring for adverse events (including seroconversion), and expert consultation in the management of exposures.

For consultation on the treatment of occupational exposures to HIV and other bloodborne pathogens, the clinician managing the exposed patient can call the National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline) at 888-448-4911. This service is available 24 hours a day at no charge. (Additional information on the Internet is available at *www.nccc.ucsf.edu.*) PEPline support may be especially useful in challenging situations, such as when drug-resistant HIV strains are suspected or the health care worker is pregnant.

Health care workers can minimize their risk of occupational HIV infection by following the CDC guidelines of July 1991, which include adherence to universal precautions, refraining from direct patient care if one has exudative lesions or weeping dermatitis, and disinfecting and sterilizing reusable devices employed in invasive procedures.