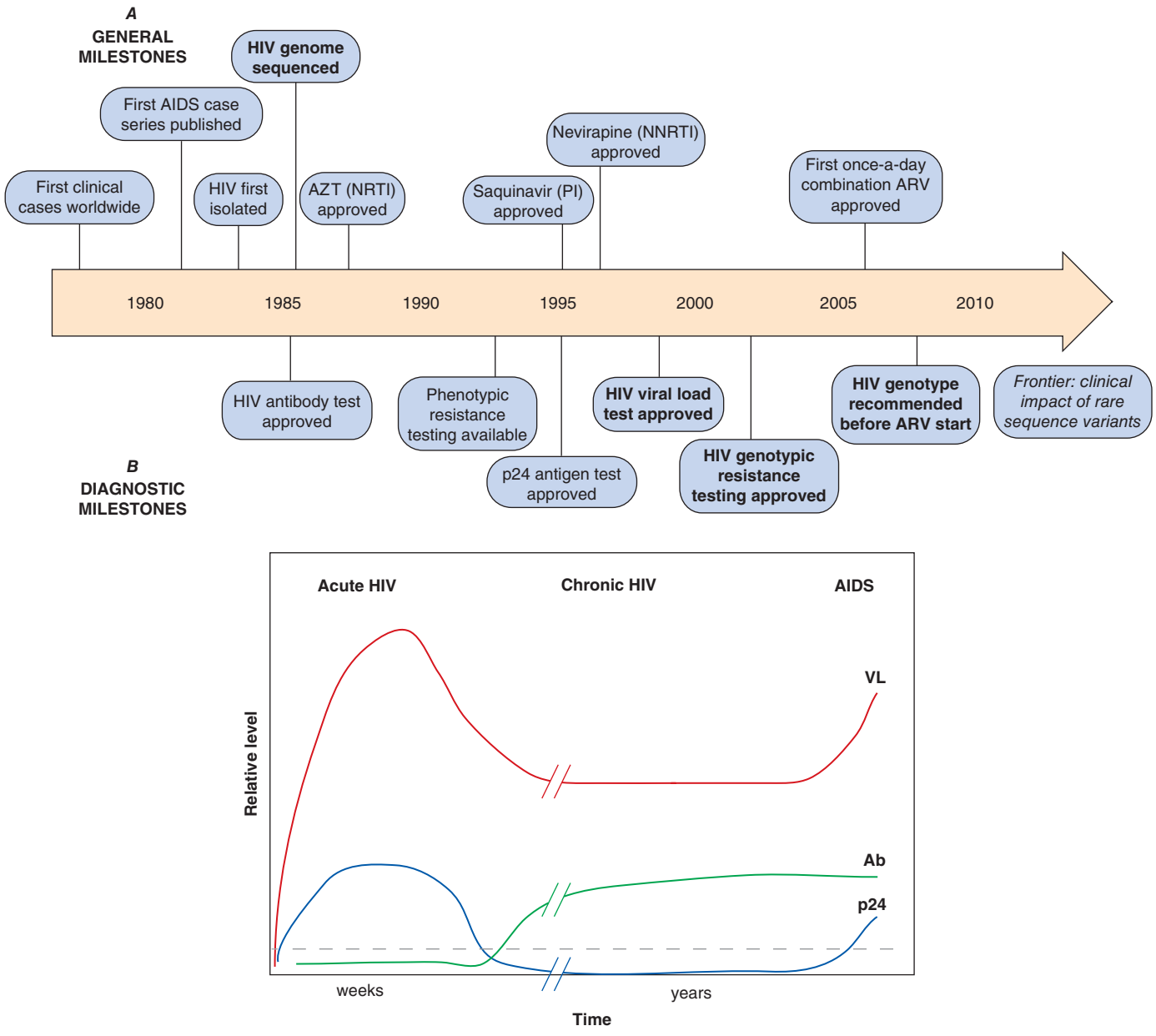

FIGURE 146-2 ***A.*** Timeline of select milestones in HIV management. Genomic advances are shown in bold type. The approvals and recommendations indicated apply to the United States. ARV, antiretroviral; AZT, zidovudine; NRTI, nucleoside reverse transcriptase (RT) inhibitor; NNRTI, non-nucleoside RT inhibitor; PI, protease inhibitor. ***B.*** Viral dynamics in the natural history of HIV infection. Three diagnostic markers are shown: HIV antibody (Ab), p24 antigen (p24), and viral load (VL). Dashed gray line represents limit of detection. *(Adapted from data in HH Fiebig et al: Dynamics of HIV viremia and antibody seroconversion in plasma donors: Implications for diagnosis and staging of primary HIV infection. AIDS 17:1871, 2003.)*

cases of severe illness. The importance of genomics in selecting loci for diagnostic assays and in monitoring test sensitivity was recently highlighted by the emergence in Sweden of a new variant of *C. trachomatis* containing a deletion that includes the gene targeted by a set of commercial NAATs. By evading detection through this deletion (which would have prompted the initiation of treatment), this strain came to be highly prevalent in some areas of Sweden. While nucleic acid–based tests remain the diagnostic approach of choice for fastidious bacteria, this example serves as a reminder of the need for careful development and ongoing monitoring of molecular diagnostics.

In contrast, for typical bacterial pathogens for which culture methods are well established, growth-based assays followed by biochemical tests still dominate in the clinical laboratory. Informed by decades of clinical microbiology, these tests have served clinicians well, yet the limitations of growth-based tests—in particular, the delays associated with waiting for growth—have left open opportunities for improvements. Molecular diagnostics, greatly informed by the vast quantity of microbial genome sequences generated in recent years, offers a way forward. First, sequencing studies may identify key genes (or noncoding nucleic acids) that can be developed into targets for clinical assays using PCR or hybridization platforms. Second, sequencing itself may eventually become inexpensive and rapid enough to be performed routinely on clinical specimens, with consequent unbiased detection of pathogens.

ORGANISM IDENTIFICATION

In order to adapt nucleic acid detection to diagnostic tests and thus to identify pathogens on a wide scale, sequences must be identified that are conserved enough within a species to identify the diversity of strains that may be encountered in various clinical settings, yet divergent enough to distinguish one species from another. Until recently, this problem has been solved for bacteria by targeting the element of a bacterial genome that is most highly conserved within a species: the 16S ribosomal RNA (rRNA) subunit. At present, 16S PCR amplification from