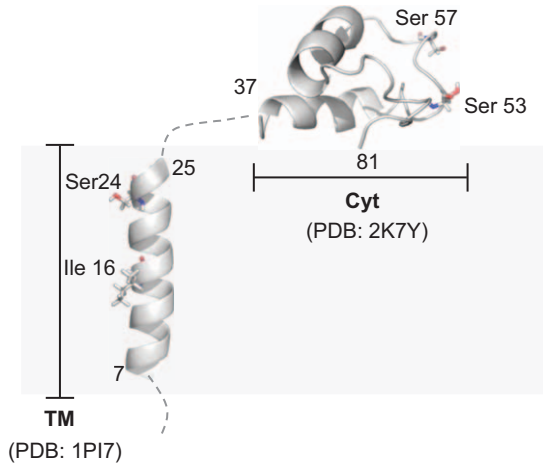

Figure 9.2 Structure of the HIV-1 Vpu channel. No structure for the complete Vpu protein is present on the PDB, yet multiple structures exist for peptides representing the Vpu *trans*-membrane (TM) domain, along with two structures for the cytosolic domain. The structure of the cytosolic domain is regulated by phosphorylation of two conserved serines, Ser53 and Ser57, while Ser23 has been shown to be essential for channel activity *in vitro* (Section 9.2.2.2). Ile16 is also believed to reside within the channel lumen (REF). Images generated in PyMol using available PDB structures.

component, yet plays a pivotal role in the release of infectious virions.[174–178] This function of the protein has been attributed in part to its ability to mediate membrane permeability and the observed channel activity of an N-terminal hydrophobic TM region in bilayers, which is sensitive to amilorides such as HMA [5-(*N*,*N*-hexamethylene)amiloride].[24–26,55,179–187] This viroporin activity of Vpu has been the subject of much research and has also been targeted by the Australian Biotech company Biotron, *via* a discovery programme which has culminated in one of the first clinical trial investigations of a viroporin-targeted small-molecule since rimantadine. The lead molecule, BIT225, displays activity in culture against HIV-1 infection of monocyte-derived macrophages, leading to the company to propose that it may further enhance HAART by targeting the long-lived macrophage virus reservoir.[86,181]

9.2.2.1 Vpu Forms an Amiloride-sensitive Channel Involved in HIV-1 Particle Production

Vpu was initially shown to mediate HIV-1 release from infected cells *via* mediating proteasomal CD4 degradation, thereby promoting trafficking of the gp120 envelope protein to the cell surface.[176,177] More recently, it was shown to ameliorate antiviral restriction conferred by the interferon-inducible factor