HIV LIFE CYCLE AND POTENTIAL TARGETS FOR DRUG ACTIVITY

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The major receptor that facilitates binding of HIV to human cells is the CD4 differentiation molecule. Table I shows the main cell types that bear CD4 or CD4-like molecules and are infected by HIV *in vivo*. Following HIV infection there is progressive depletion and/or dysfunction of CD4+ T lymphocytes that results in immunodeficiency. A viral surface glycoprotein known as gp120 binds to the CD4 molecule. On binding, a conformational change occurs in the gp120-CD4 complex that allows gp120 to interact with one or more cellular co-receptors. The gp120-co-receptor interaction triggers a further conformational change in gp41, another of the viral surface structures; hydrophobic portions of this molecule merge with the target cell membrane, inducing fusion between virus and cell.

TABLE I. MAJOR CELLULAR TARGETS FOR HIV IN VIVO

Biological process	Cell type
Attachment and/or antigen presentation	Follicular dendritic cells in lymphoid tissue M cells (Peyer's patches) Galactosylcerebroside+ cells (brain and GIT)
Infection	CD4+ T lymphocytes CD4+ monocytes and macrophages, including microglial cells CD4+ dendritic cells, including Langerhans cells

The mix of cell surface receptors and co-receptors, together with the structure of the gp120 molecule, largely determine HIV tropism for different cell types, cytolytic activity and transmissibility (Table II).

Fusion is followed by uncoating of the viral core, and deposition of the following core components into the host cell cytoplasm: viral RNA genome, reverse transcriptase (RT), integrase (IN), and virion regulatory proteins. RT begins assembling DNA copies (cDNA) of the HIV genome at a rate proportional to the activation state of the host cell. Since this is a reversal of the usual biological process – in which DNA is the template for RNA – it is described as reverse transcription. In activated cells, complete synthesis of cDNA occurs within 3 hours; in quiescent cells the process takes somewhat longer. cDNA enters the host cell nucleus as a large molecular complex comprising cDNA, RT and IN. Translocation depends upon specialised transportation molecules that are associated with pores in the nuclear membrane. The rate of nuclear translocation is also influenced by the activation state of the cell. Once inside the nucleus cDNA inserts into the host cell DNA at sites that are specially prepared by the action of IN.

Integrated cDNA is termed 'proviral DNA' and contains the blueprint for creating virus progeny. As the host cell moves through its growth cycle, proviral DNA is transcribed into messenger RNA which is exported into the cytoplasm. There mRNA is translated into new viral structural components, enzymes and genomic elements. Protease (PR) is an essential viral enzyme that is synthesised during this process.

Under the influence of PR, viral components associate with host cell membrane and then bud off as immature virions. PR activity continues after detachment from the host cell; the molecular changes that occur under the influence of

TABLE II. FACTORS AFFECTING HIV BEHAVIOUR

Dominant co-receptor use*	Major gp120 component	Cytopathic characteristic†	Transmissibility
CCR5	V3 loop	Non-syncitium-inducing	High‡
CXCR4	V3 loop	Syncitium-inducing	Low‡

* At least five other co-receptors have been identified; their role has not been fully elucidated.
† Syncitium-inducing virus generally replicates faster and is believed to be more pathogenic.
‡ Langerhans cells predominantly express CCR5 *in vivo*, explaining in part the preferential transmission of NSI virus.

this enzyme ensure maturation into a fully infectious virion.

The life-cycle of HIV presents a wide variety of potential targets for pharmacological intervention (Fig. 1). Those that are exploited by currently available antiretroviral agents are shown in Table III.

TABLE III. STAGES IN THE HIV LIFE CYCLE THAT ARE TARGETS FOR CURRENTLY AVAILABLE ANTIRETROVIRALS

Life cycle target	Antiretroviral class	Clinical status
Fusion between virus and host cell membranes	Fusion inhibitors	Significant efficacy
Reverse transcription	Reverse transcriptase inhibitors	Significant efficacy
Virus assembly and maturation	Protease inhibitors	Significant efficacy
Viral budding	Interferons	Low clinical efficacy

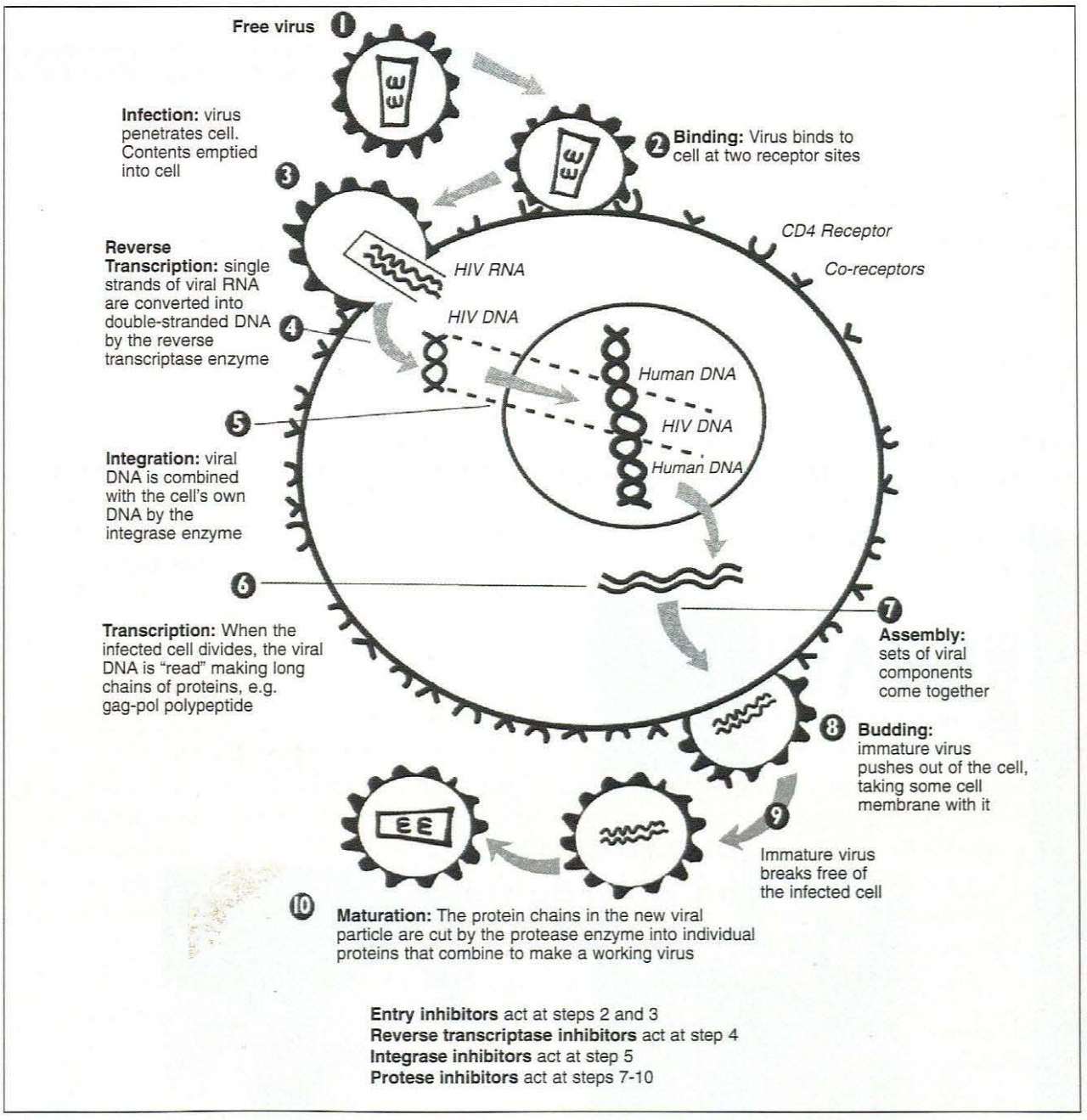

Fig. 1. Life cycle of HIV and targets for antiretroviral therapy. (Reproduced with permission from: S Miller, The Clinician's Guide to Antiretroviral Resistance, *2001.)*