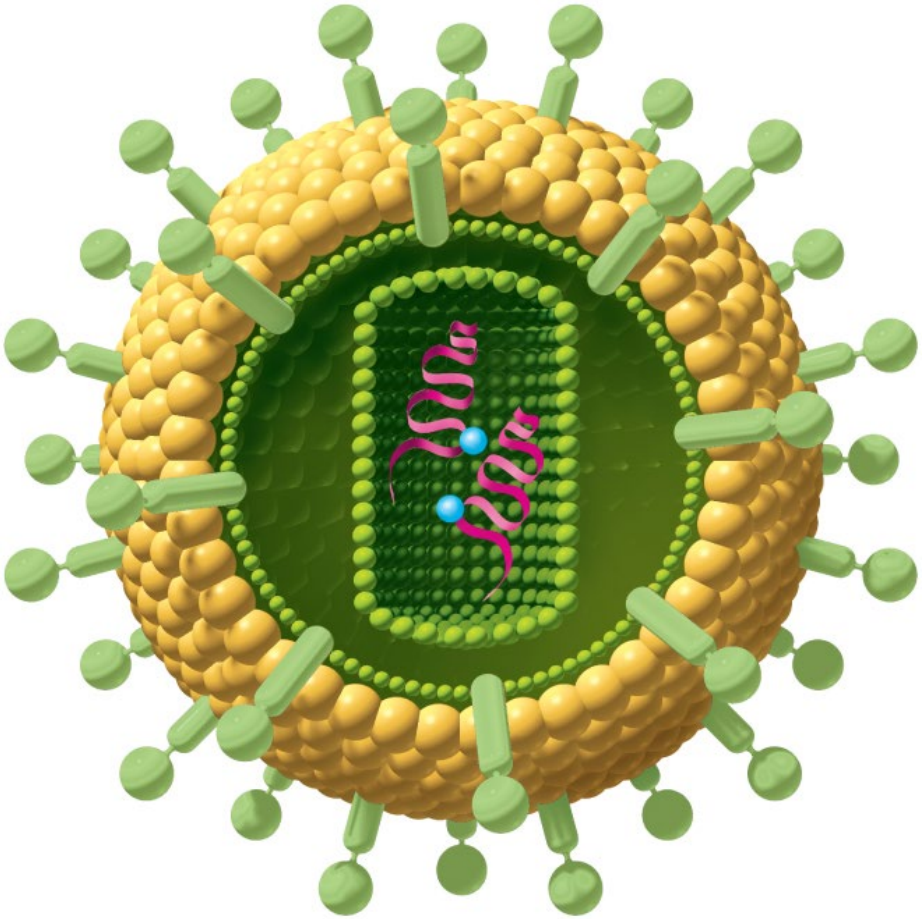
Chapter 21.9

Autoimmune and Immunodeficiency Diseases



Autoimmune Diseases

Autoimmune disease characterized by

- Failures of self-tolerance
- Immune system unable to recognize self-antigens
- Immune system produces **auto-antibodies**
- Auto-antibodies attack the host body's own tissues

Autoimmune Diseases

Reasons for lack of self-tolerance:

Cross-reactivity /// some antibodies against foreign antigens react to similar self-antigens /// rheumatic fever occurs because streptococcus antibodies react with host tissue of the heart valves

Abnormal exposure of self-antigens in the blood /// some of our native antigens are not exposed to blood // blood-testes barrier isolates sperm from blood

Changes in structure of self-antigens /// viruses and drugs may change the structure of self-antigens or cause the immune system to perceive them as foreign

Not all self-reactive cTcells eliminated in thymus during development /// these "bad" T cells are normally kept in check by the regulatory T (T_R) cells

Extreme Immunodeficiency Disease

Severe Combined Immunodeficiency Disease (SCID)

Genetic disease when immune system does not make both T cells and B cells

Now vulnerability to opportunistic infection and must live in protective enclosures

Immunodeficiency Diseases

Acquired Immunodeficiency Syndrome (AIDS)

Caused by the **human immunodeficiency virus (HIV)**

Nonhereditary diseases contracted after birth

Severely depress both cellular and humoral immunity

Also diminish some aspects of the second line of defense

Aids Associated Diseases (syndrome) // group of conditions that develop because of the original viral infection

Acquired Immunodeficiency Syndrome (AIDS)

HIV invades helper T cells // use macrophages and dendritic cells to internalize viruses using receptor mediated endocytosis

*R*everse *tr*anscriptase (*retro*virus) uses viral RNA as template to synthesize DNA

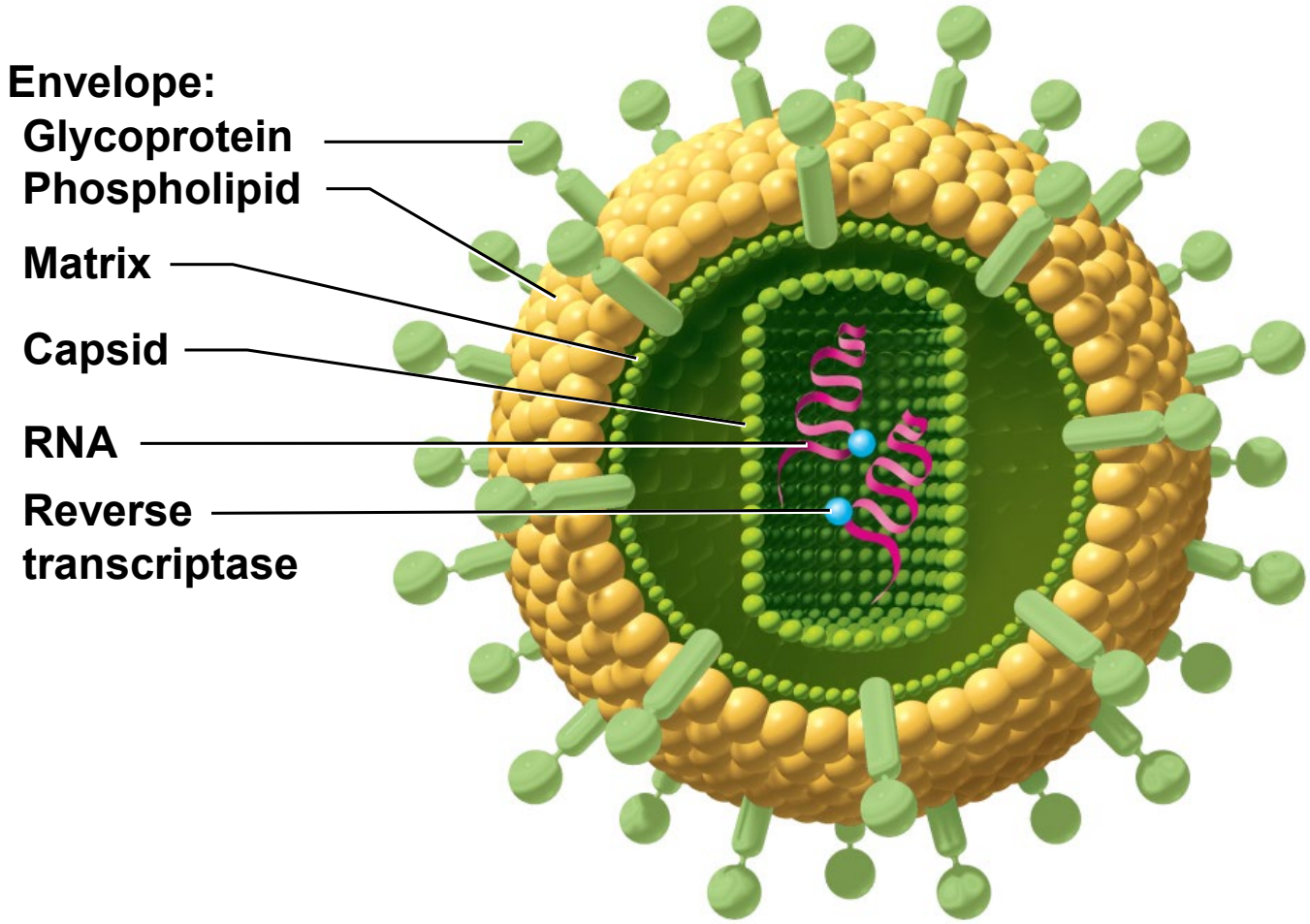
New DNA inserted into host cell DNA (may be dormant for months to years)

When activated, it induces the host cell to produce new viral RNA, capsid proteins, and matrix proteins

As virus are shed from host the virus are coated with bits of the host cell's plasma membrane

Adhere to new host cells and repeat the process

HIV Structure



AIDS – Eliminates hTcells

By destroying T_H cells, HIV strikes at the central coordinating agent of the specific defense sysem, humoral immunity, and cellular immunity // the virus (HIV) attacks the helper T cells

Incubation period ranges from several months to 12 years

Signs and symptoms

Early symptoms: flu like symptoms of chills and fever

Progresses to night sweats, fatigue, headache, extreme weight loss, lymphadenitis

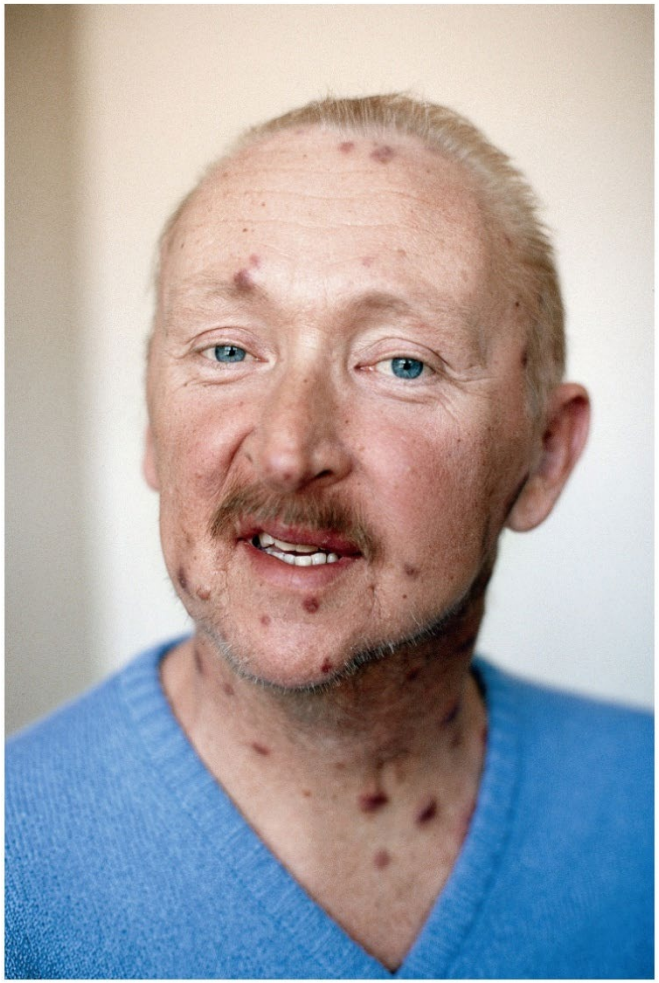
Normal T_H count is 600 to 1,200 cells/μL of blood, but in AIDS it is less than 200 cells/μL

Person susceptible to **opportunistic infections** (*Toxoplasma*, *Pneumocystis*, herpes simplex virus, cytomegalovirus, or tuberculosis)

Candida (thrush): white patches on mucous membranes

Kaposi sarcoma: cancer originates in endothelial cells of blood vessels causes purple lesions in skin

Kaposi Sarcoma



HIV Transmission

Through blood, semen, vaginal secretions, breast milk, or across the placenta

Most common means of transmission

Sexual intercourse (vaginal, anal, oral) // Contaminated blood products // contaminated needles

Not transmitted by casual contact

Undamaged latex condom is an effective barrier to HIV, especially with spermicide nonoxynol-9

Treatment Strategies

Prevent binding to CD4 proteins of T_H cells

Disrupt reverse transcriptase to inhibit assembly of new viruses or their release from host cells

Medications /// none can eliminate HIV, all have serious side-effects

HIV develops drug resistance /// medicines used in combination

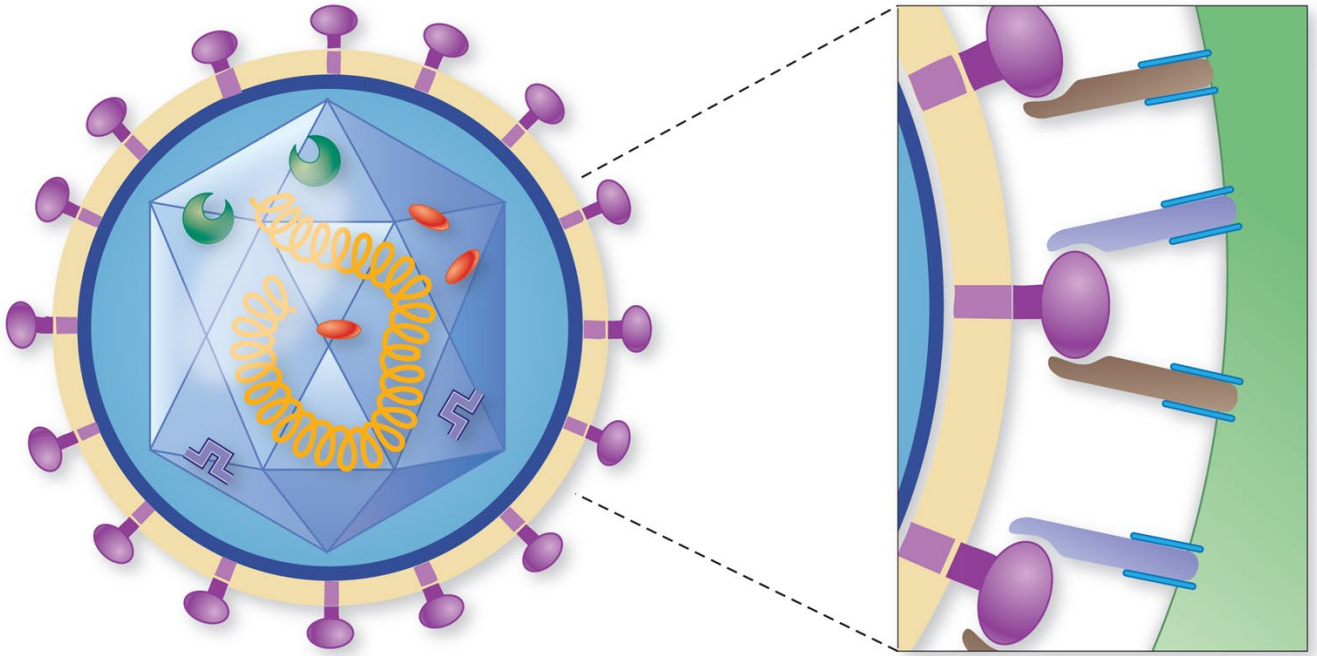
AZT (azidothymidine) /// first anti-HIV drug - inhibits reverse transcriptase

Protease inhibitors /// inhibit enzymes HIV needs to replicate

Now more than 24 anti-HIV drugs on the market

Review of HIV & AIDs

(This is Not on Exam)



Human Immunodeficiency Virus Infection (HIV) and AIDS // Signs and Symptoms

A spectrum of clinical signs and symptoms is associated with human immunodeficiency virus

Symptoms of HIV are directly tied to two things

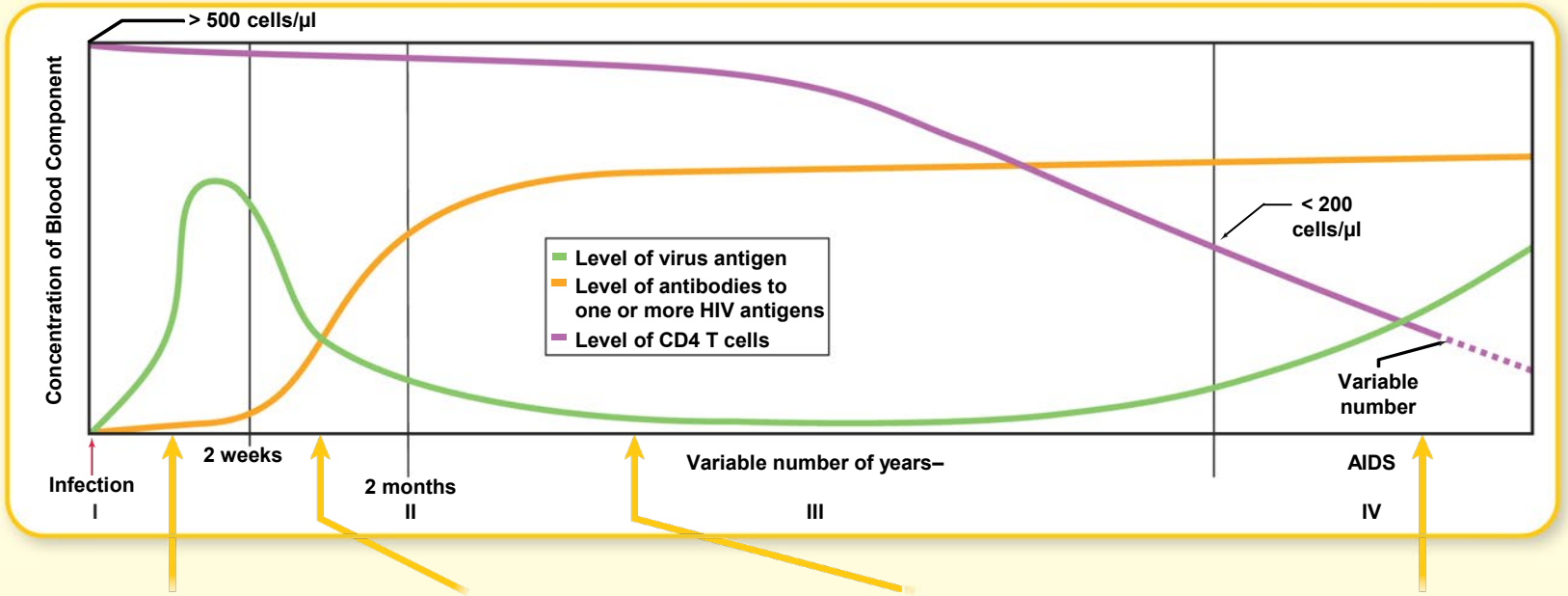
- the levels of virus in the blood
- the levels of T cells in the blood

Initial symptoms

- fatigue, diarrhea, weight loss, and neurological changes
- opportunistic infections or neoplasms (cancer)

Dynamics of Virus Antigen, Antibody, and T Cells in Circulation

Table 18.2



I	II	III	IV
Initial infection is often attended by vague, mononucleosis-like symptoms that soon disappear. This phase corresponds to the initial high levels of virus (the green line above). Antibodies are not yet abundant.	In the second phase, virus numbers in blood drop dramatically and antibody begins to appear. CD4 T cells begin to decrease in number.	A long period of mostly asymptomatic infection ensues. During this time, which can last from 2 to 15 years, lymphadenopathy may be the prominent symptom. During the mid- to late-asymptomatic period, the number of T cells in the blood is steadily decreasing. Once the T-cell level reaches a (low) threshold, the symptoms of AIDS ensue.	Once T cells drop below 200 cells/µl, AIDS results. Note that even though antibody levels remain high, virus levels in the blood begin to rise.

AIDS-defining illnesses (ADIs)

•Other disease-related symptoms appear to accompany severe immune deregulation, hormone imbalances, and metabolic disturbances

pronounced wasting of body mass: consequence of weight loss, diarrhea, and poor nutrient absorption

the virus is particularly hard on the GI tract

protracted fever, fatigue, sore throat, and night sweats

rash and generalized lymphadenopathy in several chains of lymph nodes

AIDS-Defining Illnesses

AIDS-Defining Illnesses

Skin and /or Mucous Membranes (includes eyes)	Nervous System	Cardiovascular and Lymphatic System or Multiple Organ Systems	Respiratory Tract	Gastrointestinal Tract	Genitourinary and/ or Reproductive Tract
Cytomegalovirus retinitis (with loss of vision)	Cryptococcosis, extrapulmonary	Coccidioidomycosis, disseminated or extrapulmonary	Candidiasis of trachea, bronchi, or lungs	Candidiasis of esophagus, GI tract	Invasive cervical carcinoma (HPV)
Herpes simplex chronic ulcers (>1 month duration)	HIV encephalopathy	Cytomegalovirus (other than liver, spleen, nodes)	Herpes simplex bronchitis or pneumonitis	Herpes simplex chronic ulcers (>1 month duration) or esophagitis	Herpes simplex chronic ulcers (>1 month duration)
Kaposi's sarcoma	Lymphoma; primarily in brain	Histoplasmosis	Mycobacterium avium complex	Isosporiasis, intestinal	
	Progressive multifocal leukoencephalopathy	Burkitt's lymphoma	Tuberculosis (Mycobacterium tuberculosis)	Cryptosporidiosis, chronic intestinal (>1 month duration)	
	Toxoplasmosis of the brain	Immunoblastic lymphoma	Pneumocystis jiroveci pneumonia		
		Mycobacterium kansasii, disseminated or extrapulmonary	Pneumonia, recurrent		
		Mycobacterium tuberculosis, disseminated or extrapulmonary			
		Salmonella septicemia, recurrent			
		Wasting syndrome			

Human Immunodeficiency Virus Infection (HIV) and AIDS // Signs and Symptoms

Some of the most virulent complications are neurological

lesions in the brain, meninges, spinal column, and peripheral nerves

patients with nervous system involvement show some degree of withdrawal, persistent memory loss, spasticity, sensory loss, and progressive AIDS dementia

HIV Infection and AIDS // Causative Agent

HIV is a retrovirus in the genus *Lentivirus*

- retroviruses have the potential to cause cancer
- produce dire, often fatal diseases
- capable of altering the host's DNA

Contain **reverse transcriptase (RT)**

- catalyzes the replication of double-stranded DNA from single-stranded RNA

Retroviruses can *permanently integrate viral genes into the host genome that is passed on to progeny cells*

HIV Infection and AIDS // Causative Agent

Some retroviruses transform cells (make them malignant) and regulate certain host genes

Enveloped RNA virus

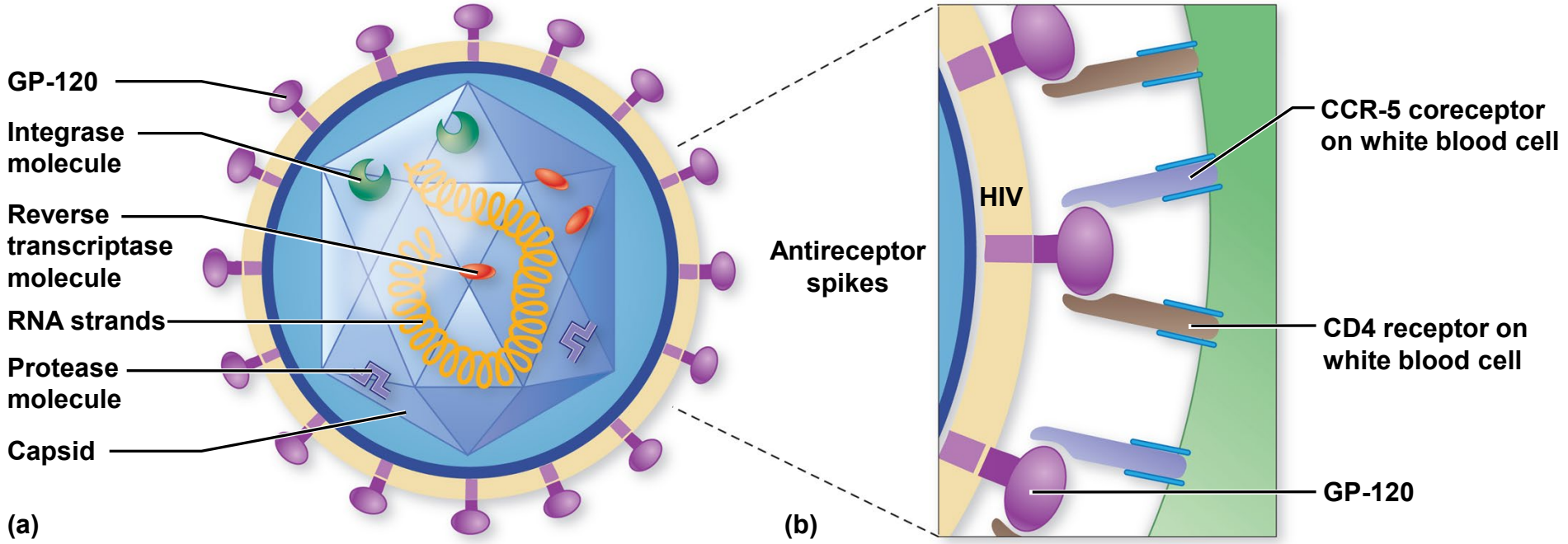
outermost layer is a lipid envelope

membrane glycoprotein spikes mediate viral adsorption to the host cell

can only infect host cells that display a combination receptor consisting of the CD4 marker plus the coreceptor CCR-5

virus uses these to gain entrance to several types of leukocytes and tissue cells

The General Structure of HIV



HIV Infection and AIDS // Pathogenesis and Virulence Factors

Viral life cycle

HIV enters a mucous membrane or the skin and travels to dendritic cells beneath the epithelium

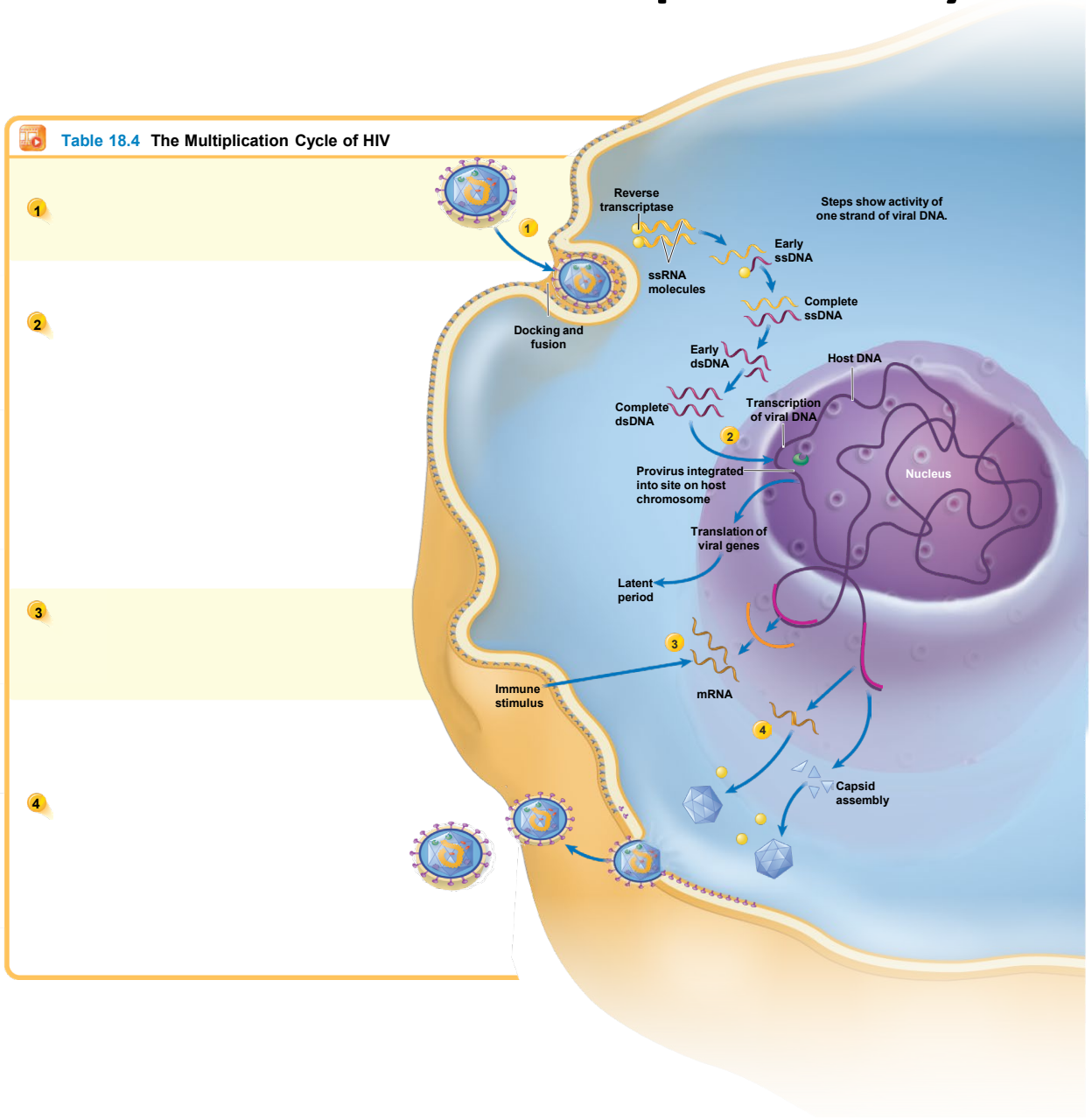
virus grows inside the dendritic cell and is shed without killing the cell

virus is amplified by macrophages in the skin, lymph organs, bone marrow, and blood

virus infects and destroys helper T4 and CD4 lymphocytes, monocytes, macrophages, and B lymphocytes

virus docks to host cell surface receptors and induces cell fusion, creating syncytia

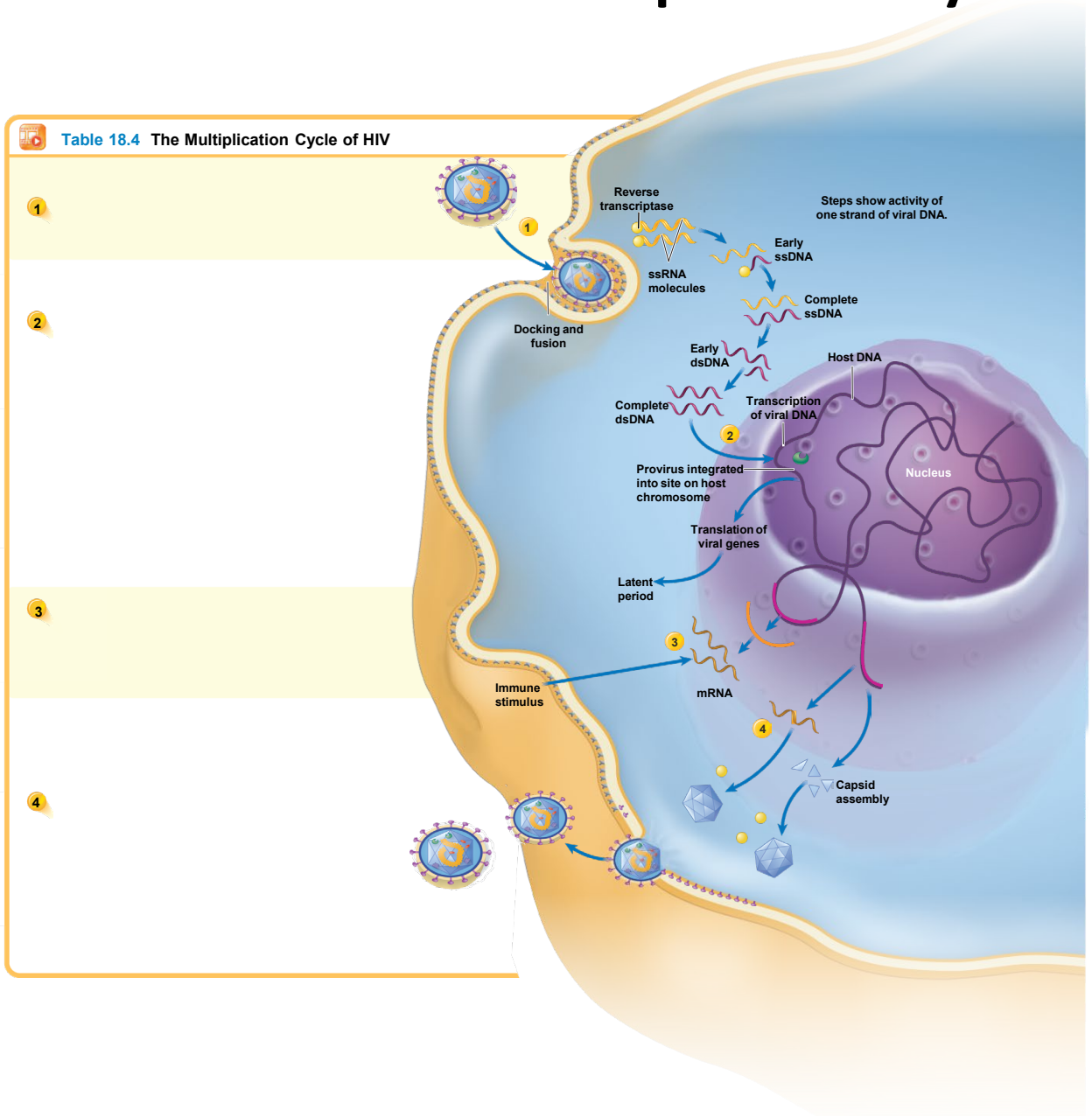
The Multiplication Cycle of HIV



#1

The virus adsorbs to receptors on the host cell, and is endocytosed. It then uncoats.

The Multiplication Cycle of HIV



#2

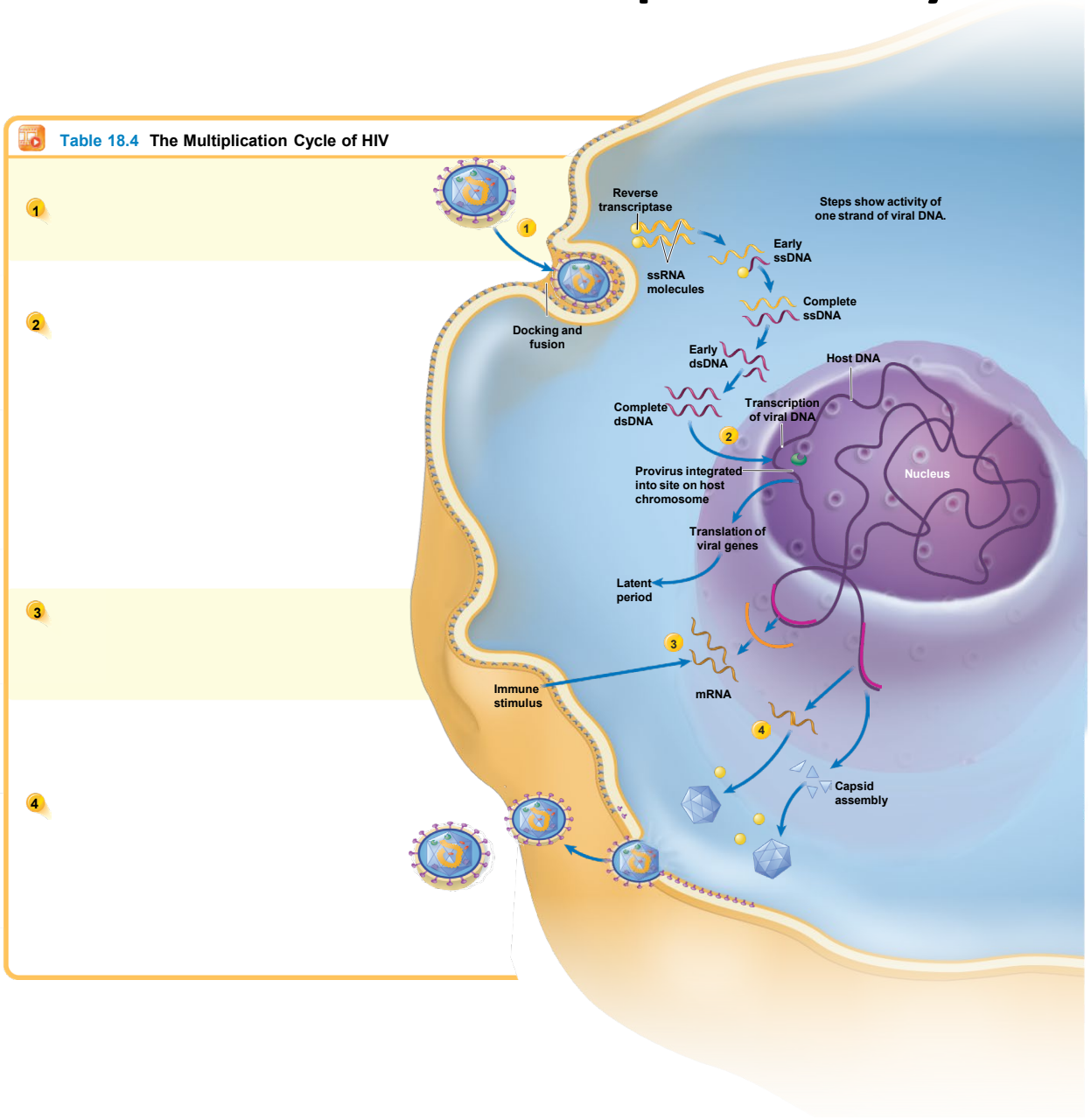
Once the virus is inside the cell, its reverse transcriptase makes its RNA into DNA. Reverse transcriptase catalyzes the synthesis of a single complementary strand of DNA (ssDNA).

This single strand serves as a template for synthesis of a double strand (ds) of DNA.

Although initially it can produce a lytic infection, in many cells it enters a latent period in the nucleus of the host cell and integrates its DNA into host DNA.

This latency accounts for the lengthy course of the disease.

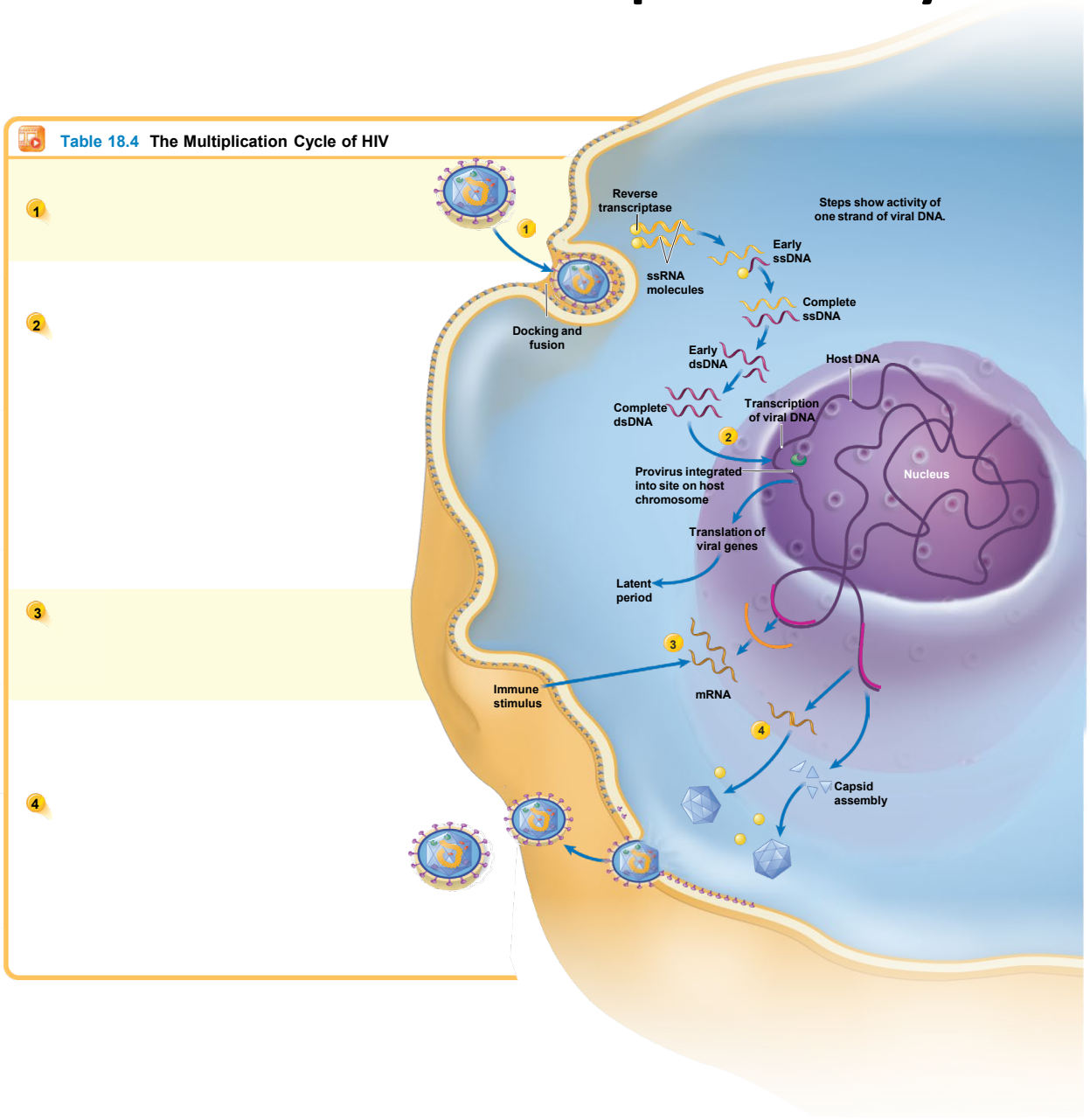
The Multiplication Cycle of HIV



#3

After a latent period, various immune activators stimulate the infected cell, causing reactivation of the provirus genes and production of viral mRNA.

The Multiplication Cycle of HIV



#4

HIV mRNA is translated by the cell's synthetic machinery into virus components (capsid, reverse transcriptase, spikes), and the viruses are assembled.

Budding of mature viruses lyses the infected cell.

HIV Infection and AIDS // Transmission

HIV is mainly transmitted through

- *sexual intercourse*
- *transfer of blood or blood products*
- *babies can be infected before or during birth, or through breastfeeding*

Mode of transmission

- similar to the hepatitis B virus, except HIV does not survive long outside the host and is more sensitive to disinfectants
- virus is not transmitted through saliva

HIV Infection and AIDS // Transmission

Health care workers *should be aware of the fluids they may come in contact with during childbirth or invasive procedures that can transmit the virus*

amniotic fluid

synovial fluid

spinal fluid

Semen and vaginal secretions harbor free virus and infected white blood cells // significant factors in sexual transmission

HIV Infection and AIDS // Transmission

Virus can be isolated from urine, tears, sweat,

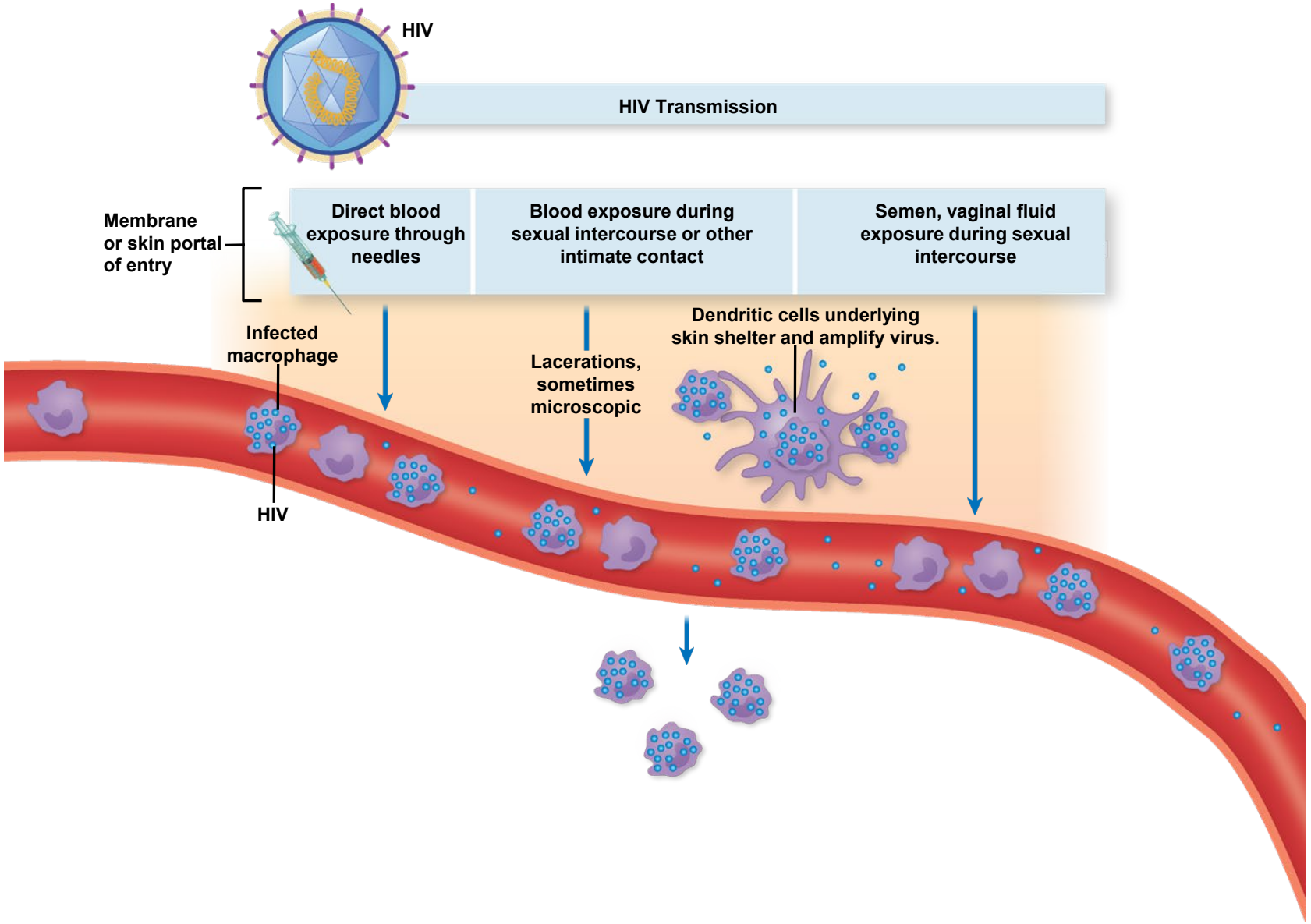
and saliva but ***not considered sources of infection***

Breast milk

contains significant numbers of leukocytes

neonates who have escaped infection prior to and during birth can still become infected through nursing

Primary Sources and Suggested Routes of Infection by HIV



HIV Infection and AIDS // Epidemiology

Since the beginning of the AIDS epidemic in the early 1980s, more than *25 million people have died Worldwide*

best global estimate of individuals infected is *33 million, with 1 million in the U.S.*

WHO estimates that 2.6 million new infections occurred in 2009, and a large number of these *people have not begun to show symptoms*

Due to global initiatives, more people in the developing world are receiving lifesaving treatments

the number of new infections is still growing faster than access to drugs

for every two people receiving treatment, five new people are diagnosed

HIV Infection and AIDS // Epidemiology

In most parts of the world, heterosexual intercourse is the primary mode of transmission

In the industrialized world, the overall rate of heterosexual infection has increased dramatically

highest rates are among adolescents and young adult women

in the U.S., about 31% of HIV infections arise from unprotected sexual intercourse with an infected partner of the opposite sex

HIV Infection and AIDS // Epidemiology

About 1% of people who are antibody positive

remain free of the AIDS

functioning immunity to the virus can develop

Non-progressor

any person who remains healthy despite HIV infection

some lack the cytokine receptors that HIV requires for entry

others are infected with a weakened mutant strain of the virus

HIV Infection and AIDS // Epidemiology

Treatment of HIV-infected mothers with a simple anti-HIV drug has dramatically reduced the rate of maternal-to-infant transmission of HIV during pregnancy

current treatment regimens result in a transmission rate of 11%

some studies with multidrug regimens claim transmission rates as low as 5%

evidence suggests that giving mothers protease inhibitors can reduce the transmission rate to around 1%

untreated mothers pass the virus to their babies at a rate of 33%

HIV Infection and AIDS // Culture and Diagnosis

A person is diagnosed as having an HIV infection if they have tested positive for the human immunodeficiency virus

this diagnosis is not the same as having AIDS

Most viral testing is based on detection of antibodies specific to the virus in serum and other fluids

ELISA: older screening method

latex agglutination and rapid antibody tests: newer methods

an at-home testing kit is also available

HIV Infection and AIDS // Culture and Diagnosis

These tests are largely accurate, but 1% of results are false positives

Western blot analysis is used to follow up

- detects several different anti-HIV antibodies
- can rule out false-positive results

False negative results

- can occur when testing is performed before the onset of detectable antibody production
- persons who are negative, but feel that they have been exposed, should be tested 3 – 6 months later

HIV Infection and AIDS // Culture and Diagnosis

Blood and blood products are sometimes tested for HIV antigens rather than HIV antibodies

- closes the window of time between infection and detectable levels of antibodies when contamination could be missed

In the U.S, diagnosis with AIDS requires // 1) testing positive for the virus and // 2) meeting one of the following criteria

- CD4 cells below 200 cells/microliter of blood
- CD4 cells account for fewer than 14% of lymphocytes
- experience one or more AIDS-defining illness

HIV Infection and AIDS // Prevention

Avoidance of sexual contact with infected persons

abstaining from sex is an obvious prevention method

sexually active individuals should consider that every partner is infected unless proven otherwise

barrier protection should be used when having sex with anyone whose HIV status is not known with certainty to be negative

HIV Infection and AIDS // Prevention

Avoiding intravenous drugs

risk decreased by not sharing needles or cleaning needles with a bleach solution

New research has shown that treating uninfected or newly-infected people with antiretrovirals can *prevent the progression to AIDS*

Problems with creating a vaccine

HIV is latent in cells

surface antigens mutate rapidly

not completely controlled by immune responses

research continues

HIV Infection and AIDS // Treatment

There is no cure for HIV

therapies only prolong life and diminish symptoms

As of mid-2011, only one person in the history of the epidemic had been declared cured of HIV after receiving a stem cell transplant

further research is needed

even if this is repeatable, it is not a practical approach for the millions who are infected

HIV Infection and AIDS // Treatment

Clear-cut guidelines that are updated regularly exist for treatment of people who test HIV positive

1 - treatment should begin soon after HIV diagnosis, *not after AIDS manifests*, as previously recommended

2 - HIV-positive individuals should receive a wide array of drugs to treat or prevent opportunistic infection in addition to antiviral chemotherapy

3 - treatment regimens vary according to each patient's profile and needs

HIV Infection and AIDS // Treatment

Highly active antiretroviral therapy (HAART)

regimen has proven to be highly effective in controlling AIDS and inevitable drug resistance

combines two reverse transcriptase inhibitors and one protease inhibitor in a "cocktail"

interrupts the virus at two different phases of its cycle

has been successful in reducing viral load to undetectable levels // facilitates the improvement of immune function

HIV Infection and AIDS // Treatment

HAART (cont'd)

reduced the incidence of viral drug resistance

has been successful in reducing viral load to undetectable levels

facilitates the improvement of immune function

reduced viral drug resistance because the virus would have to undergo three separate mutations simultaneously

patients who are HIV positive can remain healthy with this therapy

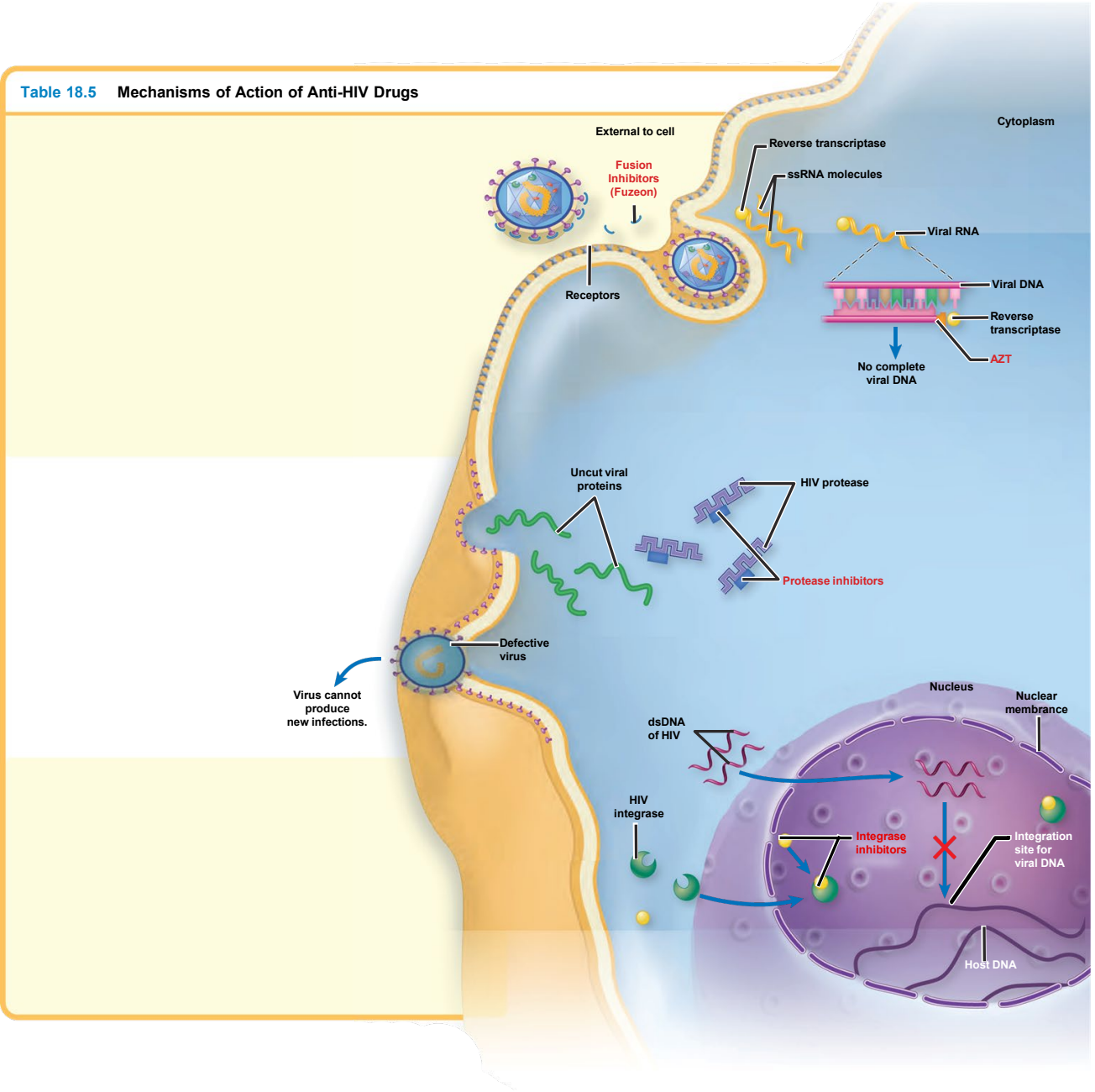
HIV Infection and AIDS // Treatment

Drawbacks of HAART

- high cost
- toxic side effects
- drug failure due to patient noncompliance
- inability to completely eradicate the virus

There is no cure for HIV, but there have been some promising advances

Mechanisms of Action of Anti-HIV Drugs



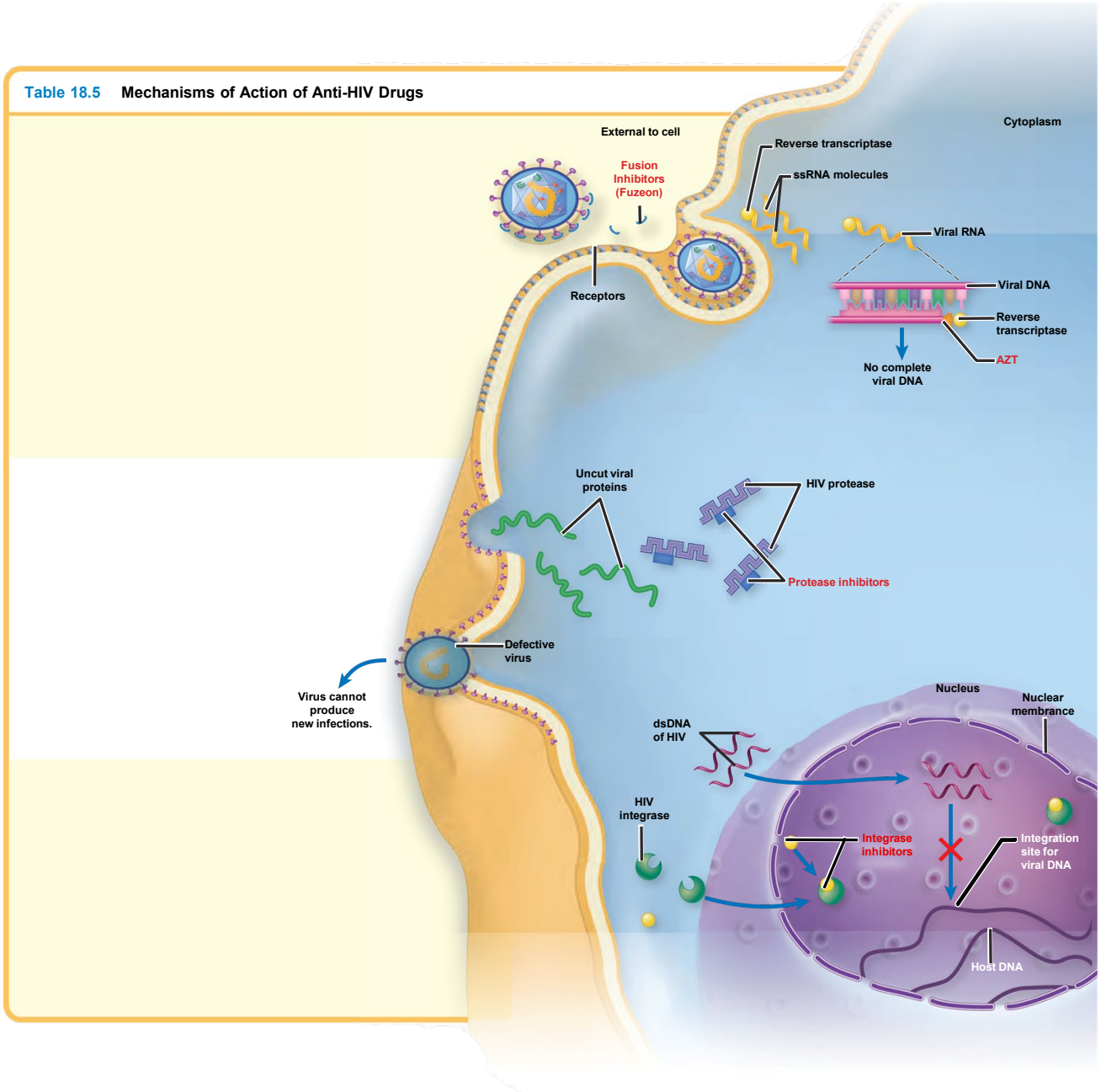
#1

The first effective drugs developed were the synthetic nucleoside analogs (reverse transcriptase inhibitors) azidothymidine (AZT), didanosine (ddI), lamivudine (Epivir) (3TC), and stavudine (d4T).

They interrupt the HIV multiplication cycle by mimicking the structure of actual nucleosides and being added to viral DNA by reverse transcriptase.

Because these drugs lack all of the correct binding sites for further DNA synthesis, viral replication and the viral cycle are terminated. Other reverse transcriptase inhibitors that are not nucleosides are nevirapine and efavirenz (Sustiva), both of which bind to the viral enzyme and restructure it.

Mechanisms of Action of Anti-HIV Drugs

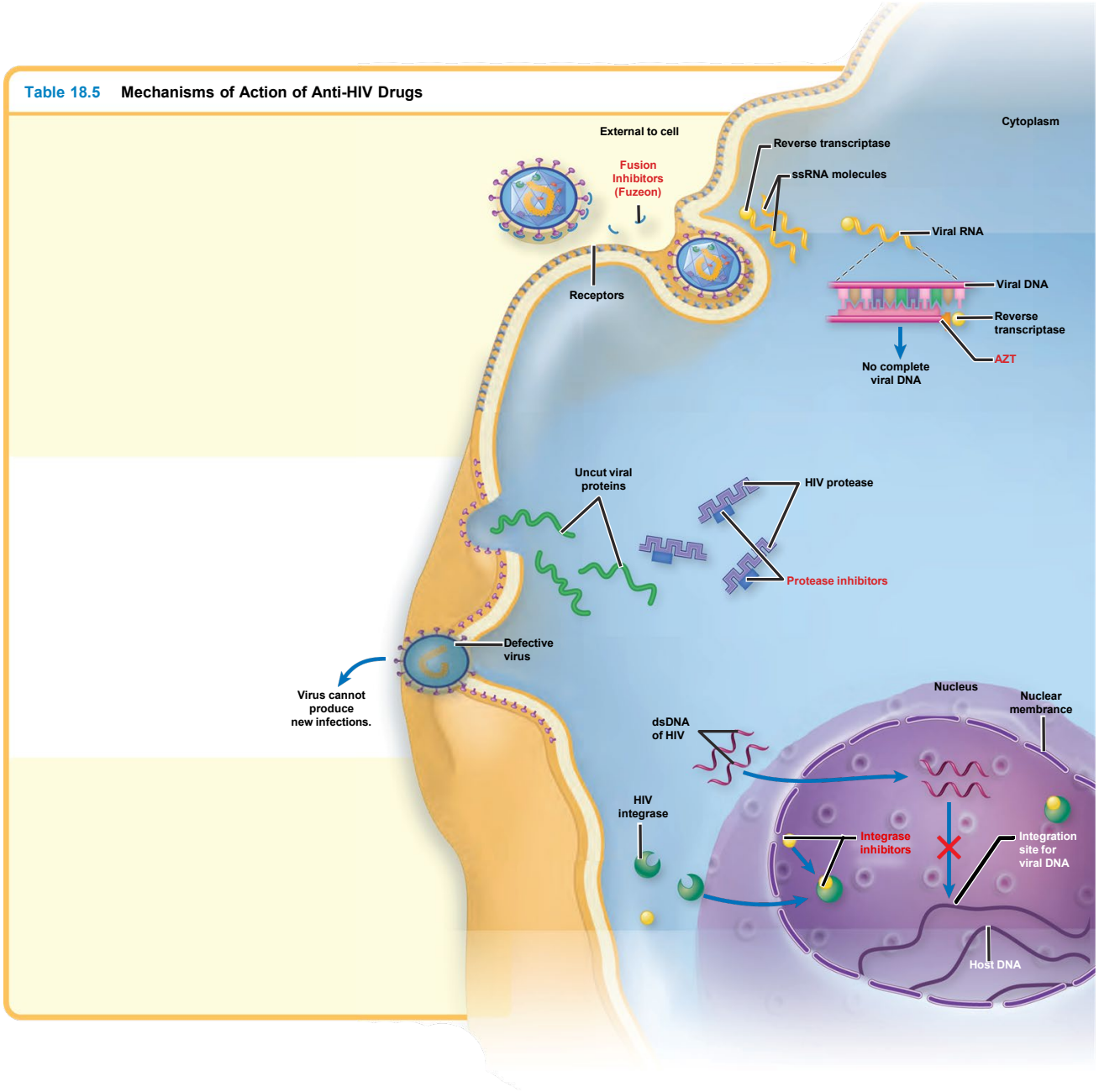


#2

Also seen here is one of the latest additions to the arsenal, enfuvirtide (Fuzeon), a drug classified as a fusion inhibitor.

It prevents the virus from fusing with the membrane of target cells, thereby stopping infection altogether.

Mechanisms of Action of Anti-HIV Drugs

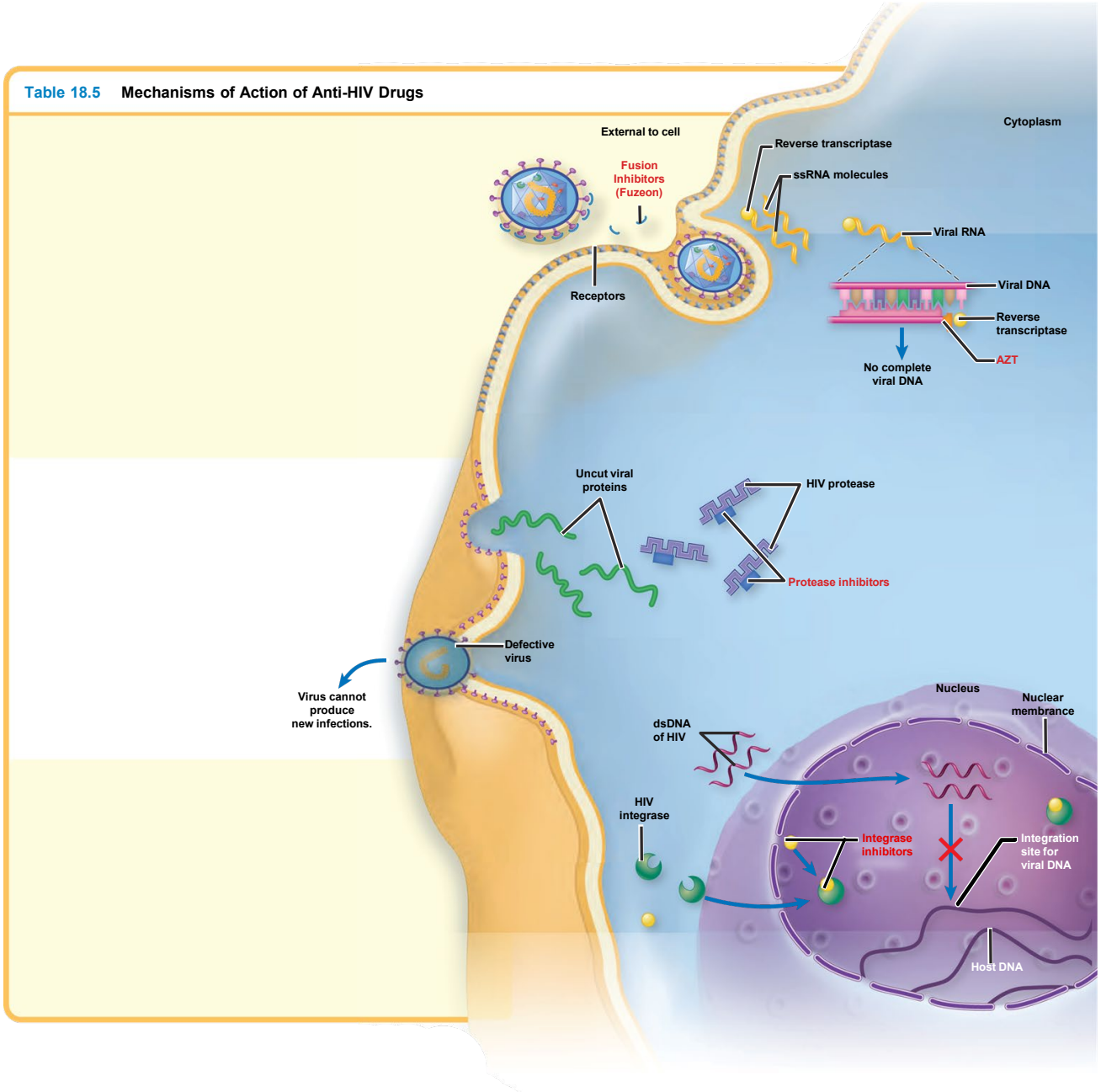


#3

Another important class of drugs is the protease inhibitors, which block the action of the HIV enzyme (protease) involved in the final assembly and maturation of the virus.

Examples of these drugs include indinavir (Crixivan), ritonavir (Norvir), and amprenavir (Agenerase).

Mechanisms of Action of Anti-HIV Drugs



#4

A class of drugs called integrase inhibitors provides a means to stop virus multiplication.

HIV Infection and AIDS

Causative Organism(s)	Human immunodeficiency virus 1 or 2
Most Common Modes of Transmission	Direct contact (sexual), parenteral (blood-borne), vertical (perinatal and via breast milk)
Virulence Factors	Attachment, syncytia formation, reverse transcriptase, high mutation rate
Culture / Diagnosis	Initial screening for antibody followed by Western blot confirmation of antibody
Prevention	Avoidance of contact with infected sex partner, contaminated blood, breast milk
Treatment	HAART (reverse transcriptase inhibitors plus protease inhibitors), Fuzeon, nonnucleoside RT inhibitors