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內文：

一、 INTRODUCTION

1 .After more than 30 years of battling a global epidemic human immunodeficiency virus (HIV) as the most challenging infectious disease.

2 discoveries about the virus, including its pathogenesis, transmission patterns and clinical course, have led to the development of potent antiretroviral drugs that offer great hopes in HIV treatment and prevention

3 Timely initiation of antiretroviral drugs, appropriate therapeutic regimens, pre and post-exposure prophylaxis contexts, treatment of comorbid conditions and addressing social and psychological factors involved in the care of individuals continue to be important considerations.

二、 THE ORIGIN OF HIV

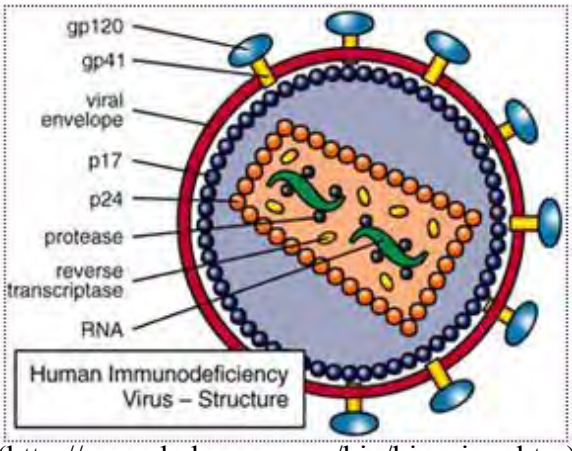
1. it is now widely accepted that HIV originated from cross species transmission of simian immunodeficiency viruses from the primates to human
2. Urbanization, spread of sexually transmitted diseases, poor infection control methods, development of a perfect environment for HIV and spread among many African nations many years before its original reports in the USA and Western Europe.

三、 GLOBAL EPIDEMIOLOGY

1. People living with the HIV or AIDS diagnoses is 34 million worldwide
2. 2.7 million new HIV infections in 2010, including 390 000 children, numbers that were 21% below the number of new infections at the peak of the epidemic in 1997
3. Coupled with the wider availability of antiretroviral (ARV or ART) therapies and intervention programs that have especially targeted maternal-child transmission, reduce new HIV infections, especially in Sub-Saharan Africa, South and South-East Asia, and in India.
4. the predominant HIV transmission mode is heterosexual
   (1) generalized epidemic pattern seen in many Sub-Saharan African countries
   (2) The at-risk populations include men who have sex with men, injecting drug users and sex workers and their sexual partners in the rest of the world

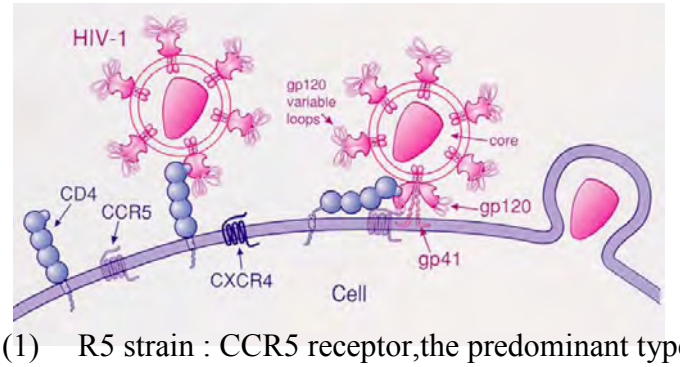
四. HIV STRUCTURE AND LIFE CYCLE

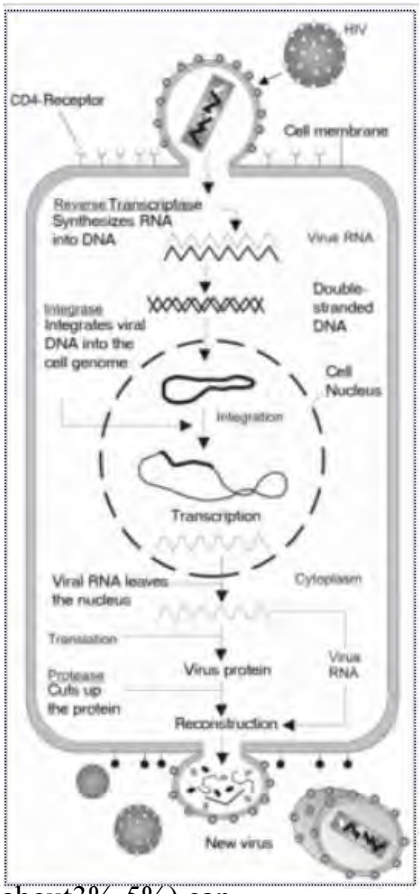
1. HIV structure



(http://www.helpcure.com/hiv/hiv-virus.htm)

2. The HIV genome consists of three structural and at least six regulatory genes
   (1) Env(viral envelope proteins gp 120 and gp 41)
   (2) Gag (matrix and core proteins p17 and p24)
   (3) Pol (protease, reverse transciptase and integrase)
   (4) The regulatory genes include Tat, Rev, Nef, Vif, Vpr, Vpx and Vpu.
3. HIV entry and life cycle





(1) R5 strain : CCR5 receptor,the predominant type of HIV in mucosal Transmissions
(2) X4 strain : CXCR4 coreceptor ,blood-borne transmissions
(3) genetically variable region of the gp120 (V3 region) plays an important role
(4) HIV may remain dormant for a long time inside the cell or begin its replication process by penetrating the host cell nucleus

五. HIV INFECTION AND HOST FACTORS

1. A small subset of ARV-untreated HIV-infected individuals (about3%-5%) can maintain normal CD4 cell counts for many years (long-term non-progressors), and an even smaller subset (1%) can maintain suppressed viral loads for years (elite controllers) without ART
2. Genetic variability : mutation in 32-base pair deletion in CCR5 receptor (CCR5-Δ32 allele) without the full coreceptor expression
3. viral strains, having protective HLA alleles (HLA -B27 and -B57), strong innate immune responses involving the natural killer cells and effective viral

restriction factors
(1) 'Apolipoprotein B or APOBEC 3G', responsible for newly synthesized viral DNA that functions in interrupting HIV replication.
(2) 'Tetherin", a membrane protein (CD317) can block the envelope protein release

六. MECHANISMS AND REGIMENS OF ANTI-RETROVIRAL DRUGS

1. Primary aim of anti-HIV treatment is to provide durable suppression of HIV replication to a level that is below the detection limits for plasma HIV quantification viral assays.
   (1) fewer drug-resistant viral variants,
   (2) prevents HIV transmission
2. commercially available ARV drugs (table1)
   (1) Nucleoside and nucleotide analog reverse transcriptase inhibitors (NRTI and NtRTI)
   (2) non-nucleoside reverse transcriptase inhibitors (NNRTI)
   (3) protease inhibitors (PI)
   (4) fusion inhibitors
   (5) integrase inhibitors (INSTI or integrase strand transfer inhibitors)
   (6) entry inhibitors that currently consist of CCR5 antagonists
   (7) combination agents.
3. recent recommended combination regimens (table2)
   (1) NNRTI-based regimen : NRTIs as the therapeutic backbone plus one NNRTI
   (2) PI-based regimen : a boosted PI
   (3) INSTI-based regimen: INSTI.
4. Virological failure in a patient can occur because of poor patient drug adherence, drug intolerance/toxicity or pre-existing (transmitted) drug resistance; it is more likely with higher HIV RNA levels and/or lower CD4 T-cell counts at baseline
   (1) HIV drug-resistance testing
   (2) the regimen should be changed as soon as possible to avoid progressive accumulation of resistance mutations

七. HIV DISEASE MANAGEMENT

1. Timing for initiating ARV treatment is as early as possible in the course of HIV infection and definitely before patient's CD4 count goes below 350 mm^{-3}
2. CD4 count and plasma HIV RNA (viral load) should be measured at baseline and every 3–4 months)
   (1). CD4 count values help guide ARV treatment initiation and prophylaxis for opportunistic infections
   (2) viral load is the most important indicator of response to ART

八. HIV PREVENTION STRATEGIES

1. Perinatal HIV transmission
   (1) Provision of lifelong ART for HIV-infected women who are in need of treatment (CD4 count <350 mm^{-3}) in order to protect their own health and also to prevent transmission to their child
   (2) Short-term combination ARV prophylaxis for HIV-infected women

who are not in need of treatment (CD4 count>350mm^{-3}) in order to prevent transmission of HIV to their child during pregnancy, delivery and breastfeeding

2. Male circumcision
Clinical trials in Kenya, South Africa and Uganda indicate that voluntary medical male circumcision reduces the risk of female-to-male sexual transmission by about 60%.

3. Treatment as prevention
ART not only averts AIDS-related complications and deaths by preventing HIV disease progression, also reduces the risk of HIV transmission by lowering individuals' viral loads

4. Universal HIV screening
(1) It can help with early identification and treatment of those infected and also because the newly diagnosed are less likely to engage in unprotected sex and with multiple partners
(2) In Kenya showed only 16% of HIV-infected adults knew that they were infected, while in the United States, this percentage is currently about 20%
(3) Because fear of social stigma is still a key prohibitive factor for universal HIV screening, home HIV testing is identified as a significant HIV prevention strategy for the next decade

5. Non-occupational post-exposure prophylaxis and pre-exposure prophylaxis
(1) Non-occupational post-exposure prophylaxis: 28-day course of ART as prophylaxis
(2) Pre-exposure prophylaxis: daily use of tenofovir/emtricitabine (Truvada)

九. NEW INTERVENTION STRATEGIES

1. Gene-based therapies
(1) Use of autologous transplantation of genetically modified CD4-positive T cells or even stem cells (CCR5-Δ32 allele)
(2) siRNAs, to interference with HIV replication

2. HIV receptor, coreceptor inhibition
CCR5 antagonist maraviroc has entered clinical use for blocking HIV entry in individuals who are primarily infected with the R5 strain

3. Elimination of the HIV reservoirs and chronic immune activation
(1) Interruption of treatment results in a rapid viral rebound even after long-term ART use, due to latently reservoir cell
-- Activate the latent cells and making them more sensitive to host immune mechanisms have included the use of cytokines like IL-2 and IL-7, raltegravir and CCR5 antagonists, all in addition to the use of ART
(2) Chronic HIV infection not only leads to progressive loss of CD4 T cells and their depletion, but also promotes thrombosis and other aging-related diseases
-- Gut-associated lymphoid tissue is a prime target of HIV and remains a chronically infected tissue and a main reservoir for the dormant T cells
-- Cox-2 inhibitors and the lipid-lowering agent atorvastatin in conjunction with ART

3. HIV vaccine

The extraordinary diversity of HIV-1, its capacity to evade host immune responses, a lack of broadly reactive antibody response in most infections, rapid mutations, and the early establishment of latent viral reservoirs have been major obstacles for those in search of an effective HIV vaccine

十.Summary

1. A major challenge in HIV eradication is the presence of HIV reservoirs that persist, despite effective treatments and optimal medication adherence and require lifelong treatment for those infected.
2. The current trends in developing new HIV treatment and prevention approaches continue, the global target of zero new infections may soon be realized.

Table 1 Major anti-retroviral drugs

	Drug class						
Properties	NRTIs/NtRTIs	NNRTIs	PIs	INSTIs	Fusion inhibitors	Entry inhibitors	Multiclass combinations
Main formulations	**Nucleoside analogs** AZT: zidovudine (*Retrovir*) ddI: didanosine (*Videx*) ddC: zalcitabine (*Hivid*) d4T: stavudine (*Zerit*) 3TC: lamivudine (*Epivir*) ABC: abacavir (*Ziagen*) FTC: emtricitabine (*Emtriva*) **Nucleotide Analogs** TDF: tenofovir (*Viread*) **Combinations** AZT/3TC (*Combivir*) ABC/3TC (*Epzicom*) AZT/ABC/3TC (*Trizivir*) TDF/FTC (*Truvada*)	**First generation** DLV: delavirdine (*Rescriptor*) EFV: efavirenz (*Sustiva*) NVP: nevirapine (*Viramune*) **Second generation** ETR: etravirine (*Intelence*) RPV: rilpivirine (*Edurant*) **In discovery/trial** Lersivirine (UK-453061)	**First generation** APV: amprenavir (*Agenerase*) SQV: saquinavir (*Invirase*) IDV: indinavir (*Crixivan*) FPV: fosamprenavir (*Lexiva*) RTV: ritonavir (*Norvir*) NFV: nelfinavir (*Viracept*) **First generation** TPV: tipranavir (*Aptivus*) DRV: darunavir (*Prezista*) ATZ: atazanavir (*Reyataz*) **Combination** Lopinavir/RTV (*Kaletra*) DRV/low dose RTV (boosted Prezista) ATZ/low dose RTV (boosted Reyataz)	RAL: Raltegravir (*Isentress*) EVG: Elvitegravir (*GS-9137) used only in combo in Stribild* **In discovery/trial** Dolutegravir (*SVGSK1349572*)	ENF: enfuvirtide (*Fuzeon*) **In discovery/trial** Ibalizumab (TMB-355)	Maraviroc (*Selzentri*) **In discovery/trial** Vicriviroc (SCH 417690) Cenicriviroc (TAK-652)	Emtricitabine/tenofovir/efavirenz (*Atripla*) Emtricitabine/tenofovir/rilpivirine (*Complera*) Emtricitabine/tenofovir/elvitegravir/cobicistat (*Stribild*)
Advantages	Easy dosing schedule Long half-life Little food effect Dual NRT established as backbone of combination Tx Fewer drug interactions	Low toxicity Impressive long-term results No food effects Less lipid abnormalities Saves PIs for future use	High genetic threshold Useful for treatment-experienced patients with NNRTI drug resistance	Useful for treatment-experienced patients with multiple drug resistance No food effects Fewer adverse effects and interactions	Useful for treatment-experienced patients with multiple drug resistance	Useful for adult patients infected with only CCR5-tropic HIV-1	Easy to use Recommended for treatment-naive patients
Disadvantages	Some members lead to serious side effects Potential for drug interactions, cross resistance, and transmission of resistance Screening for HLA-B*5701 required for abacavir	Low genetic barrier for mutation Cross resistance Potential for drug interactions	Complex food requirements Cross-resistance is common and have severe side effects CYP3A4 inhibitors and substrate Drug interaction Side effects	Lower genetic barrier for mutations than PIs	Effectiveness in treatment-naive patients still being studied	Not recommended in patients with dual/mixed or CXCR4-tropic HIV-1 Requires viral tropism assay Bronchitis Drug interactions	Rilpivirine has higher rate of virological failure if HIV-1 RNA >100 000 copies·mL^{-1}
Major side effects	Peripheral neuropathy Myopathy and myositis Cardiomyopathy Lactic acidosis Hepatic steatosis (adiposis) Lipodystrophy Pancreatitis Bone marrow suppression	Hepatic and renal toxicity Neuropsychiatric effects Drug–drug interactions Stevens–Johnson syndrome	Insulin resistance Dyslipidemia Hepatotoxicity Osteonecrosis and osteoporosis Drug–drug interactions Possible increased bleeding risk in hemophiliacs	Depression Suicidal tendencies Myopathy and rhabdomyolysis Reported Stevens–Johnson syndrome and toxic epidermal necrolysis	Risk of kidney dysfunction Injection-site reactions Hypersensitivity reaction Increased risk of bacterial pneumonia	Heaptotoxicity Cardiovascular events Bladder irritation Upper respiratory tract infection	Hepatic and renal toxicity Lactic acidosis With HBV co-infection, discontinuation can lead to severe acute HB exacerbations Neuropsychiatric effects Major drug interactions

Table1 continue

Properties	Drug class						
	NRTIs/NtRTIs	NNRTIs	PIs	INSTIs	Fusion inhibitors	Entry inhibitors	Multiclass combinations
Common side effects	Nausea, vomiting, abdominal pain, diarrhea, loss of appetite, lethargy, muscle weakness, insomnia, headache, dizziness	Nausea, vomiting, diarrhea, insomnia, unusual or vivid dreams, dizziness, rash	Nausea, vomiting, diarrhea, rash, headache	Nausea, diarrhea, fever, headache	Fatigue, numbness in feet or legs, dizziness, insomnia	Nausea, cough, fever, dizziness, headache, bloating and distention	Diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams and rash

Table 2 Initial combination regimens for the antiretroviral naive patient

Regimens	Chemical names	Common trade names
Preferred regimen		
NNRTI-based regimens		
NRTI/NRTI/ NNRTI	tenofovir/emtrcitabine/efavirenz	Atripla
PI-based regimens		
NRTI/NRTI + boosted PI	tenofovir/emtrcitabine + ritonavir/atazavir	Truvada + Boosted Reyetaz
NRTI/NRTI + boosted PI	tenofovir/emtrcitabine + ritonavir/darunavir	Truvada + Boosted Prezista
INSTI-based regimen		
NRTI/NRTI + INSTI	tenofovir/emtrcitabine + raltegravir	Truvada + Isentress
Alternative regimen		
NNRTI-based regimens		
NRTI/NRTI + NNRTI	emtricitabine/tenofovir/rilpivirine	Complera
	abacavir/lamivudine + efavirenz	Epzicom + Sustiva
	abacavir/lamivudine + rilpivirine	Epzicom + Edurant
PI-basedrRegimens		
NRTI/NRTI + boosted PI	abacavir/lamivudine + ritonavir/atazavir	Epzicom + Boosted Reyetaz
	abacavir/lamivudine + ritonavir/darunavir	Epzicom + Boosted Prezista
	abacavir/lamivudine or tenofovir/emtrcitabine + ritonavir/fosamprenavir	Epzicom or Truvada + Boosted Lexiva
	abacavir/lamivudine or tenofovir/emtrcitabine + ritonavir/loprinavir	Epzicom or Truvada + Kaltetra
INSTI-based regimen		
NRTI/NRTI + INSTI	abacavir/lamivudine + raltegravir	Epzicom + Isentress
	tenofovir/emtrcitabine/cobistat/elvitegravir	Stribid

NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside analog reverse transcriptase inhibitors; NtRTIs, nucleotide analog reverse transcriptase inhibitors; PI, protease inhibitors.

題號	題目
1	下列關於 HIV 的傳染途徑何者為非? (A) Sexual contact (B) Parenteral exposure to blood (C) Mother to fetus (D) salvia
答案 (D)	出處：oral and maxillofacial pathology (2th edition)