Medical treatment

HIV/AIDS

Mari Kajiwara
Physician
Osaka seamen's insurance hospital

[Introduction]

Global spread of the infection of HIV (human immunodeficiency virus: Human immunodeficiency virus) has been an issue.

Since the first report of HIV virus infection in early 1980s, as of the end of 2010, the total number of people positive for HIV infection was estimated to be 34 million. Compared to 2001, it was 17% increase. The number of new patients in 2010 was estimated to be 2.7 million in the world. The positive rate in Asian countries is still much lower compared to other regions. However, due to large population in the region, the number of people positive for HIV is the second largest in the world.1)

In Japan, from late 1970s through 1980s, we have experienced HIV infections mainly due to the use of contaminated blood coagulation products (non-heated products) in patients with hemophilia. This is called as "Yakugai AIDS (AIDS caused by HIV contaminated blood products)" and received so much social attention. In recent years, the number of Japanese homosexual male positive for HIV has been increasing in an accelerated manner.

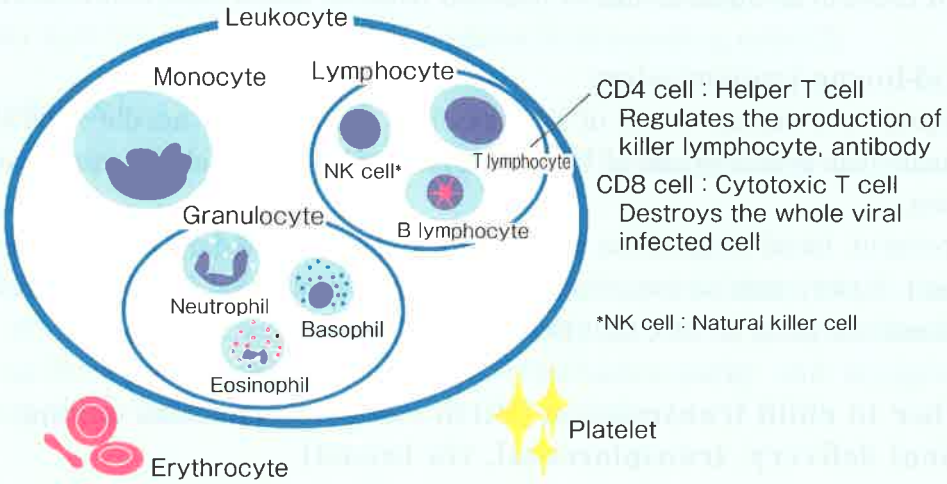
[What is HIV/AIDS?]

(1) What is HIV?

HIV is the abbreviation of Human Immunodeficiency Virus, which belongs to Retroviridae, mainly targets white blood cells called lymphocytes (CD4 positive cells), resulting in infection.

Blood cells are consisted of white blood cells, red blood cells and platelets. CD4 positive lymphocytes among white blood cells control the immune system that protects our body (Figure 1). HIV invades into and infects this CD4 positive lymphocyte and starts to replicate within the cell. Newly replicated HIV destroys

Fig.1 Celles in Blood



the original CD4 positive lymphocytes and is disseminated outside of the cell. Newly replicated HIV, then, infect other uninfected CD4 positive lymphocytes. As a result, infected lymphocytes loaded with replicated HIV are forced to death. The number of CD4 positive lymphocytes is usually approximately 700-1,300 per 1 μL of blood. Although it depends on the number of HIV virus (HIV viral load), the number of CD4 positive lymphocytes in patients infected by HIV is reduced approximately 55-60 per 1 μL in a year. In the end, the immunity that protects our body from various diseases gradually declines and results in the manifestation of AIDS.

(2) What is AIDS?

HIV infection does not mean AIDS. AIDS is the Abbreviation of Acquired Immunodeficiency Disease and is a condition of immunodeficiency due to the progression of HIV infection. In other words, it is a syndrome manifesting various complications as HIV patients infected with bacteria and/or viruses and protozoas and so on that are not usually pathogenic to healthy people due to the aforementioned condition.

[Transmission]

There are three main routes of HIV infection described below.

(1) Sexual transmission (both hetero- and homo-sexual):

HIV is in a high amount present in the body fluid such as blood, semen,

vaginal secretion. Contact to mucosal surface (oral cavity, urinary tract, vagina, penis and rectum) or injured sites of infected patients may result in infection.

(2) Blood-borne transmission:

Inappropriate repeated use of syringes like drug abuse , needle stick injuries of healthcare workers and use of HIV contaminated blood products may also result in infection.

At present, blood coagulation products are treated by heat and there is no risk of infection. Strict examination is conducted to donated blood. However, we cannot say one hundred persent sure that that there is no infection at all.

(3) Mother to child transmission (Birth canal tansmission during vaginal delivery, transplacental, via breast)

In Japan, even in case where pregnant women are positive for HIV infection, the infection rate of children is less than 1% by taking appropriate preventive interventions such as use of HIV therapeutic agents and prohibition of breast-feeding.

(4) Precautions on daily life

HIV infection is established when the body fluid containing the large amount of viruses enters into the blood through mucosa or injured skin. However, simple contact with sweat, tear, saliva, urine or feces does not result in infection. HIV can only reside within the cells of our body and continue to survive. Once discharged to the outside of our body, in the air or water, it loses contagiousness. Therefore, we do not get infected with HIV in normal life (holding on to a strap or bar in a train, going to a public bath, sharing a cup with others and getting a mosquito bite, etc.)

[Epidemiology]

As described above, the number of HIV infection in Japanese male homosexual has been rapidly increased in recent years. On the other hand, the numbers of infection due to intravenous drug abuse and mother to child transmission tend to be smaller.

The number of new HIV patients reported in 2010 was 1075. Among them, Japanese nationality were 997 and male subjects were 956. Thus, the majority was male.

The numbers of new HIV patients in 2010 by infection route were 195 (18.1%) in hetero-sexual intercourse and 744 (69.2%) in homosexual intercourse. Thus, the

total sexual intercourse was 939 (87.3%). The top 10 prefectures reported new patients in that year were Tokyo, Osaka, Aichi, Kanagawa, Chiba, Fukuoka, Shizuoka and Hyogo, Saitama, and Hiroshima in descending order.2)

[Symptoms]

When infected with HIV and not treated, the following course is in the below.

(1) Acute retroviral illness (Acute phase)

After the initial infection, HIV rapidly replicates within lymph tissues. 2-6 weeks after the initial infection, approximately 50-90% of patients demonstrate influenza-like fever, pharyngitis, fatigue, lymphadenopathy and myalgia. These signs disappear within a few weeks.

(2) Asymptomatic HIV infection

Even after the disappearance of acute symptoms, virus continues to replicate at exponential speed. It is the status that viruses with replication potential are equated with the immune trying to suppress such viruses. It was believed that this condition may last 10 years on the average. However, some recent reports mention that this period has been shortened.

Despite asymptomatic condition during this period, approximately 10 billion viruses are replicated every day and lymphocytes are infected one after another and destroyed.

(3) Symptomatic HIV infection (AIDS clinical phase)

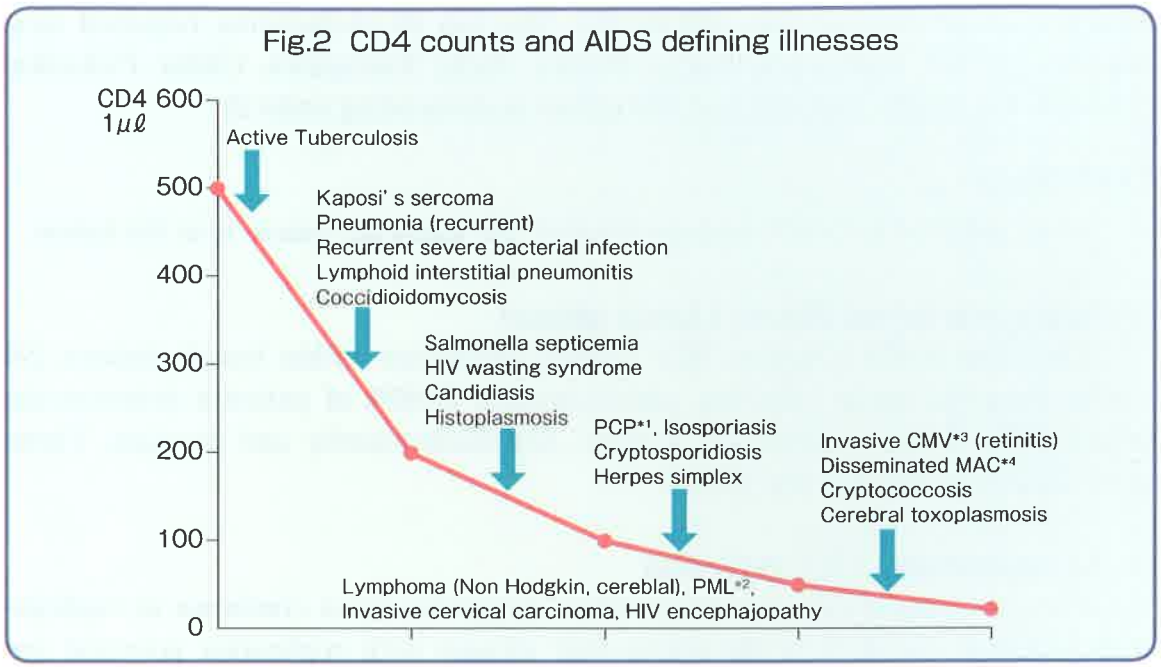
The balance between virus replication and human immune reactions can no longer be maintained. Viral load in the blood (amount of HIV RNA) is increased, followed by immunodeficiency status. Infected individuals manifest AIDS and in case of no treatment, the length of time between the manifestation of AIDS and death is considered to be about 2 years.

AIDS defining illnesses induced by the reduction of CD4 positive lymphocytes is presented in Figure 2. This is called as "opportunistic infection" and is the infection that appears when the immunity is declined.

[Diagnosis]

(1) When do we need to examine HIV infection?

In addition to the above AIDS defining illnesses, individuals who are patients of or fall under the following should receive the HIV examination: recurrent herpes zoster, unknown fever, intractable stomatitis, sexually transmitted infection



(syphilis, chlamydial infection, gonorrheal infection, condyloma acuminatum, genital herpes, amebic dysentery, etc.), acute viral hepatitis (Types A, B and C), tuberculosis, atypical courses in malignant lymphoma, pregnant women, partners of HIV-positive and sex workers.

Besides, HIV infection is considered at high risk in individuals of male homosexuals, bisexuals or heterosexuals (person who has many and unspecified partners or who goes on unprotected sexual intercourse) and individuals who received blood transfusion prior to 1985.

For Hepatitis type B, the occurrence of HIV co-infection is common since the route of infection is similar.

(2) Examination

HIV examination can be received at public health offices throughout Japan at free of charge and under anonymous. The examination, in principle, requires the consent of the individual receiving the test. Some public health offices request prior appointment. Please make an inquiry in advance or visit API-Net (http://api-net.jfap.or.jp/).

Examinations for HIV infection include a screening test and a confirmatory test. By combining these two examinations, accurate diagnosis can be made. However, at the initial phase of the infection, sufficient amount of the antibodies (proteins produced in response to immune reaction against HIV) does not present

in the blood. Therefore, the screening test may not become positive. Even during this period, there are large amount of viruses in the blood and it is highly contagious. This period is called as the window phase. Usually, 6-8 weeks after infection, the antibodies can be detected. If an individual received HIV test within 3 months of potential infection, the test must be re-performed 3 months later to confirm that the individual is free from infection 5), 6) (Figure3).

In addition, it is necessary to pay attention to the false positive that may occur in the screening test at the frequency of about 0.3% in the following individuals or patients: multipara, hematological malignancy (leukemia, multiple myeloma, etc.), connective tissue disease, alcoholic liver cirrhosis, primary biliary cirrhosis, primary sclerosing cholangitis and DNA virus infection such as herpes virus.

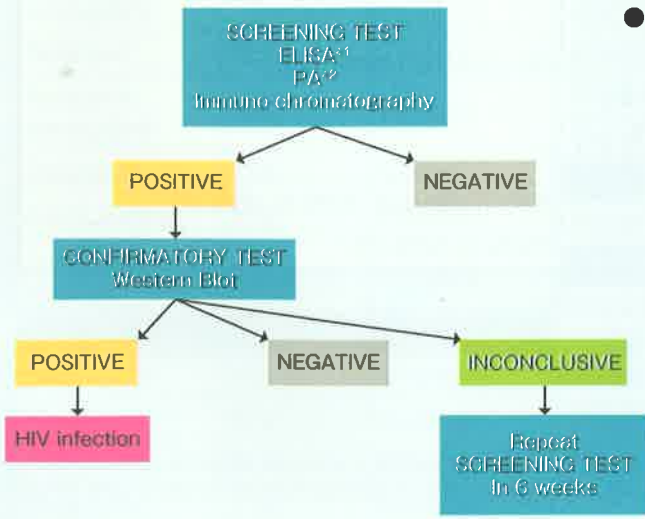
With regard to the health insurance coverage, the screening test is covered under the certain conditions such as necessity to differentiate from AIDS and sexual infection. The confirmation test will be covered only when the result of the screening test is positive.

[Treatment]

(1) Highly active antiretroviral therapy (HAART)

Oral medicine treatment is commenced in order to suppress the viral load below the limit of detection to inhibit replication, and to maintain the number of CD4 cells at the certain level to keep the immune status, which would prevent the

Fig.3 Diagnosis & routine checks



●HIV routine check
Blood test;
CBC; differential white blood count,CD4/8 count
biochemistry; electrolyte, liver/renal function
HIV RNA viral load
Serologic test for syphilis
Antibody for virus
(A, B, C hepatitis/ Cytomegalovirus/ Toxoplasma)
Amoeba antibody
Chest X-rays (Exclude TB)
Eyes; fundoscopy
Genitalia; cervical cancer

*1 : Enzyme-linked Immunosorbent assay
*2 : Particle aggulutination test

※Viral load implies speed of the HIV infetion.
The number of CD4 positive lymphocyte shows immunological state of the infected person.

development of AIDS by recovery and maintenance functions of immunocompetence.

For the suppression of drug-resistant viruses, strong multi-drug therapy using 3 or more anti-virus drugs concurrently, which is called as HAART (Highly Active Antiretroviral Therapy), is provided.

After the widespread of HAART, the prognosis of HIV infected patients has drastically improved. At present, the average life span is almost the same as non-infected individuals.

(2) Indications for starting HAART

Replication of HIV has been considered to increase the risk of non-AIDS complications (cardiovascular diseases, hepatic disorders and renal disorders) and a finding was showed that early initiation of treatment improves prognosis. In addition, since more drugs with easier to take and/or less side effects are now available, start of treatment has become earlier over the years. Since the termination of the treatment may adversely affect the prognosis, once the treatment was initiated, it should not be discontinued except special cases such as an experience of serious side reactions or difficulty in taking medication.

Table.1 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Clinical symptoms/CD4 counts	Recommendations
CD4 < 350/μℓ (A Ⅰ) Pregnancy (A Ⅰ) HIV/HBV coinfection (A Ⅱ) HIV-associated nephropathy (HIVAN) (A Ⅱ) History of an AIDS-defining illness (A Ⅰ)	Strongly recommended
CD4 350～500/μℓ (A/B-Ⅱ)	Recommended (55%-A, 45%-B)
CD4 > 500/μℓ (B/C-Ⅲ)	(50%-B, 50%-C)

〈Rating Scheme for Recommendations〉
Strength of Recommendation
A: Strong recommendation for the statement
B: Moderate recommendation for the statement
C: Optional recommendation for the statement
〈Quality of Evidence for Recommentation〉
Ⅰ: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
Ⅱ: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
Ⅲ: Expert opinion

In Japan, the initiation of the treatment follows the guidelines issued by the study group of the Ministry of Health, Labour and Welfare (March 2011) or US National Institute of Health3) (Table 1). In addition to the medical criteria, patients must be psychosocially ready to commence lifelong daily therapy, and correct adherence whith therapy is critical. Therefore, initiation of treatment should be decided based on clinical, psychological and social factors and a patient him/herself or a doctor may decide to postpone the initiation of the treatment.

(3) Anti-HIV drugs

Depending on mechanisms of action, they are classified into four main groups 4) (Table 2/3, Figure 4):

- **Nucleoside reverse transcriptase inhibitor (NRTI)**

This class of drugs is similar to nucleic acid; the raw material of virus DNA. Zidovudine (AZT [ZDV]) and tenofovir (TDF) are typically used.

Table.2 ART Drugs used in Japan

NRTIs		
一般名	略号	製品名
Zidovudine	AZT (ZDV)	Retrovir
Didanosine	ddI	Videx
Lamivudine	3TC	Epivir
Stavudine	d4T	Zerit
Lamivudine/ zidovudine	AZT/3TC	Combivir
Abacavir	ABC	Ziagen
Abacavir/ lamivudine	ABC/3TC	Epzicom
Tenofovir	TDF	Viread
Emtricitabine	FTC	Emtriva
Emtrictabine/ tenofovir	TDF/FTC	Truvade
NNRTIs		
Nevirapine	NVP	Viramune
Efavirenz	EFV	Sustiva
Delavirdine	DLV	Rescriptor
Etravirine	ETR	Intelence

Protease Inhibitors		
一般名	略号	製品名
Indinavir	IDV	Crixivan
Saquinavir	SQV	Invirase
Ritonavir	RTV	Norvir
Nelfinavir	NFV	Viracept
Lopinavir/ ritonavir	LPV/RTV	Kaletra
Atazanavir	ATV	Reyataz
Fosamprenavir	FPV	Lexiva
Darunabir	DRV	Prezista
Integrase Inhibitors		
Raltegravir	RAL	Isentress
Entry Inhibitors		
Maraviroc	MVC	Selzentry

NRTI : Nucleoside Reverse Transcriptase Inhibitor
NNRTI : Non-Nucleoside Reverse Transcriptase Inhibitor

Table.3 ART regimens in Japan

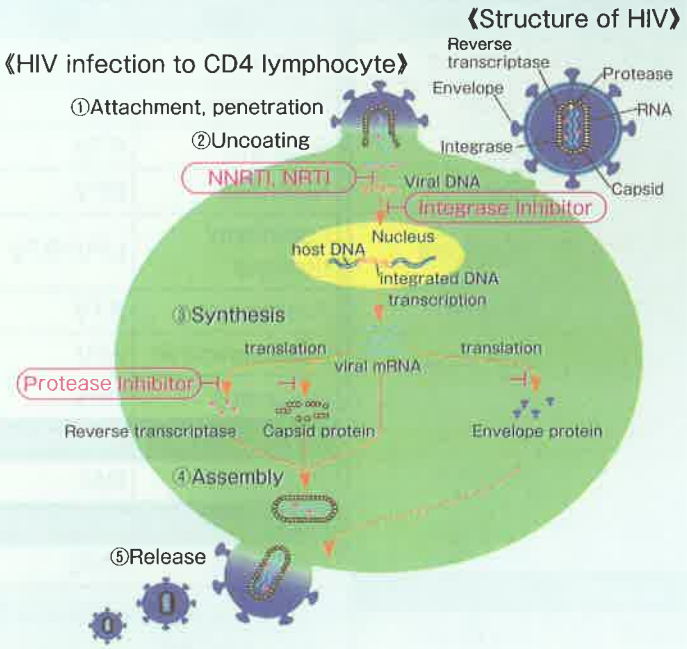
Base	Key drug	Back bone
NNRTI	EFV	+ ABC/3TC + TDF/FTC
PI	ATV + RTV DRV + RTV	+ ABC/3TC + TDF/FTC
INI	R A L	+ ABC/3TC + TDF/FTC

〈Recommended ART as first line〉

- Select one key drug (NNRTI, PI or INI) and back bone (2-NRTI).
- Select them considering their thought about the treatment, the number and frequency of pills, diet condition, severity of HIF infection, side effects, complications, interactions.

NRTI : Nucleoside Reverse Transcriptase Inhibitor
NNRTI : Non-Nucleoside Reverse Transcriptase Inhibitor
PI : Protease Inhibitor
INI : Integrase Inhibitor

Fig4. Structure of HIV and infection pathway



- Non-nucleoside reverse transcriptase inhibitor (NNRTI)

This class of drugs directly attaches to reverse transcriptase enzyme and inhibits its action. Nevirapine (NVP) and efavirenz (EFV) are typically used.

- Protease inhibitor (PI)

This class of drugs inhibits the production of virus structural protein that is necessary for the replication of progeny virus. Lopinavir (LPV) and atazanavir (ATV) are classified into this class.

- Integrase inhibitor (INI)

This class of drugs inhibits the enzymes that are necessary for the replication of HIV and inhibits the integration of HIV genes into host genes.

Major anti-HIV drugs currently approved in Japan are listed in Table 2.

Anti-HIV treatment is administered using two drugs, one from a class selected from NNRTI, PI or INI as a key drug and another from a class; 2-NRTI as a backbone4) (Table 3).

The strategy of anti-HIV treatment is still changing and developing year after year.

(4) Is HIV cured?

Antiretroviral drugs are intended to suppress the replication of viruses in the body and there is no drug that directly attacks and kills viruses. At present, similar to diabetes and anti-convulsion drugs, intake of drugs must be continued. HIV infection is a progressive infectious disease which gradually destroys the immune system. Current antiretroviral treatment cannot eradicate viruses. Hence, there is no therapy to completely cure the disease.

Reasons why we cannot eliminate HIV from the body are that the replication speed is very fast and that HIV produces many mutated strains during transcription (HIV itself commits many mistakes when replicating gene information (copy-error)). Although 10 billion viruses are replicated every day, every single reverse transcription of nucleic acid (copy of genetic information) generates single mutation on the average. When mutated viruses emerge, despite the host immune reactions against HIV work, viruses can escape such immune reactions and can continue to replicate for an extended period. Furthermore, resistant to the medication is more likely to occur.

[Prevention]

As discussed above, mutated strains are very easier to emerge in HIV. Accordingly, effective vaccine has not been developed. Therefore, following prevention of the transmission is of importance.

Prevention of sexual transmission: In order to prevent contact of body fluid to the mucosal membrane, safe sex using a condom is necessary (it is also needed for other sexual activities such as oral sex).

Prevention of blood borne infection: Donated blood is performed a screening test to prevent the contamination of blood derived products. In the case of needlestick injuries, antiretroviral drug should be given as a PEP(Post-exposure prophylaxis).

Prevention of mother to child transmission (MTCT): Irrespective of the viral load, pregnant women positive for HIV infection are indication for starting treatment. If the HIV RNA copies in the mother is measured at 1,000 copies/mL or more until just before the delivery, planned caesarian section should be conducted. Furthermore, as part of transmission preventive interventions for infant, breast feeding should be prohibited to avoid transmission via mother milk. Preventive administration of antiretroviral drugs to infants should also be considered.

[Medical fee subsidy system]

Basic principle of HIV treatment is to continue the medication. However, anti-HIV drugs are expensive and payment covered by health insurance is not enough to reduce large financial burden of patients. As a result, continuation of medication may become difficult. There are supporting systems such as physical disability certificate, high cost medical fee insurance, severely handicapped medical system and services and supports for persons with disabilities. Each local government has its own internal criteria to use such systems. For details, please contact the application desk officers, social workers or medical consultation desk officers in the medical institutions, local areas or regional hub hospitals.

Reference sites:

AIDS prevention information net (API-Net)

HIV map: http://www.hiv-map.net/

Wam net: http://www.wam.go.jp/

References:

1) UNAIDS (United Nations AIDS plan) World AIDS Day Report, 2011
2) AIDS surveillance committee, Ministry of Health, Labour and Welfare, Summary of AIDS incidence status 2010
3) Guideline published by the Department of Health and Human Sciences (DHHS, US); Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, October 14, 2011
4) HIV infection "Guideline for Treatment" ver. 15. Issued in December 2011, HIV infection treatment study group

5) Michael Eddleston, Robert Davidson, Andrew Brent, Others; Oxford Handbook of Tropical Medicine, Third Edition, OXFORD UNIVERSITY PRESS, 2008: pp 67-138
6) Makoto Aoki, "Infectious diseases manual for resident doctors" Ver. 2, Igaku-Shoin, 2008: pp 1221-1291
7) Tomohiro Morio, Masami Taniguchi, et al (supervising editors): Byoki-ga-mieru (Illustrated guide of diseases) Vol.6 Immunology, connective tissue disease and infection, ver. 1. Medic Media, 2009: pp 258-265
8) Mark Gladwin, Bill Trattler (Authors), Aikichi Iwamoto (Translation supervisor): Suguwakaru-Irasuto-Biseibutsu-gaku (Illustrated guide of basic microbiology), Maruzen, 2007: pp 248-266