

# ACQUIRED IMMUNODEFICIENCY SYNDROME PANELS

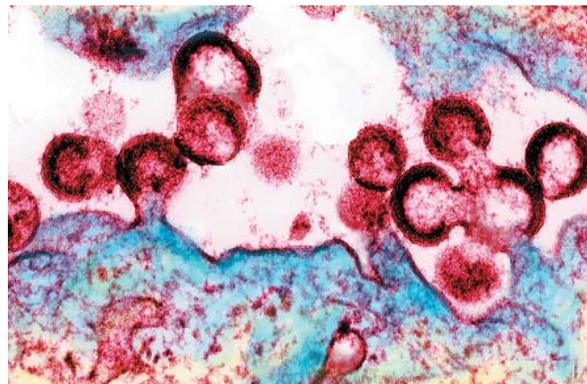
[Established in 1988]

In June 1981, the U.S. Centers for Disease Control (CDC) reported five mysterious cases of *Pneumocystis* pneumonia in previously healthy, homosexual men and noted that in the United States *Pneumocystis* pneumonia was a disease previously associated with severe immunosuppression.<sup>1</sup> By December 1982, the CDC had linked other cases of immunosuppression-associated opportunistic infections and cancers to blood transfusions, intravenous drug use, and the use of blood products by people with hemophilia A. The CDC termed the new disease entity “acquired immunodeficiency syndrome (AIDS).”<sup>2</sup>

In the mid-1980s, scientists in France and the United States isolated and identified the cause of AIDS, a human retrovirus they called human immunodeficiency virus (HIV).<sup>3</sup> HIV was similar to retroviruses that cause immunodeficiency diseases in animals, and it also resembled a retrovirus that causes human T-cell leukemia (HTLV). In 1986, the U.S. Government, through the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH), established an official program on AIDS research. At the time, the estimated cumulative number of deaths due to AIDS was 16,301.

At the 23<sup>rd</sup> meeting of the USJCMSP Joint Committee, held at NIH from July 23–24, 1987, NIAID Director and U.S. Delegation Member (1986–present) Dr. Anthony Fauci spoke about AIDS.

Dr. Fauci presented an illuminating review of the major aspects of Acquired Immunodeficiency Syndrome (AIDS) that was followed by discussion of proposed guidelines for new Panels on AIDS. After acceptance of the guidelines, the Joint Committee unanimously recommended that Joint Panels on AIDS be organized as soon as possible.<sup>4</sup>



HIV viral release

In 1988, at their 24<sup>th</sup> meeting, held in Tokyo, the Joint Committee established the Panels on AIDS as the 10<sup>th</sup> panel of the USJCMSP. Dr. Yuichi Shiokawa, Professor Emeritus, Juntendo University, was appointed the Japanese Panel Chair (1988–1994), and Dr. Ashley Haase, University of Minnesota, was named U.S. Chair (1988–1994). The initial guidelines for the AIDS Panels targeted HIV and HTLV-1 infection, perinatal infection, and epidemiology in Southeast Asia. At the time, AIDS was not prevalent in Japan, but it was clear the disease posed a global public health threat.

“Slim disease [a term for AIDS in many African countries] existed in East Africa for at least three decades before it was discovered in the U.S.,” said Dr. Adel Mahmoud in a June 2004 interview. Dr. Mahmoud served as a member of the U.S. Delegation from 1994–2000, and as Chairman of the U.S. Delegation from 2001–present. “We have to study these diseases in their global context.”

Today, nearly 38 million people worldwide, including more than 2 million children under age 15, are living with HIV/AIDS. Most of these people (25 million) live in Sub-Saharan Africa; approximately 7.4 million live in Asia and the Pacific. An estimated 14,000 new HIV infections occur worldwide each day. Since the CDC identified the first cases of AIDS

in 1981, more than 20 million people with HIV/AIDS have died.<sup>5</sup>

“AIDS infection in Asian countries is becoming a very serious issue,” said Dr. Hiroo Imura in an August 2004 interview. Dr. Imura served as a member of Japanese Delegation from 1991–2002. “HIV probably came from Africa through Caribbean countries and then to the United States,” he said. “But for Asian countries, the route was very different and the subtype of the virus is different. AIDS came to Asian countries from Africa to India, then to Southeast Asia. We are afraid that AIDS will increase remarkably in Southern China and other Asian countries.”

During the first few years after the USJCMSP AIDS Panels were established, scientists focused on disease epidemiology in the Pacific region. In 1992, Japanese and U.S. members of the AIDS Panels made a joint decision to engage scientists and epidemiologists from other countries in their meetings and research activities. At the joint annual meetings of the AIDS Panels, Japanese and U.S. scientists presented the results of studies conducted in the region and, importantly, identified epidemiologists and scientists from other countries, as well as the World Health Organization, to make presentations. The idea was to inform members of the U.S. and Japanese AIDS Panels about epidemics that were emerging in the Pacific region and to identify scientific opportunities. The hope was that the AIDS Panels could help prevent some epidemics from fully emerging and help address those that did emerge. (These efforts were analogous to those behind the now-annual International Conferences on Emerging Infectious Diseases in the Pacific Rim, although they preceded the conferences by several years.)

In addition to making important scientific progress in AIDS research, members of the AIDS Panels

have collaborated on other kinds of projects. For example, AIDS Panel members Dr. Robert Schooley (Panel member 1994–1995, Panel Chair 1995–1998), University of Colorado Health Sciences Center, and Dr. Makoto Aoki, Medical Director of AIDS Programs at the International Medical Center, Tokyo, have developed “Frequently Asked Questions” monographs used extensively among Japanese physicians in treating HIV infection. Also, since 1994, the AIDS Panels have participated in HIV research related to the U.S.-Japan Common Agenda,<sup>6</sup> as well as efforts related to the G-8 Summits. To respond to these policy forums, the Panels have increased their efforts to develop AIDS vaccine candidates, while still addressing the broader spectrum of HIV-related research.

“HIV/AIDS is one of the most serious problems today, to the whole world,” said Dr. Tadao Shimao in an August 2004 interview. Dr. Shimao was chair of the USJCMSP Japanese Delegation from 1993–2001, and a Delegation member from 1977–1993. “And now at least, we have some drugs for treatment,” he said. “They are not cures, but we can postpone the progress of disease. Both sides are trying very hard to develop a vaccine. To eradicate the disease would be a great achievement.”

The following is a list of important science advances in HIV/AIDS research associated with the U.S. and Japanese AIDS Panels. The list is adapted from information in the USJCMSP five-year reports, as well as information supplied by Dr. Linda Reck, U.S. AIDS Panel Secretariat (1990–2004); Dr. Sten Vermund, Chair of the U.S. AIDS Panel (2003–present); and Dr. Satoshi Kimura, chair of the Japanese AIDS Panel (2002–present) and Panel member (1998–2001).

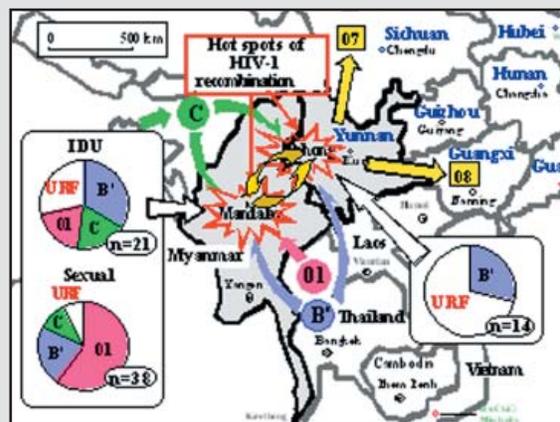
### Acquired Immunodeficiency Syndrome Panels

[Established in 1988]

[*Science Advances: 1988–2000*]

- Made important progress in the discovery and development of therapeutics for AIDS. In 1985, utilizing cultured human target cells to screen potential anti-HIV drugs, Japanese AIDS Panel member Dr. Hiroaki Mitsuya of Kumamoto University School of Medicine and the National Cancer Institute (NCI) of NIH (in the United States) and colleagues demonstrated that azidothymidine (AZT) has potent anti-HIV activity.<sup>7</sup> Based on their data, the NCI selected AZT for a clinical trial, and AZT became the first drug used to treat AIDS.<sup>8</sup> In 1994, Dr. Mitsuya and his colleagues showed that reverse transcriptase inhibitors (RTIs) can be classified into two groups: (1) cell-activation-dependent dideoxynucleosides (ddNs) such as AZT that are preferentially phosphorylated, yield higher ratios of ddN 5'-triphosphate (ddNTP)/2'-deoxynucleoside 5'-triphosphate (dNTP), and exert more potent anti-HIV activity in activated cells than in resting cells; and (2) cell-activation-independent ddNs such as dideoxyinosine (ddI) that produce higher ratios of ddNTP/dNTP and exert more potent activity against the virus in resting cells, a finding that provided the basis for the design of currently available combination chemotherapy with RTIs.<sup>9</sup> Dr. Mitsuya and his collaborators also showed that HIV develops a set of mutations that confer multidrug resistance (MDR) on the virus,<sup>10</sup> and they later began to develop novel antiviral drugs that are active against drug-resistant variants of HIV.<sup>11</sup>
- Identified and conducted phylogenetic studies of two ancestral lineages of Japanese strains of human T-cell leukemia viruses (HTLV) and their simian counterparts, STLV. (Adult T cell leukemia, which is caused by HTLV-1, has been endemic in southwestern Japan.) One strain of HTLV-1 probably came to the Americas in Paleolithic times, suggesting interspecies transmission in the origins of HTLV-1.
- Analyzed the AIDS epidemics in Guam, Hong Kong, India, Indonesia, Malaysia, the Marshall Islands, Micronesia, Papua New Guinea, the Philippines, the Republic of Korea, Samoa, and Thailand. The Joint Panels on AIDS described the pattern of the AIDS pandemic in these countries, predicted future epidemic trends elsewhere in the region, and identified research opportunities in Japan and elsewhere in Asia and Pacific Rim countries.
- Identified geographical hotspots of extensive recombination of HIV subtypes in Asia. Scientists identified two subtypes of HIV-1 strains B and E circulating in Southeast Asia by examining the sequence of the HIV coat protein, glycoprotein 120 (gp120) V3 loop. A Sendai virus-based production system for subtype gp120 proteins enabled the serological survey of the prevalence of HIV subtypes. Dr. Yutaka Tabebe of the National

Institute of Infectious Diseases and his colleagues have used genetic subtyping based on molecular epidemiological investigation to identify a “melting pot” that generates diverse forms of HIV-1 unique recombinants. Several lineages of HIV-1 strains cause the AIDS epidemics in Asia.<sup>12</sup> In addition to these strains that disseminate widely in population, various types of unique recombinant forms (URFs) have been reported in some areas in Asia, where different lineages of HIV-1 strains are cocirculating.<sup>13</sup> In 1989, one year after the AIDS outbreak in Thailand, HIV-1 epidemics occurred among injecting drug users (IDUs) in Myanmar and the western part of Yunnan Province in China. To elucidate the genesis and the interrelationship of the HIV-1 epidemic, Dr. Tabebe and his colleagues conducted molecular epidemiological investigations in Myanmar<sup>14</sup> and the nearby Yunnan Province of China.<sup>15</sup> They identified unique geographical hotspots of extensive recombination in Myanmar and western part of Yunnan Province of China, where diverse forms of recombinant strains appear to be arising continually (Fig. 1). This may reflect the presence of highly exposed individuals and social networks in these regions. Their study also represents the first evidence suggesting a possible linkage between the HIV/AIDS epidemics in Myanmar and in China. The rapid emergence and evolution of diverse forms of HIV-1 recombinants could further complicate the development of effective vaccines to limit the spread of HIV-1 in these areas of Asia.



**Fig. 1.** Schematic representation of unique geographical hotspots of extensive HIV-1 intersubtype recombination in Myanmar and the Yunnan Province of China. Western Yunnan (Dehong Prefecture) and Central Myanmar (Mandalay) (marked with “explosion” symbols) are the “melting pots” where extensive recombinations between different lineages of HIV-1 strains appear to be occurring. The pies show the prevalence of respective HIV-1 genotypes at the indicated study sites. Plausible routes of HIV-1 spread are schematically illustrated. B’, subtype B; C, subtype C; URF, unique recombinant form; O1, CRF01\_AE; O7, CRF07\_BC; O8, CRF08\_BC.

- Made progress in basic research on the development of candidate AIDS vaccines and improved understanding of the

role of mucosal immunity in vaccine development. U.S. AIDS Panel member Dr. Christopher Miller and Japanese AIDS Panel Member Dr. Hiroshi Kiyono have collaborated to investigate the molecular epidemiology, genetic analysis, and immunologic classification of HIV, and to conduct studies in primate models demonstrating that simian immunodeficiency virus (SIV) enters the vaginal mucosa within 60 minutes of intravaginal exposure, and infects primarily intraepithelial dendritic cells. Former AIDS Panel Chair Dr. Susan Zolla-Pazner of the New York University School of Medicine and her colleagues have demonstrated that immunologic classification does not correlate with genotypic classification and may be more relevant than genotypic classification for the design of polyvalent vaccines.

- Made significant strides in understanding the roles of cytotoxic T lymphocytes in the control of viremia in nonhuman primates infected with simian immunodeficiency virus (SIV). U.S. AIDS Panel member Dr. Norman Letvin and Dr. Marcelo Kuroda of Harvard University developed the SIV-infected monkey model, which is now used in many countries to develop HIV vaccine candidates for humans.

#### *[Science Advances: 2000–2004]*

- Tracked the molecular epidemiology of HIV-1 infection in Pacific Island nations. Through this collaboration, Dr. Richard Yanagihara of the University of Hawaii, and Dr. Takeshi Kurata of the National Institute of Infectious Diseases, have characterized the allele frequency of a 32 base-pair deletion within the chemokine receptor CCR5, which is associated with relative resistance to HIV-1 infection and slower progression to AIDS in non-Caucasian populations. This information is important to the development of HIV vaccine candidates that could be effective in non-Caucasian populations of Asia and the Pacific Islands.
- Developed assay systems that allow complex analyses of biological mechanisms in HIV control. These include a cross-clade neutralizing human monoclonal antibody system developed by Dr. Susan Zolla-Pazner of the New York University School of Medicine, and a cell system (MAGI-CCR5) used in neutralization assays by Dr. Julie Overbaugh of the Fred Hutchinson Cancer Research Center. Through collaborations utilizing these assay systems, Dr. Shinju Harada of Kumamoto University School of Medicine and Dr. Zolla-Pazner have elucidated mechanisms of HIV neutralization by V3-targeted antibody. Dr. Shuzo Matsushita of Kumamoto University and Dr. Zolla-Pazner have characterized the sensitivity to neutralizing antibody of viral mutants that arise during therapy with antiretroviral drugs. Dr. Masashi Tatsumi of the National Institute of Infectious Diseases and Dr. Overbaugh have developed a method for screening for drug resistance that arises during antiviral therapy.
- Identified a novel anti-HIV drug that blocks the CCR5 cytokine receptor. Japanese AIDS Panel member Dr. Hiroaki Mitsuya has recently identified a novel CCR5 antagonist AK602 (ON04128/GW873140) that is extremely potent against macrophage-tropic R5-HIV.<sup>16</sup> UIC-94017 and AK602 are undergoing phase II clinical trials in European countries and the United States, respectively.
- Demonstrated a protective immune response against HIV-1 in hu-PBL-SCID mice induced by intrasplenic immunization with HIV-1-pulsed dendritic cells. Mice with severe combined immunodeficiency (SCID), when adoptively transferred with human peripheral blood mononuclear cells (PBMC), develop a surrogate human immune system and are termed hu-PBL-SCID mice. With the ultimate goal of developing a human AIDS vaccine, Dr. Yuetsu Tanaka of the University of the Ryukyus and his colleagues explored the possibility of developing a dendritic cell-based vaccine against HIV-1 infection using hu-PBL-SCID mice. The researchers transplanted HIV-negative normal human PBMC into the spleens of SCID mice (hu-PBL-SCID-spl) together with autologous mature dendritic cells that had been pulsed with either inactivated HIV-1 (R5 or X4 strain) or ovalbumin (OVA). They found that dendritic cell-HIV-1-immunized hu-PBL-SCID-spl mice, irrespective of immunized HIV-1 strains, were protected against HIV-1 challenge, whereas none of the control mice were protected. The results suggest a new concept for AIDS vaccine design using a dendritic cell-based HIV-1 immunogen.<sup>17</sup>
- Increased understanding of the cellular and molecular biology of the mucosal immune system, and its development, as bases for developing mucosal vaccines against AIDS. M cells located in the follicle-associated epithelium (FAE) of Peyer's patches and nasopharynx-associated lymphoid tissue (NALT) are the principal sites for sampling intestinal and airway luminal antigens, respectively. A recent study by Japanese AIDS Panel member Dr. Hiroshi Kiyono of the Institute of Medical Science and his collaborators and his colleagues demonstrated the presence of a distinct gateway for the uptake of gut bacteria: clusters of non-FAE-associated UEA-1+ cells, which they designated intestinal villous M cells.<sup>18</sup> The newly identified villous M cells could be an alternative and Peyer's patch-independent gateway for inducing antigen-specific immune responses via the mucosal compartment.<sup>19</sup> This finding underscores why a thorough understanding of the molecular and cellular uniqueness of the mucosal immune system is essential to the development of novel oral and nasal vaccines for preventing mucosally transmitted HIV.
- Increased understanding of mucosal immunity and vaginal transmission of virus in nonhuman primate models. For several years, Dr. Christopher Miller, University of California at Davis, and Dr. Hiroshi Kiyono, University of Tokyo, have been studying mucosal immunity and vaginal transmission of SIV in monkeys. The studies have led to the development of candidate mucosal vaccine adjuvants, which are being tested in animal models

and may stimulate development of HIV vaccine adjuvants for humans.

- Developed novel, recombinant candidate vaccines against simian AIDS based on a prime-boost regimen that elicits strong cell-mediated responses against the virus. Members of the Japanese and U.S. AIDS Panels are collaborating to develop an AIDS vaccine that stimulates protective immune responses, including T helper cell-type 1 (Th1)-mediated immune responses and CD8+ CTL. Th1/CD8+ T-cell responses have been shown to play an important role in controlling HIV-1 replication. Recently, U.S. AIDS Panel member Normal Letvin and his collaborators showed that HIV-1 DNA-based vaccines can induce protective T cell-mediated immune responses. The immune response to DNA vaccines based on HIV-1 antigen genes was increased when the researchers combined innate and adaptive cytokine genes.<sup>20</sup> Furthermore, Japanese AIDS Panel member Dr. Mitsuo Honda of the National Institute of Infectious Diseases and his collaborators showed that recombinant Bacillus Calmette-Guerin (BCG) vectors may be able to deliver HIV immunogens that stimulate protective immune responses. They constructed new recombinant BCG and vaccinia DIs that express the SIV gag gene of the SHIV challenge viruses. (DIs is a mutant strain of vaccinia virus that cannot grow in mammalian cells but can grow in chick embryo fibroblasts.) The strongest immune responses in monkeys occurred when the researchers combined the two vaccines as a prime-boost regimen, a vaccine they also demonstrated as safe. Their newest results demonstrate that the new prime-boost regimen, based on a combination of BCG and a non-replicating, recombinant vaccinia virus, is safe and effective at inducing cell-mediated immunity against HIV-1, and it could be used as the basis of a candidate AIDS vaccine.<sup>21</sup>
- Tested the induction of HIV-specific CD8+ CTLs using viral components as a basis for AIDS vaccine development. HIV

can be transmitted via infected cells and spread by passage between fused cells. Therefore, a vaccine that primes HIV-specific CD8+ CTLs to kill cells that are producing HIV proteins may control viremia, clear the HIV genome from the host cells (by triggering apoptosis), and prevent disease progression. However, to induce virus-specific CTL responses generally requires immunization with live-virus vaccines, which is too risky for an HIV vaccine. Dr. Hidemi Takahashi of Nippon Medical School and his colleagues conducted a series of experiments and tested different strategies for inducing strong and effective CTL responses against HIV antigens and virus-infected host cells.<sup>22</sup> Their most recent experiments test whether they can induce CTLs by exposing antigen-captured immature dendritic cells (iDCs) to various stimuli for toll-like receptors (TLR) expressed on iDC. Based on the results of these and other experiments, Dr. Takahashi proposed that the induction of HIV-specific CTL responses is organized principally by iDCs arranged at the skin or mucosal surfaces, and that efficient loading of iDCs with antigenic molecules together with appropriate stimulation of the iDCs via specific TLRs may lead to a successful strategy for priming HIV-specific CTLs.<sup>23</sup>

- Developed a novel, DNA-based vaccine that partially protects monkeys against challenge with SHIV. Dr. Masanori Hayami of Kyoto University and his colleagues developed a gene-deleted SHIV as live-attenuated vaccine to induce the maximal protective effect in monkeys. To make the vaccine safer while maintaining its efficacy, they designed a semi-live vaccine that produces non-infectious virus particles, based on full-sized SHIV plasmids (pSHIV-ZF1\*IL-2), in which the nef gene was deleted and the human IL-2 gene was inserted. The vaccine induced a strong T helper cell response and partially protected monkeys from infection with challenge virus, indicating that DNA vaccination using full-sized plasmids alone is potentially efficacious.

**Footnotes — Acquired Immunodeficiency Syndrome Panels**

- <sup>1</sup> *Pneumocystis* pneumonia—Los Angeles. *MMWR Weekly* 1981 June 5;30:250–2.
- <sup>2</sup> Epidemiologic notes and reports possible transfusion-associated acquired immune deficiency syndrome (AIDS)—California. *MMWR Weekly* 1982 December 10; 31(48):652–4.
- <sup>3</sup> Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dauguet C, Axler-Blin C, Vezinet-Brun F, Rouzioux C, Rozenbaum W, and Montagnier L. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science*. 1983 May 20;220(4599):868–71; and Shaw GM, Hahn BH, Arya SK, Groopman JE, Gallo RC, and Wong-Staal F. Molecular characterization of human T-cell leukemia (lymphotropic) virus type III in the acquired immune deficiency syndrome. *Science*. 1984 Dec 7;226(4679):1165–71.
- <sup>4</sup> The United States–Japan Cooperative Medical Science Program. Fifth Five-Year Report: 1985–1990. Department of State Publication 9761: Bureau of Oceans and International Environmental and Scientific Affairs, p. 2.
- <sup>5</sup> NIAID Facts and Figures: HIV/AIDS Statistics. <http://www.niaid.nih.gov/factsheets/aidsstat.htm>.
- <sup>6</sup> In July 1993, U.S. President William J. Clinton (1992–2000) and Japanese Prime Minister Kiichi Miyazawa (November 1991–August 1993) signed the Common Agenda for Global Cooperation, which enhances collaboration through bilateral programs, including the Child Health/The Children’s Vaccine Initiative (CVI). The AIDS Panels of the USJCMSP endorsed the bilateral Common Agenda and hosted discussions among government policy representatives and scientists.
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- <sup>8</sup> Mitsuya H and Broder S. Strategies for antiviral therapy in AIDS. *Nature* 1987;325:773–8.
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- <sup>11</sup> Yoshimura K, Kato R, Yusa K, Kavlic MF, Maroun V, Nguyen A, Mimoto T, Ueno T, Shintani M, Falloon J, Masur H, Hayashi H, Erickson J, and Mitsuya H. JE-2147: a dipeptide protease inhibitor (PI) that potently inhibits multi-PI-resistant HIV-1. *Proc Natl Acad Sci U S A* 1999;96:8675–80.
- <sup>12</sup> HIV-1 subtype B′ (Thailand variant of subtype B) and CRF01\_AE triggered the epidemic in Thailand, and subtype C is the single major founder strain in India. Two closely related circulating recombinant forms (CRFs), CRF07\_BC and CRF08\_BC, are distributed among IDUs in northwestern and southeastern China, respectively.
- <sup>13</sup> Includes A/C recombinants in India, 01/B′ in Thailand and Myanmar, B′/C in Yunnan and Myanmar.
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- <sup>15</sup> Yang R, Xia X, Kusagawa S, Zhang C, Ben K, Takebe Y. On-going generation of multiple forms of HIV-1 intersubtype recombinants in the Yunnan Province of China. *AIDS* 2002;16:1401–7; and Yang R, Kusagawa S, Zhang C, Xia X, Ben K, Takebe Y. Identification and characterization of a new class of human immunodeficiency virus type 1 recombinants comprised of two circulating recombinant forms, CRF07\_BC and CRF08\_BC, in China. *J Virol* 2003;77(1):685–95.
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