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AIDS at 40th: The progress of HIV treatment in Japan

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Abstract: Forty years have passed since the first five AIDS cases in Los Angeles were reported in 1981. Looking back at the history, these 40 years could be divided into 3 phases. During the first 15 years, when there was little efficacious therapy against HIV, clinical research was directed to develop diagnosis and treatment for opportunistic infections, mainly *Pneumocystis jirovecii* pneumonia. When combination antiretroviral therapy (cART) became available in 1996, taking cART had been troublesome to most patients following 10 years because some of them had severe side effects, diet restrictions, high pill burdens, drug interactions, *etc.* It was not easy for patients to keep high adherence and, therefore, the virus easily obtained drug resistance. Although the prognosis has been dramatically improved, patients had been still living with hard times during the second phase. Along with advancement of anti-retroviral drugs that have allowed simple treatment possible, their life expectancy has further improved and is reaching almost nearly the general population in the following 15 years. However, some patients have recently faced an additional load to treat life-related comorbidities and non-AIDS defining malignancies. The problem is that these diseases start to occur in the 40s- or 50s-year-old generations and that means HIV-infected persons are suffering from pre-mature aging. AIDS no longer signifies death. However, we still have a lot to improve for their quality of life.

***Keywords*:** *Pneumocystis jirovecii* pneumonia, drug resistance, combination antiretroviral therapy, tailor-made therapy, prevention, pre-mature aging

The beginning of AIDS era: the first phase for 15 years

In 1981, adult homosexual male cases of rare pneumonias and tumors were reported from Los Angeles and New York City (*1-3*). After that, additional cases were reported from many cities in the United States (US), all of these cases exhibited severe cellular immunodeficiency (*4,5*), and then the disease was named acquired immunodeficiency syndrome, AIDS. T-lymphotropic retrovirus was isolated from AIDS patients in 1983 and named human immunodeficiency virus (HIV) (*6*). Diagnosis of AIDS equaled death at that time, spreading strong stigma and prejudice in society. Even in a hospital, medical professionals refused to care for and treat HIV patients.

Under such dark years, Japanese researchers managed to develop the first anti-HIV drug, zidovudine (ZDV), a nucleoside reverse transcriptase inhibitor (NRTI) (*7*), and the first neutralizing monoclonal antibody, named 0.5β (*8*). However, because of rapid and continuous replicating properties of HIV in infected patients (*9*), the virus can obtain drug resistance soon after treatment with one- or two- drugs (*10*) and escape variants can easily appear (*11*), keeping the prognosis still poor until three-drug combination antiretroviral treatments (cART) became possible in 1996 (*12,13*). Instead, pathogenesis of HIV infection was able to be learned watching the natural course of the disease.

In Japan, an HIV history started in hemophiliacs who had been transfused concentrated but contaminated blood products mostly imported from US until 1986. Pathogenesis of HIV and histories of Japanese hemophiliacs infected with HIV were described previously (*14*). In this first phase, 15 years, the clinical focus was directed to diagnosis and treatment of rare opportunistic infections before AIDS era such as *Pneumocystis jirovecii* pneumonia that was the leading cause of death in AIDS patients.

Diagnosis and treatment of *Pneumocystis jirovecii* (*P. jirovecii*, formerly *carinii*) pneumonia (PCP)

PCP was very rare before AIDS era. Therefore, clinical experience of diagnosis and treatment of PCP was very limited at that time. *P. jirovecii* cannot be isolated by *in vitro* culture. Therefore, diagnosis was done by direct staining of pulmonary specimens obtained from invasive methods such as bronchial endoscopy in hypoxemic patients, although sensitivity

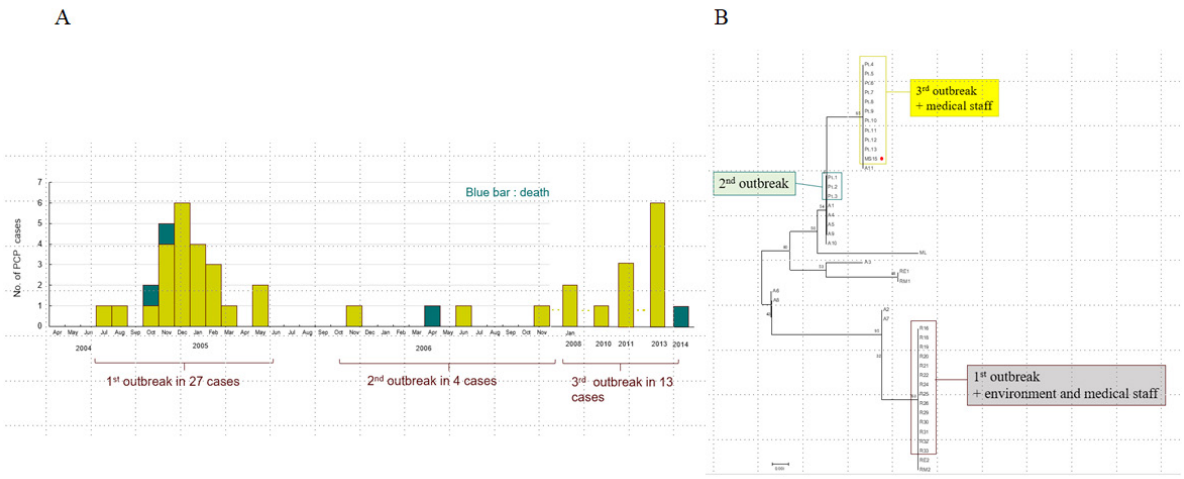

Figure 1. PCP is not the endogenous but exogeneous infection. (A) Three outbreaks of PCP in out-patient unit of renal transplant recipients; **(B)** Phylogenetic tree analysis of *P. jiroveci*. PCP, *Pneumocystis jiroveci* (*P. jiroveci*) pneumonia.

of the method was sometimes not clinically enough. Then, PCR was applied for the diagnosis of PCP amplifying 5S ribosomal DNA (*15*) that enabled us to diagnose PCP rapidly and sensitively with noninvasive specimens by using induced sputum, and follow direct monitoring of the treatment possible. Another group also developed PCR diagnosis of PCP independently (*16*). *P. jirovecii* was thought to be an infection in childhood, colonized in the lung dormantly, and developed PCP endogenously if the patient became an immunocompromised state (*17*). However, along with advancement of immunosuppressive agents, outbreaks of PCP in organ transplant recipients have been reported frequently from European countries since 2000 (*18-21*). Three outbreaks of PCP were also documented, which started in 2004 at out-patient units of renal transplant recipients and lasted for 10 years, that proved human-to-human transmission and possibly airborne, indicating *P. jirovecii* is highly contagious to susceptible hosts (*22*). The genotype of *P. jirovecii* in each outbreak was identical but different from each other (Figure 1). An environment survey revealed contamination with *P. jirovecii* around PCP patients and an oral swab from a healthy medical staff using PCR. PCP prophylaxis with oral trimethoprim-sulfamethoxazole (TMP-SMX) was strongly recommended and the outbreak has been finally mitigated since 2014 (*22*).

As PCP was to be a most common opportunistic infection in AIDS patients, basic research for *P. jirovecii* accelerated in 1980s. Morphological and ultrastructural observations concluded that the organism was a protozoan. Actually, treatment with an anti-protozoan drug, pentamidine, was documented as highly effective against PCP for treatment (*23*) and prophylaxis (*24*). However, advancement of molecular techniques and phylogenetic analysis of Pneumocystis 16S rRNA demonstrated that *P. jirovecii* is a fungi (*25*). If *P. jirovecii* was the fungi, the cell wall was thought to

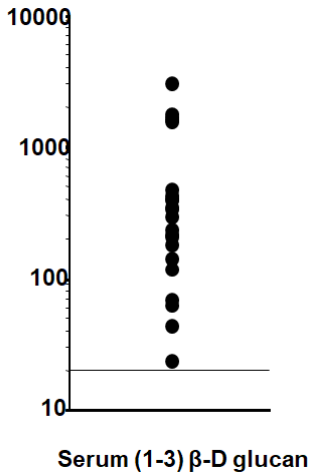

Figure 2. Serum (1→3) β-D-glucan in 22 HIV patients with PCP. Serum (1→3) β-D-glucan was elevated in all 22 patients and mean ± SD was 607 ± 771 ng/mL.

contain (1→3) β-D-glucan (*26*). Then, it was measured in PCP patients and first found that the serum titer in PCP patients was elevated (Figure 2) and it was higher than that in deep seated mycosis (*27*). Furthermore, clinical usefulness of measurement of serum (1→3) β-D-glucan was confirmed as an adjunctive diagnosis of PCP with a sensitivity of 96.4% and specificity of 87.8 % when the cutoff value was 23.2 pg/mL (*28*). Serum (1→3) β-D-glucan has been widely using clinically for diagnosis of PCP in daily practice in Japan since then.

In Japan, as the number of HIV infected patients was still not large in 1990s, most primary physicians were not familiar with diagnosis and treatment of PCP. PCP was not listed in the differential diagnosis of community acquired severe pneumonia. Then, a certain number of severe PCP cases with delayed diagnosis were referred to our hospital. If undiagnosed, PCP is a fatal disease (the mortality is 100%). Therefore, it could be supposed

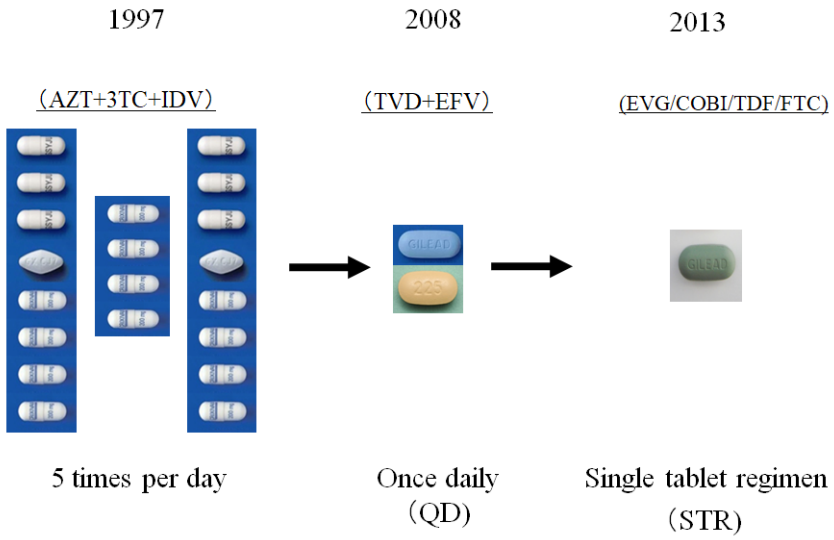

Figure 3. Advancement of cART in Japan. AZT, zidovudine; 3TC, lamivudine; IDV, indinavir; TVD, Truvada; EFV, efavirenz; EVT, elvitegravir; COB, cobicistat; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine.

that there might be a lot of undiagnosed cases with PCP during the first phase. However, if diagnosed at early to moderate stages, all cases can be cured by standard treatment with TMP-SMX or alternative treatment with Pentamidine or Atovaquone in Japan. At present, effective treatment and prophylaxis for PCP have been established (*29*) and primary physicians have been getting experience. Subsequently, PCP is no longer fatal once diagnosed. From this point of view, establishment of PCR diagnosis with noninvasive specimens and adjunctive diagnosis with serum (1→3) β-D-glucan, can both be outsourced to commercial laboratories from any hospital, and have contributed greatly to improve prognosis of PCP in Japan.

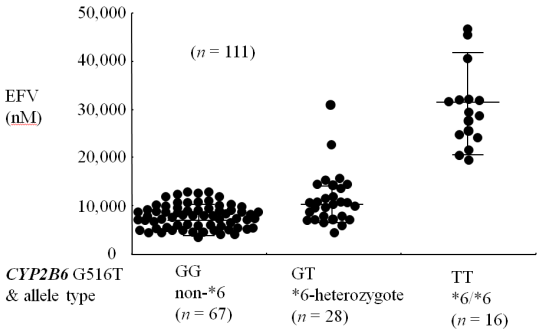

Figure 4. Genotypes of CYP 2B6 and serum efavirenz concentrations in Japanese. If patients had CYP 2B6 *6 homozygote, serum concentrations of efavirenz were elevated without exception. CYP, cytochrome P450.

The second phase of the history from 1996 to 2005

Since new classes of antiretroviral drugs, protease inhibitor (PI) including saquinavir, indinavir (IDV), ritonavir, and non-nucleoside reverse transcriptase inhibitor (NNRTI) including efavirenz (EFV) and nevirapine, have been developed (*30-32*) around 1995-1998, three-drug combination therapy (cART) has been the main strategy for HIV infection. cART consists of 2 components: key drug (PI or NNRTI) plus backbone (2 NRTIs). Especially, IDV-containing cART demonstrated strong anti-HIV activity, suppressed viremia to a undetectable level, and improved prognosis (*13*). However, patients on the IDV-containing regimen (mostly IDV plus lamivudine (3TC) plus ZDV) had to take a total of 20 tablets/day and 5 times/day (twice before and three times after meals) with 1.5 L water/day to prevent nephrotoxicity (Figure 3). In addition, patients taking the first-generation PI suffered from gastrointestinal side effects and the complicated medication patterns with high pill burdens. Then, it was very difficult to keep high adherence until a once daily regimen became possible in 2008 (Figure 3). Then, drug resistance easily occurred (*33,34*). A Japanese drug resistance surveillance network was also established in this period (*35*). Besides drug resistance, patients on the PI-containing regimen had some metabolic complications (*36-38*) and, consequently, had higher risk of cardiovascular diseases under prolonged therapy (*39,40*).

As to the other key drug of NNRTI, efavirenz (EFV), induces central nerve system (CNS) side effects such as vertigo, insomnia, nightmares, and finally depression. It was found that some patients suffered from very strong CNS side effects due to high concentrations of serum EFV because those patients, who were slow metabolizer of EFV, had cytochrome P450 2B6 *6 homozygote (Figure 4) (*41*). EFV dose was reduce from 600 mg/day to 200 mg/day with sufficient clinical efficacy and reduce the CNS side effects by checking their genotype beforehand, achieving the first tailor-made therapy in

HIV infection (*42*).

In the second phase, long term use of d-drug, especially stavudine (d4T), resulted in mitochondrial toxicities such as lipodystrophy and lactic acidosis (*43*). A combination of the generic d4T/3TC/EFV was the most widely used cART worldwide because of its low cost and combined formulation in a single tablet easy to take. Then, it contributed greatly to improve prognosis of HIV-infected patients in developing countries. However, WHO guidelines advised to stop using d4T because of irreversible and unacceptable mitochondrial toxicities of the drug (*44*) and recommended using tenofovir (TDF) in 2010 (*45*). Use of d4T has been phasing out even in developing countries and TDF/3TC/EFV was replaced thereafter (*46*).

In terms of efficacy of cART, it dramatically improved prognosis of HIV-infected patients, especially after 2000 (*47*). Life expectancy of the patients was expected to be nearly only 10 years less than the general population if not co-infected with hepatitis C. However, under these better situations, the biggest clinical question at that time was when to start cART because, as described, long term treatment caused severe side effects and complications, problems of adherence, and drug resistance. A couple of observational studies reported outcome comparisons between the early or deferred cART in asymptomatic HIV infected-patients and demonstrated that an initiation threshold of CD4 counts was around 200/mm^3 to 350/mm^3 (*48-51*). A large international randomized study, the Strategies for Management of Anti-Retroviral Therapy study (SMART study), was conducted to explore whether cART could be interrupted when CD4 counts elevated over 350/mm^3. Our clinic participated in this study as the Japan site. In this study, patients with CD4 counts > 350/mm^3 were randomly assigned to the continuous use of cART (viral suppression group) or CD4 count-guided interruption group (the drug conservation group). In the drug conservation group, patients restarted cART if CD4 counts decreased to < 250/mm^3 and then interrupted it if CD4 increased again to > 350/mm^3. The result was that patients in the drug conservation group had significantly increased the risk of opportunistic diseases or death as compared with those in the viral suppression group (*52*). After this study, it was strongly recommended that cART should continue while their CD4 counts were under 350/mm^3 and never interrupted if patients had some difficulties continuing cART. Apart from the efficacy of cART, development of better drugs or better combinations of ART such as easy to take, less toxic, and no drug-drug interactions were still desired during the second phase.

The third phase of the history from 2006 to present

The first integrase inhibitor (INSTI), raltegravir (RAL), was approved and the first once daily cART (TDF/3TC + EFV) was available in Japan in 2008. The second INSTI, elvitegravir (EVG), enabled us to treat with a single tablet regimen (STR) in 2013 (Figure 3). A simple treatment for HIV infection has become possible in this phase. However, when to start cART was still a major clinical issue around 2010. Benefits and risks of early treatment for asymptomatic HIV infection with CD4 count > 350/mm^3 were not proved by randomized trials. To explore this issue, the Strategic Timing of Anti-Retroviral Treatment (START) study was conducted. In this study, patients with CD4 counts > 500/mm^3 were randomly assigned to start cART immediately (immediately-initiation group) or to defer it until CD4 counts decreased to < 350/mm^3 (deferred-initiation group). The result was the immediately-initiation group had a better outcome over the deferred-initiation group (*53*). The issue of when to start cART was concluded in this study that it should start as soon as possible irrespective of CD4 counts even in asymptomatic HIV-infected patients.

In parallel with when to start issue, HIV prevention trial network (HTPN) study group conducted the HTPN 052 study. It enrolled 1,763 serodiscordant heterosexual couples. HIV-infected subjects with CD4 counts between 350/mm^3 and 540/mm^3 were randomly assigned to receive cART either immediately (early therapy group) or after a decline in CD4 counts (delayed therapy group). An interim analysis of this study showed that cART prevented more than 96% of genetically linked infections in the serodiscordant couples (*54*). The study continued for more than 5 years follow up to assess durability of prevention of HIV transmission and concluded that no linked infections were observed when HIV was stably suppressed by cART in the index cases (*55*). The data indicated that both personal and public health benefits from early therapy. Another important prevention study was done in serodiscordant gay couples (PARTNER study). In this study, 782 couples reported 76,088 times condom less sex for median follow up of 2.0 years, but none were genetically linked within-couple transmission. The result was similar with HPTN 052, strongly indicating that when viral load is suppressed, HIV transmission risk is suppressed to zero (*56*). These findings support the message of 'the undetectable equals untransmittable (U=U)" campaign.

Another big advancement of prevention of HIV transmission was that efficacy of pre-exposure prophylaxis (PrEP) for high-risk populations such as men and transgender women who have sex with men (MSM) was demonstrated in many clinical trials (*57,58*) and now operation of PrEP entered into the implementation phase worldwide. In theory, how to mitigate or conclude new HIV transmission can be listed: treat all for infected person to decrease viral load to undetectable level (U=U) and PrEP for high-risk populations. Taking the evidence into account, WHO

published the consolidated guidelines for treatment and prevention of HIV infection for a public health approach in 2016 (*59*). Looking back to Japanese status of treatment and prevention of HIV infection, approved antiretroviral drugs are almost the same as US and Europe, treatment cost is covered by the national health insurance plus the disabled person's coverage system, resulting that all people living with HIV can be treated with adequate treatment with affordable medical cost. In the point of treatment, the goal has arrived at some success. However, looking at prevention wise, to obtain the disabled person's coverage, patients often have to wait until their CD4 counts decrease below 500/mm^3, and that means not all patient can be treated because CD4 counts at diagnosis with more than 500/mm^3 exist at around 20%-30% of patients. Furthermore, PrEP was not approved yet as of December 2021. Above all, countermeasures to HIV prevention are almost 10 years behind the world. Implementation of the treat-all strategy and PrEP is crucial to mitigate HIV infection in Japan.

Along further improvement of the prognosis (*60*), the aging issue of patients has been getting more important in this decade. Causes of death have been changing over time. The number of deaths caused by non-AIDS defining malignancies (NADM) and related mental health issues exceeded that of AIDS-related (*61*). As an example, causes of death in my hospital in 2020 are listed in Table 1. Among 16 cases of death, 50% of patients died of NADM. The mean age of patients with NADM was 55 years old in my hospital, whereas so called cancer age in the general population is 60 years or older in Japan. Not only NADM, but also co-morbidities such as cardiovascular diseases and diabetes mellitus occurred in earlier ages than general population, indicating pre-mature aging in HIV-infected patients (*62*). Reasons for pre-mature aging are not understood clearly. One possibility might be that current cART completely suppresses plasma viral load to an undetectable level, whereas recoveries of CD4 count, CD4 percent, and CD4/CD8 ratio were not sufficient (*63*). Incomplete immune recovery might cause continuous intravascular inflammation that could cause pre-mature aging. Further clinical and basic research should be employed to answer why HIV-infected patients have pre-mature aging.

Table 1. Causes of death in 2020 in patients registered at AIDS Clinical Center

No.	Age	Sex	Category	Cause	Stage
1	30s	M	Mental health	Suicide	AC
2	30s	M	Unknown	unknown	AC
3	40s	F	NADM	Ovarian ca	AIDS
4	40s	M	Mental health	Suicide	AC
5	40s	M	NADM	Colon ca	AC
6	50s	M	Accident	Slip down at mountain	AC
7	50s	M	Mental health	Alcoholic toxication	AIDS
8	50s	M	NADM	Esophageal ca	AIDS
9	60s	M	NADM	Colon ca	AIDS
10	60s	M	NADM	Pharyngeal ca	AIDS
11	60s	M	NADM	Anal ca	AC
12	60s	M	AIDS	Wasting	AIDS
13	60s	M	CCVD	Cardiac arrest	AC
14	70s	M	NADM	Pancreas ca	AC
15	70s	M	CCVD	Cerebral infarction	AIDS
16	80s	M	NADM	Prostate ca	AC

NADM, non-AIDS defining malignancies; CCVD, cerebrocardiovascular diseases; ca, cancer.

Conclusions and Future

Treatment for HIV infection has progressed rapidly for 40 years from dark years to bright future. In the first 15 years, there had been virtually nothing that could save patients and just avoided fatal opportunistic infections. In the second phase of the subsequent 10 years, it had considered what to use, when to start, and how to treat patients with effective but troublesome ART. And in the third phase of the next 15 years, HIV-infected patients are now well recognized as people living with HIV. Their life expectancy is getting much longer with simple and much safer cART. Long-acting ART of once a month or longer is becoming a reality in the near future (*64*) in Japan. However, they have a disproportionally high incidence of comorbidities and therefore reduced health-related quality of life (*65*). For a better future of people living with HIV, broader ranges of care and comprehensive treatment are necessary for them.

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