The Korean Journal of Internal Medicine
Vol. 16, No. 1, March, 2001

Characteristics of HIV Infection/AIDS in Korea

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Since its initial appearance in 1985, human immunodeficiency virus (HIV) infection and its late-stage manifestation, the acquired immune deficiency syndrome (AIDS) have affected a growing number of persons across Korea and around the globe[1]. Worldwide, by the end of the year 2000, 36.1 million persons are living with AIDS, and an estimated 21.8 million had died since the beginning of the epidemic.

As of December 2000, more than 1,280 HIV infections and 286 deaths from AIDS in Korea have been reported to the Korean National Institute of Health (Korean Ministry of Health and Welfare, 2000). The number of cases includes only the reported cases, but the factual number is presumed to be at least three to five times larger. The epidemic in Asian countries, particularly India and Thailand, has lagged temporally behind that in Africa; however, the number of new cases in this region is accelerating rapidly, and the magnitude of the epidemic is projected to exceed that of sub-Saharan Africa in the early part of the twenty-first century[2]. In Korea, the incidence of new infections are persistently increasing each year(Figure 1).

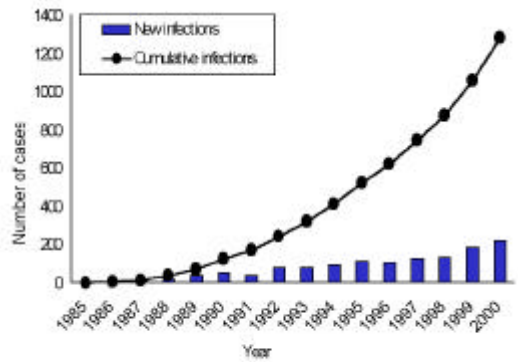

Figure 1. Cumulative prevalence of HIV infection in Korea from 1985 to 2000. The number of new cases are persistently increasing each year.(Korean Ministry of Health and Welfare, 2000)

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Age and Sex Distribution of HIV Infection in Korea

The age distribution of HIV-infected individuals in Korea is 0.4% in 0-9 years, 2.2% in 10-19 years, 31.7% in 20-29 years, 36.0% in 30-39 years, 18.3% in 40-49 years, 8.6% in 50-59 years and 2.9% in over 60 years of age. Among the total number of 1,280 cases in Korea, over 60% are in the age range of 20 to 39 which is the most socioeconomically active age. Male to female ratio is 7:1 (female, 12.5%). The proportion of women among US AIDS cases has increased annually, from 10% in 1988, to 19% in 1995, to 23% in 1999[3]. In US, the predominant exposure for women is attributed primarily to sex with a male IDU[3], while in Korea, it is attributed primarily to heterosexual contact with an infected spouse or partner. In both settings, women may be unaware of their own risk and thus may be difficult to identify and target for prevention interventions. This is why the HIV epidemic in women is complex from a prevention standpoint, and the proportion of women is expected to increase consistently.

Transmission Route of HIV Infection in Korea

While the majority of cumulative HIV infections have occurred in traditional high-risk groups, including men who have sex with men (MSM) and injection drug users (IDUs), persons in other risk categories now account for a greater proportion of AIDS cases than in years past[4]. For instance, heterosexual transmission of HIV has become the

dominant cause of new infections among women[3]. Racial and ethnic minorities represent an increased proportion of AIDS cases[5]. In Korea, 82% of the transmission is by sexual contact, among which heterosexual contact constitutes 72% and homosexual contact 28%. As the major mode of transmission in Korea appears to be heterosexual contact, rather than IDU or homosexual contact, this suggests the potential for widespread dispersion in the general population (Figure 2). Until 1992 most of the sexual contact that was highly likely to be responsible for acquiring infection was from outside of the country, but after 1992, this trend started to shift to the opposite. Other routes of transmission are by transfusion of blood and blood products, which is 3.0%, and by the perinatal route 0.2% (Figure 2).

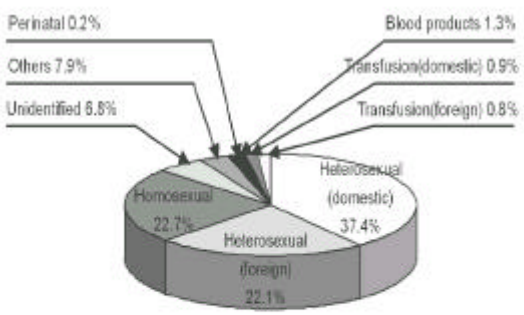

Figure 2. Modes of transmission of HIV infection in Korea. Heterosexual contact is the major transmission route in Korea. (Korean Ministry of Health and Welfare, 2000)

There has been only one case of transmission by IDU in Korea until now (unpublished data). IDU transmission is rare in Korea perhaps because Korean pharmacies sell syringes without a doctor's prescription.

HIV Subtype in Korea

Viruses have been organized into three major groups: group M, which is most common in the Americas abd group O and group N which are most commonly seen in Africa[6]. Group M HIV-1 viruses are further divided into subtypes A through J, of which subtype B is most common in north and south America, Europe, Australia and the Carribean. C type is most common in Africa and southeast Asia[7].

In a study of molecular analysis of HIV-1 in South Korea using the nef gene as an epidemiologic marker, phylogenetic analysis indicated that a majority of Korean carriers were infected with subtype B, whereas three examples for subtype A and one for subtype D were also identified[8]. Most of the subtype B sequences from this South Korean study population was seen to form a monophyletic clade[8]. Until now, subtype A, B, C, D, E, and G of HIV-1 have all been introduced into Korea[9].

AIDS-related Opportunistic Infections and Malignancies in Korea

Highly active anti-retroviral therapy (HAART) has allowed a decrease in the incidence of opportunistic infections (OIs) and Kaposi's sarcoma in HIV-infected individuals with low CD4+ T cell counts. The most common OIs of AIDS are *Pneumocystis carinii* pneumonia (PCP), disseminated Mycobacterium avium complex, esophageal candidiasis, Cytomegalovirus (CMV) retinitis and disease, and Kaposi's sarcoma[10]. The spectrum of HIV-related opportunistic diseases in Korea has been investigated in 2 large studies. In 1999, Oh et al. reported that tuberculosis (25%) was the most frequently observed OI, followed by candidiasis (21%), herpes zoster (20%), PCP (10%) and CMV disease (9.8%). Toxoplasmosis was not found[11]. This finding of high prevalence of tuberculosis in AIDS patients may be speculated by the epidemiologic characteristics of Korea in that tuberculosis has long been an endemic disease in this country. However, more recently, Kim et al. reported that the most frequently observed OI in Korea was PCP (21%), followed by tuberculosis (17%) and CMV infection (12%)[12](Table 1). This unexpected observation that PCP was one of the most important HIV-related infections in Korea, as it is in other western countries, was an interesting finding. The most common cause of death in Korea was tuberculosis and PCP (Table 2). Common AIDS-related malignancies in Korea are lymphoma (1.7%) and Kaposi"s sarcoma (1.1%)[12].

Table 1. Opportunistic Diseases of 121 HIV-infected Persons (n=317 Cases)

Opportunistic Diseases	No. of Cases (%)	Mean CD4+Cell Count (/mm^3)	Mean HIV RNA (copies/mm^3)	Mean β2MG (mg/L)
Candidiasis	50(28.4)	71	338,474	3.6
Oral	6(20.5)	77	415,274	3.5
Esophageal	14(7.9)	57	141,000	3.7
PCP	37(21.0)	63	281,967	3.2
Oral hairy leukoplakia	30(17.0)	206	236,295	3.2
Tuberculosis	29(16.5)	142	817,012	3.7
Pulmonary	8(10.2)	162	833,158	3.1
Extrapulmonary	11(6.3)	89	807,786	5.1
Folliculitis	22(12.5)	186	345,896	3.2
CMV infection	21(11.9)	32	204,093	4.1
Retinitis	15(8.5)	28	-	3.7
Other infections*	6(3.4)	37	204,093	4.4
HIV wasting syndrome	15(8.5)	67	139,890	3.9
Dermatophytosis	11(6.3)	254	355,789	4.5
HIV encephalopathy	9(5.1)	80	798,552	3.8
Herpes zoster	9(5.1)	247	46,191	3.1
Peripheral neuropathy	8(4.5)	79	24,701	4.1
Seborrheic dermatitis	7(4.0)	120	136,641	3.3
MOTT infection	6(3.4)	51	182,630	4.7
Syphilis	6(3.4)	604	239,742	3.4
Cryptococcal meningitis	4(2.3)	88	-	2.2
HIV myopathy	3(1.7)	109	-	3.7
HSV, chronic ulcer	3(1.7)	80	144,364	3.4
Toxoplasmosis, brain	3(1.7)	21	-	4.9
Malignant lymphoma	3(1.7)	46	1,422	5.4
Abscess	3(1.7)	236	261,724	2.6
Kaposi's sarcoma	2(1.1)	198	541,913	3.7
PML	2(1.1)	183	254,297	3.7
Acute pancreatitis	2(1.1)	27	260,000	2.9
Periodontitis	2(1.1)	63	19,097	3.0
Molluscum contagiosum	2(1.1)	35	51,442	2.6
Cervix cancer	1(0.6)	266	17,742	3.4
Eccrine gland cancer	1(0.6)	374	-	5.2
Spinal myelopathy	1(0.6)	272	-	2.7
Rectal cancer	1(0.6)	56	-	2.8
Clonorchiasis	1(0.6)	50	1,422	7.8
Neurocysticercosis	1(0.6)	3	-	-

PCP; pneumocystis carinii pneumonia, CMV; cytomegalovirus, HIV; human immunodeficiency virus, HSV; herpes simplex virus, PML; progressive multifocal leukoencephalopathy, MOTT; mycobacteria other than tuberculosis
*: lung, esophagus, stomach, and colon infections
-: not done

Table 2. Causes of Death in 35 Expired HIV-infected Persons (n=35 Cases)

Cause of Death	No. of Cases (%)
Tuberculosis	9(25.7)
Pulmonary	6(17.1)
Extrapulmonary	3(8.6)
PCP	9(25.7)
Bacterial pneumonia	7(20.0)
HIV encephalopathy	3(8.5)
Cryptococcal meningitis	2(5.7)
Malignant lymphoma	2(5.7)
Sepsis	1(2.9)
Toxoplasmosis, brain	1(2.9)
Myocardial infarction	1(2.9)

PCP; pneumocystis carinii pneumonia, HIV; human immunodeficiency virus

Anti-retroviral Treatment Regimens and Response in Korea

Zidovudine is the first anti-retroviral drug that was introduced into Korea. This drug is supplied free to patients by the government. Didanosine was covered by insurance from 1994, and lamivudine and indinavir from 1998. HAART has been applied to patients for over 3 years in Korea with various regimens. There are 9 available drugs in Korea, which are zidovudine, lamivudine, didanosine, stavudine, zalcitabine, efavirenz, nelfinavir, ritonavir and indinavir. Patients who are enrolled with the government are supplied with HAART and other medical financial support (restricted to insurance coverage items) by the government.

The most commonly used HAART regimen in Korea is two nucleosides combined with a protease inhibitor. A study of Koreans with a triple combination therapy, including zidovudine, didanosine, lamivudine and indinavir, has an effect of lowering the level of HIV RNA to non-detectable range of less than 500 copies/ml at 1 month in 70% and at 12 months in 90% of the Korean patients. The mean CD4+ T cell count of 206/mm3 rose to 376/mm3 after 12 months of treatment[13].

Adverse Effects of HAART in Korea

With the increasing usage of HAART, various adverse effects are being experienced in HIV-infected individuals. Common adverse effects of triple combination therapy, including zidovudine,

Table 3. Metabolic parameters in HIV-infected individuals and healthy controls.

	HIV-infected individuals		
	HAART-experienced (n=57)	HAART-naive (n=42)	Healthy controls (n=57)
Total cholesterol (mg/dl)	158.1± 20.2	152.6± 16.8	156.2± 18.0
Triglyceride (mg/dl)	148.3± 22.7	139.3± 12.1	121.3± 9.3
HDL cholesterol (mg/dl)	31.7± 1.4	32.7± 2.1	38.4± 1.9
LDL cholesterol (mg/dl)	96.3± 10.3	91.5± 11.3	95.2± 9.4
Free fatty acid (Eq/L)	352.1± 63.3	339.2± 59.3	-
Apo A1 (mg/dl)	100.1± 16.4	102.3± 24.2	-
Apo B (mg/dl)	79.5± 14.7	77.9± 18.4	-
Glucose (mg/dl)	96.4± 6.1	92.5± 7.1	98.0± 8.2
Insulin (IU/ml)	10.8± 4.2	8.9± 1.9	9.2± 1.0
C-peptide (ng/ml)	3.4± 0.7	3.1± 0.8	2.9± 0.3
Insulin resistance ($mmol^2/l^2$)	2.6± 0.8	2.1± 0.4	2.3± 0.3
Leptin (ng/ml)	3.2± 3.1	2.9± 2.3	-
Cortisol (g/dl)	8.9± 2.8	8.8± 2.6	9.1± 3.0
DHEA (ng/ml)	5.1± 4.1	5.8± 3.1	4.8± 2.8

Data are means ± SD. Statistical analysis was done by analysis of variance (ANOVA) methods and multiple comparison analysis (LSD) of the SAS system. There is no statistical difference in the metabolic parameters between the three groups of individuals ($p>0.05$).
HAART; highly active antiretroviral therapy, HIV; human immunodeficiency virus, HDL; high density lipoprotein, LDL; low density lipoprotein, Apo; apolipoprotein, DHEA; dehydroepiandrosterone

lamivudine, didanosine and indinavir, in Koreans are asymptomatic indirect hyperbilirubinemia, flank pain, nausea, fatigue and headache. Skin rash, abdominal discomfort and elevation of transaminases are some rare complications in Koreans[13]. Lipodystrophy, hyperlipidemia and hyperinsulinemia are common metabolic complications of HAART in HIV-infected individuals[14]. Protease inhibitors (PIs) can cause hyperglycemia, hyperinsulinemia, insulin resistance, hyperlipidemia and lipodystrophy.[14,15] One of the largest studies of PI-induced lipodystrophy reported an 83% prevalence rate with an 11% incidence of severe lipodystrophy.[14] Another recent study reported a 13% cumulative incidence of new onset lipodystrophy in a 5-year cohort study.[15] However, in the largest metabolic complication study in Korea, lipodystrophy was found in only 3.5% of patients who were on HAART for a mean duration of 25 months[16]. Lipid alterations associated with AIDS are known as hypertriglyceridemia, high free fatty acid, low HDL and LDL cholesterols[17]. PI use are characterized by increase of serum triglyceride, ranging from 12.9% to 80%, and increase of LDL cholesterol without ameliorating low HDL[18,19]. However, triglyceride, total cholesterol, LDL and HDL cholesterol, FFA, ApoA1, ApoB, glucose, insulin, c-peptide, leptin, cortisol and DHEA were not influenced by HAART in Koreans[16](Table 3). These findings warrant further race-specific metabolic complication studies in HIV-infected subjects receiving HAART. Osteoporosis is a recently recognized clinical feature in HIV infection that needs to be clarified through more investigations of whether it is an effect of HIV infection itself or an adverse effect of HAART. Osteoporosis and osteopenia were examined in Koreans in a recent study, and showed results of no relevance of either HIV infection or drug in Koreans[20].

Genotypic Resistance of Anti-retroviral Drugs in Koreans

The decreases in incidence of AIDS-related opportunistic illnesses and declining mortality among HIV-infected persons have been largely attributed to the availability of HAART. However, our ability to sustain these advances among HIV-positive persons is threatened by the emergence of anti-retroviral drug resistance.

Genotypic resistance of anti-retroviral drugs in Koreans was investigated in a cross-sectional study conducted with 41 HIV-infected Koreans (29 naïve and 12 HAART-experienced for a mean duration of 11.3 months) from October 1999 to September 2000 in an outpatient clinic of a university hospital and the Korean National Institute of Health. The entire protease gene and 250 amino acids of the reverse transcriptase (RT) gene were amplified and sequenced. Analysis was done by DNASTAR and the program was supported by HIV RT and Protease Sequence Stanford Database (HRP-ASAP). Primary resistance to nucleoside analogue reverse transcriptase inhibitors (NRTIs) was observed in 4 out of 29(14%) naïve individuals, whereas primary resistance to protease inhibitors (PIs) was found in none of naïve individuals. The frequently involved codons in NRTI resistance were at positions 41(50%), 69 (50%), and 215(50%). In HAART-experienced individuals, the prevalence for primary resistant genotypes was 42% for NRTIs and 25% for PIs. The most frequent NRTI mutations occurred at codons 184(42%) and 41(17%), whereas the most common PI resistance mutation was at codons 82(17%) and 48(8%). Some atypical amino acid changes such as M41I, D67G, T69A, M184V/R, G190K, L210M of the RT and L10M, K20I, G48R, L63A/V/T, G73S, V82I of the protease gene were detected in HIV-infected Koreans. Codon 63 may not be associated with resistance in Koreans but only a typical characteristic of the Korean isolates since L63A/V/T mutation in the protease gene was detected in 93% of naïve and HAART-experienced Koreans. Resistance was detected 3 times more frequently in the RT gene and more frequently in the protease gene in the HAART-experienced compared to the naïve Koreans. Genotypic resistance may be useful prior to the introduction of HAART in Korea. Since Korean isolates have some unique characteristics in genotypic resistance, phenotypic resistance and clinical correlation are to be considered for the evaluation of the effects of specific drugs.

Several studies have demonstrated that resistance testing improves virologic response to second-line HAART regimens among HIV-infected persons who have failed initial empiric therapy, and the prevalence of resistance mutations or resistance phenotypes among drug-naïve persons is generally low[21].

However, eventual recommendations regarding resistance screening to inform the choice of initial HAART regimen depend largely on the prevalence of resistance among HAART-naïve persons, so ongoing surveillance of resistance in treatment-naïve populations is critical.

Conclusion

HIV infection is persistently increasing in Korea. The most common transmission route is by sexual contact and the notable difference of transmission route in Koreans is that HIV infection by IV drug abuse is very rare. Investigations on the treatment response of HAART shows that triple combination therapy in Koreans appeared to be generally well tolerated, and was able to profoundly sustain suppression of plasma HIV-RNA to undetectable levels in most patients. A notable characteristic finding of the adverse effect of HAART in Koreans is that lipodystrophy was observed in only 3.5% of the patients on HAART, and hyperlipidemia or insulin resistance was not found. Since genotypic resistance was detected in 14% of NRTI naïve Koreans, resistance testing may be useful prior to the introduction of HAART in Korea.

HIV infection in Korea has some unique features which are different from those of other races or countries. For a more detailed and definite identification of the differences, a prospectively designed investigation on a larger scale is necessary, which will eventually enable better therapeutic and epidemiologic strategy for HIV infection/AIDS in this country.

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