

# **HIV Disease in Ethnic Minorities: Implications of Racial/Ethnic Differences in Disease Susceptibility and Drug Dosage Response for HIV Infection and Treatment**

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AIDS was originally considered a disease of the gay population (Mays & Cochran, 1987). In particular, AIDS was viewed as a White gay male disease (Cochran & Mays, 1988; Mays & Cochran, 1995). However, increasingly over the years, both the highest incidence and greatest numbers of new cases of HIV infection in the United States are within ethnic minority populations, especially among African Americans and Hispanics (Karon et al., 1996; Rosenberg & Biggar, 1998). A recent study examining the prevalence of HIV infection found that the estimated rate in White males was from 3.3 to 4.9 per 1,000, but from 16.8 to 22.5 among Black males and from 9.0 to 13.0 among Hispanic males (Karon et al., 1996). Similar patterns were found for women, with estimates of from 1.7 to 2.6, 10.6 to 14.2, and 5.6 to 8.2 for Whites, Blacks, and Hispanics, respectively. Using data from 1995, Rosenberg and Biggar (1998) showed that HIV incidence attributable to heterosexual contact is striking in its pattern among successive birth cohorts of ethnic minorities. They found that Black women have the highest incidence of infection attributable to heterosexual contact, with estimates that 1 in every 1,000 20-year-old Black women become HIV infected via heterosexual sexual routes. This compares to estimates that 1 in 2,800 similar aged Hispanic women and 1 in 15,000 White women suffer similar fates. Concurrently, the incidence of HIV infection is greater among young ethnic minority men than in White men in every transmission route, including male-to-male sexual transmission (Rosenberg, & Biggar, 1998). Here, the incidence of AIDS cases attributable to male-to-male sexual contact is four times higher in Black men and two times higher in Hispanic men when compared to White men. This discrepancy in risk is expected to widen as the incidence and numbers of new cases of HIV infection in White gay men declines (Fahey & Flemming, 1997).

In the meantime, AIDS-related research continues in the hope of finding new drugs for the treatment of AIDS and HIV infection. But the implication of these accelerating trends, shifting a greater illness burden into ethnic minority communities, presents a new challenge for researchers. Much research continues to be conducted using White male subjects. Blacks, who earlier in the history of AIDS clinical trials represented 34% of all AIDS cases (Fahey & Flemming, 1997), previously made up only 7% of the subjects in National Institute of Health (NIH) HIV/AIDS studies (Ready, 1988). Similarly, Hispanics represented 17% of AIDS cases, but were only 9% of the NIH research subjects. There are many complicated reasons for the low participation of ethnic minorities in HIV-related clinical drug and vaccine trials ranging from debatable scientific decisions to politics (El-Sadr & Capps, 1992; "Getting Cancer Patients Into Clinical Trials," 1991; Mays, 1998, 1999; Mays & Cochran, 1999). But despite this, there is growing evidence in various areas of medicine that racial/ethnic differences in disease susceptibility and drug response do exist (Pollack, Safari, & DuPont, 1983; Winchester, Chen, Rose, Selby, & Borkowsky, 1995; Zhou, Koshakji, Silberstein, Wilkinson, & Wood, 1989; Zhou, Shay, & Wood, 1993). Failure to consider these differences while attempting to develop new methods of treatment, or even possibly a cure, could have significant public health implications, particularly for ethnic minority Americans. In the hopes of encouraging consideration of these issues more fully, this chapter reviews here the existing evidence for HIV-relevant racial differences in disease susceptibility and drug dosage response.

#### GENETIC RACIAL DIFFERENCES RELATED TO HUMAN LEUKOCYTE ANTIGENS

A particularly useful area to consider in identifying possible racial/ethnic differences in HIV infection and disease is in distribution of Human Leukocyte Antigens (HLA) because of their relation to immune function. HLA molecules have a significant function in initiating the immune response through processing and presenting foreign antigens to T-cells, which then triggers clearance of the virus from the body. Racial variations in the genes encoding HLA Class I and II molecules have an effect on antigen presentation and may influence the host immune response. These tissue type antigens are used by the T-cells of the immune system to distinguish host cells from foreign cells (i.e., the self from the nonself). Every individual has a unique combination of HLA molecules on chromosome 6 called the major histocompatibility complex (MHC). HLA-A, HLA-B, and HLA-C are encoded by Class I genes, whereas HLA-DR, HLA-DQ, and HLA-DP regions are encoded by Class II genes. The Class II regions determine the selection of various cell membrane associated glycoproteins that serve numerous functions in the regulation of the T-cell immune response of the body (Callender & Dunston, 1987). A subset

of T-cells kill viral infected cells, but ironically HIV also attacks a subset of the population called the CD4+ cells. Studying specific racial variations in the Class II region may further elucidate the role they play in the T-cell mediated immune system response to HIV infection.

Because the use of HLA typing is common for the determination of the histocompatibility of tissues for transplantation, research in this area has led to the discovery of HLA determinants associated with particular racial groups. These determinants are polymorphic, resulting in differences between races in the frequency of the alleles (gene variants) at the various HLA loci. For example, in a sample drawn in Washington, DC, HLA-A23 and A30 were four times more likely to be found in Blacks than in Caucasians (Dunston, Henry, Christian, M. D. Oforu, & Callendar, 1989). Also, B45, Bw58, Bw53, Bw70, Cw7, DRw13, and DRw8 were also more likely to be found in Blacks. Further, unique HLA specificities are seen in the Black population. For instance, Aw34, Aw36, A19v, and Bw42 appear to be unique to Blacks (Callender & Dunston, 1987; Dunston, Hurley, Hartz, & Johnson, 1989).

Although a majority of previous HLA research focused on racial differences only between the Black and White population, presently DNA technology allows further identification of specific HLA alleles, suggesting HLA relatedness and differences with other racial groups. Osborne and Mason (1993) designed an HLA haplotype frequency table consisting of HLA alleles common to the U.S. Hispanic population. They reported similarities and differences in HLA A/B haplotypes among Hispanic Americans of both Caribbean and Mexican ancestry. They also reported that HLA A19/B12, A25/B12, A1/B17, A2; A34/B38, and A1; A3/B40 are common in Mexican Americans, whereas A9/B12, A19/B12, A29/B12, A2/B16, A28/B17, A19/B44, A24/B40 are shown to be common in Caribbean Hispanics. For example, HLA A28/B17 is 24 times more likely to be found in Hispanic Americans of Caribbean origin than in those of Mexican ancestry (Osborne & Mason, 1993).

Investigation of HLA Class II alleles in South American Indians show specific HLA haplotypes among those of Brazilian and Argentinean background (Cerna et al., 1993). In a study of three Argentinean tribes (Eastern Toba, Western Toba Pilaga, and Mataco Wiehi) and Xvantes from Central Brazil, the most common HLA allele was DPB1 \*0402 (Cerna et al., 1993). However, Brazilians display four DR groups: DRB1\*0404, DRB1\*0407, DRB1 \*0802, and DRB1\* 1402. Frequent alleles at the DRB1 locus in Argentineans were shown to include DRB1\*04, DRB1\*0802, and DRB1\*14.

Modern genetic studies of HLA genes have made possible comparisons between Ashkenazi Jews from Eastern and Central Europe and Non-Ashkenazi Jews from Mediterranean and Asian Countries (Martinez-Laso, Gomez-Casado, Morales, & Martinez-Quiles, 1996). Common alleles found in both Jewish groups are DRB1\*07, DRB1\*0402, DRB1\*1104, DRB1\*0102. Allelic differences within the Jewish population can be illustrated in the frequency of alleles at the DR13 loci. For example,

DRB1\*1301 is more common in Ashkenazi than in non-Ashkenazi Jews. Furthermore, DRB1\*1301 is six times more likely to be present in non-Ashkenazi Jews of Mediterranean ancestry in this subgroup (Martinez-Laso et al., 1996).

These disparate results suggest significant biological differences in HLA between races. Given the important role of HLA in immune-related disease, these racial differences may play an important, but understudied, role in HIV and may subtly influence outcomes of research directed at disease susceptibility and drug dosage response in HIV/AIDS. Studying ethnic differences in HIV disease may lead to important insights in the varied role of the viral immune response and identify new approaches for therapeutic research.

It is already known that each individual has a unique distribution of HLA alleles, and specific HLA haplotype combinations are found more frequently in different ethnic groups. Studies have also shown that with particular combinations of HLA haplotypes, the chances for long-term survival with HIV and AIDS is improved (Kaslow et al., 1990; Louie, Newman, & King, 1991; Steel et al., 1988). Yet, most of these studies have been done using data gathered from gay White men, who represent only a portion of those living with HIV and AIDS (Louie et al., 1991). In one study conducted by Louie et al. (1991) of gay White men living in 19 census tracts having the highest risk for AIDS in San Francisco, results showed that those who carried HLA DRB1\*1101, 1104, and 1201 had the worst disease outcome. The presence of DRB1\*0101 (DR1), HLA A\*2401 (A24), HLA B\*(B35), and HLA C\*0401 (C4) was associated with an increased rate of progression to AIDS, whereas those with the alleles HLA DRB1\*0701 and 0702 had a slower CD4 cell decline as well as slower progression to AIDS (Louie et al., 1991). Within the study, a comparison was made between those who were symptomatic and those who were asymptomatic. The HLA alleles DRB1\*0702 and DQA1\*0201 were more frequent among HIV+ asymptomatic men compared to HIV+ men who were symptomatic. Therefore, the presence of these alleles may confer a protection against the progression of AIDS. This study also showed that CD4+ cell counts declined faster in those with the HLA allele DQA1\*0101 present, thus resulting in the more rapid progression of AIDS. The presence of the HLA combination A1-B8-DR3 was also associated with rapid CD4 cell decline (Louie et al., 1991).

Other studies of African Americans and Caucasians offer further support for the role of HLA differences and HIV/AIDS disease progression. In the heterosexual population, HLA distribution is associated with the severity of HIV infection, and the likelihood of developing AIDS. HLA's found more frequently among HIV+ African Americans are A31(19), B35, Cw6, Cw7, DR11, DR12, DQ1, and DQ3, when compared to controls. Among the Caucasian HIV+ participants, A28, A66, B48, Cw7, Cw8, DR10, DR5, DQ1, and DQ7 are associated with HIV infection. Although some haplotypes are

common in the two groups, Cw4 and DR6 were more common among uninfected African Americans (M. N. Brackin et al., 1995). Thus, Cw4 and DR6 may provide protective resistance to HIV infection. On the other hand, A69(28)-B40 and B12-DR14(6) were associated with rapid progression in African Americans. In Caucasians, A28-B17-DR9 and DQ2 were associated with rapid progression, and A30(19)-B67 with slow progression. Studies of other ethnic groups reveal associations with different alleles of the same genes (Louie et al., 1991).

Studies have also reported other HLA associations with susceptibility to HIV-1 infection as well as to disease progression. It was shown that susceptibility to infection with HIV-1 among both African Americans and Caucasians may be influenced by HLA-DQB1 alleles (Achord, Lewis, M. N. Brackin, & Cruse, 1997). Using molecular methods, Achord and colleagues (1997) found a significantly higher frequency of DQB1\*0605 in HIV-1 positive African Americans as compared to HIV-1 negative African American controls. DQB1\*0602 was associated with HIV-1 infection in Caucasians. Although no HLA-DQB1 marker was found to be protective against HIV-1 infection in African Americans, HLA-DQB1\*0603 was found to be protective in Caucasians. These results demonstrated that different HLA molecules may be associated with HIV-1 infection or protection from infection in Caucasians and African Americans (Achord et al., 1996). Possible HLA associations with HIV-1 disease progression between different ethnic groups was also examined. HLA allele frequencies among slow progressors were compared to those of rapid progressors, stratified by race. HIV-1 infected African Americans positive for the DQB1\*0602 allele exhibited slower disease progression. Kaplan-Meier survival analysis showed a mean survival time of 71.3 months for those patients without the allele as compared to 117.8 months for the African American patients who had this allele. No marker was found to be associated with rapid disease progression in African Americans. In the HIV-1 infected Caucasian group, the DQB1\*0302 allele was more common in rapid progressors. Patients positive for the DQB1\*0302 allele had a mean survival time of 47.5 months as compared to 70.7 months for patients without the allele as shown by the Kaplan-Meier survival analysis (Achord et al., 1997).

Numerous studies have investigated the role HLA plays in response to HIV-1. It has been shown that MHC Class II DRB1 alleles of the infant influence transmission of HIV-1 from an infected mother during gestation and delivery and the association may be influenced by ethnicity (Winchester et al., 1995). Winchester et al. (1995) found a higher frequency of the DRB1\*03011 HLA allele in the infected White infants born to HIV-1 positive mothers and a higher frequency of DRB1\*1501 in the uninfected group. Also demonstrated was a higher prevalence of DR13 alleles, including DRB1\*1301, 1302, and 1303 among the African American and Hispanic infants studied. The DRB1 13 alleles are associated with an enhanced immune response to a specific HIV peptide and to resistance to HIV infection. The

frequency of the DRB 13 alleles varied with racial ethnicity. Among the African American infants, 29% of uninfected infants were positive for these alleles, in comparison to 0% of HIV-infected infants (Winchester et al., 1995). The association of specific HLA molecules with HIV-1 susceptibility was further examined in Italian children. The DRB1\*1301 allele was also found to be more frequent among infected Italian infants as compared to uninfected Italian infants born to HIV-1 positive mothers (Greggio et al., 1993; Scorza Smeraldi, et al., 1986).

In another study by Just et al. (1992), an association of HLA genotypes and susceptibility to HIV prenatal infection was found among Black infants born to HIV positive mothers. Results of this study showed the HLA DQA1\*0102 allele provided a protective role whereas the allele DPB1\*0101 was associated more with risk of infection. The uninfected infants had a higher prevalence of the DQA1\*0102 allele than the infected infants (65% vs. 43%). Whereas the DPB1\*0101 was more commonly detected among the infected infants (66%) than among the uninfected infants (43%). Additionally, infants who lack the allele DQA1\*0102 and have a specific amino acid sequence of -asp-glu-ala-val-at HLA-DPB1 positions #84-87 have a stronger association with HIV infection than those infants with the specified amino acid sequence of DPB1 and the DQA1\*0102 allele. Results of the study also show that the infants most protected from HIV infection, had a different sequence of amino acids at positions #84-87 of the DPB1 gene locus other than -asp-glu-ala-val-, and may or may not have had the DQA1\*0102 allele.

In a study (Kilpatrick, Hague, Yap, & Mok, 1991) conducted on Scottish infants born to HIV+ mothers, the frequency of HLA DR3 was three times higher in the HIV+ infants (i.e., 13% as compared with 30%). The low rate of HIV+ infants may be due to the haplotype combination they found for this group. A3-B7-DR2 was found only in the infants who were not HIV infected, perhaps offering some form of protection. The study also confirmed the results of other studies using White samples, which indicated that A1-B8-DR3 may be associated with susceptibility (Just et al., 1992; Kilpatrick et al., 1991; Yanase et al., 1986).

These studies based on infants of different ethnic backgrounds, combined with previous studies examined, hint at the possible relevance of differences in the HLA make up of different racial groups in HIV disease. Furthermore, HLA loci have also been shown to play a role in several other diseases. For example, HLA typing of Class II region reveals significant differences between African Americans with and without Grave's disease (M. H. Ofsu et al., 1996).

HLA loci are important factors in graft survival in kidney transplantation. It has been shown that the chance of graft survival increases when DRw6 allele matched in kidney transplantation (Callendar & Dunston, 1987). For kidney transplantation, in particular, race seems to have a major role in the outcome of the operation. In 1987, Blacks accounted for 12% of the U.S. population, but made up 27% of the pa-

tients with end-stage renal disease. Racial differences in ABO blood groups and MHC antigens make organ matches extremely difficult, especially because only 8% of donors are Black (Kasiske et al., 1991). For blood types O, A, B, and AB, the distribution in the White population is 45%, 40%, 11%, and 4%, respectively. On the other hand, the Black distribution is 49%, 27%, 20%, and 4%, respectively. Whereas ABO typing must be matched in the first place for tissue transplantation, exact MHC matching of HLAs is not always possible because the majority of donated kidneys are from Caucasians. Because of frequent mismatching, long-term survival of grafts is significantly lower for Blacks than for Whites (Kasiske et al., 1991). In general, when recipients had no HLA mismatches, they suffered fewer rejections and required less cyclosporine, which is the steroid administered to enhance graft survival (Callender & Dunston, 1987). Newer studies suggest that when equivalent Black and White kidney recipients are chosen and a cyclosporine regimen is followed, patient and graft survival are the same in Blacks and Whites (Friedman, 1991). Although accessibility of health services and everyday life and economic struggles that act as barriers in facilitating necessary daily health regimes may contribute to graft loss in poor Blacks (especially within the inner city), the effects of racially determined HLA typings still play a significant role in graft survival.

Sickle cell disease is another area in which—in this instance transfusion-related immune response—there is an association with several HLA specificities. Sickle cell disease patients commonly undergo blood transfusions in the treatment of their illness. Studies show that after receiving a transfusion, patients with HLA-B35 are six times more likely to produce antibodies against the transfused cells (alloimmunization) than patients without this antigen (Alarif, Castro, M. Ofofu, Dunston, & Scott, 1986). In addition, a lower incidence of alloantibodies has been associated with the presence of HLA-DR3 and of A28 and B15 (M. D. Ofofu, Saunders, Dunston, Castro, & Alarif, 1986). These associations, given the racial differences in HLA typing, indicate that Blacks may be more susceptible to alloimmunization due to transfusions received in the treatment of sickle cell disease. Indeed, in one study among Blacks, a 30% alloimmunization rate was found, whereas Whites had a 5% rate despite receiving, greater numbers of transfusions (Vichinsky et al., 1990). Because Blacks comprise a low proportion of blood donors (the donor population being mainly White), differences in the antigen mismatching between donors and recipients among African Americans may account for the resulting differences in alloimmunization frequency.

Association between HLA haplotypes and susceptibility to insulin dependent (Type 1) diabetes mellitus (IDDM) has also been studied. Specifically, it has been shown that the HLA-DQ region plays a role in IDDM susceptibility (Fletcher et al., 1988; Ronningen et al., 1993). In general, among Caucasians, DR3 is almost always associated with DQw2, whereas among Blacks, DR3 may be

associated with two phenotypes, DQw2 or DQw-. In a study of Black IDDM patients and Black non-IDDM controls, the haplotype DR3-DQw2 was found in all IDDM patients, whereas DR3-DQw-, common in the control group, was not found in the IDDM patients (Dunston et al., 1989). The DR3-DQw2 haplotype, therefore, seems to be a marker for insulin dependence in the Black diabetes patients studied, whereas DR3-DQw- is more likely to be associated with resistance to IDDM. Because IDDM is more prevalent among Black Americans than Black Africans, and DR3-DQw2 (found in nearly all Caucasians) is associated with susceptibility to IDDM, it is possible that the susceptibility genes for IDDM were introduced into the Black American population due to the admixture of Caucasian genes (Dunston et al., 1989).

Further studies also indicate genetic differences in the susceptibility and resistance to IDDM in the Mexican American population. Although the incidence of IDDM among Native Americans is low, the incidence in Non-Hispanic Whites is 15/100,000 year and 9.5/100,000 year in Mexican Americans (Eisenbarth, 1986). This pattern is consistent with the lower prevalence of the European derived HLA-DR3 haplotype in the Mexican American population, which has HLA haplotypes derived from the Native American and Hispanic Caucasian admixture heritages. Furthermore, HLA-DR3 and DR4 linkage to specific HLA DQB1 alleles influences risk of IDDM (Sanjeevi et al., 1993). Recent studies show that the Mexican population contains a variety of different DR4-DRB1 alleles (Erlich et al., 1993). Namely, there are 9 different DRB1 alleles, and 16 different DRBQ haplotypes. The risk of IDDM in this population varies from highly susceptible to protective based on the DRB1 allele present. High risk haplotypes—DRB1\*0402, DQA1\*0301, DRB1\*0405, and DQB1\*0302—are of European origin. Specifically, DRB1\*0405 is common in Spain and may illustrate the Hispanic Caucasian descent in the Mexican American population. Lower rates of IDDM in Mexican American controls corresponds to Native American ancestry.

Race has also been found to be a major contributor to the prevalence of diabetic nephropathy. In inner-city Blacks (e.g., from Brooklyn), Hispanics, and Native American Indians, the prevalence of non-insulin-dependent diabetes (NIDDM) is much higher than in non-Hispanic Whites (Friedman, 1991). Within these diabetic groups, there also seems to be a genetic predisposition to increased risk for diabetic nephropathy as compared to Caucasians. This disposition is associated with a genetic risk for hypertension. The rate of erythrocyte lithium-sodium countertransport is a marker for hypertension, and this rate is increased in those who develop nephropathy. In addition to this genetically inherited trait, end-stage renal disease (ESRD) due to diabetic nephropathy is caused mainly by NIDDM. Because Blacks, Hispanics, and American Indians suffer from NIDDM to a much greater extent than Whites, they also suffer from a higher prevalence of diabetic ESRD (Friedman, 1991).

Mixing of genes between races from interracial matings has led to changes in susceptibility. For example, following the introduction of Caucasian genes into the Pima Indian population, the prevalence of NIDDM has decreased commensurate with the decreasing prevalence of the Gm 3;0 5,13,14 haplotype, which is a risk factor for NIDDM (Friedman, 1991). Thus, as a function of the dilution of the genes associated with NIDDM susceptibility, the prevalence of NIDDM has decreased accordingly. Therefore, interracial mating is an important factor to consider when examining ethnic differences in disease susceptibility. As previously discussed, the distribution of HLA alleles are different among different racial groups. Thus, acquisition of genes from parents of different ethnic backgrounds influences biologically based responses and outcomes to disease.

HLA specificities also play a role in the susceptibility to human T-cell leukemia virus Type I (HTLV-I). In the HTLV-I endemic area of Kyushu, Japan, HLA-DQw3 is associated with HTLV-I infection that is associated with T-cell leukemia (ATL). Ninety one percent of the ATL patients had increased frequencies of HLA A26 and B39, as compared to HTLV-1 infected individuals without ATL. Thus, these alleles may be associated with predisposition to developing ATL in the course of HTLV-I infection (Uno, Kawato, Matsuoka, & Tsuda, 1988; White et al., 1996). Different alleles were observed in Black and Caribbean ATL patients in which frequencies of A36, B18, and Class II HLA-DR53 were higher (White et al., 1996).

Ethnic differences have been observed in age of onset and severity of myasthenia gravis between Chinese and Caucasians. Chinese patients were found to have less severe cases and display an earlier occurrence of this disease than Whites. Among Chinese patients, there is a strong correlation of Bw46 and DR9 with myasthenia gravis (Chen, Chiu, & Hsieh, 1993). Furthermore, the frequency of the Bw46DR9 combination was found to be increased in Chinese juvenile patients with onset before age 20 and decreased thereafter ( $20\% \geq 20$  and  $60\% \leq 20$ ). However, A1, B8, and DR3 are correlated with myasthenia gravis in Whites over age 40. Also, specific HLA combinations are associated with myasthenia gravis in other ethnic groups: HLA-DR8 and DR3 in Whites; A1, B8, and DR5 in American Blacks; and DR9 and DRw8 in Japanese.

HIV-associated diseases also show racial differences. In a study of patients with renal disease due to HIV-1 infection, known as HIV-1 associated nephropathy (HIVN), Black HIV-infected patients were more likely than Whites to develop HIVN (Bourgoignie, Ortiz-Interian, Grenn, & Roth, 1989). Moreover, whereas the majority of HIV-infected patients are White, most HIVN patients are Black. Even after taking IV drug use into account, HIVN occurs 10 times more often in Blacks. Furthermore, the predilection for HIVN cannot be attributed to differences in age, duration of disease, or to the

presence of other major opportunistic infections. This suggests a strong possibility that genetic factors are responsible for the higher frequency of HIVN among Blacks (Bourgoignie et al., 1989).

Investigations have demonstrated that non-HLA genetic factors also influence susceptibility to HIV infection and the pathogenesis of AIDS. The vast majority of people are susceptible to infection with HIV. However, rare individuals remain uninfected by HIV-1 despite multiple sexual contacts with subjects known to be HIV-1 infected (Detels et al., 1996; Liu et al., 1996). In mid-1996, a naturally occurring 32-bp deletion mutation ( $\Delta$ 32 allele) in the chemokine receptor gene CCR5 was found in subjects who remain uninfected despite repeated, extensive exposure to HIV-1 (O'Brien et al., 1998). Before the discovery of the role of chemokine receptor genes in HIV infection, only HLA genetic factors were thought to affect susceptibility of HIV infection. Studies have since identified molecular co-receptors that HIV uses in conjunction with CD4 cell entry. The macrophage-tropic, or M-tropic HIV strains use CD4 and a chemokine receptor gene called CCR5, whereas the protein CXCR4 is an entry coreceptor for T lymphocytes-tropic (T-tropic) HIV strains only (O'Brien & Goedert, 1998). Several studies confirmed the protective role of homozygosity for a 32 base pair ( $\Delta$ 32) deletion in the CCR5 gene to HIV-1 infection. Rare individuals homozygous for this  $\Delta$ CCR5 allele appear to be protected from HIV-1 infection despite repeated exposure to HIV-1 through unprotected sex with HIV-1 positive partners (Liu et al., 1996). It has been shown that genotype frequencies of the  $\Delta$ CCR5 allele vary markedly across different ethnic groups. Among Caucasians in North America or Europe, about 1% are  $\Delta$ CCR5 homozygous. Homozygous  $\Delta$ CCR5 is rarely found in non-Caucasians. Heterozygosity of the  $\Delta$ CCR5 allele is found in approximately 10% to 20% of Caucasians, approximately 6% of African Americans, 7% of Hispanics, 13% of Native Americans, and 1% or less of Asians (Dean et al., 1996; McNicholl, D. K. Smith, Qari, & Hodge, 1997; Zimmerman et al., 1997).

Similarly, Smith et al. (1997) reported that homozygosity for the  $\Delta$ CCR5 was not uncommon among exposed but uninfected individuals (1%-5%), but extremely rare among infected individuals (< .1%) (Dean et al., 1996; Huana et al., 1996). The different frequency of the homozygous  $\Delta$ CCR5 allele between Caucasian HIV-positive homosexual men (0%), and in highly exposed seronegative (4.5%), provides further support for the protective role of the  $\Delta$ CCR5 allele (Zimmerman et al., 1997).

Whereas individuals homozygous for the  $\Delta$ CCR5 allele appear to be resistant to infection, it has been shown that heterozygosity may delay the progression to AIDS in infected individuals. Infected individuals heterozygous for the  $\Delta$ CCR5 experienced a delay in the onset of AIDS of approximately 2 to 4 years, as compared to individuals with the normal CCR5 gene, in several large AIDS cohort studies (Dean et al., 1996; Huang et al., 1996; M. W. Smith et al., 1997). The long-term nonprogressors of the homosexual cohorts showed more than twice the percentage of heterozygotes compared with rapid

progressors (Dean et al., 1996). The data suggest that heterozygosity for the  $\Delta$ CCR5 allele does not affect susceptibility to infection, but rather it may postpone progression to AIDS among those already infected. Population studies have estimated the frequency of  $\Delta$ CCR5 at approximately 15% among North American or European Caucasians, but have not found any cases of  $\Delta$ CCR5 among Black populations with the exception of African Americans in the United States. A global distribution of the  $\Delta$ CCR5 allele shows the highest allele frequency recorded in the Ashkenazi Jewish population, 20.9%, descendants of ancient Israel and east European people, a frequency of from 2% to 5% throughout Europe and a general absence in sub-Saharan Africa peoples (Martinson, Chapman, Rees, Liu, & Clegg, 1997). In a study of the urban Brazilian population, comprised of Europeans, Asiatics, Arabians, Africans, and Native Amerindians, the frequency of the mutant allele in this population was 35%, but no homozygous,  $\Delta$ CCR5 individual has been discovered so far (Passos & Picanc, 1998). Differences in prevalence of the  $\Delta$ CCR5 allele continue to be examined among different ethnic groups. A study of the CCR5 gene among 377 Puerto Ricans showed 94.2% nondeletion homozygote (normal CCR5 gene), 5.8%  $\Delta$ CCR5 allele heterozygotes, and 0%  $\Delta$ CCR5 allele homozygote (Gonzales et al., 1998). Thus, Puerto Ricans appear to resemble the U.S. Hispanic population, whose genotype frequencies were 93.3% nondeletion homozygote and 6.7%  $\Delta$ CCR5 allele heterozygotes. In comparison, a study of U.S. Caucasians found 77.4% nondeletion homozygote, and 22.6%  $\Delta$ CCR5, whereas African Americans exhibited 97.7% nondeletion homozygote and 2.3%  $\Delta$ CCR5 allele heterozygotes (Gonzalez et al., 1998; Zimmerman et al., 1997). These findings underscore the possible importance of differential population distributions of the  $\Delta$ CCR5 allele in HIV-1 infection and progression.

Recent investigations reveal that the  $\Delta$ CCR5 allele is not the only genetic determinant of HIV-1 prognosis. A CCR2-64I mutation allele was discovered at a frequency of from 10% to 15% among Caucasians and African Americans (M. W. Smith et al., 1997). It was shown that CCR2-64I does not influence infection by HIV-1, but delays progression to AIDS. HIV-1 infected individuals carrying the CCR2-64I allele progressed to AIDS from 2 to 4 years later than those HIV-1 infected individuals carrying the normal CCR2 allele. Unlike the different frequency of the  $\Delta$ CCR5 allele among different ethnic groups, the CCR2-64I allele mutation was found in every ethnic group tested: 98% in Caucasians, 15.1% in African Americans, 17.2% in Hispanics, and 25% in Asians. The frequency of the CCR2-64I allele was consistently lower among those who progressed rapidly to AIDS than in the nonprogressor or slow group with delayed onset of AIDS for more than 6 to 12.5 years following infection (M. W. Smith et al., 1997).

Another genetic determinant discovered to be associated with the slower progression to AIDS, not HIV infection, is homozygosity for a mutation in the 3' untranslated region of the SDF-1 gene (Winkler

et al., 1998). The SDF-1 is the specific chemokine ligand for the chemokine receptor CXCR4, a coreceptor with CD4 for T-tropic HIV (HIV-1). It is postulated that the mutant allele (SDF1-3'A) blocks or down regulates CXCR4, effectively blocking infection by the T-tropic HIV-1 strain often present late in the course of HIV infection. Winkler et al. (1998) found different frequencies of the SDF1-3'A allele among different ethnic groups. Among Caucasians tested, the prevalence was 21.1%, among Hispanics 16%, among African Americans 5.7%, and among Asians 25.7%. In a study of 2,857 patients, there was a marked delay in progression to AIDS for those individuals homozygous for the SDF1-3'A allele. It was also found that the delay in progression associated with the SDF1-3'A allele was twice as long as the delay associated with  $\Delta$ CCR5 or CCR2-64I alleles (Winkler et al., 1998). In another study, the ethnic diversity of the SDF1-3'A allele was reported to vary widely among the different populations (Su, Chakraborty, Jin, Xiao, & Lu, 1998). The frequency of the allele ranged from 2.9% in the African populations to 71.4% in the New Guinean population. Individuals homozygous for this allele were not found among the African populations studied, but were found among populations in North America, Europe, Asia, and Oceania. The frequency of the SDF1-3'A allele was lowest in Africa (2.9%-9.1%) and higher in American Indians, Europeans, and Asians (12.2%-36.6%). The prevalence of the allele was highest among two New Guinean highlander populations (66.7%-71.4%). The frequency of homozygotes for this allele was also highest among the two New Guinean highlander populations (39.6%-47.6%). The global range of the SDF1-3'A allele and its genotype among various ethnic groups, and its role in delaying the onset of AIDS provides opportunities for exploring potential genetic-based therapeutic interventions (Su et al., 1998; Winkler et al., 1998).

Recent investigations have identified an allele that speeds up the development of AIDS. Martin et al. (1998) showed that individuals who are homozygous for the promoter allele CCR5P1, which influences the CCR5 gene, progress to AIDS more rapidly than those with other alleles of the CCR5 gene. The CCR5P1 directs the synthesis of other receptors that the virus uses for entry into the CD4+ cell. Thus, the virus can replicate more rapidly, causing the individual to develop symptoms of AIDS several years earlier than those not homozygous for the CCR5P1 allele. In a study conducted by Martin et al. (1998), the frequency of individuals homozygous for the CCR5P1 gene was 12.7% among Caucasians and 6.7% among African Americans. Homozygous Caucasian cohorts exhibited a rapid progression to AIDS, but the African American homozygous cohort failed to show accelerated progression to AIDS (Martin et al., 1998). Apparently, not everyone who is homozygous for the CCR5P1 will progress quickly to AIDS. Nevertheless, approximately 10% to 17% of those patients who develop AIDS within 3.5 years of being infected are homozygous for the CCR5P1 gene, whereas others not homozygous for the CCR5P1 gene may stay symptom-free for 15 or more years.

## OTHER RACIAL DIFFERENCES IN DISEASE

In another study of racial differences, inmates in two large prisons were assessed and retested for conversion of the tuberculin test to positive (Stead, Senner, Reddick, & Lofgren, 1990). The rate of conversion was twice as high for Blacks as for Whites, although all the inmates were exposed to the same environmental factors. The study raises the possibility that the reason for the high TB test conversion may be attributable to racially determined genetic differences.

Racial differences have also been observed in lipoprotein and cardiovascular abnormalities among renal disease patients (Burrell et al., 1991). In general, Blacks have lower total cholesterol (TC) concentrations, higher high density lipoprotein-cholesterol (HDL-C) concentrations, a lower TC/HDL-C ratio, a higher apolipoprotein (apo) A-I concentration, lower apo B concentration, and a higher A-I/B ratio than Whites (Burrell et al., 1991). This better lipid profile is significant in terms of heart disease and end-stage renal disease (ESRD). Racial disparity is also apparent in the levels of lipoprotein a, Lp(a). Lp(a) is strongly associated with coronary heart disease. Serum Lp(a) levels exceeding 25mg/dl are twice as likely to lead to myocardial infarction (Harris-Hooker & Sanford, 1994). Interestingly, Blacks are shown to have twice as much serum Lp(a) than Whites, yet there was no rise in the CHD mortality in Black participants studied (Harris-Hooker & Sanford, 1994). Overall, these findings may indicate that the reduced incidence of coronary disease and mortality in Black ESRD patients, despite increased incidence of hypertension overall, may be due to the genetically favorable lipid profile of Blacks (Burrell et al., 1991). The outcome of mortality and morbidity of cardiovascular disease in African Americans is influenced by a number of other factors ranging from lack of preventive health services to racism in health care.

For over 50 years, racial differences have also been recognized in hypertensive patients (Adams, 1932). Epidemiological evidence has demonstrated clearly that some Blacks experience higher rates of elevated blood pressure during childhood (Voors, Foster, Frerichs, Webber, & Berenson, 1976) and adulthood (Hypertension Detection and Follow-Up Program Cooperative Group, 1977; Roberts & Maurer, 1981) and higher rates of target organ damage (Saunders, 1985, 1987). The significantly reduced renin levels in Blacks, as compared to Whites, is considered to be the pathophysiologic mechanism underlying differences among White and Black hypertensive patients. Although there is certainly some evidence that environmental factors may contribute to differences in the prevalence of morbidity and mortality from hypertension between Blacks and Whites, there is also an abundance of evidence of genetic differences with associated hormonal and physiologic aberrations (Saunders, 1987; Voors et al., 1976).

HTLV infection, hypertension, tuberculosis, diabetic nephropathy, and HIV-1 associated nephropathy are not the only diseases with racially different susceptibilities. They serve, however, as examples of diseases for which environmental and lifestyle factors are not sufficient to account for the observed ethnic/racial differences in frequency and morbidity. Therefore, genetic factors are a likely candidate for causal influence. Elucidation of the biologic mechanisms associated with genetic differences would confirm their role. For example, the elucidation of the CCR5 receptor in attachment of HIV to CD4+ cells provides a biologic confirmation of genetic determinants that covary with race.

#### ARE THERE BIOLOGICALLY BASED DIFFERENCES IN DISEASE SUSCEPTIBILITY ACROSS GEOGRAPHICAL SPACE?

The recent discovery of the  $\Delta$ CCR5 allele and its differing frequency among different ethnic groups prompted numerous studies of the global distribution of the  $\Delta$ CCR5 deletion allele. As we recommended earlier, an extensive population survey conducted by Martinson et al. (1997) found geographical differences in distribution. An additional study of the frequency of the  $\Delta$ CCR5 allele across Eurasia revealed a range of from 0% to 14%, affirming the previous study of a north to south gradient in allele frequency and its near absence in East Asian, Middle Eastern and American Indian populations (Stephens et al., 1998). The highest allele frequency in North Europe is among the Swedes. Among the Mediterranean population the frequency is from 5% to 14%, among Greeks 4.4%, and among the Saudi and East Asian populations 0%. The data show high  $\Delta$ CCR5 allele frequency among northern European Caucasians (Central Asian groups such as Tatars, Tuvinians, Kazakhs, Uzbeks, Uigurs and Azerbaijanis), and an absence among the Lebanese, Georgians, Saudis, Koreans, Chinese, and American Indians (Stephens et al., 1998). Yudin et al. (1998) examined the allele distribution across the Russian part of Eurasia and found a 10.4% to 22.2% frequency among the West Siberian populations (whose descendants typically are from European parts of Russia). In contrast, very low frequencies of the  $\Delta$ CCR5 allele were found among the Far Eastern and Native East Siberian populations.

The uneven distribution of the  $\Delta$ CCR5 allele across geographic regions and racial groups has generated discussions about the rate of HIV transmission or the speed of the disease progression in different racial groups. Certain populations carrying the  $\Delta$ CCR5 allele may have an increased survival advantage in the HIV epidemic, whereas those lacking the gene variant may have a higher prevalence of HIV infection and a more rapid disease progression. African Americans, having a lower prevalence of the  $\Delta$ CCR5 allele, are at greater risk for HIV infection than Caucasians in the United States, when known risk factors were controlled. The global pattern of the  $\Delta$ CCR5 allele and its associated effect on HIV infection and disease progression calls for closer investigations (McNichol et al., 1997).

Human T-cell Leukemia Virus (HTLV-1) may also be an important cofactor in HIV disease progression. Coinfection with HTLV-1 is thought to increase the rate of development to an AIDS state (Cohen, Sande, & Volberding, 1995). Several studies have been conducted on the seroprevalence of HTLV-I in different regions of the world. From this data, different areas of the world have been found to be endemic areas of HTLV-I. In addition to areas in Japan and the Caribbean already discussed, Levine et al. (1988) found a new high risk population in a group of Native Americans from southern Florida. In addition to this group, other areas of the United States have been shown to be HTLV-I endemic areas. Williams et al. (1988) found HTLV-I seropositivity to be high in the southeastern and southwestern United States. Robert Guroff et al. (1985) also found a high prevalence in Eskimo populations in the Arctic.

Besides these areas of relatively high seroprevalence in North America, HTLV-I has been found in South America, particularly in southwestern Colombia (Maloney, Ramirez, Levin, & Blattner, 1989) and Venezuela (Merino et al., 1984). These results have implications for possible racial differences because in all of these studies, the HTLV-I antibody appeared to be less prevalent in Whites than in non-Whites. In addition, Levine et al. (1988) observed varying percentages of HTLV-I positive patients with non-Hodgkin's lymphoma (from < 5% in the Middle East, Asia, and Europe, to 84% in nonendemic areas of Japan). They attributed this variability to either different strains of HTLV-I or other retroviruses or to differences in the genetic susceptibility of the hosts.

#### IMMUNOLOGIC EVIDENCE FOR RACIAL DIFFERENCES IN HIV DISEASE

Racial differences have been found in the expression of HIV antigen p24 (HIV-Ag). HIV-Ag is used as a marker for the clinical progression of HIV infection. In HIV positive individuals, p24 prevalence increases with increasing immunodeficiency, as measured by T-cell counts. Chaisson et al. (1991) confirmed a racial difference in the prevalence of HIV p24-Ag between Blacks and Whites (18% vs. 38%). Further, anti-p24 antibodies were detected in higher proportions of Blacks (84% vs. 65%), and Blacks had higher mean immunoglobulin levels than Whites. These results may indicate that Blacks have a more sustained humoral response to HIV infection than Whites. Similar results were found in a comparative study with AIDS patients from Uganda, Kenya, and the United Kingdom. As opposed to patients from the United Kingdom, there was no significant reduction in p24 antibodies among East African asymptomatic and AIDS patients and p24 antigenemia occurred more frequently in UK individuals (65%) (Kaleebu et al., 1991).

In a study of HIV infected injecting drug users (IDU) conducted by Gorter, Vranizan, Osmond, and Moss (1992), racial and sex differences were found in the presence of the HIV marker p24 antigenemia. Black females were much less likely to have the p24 antigenemia than Black males or White males and females. Of the cohort studied, only 1% of the Black IDU women tested positive for the p24 antigen, whereas 14% of Black men, 12% of White men, and 20% of the White women were p24 antigen-positive. The low prevalence of the HIV p24 antigenemia in Black females however, does not necessarily mean a slower progression to AIDS than Whites or Black men. Results of this study should be considered in studying HIV in ethnic minority women.

There are also other reports of important immunological differences among subpopulations that may have clinical implications (Gorter et al., 1992). In an investigation by Lucey and colleagues (1992), Blacks had significantly higher IgG and IgA levels than Whites. This observation suggests that racial differences in humoral immunity may underlie the observed racial differences in HIV antibody levels and HIV antigenemia.

A study done on malaria by Hill et al. (1991) supports the hypothesis that extraordinary polymorphism of major histocompatibility complex genes has evolved primarily through natural selection by infectious pathogens. This theory of pathogen driven MHC diversity requires that individuals of different MHC types should differ in their susceptibility to at least some major infectious pathogens. In fact, the study showed that the presence of HLA Bw53 and either the HLA haplotype DRB1\*1302 or DQB1\*0501 provides the same protection as the sickle cell variant. Interestingly enough, these HLA combinations are common among West Africans (40%), but almost completely absent from Whites and Asians (0%-1%). This study suggests that malaria has influenced the evolution of polymorphic MHC genes in humans. The study opens doors into a new way of thinking. It is now possible to ask the question of whether or not HIV and AIDS are having any similar effects (Hill et al., 1991).

As suggested by the malaria study, individuals of different MHC types should differ in their susceptibility to at least some major infectious pathogens. Unfortunately, no convincing associations between HLA polymorphism and susceptibility to commonly fatal infectious diseases have yet been identified, in contrast to well-known associations between HLA and many autoimmune diseases (Hill et al., 1991).

Specific HLA combinations have been found to increase or to decrease the progression of AIDS. If each ethnic group has its own patterns of HLA combinations, then more extensive research needs to be done in order to isolate HLA or loci influencing disease progression within specific ethnic populations.

Of course, no one population is completely ethnically distinct from another, thus the high prevalence of HTLV-I and especially HTLV-II in Native American populations is particularly interesting due to the mixing of the Native American gene pool. In the United States, the Native American Indian and Black populations have intermingled, resulting in the introduction of Black genes into the Native American population. Of course, the converse is equally true. That is, a Native American predisposition could have been introduced into the American Black population. Cross-racial studies between American Blacks, American Indians, and African Blacks would further elucidate this possibility. This intermingling is useful for studies of genetic susceptibilities. Further, it cannot necessarily be assumed that all members within a particular racial/ethnic group are genetically homogeneous.

### RACIAL DIFFERENCES IN DRUG RESPONSE

Racial factors play a role in drug response as well. For example, Asians have been shown to require lower dosages of a wide variety of psychotropic drugs, including neuroleptics, tricyclics, lithium, and benzodiazepines (Lin, Poland, & Lesser, 1986). Similarly, Blacks and Hispanics also require lower clinical dosages of tricyclics. Racial differences in the metabolism and sensitivity to the drug were found between Asians and Caucasians (Zhou, Adedoyin, & Wood, 1992).

Pharmacokinetic effects can vary depending on the efficiency and extent to which a given drug is metabolized. Metabolism of drugs can be measured by observing the blood concentration of the drug as a function of drug dosage. Differences in drug sensitivity are shown by observing the effects of varying drug dosages. By looking at both of these effects, researchers have determined some of the reasons behind the racial differences in drug response (Zhou et al., 1992). For example, the effects of propranolol, a beta-blocker, were examined in Chinese and American White subjects (Zhou et al., 1989). It is already known that the dosages of propranolol prescribed in China are significantly lower than those prescribed in the United States and Europe. Zhou et al. (1989) concluded that Chinese males have a greater sensitivity to propranolol based on genetic racial differences mediating the effects of the drug on heart rate and blood pressure. Whereas the actual mechanism of the increased sensitivity in Chinese is unknown, they suggest that differences in the beta-receptor sites on the heart are partly responsible. In addition, the Chinese subjects demonstrated a dissimilar metabolism of propranolol as compared to the Caucasian subjects. Chinese males were able to metabolize propranolol two times faster than Caucasians by means of ring oxidation and conjugation. As a result, Asians had lower plasma concentrations of the drug at any given dosage (Zhou et al., 1989). The twofold higher clearance of propranolol in Asians further accentuates the sensitivity differences observed in that Asians still

showed a greater response to propranolol at a given dosage, even though the drug, was broken down at a greater rate in Asians than in Whites.

Zhou, Shay, and Wood (1993) studied the differences in plasma binding of propranolol between Caucasian and Chinese men. Chinese men not only have higher concentrations of unbound propranolol, but the ratio of unbound (-) to (+)propranolol was greater in Chinese men than in Caucasian men. A larger concentration of unbound propranolol may contribute to their heightened sensitivity to the effects of propranolol.

Differences in the effects of propranolol in Black and Caucasian men have also been documented. In one study (J. A. Johnson, 1993), Black men were less sensitive to I-propranolol than Caucasian men (Johnson & Burlew, 1992). Beta-receptors possessed a greater affinity for propranolol in Caucasian men, hence producing a greater sensitivity to beta-blockade. It was also noted that in order to occupy 92.5% of the beta-receptors, Black males needed seven times more propranolol than White males.

J. A. Johnson, Burlew, and Stiles (1995) observed that Caucasian males were more sensitive to the chronotropic effects of isoproterenol, a beta-agonist, than Black males. Black men needed twice the amount of isoproterenol than Caucasian men to attain the same response.

Ethnic differences in parasympathetic response have also been of concern to researchers. Equal doses of atropine, which induces parasympathetic blockade, were administered to eight American-born Caucasian men and Chinese men (Zhou et al., 1992). The heart rates of the Chinese participants had a significantly greater increase than those of the Caucasian participants. The plasma atropine concentration was also measured and used to correct the increase in heart rate in both groups. The Chinese men had a 2.8 fold higher heart rate for each nanogram per milliliter of plasma atropine in comparison to the Caucasian men. In addition to these findings, researchers observed that the Chinese men had a significantly higher heart rate reduction than the Caucasian men when propranolol was given along with atropine (Zhou et al., 1992). Apparently, Chinese men are much more sensitive to the effects of atropine than Caucasian men (Zhou et al., 1992). These results also support previous research described earlier that Chinese men are more sensitive to propranolol (Zhou et al., 1989).

Much research has focused on racial differences in the effects of haloperidol, a commonly used neuroleptic drug (Lin, Poland, et al., 1988). Haloperidol is a stimulator of prolactin secretion. In studies of Asians and Caucasians, Caucasians had lower plasma concentrations of haloperidol and a lower prolactin response than did the Asians subjects (Lin, Poland, et al., 1988). Even after controlling for variations in body surface area, the difference in drug response remained significant. Because researchers found no distinctions in the responses of foreign-born and American-born Asians, differences in lifestyles do not appear to be a significant factor in this aspect of drug response. Instead,

the differential drug responses are likely due to genetic differences between Asians and Caucasians (Lin, Poland, et al., 1988). Lin et al. (1989) further observed in schizophrenic patients that the racial difference in drug response was mainly due to pharmacodynamic factors. With fixed dosages, Asian patients had slightly greater serum concentrations of haloperidol and greater extra pyramidal symptoms. With variable dosages, Asian patients again required lower dosages for an optimal clinical response (Lin et al., 1989). As in their previous study, body surface area was controlled. Therefore, the lower dosages required for Asians appear to be due to increased sensitivity to haloperidol.

Building on these findings, Chang et al. (1991) discovered that in patients with schizophrenia, Chinese patients had higher haloperidol plasma levels than non-Chinese patients, which included Caucasians, Hispanics, and Blacks. In addition, this study examined "reduced haloperidol," the alcohol metabolite produced by the reduction of haloperidol at the benzylic ketone. The ratios of "reduced haloperidol" to haloperidol were lower in the Chinese patients than the non-Chinese patients. This suggests racially influenced differential rates in the metabolism of haloperidol.

Racial differences have also been observed in studies of anxiolytic medications. For example, studies with the benzodiazepine-like drug, alprazolam, also show that racial differences in pharmacokinetic effects exist between Asians and Caucasians (Lin, Lau, et al., 1988). Because of this, Asians require lower clinical dosages of alprazolam than Caucasians (Lin, Lau, et al., 1988). To what extent this is due to differences in behavioral factors, such as diet, is unknown, but evidence for genetic factors were strongly suggested. Zhang, Reviriego, Lou, Sjeoqvist, and Bertilsson (1990) found interethnic differences in the metabolism of diazepam, an anxiolytic sedative. In their study, Chinese subjects metabolized diazepam at a much slower rate than Caucasian subjects, suggesting that those of Chinese descent may require lower doses of diazepam. Finally, Caraco, Tateishi, and Wood (1995) discovered that their Chinese subjects possessed a slower metabolism of diazepam than the Caucasian subjects. They also observed ethnic differences in omeprazole's inhibitory effect on the metabolism of diazepam. After taking omeprazole, diazepam clearance was similar in both the Caucasian and Chinese participants. However, the area under the concentration time curve (AUC) for diazepam's metabolite, desmethyldiazepam, was significantly lower in the Caucasian group than in the Chinese group. Thus, it appears that not only do Chinese men metabolize diazepam at a slower rate than Caucasian men, but the effect of omeprazole among Chinese men is greatly reduced as compared to Caucasian men.

Lithium is another psychiatric medication that has been examined for possible racial differences in drug effects. In one study (Strickland, Lin, Fu, Anderson, & Zheng, 1995), African American and Caucasian bipolar patients displayed different drug-related responses. Specifically, African Americans evidenced much higher red blood cell lithium concentrations and a much higher lithium ratio when

compared to Caucasians. They also experienced a greater number of side effects. The results hint that African Americans may require lower dosages of lithium than Caucasians.

Although studies on racial differences in the effects of psychotropic medication has clearly demonstrated possible differences with relevance to dosing regimens, research in other major diseases is less developed with the exception of treatment of hypertension. Racial differences between Blacks and Whites in the prevalence and the sequelae of hypertension also have important therapeutic implications. Evidence that Blacks are relatively unresponsive to antihypertensive therapy is inconclusive. On the contrary, there is significant evidence that when pharmacologic interventions are combined with other environmental measures, Blacks benefit more (Hypertension Detection and Follow-up Program Cooperative Group, 1979a, 1979b). There is also strong evidence that in monodrug therapy, the optimal drugs to achieve effective control in Blacks are different from those likely to be successful in Whites (Cubeddu et al., 1986; Saunders, 1985).

Evidence for other race-related differences in treatment of hypertension also exists. For example, the pharmacokinetics of nifedipine, a dihydropyridine calcium channel blocker, differs among racial groups. Ahsan et al. (1993) discovered that Asians, South Asians in particular, had higher plasma concentrations of nifedipine after a standard dose than Caucasians. Also, the area under the plasma concentration time curve (AUC) was twice as high in Asians as in Caucasians. Sowunmi, Rashid, Akinvinka, and Renwick (1995) observed that South Asians as well as Nigerians had a significantly higher AUC and higher plasma concentrations than Caucasians. The difference of nifedipine metabolism between the three populations suggests differential bioavailability and/or differential systematic clearance.

### IMPLICATIONS FOR HIV/AIDS RESEARCH

From the disparate evidence presented, it is clear that racial differences exist for disease susceptibility and drug response. In many cases, increased susceptibility or resistance to a disease is associated with known racial differences in HLA specificities, CCR5, CCR2, SDF1, and the recently discovered CCR5P1 gene (Martin et al., 1998). With the recent discoveries of these host genes, new genetic therapeutic approaches may be designed to target the specific gene variant among individuals (McNicholl et al., 1997). Furthermore, different races can have varying responses to drugs. These responses are determined by differences in absorption, metabolism, or excretion (pharmacokinetic effects) or by differences in drug sensitivity (pharmacodynamic effects) that are influenced by genetic factors (Lin, Lau, et al., 1988; Lin, Poland, et al., 1988). Because of these biologically determined differences in disease susceptibility and drug response, the importance of cross-racial factors when conducting studies of disease and developing pharmacologic interventions needs to be taken into consideration.

The multigenetic influence on HIV-1 infection and progression to AIDS, and its difference in prevalence among ethnic groups, provides a basis for therapeutic opportunities. The studies presented here that show varying frequencies of the host genes among ethnic populations provide sufficient support for the importance of considering the patient's racial genetic profile in developing appropriate therapeutic strategies. Accordingly, any research conducted must take into account cross-racial factors so that what is known about the course of the disease in any given population can be elucidated accurately.

The only mechanism by which to achieve this is through the inclusion of an ethnically representative subject population in clinical trials of HIV/AIDS drugs. This would help ensure that a particular drug in standard recommended dosage has the desired therapeutic effect in one racial group as it does in another. Without cross-racial data, the results of trials on one race may not necessarily be applicable to another race. AIDS researchers must be sensitive to these issues to prevent the approval of HIV-related therapies that may not have the same efficacy or safety profile in populations outside the gay White male community. An example of one such study, Study ACTG 116-B/117, was reviewed by the food and drug administration a few years back. This study was sponsored by the National Institute on Allergies and Infectious Diseases, the leading governmental agency conducting AIDS research in the United States (Japour et al., 1995), and was designed to compare the efficacy and toxicity of didanosine (ddI) and zidovudine (ZDV or AZT) in the treatment of primary HIV infection in patients who tolerated previously more than 16 weeks of ZDV. The investigators concluded, based on information from 913 participants who were randomized at the time of analysis, ddI appeared to be more effective than ZDV in delaying time to first new AIDS-defining event or death in the study population. This benefit was seen in the subgroup of patients who entered the study with AIDS-related complex (ARC) or asymptomatic disease, but not in those with AIDS. The composition of this study population was 96% male, 82% White, and 79% from the homosexual/bisexual risk behavior group. The biological and genetic composition of this group, more homogenous than the general HIV infected population, may capitalize unknowingly on finding effects that may be influenced by unmeasured factors, thus overestimating the effectiveness of this treatment when widely applied. Although no studies have shown these findings to be detrimental, nonetheless it is important that findings from studies that lack diversity be approached cautiously as proven treatment plans for those who were not participants in the study. Further research should be conducted to determine whether results from such studies are equally effective in the populations not a part of the study.

Admittedly, the challenges of recruiting and retaining some subpopulations, especially the socially and economically disenfranchised, may be difficult, expensive and require considerable investment of

time and resources (El-Sadr & Capps, 1992; Mays, 1998, 1999; Mays & Cochran, 1999). Nonetheless, by including more representative samples of the affected populations of a particular disease, more accurate and useful information can be gained. This is especially important in the development of effective HIV-related drug, treatments as trends of incidence of HIV infection indicates a rise in new cases within ethnic minority groups who in the past have been the least likely to be recruited into studies.

Yet, despite 15 years of research in the quest for a cure or control of HIV/AIDS, HIV clinical studies, drug\_treatment, and drug and vaccine development study methodology is only in its infancy when it comes to ensuring adequate study participation by ethnic minorities (Mays, 1998, 1999; Mays & Cochran, 1990, 1999). This is because of a variety of complicated reasons (Mays, 1998, 1999; Mays & Cochran, 1999; Stone, Mauch, Steger, Janas, & Craven, 1997). But there are also a number of steps that can be taken to increase the likelihood of advancement of scientific knowledge in the area of biomedical research on HIV-related disease susceptibility, disease progression and pharmacologic interventions for ethnic minority groups.

The following steps are recommended: First and foremost, leadership by the federal government is critical in directing the research agenda to focus on possible racial/ethnic differences in susceptibility to infection, disease progression, and clinical and drug treatment options and strategies. This could be accomplished through the following:

1. A request by the President to the federal agencies and the Surgeon General to ensure that all clinical, vaccine, drug development, and drug treatment research scientifically demonstrates effectiveness across ethnic/racial groups.
2. Development of a mechanism (collaborative workgroups, advisory boards, or citizen consultants of experts on HIV and ethnic minorities drawn from senior researchers with strong research publications records, senior policy advisors and clinicians with long histories of working with minority populations) under the combined auspices of Office of AIDS Research (OAR), Office of Minority Health (OMH) and NIH with the charge to identify the gaps in the current NIH, OAR, and private-sector research portfolios; recommend new directions for biomedical research within NIH and OAR that would ensure better science on HIV-related racial/ethnic differences in genetic and immunologic aspects of HIV disease susceptibility, disease progression, and clinical and drug treatment strategies and options; and review the international HIV research portfolio to determine possible ethnic/racial difference research studies that could answer specific scientific questions.

3. A convening of a conference on biomedical research on racial/ethnic minorities with a series of commissioned papers. Publish and disseminate papers, develop regional and national data sharing collaborations, and provide seed funding for collaborators to engage in data analyses on issues identified as high priority by the conference.
4. Development of funding opportunities (RFAs, RFPs) targeting gaps in the biomedical research portfolio on racial/ethnic differences in HIV infection, disease progression/nonprogression, drug treatment, and clinical and drug development response.
5. Creation of a cooperative agreement for funding for collection of biological data from racial/ethnic minorities who are HIV seronegative high risk, HIV seropositive, and diagnosed with AIDS in order to develop a specimen repository, under the scientific direction of a multiethnic senior research team. This repository could be made accessible nationally to investigators who submit proposals to the senior multiethnic research team that maintains oversight.
6. Building on previous federal initiatives designed to increase the number of ethnic minority principal investigators, development of a RFA for three funding cycles within NIAID targeting basic genetic, immunologic, vaccine, and treatment research on racial/ethnic differences under the leadership of senior/tenured minority principal investigators.
7. Development of review guidelines for NIH review committees that address not only inclusion of minorities but the inclusion of specific scientific hypotheses that explore racial/ethnic differences in genetic and immunologic responses to HIV infection, disease progression/nonprogression, response to drug development, and clinical and drug treatment strategies and options.

Whereas leadership by the federal government is essential and necessary to accelerating the science of racial/ethnic differences in susceptibility for HIV infection, disease progression/nonprogression and responses to vaccine candidates and clinical and drug treatment strategies and options, there are others who can exert leadership in this domain. For example:

1. Medical journal editors should require that when minorities are participants in studies, evidence be provided that there are no differences from nonminorities if their data are not presented separately or in comparison to nonminorities or between ethnic groups. Analyses by race/ethnicity should be required unless there is a statistical case for foregoing such procedures.

2. Researchers must take seriously the task of mastering the scientific literature on HIV in ethnic minorities in order to develop testable hypotheses that can advance the field on ethnic/racial differences in the cause and treatment of HIV infection and disease. Many investigators will find that increased attention to this body of data will not only assist in advancing science but better equip them to design racially/ethnic diverse studies and maintain study cohorts.

Finally, although the authors could envision a number of additional recommendations to urge HIV research on biomedical research on racial/ethnic differences, none is as compelling as urging mechanisms to ensure that scientific findings are translated into prevention, intervention, and treatment strategies that reach the community. Without creating mechanisms by which the findings actually reach and benefit the population being focused on, researchers lose credibility with the community and fail to achieve the fundamental purpose of science, that is, to improve the lives of others.

#### ACKNOWLEDGMENTS

The terms, *Black* and *African American*, are often used interchangeably in the literature. Some present-day African Americans are descended from Africans brought to this country more than a 150 years ago. However over time there has been admixture in which African Americans share a mixed biological heritage with Native Americans, Whites, and other racially distinct populations. There are also a number of groups that within research studies are designated Black but maintain some genetic distinctions in their admixture from African Americans such as Haitians, Belizeans, or Black Puerto Ricans. In studies, the designation of Blacks or African Americans may vary in which biological heritage groups are included. Therefore, throughout this chapter the term adopted by the original author of the work being reviewed is used in order to remain true to their designation of the population.

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