Original Article

# Absence of Kaposi Sarcoma Among Ethiopian Immigrants to Israel Despite High Seroprevalence of Human Herpesvirus 8

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- ***Objective*: To determine the prevalence of Kaposi sarcoma (KS) and human herpesvirus 8 (HHV-8) seropositivity in Ethiopian Jewish immigrants to Israel.**
- ***Methods*: A Western blot assay was used to determine the seroprevalence of HHV-8 in serum samples from 202 randomly selected human immunodeficiency virus (HIV)–negative and 47 HIV-positive Ethiopian immigrants; samples were obtained on arrival of the immigrants in Israel. The Israel Cancer Registry provided comprehensive data on the occurrence of KS among Ethiopian immigrants and in the non-Ethiopian population of Israel.**
- ***Results*: A total of 39.1% and 57% of the HIV-negative and HIV-positive Ethiopians, respectively, were infected with HHV-8 ($P<.03$). However, none of the Ethiopians examined and none of the other HIV-negative Ethiopians among about 45,000 immigrants had KS. Moreover, only 1 (0.85%) of 118 Ethiopian patients with acquired immunodeficiency syndrome (AIDS) developed KS compared with 49 (12.5%) of 391 non-Ethiopian AIDS patients ($P<.001$).**
- ***Conclusion*: Although HHV-8 infection is common in Ethiopian Jewish immigrants to Israel, these patients almost never develop KS, in marked contrast to the strong association usually observed. The mechanism behind this population's unique protection requires further study.**

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**AIDS = acquired immunodeficiency syndrome; CI = confidence interval; HHV-8 = human herpesvirus 8; HIV = human immunodeficiency virus; ICD-O = International Classification of Diseases for Oncology; ICR = Israel Cancer Registry; KS = Kaposi sarcoma**

Kaposi sarcoma (KS) may occur sporadically, especially in elderly men of Eastern European and Mediterranean origin (classic KS), or it can occur in children and adults in Africa (endemic KS), in human immunodeficiency virus (HIV)–infected patients, particularly homosexual men (acquired immunodeficiency syndrome [AIDS]–associated KS), and after organ transplantation (iatrogenic KS).[1] In practically all cases, a newly discovered and characterized herpesvirus termed *human herpesvirus 8* (HHV-8) or Kaposi sarcoma–associated herpesvirus can be identified in the neoplastic tissues,[2] and antibodies against the virus can be detected in the serum.[3-5] Furthermore, HHV-8 infection has been proved to occur before the onset of clinical KS,[3] and the detection of virus sequences in the peripheral blood mononuclear cells is a strong predictor of the progression of KS.[6] Thus, a causal relationship between HHV-8 and KS has been well established.[7-9] Indeed, HHV-8, with or without facilitating effects of HIV, has been shown to be tumorigenic by several intriguing mechanisms.[9,10]

Serologic studies have become an invaluable tool for studying the susceptibility, transmission, and natural history of HHV-8 infection. Although important insight has been achieved, factors that confer susceptibility or resistance to the tumorigenic effects of HHV-8 have remained poorly understood.

Based on anecdotal observations, KS is rarely encountered in Ethiopian Jewish immigrants to Israel, despite the fact that they come from a highly endemic area of HHV-8 infection; thus, we attempted to determine the prevalence of HHV-8 seropositivity and KS in that population.

## METHODS

### Study Population

As a standard procedure of the Israeli Ministry of Health, all Ethiopian Jewish immigrants (except those 0-6 years old) are required to provide serum samples before or upon their arrival to Israel. These samples are tested for HIV serostatus and kept frozen. Serum samples from 202

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HIV-seronegative Ethiopian Jewish immigrants who arrived in Israel during 1991 were examined for HHV-8 seropositivity. Samples were randomly selected with stratified random tables[11] to match approximately the age and sex of that immigration wave of 15,228 persons. External validation of sex and age strata proved comparable trends (unpublished data). The group examined represents 1.3% of the 1991 immigration wave from Ethiopia to Israel. The mean age of our sample group was 29.6 years (range, 7-75 years), and 53% were female. Forty-seven HIV-seropositive Ethiopian-born patients, representing 3.9% of Ethiopian immigrants who are currently infected with HIV (n=1205), were also examined. These patients constitute carriers of HIV who emigrated between 1990 and 1995 and who were followed up at the Kaplan Medical Center, Rehovot, Israel.

### Serologic Assays

A Western blot assay was used to detect antibodies to the open reading frame of the 65.2 recombinant capsid-related antigen, vp19 (provided by Thomas F. Schulz, MD). We chose to use a conservative definition of HHV-8 seropositivity and selected this assay because preliminary analyses indicated that it has a high specificity, although it may be less sensitive. The HHV-8 truncated open reading frame 65.2 was expressed in bacteria, purified by using the Xpress System Protein Purification (Invitrogen Corporation, San Diego, Calif), and immunoblotted as previously described.[12] Serum samples were subjected to a blind test at a dilution of 1:100, and antibody reactivity was demonstrated with alkaline phosphatase–conjugated goat antiserum specific for human IgG, IgM, and IgA (Sigma Chemical Co, St Louis, Mo) at a dilution of 1:2500 and developed with 5-bromo-4-chloro-3-indolylphosphate *p*-toluidine salt and nitroblue tetra-zolium chloride as a substrate (GibcoBRL, Grand Island, NY). Serum samples from KS patients and blood donors previously shown to be seropositive and seronegative, respectively, were included as internal controls.

### Population and Morbidity Data

The population and morbidity data were obtained from the Israel Central Bureau of Statistics[13] and the Department of Tuberculosis and AIDS of the Israeli Ministry of Health, Jerusalem. The Israel Cancer Registry (ICR) provided data on the occurrence of KS in the Ethiopian and non-Ethiopian populations. The ICR has been collecting information on malignant neoplasms since 1960. Kaposi sarcoma has been registered separately since the inception of the ICR and since the late 1970s according to the International Classification of Diseases for Oncology (ICD-O).[14] Completeness of registration is estimated to be more than 90%.[15] Personal identifiers are of high quality and allow follow-up based on record linkage with other files, such as the ICR, including date of birth, sex, country of birth or origin, date of immigration for Jewish immigrants, origin of parents for Israeli-born Jews, date of KS diagnosis, topographic ICD-O codes, basis and appraisal of diagnosis, medical documentation, and mortality registers.

The KS cases were identified based on the ICR data (1980-1998), whereas the linkage to the country of origin file allowed extraction of Ethiopian immigrants with KS. In addition, ICR files were linked to the registries of the Department of Tuberculosis and AIDS of the Israeli Ministry of Health (which started to collect records in 1982) to distinguish classic KS from AIDS-associated KS.

This strategy allowed us to identify all Ethiopian KS patients, including our specific study population.

### Statistical Analysis

The $\chi^2$ test was used to compare rates of HHV-8 seroprevalence and KS incidence within the study population. Tests were 2-tailed. Incidence rates were based on the number of KS patients by 5-year age group, country of birth, and sex. The corresponding person-years at risk were calculated based on population census and intercensus figures.[13] The direct method of standardization was used, with the world standard population as a reference. Poisson regression analysis, adjusted for age at diagnosis, sex, country of birth, and calendar period, was used to assess the incidence rate of KS among different populations.[16]

## RESULTS

### Seroprevalence of HHV-8 in the Study Group

The results of the serologic study of HIV-negative Ethiopian Jews are outlined in Figure 1. Seventy-nine (39.1%) of the 202 subjects (95% confidence interval [CI], 32.9%-44.2%) were seropositive for HHV-8, 120 (59.4%; 95% CI, 53.1%-64.7%) were seronegative, and 3 (1.5%) were indeterminate. Seropositive rates represented 36.8% (95% CI, 28.3%-47.3%) when seroprevalence rates were adjusted to the entire Ethiopian immigrant population. No difference in HHV-8 antibody prevalence was found among male (35/95, 37%) and female (44/107, 41.1%) study participants ($P$=.2; adjusted rate ratio, 0.86; 95% CI, 0.72%-1.04%), except those in the 25- to 34-year age range. Notably, seropositivity started to appear in childhood (our 7- to 14-year-old group), and thereafter seroprevalence rates did not vary significantly among the different age groups ($P$=.14). One exception was the 61.9% (95% CI, 53.9%-70.3%) seropositivity of women aged 25 to 34 years compared with all other women ($P$=.04). A higher HHV-8 seroprevalence rate of 57% (27/47; 95% CI, 49.3%-64.1%) was found among HIV-seropositive Ethio-

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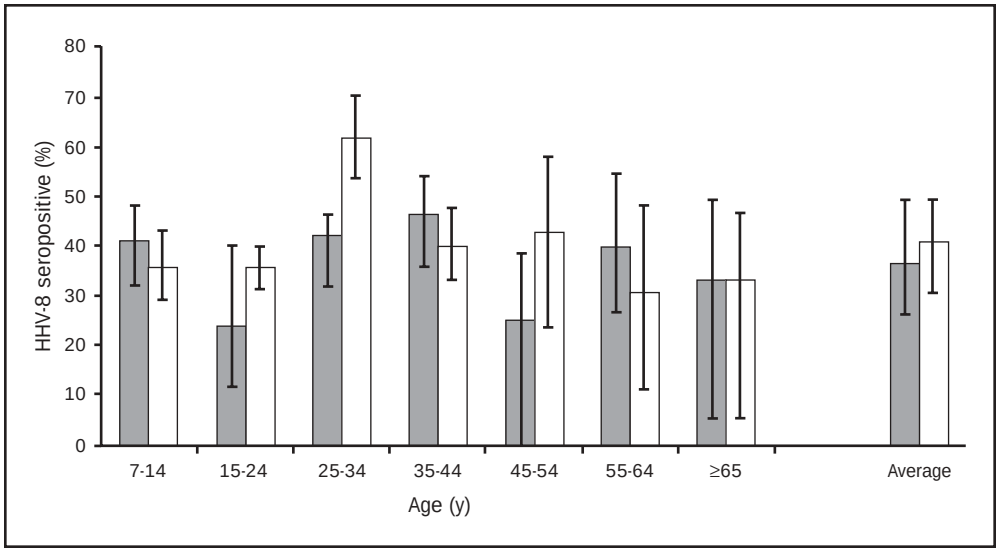


Figure 1. Age-dependent seroprevalence rates for human herpesvirus 8 (HHV-8) in 202 male (gray bars) and female (white bars) human immunodeficiency virus–negative Ethiopians in Israel. Error bars denote 95% confidence intervals.

pian patients compared with the HIV-seronegative cohort ($P<.03$).

### KS in Ethiopian Immigrants

Remarkably, no cases of KS have been reported either in our study group or in the entire HIV-negative Ethiopian immigrant population in Israel, which is based on approximately 45,500 people. This corresponds to 508,577 person-years for the period between 1982 and 1998. Even among HIV-infected Ethiopians (approximately 2% of the immigrant population), only 1 case of KS occurred between 1982 and 1998 according to the data of the ICR and the Department of Tuberculosis and AIDS of the Israeli Ministry of Health.

This zero incidence of KS among HIV-negative Ethiopian Jews in Israel is particularly striking compared with the incidence of KS in the non-Ethiopian population of Israel and other countries (Table 1). The age-standardized incidence rate of non–AIDS-associated KS during 1982 to 1994 among non-Ethiopian immigrants in the Jewish population in Israel was 3.8 (95% CI, 3.1-4.7) in males and 1.5 (95% CI, 0.4-2.1) in females per 100,000 population, whereas in Israeli-born Jews it was 3.1 (95% CI, 2.2-4.0) and 1.4 (95% CI, 0.2-2.6) in males and females, respectively (J. Iscovich, oral communication).[19] Based on the incidence rate of KS in the non-Ethiopian Jewish population, the calculated expected number of KS patients in the Ethiopian population between 1982 and 1998 is 6.4 (95% CI, 3.1-9.0) (without taking into account the high HHV-8 seroprevalence).

In addition, in comparison with the Israeli-born Jewish population, the age-adjusted incidence ratios in male and female Ethiopian immigrants were 0.1 (95% CI, 0.04-0.17) and 0 (95% CI, 0.0-0.2), whereas they were 1.1 (95% CI, 0.51-1.76) and 1.0 (95% CI, 0.12-2.15) in comparison with non-Ethiopian immigrants. Even among patients with AIDS, 49 of 391 non-Ethiopian patients developed KS compared with only 1 of 118 Ethiopian immigrant AIDS patients (12.5% vs 0.85%; $P<.001$). Thus, KS was almost 15-fold less prevalent in the Ethiopian Jewish AIDS population.

## DISCUSSION

A strong association exists between HHV-8 seropositivity and the development of KS.[8] In the United States and the United Kingdom, where less than 3% of blood donors are HHV-8 positive, the incidence of KS is also low, ranging from 0.014 to 0.165 cases per 100,000 population per year.[8] Data from Italy provide an especially poignant example. In southern Italy, 24.6% of the population is seropositive for HHV-8, and approximately 1.5 per 100,000 population per year develop KS. In other regions, where HHV-8 seropositivity is about a third of this rate (8.4%), the incidence of KS also decreases sharply (to 0.55 per 100,000 population per year).[22] Male homosexual contact, history of sexually transmitted disease, or HIV infection has been shown to increase the risk of both HHV-8 seropositivity and KS.[23] In Africa, the prevalence of antibodies to HHV-8 is the highest in the world. The rates reported in East African countries are invariably high: Zambia, 37.5%; Uganda, 53% to

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Table 1. **Human Herpesvirus 8 (HHV-8) Seroprevalence and Kaposi Sarcoma (KS) Incidence Rates per 100,000 Population in Different Human Immunodeficiency Virus (HIV)–Uninfected Populations**

| Country | HHV-8 seroprevalence in HIV-uninfected individuals (%)* | Incidence rates of classic KS per 100,000 population, male/female (period studied)† |
|---|---|---|
| United States | 0-4 | 0.29/0.07 (1973-1979) |
| United Kingdom | 0-5 | 0.21/0.05 (1988-1992) |
| Italy | 5-30 | 4.12/1.09 (1976-1984) |
| Israel | 7-10 | 3.1/1.4 (1985-1994) |
| Ethiopian immigrants to Israel | 39.1 | 0‡ (1982-1997) |

*Data are from Schulz,[8] Iscovich et al,[17] and Davidovici et al.[18]
†Data are from Iscovich et al,[19] Biggar et al,[20] and Dal Maso et al.[21]
‡No KS cases were reported between 1982 and 1998 in the Ethiopian immigrant population that reflects 508,577 person-years.

77%; and Tanzania, 33% to 84%.[4,24-27] Accordingly, African countries have the highest incidence of KS. For example, in Uganda, 43.5 males and 18.1 females per 100,000 population per year develop KS, and similar figures were obtained in neighboring countries.[28] In HIV-negative and HIV-positive patients, KS is now the most frequently occurring tumor in central Africa and ranks high among the most common malignancies in eastern and southern Africa as well.[29]

Our data, however, reveal a unique lack of association between HHV-8 infection, as reflected by seroprevalence, and KS. We found a 39.1% (age and sex adjusted, 36.8%) prevalence of HHV-8 seropositivity among a representative group of 202 Ethiopian Jews on arrival in Israel in 1991. This figure is in entire agreement with previous studies of HHV-8 seroprevalence in other East African countries reported herein.[24,26,27] In addition, HIV infection is encountered in Ethiopian Jewish immigrants as expected among immigrants from an endemic area. However, in marked contrast to all other reported populations from that region, we found a close-to-zero occurrence of KS among the entire cohort of Ethiopian Jewish immigrants, despite their high initial rate of HHV-8 infection, a decade of follow-up, and the relatively high occurrence of HIV infection (approximately 2%). This result is even more striking compared with a significantly higher KS incidence in the non-Ethiopian population in Israel (Table 1), whose HHV-8 seroprevalence rate is much lower than that of the Ethiopians studied (7%-10% vs 39.1%).[17,18] In Ethiopians, AIDS-associated KS is likewise a rare occurence. The total number of AIDS cases in Israel during 1982 to 1998 was reported as 509, of which 118 patients were of Ethiopian origin. Yet, the numbers of AIDS-associated KS cases were 49 and 1, respectively, a 14.7-fold lower incidence. Therefore, the KS prevalence in AIDS patients in Israel was 0.125 in the non-Ethiopian population and 0.0085 in the Ethiopian immigrants (age-adjusted rate ratio of Ethiopian to non-Ethiopian AIDS patients, 13.8; 95% CI, 12.6-15.3).

This incidence of KS in Ethiopians, whether they are HIV infected or not, was not previously recognized as such but can be supported by previous observations. Thus, only 39 cases of KS were identified among 12,402 Ethiopian AIDS patients before 1994,[30] and the general rarity of KS in Ethiopia was occasionally noted.[31-33] Therefore, the postulated "resistance" of Ethiopians to the tumorigenic effects of HHV-8 does not appear to be unique to Ethiopian Jews and in fact may exist in Gambia as well.[27,34] An intriguing genetic difference in Ethiopians might account for this putative resistance to HHV-8–induced tumorigenicity. Its characterization remains a target for future research that might have important implications.

Several limitations of our study should be recognized. Cases of KS among Ethiopian immigrants may have occurred but may not have been reported to the health authorities and central registries. However, this is highly unlikely. The Ethiopian immigrants to Israel live together in communities, they have free access to medical services, and, moreover, their successful integration is a national goal. Thus, they are closely followed up and supported by a network of experienced physicians and health care workers who are in close contact with the Israeli Ministry of Health. It may be argued that changed conditions in Israel following immigration (eg, improved nutrition and sanitation, decrease in intestinal parasitic infestations) may have affected the development of KS. There is no evidence that this is the case, and, moreover, our findings are supported by indirect data from Ethiopia.[31,32] Official cancer registry data from Ethiopia are not available; however, the cohort sampled after arrival in Israel is representative of Ethiopia, as other reports of seroprevalence of HHV-8 from the region show. Finally, the serologic assay used is highly specific, but its sensitivity may be approximately 80% to 95%. However, the conclusions would not be affected by a few additional cases of HHV-8 positivity.

In conclusion, we have shown that, although HHV-8 infection is highly prevalent in Ethiopian Jewish immigrants to Israel, these people almost never develop HHV-8–induced KS, whether they are HIV infected or not. This is in marked contrast to the strong correlation observed worldwide between HHV-8 seroprevalence and the incidence of KS. Elucidation of the mechanism of this postulated resistance to HHV-8 tumorigenicity among Ethiopians should be a target of future study.

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