

# Men Who Have Sex With Men, Risk Behavior, and HIV Infection: Integrative Analysis of Clinical, Epidemiological, and Laboratory Databases

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(See the editorial commentary by Mayer and Mimiaga, on pages 1371–1373.)

**Background.** Centralized data collection and analytic tools facilitate tracing HIV transmission trends at the patient-population level with increasing resolution, complementing behavioral studies while avoiding sampling biases. By several measures, the rate of HIV infection among men who have sex with men (MSM) in Israel increased in the past several years more rapidly than was expected. We describe features of the data that connect this increase to behavioral changes.

**Methods.** We retrospectively analyzed data from the national HIV reference laboratory and the national HIV and sexually transmitted infections registries. We examined changes in selected epidemiologic and clinical parameters and in the pattern of drug-resistant virus transmission among MSM in Israel. In particular, virus isolates from 296 MSM (23.8% of all MSM who received a diagnosis) were genotyped, drug-resistance conferring mutations were characterized, and phylogenetic trees were constructed.

**Results.** Compared with earlier years, during 2007–2009 MSM were more often infected with drug-resistant virus before treatment initiation, were coinfecting with syphilis, and received a diagnosis during acute retroviral syndrome. Phylogenetic analysis suggested frequent transmission of drug-resistant HIV by drug-treated individuals to >1 partner. Secondary transmission of resistant virus by drug-naive patients is also consistent with the phylogenetic patterns. In addition, non-B HIV subtypes began to appear among MSM.

**Conclusions.** Together, our findings suggest that the sexual behavior of MSM, both HIV-infected and uninfected, has become riskier, contributing to the number of those seeking early clarification of status, to syphilis comorbidity, and to the spread of drug resistance. These findings call for action by public health planners and community-based organizations aimed at increasing awareness of the risks, bringing a change in attitude and establishing safe sex norms.

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Data regarding the frequency and distribution of HIV infection in populations at risk are important in monitoring and controlling the epidemic. Incidence rates of HIV infection are influenced by several factors, including the sizes of the infected populations, migration, availability of highly active antiretroviral therapy (HAART), and various behavioral activities [1].

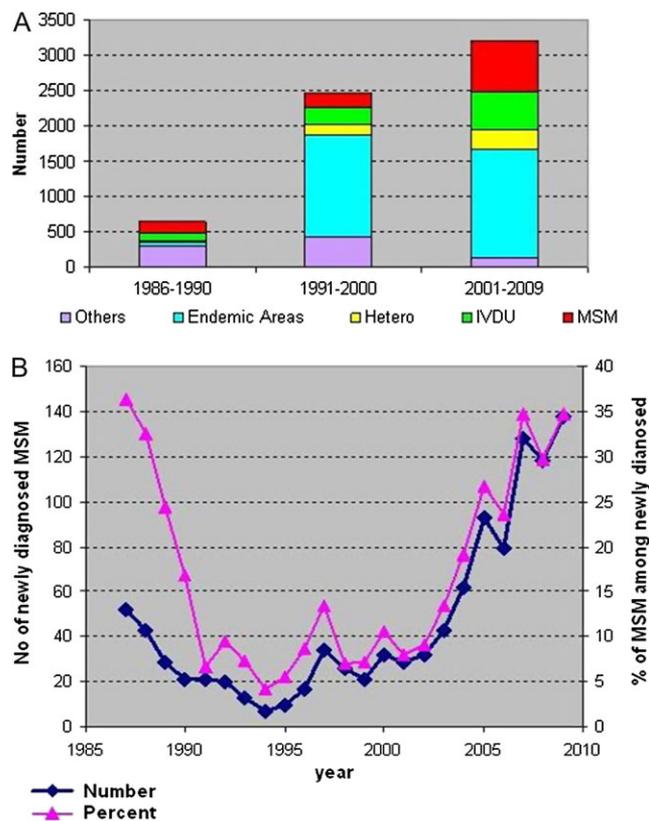
By the end of 2009, 3800 male adults infected with HIV-1 were reported in Israel, of whom 1243 (32.7%) were men who have sex with men (MSM). Until

1991, HIV-infected MSM were the group with the greatest number of reported cases in the country [1–3] (Figure 1A). During the early 1990s, MSM adopted risk-reducing strategies, and at the same time, there was a large wave of immigrants from Ethiopia, among whom prevalence of HIV infection is high, reducing the absolute number of new cases per year among MSM and the proportion of MSM in the population of HIV-infected persons [3, 4]. These trends were reversed during the later 1990s, and during the past decade, the annual number of MSM with a new diagnosis of HIV infection in Israel has increased by 4–5-fold (Figure 1B). This phenomenon requires an explanation, while the (more modest) increases in annual numbers of newly diagnosed cases in members of other transmission groups in the same period, especially injection drug users, can be readily accounted for by changes in the immigration to Israel from the former Soviet Union and East Africa.

Part of the increase in the incidence rate of HIV infection during 2002–2009 in Israel could be accounted for by the growth in the overall population of infected MSM during that period. Thus, we would have expected the number of new transmissions among MSM in 2009 to have increased in proportion to the growth in the total number of infected MSM even if the mean probability of an infected individual of infecting other men in 2009 remained the same as that in 2002. This is the case because, in the meantime, the collective source of virus expanded and the number of uninfected MSM is not limiting. In fact, it can be estimated roughly that the total number of HIV carriers among MSM in Israel less than doubled during the considered period, which leaves more than half of the 4.3-fold difference in the number of MSM with newly diagnosed HIV infection during 2002–2009 (Figure 1B) unaccounted for.

Developing solid understanding of the dynamics of HIV infection trends requires collecting and rigorously analyzing a large body of data, and the best way of doing it is in a centralized manner [5]. A national HIV registry and a National HIV Reference Laboratory (NHRL) were established in Israel in 1986. All physicians and laboratories are required to report every newly diagnosed case to the national registry, reporting patient identification details, sex, year and country of birth, year of arrival in Israel, and mode of HIV transmission. In addition, all the peripheral laboratories send their positive enzyme-linked immunosorbent assay results to the NHRL, which performs the confirmatory Western blot assay and reports to the national registry. Thus, the registry is both accurate and sensitive to changes in the overall trends of the epidemic. The NHRL also performs the majority of drug resistance analyses, facilitating integrative studies.

Assessing behavioral changes usually relies on the direct collection of behavioral data from the target population. This approach is not always feasible, and performing appropriate



**Figure 1.** Patients with newly diagnosed HIV-1 infection in Israel. A. Patients with newly diagnosed HIV-1 infection, by period and transmission group. "Endemic Areas," stands for immigrants from areas where HIV infection is endemic (mostly Eritrea, Ethiopia, and Sudan). B. Absolute number and proportion of men who have sex with men (MSM) with newly diagnosed HIV infection, by year of diagnosis. IVDU, intravenous drug user.

probability sampling in a population such as MSM is inherently difficult [6]. It is desirable to combine information based on directly investigating the behavior of persons with the results of studies that rely primarily on laboratory data, including in particular, evolution of the virus in the population.

The purpose of the present study was to assess the possible role of behavioral changes in accelerating the spread of HIV infection among MSM in Israel over time through a detailed examination of the shifting patterns of drug-resistant virus transmission in this group and of other parameters, including presentation with syphilis at the time of diagnosis of HIV infection and the frequency of cases in which HIV positivity is detected relatively soon after infection. Drug-resistant virus transmission is a marker of unsafe sex practiced by actively treated patients and their sex partners. The frequency at which new cases are diagnosed soon after the infection occurred may indicate to what degree sexually active MSM are collaborating with efforts by doctors and public health officials to minimize

the time between infection and its detection, for the patient's benefit but also to reduce the risk of secondary infections during the time after infection when such risk is particularly high. Early diagnosis might also reflect awareness by patients who received a diagnosis of having practiced unsafe sex. In any case, a trend toward earlier diagnosis can be considered to be indirect evidence that the increasing rates of infection among MSM are not attributable to a widespread ignorance regarding the risks of unsafe sex (although they might be attributable to ignoring those risks). Coinfection with syphilis can be regarded as a surrogate marker for unsafe sexual practices. Indeed, syphilis is the most infectious of all sexually transmitted diseases.

Increase in incidence of HIV infection among MSM was also noted during the early 2000s in the United States [7] and several European [8, 9] and African [10] countries. It was related to behavioral changes, especially an increase in unprotected anal intercourse [11]. Although our study was limited to a relatively small MSM population in a small country, the issues considered, the methods implemented, and the lessons from this study are pertinent to many other communities of broadly similar characteristics [12].

## METHODS

We identified cases of recent HIV infection at diagnosis retrospectively either by documented evidence that seroconversion occurred in the preceding 12 months or when acute retroviral syndrome was documented, based on a compatible pattern of viral load, CD4 cell count, and clinical history [13, 14].

Infectious syphilis (primary, secondary, or early latent) was defined by a Venereal Disease Research Laboratory (Becton-Dickenson) titer >1:8 in a patient with positive *Treponema Pallidum* Haemagglutination (Axis Shield) and/or positive Fluorescent *Treponemal* Antibody (BioMérieux) results, with a compatible clinical history. Because syphilis is a notifiable disease, data from the national sexually transmitted diseases registry at the Ministry of Health was cross-checked with the national HIV registry data. Data on syphilis prevalence in the entire MSM population was not available to us.

Viruses from a total of 884 male patients (23.3% of all identified in Israel until the end of 2009) were genotyped at the NHRL before initiation of treatment. These patients include 3 groups that together are representative of resistance among drug-naïve patients. First, from 2002 through 2006, isolates from a group of persons with newly diagnosed cases were genotyped as part of the international SPREAD program, carefully selected to be representative of drug-naïve HIV-infected persons in the participating countries [15–17]. Second, since 2007, isolates from all persons with newly diagnosed cases are genotyped

as part of clinical evaluation; >80% of isolates are genotyped at NHRL. Isolates from only 94 drug-naïve patients (11 MSM and 83 others) who received a diagnosis before 2002 were genotyped without particular selection.

We retrospectively analyzed all the available molecular data, focusing on the 296 MSM found among the 884 infected male patients. These MSM included 165 drug-naïve and 148 drug-treated patients from 6 of the 7 AIDS centers in the country (for 17 individuals, we had samples obtained both before and after treatment initiation). Genotyping was performed using the HIV-I Truegene kit (Siemens). Only the first available sequence from each patient was included. Resistance-conferring mutations were defined according to the criteria suggested by Bennett et al [18]. For comparisons of mutation frequencies among MSM and other patients, we used the  $\chi^2$  test for the categorical independent variables or Student's *t* test for the continuous independent variables; *P* values <.05 were considered to be statistically significant. Analyses were conducted using SPSS, version 14.0, for Windows.

Phylogenetic and molecular evolutionary analyses of 270 sequences from 165 drug-naïve and 105 drug-treated patients were conducted using MEGA, version 4 [19] and the CluslX method (MegAlign, Lasergene, version 5.01, DNASTar). Phylogenetic trees were drawn using FigTree, version 1.3.1, and branch reproducibility was performed on 1000 replicates using Seqboot. Subtyping was based on the Stanford Rapid Subtyping tool ([www.hivdb.stanford.edu/hiv/](http://www.hivdb.stanford.edu/hiv/)).

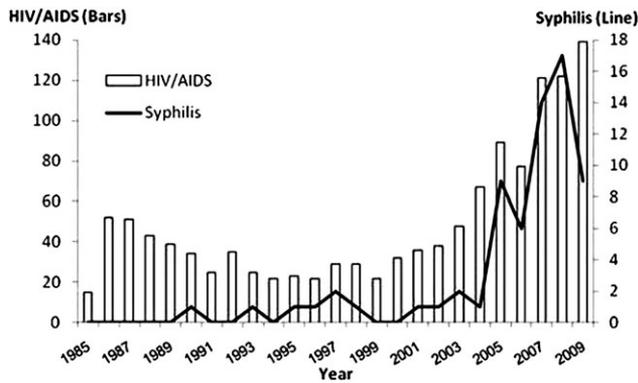
The study was approved by the Ethical Committee of the Sheba Medical Center.

## RESULTS

### Number and Proportion of MSM Newly Diagnosed With HIV

By the end of 2009, 6250 persons infected with HIV-1, including 3800 men >15 years of age, were reported in Israel (Figure 1A). They consisted of MSM (32.7%), immigrants from Ethiopia (32.3%) and from other areas of endemicity (mainly Sudan and Eritrea, 15.4%), and injection drug users (17.9%) (Figure 1A). Of the latter, 61% emigrated from the former Soviet Union (mainly, Ukraine and Russia). The proportion of MSM among all persons with newly diagnosed HIV infection was 38% during the late 1980s, decreased to 7% during the 1990s, and has been increasing constantly since 2000, reaching 35% in 2009 (Figure 1B).

Most of the infected MSM (68.9%) were born in Israel and 6.9% in the former Soviet Union, mainly Ukraine. Fifty-two percent were infected in Israel and 7% in the United States or Western Europe; for 41%, place of infection was not known. The implication of this and the fact that most infected MSM carry subtype B viruses is that the MSM epidemic in Israel is



**Figure 2.** Syphilis among men who have sex with men (MSM) who have received a diagnosis of HIV infection. HIV-infected MSM received a diagnosis of syphilis in Israel during 1987–2009. Bars represent patients with newly diagnosed HIV infection or AIDS. Line represents patients with syphilis among all MSM with newly diagnosed HIV infection.

essentially homegrown and that factors, such as tourism and immigration, do not significantly confound the results.

### Recent Infection With HIV-1 Among MSM With Newly Diagnosed HIV Infection

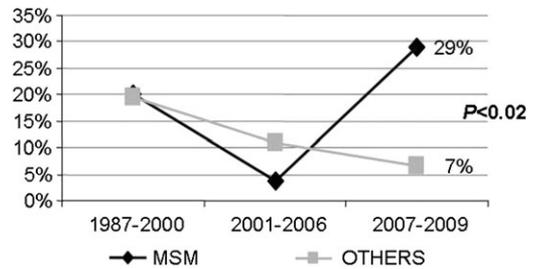
Until the end of 2009, 237 individuals were recently infected at the time of diagnosis (as defined in Methods). Eighty-six of these were MSM (7.9% of all MSM who received a diagnosis)—a proportion significantly higher than in the other known risk groups ( $P < .001$ ). A significant increase in the proportion of MSM with newly diagnosed cases who were recently infected, many of them before or during seroconversion, was seen in recent years. Whereas during 1986–2006, only 4% of MSM who received a diagnosis had been recently infected; during 2007–2009, the proportion increased to 14% ( $P = .02$ ). Data extracted from the AIDS clinic at the Sheba Medical Center (1 of 7 centers in the country, serving the Tel-Aviv metropolitan area) demonstrated an increase that was even greater: during 1986–2006, only 4 (2%) of 198 MSM who received a diagnosis at this clinic were recently infected, and during 2007–2009, 32 (28%) of 116 MSM with newly diagnosed cases were recently infected ( $P < .0001$ ).

### MSM Coinfected With HIV and Syphilis

Cross-checking data from the national sexually transmitted diseases registry and the national HIV registry showed a trend of increase in syphilis incidence rates among HIV-infected MSM similar to the increase in incidence rates of HIV infection during most of the 2000s, with some limited decrease in 2009 (Figure 2).

### Drug Resistance Among Patients With Newly Diagnosed HIV Infection

Isolates from 884 male patients (23.3% of all identified in Israel until the end of 2009) were genotyped at the NHRL before



**Figure 3.** Drug resistance among drug-naive men who have sex with men (MSM) and in the total HIV-infected population. Percentage of individuals found to carry resistant virus at the time of diagnosis in different periods.

treatment initiation. Drug resistance among isolates from patients with newly diagnosed cases was high during the 1990s (20%), decreased during the early 2000s (8%) [4], and increased until the end of the study period. Among the different risk groups, drug-resistant viruses were most frequently found in MSM. During 2007–2009, ~29% of all MSM with newly diagnosed cases carried HIV bearing at least 1 major resistance-conferring mutation, while only 7% of all other patients who received a diagnosis during this period had such mutations (Table 1 and Figure 3;  $P = .015$ ).

The most common drug resistance mutations in samples from drug-naive patients occurred in reverse transcription amino acids 103 (6%) and 215 (4%) and in Pr amino-acid 90 (2%), reflecting the common pattern of resistance development in patients experiencing failure of drug-combination treatment. Transmission of drug-resistant virus to drug-naive patients was more common during 2007–2009 (Table 2, Figure 4).

### Phylogenetic Analysis of Viral Protease and Reverse Transcriptase From Infected MSM

Phylogenetic trees of Pr-RT sequences from 270 patients (165 drug-naive and 105 treated) were constructed. We divided the sequences into early (1986–2006; 145 patients) (Figure 4A) and

**Table 1. Subtypes, Drug Treatment, and Resistance Status of Screened HIV-Infected Men Who Have Sex With Men (MSM)**

Subtype	drug-naive	Treated	Total	Drug-naive patients carrying resistant virus	
				No	%
A/AE	15	2	17	1	6.7
B	145	123	268	21	14.5
C	4	4	8	1	25
D,F,G	1	2	3	0	0
Total	165	131	296	23	13.9

**NOTE.** Subtypes and resistance status among drug-naive HIV-infected MSM. Of note, while subtype-C virus is prevalent among heterosexuals and subtypes A and AE among IDU, most MSM in Israel have subtype B.

**Table 2. Drug Resistance Among Drug-Naive and Drug-Treated HIV-Infected Men Who Have Sex With Men (MSM)**

	Amino Acids	Naive N = 148		Treated N = 148 <sup>a</sup>		P	Clustering in naive
		Number	Percentage	Number	Percentage		
NRTI	M41L	1	1	35	24	<.00001	
	K65R	0	0	5	3	0.06	
	D67NGdel	0	0	38	26	<.00001	
	T69Dins	0	0	0	0	-	
	K70R	0	0	27	18	<.00001	
	F77I	0	0	1	1	1	
	F116Y	0	0	3	2	0.2	
	M184VI	0	0	64	43	<.00001	
	L210W	0	0	24	16	<.00001	
	T215YFCDESIV	6	4	54	36	<.00001	clustered
K219QER	2	1	28	19	<.00001		
NNRTI	K101E	1	1	10	7	0.01	
	K103NST	9	6	28	19	<.00001	clustered
	V106MA	0	0	3	2	0.2	
	Y181CI	0	0	17	11	<.00001	
	G190ASEQ	0	0	17	11	<.00001	
PI	M46LI	1	1	30	20	<.00001	
	I50VL	1	1	1	1	1	
	F53I	0	0	2	1	0.5	
	I54VLMATS	2	1	21	14	<.00001	
	V73CSTA	1	1	7	5	0.2	
	V82AFTSM	2	1	22	15	<.00001	
	V84AC	0	0	14	9	<.00001	
	D88NS	0	0	6	4	0.03	
	L90M	4	2	27	18	0.01	clustered
Summary	Any NRTI Mutation	10	7	97	66	<.00001	
	Any NNRTI Mutation	9	6	47	32	<.00001	
	Any PI Mutation	7	5	57	39	<.00001	
	Any Resistant Mutation	23	16	103	70	<.00001	
	No resistance	118	80	45	30	<.00001	
	Resistance to 1 family	22	15	24	16	1	
	Resistance to 2 families	2	1	60	41	<.00001	
Resistance to 3 families	0	0	19	13	<.00001		

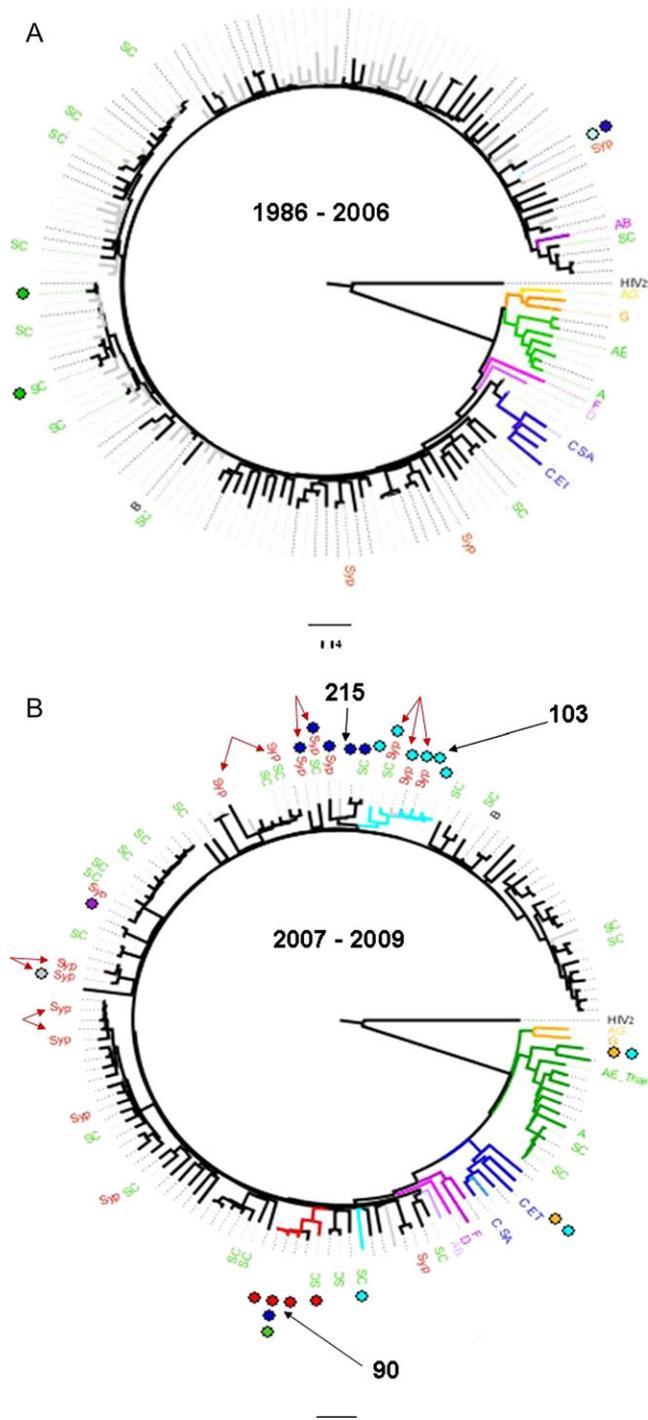
**NOTE.** Numbers and percentages of resistance-conferring mutations among drug-naive and drug-treated MSM. Note that drug-naive patients with drug-resistant virus typically carry a single resistance-conferring mutation while most treated patients, as expected, have several mutations, conferring resistance to more than one family of drugs. Resistance-conferring mutations were defined according to Bennett et al [18]. MSM—men who have sex with men; NRTI—nucleoside reverse-transcriptase inhibitors; NNRTI—non-nucleoside reverse-transcriptase inhibitors; PI—protease inhibitors.

<sup>a</sup> 17 subtype-B infected MSM had samples taken both before and after treatment failure. The 17 treated samples were included in the mutation analysis in this table but not in the phylogenetic analysis, Figure 4.

late (2007–2009) (125 patients) (Figure 4B), according to time of diagnosis. This enabled us to better envision and characterize trends of change (Table 3).

During the first years of the epidemic, all MSM in Israel were infected with HIV subtype B. Other subtypes have been identified in this transmission group only since the beginning of this century; in 2001, the first (of 17) A/AE case and, in 2003, the first (of 8) subtype C case were identified. Establishment of A/AE infection among MSM is particularly evident since 2007 (Figure 4). Drug-resistant virus of all subtypes was found in the population of drug-naive patients (Table 1).

The phylogenetic trees show frequent transmission of drug-resistant viruses during the last 3 years of the study. In addition to resistance transmission from treated patients to uninfected individuals, drug-resistant virus might have also been transmitted to such individuals by other drug-naive carriers of the virus. Thus, the drug-naive individuals infected with closely related viruses bearing the protease mutation L90M (4 cases) or the reverse transcriptase mutations K103N (6) or T215Y (3 and 2) (Figure 4B) might, in each case, have been infected by a single patient receiving HAART or, alternatively, infected each other in a relatively short period (the original drug-treated patients are



**Figure 4.** Phylogenetic trees of sequences from 270 MSM. A. Sequences of individuals diagnosed before 2007. B. Sequences of individuals diagnosed after 2007. 270 samples of MSM diagnosed before 2007 (145 samples: 64 naive and 81 treated; A) or after 2007 (125 samples: 118 naive and 7 treated; B) were analyzed. First available sequence of each individual was included in the analysis. Specifically indicated are coinfection with syphilis (Syp, in red; red arrows show clustering), diagnosis before or soon after seroconversion (SC, in green), and selected resistance-conferring mutations in drug-naive individuals (colored circles). Black line—drug-naive subtype B; gray line—drug-treated subtype B; dark-blue line—drug-naive subtype C; light-blue line—drug-treated subtype C; dark-green line—drug-

unknown). This would mean that transmission of resistant virus by drug-naive carriers of such virus could have involved up to 65% of all transmissions (15 of 23 infection events) in the studied group. Other clusters showing sequence similarity but not shared resistance mutations also suggest the same phenomenon of virus being increasingly transmitted by single individuals to several uninfected partners and/or chain transmission. Overall, clustering was more common in the late group than in the pre-2007 group (Figure 4).

Figure 4B shows that syphilis was in correlation with clustering. Of the 16 MSM with newly diagnosed HIV infection who were found to be coinfecting with syphilis during 2007–2009, 11 (69%) were found in multiples in clusters of closely related viruses. Although the numbers are modest, the probability that the observed distribution resulted from random associations is small.

## DISCUSSION

In recent years, the majority of men with newly diagnosed HIV infection in Israel were MSM. Infected MSM were typically Caucasian Jews (median age  $\pm$  SD,  $33 \pm 10$  years) who contracted the virus in Israel or in other industrial countries [17]. Until recently, all MSM had subtype B, but recently, MSM carrying A/AE and C viruses were identified. The greater variety suggests risky sexual behavior with larger groups of sex partners.

In addition to these trends, higher rates of syphilis were detected among HIV-infected MSM, as reported also in other countries [20, 21], indicating an increasing tendency of practicing unsafe sex in this group. Syphilis may increase viral load, thus facilitating further spread of virus and exacerbating the consequences of irresponsible conduct [22, 23]. HIV infection, in turn, might facilitate the spread of the spirochete [24] in a vicious cycle. Although, in Israel, there is general awareness of the risks, it appears that the success of HAART and other factors have diminished concerns regarding the risk and consequences of HIV transmission, resulting in behavioral disinhibition among MSM [25].

Frequent engagement in risky behavior was also reflected by the spread of drug-resistant virus. The increasing number of patients with newly diagnosed HIV infection who were carrying resistance-conferring mutations indicates that treated patients increasingly practice unprotected sex. Indeed, the same mutations prevalent in the treated population are now also those

naive subtype A/AE; purple line—drug-naive subtype F; orange line—drug-naive subtype G; red line and circles—drug-naive carrying mutation L90M; turquoise line and circles—drug-naive carrying mutation K103N; Blue circles - mutation T215Y. Accession numbers: A - AF193275; AE - AF197340; AB - AF193276; AG - AF063223; B - K03455; C-ET - AF286233; C-SA - AY585268; D - AY322189; F - AJ249238; G - AF450098; HIV-II - BD413542. Red arrows show clustered patients coinfecting with syphilis.

**Table 3. Coinfection With Syphilis, Early Diagnosis, and Resistance Transmission**

Attributes	Early (1986–2006) No. = 145		Late (2007–2009) No = 125		P
	Number	Percentage	Number	Percentage	
Seroconversion	10	7	25	20	.002
Syphilis	3	2	16	13	.001
Resistance	4	3	19	15	<.0001
Syphilis + resistance	0	0	7	6	.004
Seroconversion + syphilis	0	0	3	2	.1

**NOTE.** Infection attributes during the two periods of the study

most prevalent in the drug-naive population (with the exception of M184V, which affects the active site of the reverse-transcriptase enzyme and, therefore, disappears rapidly when the selection pressure of the drug is removed [26]). Responsibility for the risky behavior underlying the observed trends may be ascribed, perhaps to a different degree, to both uninfected and infected partners; certainly, the drug-treated partner is aware of his HIV status. The higher percentage of MSM who received a diagnosis relatively soon after being infected and even before seroconversion suggest also that many MSM may be aware of having practiced risky sexual contact and/or are sensitive to initial signs of infection. Although such awareness did not prevent their initial risky behavior, they appear to seek immediate clarification of their infection status and medical advice. Collection of relevant behavioral data is required to assess the validity of this conjecture. In any case, the data are consistent with a higher degree of risk awareness rather than the opposite. Detection of HIV positivity at an earlier stage after infection, as observed, should tend to diminish the rate of virus transmission among MSM, but evidently, this was not enough to reverse the present trends.

Our phylogenetic analysis provided further insights that corroborate the aforementioned inferences regarding the trend of increased risky behavior among MSM. This analysis revealed a considerable increase after 2007 in the proportion of MSM infected with closely related viruses. In particular, several clustered viruses share a common resistant-conferring mutation, and most drug-resistant viruses reside in clusters. Such clustering suggests either a common source of virus (drug-treated patient) or secondary transmission among drug-naive carriers of the virus in a relatively short time, as was suggested in other studies [13, 27]. We cannot distinguish between the 2 possibilities, because such distinction would require analyzing larger numbers of treated and untreated HIV-infected MSM and/or a detailed epidemiological investigation. However, because the observed clusters represent a significant proportion of all those MSM infected with drug-resistant virus and because finding the mode of transmission of the same drug-resistant virus to  $\geq 2$  men could be particularly instructive, additional studies would be of interest. In clusters, there was an increased representation

of syphilis coinfection, consistent both with the association of syphilis with unsafe sex and with the potential synergy between syphilis and HIV infection.

Beyond the concrete findings that we have reported, this work and the work of others reveals that centralized databases and modern analytic tools allow the tracing of virus transmission trends, at the patient population level, with increasing resolution, potentially complementing behavioral studies while avoiding some of the sampling biases of those [6]. The major limitation of the present study is that the number of MSM infected with drug-resistant virus in Israel is still relatively small. Moreover, our analysis did not incorporate all the data gathered in Israel on this subpopulation of MSM infected with drug-resistant HIV, because data from 1 major AIDS center (of seven) was not available to us.

Our finding of an increasing number of recent infections, syphilis comorbidity, expanding range of subtypes, HIV drug resistance spread, and phylogenetic clustering of multiple infections indicates that unprotected sex has become more common among MSM in Israel and that this is not entirely a problem of insufficient awareness of the risks, as suggested also in some behavioral surveys in different countries. Action by public health planners and community-based organizations to further increase awareness of the risks and to establish community norms of safe sex practices are called for.

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