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Research article

A Population-Based and Longitudinal Study of Sexual Behavior and Multidrug-Resistant HIV Among Patients in Clinical Care

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Abstract

Background: Population-based and longitudinal information regarding sexual risk behavior among patients with multidrug resistant (MDR) HIV and their sexual partners is of great public health and clinical importance.

Objective: To characterize the HIV sexual risk behaviors of patients with and without drug-resistant HIV in the clinical care setting over time.

Measurements: 393 HIV-positive patients completed questionnaires of self-reported sexual risk behaviors at approximate 6-month intervals extending over 24 months. HIV viral load and genotypic drug resistance obtained during the same time points were matched to the behavioral data. Multidrug resistance was defined as having resistance to 2 or 3 antiretroviral (ARV) drug classes.

Results: In serial cross-sectional analyses, 393 patients (44% female and 79% heterosexual) contributed 919 matched behavioral and virologic results over the 24 months of data collection. Of these, 250 patients (64%) reported having sex during at least 1 survey period resulting in greater than 10,000 sexual events with more than 1000 partners. Unprotected sexual behavior was reported by 45% of sexually active patients, resulting in 34% of all sex events that exposed 29% of all partners. Of these patients with unprotected sexual events, 31% had HIV drug resistance 11.6% with resistance to 2 classes of ARVs (2-class), and 1.8% with 3-class ARV resistance at the time of a sexual risk event. Close to 1000 or 28% of all unprotected sexual events involved resistant strains (11% of these with resistance to 2 classes and 0.2% with 3-class resistance, exposing 20% of unprotected sexual partners to resistant HIV (8% to 2-class and 0.6% to 3-class resistance).

In longitudinal analysis among the 78 patients who reported a cumulative total of 12 months of sexual history and had resistance testing, 38% reported engaging in unprotected sexual behavior. There was substantial and complex variation in the distribution of unprotected sexual events and in the detection of resistance over time.

Conclusion: In this study of HIV sexual risk and resistance over time among HIV-infected patients in clinical care, a substantial proportion engaged in unprotected sex and had drug-resistant HIV, frequently exposing partners to 1- or 2-class resistant HIV strains. However, relatively few exposures involved 3-class resistance. The dynamics of sexual risk behavior and HIV drug resistance are complex and vary over time and urgently require both general and targeted interventions to reduce transmission of resistant HIV.

Introduction

The transmission of drug-resistant strains of HIV-1 to newly infected persons is now a major clinical and public health problem in developed countries with availability of antiretroviral (ARV) therapy during the past decades. In the United States, an estimated 10% to 15% of incident HIV infections involve drug-resistant strains,[1-4] and superinfection with resistant strains has been reported.[5-7] Transmitted multidrug resistant (MDR) HIV-1 strains that possess viral mutations that result in 2- or 3-class drug resistance can profoundly affect the response to ARV therapy.[1,2,8] The likelihood of transmission of MDR HIV may not only depend on the HIV viral load and viral fitness, but also on the frequency of risky behavioral exposures to MDR strains.[9,10] Information on sexual risk behavior among HIV-positive patients who may transmit HIV with 2-class or 3-class drug resistance is of great public health importance, but is currently very limited in the published literature. Although important anecdotal and cross-sectional information on sexual risk behavior of patients with drug-resistant HIV is available,[8,11,12] studies have generally not provided population-based information over time on the quantitative aspects and dynamics of the relationship of sexual risk and resistance. The data needed to more fully understand this relationship include: (1) cumulative proportion of patients with MDR HIV strains who engage in unprotected sexual behavior, (2) the number of sexual events involving such individuals, and (3) the number of partners thereby exposed to resistant strains.

We have previously performed and reported the baseline results of the study of prevalence and predictors of HIV drug resistance among HIV-positive patients in clinical care who have engaged in sexual behaviors that may transmit HIV to others.[9] To further characterize and extend our understanding of this behavioral and biologic relationship, we now present cumulative and longitudinal data on sexual risk involving MDR HIV over an approximate 2-year period in this HIV-infected clinic population.

Methods

Patient Population, HIV Sexual Risk Behavior, and HIV Drug Resistance

Patients were recruited from the 2 largest adult HIV clinical care settings in Connecticut. Patients had been previously enrolled in a parent study the Options Project a longitudinal intervention outcome study of HIV transmission risk in HIV-positive patients in clinical care.[9] The HIV drug resistance and transmission risk substudy was nested within the parent study and involved agreeing to have a resistance test performed on archived plasma samples. A separate informed consent was obtained. Inclusion criteria were written informed consent, at least 18 years old, and healthy enough to complete the procedures. All of the 497 patients enrolled in the Options Project were offered participation in the resistance substudy. The study was approved by the Institutional Review Boards at the University of Connecticut, Hartford Hospital, and the Human Investigations Committee at Yale University.

From 2000 to 2003, HIV-positive patients completed surveys at approximate 6-month intervals via a computer-administered self-interview of sexual risk behaviors during the previous 3 months; the cumulative time covered by the survey was 12 months over the approximate 24-months of the study.[9,13] HIV viral load and HIV genotypic resistance data were obtained and matched to the behavioral data by coded identifier as previously described.[9,14] Patients were included if they had an HIV viral load or a genotypic resistance test result within 3 months of a behavioral survey. Standard DNA sequencing of the HIV-1 *pol* gene was used to detect HIV genotypic resistance (*ABI*, Applied Biosystems, Foster City, California).[9,14] An HIV genotypic resistance test was performed if the HIV viral load was > 400 HIV RNA copies/mL.[9] Patients with a viral load of < 400 HIV RNA copies/mL were classified as having a nondetectable viral load. MDR resistance was defined as having major resistance mutations to 2 or 3 antiretroviral drug classes (IAS-USA 2004 mutation table[15]).

Definitions of sexual behavior and unprotected sexual behavior (sexual risk) were (1) no sexual behavior no vaginal, anal, or oral insertive sex events; (2) sexual behavior and events all vaginal, anal, and oral insertive sexual events, protected (condom used) and unprotected; and (3) unprotected sexual behavior and events: unprotected vaginal, anal, and oral sexual events.

For the purposes of this study, sexual behavior was defined as penile-vaginal and penile-anal intercourse for women; penile-vaginal, penile-anal, and insertive penile-oral sex for men who were HIV-positive, and who had HIV-negative or status-unknown partners (oral-insertive sex was restricted to HIV-negative or status-unknown partners).[9]

Analysis and Statistical Methods

Analyses of the current data consisted of descriptive statistics to quantify the total number of sexual events and proportion of sexual events involving sexual risk, as well as the total number and HIV sero-status of partners potentially exposed, across the entire sample and specific to those with known drug-resistant strains of HIV. These quantities were derived and analyzed in 2 ways: (1) a cross-sectional cohort, where all available observations from all participants contributed to a single sample of data; and (2) as a longitudinal sample where only those contributing all 4 waves of data collection (4 time points

with behavioral, resistance, and viral load data) were included. All descriptive statistics and data management procedures used SPSS version 11.01 (SPSS, Inc., Chicago, Illinois).[16]

Results

Four hundred and four of the 497 Options Project enrolled patients (81%) consented and enrolled in the Options drug resistance and risk substudy. Of the 404 consented patients, 393 had a matched HIV genotypic resistance test and behavioral survey result and were included for analysis. Of these 393, 44% were female, 79% were heterosexual, 11% were men who had sex with men, and 10% reported being bisexual. The mean age was 43 years; 38% were African American, 34% Hispanic, 22% white, and 6% reported "other." Of the 393 patients, at baseline 180 (46%) had an injection drug use history and 57 (14%) reported using injection drugs during the previous month. The mean duration of HIV infection was 8 years (median of 9 years) and duration of ARV therapy was 23 years for those on ARV at baseline. The mean CD4+ cell count at first survey was 414 cells/microliter (mcL) (SD = 299 cells/mcL, median = 365 cells/mcL), and 48% had nondetectable HIV viral load. At least 263 patients were prescribed ARVs at the outset of the study. A total of 919 matched data points consisting of both behavioral and virologic data were available. Seventy-eight patients contributed 4 matched behavioral and resistance and viral load results obtained within the same time period, 99 patients had 3, 94 had 2, and 122 contributed 1 matched result. As behavioral data were collected for the preceding 3 months on multiple occasions, the most complete matched population, those with 4 matched time points, represented 12 months of cumulative sexual experience over an approximate 2-year period.

Total Sexual Events and HIV Drug Resistance

Of the 393 patients, 250 (64%) reported any sexual behavior (protected or unprotected) during their participation in the study. These 250 patients reported a total of 10,116 sexual events with a maximum of 1225 partners. Because assessments were collected over time and reports of partners did not include any partner identifying information, the number of partners across the study may have included the same partner reported on multiple assessments. If partners who are possibly redundant are excluded (eg, if a patient reported risk events with 4 partners at time 1 and 6 partners at time 2, a maximum number of 6 partners was used, not 10), the total adjusted number of sexual partners was 867.

Nine of the 250 patients (3.6%) who engaged in any sexual behavior (protected or unprotected) had 3-class resistance at the time of a sexual event, for a total of 242 sexual events (2.4% of all sexual events) with an adjusted number of 12 exposed partners (1% of all partners).

Unprotected Sex Events and HIV Drug Resistance

Of the 250 patients engaging in sexual behavior, 112 (45%) reported engaging in unprotected sex. These 112 patients with unprotected sexual risk engaged in 3476 risk events (34% of all sex events), and exposed 354 partners (252 of these (71%) were reported by the patients as being HIV negative or status unknown). Of the 112 patients with sexual risk events, 60 (54%) had a viral load above 1500 HIV RNA copies/mL at the time of the reported unprotected sexual event (a viral load threshold associated with greater risk of HIV transmission[17]), cumulatively reporting a total of 1156 unprotected sex events over the course of the study. Across these specific sexual risk events, viral load at the time of the event ranged from 1500 to 750,000; had a median of 27,420 and interquartile ranges (IQR) of 8417 (25th) to 103,439 (75th) HIV RNA copies/mL.

Of all of the patients reporting unprotected sex events, 35 (31%) had resistant virus at the time of 1 or more of their risk events, 24 (21%) had only a single-class drug resistance, 13 (11.6%) had 2-class only drug resistance, and 2 (1.8%) had a 3-class resistance at the time of a sexual unprotected risk event (Figure 1). Note that resistant patients engaging in risk often had viral loads that fluctuated over time during the study but almost uniformly had viral loads greater than the 1500 HIV RNA copy threshold associated with transmission risk at the time of the risk event. For this group median viral load across the reported transmission risk events was 14,244 copies/mL (IQR of 6410 25th] to 750,000 [75th]).

Of the 3476 total reported unprotected sexual events, 978 (28%) involved ARV-resistant strains; 577 (16.6%) risk events involved a single-class resistance, 393 (11%)

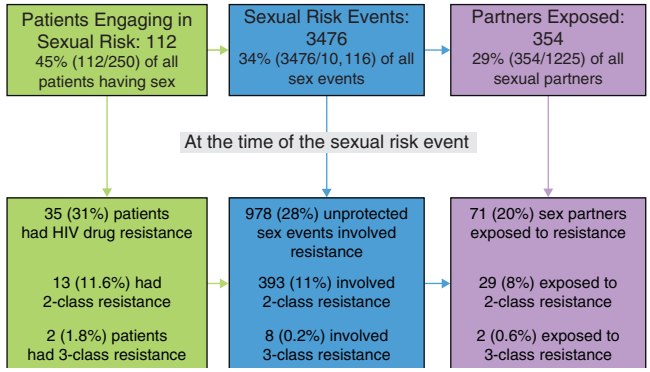

Figure 1
Sexual risk events and HIV drug resistance.

involved 2-class, and 8 risk events (0.2%) 3-class resistance. Seventy-one of 354 (20%) sexual risk partners were exposed to resistant HIV with 29 (8%) exposed to 2-class resistance and 2 (0.6%) exposed to 3-class resistance. Of the 71 partners exposed to drug-resistant HIV, 59 (83%) were reported by the patient as being HIV negative or status unknown. If possible redundant partners are excluded, 58 partners or 21% of all adjusted total partners (273) were exposed to drug resistance. Of these 58 partners exposed to drug-resistant virus, 47 (81%) were reportedly HIV negative or status unknown.

The prevalence of specific resistance mutations in patients engaging in sexual risk can be found in Table 1 and the resistance patterns of the viral strains from the 2 patients engaging in sexual risk with 3-class resistance are listed in Table 2.

Longitudinal Results in Patients With 4 Behavioral Surveys and Resistance Results

Recognizing that both sexual risk behaviors and resistance might change over time, we sought to provide a more complete picture of sexual transmission risk and drug resistance dynamics over time by analyzing the 78 patients (20% of total population) with 4 surveys, viral load, and matched resistance data. This subset of the population provided a cumulative total of 12 months of sexual behavior experience over time. Sixty-six of the 78 (85%) patients engaged in vaginal, anal, or oral insertive sexual behavior during the 12-month cumulative period and reported a total of 3034 sexual events (median, 24/patient; range, 1427). Patients with resistance at the time of a sexual event contributed 549 sexual events (18% of all events). Patients had 3-class drug resistance during 62 or 2% of these sexual events. Thirty of the 78 patients (38%) engaged in unprotected vaginal, anal, or oral insertive sex at some time during the study, resulting in 789 sexual transmission risk events (median, 1/patient; range, 1131) exposing 70 partners (adjusted for redundancy; median, 1/patient; range, 115). As can be seen in Figure 2, there is a wide variation and uneven distribution in sexual risk events among the 30 patients. In addition, this wide variation extends to differences in sexual risk events with resistant and sensitive strains and numbers of partners exposed. For example, 3 patients contributed 7% (48/655) of the unprotected sex events with wild type virus and 74% (99/134) of the unprotected risk events that occurred with resistant strains.

The dynamics of risk and resistance were complex and varied over time. Patients had transitions in the viral resistance genotype (eg, from 1-class resistance to 2-class resistance, to nondetectable viral load or wild type virus) as patients went on new regimens or were taken off drugs, and some patients went in and out of sexual risk during their course of participation in the study. Risk behavior could be matched with confirmed viral load and viral resistance results within the specified time for 78 patients. Focusing on sexual transmission risk events involving resistance, 9 of the 78 patients (12%) had drug resistance at the time of unprotected sexual risk behavior and engaged in 134 (17%) of all unprotected sexual risk events. These 9 patients exposed 19 (27%) of all partners to drug-resistant virus (Figure 2). Of the unprotected sex events, 89 (11%) involved 2-class resistance and 7 (1%) involved 3-class resistance. Ten sexual risk partners (14%)

Table 1: HIV Genotypic Resistance Mutations for Patients Engaging in Sexual Risk

Antiretroviral Class Resistance and Number of Patients With Resistance	Mutation* and % of Patients With a Mutation
Nucleoside reverse transcriptase inhibitor (N = 29)	215Y/F/C/S/D (79%) 184V (52%) 41L (34%) 219Q/E (34%) 70R (28%) 67N (10%) 74V (3%) 151M (3%) 69SSS (3%)
Nonnucleoside reverse transcriptase inhibitor (N = 15)	103N (53%) 181C (40%) 190A/S (38%)
Protease inhibitor (N = 16)	90M (50%) 82A/F/D (31%) 30N (20%) 84V (6%) 48V (6%)

*Only major mutations are listed.

Table 2: HIV Resistance Genotypes of the 2 Patients With 3-Class Antiretroviral Drug Resistance at the time of the Sexual Risk Events

Patient Engagingin Sexual Risk	CD4+ Cell Count and HIV Viral Load	HIV Genotype	# Unprotected Sexual Events (# penile-vaginal or anal) [Partners exposed]
White Female IDU	429 cells/mcL 10,400 HIV RNA copies/mL	PI-46L, 82A NNRTI-103N RTI-41L, 184V, 210W, 215Y, 219Q	7 (7) [1]
Black Male MSM	51 cells/mcL 75,000 HIV RNA copies/mL	PI-10I, 46L, 54L, 71V, 82A NNRTI 181C, 190A RTI-67N, 210W, 215Y, 219N	1 (1) [1]

IDU = injection-drug user; mcL = microliter; PI = protease inhibitor; NNRTI-nonnucleoside reverse transcriptase inhibitor; NRTI = reverse transcriptase inhibitor; MSM = man who has sex with men.

were exposed to 2-class resistance and 1 (1.4%) to 3-class resistance during these unprotected events.

Assuming the partners for each patient were the same at all other time points, the minimum number of partners exposed (adjusted number) was 43; if all partners were different, the maximum number of partners exposed was 70. Using 70 and 43 separately as denominators to create conservative and more liberal estimates of proportion of partners exposed to ARV resistance, the percent of total partners exposed to 3-class resistance ranged from 1.4% (1/70) to 2.3% (1/43). The percent of partners exposed to any type of resistance ranged from 27% (19/70) to 30% (13/43).

Discussion

In this study of a diverse population of HIV-positive patients in clinical care, we obtained serial cross-sectional population-based data on the number of unprotected sexual events involving drug-resistant strains of HIV, and the number of partners potentially exposed to these resistant strains over time. In addition, in a subset of patients followed longitudinally, with matched biologic and behavioral data, we documented 12 months of reported cumulative unprotected sexual behavior over a period of observation of approximately 2 years. Both cross-sectional and longitudinal data from this diverse HIV-positive population receiving care indicate that those with drug-resistant HIV had a substantial amount of continued unprotected sexual risk behavior that could result in HIV transmission. In addition to the risk of HIV transmission in general, it is of further concern that during the time period in which the unprotected sexual events took place, approximately 11% of total risk events and 9% of the partners involved in these events were exposed to MDR HIV. It is of some comfort to note that in this sample, most were 2-class resistance and only approximately 1% of patients, events, and partners involved 3-class resistant strains.

These data are unique and help provide a more complete picture of the risk of drug resistance transmission via sexual risk behavior among patients with HIV infection and provide insight into the growing rate of drug resistance in incident HIV infections in areas where ARVs has been available for several decades.

In our previous baseline cross-sectional survey of risk behaviors in this population, approximately 23% of patients reported unprotected sexual behavior during a single 3-month period.[9] By capturing longitudinal behavioral data over the ensuing time period of approximately 2 years, 38% of patients who reported 12 months of cumulative sexual history engaged in unprotected sex at some time during the study. This is a larger proportion than that reported in previous single time point cross-sectional and nonquantitative resistance and risk studies,[9,12,18] and makes it clear that patients' sexual behavior is not static and changes over time. Some patients moved in and out of unprotected sexual risk behaviors at different times.

The majority of sexual risk partners (71%) involved in unprotected sexual events reported by this sample of HIV-positive patients in clinical care were HIV-negative or HIV serostatus unknown. Furthermore, of the sexual risk partners exposed to resistant strains, 83% were reported as being HIV negative or serostatus unknown. This suggests that in this predominately heterosexual population serosorting, or choosing partners of the same HIV serostatus, among patients with resistance who engaged in risk behaviors occurred at a low frequency.

One of the most interesting findings in this study is the wide variability in distribution of sexual risk in the population. The number of individuals engaging in risk behaviors, sexual risk events, and partners exposed were all unevenly distributed. Relatively few patients contributed a large number of unprotected sex events with drug-resist-

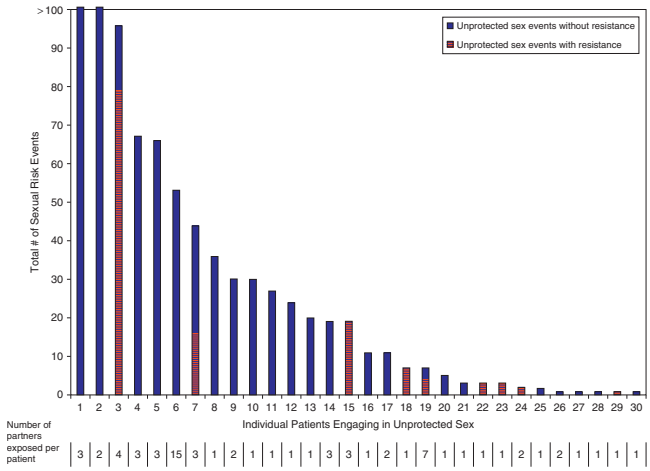

Figure 2

Distribution and relationship of unprotected sexual events; antiretroviral resistance and partners exposed among 30 patients engaging in sexual risk followed longitudinally in clinical care. Thirty patients engaging in unprotected sex during a cumulative total of 12 months: Cumulative number of unprotected sex events represented in bars, number of unprotected events with resistance (red stripe) and without (solid blue), and total number of partners exposed for all unprotected sex events for each patient (in column below each patient number). Cumulative unprotected sexual events (n = 789; median number of events = 11 [range 1131]), unprotected sex events with resistance (n = 134), and number of partners exposed (n = 70). Over the 4 three-month time periods, patients had back-and-forth transitions in the viral resistance genotype (eg, from 1-class resistance to 2-class resistance, or back to non-detectable viral load or wild-type virus (as patients received new regimens or were taken off drugs). In addition, some patients moved in and out of unprotected sexual risk during these time periods. Note that 7 patients provided 72% of unprotected risk events (patients 17) and 3 patients provided 85% of unprotected sexual risk events with resistant virus.

ant strains. This was particularly apparent in the sample of 78 patients who were followed longitudinally and had 12 months of sexual history matched with resistance data. In this subset of patients, 9 carried resistant virus and engaged in unprotected sex, with unprotected events ranging from 3 to 79, and exposed partners from 1 to 7 per patient. Furthermore, among these patients, 3 contributed 85% of the unprotected sex events involving resistant virus. Some patients exposed many partners in the 12-month period but with few unprotected events, whereas other patients exposed a single partner with many unprotected events. It is apparent from these data that not all patients or partners confer or receive similar transmission risk and, importantly, in this patient population, it appears that there is a small core group of individuals who contribute a large proportion of the sexual transmission risk events with resistant virus.

The opportunity to follow a subset of the patients longitudinally has enabled us to document that HIV-positive patients in this study had transitions over time in their predominant detectable viral genotype from 1-class to 2-class or 3-class resistance or back to a nondetectable viral load or to wild type virus (in concert with initiating new regimens or discontinuing medications). Along with the variations in transmission risk over time, this illustrates the dynamic process at the interface of drug resistance and unprotected sexual risk behavior (both persistent as well as intermittent).[12,18-22] The associations between overall sexual behavior, unprotected sex, and HIV drug resistance are complex and dynamic and further studies are needed to better elucidate these interrelationships over time.

In this study, all risk groups were represented and the demography and risk profile was that typical for HIV clinic populations in inner city urban areas of the northeastern United States where the HIV/AIDS epidemic is mature.[23] Notably, women, non-whites and heterosexual and intravenous drug users were most prominent in this population. One limitation of the study is that men who have sex with men were underrepresented and therefore characteristics and dynamics related to risk and resistance that may differ in this population may have been undetected. In addition, our study results may only be characteristic of the geographic region urban northeastern United States studied or the period when assessments were collected. They are, however, quite consistent with the small but growing data from other regions and populations,[9,18,22,24] where men who have sex with men were well represented.[12] Moreover, these data are of pressing clinical and public health importance, and warrant similar and additional investigation in different populations and geographic areas.

An additional limitation in the current study was our inability to identify and test partners of the patients for HIV infection to determine incident rates of transmission of resistant viruses. This would have enabled us to explore actual transmission rates rather than risk of resistant virus transmission from the clinic population. Such an effort was beyond the scope of this study. Furthermore, the study provided strict assurances of confidentiality to the participants and would have required participants to divulge information that in some areas in the United States is considered a criminal offense.[25] We used standard DNA sequencing to detect resistance mutations and such methods are limited in their ability to detect minor resistant viral variants in a sample. Thus, we may have underestimated resistant transmission risk events that could have involved minor resistant populations that were not detected with standard methods.

It is not known presently if the transmission of MDR HIV strains will continue to increase over time. If transmission risk behaviors remain stable over time in a population but drug resistance as a result of therapeutic failure develops in more patients, the total transmission events involving MDR strains may increase. Patients in care with and without resistant strains are only 1 portion of those who transmit HIV; however, those in care are more likely to carry resistant strains because of ARV exposure and longer duration of therapy. Alternatively, the transmission of resistance strains may decrease if more patients remain off drugs for longer periods or if they undergo monitored structured treatment interruptions and wild type virus predominates. Furthermore, future antiretroviral therapy that is more potent and easier to take may lead to lower viral load levels and decreased viral fitness.

Results from this study suggest that a likely major source of new resistant infections is a core group of patients within the clinic setting itself who have both resistance and ongoing unprotected HIV sexual transmission risk behaviors. Additionally, because many and likely increasing numbers of patients with or without drug-resistant strains engaging in sexual risk behavior are followed in clinical care, targeted prevention and risk reduction strategies situated within the clinical care setting may be an effective critical addition to HIV prevention efforts. Risk reduction strategies targeting HIV-positive patients in general and particularly those with highest potential for transmission of resistant HIV are a central component of current HIV prevention recommendations.[23] This issue takes on additional timeliness and relevance as growing populations of patients with HIV in resource-limited settings begin to receive ARV therapy and before resistance transmission becomes widespread.[26]

The findings of this study support the development, testing, and deployment of targeted prevention and risk reduction strategies in the clinical care setting, where ARV resistance is present among the patient population continuing to engage in behaviors that may transmit HIV, and prevention strategies may benefit from the frequent contacts and trusting relationships that occur between clinicians and their patients.[23,26,27]

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Authors and Disclosures

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