Use of Flexible Sigmoidoscopy to Screen for Colorectal Cancer in HIV-Infected Patients 50 Years of Age and Older

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Background: Although many patients with human immunodeficiency virus (HIV) infection are now living well beyond 50 years of age, there are no data available on colorectal cancer screening in this population. The aim of this study was to determine the utility of screening flexible sigmoidoscopy in patients with HIV.

Methods: Consecutive patients at average risk for colorectal cancer who were referred for screening flexible sigmoidoscopy were prospectively identified. A detailed medical history was obtained from all patients before flexible sigmoidoscopy, and colonoscopy was recommended for all subjects with positive sigmoidoscopic findings.

Results: A total of 2382 patients were enrolled in the study; 165 were HIV positive. The prevalence of neoplastic lesions (adenomas or adenocarcinomas) in the distal colon was significantly higher in HIV-infected patients than in control subjects (25.5% vs 13.1%, $P<.001$), and the odds of HIV-infected patients having a neoplastic lesion was significantly higher even after adjustment for potential confounding variables (odds ratio, 2.34; 95% confidence interval, 1.60-3.44). The prevalence of adenomas of any size (25.5% vs 12.9%, $P<.001$) and advanced neoplasia (7.3% vs 3.8%, $P=.03$) in the distal colon was significantly higher in HIV-infected patients. Among individuals with positive results on flexible sigmoidoscopy, proximal colonic neoplastic lesions on follow-up colonoscopy were more common in HIV-infected patients after adjustment for age, sex, and race/ethnicity (odds ratio, 1.88; 95% confidence interval, 1.02-3.46).

Conclusions: Patients infected with HIV are more likely to have colonic neoplasms on screening flexible sigmoidoscopy than those without HIV, and these individuals should be offered colorectal cancer screening.

Arch Intern Med. 2006;166:1626-1631

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SINCE THE INTRODUCTION OF highly active antiretroviral therapy (HAART), significant shifts have occurred in the frequency and clinical presentation of AIDS-defining conditions and AIDS-related deaths.[1-5] Improvements in the life expectancy of patients infected with human immunodeficiency virus (HIV) make it possible and important to evaluate and plan for the long-term health maintenance of these individuals.[6-9]

Although colorectal cancer (CRC) is the fourth most common cancer in the United States, it remains the second leading cause of cancer-related mortality, with more than 56 000 deaths resulting from the disease in 2005.[10] It is estimated that a person dying of CRC loses 14 years of life.[11] Screening for CRC starting at the age of 50 years for average-risk individuals reduces mortality from the disease and is recommended by the US Preventive Services Task Force,[12] the American Cancer Society,[13] the US Multi-Society Task Force on Colorectal Cancer,[14] and others.[15,16]

Even though the life expectancy of many HIV-infected patients has increased well beyond the age of 50 years, there are no published data on the utility of CRC screening in this population. Therefore, the aims of this study were to evaluate the prevalence of colonic neoplasms detected by flexible sigmoidoscopy among patients with HIV and to determine factors associated with colonic neoplasms in this population. Because patients with HIV are chronically immunosuppressed, which may increase their risk for the development of malignancies, we hypothesized that they would be more likely to have colonic neoplasms than those without HIV.

METHODS

STUDY POPULATION

We prospectively identified all patients referred for screening flexible sigmoidoscopy at the Veterans Affairs New York Harbor Healthcare System in New York City from January 1998 through December 2003. Patients were eli-

gible for the study if they were 50 years of age or older, were asymptomatic, and were at average risk for CRC. *Asymptomatic* was defined as the absence of gastrointestinal symptoms, including abdominal pain, constipation, diarrhea, change in stool caliber or frequency, unexplained weight loss, rectal bleeding, or other alarming symptoms suggestive of an underlying malignancy. *Average risk* was defined as no personal history of CRC or adenomatous polyps, no family history of colorectal neoplasia in a first-degree relative, and no inflammatory bowel disease.[14,15]

Patients were excluded from the study if they had a positive fecal occult blood test result, underwent a flexible sigmoidoscopy or barium enema within the last 5 years, or underwent a colonoscopy within the last 10 years. It is standard practice for physicians at our medical center to use flexible sigmoidoscopy to screen asymptomatic average-risk patients for CRC. At the time of the study, HIV status was not used by the referring physicians as a risk-modifying criterion that might alter referral patterns. The study protocol was reviewed and approved by the institutional review board at our medical center.

STUDY DESIGN

Before endoscopy, demographic and clinical information on all patients was obtained by means of a detailed self-administered questionnaire. Information collected included age, sex, race/ethnicity, level of education, annual household income, use of alcohol (≥2 drinks per day), tobacco use, use of nonsteroidal anti-inflammatory drugs or aspirin, and comorbid medical illnesses, including HIV. For HIV-infected patients, we also collected data on the duration of infection and the medications taken and reviewed the electronic medical record to confirm HIV status as well as to obtain the results of plasma HIV RNA testing and CD4 lymphocyte counts closest to the time of sigmoidoscopy. Patients who were not tested for HIV were considered HIV indeterminate and were included in the control group.

Before flexible sigmoidoscopy, patients received a bowel preparation of oral bisacodyl in combination with either an oral sodium phosphate solution or 2 enemas. Flexible sigmoidoscopy was performed without sedation of the patients. Polyps and masses were not removed during flexible sigmoidoscopy, and individuals were referred for colonoscopy on a separate day. The examining physicians were not blinded to the patient's HIV status.

All patients received an oral sodium phosphate solution or a polyethylene glycol–based electrolyte solution for bowel preparation before colonoscopy. After intravenous meperidine hydrochloride and midazolam were administered for conscious sedation, the colon was evaluated to the cecum and the location and size of each polyp were recorded. The size of small polyps was estimated using an open-biopsy forceps, which is 7 mm in diameter. The size of large polyps removed by snare polypectomy was confirmed during histologic evaluation. All retrieved polyps and biopsy specimens were sent to our local pathology laboratory for histologic evaluation.

STUDY OUTCOMES

The primary outcome of our study was the prevalence of neoplastic lesions (adenomas of any size or adenocarcinomas) in the distal colon detected by flexible sigmoidoscopy among HIV-positive patients compared with control subjects. The secondary outcomes included the proportion of patients with advanced neoplasia in the distal colon, the predictors of finding a distal neoplastic lesion, and the findings in the proximal colon among the patients with positive results on flexible sigmoidoscopy who underwent follow-up colonoscopy. *Advanced neoplasia* was defined as adenomas 10 mm or larger in diameter or any adenoma, regardless of size, with villous histologic features, high-grade dysplasia, or cancer.[17] *The distal colon* was defined as the segment of colon that was within reach of the 60-cm flexible sigmoidoscope, whereas *the proximal colon* was defined as the segment of colon evaluated by colonoscopy that was beyond the reach of the sigmoidoscope.

Table 1. Baseline Demographic and Clinical Characteristics of 2382 Patients Who Underwent Screening Flexible Sigmoidoscopy*

Characteristic	HIV-Positive Patients (n = 165)	Control Subjects (n = 2217)	*P* Value
Age, mean ± SD, y	64.0 ± 9.3	66.3 ± 9.3	.003
Male	159 (96.4)	2165 (97.7)	.30
Race/ethnicity			<.001
White, non-Hispanic	49 (29.7)	970 (43.8)	
Black, non-Hispanic	83 (50.3)	765 (34.5)	
Hispanic	31 (18.8)	395 (17.8)	
Asian	2 (1.2)	77 (3.5)	
Other	0 (0.0)	10 (0.5)	
Education <12 y	38 (23.0)	553 (24.9)	.58
Annual household income <$15 000	85 (51.5)	1187 (53.5)	.62
Alcohol use			.78
Never	61 (37.0)	852 (38.4)	
Former	62 (37.6)	773 (34.9)	
Current	42 (25.5)	592 (26.7)	
Smoker			.06
Never	49 (29.7)	743 (33.5)	
Former	71 (43.0)	1039 (46.9)	
Current	45 (27.3)	435 (19.6)	
Current NSAID use	39 (23.6)	497 (22.4)	.72
Current aspirin use	62 (37.6)	1057 (47.7)	.01

Abbreviations: HIV, human immunodeficiency virus; NSAID, nonsteroidal anti-inflammatory drug.
*Values other than age are expressed as number (percentage).

STATISTICAL ANALYSIS

Continuous variables were compared using the unpaired 2-tailed *t*-test or the Mann-Whitney *U* test. Data are expressed as mean ± SD for those variables that were normally distributed, and medians and interquartile ranges (25th-75th percentiles) are expressed for those with a nonnormal distribution. Categorical variables were compared using the χ^2 test or the Fisher exact test.

Multivariable logistic regression analysis was used to assess the effect of HIV infection on the odds of a neoplastic lesion being present after adjustment for potential confounding variables. The strength of the association between HIV infection and the presence of colonic neoplasia is expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical analysis was performed using SPSS software (Version 13.0; SPSS Inc, Chicago, Ill), and a 2-tailed *P* value of less than .05 was considered statistically significant.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

A total of 2382 patients met the eligibility criteria, and 165 (6.9%) were HIV positive. The baseline demographic and clinical characteristics of the 165 HIV-infected patients and the 2217 control subjects are shown in **Table 1**. Com-

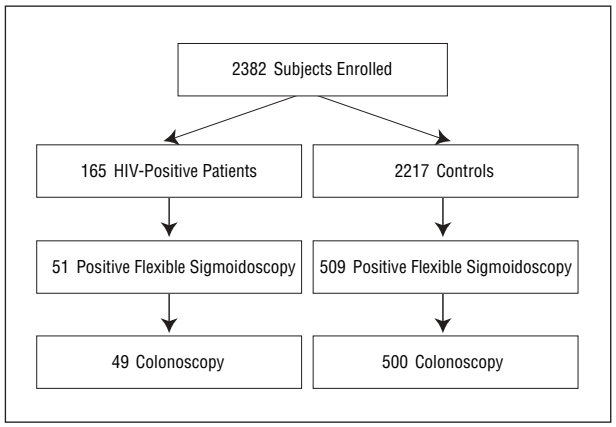

Figure 1. Flow of participants through the study. HIV indicates human immunodeficiency virus.

pared with control subjects, HIV-infected patients were significantly younger, more likely to be of a racial or ethnic minority, more likely to smoke, and less likely to be taking aspirin.

Among the HIV-infected patients, the median duration of HIV infection was 10.0 years (interquartile range, 7.5-15.0 years), and 82 individuals (49.7%) had been diagnosed as having HIV more than 10 years earlier. The patients had a median CD4 cell count of 346/μL (interquartile range, 187/μL-540/μL), with 47 (28.5%) having a CD4 cell count of less than 200/μL. A total of 141 patients (85.5%) were taking HAART, and plasma HIV RNA levels were undetectable in 75 (45.5%) of the 165 HIV-infected patients.

FINDINGS IN THE DISTAL COLON ON SCREENING FLEXIBLE SIGMOIDOSCOPY

The proportion of patients who underwent a complete flexible sigmoidoscopy to 50 cm (89.1% vs 91.9%, $P=.21$) or 60 cm (84.8% vs 87.7%, $P=.29$) was similar in the HIV-positive group and the control group. The flow of participants through the study is shown in **Figure 1**. One or more polyps or masses (a positive screening test result) were identified in 30.9% of HIV-infected patients and in 23.0% of control subjects ($P=.02$), a difference of 7.9% (95% CI, 1.2%-14.7%).

The prevalence of neoplastic lesions detected by flexible sigmoidoscopy was significantly higher in HIV-infected patients than in control subjects (25.5% vs 13.1%, $P<.001$), a difference of 12.4% (95% CI, 6.9%-17.8%). Compared with control subjects, HIV-infected patients had significantly increased odds of having neoplastic lesions (OR, 2.27; 95% CI, 1.57-3.29), and this association remained highly significant even after adjustment for age, sex, race/ethnicity (OR, 2.45; 95% CI, 1.68-3.57), and all baseline characteristics listed in Table 1 (OR, 2.34; 95% CI, 1.60-3.44).

The type of lesions identified by flexible sigmoidoscopy in the 165 HIV-infected patients and the 2217 control subjects is shown in **Table 2**. Compared with control subjects, HIV-infected patients were significantly more likely to have adenomas and advanced neoplasia. Also, adenocarcinomas of the distal colon were more common in HIV-infected patients, although this difference did not reach statistical significance.

Table 2. Prevalence of Distal Neoplastic Lesions on Screening Flexible Sigmoidoscopy

Distal Colon Lesions*	HIV-Positive Patients, No. (%) (n = 165)	Control Subjects, No. (%) (n = 2217)	*P* Value
Any adenoma	42 (25.5)	287 (12.9)	<.001
Adenoma <5 mm	24 (14.5)	156 (7.0)	<.001
Adenoma 6-9 mm	14 (8.5)	73 (3.3)	.001
Adenoma ≥10 mm	11 (6.7)	76 (3.4)	.03
Villous adenoma	5 (3.0)	19 (0.9)	.007
Adenocarcinoma	3 (1.8)	10 (0.5)	.06
Advanced neoplasia	12 (7.3)	85 (3.8)	.03
Carcinoid	0	3 (0.1)	>.99
Gastrointestinal stromal tumor	0	1 (0.1)	>.99
Lymphoma	1 (0.6)	0	.07
Hyperplastic polyp	10 (6.1)	214 (9.7)	.13

Abbreviation: HIV, human immunodeficiency virus.
*The categories are not mutually exclusive, as advanced neoplasia includes patients with adenomas 10 mm or larger, patients with adenomas of any size with villous histologic features or high-grade dysplasia, and patients with adenocarcinoma.

FACTORS ASSOCIATED WITH DISTAL NEOPLASTIC LESIONS AMONG PATIENTS WITH HIV

To evaluate factors associated with adenomas and cancers in the distal colon among HIV-infected patients, we determined the proportion of subjects who had neoplastic lesions detected by sigmoidoscopy according to select demographic and clinical characteristics (**Table 3**). In the univariate analysis, HIV infection of more than 10 years and lower CD4 lymphocyte counts were the only 2 variables that were significantly associated with having a distal neoplastic lesion detected by flexible sigmoidoscopy.

In the multivariable analysis, HIV infection of more than 10 years (OR, 9.96; 95% CI, 3.75-26.42) and lower CD4 lymphocyte counts both remained independently associated with distal neoplastic lesions. Compared with subjects with CD4 cell counts lower than 200/μL, patients with CD4 cell counts ranging from 200/μL to 350/μL (OR, 0.17; 95% CI, 0.05-0.52) and those with CD4 cell counts higher than 350/μL (OR, 0.15; 95% CI, 0.06-0.42) had lower odds of having a distal neoplastic lesion. Both duration of HIV infection and CD4 cell count remained independently associated with distal neoplastic lesions when multivariable logistic regression was repeated with age, sex, and race forced into the model.

FINDINGS IN THE PROXIMAL COLON ON FOLLOW-UP COLONOSCOPY

Among participants with positive results on screening sigmoidoscopy, the proportion who underwent a follow-up colonoscopy was similar in the 2 groups (96.1% vs 98.2%, $P=.29$). The remaining patients refused colonoscopy or were unavailable for follow-up, and none of

Table 3. Proportion of HIV-Infected Patients With Neoplastic Lesions on Screening Flexible Sigmoidoscopy According to Select Demographic and Clinical Characteristics

Characteristic	No. of Subjects in Each Category	Proportion With Neoplastic Lesions, %	*P* Value
Age, y			.10
50-59	55	18.2	
60-69	67	26.9	
≥70	43	32.6	
Sex			.65
Female	6	33.3	
Male	159	25.2	
Race/ethnicity			.31
White, non-Hispanic	49	18.4	
Black, non-Hispanic	83	25.3	
Hispanic	31	35.5	
Asian	2	50.0	
Education <12 y			.78
No	127	26.0	
Yes	38	23.7	
Annual household income <$15 000			.56
No	80	27.5	
Yes	85	23.5	
Alcohol use			.08
Never	61	23.0	
Former	62	19.4	
Current	42	38.1	
Smoker			.57
Never	49	22.4	
Former	71	29.6	
Current	45	22.2	
Current NSAID use			.22
No	126	27.8	
Yes	39	17.9	
Current aspirin use			.77
No	103	26.2	
Yes	62	24.2	
Duration of HIV Infection >10 y			<.001
No	83	9.6	
Yes	82	41.5	
Currently taking HAART			.57
No	24	20.8	
Yes	141	26.2	
Undetectable HIV viral load			.74
No	90	24.4	
Yes	75	26.7	
CD4 cell count, /μL			<.001
<200	47	44.7	
200-350	36	22.2	
>350	82	15.9	

Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NSAID, nonsteroidal anti-inflammatory drug.

these individuals had a polyp greater than or equal to 10 mm in diameter or a mass on sigmoidoscopy. Colonoscopy was complete to the cecum in 47 (95.9%) of the 49 HIV-infected patients and 487 (97.4%) of the 500 control subjects who underwent colonoscopy ($P=.54$).

Among patients with positive results on screening sigmoidoscopy, the prevalence of neoplastic lesions in the proximal colon detected by colonoscopy was higher in the HIV-infected group than in the control group (61.2% vs 47.8%, $P=.07$), although this difference was not statistically significant. However, the odds of having a proximal neoplastic lesion was significantly greater in HIV-positive patients than in control subjects after adjustment for age, sex, and race/ethnicity (OR, 1.88; 95% CI, 1.02-3.46). The small sample size did not allow adjustment for other potential confounding variables.

Table 4. Prevalence of Proximal Neoplastic Lesions on Follow-up Colonoscopy Among Patients With Positive Results on Flexible Sigmoidoscopy

Distal Colon Lesions*	HIV-Positive Patients, No. (%) (n = 49)	Control Subjects, No. (%) (n = 500)	*P* Value
Any adenoma	30 (61.2)	236 (47.2)	.06
Adenoma <5 mm	16 (32.7)	133 (26.6)	.36
Adenoma 6-9 mm	13 (26.5)	114 (22.8)	.56
Adenoma ≥10 mm	15 (30.6)	94 (18.8)	.048
Adenocarcinoma	4 (8.2)	15 (3.0)	.08
Villous adenoma	3 (6.1)	23 (4.6)	.50
Advanced neoplasia	16 (32.7)	107 (21.4)	.07
Hyperplastic polyp	6 (12.2)	67 (13.4)	.82

Abbreviation: HIV, human immunodeficiency virus.
*The categories are not mutually exclusive, as advanced neoplasia includes patients with adenomas 10 mm or larger, patients with adenomas of any size with villous histologic features or high-grade dysplasia, and patients with adenocarcinoma.

The type of proximal colonic lesions identified by colonoscopy in the 49 HIV-infected patients and the 500 control subjects with positive flexible sigmoidoscopy results is shown in **Table 4**. Compared with control subjects, HIV-infected patients were significantly more likely to have adenomas greater than or equal to 1 cm. Also, there was a trend toward adenomas of any size, adenocarcinoma, and advanced neoplasia being more common in HIV-infected patients than in control subjects.

To determine whether distal lesions on sigmoidoscopy were predictive of neoplasms being found in the proximal colon on follow-up colonoscopy among HIV-infected patients, we evaluated the prevalence of proximal neoplastic lesions stratified according to the most advanced distal lesion (**Figure 2**). Although limited by the small sample size, we did find significant differences in the prevalence of proximal neoplastic lesions according to the most advanced distal lesion ($P=.02$). The prevalence of proximal neoplastic lesions was highest in patients with adenomas greater than or equal to 10 mm in diameter and in individuals with adenocarcinoma. Also, patients with an advanced neoplasm in the distal colon were significantly more likely to have a neoplastic lesion detected in the proximal colon than those without advanced neoplasms in the distal colon in both the HIV-infected group (100.0% vs 48.6%, $P=.001$) and the control group (71.8% vs 42.9%, $P<.001$).

COMMENT

In the present study, we demonstrated that neoplastic lesions detected by screening flexible sigmoidoscopy were significantly more common in HIV-infected patients than in control subjects without HIV. This clinically important finding has substantial implications for the esti-

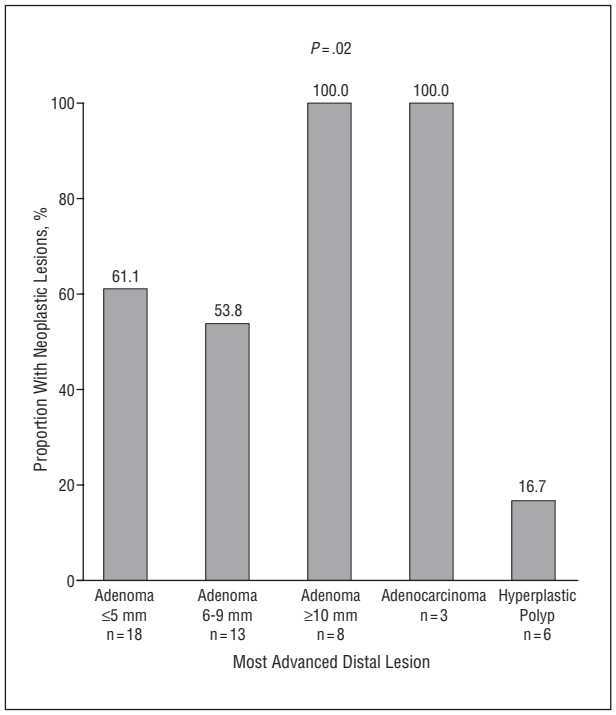

Figure 2. Prevalence of proximal neoplastic lesions among human immunodeficiency virus–positive patients who underwent a follow-up colonoscopy stratified according to distal findings.

mated 1 million persons living with HIV in the United States,[18] especially since many of these individuals are now living well beyond 50 years of age.

Compared to the pre-HAART era, patients with HIV in the HAART era have a lower incidence of AIDS-defining malignancies such as non-Hodgkin lymphoma, Kaposi sarcoma, and cervical cancer, although the incidence of these malignancies is still higher than in the general population. Several recent studies have demonstrated that non–AIDS-defining malignancies account for an increasing proportion of cancers seen in HIV-infected patients,[19-27] with the proportion of individuals dying as a result of these malignancies increasing from less than 1% in the pre-HAART era to 13% currently.[27,28] Colorectal cancer has been identified as one of the non–AIDS-defining malignancies that may be increasing in incidence in the HIV population.[20,26,29] For example, a prospective cohort study of 2882 patients with HIV reported that the annual incidence of CRC increased from 0.65 per 1000 patient-years in the pre-HAART era to 2.34 per 1000 patient-years between 1997 and 2002.[26] However, other studies showed that the incidence of CRC is not higher in HIV-infected patients than in the general population[22,23,30-32] and that, when compared with the pre-HAART era, there has not been an increase in CRC incidence in HIV-infected subjects.[33,34] These contradictory findings highlight the need for large, well-designed studies to evaluate CRC in this population.

Non–AIDS-defining malignancies such as CRC may develop at an earlier age and be more aggressive in HIV-infected patients than in individuals without HIV.[24,29,35-38] Despite the potential increase in incidence, younger age at onset, and more aggressive course of CRC in patients with HIV, a recent study showed that CRC screening is underused in these individuals.[39] In a retrospective study of 302 HIV-infected patients 50 years of age and older who were seen in the outpatient clinics at a single medical center, only 5.3% of the patients with HIV had ever undergone a flexible sigmoidoscopy compared with 17.5% of age-matched controls without HIV. Furthermore, that study demonstrated that other screening modalities, such as fecal occult blood testing and colonoscopy, were also underused in HIV-infected patients.

Another interesting and important finding in our study was the significant independent association between a longer duration of HIV infection and neoplastic lesions in the distal colon. One possible explanation is that the risk for developing neoplastic colonic lesions among patients with HIV increases with age, as it does among patients without HIV. As survival times increase as a result of the use of HAART, the risk of the development of neoplastic lesions also increases as a result of the aging of the population.

However, given that HIV-infected patients may develop colonic lesions at a younger age than those without HIV, it is possible that either HIV itself or immune system dysfunction contributes to the development of neoplastic colonic lesions. The concept of immune system dysfunction being associated with an increased risk of colorectal neoplasia is supported by our study, because we found that lower CD4 lymphocyte counts were also independently associated with neoplastic lesions in the distal colon. This association suggests the possibility that there is an antineoplastic response associated with higher CD4 cell counts, and this hypothesis is supported by data demonstrating the importance of CD4 and CD8 cells as part of the antitumor response.[40-43] Taken together, the duration of HIV infection and the CD4 lymphocyte count may be useful markers to target HIV-infected individuals for CRC screening.

The strengths of our study include the prospective study design, the collection of detailed demographic and clinical data, the inclusion of a control group, and the performance of colonoscopy in a high proportion of subjects with positive results on flexible sigmoidoscopy. Also, this study is unique because we are unaware of any published studies that have evaluated screening flexible sigmoidoscopy in patients with HIV.

However, several limitations should be considered when interpreting our findings. First, the study was conducted at a single Veterans Affairs Medical Center and the majority of our patients were men. Therefore, our findings may not be generalizable to other clinical settings or to women. Second, our study population included only 165 HIV-infected patients, and larger prospective studies are needed to address this clinically important issue. Third, HIV testing was not performed on all subjects in the control group, and it is possible that some of these individuals had undiagnosed HIV infection. Nonetheless, we do not think that this had a substantial impact on our findings, because the prevalence of polyps or masses in the distal colon of our control subjects (23.0%) was remarkably similar to the frequency reported among the 64 658 average-risk subjects evaluated in the multicenter Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (23.4%).[44]

Because the endoscopists who performed the sigmoidoscopies were not blinded to the HIV status of the pa-

tients, it is possible that there was ascertainment bias. However, this was unlikely to be a major factor, as the endoscopists were not aware of the specific aims of this study. Although flexible sigmoidoscopy is less sensitive than colonoscopy for the detection of neoplastic lesions, this should not have biased our results in favor of detecting more lesions in patients with HIV, as both groups underwent the same procedure and had a similar depth of insertion of the sigmoidoscope. Finally, we were not able to determine the prevalence of proximal neoplastic lesions in patients without distal neoplastic lesions because colonoscopy was only performed in those with positive results on flexible sigmoidoscopy. This important limitation highlights the need for screening colonoscopy studies in this population.

In conclusion, flexible sigmoidoscopy is a valuable tool to screen for CRC in patients with HIV. The high prevalence of colonic neoplasms in patients with HIV underscores the need to increase awareness of CRC screening in this population. Also, large, well-designed, multicenter studies are needed to confirm our findings and to evaluate the utility of screening colonoscopy in patients with HIV infection.

Accepted for Publication: May 11, 2006.
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Financial Disclosure: None reported.

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