Colon Cancer Screening in HIV-Infected Patients Age 50 and Older: Data from an Outpatient HIV Clinic

by Robert D. Kung, Ashley L. Reid, Matthew M. McMahon, Ying Guo, Ryan M. Ford

Background and Aims: It is unclear whether infection with Human Immunodeficiency Virus (HIV) increases the risk of developing colorectal cancer.

Methods: A retrospective cohort study to determine colon cancer screening results was conducted. 298 HIV-infected subjects, 50 years of age or older, were randomly selected from an outpatient HIV clinic; comparisons were made to 102 uninfected controls. Frequency and type of screening methods were evaluated; polyp pathology was analyzed for those who underwent colonoscopy.

Results: In the HIV-infected cohort, 72% (216/298) were screened for colorectal cancer. Colonoscopy was utilized in 45% (98/216) of patients and fecal occult blood test (FOBT) in 44% (95/298). There was no difference between the prevalence of polyps between the HIV-infected and uninfected groups (18% vs. 22%, p=0.42). There was a trend that HIV-infected patients were more likely to have advanced neoplasms (46% vs. 19%, p=0.13).

Conclusions: HIV-infected subjects did not have a higher prevalence of colorectal polyps in our review but may be at higher risk for advanced neoplasia.

INTRODUCTION

With the advent of highly active antiretroviral therapy (HAART), the survival of patients with Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome (HIV/AIDS) has dramatically improved, and the natural history and course of the disease has changed.[1-4] Whereas the incidence of AIDS defining cancers, such as Kaposi's sarcoma or Non-Hodgkins lymphoma has fallen,[4-8] the incidence of non-AIDS defining cancers has increased.[4,9-12] These non-AIDS defining cancers have become an increasingly important cause of mortality in this population.[13,14]

It is unclear whether patients with HIV/AIDS are at an increased risk for developing colorectal cancer (CRC). Case reports and retrospective studies have suggested an increased risk of CRC and a younger age at presentation in HIV-infected patients. On the other hand, several large epidemiological studies utilizing AIDS and cancer registries have not identified an association between HIV infection and CRC.[9-22] However, none of those studies included information on prevalence and type of CRC screening. Furthermore, Reinhold et al. found that HIV positive patients were 22.1% less likely to have ever been screened and 16.3% less likely to be

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Table 1. Baseline Characteristics of All Study Patients According to HIV Status

Characteristic	HIV-infected (N=298)	HIV uninfected (N=102)
Age – yr		
Average	53.9	57
Range	50-76	50-79
Male sex- no. (%)	209 (70)	30(29)
Race - no. (%)		
African American	233 (78)	92(90)
Caucasian/Other	66 (22)	10(10)
CD4 count < 200 - no. (%)	100 (33)	N/A
HIV RNA Viral load undetectable - no. (%)	145 (48)	N/A
HAART therapy - no. (%)	221 (74)	N/A

HAART = highly active antiretroviral therapy

up to date with recommended screening when compared to controls.[23]

Another study by Bini and colleagues showed that HIV-infected patients had a higher prevalence of colorectal neoplasms and presented at a younger age than HIV negative controls.[24,25] Our study aims to better define prevalence and modality of CRC screening in an HIV-infected population. We also aim to define the risk of polyps, advanced neoplasia and cancer in an age appropriate population of HIV-infected patients undergoing colonoscopy.

METHODS

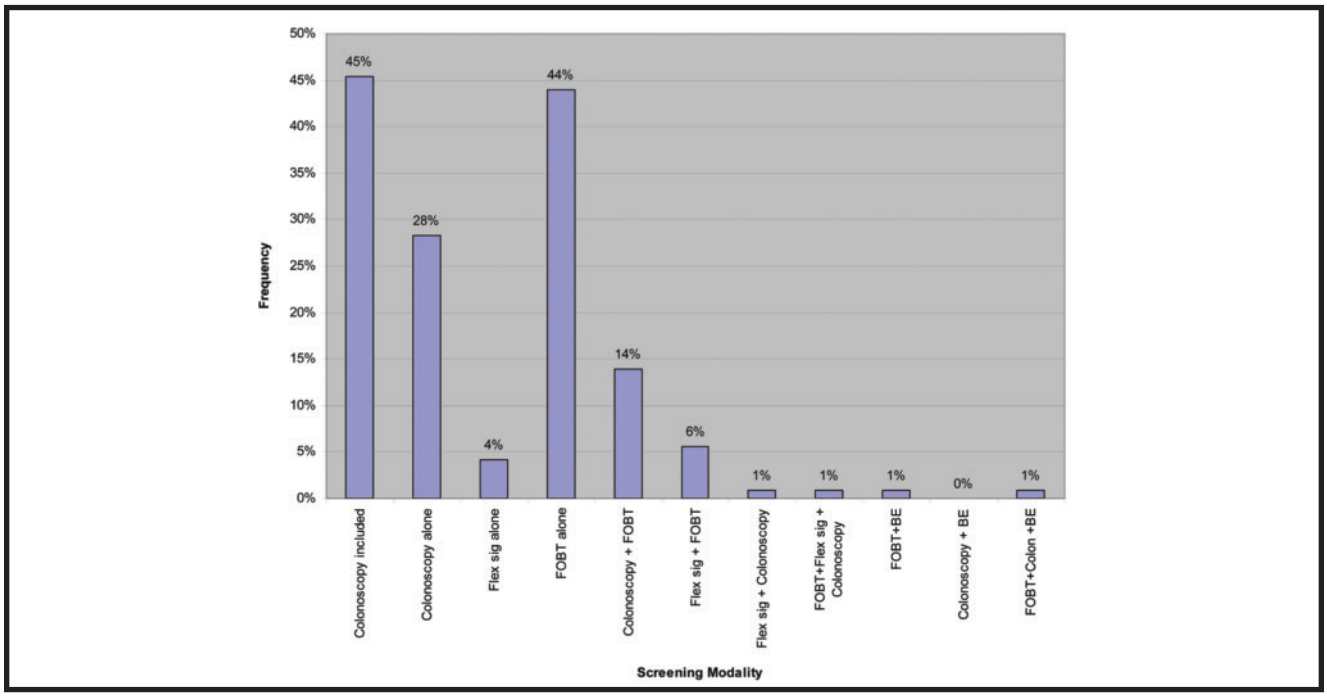
Study Population and Design

After Institutional Review Board approval, we obtained a list of all patients age 50 and older who were seen at least once at the comprehensive HIV clinic on Ponce de Leon Avenue in downtown Atlanta, Georgia between January 2000 and December 2006. 298 out of a possible 849 patients were randomly identified for chart review. Data regarding age, gender, family history of CRC, CD4 count, viral load, active HAART therapy, presence of colon cancer screening and selected modality of colon cancer screening were collected. For those patients who underwent colonoscopy at Grady Hospital, the major urban referral site for the Infectious Disease clinic, colonoscopy reports were reviewed for indication of exam, location of polyp, and size of polyps. Pathology reports were reviewed to determine histologic findings. Advanced neoplasias were defined as any of the following: adenoma > 10mm, adenoma with villous features or high-grade dysplasia, or invasive cancer. The control group was composed of 102 HIV negative age-matched contemporary clinic patients who underwent colonoscopy in 2006 and the corresponding endoscopy and pathology reports were reviewed.

Statistical Analysis

Demographic and clinical characteristics were compared between the HIV-infected and uninfected control groups. Continuous variables and relative frequency of various polyps were compared using the independent sample Student t-test. Categorical variables were compared using the Chi-square test or Fisher's exact test when appropriate. Multivariate logistic regression analysis was used to assess the effect of HIV infection on the presence of polyps or advanced neoplasms while adjusting for potential confounding variables: age, sex, race, family history of CRC, and CD4 count. The strength of the association between

Figure 1. Frequency of Colorectal Cancer Screening in HIV Patients According to Modality



FOBT, fecal occult blood test; flex sig, flexible sigmoidoscopy; BE, barium enema; colon, colonoscopy

HIV infection and the presence of colorectal neoplasia is expressed as an odds ratio (OR) with 95% confidence intervals (CI). Statistical analysis was performed using SPSS and SAS (version 9.2; SAS Institute, Cary, NC) software. All statistical tests were two-sided and a p value of < 0.05 was considered statistically significant.

RESULTS

Patient Demographic and Clinical Characteristics

A total of 298 HIV-infected subjects and 102 uninfected controls were analyzed. The baseline demographic and clinical characteristics of the study subjects are shown in Table 1.

Pattern of Colorectal Cancer Screening in HIV-Infected Group

Of the 298 HIV-infected patients studied, 216 (72%) patients underwent some form of colon cancer screening (see Figure 1). Colonoscopy alone was performed in 61 patients (28%) and used in combination with other modalities in 98 (48%) patients. FOBT testing alone was performed in 95 patients (44%); however, it was never performed on a consistent annual basis. Flexible sigmoidoscopy alone was used in 4% and barium enema in 1%.

Prevalence and Types of Neoplasms Detected by Colonoscopy

Of the 98 HIV-infected patients who underwent screening colonoscopy, 80 (82%) had endoscopy and pathology reports at Grady Hospital that were available for review. One patient was excluded because the indication for colonoscopy was to evaluate rectal bleeding. An additional five were excluded due to poor bowel preparation. 74 patients were thus included in the statistical analysis. 102 HIV negative patients in the control group had endoscopy and pathology reports from a colonoscopy that was performed at Grady Hospital. In the control group, 8 patients were excluded due to poor bowel preparation; therefore, 94 control patients were analyzed. (See table 2 for demographics). The HIV-infected group had significantly more males (64% vs. 31%, $p < 0.0001$) and was slightly younger (55.2 vs. 57.3 years, $p = 0.05$). Both groups were predominantly African American (81% vs. 90%, $p = 0.13$).

Figure 2 and Table 3 identify and describe the pathology of the polyps removed in those patients who underwent colonoscopy. The prevalence of adenomatous polyps in HIV-infected patients did not differ relative to uninfected controls (18% vs. 22%, p=0.42). The prevalence of advanced neoplasms, however, was twice as high in the HIV-infected group (8% vs. 4%, p=0.34)

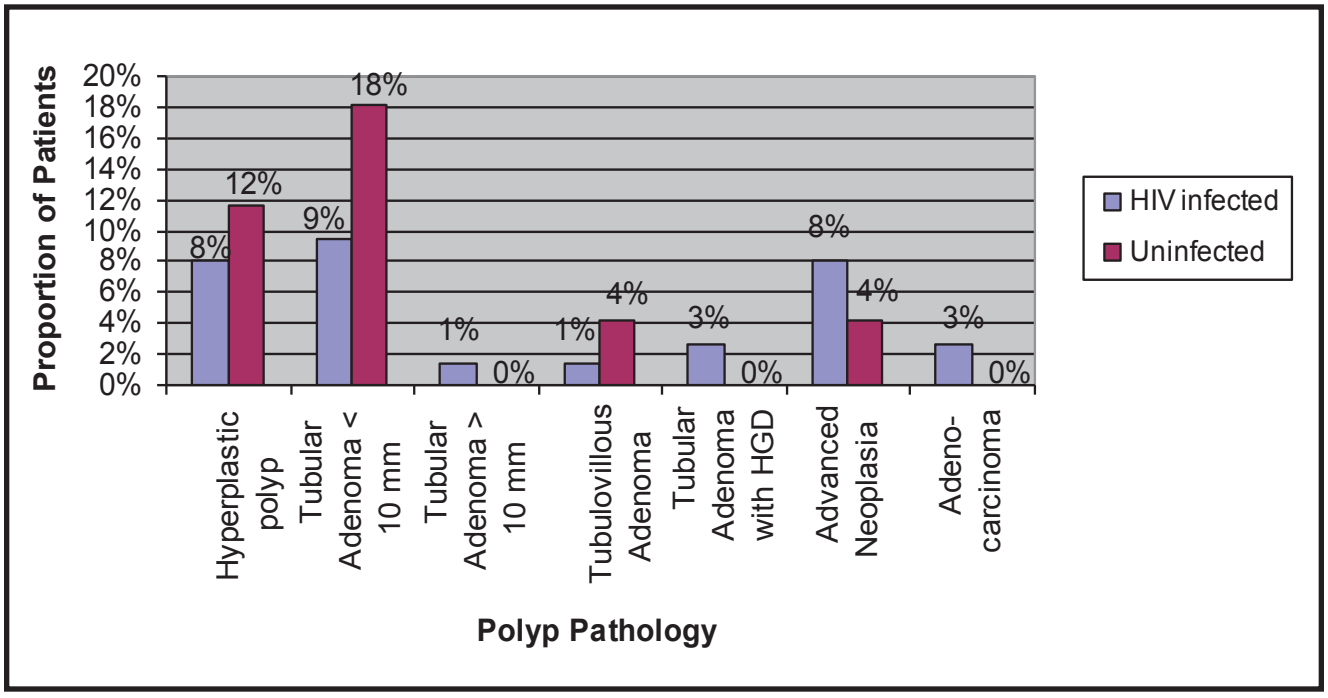
Table 2. Baseline Characteristics of Patients Undergoing Screening Colonoscopy

	HIV positive (N=74)	HIV negative (N=94)	p-value
Age - year			
Average (SD)	55.2	57.3	0.05
Range	50-76	50-79	
Male sex- no. (%)	47(64)	29(31)	<0.0001
Race-no. (%)			
African American	60(81)	85(90)	0.13
Caucasian/Other	14(19)	9(10)	-
Family History of CRC (%)	4(5.4)	6(6.3)	0.79
CD4 count < 200 - no. (%)	14(19)	N/A	-
HIV RNA Viral load undetectable - no. (%)	35(47)	N/A	-
HAART therapy - no. (%)	45(61)	N/A	-

Table 3. Results of Screening Colonoscopy

	HIV positive subjects (N=74)		Control subjects (N=94)		p-value
Result					
No polyps	55	74%	62	66%	0.28
Any Polyp or Neoplasm	13	18%	21	22%	0.42
Polyp Pathology-no. (%)					
Hyperplastic polyp	6	8%	11	12%	0.08
Tubular Adenoma < 10 mm	7	9%	17	18%	0.44
Tubular Adenoma > 10 mm	1	1%	0	0%	0.11
Tubulovillous Adenoma	1	1%	4	4%	0.44
Tubular Adenoma with High Grade Dysplasia	2	3%	0	0%	0.39
Advanced Neoplasia	6	8%	4	4%	0.11
Adenocarcinoma	2	3%	0	0%	0.34

Figure 2. Results of Screening Colonoscopy



HGD, High-grade dysplasia

but did not reach statistical significance. There were two cases of adenocarcinoma in the HIV-infected group, but no cases in the uninfected control group (3% vs. 0%, p = 0.44). There were two cases of tubular adenomas with high-grade dysplasia in the HIV-infected group but no such cases in the control group (3% vs. 0%, p = 0.11).

Multivariate analysis (Table 4) did not show a statistically significant difference in the risk of colorectal polyps between the HIV-infected patients and controls (OR= 0.86, 95% CI: 0.35-2.07, p=0.72).

Of those patients with polyps, Chi-square test showed a trend toward increased prevalence of advanced neoplasms in the HIV-infected group (46% vs. 19%, p=0.13). Multivariate analysis (Table 5) suggested that HIV-infection was associated with a higher odds ratio of having an advanced neoplasm, which trended toward statistical significance (OR=3.61, 95% CI: 0.60-21.61, p=0.16).

Two cases of adenocarcinoma were identified in the HIV positive group but none in the control group. The first case was a 64 year-old African-American male with a rectal adenocarcinoma and several synchronous tubular adenomas. He was not on HAART, had a CD4 count of 422 and had a detectable HIV viral load. The second case involved a 60 year-old African-American female with a rectosigmoid adenocarcinoma. She was on HAART and had a CD4 count of 229 with an undetectable viral load.

In the HIV positive group, the four patients with nonmalignant advanced neoplasia had an average age of 53, were on HAART (100%), 75% had an undetectable viral load and 75% had a CD4 count above 200. In the control group, the four patients with advanced neoplasia had an average age of 53.

HIV-infected subjects were significantly less likely to have any polyps proximal to the splenic flexure (8% vs. 22%, p=0.01). Only 6 (17%) advanced neoplasms in the HIV-infected group occurred proximally, compared to 3 of 4 (75%) advanced neoplasms in the control group. The average age of those with advanced neoplasms did not differ.

DISCUSSION

Estimates are that over 1 million people in the United States are infected with HIV and the number living beyond fifty years of age continues to grow.[26] The prevalence of colorectal cancer in patients with HIV has increased over time.[5,9] However, whether this is due to an increased risk conferred by infection with HIV, or is a result of improved life expectancy in an average risk population is not clear. The current study is one of

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the first to report rates and modalities of CRC screening from a comprehensive HIV clinic while also describing endoscopic and pathologic findings from colonoscopy.

The proportion of HIV patients who underwent colorectal cancer screening during the 7 year study period was 78%, which is higher than the previously reported rate of 55.6% in HIV patients[23] and the rate of 65.4% in the U.S. population.[27] Not all of these ptients were screened with colonoscopy, and those who were screened with FOBT did not get screened annually with this modality as recommended by the United States Preventive Services Task Force.[28] Reinhold et al. showed that a CD4 count <100 was associated with a lower screening rate. At the same time, variables associated with a higher screening rate included more than 10 visits with a primary care provider in the last 24 months, currently taking HAART and having an undetectable viral load.[23] Such characteristics are likely surrogate markers for access to health care. Our study evaluated CRC screening prevalence and modality in a patient population who had access to health care while being treated at a comprehensive HIV clinic in downtown Atlanta.

In our study, although not reaching statistical significance, there is a trend toward higher risk of advanced neoplasia and cancer in patients who are HIV positive. The HIV positive group was also slightly younger than the HIV negative control group. There were two cases of adenocarcinoma in the HIV positive group, but no cases of cancer in the control group. Our findings suggest that the pathogenesis of advanced colonic neoplasia in HIV positive patients may differ from the traditional multi-hit model of CRC progression in the general population. This may be due to altered immune surveillance, direct cytotoxic effects of HIV or other opportunistic pathogens, effects of HAART therapy on colonic mucosa, microsatellite instability or other unknown derangements. Bini et al. reported that HIV-infected patients with colorectal adenocarcinoma presented on average eight years earlier than uninfected controls.[25] HIV infection may lead to a more aggressive disease phenotype.

It is unclear whether altered host immunity contributes to CRC pathogenesis. Our subgroup analysis does not show any increased rate of neoplasms associated with CD4 count<200, not being on HAART, or having a detectable viral load, which was well represented in our HIV-infected cohort (19%, 39%, and 53%, respectively). Bini et al. showed HAART to be associated with a decreased risk of neoplasm (OR: 0.14, 95% CI: 0.02-0.75, p=0.03), but no significant association with CD4 count<200 or detectable viral load.[25] Whether or not the virus plays any direct role (e.g. cytotoxic) or indirect role (e.g. via systemic inflammation) remains to be determined.

Bini et al. also reported that HIV-infected patients were at higher risk of developing neoplasms proximal to the splenic flexure. In our study, we observed that HIV-infected patients had less proximal neoplasia. Further studies are needed to address the optimal age to begin screening and the most effective modality (flexible sigmoidoscopy vs. colonoscopy) of CRC screening in the HIV positive population.

Table 4. Multivariate Logistic Regression for Presence of Colorectal Polyps

Effect	Estimated Odds Ratio	95% CI for Odds Ratio	p-value
HIV Infection (Yes or No)	0.86	(0.35, 2.07)	0.72
Age	0.99	(0.94, 1.04)	0.67
Gender (Female vs. Male)	2.46	(1.02, 5.82)	0.05
Race	0.68	(0.21, 2.01)	0.45
CD4<200 (Yes vs. No)	1.55	(0.36, 7.18)	0.54

Table 5. Multivariate Logistic Regression for Presence of Advanced Colorectal Neoplasms Amongst Subjects with Polyps/Lesions

Effect	Estimated Odds Ratio	95% CI for Odds Ratio	p-value
HIV Infection (Yes or No)	3.61	(0.60, 21.61)	0.16
Age	0.91	(0.78, 1.07)	0.25
Gender (Female vs. Male)	0.34	(0.05, 2.44)	0.28
Race	1.22	(0.09, 15.81)	0.88
CD4<200 (Yes vs. No)	0.52	(0.03, 10.42)	0.67

The strengths of our study include the comprehensive analysis of CRC screening and neoplasia prevalence in a specific population. Our description of the patterns and prevalence of CRC screening in the HIV positive population provides quality improvement analysis to hopefully improve future care for patients with HIV. Our study includes HIV positive patients in an urban community with a high prevalence of HIV infection (1.7%) and a high prevalence of African-Americans. Although many of our findings did not reach statistical significance, there were several observations and trends that still suggest a possible benefit to earlier CRC screening with colonoscopy in the HIV positive population.

There are, however, several limitations to consider when interpreting our findings. First, the retrospective design of our study limits our data analysis to what was available in the chart. Second, our experimental and control groups differed with regard to gender and race. Third, data on other potential confounding variables, such as family history of colon cancer, were not complete, although none of the cancer cases in the HIV positive group had a positive family history. Fourth, our sample size was likely too small to show a statistically significant difference in risk of CRC. Fifth, our control group was only presumed to be HIV negative, as we did not have negative serologies to confirm such status. Lastly, our results may not be applicable to patients with advanced HIV/AIDS since our HIV-infected patients were predominantly on HAART therapy with a CD4>200. Nearly half of our HIV positive patients had an undetectable viral load. These are representative characteristics of most patients who attend the comprehensive HIV clinic in downtown Atlanta (selection bias for more adherent patients).

Based on our findings, we recommend that HIV-infected patients continue to be screened for CRC according to current USPSTF guidelines for individuals at average risk. We recommend colonoscopy as the preferred modality of screening in the HIV positive population. Systems based changes and quality initiatives are needed to continue to improve the overall rate of CRC screening in this patient population. ■

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