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# Colorectal cancer in HIV positive individuals: The immunological effects of treatment

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ABSTRACT

*Background and objectives:* Since the introduction of highly active antiretroviral therapy (HAART), non-AIDS defining malignancies including colorectal cancer (CRC) have emerged as major health concerns for people living with HIV.

*Methods:* From a prospective database of 11,112 HIV seropositive individuals, we identified 11 patients with CRC. Clinicopathological details on the presentation, treatment and outcomes were collected.

*Results:* All were male with a median age of 50 years (range 36–67) and median duration of HIV infection of 7.2 years (range 0–21). Five had metastatic disease at presentation, including 1 patient with a small cell cancer of the rectum. Patients were treated along conventional lines for CRC with concomitant HAART and opportunistic infection prophylaxis. During treatment, median CD4 cell counts fell from 357/mm$^3$ at CRC diagnosis to 199/mm$^3$, although no opportunistic infections were recorded. Three patients have died and the 5-year overall survival measured 65% (95% confidence interval 32–98%).

*Conclusions:* Treatment for CRC reduces cellular immunity and potentially puts HIV patients at risk of opportunistic infections; knowledge of HIV status prior to starting treatment is essential. This risk may be reduced by concomitant HAART and prophylaxis. Clinicians managing CRC should consider screening patients for HIV before starting chemotherapy or radiotherapy.



## 1. Introduction

Whilst the three AIDS defining cancers (Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer in women) have long been associated with HIV infection, there is growing recognition of the clinical importance of non-AIDS defining malignancies (NADM). In particular, the incidence of these NADM, especially those with established links to oncogenic infections, appears unrelated to the degree of immunosuppression as measured by CD4 cell counts and it is not declining following the introduction of highly active antiretroviral therapy (HAART).[1,2] Although, HAART has decreased the number of HIV related death,[3] the number of deaths due to non-AIDS defining cancers, such as colorectal cancer, exceeds those due to AIDS related malignancies in the DAD study of over 23,000 HIV positive patients.[4]

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Numerous epidemiological studies have investigated the incidence of colorectal cancer (CRC) along with other non-AIDS defining malignancies to assess the relative risk of these cancers. Although it was hypothesised in one case series that the incidence of CRC may be elevated in people living with HIV,[5] two cohort studies[6,7] and two meta-analyses[1,8] have failed to demonstrate an elevated risk. However, the prevalence of colorectal tumours, mainly adenomas, identified predominantly by screening sigmoidoscopy, may be significantly higher in asymptomatic HIV seropositive individuals than in control populations.[9–11] In contrast a study of screening colonoscopy reported similar rates of adenomas and carcinomas in HIV positive individuals and controls.[11]

A case series of 7 patients with HIV associated colorectal cancer and a comprehensive literature review that includes a further 10 individuals was published in 2009.[12] This paper covered all published cases and concluded that the disease appeared to affect young men with a high incidence of right-sided tumours. No uncommon histological subtypes were reported amongst these 17 patients. To investigate this further, we undertook a retrospective study of all cases of colorectal cancer in our cohort of 11,112 HIV positive individuals with 71,687 patient-years of follow-up. We identified 11 HIV seropositive patients with colorectal cancer, including 1 patient with a poorly differentiated small cell cancer of the rectum. We also measured the effects of treatment for colorectal cancer on cellular innate and adaptive immunity in our patients.

## 2. Materials and methods

### 2.1. Patients and methods

Since 1986 a prospective database has been collected of all HIV seropositive patients treated at the Chelsea & Westminster Hospital that includes 11,112 patients and represents 71,687 patient years of follow-up, the largest HIV cohort in Europe. This database includes 11 patients with histologically confirmed colorectal cancer.

Routine cancer staging was undertaken in all patients using the American Joint Committee tumour-node-metastasis (TNM) system.[13] Performance status was documented according to the Eastern Co-operative Oncology Group (ECOG).[14]

Total lymphocyte and subset analysis was performed using whole blood stained with murine anti-human monoclonal antibodies to CD3, CD4, CD8, CD16, CD19 and CD56 (Tetra-One; Beckman Coulter, High Wycombe, United Kingdom) and were evaluated on an Epics® XL-MCL™ (Beckman Coulter) flow cytometer.

### 2.2. Statistical analysis

Survival was calculated from the day of CRC diagnosis until death or the date of last follow-up. Overall survival duration curves were plotted according to the method of Kaplan and Meier.[15]

**Table 1A – Clinicopathological details of patients with HIV and CRC.**

| Patient number | Age (years) | HIV duration (years) | Prior AIDS diagnosis | CD4 cell count at CRC diagnosis (cells/mm$^3$) | Plasma HIV viral load at CRC diagnosis (copies/mL) | On HAART at CRC diagnosis | CRC tumour site | CRC tumour grade | TNM (stage grouping) | Survival from CRC diagnosis (months) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 50 | 18 | Y | 200 | <50 | Y | Rectum | Poor, small cell | T4N2M1 (IV) | 4.6 |
| 2 | 50 | 15 | N | 1300 | <50 | Y | Sigmoid colon | Mod | T4N1M0 (IIIB) | 7.0* |
| 3 | 37 | 5 | N | 544 | <50 | Y | Rectum | Poor | T3N2M0 (IIIC) | 14.7* |
| 4 | 53 | 20 | Y | 242 | <50 | Y | Rectum | Mod | T3N0M0 (IIA) | 8.0* |
| 5 | 49 | 22 | N | 59 | <50 | Y | Sigmoid colon | Poor | T4N1M1 (IV) | 15.0* |
| 6 | 62 | 5 | N | 959 | NA | N | Sigmoid colon | Poor | TX NX M1 (IV) | 0.1 |
| 7 | 68 | 7 | N | 407 | <50 | Y | Rectum | Mod | T3N2M0 (IIIC) | 1.8* |
| 8 | 41 | 0 | Y | 20 | NA | N | Rectum | NA | T3N1M0 (IIIB) | 145.6* |
| 9 | 67 | 6 | Y | 116 | <50 | Y | Hepatic flexure | Mod | T4N2M1 (IV) | 3.7 |
| 10 | 59 | 0 | N | 371 | NA | N | Ascending colon | Poor | T3N1M1 (IV) | 0.8* |
| 11 | 47 | 15 | Y | 357 | <50 | Y | Caecum | Poor | T4N0M0 (IIB) | 13.4* |

NA = not available, Mod = moderately differentiated, Y = Yes, N = No.
* = Alive.

## 3. Results

We identified 11 patients with HIV associated colorectal cancer with presentations similar to the general population of change in bowel habit, bleeding per rectum and abdominal pain. All were male; 10 were Caucasian and one black African. All patients were diagnosed with CRC in the HAART era. The median age at CRC diagnosis was 50 years (range 36–67). The median duration of known HIV seropositivity prior to CRC diagnosis was 7.2 years (range 0–21), including 2 patients diagnosed HIV positive at the time of CRC presentation. Five patients had a prior AIDS defining illness and eight were on HAART at the time of CRC diagnosis, all of whom had undetectable plasma HIV viral loads. The median CD4 cell count at CRC diagnosis was 357/mm$^3$ (range 20–1300), whilst the median nadir CD4 cell count for these patients was 60/mm$^3$ (range 6–371). One patient had a poorly differentiated small cell carcinoma of the rectum whilst the remaining 10 patients had adenocarcinomas. At diagnosis 5 patients had metastatic disease, 4 patients had group III stage disease and 2 patients group II disease. Only 2 patients had an ECOG performance status above 1. The clinicopathological details are shown in Table 1A.

The oncological management of these patients was dependent on the disease histology and stage but followed similar strategies to those used in the general population. Four patients received neoadjuvant chemoradiotherapy (45 Gy in 25 fractions with capecitabine and oxaliplatin[3] or capecitabine alone[1]) followed by surgery, 1 patient had a right hemicolectomy followed by adjuvant CAPOX chemotherapy and 1 patient with a diagnosis of familial adenomatous polyposis (FAP) had a pancolectomy with no adjuvant therapy. Three individuals had palliative defunctioning surgery (two following palliative chemotherapy) and the remaining 2 patients with metastatic disease had no surgery (one had palliative chemotherapy and one best supportive care). Four patients had post-operative complications; 3 patients had pelvic collections, which were managed with radiological drainage and antibiotics. One patient developed a wound dehiscence which, required surgical management.

All the patients who received surgery, chemotherapy or radiotherapy were treated with concomitant HAART and opportunistic infection prophylaxis in line with national guidelines.[16] The HAART consisted of non-nucleoside reverse transcriptase inhibitor based combinations for 7 patients, rtionavir boosted protease inhibitor based combinations for 3 patients and integrase inhibitor based combination for 1 patient. No patient developed an opportunistic infection during therapy. However, the treatment for CRC was associated with a fall in the median CD4 cell count from 357/mm$^3$ at CRC diagnosis to 199/mm$^3$ 6 months later. This fall was less marked for other immune lymphocyte subsets including CD8 T-cells, CD19 B-lymphocytes and CD16/CD56 natural killer cell counts (Table 1B). The fall in CD4 cell count occurred despite continuing effective HAART therapy and the plasma HIV viral load remained fully suppressed in all the patients during this time. Indeed the CD4 cell count fell below 200/mm$^3$ in 6 out of the 11 (54%) patients at some time during therapy for CRC.

Three patients died, two from metastatic CRC and 1 patient who also had metastatic disease, died from a leaking abdominal aortic aneurysm graft. The median survival has not yet been reached. The 5-year overall survival is 65 per cent (95% confidence interval 32–98%). No patients died of HIV related causes following a diagnosis of CRC.

## 4. Discussion

The relative risk of colorectal cancer in people living with HIV remains uncertain. Studies have suggested that NADM including CRC are unrelated to immunosuppression and that the incidence of these malignancies in not declining with HAART, as supported by other studies.[1,17–19] Moreover, as the survival with HIV improves due to HAART, the accompanying increasing longevity will augment the risk of many NADM that occur more commonly in the elderly including CRC. The recognition of a high prevalence in HIV of asymptomatic colorectal adenomas and adenocarcinoma in two series[9,10] have not been confirmed in a recent study[11] and indeed people with HIV may be missing out on CRC screening opportunities.[20]

The clinicopathological features in several small series including this one, suggest that people with HIV associated CRC tend to be younger and have more extensive stage disease at presentation.[12,21,22] In one case-control series from Italy it has been suggested that patients with CRC and HIV also had poorer performance status and higher grade tumours and that the overall survival was worse.[21] Another case-controlled study, suggested a trend towards shorter disease-free survival in HIV-infected patients had than controls.[22] Despite the fact that a high proportion of patients were presented with metastatic disease, the overall survival is not dramatically worse than for the general population with similar tumour stage disease.

Both chemotherapy and radiotherapy are well known to cause myelosuppression, which is usually the dose limiting toxicity. In addition, they also cause significant suppression of both adaptive and innate cell mediated immunity by depleting immune cell subsets. When administered to immu-

**Table 1B – Median lymphocyte subsets during treatment for HIV associated colorectal cancer.**

| | At CRC diagnosis | 1 month post diagnosis | 3 months post diagnosis | 6 months post diagnosis |
|---|---|---|---|---|
| Samples available | 11 | 8 | 7 | 5 |
| Median CD4 cell count (/mm$^3$) | 357 | 303 | 185 | 199 |
| Median CD8 cell count (/mm$^3$) | 550 | 453 | 350 | 349 |
| Median CD19 cell count (/mm$^3$) | 103 | 157 | 80 | 96 |
| Median CD56 cell count (/mm$^3$) | 62 | 46 | 56 | 61 |

nocompetent individuals, chemotherapy causes a profound decline in CD4 cell counts and a more modest fall in CD8 T-cells,[23] whilst the natural killer cell population is relatively spared.[24] The most striking finding from studies in immunocompetent patients is the protracted recovery of the CD4 cells. In people with HIV there is therefore concern that prolonged CD4 suppression induced by chemotherapy may have a major adverse influence on the course of HIV-1 disease even when suppression of HIV viraemia is maintained with HAART. Declines in CD4 T helper cell counts, as well as variable falls in CD8 T cytotoxic cell, CD56 natural killer cell and CD19 B lymphocyte counts, have been documented with chemotherapy in HIV associated non-Hodgkin lymphoma[25–27] and to a lesser extent in Kaposi sarcoma.[28] Here we show similar declines in CD4 cell counts in a small number of patients receiving oncological treatments with concomitant HAART for HIV-associated CRC. Even with HAART and undetectable plasma HIV viral loads, the CD4 cell count fell below 200/mm$^3$ in more than half the patients who were thus at risk of *Pneumocystis jirovecii* and other opportunistic infections including Mycobacteria.[29] In spite of this fall in CD4 cell count, no opportunistic infections were observed in these patients and this may be attributable to the prescribing of prophylaxis against *P. jirovecii*, fungal infections and *Mycobacterium avium* complex regardless of their initial CD4 cell count. This observation underscores the clinical importance of knowing the HIV status of patients before commencing chemotherapy so that both HAART and opportunistic infection prophylaxis may be prescribed, particularly as two of the patients in our cohort were not diagnosed with HIV until they presented with CRC.

As the management of HIV and AIDS improves and the longevity of HIV patients increases, an increase in the incidence of common malignancies as seen in the general population is anticipated. Clinicians need to be aware of the profound immunological effects of oncological treatment for CRC and ensure HIV positive patients with CRC are identified and are prescribed HAART and opportunistic infection prophylaxis with therapy.

## Conflict of interest statement

None declared.

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