Upper and lower gastrointestinal symptoms in HIV-infected adults in a clinical cohort in Midwestern Brazil: incidence and associated factors

Annelisa Silva e Alves de Carvalho Santos and Erika Aparecida Silveira

1Professor at the United Faculty of Campinas, Goiânia, Goiás, Brazil
2Post-Graduation Program in Health Sciences, Faculty of Medicine, Federal University of Goiás, Goiânia, Goiás, Brazil

Abstract

Aim: The present study aimed to investigate the incidence of both upper and lower gastrointestinal symptoms and associated factors in HIV-infected adults with or without antiretroviral therapy (ART). Methodology: This study is part of a clinical cohort conducted with adult HIV-infected adults in Midwestern Brazil on outpatient care. Outcome variables were the presence of upper (nausea/vomiting, dyspepsia, and heartburn) and lower (diarrhea, constipation, and flatulence) gastrointestinal symptoms incident on the week before data collection. Explanatory variables were sex, tobacco use, nutritional status, waist circumference (WC), duration of ART, protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) use, and CD4+ T lymphocyte count. The estimate of the effect was analyzed by the incidence ratio (IR) and 95% confidence interval (CI). Statistical significance level was set at p<0.05.

Results: Of 290 study participants, 69.0% were on ART. The most incident gastrointestinal symptom was heartburn (49.3%), followed by flatulence (43.4%), dyspepsia (24.5%), nausea/vomiting (22.8), diarrhea (18.3%), and constipation (16.2%). No difference was observed in the incidence of gastrointestinal symptoms in participants with or without ART. The associated factors with upper and/or lower gastrointestinal symptoms were female sex, excess of body weight, abdominal obesity, less than one year of ART use, tobacco exposure, and CD4+ T lymphocyte count.

Conclusion: A high incidence of several gastrointestinal symptoms was found in HIV-infected adults, associated with both modifiable and non-modifiable risk factors. These findings contribute to gastrointestinal symptoms management in clinical practice for people living with HIV/AIDS, mainly those in risk categories, as gastrointestinal symptoms could result in adverse outcomes for this population.

Introduction

HIV-infection is a major public health problem worldwide. At the end of 2018, 37.9 million people were living with HIV, and 1.7 million people were newly infected globally [1]. Antiretroviral therapy (ART) have contributed to opportunistic infection-associated morbimortality improving the quality of life of people living with HIV/AIDS (PLWHA) significantly. However, some adverse effects may compromise treatment success [2,3]. Gastrointestinal symptoms are among the most common related ART adverse effects, mainly nausea, vomiting, and diarrhea [4].

The expansion of scientific knowledge on gastrointestinal symptoms in PLWHA is quite relevant, once it may result in several negative outcomes in this population, as malnutrition and micronutrient deficiency, lack to ART adherence and quality of life impairment [5,6]. In this context, our study aimed to estimate gastrointestinal symptoms incidence and associated factors in HIV-infected adults with and without ART.

Methodology

The present study is part of a clinical cohort conducted in Midwestern Brazil with HIV-infected adults with or without ART on outpatient care [7-9]. The study was approved by the Institutional Ethics Committee and all study participants signed an informed consent. A trained and qualified researcher applied a structured questionnaire for data collection. After the interview, body weight, height, and waist circumference (WC) were measured according to standardized procedures [10,11].

The investigated gastrointestinal symptoms were nausea and/or vomiting, dyspepsia, heartburn, diarrhea, constipation, and flatulence, evaluated as present or absent in the week prior the interview. We used Rome III criteria to define all gastrointestinal symptoms. Explanatory variables were sex, tobacco use, nutritional status, WC, and clinical data (time of ART, use of protease inhibitors – PI, use of non-nucleoside reverse transcriptase inhibitors – NNRTI, and CD4+ T lymphocyte count).

Tobacco use was investigated according to the Pan American Health Organization [12]. Nutritional status was classified according to Body Mass Index (BMI) ranges [11]: underweight/normal weight (BMI up to 24.9 kg/m²), overweight (BMI 25.0-29.9 kg/m²), and obesity (BMI ≥ 30 kg/m²).

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≥ 30.0 kg/m²). WC was classified as normal, increased (WC 80-88 cm for women and 90-94 cm for men), and abdominal obesity (WC ≥ 88 cm for women and ≥ 102 for men) [11]. Duration of ART was based on the difference from the date of the interview and the date of ART initiation informed by the study participant. CD4+ T lymphocyte count was analyzed in absolute value in cells per mm³ from the most recent count and categorized into ≤ 350 cells/mm³ and > 350 cells/mm³ WHO 2010 [13].

All statistical analysis was conducted on Stata 12.0. Absolute and relative frequency of each gastrointestinal symptom were calculated. The estimate of the effect was analyzed by the incidence ratio (IR) and 95% confidence interval (CI), considering the following reference categories: no tobacco use, no ITRNN use, underweight/normal weight, and normal WC. For the other variables, the reference category was that of lower prevalence concerning the respective gastrointestinal symptom. Statistical significance level was set at p<0.05.

Results

Two hundred and ninety HIV-infected adults participated in the present study; mostly male (n=226, 77.9%). Participants mean age was 37.2 ± 11.0 years with mean 3.3 ± 3.1 years of HIV-infection diagnosis. About 69.0% of study participants were on ART (n=200), being 35.9% with less than a year of ART duration. Of those on ART, all were on nucleoside reverse transcriptase inhibitors (NRTI) use; 77.7% were on NNRTI use; and 26.5% were on PI use.

The most incident gastrointestinal symptom was heartburn (49.3%), followed by flatulence (43.4%), dyspepsia (24.5%), nausea/vomiting (22.8), diarrhea (18.3%), and constipation (16.2%). There was no statistical difference in the gastrointestinal symptoms’ incidence regarding ART use (Table 1). The associated factors with upper and/or lower gastrointestinal symptoms were female sex, excess of body weight, abdominal obesity, less than one year of ART use, tobacco exposure and CD4+ T lymphocyte count (Tables 2 and 3).

| Gastrointestinal Symptoms | Incidence n (%; 95%CI) | With ARTb n (%) | Without ARTb n (%) | p-valuec |
|---------------------------|------------------------|-----------------|-------------------|----------|
| Constipation              | 47 (16.2; 12.16 – 20.96) | 28 (14.14) | 19 (20.65) | 0.160    |
| Diarrhea                  | 53 (18.28; 14.05 – 23.29) | 41 (20.81) | 12 (13.04) | 0.124    |
| Nausea/Vomiting           | 66 (22.84; 18.12 – 28.12) | 50 (25.25) | 16 (17.58) | 0.161    |
| Dyspepsia                 | 71 (24.48; 19.64 – 29.85) | 50 (25.25) | 21 (22.83) | 0.657    |
| Flatulence                | 126 (43.45; 37.80 – 49.53) | 82 (41.41) | 44 (48.35) | 0.260    |
| Heartburn                 | 143 (49.31; 43.42 – 55.22) | 94 (47.47) | 49 (53.26) | 0.351    |

Table 1. Incidence of gastrointestinal symptoms by antiretroviral therapy use in HIV-infected adults (n=290)

| Sex                      | IR (95%CI) | IR (95%CI) | IR (95%CI) |
|--------------------------|------------|------------|------------|
| Male                     | 1.00       | NS         | NS         |
| Female                   | 2.30 (1.56-3.39) | NS         | NS         |

| Tobacco use              | IR (95%CI) | IR (95%CI) | IR (95%CI) |
|--------------------------|------------|------------|------------|
| No                       | 1.00       | NS         | NS         |
| Former smoker            | 1.20 (0.67-2.14) | NS         | 0.95 (0.69-1.31) |
| Yes                      | 2.16 (1.36-3.43) | NS         | 1.38 (1.07-1.77) |

| Nutritional status       | IR (95%CI) | IR (95%CI) | IR (95%CI) |
|--------------------------|------------|------------|------------|
| Underweight/Normal weight| 1.00       | NS         | NS         |
| Overweight               | 1.69 (1.08-2.63) | NS         | NS         |
| Obesity                  | 2.43 (1.25-4.71) | NS         | NS         |

| Waist circumference      | IR (95%CI) | IR (95%CI) | IR (95%CI) |
|--------------------------|------------|------------|------------|
| Normal                   | 1.00       | NS         | NS         |
| Increased                | 1.45 (0.84-2.51) | NS         | NS         |
| Abdominal obesity        | 2.47 (1.56-3.92) | NS         | NS         |

| Duration of ARTd         | IR (95%CI) | IR (95%CI) | IR (95%CI) |
|--------------------------|------------|------------|------------|
| < 1 year                 | 2.16 (1.20-3.87) | NS         | NS         |
| 1 to 3 years             | 1.21 (0.58-2.54) | NS         | NS         |
| > 3 year                 | 1.00       | NS         | NS         |

| PI use                   | IR (95%CI) | IR (95%CI) | IR (95%CI) |
|--------------------------|------------|------------|------------|
| No                       | NS         | NS         | NS         |
| Yes                      | NS         | NS         | NS         |

| NNRTI use                | IR (95%CI) | IR (95%CI) | IR (95%CI) |
|--------------------------|------------|------------|------------|
| No                       | NS         | NS         | NS         |
| Yes                      | NS         | NS         | NS         |

| CD4+ cells count         | IR (95%CI) | IR (95%CI) | IR (95%CI) |
|--------------------------|------------|------------|------------|
| ≤ 350 cells/mm³          | NS         | NS         | 1.00       |
| > 350 cells/mm³          | NS         | NS         | 1.46 (1.06-2.02) |

*IR: incidence ratio, 95%CI: 95% confidence interval, *ART: antiretroviral therapy, *PI: protease inhibitors, *NNRTI: non-nucleoside reverse-transcriptase inhibitors.
Table 3. Lower gastrointestinal symptoms incidence ratio by sex, tobacco use, nutritional and clinical variables in HIV-infected adults (n=290)

|                                      | Diarrhea | Constipation | Flatulence |
|--------------------------------------|----------|--------------|------------|
| **Sex**                              |          |              |            |
| Male                                 | NS       | 1.00         | 1.00       |
| Female                               | NS 3.11 (1.88-5.13) | 1.41 (1.07-1.84) |
| **Tobacco use**                      |          |              |            |
| No                                   | NS       | 1.00         | NS         |
| Former smoker                        | NS 2.07 (1.13-3.76) | NS         |
| Yes                                  | NS 1.44 (0.73-2.82) | NS         |
| **Nutritional status**               |          |              |            |
| Underweight/Normal weight            | NS       | NS           | NS         |
| Overweight                           | NS       | NS           | NS         |
| Obesity                              | NS       | NS           | NS         |
| **Waist circumference**              |          |              |            |
| Normal                               | NS       | 1.00         | 1.00       |
| Increased                            | NS 1.28 (0.58-2.82) | 0.94 (0.63-1.39) |
| Abdominal obesity                    | NS 3.03 (1.66-5.54) | 1.41 (1.01-1.95) |
| **Duration of ART**                  |          |              |            |
| ≤ 1 year                             | NS       | NS           | NS         |
| 1 to 3 years                         | NS       | NS           | NS         |
| > 3 year                             | NS       | NS           | NS         |
| **PI** use                           |          |              |            |
| No                                   | 1.00     | NS           | NS         |
| Yes                                  | 1.95 (1.14-3.34) | NS         |
| **NNRTI** use                        |          |              |            |
| No                                   | 0.50 (0.29 – 0.86) | NS         |
| Yes                                  | NS       | NS           | NS         |
| **CD4+ cells count**                 |          |              |            |
| ≤ 350 cells/μl                       | NS       | NS           | NS         |
| > 350 cells/μl                       | NS       | NS           | NS         |

*IR: incidence ratio, 95%CI: 95% confidence interval, NS: nonsignificant, *ART: antiretroviral therapy, *PI: protease inhibitors, *NNRTI: non-nucleoside reverse-transcriptase inhibitors.

Discussion

The present study contributes to expand the scientific knowledge on gastrointestinal symptoms in PLWHA, providing relevant information for clinical care of this population. Among the associated factors are female sex, tobacco exposure, excess of body weight, abdominal obesity, duration of ART and protease inhibitors use.

Sex differences in gastrointestinal physiology may partially explain why women were more prompt to present higher incidence of gastrointestinal symptoms than men, as dyspepsia, constipation and flatulence. Intestinal motility tends to be slower in women, contributing to constipation symptoms, which could be altered due to the levels of steroid hormones, for example [14].

Regarding tobacco exposure, there are evidence of the role of nicotine toxicity and/or its byproducts in the development of several gastrointestinal disorders and diseases [15,16]. One of the possible mechanisms is the stimulation of parasympathetic autonomic system, increasing muscular tonus and gastrointestinal motility [17].

Abdominal obesity and excess body weight are associated with gastrointestinal complications [18], and HIV-infection may potentize this relationship. In our study, being overweight/obese or having abdominal obesity were associated with a higher incidence of dyspepsia. In obese subjects, esophageal transit time is significantly prolonged compared with lean individuals [18], which could be due to increased gastric and gastroesophageal junction resistance [19]. Regarding constipation, abdominal obesity was an important associated factor in our study, although the relationship between obesity and constipation is not fully understood [20].

Since the beginning of HIV-infection, opportunistic infections in the gastrointestinal tract have been described, which may lead to gastrointestinal symptoms manifestation. After ART introduction, gastrointestinal symptoms caused by opportunistic infections reduced significantly. However, the use of some antiretroviral drug classes has been associated with gastrointestinal symptoms, being the most common complaints among patients on ART, primarily in its first year of use [21]. In our study this association was also observed, once nausea/vomiting were more incident in those individuals with less than a year of ART and diarrhea in those in PI use.

In conclusion, this study brings important contributions to the field of clinical management of PLWHA, mainly those in outpatient care, providing relevant information on the incidence of the most common gastrointestinal complaints in this population and the potential risk factors. Along with ART use, which is the main factor associated with gastrointestinal symptoms in PLWHA nowadays, other important factors as sex, tobacco exposure and excess of body weight and abdominal obesity may be taken into consideration when evaluating these patients in a clinical setting, directing treatment with effective strategies for each situation.

Authorship and contributions

EAS designed the research. ASACS participated in data collection. ASACS and EAS analyzed the data and wrote the paper. All authors revised the content of this manuscript and approved the final version of the paper.

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Competing interest

None to declare.

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