Acute toxicity of second generation HIV protease-inhibitors in combination with radiotherapy: a retrospective case series

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Abstract

Background: There is little data on the safety of combining radiation therapy and human immunodeficiency virus (HIV) protease inhibitors to treat cancers in HIV-positive patients. We describe acute toxicities observed in a series of HIV-positive patients receiving modern radiation treatments, and compare patients receiving HIV protease inhibitors (PI) with patients not receiving HIV PIs.

Methods: By reviewing the clinical records beginning January 1, 2009 from the radiation oncology department, we identified 29 HIV-positive patients who received radiation therapy to 34 body sites. Baseline information, treatment regimen, and toxicities were documented by review of medical records: patient age, histology and source of the primary tumor, HIV medication regimen, pre-radiation CD4 count, systemic chemotherapy, radiation therapy dose and fractionation, irradiated body region, toxicities, and duration of follow-up. Patients were grouped according to whether they received concurrent HIV PIs and compared using Pearson’s chi-square test.

Results: At baseline, the patients in the two groups were similar with the exception of HIV medication regimens, CD4 count and presence of AIDS-defining malignancy. Patients taking concurrent PIs were more likely to be taking other HIV medications (p = 0.001) and have CD4 count >500 (p = 0.006). Patients taking PIs were borderline less likely to have an AIDS-defining malignancy (p = 0.06). After radiation treatment, 100 acute toxicities were observed and were equally common in both groups (64 [median 3 per patient, IQR 1-7] with PIs; 36 [median 3 per patient, IQR 2-3] without PIs). The observed toxicities were also equally severe in the two groups (Grades I, II, III respectively: 30, 30, 4 with PIs; 23, 13, 0 without PIs; p = 0.38). There were two cases that were stopped early, one in each group; these were not attributable to toxicity.

Conclusions: In this study of recent radiotherapy in HIV-positive patients taking second generation PIs, no difference in toxicities was observed in patients taking PIs compared to patients not taking PIs during radiation therapy. This suggests that it is safe to use unmodified doses of PIs and radiation therapy in HIV cancer patients, and that it is feasible to use PIs as a radiosensitizer in cancer therapy, as has been suggested by pre-clinical results.

Background

HIV and malignancies

Historically, HIV infection is associated with a much higher risk of specific cancers [1-4]. In particular, diagnosis of Kaposi sarcoma, non-Hodgkin lymphoma (NHL), or cervical cancer are considered acquired immunodeficiency syndrome (AIDS)-defining malignancies [5]. However, increasing effectiveness of anti-retroviral therapy (ART) has led to decreased mortality in Europe and North America from opportunistic infections and AIDS-defining malignancies [5-8], while mortality from non-AIDS-defining and non-HIV-associated cancers has been increasing [8,9].

Response to cancer therapy is also different in the HIV patient population. Initial reports found increased radiotoxicity in HIV patients receiving treatment for Kaposi sarcoma, cervical carcinoma, while there was no difference in adverse effects of radiation therapy for...
other malignancies [10,11]. Systemic glutathione deficiency [12], DNA repair deficiency, or cell cycle dysregulation may increase radiosensitivity [13-15]. However, radiation therapy remains a cornerstone of therapy in a number of cancers such as anal cancer [16], prostate [17], breast [18-20], and cervical cancer [16,21].

Protease inhibitors in the treatment of HIV

PIs are anti-viral drugs that inhibit proteases, viral enzymes which cleave polyprotein precursors into mature viral proteins [22]. PIs are one class of anti-virals that is used as the ‘base’ in combination with two ‘backbone’ drugs for treatment of HIV, antiretroviral therapy (ART). There are currently ten PIs available; in chronological order of FDA approval, saquinavir, ritonavir, indinavir, nelfinavir, lopinavir, atazanavir, fosamprenavir (pro-drug of amprenavir, which is no longer available), tipranavir, and darunavir.

Although PIs act by inhibiting HIV aspartyl protease, they also have off-target effects. The entire class is associated with dysregulation of glucose and lipid metabolism due to homology between HIV-1 protease and various human proteins [23-26]. In addition, some PIs inhibit the phosphatidylinositol 3-kinase (PI3K)-Akt pathway, which is shared by numerous cell homeostasis pathways [27,28].

Non-target effects of protease inhibitors

A number of PIs have been associated with anti-cancer activity [29]. Through PI3K-Akt and closely related pathways, PIs induce apoptosis of tumor cells [30-36]. Although PIs have been shown to directly effect tumor cell death, use of PIs has not reduced cancer risk in HIV patients, suggesting that PIs would not be clinically effective anti-cancer monotherapies [37]. Although ineffective alone, PIs synergize with other cancer therapies such as radiotherapy [38].

Initial studies suggested that nelfinavir upregulates vascular endothelial growth factor (VEGF) and downregulates hypoxia-inducible factor 1 alpha (HIF-1α). Although VEGF can increase tumor oxygenation, the HIF1-α hypoxia factor can mediate radiation resistance [39,40]. However, HIF-1α knockdown studies suggest that radiosensitivity induced by PIs is independent of HIF-1α [28,40-42]. In a number of cancers, resistance to radiotherapy is mediated by the PI3K-Akt pathway, suggesting an alternative mechanism of PI-induced radiosensitization [43-45]. Preclinical studies with nelfinavir in head-and-neck cancer [46] and non-small cell lung cancer [28] cell lines found downregulation of Akt to be associated with increased sensitivity to radiation.

Although PI-induced radiosensitization of cancers was shown to be independent of HIF-1α, PIs have been shown to induce systemic vascular stress [47]. Preclinical in vivo studies suggest that in addition to direct effect on the tumor cells, PIs may inhibit PI3K-Akt activation in tumor vasculature, suppressing hypoxia pathways and leading to reduced radiation resistance [48,49]. Other clinical reports also suggest that PIs and radiotherapy interact on tumor vasculature similar to the effects of radiation and bevacizumab, an anti-angiogenic antibody [50].

Protease inhibitors and radiotherapy

A retrospective review (14 patients receiving PIs and 28 controls) did not find severe toxicities attributable to combination of PIs and radiotherapy for cancer in HIV+ patients [11,51-54]. There are ten prospective trials, nine of which are on-going (a phase II trial was terminated due to poor enrollment): five phase I studies, and four studies that have a phase II component. One published phase I trial in pancreatic cancer showed the following toxicities one of which was life-threatening: severe nausea and vomiting and increase in liver enzymes and bilirubin due to stent occlusion [55]. Given the inconclusive safety data on combining PIs and radiation therapy to treat cancer in HIV patients, we reviewed a series of HIV patients receiving radiation therapy for malignancies.

Methods

Patient identification

In accordance with a research protocol approved by the Institutional Review Board, patients were identified by review of clinical records from January 1, 2009-October 31, 2010 in the Department of Radiation Oncology at The Johns Hopkins Hospital. Patients were included if they had documented HIV infection and received radiation therapy at Johns Hopkins.

Retrospective review

Medical records for included patients were reviewed for HIV medications, cancer diagnosis and stage, radiation therapy (site, dose, fractionation, completion or early stopping), age at time of radiation therapy, cancer chemotherapy, acute (< 6 weeks after end of radiation therapy) toxicities categorized by Common Toxicity Criteria for Adverse Events version 3.0 (CTCAE) grade. All patients receiving radiation therapy were evaluated at least once per week for treatment toxicity, and side effects were recorded prospectively in an electronic record system.

Statistical analysis

Patients were categorized by type of malignancy (AIDS-defining, HIV-associated, non-HIV associated), taking non-PI HIV medications (yes/no), and by baseline CD4 count (< 50, <200, <500, 500). Toxicities were categorized
by CTCAE grade. Differences between the groups were analyzed using Pearson’s chi-square test with JMP 8.0 (SAS Institute Inc.). Statistical significance was defined as a Pearson’s chi-square p-value < 0.05.

Results
We retrospectively reviewed acute toxicities in a series of patients with a history of HIV infection and receiving radiation therapy; in this series, we compared patients who received concurrent PIs with patients who did not receive concurrent PIs. Eighteen patients received concurrent PIs and radiation therapy; one patient received radiation therapy for two different malignancies, and one patient received radiation therapy for three recurrences of NHL. There were eleven patients with a history of HIV infection but not treated with PIs who received radiation therapy; one patient received three regimens of radiation therapy; one patient received three regimens of radiation therapy, twice for brain metastasis and once for testicular metastasis.

Patient characteristics
Characteristics of patients receiving concurrent protease inhibitor are presented in Table 1 while characteristics of patients not receiving concurrent protease inhibitor are presented in Table 2. There were 34 total courses of radiation treatment delivered (21 with PIs, 13 without PIs) for a variety of histologies, including HIV-defining (0 with PIs; 3 [23%] without PIs), HIV-associated (11 [58%] with PIs; 5 [38%] without PIs), non-HIV-associated malignancies (8 [42%] with PIs, 5 [38%] without PIs), and non-malignancies (keloid scar and dural arteriovenous fistula with PIs, none without PIs). The median age was 50 (interquartile range [IQR] 47-56). The difference between the two groups in number of AIDS-

Table 1 Baseline data: patients receiving concurrent protease inhibitor

| #  | Cancer diagnosis                      | Age | Concurrent systemic therapy | Baseline CD4 | Non-PI HIV regimen | PI     |
|----|--------------------------------------|-----|-----------------------------|--------------|--------------------|--------|
| 1a | Ductal carcinoma, breast T2N1M0      | 47  | None                        | 104          | lamivudine, raltegravir | RTV, DRV |
| 1b | SCC, anus T3N0M0                      | 49  | 5-FU, mitomycin C           | 68           | lamivudine, raltegravir | RTV, DRV |
| 2  | SCC, vulva T1bN1b, stage IIIa        | 26  | cisplatin                   | 1647         | emtricitabine, tenofovir, raltegravir | RTV, ATZ |
| 3  | Ductal carcinoma, breast T1cN0M0, stage I | 47  | None                        | 474          | emtricitabine, tenofovir, raltegravir | RTV, ATZ |
| 4  | SCC, anus T2N0M0, stage II            | 47  | None                        | NR           | emtricitabine, tenofovir, raltegravir | RTV, DRV |
| 5  | Adenocarcinoma, prostate cT2bN0M0, GS 3+3, PSA 8.7, stage II | 58  | None                        | WNL          | efavirenz, emtricitabine, tenofovir | RTV, LPV |
| 6  | Adenocarcinoma, prostate cT1cN0M0, GS 3+4, PSA 4.9, stage II | 73  | androgen deprivation        | 1105         | raltegravir         | RTV, DRV |
| 7  | Adenocarcinoma, prostate cT1cN0M0, GS 4+3, PSA 5.1 stage II | 69  | androgen deprivation        | 536          | abacavir, lamivudine | RTV, ATZ |
| 8  | Renal cell carcinoma, lateral chest wall, metastatic, stage IV | 50  | suten                       | 766          | emtricitabine, tenofovir, efavirenz | RTV, ATZ |
| 9  | Arteriovenous fistula, dura mater     | 57  | None                        | 944          | abacavir, lamivudine, raltegravir | RTV, LPV |
| 10 | SCC, tonsil T2N2bM0                   | 53  | cisplatin                   | 956          | emtricitabine, tenofovir | RTV, LPV |
| 11 | Primary CNS lymphoma, CNS             | 44  | None                        | 4            | None                | RTV, DRV |
| 12 | NHL, neck and axilla, stage IV        | 53  | vincristine, prednisone     | 57           | abacavir, lamivudine | RTV |
| 13a | NHL, pelvis, stage IV                 | 53  | None                        | 120          | abacavir, lamivudine | RTV, ATZ |
| 13b | NHL, axilla, stage IV                 | 55  | None                        | 39           | abacavir, lamivudine | RTV, LPV |
| 13c | NHL, temple, stage IV                 | 56  | None                        | 87           | abacavir, lamivudine | RTV, LPV |
| 14 | Primary CNS lymphoma, CNS             | 21  | None                        | 0            | emtricitabine, tenofovir | RTV, DRV |
| 15 | Ductal carcinoma, breast T2N0M0, stage IIa | 58  | None                        | NR           | emtricitabine, tenofovir | RTV, LPV |
| 16 | SCC, anus T1N0M0, stage I             | 43  | 5-FU, mitomycin C           | 547          | abacavir, lamivudine | RTV, LPV |
| 17 | Primary CNS lymphoma, CNS             | 23  | None                        | 10           | emtricitabine, tenofovir | RTV, DRV |
| 18 | Keloid scar, posterior scalp          | 47  | None                        | WNL          | zidovudine 300 mg, lamivudine 150 mg | NFV |

Patients are uniquely identified by numbers, repeated treatments on a patient are distinguished by a letter after the number.

NHL = non-Hodgkin lymphoma.
cT = clinical tumor, pT = pathological tumor, GS = Gleason score, PSA = prostate specific antigen.
RTV = ritonavir, DRV = darunavir, ATZ = atazanavir, LPV = lopinavir, NFV = nelfinavir.
WNL = Reported as within normal limits, NR = not reported.
defining malignancies almost reached statistical significance (p = 0.06), but the remainder of the malignancies (HIV-associated and non-HIV-associated) are not differently distributed in the two groups (p = 0.9). 29 cases had documented pre-treatment CD4 counts; 4 were <50 (4 [24%] with PIs), 13 were <200 (9 [53%] with PIs, 4 [33%] without PIs), and 21 were <500 (10 [59%] with PIs; 11 [92%] without PIs). Patients taking PIs were more likely than patients not taking PIs to have a CD4 count \( \geq 500 \) (7 [41%] with PIs; 1 [8%] without PIs; p = 0.006).

Radiation treatment
For the 29 patients receiving radiation therapy, 15 patients were treated with definitive or adjuvant dose regimens (9 receiving PIs, 6 without PIs), while 14 patients received palliative radiation doses (9 receiving PIs, 5 without PIs). The exact definition of definitive/adjuvant versus palliative dose varied based on body site. Definitive/adjuvant dose was at least 5400 cGy for brain (conventional fractionation equivalent), 7000 cGy for head and neck, 5400 cGy for breast, 4500 cGy for pelvis, and 7800 cGy for prostate. Palliative doses also varied based on body site and disease histology, but were lower than definitive/adjuvant dose regimens.

Table 2 Baseline data: patients not receiving concurrent protease inhibitor

| #  | Cancer diagnosis                      | Age | Concurrent systemic therapy | Baseline CD4 | Non-PI HIV regimen |
|----|--------------------------------------|-----|----------------------------|--------------|--------------------|
| 1  | SCC, cervix T4N1M0, stage IVa         | 29  | cisplatin                  | 189          | None               |
| 2  | SCC, cervix, stage Iib               | 34  | cisplatin                  | 189          | None               |
| 3  | Cholangiocarcinoma, abdomen pT3N1M0  | 53  | xeloda                     | 300          | efavirenz, emtricitabine, tenofovir |
| 4  | Adenocarcinoma, prostate TXNMX1, stage IV | 48 | None                       | 399          | None               |
| 5  | Meningioma, CNS                      | 46  | None                       | 408          | None               |
| 6  | Adenocarcinoma, prostate cT1cN0M0, GS | 62 | androgen                   | 1047         | None               |
| 7  | NSCLC, brain met, stage IV           | 57  | None                       | NR           | None               |
| 8a | DLBCL, brain met, stage IV           | 46  | None                       | 214          | efavirenz, emtricitabine, tenofovir |
| 8b | DLBCL, brain met recurrence, stage IV| 46  | None                       | 214          | efavirenz, emtricitabine, tenofovir |
| 8c | DLBCL, testicular met, stage IV      | 46  | None                       | 214          | efavirenz, emtricitabine, tenofovir |
| 9  | Adenocarcinoma, prostate cT2aN0M0, GS| 61  | None                       | 150          | efavirenz, emtricitabine, tenofovir |
| 10 | SCC, cervix, stage Iib               | 57  | cisplatin                  | 116          | None               |
| 11 | SCC, anal                             | 49  | mitomycin C and xeloda     | 450          | efavirenz, emtricitabine, tenofovir |

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NHL = non-Hodgkin lymphoma, DLBCL = diffuse large B-cell lymphoma.
cT = clinical tumor, pT = pathological tumor, GS = Gleason score, PSA = prostate specific antigen.
NR = not reported.

In the group receiving PIs, the most common PI was ritonavir (20 [95%]), followed by darunavir and lopinavir (7 [33%] each), atazanavir (5 [24%]), and only one [5%] patient received nelfinavir (Table 1 and 2).

Toxicities
Follow-up and observed toxicities are presented in Table 3 and 4. The median follow-up of all patients was 18 weeks [IQR 8-30], but the follow-up for patients not taking PIs (median 13 weeks [IQR 5-18]) was much shorter than the follow-up for patients taking PIs (median 21 weeks [IQR 10-38]). The limited follow-up in the group not taking PIs prevented comparison of long-term toxicities.

There were 64 acute toxicities in the group receiving PIs (30 grade 1, 30 grade 2, 4 grade 3). In the group not receiving PIs, there were 36 acute toxicities (23 grade 1, 13 grade 2). The median number of toxicities experienced per patient was not different between the groups (3 [IQR 1-7] with PIs; 3 [IQR 2-3] without PIs). Chi-square analysis of the distribution of severity did not find statistically significant difference in the severity of toxicities between the two groups (p = 0.38). One radiation treatment in each group was stopped early, but neither of these was secondary to toxicity (no grade 3 toxicities in either patient).
Discussion

Our retrospective review of HIV-positive patients receiving radiation therapy found no increased toxicity in patients receiving concurrent PIs. The number and severity of toxicities experienced per patient were not found to be different in patients who were concurrently taking PIs compared to those who were not. There were differences in the baseline characteristics and medication regimens of the two groups. First, there were no cases of AIDS-defining malignancies in the group treated with PIs. This difference coincided with a difference in all HIV treatment and CD4 count. Significantly more patients in the non-PI group did not receive any medication to manage HIV, and significantly more patients in the non-PI group had CD4 counts below 500. This difference may reflect the efficacy of PIs and ART in controlling HIV, and a resulting decrease in opportunistic malignancies that has been observed with progressive generations of ART[9]. Although ART is typically initiated if the CD4 count is below 500, there are a number of other factors that contribute to the decision to initiate therapy, such as patient preference, adherence to prescriptions, and HIV strain. There was no association between CD4 count and adverse events.

There have been a number of case reports and small case series documenting severe toxicities in HIV patients receiving radiation therapy. A meta-analysis of case reports and case series found severe toxicities in HIV patients receiving radiation therapy for Kaposi sarcoma, but not in other malignancies [10]. Our results are in accordance with the only published study evaluating toxicities from interaction between PIs and radiation therapy [11]. Plastaras et al. reviewed 14 patients with concurrent PIs and 28 patients in the absence of PI, and found no difference in toxicity from radiation therapy. Although this group

| #  | F/U [weeks] | Region treated | Dose (fractionation) [cgy] | Complete RT regimen | Acute toxicity and CTC grade |
|----|-------------|----------------|-----------------------------|---------------------|----------------------------|
| 1a | 75          | right breast  | 5800 (200)                  | yes                 | dermatitis 2, pruritus 1, hyperpigmentation 2, fatigue 1, pain 1 |
| 1b | 0           | pelvis        | 3600 (180)                  | no, prescribed 5400 | fatigue 2, pain 2, nocturia 2, anorexia 1, proctitis 2 |
|    |             |                |                             |                      | fatigue 1, pain 1, nocturia and urinary frequency 1, dysuria 2, proctitis 1, diarrhea 1, mucosal drainage 1 |
| 2  | 9           | pelvis and left vulva | 4500 (180)                  | yes                 | fatigue 2, pain 3, dermatitis 1, hyperpigmentation 2 |
| 3  | 36          | right breast  | 5130 (270)                  | yes                 | dysuria 1 |
| 4  | 18          | pelvis and anus | 3000 (200)                  | yes                 | dysuria and nocturia and urinary frequency 2, anorexia 1, diarrhea 1, hematochezia 1 |
| 5  | 82          | prostate and SV | 6720 (320)                  | yes                 | nausea and urinary frequency 2 |
| 6  | 18          | prostate and SV | 8000 (200)                  | yes                 | nocturia and urinary frequency 2 |
| 7  | 7           | prostate and SV | 7800 (200)                  | yes                 | pain 1, dysuria and urinary frequency and incontinence 2, constipation 1, diarrhea 1 |
| 8  | 8           | left lateral chest wall | 3600 (300)                  | yes                 | dermatitis 1 |
| 9  | 38          | brain         | 2000 (2000)                 | yes                 | none |
| 10 | 25          | head and neck | 7000 (200)                  | yes                 | dermatitis 3, fatigue 3, dysphonia 1, xerostomia 2 |
| 11 | 21          | brain         | 3000 (300)                  | yes                 | fatigue 2, pain 2, nausea 2, insomnia 2, anorexia 2, vomiting 2, ataxia 2 |
| 12 | 23          | right neck and left axilla | 3000 (200)                  | yes                 | fatigue 1, pain 1, dermatitis 1, dysgeusia 1, dysphonia 1, xerostomia 1 |
| 13a| 147         | right pelvis  | 3000 (250)                  | yes                 | fatigue 1 |
| 13b| 13          | right axilla and ulcerating skin lesion | 3060 (180)                  | yes                 | dermatitis 2, drainage 3, pruritus 1 |
| 13c| 7           | right temple and subcutaneous skin lesion | 3060 (180)                  | yes                 | dermatitis 2 |
| 14 | 19          | brain         | 3000 (300)                  | yes                 | fatigue 1 |
| 15 | 86          | right breast  | 6000 (200)                  | yes                 | dermatitis 1 |
| 16 | 85          | pelvis        | 5040 (180)                  | yes                 | urinary frequency 1, anorexia 2, proctitis 1, diarrhea 2, dermatitis 2 |
| 17 | 10          | brain         | 3000 (300)                  | yes                 | altered mental status in intensive care throughout treatment |
| 18 | 31          | posterior scalp | 1600 (400)                  | yes                 | none |

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F/U = follow-up.
found no increase in toxicity from radiation therapy, the patient series was treated between 1993-2007 for the control group and 1997-2006 for the PI group. Inclusion of patients from this time period may have been reflected in the distribution of PIs and the distribution of malignancies treated. Nearly all patients in the Plastaras et al. study were treated with nelfinavir, three were treated with saquinavir (the oldest available PI), and one was treated with amprenavir (no longer available). 29 (69%) of 42 malignancies were AIDS-defining or strongly associated with HIV. These results may be limited by the baseline characteristics: AIDS-defining and HIV-associated malignancies are more heavily represented than in the current HIV+ population and PI regimens are evolving rapidly. Although not related to the years from which the patients were sampled, only 6 of the 14 patients from the PI group had documented CD4 count: one was <50, two were <200, and three <500. No association was observed between CD4 count and radiation toxicity, but the data is limited.

Our study characterizes the safety of radiation therapy combined with the newer generation of PIs in treatment of non-AIDS defining malignancies which are increasingly common in the era of improved ART. The series included only patients treated from January 1, 2009 onwards: of the 18 patients receiving PIs, 16 (89%) were receiving a dual-PI regimen; only two were taking a mono-PI regimen (one ritonavir and one nelfinavir). The case series included more malignancies not associated with HIV or AIDS (ductal carcinoma of the breast, renal cell carcinoma, cholangiocarcinoma, and meningioma), and two non-malignancies (dural AVM, and keloid scar) that were treated with radiation. Half of the patients in this case series received definitive or adjuvant radiation dose regimens (45-78 Gy). These patients were distributed equally in the group with PIs and in the group without PIs, and combination of definitive/adjuvant doses of radiation with PIs did not increase toxicities over definitive/adjuvant radiation doses alone. The present study more than doubles the reported number of patients treated with HIV PIs and radiation from 14 to 32.

The limitations of this study include the small size, short follow-up, heterogeneous nature of our cohort, and the differences between the control group and the PI treatment group. As discussed before, in addition to not taking PI, the control group also received less non-PI HIV medications and had a lower median CD4 count. The factors that underlie these two differences may confound the results. In addition, although we collected data on late toxicities, there was insufficient follow-up (21 weeks [IQR 10-38] with PIs, 13 [IQR 5-18] without PIs) to assess differences in late toxicities. Extended follow-up is necessary to determine the impact on long term toxicities. In addition, the majority of the cases received ritonavir combined with a second PI. Ritonavir does not inhibit Akt, which is a proposed

### Table 4 Radiation regimen, follow-up and toxicities in patients not receiving concurrent protease inhibitor

| #  | F/U [weeks] | Region treated | Dose (fractionation) [cgy] | Complete RT regimen | Acute toxicity and CTC grade |
|----|-------------|----------------|----------------------------|---------------------|-----------------------------|
| 1  | 6           | Pelvis         | 5400 (180)                 | yes                 | fatigue 1, nocturia 1, proctitis 2, gastrointestinal bleed 3, dermatitis 2 |
| 2  | 6           | vaginal cuff brachytherapy | 4500 and 2500 HDR (180 and 500 HDR) | yes                 | fatigue 1, anorexia 1, nausea 1 |
| 3  | 18          | Abdomen        | 5040 (180)                 | yes                 | fatigue 1 |
| 4  | 13          | thoracic spine | 3000 (300)                 | yes                 | pain 2, edema 2 |
| 5  | 29          | Brain          | 5400 (180)                 | yes                 | nocturia and urinary frequency and urgency 2, urinary retention 1 |
| 6  | 44          | prostate and SV | 7800 (200)                | yes                 | memory impairment 1, concentration impairment 1 |
| 7  | 20          | Brain          | 5300 (250 and 18 Gy gamma-knife boost) | yes                 | dysuria and nocturia 2, urinary retention 1, constipation 1 |
| 8a | 0           | prostate and SV | 7800 (200)                | yes                 | fatigue 2, anorexia 1, dermatitis 2 |
| 8b | 13          | Pelvis         | 3780 and 1400 HDR (180 and 700 HDR) | no                 | fatigue 2, pain 1, anorexia 1, constipation 1, dermatitis 1 |
| 8c | 4           | Pelvis         | 3000 and 1200 IORT (200 and 1200 HDR) | yes                 | fatigue 1, pain 1, anorexia 1, proctitis 1, diarrhea 1 |
| 9  | 13          | Brain          | 2400 (200)                 | yes                 | fatigue 2, pain 2, |
| 10 | 5           | brain (repeated) | 2400 (200)               | yes                 | fatigue 2, anorexia 1, constipation 1, dermatitis 1, |
| 11 | 0           | Testicles      | 2700 (180)                 | no, prescribed      | pain 1, constipation 1, dermatitis 1 |

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F/U = follow-up.
HDR = high dose radiation.

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mechanism of radiosensitization by PIs [27]. However, there are no published studies evaluating the radiosensitizing effect of darunavir, atazanavir, or lopinavir, which were used in combination with ritonavir by the majority of the patients. Prior studies on radiosensitization by PIs have not found a defining structural characteristic which would predict whether a PI will increase radiosensitivity. In spite of these limitations, this retrospective review provides valuable information about the acute toxicity of combining radiation with current PI therapies. Review of this contemporary series of patients did not find an increase in acute toxicity from the combination of the newest generation of HIV PIs and radiation therapy to treat diverse pathologies.

Conclusions
Preclinical data has suggested that PIs used in the treatment of HIV may radiosensitize cancer cells, but case reports have suggested that PIs may exacerbate radio-toxicity in normal tissue. Review of a set of HIV-positive radiation therapy patients did not reveal increased toxicity in patients taking PIs during radiation therapy. Our cohort doubles the number of patients in the current literature on the acute safety profile of combining PIs and radiation therapy. These data suggest that clinical trials of PIs as radiosensitizers will not encounter increased acute toxicity.

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Authors’ contributions
APS identified the HIV-positive patients receiving radiation treatment, performed the statistical analysis and helped draft the manuscript. JZ designed the protocol, collected clinical variables in review of the patient records and helped draft the manuscript. PT and ML conceived of the study, designed the study and edited the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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