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# Incidence of cancer in individuals treated with raltegravir-based and non-raltegravir-based cART regimens

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**BACKGROUND:** In the early stages of clinical trials with raltegravir (RAL) – drug approved in 2007-there were reports of an apparent increase in cancers seen in some RAL users. Concerned about this finding, researchers compared cancer cases seen in several raltegravir clinical trials over time. However, there is currently little data on the long-term risk of cancer in individuals taking RAL.

**OBJECTIVES:** To compare the incidence of malignancies among individuals taking RAL-based and non-RAL-based cART regimens.

**METHODS:** The EuroSIDA cohort was divided into 3 comparison groups, RAL individuals: starting a RAL-based cART regimen after December 2007; historical cohort (HIST): individuals adding a new antiretroviral (ARV) to their cART regimen between January 2005 and December 2007, concurrent cohort (CONC): individuals adding a new ARV (excluding RAL) after December 2007. Baseline characteristics were compared using logistic regression. The incidence of newly diagnosed AIDS and non-AIDS malignancies was compared using Poisson regression. Because of the large number of potential measured confounders propensity scores have been used in for the adjustment in the multivariable analysis. All factors showing an univariable association with alpha=0.1 were included in the propensity score vector. For the main Poisson regression analysis, an intention to treat (ITT) approach, ignoring treatment switches was used.

**RESULTS:** The RAL cohort included 1,470 individuals (PYFU: 4,058) compared to 3,787 (4,472) and 4,467 (10,691) in the HIST and CONC cohorts, respectively. Baseline characteristics were generally well-matched between cohorts (**Table 1**). However, in multivariable logistic regression individuals included in the RAL-cohort tended to have higher adjusted odds ratios (aOR) of a number of previous clinical events (AIDS, severe non-AIDS events such as malignancies and cardiovascular events) as well as prior use/failure of antiretroviral therapy vs. the concurrent control group (**Table 2**) and also vs. the historical group (data not shown). In the ITT analysis (events: 50 RAL, 45 HIST, 127 CONC), the incidence of all new malignancies was 1.11 (95% CI 0.84-1.46) per 100 PYFU in the RAL cohort vs. 1.20 (0.90-1.61) and 0.83 (0.70-0.99) for the HIST and CONC cohorts, respectively. After adjustment using propensity scores, there was no significant difference in the incidence of malignancies between the RAL cohort and the HIST or CONC cohorts (**Table 3**).

**CONCLUSIONS:** *At baseline individuals in the RAL cohort tended to have more co-morbidities than those in the HIST and CONC control groups. Once these differences were taken into account, there was no difference in the risk of malignancy among RAL-exposed individuals compared to those starting other historical or concurrent cART regimens.*

**Table 1.** Baseline characteristics of participants according to inclusion in raltegravir, historical and concurrent cohorts

| | RAL | Historical | Concurrent |
|---|---|---|---|
| **Total** | N= 1470 | N= 3787 | N= 4467 |
| **No. of patients (%)** | | | |
| **Gender** | | | |
| **Female** | 361 (24.6%) | 949 (25.1%) | 1229 (27.5%) |
| **Mode of HIV transmission** | | | |
| **Homosexual contacts** | 640 (43.5%) | 1623 (42.9%) | 1782 (39.9%) |
| **Heterosexual contacts** | 255 (17.3%) | 764 (20.2%) | 860 (19.3%) |
| **IDU** | 451 (30.7%) | 1129 (29.8%) | 1539 (34.5%) |
| **Other/unknown** | 124 (8.4%) | 271 (7.2%) | 286 (6.4%) |
| **Race** | | | |
| **White** | 1232 (83.8%) | 3274 (86.5%) | 3942 (88.2%) |
| **Asian** | 20 (1.4%) | 62 (1.6%) | 56 (1.3%) |
| **Black** | 90 (6.1%) | 239 (6.3%) | 282 (6.3%) |
| **Other/unknown** | 128 (8.7%) | 212 (5.6%) | 187 (4.2%) |
| **Geographical region** | | | |
| **South** | 458 (31.2%) | 1131 (29.9%) | 1053 (23.6%) |
| **Central West** | 523 (35.6%) | 892 (23.6%) | 889 (19.9%) |
| **North** | 315 (21.4%) | 1071 (28.3%) | 891 (19.9%) |
| **Central East** | 138 (9.4%) | 394 (10.4%) | 777 (17.4%) |
| **East** | 21 (1.4%) | 190 (5.0%) | 696 (15.6%) |
| **Argentina** | 15 (1.0%) | 109 (2.9%) | 161 (3.6%) |
| **Viral load, copies/mL** | | | |
| **<500** | 1082 (73.6%) | 2278 (60.2%) | 2584 (57.8%) |
| **500-10,000** | 179 (12.2%) | 486 (12.8%) | 411 (9.2%) |
| **>10,000** | 209 (14.2%) | 1023 (27.0%) | 1472 (33.0%) |
| **Median(IQR)** | | | |
| **Age (years)** | 49 (44, 56) | 44 (39, 50) | 44 (35, 51) |
| **CD4 count (cells/mm$^{3)}$** | | | |
| **Baseline** | 468 (300, 673) | 392 (237, 614) | 404 (255, 630) |
| **Nadir** | 118 (41, 208) | 140 (50, 225) | 175 (75, 266) |
| **Time since nadir (years)** | 10 (4, 13) | 6 (2, 9) | 4 (0, 10) |
| **Viral load ($log_{10}$ copies/mL)** | | | |
| **Baseline** | 1.7 (1.6, 2.9) | 1.9 (1.7, 4.2) | 1.8 (1.6, 4.5) |
| **Peak** | 5.0 (4.3, 5.6) | 4.9 (4.2, 5.5) | 5.0 (4.3, 5.5) |
| **Index date (baseline)** | 2010 (2009, 2012) | 2006 (2005, 2006) | 2009 (2008, 2011) |
| **Length of follow-up (months)** | 32 (15, 52) | 13 (6, 22) | 25 (11, 45) |
| **Length of enrolment (months)** | 11 (5, 14) | 7 (2, 9) | 4 (1, 10) |
| **Time since HIV-1 positive (years)[a]** | 17 (13, 21) | 12 (8, 16) | 10 (4, 16) |

**Table 3.** RH from fitting a Cox regression model and adjustment using propensity scores

| | Unadjusted | | Adjusted | |
|---|---|---|---|---|
| | RR (95% CI) | p-value | RR (95% CI) | p-value |
| **Model 1*** | | | | |
| **Historical control** | 1.00 | | 1.00 | |
| **Raltegravir** | 0.92 (0.62, 1.38) | 0.703 | 0.74 (0.48, 1.15) | 0.184 |
| **Model 2**** | | | | |
| **Concurrent control** | 1.00 | | 1.00 | |
| **Raltegravir** | 1.33 (0.96, 1.85) | 0.086 | 1.02 (0.70, 1.49) | 0.904 |
| | | | | |
| ***Adjusted for the following covariates:** | | | | |
| **Geographical region, HBV co-infection, age, time since CD4 count nadir, viral load - baseline and peak, length of enrolment in EuroSIDA, loss or accumulation of fat, OI treatment, time since started ART, No. of previous treatment failures, No. of previous NRTIs, No. of previous NNRTIs and No. of previous PIs** | | | | |
| ****Adjusted for the following covariates:** | | | | |
| **Geographical region, HBV co-infection, age, CD4 count nadir, No. of previous AIDS diagnosis, OI treatment, No. of previous treatment failures, No. of previous NRTIs, No. of previous NNRTIs and No. of previous PIs** | | | | |

**Table 2.** Univariable and multivariable odds ratios (ORs) for initiation of RAL, compared to concurrent cohort (selected factors)

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| **Factor** | OR (95% CI) | p-value | OR (95% CI) | p-value |
| **No. of previous AIDS diagnoses** | | | | |
| **0** | 1.00 | | 1.00 | |
| **1** | 1.48 (1.28, 1.71) | <.001 | 0.97 (0.81, 1.15) | 0.708 |
| **>=2** | 2.45 (2.07, 2.90) | <.001 | 1.27 (1.01, 1.60) | 0.037 |
| **AIDS malignancy** | 2.04 (1.64, 2.54) | <.001 | 0.92 (0.70, 1.21) | 0.559 |
| **Non-AIDS malignancy** | 3.12 (2.39, 4.08) | <.001 | 1.89 (1.37, 2.61) | <.001 |
| **Cardiovascular event** | 2.69 (2.06, 3.53) | <.001 | 1.35 (0.99, 1.83) | 0.055 |
| **Loss or accumulation of fat** | 2.91 (2.60, 3.27) | <.001 | 0.95 (0.81, 1.11) | 0.516 |
| **Discontinued drug due to toxicity** | 1.94 (1.53, 2.46) | <.001 | 1.09 (0.83, 1.42) | 0.550 |
| **Discontinued drug due to lipodistrophy/atrophy** | 1.78 (1.56, 2.04) | <.001 | 1.04 (0.88, 1.23) | 0.642 |
| **Prior medication (versus no medication)** | | | | |
| **OI treatment[a]** | 2.51 (2.23, 2.82) | <.001 | 0.88 (0.75, 1.03) | 0.109 |
| **Lipid lowering agents** | 1.88 (1.54, 2.28) | <.001 | 0.75 (0.60, 0.94) | 0.012 |
| **Prior antiretroviral therapy** | | | | |
| **Time since started ART (per year longer)** | 1.16 (1.15, 1.17) | <.001 | 0.99 (0.96, 1.01) | 0.281 |
| **No. of previous treatment failures (per one higher)** | 2.33 (2.20, 2.47) | <.001 | 1.29 (1.17, 1.42) | <.001 |
| **No. of previous NRTIs** | | | | |
| **3-4** | 1.00 | | 1.00 | |
| **0-2** | 0.31 (0.26, 0.37) | <.001 | 0.89 (0.70, 1.12) | 0.313 |
| **>=5** | 3.35 (2.89, 3.88) | <.001 | 1.70 (1.43, 2.03) | <.001 |
| **No. of previous NNRTIs** | | | | |
| **1** | 1.00 | | 1.00 | |
| **0** | 0.26 (0.23, 0.30) | <.001 | 0.35 (0.25, 0.49) | <.001 |
| **>=2** | 2.39 (2.02, 2.83) | <.001 | 1.38 (1.14, 1.68) | <.001 |
| **No. of previous PIs** | | | | |
| **1-2** | 1.00 | | 1.00 | |
| **0** | 0.22 (0.18, 0.26) | <.001 | 0.34 (0.24, 0.47) | <.001 |
| **3-4** | 2.53 (2.19, 2.94) | <.001 | 1.52 (1.28, 1.80) | <.001 |
| **>=5** | 7.04 (5.60, 8.86) | <.001 | 2.82 (2.12, 3.74) | <.001 |
| **Previously taken NRTIs, NNRTIs, PIs** | 5.55 (4.91, 6.27) | <.001 | 0.54 (0.37, 0.78) | 0.001 |

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