**Non-Hodgkin lymphoma risk in adults living with HIV across five continents: a multicohort study**

The AIDS-defining Cancer Project Working Group of IeDEA and COHERE in EuroCoord

**Supplementary material**

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**Detailed acknowledgements**

* **Detailed acknowledgements of consortia contributing data to this analysis.**

**Supplementary Box S1: Collection and merging of cohort data.**

We analyzed longitudinal routine clinical care data of adults living with HIV within the framework of the International epidemiology Databases to Evaluate AIDS (IeDEA) and the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. The following IeDEA regions contributed data to this analysis: The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD);1 the Caribbean, Central and South America network for HIV epidemiology (CCASAnet);2 IeDEA Southern Africa;3 and IeDEA Asia-Pacific.4 COHERE in EuroCoord contributed data from 24 cohorts covering 36 countries through the 2014 merger.5 Cohorts participating in IeDEA and COHERE in EuroCoord routinely collect clinical, demographic, laboratory, and treatment data during enrollment and follow-up visits. Patient data are then de-identified and transferred to regional data centres for merging. Through standard procedures for data request we obtained regional data sets in their respective standard data exchange formats from the data centers in 2014. We performed quality checks, harmonized the regional data sets by renaming variables and creating new variables based on available information, and eventually combined them into one multiregional data set for use in this analysis.

Cancer data collection is not standardized across regions. Most cohorts prospectively capture information on AIDS-defining cancers including NHL. In addition, cohorts participating in NA-ACCORD validated cancer cases using information from medical records, histopathology reports, and linkages with cancer registries.6 CCASAnet retrospectively added cancer data through review of medical charts, local databases, and pathology reports in 2007 to 2009.7 Sites contributing data to the IeDEA Asia-Pacific previously reviewed medical charts to retrospectively identify cancer cases up to 2008.8 For IeDEA Southern Africa we restricted the analysis to two South African cohorts, which had been linked with the National Cancer Registry, to reduce under-reporting of cancer cases in the HIV cohorts.9 The French hospital database on HIV (FHDH-ANRS CO4), which is the largest COHERE cohort contributing data to the current analysis, performs regular audits comparing cancer data in the cohort database with medical records.10

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**Supplementary Figure S1:** Identification of study population for analysis.The flow diagram shows the number of included and excluded adults.



**Supplementary Figure S2:** **NHL incidence rates by time since ART start in MSM, heterosexual men, and women across regions.** Incidence rates are predicted for adults with a current CD4 cell count of 450 cells/µl who started an NNRTI-based first-line ART regimen between 2008-2014 at the age of 40 years and did not inject drugs (model 3).



ART, antiretroviral therapy; MSM, men who have sex with men; NHL, non-Hodgkin lymphoma; NNRTI, non-nucleoside reverse-transcriptase inhibitors; pys, person-years.

**Supplementary Table S1:** Characteristics of adults with incident NHL.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Asia-Pacific** | **South Africa** | **Latin America** | **North America** | **Europe** |
| **All NHL cases** | 9 (100%) | 63 (100%) | 51 (100%) | 204 (100%) | 1,225 (100%) |
| **Median time to NHL diagnosis (IQR) [years]** | 0.6 (0.5 - 1.4) | 1.3 (0.6 - 2.9) | 0.8 (0.2 - 3.6) | 1.9 (0.4 - 4.7) | 1.1 (0.3 - 3.5) |
| **Sex** |  |  |  |  |  |
|  Women | 1 (11%) | 41 (65%) | 4 (8%) | 33 (16%) | 210 (17%) |
|  Men | 8 (89%) | 22 (35%) | 47 (92%) | 171 (84%) | 1,015 (83%) |
| **Median age at NHL diagnosis (IQR) [years]** | 53.0 (48.1 - 59.8) | 38.6 (35.0 - 42.5) | 41.4 (34.7 - 49.6) | 44.9 (38.1 - 50.2) | 43.0 (36.6 - 51.1) |
| **First line treatment** |  |  |  |  |  |
|  NNRTI-based | 7 (78%) | 60 (95%) | 40 (78%) | 63 (31%) | 452 (37%) |
|  PI-based | 2 (22%) | 3 (5%) | 10 (20%) | 125 (61%) | 675 (55%) |
|  Other ART | 0 (0%) | 0 (0%) | 1 (2%) | 16 (8%) | 98 (8%) |
| **Calendar period of ART intiation** |  |  |  |  |  |
|  1996-1998 | 0 (0%) | 0 (0%) | 2 (4%) | 94 (46%) | 256 (21%) |
|  1999-2003 | 0 (0%) | 0 (0%) | 12 (24%) | 71 (35%) | 431 (35%) |
|  2004-2007 | 1 (11%) | 44 (70%) | 18 (35%) | 27 (13%) | 296 (24%) |
|  2008-2014 | 8 (89%) | 19 (30%) | 19 (37%) | 12 (6%) | 242 (20%) |
| **Median CD4 cell count at NHL diagnosis (IQR) [cells/µl]** | 76 (26 - 465) | 225 (97 - 352) | 159 (84 - 280) | 153 (54 - 326) | 235 (104 - 390) |
| **CD4 cell count at NHL diagnosis (IQR) [cells/µl]** |  |  |  |  |  |
|  <50 | 2 (22%) | 4 (6%) | 9 (18%) | 42 (21%) | 142 (12%) |
|  50-99 | 2 (22%) | 8 (13%) | 5 (10%) | 24 (12%) | 118 (10%) |
|  100-199 | 0 (0%) | 7 (11%) | 14 (27%) | 44 (22%) | 203 (17%) |
|  200-349 | 1 (11%) | 16 (25%) | 9 (18%) | 29 (14%) | 291 (24%) |
|  350-499 | 0 (0%) | 7 (11%) | 6 (12%) | 25 (12%) | 170 (14%) |
|  500-699 | 0 (0%) | 3 (5%) | 3 (6%) | 12 (6%) | 92 (8%) |
|  ≥700 | 1 (11%) | 2 (3%) | 0 (0%) | 6 (3%) | 63 (5%) |
|  missing | 3 (33%) | 16 (25%) | 5 (10%) | 22 (11%) | 146 (12%) |
| **Median HIV RNA at NHL diagnosis (IQR) [log10 copies/ml]** | 1.8(1.7 - 5.7) | 1.7(1.7 - 2.6) | 2.1(1.7 - 4.9) | 2.7(2.3 - 4.7) | 2.6(1.7 - 4.7) |
| **HIV RNA at NHL diagnosis (IQR) [log10 copies/ml]** |  |  |  |  |  |
|  <2.7 | 5 (56%) | 30 (48%) | 21 (41%) | 90 (44%) | 555 (45%) |
|  2.7-3.9 | 0 (0%) | 5 (8%) | 5 (10%) | 22 (11%) | 131 (11%) |
|  4.0-4.9 | 0 (0%) | 3 (5%) | 3 (6%) | 36 (18%) | 126 (10%) |
|  5.0-5.9 | 1 (11%) | 0 (0%) | 6 (12%) | 31 (15%) | 174 (14%) |
|  ≥6.0 | 1 (11%) | 0 (0%) | 2 (4%) | 1 (<1%) | 26 (2%) |
|  missing | 2 (22%) | 25 (40%) | 14 (27%) | 24 (12%) | 213 (17%) |

ART, antiretroviral therapy; IQR, interquartile range; NHL, non-Hodgkin lymphoma; MSM, men who have sex with men; NNRTI, non-nucleoside reverse-transcriptase inhibitor; PI, protease-inhibitor; RNA, ribonucleic acid.

**Supplementary Table S2:** RawNHL incidence rates per 100,000 pys and 95% CIs, stratified by region and risk factor.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Asia-Pacific** | **South Africa** | **Latin America** | **North America** | **Europe** |
| **Cases and total number** **of persons** | 9 / 2,638 | 63 / 21,656 | 51 / 8,569 | 204 / 16,986 | 1,225/161,049 |
| **Person years** | 7,772 | 54,307 | 45,614 | 90,818 | 891,834 |
| **Overall** | 116 (60-223) | 116 (91-149) | 112 (85-147) | 225 (196-258) | 137 (130-145) |
| **Sex and exposure group**  |  |  |  |  |  |
|  Female | 42 (6-295) | 116 (85-157) | 32 (12-85) | 129 (92-181) | 85 (74-97) |
|  Male | 149 (75-298) | 116 (77-177) | 142 (107-189) | 262 (226-305) | 157 (148-167) |
|  Heterosexual male | 144 (60-345) | - | 136 (80-229) | 271 (201-364) | 159 (144-175) |
|  MSM | 162 (52-503) | - | 162 (114-231) | 245 (204-295) | 152 (139-165) |
| **PWID** |  |  |  |  |  |
|  Yes | - | - | 310 (100-961) | 163 (105-253) | 135 (114-158) |
|  No | - | - | 108 (81-143) | 234 (203-271) | 138 (130-146) |
| **Age at ART start [years]** |  |  |  |  |  |
|  16-25 | 166 (23-1,181) | 69 (22-215) | 61 (20-189) | 190 (95-379) | 75 (58-98) |
|  26-35 | - | 105 (70-156) | 103 (66-162) | 168 (125-225) | 103 (93-114) |
|  36-45 | 38 (5-268) | 163 (114-231) | 97 (57-164) | 222 (180-274) | 141 (128-155) |
|  46-55 | 274 (88-849) | 59 (22-158) | 172 (93-320) | 335 (257-436) | 196 (173-223) |
|  ≥56 | 1,138 (427-3,032) | 80 (11-570) | 247 (103-592) | 214 (111-411) | 300 (256-353) |
| **KS history** |  |  |  |  |  |
|  Yes | - | - | 373 (93-1,493) | 737 (397-1,370) | 245 (183-328) |
|  No | 144 (75-276) | 135 (105-174) | 128 (91-179) | 219 (188-255) | 145 (136-153) |
| **First line treatment** |  |  |  |  |  |
|  NNRTI-based | 103 (49-216) | 118 (92-152) | 120 (88-164) | 237 (185-303) | 133 (121-146) |
|  PI-based | 236 (59-944) | 87 (28-271) | 90 (48-167) | 222 (187-265) | 139 (129-150) |
|  Other ART | - | - | 83 (12-590) | 200 (122-326) | 146 (120-178) |
| **Calendar period at ART start** |  |  |  |  |  |
|  1996-1998 | - | - | 151 (38-604) | 212 (173-259) | 128 (113-144) |
|  1999-2003 | - | - | 69 (39-122) | 231 (183-292) | 120 (109-132) |
|  2004-2007 | 40 (6-280) | 115 (86-155) | 101 (63-160) | 203 (139-296) | 142 (127-159) |
|  2008-2014 | 170 (85-339) | 122 (78-192) | 210 (134-330) | 502 (285-884) | 194 (171-220) |
| **CD4 cell count at ART start [cells/µl]** |  |  |  |  |  |
|  <50 | 212 (80-564) | 107 (64-177) | 122 (66-227) | 402 (308-523) | 186 (162-213) |
|  50-99 | - | 183 (116-286) | 103 (46-230) | 383 (261-562) | 207 (176-243) |
|  100-199 | 54 (8-381) | 102 (65-159) | 122 (68-220) | 262 (191-360) | 176 (156-198) |
|  200-349 | 95 (24-381) | 120 (57-251) | 79 (39-157) | 165 (119-230) | 116 (104-130) |
|  350-499 | 378 (53-2,681) | - | 83 (21-332) | 107 (63-181) | 81 (67-99) |
|  500-699 | - | - | 128 (18-906) | 108 (54-215) | 93 (71-121) |
|  ≥700 | - | - | - | 162 (73-360) | 79 (53-119) |

ART, antiretroviral therapy; IQR, interquartile range; NHL, non-Hodgkin Lymphoma; KS, Kaposi Sarcoma; MSM, men who have sex with men; NNRTI, non-nucleoside reverse-transcriptase inhibitor; PI, protease-inhibitor; PWID, people who inject drugs; pys, person-years.

**Supplementary Table S3:** RawNHL incidence rates per 100,000 pys and 95% CIs, stratified by region and current CD4 cell count.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Asia-Pacifc** | **South Africa** | **Latin America** | **North America** | **Europe** |
| **Current CD4 cell count [cells/µl]** | **pys** | **N** | **IR (95% CI)** | **pys** | **N** | **IR (95% CI)** | **pys** | **N** | **IR (95% CI)** | **pys** | **N** | **IR (95% CI)** | **pys** | **N** | **IR (95% CI)** |
|  ≤50 | 464 | 2 | 431 (108 - 1,725) | 2,671 | 4 | 150 (56 - 399) | 1,424 | 9 | 632 (329 - 1,215) | 4,118 | 47 | 1,141 (858-1,519) | 14,722 | 157 | 1,066 (912-1,247) |
|  51-100 | 410 | 2 | 488 (122 - 1,953) | 3,211 | 10 | 311 (168 - 579) | 1,661 | 5 | 301 (125 - 723) | 3,537 | 26 | 735 (501 – 1,080) | 18,790 | 131 | 697 (587 - 827) |
|  101-200 | 1,222 | 0 | - | 10,515 | 8 | 76 (38 - 152) | 5,409 | 17 | 314 (195 - 506) | 10,024 | 48 | 479 (361 - 635) | 66,333 | 232 | 350 (308 - 398) |
|  201-350 | 2,224 | 4 | 180 (67 - 479) | 16,166 | 20 | 124 (80 - 192) | 11,137 | 10 | 90(48 - 167) | 20,458 | 35 | 171 (123 - 238) | 171,399 | 335 | 195 (176 - 218) |
|  351-500 | 1,812 | 0 | - | 11,440 | 14 | 122 (72 - 207) | 10,334 | 6 | 58 (26 - 129) | 19,917 | 27 | 136 (93 - 198) | 209,252 | 195 | 93 (81 - 107) |
|  501-700 | 1,153 | 0 | - | 7,041 | 5 | 71 (30 - 171) | 8,758 | 4 | 46 (17 - 122) | 18,219 | 14 | 77 (46 - 130) | 213,832 | 107 | 50 (41 - 60) |
|  >700 | 434 | 1 | 230 (32 - 1,634) | 2,802 | 2 | 71 (18 - 285) | 6,214 | 0 | - | 14,480 | 7 | 48 (23 - 101) | 187,320 | 68 | 36 (29 - 46) |

NHL, non-Hodgkin Lymphoma; pys, person-years; N number of cases; IR, incidence rate; CI, confidence interval.

**Supplementary Table S4:** Crude and adjusted hazard ratios for the effect of age, calendar period of ART start and first-line ART regimen on the risk of developing NHL in adults who started ART.

|  |  |  |
| --- | --- | --- |
|  | **Crude hazard ratio****(95% CI)** | **Adjusted hazard ratio (95% CI)\*** |
| **Age at ART start** |  |  |
|  per decade increase | 1.35 (1.29 - 1.41) | 1.29 (1.23 - 1.35) |
| **Calendar year of ART start** |  |  |
|  1996-1998 | 1.52 (1.28 - 1.80) | 1.25 (1.04 - 1.49) |
|  1999-2003 | 1.27 (1.09 - 1.48) | 1.02 (0.87 - 1.19) |
|  2004-2007 | 1.12 (0.96 - 1.31) | 0.97 (0.83 - 1.14) |
|  2008-2014 | 1.00 | 1.00 |
| **First line treatment** |  |  |
|  NNRTI-based | 1.00 | 1.00 |
|  PI-based | 1.11 (1.00 - 1.24) | 0.96 (0.85 - 1.08) |
|  Other ART | 1.13 (0.92 - 1.38) | 1.09 (0.89 - 1.34) |

\* Adjusted for region, age at ART start, calendar year of ART start, first-line ART regimen, current CD4 cell count and its interaction with region, sex and its interaction with region (model 1).

ART, antiretroviral therapy; CI, confidence interval; NHL, non-Hodgkin Lymphoma; NNRTI, non-nucleoside reverse-transcriptase inhibitor; PI, protease-inhibitor.

**Supplementary Table S5:** Raw NHL incidence rates by region; sensitivity analysis excluding NHL cases diagnosed within the first six months after ART start.

|  |  |
| --- | --- |
|  | **Incidence rate per 100,000 pys (95% CI)** |
| **Overall** | 100 (94 - 106) |
| **Asia-Pacific** | 84 (38 - 188) |
| **Latin America** | 69 (48 - 99) |
| **Europe** | 95 (89 - 102) |
| **South Africa** | 100 (76 - 132) |
| **North America** | 169 (143 - 198) |

ART, antiretroviral therapy; CI, confidence interval; NHL, non-Hodgkin Lymphoma; pys, person-years.

**Supplementary Table S6:** Crude and adjusted hazard ratios for the regional effect of sex and current CD4 cell count on the risk of developing NHL in adults who started ART; sensitivity analysis excluding NHL cases diagnosed within the first six months after ART start.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **South Africa** | **Latin America** | **North America** | **Europe** |
|  | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** |
| **Sex** |  |  |  |  |
| Men | 1.00 | 1.00 | 1.00 | 1.00 |
|  Women (crude) | 1.20 (0.65 - 2.21) | 0.29 (0.09 - 0.97) | 0.53 (0.34 - 0.82) | 0.55 (0.46 - 0.66) |
|  Women (adjusted\*) | 1.34 (0.72 – 2.47) | 0.31 (0.09 - 1.02) | 0.52 (0.34 - 0.81) | 0.61 (0.51 - 0.73) |
| **Current CD4 cell count** |  |  |  |  |
| Per 100 cells/µl increase (crude) | 0.95 (0.80 - 1.13) | 0.69 (0.56 - 0.86) | 0.65 (0.59 - 0.71) | 0.72 (0.69 - 0.74) |
| Per 100 cells/µl increase (adjusted\*\*) | 0.95 (0.80 - 1.13) | 0.70 (0.56 - 0.87) | 0.64 (0.59 - 0.71) | 0.73 (0.70 - 0.75) |

\* Adjusted for age at ART start, calendar year of ART start, first-line ART regimen, current CD4 cell count and its interaction with region (model 1).

\*\* Adjusted for age at ART start, calendar year of ART start, first-line ART regimen, sex and its interaction with region (model 1).

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; NHL, non-Hodgkin Lymphoma.

**Supplementary Table S7:** Crude and adjusted hazard ratios for the effect of exposure group and injection drug use on the risk of developing NHL in adults who started ART, restricted to North America, Latin America, and Europe; sensitivity analysis excluding NHL cases diagnosed within the first six months after ART start.

|  |  |  |
| --- | --- | --- |
|  | **Crude** | **Adjusted\*** |
|  | **HR (95% CI)** | **HR (95% CI)** |
| **Exposure group** |  |  |
|  Women | 0.53 (0.44 - 0.64) | 0.68 (0.56 - 0.83) |
|  Heterosexual men | 1.00 | 1.00 |
|  MSM | 0.93 (0.80 - 1.08) | 1.28 (1.09 - 1.50) |
| **PWID** |  |  |
|  No | 1.00 | 1.00 |
|  Yes | 1.05 (0.87 - 1.27) | 0.96 (0.78 - 1.18) |

\*Adjusted for region, age at ART start, calendar year of ART start, first-line ART regimen, current CD4 cell count, and exposure group or PWID, respectively (model 2)

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; MSM, men who have sex with men; NHL, non-Hodgkin Lymphoma; PWID, people who inject drugs.

**Supplementary Table S8: Comparison of NHL rates between different regions and Europe:** Crude and adjusted HRs for being diagnosed with NHL at 2 years after ART start in different population groups; sensitivity analysis excluding NHL cases diagnosed within the first six months after ART start.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Women1** | **All men1** | **Heterosexual men2** | **MSM2** |
|  | **Crude HR** **(95% CI)** | **Adjusted HR\* (95% CI)** | **Crude HR** **(95% CI)** | **Adjusted HR\* (95% CI)** | **Crude HR** **(95% CI)** | **Adjusted HR\*\* (95% CI)** | **Crude HR** **(95% CI)** | **Adjusted HR\*\* (95% CI)** |
| **Region** |  |  |  |  |  |  |  |  |
|  Europe | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
|  North America | 1.75 (1.12 - 2.72) | 0.91(0.55 - 1.49) | 1.82 (1.45 - 2.28) | 1.06 (0.78 - 1.44) | 2.14(1.48 - 3.09) | 1.53 (1.06 - 2.21) | 1.68 (1.27 - 2.21) | 1.13 (0.85 - 1.49) |
|  Latin America | 0.38 (0.12 - 1.21) | 0.32 (0.09 - 1.06) | 0.72 (0.47 - 1.09) | 0.62 (0.35 - 1.10) | 0.96 (0.51 - 1.81) | 0.91 (0.49 - 1.72) | 0.74(0.43 - 1.29) | 0.64 (0.37 - 1.10) |
|  South Africa | 1.71 (1.14 - 2.58) | 2.19(1.42 - 3.39) | 0.79 (0.46 - 1.35) | 1.00(0.56 - 1.80) | - | - | - | - |

1 From models including the variable “sex” and its interaction with region.

2 From models including the variable “exposure group” and its interaction with region.

\* Adjusted for age at ART start, calendar period of ART start, first-line ART regimen, current CD4 cell count and its interaction with region, and sex and its interaction with region (model 1).

\*\* Adjusted for age at ART start, calendar period of ART start, first-line ART regimen, current CD4 cell count, drug use, and exposure group and its interaction with region (model 3).

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; NHL, non-Hodgkin Lymphoma.

**Supplementary Table S9: Comparison of NHL rates between different regions and Europe:** Crude and adjusted HRs for being diagnosed with NHL at 5 years after ART start in different populations groups.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Women1** | **All men1** | **Heterosexual men2** | **MSM2** |
|  | **Crude HR** **(95% CI)** | **Adjusted HR\* (95% CI)** | **Crude HR** **(95% CI)** | **Adjusted HR\* (95% CI)** | **Crude HR** **(95% CI)** | **Adjusted HR\*\* (95% CI)** | **Crude HR** **(95% CI)** | **Adjusted HR\*\* (95% CI)** |
| **Region** |  |  |  |  |  |  |  |  |
|  Europe | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
|  North America | 1.95(1.32 - 2.89) | 1.11(0.72 - 1.70) | 2.04(1.63 - 2.55) | 1.25 (0.95 - 1.65) | 2.04(1.44 - 2.90) | 1.39 (0.98 - 1.98) | 2.02(1.56 - 2.60) | 1.32 (1.02 - 1.71) |
|  Latin America | 0.31 (0.11 - 0.91) | 0.25 (0.08 - 0.75) | 0.74 (0.45 - 1.22) | 0.61 (0.34 - 1.09) | 0.73 (0.38 - 1.41) | 0.68 (0.35 - 1.32) | 0.93(0.55 - 1.59) | 0.79 (0.46 - 1.36) |
|  South Africa | 1.99 (1.18 - 3.38) | 2.30(1.34 - 3.95) | 1.08(0.59 - 1.95) | 1.20(0.65 - 2.21) | - | - | - | - |

1 From models including the variable “sex” and its interaction with region.

2 From models including the variable “exposure group” and its interaction with region.

\* Adjusted for age at ART start, calendar period of ART start, first-line ART regimen, current CD4 cell count and its interaction with region, and sex and its interaction with region (model 1).

\*\* Adjusted for age at ART start, calendar period of ART start, first-line ART regimen, current CD4 cell count, drug use, and exposure group and its interaction with region (model 3).

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; NHL, non-Hodgkin lymphoma.

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