

Low Risk of Malignancy With Maraviroc in Treatment-Experienced and Treatment-Naïve Patients Across the Maraviroc Clinical Development Program

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Background

- Combination antiretroviral therapy for HIV has resulted in a decrease in the incidence of AIDS-defining malignancies; however, the incidence of non-AIDS-defining malignancies in this population remains higher relative to the HIV-uninfected population¹⁻⁴
- Many of the non-AIDS-defining malignancies commonly reported in HIV-infected patients have known or suspected infectious causes¹⁻⁶
- Maraviroc (MVC) is a CCR5 antagonist and the first clinically available antiretroviral agent designed to act on a host cell target
- Since CCR5-mediated signaling plays a role in immune surveillance, an increased incidence of malignancies or infections is a theoretical concern
 - Although no clinical or preclinical malignancy signals have been detected during the clinical development of MVC, an apparent malignancy excess had been observed during the development of another CCR5 antagonist⁷
- The objective of this retrospective analysis was to assess the incidence of and risk factors for malignancies among more than 1400 MVC-treated patients included in the phase 2b/3 studies of the MVC development program

Methods

- In the MVC phase 2b/3 studies (Table 1) treatment-emergent malignancies were reported prospectively
- This is a retrospective analysis of treatment-emergent malignancies among patients treated with MVC or placebo/active control during MOTIVATE 1 and 2,^{8,9} MERIT¹⁰ and study A4001029¹¹
- The analysis included data from
 - The blinded treatment period for all treatment arms of all studies
 - The open-label treatment period for all treatment arms of all studies except the placebo arm of the MOTIVATE studies
- Malignancies were categorized in two non-mutually exclusive ways
 - AIDS-defining versus non-AIDS-defining
 - Infection-related versus non-infection-related
 - Potentially related to infection with HPV, EBV, HBV, HCV, HHV-8, or HTLV-15,6

Table 1. Description of MVC Phase 2b/3 Study Design

	MOTIVATE 1 & 2 (N = 1049)	MERIT (N = 895)	A4001029 (N = 186)
Patients	Treatment-experienced (TE)	Treatment-naïve (TN)	Treatment-experienced (TE)
Tropism and entry viral load	R5 HIV-1 HIV-1 RNA ≥ 5000 copies/mL	R5 HIV-1 HIV-1 RNA ≥ 5000 copies/mL	Non-R5 HIV-1 HIV-1 RNA ≥ 5000 copies/mL
Randomized treatment arms	OBT plus • MVC 150 mg ^a once daily (n = 414) • MVC 150 mg ^a twice daily (n = 426) • PBO (n = 209)	AZT/3TC (CBV) plus • MVC 300 mg once daily (n = 174) • MVC 300 mg twice daily (n = 360) • EFV 600 mg twice daily (n = 361)	OBT plus • MVC 150 mg ^a once daily (n = 63) • MVC 150 mg ^a twice daily (n = 62) • PBO (n = 61)
Duration of blinded treatment	48 weeks	96 weeks ^b	48 weeks
Open-label treatment	Open-label MVC twice-daily for eligible patients	Open-label continuation of therapy within treatment groups ^b	Open-label MVC for eligible patients in MVC arms

3TC, lamivudine; AZT, zidovudine; CBV, Combivir; EFV, efavirenz; OBT, optimized background therapy; PBO, placebo
^aPatients receiving protease inhibitors (except tipranavir) and/or delamanvir received 150 mg MVC, all others received 300 mg
^bThe MVC once-daily arm was discontinued at 16 weeks following the results of an interim analysis. Patients in this arm were subsequently eligible to receive open-label MVC 300 mg twice-daily.

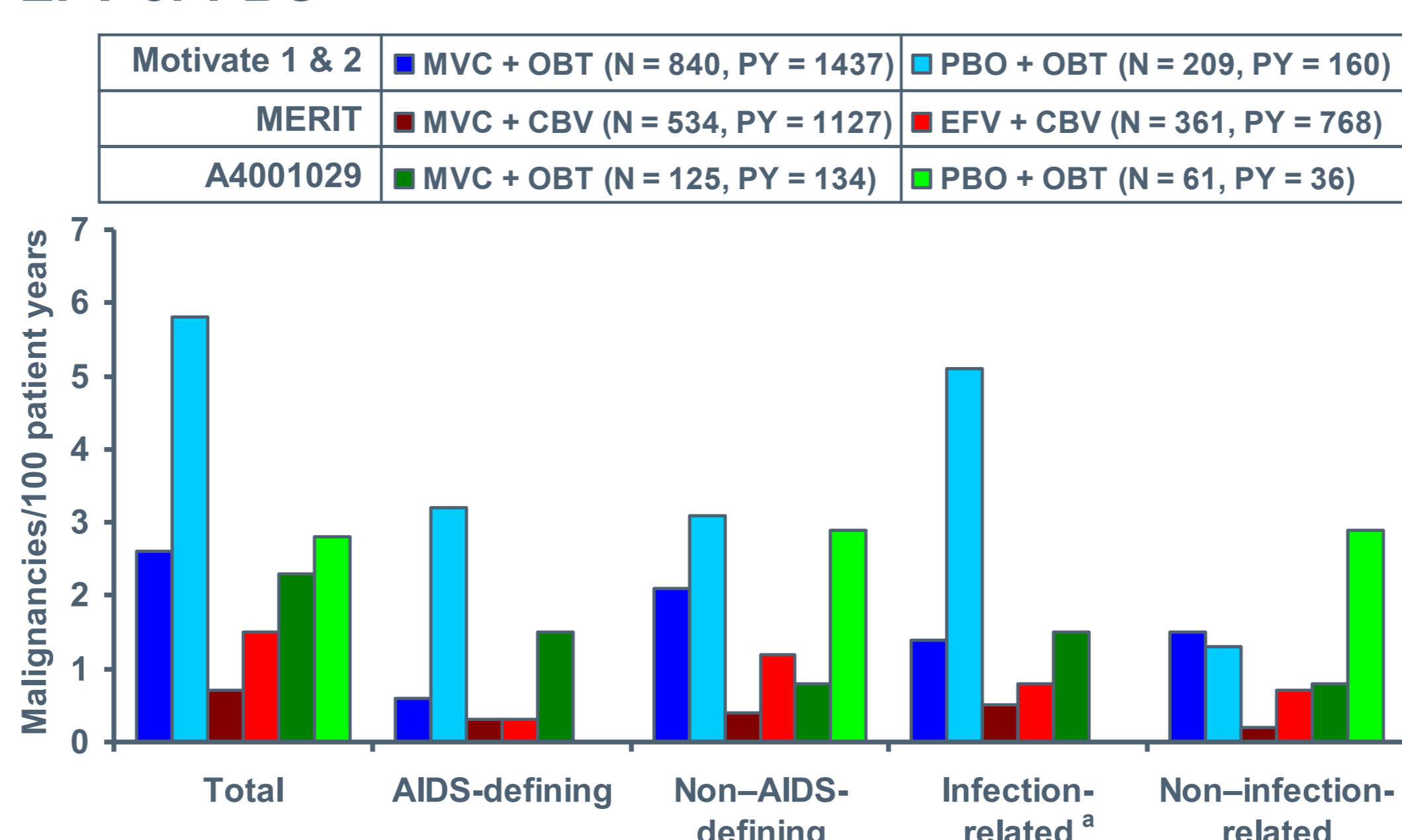
- Treatment-emergent malignancies are presented separately for each of the 3 study cohorts
 - Descriptive statistics were calculated within treatment groups
 - Patients with more than 1 malignancy contributed once to each applicable category, hence categories are not mutually exclusive
- Malignancies present at baseline were included only if they worsened in severity during treatment
 - Exposure-adjusted malignancy rates were calculated to adjust for the longer duration spent on MVC relative to the PBO arms in MOTIVATE 1 and 2 and A4001029
 - Risk ratios and 95% confidence intervals were calculated for MVC versus placebo or EFV
- Predictive factors for malignancies were assessed for the pooled population from the 3 studies using univariate and stepwise multivariate Cox proportional hazard regression models
 - Baseline covariates included age (in 1-year increments), gender, baseline CD4⁺ count and HIV-1 RNA level, mode of infection, hepatitis B or C co-infection at screening, prior treatment status (TE vs TN), past history of malignancy, and treatment arm (MVC vs comparator)
 - Time-dependent covariates included change from baseline in CD4⁺ count (in increments of 25 cells/mm³) and HIV-1 RNA level (< 50 copies/mL vs ≥ 50 copies/mL)

Results

- The exposure-adjusted incidences of malignancies across the 3 studies were generally lower in the combined MVC arms than in the comparator arms, with the differences particularly marked for the MOTIVATE studies where the duration of MVC exposure was 9 times greater than placebo exposure (Figure 1)
- These differences were associated with a significantly lower overall risk of malignancy and significantly lower risks of AIDS-defining and infection-related malignancies among patients receiving MVC than among patients receiving placebo in MOTIVATE (Figure 2)

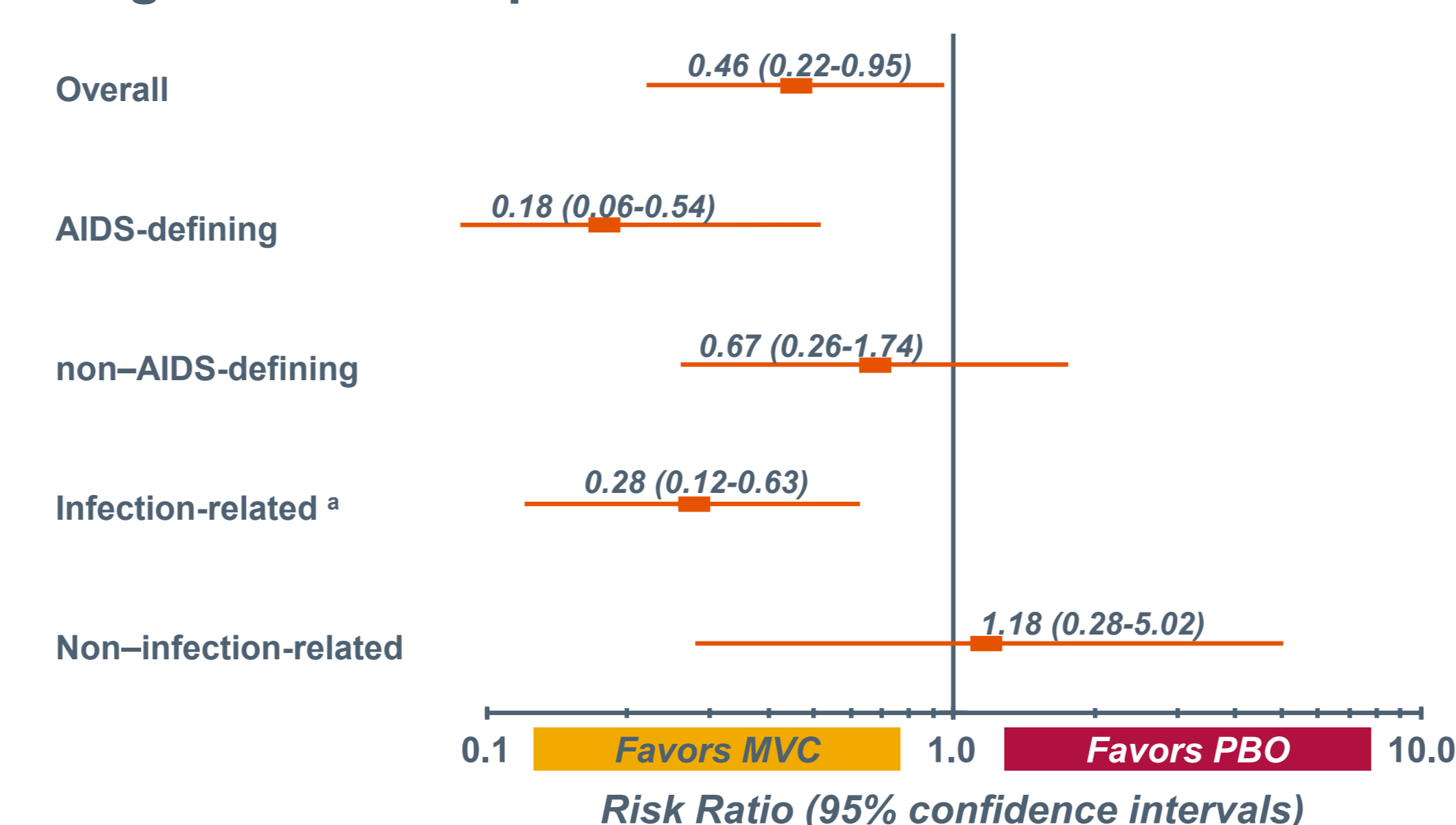
- In the MERIT study of TN patients, the exposure-adjusted risk of malignancy was not significantly different between those receiving MVC and those receiving the active comparator EFV; although nonsignificant, lower exposure-adjusted rates for overall, non-AIDS-defining and non-infection-related malignancies were seen in the MVC arms (Figure 3)
- There were too few malignancies observed in A4001029 to draw meaningful risk comparisons between treatment arms (Table 2)

Figure 1. Exposure-adjusted Incidence of Malignancies Was Generally Numerically Lower on MVC Compared to EFV or PBO



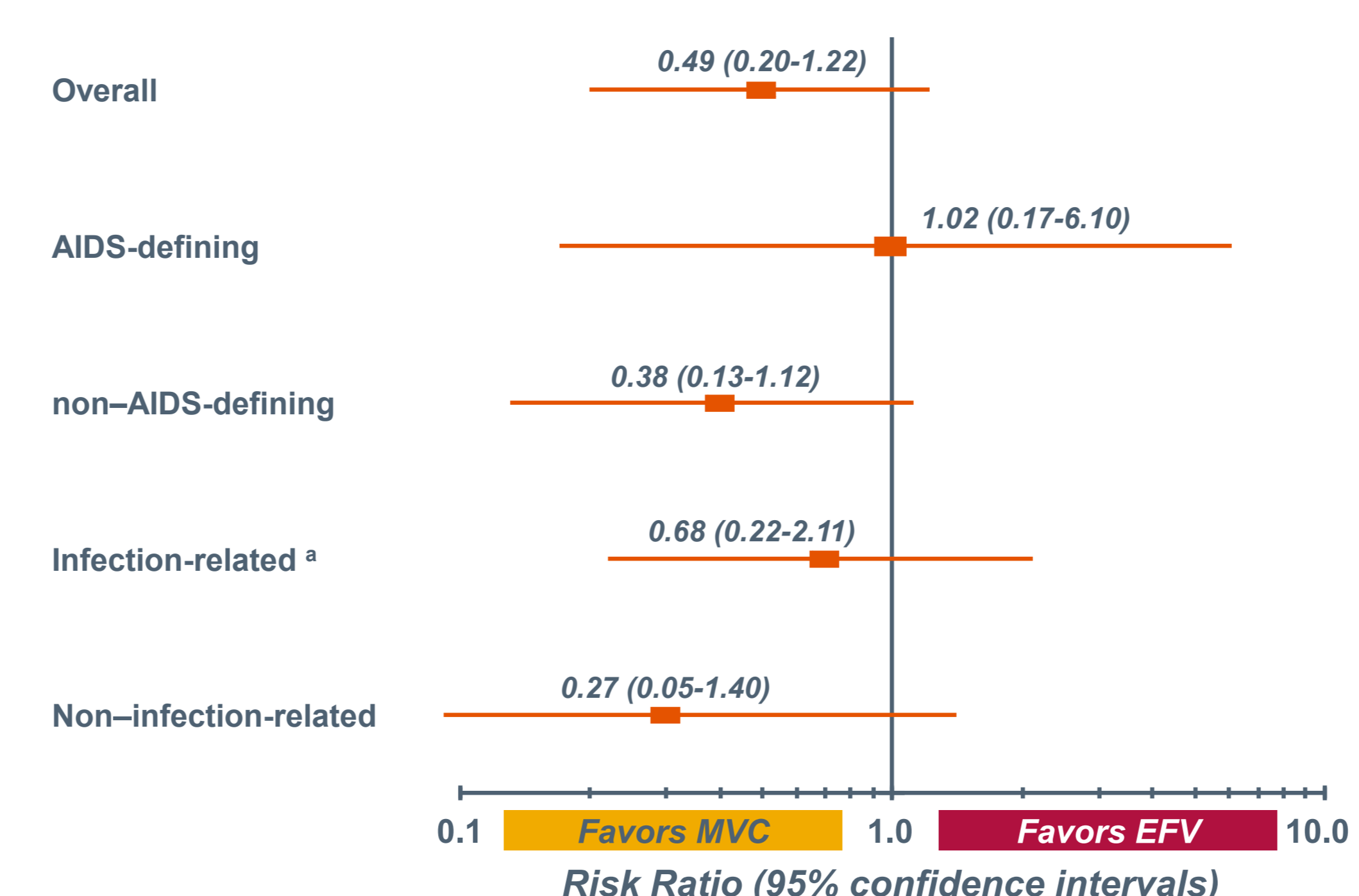
CBV, combivir; EFV, efavirenz; OBT, optimized background therapy; PBO, placebo; PY, patient year
^aPotentially related to infection with HPV, EBV, HBV, HCV, HHV-8, or HTLV-15,6

Figure 2. Patients in the MOTIVATE Studies Receiving MVC Had Significantly Lower Exposure-adjusted Risks of Overall, AIDS-Defining and Infection-Related Malignancies Compared to the PBO arm



^aPotentially related to infection with HPV, EBV, HBV, HCV, HHV-8, or HTLV-15,6

Figure 3. Although Not Significant, Lower Exposure-Adjusted Rates for Overall, Non-AIDS-Defining and Non-Infection-Related Malignancies Were Seen in the MVC Arms of MERIT



^aPotentially related to infection with HPV, EBV, HBV, HCV, HHV-8, or HTLV-15,6

Table 2. The Most Frequently Reported Malignancy Types Were Anal Cancer, Lymphoma and Basal Cell Carcinoma

Unadjusted incidence	MOTIVATE 1 & 2		MERIT		A4001029	
	MVC+OBT N = 840	PBO+OBT N = 209	MVC+CBV N = 534	EFV+CBV N = 361	MVC+OBT N = 125	PBO+OBT N = 61
Total patients, n (%)	37 (4.4)	9 (4.3)	8 (1.5)	11 (3.1)	3 (2.4)	1 (1.6)
Total malignancies, n ^a	44	10	9	11	3	1
Malignancy type, n (% of all patients in treatment arm)						
Gastrointestinal tract	13 (1.5)	3 (1.4)	2 (0.4)	2 (0.6)	0	0
Anal cancer ^b	8 (1.0)	3 (1.4)	1 (0.2)	0	0	0
Bile duct cancer	1 (0.1)	0	0	0	0	0
Esophageal carcinoma	2 (0.2)	0	0	0	0	0
Rectal cancer	1 (0.1)	0	0	1 (0.3)	0	0
Tongue neoplasm	1 (0.1)	0	0	0	0	0
Nasopharyngeal cancer	0	0	1 (0.2)	0	0	0
Salivary gland neoplasm	0	0	0	1 (0.3)	0	0
Lymphoma	9 (1.1)	2 (1.0)	3 (0.6)	3 (0.8)	2 (1.6)	0
Hodgkin	3 (0.4)	0	1 (0.2)	2 (0.6)	0	0
Non-Hodgkin ^c	6 (0.7)	2 (1.0)	2 (0.4)	1 (0.3)	2 (1.6)	0
Kaposi's Sarcoma	3 (0.4)	3 (1.4)	1 (0.2)	1 (0.3)	0	0
Lung	1 (0.1)	0	0	0	1 (0.8)	0
Bronchial carcinoma	1 (0.1)	0	0	0	0	0
Lung adenocarcinoma	0	0	0	0	1 (0.8)	0
Skin	10 (1.2)	1 (0.5)	1 (0.2)	2 (0.6)	0	1 (1.6)
Basal cell carcinoma	7 (0.8)	0	0	2 (0.6)	0	1 (1.6)
Squamous cell carcinoma	3 (0.4)	1 (0.5)	0	0	0	0
Skin cancer	0	0	1 (0.2)	0	0	0
Metastases	4 (0.5)	0	1 (0.2)	1 (0.3)	0	0
Bone	1 (0.1)	0	1 (0.2)	0	0	0
Liver	2 (0.2)	0	0	0	0	0
Peritoneum	1 (0.1)	0	0	0	0	0
Metastatic neoplasm	0	0	0	1 (0.3)	0	0
Genitourinary	2 (0.2)	0	0	1 (0.3)	0	0
Prostate cancer	1 (0.1)	0	0	0	0	0
Testicular neoplasm	1 (0.1)	0	0	0	0	0
Vulval neoplasm	0	0	0	1 (0.3)	0	0
Neoplasm^d	1 (0.1)	1 (0.5)	0	0	0	0
Leukemia	1 (0.1)	0	0	0	0	0
Castleman's disease	0	0	0	1 (0.3)	0	0
Multiple myeloma	0	0	1 (0.2)	0	0	0

CBV, Combivir; EFV, efavirenz; MVC, Maraviroc; OBT, optimized background therapy.
^aAll on-study malignancy events are listed for patients who had one or more malignancy event on study.
^bIncludes anal cancer stage 0.
^cIncludes Burkitt's lymphoma, T-cell lymphoma, B-cell lymphoma, diffuse large B-cell lymphoma, lymphoma, and other non-Hodgkin lymphoma.
^dInvestigator terms "Lump left side neck" and "Right thigh lump" reported under the MedDRA preferred term of neoplasm. Further investigation into the clinical status of these neoplasms is ongoing.

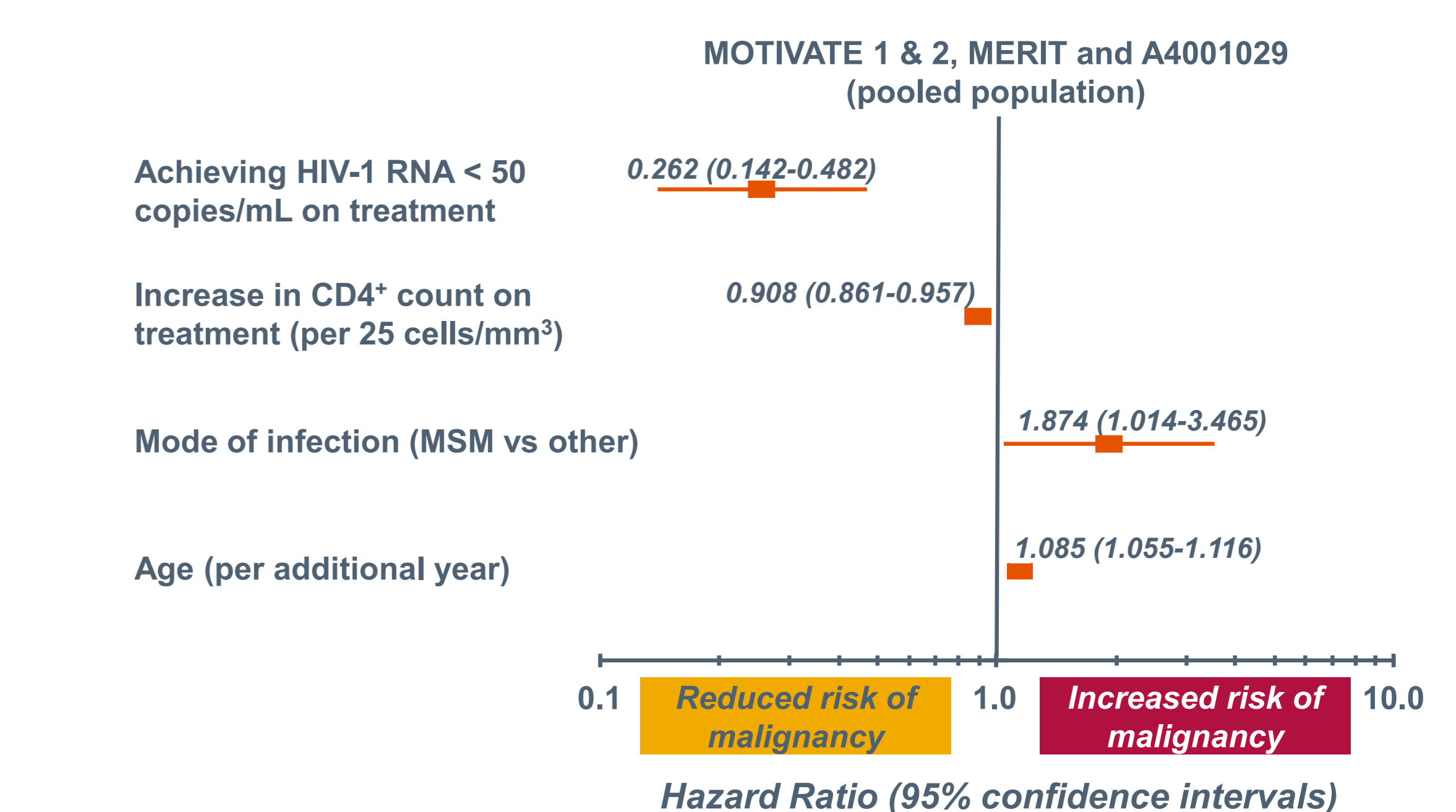
- The most commonly reported malignancies among the 3 studies were anal cancers, lymphomas and basal cell carcinomas (Table 2)
- In each study, substantial proportions of patients who developed an on-treatment malignancy had achieved undetectable (<50 copies/mL) HIV-1 RNA prior to the event (Table 3)
- In the MERIT study, patients from both the MVC and EFV treatment arms who developed an on-treatment malignancy had smaller CD4⁺ cell increases prior to the event than those who did not develop a malignancy (Table 3)
- CD4⁺ cell increase on treatment was associated with a reduced risk of malignancy in a multivariate analysis of pooled data from all 3 studies (Figure 4). Achieving HIV-1 RNA levels <50 cells/mm³ was also associated with a reduced risk of malignancy
- By contrast, older age and MSM transmission were both associated with an increased risk of malignancy (Figure 4)

Table 3. Substantial Proportions of Patients With an On-Treatment Malignancy Had Undetectable HIV-1 RNA Prior to Onset

	MOTIVATE 1 & 2				MERIT				A4001029			
	Malignancy + OBT	No Malignancy + OBT	Malignancy + OBT	No Malignancy + OBT	Malignancy + OBT	No Malignancy + OBT	Malignancy + OBT	No Malignancy + OBT	Malignancy + OBT	No Malignancy + OBT	Malignancy + OBT	No Malignancy + OBT
Total patients	37	9	803	200	7 (88)	9 (82)	379 (72)	250 (71)	2 (87)	1 (100)	107 (88)	51 (85)
Male, n (%)	37 (100)	8 (89)	708 (88)	177 (89)	7 (88)	9 (82)	379 (72)	250 (71)	2 (87)	1 (100)	107 (88)	51 (85)
Age, median (IQR) years	50 (43-56)	45 (41-52)	45 (40-51)	45 (41-50)	53 (49-56)	38 (38-57)	30 (30-43)	37 (30-43)	40 (32-52)	52 (40-49)	43 (39-47)	44 (40-49)
Pre with prior malignancy, n (%)	10 (27)	2 (22)	144 (18)	35 (18)	1 (13)	1 (9)	11 (2)	12 (3)	0	0	24 (20)	11 (18)
Baseline CD4 count, median (IQR) cells/mm ³	152 (59-264)	164 (4-252)	169 (74-288)	171 (84-279)	272 (193-366)	232 (127-277)	244 (173-320)	259 (189-328)	84 (63-148)	154 (154-154)	54 (49-125)	43 (7-156)
Baseline HIV-1 RNA, median (IQR) copies/mL	5.1 (4.8-5.5)	5.1 (4.8-5.7)	4.9 (4.4-5.3)	4.9 (4.3-5.3)	4.8 (4.5-5.3)	5.2 (4.5-5.7)	4.9 (4.4-5.3)	4.9 (4.5-5.2)	4.8 (3.9-5.3)	5.5 (5.5-5.5)	5.3 (4.8-5.5)	5.1 (4.8-5.4)
HIV-1 RNA < 50 copies/mL prior to event ^a , n (%)	18 (49)	2 (22)	504 (63)	70 (35)	6 (75)	8 (73)	428 (81)	306 (87)	3 (100)	0	43 (35)	17 (28)
CD4 count prior to event ^a , median (IQR) cells/mm ³	308 (172-462)	235 (51-354)	294 (171-438)	224 (109-353)	327 (272-383)	301 (289-369)	458 (322-581)	462 (320-562)	259 (161-264)	361 (361-361)	128 (46-284)	130 (21-275)
Change in CD4 from baseline to event, median (IQR) cells/mm ³	82 (48-172)	28 (1-91)	106 (36-199)	29 (-4-113)	64 (-37-161)	85 (45-97)	204 (105-336)	187 (86-313)	116 (77-197)	208 (208-208)	46 (9-129)	23 (0-104)

CBV, combivir; EFV, efavirenz; IQR, interquartile range; OBT, optimized background therapy; PBO, placebo.
^aFor patients without malignancies, listed values are the last on-treatment measurement.

Figure 4. CD4⁺ Cell Increases and Undetectable HIV-1 RNA Were Associated With Decreased Malignancy Risk, While Older Age and Infection by MSM Transmission Were Associated With Increased Risk (Multivariate Analysis)^a



^aStepwise Cox proportional hazard model; only terms remaining in the model are presented

Conclusions

- In this retrospective analysis of more than 1400 patients:
 - MVC-treated patients had a low incidence of malignancies, regardless of virus tropism or degree of antiretroviral treatment experience
 - Long-term blinded and open-label treatment with MVC did not reveal any increased incidence of malignancies, compared to published rates at 48 weeks^{8,10,11}
 - The exposure-adjusted incidence of malignancies was generally numerically lower in the MVC group compared to PBO or EFV; in MOTIVATE, the difference between MVC and PBO was statistically significant for overall, AIDS-defining, and infection-related malignancies
 - Across the 3 cohorts, the incidence of non-AIDS-defining malignancies was generally greater than that of AIDS-defining malignancies
 - Older age and mode of infection were associated with increased risk of malignancy
 - On-treatment increase in CD4⁺ cell count and undetectable HIV-1 RNA were associated with reduced risk of malignancy
 - Every increase in CD4⁺ count of 25 cells/mm³ was associated with an approximate 10% decrease in risk of malignancy
 - A large percentage of patients who developed a malignancy did so after having achieved an undetectable viral load

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