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An integrative analysis of the fluoroquinolone phase III TB clinical trials

TB Re-analysis of Floroquinolone Clinical Trials

(TB-ReFLECT)

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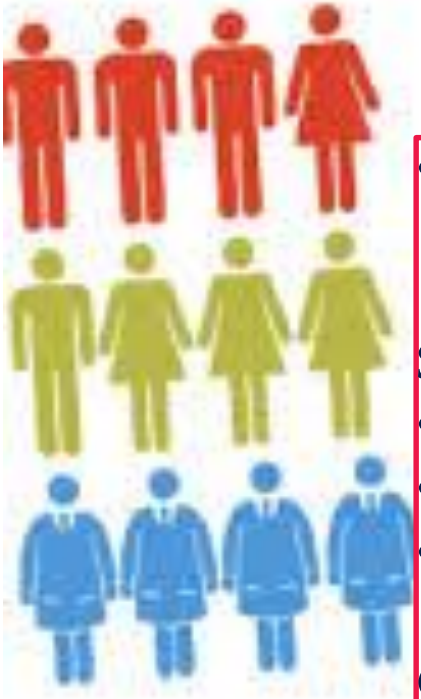
UCSF

3/29/2017

One Regimen Does **NOT** Fit All

Towards Patient Stratification



- 4 month regimen worked well in 80% patients
  - Hard/Easy to treat and all in between

Stratification based on

- Clinical characteristics (X-ray, Gene Xpert, Baseline Smear, HIV))
- Demographics (Nutrition, Age, Weight, etc)
- More refined biomarker (Scans + Immunological)

Goal: Identify the **right regimen** for the **right patient** at the right time

Deliverable: Smart and Easy to Use/Implement Dosing Algorithms

Analysis Goal

- To assess predictors of treatment response after oral administration of 6 month standard of care treatment and various experimental 4 and 6 months regimens in Pulmonary Tuberculosis Patients
  - To identify patient groups eligible for 4 month treatment
  - To profile “hard-to-treat” patient populations
  - To identify drug-specific factors predicted of unfavorable response
  - To provide directions for future clinical trials
  - To provide data-driven evidence for immediate impact on TB treatment implementation

Data Base

- Integrated and standardized Individual level data from 3 recent Phase III trials (OFLOTUB, REMox and Rifaquin) through the Platform for Aggregation of Clinical TB Studies (TB-PACTS)
- Data sharing governed by comprehensive Data Contribution Agreements with sponsors.
- Data standardization and curation facilitated and enabled by CPTR.
- Data base architecture and access to qualified researchers maintained by CPTR.

Outcome definition (challenge #1)

- Unfavorable outcome
  - Diverse definitions in the three studies
- Recurrence (Unfavorable outcome – treatment failures)
  - Removed individuals with unfavorable events before 114 days for 4 month arms
  - Removed individuals with unfavorable events before 170 days for SOC

Predictors

- Demographics (weight, bmi, age, sex)
- Clinical (Baseline Smear, HIV status, Cavity status (yes/no))
- On treatment: Month 2 and Month 4 culture (solid or liquid)
- Drug: adherence, treatment duration (time dependent)

- **Other relevant predictors non consistent across 3 trials:**
  - Smoking
  - Detailed readouts from Chest X-ray (zone scoring, bilateral disease, cavity size)
  - Longitudinal MGIT (no Gene Xpert)
  - PK

Demographics

		6 month arm		4 month arm	
Study		N=1404	Rifaquin: 188 REMox: 555 Oflotub: 661	N=2001	Rifaquin: 193 REMox: 1119 (2 arms) Oflotub: 689
Females, n (%)		415 (30%)		592 (30%)	
Ethnicity	Black	1066 (76%)		1326 (66%)	
	Asian	178 (13%)		349 (17%)	
	Other	160 (11%)		329 (16%)	
Age, yrs, median,(min,max)		29 (17-77)		30 (16-81)	
Weight, kg, median,(min,max)		52 (35-137)		52 (35-98)	
BMI kg/m^2 median,(min,max)		18.3 (12.1-50.9)		18.4 (12.0-40.7)	

HIV Status and Baseline Disease Severity

		6 month arm		4 month arm	
Study		N=1404	Rifaquin: 188 REMox: 555 Oflotub: 661	N=2001	Rifaquin: 193 REMox: 1119 (2 arms) Oflotub: 689
HIV-infected, n, (%)		220 (16%)		248 (12%)	
Smear	Negative/Scanty	85 (6%)		151 (8%)	
	1+	232 (17%)		332 (17%)	
	2+	404 (29%)		503 (25%)	
	3+	666 (47%)		988 (49%)	
Cavity presence (yes)		847 (60%)		1247 (62%)	
CD4 cells/uL (median)*		317 (19-1155)		363 (25 - 1134)	

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Missing On-treatment Predictors

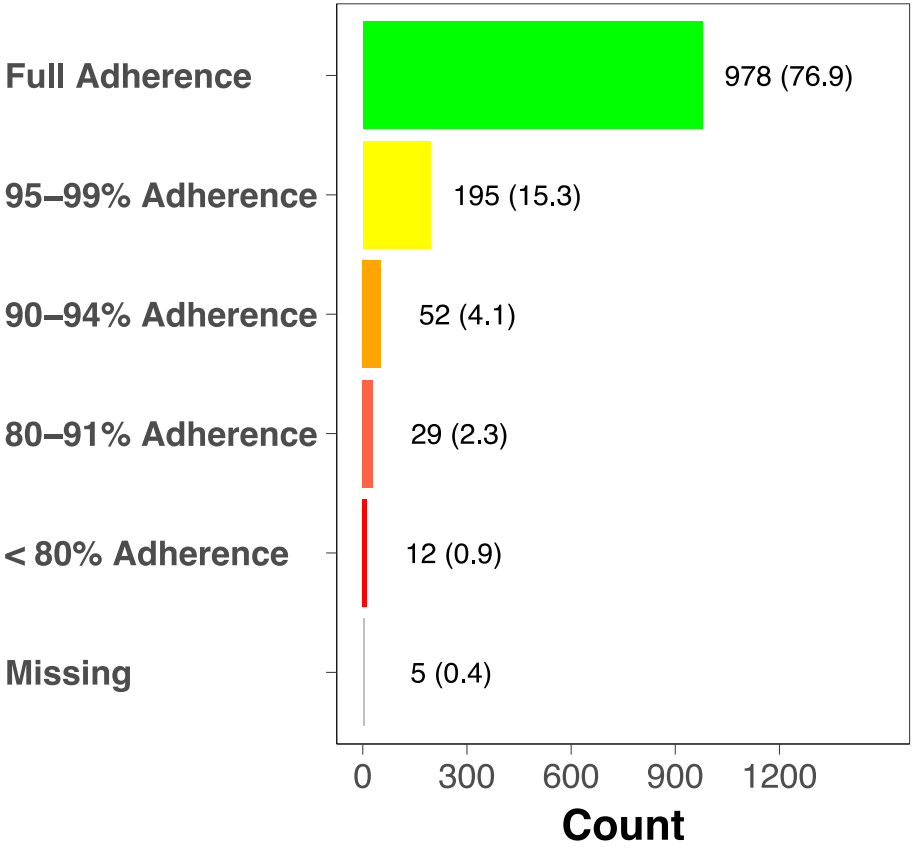
	Smear	
	SOC	4 month
Baseline	1.2% (17)	1.3% (26)
Month 1	60.4% (846)	44.3% (887)
Month 2	7.7% (108)	8.7% (174)
Month 3	47.1% (661)	37.2% (744)
Month 4	15.7% (220)	10.9% (218)
Month 6	12.3% (173)	17.0% (340)

Missing On-treatment Predictors

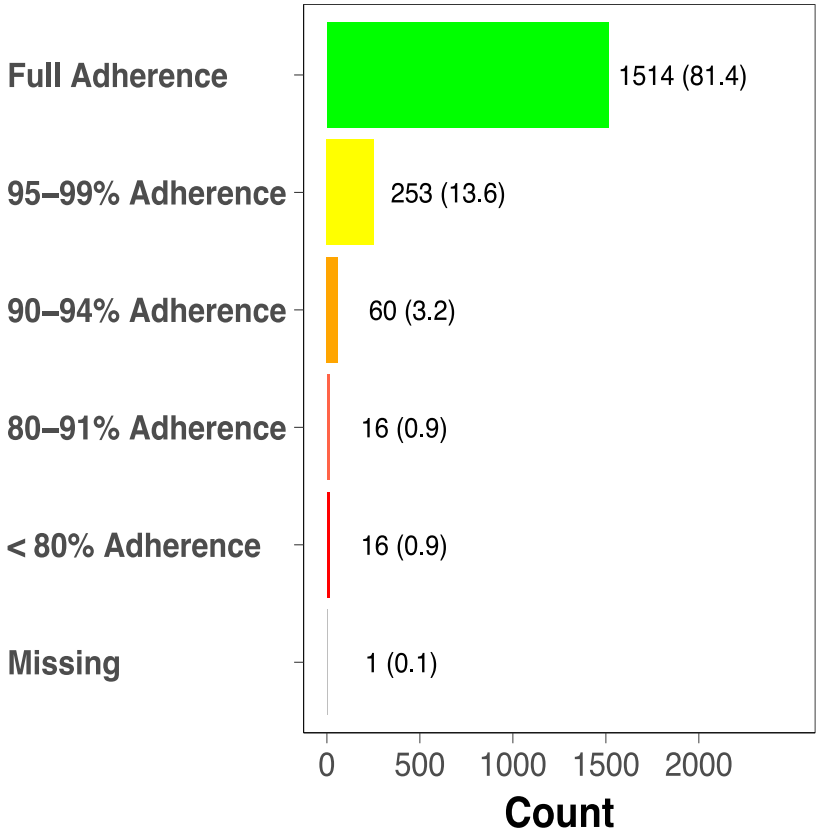
	Solid Culture Growth		Liquid Culture Growth		Solid or Liquid Culture	
	SOC	4 month	SOC	4 month	SOC	4 month
Baseline	**21.9%** (307)	**15.7%** (314)	**52.5%** (737)	**39.2%** (784)	**12.7%** (178)	**9.4%** (188)
Month 1	**60.4%** (846)	**44.3%** (887)	**60.4%** (846)	**44.3%** (887)	**60.4%** (846)	**44.3%** (887)
Month 2	**16.6%** (233)	**15.3%** (306)	**56.8%** (797)	**45.5%** (910)	**9.0%** (126)	**9.8%** (196)
Month 3	**55.3%** (776)	**42.2%** (844)	**58.6%** (823)	**45.7%** (914)	**47.8%** (671)	**37.3%** (746)
Month 4	**24.8%** (348)	**17.2%** (344)	**57.1%** (802)	**46.5%** (930)	**16.8%** (236)	**12.1%** (242)
Month 6	**21.2%** (298)	**23.0%** (460)	**58.0%** (814)	**47.5%** (950)	**13.4%** (188)	**17.9%** (358)

Drug Adherence

HRZE recurrence

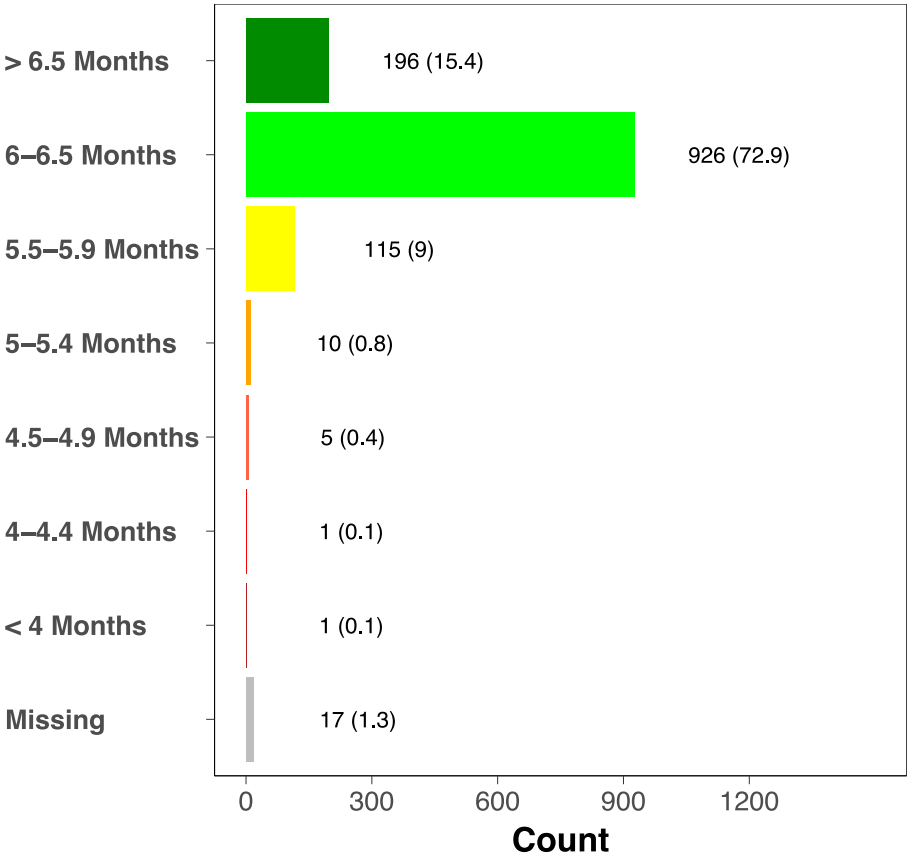


4-month recurrence

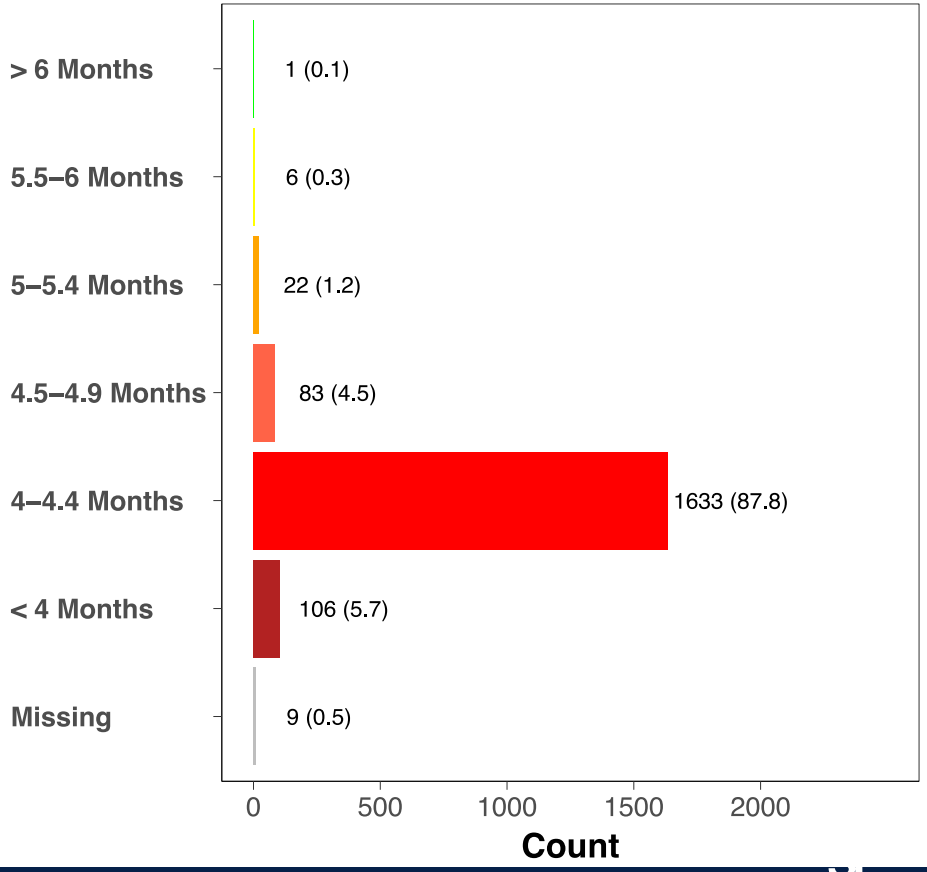


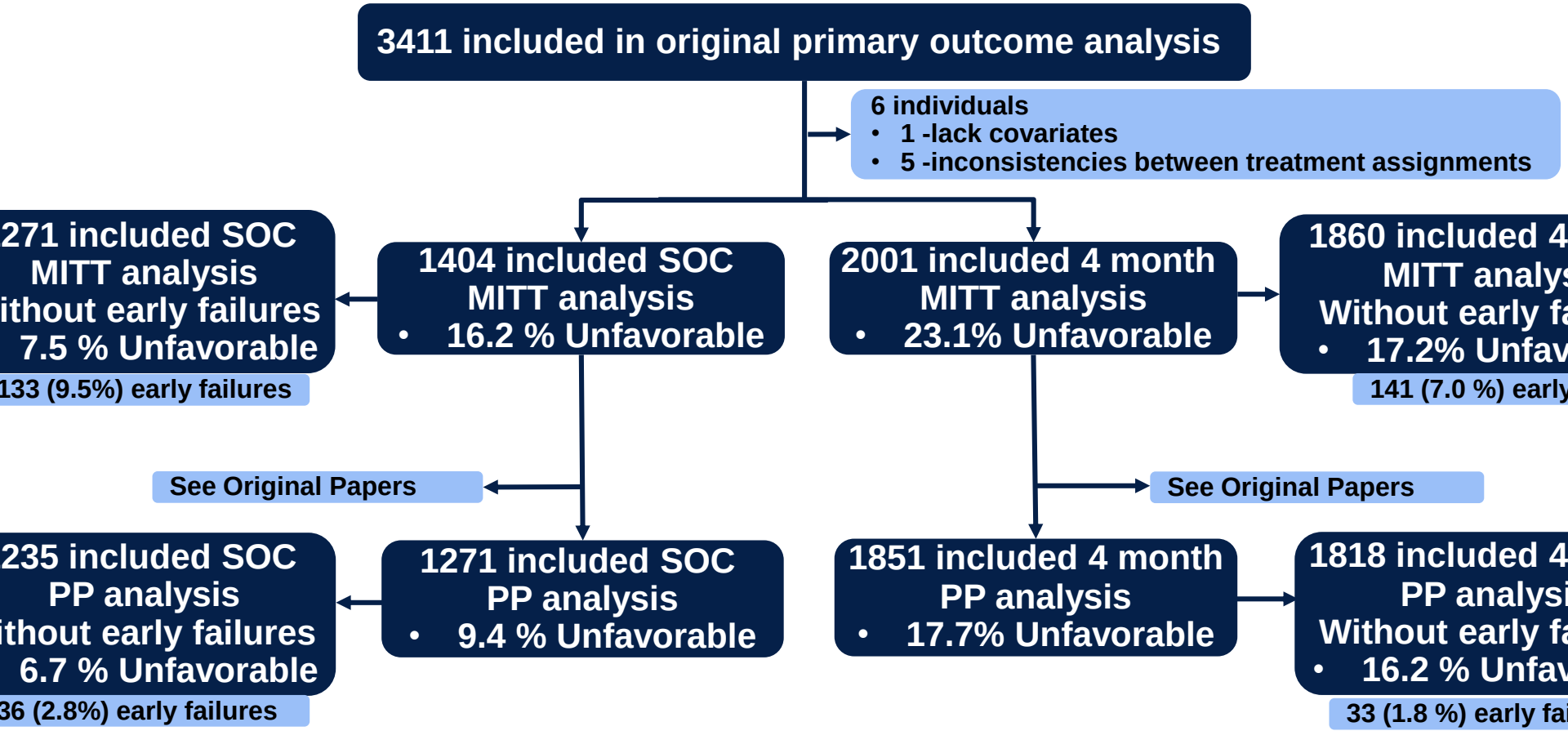
Treatment Duration

HRZE recurrence



4-month recurrence

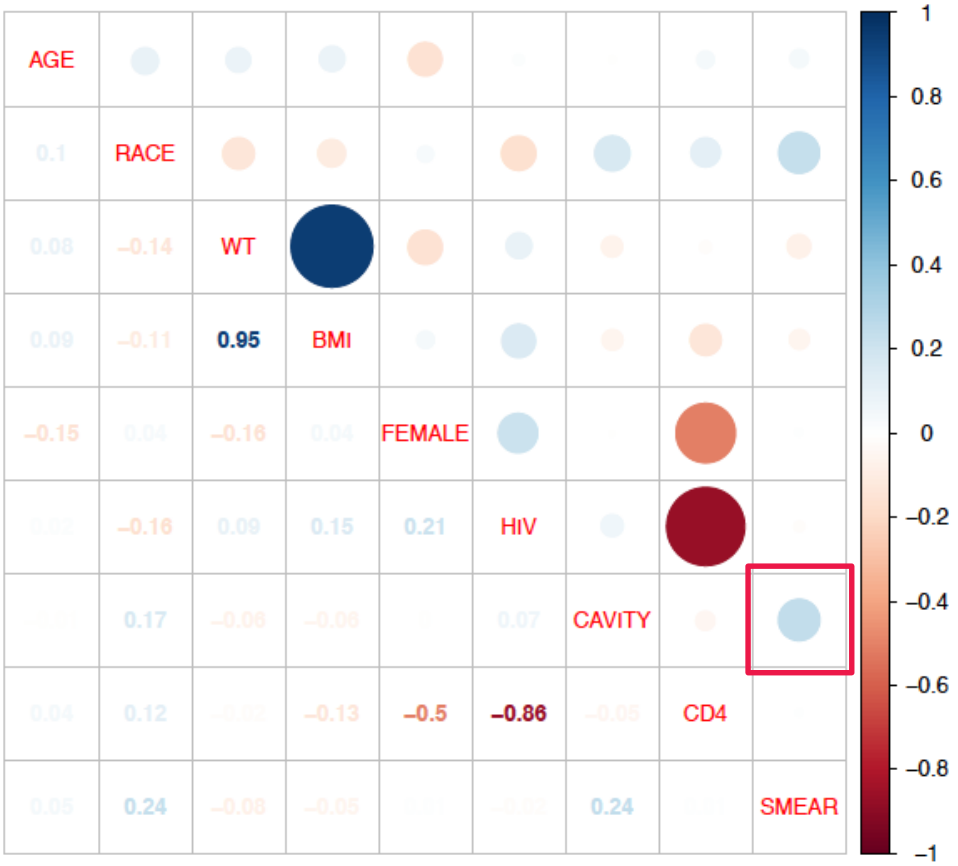



3411 included in original primary outcome analysis
6 individuals
• 1 -lack covariates
• 5 -inconsistencies between treatment assignments
271 included SOC
MITT analysis
ithout early failures
7.5 % Unfavorable
133 (9.5%) early failures
1404 included SOC
MITT analysis
• 16.2 % Unfavorable
2001 included 4 month
MITT analysis
• 23.1% Unfavorable
1860 included 4
MITT analys
Without early fa
• 17.2% Unfav
141 (7.0 %) early
See Original Papers
See Original Papers
235 included SOC
PP analysis
ithout early failures
6.7 % Unfavorable
36 (2.8%) early failures
1271 included SOC
PP analysis
• 9.4 % Unfavorable
1851 included 4 month
PP analysis
• 17.7% Unfavorable
1818 included 4
PP analysi
Without early fa
• 16.2 % Unfav
33 (1.8 %) early fai

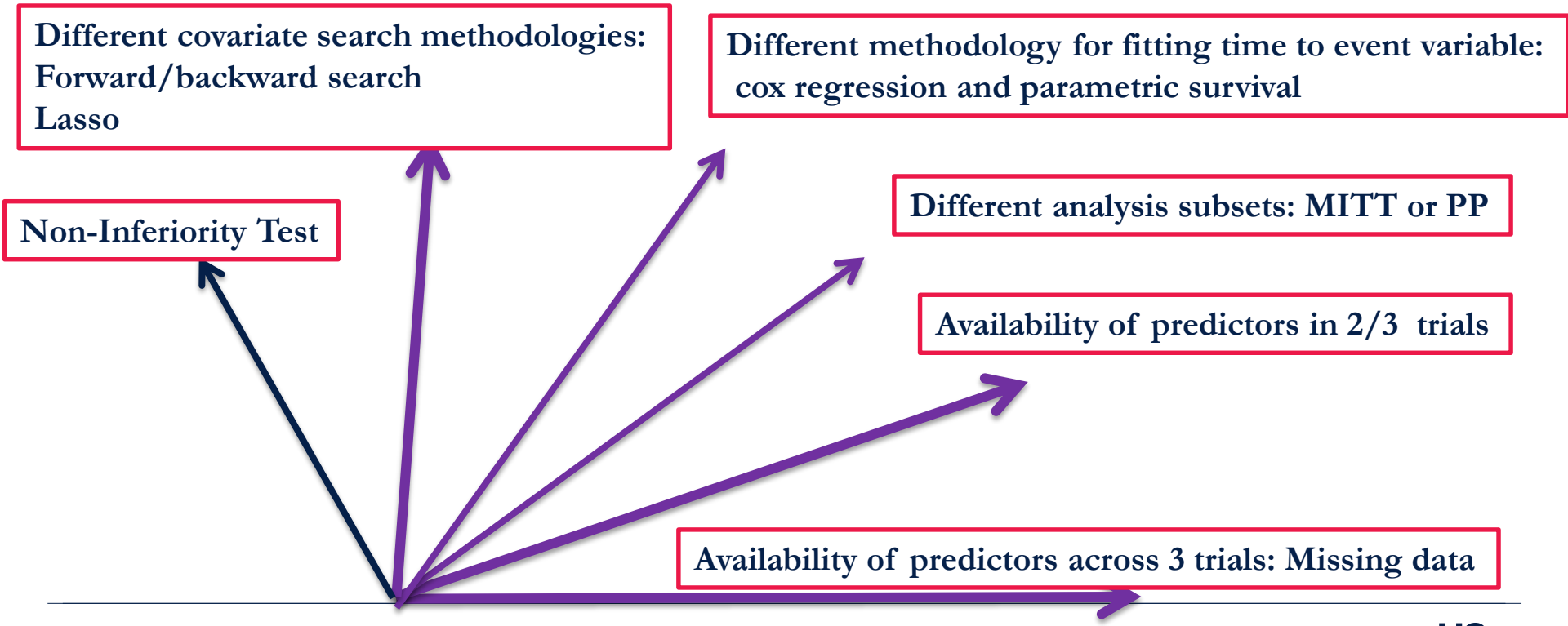
Clinical predictors
No major correlation

Subjects in standard of care

Examples:
- Positive correlation between BMI and weight.
- Negative correlation between CD4 counts and HIV status



Analysis Methodology: Matrix Approach



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RESULTS
6 month HRZE

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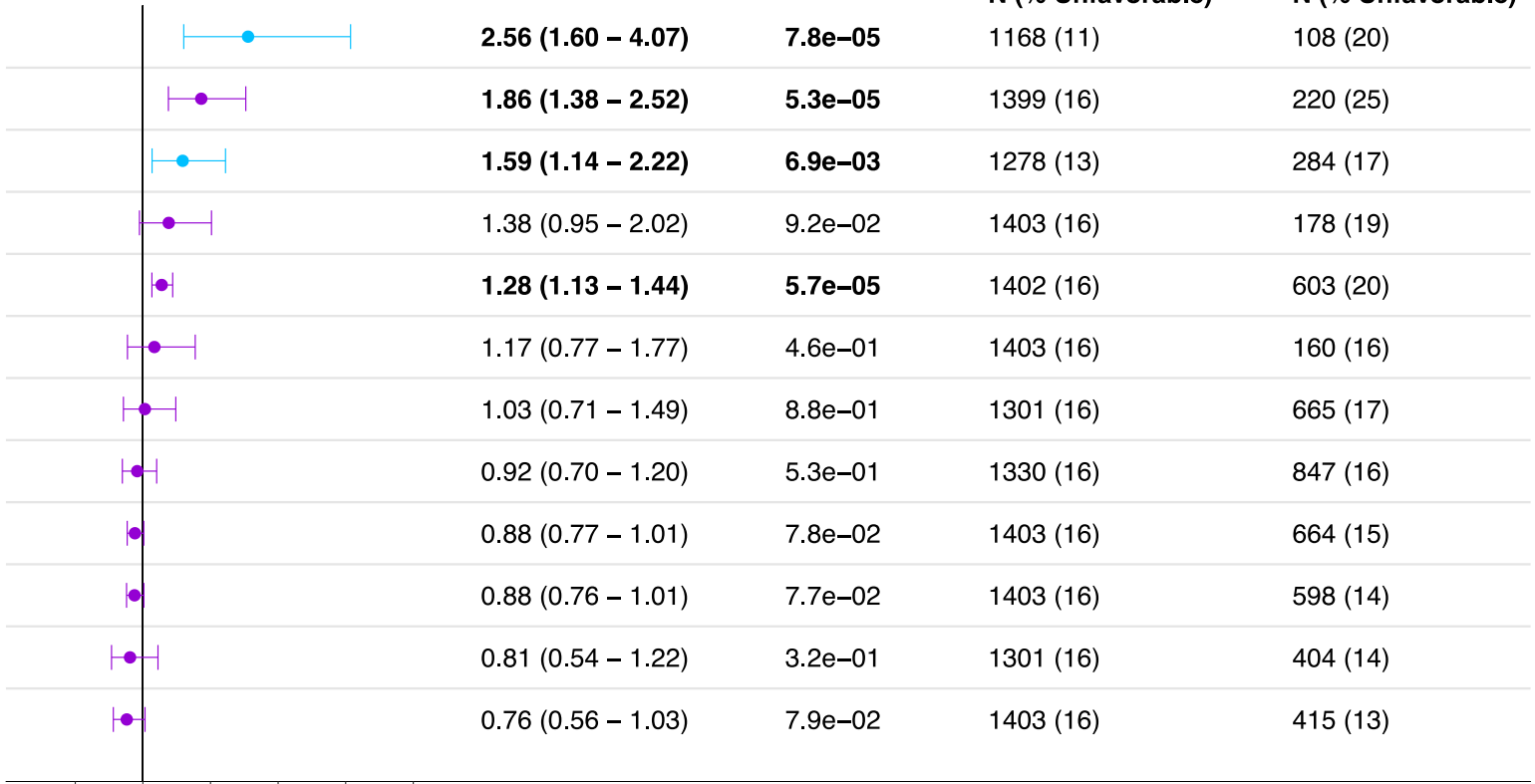
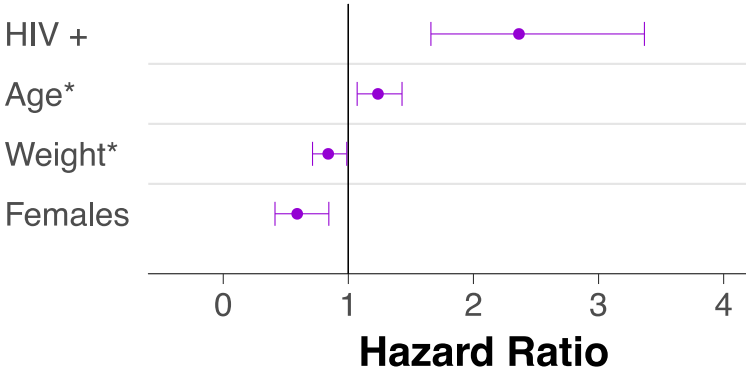
HRZE MITT– univariate analysis (no drug)



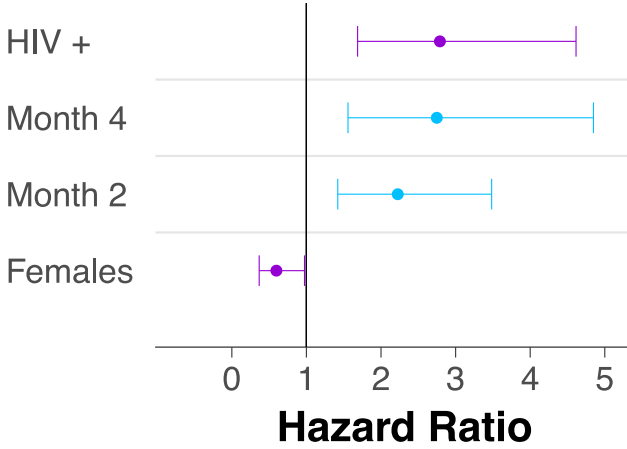
	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 4	**2.56 (1.60 – 4.07)**	**7.8e–05**	1168 (11)	108 (20)
HIV +	**1.86 (1.38 – 2.52)**	**5.3e–05**	1399 (16)	220 (25)
Month 2	**1.59 (1.14 – 2.22)**	**6.9e–03**	1278 (13)	284 (17)
Asian:Black	1.38 (0.95 – 2.02)	9.2e–02	1403 (16)	178 (19)
Age*	**1.28 (1.13 – 1.44)**	**5.7e–05**	1402 (16)	603 (20)
Other:Black	1.17 (0.77 – 1.77)	4.6e–01	1403 (16)	160 (16)
Smear 3+ to 1+	1.03 (0.71 – 1.49)	8.8e–01	1301 (16)	665 (17)
Cavity Present	0.92 (0.70 – 1.20)	5.3e–01	1330 (16)	847 (16)
Weight*	0.88 (0.77 – 1.01)	7.8e–02	1403 (16)	664 (15)
BMI*	0.88 (0.76 – 1.01)	7.7e–02	1403 (16)	598 (14)
Smear 2+ to 1+	0.81 (0.54 – 1.22)	3.2e–01	1301 (16)	404 (14)
Females	0.76 (0.56 – 1.03)	7.9e–02	1403 (16)	415 (13)

HRZE MITT, multivariate analysis, Baseline factors only



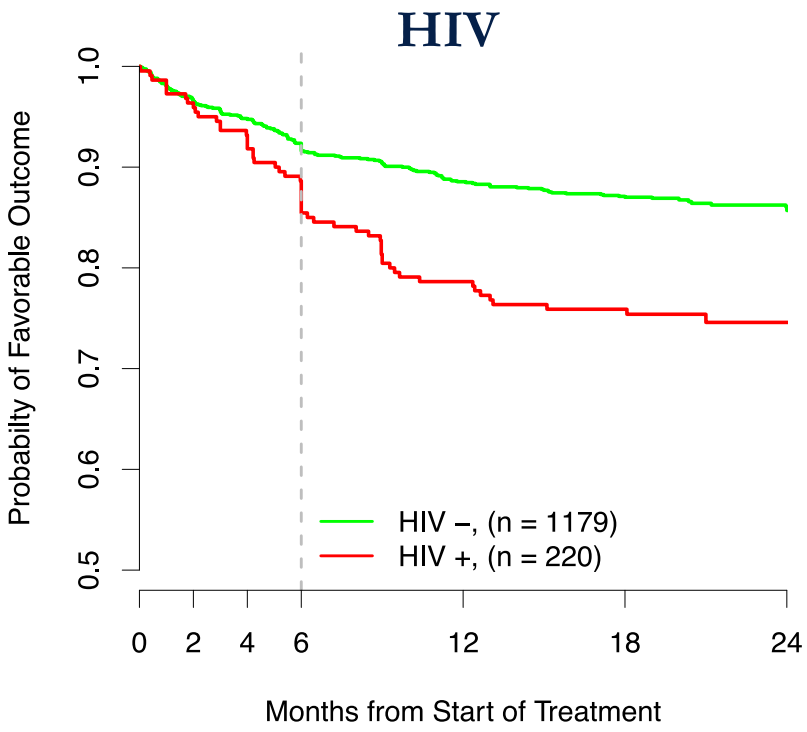
	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
HIV +	**2.36 (1.66 – 3.37)**	**1.9e–06**	1234 (16)	198 (26)
Age*	**1.24 (1.07 – 1.43)**	**4.0e–03**	1234 (16)	527 (20)
Weight*	**0.84 (0.71 – 0.99)**	**3.4e–02**	1234 (16)	588 (15)
Females	**0.59 (0.41 – 0.84)**	**3.8e–03**	1234 (16)	356 (12)

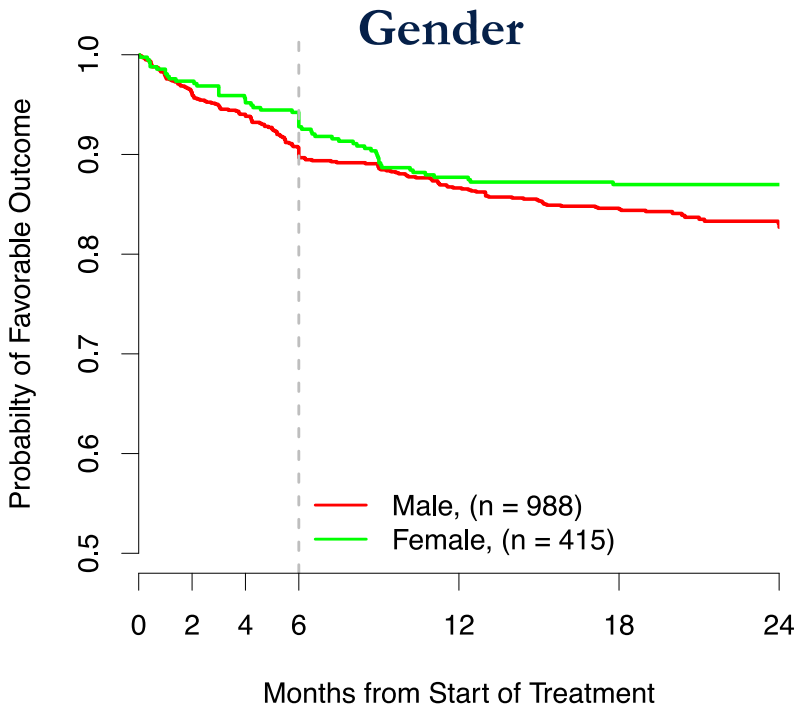
HRZE MITT, multivariate analysis
Baseline and Culture



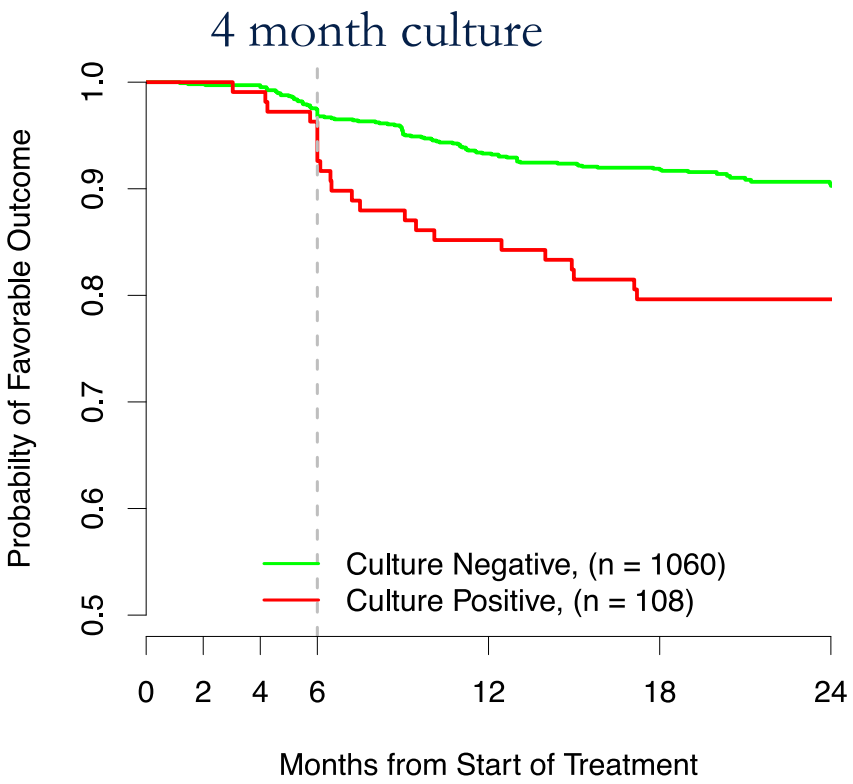
	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
HIV +	**2.79 (1.69 – 4.61)**	**6.5e–05**	977 (11)	156 (17)
Month 4	**2.75 (1.56 – 4.85)**	**4.8e–04**	977 (11)	88 (20)
Month 2	**2.22 (1.42 – 3.48)**	**4.8e–04**	977 (11)	228 (17)
Females	**0.60 (0.37 – 0.97)**	**3.9e–02**	977 (11)	284 (8)

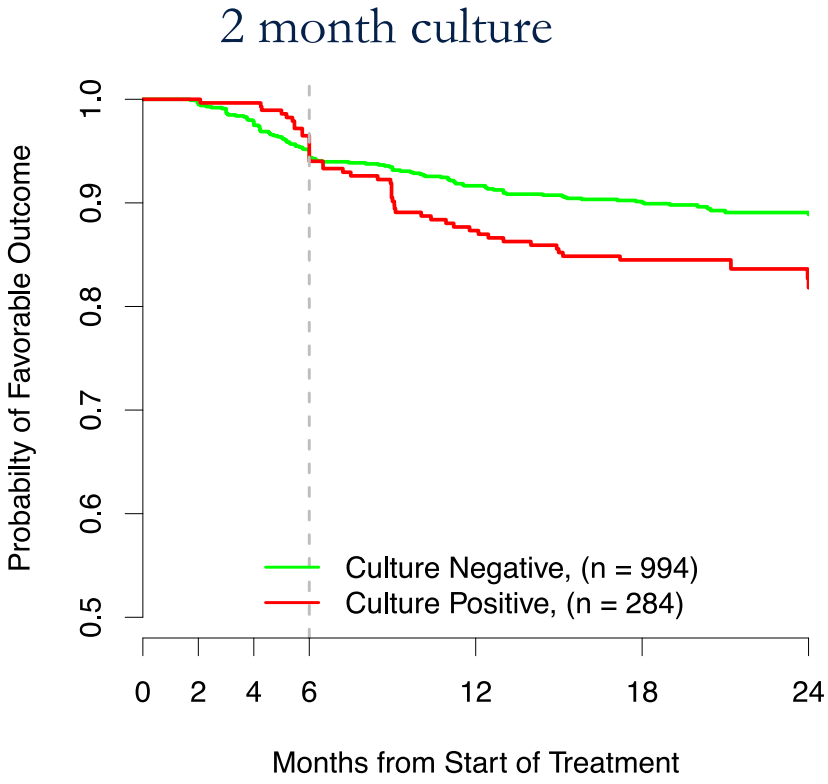
HRZE: Baseline factors





HRZE: On treatment factors





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SOC Analysis of Recurrences (MITT)

Incorporating treatment-related factors

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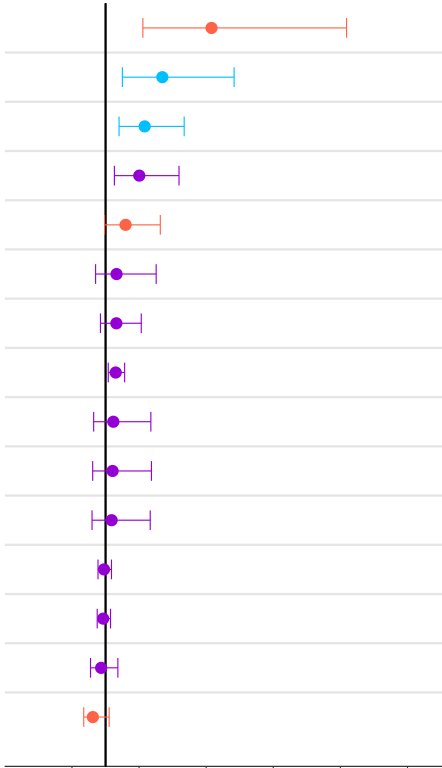
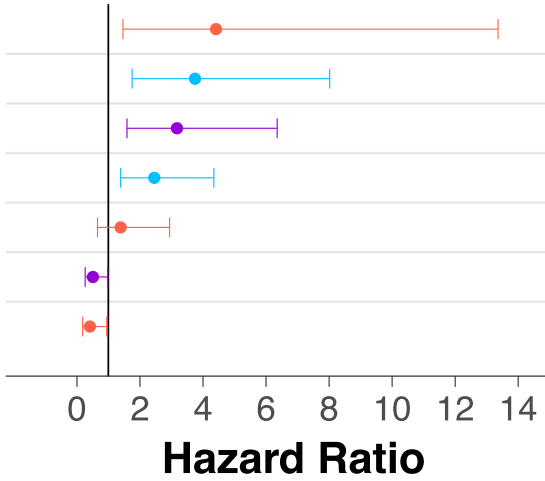
HRZE, recurrence, univariate analysis



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Adherence < 90%	**4.16 (2.11 – 8.19)**	**3.7e–05**	1266 (7)	41 (24)
Month 4	**2.69 (1.50 – 4.83)**	**8.9e–04**	1126 (7)	100 (14)
Month 2	**2.17 (1.40 – 3.34)**	**4.8e–04**	1205 (7)	267 (12)
HIV +	**2.01 (1.26 – 3.19)**	**3.2e–03**	1268 (7)	188 (13)
Adherence 99–90%	1.60 (0.97 – 2.63)	6.6e–02	1266 (7)	247 (9)
Smear 3+ to 1+	1.33 (0.70 – 2.51)	3.8e–01	1179 (7)	598 (8)
Cavity Present	1.32 (0.85 – 2.07)	2.2e–01	1202 (7)	775 (8)
Age*	**1.30 (1.08 – 1.57)**	**5.3e–03**	1270 (7)	537 (11)
Asian:Black	1.23 (0.65 – 2.35)	5.3e–01	1271 (7)	156 (7)
Other:Black	1.21 (0.62 – 2.37)	5.8e–01	1271 (7)	144 (7)
Smear 2+ to 1+	1.18 (0.60 – 2.33)	6.3e–01	1179 (7)	375 (7)
BMI*	0.96 (0.78 – 1.18)	6.7e–01	1271 (7)	550 (6)
Weight*	0.93 (0.75 – 1.15)	5.0e–01	1271 (7)	606 (7)
Females	0.87 (0.55 – 1.37)	5.5e–01	1271 (7)	385 (7)
Treatment Duration*	0.62 (0.35 – 1.11)	1.1e–01	1254 (7)	803 (7)

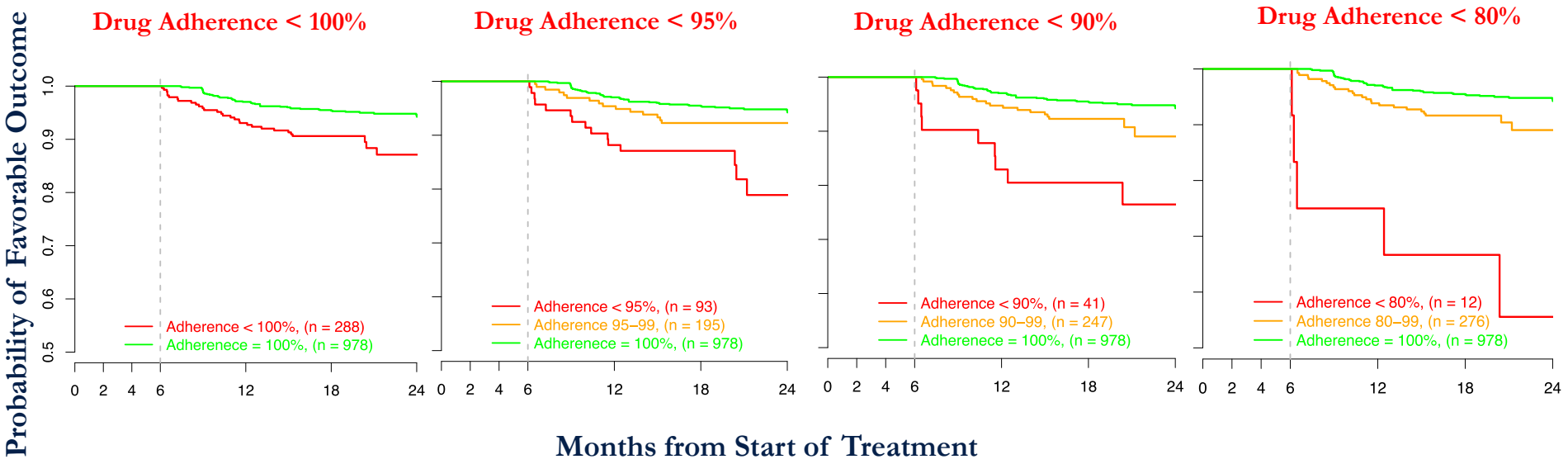
HRZE, recurrence, multi-variate analysis



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Adherence < 90%	**4.41 (1.46 – 13.36)**	**8.6e–03**	929 (7)	26 (23)
Month 4	**3.75 (1.75 – 8.02)**	**6.7e–04**	929 (7)	81 (14)
HIV +	**3.17 (1.59 – 6.35)**	**1.1e–03**	929 (7)	145 (11)
Month 2	**2.45 (1.39 – 4.34)**	**2.1e–03**	929 (7)	213 (11)
Adherence 99–90%	1.38 (0.65 – 2.94)	4.0e–01	929 (7)	158 (6)
Females	**0.51 (0.26 – 0.98)**	**4.3e–02**	929 (7)	273 (5)
Treatment Duration*	**0.41 (0.18 – 0.94)**	**3.6e–02**	929 (7)	575 (6)

On Treatment Culture Drug Baseline

HRZE, impact of adherence on recurrence



HRZE, results summary

- Failures in SOC were mostly associated with insufficient drug levels (adherence)
- **Baseline covariates:**
  - HIV+, older, underweight patients have higher risk of unfavorable outcome
- **Longer duration** of treatment beneficial
- **Culture based predictors**:
  - 4 month + 2 month > 4 month > 2 month
- Strategies to improve outcomes for HRZE
  - Full adherence
  - Longer duration for patients at risk

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RESULTS

4 month regimen

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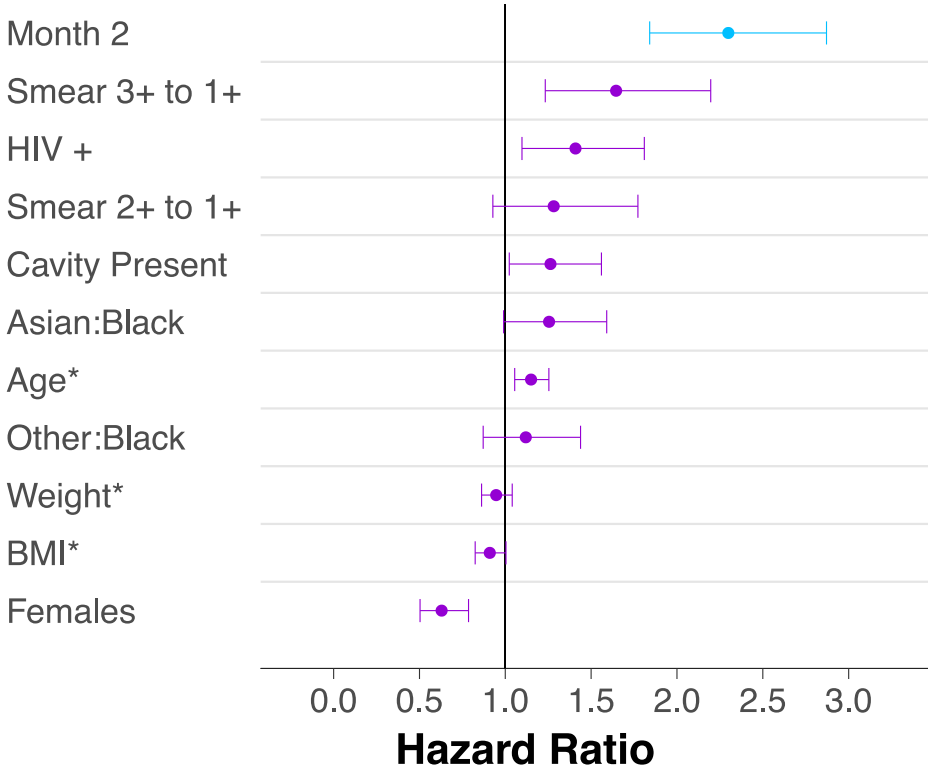
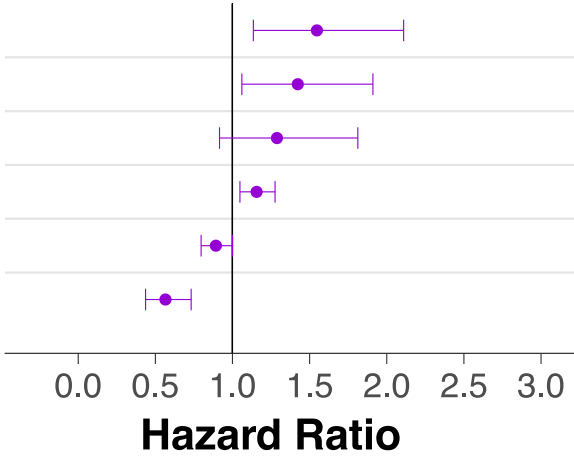
4 - month arms, MITT– univariate analysis (no drug)



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 2	**2.30 (1.84 – 2.87)**	**2.1e–13**	1804 (20)	335 (34)
Smear 3+ to 1+	**1.65 (1.23 – 2.20)**	**7.3e–04**	1819 (23)	988 (26)
HIV +	**1.41 (1.10 – 1.81)**	**7.3e–03**	1992 (23)	248 (29)
Smear 2+ to 1+	1.28 (0.93 – 1.77)	1.3e–01	1819 (23)	501 (21)
Cavity Present	**1.26 (1.02 – 1.56)**	**3.0e–02**	1870 (23)	1246 (24)
Asian:Black	1.25 (0.99 – 1.59)	6.0e–02	1997 (23)	349 (26)
Age*	**1.15 (1.05 – 1.25)**	**1.5e–03**	1993 (23)	797 (27)
Other:Black	1.12 (0.87 – 1.44)	3.8e–01	1997 (23)	326 (24)
Weight*	0.95 (0.86 – 1.04)	2.6e–01	1997 (23)	952 (22)
BMI*	0.91 (0.82 – 1.00)	6.0e–02	1997 (23)	857 (21)
Females	**0.63 (0.50 – 0.79)**	**4.5e–05**	1997 (23)	591 (17)

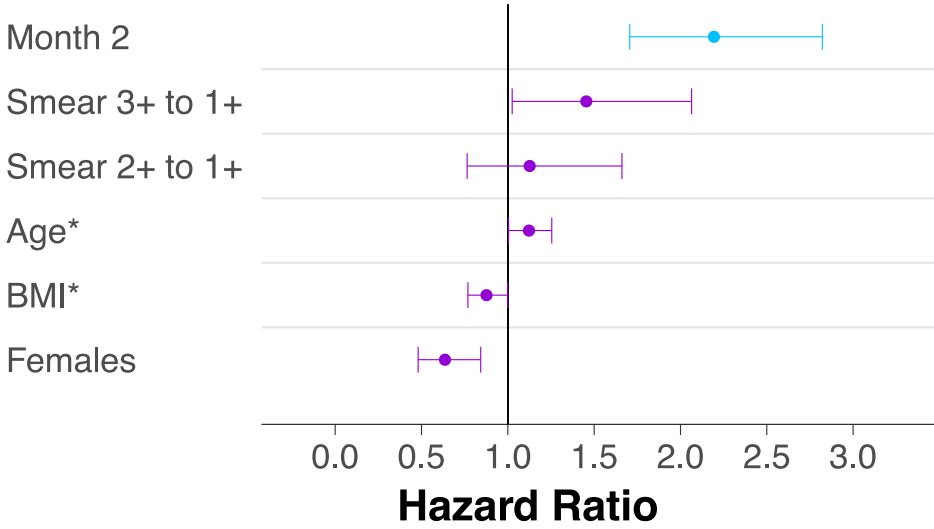
On Treatment Culture — Drug — Baseline

4-month arms, MITT– multi-variate analysis
Baseline



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Smear 3+ to 1+	**1.55 (1.13 – 2.11)**	**5.8e–03**	1698 (23)	919 (25)
HIV +	**1.42 (1.06 – 1.91)**	**1.9e–02**	1698 (23)	213 (27)
Smear 2+ to 1+	1.29 (0.92 – 1.81)	1.5e–01	1698 (23)	479 (21)
Age*	**1.16 (1.05 – 1.28)**	**3.7e–03**	1698 (23)	677 (27)
Weight*	0.89 (0.80 – 1.00)	5.0e–02	1698 (23)	825 (23)
Females	**0.57 (0.44 – 0.73)**	**1.5e–05**	1698 (23)	497 (16)

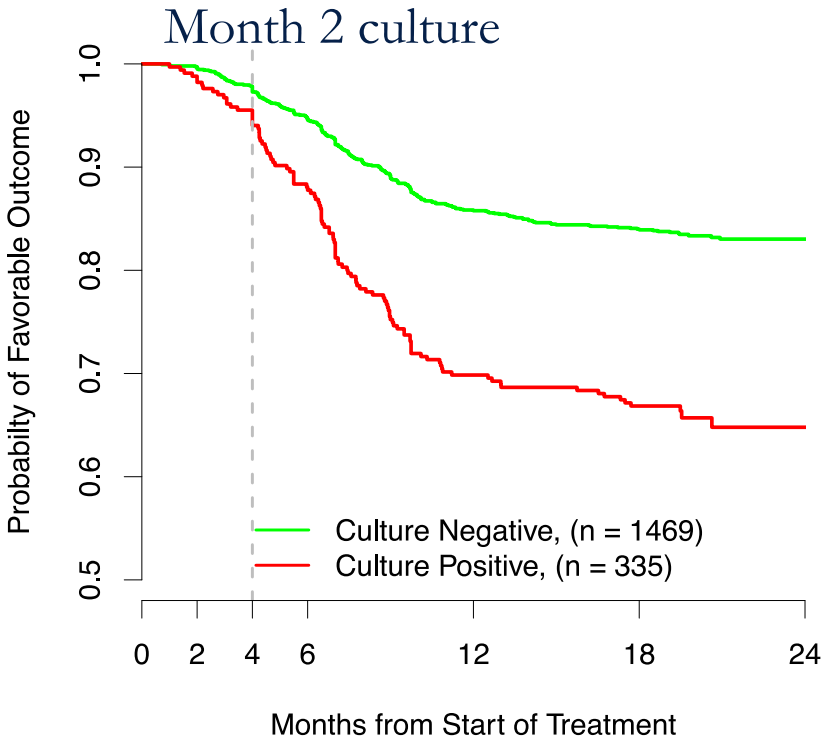
4-month arms, MITT– multi-variate analysis
Baseline and on treatment predictors

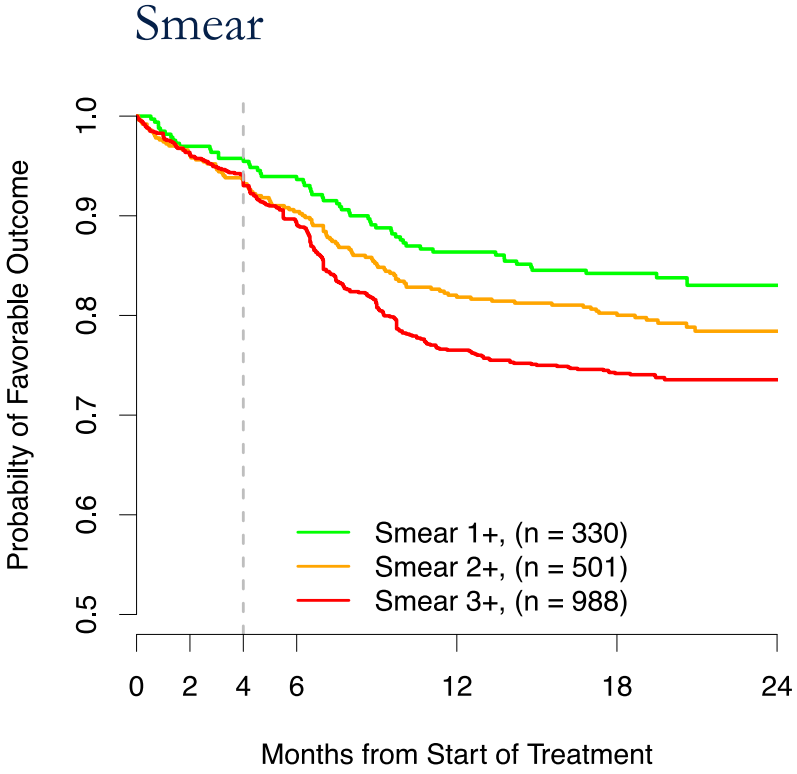


	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 2	**2.19 (1.71 – 2.82)**	**9.2e–10**	1552 (20)	297 (35)
Smear 3+ to 1+	**1.45 (1.03 – 2.06)**	**3.6e–02**	1552 (20)	850 (23)
Smear 2+ to 1+	1.13 (0.76 – 1.66)	5.5e–01	1552 (20)	436 (18)
Age*	**1.12 (1.00 – 1.25)**	**4.1e–02**	1552 (20)	619 (24)
BMI*	**0.88 (0.77 – 1.00)**	**4.9e–02**	1552 (20)	670 (18)
Females	**0.64 (0.48 – 0.84)**	**1.6e–03**	1552 (20)	449 (14)

On Treatment Culture — Drug — Baseline

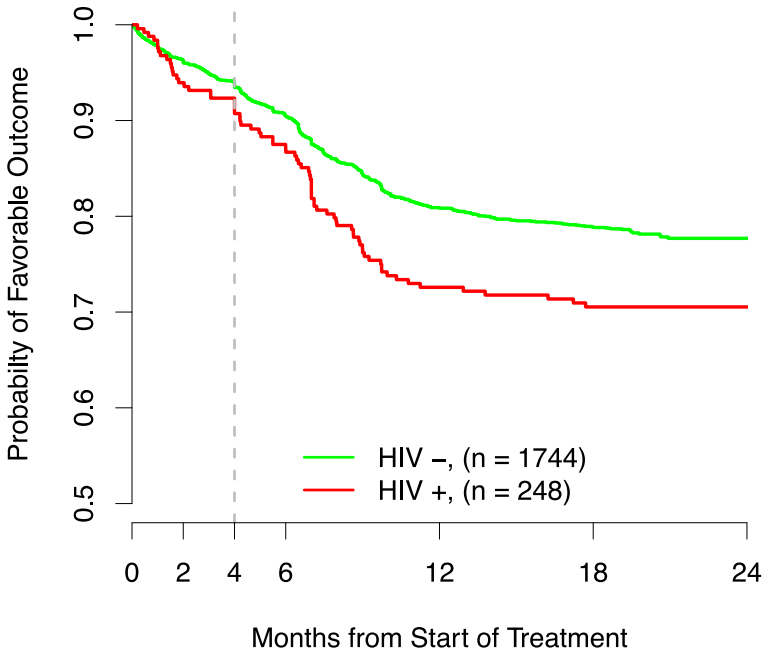
4-month: Smear and Culture



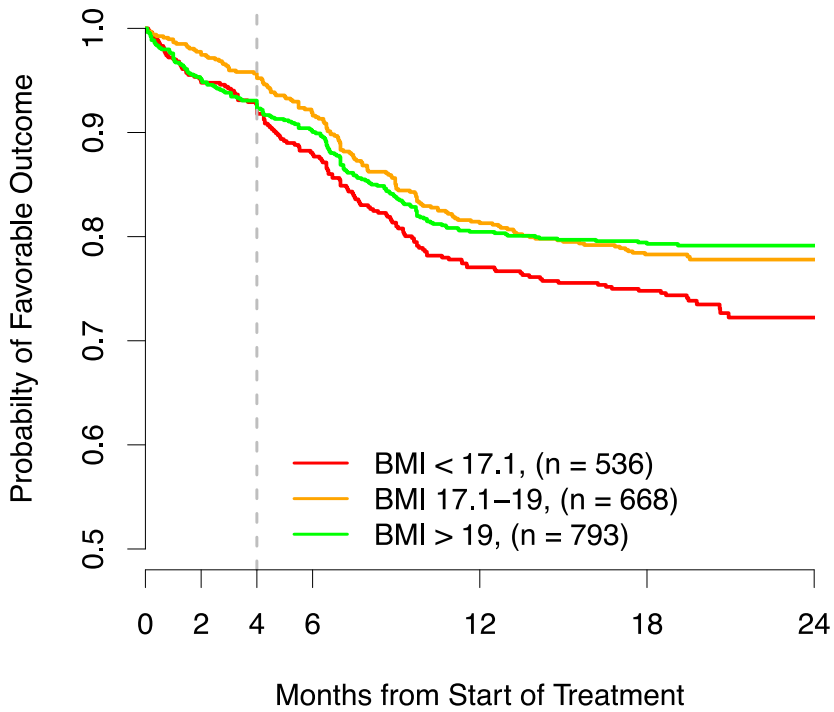


4-month: Baseline factors

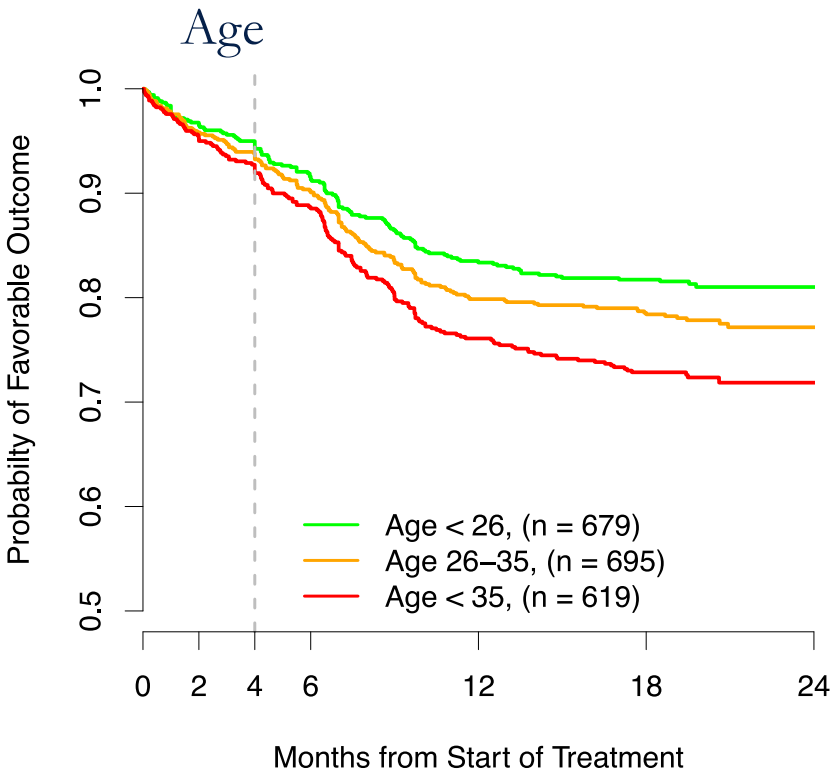
HIV

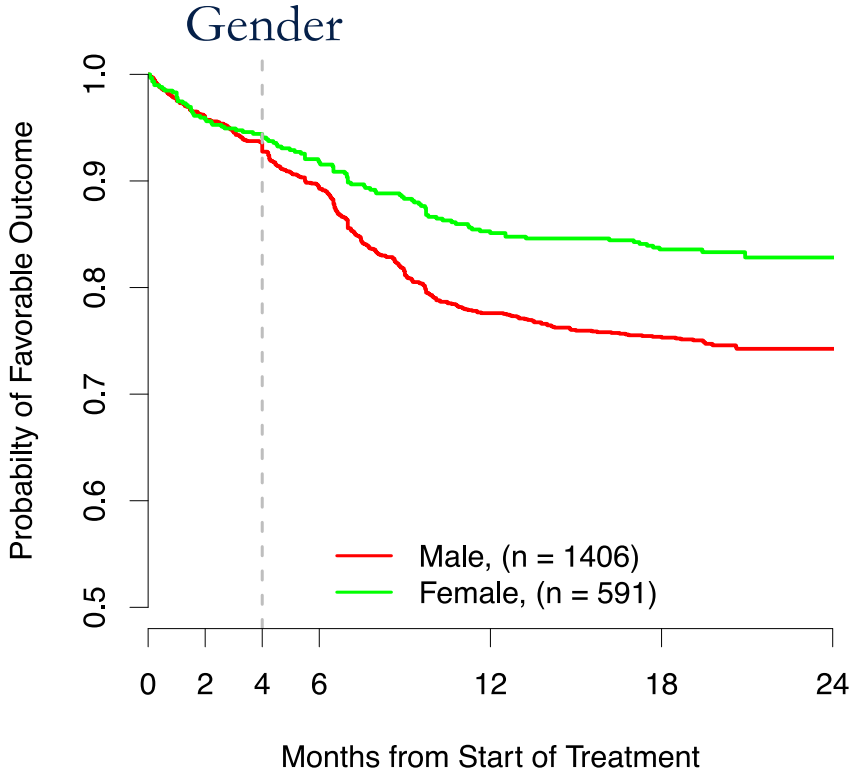


BMI



4-month: Baseline factors





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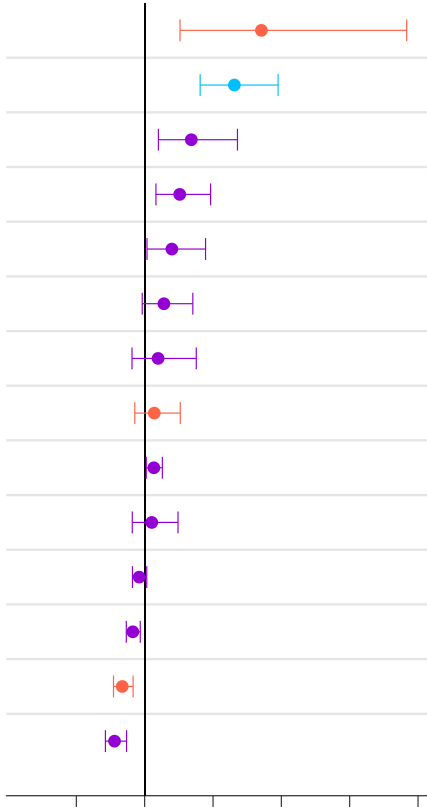
4-month regimens, Analysis of Recurrences (MITT)

Incorporating treatment-related factors

3/29/2017

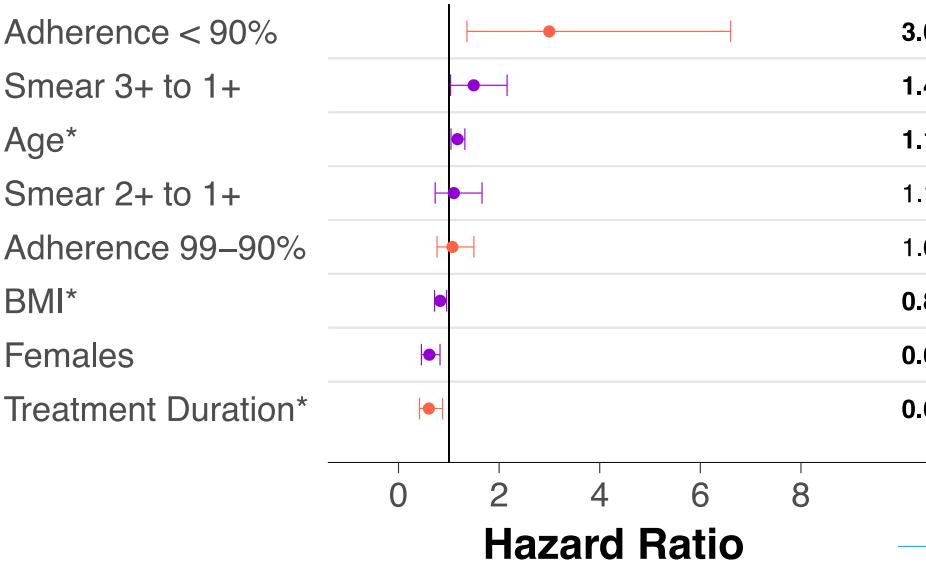
4 - month arms, MITT– univariate analysis



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Adherence < 90%	**2.71 (1.52 – 4.83)**	**7.5e–04**	1859 (17)	32 (38)
Month 2	**2.31 (1.81 – 2.95)**	**1.6e–11**	1744 (17)	315 (30)
Smear 3+ to 1+	**1.68 (1.20 – 2.36)**	**2.5e–03**	1701 (18)	919 (21)
Cavity Present	**1.51 (1.17 – 1.96)**	**1.9e–03**	1745 (17)	1167 (19)
HIV +	**1.40 (1.03 – 1.89)**	**2.9e–02**	1855 (17)	225 (22)
Other:Black	1.28 (0.96 – 1.70)	8.8e–02	1860 (17)	310 (20)
Smear 2+ to 1+	1.20 (0.82 – 1.76)	3.6e–01	1701 (18)	467 (15)
Adherence 99–90%	1.14 (0.86 – 1.52)	3.7e–01	1859 (17)	313 (18)
Age*	**1.13 (1.02 – 1.26)**	**1.7e–02**	1857 (17)	732 (20)
Asian:Black	1.10 (0.82 – 1.49)	5.2e–01	1860 (17)	314 (18)
Weight*	0.92 (0.82 – 1.03)	1.5e–01	1860 (17)	883 (16)
BMI*	**0.83 (0.73 – 0.94)**	**2.5e–03**	1860 (17)	793 (15)
Treatment Duration*	**0.67 (0.54 – 0.83)**	**2.3e–04**	1851 (17)	1395 (17)
Females	**0.56 (0.42 – 0.73)**	**3.1e–05**	1860 (17)	556 (12)

On Treatment Culture Drug Baseline

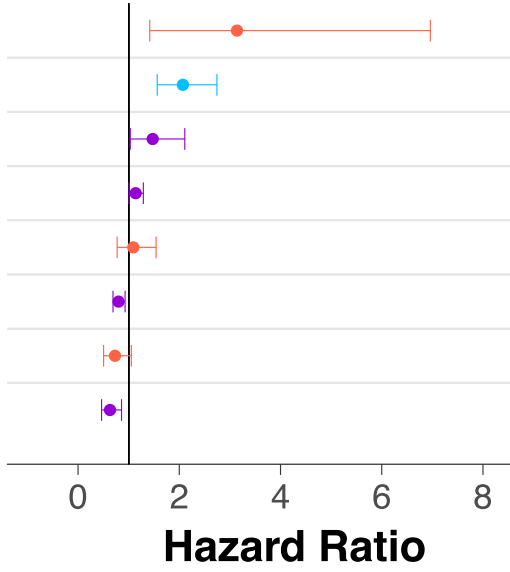
4-month arms, MITT: Multi-variate analysis (baseline and drug)



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Adherence < 90%	**3.00 (1.36 – 6.60)**	**6.5e–03**	1582 (17)	25 (36)
Smear 3+ to 1+	**1.49 (1.04 – 2.16)**	**3.2e–02**	1582 (17)	855 (20)
Age*	**1.17 (1.04 – 1.32)**	**7.9e–03**	1582 (17)	623 (21)
Smear 2+ to 1+	1.10 (0.73 – 1.66)	6.5e–01	1582 (17)	442 (15)
Adherence 99–90%	1.07 (0.77 – 1.50)	6.9e–01	1582 (17)	264 (17)
BMI*	**0.83 (0.72 – 0.96)**	**1.1e–02**	1582 (17)	676 (15)
Females	**0.61 (0.45 – 0.83)**	**1.3e–03**	1582 (17)	473 (12)
Treatment Duration*	**0.60 (0.42 – 0.88)**	**7.9e–03**	1582 (17)	1136 (18)

On Treatment Culture — Drug — Baseline

4-month arms, MITT: Multi-variate analysis (baseline, culture and drug)

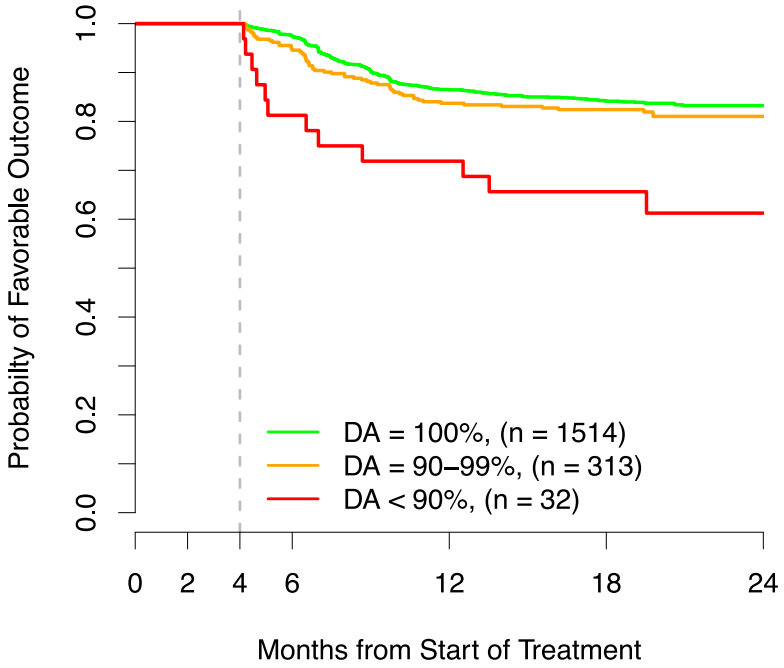


	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Adherence < 90%	**3.14 (1.42 – 6.96)**	**4.8e–03**	1493 (17)	23 (39)
Month 2	**2.07 (1.56 – 2.74)**	**3.7e–07**	1493 (17)	277 (30)
HIV +	**1.48 (1.03 – 2.11)**	**3.3e–02**	1493 (17)	187 (21)
Age*	**1.14 (1.01 – 1.29)**	**3.9e–02**	1493 (17)	592 (21)
Adherence 99–90%	1.09 (0.77 – 1.54)	6.2e–01	1493 (17)	249 (18)
BMI*	**0.80 (0.69 – 0.93)**	**3.5e–03**	1493 (17)	644 (15)
Treatment Duration*	0.73 (0.51 – 1.05)	9.3e–02	1493 (17)	1061 (18)
Females	**0.63 (0.46 – 0.86)**	**3.5e–03**	1493 (17)	440 (12)

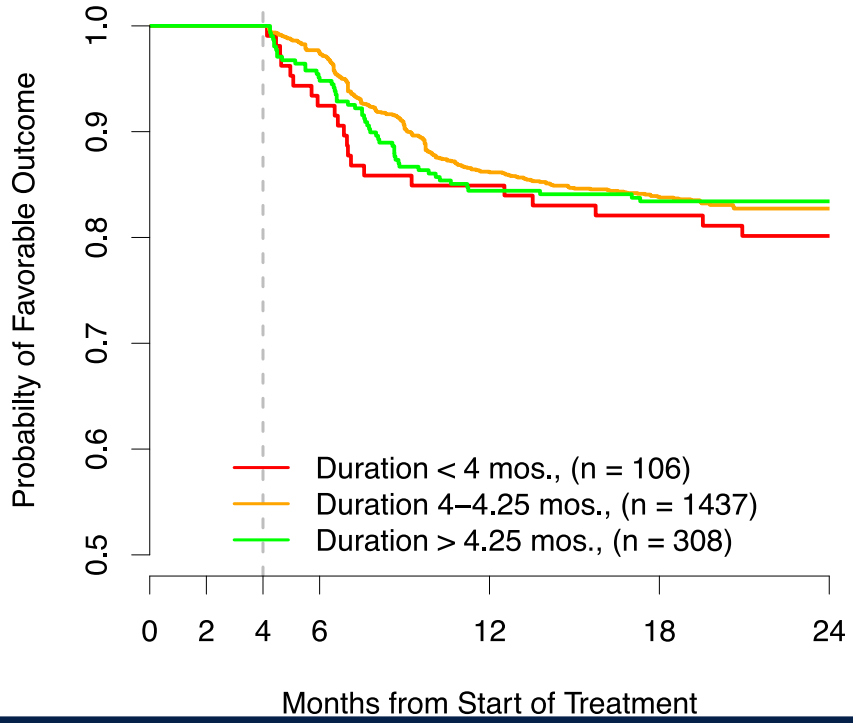
On Treatment Culture Drug Baseline

Survival Plots for multivariate predictors: Drug

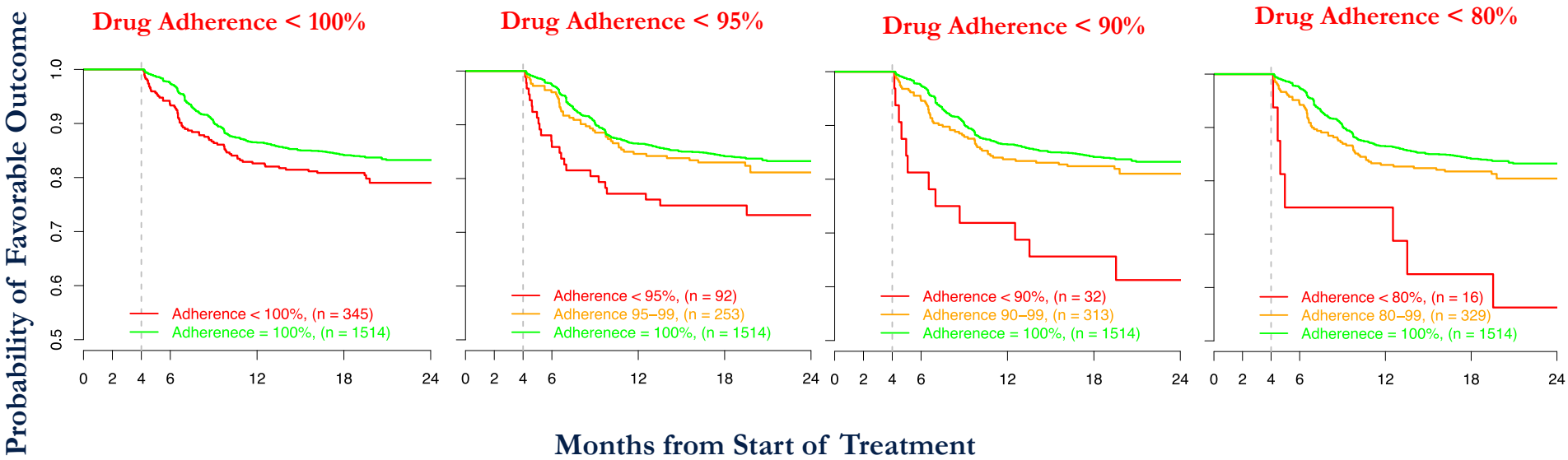
Drug Adherence



Treatment Duration



4-month, impact of adherence on recurrence



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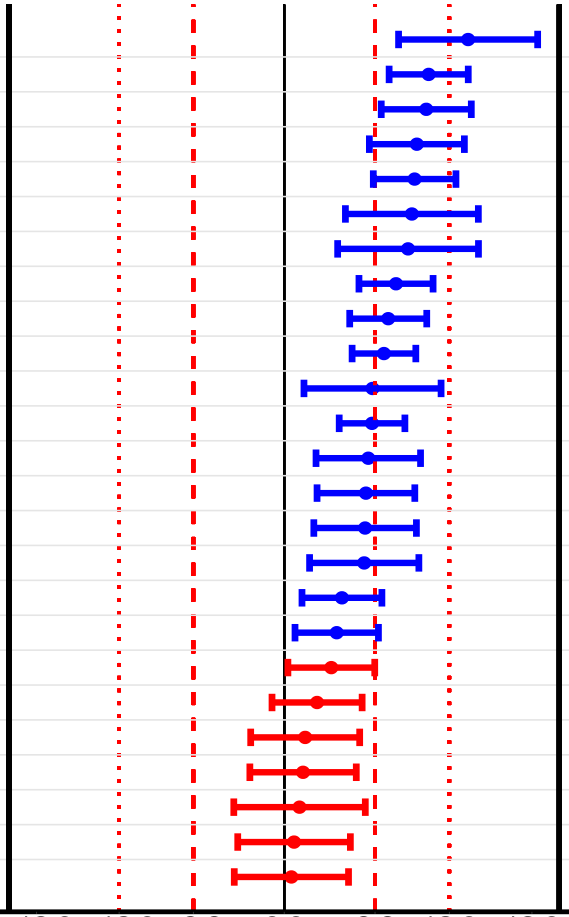
Results:
Non-Inferiority Test

3/29/2017

(4 month / full HRZE)

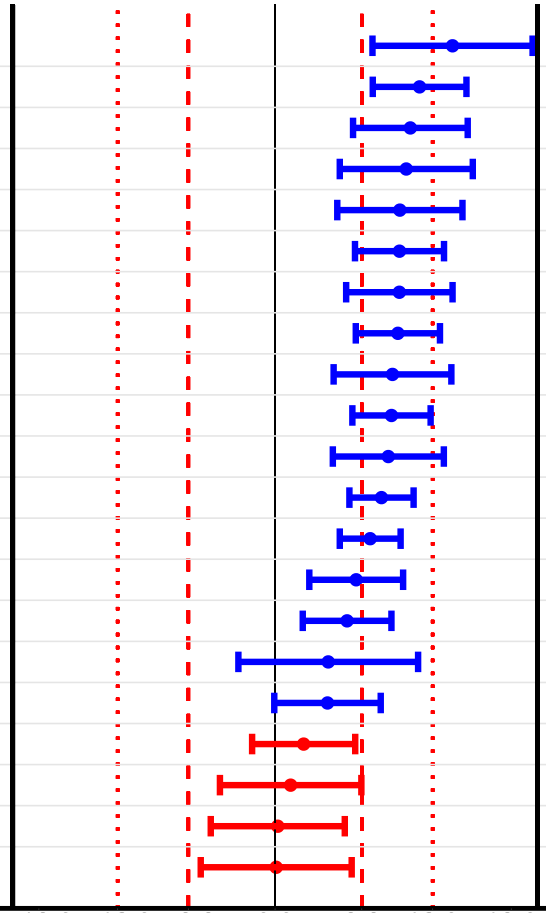
Favors shorter ← → Favors longer



			No. Patients		% Unfavorable		
			CTRL	TEST	CTRL	TEST	% Point Diff (90% CI)
all	all	HIV +	1400	248	16.1	29.5	13.4 (8.3, 18.4)
Smear 3+	all	all	1387	988	16	26.4	10.5 (7.6, 13.4)
Smear 3+	Cavity +	all	1315	708	16.2	26.5	10.3 (7.1, 13.6)
Smear 3+	Cavity +	HIV −	1311	608	16.1	25.8	9.6 (6.2, 13.1)
Smear 3+	all	HIV −	1383	852	15.9	25.4	9.5 (6.5, 12.5)
Smear 2+	Cavity +	all	1315	282	16.2	25.4	9.3 (4.4, 14.1)
Smear 2+	Cavity +	HIV −	1311	255	16.1	25.1	9 (3.9, 14.1)
all	Cavity +	all	1331	1247	16.4	24.5	8.1 (5.4, 10.8)
all	Cavity +	HIV −	1327	1095	16.3	23.9	7.6 (4.8, 10.4)
all	all	all	1404	2001	16.1	23.4	7.2 (4.9, 9.6)
Smear 3+	Cavity −	all	1315	217	16.2	22.6	6.4 (1.4, 11.4)
all	all	HIV −	1400	1748	16.1	22.5	6.4 (4, 8.8)
Smear 1+ or 2+	Cavity +	all	1315	451	16.2	22.3	6.1 (2.3, 9.9)
Smear 2+	all	all	1387	503	16	21.9	5.9 (2.4, 9.5)
Smear 2+	all	HIV −	1383	451	15.9	21.8	5.9 (2.1, 9.6)
Smear 1+ or 2+	Cavity +	HIV −	1311	408	16.1	22	5.8 (1.8, 9.8)
Smear 1+ or 2+	all	all	1387	835	16	20.1	4.2 (1.3, 7.1)
Smear 1+ or 2+	all	HIV −	1383	736	15.9	19.7	3.8 (0.8, 6.8)
all	Cavity −	all	1331	627	16.4	19.8	3.4 (0.3, 6.6)
all	Cavity −	HIV −	1327	545	16.3	18.7	2.4 (−0.9, 5.7)
Smear 1+	all	all	1387	332	16	17.5	1.5 (−2.4, 5.5)
Smear 1+ or 2+	Cavity −	all	1315	335	16.2	17.5	1.4 (−2.5, 5.2)
Smear 2+	Cavity −	all	1315	200	16.2	17.3	1.1 (−3.7, 5.9)
Smear 1+ or 2+	Cavity −	HIV −	1311	283	16.1	16.9	0.7 (−3.4, 4.8)
Smear 1+	all	HIV −	1383	285	15.9	16.4	0.5 (−3.6, 4.7)

(4 month/subgroup HRZE)

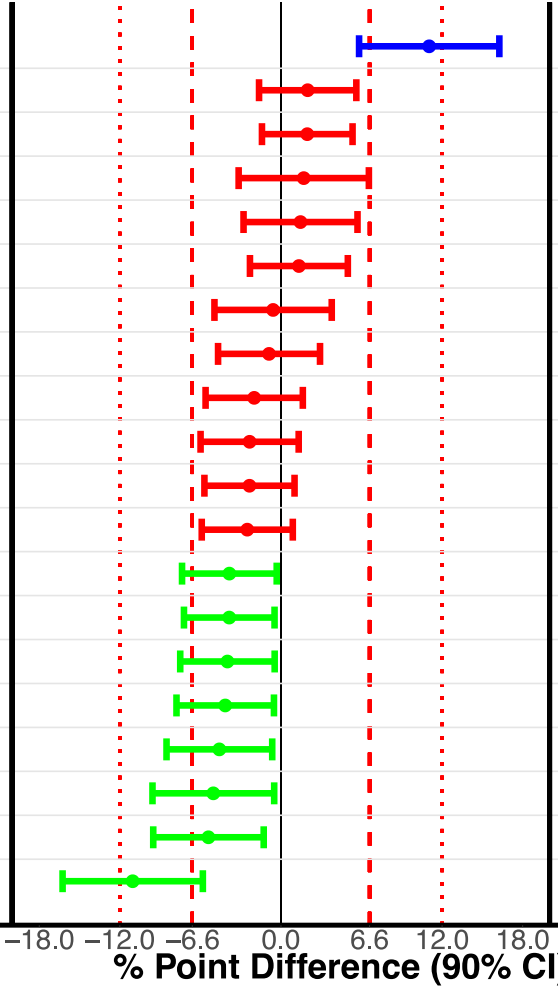
Favors shorter ← → Favors longer



			No. Patients		% Unfavorable		
			CTRL	TEST	CTRL	TEST	% Point Diff (90% CI)
Smear 2+	Cavity +	all	203	282	11.9	25.4	13.5 (7.4, 19.6)
Smear 3+	all	HIV −	544	852	14.4	25.4	11 (7.4, 14.6)
Smear 3+	Cavity +	HIV −	371	608	15.5	25.8	10.3 (5.9, 14.7)
Smear 1+ or 2+	Cavity +	HIV −	283	408	12	22	10 (4.9, 15.1)
Smear 1+ or 2+	Cavity +	all	328	451	12.8	22.3	9.5 (4.7, 14.3)
Smear 3+	all	all	666	988	17	26.4	9.5 (6.1, 12.9)
Smear 3+	Cavity +	all	453	708	17	26.5	9.5 (5.4, 13.5)
all	Cavity +	HIV −	715	1095	14.5	23.9	9.4 (6.2, 12.6)
Smear 2+	all	HIV −	354	451	12.9	21.8	8.9 (4.5, 13.4)
all	Cavity +	all	847	1247	15.6	24.5	8.9 (5.9, 11.9)
Smear 2+	all	all	404	503	13.3	21.9	8.6 (4.4, 12.9)
all	all	HIV −	1180	1748	14.4	22.5	8.1 (5.7, 10.6)
all	all	all	1404	2001	16.1	23.4	7.2 (4.9, 9.6)
Smear 1+ or 2+	all	HIV −	546	736	13.6	19.7	6.2 (2.6, 9.8)
Smear 1+ or 2+	all	all	636	835	14.7	20.1	5.5 (2.1, 8.9)
all	all	HIV +	220	248	25.4	29.5	4.1 (−2.8, 10.9)
all	Cavity −	HIV −	404	545	14.7	18.7	4 (−0.1, 8.1)
all	Cavity −	all	484	627	17.6	19.8	2.2 (−1.8, 6.1)
Smear 1+ or 2+	Cavity −	HIV −	241	283	15.7	16.9	1.2 (−4.2, 6.6)
Smear 1+ or 2+	Cavity −	all	282	335	17.3	17.5	0.2 (−4.9, 5.3)
Smear 1+	all	all	232	332	17.4	17.5	0.1 (−5.7, 5.8)

(subgroup HRZE/HRZE)

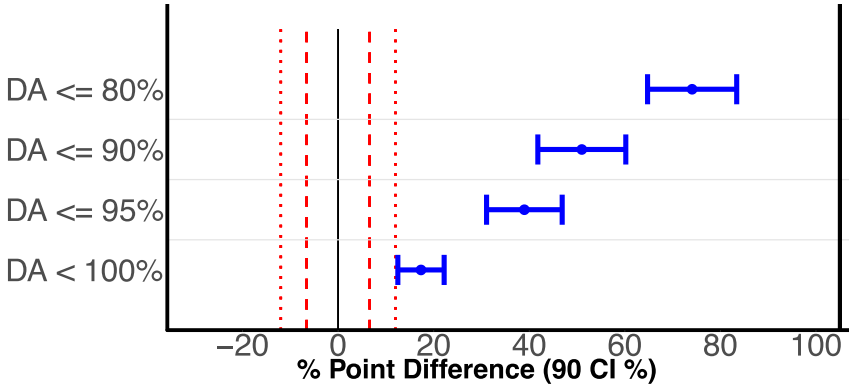
Favors shorter ← → Favors longer



			No. Patients		% Unfavorable		
			CTRL	TEST	CTRL	TEST	% Point Diff (90% CI)
all	all	HIV +	1180	220	14.4	25.4	11 (5.8, 16.3)
all	Cavity –	all	847	484	15.6	17.6	2 (–1.6, 5.6)
Smear 3+	all	all	721	666	15	17	2 (–1.4, 5.3)
Smear 1+	all	all	1155	232	15.7	17.4	1.7 (–3.2, 6.5)
Smear 1+ or 2+	Cavity –	all	1033	282	15.9	17.3	1.5 (–2.8, 5.7)
Smear 3+	Cavity +	all	862	453	15.7	17	1.3 (–2.3, 5)
Smear 1+ or 2+	Cavity –	HIV –	1070	241	16.3	15.7	–0.6 (–5, 3.8)
Smear 3+	Cavity +	HIV –	940	371	16.4	15.5	–0.9 (–4.7, 2.9)
all	Cavity +	all	484	847	17.6	15.6	–2 (–5.6, 1.6)
all	Cavity –	HIV –	923	404	17.1	14.7	–2.3 (–6, 1.3)
Smear 1+ or 2+	all	all	751	636	17	14.7	–2.3 (–5.7, 1)
Smear 3+	all	HIV –	839	544	16.9	14.4	–2.5 (–5.9, 0.9)
Smear 2+	all	all	983	404	17.1	13.3	–3.8 (–7.4, –0.3)
Smear 1+ or 2+	all	HIV –	837	546	17.4	13.6	–3.9 (–7.2, –0.5)
all	Cavity +	HIV –	612	715	18.5	14.5	–4 (–7.5, –0.5)
Smear 2+	all	HIV –	1029	354	17	12.9	–4.1 (–7.8, –0.5)
Smear 1+ or 2+	Cavity +	all	987	328	17.4	12.8	–4.6 (–8.5, –0.7)
Smear 2+	Cavity +	all	1112	203	17	11.9	–5 (–9.6, –0.5)
Smear 1+ or 2+	Cavity +	HIV –	1028	283	17.4	12	–5.4 (–9.5, –1.3)
all	all	HIV –	220	1180	25.4	14.4	–11 (–16.3, –5.8)

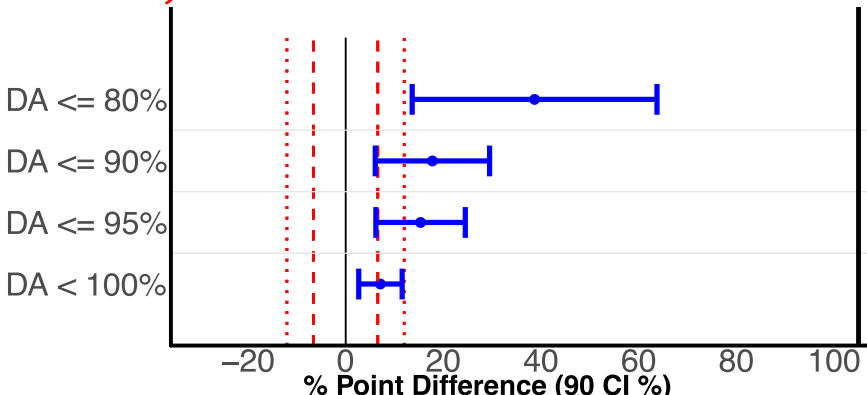
HRZE Non-inferiority test: Adherence as a stratifying factor

HRZE, MITT



	No. Patients		% Unfavorable		
	DA = 100%	Test Group	DA = 100%	Test Group	% Point Diff (90% CI)
DA <= 80%	1033	44	10.8	84.8	74.1 (64.8, 83.4)
DA <= 90%	1033	82	10.8	61.8	51 (41.8, 60.2)
DA <= 95%	1033	146	10.8	49.7	39 (31.1, 46.9)
DA < 100%	1033	349	10.8	28.1	17.3 (12.5, 22.2)

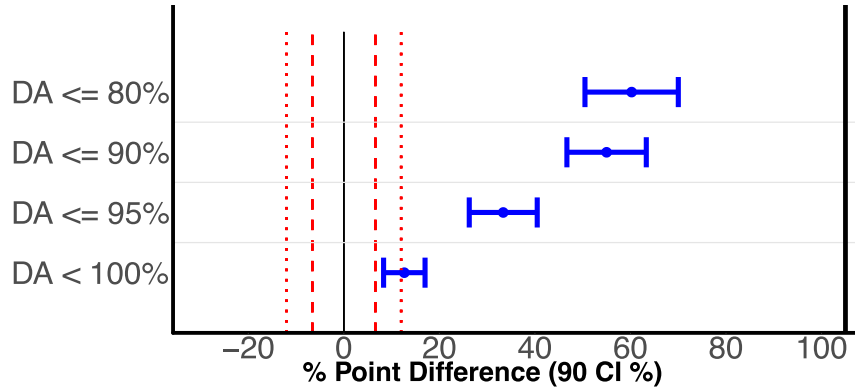
HRZE, MITT recurrence



	No. Patients		% Unfavorable		
	DA = 100%	Test Group	DA = 100%	Test Group	% Point Diff (90% CI)
DA <= 80%	978	12	5.8	44.4	38.7 (13.6, 63.8)
DA <= 90%	978	41	5.8	23.5	17.8 (6.1, 29.5)
DA <= 95%	978	93	5.8	21.1	15.4 (6.2, 24.5)
DA < 100%	978	288	5.8	12.9	7.1 (2.7, 11.6)

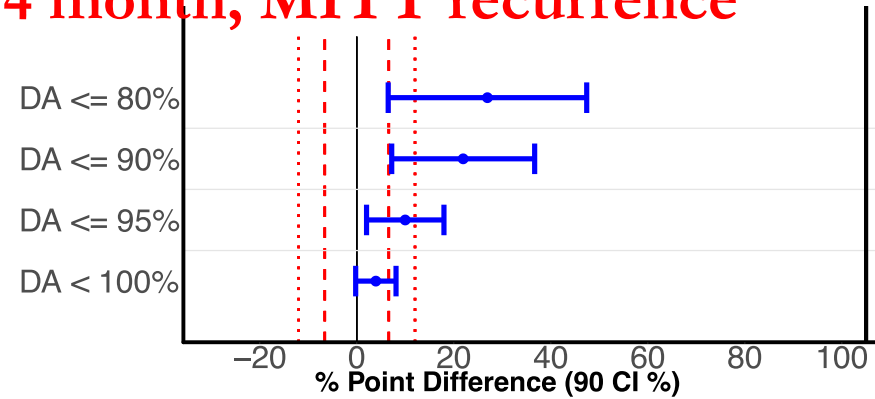
4 month non-inferiority test: Adherence as a stratifying factor

4 month, MITT



	No. Patients		% Unfavorable		
	DA = 100%	Test Group	DA = 100%	Test Group	% Point Diff (90% CI)
DA <= 80%	1579	46	20.2	80.4	60.2 (50.5, 70)
DA <= 90%	1579	79	20.2	75.2	55 (46.7, 63.3)
DA <= 95%	1579	145	20.2	53.6	33.4 (26.3, 40.5)
DA < 100%	1579	406	20.2	32.8	12.7 (8.3, 17)

4 month, MITT recurrence



	No. Patients		% Unfavorable		
	DA = 100%	Test Group	DA = 100%	Test Group	% Point Diff (90% CI)
DA <= 80%	1515	16	16.8	43.8	26.9 (6.5, 47.4)
DA <= 90%	1515	32	16.8	38.8	21.9 (7.2, 36.7)
DA <= 95%	1515	92	16.8	26.8	10 (2, 18)
DA < 100%	1515	344	16.8	20.7	3.9 (–0.2, 8.1)

Stratifying Patient Population: Total Patient Numbers

		HIV+		HIV-	
CAVITY -	Smear 1+	1.7 %	n=50	6.1 %	n=180
	Smear 2+	1.4 %	n= 42	11.7 %	n=344
	Smear 3+	1.9 %	n= 56	11.4 %	n=336
CAVITY +	Smear 1+	1.1 %	n= 31	8.9 %	n=263
	Smear 2+	1.9 %	n= 55	14.5 %	n= 428
	Smear 3+	6.1 %	n= 178	33.3 %	n= 979

Stratifying Patient Population: Total Patient Numbers

		HIV+		HIV-	
CAVITY -	Smear 1+	1.7 %	4 months	6.1 %	4 months
	Smear 2+	1.4 %	?	11.7 %	4 months
	Smear 3+	1.9 %	?	11.4 %	4 months
CAVITY +	Smear 1+	1.1 %	4 months	8.9 %	4 months
	Smear 2+	1.9 %		14.5 %	
	Smear 3+	6.1 %		33.3 %	

Cumulative: 40.9 % "Easy to treat"

Stratifying Patient Population: Total Patient Numbers

		HIV+		HIV-	
CAVITY -	Smear 1+	1.7 %	4 months	6.1 %	4 months
	Smear 2+	1.4 %	?	11.7 %	4 months
	Smear 3+	1.9 %		11.4 %	4 months
CAVITY +	Smear 1+	1.1 %	4 months	8.9 %	4 months
	Smear 2+	1.9 %		14.5 %	
	Smear 3+	6.1 %	6 months	33.3 %	6 months

Cumulative: 39.4% Hard to Treat

Stratifying Patient Population: Total Patient Numbers

		HIV+		HIV-	
CAVITY -	Smear 1+	1.7 %	4 months	6.1 %	4 months
	Smear 2+	1.4 %	?	11.7 %	4 months
	Smear 3+	1.9 %	?	11.4 %	4 months
CAVITY +	Smear 1+	1.1 %	4 months	8.9 %	4 months
	Smear 2+	1.9 %	?	14.5 %	?
	Smear 3+	6.1 %	6 months	33.3 %	6 months

Middle ground: 19.7%

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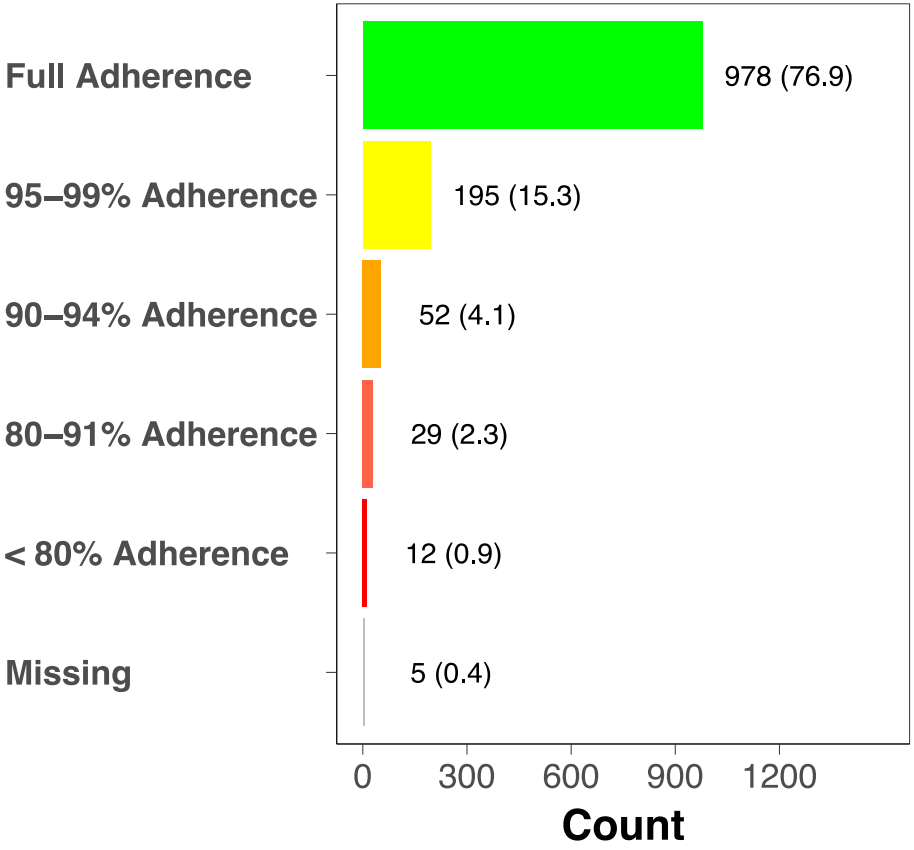
Results:
Merging entire data-base

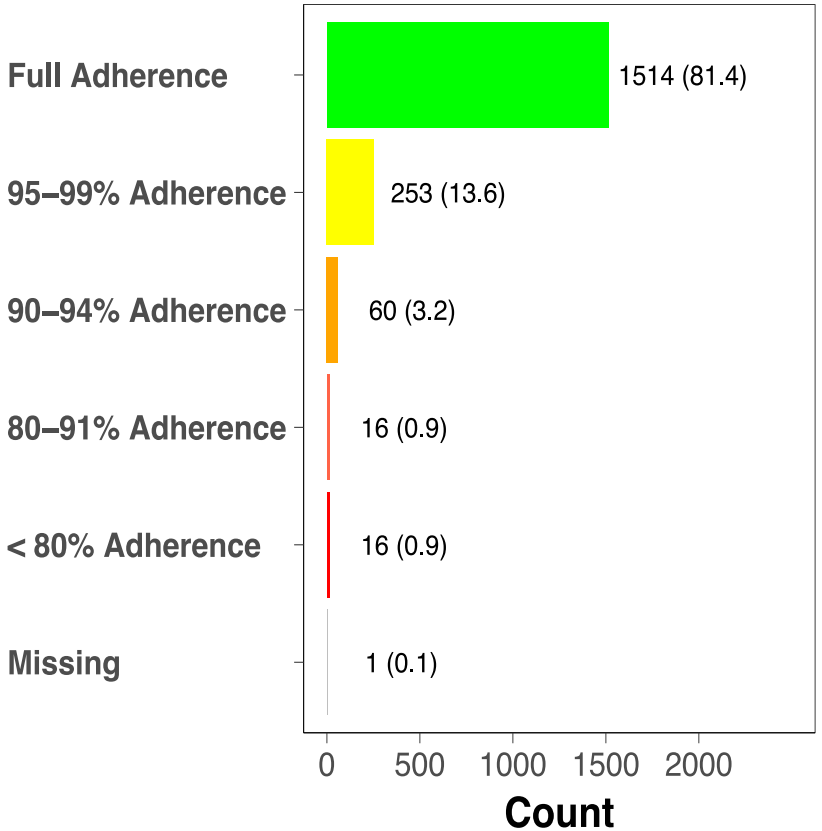
3/29/2017

Drug Adherence

HRZE recurrence

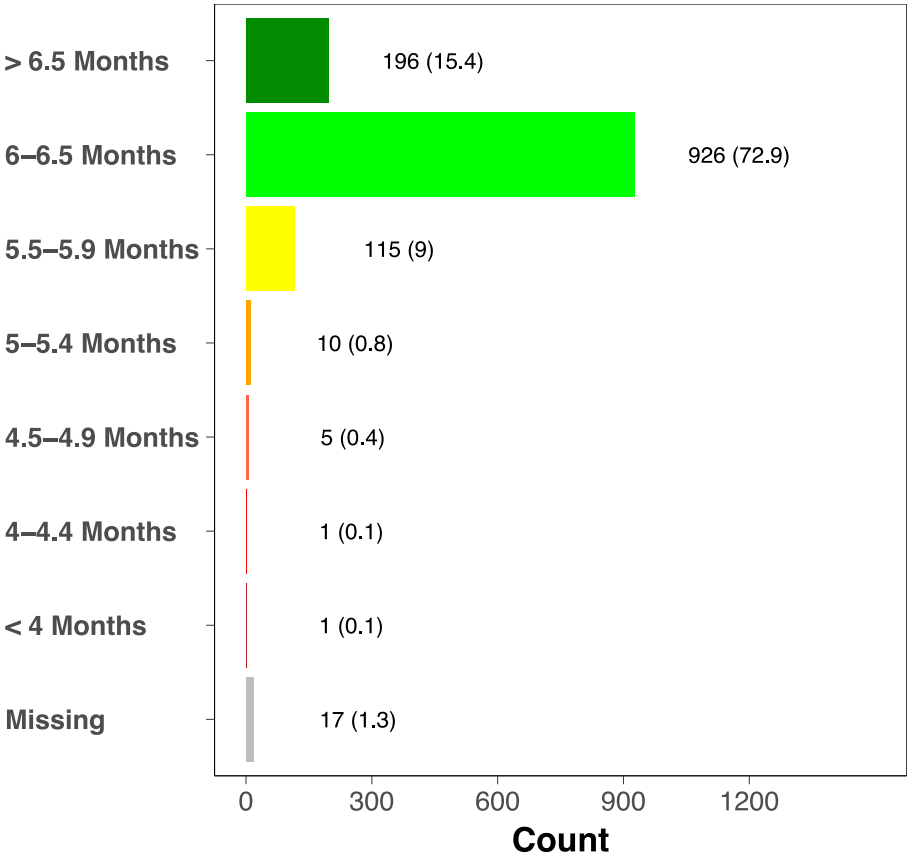


4-month recurrence

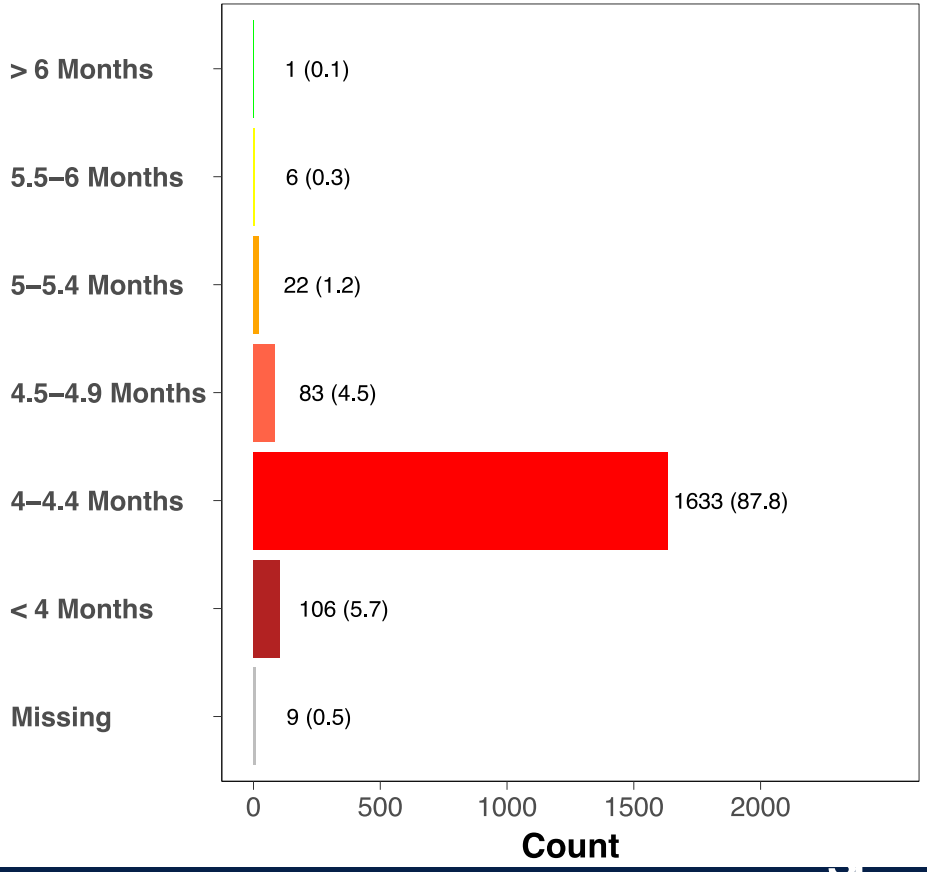


Treatment Duration

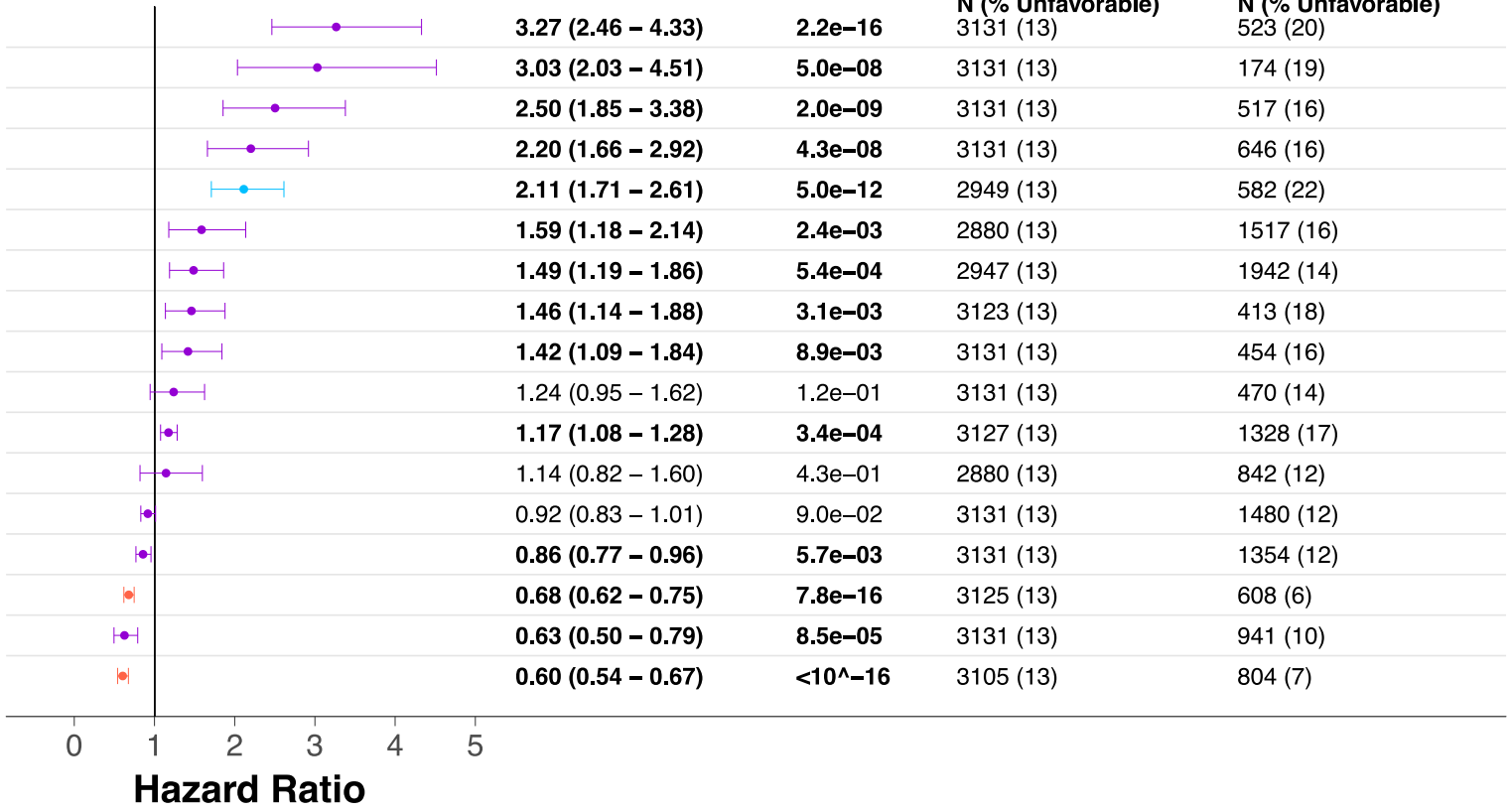
HRZE recurrence



4-month recurrence

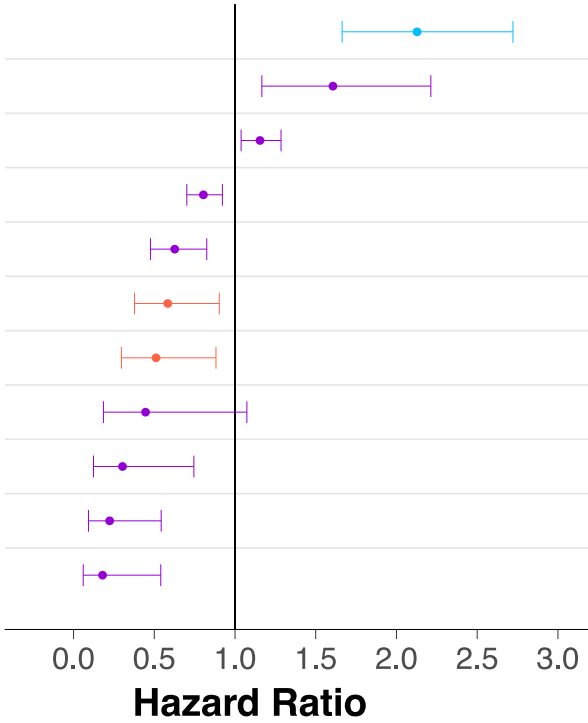


Full data base – recurrence, univariate



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
ReMOX, 2MERZ/2MR	**3.27 (2.46 – 4.33)**	**2.2e–16**	3131 (13)	523 (20)
RIFAQUIN, 2MERZ/2P2M2	**3.03 (2.03 – 4.51)**	**5.0e–08**	3131 (13)	174 (19)
ReMOX, 2MHRZ/2MHR	**2.50 (1.85 – 3.38)**	**2.0e–09**	3131 (13)	517 (16)
OFLOTUB, 2GHRZ/2GHR	**2.20 (1.66 – 2.92)**	**4.3e–08**	3131 (13)	646 (16)
Month 2	**2.11 (1.71 – 2.61)**	**5.0e–12**	2949 (13)	582 (22)
Smear 3+ to 1+	**1.59 (1.18 – 2.14)**	**2.4e–03**	2880 (13)	1517 (16)
Cavity Present	**1.49 (1.19 – 1.86)**	**5.4e–04**	2947 (13)	1942 (14)
HIV +	**1.46 (1.14 – 1.88)**	**3.1e–03**	3123 (13)	413 (18)
Other:Black	**1.42 (1.09 – 1.84)**	**8.9e–03**	3131 (13)	454 (16)
Asian:Black	1.24 (0.95 – 1.62)	1.2e–01	3131 (13)	470 (14)
Age*	**1.17 (1.08 – 1.28)**	**3.4e–04**	3127 (13)	1328 (17)
Smear 2+ to 1+	1.14 (0.82 – 1.60)	4.3e–01	2880 (13)	842 (12)
Weight*	0.92 (0.83 – 1.01)	9.0e–02	3131 (13)	1480 (12)
BMI*	**0.86 (0.77 – 0.96)**	**5.7e–03**	3131 (13)	1354 (12)
Total Number of Doses*	**0.68 (0.62 – 0.75)**	**7.8e–16**	3125 (13)	608 (6)
Females	**0.63 (0.50 – 0.79)**	**8.5e–05**	3131 (13)	941 (10)
Treatment Duration*	**0.60 (0.54 – 0.67)**	**<10^–16**	3105 (13)	804 (7)

Full data base – recurrence, multivariate



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 2	**2.13 (1.66 – 2.72)**	**1.8e–09**	2538 (13)	506 (22)
HIV +	**1.61 (1.17 – 2.21)**	**3.7e–03**	2538 (13)	346 (17)
Age*	**1.15 (1.04 – 1.28)**	**8.3e–03**	2538 (13)	1092 (17)
BMI*	**0.80 (0.70 – 0.92)**	**1.8e–03**	2538 (13)	1112 (11)
Females	**0.63 (0.48 – 0.83)**	**8.7e–04**	2538 (13)	748 (9)
Total Number of Doses*	**0.58 (0.38 – 0.90)**	**1.5e–02**	2538 (13)	448 (5)
Treatment Duration*	**0.51 (0.30 – 0.88)**	**1.6e–02**	2538 (13)	635 (6)
ReMOX, 2MERZ/2MR	0.45 (0.19 – 1.07)	7.1e–02	2538 (13)	371 (21)
ReMOX, 2MHRZ/2MHR	**0.30 (0.12 – 0.75)**	**9.3e–03**	2538 (13)	374 (16)
OFLOTUB, 2GHRZ/2GHR	**0.22 (0.09 – 0.54)**	**9.3e–04**	2538 (13)	603 (15)
RIFAQUIN, 2MERZ/2P2M2	**0.18 (0.06 – 0.54)**	**2.2e–03**	2538 (13)	145 (19)

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Results:
Other candidate predictors

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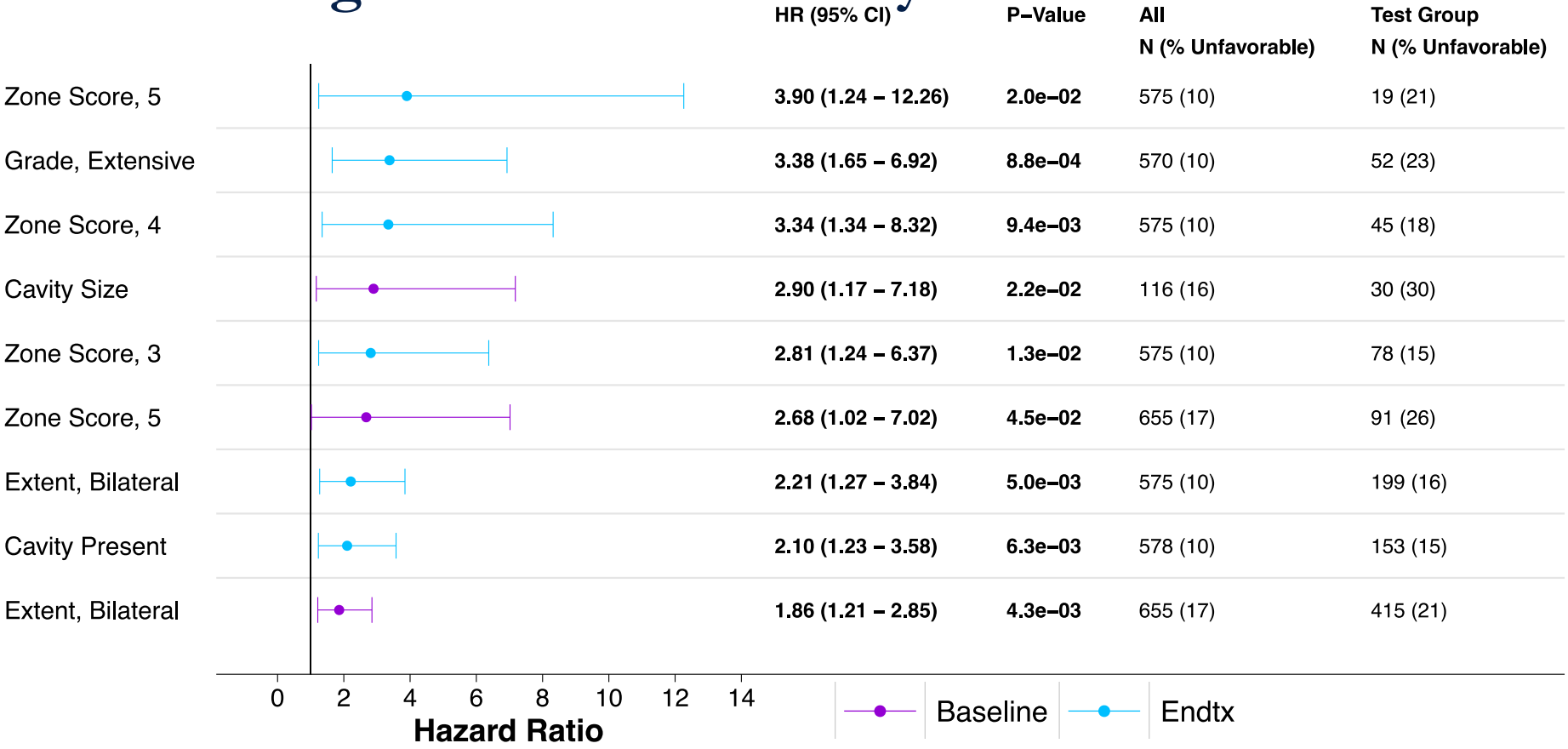
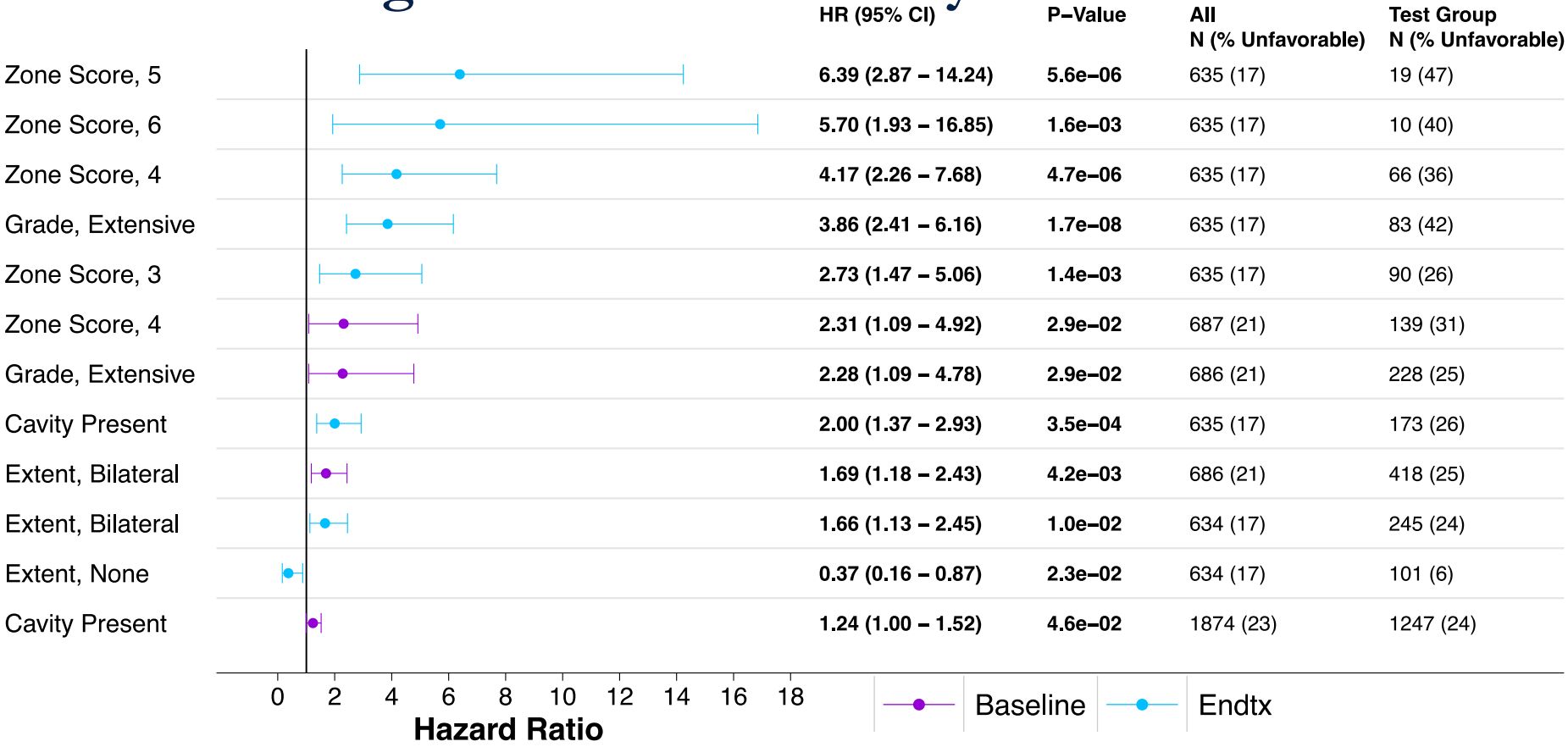
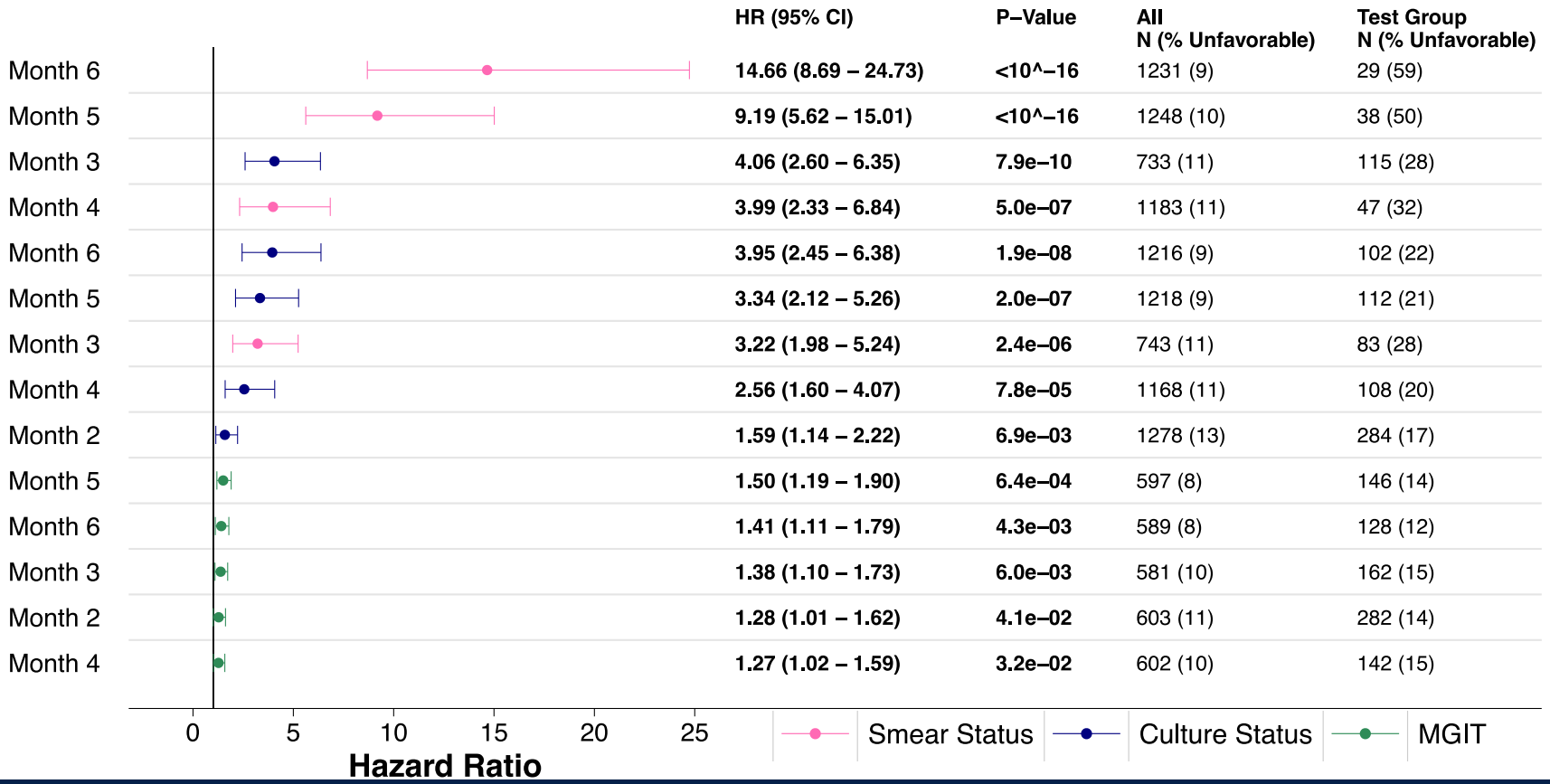
HRZE: Significant Chest X-Ray Predictors



4 month: Significant Chest X-Ray Predictors

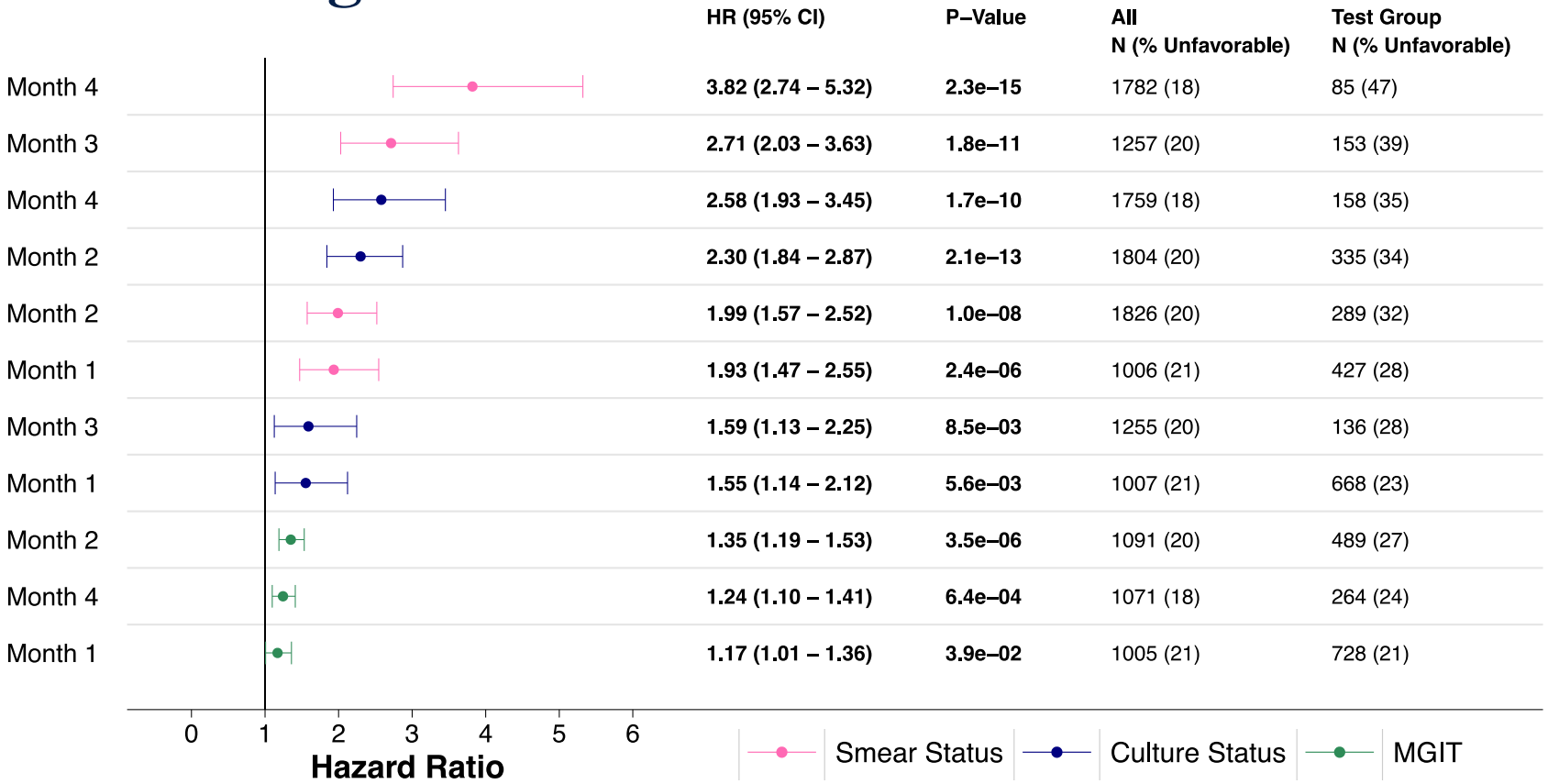


HRZE: Significant On Treatment MB Predictors



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 6	**14.66 (8.69 – 24.73)**	**<10^–16**	1231 (9)	29 (59)
Month 5	**9.19 (5.62 – 15.01)**	**<10^–16**	1248 (10)	38 (50)
Month 3	**4.06 (2.60 – 6.35)**	**7.9e–10**	733 (11)	115 (28)
Month 4	**3.99 (2.33 – 6.84)**	**5.0e–07**	1183 (11)	47 (32)
Month 6	**3.95 (2.45 – 6.38)**	**1.9e–08**	1216 (9)	102 (22)
Month 5	**3.34 (2.12 – 5.26)**	**2.0e–07**	1218 (9)	112 (21)
Month 3	**3.22 (1.98 – 5.24)**	**2.4e–06**	743 (11)	83 (28)
Month 4	**2.56 (1.60 – 4.07)**	**7.8e–05**	1168 (11)	108 (20)
Month 2	**1.59 (1.14 – 2.22)**	**6.9e–03**	1278 (13)	284 (17)
Month 5	**1.50 (1.19 – 1.90)**	**6.4e–04**	597 (8)	146 (14)
Month 6	**1.41 (1.11 – 1.79)**	**4.3e–03**	589 (8)	128 (12)
Month 3	**1.38 (1.10 – 1.73)**	**6.0e–03**	581 (10)	162 (15)
Month 2	**1.28 (1.01 – 1.62)**	**4.1e–02**	603 (11)	282 (14)
Month 4	**1.27 (1.02 – 1.59)**	**3.2e–02**	602 (10)	142 (15)

4 month: Significant On Treatment MB Predictors



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PK and Dose predictors

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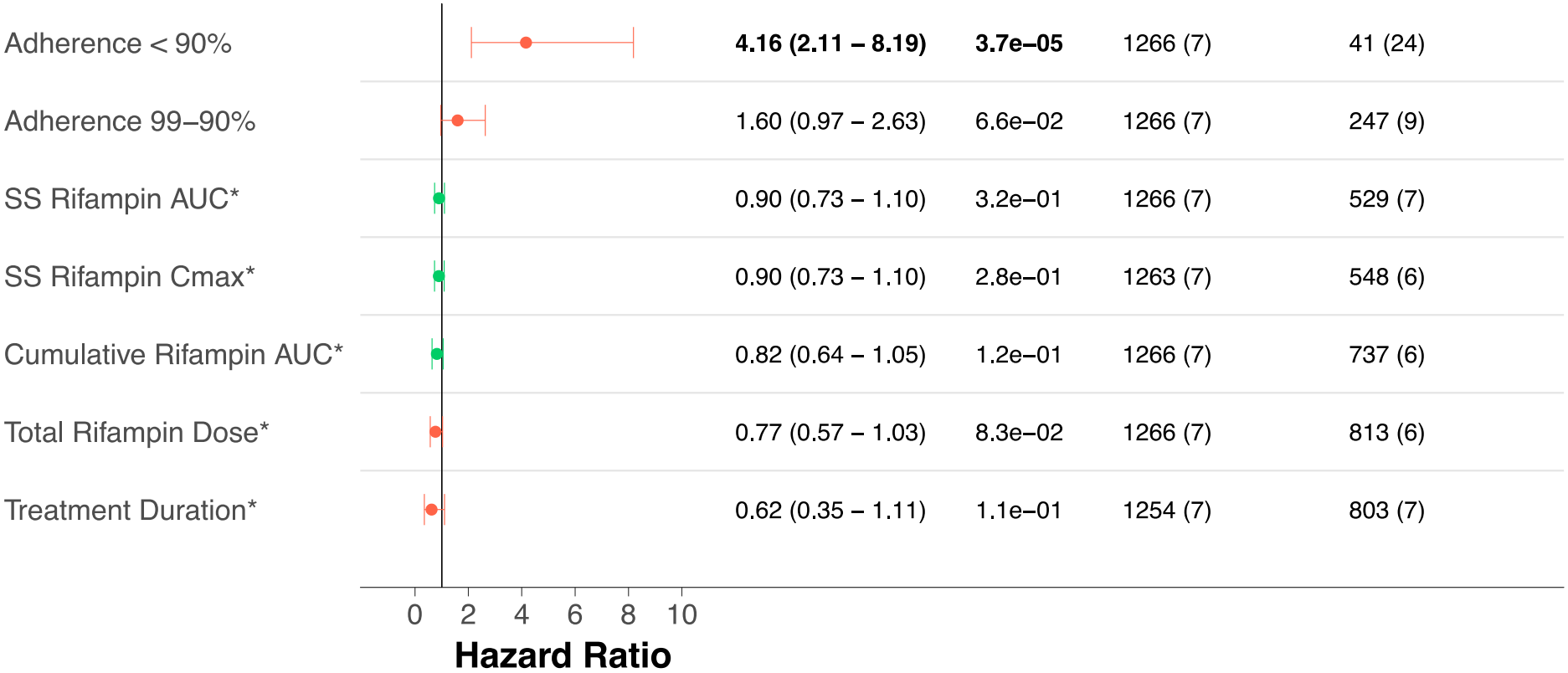
PK Specific Predictors

- 343 individuals had HRZ PK data in OFLOTUB
- 169 subjects had Gatifloxacin PK in OFLOTUB
- 241 subjects had Moxifloxacin and Rifapentine PK in Rifaquin
- For the remaining subjects, PK imputed as combination of Dose, cumulative adherence, and individualized PK parameters (based on set of baseline characteristics)
- FQ merged in one predictor based on relative distribution

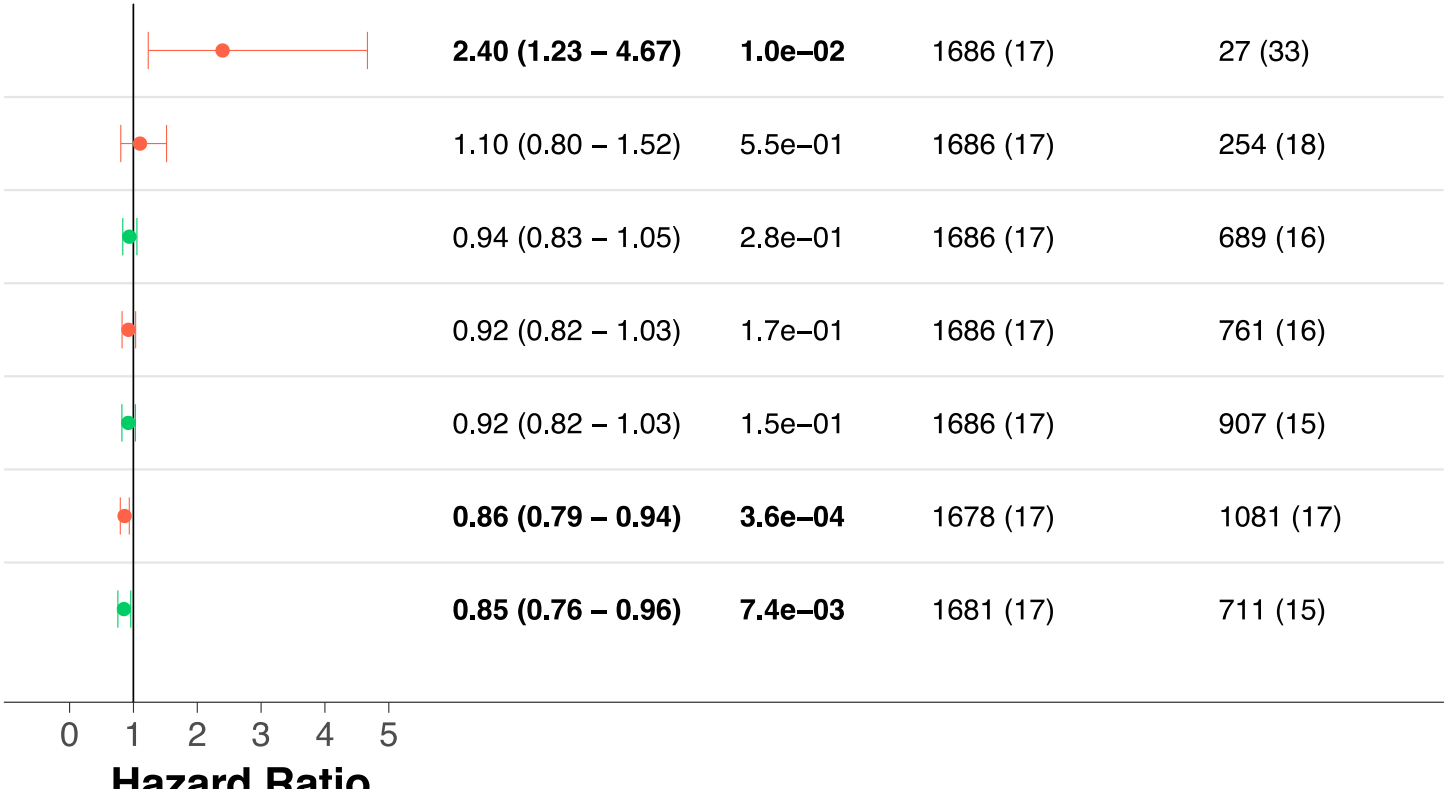
PK – specific predictors

	AUCss (mg*h/L)		cAUC (mg*h/L)		Cmax (mg/L)	
	6 months	4 months	6 months	4 months	6 months	4 months
Rifampin	35 (18-86)	35 (20 - 91)	5619 (120 - 12348)	3745 (35-8742)	9 (5-14)	9 (4-13)
Isoniazid	23 (2-54)	24 (3 – 50)	3455 (61 –9768)	2369 (34-5854)	6 (0.7-12)	6 (1-12)
Pyrazinamide	391 (248-797)	379 (203 –651)	20142 (1210-38261)	19616 (396-31255)	38 (23-56)	37 (24-58)
Ethambutol	24 (12 – 53)	23 (16 – 33)	1170 (295-2522)	1266 (409-1860)	7 (2-9)	7 (5-9)
Gatifloxacin	-	37 (7.5 – 63)		3499 (58-6010)	-	4 (2-7)
Moxifloxacin	-	29 (28-53)		3400 (71-4209)	-	3 (3-6)
Rifapentine	-	768 (0-1133)		13751 (0-20400)	-	31 (0-43)

HRZE MITT recurrence, univariate

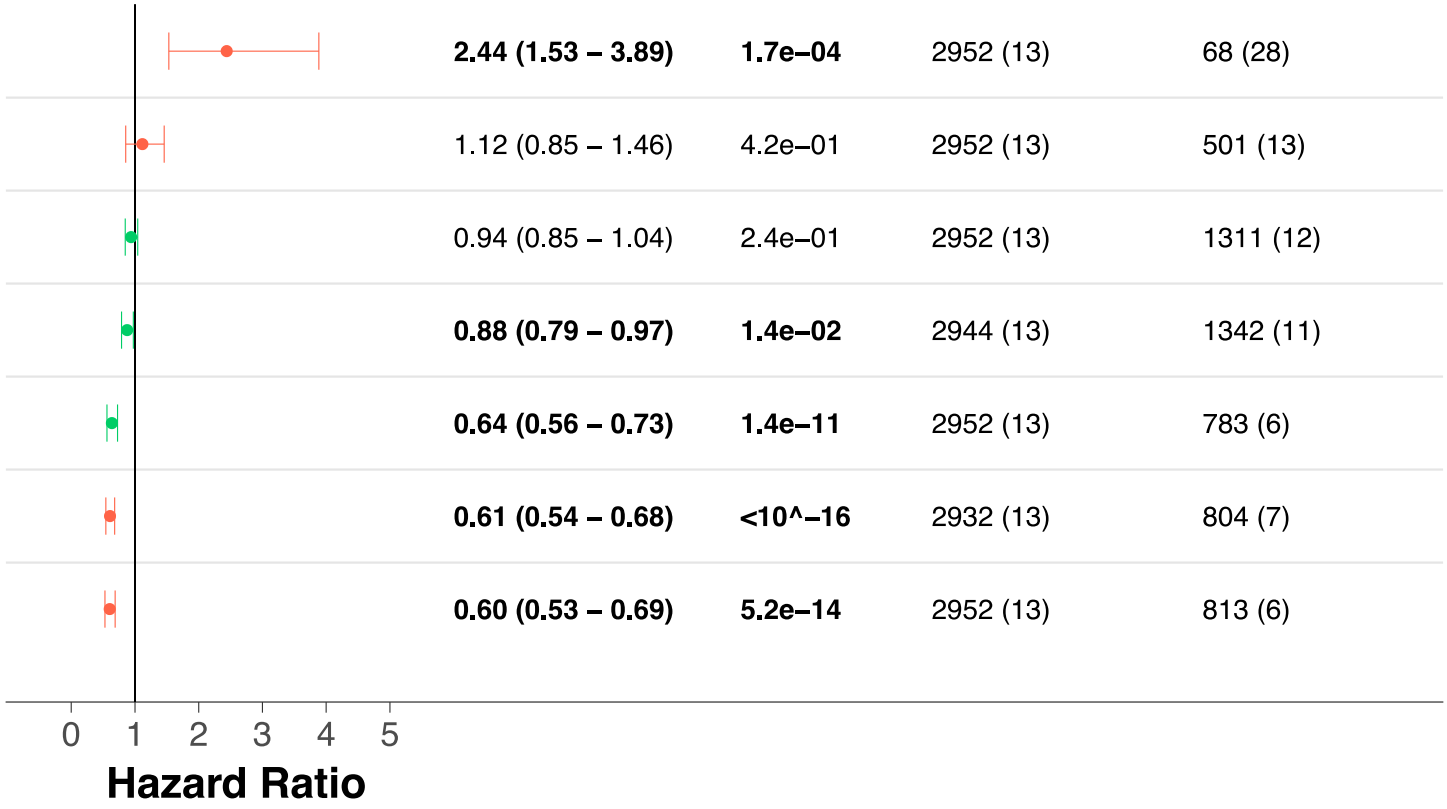


4-month MITT recurrence, univariate



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable
Adherence < 90%	**2.40 (1.23 – 4.67)**	**1.0e–02**	1686 (17)	27 (33)
Adherence 99–90%	1.10 (0.80 – 1.52)	5.5e–01	1686 (17)	254 (18)
SS Rifampin AUC*	0.94 (0.83 – 1.05)	2.8e–01	1686 (17)	689 (16)
Total Rifampin Dose*	0.92 (0.82 – 1.03)	1.7e–01	1686 (17)	761 (16)
Cumulative Rifampin AUC*	0.92 (0.82 – 1.03)	1.5e–01	1686 (17)	907 (15)
Treatment Duration*	**0.86 (0.79 – 0.94)**	**3.6e–04**	1678 (17)	1081 (17)
SS Rifampin Cmax*	**0.85 (0.76 – 0.96)**	**7.4e–03**	1681 (17)	711 (15)

Full data base, MITT recurrence, univariate



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Adherence < 90%	**2.44 (1.53 – 3.89)**	**1.7e–04**	2952 (13)	68 (28)
Adherence 99–90%	1.12 (0.85 – 1.46)	4.2e–01	2952 (13)	501 (13)
SS Rifampin AUC*	0.94 (0.85 – 1.04)	2.4e–01	2952 (13)	1311 (12)
SS Rifampin Cmax*	**0.88 (0.79 – 0.97)**	**1.4e–02**	2944 (13)	1342 (11)
Cumulative Rifampin AUC*	**0.64 (0.56 – 0.73)**	**1.4e–11**	2952 (13)	783 (6)
Treatment Duration*	**0.61 (0.54 – 0.68)**	**<10^–16**	2932 (13)	804 (7)
Total Rifampin Dose*	**0.60 (0.53 – 0.69)**	**5.2e–14**	2952 (13)	813 (6)

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Safety HRZE

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Limitations of Safety Analysis

Adverse events

- Only OFLOTUB captured and coded adverse events
- In REMox, AEs were captured, but not coded (Contrary to ICE guideline E9)
- In RIFAQUIN, only SAEs were captured. Non-serious AEs were not captured (Contrary to ICH guidelines E3 and E9).

Lab collection

- In RIFAQUIN, labs were not captured after baseline. No useful safety lab data.
- Incomplete data management: no normal ranges for OFLOTUB, 155 lab values dropped due to implausibility (not consistent with life). Some look like data errors.
- Biochemistry & hematology panels were incomplete in REMox and OFLOTUB

Schedule of Laboratory Tests

	Baseline	Week 2	Week 4	Week 8	Week 12	Month 4	Month 6
REMox	X	X	X	X	X	X	
OFLOTUB	X		X		X	X	X
RIFAQUIN	X						

- Amylase, glucose not captured in REMox
- Bilirubin not captured in OFLOTUB
- Lipids, GGT, RBC, WBC + differential not captured in either study

	AST /ALT	Bilirubin	Amylase	Creatinine Urea	Glucose	K	Na	Hemoglobin Platelets	PT, aPTT, INR
REMox	X	X		X		X	X	X	X
OFLOTUB	X		X		X	X		X	

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Summary points

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Treatment Implications

- 4 month regimens can be administered to identified 35% of the patients (**Smear 1+, Smear 2+ HIV negative, Cavity -)**
- SOC can be considered for 4 months in these patient groups (over-treatment) if full adherence
  - Immediate programmatic impact
- Most impactful intervention is ensuring **adequate adherence** and doses
- **Low forgiveness of HRZE**
- More variation due to disease than due to a regimen
- **Treatment duration** has independent impact

Design of future clinical trials: Patient stratification

- Evidence that different patient groups require different treatment duration
  - Concept of “one duration for all” is not valid
- More aggressive regimens for hard-to-treat patient categories
- These algorithms are intended to evolve and will become more precise with more detailed data (Chest X-ray readouts + biomarkers)

Clinical Trial Design: Data aspects

- Consistency across the trials in collecting clinical data is needed to expedite integrated learning
- Definition of Phase 3 clinical trial endpoint should be at minimum recurrence/relapse
- Culture results are relevant risk factors, but not capable of predicting individual relapse
- MITT and PP definition need re-examination (impact of adherence)
- Set of standardized predictors
- Incorporation of PK data and detailed adherence histories

Future TB ReFLECT work:

- Incorporation of individual PK data –separation of duration and individual drug pressure (dose, pk)
- Analysis of treatment failures
- Parametric survival modeling – models suitable for clinical trial simulations and incorporation of nonlinear relationships (U-type, Emax)
- Modeling of longitudinal culture data (solid & liquid) – additional on treatment predictor
- Safety analysis

Acknowledgements

World Health Organization

Critical Path to TB Drug Regimens

BILL & MELINDA GATES foundation

Data Contributors:

- TB Alliance
- St. George's, University of London
- WHO
- UCT

UCSF Lab

TB ReFLECT steering committee:

- Christian LIENHARDT
- Debra HANNA
- Klaus ROMERO
- David HERMAN
- Katherine Fielding
- Patrick Phillips
- Dan Hartley
- Bob Stafford

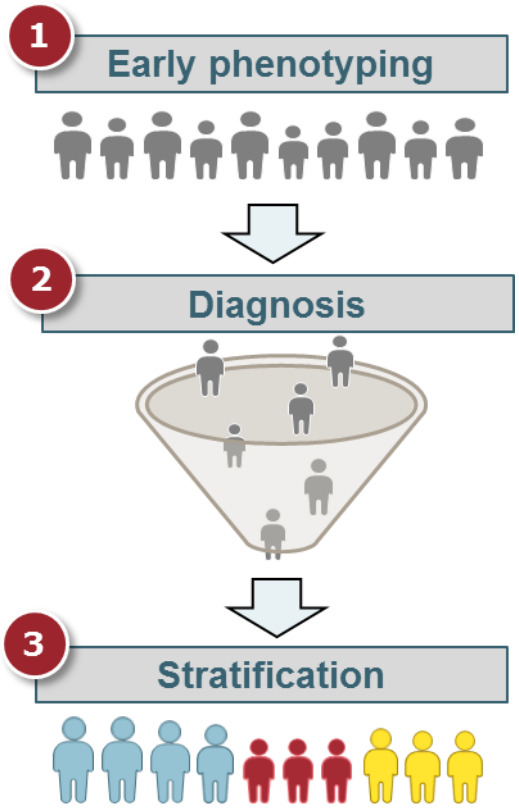
Conclusions: Treatment Implications

- 4 month regimens can be administered to identified 35% of the patients (Smear1+ and Smear 2+ HIV negative)
- SOC can be considered for 4 months in these patient groups (over-treatment)
  - Immediate programmatic impact
- Most impactful intervention is ensuring adequate doses and adherence of treatment (Rifamycins)
- Evaluated 4 months regimens seem to be equivalent for given duration
- More variation due to disease than due to regimen

Design of future clinical trials

- Further work for dose optimization of TB drugs (R, P, M, Z, G)
- Evidence that different patient groups require different treatment duration
  - Concept of “one duration for all” needs re-examination
- More aggressive regimens are needed for hard to treat patient categories
- Consistency across the trials in collecting clinical data is needed to expedite integrated learning
- These algorithms are intended to evolve and will become even more precise with more detailed data (Chest X-ray readouts + biomarkers)

Towards Patient Stratification



Goal:

Identify the **right regimen** for the **right patient** at the **right time:**

All patients with TB should be CURED

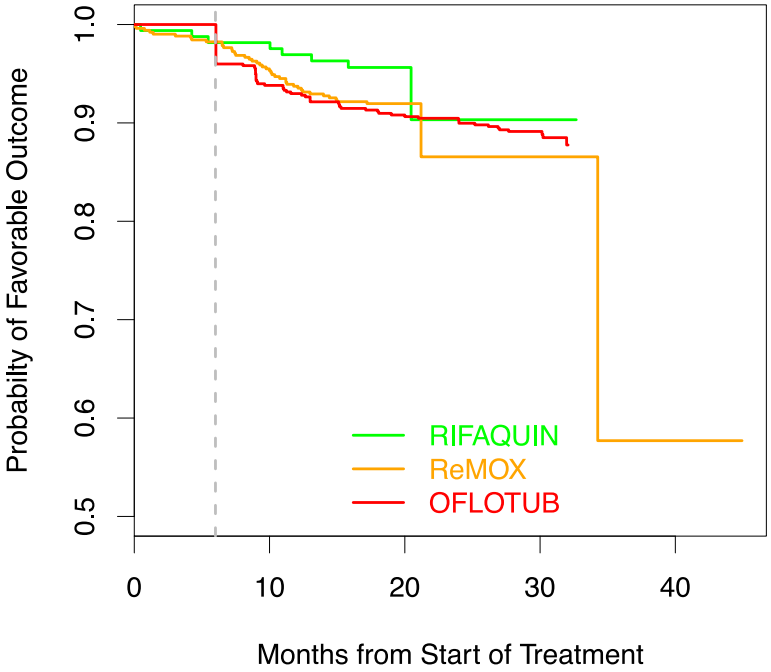
Deliverable:

Smart and Easy to Use/Implement Dosing Algorithms

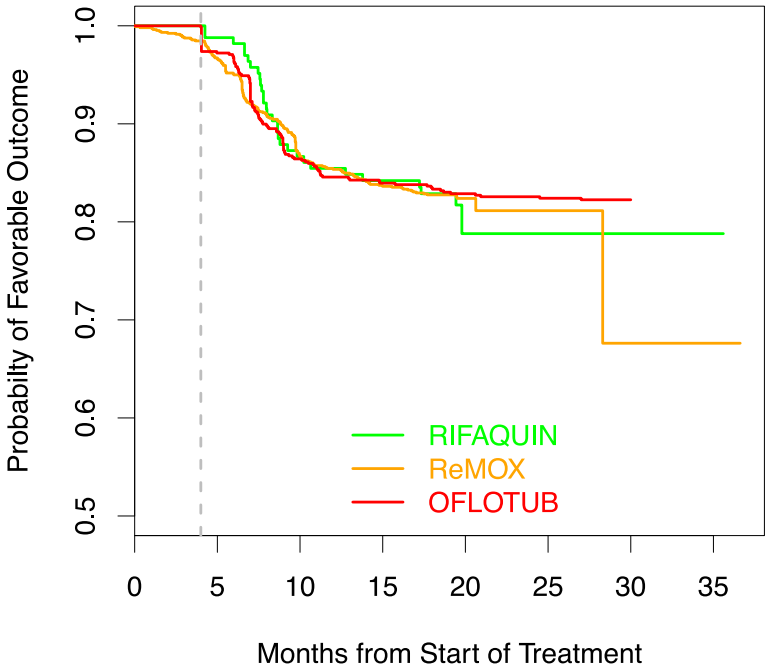
Adherence

	ReMOX	Rifaquin	OFLOTUB
Adherence	1 (0.14-1)	0.99 (0.66-1)	1 (0.33-1)
% patients < 50% adherence	24/471 (5%)	2/142 (1%)	50/604 (8%)
% patients < 80% adherence	36/471 (8%)	8/142 (6%)	53/604 (9)
% patients < 80% adherence	40/471 (8%)	15/142 (11%)	66/604 (11%)

Standard of Care



4 Month Experimental Arms



Stratifying Patient Population: Relapse Rate

		HIV +				HIV -			
		SOC		4 months		SOC		4 months	
CAVITY -	Smear 1+	34.8 %	n=23	22.7 %	n=22	16.4 %	n=73	19.3 %	n=114
	Smear 2+	17.7 %	n=18	23.1%	n=26	16.3%	n=147	17.5%	n=166
	Smear 3+	40.0 %	n=30	21.7 %	n=23	14.3 %	n=140	21.1 %	n=170
	Smear 4+	0 %	n=5	40.0 %	n=5	8.8 %	n=34	17.4%	n=69
CAVITY +	Smear 1+	28.6 %	n=14	13.3 %	n=15	11.1 %	n=90	13.7%	n=95
	Smear 2+	8.7 %	n=23	22.7 %	n=22	10.3 %	n=136	20.5 %	n=176
	Smear 3+	24.3 %	n=74	30.6 %	n=72	13.5 %	n=259	24.1 %	n=390
	Smear 4+	35.7 %	n=14	37.5 %	n=32	17.4 %	n=195	26.2 %	n=389

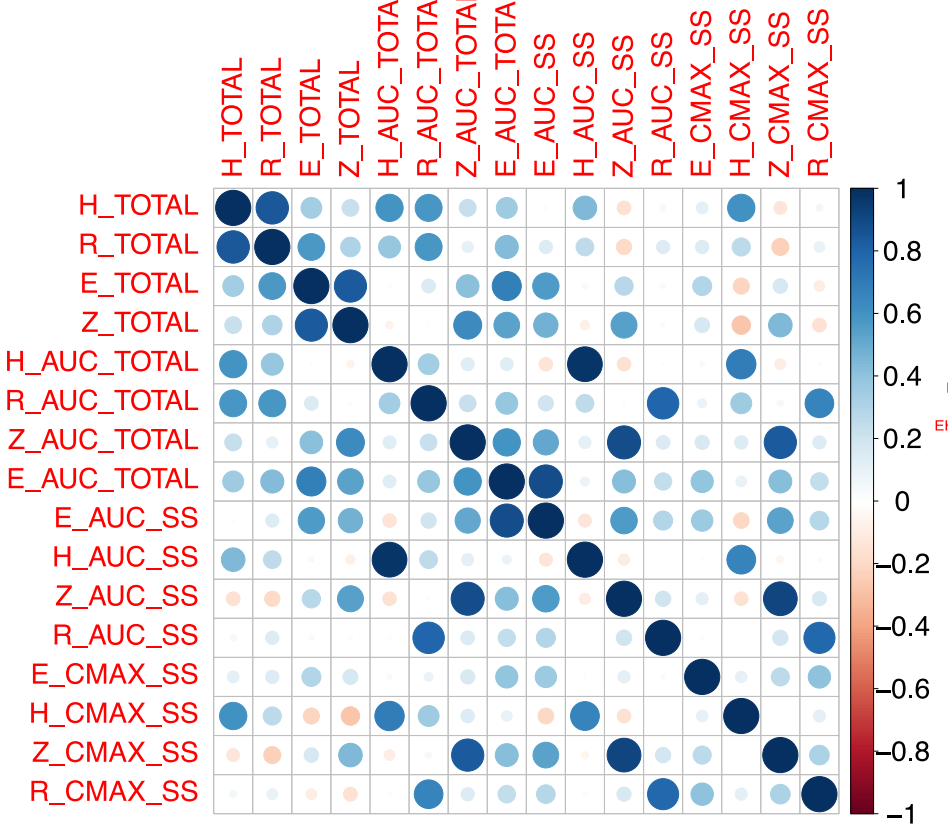
Stratifying Patient Population: Relapse Rate

		SOC		4 month		4month/SOC
CAVITY -	Smear 1+	20.8 %	n=96	19.9 %	n=136	0.97
	Smear 2+	16.4 %	n=165	18.2 %	n=192	1.11
	Smear 3+	18.8 %	n=170	21.2 %	n=193	1.13
	Smear 4+	7.7 %	n=39	18.9 %	n=74	2.45
CAVITY +	Smear 1+	13.5 %	n=104	13.6 %	n=110	1.01
	Smear 2+	10.1 %	n=159	20.7 %	n=198	2.05
	Smear 3+	15.9 %	n=333	25.1 %	n=462	1.57
	Smear 4+	18.7 %	n=209	27.1 %	n=421	1.45

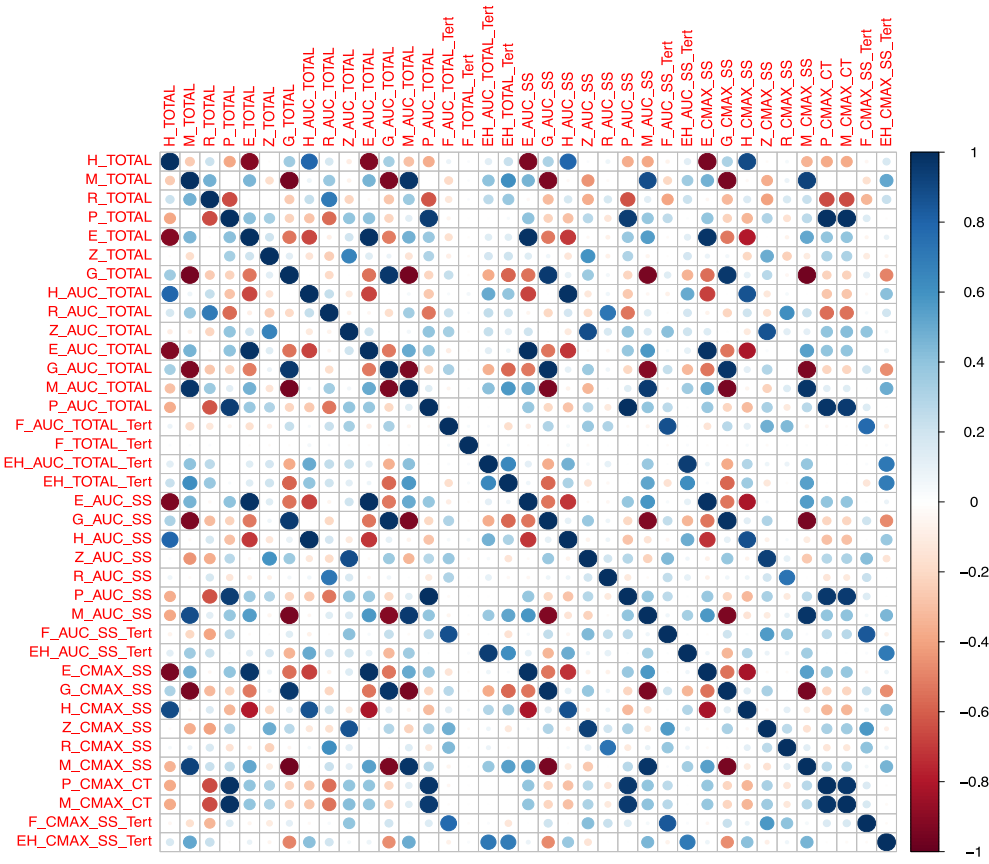
Stratifying Patient Population: Relapse Rate

		HIV +				HIV -			
		SOC		4 months		SOC		4 months	
CAVITY -	Smear 1+	17.7 %	n=17	5.9 %	n=17	10.9 %	n=64	10.8 %	n=102
	Smear 2+	6.3 %	n=16	16.7%	n=24	6.3%	n=127	12.4%	n=153
	Smear 3+	34.6 %	n=26	18.2 %	n=22	9.4 %	n=128	17.0 %	n=159
	Smear 4+	0 %	n=5	40.0 %	n=5	3.1%	n=32	9.5%	n=63
CAVITY +	Smear 1+	0 %	n=10	14.3 %	n=14	6.0 %	n=83	11.1%	n=90
	Smear 2+	8.7 %	n=23	15.0 %	n=20	6.9 %	n=131	15.2 %	n=164
	Smear 3+	20.3 %	n=69	29.0 %	n=69	8.3 %	n=241	19.0 %	n=363
	Smear 4+	25.0 %	n=12	35.5 %	n=31	7.5 %	n=174	21.8 %	n=367

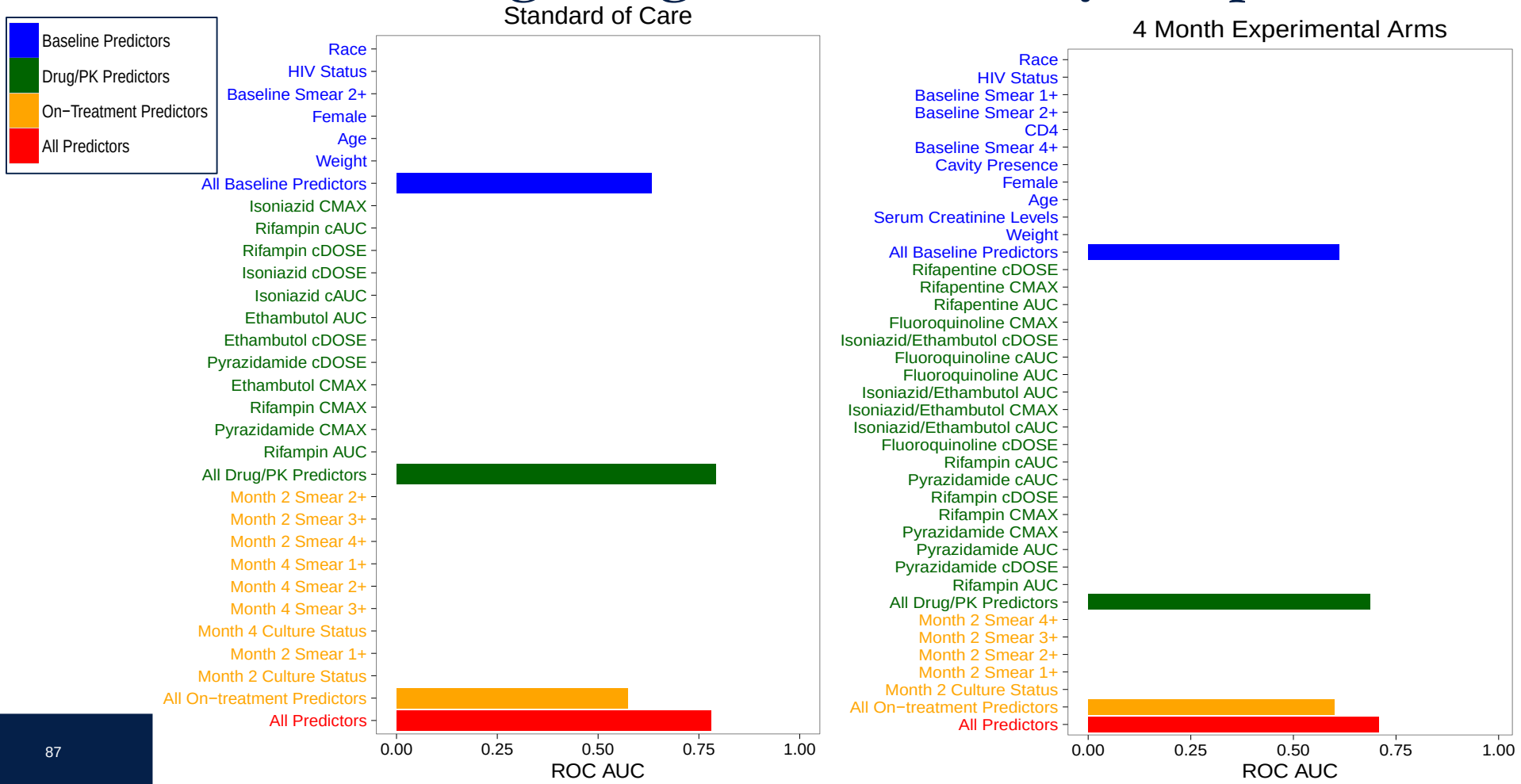
Standard of Care



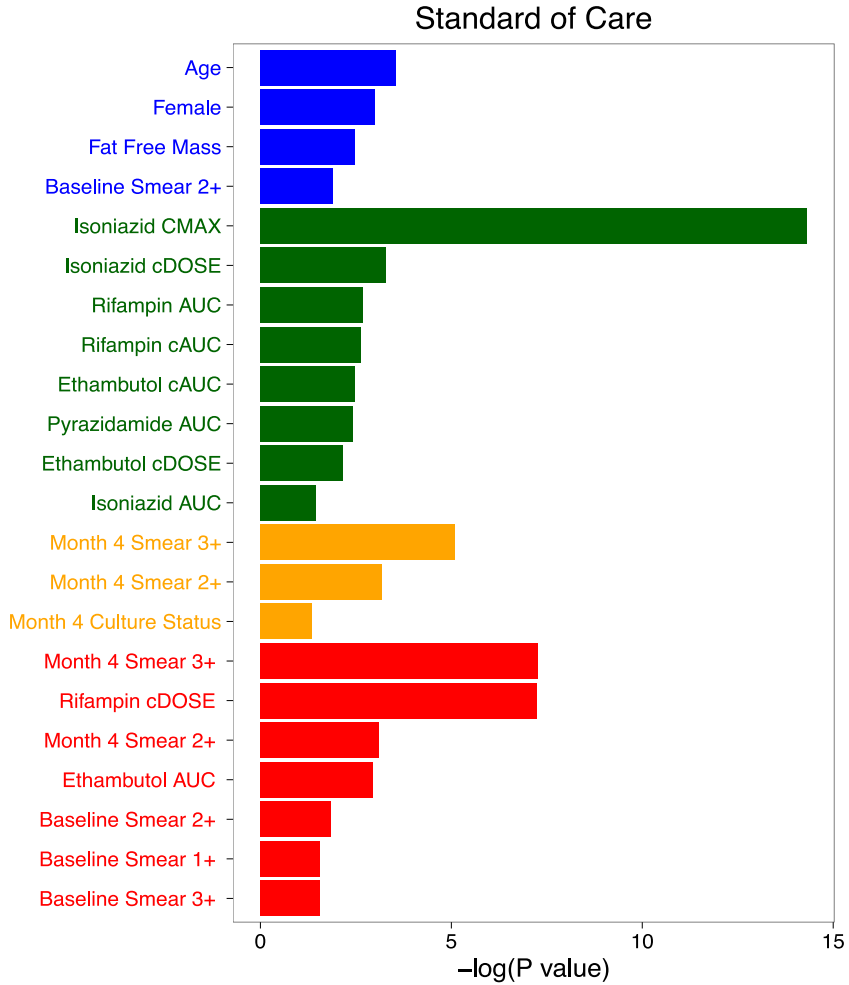
4 Month Experimental Arms

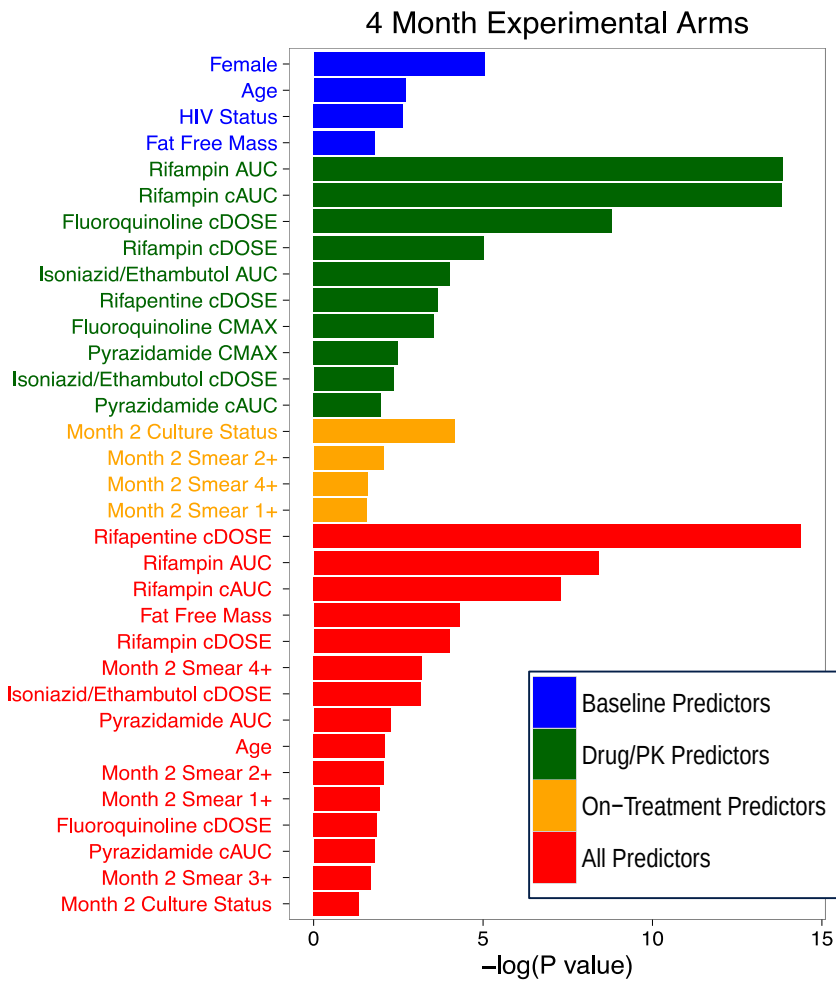


Predictors for Logit Regression- Primary Endpoint

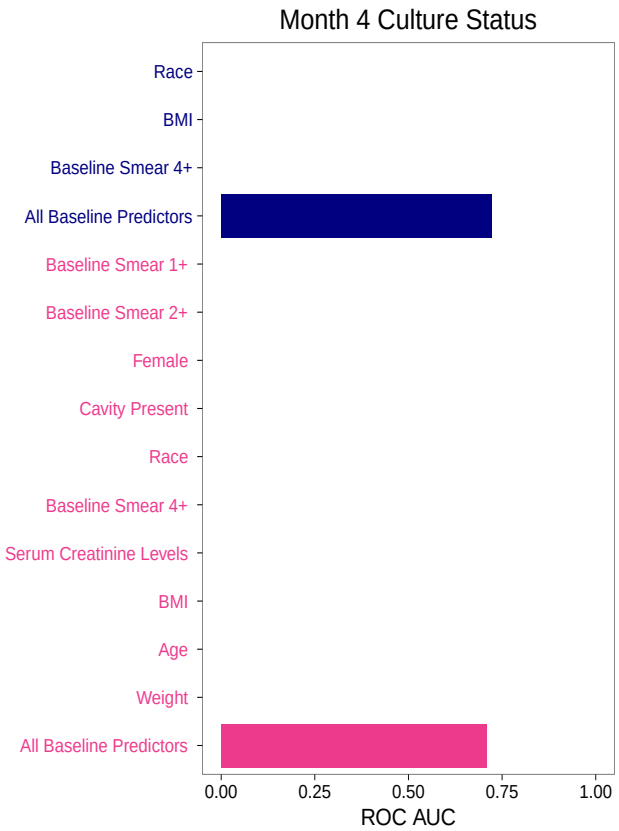


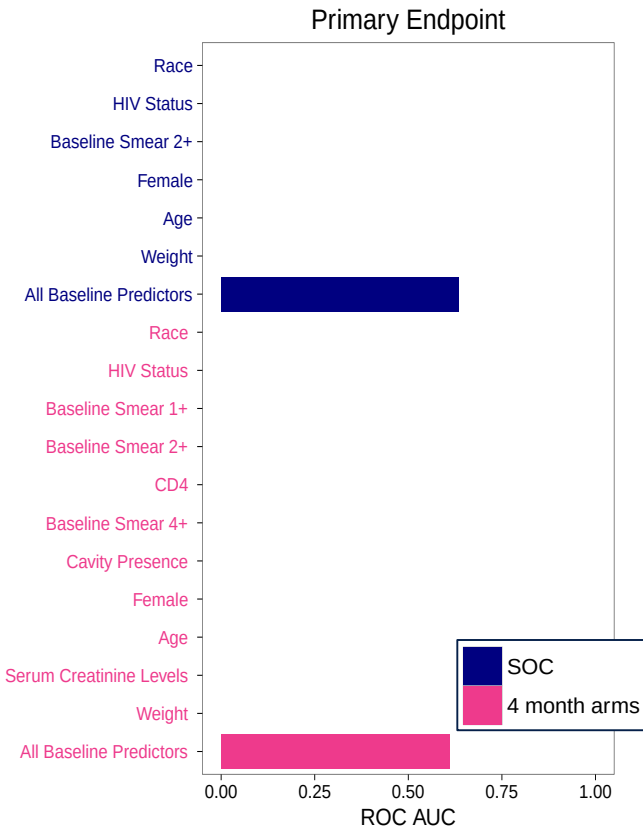
Predictors for Cox Regression- Primary Endpoint



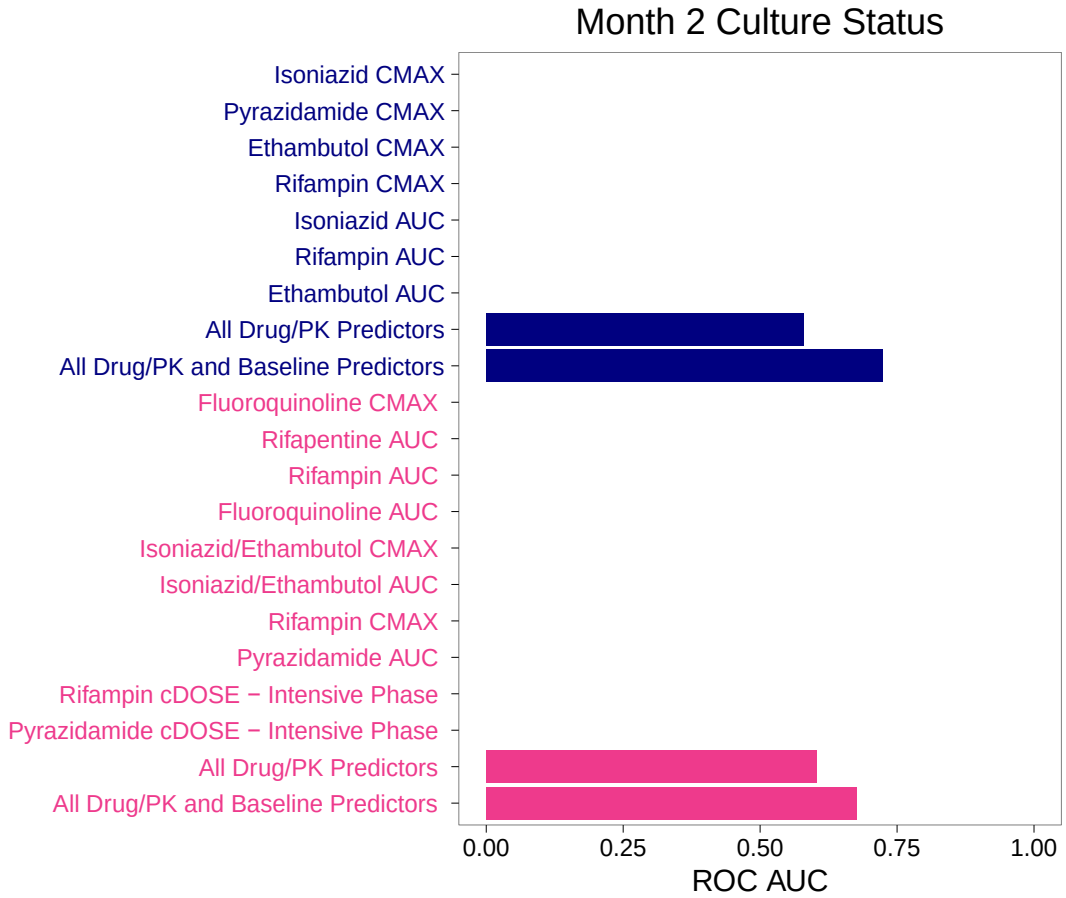


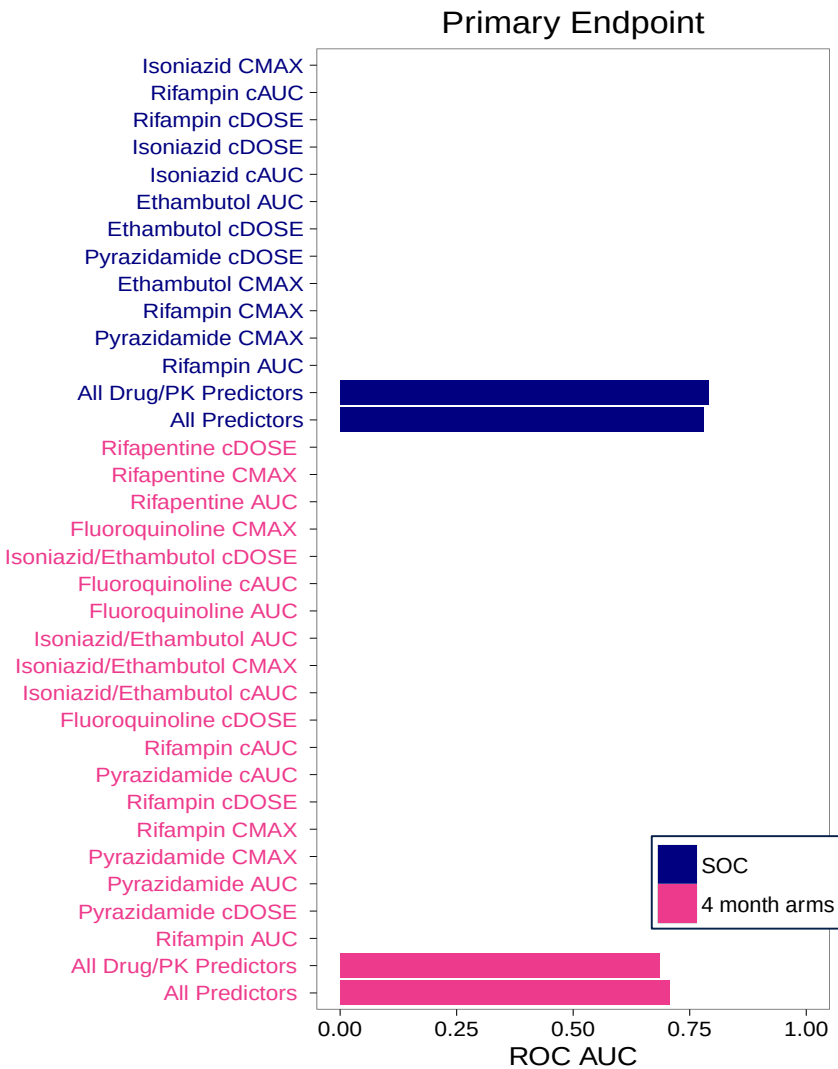
Baseline Predictors for On-Treatment Culture Status





Drug/PK Predictors for On-Treatment Culture Status



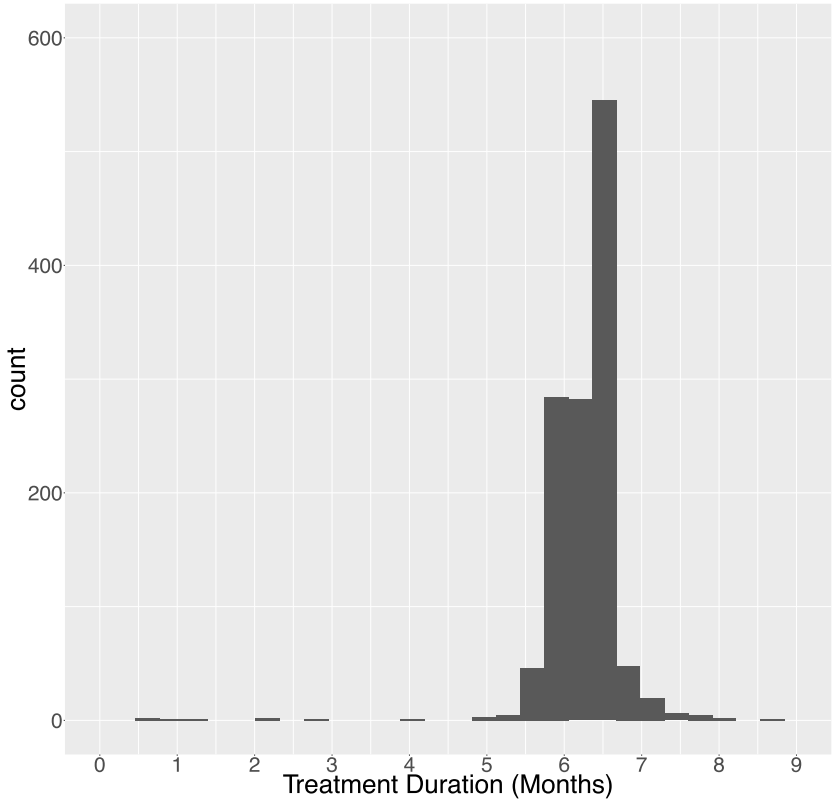


Hazard Ratio and Survival Plots – all adjusted by SITEID

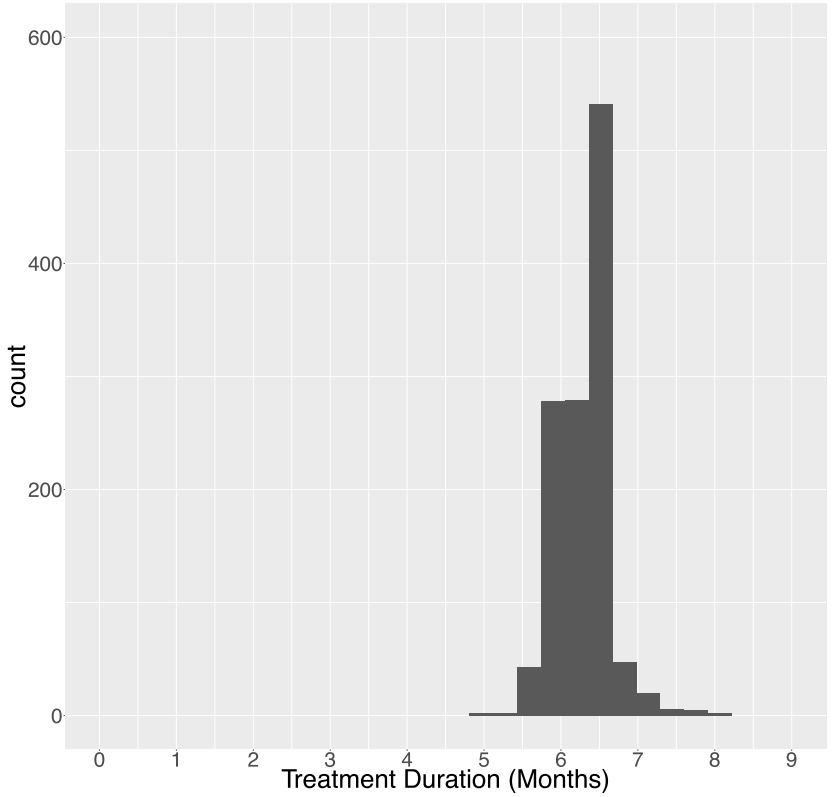
SOC MITT without early failures

SOC

PP

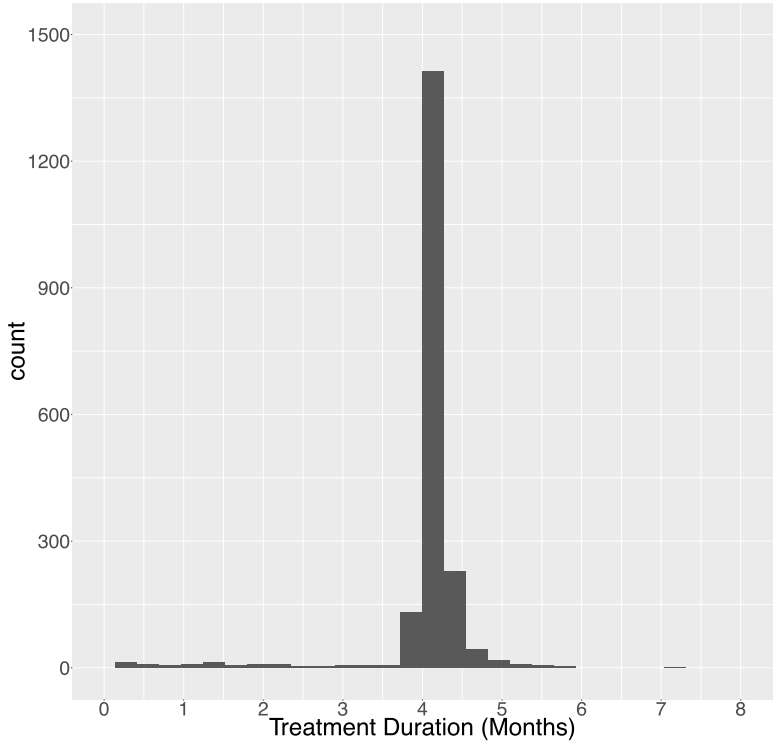


PP without early

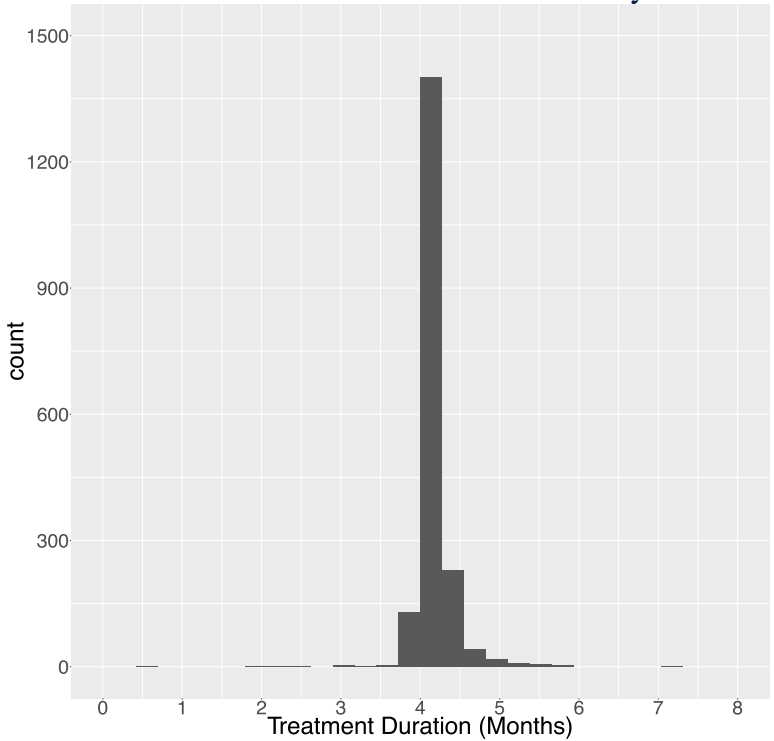


EXP

MITT

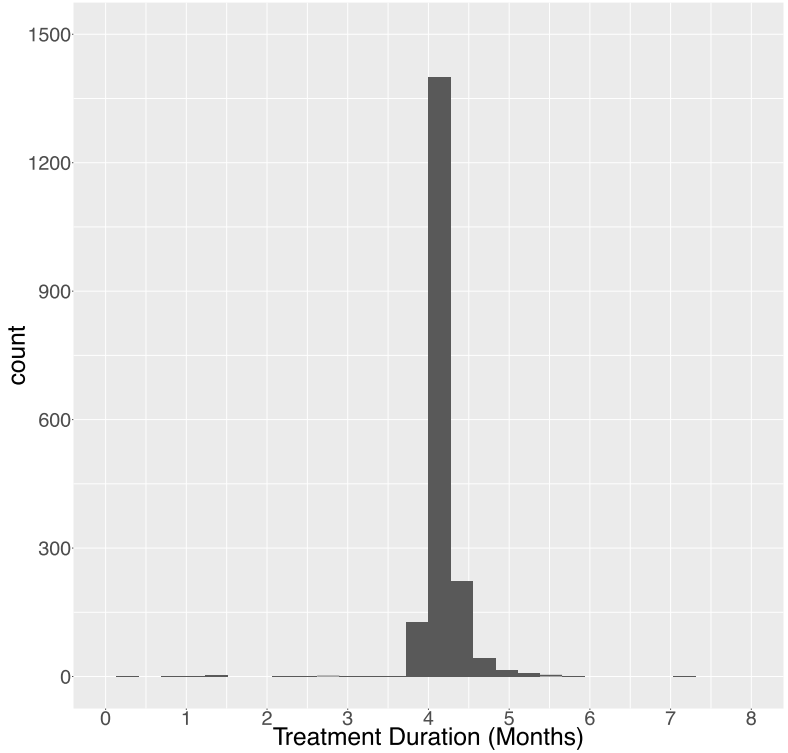


MITT without early

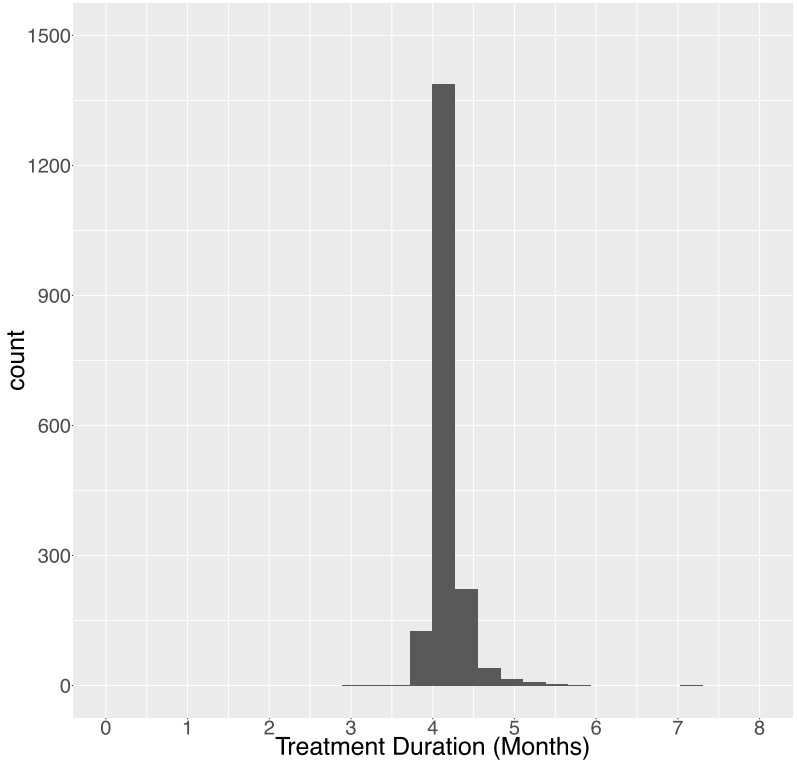


EXP

PP



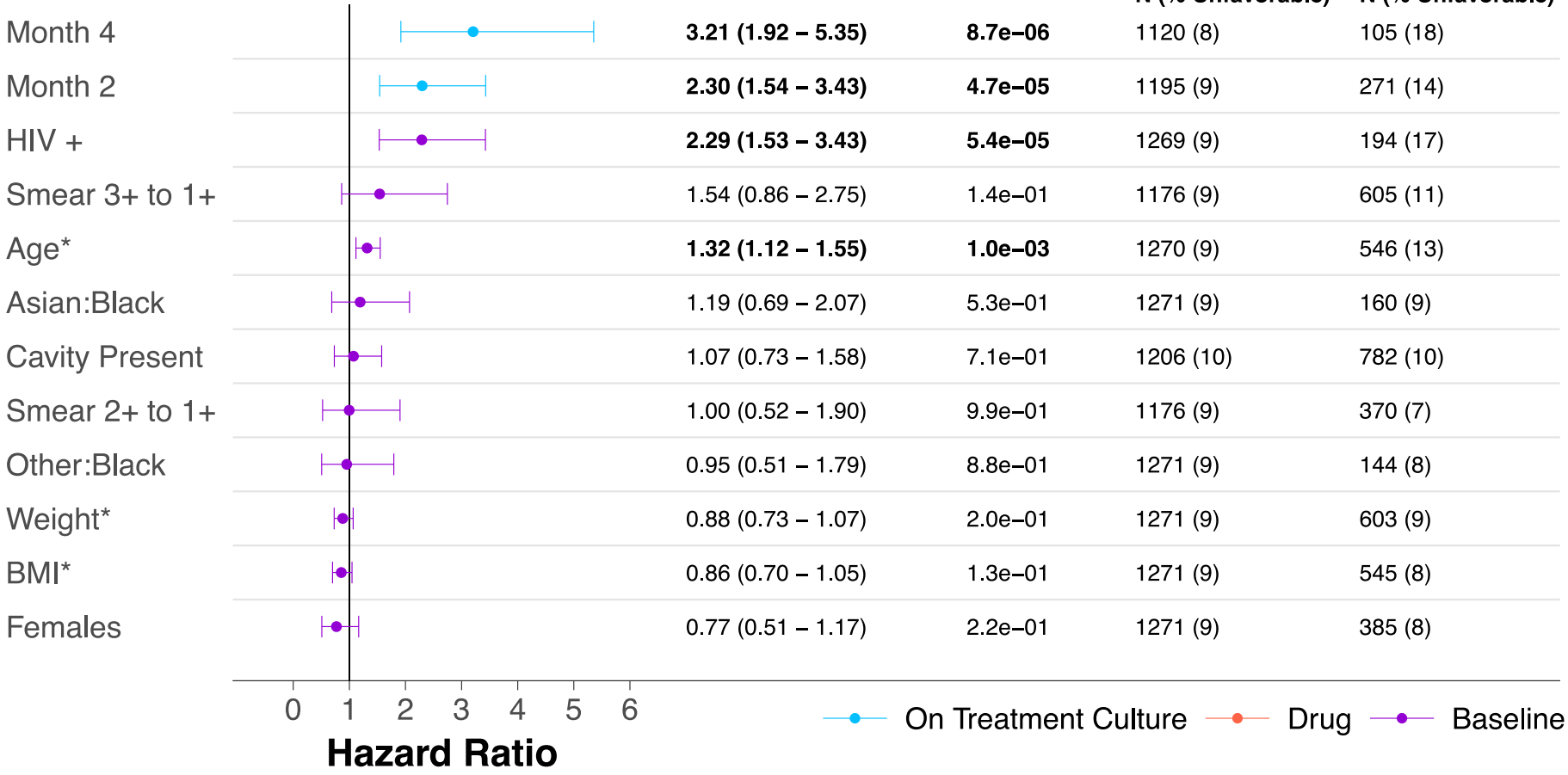
PP without early



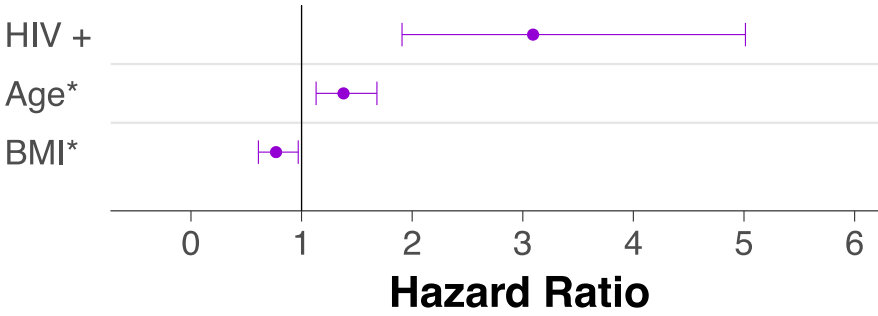
SOC MITT

SOC PP

SOC-PP– univariate (without DA or Duration)



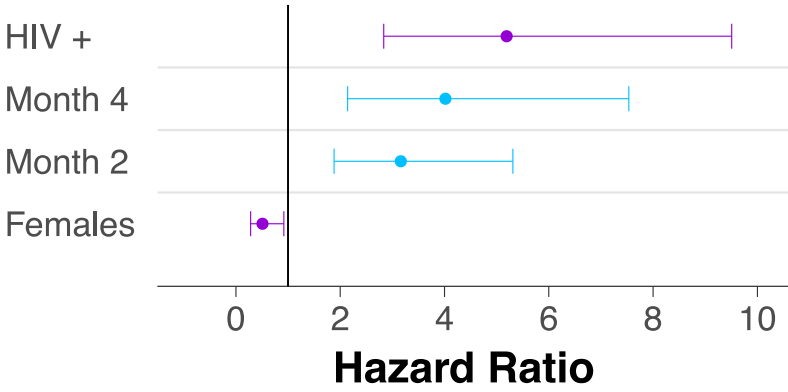
SOC-PP–multi- baseline only



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
HIV +	**3.09 (1.91 – 5.01)**	**4.6e–06**	1118 (9)	175 (18)
Age*	**1.38 (1.13 – 1.68)**	**1.4e–03**	1118 (9)	477 (13)
BMI*	**0.77 (0.61 – 0.97)**	**2.7e–02**	1118 (9)	475 (7)

On Treatment Culture Drug Baseline

SOC-PP –muti (without DA or Duration)

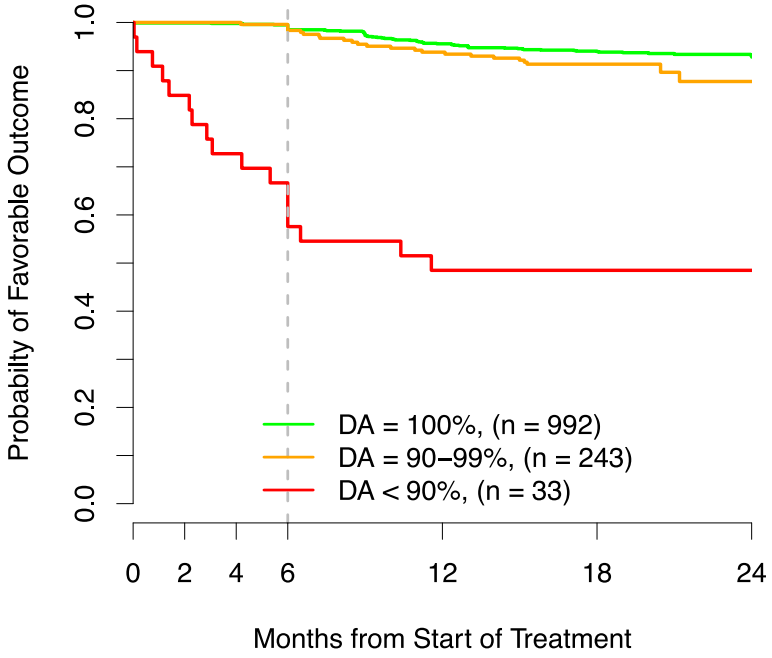


	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
HIV +	**5.19 (2.84 – 9.51)**	**9.5e–08**	938 (8)	149 (15)
Month 4	**4.02 (2.14 – 7.53)**	**1.5e–05**	938 (8)	86 (19)
Month 2	**3.16 (1.88 – 5.31)**	**1.4e–05**	938 (8)	220 (15)
Females	**0.51 (0.28 – 0.92)**	**2.5e–02**	938 (8)	275 (6)

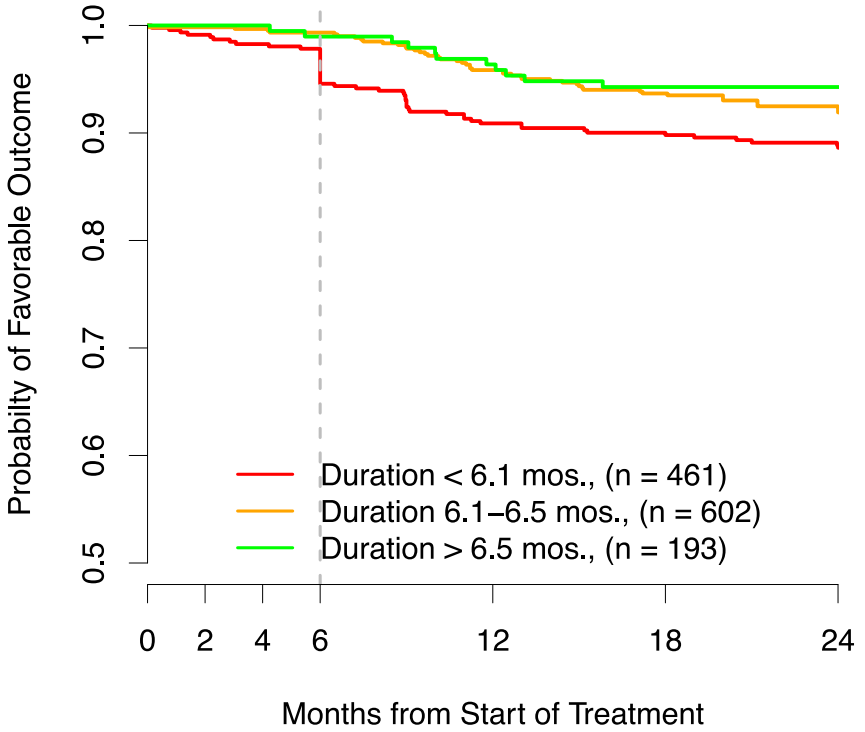
On Treatment Culture Drug Baseline

Survival Plots for significant multivariate predictors

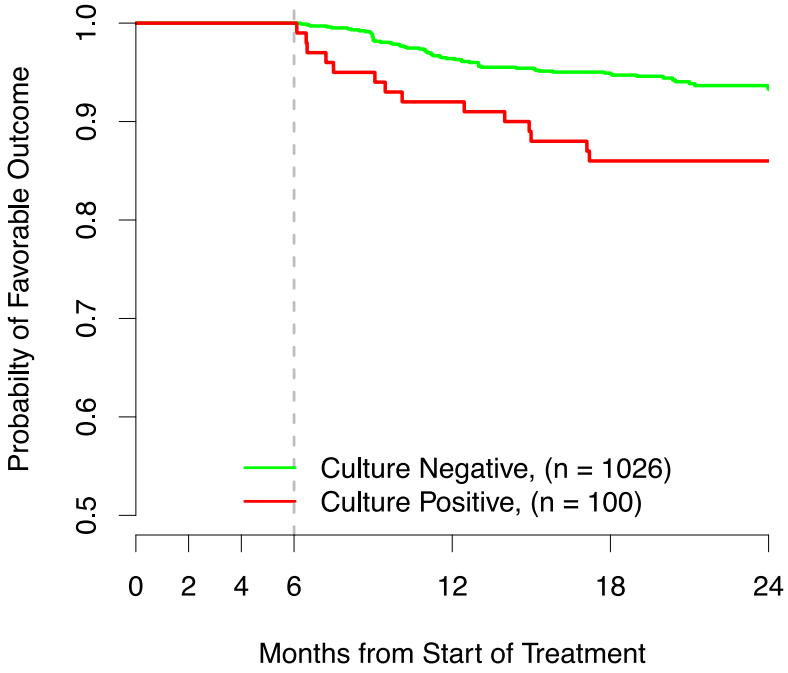
Drug Adherence



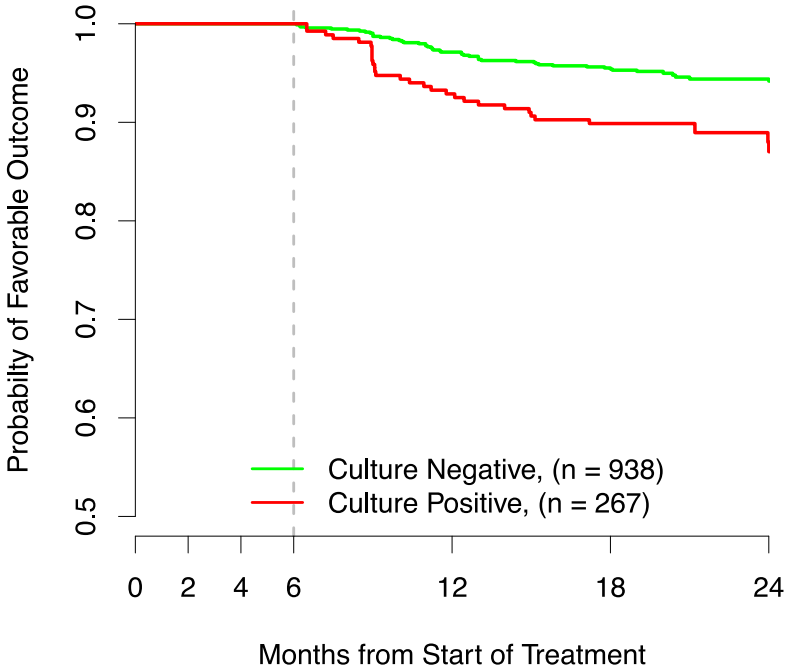
Treatment Duration

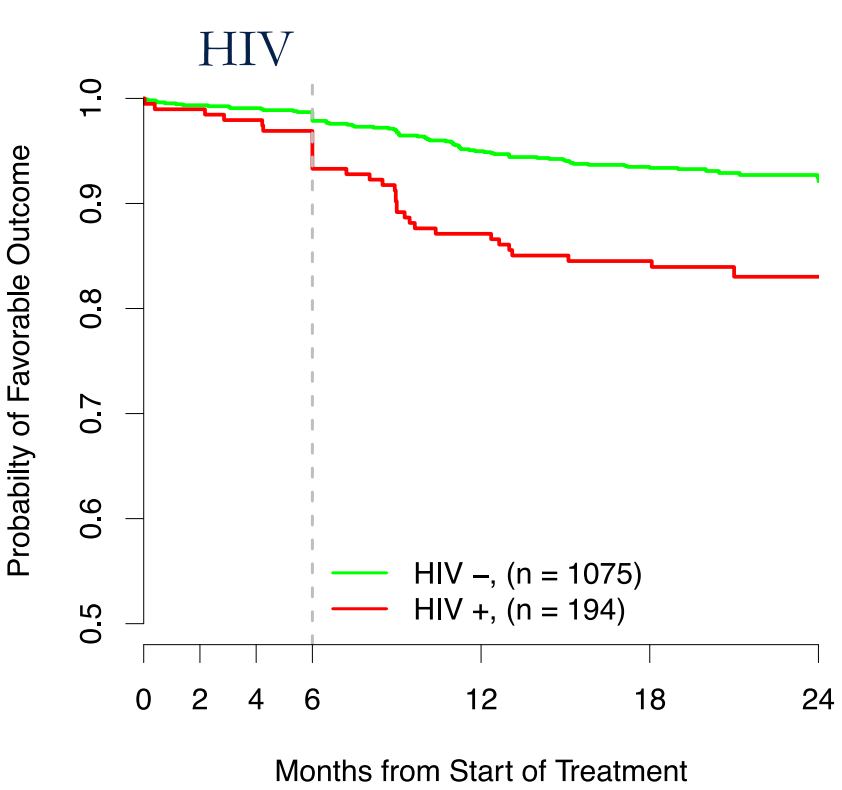


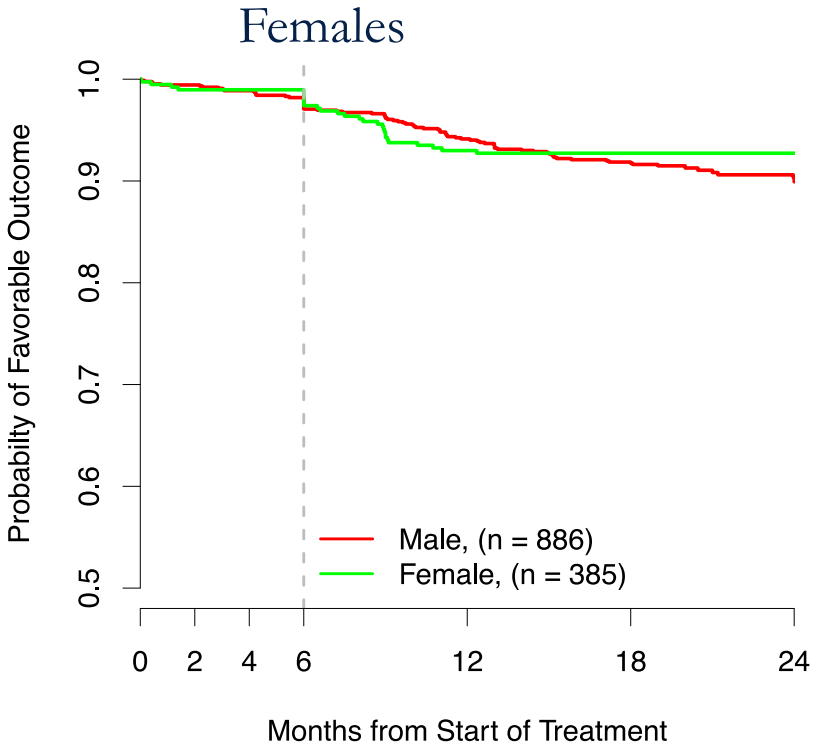
4 month culture



2 month culture

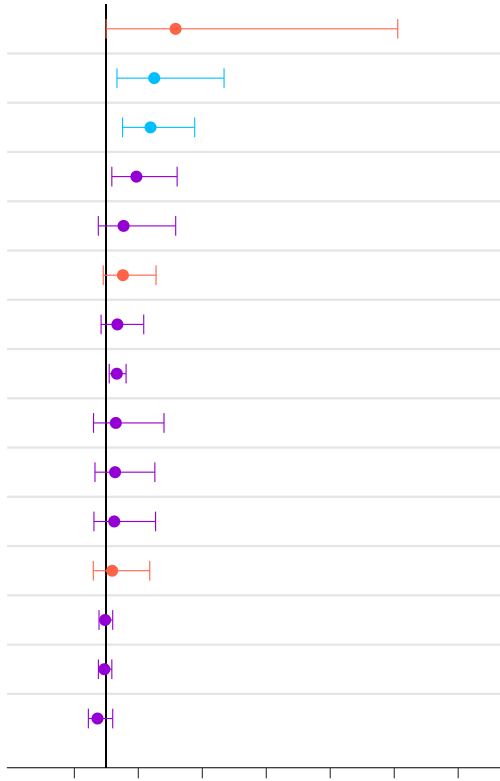



HIV
Probabilty of Favorable Outcome
1.0
0.9
0.8
0.7
0.6
0.5
HIV –, (n = 1075)
HIV +, (n = 194)
0
2
4
6
12
18
24
Months from Start of Treatment


Females
Probabilty of Favorable Outcome
1.0
0.9
0.8
0.7
0.6
0.5
Male, (n = 886)
Female, (n = 385)
0
2
4
6
12
18
24
Months from Start of Treatment

SOC PP without early failures

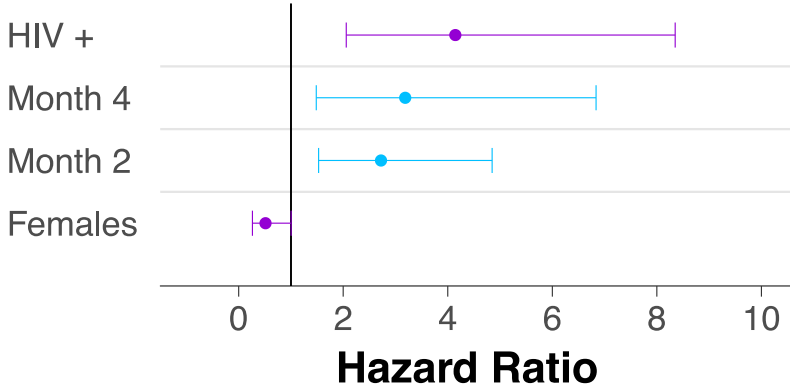
SOC- PP without early – uni



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Adherence < 90%	3.17 (0.99 – 10.11)	5.2e–02	1235 (7)	19 (16)
Month 4	**2.50 (1.33 – 4.68)**	**4.3e–03**	1102 (7)	98 (12)
Month 2	**2.38 (1.51 – 3.76)**	**2.0e–04**	1171 (7)	262 (11)
HIV +	**1.94 (1.17 – 3.21)**	**1.0e–02**	1233 (7)	181 (11)
Smear 3+ to 1+	1.54 (0.75 – 3.17)	2.4e–01	1144 (6)	582 (7)
Adherence 99–90%	1.52 (0.90 – 2.55)	1.2e–01	1235 (7)	239 (8)
Cavity Present	1.35 (0.84 – 2.17)	2.2e–01	1170 (7)	762 (7)
Age*	**1.33 (1.09 – 1.62)**	**5.0e–03**	1234 (7)	526 (10)
Smear 2+ to 1+	1.30 (0.60 – 2.80)	5.1e–01	1144 (6)	366 (6)
Asian:Black	1.27 (0.64 – 2.52)	4.9e–01	1235 (7)	155 (6)
Other:Black	1.25 (0.61 – 2.54)	5.4e–01	1235 (7)	142 (6)
Treatment Duration*	1.18 (0.59 – 2.36)	6.4e–01	1225 (7)	789 (6)
Weight*	0.96 (0.77 – 1.20)	7.3e–01	1235 (7)	590 (7)
BMI*	0.94 (0.75 – 1.17)	5.7e–01	1235 (7)	534 (6)
Females	0.72 (0.44 – 1.20)	2.1e–01	1235 (7)	375 (5)

On Treatment Culture Drug Baseline

SOC- PP without early – multi

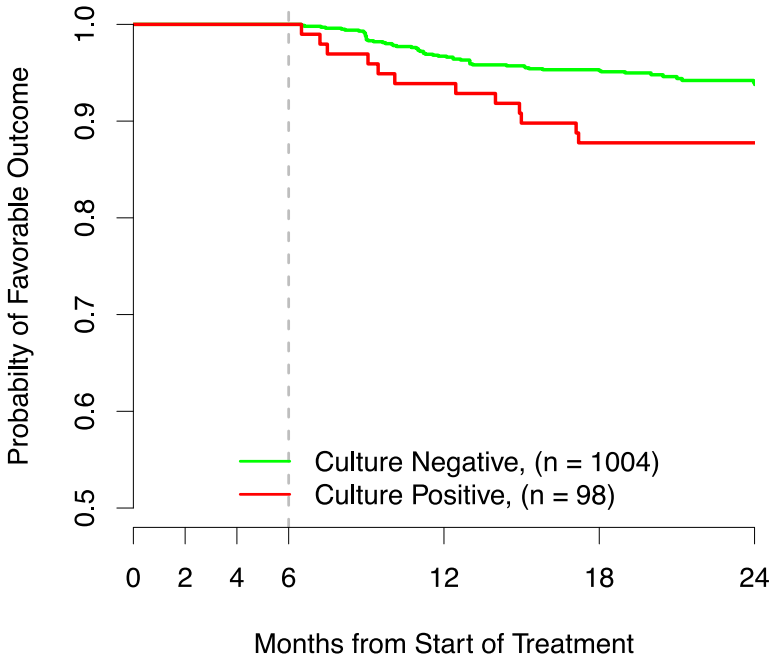


	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
HIV +	**4.15 (2.06 – 8.35)**	**6.9e–05**	914 (7)	142 (11)
Month 4	**3.19 (1.49 – 6.84)**	**2.9e–03**	914 (7)	80 (12)
Month 2	**2.72 (1.53 – 4.85)**	**6.7e–04**	914 (7)	211 (11)
Females	0.51 (0.26 – 1.00)	5.1e–02	914 (7)	270 (4)

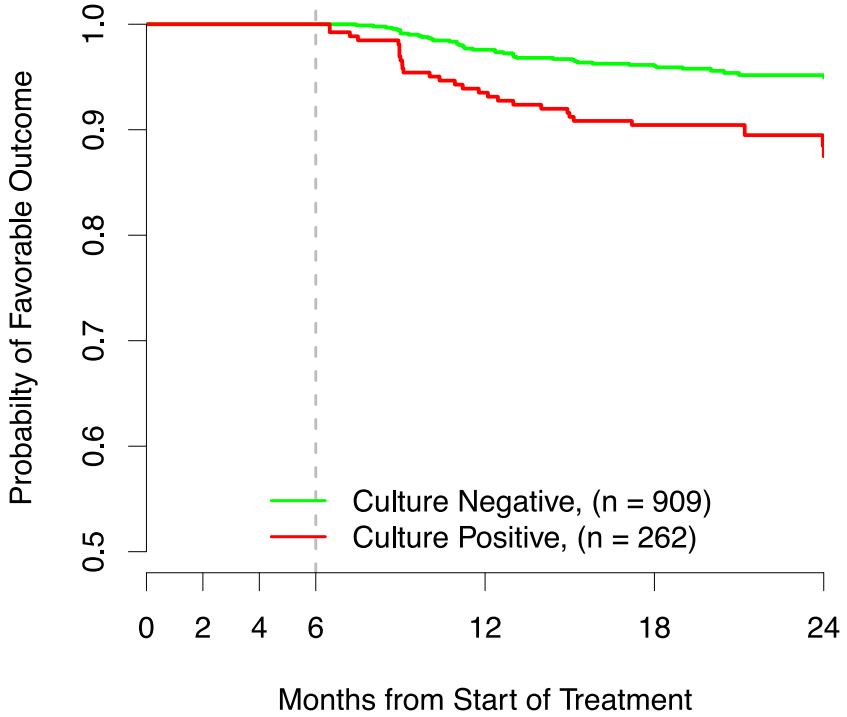
On Treatment Culture Drug Baseline

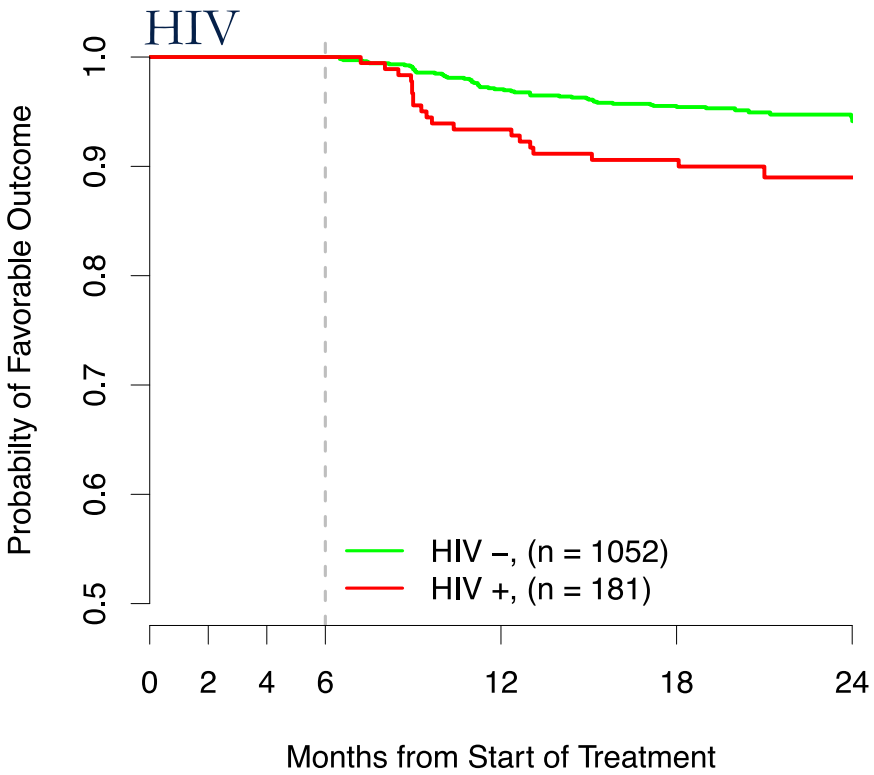
Survival Plots for significant multivariate predictors

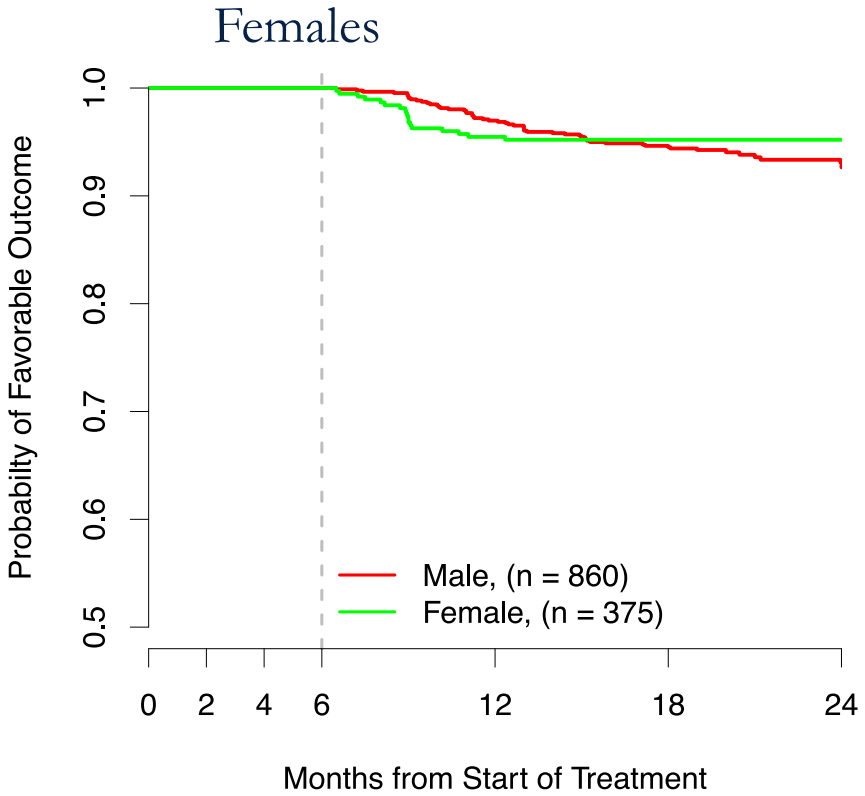
4 month culture



2 month culture



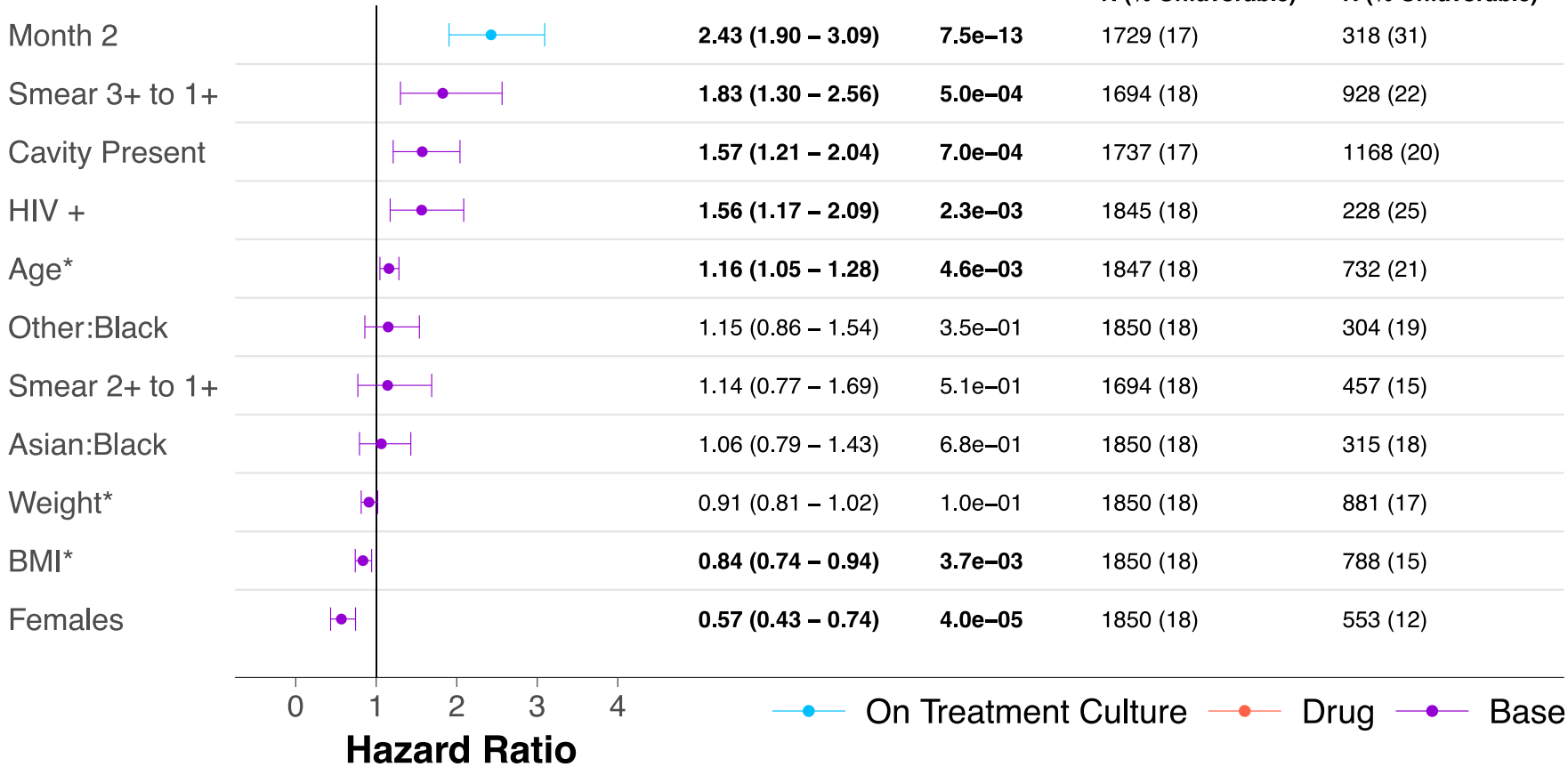

HIV
Probabilty of Favorable Outcome
1.0
0.9
0.8
0.7
0.6
0.5
HIV –, (n = 1052)
HIV +, (n = 181)
0
2
4
6
12
18
24
Months from Start of Treatment


Females
Probabilty of Favorable Outcome
1.0
0.9
0.8
0.7
0.6
0.5
Male, (n = 860)
Female, (n = 375)
0
2
4
6
12
18
24
Months from Start of Treatment

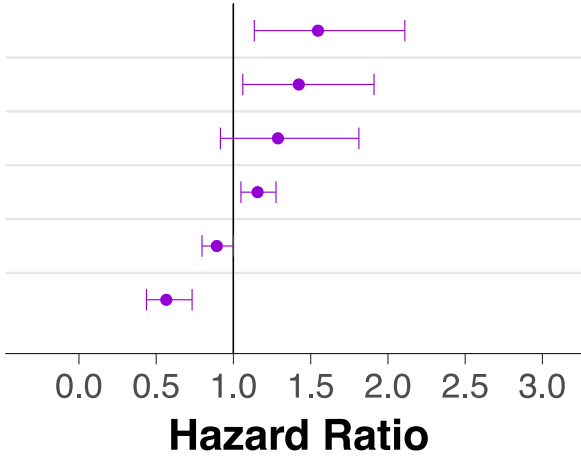
4 months MITT

4 months PP

EXP-PP uni (without DA or Duration)

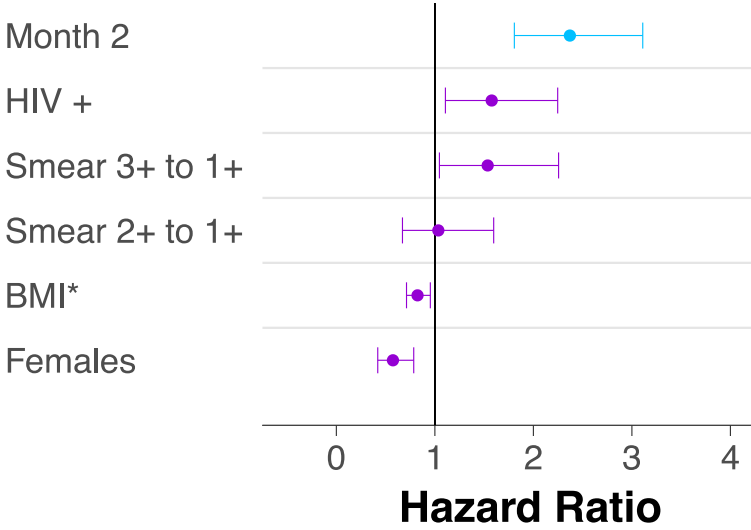


EXP-pp multi baseline only



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Smear 3+ to 1+	**1.55 (1.13 – 2.11)**	**5.8e–03**	1698 (23)	919 (25)
HIV +	**1.42 (1.06 – 1.91)**	**1.9e–02**	1698 (23)	213 (27)
Smear 2+ to 1+	1.29 (0.92 – 1.81)	1.5e–01	1698 (23)	479 (21)
Age*	**1.16 (1.05 – 1.28)**	**3.7e–03**	1698 (23)	677 (27)
Weight*	0.89 (0.80 – 1.00)	5.0e–02	1698 (23)	825 (23)
Females	**0.57 (0.44 – 0.73)**	**1.5e–05**	1698 (23)	497 (16)

EXP-pp multi (without DA or Duration)

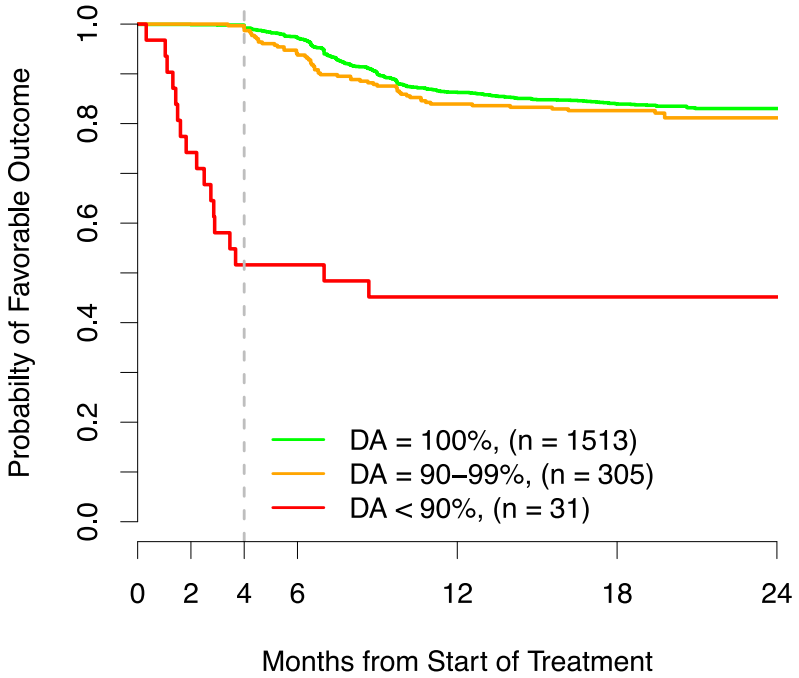


	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 2	**2.37 (1.81 – 3.11)**	**4.6e–10**	1488 (18)	282 (32)
HIV +	**1.58 (1.11 – 2.25)**	**1.2e–02**	1488 (18)	188 (22)
Smear 3+ to 1+	**1.54 (1.05 – 2.26)**	**2.9e–02**	1488 (18)	820 (21)
Smear 2+ to 1+	1.04 (0.67 – 1.60)	8.8e–01	1488 (18)	413 (14)
BMI*	**0.82 (0.71 – 0.95)**	**9.6e–03**	1488 (18)	639 (15)
Females	**0.57 (0.42 – 0.79)**	**5.2e–04**	1488 (18)	433 (12)

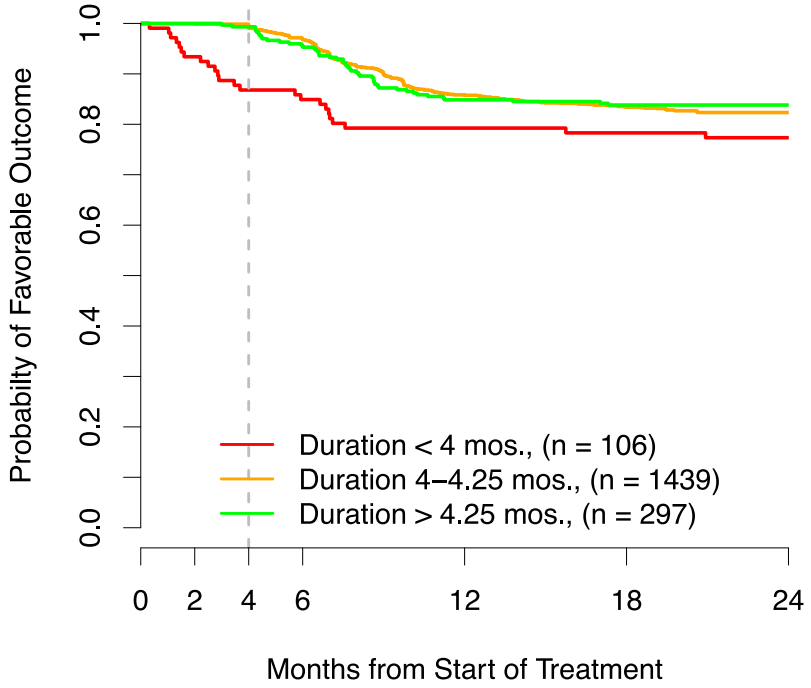
On Treatment Culture — Drug — Baseline

Survival Plots for significant multivariate predictors

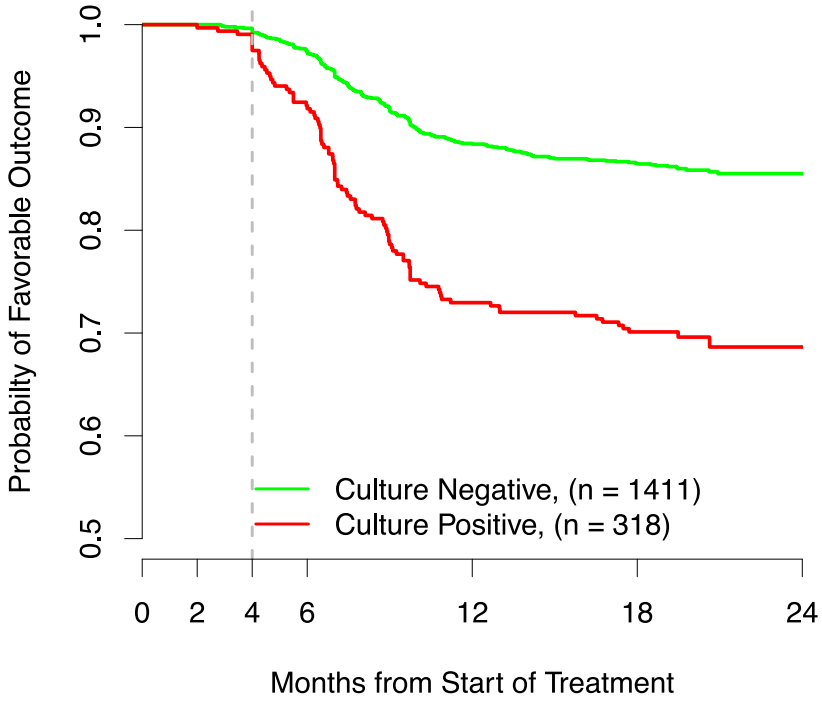
Drug Adherence



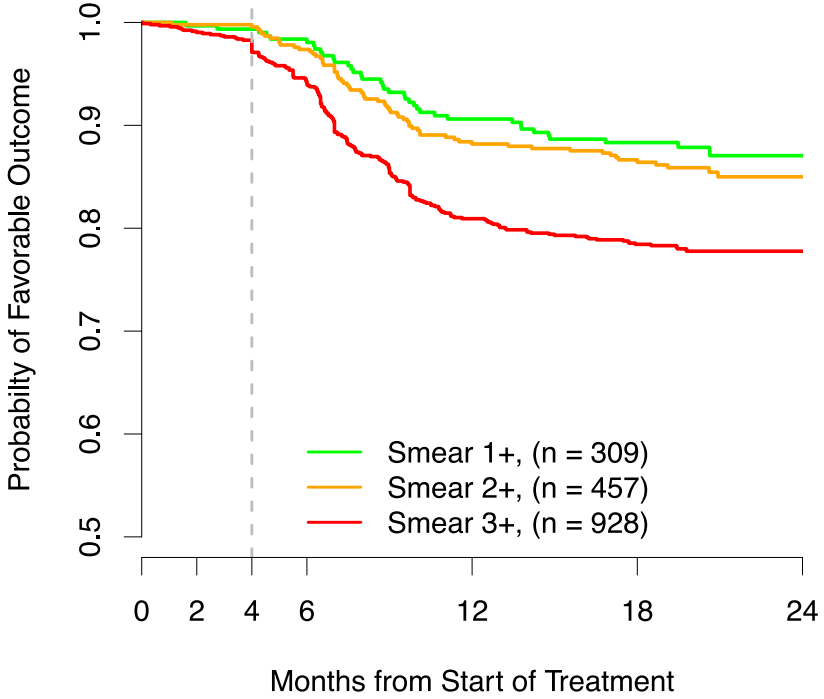
Treatment Duration

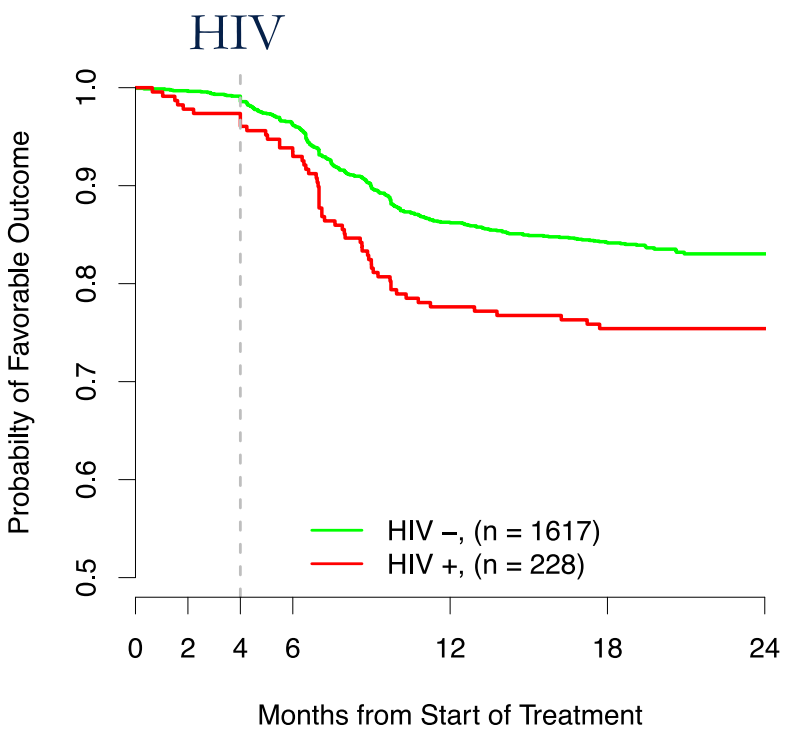


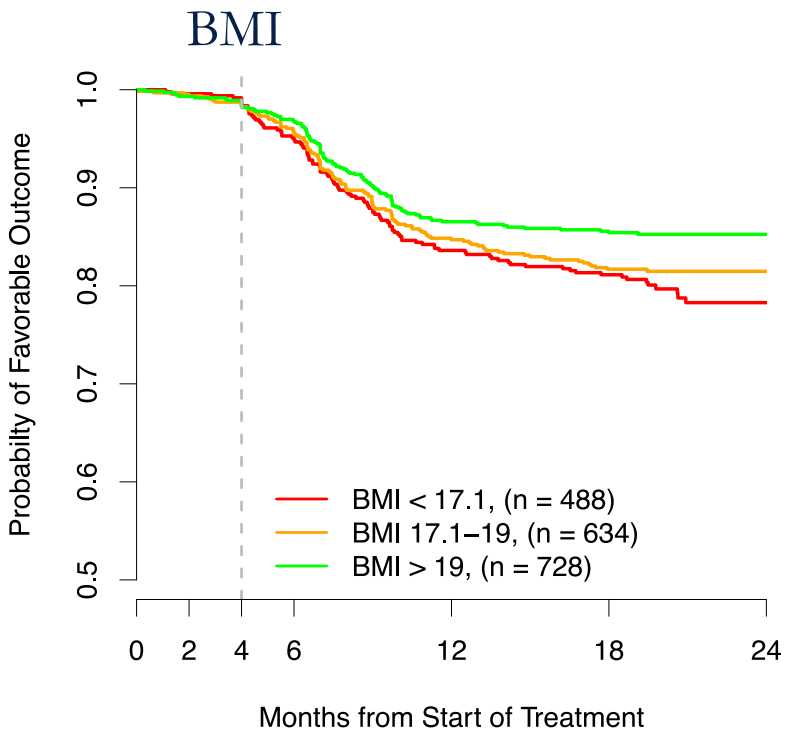
Month 2 culture

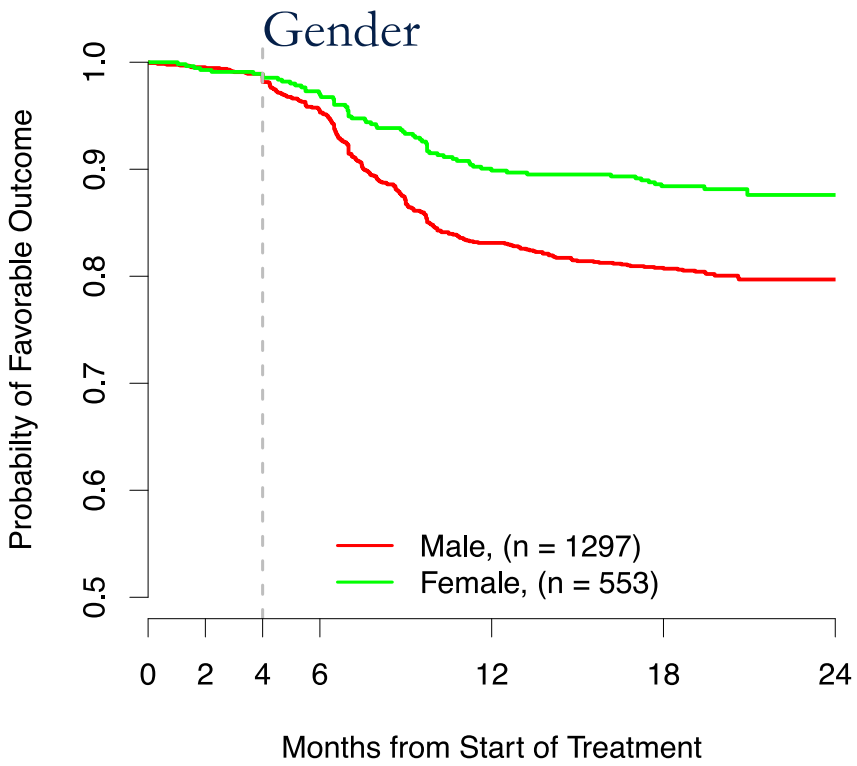


Smear



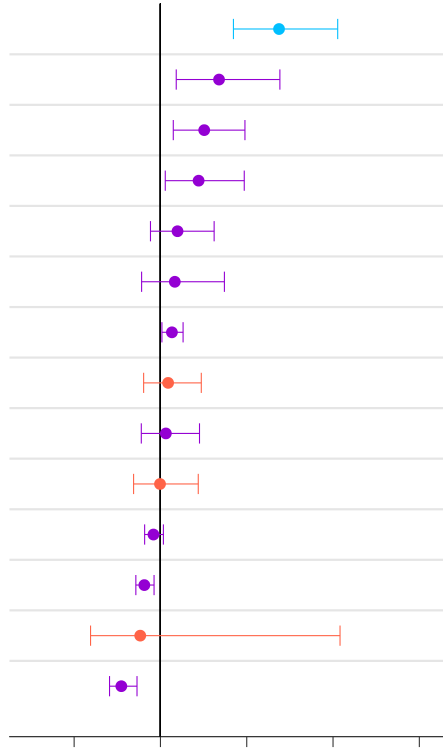

HIV
Probabilty of Favorable Outcome
1.0
0.9
0.8
0.7
0.6
0.5
HIV –, (n = 1617)
HIV +, (n = 228)
0
2
4
6
12
18
24
Months from Start of Treatment


BMI
Probabilty of Favorable Outcome
1.0
0.9
0.8
0.7
0.6
0.5
BMI < 17.1, (n = 488)
BMI 17.1–19, (n = 634)
BMI > 19, (n = 728)
0
2
4
6
12
18
24
Months from Start of Treatment


Gender
Probabilty of Favorable Outcome
1.0
0.9
0.8
0.7
0.6
0.5
Male, (n = 1297)
Female, (n = 553)
0
2
4
6
12
18
24
Months from Start of Treatment

4 months PP without early failures

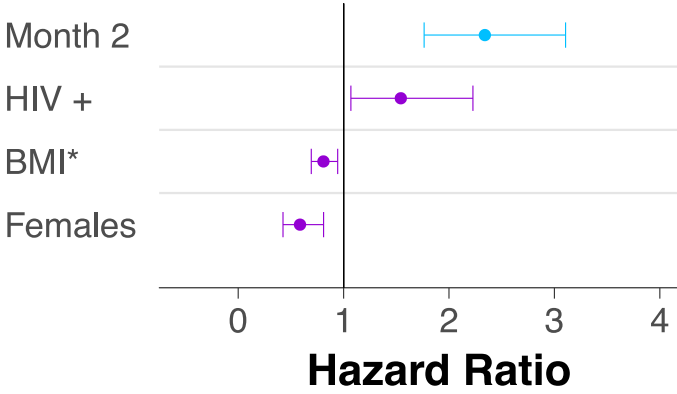
EXP-PP without early – uni



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 2	**2.37 (1.85 – 3.05)**	**1.7e–11**	1710 (16)	310 (29)
Smear 3+ to 1+	**1.68 (1.18 – 2.38)**	**3.7e–03**	1663 (17)	901 (20)
Cavity Present	**1.51 (1.15 – 1.98)**	**3.1e–03**	1707 (16)	1143 (18)
HIV +	**1.44 (1.06 – 1.97)**	**2.1e–02**	1813 (16)	219 (21)
Other:Black	1.20 (0.88 – 1.62)	2.4e–01	1818 (16)	300 (18)
Smear 2+ to 1+	1.17 (0.78 – 1.74)	4.5e–01	1663 (17)	455 (14)
Age*	**1.13 (1.02 – 1.26)**	**2.3e–02**	1815 (16)	715 (19)
Adherence 99–90%	1.09 (0.81 – 1.47)	5.8e–01	1818 (16)	301 (17)
Asian:Black	1.06 (0.78 – 1.45)	7.0e–01	1818 (16)	309 (16)
Treatment Duration*	1.00 (0.69 – 1.44)	9.8e–01	1812 (16)	1375 (17)
Weight*	0.92 (0.82 – 1.03)	1.6e–01	1818 (16)	865 (15)
BMI*	**0.81 (0.71 – 0.93)**	**1.8e–03**	1818 (16)	774 (14)
Adherence < 90%	0.77 (0.19 – 3.08)	7.1e–01	1818 (16)	16 (12)
Females	**0.55 (0.41 – 0.73)**	**3.8e–05**	1818 (16)	545 (11)

On Treatment Culture Drug Baseline

EXP-PP without early –multi

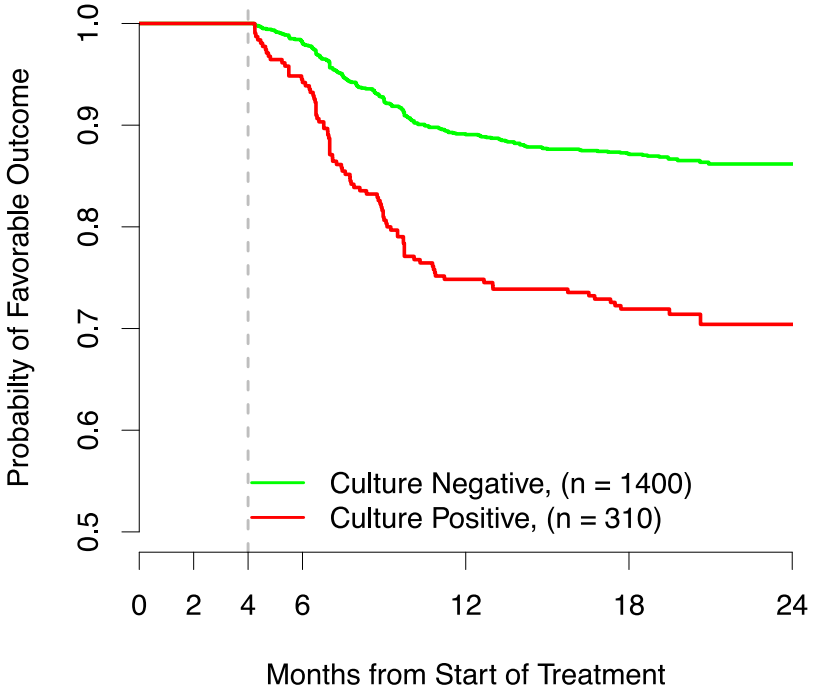


	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 2	**2.34 (1.76 – 3.11)**	**3.8e–09**	1465 (16)	273 (29)
HIV +	**1.54 (1.07 – 2.23)**	**2.1e–02**	1465 (16)	184 (21)
BMI*	**0.81 (0.69 – 0.94)**	**6.9e–03**	1465 (16)	630 (14)
Females	**0.59 (0.42 – 0.81)**	**1.2e–03**	1465 (16)	430 (11)

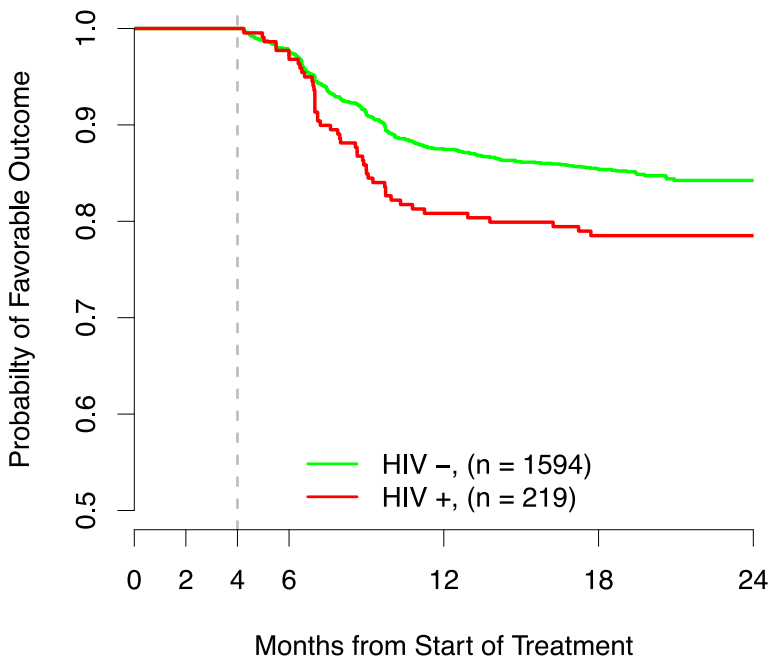
On Treatment Culture — Drug — Baseline

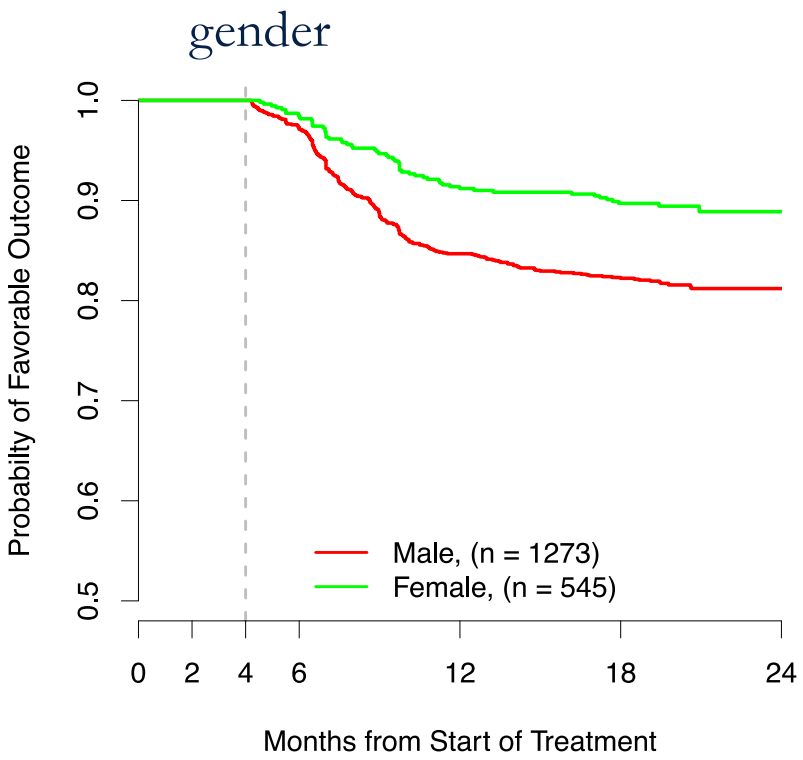
Survival Plots for significant multivariate predictors

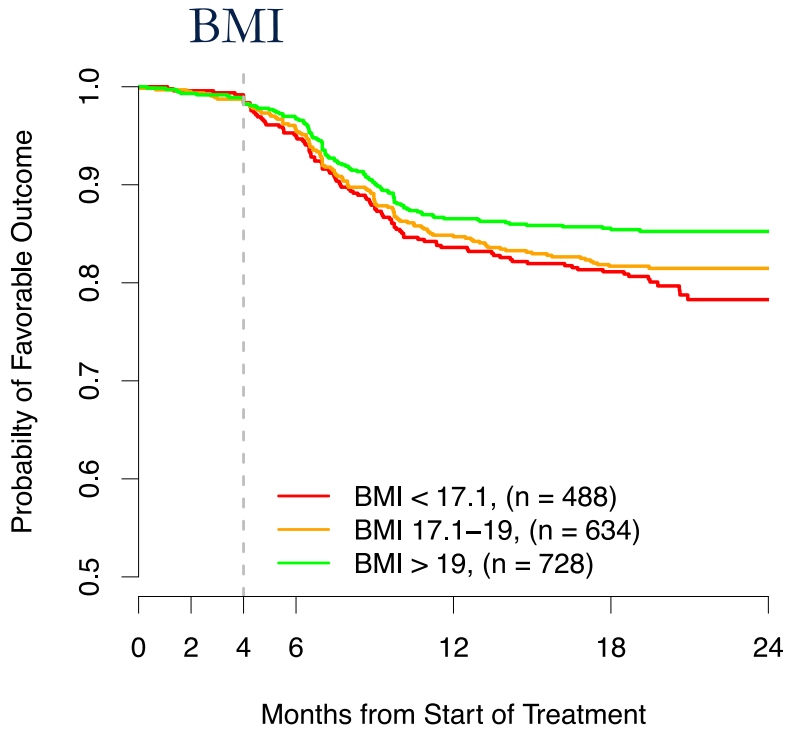
Month 2 culture



HIV

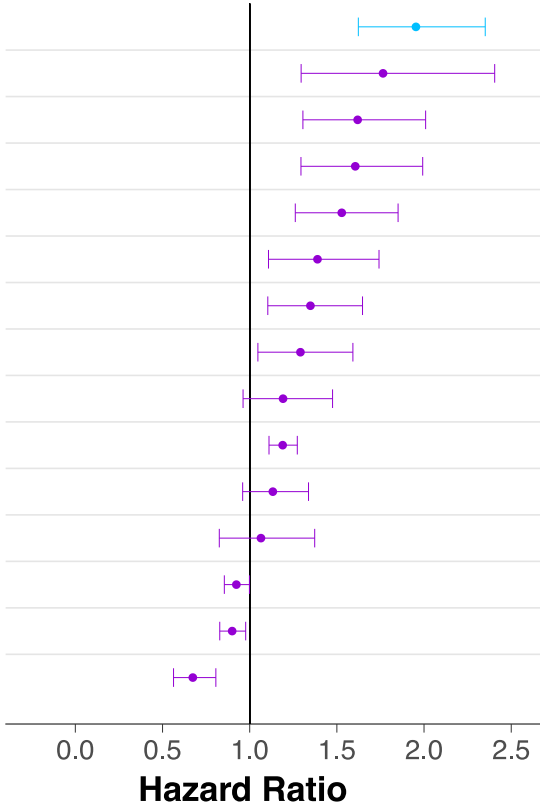



gender
Probabilty of Favorable Outcome
1.0
0.9
0.8
0.7
0.6
0.5
Male, (n = 1273)
Female, (n = 545)
0
2
4
6
12
18
24
Months from Start of Treatment


BMI
Probabilty of Favorable Outcome
1.0
0.9
0.8
0.7
0.6
0.5
BMI < 17.1, (n = 488)
BMI 17.1–19, (n = 634)
BMI > 19, (n = 728)
0
2
4
6
12
18
24
Months from Start of Treatment

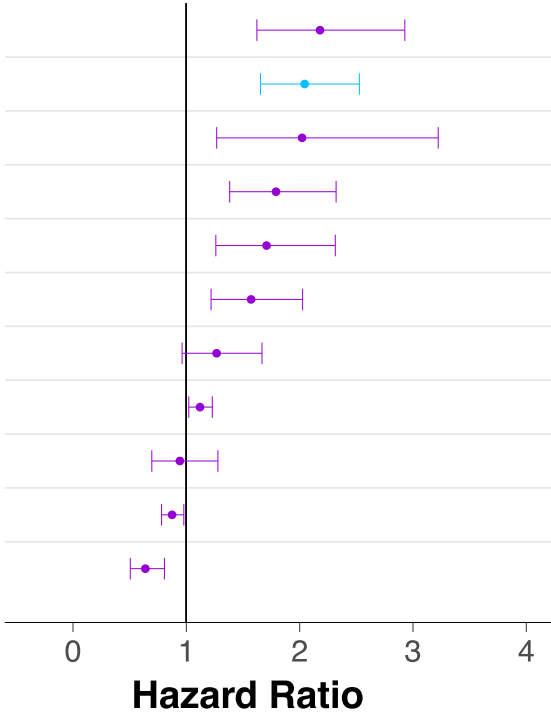
SOC + 4 months MITT

Both SOC and EXP- MITT uni (without DA or Duration)



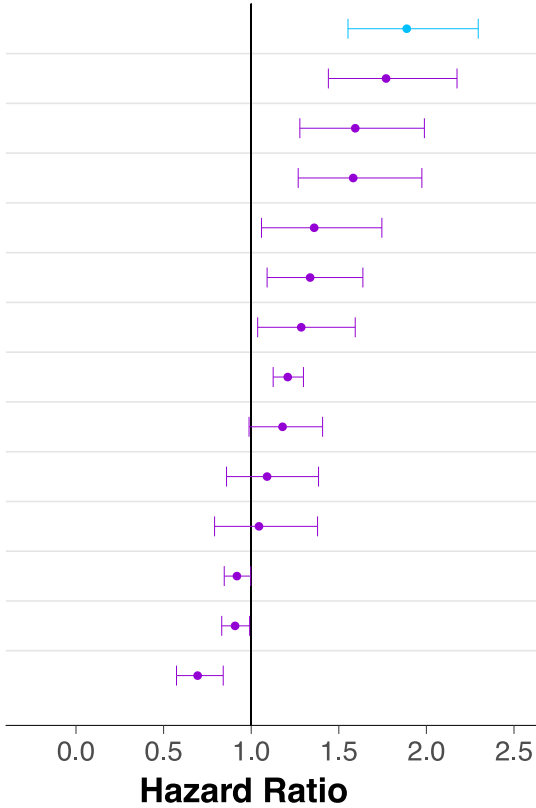
	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 2	**1.95 (1.62 – 2.35)**	**1.4e–12**	3082 (17)	619 (26)
RIFAQUIN, 2MERZ/2P2M2	**1.76 (1.30 – 2.41)**	**3.2e–04**	3400 (20)	190 (26)
ReMOX, 2MERZ/2MR	**1.62 (1.31 – 2.01)**	**1.2e–05**	3400 (20)	551 (24)
ReMOX, 2MHRZ/2MHR	**1.61 (1.29 – 1.99)**	**1.7e–05**	3400 (20)	568 (23)
HIV +	**1.53 (1.26 – 1.85)**	**1.5e–05**	3391 (20)	468 (28)
Smear 3+ to 1+	**1.39 (1.11 – 1.74)**	**4.4e–03**	3120 (20)	1653 (23)
Asian:Black	**1.35 (1.10 – 1.65)**	**3.4e–03**	3400 (20)	527 (23)
OFLOTUB, 2GHRZ/2GHR	**1.29 (1.05 – 1.59)**	**1.7e–02**	3400 (20)	688 (21)
Other:Black	1.19 (0.96 – 1.48)	1.1e–01	3400 (20)	486 (21)
Age*	**1.19 (1.11 – 1.27)**	**6.3e–07**	3395 (20)	1467 (25)
Cavity Present	1.13 (0.96 – 1.34)	1.4e–01	3200 (20)	2093 (21)
Smear 2+ to 1+	1.06 (0.83 – 1.37)	6.3e–01	3120 (20)	905 (18)
Weight*	**0.92 (0.85 – 1.00)**	**4.5e–02**	3400 (20)	1606 (19)
BMI*	**0.90 (0.83 – 0.98)**	**1.2e–02**	3400 (20)	1468 (19)
Females	**0.67 (0.56 – 0.81)**	**1.6e–05**	3400 (20)	1006 (15)

Both SOC- EXP MITT- multi (without DA or Duration)



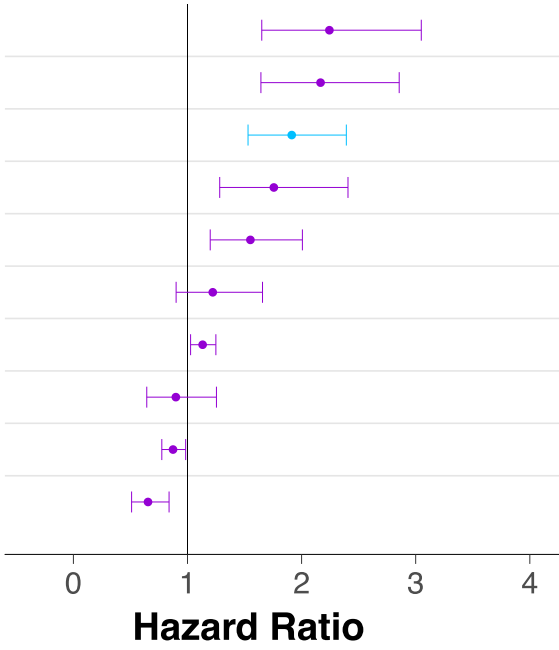
	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
ReMOX, 2MERZ/2MR	**2.18 (1.62 – 2.93)**	**2.3e–07**	2683 (17)	377 (23)
Month 2	**2.04 (1.65 – 2.53)**	**3.7e–11**	2683 (17)	544 (27)
RIFAQUIN, 2MERZ/2P2M2	**2.02 (1.27 – 3.22)**	**3.1e–03**	2683 (17)	150 (21)
HIV +	**1.79 (1.38 – 2.32)**	**1.0e–05**	2683 (17)	374 (23)
ReMOX, 2MHRZ/2MHR	**1.71 (1.26 – 2.31)**	**5.6e–04**	2683 (17)	386 (19)
OFLOTUB, 2GHRZ/2GHR	**1.57 (1.22 – 2.03)**	**4.9e–04**	2683 (17)	639 (20)
Smear 3+ to 1+	1.27 (0.96 – 1.67)	9.1e–02	2683 (17)	1424 (20)
Age*	**1.12 (1.02 – 1.23)**	**1.5e–02**	2683 (17)	1158 (21)
Smear 2+ to 1+	0.94 (0.70 – 1.28)	7.0e–01	2683 (17)	792 (14)
BMI*	**0.87 (0.78 – 0.98)**	**1.9e–02**	2683 (17)	1168 (15)
Females	**0.64 (0.51 – 0.81)**	**1.7e–04**	2683 (17)	777 (12)

Both SOC and EXP- MITT uni (without DA or Duration)- without RIFAQUIN



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 2	**1.89 (1.55 – 2.30)**	**2.0e–10**	2739 (17)	572 (26)
HIV +	**1.77 (1.44 – 2.17)**	**5.6e–08**	3013 (20)	359 (31)
ReMOX, 2MERZ/2MR	**1.59 (1.28 – 1.99)**	**3.6e–05**	3022 (20)	551 (24)
ReMOX, 2MHRZ/2MHR	**1.58 (1.27 – 1.97)**	**4.8e–05**	3022 (20)	568 (23)
Smear 3+ to 1+	**1.36 (1.06 – 1.75)**	**1.6e–02**	2779 (20)	1514 (22)
Asian:Black	**1.34 (1.09 – 1.64)**	**5.1e–03**	3022 (20)	527 (23)
OFLOTUB, 2GHRZ/2GHR	**1.29 (1.04 – 1.59)**	**2.2e–02**	3022 (20)	688 (21)
Age*	**1.21 (1.13 – 1.30)**	**2.1e–07**	3017 (20)	1282 (25)
Cavity Present	1.18 (0.99 – 1.41)	6.9e–02	2849 (20)	1861 (21)
Other:Black	1.09 (0.86 – 1.38)	4.8e–01	3022 (20)	409 (20)
Smear 2+ to 1+	1.04 (0.79 – 1.38)	7.6e–01	2779 (20)	827 (18)
Weight*	**0.92 (0.85 – 1.00)**	**4.2e–02**	3022 (20)	1416 (19)
BMI*	**0.91 (0.83 – 0.99)**	**3.0e–02**	3022 (20)	1280 (18)
Females	**0.69 (0.57 – 0.84)**	**1.8e–04**	3022 (20)	867 (16)

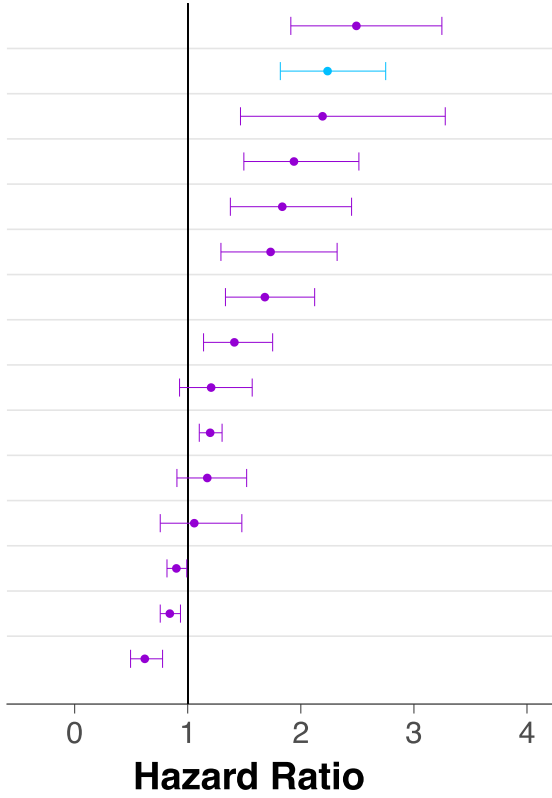
Both SOC- EXP MITT- multi (without DA or Duration)- without RIFAQUIN



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
ReMOX, 2MERZ/2MR	**2.24 (1.65 – 3.05)**	**2.4e–07**	2393 (17)	377 (23)
HIV +	**2.17 (1.64 – 2.86)**	**4.1e–08**	2393 (17)	296 (26)
Month 2	**1.91 (1.53 – 2.39)**	**1.2e–08**	2393 (17)	501 (27)
ReMOX, 2MHRZ/2MHR	**1.76 (1.28 – 2.41)**	**4.5e–04**	2393 (17)	386 (19)
OFLOTUB, 2GHRZ/2GHR	**1.55 (1.20 – 2.01)**	**8.3e–04**	2393 (17)	639 (20)
Smear 3+ to 1+	1.22 (0.90 – 1.66)	2.0e–01	2393 (17)	1309 (19)
Age*	**1.13 (1.03 – 1.25)**	**1.2e–02**	2393 (17)	1018 (21)
Smear 2+ to 1+	0.90 (0.64 – 1.25)	5.3e–01	2393 (17)	728 (14)
BMI*	**0.87 (0.78 – 0.98)**	**2.6e–02**	2393 (17)	1022 (15)
Females	**0.65 (0.51 – 0.84)**	**8.1e–04**	2393 (17)	669 (13)

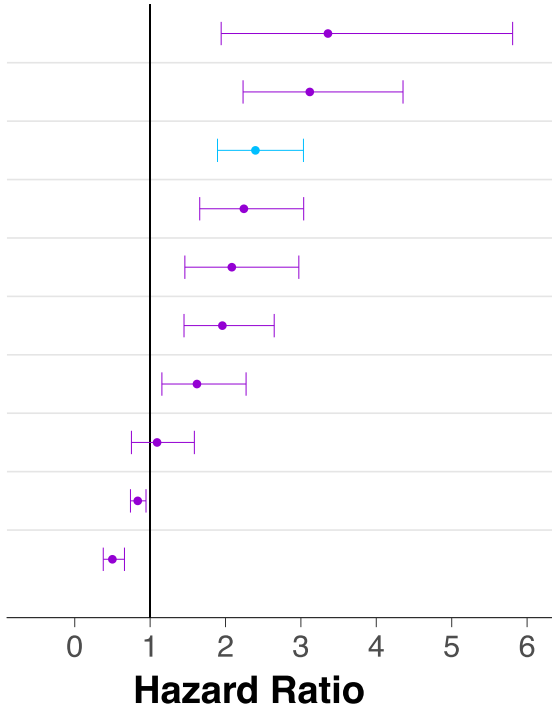
SOC + 4 months PP

Both SOC and EXP- PP uni (without DA or Duration)



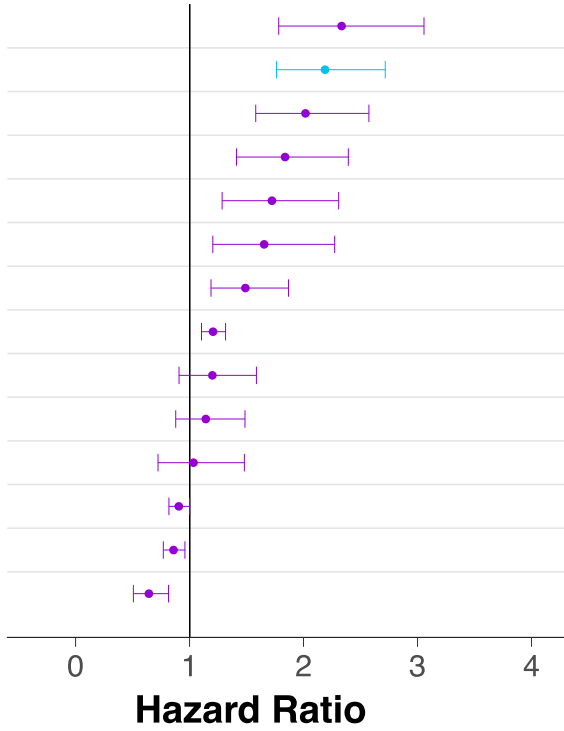
	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
ReMOX, 2MERZ/2MR	**2.49 (1.91 – 3.25)**	**1.5e–11**	3121 (14)	524 (20)
Month 2	**2.24 (1.82 – 2.75)**	**2.4e–14**	2924 (14)	589 (23)
RIFAQUIN, 2MERZ/2P2M2	**2.19 (1.47 – 3.28)**	**1.3e–04**	3121 (14)	165 (18)
OFLOTUB, 2GHRZ/2GHR	**1.94 (1.50 – 2.51)**	**5.6e–07**	3121 (14)	647 (18)
ReMOX, 2MHRZ/2MHR	**1.84 (1.38 – 2.45)**	**3.6e–05**	3121 (14)	514 (15)
Smear 3+ to 1+	**1.73 (1.29 – 2.32)**	**2.3e–04**	2870 (14)	1533 (17)
HIV +	**1.68 (1.33 – 2.12)**	**1.2e–05**	3114 (14)	422 (21)
Cavity Present	**1.41 (1.14 – 1.75)**	**1.6e–03**	2943 (14)	1950 (16)
Other:Black	1.21 (0.93 – 1.57)	1.6e–01	3121 (14)	448 (15)
Age*	**1.20 (1.10 – 1.30)**	**2.4e–05**	3117 (14)	1337 (18)
Asian:Black	1.17 (0.90 – 1.52)	2.3e–01	3121 (14)	475 (15)
Smear 2+ to 1+	1.06 (0.76 – 1.48)	7.4e–01	2870 (14)	827 (11)
Weight*	**0.90 (0.82 – 0.99)**	**3.2e–02**	3121 (14)	1476 (13)
BMI*	**0.84 (0.76 – 0.94)**	**1.4e–03**	3121 (14)	1343 (12)
Females	**0.62 (0.49 – 0.78)**	**3.5e–05**	3121 (14)	938 (10)

Both SOC- EXP PP multi (without DA or Duration)



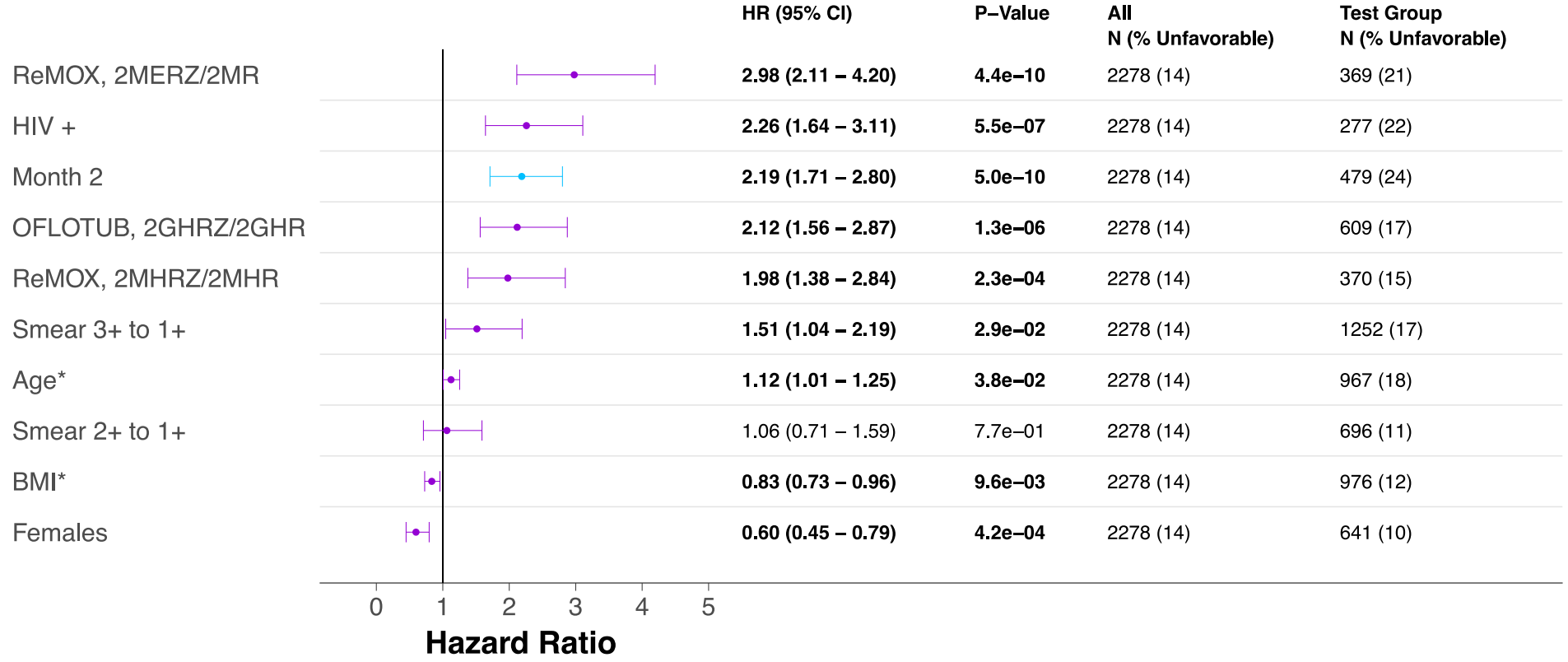
	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
RIFAQUIN, 2MERZ/2P2M2	**3.36 (1.94 – 5.81)**	**1.5e–05**	2542 (14)	140 (18)
ReMOX, 2MERZ/2MR	**3.12 (2.23 – 4.35)**	**2.5e–11**	2542 (14)	369 (21)
Month 2	**2.40 (1.89 – 3.03)**	**3.7e–13**	2542 (14)	516 (24)
OFLOTUB, 2GHRZ/2GHR	**2.24 (1.66 – 3.04)**	**1.7e–07**	2542 (14)	609 (17)
ReMOX, 2MHRZ/2MHR	**2.08 (1.46 – 2.97)**	**5.1e–05**	2542 (14)	370 (15)
HIV +	**1.96 (1.45 – 2.65)**	**1.2e–05**	2542 (14)	350 (19)
Smear 3+ to 1+	**1.62 (1.16 – 2.27)**	**5.1e–03**	2542 (14)	1358 (17)
Smear 2+ to 1+	1.09 (0.75 – 1.59)	6.4e–01	2542 (14)	753 (11)
Weight*	**0.84 (0.74 – 0.95)**	**4.3e–03**	2542 (14)	1234 (13)
Females	**0.50 (0.38 – 0.66)**	**9.6e–07**	2542 (14)	743 (9)

Both SOC and EXP- PP uni (without DA or Duration)- without RIF



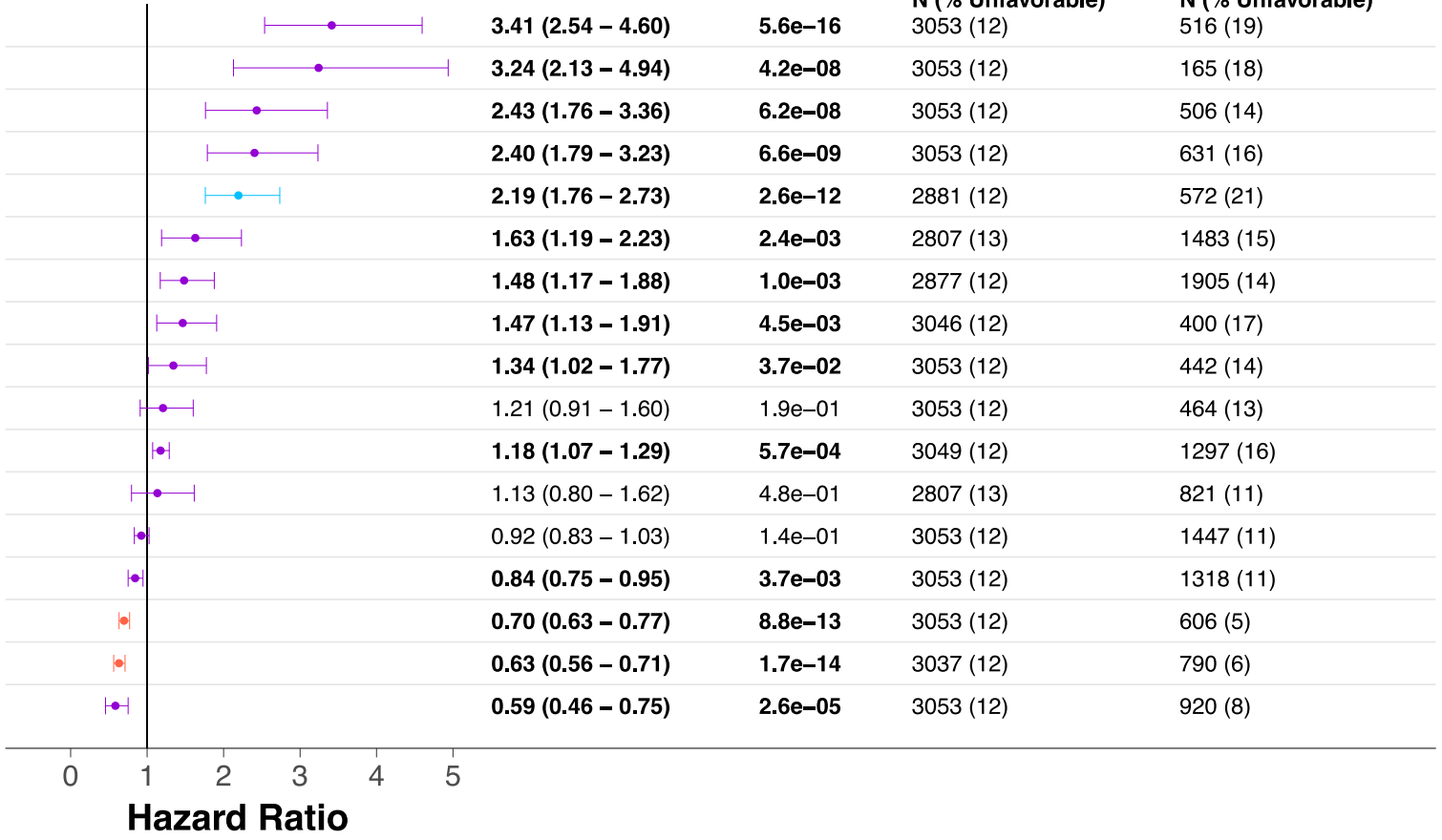
	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
ReMOX, 2MERZ/2MR	**2.33 (1.78 – 3.06)**	**7.4e–10**	2793 (15)	524 (20)
Month 2	**2.19 (1.76 – 2.72)**	**1.2e–12**	2612 (14)	548 (23)
HIV +	**2.02 (1.58 – 2.57)**	**1.7e–08**	2786 (15)	326 (25)
OFLOTUB, 2GHRZ/2GHR	**1.84 (1.41 – 2.39)**	**6.2e–06**	2793 (15)	647 (18)
ReMOX, 2MHRZ/2MHR	**1.72 (1.29 – 2.31)**	**2.7e–04**	2793 (15)	514 (15)
Smear 3+ to 1+	**1.65 (1.20 – 2.27)**	**1.9e–03**	2570 (15)	1409 (18)
Cavity Present	**1.49 (1.19 – 1.87)**	**5.6e–04**	2639 (15)	1747 (16)
Age*	**1.21 (1.11 – 1.32)**	**2.7e–05**	2789 (15)	1175 (19)
Other:Black	1.20 (0.91 – 1.59)	2.0e–01	2793 (15)	388 (16)
Asian:Black	1.14 (0.88 – 1.49)	3.2e–01	2793 (15)	475 (15)
Smear 2+ to 1+	1.03 (0.72 – 1.48)	8.5e–01	2570 (15)	761 (12)
Weight*	0.91 (0.82 – 1.00)	5.3e–02	2793 (15)	1315 (14)
BMI*	**0.86 (0.77 – 0.96)**	**7.1e–03**	2793 (15)	1187 (13)
Females	**0.64 (0.51 – 0.82)**	**2.7e–04**	2793 (15)	812 (11)

Both SOC- EXP PP multi (without DA or Duration)- without RIF



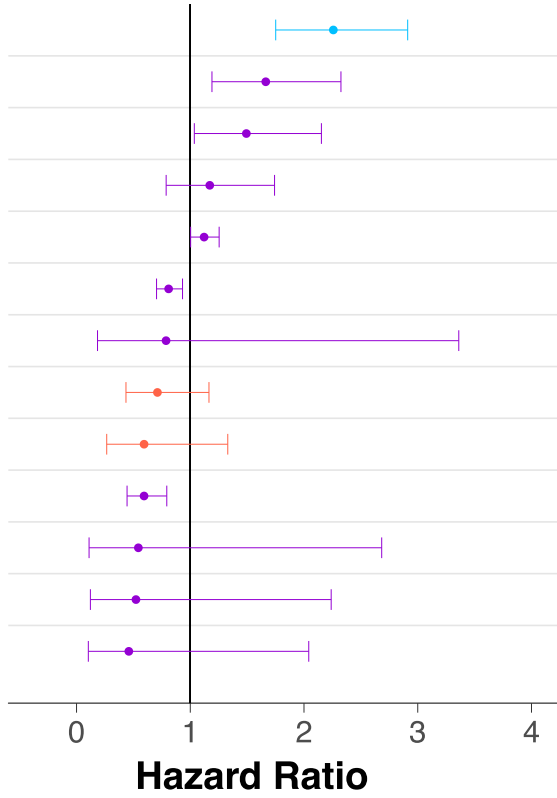
SOC + 4 months PP without early failures

Both SOC and EXP- PP without early uni



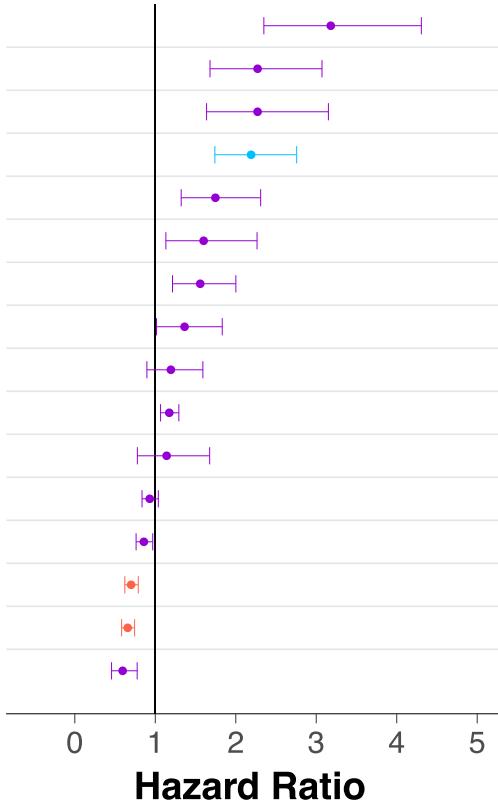
	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
ReMOX, 2MERZ/2MR	**3.41 (2.54 – 4.60)**	**5.6e–16**	3053 (12)	516 (19)
RIFAQUIN, 2MERZ/2P2M2	**3.24 (2.13 – 4.94)**	**4.2e–08**	3053 (12)	165 (18)
ReMOX, 2MHRZ/2MHR	**2.43 (1.76 – 3.36)**	**6.2e–08**	3053 (12)	506 (14)
OFLOTUB, 2GHRZ/2GHR	**2.40 (1.79 – 3.23)**	**6.6e–09**	3053 (12)	631 (16)
Month 2	**2.19 (1.76 – 2.73)**	**2.6e–12**	2881 (12)	572 (21)
Smear 3+ to 1+	**1.63 (1.19 – 2.23)**	**2.4e–03**	2807 (13)	1483 (15)
Cavity Present	**1.48 (1.17 – 1.88)**	**1.0e–03**	2877 (12)	1905 (14)
HIV +	**1.47 (1.13 – 1.91)**	**4.5e–03**	3046 (12)	400 (17)
Other:Black	**1.34 (1.02 – 1.77)**	**3.7e–02**	3053 (12)	442 (14)
Asian:Black	1.21 (0.91 – 1.60)	1.9e–01	3053 (12)	464 (13)
Age*	**1.18 (1.07 – 1.29)**	**5.7e–04**	3049 (12)	1297 (16)
Smear 2+ to 1+	1.13 (0.80 – 1.62)	4.8e–01	2807 (13)	821 (11)
Weight*	0.92 (0.83 – 1.03)	1.4e–01	3053 (12)	1447 (11)
BMI*	**0.84 (0.75 – 0.95)**	**3.7e–03**	3053 (12)	1318 (11)
Total Number of Doses*	**0.70 (0.63 – 0.77)**	**8.8e–13**	3053 (12)	606 (5)
Treatment Duration*	**0.63 (0.56 – 0.71)**	**1.7e–14**	3037 (12)	790 (6)
Females	**0.59 (0.46 – 0.75)**	**2.6e–05**	3053 (12)	920 (8)

Both SOC and EXP- PP without early multi



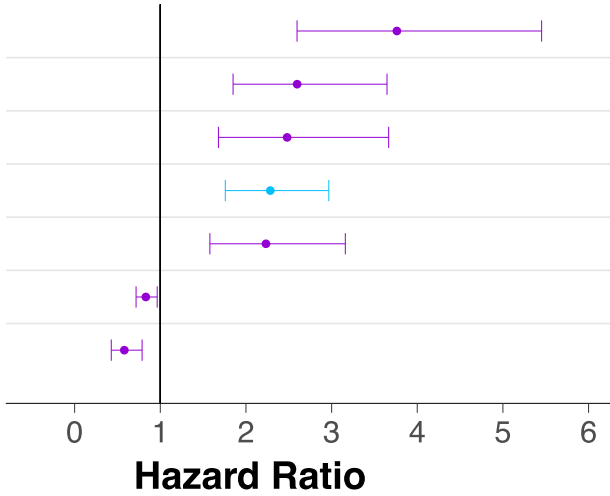
	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 2	**2.26 (1.75 – 2.91)**	**3.4e–10**	2486 (12)	498 (21)
HIV +	**1.66 (1.19 – 2.33)**	**2.9e–03**	2486 (12)	338 (16)
Smear 3+ to 1+	**1.49 (1.04 – 2.15)**	**3.2e–02**	2486 (12)	1319 (15)
Smear 2+ to 1+	1.17 (0.79 – 1.74)	4.3e–01	2486 (12)	744 (10)
Age*	**1.12 (1.00 – 1.25)**	**4.3e–02**	2486 (12)	1072 (16)
BMI*	**0.81 (0.70 – 0.93)**	**3.3e–03**	2486 (12)	1086 (10)
ReMOX, 2MERZ/2MR	0.79 (0.18 – 3.36)	7.5e–01	2486 (12)	365 (20)
Total Number of Doses*	0.71 (0.43 – 1.16)	1.8e–01	2486 (12)	448 (5)
Treatment Duration*	0.59 (0.27 – 1.33)	2.0e–01	2486 (12)	623 (6)
Females	**0.59 (0.44 – 0.79)**	**4.3e–04**	2486 (12)	733 (8)
RIFAQUIN, 2MERZ/2P2M2	0.54 (0.11 – 2.68)	4.5e–01	2486 (12)	140 (18)
ReMOX, 2MHRZ/2MHR	0.52 (0.12 – 2.24)	3.8e–01	2486 (12)	367 (14)
OFLOTUB, 2GHRZ/2GHR	0.46 (0.10 – 2.04)	3.1e–01	2486 (12)	593 (15)

Both SOC and EXP- PP without early uni-without RIF



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
ReMOX, 2MERZ/2MR	**3.18 (2.35 – 4.31)**	**7.1e–14**	2728 (13)	516 (19)
OFLOTUB, 2GHRZ/2GHR	**2.27 (1.68 – 3.07)**	**9.7e–08**	2728 (13)	631 (16)
ReMOX, 2MHRZ/2MHR	**2.27 (1.64 – 3.15)**	**9.1e–07**	2728 (13)	506 (14)
Month 2	**2.19 (1.74 – 2.76)**	**2.3e–11**	2571 (13)	533 (21)
HIV +	**1.75 (1.32 – 2.31)**	**8.9e–05**	2721 (13)	305 (20)
Smear 3+ to 1+	**1.60 (1.13 – 2.26)**	**7.8e–03**	2510 (13)	1362 (15)
Cavity Present	**1.56 (1.21 – 2.00)**	**5.0e–04**	2576 (12)	1703 (14)
Other:Black	**1.36 (1.02 – 1.83)**	**3.9e–02**	2728 (13)	383 (15)
Asian:Black	1.19 (0.90 – 1.59)	2.3e–01	2728 (13)	464 (13)
Age*	**1.17 (1.07 – 1.29)**	**1.1e–03**	2724 (13)	1136 (16)
Smear 2+ to 1+	1.14 (0.78 – 1.68)	5.0e–01	2510 (13)	755 (11)
Weight*	0.93 (0.84 – 1.04)	2.0e–01	2728 (13)	1288 (12)
BMI*	**0.86 (0.76 – 0.97)**	**1.3e–02**	2728 (13)	1162 (11)
Total Number of Doses*	**0.70 (0.62 – 0.79)**	**3.8e–09**	2728 (13)	490 (6)
Treatment Duration*	**0.66 (0.58 – 0.74)**	**2.0e–11**	2712 (13)	670 (7)
Females	**0.59 (0.46 – 0.77)**	**1.2e–04**	2728 (13)	794 (9)

Both SOC and EXP- PP without early multi-without RIF

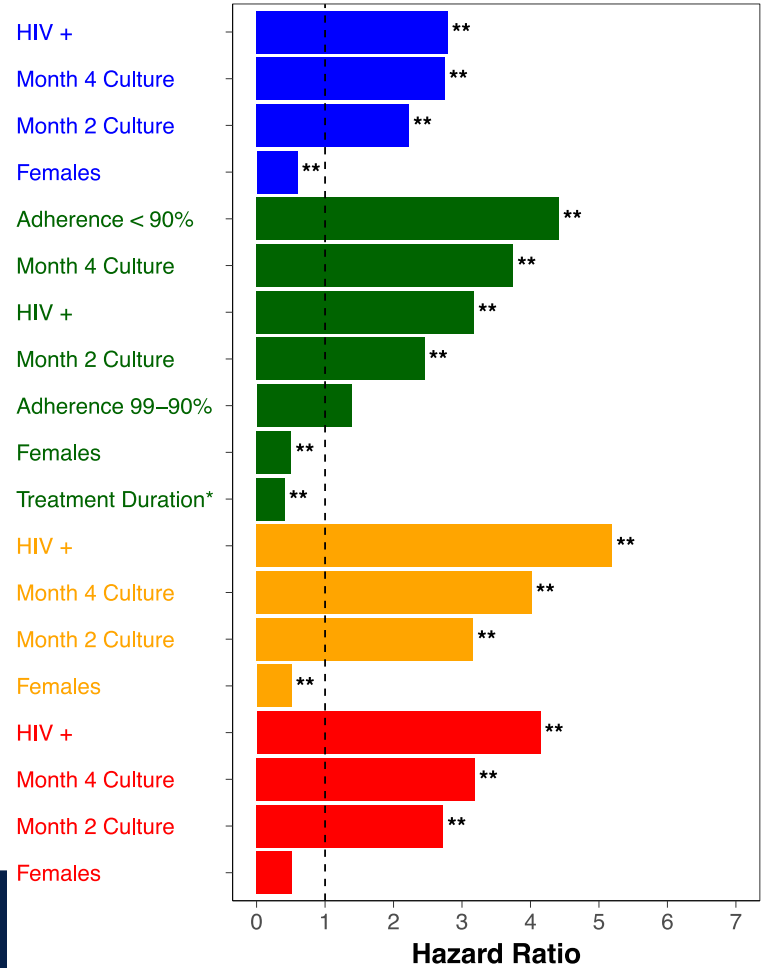


	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
ReMOX, 2MERZ/2MR	**3.76 (2.60 – 5.45)**	**2.5e–12**	2224 (13)	365 (20)
OFLOTUB, 2GHRZ/2GHR	**2.60 (1.85 – 3.65)**	**3.6e–08**	2224 (13)	593 (15)
ReMOX, 2MHRZ/2MHR	**2.48 (1.68 – 3.67)**	**5.1e–06**	2224 (13)	367 (14)
Month 2	**2.28 (1.76 – 2.97)**	**6.0e–10**	2224 (13)	463 (21)
HIV +	**2.23 (1.58 – 3.16)**	**5.6e–06**	2224 (13)	266 (19)
BMI*	**0.83 (0.72 – 0.96)**	**1.4e–02**	2224 (13)	957 (11)
Females	**0.58 (0.43 – 0.79)**	**4.7e–04**	2224 (13)	631 (9)

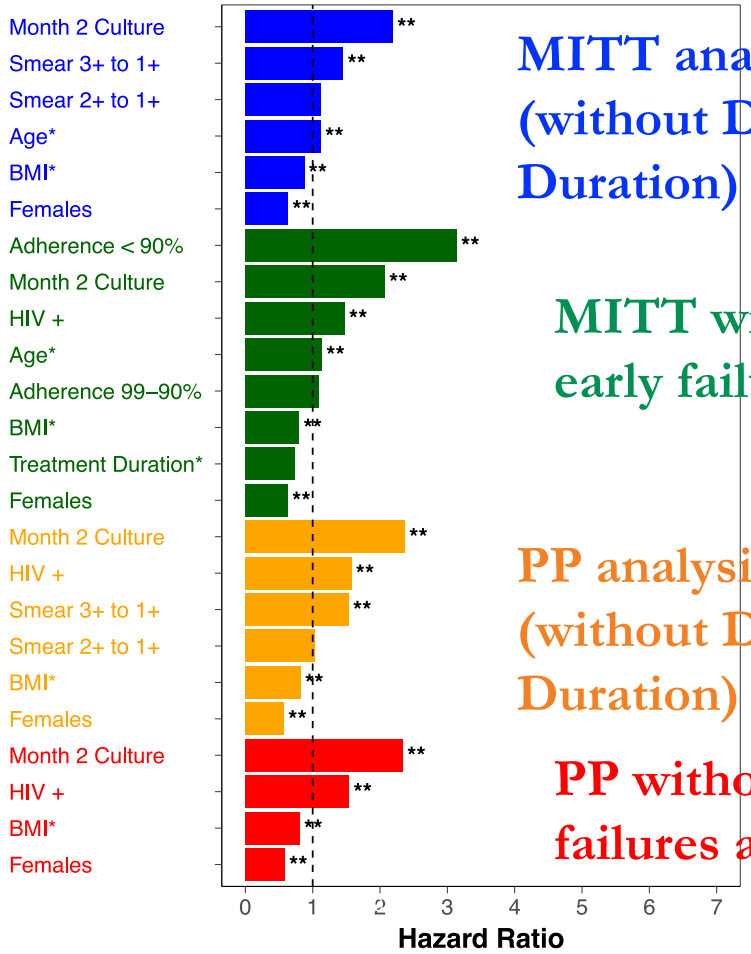
Summarizing Bar plots

Comparing results from SOC and EXP multivariate analysis

Standard of Care



4 Month Arms



MITT analysis (without DA or Duration)

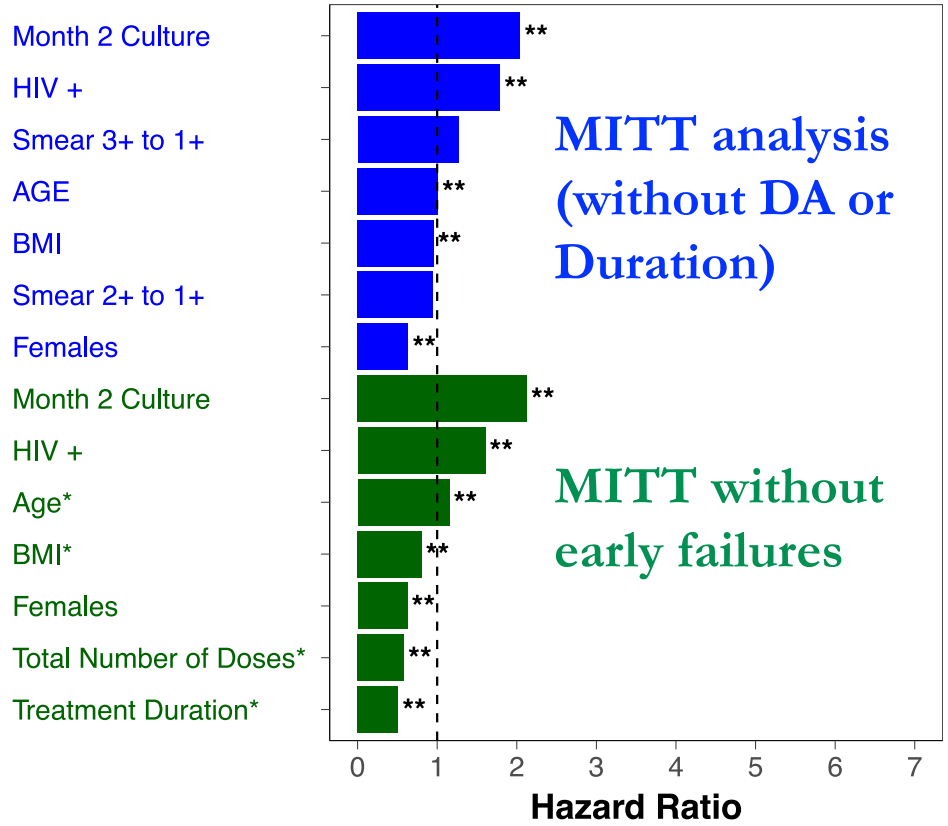
MITT without early failures

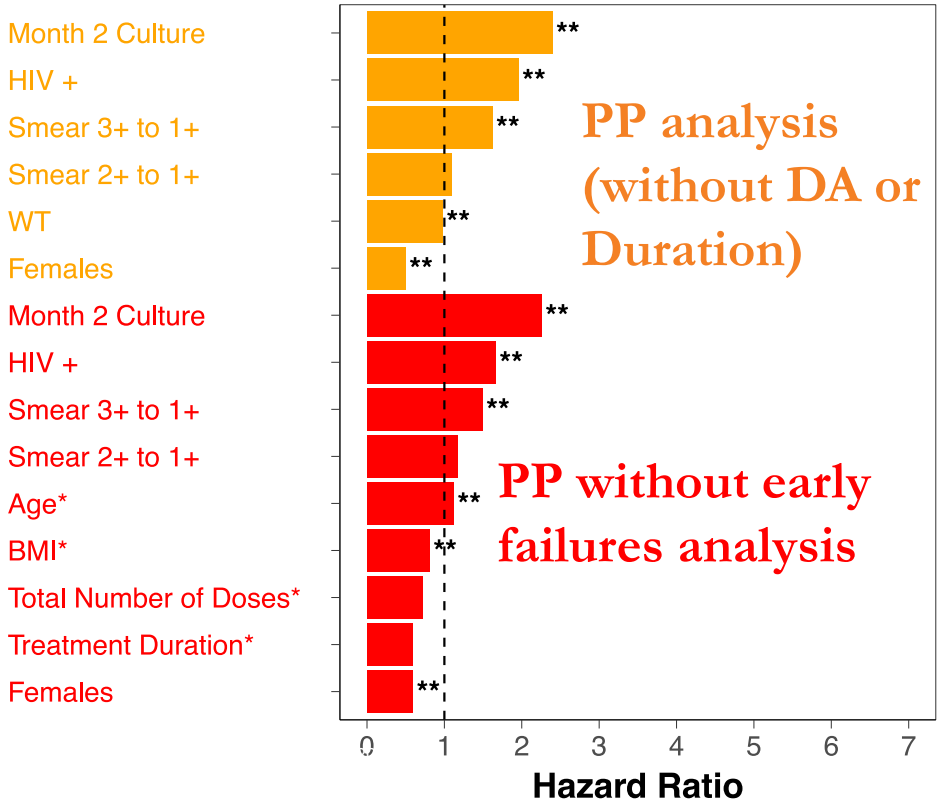
PP analysis (without DA or Duration)

PP without early failures analysis

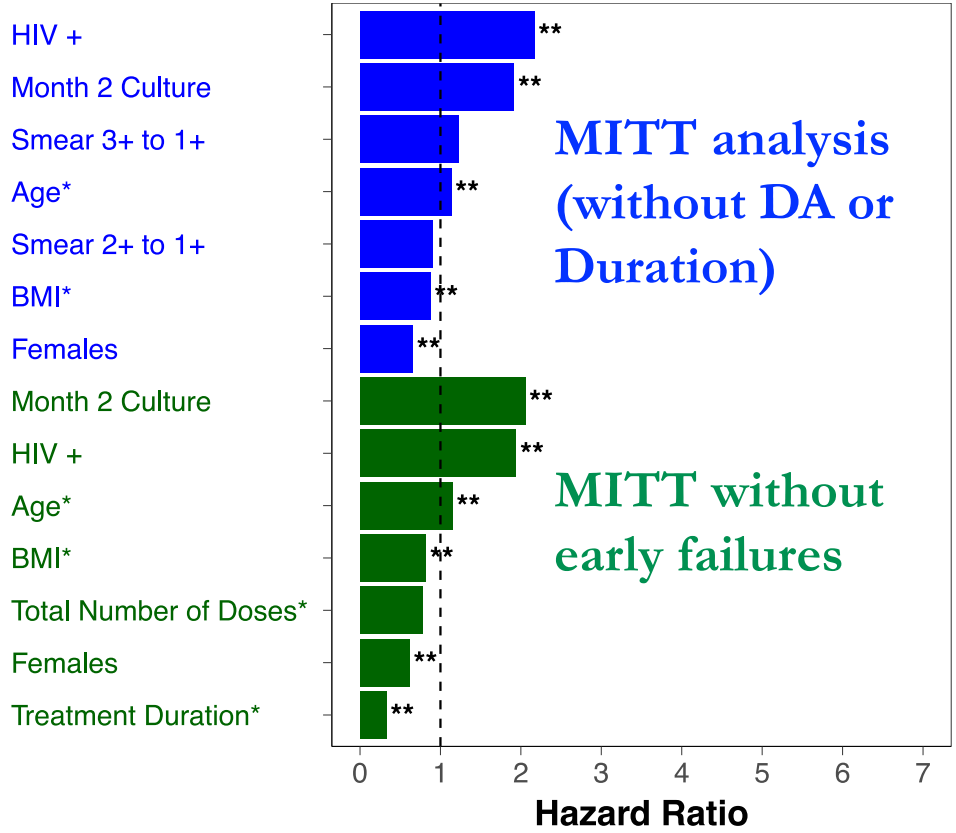
UCSF

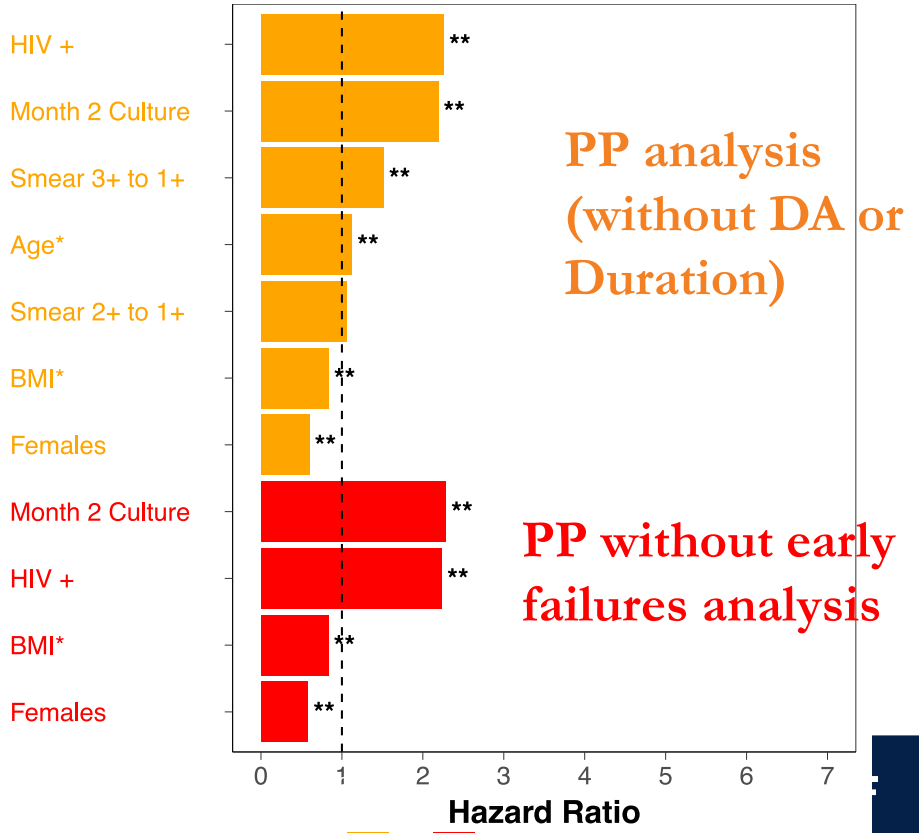
SOC + EXP analysis summary of multivariate analysis





SOC + EXP analysis summary of multivariate analysis- without RIF





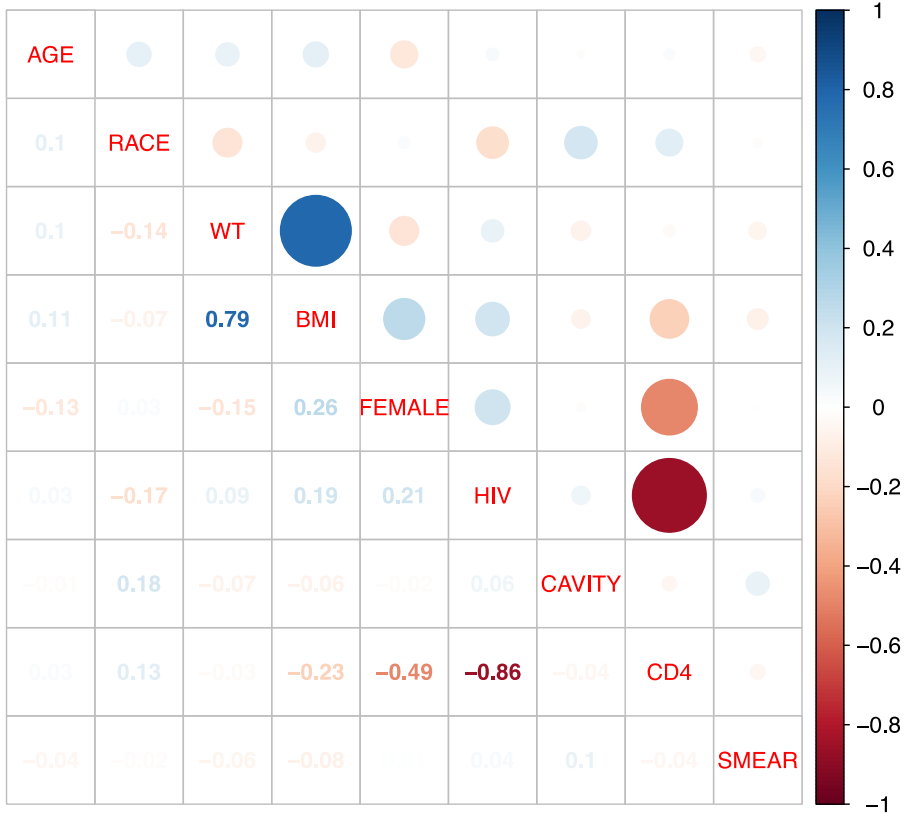
Non-inferiority Plots

4 month compared to SOC

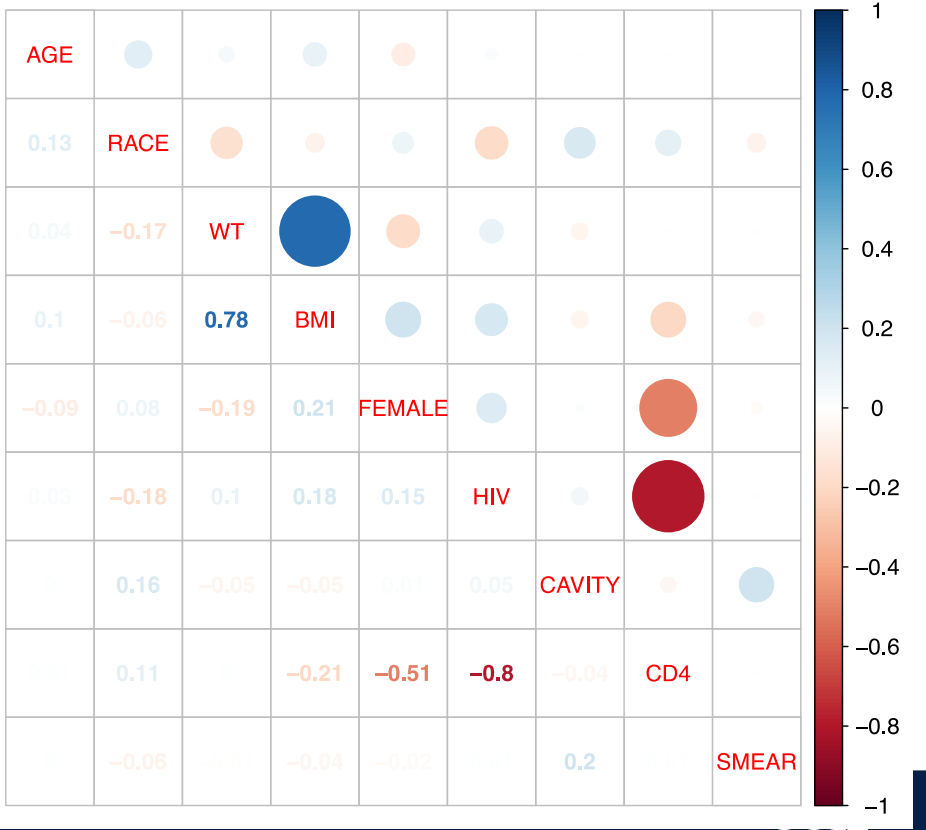
Correlations

Baseline Predictors- Pearson

SOC MITT

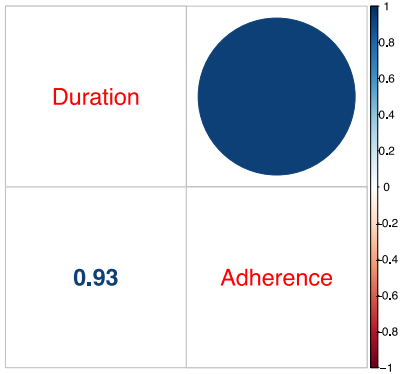


EXP MITT

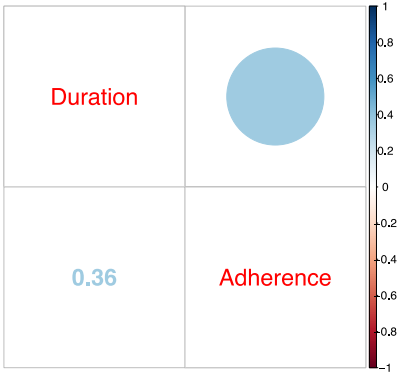


Pearson Correlation

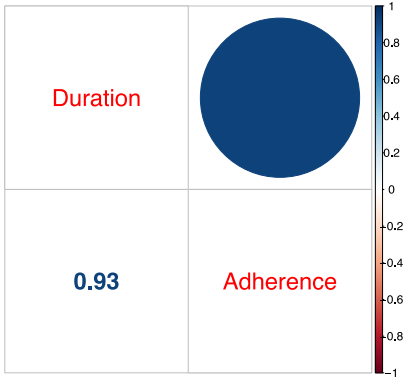
SOC MITT



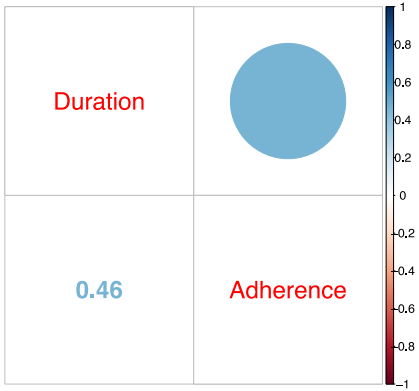
SOC-MITTendtx



EXP MITT

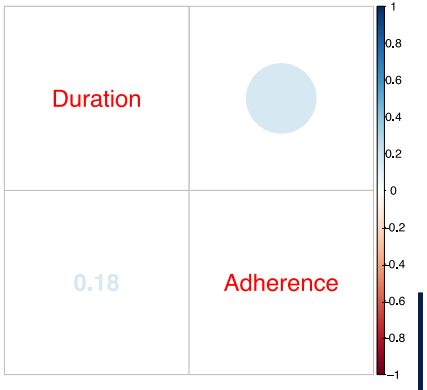


EXP MITTendtx

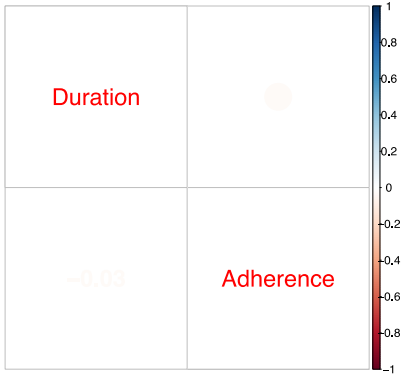


Spearman Correlation

SOC MITT



SOC-MITTendtx



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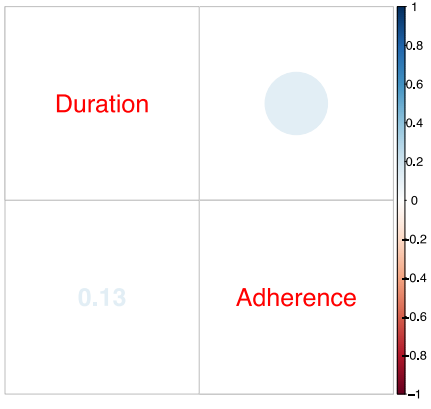
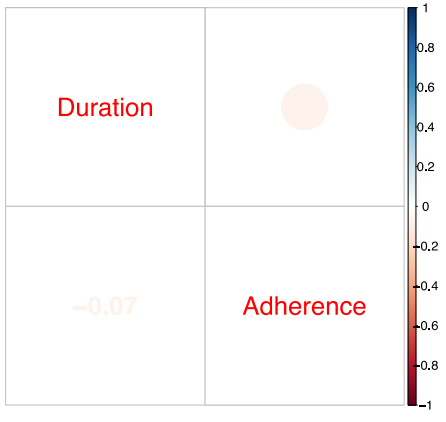


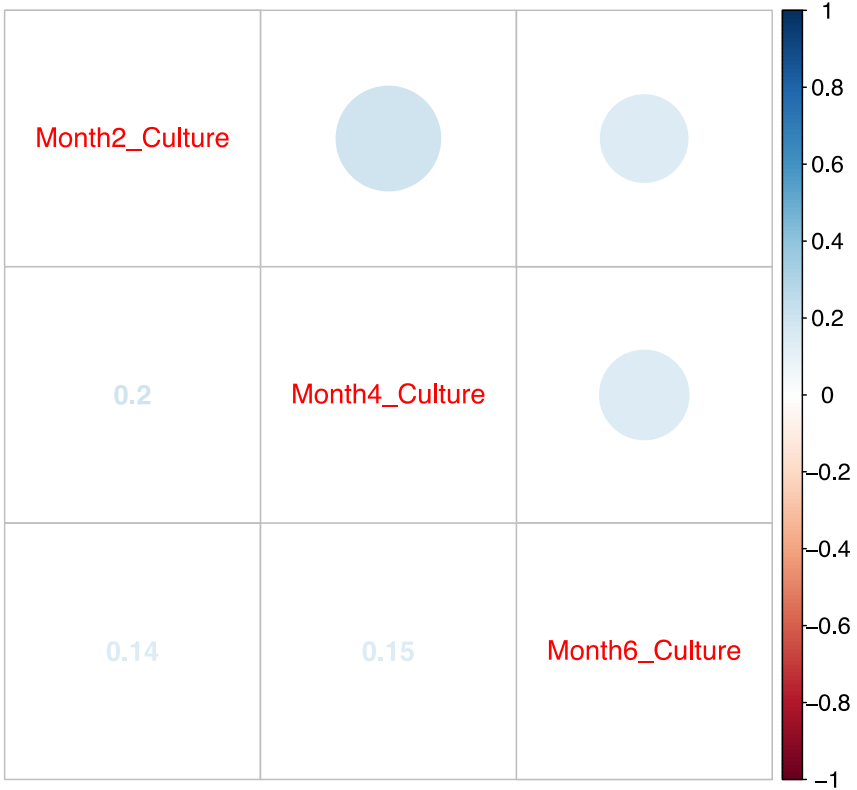
EXP MITTendtx



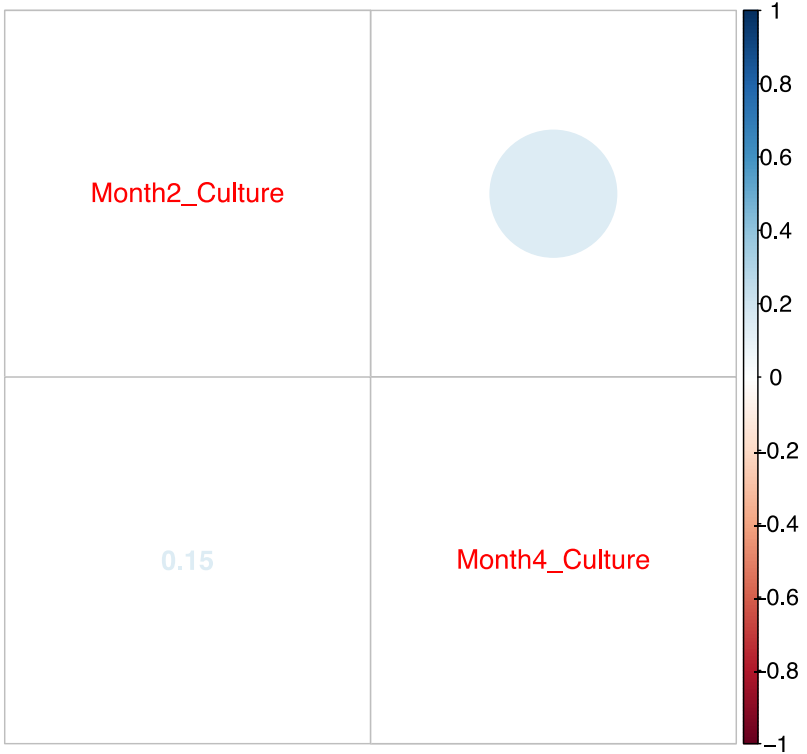
UCSF

Culture Predictors- Pearson

SOC MITT



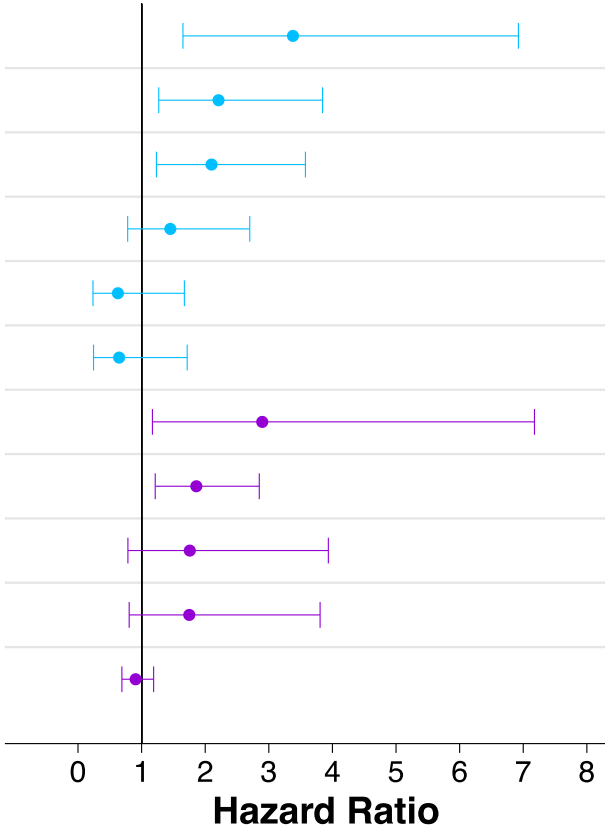
EXP MITT



Other Predictors of Interest

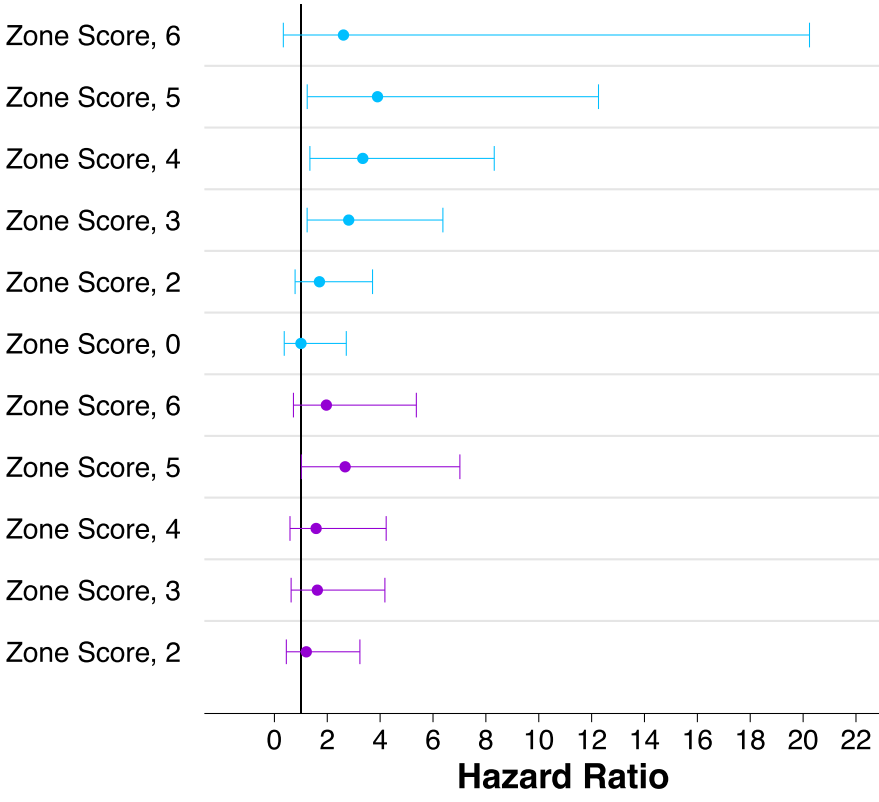
Standard of Care- Other predictors of interest

Chest X-Ray Predictors



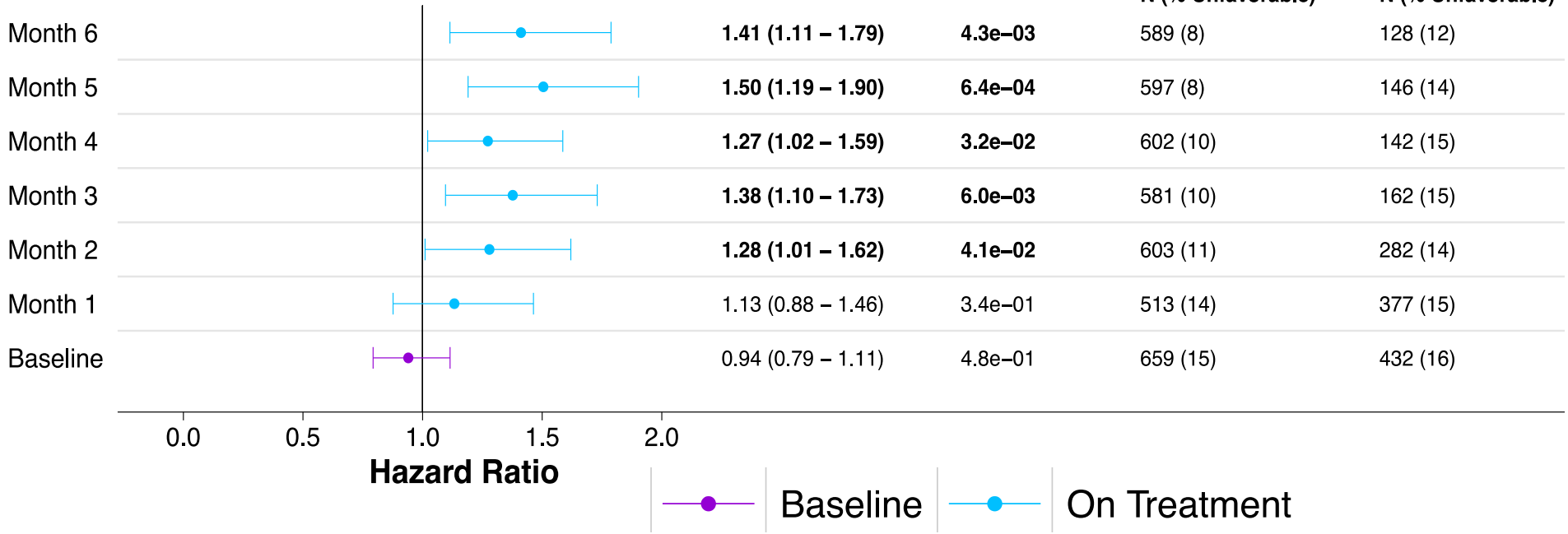
	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Grade, Extensive	**3.38 (1.65 – 6.92)**	**8.8e–04**	570 (10)	52 (23)
Extent, Bilateral	**2.21 (1.27 – 3.84)**	**5.0e–03**	575 (10)	199 (16)
Cavity Present	**2.10 (1.23 – 3.58)**	**6.3e–03**	578 (10)	153 (15)
Grade, Moderate	1.45 (0.78 – 2.70)	2.4e–01	570 (10)	178 (11)
Grade, Normal	0.63 (0.24 – 1.67)	3.5e–01	570 (10)	93 (5)
Extent, None	0.65 (0.24 – 1.72)	3.8e–01	575 (10)	97 (5)
Cavity Size	**2.90 (1.17 – 7.18)**	**2.2e–02**	116 (16)	30 (30)
Extent, Bilateral	**1.86 (1.21 – 2.85)**	**4.3e–03**	655 (17)	415 (21)
Grade, Extensive	1.76 (0.78 – 3.94)	1.7e–01	654 (17)	209 (18)
Grade, Moderate	1.75 (0.80 – 3.81)	1.6e–01	654 (17)	379 (18)
Cavity Present	0.91 (0.69 – 1.19)	4.7e–01	1331 (16)	847 (16)

Chest X-Ray Predictors



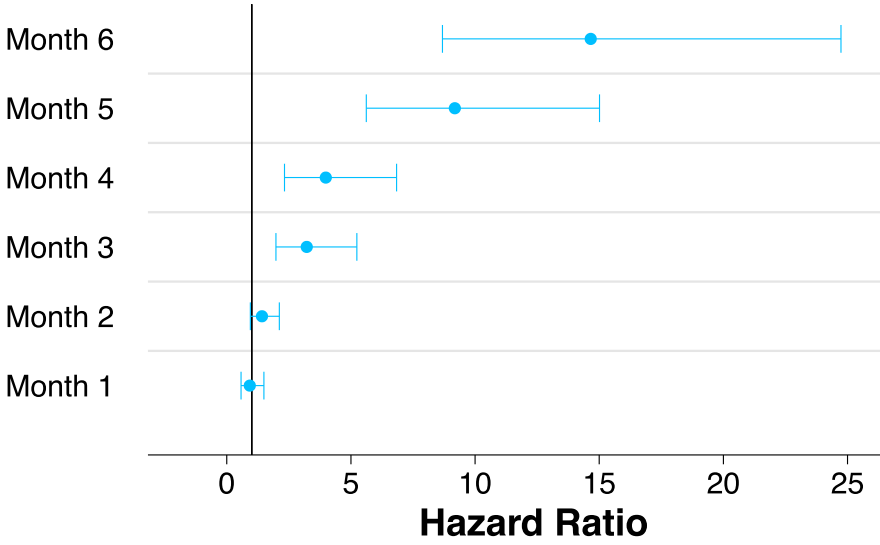
	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Zone Score, 6	2.61 (0.34 – 20.24)	3.6e–01	575 (10)	7 (14)
Zone Score, 5	**3.90 (1.24 – 12.26)**	**2.0e–02**	575 (10)	19 (21)
Zone Score, 4	**3.34 (1.34 – 8.32)**	**9.4e–03**	575 (10)	45 (18)
Zone Score, 3	**2.81 (1.24 – 6.37)**	**1.3e–02**	575 (10)	78 (15)
Zone Score, 2	1.70 (0.78 – 3.71)	1.8e–01	575 (10)	150 (10)
Zone Score, 0	1.01 (0.37 – 2.72)	9.9e–01	575 (10)	95 (6)
Zone Score, 6	1.97 (0.72 – 5.37)	1.9e–01	655 (17)	78 (21)
Zone Score, 5	**2.68 (1.02 – 7.02)**	**4.5e–02**	655 (17)	91 (26)
Zone Score, 4	1.58 (0.59 – 4.23)	3.6e–01	655 (17)	112 (17)
Zone Score, 3	1.62 (0.63 – 4.18)	3.1e–01	655 (17)	181 (17)
Zone Score, 2	1.21 (0.45 – 3.23)	7.1e–01	655 (17)	145 (13)

On Treatment MGIT



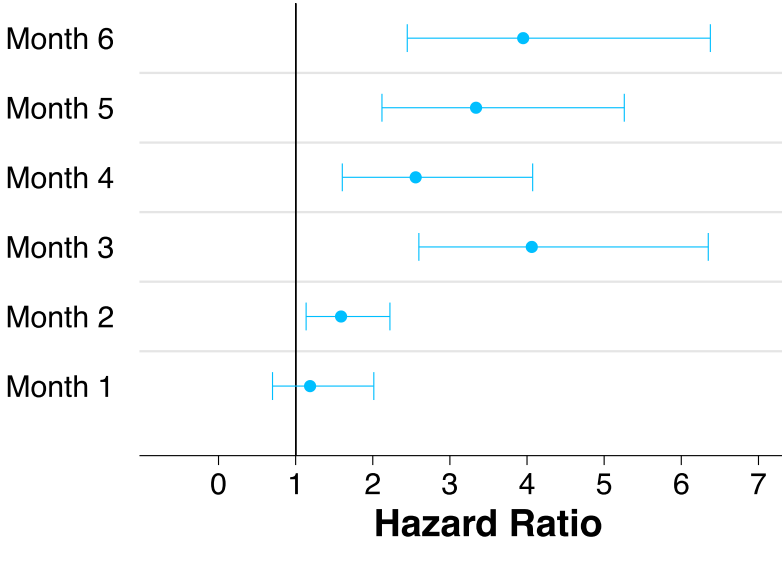
	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 6	**1.41 (1.11 – 1.79)**	**4.3e–03**	589 (8)	128 (12)
Month 5	**1.50 (1.19 – 1.90)**	**6.4e–04**	597 (8)	146 (14)
Month 4	**1.27 (1.02 – 1.59)**	**3.2e–02**	602 (10)	142 (15)
Month 3	**1.38 (1.10 – 1.73)**	**6.0e–03**	581 (10)	162 (15)
Month 2	**1.28 (1.01 – 1.62)**	**4.1e–02**	603 (11)	282 (14)
Month 1	1.13 (0.88 – 1.46)	3.4e–01	513 (14)	377 (15)
Baseline	0.94 (0.79 – 1.11)	4.8e–01	659 (15)	432 (16)

On Treatment Smear Status



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 6	**14.66 (8.69 – 24.73)**	**<10^–16**	1231 (9)	29 (59)
Month 5	**9.19 (5.62 – 15.01)**	**<10^–16**	1248 (10)	38 (50)
Month 4	**3.99 (2.33 – 6.84)**	**5.0e–07**	1183 (11)	47 (32)
Month 3	**3.22 (1.98 – 5.24)**	**2.4e–06**	743 (11)	83 (28)
Month 2	1.42 (0.95 – 2.12)	8.8e–02	1296 (13)	173 (17)
Month 1	0.93 (0.57 – 1.50)	7.6e–01	513 (14)	214 (13)

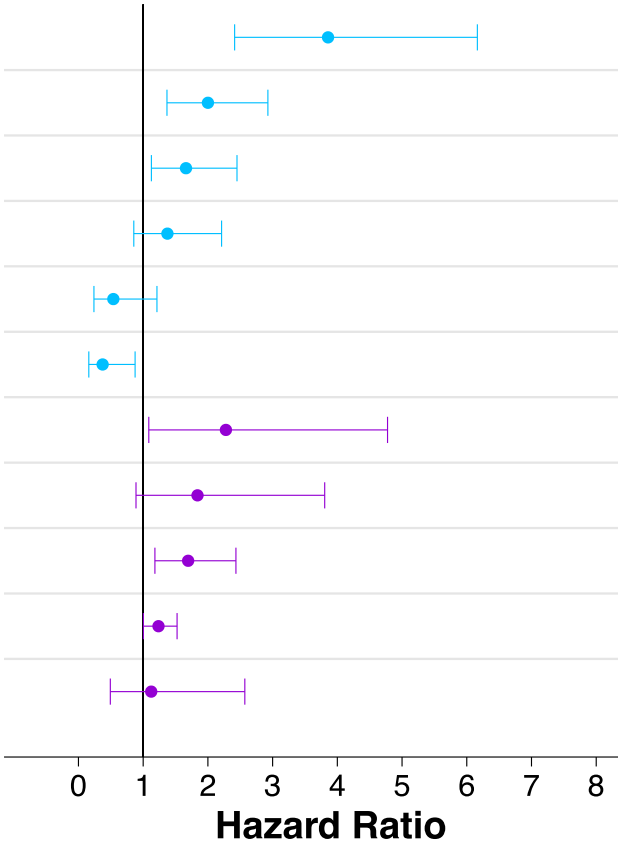
On Treatment Culture Status



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 6	**3.95 (2.45 – 6.38)**	**1.9e–08**	1216 (9)	102 (22)
Month 5	**3.34 (2.12 – 5.26)**	**2.0e–07**	1218 (9)	112 (21)
Month 4	**2.56 (1.60 – 4.07)**	**7.8e–05**	1168 (11)	108 (20)
Month 3	**4.06 (2.60 – 6.35)**	**7.9e–10**	733 (11)	115 (28)
Month 2	**1.59 (1.14 – 2.22)**	**6.9e–03**	1278 (13)	284 (17)
Month 1	1.19 (0.70 – 2.01)	5.3e–01	514 (14)	353 (14)

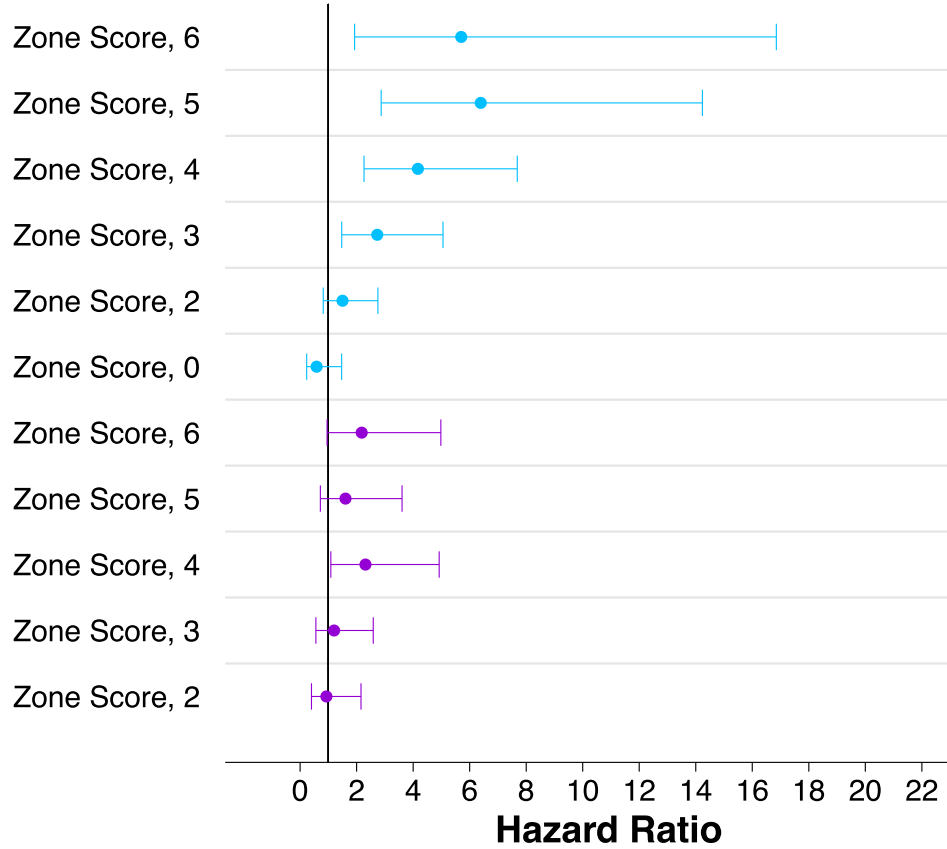
4 month - Other predictors of interest

Chest X-Ray Predictors



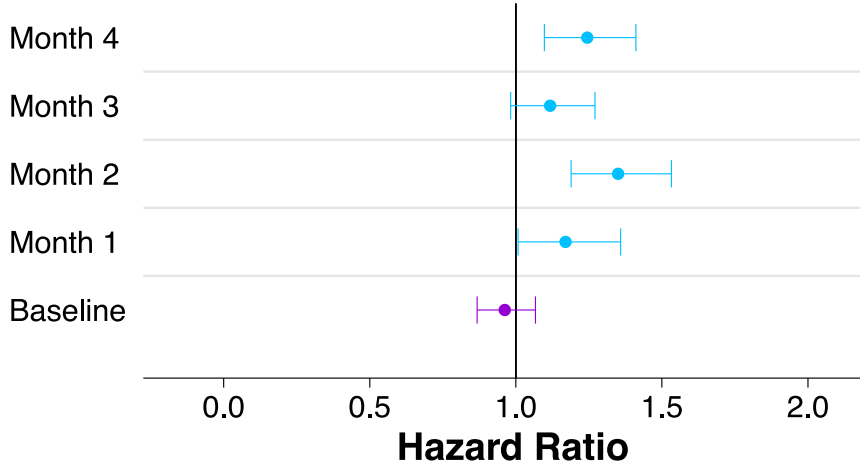
	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Grade, Extensive	**3.86 (2.41 – 6.16)**	**1.7e–08**	635 (17)	83 (42)
Cavity Present	**2.00 (1.37 – 2.93)**	**3.5e–04**	635 (17)	173 (26)
Extent, Bilateral	**1.66 (1.13 – 2.45)**	**1.0e–02**	634 (17)	245 (24)
Grade, Moderate	1.37 (0.85 – 2.21)	1.9e–01	635 (17)	189 (17)
Grade, Normal	0.54 (0.24 – 1.21)	1.4e–01	635 (17)	98 (7)
Extent, None	**0.37 (0.16 – 0.87)**	**2.3e–02**	634 (17)	101 (6)
Grade, Extensive	**2.28 (1.09 – 4.78)**	**2.9e–02**	686 (21)	228 (25)
Grade, Moderate	1.84 (0.89 – 3.80)	1.0e–01	686 (21)	386 (21)
Extent, Bilateral	**1.69 (1.18 – 2.43)**	**4.2e–03**	686 (21)	418 (25)
Cavity Present	**1.24 (1.00 – 1.52)**	**4.6e–02**	1874 (23)	1247 (24)
Cavity Size	1.12 (0.49 – 2.57)	7.8e–01	117 (23)	32 (25)

Chest X-Ray Predictors

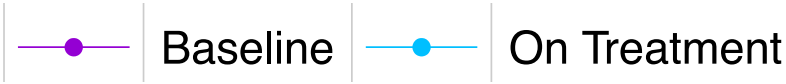


	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Zone Score, 6	**5.70 (1.93 – 16.85)**	**1.6e–03**	635 (17)	10 (40)
Zone Score, 5	**6.39 (2.87 – 14.24)**	**5.6e–06**	635 (17)	19 (47)
Zone Score, 4	**4.17 (2.26 – 7.68)**	**4.7e–06**	635 (17)	66 (36)
Zone Score, 3	**2.73 (1.47 – 5.06)**	**1.4e–03**	635 (17)	90 (26)
Zone Score, 2	1.50 (0.82 – 2.75)	1.9e–01	635 (17)	171 (15)
Zone Score, 0	0.58 (0.23 – 1.47)	2.5e–01	635 (17)	102 (6)
Zone Score, 6	2.18 (0.95 – 4.98)	6.5e–02	687 (21)	65 (29)
Zone Score, 5	1.61 (0.72 – 3.61)	2.5e–01	687 (21)	97 (23)
Zone Score, 4	**2.31 (1.09 – 4.92)**	**2.9e–02**	687 (21)	139 (31)
Zone Score, 3	1.20 (0.56 – 2.59)	6.4e–01	687 (21)	204 (18)
Zone Score, 2	0.93 (0.40 – 2.16)	8.7e–01	687 (21)	123 (14)

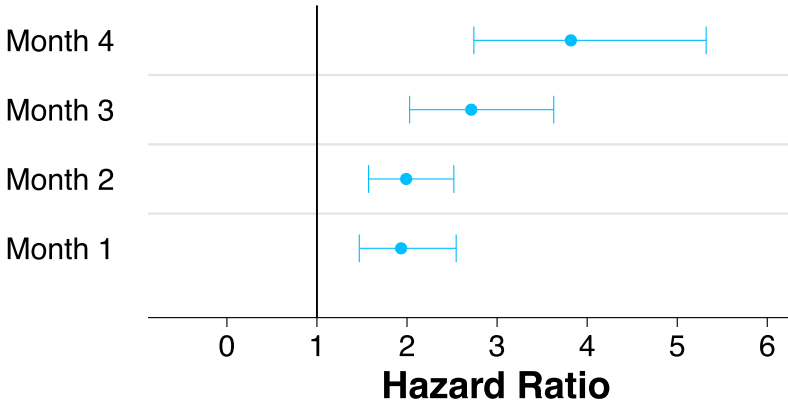
On Treatment MGIT



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 4	**1.24 (1.10 – 1.41)**	**6.4e–04**	1071 (18)	264 (24)
Month 3	1.12 (0.98 – 1.27)	9.1e–02	1086 (19)	302 (24)
Month 2	**1.35 (1.19 – 1.53)**	**3.5e–06**	1091 (20)	489 (27)
Month 1	**1.17 (1.01 – 1.36)**	**3.9e–02**	1005 (21)	728 (21)
Baseline	0.96 (0.87 – 1.07)	4.7e–01	1208 (24)	841 (24)

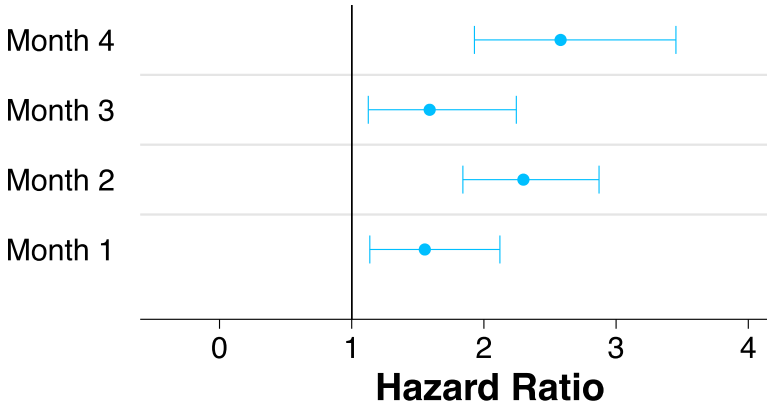


On Treatment Smear Status



	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 4	**3.82 (2.74 – 5.32)**	**2.3e–15**	1782 (18)	85 (47)
Month 3	**2.71 (2.03 – 3.63)**	**1.8e–11**	1257 (20)	153 (39)
Month 2	**1.99 (1.57 – 2.52)**	**1.0e–08**	1826 (20)	289 (32)
Month 1	**1.93 (1.47 – 2.55)**	**2.4e–06**	1006 (21)	427 (28)

On Treatment Culture Status

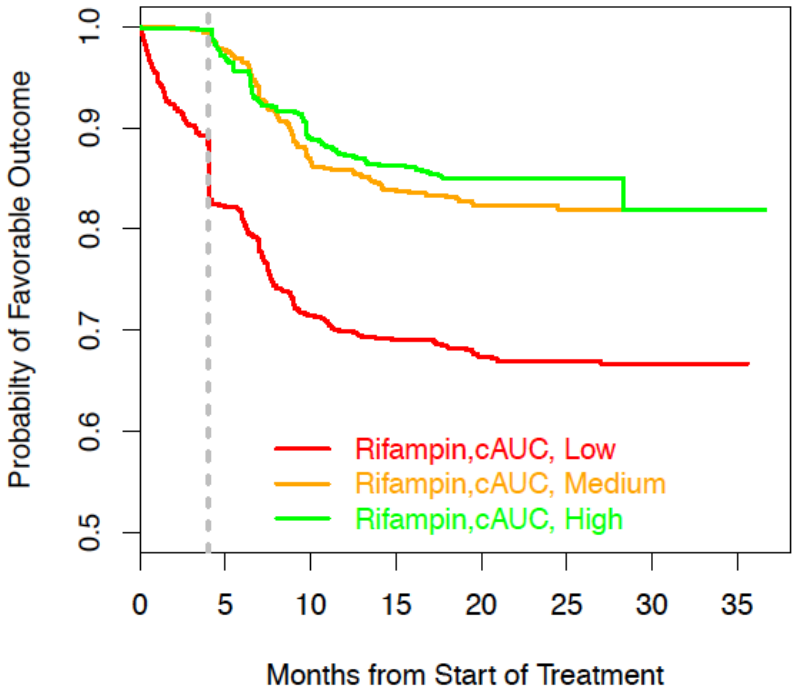


	HR (95% CI)	P–Value	All N (% Unfavorable)	Test Group N (% Unfavorable)
Month 4	**2.58 (1.93 – 3.45)**	**1.7e–10**	1759 (18)	158 (35)
Month 3	**1.59 (1.13 – 2.25)**	**8.5e–03**	1255 (20)	136 (28)
Month 2	**2.30 (1.84 – 2.87)**	**2.1e–13**	1804 (20)	335 (34)
Month 1	**1.55 (1.14 – 2.12)**	**5.6e–03**	1007 (21)	668 (23)

4 month arms: Summary Results (Hazard ratios)

Predictor	MITT		PP	
	HR (95% CI)	p- value	HR (95% CI)	p-value
Moxifloxacin	3.1 (2.2-4.3)	$<10^{-9}$	4.7 (2.2-10)	$<10^{-4}$
Cumulative R AUC	0.02 (0.01-0.11)	$<10^{-5}$	0.001 (0.0001-0.01)	$<10^{-7}$
SMEAR 4+	1.5 (1.1-1.9)	$<10^{-2}$	1.8 (1.2-2.7)	$<10^{-2}$
HIV+	-	-	2.2 (1.4-3.6)	$<10^{-2}$
CAVITY	-	-	1.4 (1-2)	$<10^{-2}$
Other predictors of interest				
FQ C_{max} (high)	0.55 (0.33-0.95)	<0.05		

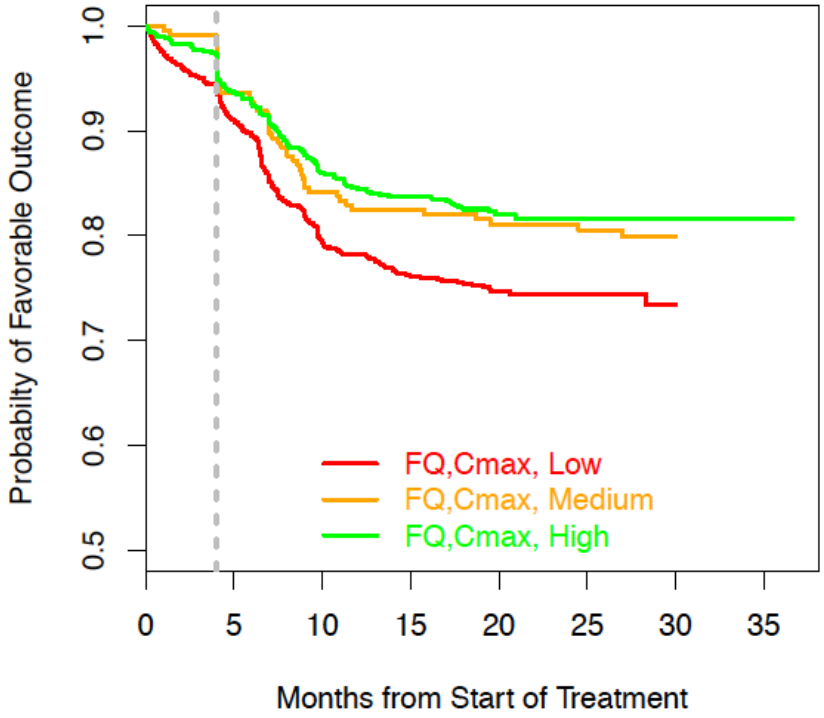
Impact of Rifampin PK (4 month cumulative exposure)



cAUC <3314 - Low
cAUC <4140 – Median
cAUC >4140 – High

Reference: Typical Patient having 120 tablets of R: cAUC=4200 mg*h/L

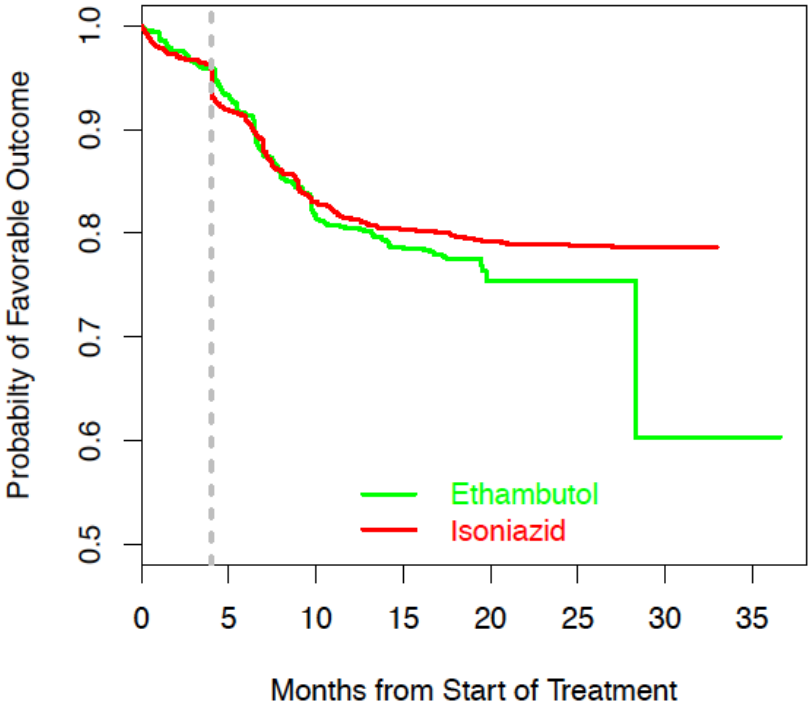
Impact of FQ PK (Cmax at SS)

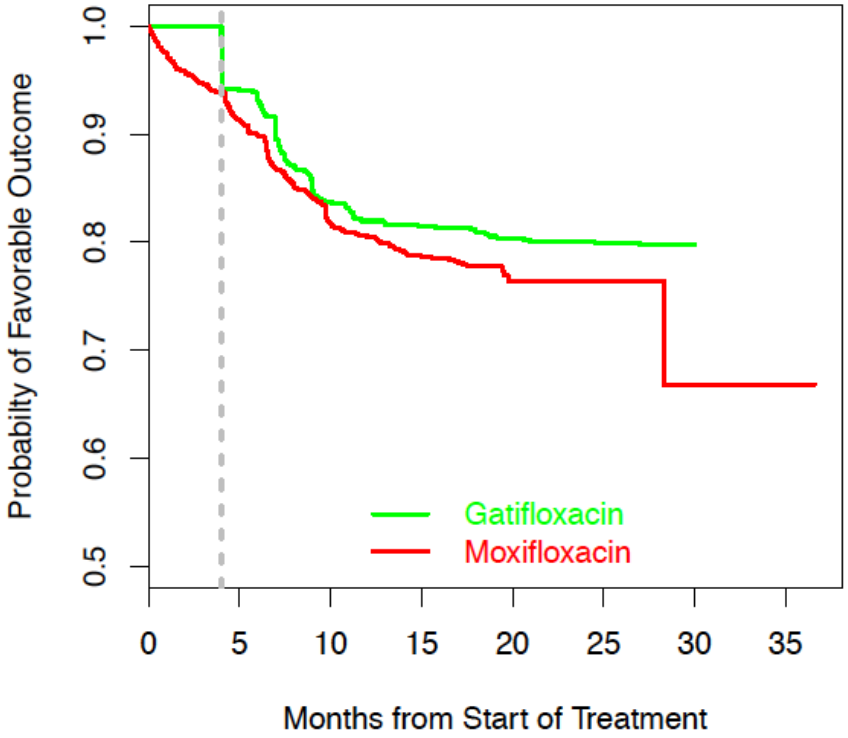


Patients divided in 3 groups depending on their relative FQ PK compared to the rest of the group:

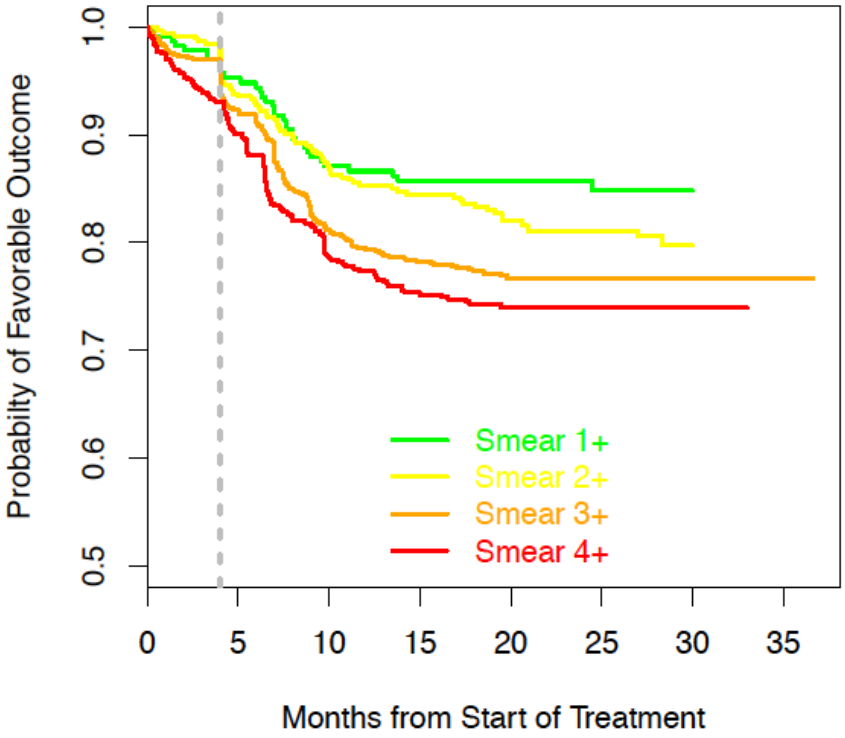
Low Cmax – all patients having Moxi or Gati Cmax in lower tertile

Indications: H and G performing slightly better



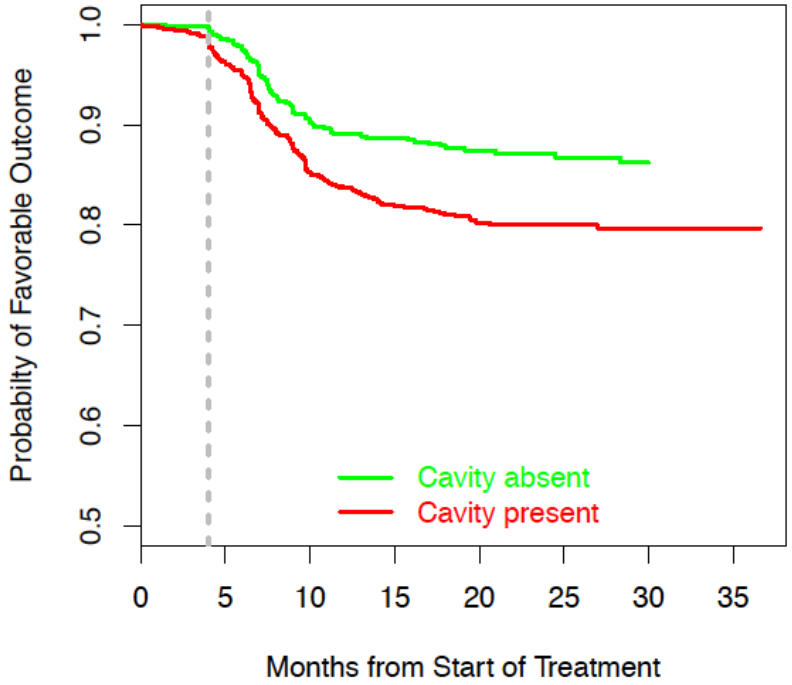


Impact of Baseline Severity (Smear)



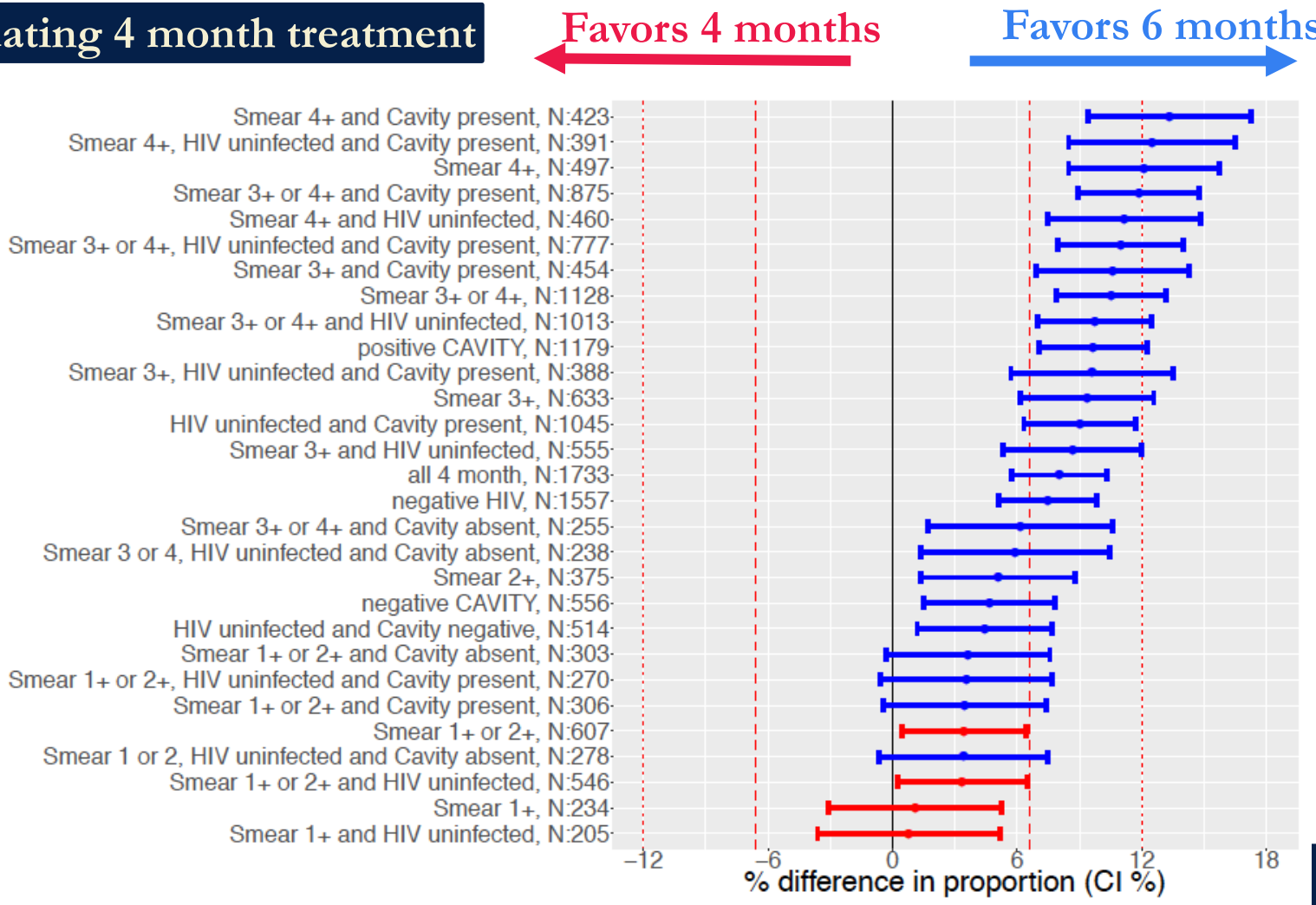
Smear 4+: HR 2.7(1.8-4.1)
Smear 3+: 1.6 (1.1 – 2.3)

Impact of Baseline Severity (Cavity)

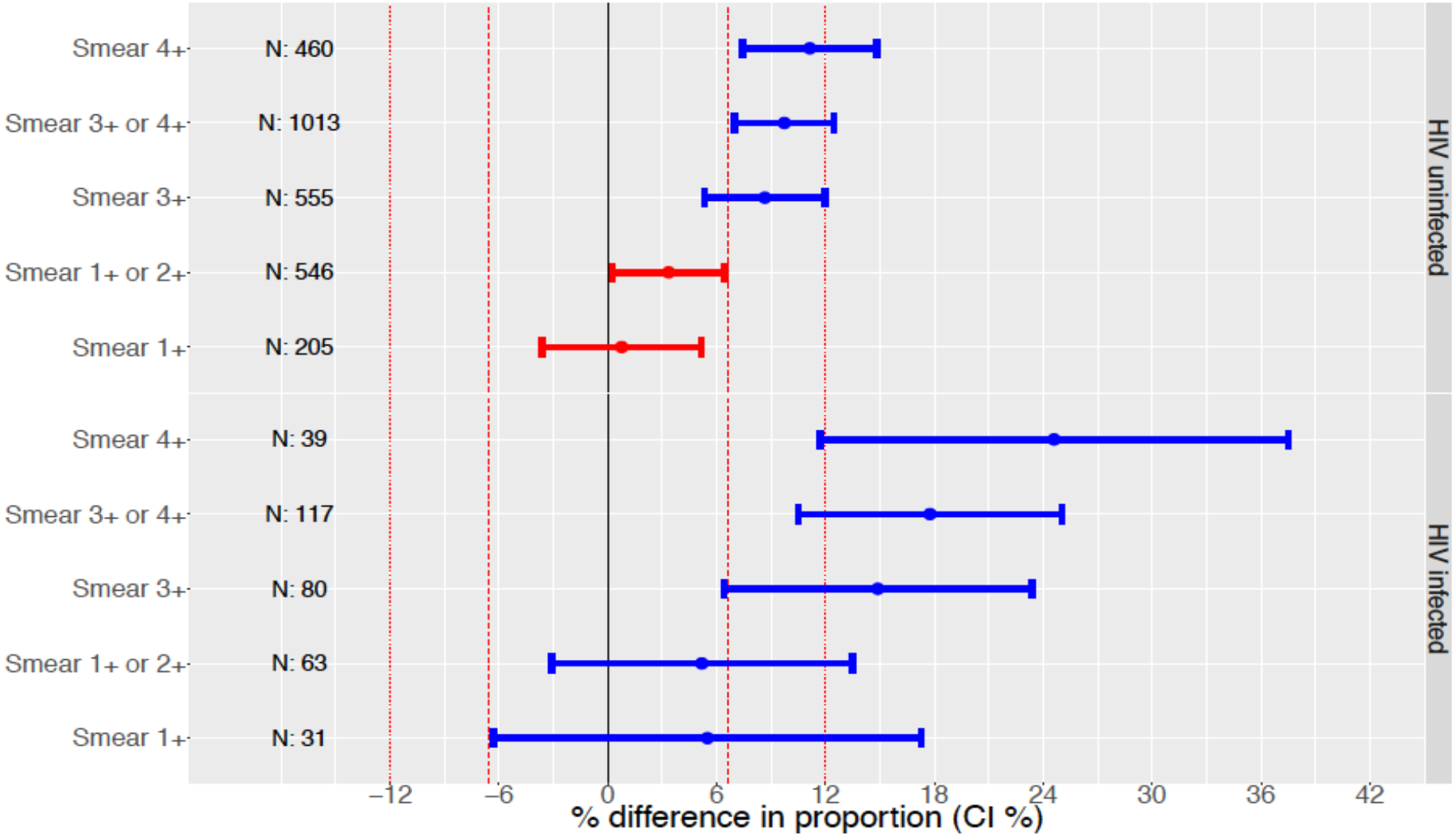


Cavity: HR 1.4(1-2)

Evaluating 4 month treatment

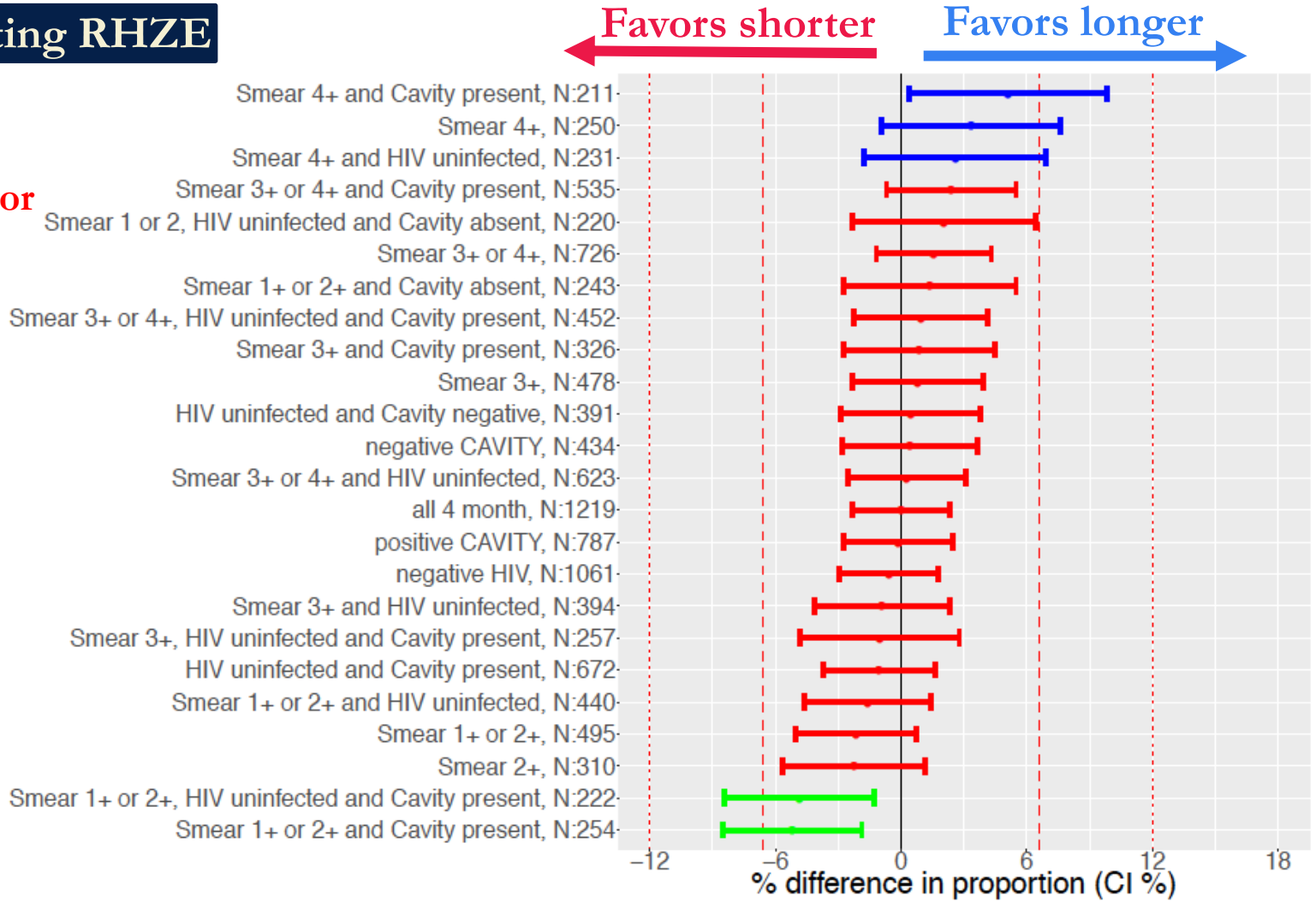


UCSF


Smear 4+
N: 460
Smear 3+ or 4+
N: 1013
Smear 3+
N: 555
Smear 1+ or 2+
N: 546
Smear 1+
N: 205
Smear 4+
N: 39
Smear 3+ or 4+
N: 117
Smear 3+
N: 80
Smear 1+ or 2+
N: 63
Smear 1+
N: 31
HIV uninfected
HIV infected
−12
−6
0
6
12
18
24
30
36
42
% difference in proportion (CI %)

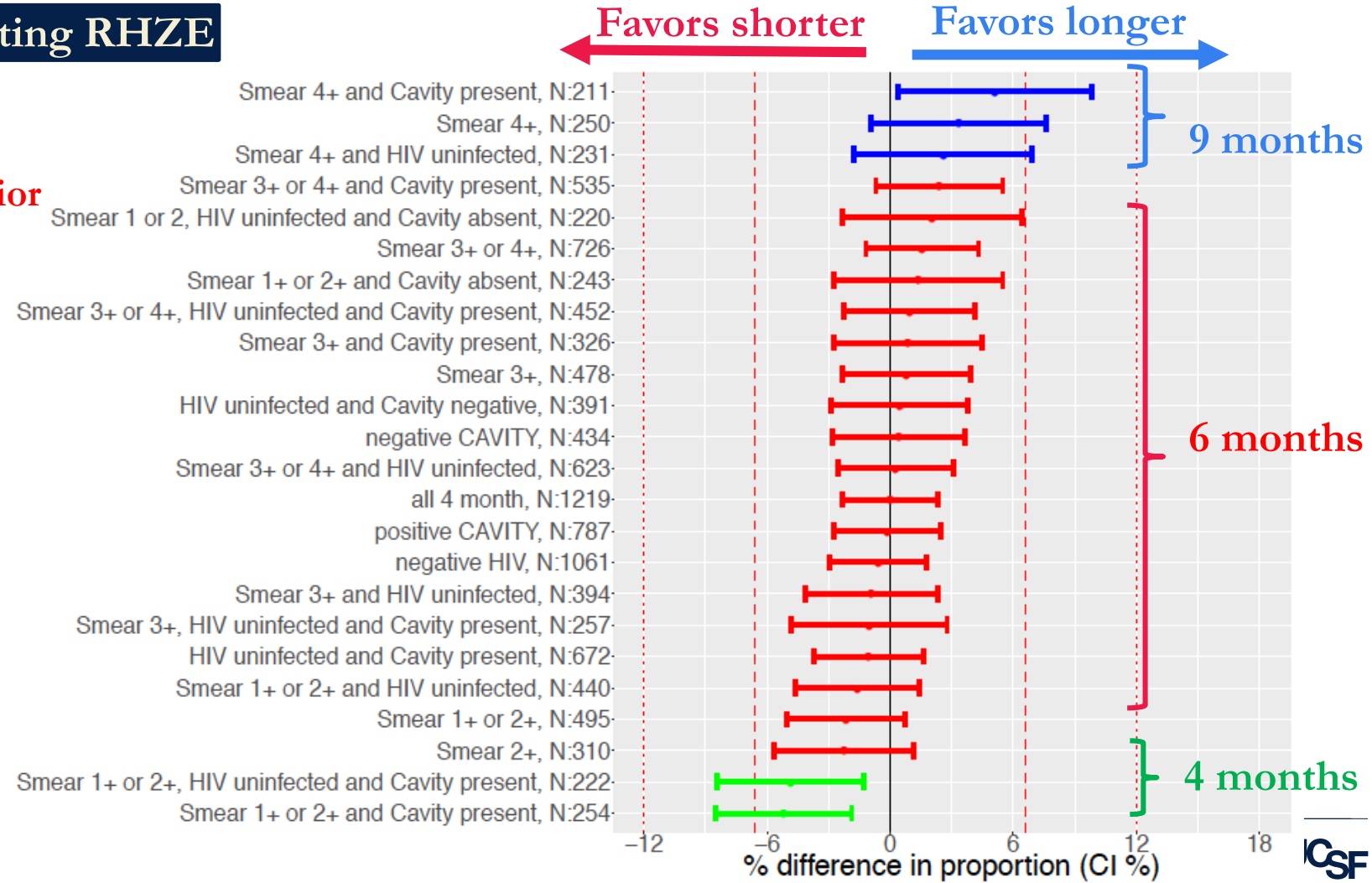
Evaluating RHZE

Superior
Non-Inferior
Inferior

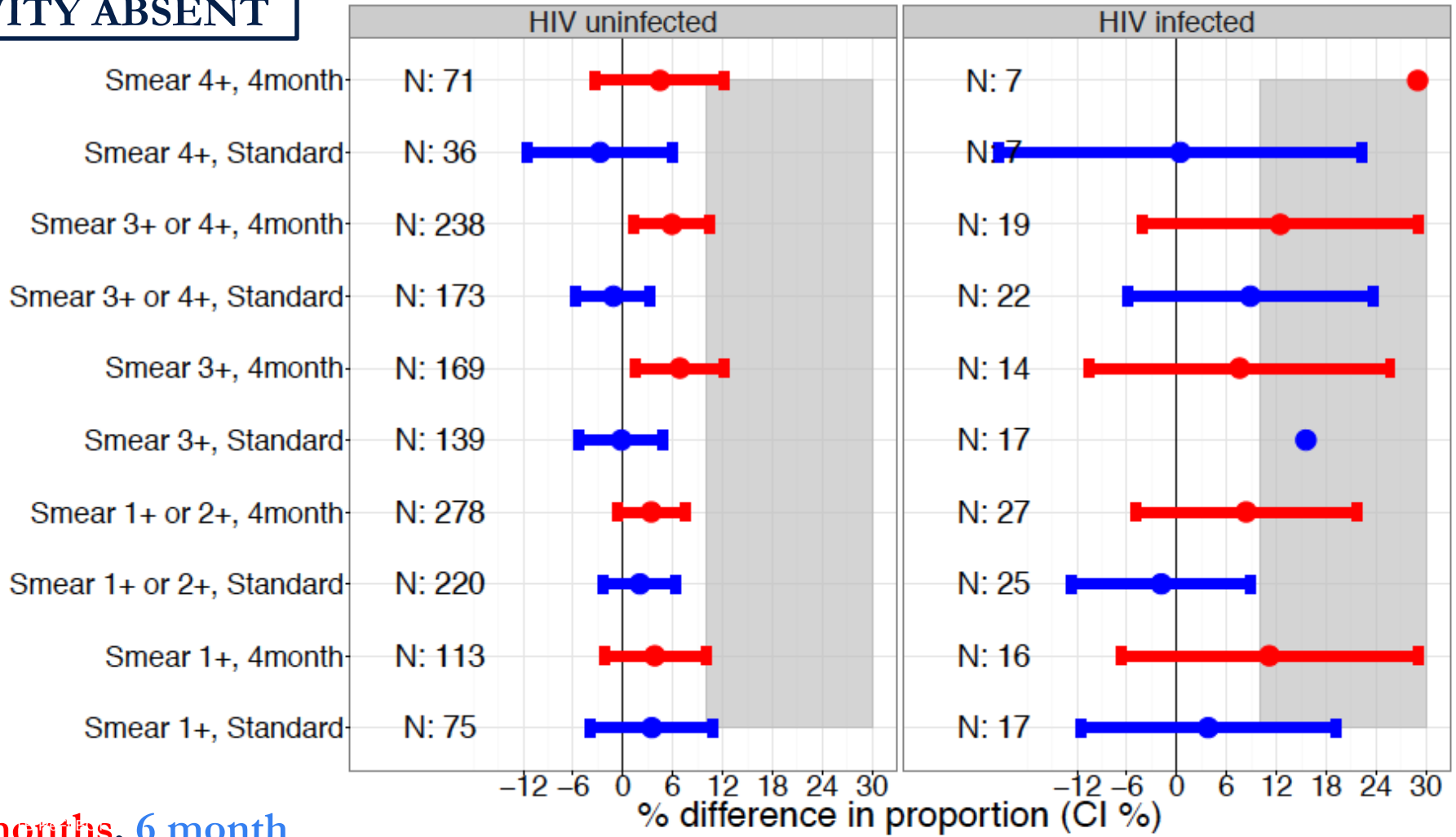


Evaluating RHZE

Superior
Non-Inferior
Inferior

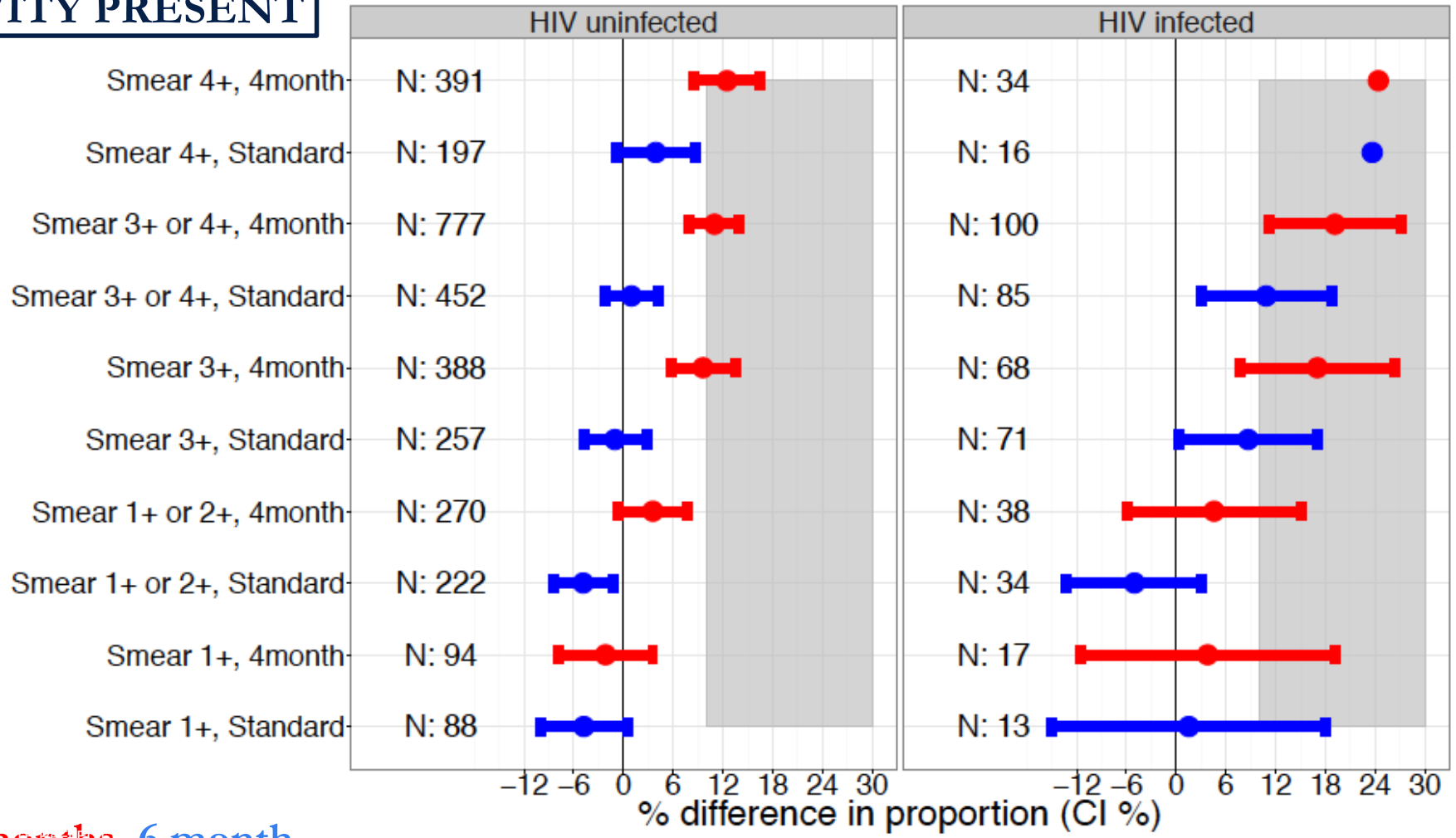


CAVITY ABSENT



4 months, 6 month

CAVITY PRESENT



4 months, 6 month