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Supplementary appendix 4

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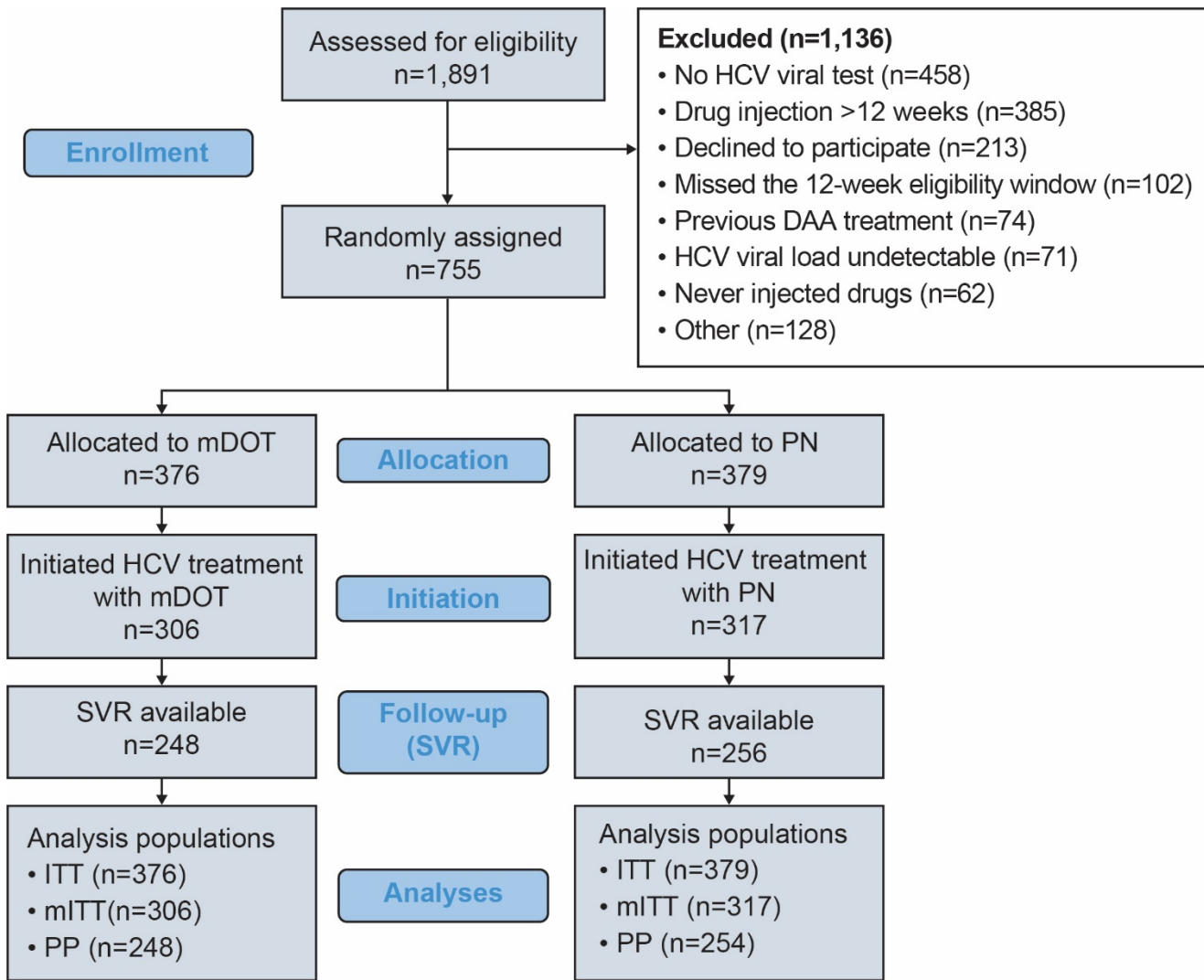
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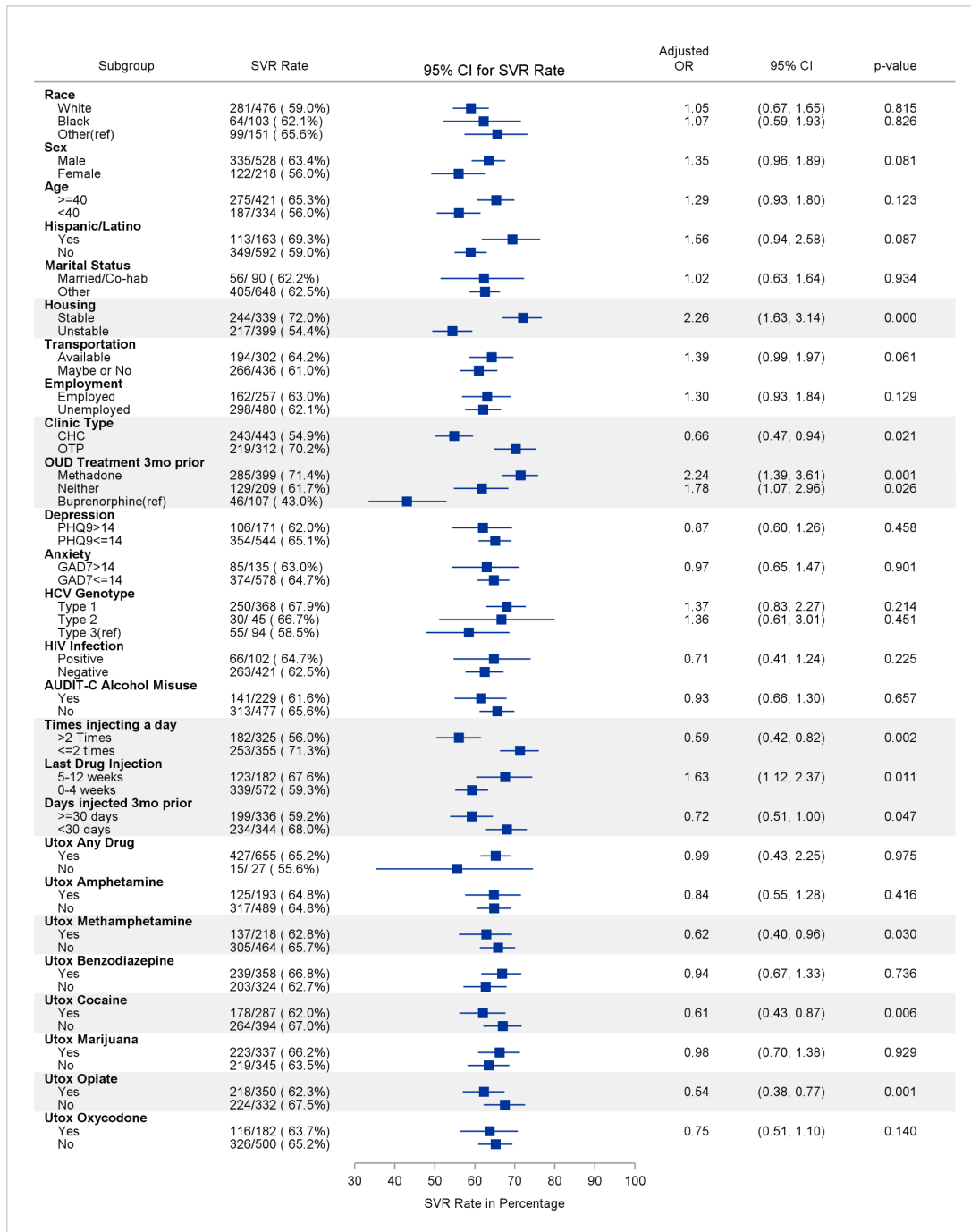
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Figure S1. CONSORT Flow Chart.

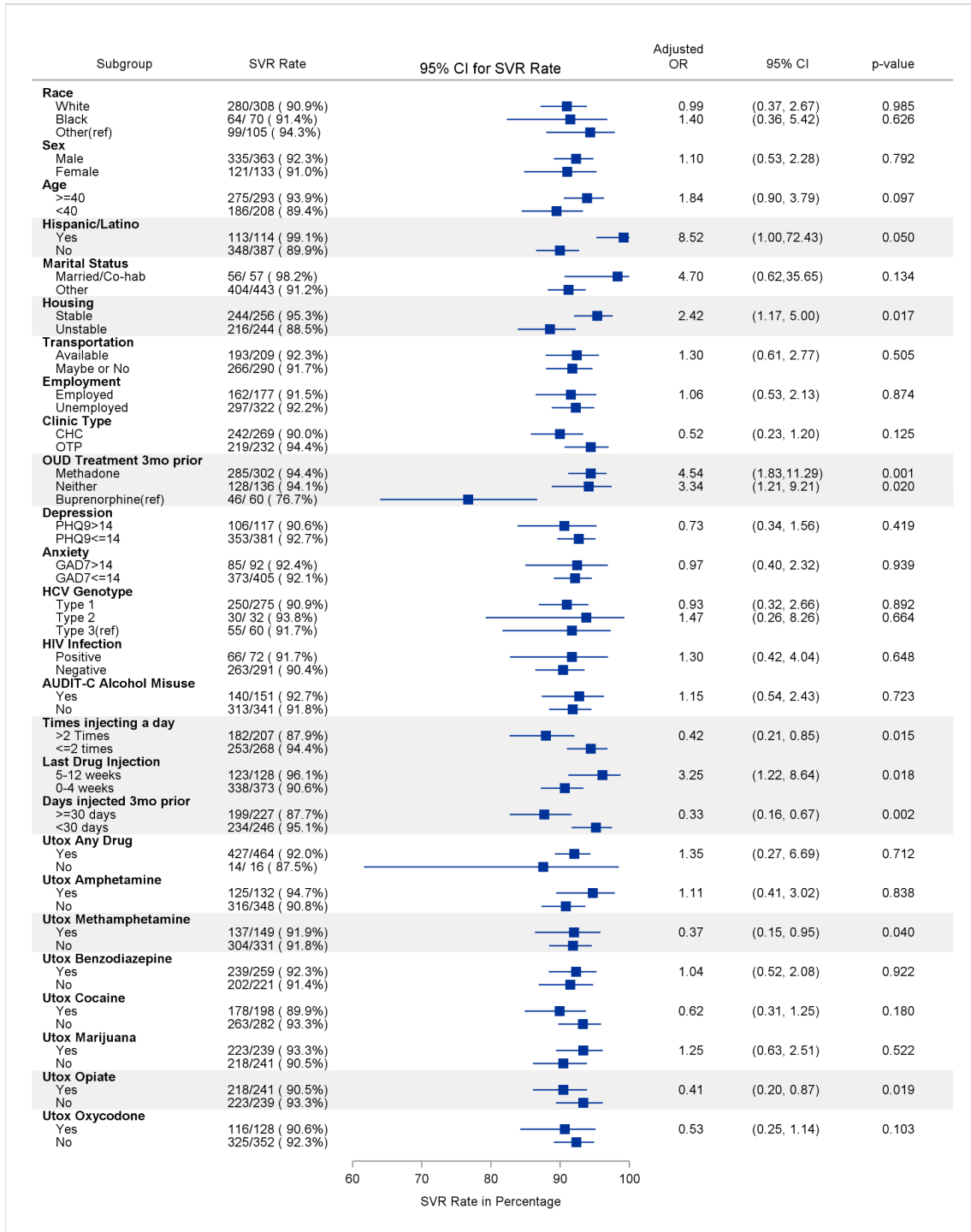


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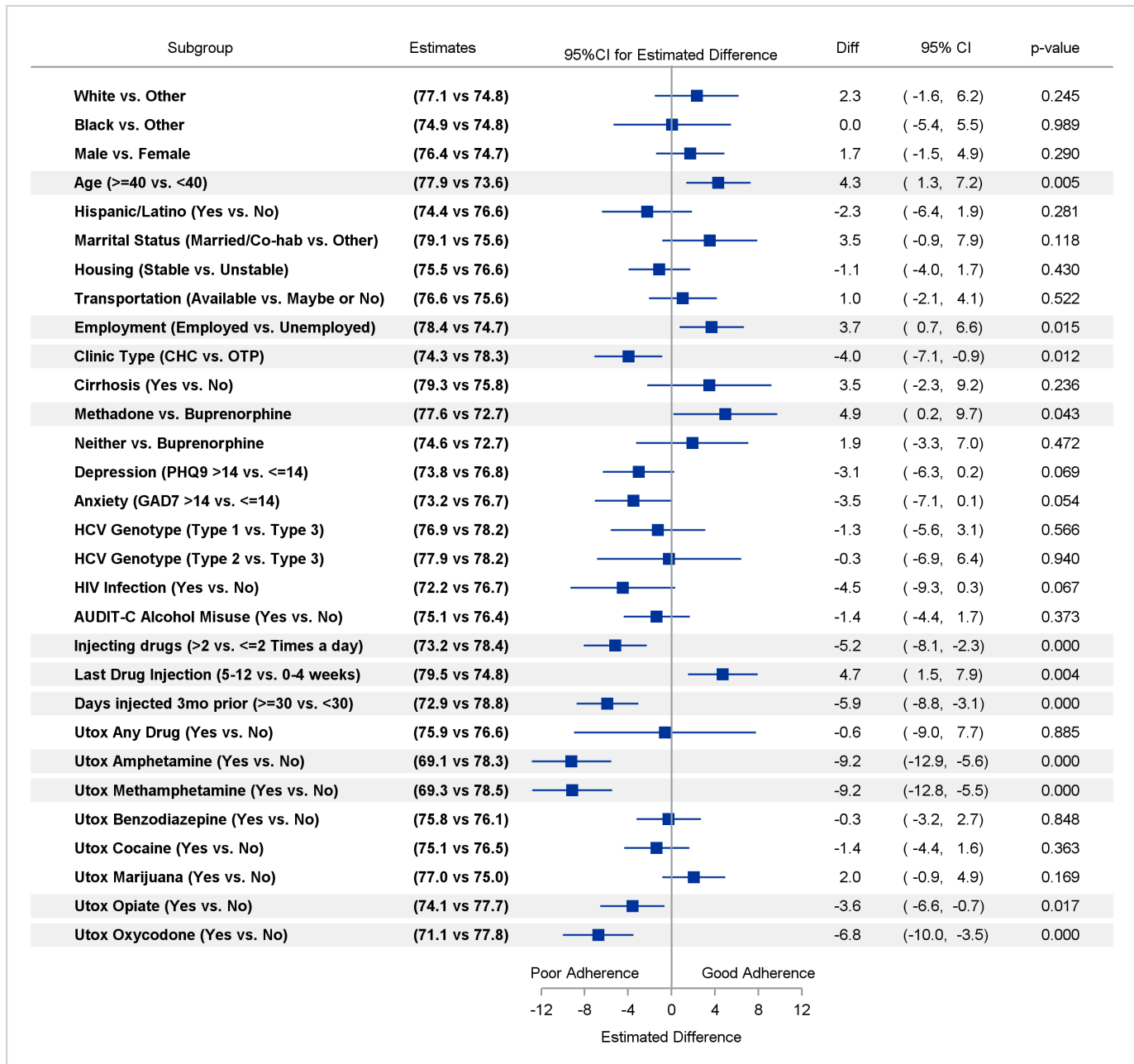


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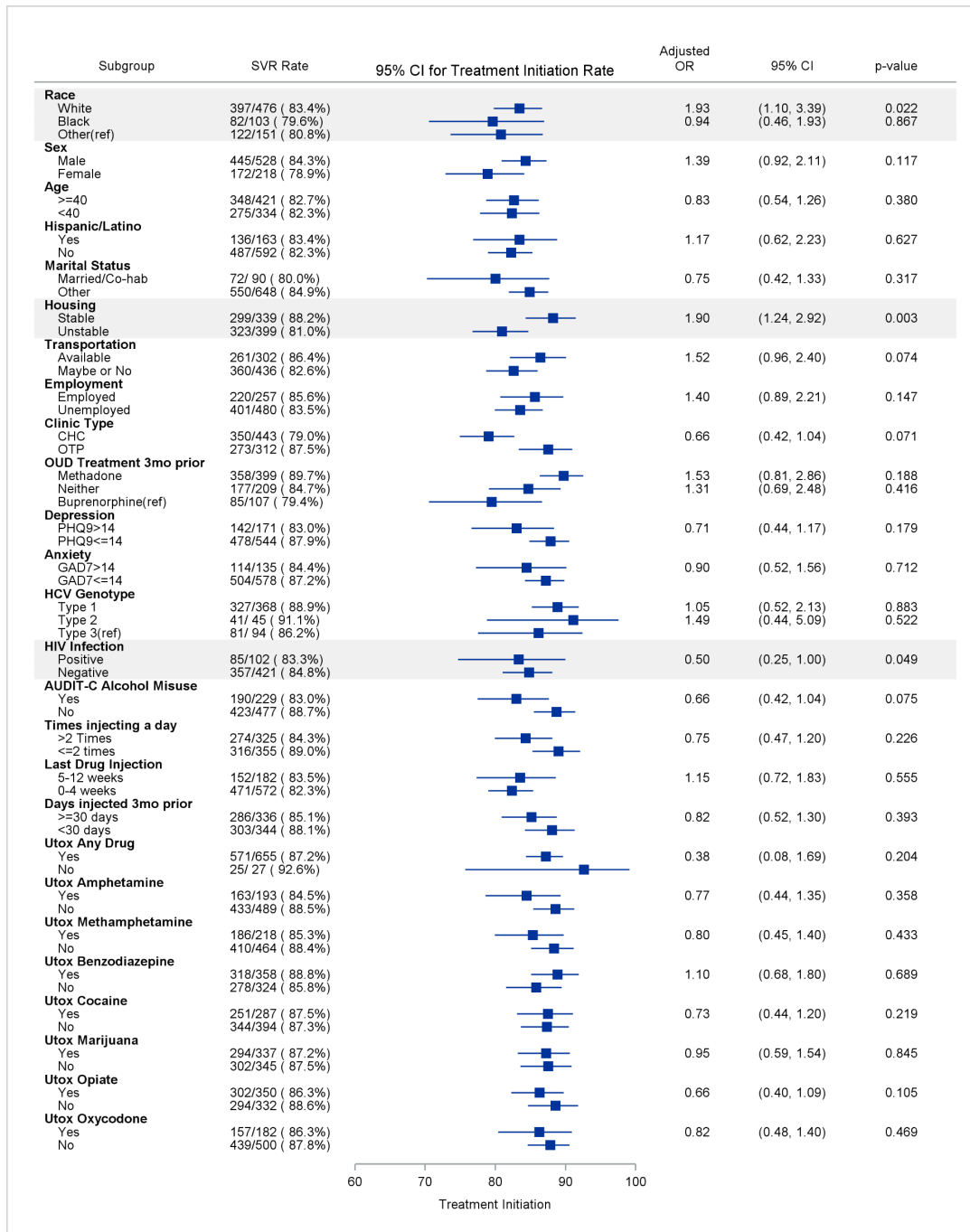
AUDIT-C, Alcohol Use Disorders Identification Test; CHC, community health centers; Co-hab, cohabitation; GAD7, general anxiety disorder 7-item; HCV, hepatitis C virus; ITT, intention to treat; OR, odds ratio; OTP, opioid treatment programs; OUD, opioid use disorder; PHQ-9, Patient Health Questionnaire-9; SVR, sustained virologic response; UTOX, urine toxicology screen.

Figure S3. Factors Associated With Adherence in the PP Population.



AUDIT-C, Alcohol Use Disorders Identification Test; CHC, community health centers; Co-hab, cohabitation; diff, difference; GAD7, general anxiety disorder 7-item; HCV, hepatitis C virus; OR, odds ratio; OTP, opioid treatment programs; OUD, opioid use disorder; PHQ-9, Patient Health Questionnaire-9; SVR, sustained virologic response; UTOX, urine toxicology screen.

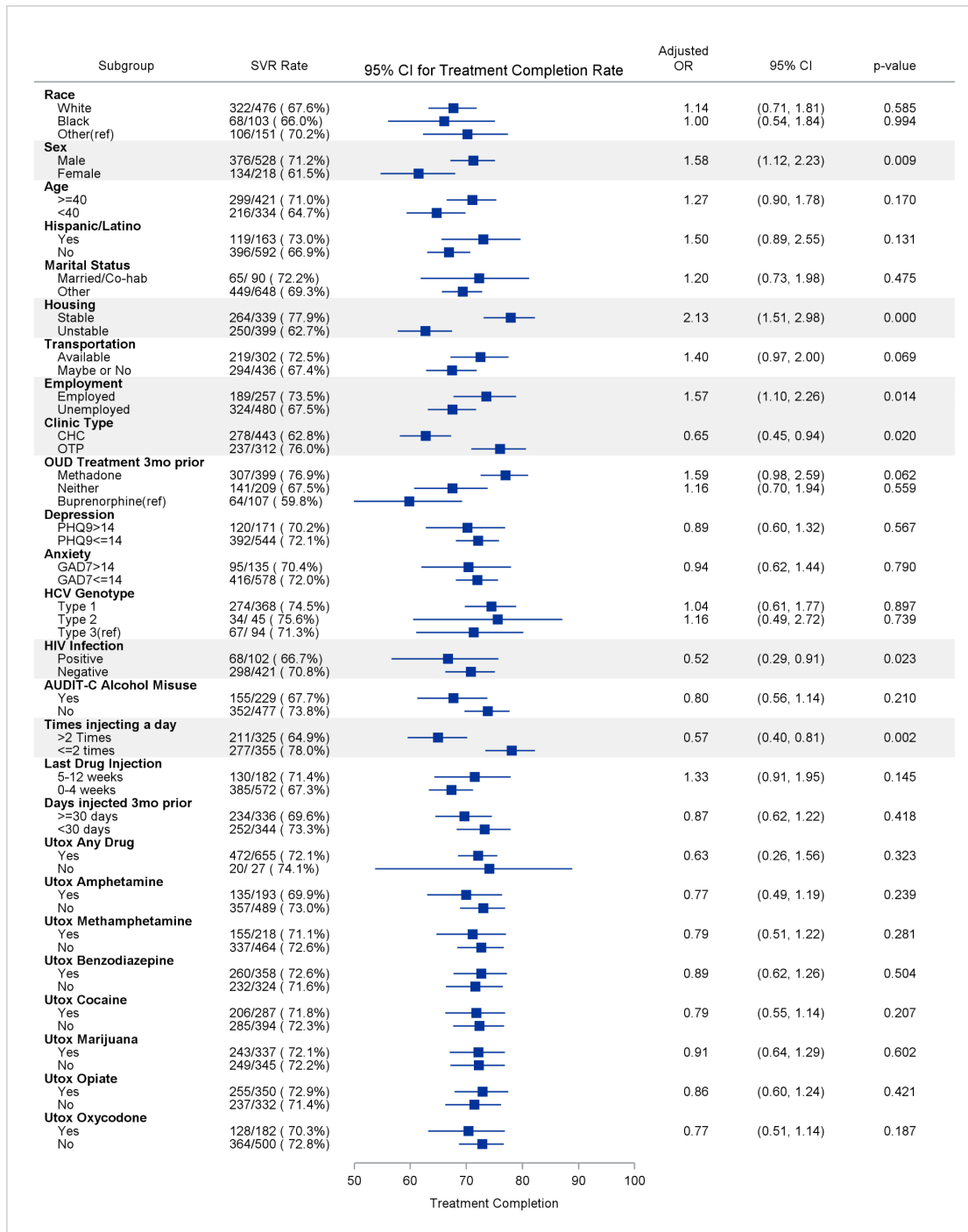
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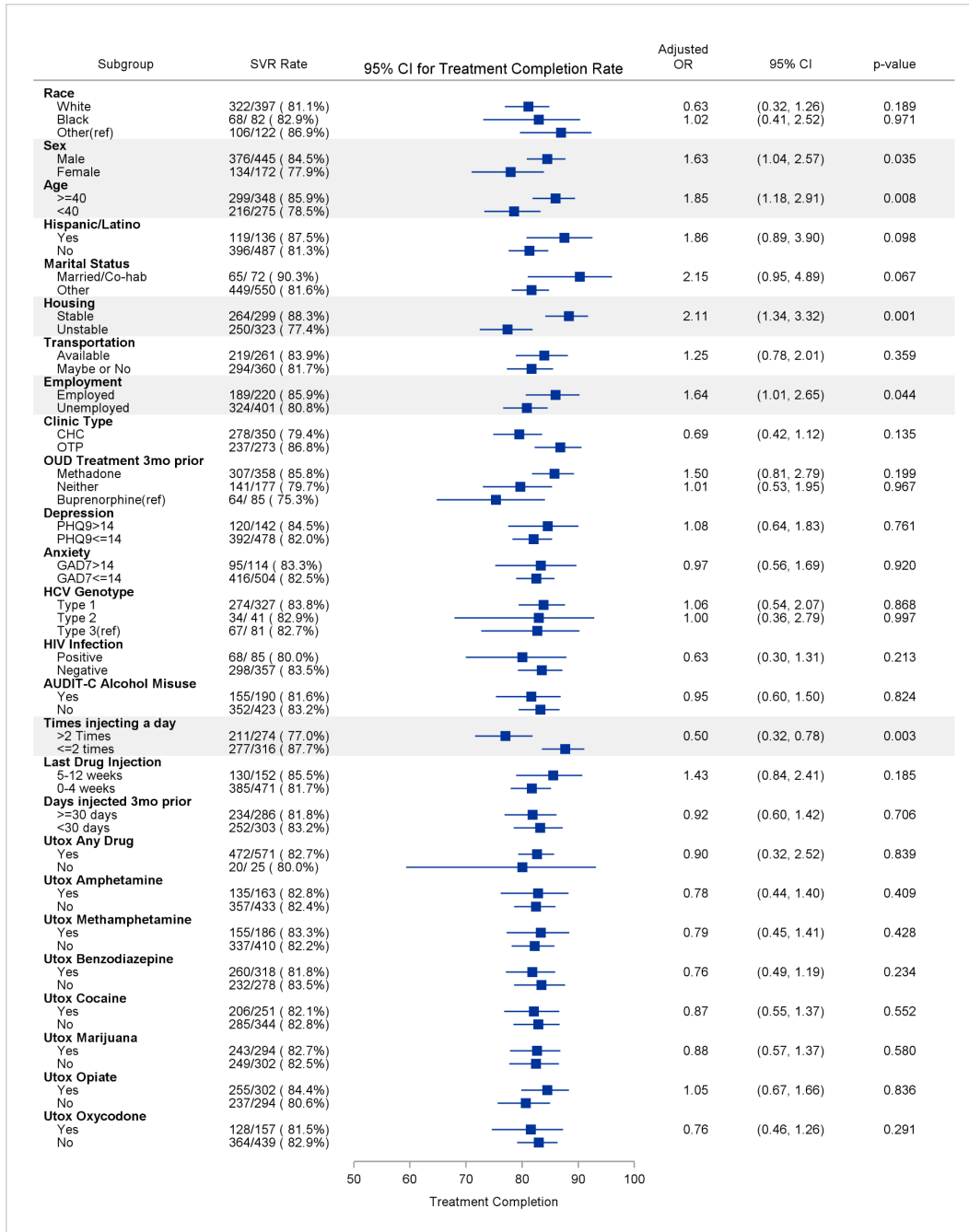
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Figure S5. Factors Associated With Treatment Completion in the ITT (Panel A), mITT (Panel B), and PP (Panel C) Populations.

A



B



C

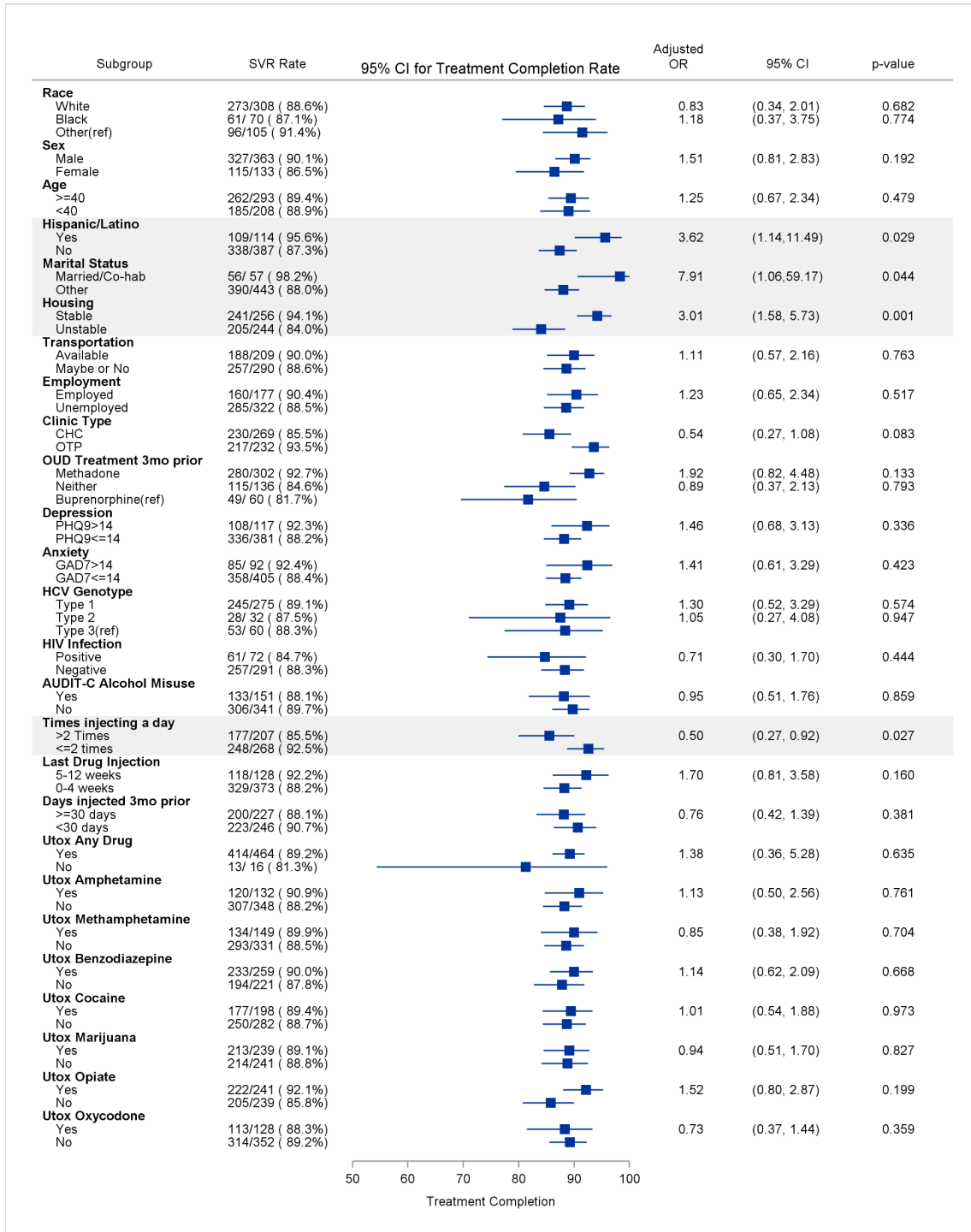


Figure S6. Proportion of Patients With Active Drug Use.

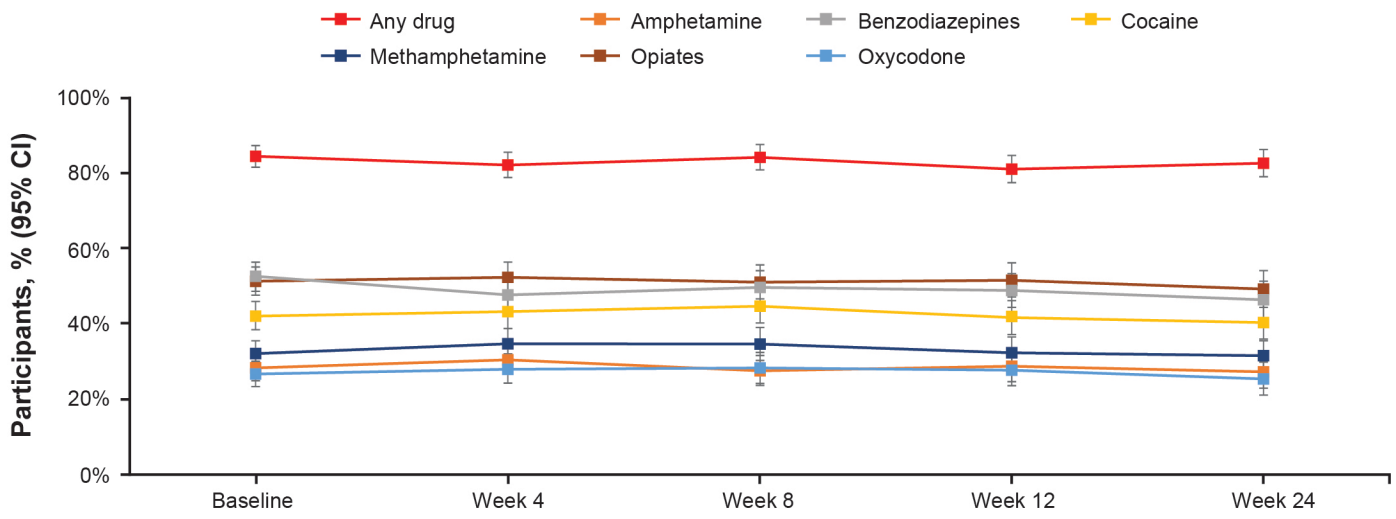
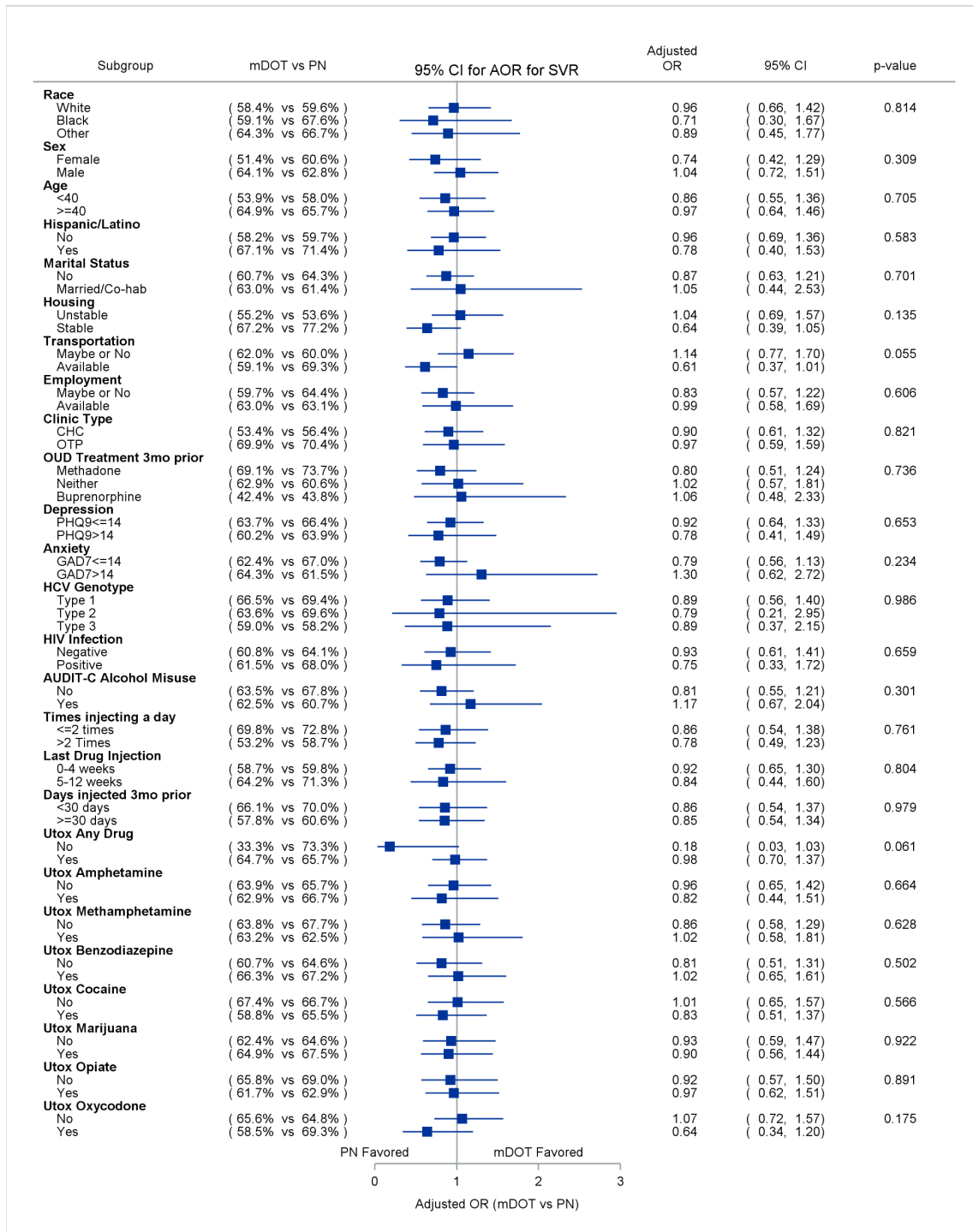
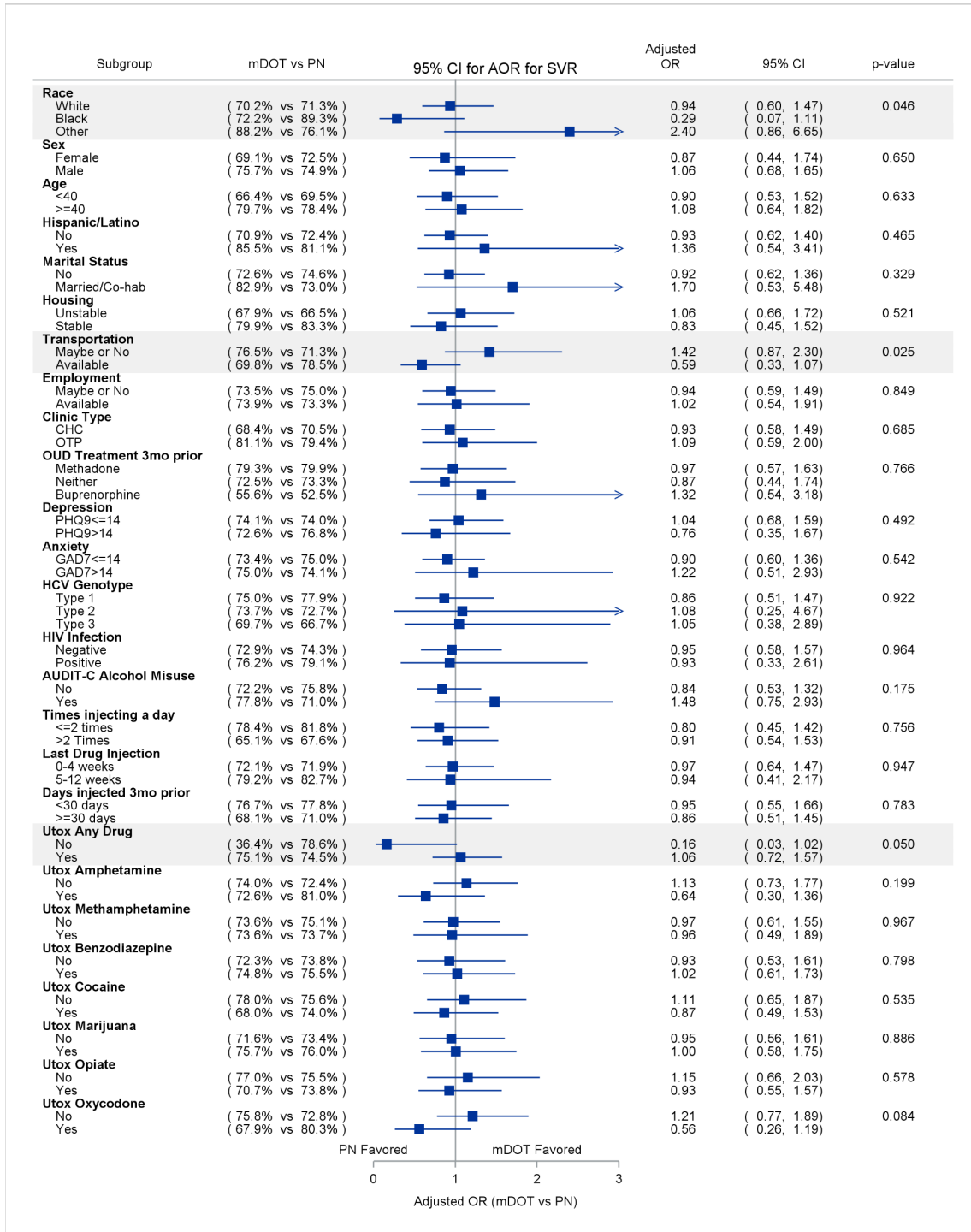


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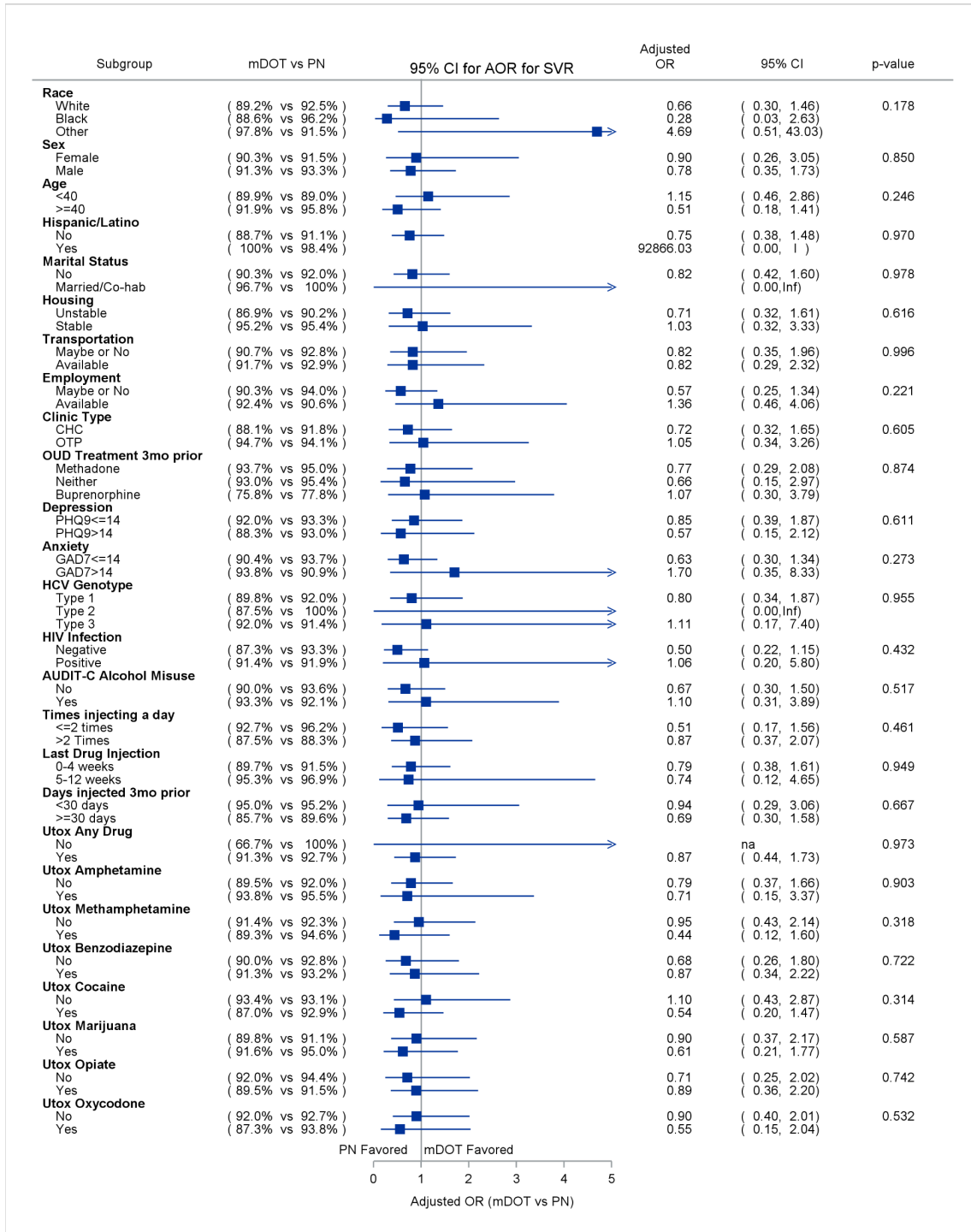
A



B

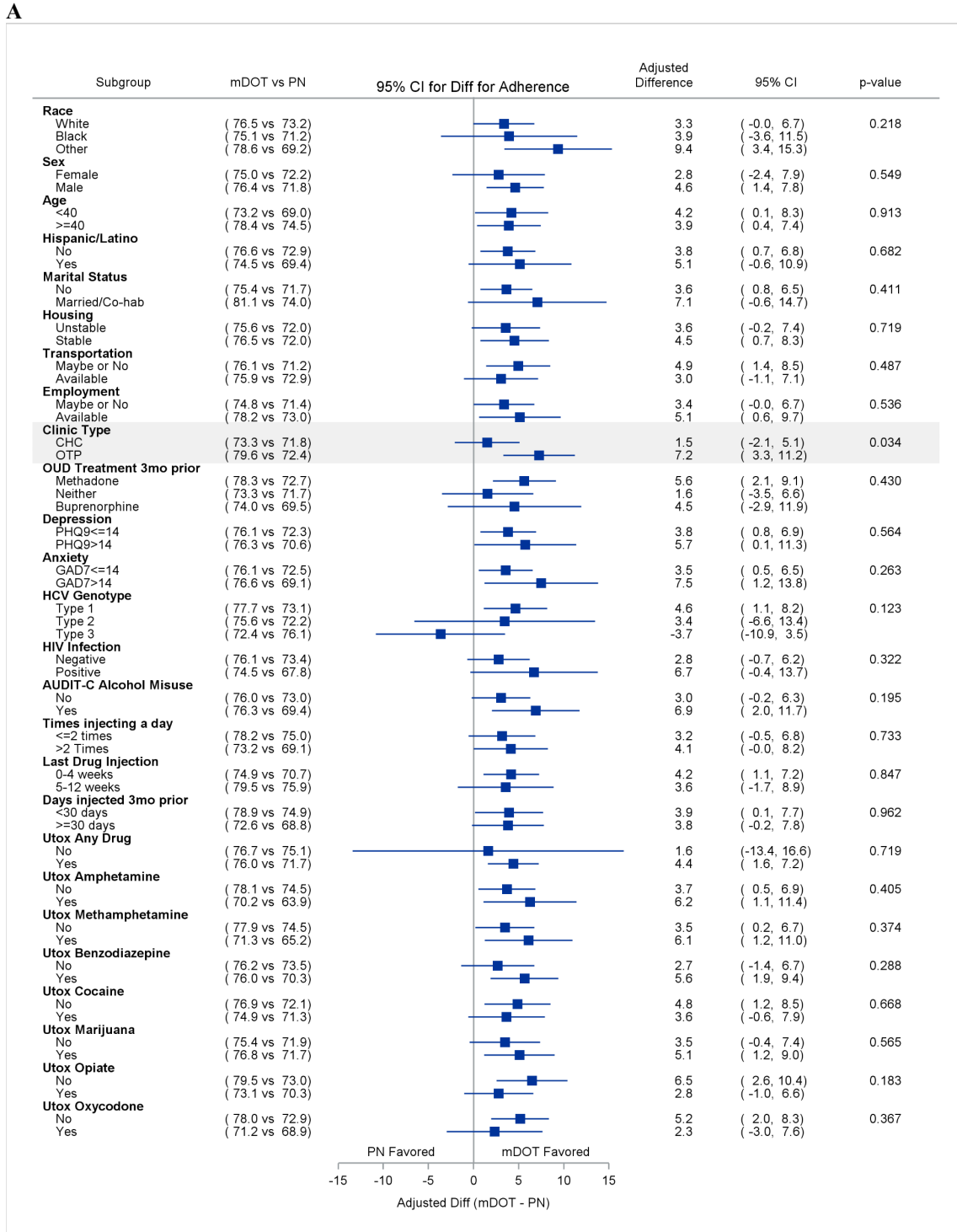


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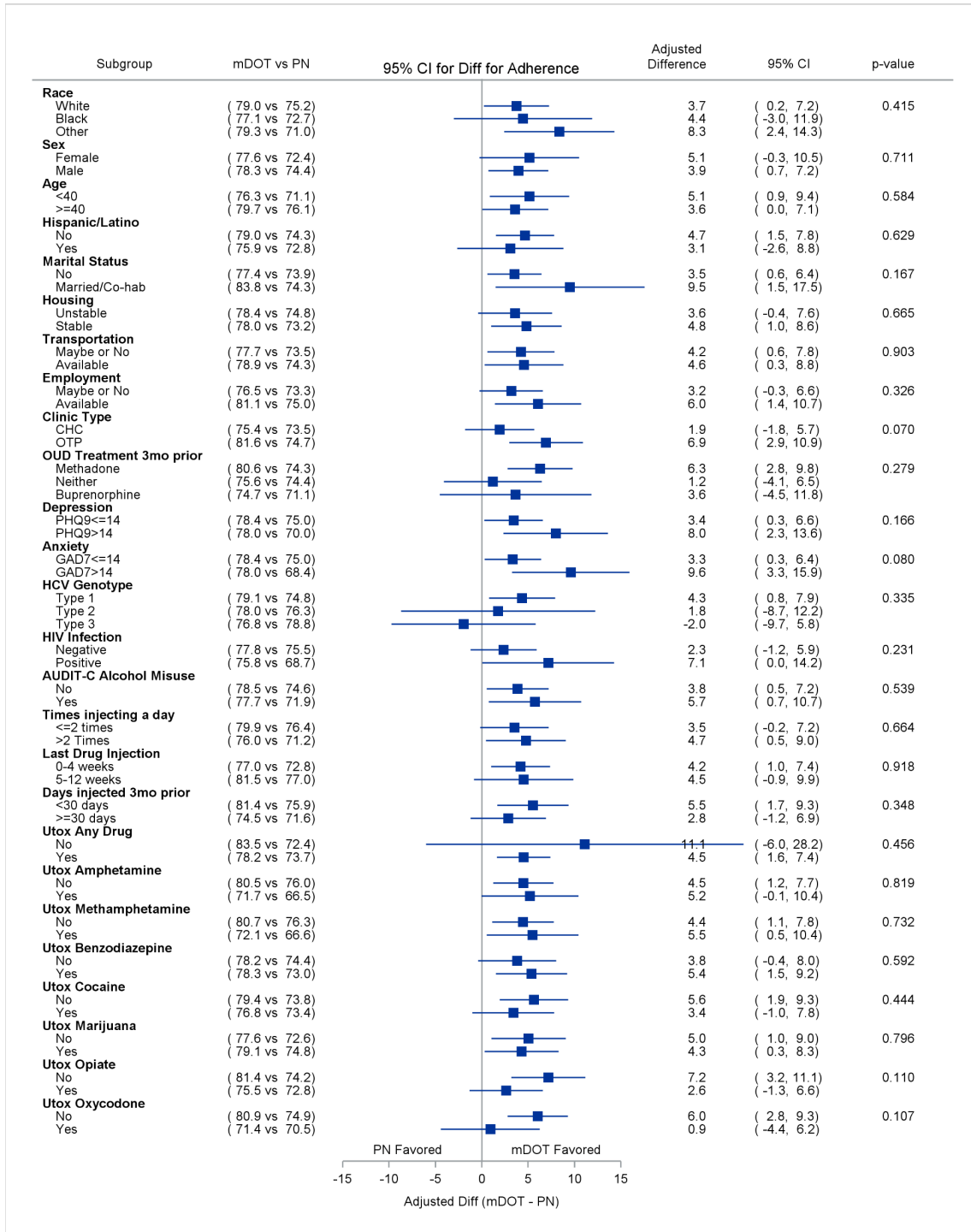


AOR, adjusted odds ratio; AUDIT-C, Alcohol Use Disorders Identification Test; CHC, community health centers; Co-hab, cohabitation; GAD7, general anxiety disorder 7-item; HCV, hepatitis C virus; ITT, intention to treat; mDOT, modified directly observed therapy; OR, odds ratio; OTP, opioid treatment programs; OUD, opioid use disorder; PHQ-9, Patient Health Questionnaire-9; PN, patient navigator; SVR, sustained virologic response; UTOX, urine toxicology screen.

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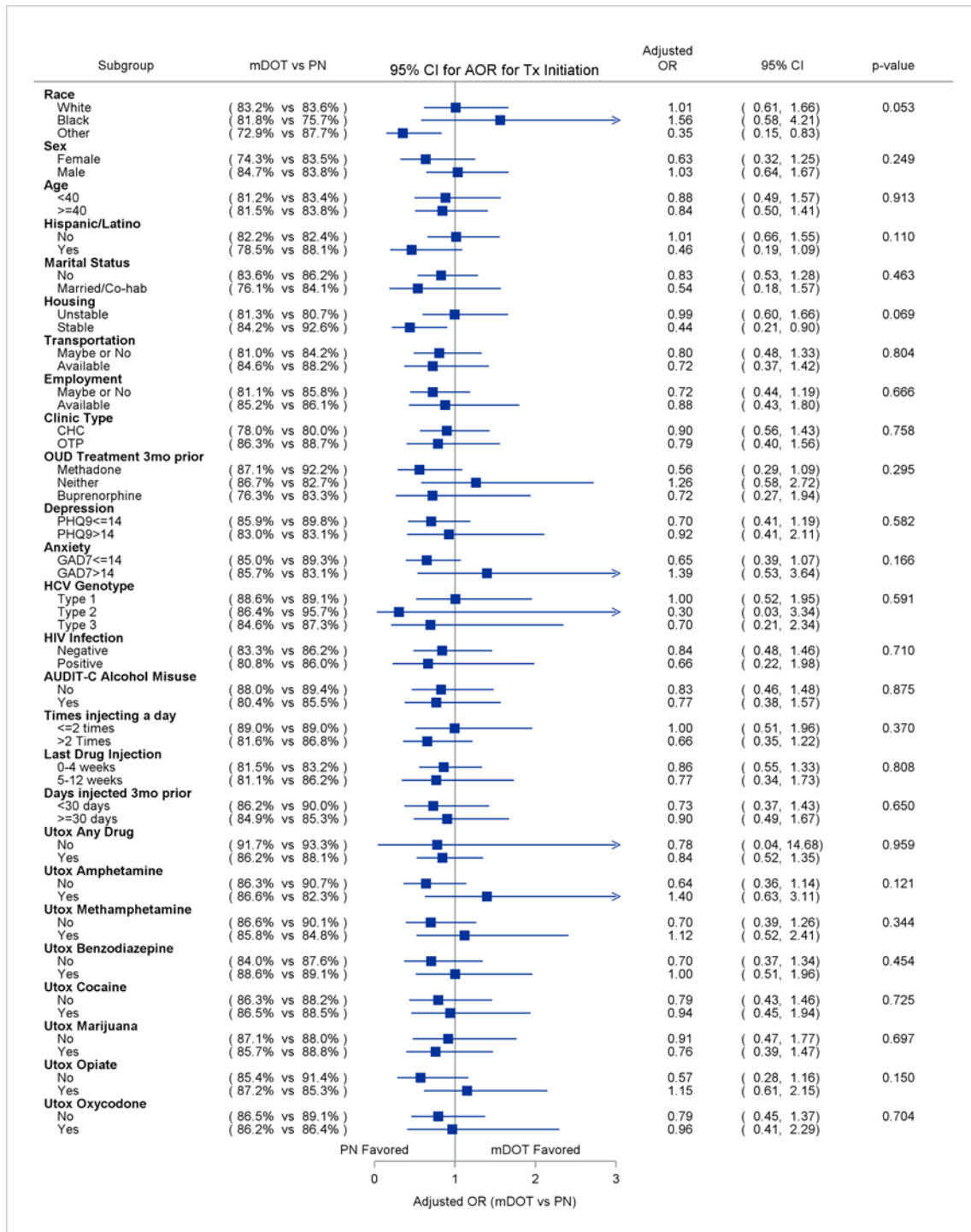


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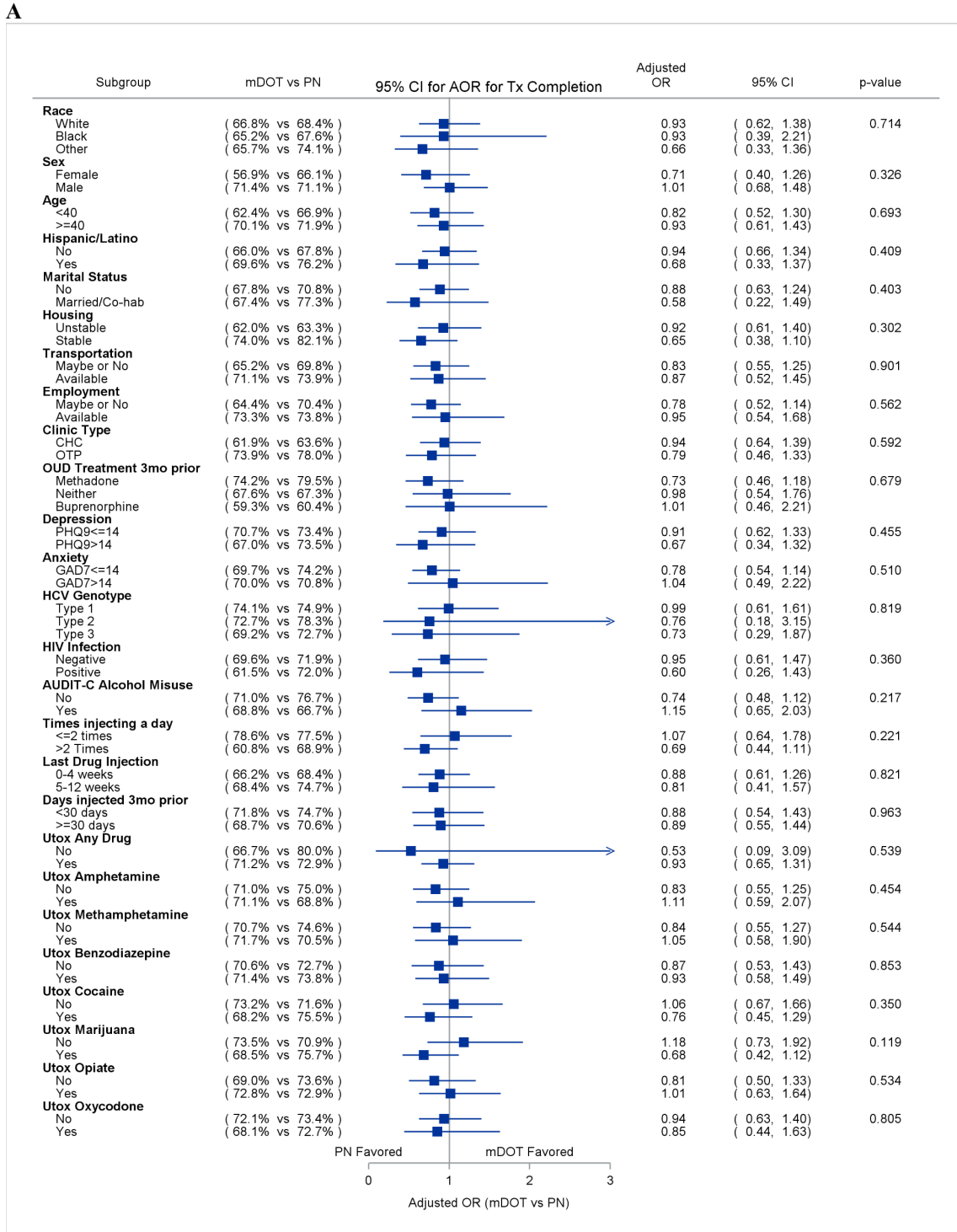
AOR, adjusted odds ratio; AUDIT-C, Alcohol Use Disorders Identification Test; CHC, community health centers; Co-hab, cohabitation; GAD7, general anxiety disorder 7-item; HCV, hepatitis C virus; ITT, intention to treat; mDOT, modified directly observed therapy; OR, odds ratio; OTP, opioid treatment programs; OUD, opioid use disorder; PHQ-9, Patient Health Questionnaire-9; PN, patient navigator; SVR, sustained virologic response; UTOX, urine toxicology screen.

Figure S9. Factors With Between-Subgroup Heterogeneous Intervention Effects on Treatment Initiation in the ITT Population

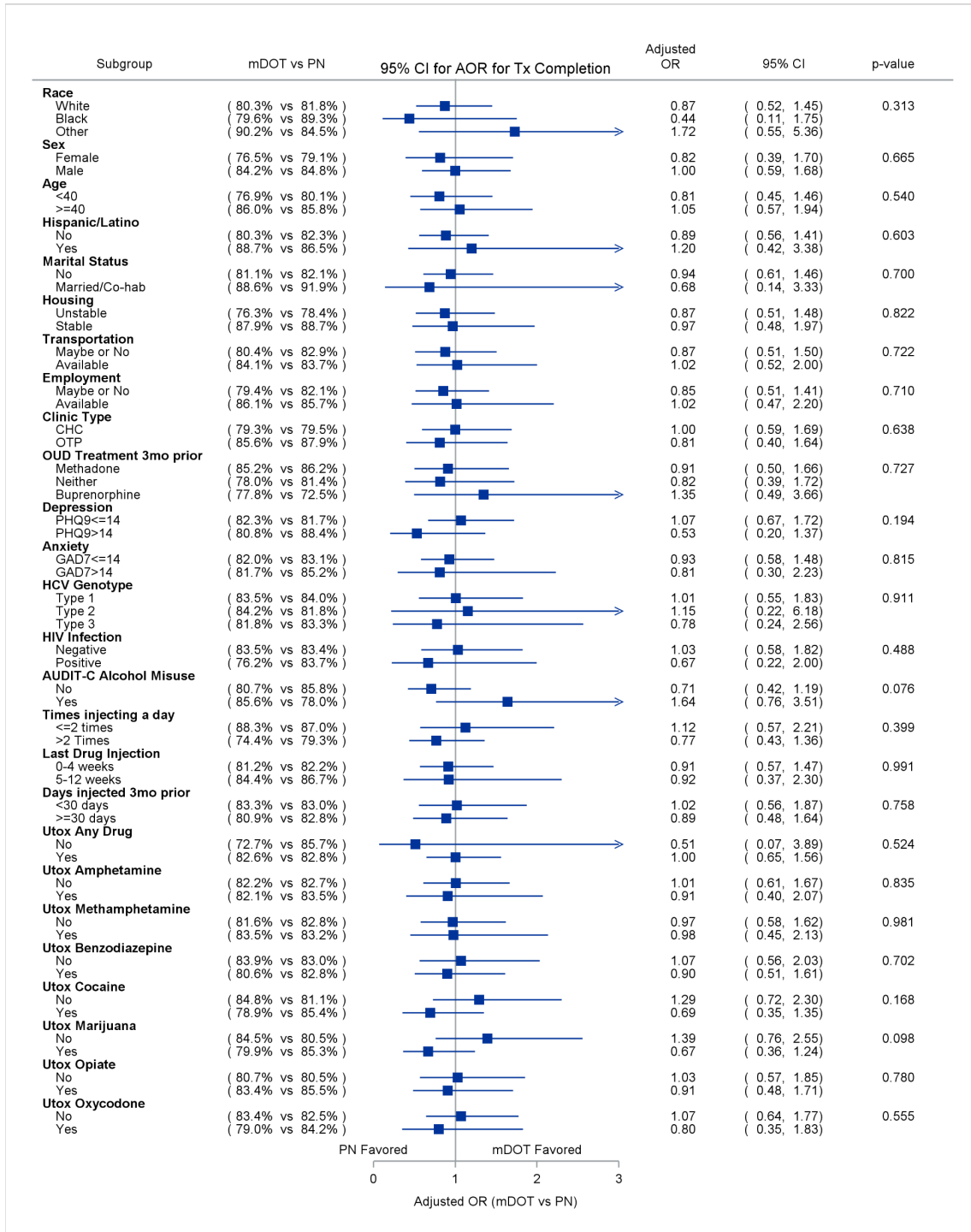


AOR, adjusted odds ratio; AUDIT-C, Alcohol Use Disorders Identification Test; CHC, community health centers; Co-hab, cohabitation; GAD7, general anxiety disorder 7-item; HCV, hepatitis C virus; ITT, intention to treat; mDOT, modified directly observed therapy; OR, odds ratio; OTP, opioid treatment programs; OUD, opioid use disorder; PHQ-9, Patient Health Questionnaire-9; PN, patient navigator; SVR, sustained virologic response; Tx, treatment; UTOX, urine toxicology screen.

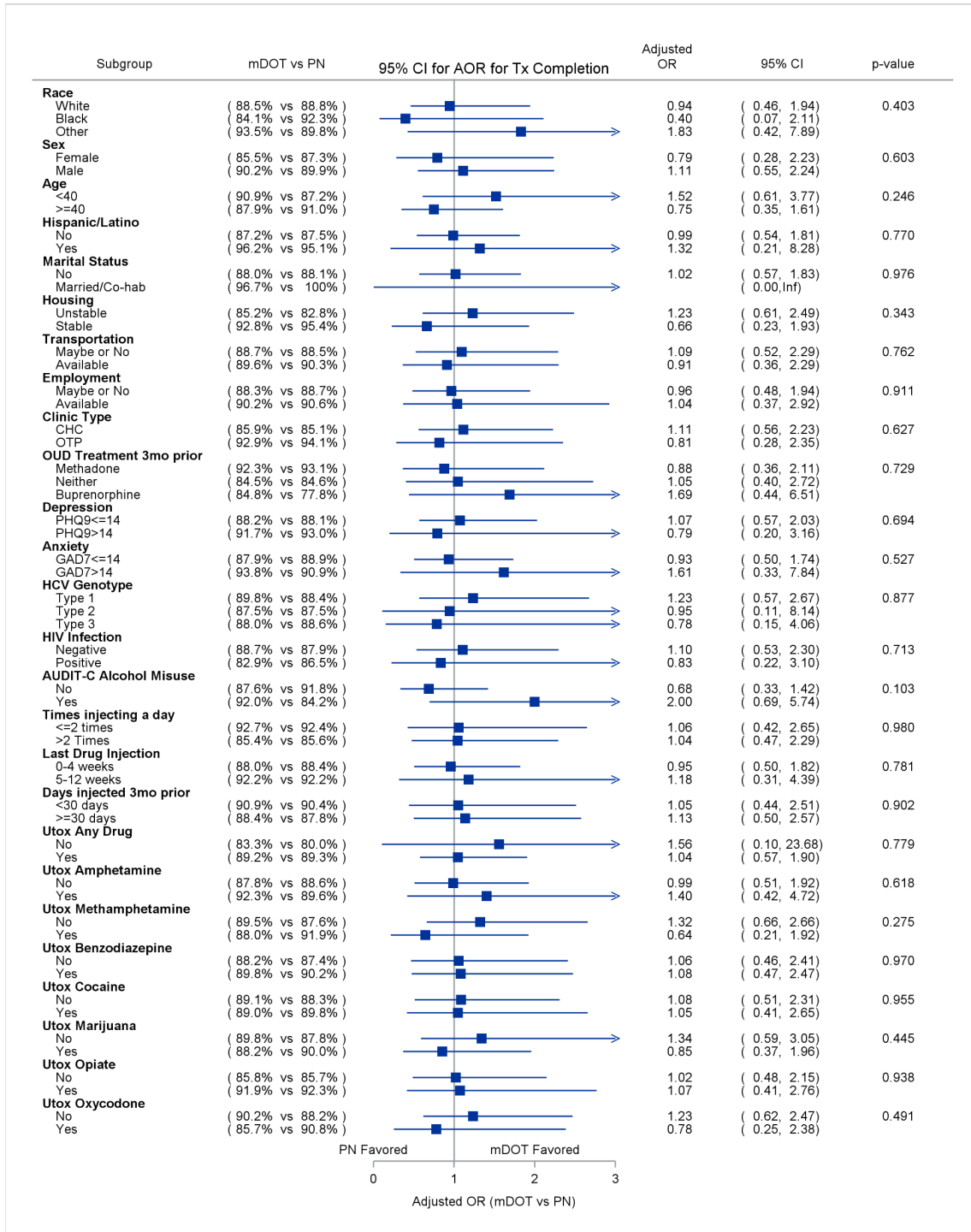
Figure S10. Factors With Between-Subgroup Heterogeneous Intervention Effects on Treatment Completion in the ITT (Panel A), mITT (Panel B), and PP (Panel C) Populations



B



C



AOR, adjusted odds ratio; AUDIT-C, Alcohol Use Disorders Identification Test; CHC, community health centers; Co-hab, cohabitation; GAD7, general anxiety disorder 7-item; HCV, hepatitis C virus; ITT, intention to treat; mDOT, modified directly observed therapy; OR, odds ratio; OTP, opioid treatment programs; OUD, opioid use disorder; PHQ-9, Patient Health Questionnaire-9; PN, patient navigator; SVR, sustained virologic response; Tx, treatment; UTOX, urine toxicology screen.

Table S1. Baseline Characteristics of HERO Participants Among PP Sample.

Characteristic	Category	Total (N=501) ^a	DOT (N=248) ^a	PN (N=253) ^a	<i>P</i> ^b
Demographic Characteristics					
Gender, n (%)	Female	133 (26.5)	62 (25.0)	71 (28.1)	0.654
	Male	363 (72.5)	184 (74.2)	179 (70.8)	
	Transgender or gender non-conforming	5 (1.0)	2 (0.8)	3 (1.2)	
Age	Mean (SD)	44.0 (11.5)	44.6 (11.7)	43.4 (11.3)	0.211
	Median (Q1, Q3)	42.6 (35.3, 53.7)	44.0 (35.7, 54.6)	41.6 (35.1, 51.1)	
Race, n (%)	White/Caucasian	308 (63.8)	148 (62.2)	160 (65.3)	0.037
	Black/African American	70 (14.5)	44 (18.5)	26 (10.6)	
	Other	105 (21.7)	46 (19.3)	59 (24.1)	
Latino/Hispanic ethnicity, n (%)	Yes	114 (22.8)	53 (21.4)	61 (24.1)	0.465
	No	387 (77.2)	195 (78.6)	192 (75.9)	
Marital/cohabitation status, n (%)	Single/separated/divorced/widowed	438 (87.6)	215 (87.0)	223 (88.1)	0.795
	Married/living together as married	57 (11.4)	30 (12.1)	27 (10.7)	
	Other	5 (1.0)	2 (0.8)	3 (1.2)	
Education, n (%)	Less than HS	118 (23.6)	67 (27.1)	51 (20.2)	0.183
	HS diploma or GED	189 (37.8)	90 (36.4)	99 (39.1)	
	Some college or more	193 (38.6)	90 (36.4)	103 (40.7)	
Living situation ^c , n (%)	Shelter	34 (6.8)	20 (8.1)	14 (5.5)	0.741
	Street/Outdoors	27 (5.4)	16 (6.5)	11 (4.3)	
	Someone else's apartment, room, or house	127 (25.4)	60 (24.3)	67 (26.5)	
	Institution	37 (7.4)	17 (6.9)	20 (7.9)	
	Own/rent apartment, room, or house	256 (51.2)	125 (50.6)	131 (51.8)	
	Other	19 (3.8)	9 (3.6)	10 (4.0)	
Availability of transportation, n (%)	Yes	209 (41.9)	96 (38.9)	113 (44.8)	0.414
	Maybe, if I can get a ride	26 (5.2)	16 (6.5)	10 (4.0)	
	Maybe, if public transportation is available	260 (52.1)	133 (53.8)	127 (50.4)	
	No	4 (0.8)	2 (0.8)	2 (0.8)	
	Yes	177 (35.5)	92 (37.4)	85 (33.6)	0.375

Characteristic	Category	Total (N=501) ^a	DOT (N=248) ^a	PN (N=253) ^a	P ^b
Employed with a regular job or informal work ^d , n (%)	No	322 (64.5)	154 (62.6)	168 (66.4)	
Clinical Characteristics					
Clinical setting, n (%)	OTP	232 (46.3)	113 (45.6)	119 (47.0)	0.741
	CHC	269 (53.7)	135 (54.4)	134 (53.0)	
Any medication for OUD in the past 3 months, n (%)	Buprenorphine				
	Yes	70 (14.1)	39 (15.8)	31 (12.4)	0.270
	No	428 (85.9)	208 (84.2)	220 (87.6)	
	Methadone				
	Yes	302 (60.6)	143 (57.9)	159 (63.3)	0.213
	No	196 (39.4)	104 (42.1)	92 (36.7)	
Depression PHQ-9 severity, n (%)	Mild (<10)	259 (52.0)	130 (52.6)	129 (51.4)	0.751
	Moderate (10-14)	122 (24.5)	57 (23.1)	65 (25.9)	
	Moderately severe/severe (>14)	117 (23.5)	60 (24.3)	57 (22.7)	
Anxiety GAD-7 severity, n (%)	Mild (<10)	309 (62.2)	144 (58.5)	165 (65.7)	0.218
	Moderate (10-14)	96 (19.3)	54 (22.0)	42 (16.7)	
	Moderately severe/severe (>14)	92 (18.5)	48 (19.5)	44 (17.5)	
Genotype, n (%)	Type 1	275 (73.7)	137 (75.3)	138 (72.3)	0.714
	Type 2	32 (8.6)	16 (8.8)	16 (8.4)	
	Type 3	60 (16.1)	25 (13.7)	35 (18.3)	
	Type 4	3 (0.8)	2 (1.1)	1 (0.5)	
	Mixed	3 (0.8)	2 (1.1)	1 (0.5)	
HIV infection (positive), n (%)	Yes	72 (19.8)	35 (19.8)	37 (19.9)	1.000
	No	291 (80.2)	142 (80.2)	149 (80.1)	
Cirrhosis (positive), n (%)	Yes	31 (6.2)	16 (6.5)	15 (5.9)	0.808
	No	470 (93.8)	232 (93.5)	238 (94.1)	
Alcohol misuse ^e , n (%)	Yes	151 (30.7)	75 (30.6)	76 (30.8)	0.970
	No	341 (69.3)	170 (69.4)	171 (69.2)	
Last drug injection (within 3 months of screening), n (%)	0-4 weeks	373 (74.5)	184 (74.2)	189 (74.7)	0.640
	5-8 weeks	85 (17.0)	45 (18.1)	40 (15.8)	
	9-12 weeks	43 (8.6)	19 (7.7)	24 (9.5)	
	Yes	475 (95.2)	233 (94.3)	242 (96.0)	0.375

Characteristic	Category	Total (N=501) ^a	DOT (N=248) ^a	PN (N=253) ^a	<i>P</i> ^b
Drug injection reported within 3 months of baseline ^{f, n} (%)	No	24 (4.8)	14 (5.7)	10 (4.0)	
Number of days injected drugs in the past 3 months ^{f,g}	Mean (SD)	32.6 (30.5)	32.0 (29.1)	33.2 (31.8)	0.938
	Median (Q1, Q3)	24.0 (5.0, 60.0)	25.0 (6.0, 50.0)	21.0 (5.0, 60.0)	
Times injecting drugs a day ^{f,h}	Mean (SD)	2.9 (2.7)	2.8 (2.3)	3.0 (2.9)	0.305
	Median (Q1, Q3)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	
	≤2 times per day	268 (56.4%)	137 (58.8%)	131 (54.1%)	
	>2 times per day	207 (43.6%)	96 (41.2%)	111 (45.9%)	
Urine Drug Screen Results at Baseline Visitⁱ, n (%)					
Any drug ^j	Yes	464 (96.7)	231 (97.5)	233 (95.9)	0.334
	No	16 (3.3)	6 (2.5)	10 (4.1)	
Amphetamine	Yes	132 (27.5)	65 (27.4)	67 (27.6)	0.972
	No	348 (72.5)	172 (72.6)	176 (72.4)	
Methamphetamine	Yes	149 (31.0)	75 (31.6)	74 (30.5)	0.778
	No	331 (69.0)	162 (68.4)	169 (69.5)	
Benzodiazepine	Yes	259 (54.0)	127 (53.6)	132 (54.3)	0.872
	No	221 (46.0)	110 (46.4)	111 (45.7)	
Cocaine	Yes	198 (41.3)	100 (42.2)	98 (40.3)	0.678
	No	282 (58.8)	137 (57.8)	145 (59.7)	
THC/cannabis	Yes	239 (49.8)	119 (50.2)	120 (49.4)	0.856
	No	241 (50.2)	118 (49.8)	123 (50.6)	
Opiate	Yes	241 (50.2)	124 (52.3)	117 (48.1)	0.361
	No	239 (49.8)	113 (47.7)	126 (51.9)	
Oxycodone	Yes	128 (26.7)	63 (26.6)	65 (26.7)	0.967
	No	352 (73.3)	174 (73.4)	178 (73.3)	

CHC denotes community health centers, DOT directly observed therapy, GAD-7 General Anxiety Disorder-7 scale, GED General Educational Development, HS high school, ITT intention-to-treat, mITT modified intention-to-treat, OTP opioid treatment program, OUD opioid use disorder, PHQ-9 Patient Health Questionnaire-9, PN patient navigation, PP per-protocol, THC tetrahydrocannabinol.

^aExtent of missing observations varies across the characteristics.

^b*P* values are based on Chi-square, Fisher exact, t, or Wilcoxon test comparing between DOT and PN groups among the mITT sample.

^cParticipants were asked: "In the last 3 months, where have you been living most of the time?" Answers included: shelter; street/outdoors; someone else's apartment, room, or house; institution (institution, hallway house, residential treatment facility/program); own/rent apartment, house, or room; other (dormitory/college residence, other, refused, don't know).

^dParticipants were asked: "In the last 3 months, what were your sources of income?" Employed was defined as including (a) a regular job and (b) informal work.

^eBased on the Alcohol Use Disorders Identification Test score: yes (alcohol misuse vs no). Note that

cutoffs are different for male and female participants.

^fPercentage calculated based upon the Behavioral Risk Assessment administered at baseline visit.

^gParticipants were asked: "In the past 3 months, on how many DAYS did you shoot up anything, including prescribed medications not intended to be injected?"

^hParticipants were asked: "How many times a day did you usually inject on the days you injected?"

ⁱPercentages calculated based upon conducted urine drug screen at baseline visit.

^jPositive for any drug toxicology (including cannabis, barbituates, buprenorphine, and methadone).

Table S2 . Distribution of SAE by the study arms from N=219 participants (N=109 from mDOT and N=110 for PN)

Serious Adverse Event	Total N(%)	mDOT	PN
Death	35 (8.3%)	17 (7.8%)	18 (8.8%)
Life threatening	17 (4.0%)	6 (2.8%)	11 (5.4%)
Hospitalization	337 (80.1%)	176 (81.1%)	161 (78.9%)
Disability or permanent change	1 (0.2%)	0 (0.0%)	1 (0.5%)
Required intervention to prevent impairment/damage	2 (0.5%)	1 (0.5%)	1 (0.5%)
Other serious important medical event	29 (6.9%)	17 (7.8%)	12 (5.9%)
Total	421	217	204