Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

The LATITUDE Study: Long-Acting Therapy to Improve Treatment SUccess in Daily LifE - A Phase III Study to Evaluate Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals

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Section 2 Supplementary Tables and Figures

Figure S1a Step 1 Consort Diagram by Protocol Version

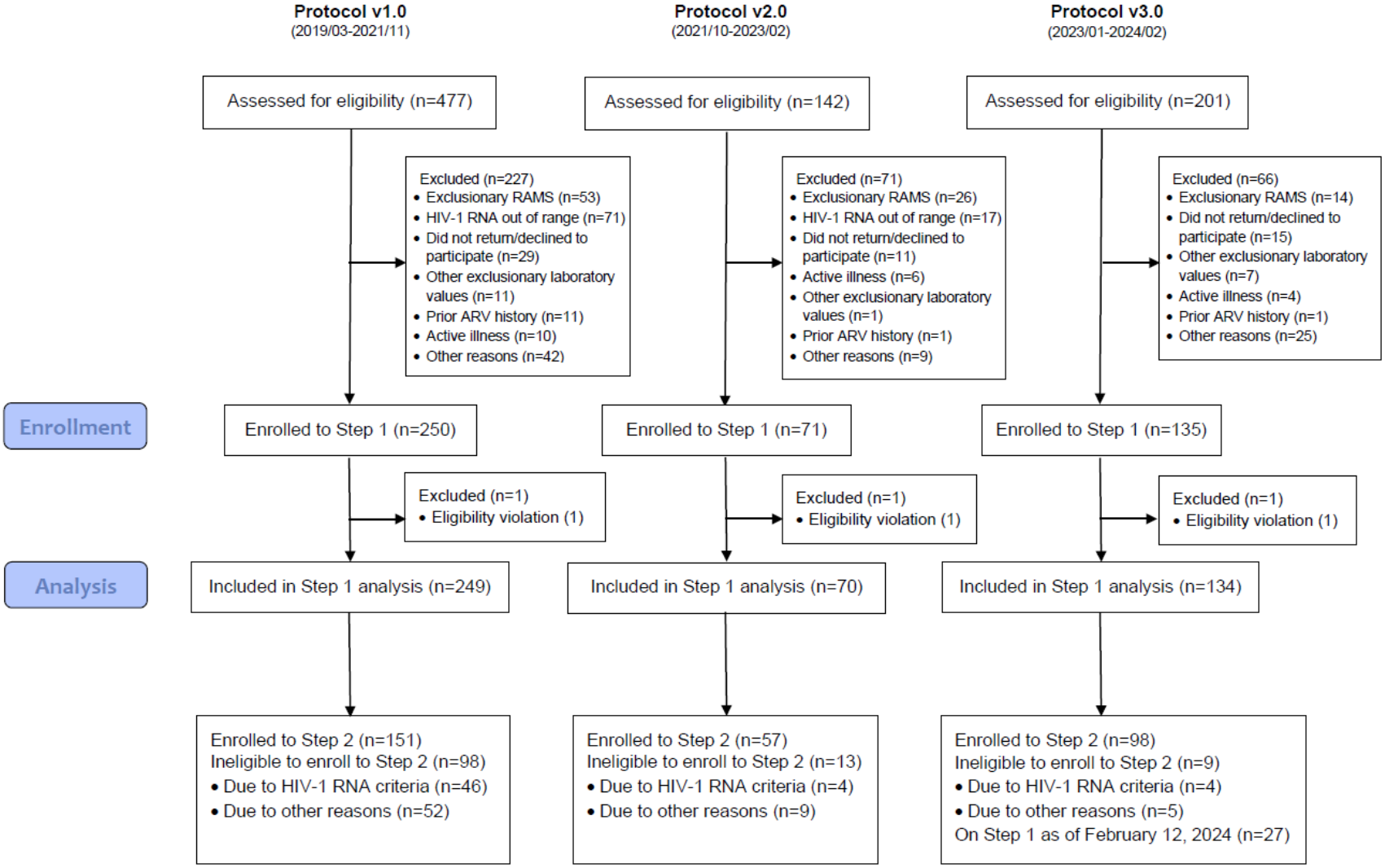
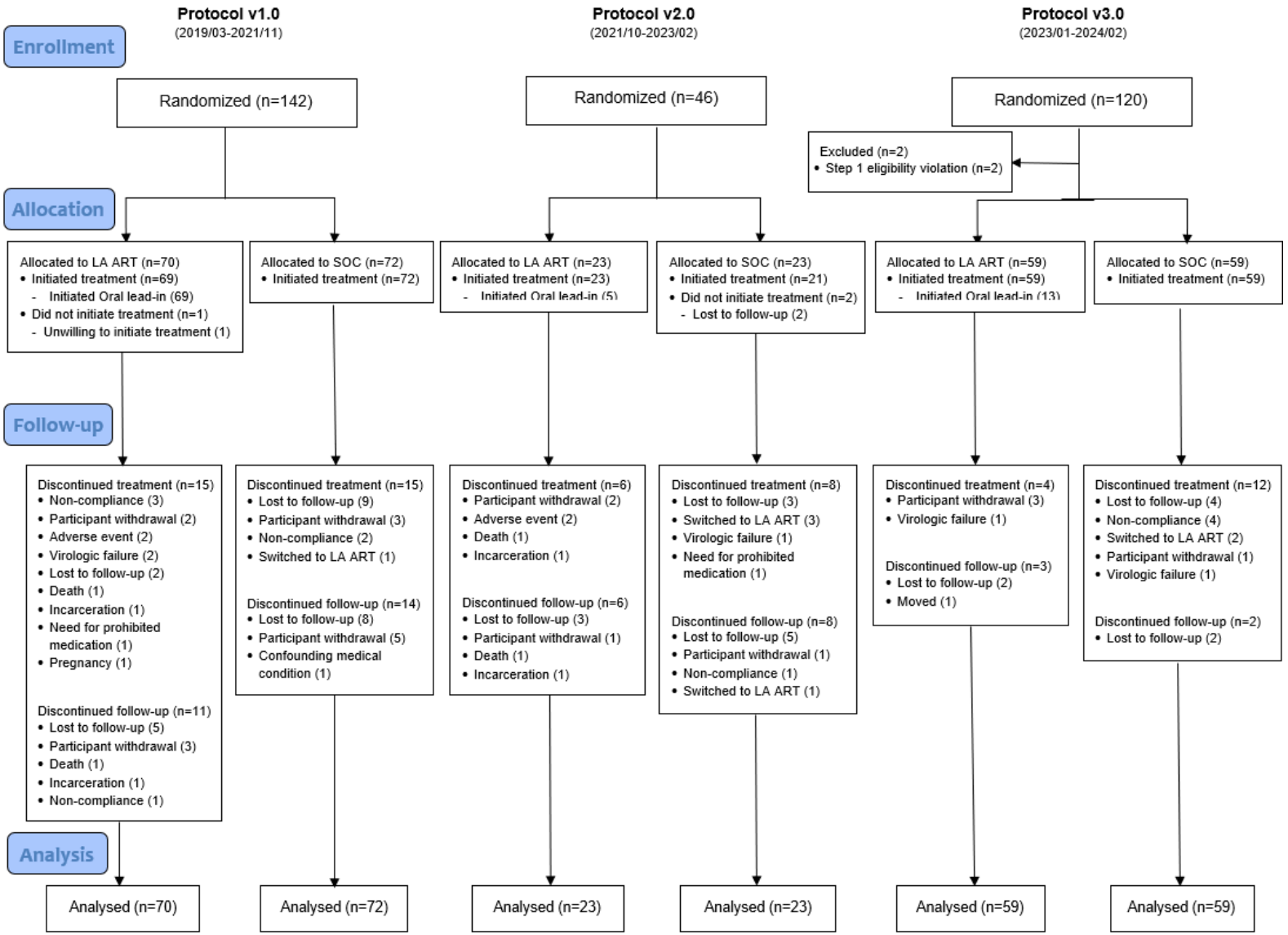


Figure S1b Step 2 Consort Diagram by Protocol Version



Step 1 Full Baseline Characteristics

Appendix Table S 2.1: Step 1 Baseline Sociodemographic Characteristics

		Total (N=453)
Age, years	Median (Q1, Q3)	40 (32, 51)
	18-24	29 (6%)
	25-30	64 (14%)
	31-40	142 (31%)
	41-50	102 (23%)
	51+	116 (26%)
Sex at Birth	Female	133 (29%)
	Male	320 (71%)
Gender Identity	Cisgender	429 (95%)
	Transgender Spectrum	22 (5%)
	Information Not Collected	2
Race	Black or African American	286 (63%)
	White	125 (28%)
	Asian	3 (1%)
	Multiple	11 (2%)
	Unknown	28 (6%)
Ethnicity	Hispanic or Latino	79 (17%)
	Not Hispanic or Latino	369 (81%)
	Unknown	5 (1%)
History of IV drug use	Currently	20 (4%)
	Previously	43 (9%)
	Never	390 (86%)

Appendix Table S2.2 Step 1 Baseline Characteristics: History and HIV Disease Progression

		Total (N=453)
Step 1 Baseline BMI kg/m²	n	453
	Median (Q1, Q3)	26 (22, 30)
Time since HIV diagnosis, years	Median (Q1, Q3)	13 (7, 21)
	# missing	71
Non-Adherence Information	Lost To Follow-Up	93 (21%)
	Poor Virologic Response	294 (65%)
	Poor Virologic Response And Lost To Follow-Up	66 (15%)
Step 1 Baseline HIV-1 RNA [log_{10} copies/mL][a]	n	453
	Median (Q1, Q3)	3.45 (1.91, 4.57)
Step 1 Baseline HIV-1 RNA levels [copies/mL]	<40	85 (19%)
	40-200	69 (15%)
	201-399	16 (4%)
	400-1,000	28 (6%)
	1,001-5,000	48 (11%)
	5,001-10,000	22 (5%)
	10,001-100,000	123 (27%)
	100,001-1,000,000	58 (13%)
	>1,000,000	4 (1%)
Step 1 Baseline CD4 count/mm³	n	453
	Median (Q1, Q3)	273 (119, 511)
Step 1 Baseline CD8 count/mm³	n	453
	Median (Q1, Q3)	843 (586, 1225)

Appendix Table S2.3 Step 1 Sociodemographic at Baseline

		Total (N=453)
Education Level	11th grade or less	89 (20%)
	High school graduate or GED	141 (32%)
	Some college/AA degree/Technical school training	162 (36%)
	College graduate (BA or BS)	40 (9%)
	Master's degree	6 (1%)
	Doctorate/medical degree/law degree	6 (1%)
	Missing	9
Employment or School	Part-time employment	61 (14%)
	Full-time employment	117 (26%)
	Part-time student	3 (<1%)
	Full-time student	13 (3%)
	On disability	96 (21%)
	Pension/Retired	11 (2%)
	OTHER	147 (33%)
	Missing	5
Having Children	Y	189 (42%)
	N	259 (58%)
	Missing	5
How Many Children Live with You	n	188
	Median (Q1, Q3)	1 (0, 2)
	Min, Max	0, 5
How to Pay Healthcare	Government Funding	350 (81%)
	Government Funding,Private Insurance	15 (3%)
	Government Funding,Private Insurance,Self Pay/Out of Pocket	3 (<1%)
	Government Funding,Self Pay/Out of Pocket	20 (5%)
	Private Insurance	30 (7%)
	Private Insurance,Self Pay/Out of Pocket	3 (<1%)
	Self Pay/Out of Pocket	12 (3%)
	Missing	20
Provide Support to Friend/Family Member	Y	116 (26%)
	N	332 (74%)
	Missing	5

		Total (N=453)
Living Situation	In Own House/Apartment	270 (61%)
	At Parents House	64 (14%)
	Someone Elses House/Apartment	57 (13%)
	Rooming Boarding Or Halfway House	17 (4%)
	Shelter/Welfare Hotel	15 (3%)
	On The Street(S)	9 (2%)
	Residential Drug/Alcohol Treatment Facility	1 (<1%)
	Other	11 (2%)
	Missing	9
Treated for Depression or Mental Health	Y	124 (28%)
	N	323 (72%)
	Missing	6

Appendix Table S2.4: Step 1 Sociodemographic at Baseline -- Likely Route of HIV Infection

		Total (N=453)
Sex with a man who was HIV+	Y	308 (70%)
	N	131 (30%)
	Missing	14
Sex with a woman who was HIV+	Y	76 (18%)
	N	354 (82%)
	Missing	23
Shared needles with a person who was HIV+	Y	27 (6%)
	N	401 (94%)
	Missing	25
Blood transfusion or other medical procedure	Y	9 (2%)
	N	416 (98%)
	Missing	28
Do not know	Y	60 (14%)
	N	359 (86%)
	Missing	34
Perinatally acquired	Y	24
Tattoo	Y	2
Raped/bitten	Y	2

Appendix Table S2.5: Step 1 DUDIT Test at Baseline

		Total (N=453)
Drug Use Disorders Identification Test	n	452
	Median (Q1, Q3)	4 (0, 10)
	Min, Max	0, 44
	# missing	1
Drug Dependency**	No Drug Problems	224 (50%)
	Drug-Use-Related Problems	205 (45%)
	Drug Dependency	23 (5%)
	Missing	1

*** Drug Dependency is defined as: No Drug Problems [<6 for male and <2 for female]; Drug-Use-Related problems [between [6, 25) for male and [2, 25) for female]), Drug Dependency [>=25 regardless of sex] by Drug Use Disorders Identification Test result.*

Appendix Table S2.6: Step 1 Participant Health Questionnaire (PHQ-9) at Baseline

		Total (N=453)
PHQ-9 total score [0-27]	n	450
	Median (Q1, Q3)	4 (2, 10)
	Min, Max	0, 27
	# missing	3
	No Depression [0-4]	228 (51%)
	Mild Depression [5-9]	106 (24%)
	Moderate Depression [10-14]	56 (12%)
	Severe Depression [15-27]	60 (13%)
	Missing	3

Appendix Table S2.7 Step 1 General Anxiety Disorder (GAD-7) and Domestic Violence Screening (DVST-HITS) at Baseline

		Total (N=453)
GAD-7 Assessment	n	452
	Median (Q1, Q3)	5 (1, 10)
	Min, Max	0, 21
	# missing	1
	No Anxiety [<5]	220 (49%)
	Mild [5-<10]	111 (25%)
	Moderate [10-<15]	69 (15%)
	Severe Anxiety [15+]	52 (12%)
	Missing	1
DVST-HITS	n	436
	Median (Q1, Q3)	4 (4, 4)
	Min, Max	4, 19
	# missing	17
Domestic Violence [>10]	Y	12 (3%)
	N	424 (97%)
	Missing	17

Appendix Table S2.8: Step 1 Suicide Severity Rating at Baseline

		Total (N=453)
Suicide Severity Rating	No Risk	358 (81%)
	Low Risk	31 (7%)
	Moderate Risk	45 (10%)
	High Risk	10 (2%)
	Missing	9

Step 2 Baseline Characteristics by Protocol Version

Appendix S3.1: Step 2 Baseline Characteristics: History and HIV Disease Progression by Step 2 Protocol Version

		Protocol Version			
		1.0 (N=142)	**2.0 (N=46)**	**3.0 (N=118)**	**Total (N=306)**
Age at Step 2 Randomization, years	Median (Q1, Q3)	42 (33, 54)	41 (34, 52)	41 (31, 52)	42 (32, 52)
	Min, Max	21, 75	23, 70	20, 69	20, 75
	18-24	4 (3%)	3 (7%)	8 (7%)	15 (5%)
	25-30	17 (12%)	4 (9%)	20 (17%)	41 (13%)
	31-40	41 (29%)	16 (35%)	29 (25%)	86 (28%)
	41-50	33 (23%)	10 (22%)	29 (25%)	72 (24%)
	51+	47 (33%)	13 (28%)	32 (27%)	92 (30%)
Sex at Birth	Female	40 (28%)	11 (24%)	33 (28%)	84 (27%)
	Male	102 (72%)	35 (76%)	85 (72%)	222 (73%)
Gender Identity	Cisgender	134 (94%)	46 (100%)	110 (93%)	290 (95%)
	Transgender Spectrum	8 (6%)	0 (0%)	7 (6%)	15 (5%)
	Information Not Collected	0	0	1	1
Race	Black or African American	96 (68%)	26 (57%)	75 (64%)	197 (64%)
	White	31 (22%)	16 (35%)	33 (28%)	80 (26%)
	Asian	1 (<1%)	0 (0%)	1 (<1%)	2 (<1%)
	Multiple	0 (0%)	1 (2%)	5 (4%)	6 (2%)
	Unknown	14 (10%)	3 (7%)	4 (3%)	21 (7%)
Ethnicity	Hispanic or Latino	27 (19%)	7 (15%)	21 (18%)	55 (18%)
	Not Hispanic or Latino	112 (79%)	38 (83%)	96 (81%)	246 (80%)
	Unknown	3 (2%)	1 (2%)	1 (<1%)	5 (2%)
History of IV drug use	Currently	4 (3%)	4 (9%)	4 (3%)	12 (4%)
	Previously	13 (9%)	9 (20%)	5 (4%)	27 (9%)
	Never	125 (88%)	33 (72%)	109 (92%)	267 (87%)

Appendix Table S3.2: Step 2 Baseline Characteristics: History and HIV Disease Progression by Step 2 Protocol Version

		Protocol Version			
		1.0 (N=142)	2.0 (N=46)	3.0 (N=118)	Total (N=306)
Step 2 Baseline BMI kg/m²	n	141	44	114	299
	Median (Q1, Q3)	26 (23, 31)	25 (22, 30)	27 (23, 31)	26 (23, 31)
	Min, Max	17, 66	20, 50	17, 60	17, 66
Time since HIV diagnosis, years	Median (Q1, Q3)	13 (7, 21)	12 (8, 18)	13 (7, 22)	13 (7, 20)
	Min, Max	1, 35	3, 36	2, 33	1, 36
	# missing	28	5	16	49
Non-Adherence Information	Lost To Follow-Up	29 (20%)	17 (37%)	24 (20%)	70 (23%)
	Poor Virologic Response	90 (63%)	25 (54%)	79 (67%)	194 (63%)
	Poor Virologic Response And Lost To Follow-Up	23 (16%)	4 (9%)	15 (13%)	42 (14%)
Step 2 Baseline HIV-1 RNA levels [copies/mL][a]	<50	118 (84%)	31 (70%)	82 (70%)	231 (76%)
	50-200	9 (6%)	9 (20%)	19 (16%)	37 (12%)
	201-399	3 (2%)	1 (2%)	4 (3%)	8 (3%)
	400-1,000	5 (4%)	0 (0%)	2 (2%)	7 (2%)
	1,001-5,000	3 (2%)	1 (2%)	4 (3%)	8 (3%)
	5,001-10,000	0 (0%)	1 (2%)	1 (<1%)	2 (<1%)
	>10,000	3 (2%)	1 (2%)	5 (4%)	9 (3%)
	Not Done	1	1	1	3
	# missing	0	1	0	1
Step 2 Baseline HIV-1 RNA categories [copies/mL]	≤200	127 (90%)	40 (91%)	101 (86%)	268 (89%)
	>200	14 (10%)	4 (9%)	16 (14%)	34 (11%)
	Not Done	1	1	1	3
	# missing	0	1	0	1
Step 2 Baseline CD4 count/mm³	n	139	44	116	299
	Median (Q1, Q3)	389 (196, 578)	381 (181, 594)	401 (208, 699)	389 (199, 638)
	Min, Max	59, 1336	59, 1255	17, 1919	17, 1919
	# missing	3	2	2	7
Step 2 Baseline CD8 count/mm³	n	139	44	115	298
	Median (Q1, Q3)	809 (590, 1144)	892 (638, 1069)	917 (678, 1263)	861 (616, 1179)
	Min, Max	226, 2684	399, 1928	169, 4690	169, 4690
	# missing	3	2	3	8

Appendix Table S3.3: Step 2 Sociodemographic at Baseline

		Protocol Version			
		1.0 (N=142)	2.0 (N=46)	3.0 (N=118)	Total (N=306)
Education Level	11th grade or less	30 (22%)	7 (16%)	22 (19%)	59 (20%)
	High school graduate or GED	41 (30%)	15 (35%)	39 (33%)	95 (32%)
	Some college/AA degree/Technical school training	55 (40%)	15 (35%)	38 (32%)	108 (36%)
	College graduate (BA or BS)	8 (6%)	5 (12%)	11 (9%)	24 (8%)
	Master's degree	1 (<1%)	1 (2%)	4 (3%)	6 (2%)
	Doctorate/medical degree/law degree	2 (1%)	0 (<1%)	3 (3%)	5 (2%)
	Missing	5	3	1	9
Employment or School	Part-time employment	18 (13%)	6 (14%)	16 (14%)	40 (13%)
	Full-time employment	35 (25%)	15 (34%)	44 (37%)	94 (31%)
	Part-time student	1 (<1%)	0 (<1%)	1 (<1%)	2 (<1%)
	Full-time student	2 (1%)	0 (<1%)	3 (3%)	5 (2%)
	On disability	36 (26%)	5 (11%)	22 (19%)	63 (21%)
	Pension/Retired	5 (4%)	2 (5%)	2 (2%)	9 (3%)
	OTHER	41 (30%)	16 (36%)	30 (25%)	87 (29%)
	Missing	4	2	0	6
Average Yearly Household Income	Less than $5000 per year	37 (27%)	19 (43%)	33 (28%)	89 (30%)
	$5000 - 9999	26 (19%)	2 (5%)	18 (15%)	46 (15%)
	$10000 - 19999	36 (26%)	8 (18%)	19 (16%)	63 (21%)
	$20000 - 29999	17 (12%)	3 (7%)	13 (11%)	33 (11%)
	$30000 - 39999	11 (8%)	6 (14%)	16 (14%)	33 (11%)
	$40000 - 49999	3 (2%)	2 (5%)	7 (6%)	12 (4%)
	$50000 or more per year	9 (6%)	4 (9%)	11 (9%)	24 (8%)
	Missing	3	2	1	6
Having Children	Y	72 (51%)	15 (34%)	50 (42%)	137 (45%)
	N	68 (49%)	29 (66%)	68 (58%)	165 (55%)
	Missing	2	2	0	4
How Many Children Live with You	n	72	15	50	137
	Median (Q1, Q3)	1 (0, 2)	0 (0, 2)	1 (0, 2)	1 (0, 2)
	Min, Max	0, 5	0, 5	0, 4	0, 5
How to Pay Healthcare	Government Funding	113 (84%)	31 (74%)	85 (75%)	229 (79%)
	Government Funding,Private Insurance	6 (4%)	1 (2%)	7 (6%)	14 (5%)

		Protocol Version			
		1.0 (N=142)	2.0 (N=46)	3.0 (N=118)	Total (N=306)
	Government Funding,Private Insurance,Self Pay/Out of Pocket	2 (1%)	0 (<1%)	2 (2%)	4 (1%)
	Government Funding,Self Pay/Out of Pocket	3 (2%)	3 (7%)	5 (4%)	11 (4%)
	Private Insurance	7 (5%)	5 (12%)	8 (7%)	20 (7%)
	Private Insurance,Self Pay/Out of Pocket	1 (<1%)	0 (<1%)	1 (<1%)	2 (<1%)
	Self Pay/Out of Pocket	3 (2%)	2 (5%)	6 (5%)	11 (4%)
	Missing	7	4	4	15
Provide Support to Friend/Family Member	Y	32 (23%)	16 (36%)	33 (28%)	81 (27%)
	N	108 (77%)	28 (64%)	85 (72%)	221 (73%)
	Missing	2	2	0	4
Living Situation	In Own House/Apartment	93 (66%)	24 (55%)	83 (70%)	200 (66%)
	At Parents House	15 (11%)	8 (18%)	13 (11%)	36 (12%)
	Someone Elses House/Apartment	21 (15%)	5 (11%)	15 (13%)	41 (14%)
	Rooming Boarding Or Halfway House	2 (1%)	3 (7%)	1 (<1%)	6 (2%)
	Shelter/Welfare Hotel	6 (4%)	1 (2%)	2 (2%)	9 (3%)
	On The Street(S)	2 (1%)	1 (2%)	1 (<1%)	4 (1%)
	Residential Drug/Alcohol Treatment Facility	0 (<1%)	1 (2%)	1 (<1%)	2 (<1%)
	Other	1 (<1%)	1 (2%)	2 (2%)	4 (1%)
	Missing	2	2	0	4
Treated for Depression or Mental Health	Y	37 (26%)	11 (25%)	29 (25%)	77 (25%)
	N	103 (74%)	33 (75%)	89 (75%)	225 (75%)
	Missing	2	2	0	4
Zip code	Available	139 (98%)	43 (93%)	117 (>99%)	299 (98%)
	Not Available	3 (2%)	3 (7%)	1 (<1%)	7 (2%)

Appendix Table S3.4: Step 2 Sociodemographic at Baseline -- Likely Route of HIV Infection

		Protocol Version			
		1.0 (N=142)	2.0 (N=46)	3.0 (N=118)	Total (N=306)
Sex with a man who was HIV+	Y	89 (67%)	31 (70%)	87 (76%)	207 (71%)
	N	44 (33%)	13 (30%)	28 (24%)	85 (29%)
	Missing	9	2	3	14
Sex with a woman who was HIV+	Y	30 (23%)	5 (11%)	16 (14%)	51 (18%)
	N	98 (77%)	39 (89%)	98 (86%)	235 (82%)
	Missing	14	2	4	20
Shared needles with a person who was HIV+	Y	16 (13%)	6 (14%)	1 (<1%)	23 (8%)
	N	112 (88%)	38 (86%)	111 (>99%)	261 (92%)
	Missing	14	2	6	22
Blood transfusion or other medical procedure	Y	5 (4%)	1 (2%)	1 (<1%)	7 (2%)
	N	121 (96%)	43 (98%)	111 (>99%)	275 (98%)
	Missing	16	2	6	24
Do not know	Y	14 (11%)	9 (21%)	18 (16%)	41 (15%)
	N	109 (89%)	34 (79%)	93 (84%)	236 (85%)
	Missing	19	3	7	29
Perinatally acquired	Y	8	1	6	15
Tattoo	Y	2			2
Raped/bitten	Y	1		2	3

Step1 Baseline Characteristics by Step 2 Enrollment Status

Appendix Table S4.1: Step 1 Baseline Characteristics by Step 2 Enrollment Status

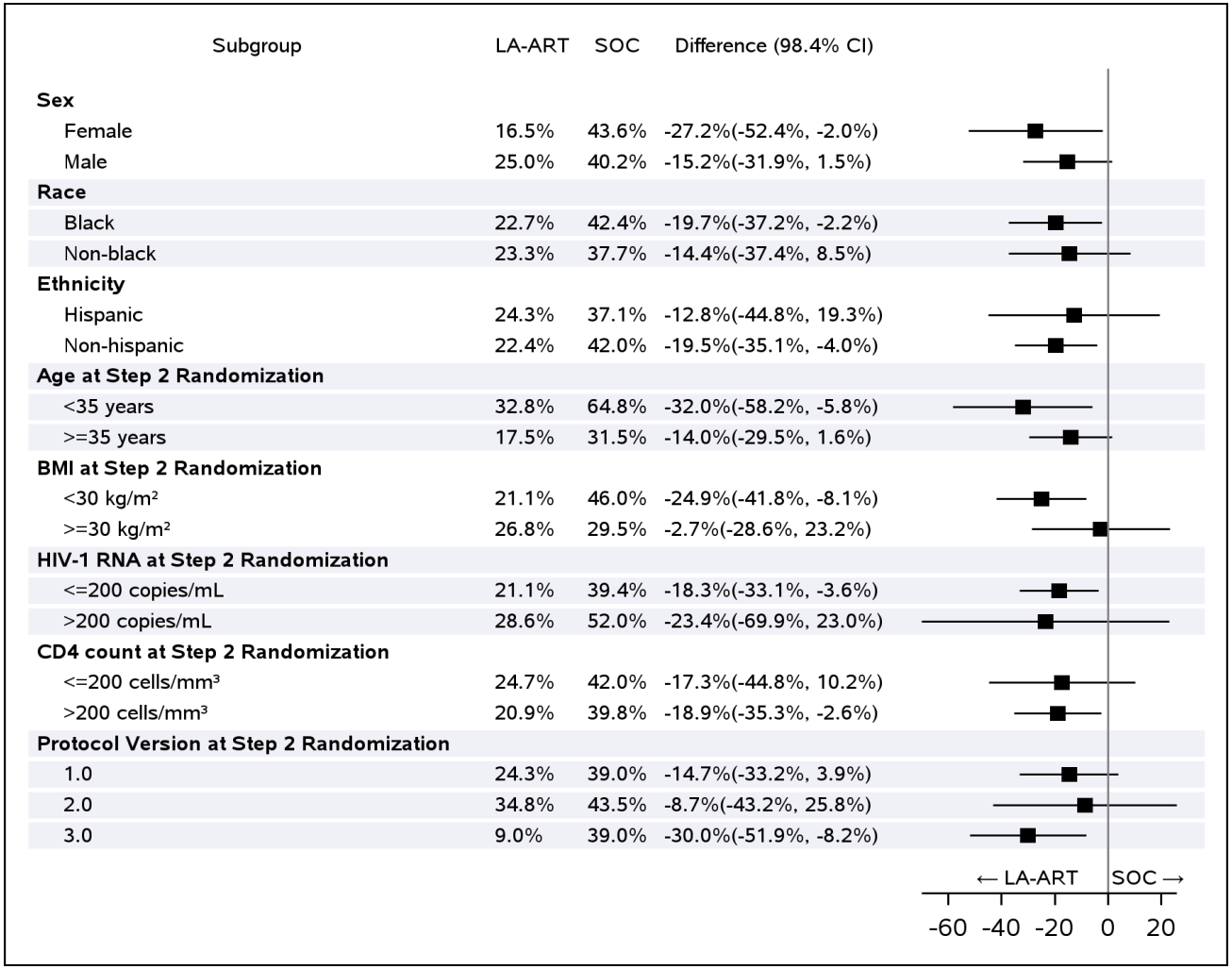
		Enrolled to Step 2	
		Yes (N=306)	**No (N=120)**
Age, years	Median (Q1, Q3)	41 (32, 52)	39 (31, 46)
	Min, Max	20, 75	18, 64
	18-24	17 (6%)	9 (8%)
	25-30	42 (14%)	19 (16%)
	31-40	88 (29%)	38 (32%)
	41-50	69 (23%)	31 (26%)
	51+	90 (29%)	23 (19%)
Sex at Birth	Female	84 (27%)	40 (33%)
	Male	222 (73%)	80 (67%)
Gender Identity	Cisgender	290 (95%)	113 (94%)
	Transgender Spectrum	15 (5%)	6 (5%)
	Information Not Collected	1	1
Race	Black or African American	197 (64%)	73 (61%)
	White	80 (26%)	36 (30%)
	Asian	2 (<1%)	1 (<1%)
	Multiple	6 (2%)	5 (4%)
	Unknown	21 (7%)	5 (4%)
Ethnicity	Hispanic or Latino	55 (18%)	20 (17%)
	Not Hispanic or Latino	246 (80%)	100 (83%)
	Unknown	5 (2%)	0 (0%)
History of IV drug use	Currently	12 (4%)	7 (6%)
	Previously	27 (9%)	15 (13%)
	Never	267 (87%)	98 (82%)

Appendix Table S4.2: Step 1 Baseline Characteristics: History and HIV Disease Progression by Step 2 Enrollment Status

		Enrolled to Step 2	
		Yes (N=306)	**No (N=120)**
Step 1 Baseline BMI kg/m²	n	306	120
	Median (Q1, Q3)	26 (22, 30)	25 (21, 29)
	Min, Max	17, 63	17, 45
Time since HIV diagnosis, years	Median (Q1, Q3)	13 (7, 20)	13 (6, 20)
	Min, Max	1, 36	1, 32
	# missing	49	18
Non-Adherence Information	Lost To Follow-Up	70 (23%)	17 (14%)
	Poor Virologic Response	194 (63%)	82 (68%)
	Poor Virologic Response And Lost To Follow-Up	42 (14%)	21 (18%)
Step 1 Baseline HIV-1 RNA [log_{10} copies/mL][a]	n	306	120
	Median (Q1, Q3)	2.91 (1.63, 4.37)	4.23 (3.01, 5.00)
	Min, Max	1.28, 6.02	1.28, 6.28
	# missing	0	0
Step 1 Baseline HIV-1 RNA categories [copies/mL]	≤200	124 (41%)	30 (20%)
	>200	182 (59%)	117 (80%)
Step 1 Baseline CD4 count/mm³	n	306	120
	Median (Q1, Q3)	300 (152, 572)	206 (60, 420)
	Min, Max	7, 1781	4, 1486
	# missing	0	0
Step 1 Baseline CD8 count/mm³	n	306	120
	Median (Q1, Q3)	872 (614, 1281)	799 (498, 1195)
	Min, Max	153, 4165	149, 2606
	# missing	0	0

Primary Outcome of Regimen Failure by subgroup analysis and supportive analyses

Appendix Figure S5.2: Subgroup Analysis: Cumulative Probability of Regimen Failure in Step 2 up to Step 2 Week 48



The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects for secondary outcomes and subgroup analyses

Appendix Table S5.3: Supportive Analysis: Cumulative Probability of Regimen Failure in Step 2 up to Step 2 Week 48

	Step 2 Treatment Arm						
	LA-ART			SOC			
Analysis	No. of PIDs	No. of failures	Cumulative Probability	No. of PIDs	No. of failures	Cumulative Probability	Difference % [SE] (Nominal 98.4% CI) (LA-ART - SOC)
Supportive 1: Modified ITT Population	151	28	22.3%	152	53	40.5%	-18.1%[5.8%](-32.2%, -4.1%)
Supportive 2: censoring at first positive pregnant test	152	27	21.5%	154	55	41.2%	-19.7%[5.8%](-33.7%, -5.8%)
Supportive 3: excluding participants with Step 2 eligibility violation	152	29	22.8%	152	54	41.2%	-18.3%[5.9%](-32.4%, -4.2%)
Supportive 4: censoring at start of COVID disruption at sites	152	28	23.0%	154	55	41.7%	-18.7%[6.0%](-33.0%, -4.3%)
Supportive 5: excluding all participants at COVID disrupted sites	146	28	23.3%	150	53	41.1%	-17.8%[6.0%](-32.2%, -3.4%)

The modified intention-to-treat population excluded participants who did not initiate randomized treatment

The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects for secondary outcomes and subgroup analyses

Appendix Table S5.4:Virologic Non-Success Defined by FDA Snapshot Algorithm at Step 2 Week 48 Restricted to Participants Randomized 50 Weeks Prior to Follow-up Cutoff Date

	LA-ART (N=94)	95% CI	SOC (N=96)	95% CI	% Difference [95% CI]*
HIV-1 RNA < 50 copies/ml	62 (66.0%)		49 (51.0%)		
HIV-1 RNA >= 50 copies/ml	14 (14.9%)	[7.7%,22.1%]	33 (34.4%)	[24.9%,43.9%]	-21.8%[-35.6%,-8.1%]
No Virologic Data at Week 48 Window					
Treatment Discontinuation due to AE or Death	6 (6.4%)		0 (0.0%)		
Treatment Discontinuation due to other reasons with HIV-1 RNA < 50 copies/ml	10 (10.6%)		13 (13.5%)		
On treatment but missing data	2 (2.1%)		1 (1.0%)		
HIV-1 RNA < 200 copies/ml	69 (73.4%)		55 (57.3%)		
HIV-1 RNA >= 200 copies/ml	5 (5.3%)	[0.8%,9.9%]	25 (26.0%)	[17.3%,34.8%]	-24.5%[-36.1%,-12.8%]
No Virologic Data at Week 48 Window					
Treatment Discontinuation due to AE or Death	6 (6.4%)		0 (0.0%)		
Treatment Discontinuation due to other reasons with HIV-1 RNA < 200 copies/ml	12 (12.8%)		15 (15.6%)		
On treatment but missing data	2 (2.1%)		1 (1.0%)		

The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects for secondary outcomes and subgroup analyses

Appendix Table S5.5 Adults with HIV Out-of-Care and In-Care, in the United Sates by Age, Sex, and Race/Ethnicity, adapted from Dawson L., Kates J *What Do We Know About People with HIV Who Are Not Engaged In Regular HIV Care? KFF/CDC Analysis of the Medical Monitoring Report 2018 &2019,* KFF June 2023

	Out of Care[a]	In Care
Age		
18-29	12%	8%
30-39	20%	16%
40-49	24%	21%
50-64	38%	45%
65+	7%	10%
Sex at Birth		
Male	72%	75%

Female	26%	23%
Race/Ethnicity		
White	26%	30%
Black	50%	39%
Hispanic	16%	24%

a having fewer than two CD4 or viral load tests at least 3 months apart within a 12-month period

KFF Methodology: Data on people with HIV are based on 2018 and 2019 data cycles (which cover data through part of 2020) from the Medical Monitoring Project (MMP), a Centers for Disease Control and Prevention (CDC) surveillance system which produces national and state-level representative estimates of behavioral and clinical characteristics of adults with diagnosed HIV in the United States.

MMP employs a two-stage, complex sampling design. First, jurisdictions are selected from all U.S. states, the District of Columbia, and Puerto Rico using a probability proportional to size sampling strategy based on AIDS prevalence at the end of 2002, such that areas with higher prevalence had a higher probability of selection. Next, adults (aged 18 years and older) with diagnosed HIV were sampled from selected jurisdictions from the National HIV Surveillance System (NHSS), a census of U.S. persons with diagnosed HIV. During the 2018 and 2019 MMP data cycles, data came from: California (including the separately funded jurisdictions of Los Angeles County and San Francisco), Delaware, Florida, Georgia, Illinois (including the separately funded jurisdiction of Chicago), Indiana, Michigan, Mississippi, New Jersey, New York (including the separately funded jurisdiction of New York City), North Carolina, Oregon, Pennsylvania (including the separately funded jurisdiction of Philadelphia), Puerto Rico, Texas (including the separately funded jurisdiction of Houston), Virginia, and Washington.

Data used in this analysis were collected via telephone or face-to-face interviews and medical record abstractions during the following periods:

- 2018 data was collected between June 1, 2018–May 31, 2019
- 2019 data was collected between June 1, 2019–May 31, 2020

The response rate was 100% at the first stage, and was 45% for each of the 2 cycles included in this analysis. Data were weighted based on known probabilities of selection at state or territory and patient levels. In addition, data were weighted to adjust for non-response using predictors of person-level response, and post-stratified to NHSS population totals by age, race/ethnicity, and sex at

birth. This analysis includes information on 7,642 adults with HIV. Of the 7,642 adults sampled, 1,604 (21%) were identified as being out-of-care (having fewer than two CD4 or viral load tests at least 3 months apart within a 12-month period) and 1,215 (16%) were identified as being out-of-care (having fewer than two CD4 or viral load tests at least 3 months apart within a 12-month period) *and* also being virally unsuppressed (having a viral load of equal to or more than 200 copies of HIV per milliliter of blood).

Section 3 Protocol Adherence Support Measures

Recruitment and Entry

I. Study population will likely not self-refer; will need to consider active modalities to recruit and screen
   A. Work with your local clinic and any clinician who can serve as a study champion to spread the word about the study and help identify referrals of potential participants
   B. "Ready to screen": potential participants may need to be recruited from outside the clinical trials space (e.g., ER, hospitalized individuals)
   C. Consider community partners who engage with potential participants
   D. Advertisement, social media awareness
   E. Consultation with the site CAB on recruitment is recommended.

Adherence and Retention

I. Overview. Supporting adherence is critical to the success of this (and any) protocol. This includes adherence to oral medications in Step 1 and the oral medication for those randomized to SOC arm in Step 2, as well as appointment attendance to support adherence in the LA regimen arm. The A5359 Manual of Procedures (MOPS) provides a planning approach and evidence-based options/tools that sites can use to develop individualized support plans for participants.

   A. The Challenges
      1. About one-third of US participants in care lack consistent viral suppression (see Crepaz 2016).
      2. About 40% of US HIV participants are poorly retained in primary care (see Marks 2010).
      3. Changing behavior is hard when people lack the motivation, skills, and resources to make meaningful change in their lives.
      4. Maintaining contact with people who are highly marginalized can be difficult due to frequent changes in their address, cell service, etc.

   B. The Opportunity
      1. People receive substantial clinical benefit when we help them engage in care and take ART medicines.
      2. Many evidence-based strategies to help people with adherence and retention are available; evidence exists that active approaches can facilitate re-linkage to care.
      3. Knowledge that "treatment is prevention" provides added motivation to achieve viral suppression for many people living with HIV.
      4. Text messaging and social media provide new avenues to stay in contact with people, even when they are not otherwise easily reached.

5. This study will help capacitate future research and further improvement in trial performance measures at the CTU.
6. Your protocol involvement will advance your expertise in state-of-the-art approaches to adherence and retention support.
7. We have a chance to make a difference for people who are in need and to meaningfully advance the use and impact of LA HIV treatment regimens.

C. The Approach
1. Warmth and rapport are the core of our Adherence & Retention support strategy.
2. The goal is to provide participants with a multicomponent backbone of adherence and retention support throughout their trial participation.
3. Adherence support will be tailored to individual participant needs.
4. Each participant will develop an adherence action plan to follow throughout the study; this plan provides the backbone of support and it will be revisited and updated at each counseling touch-point.
5. In addition to this consistent and ongoing backbone of support, the trial will also offer a special, limited-time opportunity to "kick-start" progress toward viral suppression through conditional economic incentives (CEI).
6. When the special, limited-time CEI end, we will continue to provide a backbone of multicomponent adherence and retention support.

D. The Plan
1. Sites are strongly encouraged to go through a systematic planning process for A5359 adherence and retention support before the launch of protocol implementation.
   i. Sites will create a voluntary adherence support team (the A5359 STARS: Support Team for Adherence and Retention Strategies).
   ii. Sites will then create site-specific adherence and retention procedures by considering the Menu of Adherence and Retention Support Strategies (MARSS) and associated guidance in the MOPS, as well as the resources and know-how of the local STARS.
   iii. An implementation plan for the site adherence and retention procedures (SARP) that outlines the participant flow, individual staff roles, and the integration of multicomponent support will need to be developed, too.
2. Upon protocol implementation, the study coordinator will anchor all efforts, working in partnership and coordination with the A5359 STARS.
   i. We encourage the STARS to meet at regular intervals (if not weekly) throughout the trial.
   ii. The STARS should also review the SARP the appointment conduct checklist (see section VII: Coordinating/choreographing integrated multicomponent support from the site adherence and retention plan) on a quarterly basis to address any emergent needs and make associated adjustments/improvements.

II. Preparatory Activities: Reaching for the STARS and Considering the MARSS

A. Create the STARS. Sites will benefit from specifically identifying local staff and volunteers who will become the A5359

STARS.

1. The STARS will provide substantive, logistic, and/or strategic support for adherence and retention through multiple roles and routes. The STARS may include the following people. Some of these roles may be filled by the same person:
    i. Nurse Coordinator or Study Coordinator. This individual will be the lead person for the protocol and will oversee all aspects
    ii. Adherence Counselor(s). This individual (or individuals) will be charged with delivering adherence counseling to the participants, including the development and monitoring of a tailored adherence action plan with each participant. We strongly recommend that each participant meet with the same adherence counselor over the course of the trial, to foster better connection and rapport.
    iii. CEI Manager. This person will help manage and administer the CEI that are designed to motivate participants to achieve viral suppression in the initial phase of the A5359 protocol. This individual will learn how to use the local site system for disbursing the CEI (e.g., Greenphire ClinCard system, another web-based system, or other procedures). This person will need rapid access to the viral load assays results in order to administer the incentives. We recommend that the CEI Manager and the Adherence Counselor are NOT the same person, particularly if the site uses in-person disbursement of incentives. This will keep the Adherence Counselor role focused on assisting the participant.
    iv. Outreach Worker or Peer Navigators. These individuals may be engaged through the protocol and/or the local site or clinic; they would provide community-based outreach services and additional support for study recruitment and retention. They may visit the local clinic or other community-based venues to assist with study recruitment and retention efforts. Their work might also include management of appointment reminders through letters, phone, or text messages.
    v. CAB member(s). We have heard that some Community Advisory Board members may be interested to play a more active role in a study like A5359. This is their chance to get involved. One or more CAB members could become STARS and could contribute to the trial in a variety of ways. For example, they might attend STARS meetings to offer input and provide troubleshooting; or they could provide direct assistance with study recruitment, outreach, and retention efforts; or they could take-on a specific role or responsibility in the project (e.g., Adherence Counselor; Lead Social Worker Contact, etc.). The CAB will likely be an asset to the study, more generally.
    vi. Lead social worker or case manager contact. This individual would be the chief point of contact for connection to case management and social worker services. They may provide services as needed to study participants or could connect them to other social workers and case managers. If a Lead Social Worker or Case Manager is not available through the local site or clinic, could an appropriate one be identified in partnership with the CAB?
    vii. Clinic champion. This individual would be a clinician in the local clinic who is willing to champion the study. As a study champion, they would volunteer to advocate for the study within the clinic and among their colleagues, and to facilitate occasional logistic support as needed.
    viii. CTU leader. This person heads the local CTU and is critical to facilitating the study hours, resources, and operations.
    ix. Protocol team. The protocol team is a part of your wider support network. This includes the provision of the guidance

in the MOPS, as well as other training and guidance over the course of the study.

x. Other Members. Your local expertise and knowledge is a strength to build on. Sites are invited to consider others who would be interested to volunteer and who could meaningfully contribute to the A5359 STARS. Someone from the clinic front desk? A local adherence specialist? An addictions counselor? A member of the laboratory that receives study samples? A member of a partnering CBO? There are many possibilities.

2. Identifying and documenting the individual or individuals who will fill each role on the Support Team for Adherence and Retention Strategies (STARS) prior to the study launch will help ensure successful support.
   i. The MOPS appendix includes an example of a local STARS member roster, which can be modified for local use.
   ii. Some team members may wear multiple "hats" (e.g., perform more than one role); and some roles may be performed by multiple team members
   iii. It will be important to gain each person's voluntary agreement to contribute to the adherence support team, by discussing the study with each member and the expectations for their role(s) and participation
   iv. Strongly consider getting each person's commitment in writing (e.g., complete a written agreement about their role on the study).
   v. Also consider offering a small token of appreciation such as an "A5359 Support Team for Adherence and Retention Strategies (STARS) certificate" (see MOPS Appendix for example) that thanks the individual for their involvement and specifies their voluntary contributions to the study. The certificate can be signed by themselves and the study coordinator. See an example in the MOPS Appendix.

3. Regular meetings of the STARS will help improve study conduct and participation metrics.
   i. Meetings of the adherence support team offer a chance to review upcoming appointments and participant flow, and to troubleshoot difficult cases and update one another on study developments.
   ii. The optimal meeting frequency and format can be set by the site. Is it weekly or something else? In person or teleconference?
   iii. Sites might consider holding this meeting as a subcomponent of any larger study-oriented meeting.
   iv. If more feasible, a core group of the STARS might meet routinely, with only occasional or as-needed participation from some wider team members.

B. Choose from the Menu of Adherence and Retention Support Strategies (MARSS). The MOPS outlines many adherence and retention support strategies. Sites should use this list and the attendant guidance—in combination with their local STARS resources and know-how—to identify the specific strategies that the site will deploy in A5359.

1. Specifying the site-specific support strategies
   a. At the start of the study, each site should identify the strategies that it will offer to any A5359 participants.
      i. Some strategies will be used with all participants, others will only be used with select participants, as needed.

ii. Sites are not expected to offer every strategy identified within the A5359 MOPS. The MOPS only provides an outline of the range of possible strategies. The strategies selected by each site will depend upon local resources, expertise, and decision-making.

2. Per the A5359 protocol, sites will need to update the list of "Site Adherence and Retention Procedures" (SARP) Instrument at six-month intervals following enrollment start.
   a. We strongly recommend that each site should revisit their site-specific Adherence and Retention Procedures and the A5359 MARSS on a more frequent (possibly quarterly) basis.
   b. These discussions should be held with the STARS and they would reflect on the successes and challenges that the trial is encountering; consultations with the site CAB could be helpful, too.
   c. The goal is to identify whether there is any need to:
      i. Further strengthen/coordinate current strategies;
      ii. Enhance the site procedures with new support strategies;
      iii. Or discontinue unproductive strategies.
   d. Resulting products would include
      i. An updated site-specific Adherence and Retention Plan
      ii. Addition of any new STARS
      iii. Any new/updated STARS certificates/agreements

3. Menu of Adherence and Retention Support Strategies (MARSS)
   Below is an overall list of the available support strategies.

A5359 Menu of Adherence and Retention Support Strategies (MARSS)	
Communications and keeping in touch	Retention support
1. Regularly updated locator form 2. Routine study appointment reminders a. Palm cards b. Calendars c. Mailed letters d. Text messages and calls e. E-mails 3. Digital connections a. Facebook	1. Expanded daytime, evening, and/or weekend hours 2. Transportation assistance 3. Appointment stipends/reimbursements and travel vouchers 4. Grab bags: Snacks/candy and toiletries 5. Notes of appreciation a. "Thank you" cards b. Birthday cards

b. Google Voice
c. Weekly interactive text messages
4. Other approaches (sites should specify)

Adherence support

1. One-on-one adherence counseling
2. Offering pill organizers
3. Electronic adherence reminder texts
4. CEI (in Protocol Step 1)
5. Other approaches (sites should specify)

6. Outreach worker/teams
7. Other approaches (sites should specify)

Meeting deeper needs

1. "Warm" connection to case management
2. Facilitated connection to alcohol and drug treatment or behavioral health specialists
3. Providing a referral resource list
4. Other approaches (sites should specify)

NOTE: Detailed guides for each strategy follow below.

III. Communications and Keeping in Touch. Establishing multiple avenues of communication is essential in engaging a challenging population.

A. <u>Regularly updated locator form</u>
   1. We will collect detailed contact and locator information from each participant at study entry.
   2. *Refer to section 4 of the MOPS for the sample locator form. The form can be modified/customized to meet any local site needs/interests.*
   3. The locator form will provide basic contact information for routine contact, as well as further information that could be useful for finding a participant who has been lost or out of touch (through community outreach, database searches, or other means).
      a. The locator form will ask participants for permission to contact them in a variety of ways—by phone, text, mail, Facebook, etc.
      b. The form also asks if study staff can make a photocopy of personal identification (e.g., driver's license).
      c. The form will also include a request for any friends or family who could help locate the participant if they were out of touch, as well as places that the participant likes to hang out.
      d. We will emphasize to the participant that any outreach to these contacts or places will only be utilized for contact with participant and no one will be notified of the participant's HIV/medical status or the study purpose.
   4. The locator form should be updated at each visit (e.g., when meeting, read out their address and phone number and ask, "Is this your correct address and phone number? Any other updates?").

B. <u>Routine study appointment reminders. Appointment reminders can be offered through multiple modalities over different time</u>

junctures for optimal impact.

1. Palm cards
    a. We recommend each participant leave every appointment with a written palm card that features the date and time of their next appointment.
    b. If a reimbursement for time or travel is associated with the next appointment, this amount should also be indicated on the card.
    c. Palm cards should further provide a phone number, pager number, or email for reaching the study with any issues.
    d. Based on your local requirements, these Palm cards may need to be IRB approved.

2. Calendars
    a. We can also ask the participant at the end of each appointment if they use any kind of written datebook or electronic calendar to keep track of appointments.
    b. If they do: “That’s great. Let me give you a moment to enter this next appointment (show reminder card) into your calendar.”

3. Mailed letters
    a. A mailed postal letter that provides an appointment reminder approximately 5-7 days before a study appointment can be helpful.
    b. Permission to send a letter is indicated in the locator form (see Section 1 of the MOPS). When sending such a letter, it is important to protect privacy and confidentiality.
        i. The return address on the envelope and the letter should not mention the study purpose, hospital, or the words “HIV/AIDS”.
        ii. Alternative approaches include listing the participant’s main point of contact with the study (e.g., adherence counselor or outreach worker) as the return address name, and having the letter indicate that the participant’s next appointment “with us” is at a certain date/time, and that we look forward to seeing you.
        iii. Provide a number where the participant could call if they need to reschedule.
    c. Letters returned by the post office as “addressee unknown” are helpful for identifying a change of address that could be looked into by the outreach worker or staff

4. Text messages and calls
    a. Text messages can be a particularly effective way to reach people
        i. They are more likely to be seen and responded to than phone calls or voicemail messages
        ii. Text messages can have a more intimate feel than other modes of communication (e.g., email).
    b. If the participant has provided permission to be contacted by phone or text message, these reminders can be helpful 2-3 days before an appointment, and even the day of the appointment.
    c. This contact provides the opportunity for the team to confirm any needs with participant, e.g. transportation assistance.

Does the site maintain a site cellphone, staff cellphones, or computer software/accounts (e.g., Google Voice) that it can use for sending and receiving text messages?

5. Email
   a. If the participant has provided permission to be contacted by phone or text message, these reminders can be helpful 2-3 days before an appointment, and even the day of the appointment.
   b. This contact provides the opportunity for the team to confirm any needs with participant (e.g., transportation assistance).
   c. Even when homeless or lacking a cellphone, clinical trial participants have been found to maintain email access through public libraries or other means (Mitchell, SG, et al. The use of technology in participant tracking and study retention: lessons learned from a clinical trials network study. Subst Abuse 2015;36:420-6.)

C. Digital connections. Modern technologies offer remarkable new tools for keeping in touch with study participants. We highlight three approaches here.

1. Facebook
   a. Facebook use is widespread in the US, according to Pew 2016:
      i. 68% of all Americans use Facebook
      ii. 79% of online adults use Facebook
      iii. 84% of lower-income individuals use Facebook
      iv. 88% of younger individuals (ages 18-29) use Facebook
   b. The widespread use of Facebook offers an important route for reaching study participants.
   c. The suggested “Locator Form” in the MOPS includes a request for Facebook information and permission to contact the participant through Facebook.
   d. Site STARS can think carefully about whether and how they would like to use Facebook, and what approach feels most feasible and appropriate. This might include:
      i. A unique work-related Facebook account for the individual Outreach Coordinator
      ii. A public Facebook page associated with the site
   e. When a participant cannot be readily located or reached, one possible option is to look for them on Facebook Messenger, and to send a carefully worded note (for any privacy concerns): “Hey. I am reaching out about your schedule. Can we set an appt?” Although non-friend messages are not typically sent to a person’s regular “Inbox” on Facebook, for a small fee, private messages can be sent from the study team’s account to the participant’s inbox. This will notify the account holder that a new message has been received, and permit the study team to see when the message had been viewed (Mitchell SG, et al. The use of technology in participant tracking and study retention: lessons learned from a clinical trials network study. Subst Abuse 2015;36:420-6).

f. For privacy protection, Facebook pages and communications should never directly mention the study purpose or the words HIV/AIDS.
g. Based on your local requirements, this approach may need to be IRB approved.

2. Google Voice
   a. Google Voice is a free service that offers a single number for reaching multiple forms of communication (cellphone, landline, email)
   b. A brief overview of Google Voice is here: https://www.youtube.com/embed/cOZU7BOeQ58?autoplay=1
   c. Why would this be of value to the participant and the study?
      i. Setting up a Google Voice number for the study or the site could benefit the study because:
         a) The study can use it to manage a large set of participant contacts through multiple channels (text, phone, email).
         b) It provides a centralized communications resource that is accessible by multiple team members.
      ii. Setting up a Google Voice number for an individual participant can benefit the participant because:
         a) It becomes a permanent number that anyone can reach them through, even if their cellphone service is disconnected or interrupted.
         b) If their cell number changes they can just update the new cell number in Google Voice and people will be able to reach them, even without knowing the new cell number.
         c) They can customize how calls are handled (e.g., where/when they ring, and whether they go to voicemail).
      iii. Setting up a Google Voice number for the participant benefits the study because:
         a) It can facilitate a connection to participants even when they have changed cell numbers.
         b) If their numbers are not current, they can still get an email with a voicemail readout.
         c) Setting this up for the participant offers them a "free service" and some added value for their study participation.
   d. The STARS could consider whether this tool would be useful for the study, and what would be the best approach/timing for talking with participants about whether they would like to set-up a Google Voice account, and assisting them accordingly.

3. Weekly text messages
   a. Weekly text messages are another way to keep in touch with participants. They provide a "heartbeat" to study participation between protocol appointments, and a chance to troubleshoot any problems. They can be accomplished in a manner that protects confidentiality, and can be sent manually or in an automated system.
   b. Indicate in the Locator form whether the participant wants to receive these optional text messages.
   c. The simplest approach is a personal one-way message to the participant from the study coordinator or another primary point of contact, such as the adherence counselor or the outreach coordinator. Examples:
      i. "Ron here. Just checking in. Hope all's well and let me know if you need anything."

ii. “Janice here. How are you? Have a nice day.”

d. We mention this approach because one study of ART initiators in Kenya found improved viral suppression at 12 months if participants received a once-weekly text message that asked, “How are you?” (Lester, 2010). Participants were instructed to respond to the message by stating “Fine” or “Problem,” and those who stated “Problem” or who did not reply after three days got a call from a nurse to address any problems they may have. A similar approach was recently demonstrated to improve PrEP medication adherence (Liu, IAPAC 2017).
e. Text messages can be sent manually, but there are computer programs/apps that can automate this process.
f. Any pursuit of this strategy would need to recognize that the long period of follow-up in the A5359 trial will require an extended and extensive commitment.
g. Give the participants’ flexibility to opt in or out of this messages at any time.

4. Other approaches for keeping in touch. There may be other strategies for keeping in touch that the site currently uses or would like to consider. We defer to the site know-how and the creativity and expertise of the local STARS, as well as the CAB.

IV. Retention Support

A. <u>Expanded daytime hours and/or evening and weekend hours</u>

1. Our experience working with this population tells us that greater flexibility in appointment scheduling can be very helpful for furthering study enrollment and retention.
   a. When available appointment times are limited to specific intervals on weekdays, this creates barriers to participation for individuals who work weekdays, and especially for those who work hourly and lack leave, as well as individuals who have daytime caregiving duties.
   b. We recognize that there are many constraints on the site hours of operation—including staff availability, safety considerations, building policies—and particularly pharmacy and laboratory coordination, since the drug will need to be prepared for participant in the LA arm.
   c. Some sites have nonetheless indicated capacity for flexible weekday schedules and some availability weeknight evenings or weekend mornings.
2. We encourage each site to explore as much flexibility as feasible when setting available appointment hours for study participation.
   a. What plans and coordination could be undertaken with the local laboratory and pharmacy to expand the range of weekday daytime hours that are available for appointments? Are there opportunities for early morning appointments (before 9:00 am) or later afternoon appointments (after 3:00 pm)?
   b. Is there any opportunity to offer a limited evening session—on an ad hoc/ as needed basis—or one night a week?
   c. Is there any chance of limited weekend hours, perhaps via a Saturday morning session?

B. Transportation assistance
   1. This strategy directly offers transportation to participants to facilitate their appointment attendance.
   2. Sites may consider offering this option to participants as an alternative to a transportation reimbursement.
   3. Sites that are capacitated to manage an Uber or Lyft account can dispatch a car to pick up a participant.
      a. Here is how this can be done with Uber: https://www.uber.com/us/en/ride/how-it-works/request-for-a-guest/
      b. Here is how this can be done with Lyft: https://help.lyft.com/hc/en-us/articles/115013080388-Policies-for-passenger-use-of-Lyft
      c. A text message reminder sent 2-3 days before the appointment, or the day of the appointment, offers a good opportunity to ask, “Can we send a car to pick you up?”.
      d. Some nice aspects of this approach are that the site gets to track the progress and arrival time of the participant, and it can help to make the participant feel special.
      e. Keep in mind that the participant may require a trip home as well.
      f. Certain participants might require a Paratransit option if they have a disability that prevents them from using routine car, bus, or rail options.

C. Appointment stipends/reimbursements and travel vouchers
   1. The provision of a stipend for each study visit is a common practice across many sites, and it can be very helpful for promoting appointment attendance.
   2. Sites are encouraged to provide study visit stipends to participants (to compensate for their appointment visit/time, blood draws, etc.).
   3. These stipends are distinct/separate from the viral suppression conditional economic incentives offered in Step 1 of A5359. They would be offered to all participants regardless of trial arm assignment or viral suppression status.
   4. Sites would have to make choices about the appropriate stipend amount for each appointment. Some scale the amount according to the appointment length or burden. We have also seen approaches where the appointment attendance stipend escalates over the course of the study, to help ensure continued attendance.
   5. Sites can also consider offering participants mileage reimbursement, parking reimbursement, or public transit coupons.

D. Grab bag: Snacks/candy and toiletries
   1. This simple approach can be very meaningful and impactful with people who don’t have a lot.
   2. Put together two covered plastic containers which contain (1) some snack packets, candy, and gum, and (2) some basic toiletries and supplies (toothpaste, toothbrush, mouthwash, deodorant, tampons, etc.).
   3. Offer participants a chance to select a few items from these “grab bags” at the end of their appointment.
   4. The snack box can also be used to provide snacks to participants during their study appointments.
   5. This method may need to be IRB approved based on your local requirements.

E. Notes of appreciation. A simple note of appreciation can work wonders. We see two main routes for doing this on the study.

1. “Thank you” cards. These could be helpfully deployed at a few key junctures:
    a. upon enrollment
    b. following completion of Step 1 and before transition to the randomized Step 2
    c. after any unusually lengthy appointment
2. Thank you notes are very easy to effect
    a. Acquire some inexpensive thank you stationery
    b. In under a minute, one can write a quick note of appreciation while the participant is completing other study procedures (“Thank you for your time and help! Your contributions are much appreciated, and you are making a difference. It is always great to see you and I look forward to our next meeting.”).
    c. Hand them the note on the way out the door, or ask if you can mail a note of appreciation home (just drop it in the mail afterwards).
3. These notes may need to be IRB approved based on your local requirements.
4. Birthday cards
    a. Our involvement with each participant will span more than 2 years.
    b. Participant birthday dates should be available from the locator form.
    c. If these birthdays are entered on a calendar, a member of the STARS can send a birthday card a week in advance or placed in the chart to be given in person at their next study visit.
    d. A batch of birthday cards is inexpensive and can be purchased at the same time that “thank you” cards are acquired.
    e. The birthday card is a chance to say, “Happy birthday! Thanks for your involvement with our project. Very glad to know you. Have a great day!”

F. <u>Outreach worker or team</u>
1. Having dedicated time from an outreach worker or team can be one of the strongest assets for promoting study retention.
    a. The A5359 protocol may provide provisional support for a part time outreach worker to assist in recruitment and retention efforts.
    b. Certain sites may alternatively or additionally have local site- or clinic-based outreach teams available to them that could be leveraged.
2. The local STARS should identify the optimal responsibilities and roles for any outreach coordinator. These might include one or more of the following:
    a. Managing appointment reminders
    b. Conducting digital outreach efforts
    c. Assisting warm connection to case management services
    d. Clinic-based surveillance to intercept potential or enrolled trial participants who have scheduled clinical appointments
    e. Peer navigation or accompaniment for participants who are re-engaging after missing one or more appointments or who are otherwise at-risk for not returning
    f. Locating out-of-touch enrolled participants in community locations

g. With appropriate permissions, seeking out-of-touch or lost-to-follow-up participants by searching the Internet, paid databases, obituaries, judiciary websites, or credit reports.

G. Other retention support approaches. There may be other strategies to promote retention that the site currently uses or would like to try. We defer to the site know-how and the creativity and expertise of the local STARS. A few possibilities are below but these are not intended to be exhaustive or limiting.
   1. A special prize drawing for any participant who completes an on-time appointment without rescheduling (select one item from a unique grab bag with headphones, gift certificates/cards, umbrellas, etc.)
   2. Branded study "swag" (pens, etc.) with a number for the site
   3. Couple-based or partner-inclusive appointments
   4. Provision of childcare
   5. Other creative ideas from the STARS and the CAB
   6. Again, any or all of these methods may need to be IRB approved based on your local requirements.

V. Adherence Support. Promoting oral medication adherence is crucial to achieving viral suppression by the end of protocol Step 1. In Step 2, we will also support adherence to oral medications for those randomized to the SOC arm, and adherence to trial/clinic appointments for those in the injection arm. The primary adherence support options are outlined below.

A. Adherence Counseling
   1. We strongly recommend that participants receive one-on-one ART education upon study entry and adherence counseling at each study visit.
   2. ART education and adherence counseling are recommended as evidence-based approaches in the IAPAC Adherence and Retention Guidelines (Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. Ann Intern Med 2012;156:817-33.).
   3. Overall frame for counseling approach:
      a. "This is an opportunity to reset the clock and get a fresh start."
      b. "We'll talk about what gets in the way and what might help."
      c. "We are here to support you, to achieve your goals, and give you the best shot at the study incentives."
   4. Counseling curriculum
      a. A number of evidence-based medication adherence counseling approaches are available, including interventions grounded in motivational interviewing, problem solving approaches, and others.
         i. Does your local site or STARS personnel have prior expertise in a particular adherence counseling approach? This might be a good avenue to consider and build upon.
         ii. We provide an examples of one adherence counseling curriculum in the MOPS Appendix.
            a) This is a "motivational interviewing"-based adherence counseling intervention (MICARE approach and cheat

sheet).

b) In the MOPS Appendix, you will find these resources:
- A flowchart of the counseling session
- A one-page "cheat-sheet" for the session
- A longer session protocol
- Several worksheets and handouts that may accompany a counseling session.

b. Other helpful handouts and tools
   i. See the "Additional Online Resources and Links" section at the end of the MOPS for additional adherence counseling curricula, tools, and handouts.
   ii. Within the context of adherence counseling, we can also support the use of adherence tools such as pill organizers and electronic reminders (see below).

B. Pill organizers
1. These are generally inexpensive to obtain and can be very helpful for those interested in using them.
2. Offering a variety of pill organizer shapes, formats, and colors will facilitate selection, choice, and use.
3. Use is voluntary and the offer can follow the initial counseling session or subsequent ones.
4. This method may need to be IRB approved based on your local requirements.

C. Electronic Reminders
1. Consider setting up daily medication and weekly appointment reminders in participants' personal mobile devices.
2. Use is voluntary.
3. Options for doing this include:
   a. Programming an alarm into participant's cellphone or watch as a medication reminder
   b. Downloading a smartphone "app" such as the CDC "Every Dose Every Day" app, which provides reminders for medication doses, refills, and medical appointments. See links to this app in APPENDIX B: Additional Online Resources and Links at the end of the MOPS.
4. Ask if they would like set up these things onsite, or have help with the process.

D. Conditional economic incentives (per Step 1 of the protocol) Conditional economic incentives (CEI) will be provided to participants for achieving benchmarks in step 1 as outlined in the protocol.

1. We recommend that a specific individual be charged with implementing the CEI program (the CEI Manager). At sites where CEI are provided in-person to participant, it may be preferable if this was someone other than the Adherence Counselor.
2. In step 1 of A5359, all participants will receive additional CEI beyond usual study visit remuneration for achieving certain benchmarks:

Step 1, Week	Milestone	Incentive
2	Completed visit (in person or virtual)	$75.00
4	HIV-1 RNA >1 $\log_{10}$ drop or HIV-1 RNA ≤200 copies/mL or completed virtual visit	$75.00*****
8 **(if needed)**	HIV-1 RNA >2 $\log_{10}$ drop or HIV-1 RNA ≤200 copies/mL or completed virtual visit	$75.00*****
12 **(if needed)**	HIV-1 RNA ≤200 copies/mL or completed virtual visit	$150.00*
16 (if needed)	HIV-1 RNA ≤200 copies/mL or completed virtual visit	$150.00*
20 (if needed), or Confirmation viral load after week 20 (but prior to week 24)	HIV-1 RNA ≤200 copies/mL	$150.00
Additional Continuity Visits during the COVID-19 pandemic (only applicable if in-person visits are not permitted by the site's institution)	HIV-1 RNA ≤200 copies/mL or completed virtual visit	$150.00

* NOTE: Virally suppressed participants (≤200 copies/mL) who receive CEI at week **4, 8,** 12 or week 16 will be eligible for randomization into Step 2 and should not continue further visits in Step 1, and will additionally receive the CEI that would have been distributed at the later Step 1 visits.

3. For visits at Step 1, Weeks 4-20, the CEI is based on results of viral load testing which will be completed locally, with results expected within 2-4 days from the blood draw.
4. Research on use of CEI suggests that this strategy works better if: 1) it is based on objective measures and 2) is delivered as soon as possible after the target behavior was achieved (Haug NA, Sorensen JL. Contingency management interventions for HIV-related behaviors. Curr HIV/AIDS Rep 2006;3:154-9; Galarraga O, et al. Conditional economic incentives to improve HIV treatment adherence: literature review and theoretical considerations. AIDS Behavior 2013;17:2283-92).
5. We encourage use of a Greenphire ClinCard (or another web-based system) to electronically disburse the CEI.
   a. Use of web-based automated payments allows us to deliver the CEI to participants who achieve the benchmark as immediately as we have the results available.
   b. Your site may already have expertise in the Greenphire system or related systems (WebPay, Scrip, Vpay, reloadable

Bank of America Visa card, etc.).
   c. If your site does not have prior experience with such a system, this protocol is a great opportunity to pioneer use of such a system.
   d. Sites may want to explore use this electronic approach for sending remuneration for standard study visits as well.
   e. The system does not require a social security number, though there is capability to add a provision to prompt entry of social security number if calendar year payments go above $600.
   f. If participants do not want to use a debit card, there is also an option for disbursement via direct deposit or check.
   g. At the end of each calendar year, sites will be able to generate a report using participant numbers or social security number to determine which participants will need to be issued a 1099.
6. The STARS should select a point-person for adjudicating the conditional economic incentives (that ideally should not be the same person providing adherence counseling).
7. If a participant misses one incentive, then we skip to the next.

VI. Meeting Deeper Needs

A. <u>"Warm" Connections to Case management</u>

1. The study and many participants will benefit from having connections to local case management or social work services.
2. These services may be located at the local treatment clinic and/or community based agencies.
3. We encourage connecting trial participants who have unmet needs to case management services.
   a. Connection to these services can be offered under a "normalized" process, e.g., "We offer all our participants the opportunity to connect with case management services. Case managers can help you with many different needs, including transportation, benefits, and housing. Do you have a case manager? May we connect or reconnect you to this service?"
   b. Participants may also/alternatively benefit from a needs assessment at study screening and periodically throughout the study. This should be performed in conjunction with clinical support staff including case managers or social workers or adherence specialists as applicable. This includes identification of barriers such as transportation, substance use, mental health needs, and homelessness with appropriate supportive case management referrals as needed.
4. Whenever possible, we recommend making a "warm connection" to case management by having someone walk the participant over and make a personal introduction to the case manager or case management team.
5. If connected to a case management service, participant can sign a release allowing contact between study staff and case management service to help facilitate study visits.
6. Consider coordinating study visits with social worker/case management visits where possible.

B. <u>Facilitated connection to alcohol/drug treatment or behavioral health specialists</u>

1. Some participants may benefit from alcohol/drug treatment or mental health care.

2. These assessments may be best conducted by a case manager or social worker who is working with the study participant as a client.
3. Participants who meet certain cutoffs on the protocol assessments may also be directly referred to these services.

C. Providing a referral resource list
   1. Sites will benefit from assembling a list of referral resources.
   2. The referral resource list could be provided to study participants at routine intervals; it may also provide helpful information to the study staff when referrals are requested or needed.
   3. The referral list could identify a wide range of local services which might include the following:
      a. ADAP
      b. Food pantries
      c. Housing assistance (local HOPWA programs)
      d. Transportation assistance / paratransit services
      e. Sexual assault, intimate partner violence, and domestic shelter programs
      f. Mental health services
      g. Drug treatment and recovery services
      h. Needle exchange, syringe service, and overdose prevention programs
      i. Legal projects or clinics
      j. Support groups
      k. Spiritual services
   4. The local CAB may be helpful for composing this referral resource list.

VII. Coordinating/Choreographing Integrated Multicomponent Support from the Site Adherence and Retention Plan

A. Sites will need to develop a coordination plan for the integrated adherence and retention support.
Identify activities that should be accomplished daily, weekly, and periodically and

Appendix Table S6.1 : Number Of Sites Providing Each Support Service

		First* Number of sites (=Yes)	Last** Number of sites (=Yes)	Difference* Number of sites (=Yes)
Communication Support Service	Was a participant locater form used?	22	13	-9
	Was a participant contacted via palm card?	0	3	3
	Was a participant given a calendar?	12	11	-1
	Was a participant contacted via mailed letter?	6	7	1
	Was a participant contacted via text message?	25	24	-1

		First* Number of sites (=Yes)	Last** Number of sites (=Yes)	Difference* Number of sites (=Yes)
	Was a participant contacted via phone call?	29	28	-1
	Was a participant contacted via facebook?	4	0	-4
Retention Support Service	Were extended hours services provided?	8	9	1
	Were transportation services provided?	20	17	-3
	Were grab bag services provided?	7	11	4
	Were appreciation notes provided?	5	9	4
	Were outreach worker services provided?	15	10	-5
Adherence Support Service	Were adherence counseling services provided?	27	23	-4
	Were pill organizer services provided?	20	17	-3
	Were reminder text services provided?	19	23	4
Referral Support Service	Were case management services provided?	16	14	-2
	Were alcohol and/or drug treatment services provid	6	7	1
	Were mental health services provided?	15	15	0
	Were other referral services provided?	10	14	4

*First report after the first enrollment of Step 1

**Last report prior to February 12, 2024

Section 4 Randomization Procedure and Statistical Methods

Randomization

Treatment allocation was done by a computerized algorithm at the Data Management Center of the ACTG, a permuted block size of 4 was used across sites. The algorithm tracked the prior assignments to allow for monitoring of the numbers assigned to the two arms at each site. If a pre-set threshold for imbalance was reached at a site, the computer assigned the next participant to the less represented arm.

Data and Safety Monitoring Board (DSMB) efficacy reviews and statistical significance

A5359 was reviewed by Therapeutics and Prevention DSMB appointed by DAIDS. Two interim efficacy reviews were planned when approximately 33% and 67% of the total expected information on the primary outcome measure was available. Interim efficacy analyses were based on group-sequential repeated confidence intervals for the difference between treatment groups, using the Lan-DeMets approach with an O'Brien-Fleming spending function.

At the second planned DSMB efficacy review on February 12, 2024, based on the interim efficacy results, the DSMB concluded that "… *all endpoint estimates favor the LA-ART arm and the important endpoints of virologic failure and treatment related failure significantly favor LA-ART when using the interim monitoring level. Although the primary endpoint (which was a composite endpoint that included virologic failure) does not meet the strict criteria of the 98.75% CI, the point estimate and 98.75% confidence interval for the cumulative probability difference were -14.4% (-29.8%, 0.8%). The statistically significant difference of the secondary endpoints clearly suggests efficacy of the test regimen. When considering all endpoints together, the evidence indicates superior efficacy of LA-ART over SOC.*" The DSMB recommended to stop randomization in Step 2 and transition all participants in Step 2 to LA-ART.

This final analysis included additional 6 weeks of data from the date of data cutoff for the DSMB review (January 3, 2024) and the DSMB review date (February 12, 2024). These data are called overrun data, which are considered valid and should be included in the analyses according to regulatory bodies [1-4]. The final confidence interval was adjusted for Type I error spent at the interim efficacy analyses and the fact that randomization and Step 2 follow-up were terminated early, to preserve an overall two-sided Type I error rate of 0.05 for the comparison of the primary outcome measure. Specifically, a new information fraction was calculated including additional data from the time of interim analysis data cut (January 3, 2024) used in the DSMB review that led to termination of Step 2 enrollment, to the date of the DSMB review (February 12, 2024). The level of the final confidence interval was recomputed using the O'Brien-Fleming spending function at the new information fraction.

The information fraction was calculated based on the primary outcome measure of regimen failure using the effective sample size approach taking account of all available data [5]. Using the Lan-DeMets approach with an O'Brien-Fleming spending function, based on the information fraction of 76.6% on the primary outcome measure and accounting for prior efficacy reviews, a nominal 98.4% two-sided confidence interval (corresponding to a significance level of 0.0161) was used in this final analysis of the primary outcome measure. For simplicity, the same nominal 98.4% confidence interval was also used for the secondary efficacy outcome measures (virologic failure, treatment-related failure, permanent treatment discontinuation) although the level of information available at this time for the secondary outcomes may be different from the primary outcome measure.

Analysis details of primary and secondary efficacy outcomes

Primary outcome: regimen failure

The primary estimand was the absolute difference in the cumulative probability of regimen failure over 48 weeks of LA ART (using LA RPV and LA CAB) compared to SOC, among previously non-adherent, individual living with HIV who successfully achieved virologic suppression after a period of incentivized SOC ART regimen. Regimen failure was defined as the occurrence of the first of the two following events at any time post randomization to Step 2, week 48 visit:

- Virologic failure
- Permanent discontinuation of randomized study treatment

For intercurrent events of failure to initiate randomized treatment, death or loss to follow-up, a composite strategy was used, e.g., occurrence of these events was included as part of the outcome measure definition. For intercurrent events of missed injections and COVID disruption to clinical operation, a treatment policy strategy was used.

Participants who did not experience a regimen failure on Step 2:

1) For participants on LA-ART, their follow-up time was censored at later of the last injection plus 28 days or last HIV-1 RNA measurement prior to or on February 12, 2024.
2) For participants on SOC, their follow-up time was censored at later of last study visit or last HIV-1 RNA measurement prior to or on February 12, 2024.

Comparison of treatment arms was made using the difference in the Kaplan-Meier estimates for the week 48 cumulative probability of regimen failure. Specifically, Kaplan-Meier estimates of the week 48 cumulative probability of regimen failure and associated Greenwood variance were calculated. A Z-test and corresponding two-sided confidence interval was constructed using the difference between the treatment arms and associated variance of the difference. Missing data were assumed to be randomly censored.

Supportive and subgroup analyses:

Supportive analyses were carried out applying different handling strategies for the intercurrent events. For intercurrent event of never initiated randomized treatment, a modified intention-to-treat analysis was conducted excluding those participants who did not initiate randomized treatment. For intercurrent event of COVID disruption to clinical operation, two supportive analyses were carried out: censoring at start of COVID disruption at sites and excluding all participants at COVID disrupted sites. Additional supportive analyses were carried out censoring at first positive pregnancy test and excluding participants with Step 2 eligibility violations but were permitted to include in analysis by study team.

An ad-hoc supportive analysis of treatment difference stratified by protocol version was carried out to account for different protocol versions. In this analysis, Kaplan-Meier estimates of the cumulative failure probabilities and associated Greenwood variance were obtained for each stratum level (protocol version). The difference between arms and the corresponding variance within each stratum was used to get a weighted average and associated variance for the difference across strata. The inverse of the within stratum variance was used to weight each stratum.

Treatment effect for the primary outcome was evaluated in pre-specified subgroup based on sex (at birth), race (Black vs. non-Black), ethnicity (Hispanic vs non-Hispanic), age (<35 vs. ≥35 years), body mass index (BMI, <30 vs ≥30 kg/m^2), HIV-1 RNA at randomization (≤200 vs >200 copies/mL), CD4+ T cell count at randomization (≤200 vs >200 cells/mm3) and protocol version (1, 2, and 3). The same analysis approach outlined for the primary outcome was implemented for each subgroup. Within each subgroup, the difference between randomized arms in cumulative failure probability and two-sided confidence intervals were estimated.

No multiplicity adjustment was done for the subgroup analysis, the widths of the confidence intervals should not be used to infer definitive treatment effects.

Secondary efficacy outcomes:

Virologic failure

Virologic failure was defined as two consecutive HIV-1 RNA > 200 copies/mL after Step 2 randomization and up to Step 2 Week 48 visit, regardless of the time between them.

For participants with an initial failing measurement obtained prior to or on February 12, 2024, confirmation measurements may be obtained prior to or on March 4, 2024 (within 21 days after February 12, 2024). If no confirmatory measurements were available

within the time frame, participants with an initial failing HIV-1 RNA prior to or on February 12, 2024 would be considered as virologic failure at the study visit week of the unconfirmed value.

Participants with an unconfirmed virologic failure (last Step 2 HIV-1 RNA > 200 copies/mL after Step 2 randomization) would be considered as virologic failure at the study visit week of the unconfirmed result.

The analysis of virologic failure followed the same approach as the primary outcome of regimen failure. Virologic failure was evaluated regardless randomized treatment status, e.g., failure to initiate randomized treatment or permanent discontinuation of randomized treatment was ignored. Missed injection and COVID disruption were also ignored. Participants who died or lost to follow-up without experiencing VF had their follow-up time censored at the study week of their last measured plasma HIV-1 RNA on Step 2. For all other participants without experiencing VF, their follow-up time was censored at the study week of their last measured plasma HIV-1 RNA up to Step 2 week 48 visit prior to or on February 12, 2024. For participant did not have plasma HIV-1 RNA on Step 2, their follow-up time was censored at the Step 2 entry.

Supportive analysis of virologic outcome at week 48 by FDA Snapshot algorithm was conducted using threshold of 50 and 200 copies/mL. The analyses were restricted to participants who could have had the week 48 visit by the follow-up cutoff date (February 12, 2024) to ensure sufficient follow-up time. More specifically, the analysis population was restricted to participants randomized at least 50 weeks prior to the follow-up cutoff date.

Treatment-related failure

Treatment-related failure was defined as the occurrence of the first of virologic failure or permanent Step 2 treatment discontinuation due to AE up to Step 2 week 48 visit. Treatment discontinuation due to treatment-related AE was used to define the outcome measure.

Comparison of the cumulative probability of treatment-related failure up to Step 2 week 48 visit between randomized treatment was carried out following the same analysis approach for the primary outcome. For participants without experiencing a treatment-related failure, their follow-up time was censored at their last study visit (regardless of visit type) up to Step 2 week 48 visit prior to or on February 12, 2024.

Permanent Step 2 treatment discontinuation

Permanent discontinuation of randomized study treatment was defined as the first of the following events prior to Step 2 week 48 visit:

- Participants randomized to LA ART arm prematurely discontinue oral RPV or CAB before Step 2, week 4
- Participants randomized to LA ART arm never initiate injectable RPV or CAB
- Participants randomized to LA ART arm prematurely discontinue injectable RPV or CAB
- Participants randomized to SOC arm prematurely discontinue oral ART regimen. Switching to another oral ARV was not considered treatment discontinuation.
- Participants prematurely discontinue study treatment/participation for any reason including death and loss to follow up.

Comparison of the cumulative probability of permanent Step 2 treatment discontinuation up to Step 2 week 48 visit between randomized treatment was carried out following the same analysis approach for the primary outcome. For participants without premature treatment discontinuation,

1) For participants on LA-ART, their follow-up time was censored at last injection plus 28 days.
2) For participants on SOC, their follow-up time was censored at last visit prior to or on February 12, 2024.

References:

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Section 5 Additional Patient Reported Outcomes

The HIV Treatment Adherence Self-Efficacy Scale was a 12-item measure used to measure social and psychological determinants of adherence to ART among individuals living with HIV. The response scale to each individual item ranged from 0 (“cannot do at all”) to 10 (“completely certain can do”). The total score reported was the average of all item scores, ranging from 0 to 10, with higher scores indicating higher adherence self-efficacy. HIV-ASES was scheduled at Weeks 24 and 48 on Step 2. The most recent evaluation participants completed during Step 1 was used as Step 2 baseline. The median summary score was 9 in both arms at Step 2 entry and was 10 in both arms at Weeks 24 and 48.

Appendix Table S7.1: Step 2 HIV Treatment Adherence Self-Efficacy Scale Score (HIV-ASES)

Week	Statistic	LA-ART (N=151)	SOC (N=152)
Week 0	n	151	152
	Median (Q1, Q3)	9 (8, 10)	9 (8, 10)
	Min, Max	0, 10	0, 10
Week 24	n	108	105
	Median (Q1, Q3)	10 (8, 10)	10 (8, 10)
	Min, Max	2, 10	3, 10
Week 48	n	77	69
	Median (Q1, Q3)	10 (9, 10)	10 (8, 10)
	Min, Max	0, 10	4, 10

The HIV Treatment Satisfaction Questionnaire (HIVTSQ) was designed specifically to measure satisfaction with medication for people living with HIV. The questionnaire had 12 items rated using a 7-point Likert scale. Results were summarized as a total score that included 11 items, with the “pain/discomfort” item reported separately. The status version (HIVTSQs) measured participant satisfaction with their current treatment with individual item rated ranging from 0 (“very dissatisfied”) to 6 (“very satisfied”) and the total score ranging from 0 to 66, where higher scores indicated a greater level of satisfaction with their HIV-1 treatment. The HIVTSQ “change version” (HIVTSQc) was designed to assess the change in treatment satisfaction between a participant’s previous and current treatment. The individual items were rated from -3 (“much less satisfied”) to 3 (“much more satisfied”) with a total score ranging from -33 to 33, where higher scores indicated a greater improvement in treatment satisfaction with the new treatment, and lower scores indicated lower treatment satisfaction with the new treatment, and a score of zero represented no change in

satisfaction. HIVTSQs was completed by participants on both arms at Step 2 entry and Week 24, and also at Week 48 for those randomized to SOC.

At Week 48, participants on the LA-ART arm completed the change version of the questionnaire(HIVTSQc). At week 48, the HIVTSQc total score for satisfaction with current vs. prior treatment was high in LAI arm (median 33, [IQR 31, 33].

Appendix Table S7.2: Step 2 HIV Treatment Satisfaction Questionnaire

eCRF	Study week	Question	Statistic	LA-ART (N=151)	SOC (N=152)
QLW10086: HIVTSQs[1]	Week 0	11-item total score	n	149	149
			Median (Q1, Q3)	63 (55, 66)	62 (53, 66)
			Min, Max	2, 66	0, 66
		Satisfaction with Pain/Discomfort	n	148	149
			Median (Q1, Q3)	6 (5, 6)	6 (4, 6)
			Min, Max	0, 6	0, 6
	Week 24	11-item total score	n	147	146
			Median (Q1, Q3)	66 (60, 66)	62 (51, 66)
			Min, Max	22, 66	0, 66
		Satisfaction with Pain/Discomfort	n	143	142
			Median (Q1, Q3)	6 (5, 6)	6 (5, 6)
			Min, Max	1, 6	0, 6
		Change in 11-item total score	n	147	143
			Median (Q1, Q3)	0 (0, 4)	0 (0, 1)
			Min, Max	-30, 60	-47, 35
			Wilcoxon Test		
		Change in Satisfaction with Pain/Discomfort	n	142	139
			Median (Q1, Q3)	0 (0, 0)	0 (0, 0)
			Min, Max	-5, 3	-5, 6
			Wilcoxon Test		
	Week 48	11-item total score	n		146
			Median (Q1, Q3)		63 (51, 66)
			Min, Max		0, 66
		Satisfaction with Pain/Discomfort	n		143
			Median (Q1, Q3)		6 (5, 6)
			Min, Max		0, 6

eCRF	Study week	Question	Statistic	LA-ART (N=151)	SOC (N=152)
QLW10067: HIVTSQc[2]	Week 48	Change in 11-item total score	n	71	
			Median (Q1, Q3)	33 (31, 33)	
			Min, Max	24, 33	

A single-item question regarding preference for LAI or oral therapy at Step 2 week 48 was administered in the LAI group. Among participants on LAI who completed a dichotomous preference questionnaire at Week 48, 95% preferred LAI over SOC.

Appendix Table S7.3: Step 2 Dichotomous Preference Question: LA ART vs. Oral ART among Those who Initiated Injection

Week	Preference	LA-ART (N=141)
Week 48	Daily oral HIV Treatment	4 (5%)
	Monthly injections of Long-Acting HIV Treatment	72 (95%)
	Not Done	2
PREMATURE TREATMENT DISCONTINUATION	Daily oral HIV Treatment	2 (50%)
	Monthly injections of Long-Acting HIV Treatment	2 (50%)
PREMATURE STUDY DISCONTINUATION	Monthly injections of Long-Acting HIV Treatment	2 (100%)
	Not Done	1

Participants were asked at Step 2 Entry and at Step 2 Week 8 their perceptions regarding the discontinuation of the Step 1 Conditional Economic Incentives (CEI).

Appendix Table S7.4: Step 2 Conditional Economic Incentive (CEI) Withdrawal Question

Week	Statistic	LA-ART (N=151)	SOC (N=152)
Week 0	n	149	152
	Not at all upset or disappointed	71 (48%)	75 (49%)
	Not very upset or disappointed	20 (13%)	13 (9%)
	Somewhat upset or disappointed	27 (18%)	27 (18%)

Week	Statistic	LA-ART (N=151)	SOC (N=152)
	Extremely upset or disappointed	17 (11%)	16 (11%)
	Undecided	14 (9%)	21 (14%)
Week 8	n	128	120
	Not at all upset or disappointed	55 (43%)	44 (37%)
	Not very upset or disappointed	20 (16%)	17 (14%)
	Somewhat upset or disappointed	31 (24%)	27 (23%)
	Extremely upset or disappointed	15 (12%)	20 (17%)
	Undecided	7 (5%)	12 (10%)