A5359: Decreasing oral induction duration in support of LAI ART use with hardly-reached populations

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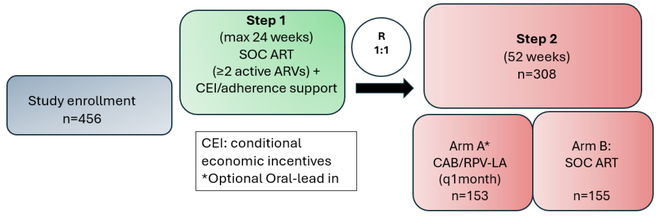
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BACKGROUND

- Large randomized clinical trials of investigational agents among people with HIV (PWH) routinely exclude participants with adherence challenges.
- ACTG 5359, LATITUDE (NCT03635788) is a phase III, prospective, randomized, open-label trial that demonstrated superiority of monthly long acting cabotegravir + rilpivirine (LAI) vs. oral standard of care (SOC) ART in PWH with a history of suboptimal adherence (persistent HIV-1 RNA >200 c/mL or loss to follow-up).[1]
- After an induction phase (Step 1) on oral SOC of up to 24 weeks, participants were eligible to enter the randomization phase comparing LAI to SOC (Step 2). (**Figure 1)**

Figure 1. Study enrollment and design



OBJECTIVES

- To examine the transition status from Step 1 to Step 2 with successive shortening the oral induction phase.

METHODS

- After study initiation (March 2019), the HIV-1 RNA threshold for Step 2 was changed from <50 copies/mL to <200 copies/mL, and the minimum duration of Step 1 was progressively shortened from 20 weeks to 12 weeks (Version 2, Dec 2021), and then to 4 weeks (Version 3, Jan 2023) (**Figure 2**)

Figure 2. Step 2 Eligibility Criteria by Protocol Version*



*3 enrolled participants were subsequently considered ineligible and removed from study

- Transition status of all Step 1 participants who would have been eligible to enter Step 2 at the time of protocol data freeze on February 12, 2024, were summarized. Participants still in Step 1 (n=27) are excluded from the transition analysis.
- Step 2 baseline characteristics of participants were descriptively summarized overall and compared by protocol version.

Shortening the required duration of virologic suppression during the oral induction phase significantly increased enrollment for the randomized strategy comparison in A5359.

RESULTS

Table 1. Baseline Socio-demographics at Step 1 Entry

Characteristic		Total (n=453)	Characteristic		Total (n=453)
Age, years	Median (Q1, Q3)	40 (32, 51)	Time since HIV Dx, years	Median (Q1, Q3)	13 (7, 21)
Sex at birth	Female	133 (29%)	Baseline BMI kg/m^2	Median (Q1, Q3)	26 (22, 30)
Race, n (%)	Black/African American	286 (63%)	Education, n (%) [a]		
	White	125 (28%)	<High School		89 (20%)
	Other/multiple/unknown	42 (9%)	High School		141 (32%)
			Some College or Higher		214 (47%)
Ethnicity	Hispanic/Latinx	79 (17%)	IV Drug Use, n (%)		
			Current		20 (4%)
			Prior		43 (9%)
Non-Adherence Enrollment Criteria			Income[a]		
Lost to follow-up		93 (20%)	<$5000		128 (29%)
Poor virologic response		294 (65%)	$5000-9999		59 (13%)
Both		66 (15%)	$10000-19999		99 (23%)
			>$20,000		153 (34%)
Step 1 Baseline HIV-1 RNA, n (%)	≤200	154 (34%)	Housing Status[a]		
[copies/mL]	201-10,000	114 (25%)	In own house/apartment		270 (61%)
	10,001-100,000	123 (27%)	Parents' House		64 (14%)
	>100,000	62 (14%)	Someone Else's Housing		57 (13%)
			Unstable/Homeless[b]		42 (9%)
			Other		11 (2%)
Baseline CD4+ T (cells/mm^3)	Median (Q1, Q3)	273 (119, 511)			

[a] percentages may not equal 100 due to rounding or missing data
[b] Unstable/Homeless includes: Shelter/Welfare hotel, Halfway/Boarding House On the Street, Residential Treatment Facility

Table 2. Baseline Mental Health/Substance Use Assessments at Step 1 Entry[c]

Assessment	Total (n=453)	Assessment	Total (n=453)
PHQ-9[2] Depression Category, n (%)		Generalized Anxiety Disorder-7 Category[6], n (%)	
None	228 (51%)	None	220 (49%)
Mild	106 (24%	Mild	111 (25%)
Moderate	56 (12%)	Moderate	69 (15%)
Severe	60 (13%)	Severe	52 (12%)
Alcohol Use AUDIT-C Score[3]		DUDIT Score[7], n (%)	
Hazardous Drinking, n (%)	144 (32%)	Drug-use problems (males ≥6, females ≥2)	205 (45%)
(≥4 (males) or ≥3 (females)		Drug Dependence (≥25)	23 (5%)
Suicide Severity Rating[4], n (%)		Urine Drug Screen Positivity During Step 1, n (%)	
No risk	358 (81%)	Cocaine	98 (24%)
Low risk	31 (7%)	Amphetamine/Methamphetamine	113 (28%)
Moderate risk	45 (10%)	Opiate/Methadone	45 (11%)
High risk	10 (2%)	Marijuana	239 (59%)
		≥2 drugs	186 (41%)
Domestic Violence Screening[5]		HIV Treatment Self-Efficacy Scale (HIV-ASES)[8]	
Yes	12 (3%)	median (Q1, Q3)	9 (7, 10)
No	424 (97%)		

[c] percentages may not equal 100 due to rounding or missing data

Table 3. A5359 Step 1 to Step 2 Transitions by Protocol Version

Protocol Version Step 1 to Step 2 Transition Status	1.0 (N=249)	2.0 (N=70)	3.0 (N=107)	Total (N=426)
Enrolled to Step 2[d] n (%)	151 (61%)	57 (81%)	98 (92%)	306 (72%)
At Week 4	0 (0%)	3 (5%)	78 (80%)	81 (26%)
At Week 8	0 (0%)	4 (7%)	15 (15%)	19 (6%)
At Week 12	4 (3%)	42 (74%)	4 (4%)	50 (16%)
At Week 16	3 (2%)	6 (11%)	0 (0%)	9 (3%)
At/after Week 20	144 (95%)	2 (4%)	1 (1%)	147 (48%)
Ineligible to enroll in Step 2 due to HIV-1 RNA criteria				
n (%)	46 (18%)	4 (6%)	4 (4%)	54 (13%)
Off study in Step 1 due to reasons other than HIV-1 RNA criteria				
Lost to follow-up	23 (58%)	5 (56%)	3 (60%)	31 (57%)
Participant withdrawal	12 (30%)	1 (11%)	0 (0%)	13 (24%)
Other reasons[e]	17(30%)	3 (44%)	2 (44%)	22 (34%)

[d] Participants enrolled in Step 1 could transition to Step 2 under subsequent version eligibility criteria once approved at site.
[e] Includes protocol non-compliance (9), discontinuation of ART (5), prohibited medication/confounding medical condition (4), death (1), pregnancy (1), site error (1) and incarceration (1).

Table 4. Key Differences in Sociodemographic and Behavioral Assessments at Step 2 Entry By Protocol Version

	V1.0 n= 142	V2.0 n=46	V3.0 n=118	Chi-Square Test
Current or Prior IV Drug use, n (%)	17 (12%)	13 (29%)	9 (7%)	.008
Average number of cigarettes smoked daily	6	5	10	.042
Moderate/severe anxiety on GAD-7, n (%)	21 (15%)	11 (24%)	30 (26%)	.016
HIV Treatment Adherence Self-Efficacy Score (median)	10	10	9	<0.001
Moderate/high suicide risk, n (%)	7 (5%)	2 (4%)	20 (17%)	.005

- Other sociodemographic and behavioral characteristics were not significantly different across protocol versions.

CONCLUSIONS

- A5359 successfully enrolled a priority population not generally included in studies of investigational ART strategies
- Participants in later protocol versions had higher proportions with moderate/severe anxiety and moderate/high suicide risk, and lower HIV Treatment Adherence Self-Efficacy scale scores, with version 2 participants having higher proportions of history of IV Drug use.
- In-trial shortening of the required duration of virologic suppression significantly increased enrollment for the randomized strategy comparison from 61% to 92% in this vulnerable population.

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ClinicalTrials.gov registration: NCT03635788 | **Correspondence:** Aadia Rana, University of Alabama Heersink School of Medicine 1808 7th Avenue South BDB 847 | Birmingham, AL 35233, airana@uabmc.edu| **Acknowledgements:** The study team would like to thank the study participants and sites. The ACTG Network is funded by the National Institute of Allergy and Infectious Diseases, as part of the NIH (ACTG SDAC UM1 AI068634, LOC UM1 AI068636 and LC UM1 AI106701).

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