Data-informed Stepped Care (DiSC) to Improve Adolescent HIV Outcomes (UH3): A cluster randomized trial on a Data Informed Stepped Care intervention to improve retention among adolescents living with HIV

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Data-informed Stepped Care (DiSC)

Statistical Analysis Plan for of the Cluster Randomized Trial (Aim 2)

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Section 1. Study summary and aims

1.1. Rationale

UNAIDS '95-95-95' targets cannot be achieved without additional support for adolescents living with HIV (ALHIV) to increase retention in care and to support viral suppression. A stepped care approach to care can support allocation of ALHIV to tailored care based on risk.

This study aims to test a data-informed stepped care approach to improve retention among ALHIV. We will also study HIV cascade outcomes (viral non-suppression, receiving differentiated care, adherence).

1.2. DiSC Cluster RCT Objectives

Primary: To compare retention during 12-month follow-up among ALHIV in 12 HIV clinics receiving DiSC intervention to retention among ALHIV in 12 similar control clinics receiving standard of care. Participating clinics will be high-volume HIV clinics in Homabay, Kisumu and Migori counties, all in Western Kenya.

Secondary: To evaluate the effect of the DiSC intervention on HIV cascade outcomes (viral non-suppression, receiving differentiated care, adherence).

Section 2. Study outcomes

2.1. Summary of primary and secondary outcomes

Table 1. Outcome definitions and assessment

Outcome	Indicator	Source	Timing
Primary outcome			
Retention in care	Missed visits: Not seen within 30 days of a scheduled visit.	EMR data (Visit Date, TCA)	All visits occurring during the 12-month period after the study enrollment visit*
Secondary outcomes			
Loss to follow-up	Not return to care within the 12 months study interval	EMR data (Visit Date, TCA)	All visits after the first study visit until event or end of follow-up at 12 months. Participants marked as 'transferred out' or 'died' will be censored.
Viral non-suppression	Having HIV viral load (VL) >1,000 copies/mL	NASCOP data, abstraction of paper records	All visits from enrollment to 12 months follow-up*
Receiving differentiated care	• Long inter-visit interval • Fast-track visit	EMR data (TCA, Care Model)	All visits from enrollment to 12 months follow-up*
Adherence	Pill coverage estimated by days of dosing and inter-visit interval since last visit >80%	EMR data (Visit Date, next Visit Date, Duration)	All visits from enrollment to 12 months follow-up*

*time window up to 12 months + 30 days

2.2. Sample size considerations

2.2.1. Sample size and power for primary outcome

In our sample of HIV care facilities with >1,000 clients enrolled overall, we anticipate at least 10% will be eligible adolescents and young adults (AYA), with about 100-200 AYA per clinic on average. Based on our UG3 data, we assume that 75% will be in care (not LTFU) by the end of 12-month follow-up period. Given a minimum of 24 facilities in the trial (minimum 12 per arm), we estimated the minimum average number of AYA per facility to detect a 14-18% point change in retention using EMR data. Assuming 12 facilities per arm, 80% power, α=0.05 and coefficient of variation of 0.10 (Table 2), we can detect a 14%-point difference (75% to 89%) with at least 150 AYA per facility, and a 15%-point difference (75% to 90%) with at least 50 AYA per facility. Assuming coefficient of variation of 0.15, we can detect a 17%-point difference (75% to 92%) with at least 50 AYA per facility (Table 2). Detecting a less than 14%-point difference or if assuming a larger correlation coefficient of individuals within a facility would require more participants per facility or more facilities per arm.

2.2.2. Secondary outcomes and assumptions

Viral suppression: An average of 50 AYA VL records per facility and a minimum of 12 facilities per arm would be sufficient to detect a change from 64% to 82%, assuming 80% power, an α=0.05 and coefficient of variation of 0.10 (Table 2).

Table 1. Sample size calculation of number of facilities per arm for the ITT analysis of retention and viral suppression

AYA per facility	ICC	Estimated proportion in study arm									
		Control	Intervention								
		75%	85%	86%	87%	88%	89%	90%	91%	92%	93%
200	0.10		26	21	18	15	**12**	**11**	**9**	**8**	**7**
150			27	22	18	15	**12**	**11**	**9**	**8**	**7**
100			27	22	18	15	13	**11**	**9**	**8**	**7**
50			30	24	20	17	14	**12**	**10**	**9**	**8**
	0.15	75%	85%	86%	87%	88%	89%	90%	91%	92%	93%
200			39	31	26	21	18	15	13	**11**	**10**
150			39	32	26	22	18	16	13	**12**	**10**
100			40	32	26	22	19	16	14	**12**	**10**
50			42	34	28	23	20	17	14	**12**	**11**
		64%	80%	81%	82%	83%	84%	85%	86%	87%	88%
200	0.10		13	**11**	**10**	**9**	**8**	**7**	**6**	**6**	**5**
150			13	**12**	**10**	**9**	**8**	**7**	**7**	**6**	**5**
100			13	**12**	**10**	**9**	**8**	**7**	**7**	**6**	**5**
50			15	13	**11**	**10**	**9**	**8**	**7**	**7**	**6**
	0.15	64%	80%	81%	82%	83%	84%	85%	86%	87%	88%
200			19	17	15	13	**12**	**10**	**9**	**8**	**8**
150			19	17	15	13	**12**	**10**	**9**	**8**	**8**
100			19	17	15	13	**12**	**11**	**10**	**9**	**8**
50			20	18	16	14	**12**	**11**	**10**	**9**	**8**

ICC: intraclass correlation coefficient; sample size estimated by assuming study power of 80%, significance level of 0.05 and coefficient of variation of 0.10

Section 3. Study Data Analysis

3.1. Study accrual

Per CONSORT guidelines, we will report the number of facilities who:

- Underwent screening
- Met inclusion criteria
- Did not meet inclusion criteria (and reasons)
- Enrolled in the study and were randomized
- # of people at facility that were treated as per study protocol

3.2. Trial profile

A CONSORT diagram will show the number of clinics and ALHIV clients per clinic (cluster) randomized to each arm (see Figure 1). We will report the number of clinics selected for inclusion, assignment to intervention or control, and the number of HCWs enrolled per site. Clinic-specific information, including ALHIV client volume, number of HCWs, and any pre-trial adolescent-specific services will be reported.

3.3. Baseline characteristics

We will describe the distribution of baseline characteristics, using appropriate summary statistics. We will present these summary statistics in tables overall and by study arm (see Table 3).

Figure 1. DiSC UH3 CONSORT Diagram

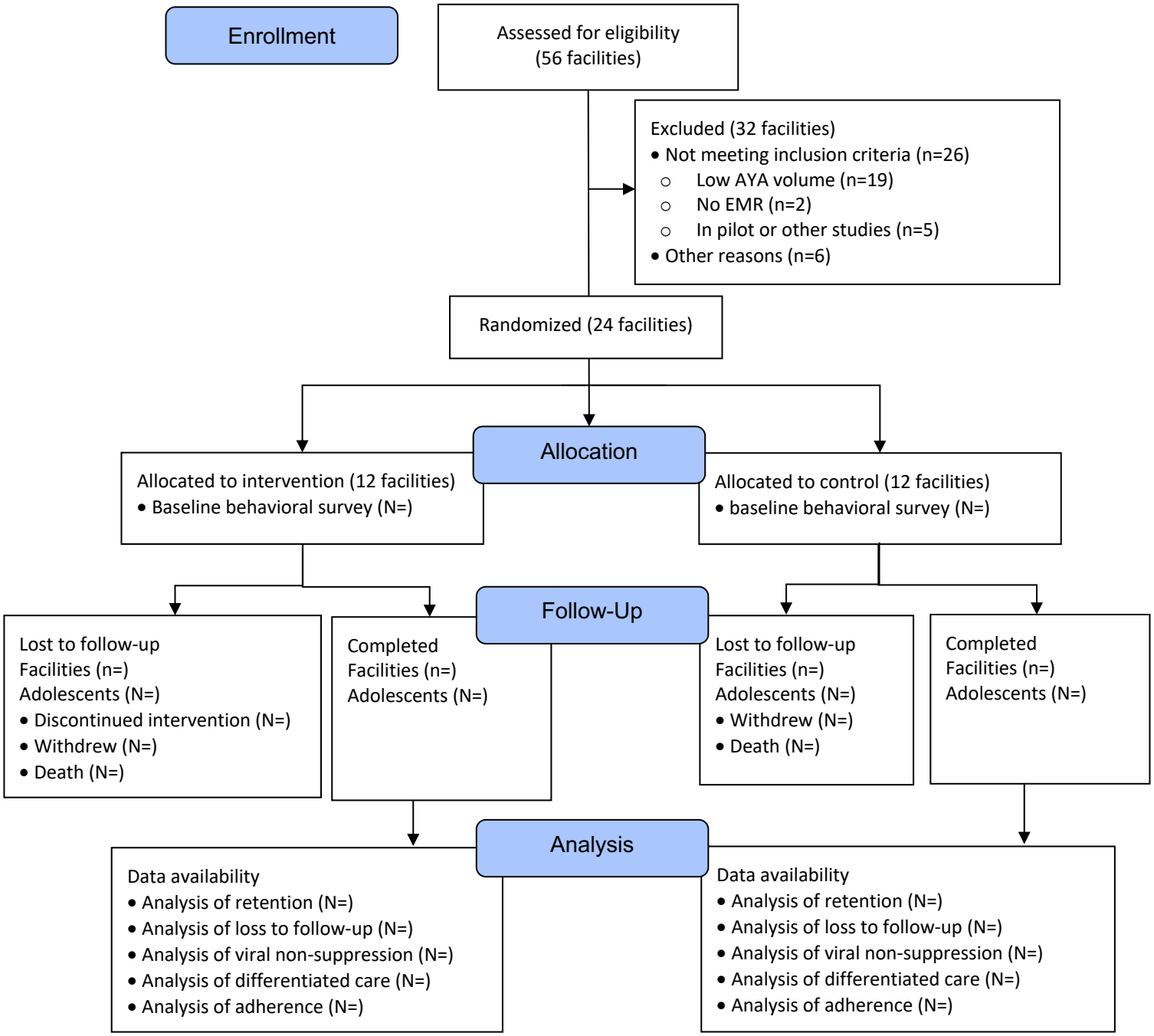

Table 3. Baseline characteristics of study participants by study arm

Characteristic	Overall	Control	Intervention
Age			
Median (IQR)			
Gender			
Male			
Female			
Currently in school			
Completed secondary school			
At least one parent alive			
At least one parent died			
Depression category [a]			
None/minimal (0-4)			
Mild (5-9)			
Moderate (10-14)			
Severe (15+)			
Anxiety category [b]			
None/minimal (0-4)			
Mild (5-9)			
Moderate (10-14)			
Severe (15+)			
Any alcohol or drug use in life [c]			
Social support [d]			
Resilience [e]			
Adherence self-efficacy [f]			
Stigma [g]			
Part of a peer support group			
Violence in the last 6 months			
Transport to clinic ≥1 hour			
Wait time in clinic ≥1 hour			
Use at least 1 differentiated care model			
Report service needed but not received			
Able to come for appointments without help from caregiver			
Able to take medication without reminders from caregiver			
Always coming to this clinic by yourself			
Other person in charge of healthcare decision			
Disclosed to anyone			
ART regimen TDF/3TC/DTG ABC/3TC/DTG ABC/3TC/EFV ABC/3TC/NVP AZT/3TC/NVP Others			

[a] evaluated using Patient Health Questionnaire-9 (PHQ-9) with a score of 0-4 indicating none/minimal depression, 5-9 mild depression, 10-14 moderate depression, ≥15 severe depression; [b] evaluated using General Anxiety Disorder-7 (GAD-7) with a score of 0-4 indicating none/minimal anxiety, 5-9 mild anxiety, 10-14 moderate anxiety, ≥15 severe anxiety; [c] using WHO Alcohol, Smoking and Substance Involvement Screening Test for Young people (ASSIST-Y); [d] evaluated using Multidimensional Scale of Perceived Social Support (MSPSS) 12-item scale with a score >3 indicating high social support; [e] evaluated using Connor-Davidson Resilience Scale-2 (CDRS-2) with a score ≥3 indicating high resilience; [f] evaluated using Arthritis Self-Efficacy Scale (ASES) with a score ≥5 indicating high adherence; [g] evaluated using Youth HIV Brief Stigma Scale (YHBSS) with a score ≥3 indicating high stigma experience

3.4. Analysis of retention

Retention will be evaluated using an indicator of missed visits. A missed visit will be defined as a participant not seen within 30 days of a scheduled visit during follow-up since the first stepped care visit to 12 months. Each scheduled visit will be classified as missed versus not missed and analysis will use repeated measures per participant. The proportion of missed visits will be compared between study arms using mixed-effects Poisson regression with random effects for facility and participant and robust standard errors.

Sub-group analyses for retention will be performed by gender and age-group. Facility factors, including concurrent adolescent-friendly services and high/low performance will be evaluated as modifiers of intervention effectiveness.

Table 4. Analysis of missed visits

	Overall	Control	Intervention	Intervention vs. control
Missed visits per participant				[a]RR (95% CI)
	Median (IQR)			
Number of scheduled visits Number of missed visits (%)				
Missed visits over all participants				
	Count (proportion)			
Number of scheduled visits Number of missed visits (%) Number of AYA ever missed a visit (%)				

[a] Estimated by mixed-effects Poisson regression with random effects for facility and participant and robust standard errors

*Excluding TCA that had miss/no-miss status censored or missing

*Models adjusted for any factors differing between arm with statistical significance at enrollment

3.5. Analysis of secondary study outcomes

3.5.1. Loss to follow-up:

- Loss to follow-up will be defined as a participant missed a visit and did not return to care within the 12-month study period. The proportion of loss to follow-up during 12-month study interval (window up to 12 months +30 days) will be compared between study arms using Poisson regression with robust errors.
- Time to loss to follow-up will be compared between arms by survival curves, and death or transfers will be censored. The hazard of loss to follow-up will be compared between study arms using Cox proportional hazards regression.

3.5.2. Viral non-suppression:

- Viral non-suppression will be defined as having HIV viral loads (VL) >1,000 copies/mL. Each VL testing result will be classified as VL suppressed vs. unsuppressed. The proportion of viral non-suppression during follow-up will be compared between study arms using mixed-effects Poisson regression with random effects for facility and participant and robust standard errors.

3.5.3. Receiving differentiated care:

- Receiving differentiated care will be defined in two ways. One approach will evaluate the next visit appointment date (scheduled inter-visit interval) – visits scheduled for ≥3 months after visit will be considered as differentiated care, in comparison to monthly visits recommended for AYA in current guidelines. The second approach will use the variable 'fast-track' at each visit – 'fast track' visits are considered as a component of differentiated care. Two analyses will be conducted (one for long scheduled inter-visit interval and one for 'fast track'), each will be compared between study arms using mixed-effects Poisson regression with random effects for facility and participant and robust standard errors.

3.5.4. Adherence:

- Adherence will be evaluated using the proportion of days of pill dosing over days of inter-visit interval. The level of adherence during the past inter-visit interval will be assessed at each visit. A proportion over 80% as good adherence. The dichotomized adherence will be compared between arms using mixed-effects Poisson regression with random effects for facility and participant and robust standard errors.

Table 5. Analysis of secondary study outcomes

Loss to follow-up				
	Overall	Control	Intervention	Intervention vs. control
	Count (proportion)			[a]RR (95% CI) [b]HR (95% CI)
Event Person-year Cumulative incidence Incidence rate (per 100 person-years)				
Viral non-suppression				
	Overall	Control	Intervention	Intervention vs. control
	Count (proportion) / Median (IQR)			[c]RR (95% CI)
Per participant Number of viral load assays **Over all participants** Number of viral load assays Number of non-suppression results (%)				
Differentiated care: long-interval visits scheduled				
	Overall	Control	Intervention	Intervention vs. control
	Count (proportion) / Median (IQR)			[c]RR (95% CI)
Per participant Number of scheduled visits **Over all participants** Number of scheduled visits Number of long-duration interval (%)				
Differentiated care: fast-track visits				
	Overall	Control	Intervention	Intervention vs. control

	Count (proportion) / Median (IQR)			[c]RR (95% CI)
Per participant Number of visits with non-missing care model **Over all participants** Number of visits with non-missing care model Number of fast-track visits (%)				
Adherence				
	Overall	Control	Intervention	Intervention vs. control
	Count (proportion) / Median (IQR)			[c]RR (95% CI)
Per participant Number of intervals with good adherence **Over all participants** Number of intervals with good adherence Number of intervals with good adherence (%)				

[a] Estimated by Poisson regression with robust errors
[b] Estimated by Cox proportional hazards regression
[c] Estimated by mixed-effects Poisson regression models with random effects for facility and participant and robust standard errors
*Models adjusted for any factors differing between arm with statistical significance at enrollment

Section 4. Missing data

While we will attempt to follow all participants at 12 months, we anticipate that EMR data and VL data may be incomplete for some participants might be a challenge due to participant loss to follow-up – either due to loss from care, or silent transfer to another facility. Due to the level of missingness we expect, we will not conduct any formal imputation.

Section 5. Safety monitoring

Adverse and severe adverse events, including social harms such as violence or breach of confidentiality, will be monitored as they arise, and unblinded results will be reviewed by the DSMB. The DSMB will make recommendations regarding any imbalances in safety outcomes.

SAE #	PTIDNO	Study arm	SAE description	Onset date	Duration (days / unresolved)	Onset since randomization (days)	Relatedness to study