CONCEPT SHEET: MULTIREGIONAL ANALYSIS

Date of EC approval:	*(to be added by UCT data centre)*
Tracking number:	*(to be added by UCT data centre after EC approval)*
Title:	**Time to ART initiation as a predictor of loss to care and viral suppression among PLWH entering HIV care under Treat All**
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Where will data be merged?	CUNY ISPH
Where will statistical analyses be done?	Einstein / CUNY
Abstract: (±200 words)	**Background and objectives** Nearly all countries have adopted WHO "Treat All" guidelines to initiate antiretroviral therapy (ART) for all people living with HIV (PLWH) as soon as possible after diagnosis. An emerging literature suggests it is important to characterize the relationship between time to ART initiation and subsequent clinical outcomes under Treat All. We propose to conduct a multi-regional

	cohort study of patients who entered care after Treat All was implemented in the four sub-Saharan Africa IeDEA regions to examine associations between time from diagnosis to ART initiation and outcomes of loss to clinic and viral suppression. **Methods** We propose to conduct a cohort study of adult patients in IeDEA-affiliated health centers newly diagnosed with HIV after Treat All implementation. We will use time-to-event methods to examine associations between time from diagnosis to ART initiation (same day, 1-7, 8-30, >30 days) and loss to clinic (>120 days since last clinic visit and did not knowingly die or transfer). Among patients with measured viral loads after ART initiation, we will use logistic or log binomial regression to calculate risk ratios for viral suppression by time to ART.
Project outline: (±1000 words)	**Background** Current WHO guidelines recommend provision of antiretroviral therapy (ART) to all people living with HIV regardless of clinical stage or CD4 count ("Treat All"), and further recommend that newly diagnosed patients be offered ART within 7 days of diagnosis ("Rapid ART"), or even on the day of diagnosis ("Same-day ART"). Data from multiple settings have demonstrated substantial decreases in time from diagnosis to both ART initiation and viral suppression among patients offered Rapid ART.[1,2] There are conflicting data regarding the associations of same day- and rapid ART initiation with loss to care and viral suppression. Randomized controlled trials in Haiti and in South Africa, as well as public health settings in the U.S., have described retention outcomes that are as good as or better among patients offered rapid ART compared to more lengthy initiation processes.[1,3-5] In these same studies, time to viral suppression was much shorter among those initiating ART rapidly compared to more standard ART initiation times. However, population-based surveillance data on all persons with newly diagnosed HIV in Haiti following 'treat all' implementation demonstrated lower odds of 12-month retention in care among patients initiating ART on the same day as diagnosis compared to those with longer intervals between diagnosis and ART initiation.[6] To date, no observational data from sub-Saharan Africa have been published describing the association between time to ART initiation and loss to care or viral suppression under Treat All. However, a recent analysis of data from Rwanda by the CA-IeDEA team found that loss to clinic was highest among those initiating ART on the day of diagnosis compared to later times (see Appendix). In qualitative work conducted by the CA-IeDEA team in Rwanda, both patients and care providers expressed appreciation for the potential benefits of rapid ART, but also concern about insufficient time to process a new HIV diagnosis and insufficient pre-ART counseling that may potentially lead to negative outcomes. We therefore propose to examine associations between Same-day ART as well as Rapid ART and outcomes of loss to care

and viral suppression among patients who entered care after Treat All was implemented in the four sub-Saharan Africa IeDEA regions.

Members of the Central Africa IeDEA team are well-positioned to lead this collaborative, multi-regional study and do so rapidly. We recently published studies examining changes in time to ART ART initiation before and after national 'Treat All' guideline adoption[7,8] (time to ART is the proposed "exposure" variable in the analyses described below), and can potentially leverage these cleaned data for the proposed concept. These early steps will facilitate conducting a multi-regional analysis that can provide richer and more generalizable results

Objectives and hypotheses

Aim 1: To characterize the frequency, describe trends, identify predictors of same-day (ART initiation on day of diagnosis) and rapid ART (within 7 days of diagnosis) initiation among patients newly enrolling in HIV care after Treat All implementation:

• *H1: Predictors of same-day and rapid ART initiation will include a) pregnant (vs. non-pregnant) status; b) WHO Stage I or II (vs. III or IV); c) TB status negative (vs positive); d) missing (vs. non-missing) CD4 count.*

Aim 2: To describe the association between same-day and rapid ART initiation and loss to clinic among patients initiating ART after Treat All implementation

• *H2: Loss to clinic will be higher among those who initiated ART on the same day as enrollment compared to those who initiated ART after the day of enrollment;*

• *H3: Loss to clinic will be higher among those who initiated ART within 7 days of diagnosis compared to those who initiated ART >7 days after enrollment*

Aim 3: To describe the association between same-day and rapid ART initiation and viral suppression at 6 months after ART initiation among patients retained in HIV care.

• *H4: 6-month viral suppression will be higher among those who initiated ART within 7 days of diagnosis (including on the same day as diagnosis) compared to those who initiated ART >7 days*

**** NOTE: Not all patients will have available data for date of diagnosis, and the quality of these data may not be high. If there are not sufficient nor sufficiently high-quality data for date of diagnosis, we will conduct the above analyses examining time from enrollment in HIV care to ART initiation ****

Study Population and Inclusion/Exclusion Criteria

All patients at health centers affiliated with Central-, East-, Southern- and West-Africa IeDEA who: (1) are ≥15 years old, (2) are HIV-infected, (3) initiated ART (ART initiation date available in dataset); (4) have an HIV diagnosis date available in the dataset*, (5) were diagnosed with HIV on/after

date of Treat All implementation, (6) have at least 12 months of potential follow-up time following date of HIV diagnosis

**as noted above, if data quality for HIV diagnosis date is poor, we will use enrollment date instea*d

Key variables and definitions

OUTCOMES

• **Loss to clinic**, defined as no contact with health center for 120 days

• **Viral suppression**¸ defined as VL < 200 on the last viral load performed within 1 year after ART initiation

We will consider VL suppression as the last VL performed to account for the fact that patients whose first VL was not suppressed may have a second VL performed within a relatively short time after the first VL to assess whether clinical changes have resulted in VL suppression

PRIMARY EXPOSURE OF INTEREST

• **Time to ART initiation** – we will examine ART initiation time based on diagnosis (or enrollment) and ART initiation dates, categorized as:

1. ART initiation on the same day as diagnosis (or enrollment) date (Same Day ART)
2. ART initiation between 1 and 7 days after diagnosis (or enrollment) date (Rapid ART)
3. ART initiation between 8 and 30 days after diagnosis (or enrollment) date
4. ART initiation >30 days after diagnosis (or enrollment) date

OTHER VARIABLES OF INTEREST

- Year of enrollment
- Method of enrollment (VCT, PMTCT, TB, etc)
- Age at enrollment
- Sex (female/male)
- BMI (m/kg2)
- Pregnant at enrollment (yes/no)
- Baseline WHO stage (I-IV, missing)
- Baseline TB status (active infection: yes/no)
- Baseline CD4 count (<200, 200-349, 350-499, ≥500 cells/µl, missing)
- ART regimen, clinic and pharmacy visit dates.

Study Design, Methods and Planned Statistical Analyses

This will be a cohort study of data from patients newly diagnosed with HIV in health centers from the 4 Africa regional IeDEA cohorts.

Same-day or rapid ART initiation

	• Among newly enrolled patients meeting inclusion criteria, we will conduct a logistic regression analysis to determine predictors of same-day ART initiation (yes vs. no) and rapid ART initiation (yes vs. no) • We will first describe proportions of patients who: a) started ART on the same day as diagnosis (or enrollment), b) started ART between 1-7 days after diagnosis (or enrollment), c) started ART between 8-30 days after diagnosis (or enrollment), d) started ART >30 days after diagnosis (or enrollment). • We will develop bivariate and multivariate logistic regression models to identify predictors of same-day and rapid ART initiation. **Loss to clinic** • Among newly enrolled patients meeting inclusion criteria (defined in section 3), we will conduct a time to event analysis to determine the association between rapid ART initiation and loss to clinic (defined as >120 days between last health center appointment and censoring date). • We will first conduct descriptive statistics of baseline characteristics. • We will conduct Kaplan-Meier analyses to compare the proportion of patients "surviving" (not lost to care) by whether or not they initiated ART rapidly. • We will then use multivariable Cox proportional hazard models to determine the relative hazard of loss to care controlling for baseline characteristics. • We will test for interactions between the exposure of interest and other independent variables (including sex, age and baseline clinical status) and stratify analyses as appropriate. • If a large proportion of patients have no follow-up data (i.e., never returned after initial visit), we will consider the following methods to address this problem: 1. Assign a value of 1 day of follow-up time to these patients such that we will be able to include them in time-to-event analyses; 2. Limit time-to-event analyses to patients who had at least 1 follow-up visit **Viral suppression** • Among newly enrolled patients meeting inclusion criteria, and who have had ≥1 viral load measured within 1 year after ART initiation, we will conduct a log binomial regression analysis to determine association between same-day or rapid ART initiation and viral suppression • We will first present descriptive statistics • We will conduct bivariate and multivariate log binomial models to determine probability of viral suppression • We will test for interactions between the exposure of interest and other independent variables (including sex, age and baseline clinical status) and stratify analyses as appropriate.

	References 1. Koenig S, et al. Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: A randomized unblinded trial. PLoS Med. 2017 Jul 25;14(7):e1002357 2. Bacon O, et al. THE RAPID ART PROGRAM INITIATIVE FOR HIV DIAGNOSES (RAPID) IN SAN FRANCISCO. Presented at CROI 2019. 3. Pilcher CD, et al. The Effect of Same-Day Observed Initiation of Antiretroviral Therapy on HIV Viral Load and Treatment Outcomes in a US Public Health Setting. J Acquir Immune Defic Syndr. 2017 Jan 1;74(1):44-51. 4. Rosen S, et al. Initiating Antiretroviral Therapy for HIV at a Patient's First Clinic Visit: The RapIT Randomized Controlled Trial. PLoS Med. 2016 May 10;13(5):e1002015. 5. Colasanti J, et al. Implementation of a Rapid Entry Program Decreases Time to Viral Suppression Among Vulnerable Persons Living With HIV in the Southern United States. Open Forum Infect Dis. 2018 Jun 28;5(6):ofy104. 6. Puttkammer N, et al. OUTCOMES OF 'TEST AND START" AT SCALE WITHIN HAITI'S NATIONAL ART PROGRAM. Presented at CROI 2019. 7. Tymejczyk O, et al. Rapid HIV treatment initiation increases after national Treat All policy adoption in six sub-saharan African countries: regression discontinuity analysis. Plos Medicine 16(6):e1002822. 8. Ross J, et al. Early outcomes after implementation of treat all in Rwanda: an interrupted time series study. J Int AIDS Soc. 2019 Apr 16; 22(4); e25279
Ethics:	x This concept uses only the IeDEA standard dataset and is covered by the core IeDEA ethics approvals. ☐ This concept requires additional collection of health-related data, measurements or tests, or sampling of biological material not included in the IeDEA standard dataset. Additional ethics approval is required. ☐ This concept does not fall into either ethics category above. *Describe*:
Dataset:	x This concept requires new patient-level datasets. ☐ This concept uses existing patient-level datasets submitted for a previous concept: *Concept title:* *Concept number*: MR_____ ☐ This concept uses IeDEA Site Assessment or other IeDEA survey data. ☐ This concept does not use any IeDEA data (e.g., viewpoint paper).
Target journal(s):	*To be determined*
Milestones:	Circulation of concept sheet: <date> Circulation of draft paper: <date> Submission to target journal: <date>