SCHARP
Statistical Center for HIV/AIDS Research and Prevention

STATISTICAL ANALYSIS PLAN FOR HVTN SAFETY

Protocol HVTN 804/HPTN 095(v3.0)

Antiretroviral analytical treatment interruption (ATI) to assess immunologic and virologic responses in participants who received VRC01 or placebo and became HIV-infected during HVTN 704/HPTN 085

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Statistical Analysis Plan for Safety

Protocol: HVTN 805/ HPTN 095 (v3.0)

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SAP Modification History

The version history of, and modifications to, this statistical analysis plan are described below.

SAP Version	Modification
1.0	Initial
2.0	Update include: • Use latest HVTN Safety SAP template. • Add additional analysis for FSR

Table of Contents

1 LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse Experience
EAE	Expedited Adverse Experience
FSR	Final Study Report
RSC	Regulatory Support Center
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STI	Sexually Transmitted Infection
DSMB	Data Safety Monitoring Board

2 OVERVIEW

The following describes the Statistical Analysis Plan (SAP) for the analysis of safety data from HVTN 804/HPTN 095 for Data Safety Monitoring Board (DSMB) reports and the Final Study Report (FSR) for Safety.

3 PROTOCOL SUMMARY

Full title: Antiretroviral analytical treatment interruption (ATI) to assess immunologic and virologic responses in participants who received VRC01 or placebo and became HIV-infected during HVTN 704/HPTN 085

Short title: HVTN 804/HPTN 095

Sponsor: NIAID Division of AIDS

Conducted by: HIV Vaccine Trials Network (HVTN) and HIV Prevention Trials Network (HPTN)

Protocol chairs: Shelly Karuna, MD, MPH; Katharine Bar, MD

Sample size: 16 – 46

Study population: HIV-1–infected HVTN 704/HPTN 085 participants who met criteria for transition to Schedule 2 or Schedule 3 in that trial

Study design: An exploratory study of HIV-infected participants undergoing an analytical treatment interruption after receiving VRC01 or placebo infusions in HVTN 704/HPTN 085. The study schema is provided in Appendix I.

Study duration: Study duration is potentially indefinite for a participant maintaining extreme and extended viral control during ATI. Study duration for most participants is expected to be 13-18 months. The maximum anticipated duration for any participant is expected to be approximately 2½ to 3 years.

Study products: None. Drugs for anti-retroviral therapy (ART) and for pre-exposure prophylaxis (PrEP) will not be provided by the study or paid for using sponsor funds. Procedures for accessing external funding sources for PrEP and ART provision are detailed in the HVTN 804/HPTN 095 Study Specific Procedures (SSP).

4 HYPOTHESIS

4.1 Primary hypothesis

- *VRC01 recipients who became HIV-infected during HVTN 704/HPTN 085 within 8 weeks of their last study product administration will suppress plasma viremia and maintain CD4+ T-cell counts longer during ATI than placebo recipients who became HIV-infected during HVTN 704/HPTN 085.*
- *ATI will be safe and well-tolerated in individuals who became HIV-infected in HVTN 704/HPTN 085*

4.2 Secondary hypothesis

- *VRC01 recipients who became HIV-infected during HVTN 704/HPTN 085 within 8 weeks of their last study product administration will have enhanced cellular and humoral responses compared to placebo recipients who became HIV-infected during HVTN 704/HPTN 085.*
- *VRC01 recipients who became HIV-infected during HVTN 704/HPTN 085 within 8 weeks of their last study product administration will have more limited viral reservoirs, before and after ATI, than placebo recipients who became HIV-infected during HVTN 704/HPTN 085.*

5 SAFETY/VIROLOGIC(?) OBJECTIVES AND ENDPOINTS

Primary objective 1

- *To evaluate the effect of VRC01 received in the immediate pre-HIV acquisition period and/or during early infection on the time to meeting ART re-initiation criteria in participants undergoing ATI*

Primary endpoint 1

- *Time to meeting criteria for ART re-initiation*
- *Frequency of sustained post-treatment HIV control, defined as ≥ 24 weeks off ART without meeting ART re-initiation criteria*

Primary objective 2

- *To evaluate the safety of ATI among HVTN 804/HPTN 095 participants*

Primary endpoint 2

- *Laboratory measures of safety, adverse events (AEs), SAEs (serious AEs), and rates of discontinuation*

Secondary objective 2

- *To evaluate the effect of VRC01 received in the immediate pre-HIV acquisition period and/or during early infection on viral load in participants undergoing ATI*

Secondary endpoint 2

- *Cumulative incidence of participants with viral load ≥ 200 at weeks 8, 16, and 24*

Secondary objective 3

- *To evaluate the effect of VRC01 received in the immediate pre-HIV acquisition period and/or during early infection on HIV reservoir size before and after ATI, and whether HIV reservoir measurements are associated with time to meeting criteria for ART re-initiation in participants undergoing ATI*

Secondary endpoint 3

- *Frequency of CD4+ T cells carrying intact and/or total pro-viral HIV DNA, replication competent virus, and/or cell-associated HIV RNA*

6 COHORT DEFINITION

Participants for this trial will be recruited from among former HVTN 704/HPTN 085 (NCT02716675) study participants who met criteria for transition to Schedule 2 or Schedule 3 in that study and who meet the inclusion/exclusion criteria that are specified in protocol section 5.

7 RANDOMIZATION

This study is not randomized. Outcomes will be compared using randomized treatment assignment from HVTN 704/HPTN 085.

8 BLINDING

Although this study is not randomized, and study product is not administered, precautions have been taken to protect the integrity of the ongoing HVTN 704/HPTN 085 study.

Participants eligible for screening and enrollment into this study are a subset of all HVTN 704/HPTN 085 HIV-infected participants. Participant recruitment lists are restricted to study staff who already have knowledge of HVTN 704/HPTN 085 HIV-infected participants (details in the HVTN 804/HPTN 095 SSP). HVTN 704/HPTN 085 participant identifiers were masked in this study's database until HVTN 704/HPTN 085 was fully completed and unblinded. Unlike other HVTN studies in which enrollment data is available to all HVTN members, enrollment data for this study are restricted to study team members.

9 SAMPLE SIZE

We calculate the expected trial sized under different scenarios for the percentage of enrolled participants out of the total number of endpoint infected cases from HVTN 704/HPTN 085; scenarios include 25%, 50%, and 75%. Eligible placebo recipients will be capped such that the overall placebo to VRC01 recipient ratio of enrolled participants is at most approximately 1:1. Given that the parent HVTN 704/HPTN 085 study was randomized at a 1:2 placebo to VRC01 ratio, we would only expect to cap the number of eligible placebo recipients if prevention efficacy (PE) exceeds 50%. Given this constraint, along with an assumption of a common prevention efficacy at each dose (PE10 and PE30), the expected trial size will depend on different levels of PE. Under the null hypothesis (PE10 = PE30 = 0%), the total expected number of endpoint infections among placebo recipients is 26 and VRC01 recipients is 55 (Table 4-3 in the parent protocol HVTN 704/HPTN 085); therefore, we assume a trial size of 7, 13 or 20 placebo recipients and 14, 28, or 41 VRC01 recipients depending on the enrollment ratio. Under the alternative hypothesis (PE10 = PE30 = 60%), the total expected number of endpoint infections among placebo recipients is 37 and VRC01 recipients is 30 (Table 4-3 in the parent protocol); therefore, under the different enrollment ratio scenarios, we assume a trial size of 8, 15, or 23 placebo recipients and an equal number of VRC01 recipients so as not to exceed a 1:1 ratio. These six sample size scenarios represent estimated upper and lower bounds for sample size

given the expected number of endpoint infections under the null and alternative hypotheses respectively, as well as various scenarios for the percentage of eligible participants who will ultimately enroll in HVTN 804/HPTN 095.

Sample size considerations for time to ART re-initiation criteria (primary objective 1)

Using data from the placebo arm of a therapeutic vaccine study which enrolled early treated patients (80), we modeled the time T (in weeks) to meet re-initiation criteria as a Weibull distribution with survival function $P(T > t) = \exp[-(\lambda t)p]$, where $\lambda = \exp(-2.932) = 0.053$ and $p = 2.014$. From these parameters, we estimated the median time to meet re-initiation criteria as 15.6 weeks in the AMP placebo recipients. We can express the treatment effect in terms of either the hazard ratio θ or the factor β by which treatment increases the median time to meet re-initiation criteria; β and θ are related by $\beta = \theta^{1/p}$.

We model censoring of time to re-initiation criteria using an exponential model and a maximum follow-up time of 72 weeks, where follow-up is censored at a rate of 20% per year due to either study termination or re-initiation of ART before reaching the re-initiation criteria. Simulating 10,000 trials based on these models of time to re-initiation criteria and censoring, we computed power using a log rank test with alpha equal to 0.05. Power for a 40%, 50%, 60%, and 70% reduction in hazard under different enrollment rate and prevention efficacy scenarios are shown in Table 4-1. These hazard reductions correspond to 29%, 41%, 58%, and 82% increases in the median time to meet re-initiation criteria. Therefore, if VRC01 increases the median time to re-initiation criteria 58% and the enrollment rate is 50%, then under the parent study null hypothesis power to detect a difference in time to re-initiation criteria is 72% while under the alternative hypothesis power is 62%.

Table 4-1 Power under different prevention efficacy results, different enrollment rates and different treatment effects, expressed as either reduction in hazard or percent increase in median time to meet re-initiation criteria

		Null hypothesis			Alternative hypothesis		
Enrollment Rate		25%	50%	75%	25%	50%	75%
Expected number of placebos		7	13	20	8	15	23
Expected number of VRC01		14	28	41	8	15	23
Reduction in hazard	% Increase in median time to meet re-initiation criteria						
40%	29%	20%	32%	44%	16%	26%	37%
50%	41%	31%	50%	67%	24%	42%	58%
60%	58%	46%	72%	89%	36%	62%	81%
70%	82%	65%	91%	98%	54%	83%	96%

Sample size considerations for safety (primary objective 2)

The goal of the safety evaluation for this study is to identify safety concerns associated with ATI. The ability of the study to detect serious adverse events (SAEs) (see protocol Section 4.2.4.1) can be expressed by the true event rate above which at least 1 SAE would likely be observed and the true event rate below which no events would likely be observed. Under the enrollment rate and PE scenarios described in protocol Section 4.1, Table 4-2 shows the true event rate such that there is a 90% chance of observing at least 1 event (or no events) among three groups; 1) the placebo recipients only, 2) the VRC01 recipients only, or 3) all enrolled participants.

Table 4-2 True event rates above which at least 1 SAE (or below which no events) would likely be observed in a group of size *n* participants. Event rates are computed separately for various values of *n* given by the range and midpoint for the estimated number of participants among 3 groups; 1) the placebo recipients only, 2) the VRC01 recipients only, or 3) all enrolled participant based on the enrollment scenarios described in Section 4.1.

	Placebo recipients			VRC01 recipients			All enrolled		
n	7	15	23	8	25	49	16	38	61
At least 1 event	28.0%	14.2%	9.5%	25.0%	8.8%	4.6%	13.4%	5.9%	3.7%
No events	1.5%	0.7%	0.5%	1.3%	0.4%	0.2%	0.7%	0.3%	0.2%

10 STATISTICAL ANALYSIS

Analyses for primary endpoints will be performed using SAS and R. All other descriptive and inferential statistical analyses will be performed using SAS, StatXact, or R statistical software.

No formal multiple comparison adjustments will be employed for multiple safety endpoints or secondary endpoints. However, multiplicity adjustments will be made for certain laboratory assays, as discussed below, when the assay endpoint is viewed as a collection of hypotheses (eg, testing multiple peptide pools to determine a positive response).

10.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, and laboratory outcomes for primary- and secondary-objective analyses.

10.2 Baseline comparability

Groups defined by the parent protocol treatment arms will be compared for baseline participant characteristics using descriptive statistics.

10.3 Primary virologic analysis

In this study we condition on HIV-infection with the intention of comparing virologic outcomes by randomized treatment assignment from HVTN 704/HPTN 085. Since we are conditioning on a postrandomization event, HIV-infection, a two-sample test for a difference in outcome is subject to postrandomization selection bias. A direct comparison of virologic outcomes between treatment groups, which measures the "net treatment effect," does not have a causal interpretation (1). As an example of the type of bias that can occur, suppose VRC01 protects against mild viruses but is not effective against virulent viruses. If this were true, we might see longer time to re-initiation criteria in VRC01 recipients than placebo recipients whereas, if we restricted only to those participants infected with a virulent HIV strain, we might see shorter time to re-initiation criteria in the VRC01 group. Therefore, a two - sample test comparing time to re-initiation criteria between treatment groups could give a misleading impression that VRC01 shortens viral suppression time during ATI while the causal interpretation of this hypothetical example would be that for virulent viruses, VRC01 increases viral suppression time during ATI compared to placebo.

Approaches will be taken to ensure robust and unbiased results. Implementation of targeted minimum loss-based estimation (TMLE) methods, used to address the objectives in the following sections, will be fully prespecified in the statistical analysis plan (SAP) to ensure objective and reproducible inference.

Each analysis will be done pooling the VRC01 recipients versus placebo recipients with supplemental analyses done separately for each dose group versus the placebo recipients.

10.3.1 Time to ART re-initiation

The primary outcome is the time from the start of treatment interruption until the participant meets criteria to re-initiate ART.

A Cox proportional hazards model with the indicator of assignment to a mAb group versus the control group will be used to estimate the cumulative incidence in each of the infected VRC01 and infected placebo groups, as well as the hazard ratio, all with 95% confidence intervals and associated 2-sided p-values, where the model controls for baseline covariates thought to potentially predict both HIV-1 infection and the instantaneous hazard of meeting the ART re-initiation criteria. This is needed for controlling for potential postrandomization selection bias given that analyzed treatment groups are selected postrandomization. Plots of the estimated cumulative incidence will be shown by treatment group.

As a supportive analysis of this hypothesis, targeted minimum loss-based estimation (TMLE) may be used to estimate cumulative incidences of the primary efficacy endpoint over time for the pooled mAb arm and the control arm. Iterative mean-based TMLE is used for this analysis as described by Benkeser et al (2). The Super Learner (3) is used to generate initial estimates of the conditional censoring distribution and the iterated conditional means. This analysis will use TMLE as implemented in the R package survtmle available on CRAN (4).

10.3.2 Frequency of sustained post-treatment HIV control

The same covariate adjusted model used to estimate cumulative incidence of meeting the re-initiation criteria for ART over time, described in the previous section, will be used to compare the rates of failure to maintain HIV control at 24 weeks between the two treatment groups.

10.3.3 Time to viral load ≥*200*

Secondary endpoint 2 is time until the participant has a viral load ≥ 200. The same methodology used to assess time to ART re-initiation criteria will be used for this endpoint. In this analysis we will compare cumulative incidence at week 8 in each of the infected VRC01 and infected placebo groups supplemented by a sensitivity analysis based on cumulative incidence at weeks 8, 16, and 24.

10.4 Primary safety analysis

10.4.1 AE and SAEs

AEs will be summarized using MedDRA System Organ Class and preferred terms. Tables will show by treatment arm the number and percentage of participants experiencing an AE within a System Organ Class or within preferred term category by severity or by relationship to treatment interruption. For the calculations in these tables, a participant with multiple AEs within a category will be counted once under the maximum severity or the strongest recorded causal relationship to treatment interruption. Formal statistical testing comparing arms is not planned since interpretation of differences must rely heavily upon clinical judgment.

10.4.2 Local laboratory values

Box plots of local laboratory values will be generated for baseline values and for values measured during the course of the study by treatment arm and visit. Each box plot will show the first quartile, the median, and the third quartile. Outliers (values outside the box plot) will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

For each local laboratory measure, summary statistics will be presented by treatment arm and timepoint, as well as changes from baseline for postenrollment values. In addition, the number (percentage) of participants with local laboratory values recorded as meeting Grade 2 AE criteria or above as specified in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events will be tabulated by treatment arm for each timepoint after initiation of treatment interruption. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

10.4.3 Reasons for discontinuation of ATI and early study termination

The number and percentage of participants who discontinue ATI and who terminate the study early will be tabulated by reason and treatment arm.

10.5 Secondary analyses of immune responses and reservoir measurement

Analyses of immune responses and reservoir measurements will be descriptive using appropriate plotting techniques for describing measurements at a fixed time point (eg, boxplots and barplots) or longitudinally (eg, spaghetti plots) separately by treatment group. In addition, if enough samples are assayed we plan to do inferential and descriptive analyses as described in the following sections.

10.5.1 Evaluate the difference in anti-HIV immune responses or reservoir size between VRC01 and placebo recipient

TMLE will be used to estimate mean endpoints in each of the infected VRC01 and infected placebo groups, as well as the mean difference, all with 95% confidence intervals and associated 2-sided p-values, where the TMLE controls for all baseline covariates thought to potentially predict both HIV-1 infection and one of the secondary endpoints under study. This is needed for controlling for potential postrandomization selection bias given that analyzed treatment groups are selected postrandomization.

10.5.2 Assess whether anti-HIV immune responses or reservoir size are associated with time to meeting ART re-initiation criteria

Cox regression will be used to estimate cumulative incidence over time for groups defined by levels of immune response or reservoir size for each treatment group

11 SAFETY TABLES, PARTICIPANT LISTINGS, AND FIGURES

Approximately 6 months after enrollment of the first participant or after the 10th participant has completed 12 weeks of ATI (whichever comes first), an interim review of the study will occur. The Data Safety Monitoring Board (DSMB) will review accrual; retention; AE summaries, including all reported AEs ≥ Grade 3 and all STIs; summaries of the time to meeting ART re-initiation criteria; and longitudinal summaries of HIV-1 RNA and CD4+ T-cell count. Subsequent DSMB reviews will occur at least annually while participants remain on study. A DSMB may also be convened if a reason is identified by the DAIDS MO, study Co-chairs, or study statisticians in consultation with the HVTN 804/HPTN 095 Protocol Team leadership.

The following tables and figures will be presented to the DSMB and or FSR for safety.

11.1 List of Tables and Listings

The following tables are included in the DSMB reports and FSR for Safety:

- Enrollment by study site
- Baseline participant characteristics
- Study status and reasons for early termination
- Visit retention, Schedule 1
- Visit retention, Schedule 2
- Visit retention, Schedule 3
- Reasons for meeting ART re-initiation criteria
- Summary of time to meeting ART re-initiation criteria
- Turnaround times for ART Re-Initiation
- SAE listing
- STI listing
- Grade 1-5 Adverse Events by System Organ Class, Ordered by Decreasing Frequency
- Grade 3+ Adverse Events by System Organ Class, High Level Term, and Severity
- Grade 1-5 Adverse Events Related to ATI by System Organ Class, High Level Term, and Severity

Additional tables include in the FSR for Safety:

- Local Lab Value Summary Statistics
- Local Laboratory Values Meeting Grade 2 AE Criteria or Above

11.2 List of Figures

These graphs are included in the DSMB reports and FSR for Safety:

- Longitudinal Summaries of HIV-1 RNA Viral Load and CD4+ T-Cell Count (participant level) – all participants
- Longitudinal Summaries of HIV-1 RNA Viral Load and CD4+ T-Cell Count, restricted to participants who entered schedule 2 and to schedule 1 and 2 data points
- Cumulative Incidence of Meeting ART Re-Initiation Criteria
- Survival Plot of Time to Viral Load $\geq$ 200 (copies/ml)

Additional graphs included in FSR for Safety:

- Boxplots for local laboratory value (ALT, Direct Bilirubin, eGFR, Hemoglobin, Platelets, Absolute Neutrophil Count) at schedule 1 (visit 4, 8, 12, 14, 16, 18, 20, 21, 22, 23, 25, 27), schedule 2 (visit 40, 44, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66), and schedule 3 (82, 84, 86, 89, 91)

12 REFERENCES

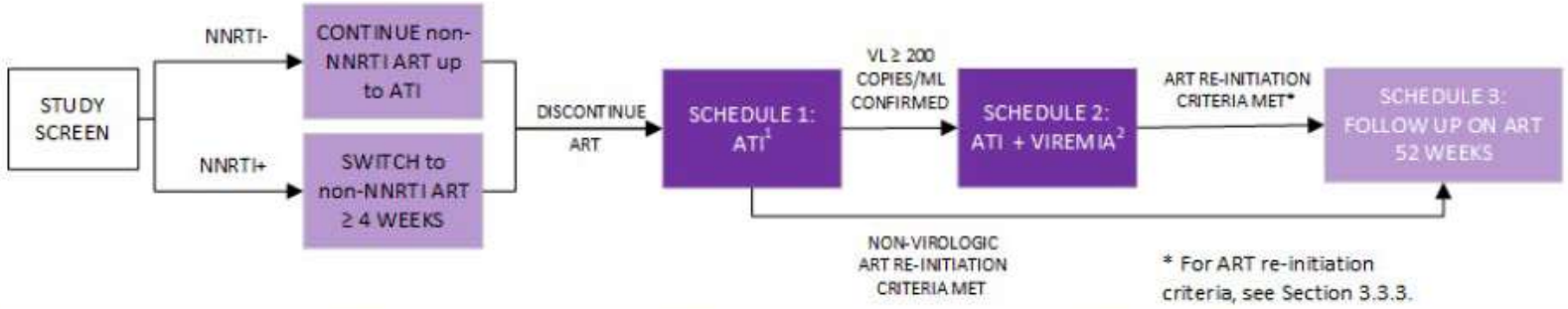
1. Gilbert PB, Bosch RJ, Hudgens MG. Sensitivity analysis for the assessment of causal vaccine effects on viral load in HIV vaccine trials. Biometrics. 2003;59(3):531-41.

2. Benkeser D, Carone M, Gilbert PB. Improved estimation of the cumulative incidence of rare outcomes. Stat Med. 2018;37(2):280-93.

3. van der Laan MJ, Polley EC, Hubbard AE. Super learner. Stat Appl Genet Mol Biol. 2007;6:Article25.

4. Benkeser D, Hejazi N. survtmle: Compute Targeted Minimum Loss-Based Estimates in Right-Censored Survival Settings [R package]. 2018 [Available from: https://cran.r-project.org/web/packages/survtmle/index.html]

Appendix I: Schema



			SCHEDULE 1			SCHEDULE 2				SCHEDULE 3		
	SCREEN	PRE-DISCONTINUE ART	ATI WEEKS 0-8	ATI WEEKS 10-24	ATI WEEKS 28-52[1]	ATI + Viremia WEEKS 0-8	ATI + Viremia WEEKS 10-36	ATI + Viremia WEEKS 40-52[2]	PRE-REINITIATE ART	FOLLOW UP ON ART WEEKS 0-12	FOLLOW UP ON ART WEEKS 12-28	FOLLOW UP ON ART WEEKS 40-52
Plasma HIV RNA	√	√	WEEKLY	Q2 WEEKS	Q4 WEEKS	WEEKLY	Q2 WEEKS[3]	Q4 WEEKS	√	Q2 WEEKS	Q4 WEEKS	Q12 WEEKS
CD4+ & CD8+ T cell counts	√	√	Q2 WEEKS	Q4 WEEKS	Q8 WEEKS	Q2 WEEKS	Q4 WEEKS[4]	Q8 WEEKS	√	Q4 WEEKS	Q8 WEEKS	Q12 WEEKS
Hematology & Chemistries	√	√	Q4 WEEKS		Q8 WEEKS	Q4 WEEKS		Q8 WEEKS	–	Q4 WEEKS	Q12 WEEKS	Q12 WEEKS

[1] QUARTERLY FOLLOW-UP VISITS MAY CONTINUE BEYOND WEEK 52 FOR PARTICIPANTS WHO DO NOT MEET CRITERIA FOR TRANSITION TO SCHEDULE 2.
[2] QUARTERLY FOLLOW-UP VISITS MAY CONTINUE BEYOND WEEK 52 FOR PARTICIPANTS WHO DO NOT MEET CRITERIA FOR ART RE-INITIATION.
[3] OR WEEKLY FOR WEEKS 10-24, IF VL ≥ 200 copies/mL
[4] OR Q2 WEEKS FOR WEEKS 10-24 IF VL ≥ 200 copies/mL