Intra-Cluster Correlation Estimates for HIV-related Outcomes from Care and Treatment Clinics in Dar es Salaam, Tanzania

Dale Barnhart[1], **Ellen Hertzmark**[1], **Enju Liu**[3], **Ester Mungure**[3], **Aisa N. Muya**[6], **David Sando**[3,6], **Guerino Chalamilla**[6,*], **Nzovu Ulenga**[4,6], **Till Bärnighausen**[3,7], **Wafaie Fawzi**[1,3,5], and **Donna Spiegelman**[1,2]

Dale Barnhart: dab000@mail.harvard.edu; Ellen Hertzmark: stleh@channing.harvard.edu; Enju Liu: stliu@channing.harvard.edu; Ester Mungure: stemm@channing.harvard.edu; Aisa N. Muya: aisamuya@gmail.com; David Sando: dsando.tz@gmail.com; Nzovu Ulenga: nulenga@mdh-tz.org; Till Bärnighausen: tbaernig@hsph.harvard.edu; Wafaie Fawzi: mina@hsph.harvard.edu; Donna Spiegelman: stdls@hsph.harvard.edu

[1]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Huntington Avenue, Boston, Massachusetts 02115, USA

[2]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Huntington Avenue, Boston, Massachusetts 02115, USA

[3]Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Huntington Avenue, Boston, Massachusetts 02115, USA

[4]Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Huntington Avenue, Boston, Massachusetts 02115, USA

[5]Department of Nutrition, Harvard T.H. Chan School of Public Health, Huntington Avenue, Boston, Massachusetts 02115, USA

[6]Management and Development of Health, Mwai Kibaki Road, Dar es Salaam, Tanzania

[7]Wellcome Trust Africa Centre for Population Health, A2074 Road, Mtubatuba, KwaZulu-Natal 3935, South Africa

Abstract

Introduction—Researchers planning cluster-randomized controlled trials (cRCTs) require estimates of the intra-cluster correlation coefficient (ICC) from previous studies for sample size calculations. This paper fills a persistent gap in the literature by providing estimates of ICCs for many key HIV-related clinical outcomes.

Please send direct correspondence to: Dale Barnhart, dab000@mail.harvard.edu, 677 Huntington Avenue, Kresge Building, 9th Floor, Boston, MA 02115.
*Deceased

Methods—Data from HIV-positive patients from 47 HIV care and treatment clinics in Dar es Salaam, Tanzania were used to calculate ICCs by site of enrollment or site of ART initiation for various clinical outcomes using cross-sectional and longitudinal data. ICCs were estimated using linear mixed models where either clinic of enrollment or clinic of ART initiation served as the random effect.

Results—ICCs ranged from 0 to 0.0706 (95% CI: 0.0447, 0.1098). For most outcomes, the ICCs were large enough to meaningfully affect sample size calculations. For binary outcomes, the ICCs for event prevalence at baseline tended to be larger than the ICCs for later cumulative incidences. For continuous outcomes, the ICCs for baseline values tended to be larger than the ICCs for the change in values from baseline.

Conclusion—The ICCs for HIV-related outcomes cannot be ignored when calculating sample sizes for future cluster-randomized trials. The differences between ICCs calculated from baseline data alone and ICCs calculated using longitudinal data demonstrate the importance of selecting an ICC that reflects a study's intended design and duration for sample size calculations. While not generalizable to all contexts, these estimates provide guidance for future researchers seeking to design adequately powered cRCTs in Sub-Saharan African HIV treatment and care clinics.

Keywords

Intra-cluster Correlation Coefficient; HIV Infections; Multicenter Studies; Cluster Randomized Controlled; Sample Size

Introduction[1]

HIV treatment programs in sub-Saharan Africa currently deliver antiretroviral treatment (ART) and pre-ART care to millions of patients (1). However, the long-term success of HIV treatment programs depends on identifying models of treatment delivery that provide quality care at a low cost. For many of the most important aspects of HIV treatment delivery, the smallest unit which allows variation in delivery approaches is the treatment facility. For instance, health systems integration, health worker team composition, and location of treatment are inherent characteristics of facilities that cannot be varied at the level of individual patients. Many other factors, such monitoring and screening approaches, which theoretically could be varied at the level of the patient, will be impractical or impossible to vary within a facility for managerial or political reasons. Because treatment facility is often the smallest unit that allows for randomization, cluster randomized controlled trials (cRCTs) have become a methodological mainstay for HIV treatment implementation research, as evidenced by their use in trials investigating testing and counseling (2), treatment as prevention (3, 4), provision of care by peer health workers (5, 6) and tuberculosis prevention (7).

Unlike traditional randomized trials, cRCTs randomize entire pre-existing groups, such as health centers or neighborhoods, to different study arms. cRCTs are advantageous when interventions are naturally implemented at the group level, when denying some group

[1]**Abbreviations:** ART: antiretroviral treatment; CTC: care and treatment clinics; ICC: intra-cluster correlation coefficient; MDH: Management and Development for Health; PEPFAR: US President's Emergency Plan for AIDS Relief;

members access to the intervention would be challenging or unacceptable, or to minimize contamination of study arms (8–10). However, combining group-level randomization with individual-level analysis creates challenges for study design. Because subjects from the same cluster often share characteristics such as beliefs, behaviors, or environments, their outcomes are often correlated. Consequently, each subject in a cRCT provides less independent information than a subject in a comparable individually randomized trial. In the analysis phase, ignoring the correlation between cluster members will increase the type-I error rate. However, if the correlation between cluster members is accounted for in the analysis phase but ignored during the design phase, sample size calculations will underestimate the true number of subjects required to adequately power the cRCT, increasing the type-II error rate. (11–13).

Researchers commonly adjust for this correlation by multiplying the sample size required for a comparable individually randomized trial by the "Design Effect," also known as the "Variance Inflation Factor." The Design Effect is a function of the number of individuals per cluster, m, and the intra-cluster correlation coefficient (ICC), a parameter that describes the proportion of the total variation in outcomes that is due to variation between clusters (9).

$$Design\ Effect = 1 + (m - 1) * ICC$$

Typically, researchers designing cRCTs rely on previously published ICCs for their sample size calculations. However, because ICCs depend on a study's outcome, design, analytic plan, and population, researchers often struggle to find published ICCs that apply to their study (14). Despite calls for increased publications of ICCs for a range of outcomes, (15) fewer than 20% of both health-related and HIV-related cRCTs report their ICCs (16, 17).

Only three previous studies have attempted to fill this gap by reporting ICCs for a range of HIV-related outcomes. Of these studies, two focused on sexual attitudes and behaviors among adolescents and young adults in the United States (18, 19). One study calculated ICCs for outcomes among people living with HIV, but included only a limited number of clinical outcomes and calculated ICCs using baseline data alone, which is applicable to future cross-sectional studies but not necessarily prospective studies (20). This paper aims to provide estimates of the ICC for HIV-related clinical outcomes calculated both cross-sectionally and longitudinally among clinics supporting patients enrolled in a large urban HIV care and treatment program in Dar es Salaam, Tanzania.

Methods

Study Population

Data were obtained from an ongoing cohort of HIV-infected adult patients (>15 years old) from 47 HIV care and treatment clinics (CTCs) in Dar es Salaam, Tanzania (21). These clinics are supported by the local NGO, Management and Development for Health (MDH), with additional support from the President's Emergency Plan for AIDS Relief (PEPFAR) and a longstanding collaborative relationship with the Harvard T.H. Chan School of Public Health. All adult patients with data on their site of enrollment or site at the time of ART

initiation who were enrolled between October 2004 and September 2012 were eligible for inclusion in the study. Only ART-initiated patients were considered when calculating ICCs for ART non-adherence, immunologic failure endpoints, elevated alanine transaminase (ALT) levels, and weight loss after ART initiation. Pregnant women were excluded when calculating ICCs for anemia, weight-related outcomes, and plasma lipid level outcomes. Patients who received tuberculosis treatment, had severe anemia, or were overweight or obese at enrollment, as well as patients who had elevated ALT levels at ART initiation were excluded when calculating cumulative incidences for these outcomes. The study was approved by institutional review boards for human research at the Muhimbili University of Health and Allied Sciences and the Harvard T.H. Chan School of Public Health.

Data Collection

Outcomes included in this paper had been previously studied in this cohort, and data collection methods are described in detail elsewhere (21–28). Briefly, patients received treatment according to Tanzanian National and World Health Organization guidelines (29, 30). ART-eligible patients returned for monthly visits while ART-ineligible patients returned for care and monitoring visits every 4 months. A comprehensive patient tracking system ensured that patients could be encouraged to return to the clinic as needed.

At each visit, health care providers completed standardized forms including demographic, clinical, laboratory, and therapeutic information. Data reviewers at each clinic ensured that data recorded by healthcare workers were accurate and complete, and professional data entry clerks entered these data into a secure computerized database daily. A data management team performed weekly quality assurance checks.

Study variables

Data on deaths were obtained through notification by family, friends, or community-based patient tracking teams. If the death date was unknown but the patient was known to have died, the date of the last clinical visit was used as the death date. Loss to follow up was defined as having no clinic visits for >6 months from the date of file closing among patients not initiated on ART or as having no clinic visits or ART refills for >3 months from the date of file closing among ART-initiated patients. Any patients prescribed anti-tuberculosis medications within the first 30 days of enrollment were considered to have prevalent tuberculosis at enrollment. Incident tuberculosis was defined as having been prescribed anti-tuberculosis medications during follow-up among patients who were not diagnosed with tuberculosis within 30 days of enrollment. Severe anemia was defined as hemoglobin levels <8.5 g/dL. Underweight was defined as having a BMI<18.5, overweight as having a BMI 25, and obesity as having a BMI 30 (31). Abnormal lipid levels included high triglycerides (TG 150 mg/dL), high total cholesterol (TC 200 mg/dL), high low-density lipoprotein cholesterol (LDL-c 130mg/dL), low high-density lipoprotein cholesterol (HDL-c<40 mg/dL), and dyslipidemia (TG 150 mg/dL, TC 200 mg/dL, LDL-c 130mg/dL, or HDL-c<40 mg/dL)(31). When calculating ICCs for continuous variables and for lipid level-related outcomes, the time windows used for the baseline, 6, 12, and 24-month measurements were 0–2, 3–8, 9–17, and 18–29 months, respectively.

Patients became eligible for immunologic failure 168 days after ART initiation, at which point immunologic failure was evaluated according to 5 alternative definitions: (a) CD4+ count <100, (b) 50% drop in CD4+ count from its peak value, (c) a return to pre-ART CD4+ count or lower, (d) failure by Tanzanian criteria, defined as either a 50% drop in CD4+ count from its peak value or a return to pre-ART CD4+ count or lower, or (e) by any of the above criteria (29, 30). Eligibility for second-line ART was defined as either a 50% drop in CD4+ count from its peak value and a return to pre-ART CD4+ count after 168 days on ART or a viral load greater than 10,000 after 168 days on ART. Hepatotoxicity was defined as ALT>40 IU/L and ALT>120 IU/L. Significant weight loss after ART initiation was defined as weight loss 5% of the weight recorded at ART initiation. Because 95% adherence to ART or better is required for optimal viral suppression (32), non-adherence was said to have occurred when the number of days late to an appointment or ART pick-up was 5% or more of the total days between scheduled appointments or ART pick-ups.

Statistical Methods

To reflect the unadjusted, intent-to-treat analysis that would typically be used for most cRCTs, we calculated unadjusted ICCs using linear mixed models with the patients' site of enrollment as the random effect for outcomes calculated among all patients and site of ART initiation as the random effect for outcomes calculated only among ART-initiated patients:

$$Y_{ij} = \beta_0 + b_i + e_{ij},$$

where $var(b_i) = \sigma_B^2$, $var(e_{ij}) = \sigma_W^2$, $cov(b_i, e_{ij}) = 0$, $E(b_i) = E(e_{ij}) = 0$, Y_{ij} is the measured outcome for patient j from site i, σ_B^2 is the between-clinics variance, and e_{ij} is the within-clinic variance. The ICC was calculated as:

$$\widehat{ICC} = \frac{\widehat{\sigma_B^2}}{\widehat{\sigma_B^2} + \widehat{\sigma_W^2}}$$

Lower and upper limits of the 95% confidence intervals were estimated as described in Hankinson et al. (33):

$$\left(\widehat{ICC}^{-1} \pm 1.96 \sqrt{\widehat{var}\left(\widehat{ICC}^{-1}\right)}^{-1} \right)$$

where

$$\widehat{var}\left(\widehat{ICC}^{-1}\right) \cong \frac{1}{\hat{\sigma}_B^2} \widehat{var}\left(\hat{\sigma}_W^2\right) + \frac{\left(\hat{\sigma}_W^2\right)^2}{\left(\hat{\sigma}_B^2\right)^4} \widehat{var}\left(\hat{\sigma}_b^2\right) - 2\frac{\left(\hat{\sigma}_W^2\right)^2}{\left(\hat{\sigma}_B^2\right)^3} \widehat{cov}\left(\hat{\sigma}_w^2, \hat{\sigma}_b^2\right)$$

To ensure stability of the ICCs, sites with fewer than 5 events for binary outcomes or fewer than 10 measurements for continuous outcomes were excluded from the ICC calculation.

Sites were also excluded from the ICC calculation if they were extreme outliers, defined as having a site-specific outcome greater than 3 interquartile ranges (IQRs) below the 25th percentile or above the 75th percentile. These exclusion criteria were selected to improve the stability of the estimates for the ICCs. However, because researchers designing their own cRCTs would typically select appropriately sized clusters containing more than 10 continuous observations or 5 binary events, using the current exclusion criteria may also reasonably reflect the conditions of a real cRCT. Due to these exclusion criteria, although a total of 47 sites are included in the MDH database, the number of sites used in the calculation of the ICCs ranged from 7 to 44, with median of 26. Analyses were calculated using SAS, Release 9.2 (SAS Institute, Cary, NC, USA). ICCs and their confidence intervals were calculated with a publically available SAS macro available on the last author's website (34).

Results

Of the 109,943 patients enrolled in MDH since 2004, 109,320 had information on their site of enrollment and 73,862 of the 74,067 patients who were initiated on ART over follow-up had information on their site of ART initiation. Table 1 presents the distribution of patients and patient visits by site of enrollment and ART initiation. A detailed description of the baseline sociodemographic and clinical characteristics of the study population has been discussed elsewhere (26, 27). Over the first 2 years of follow up, only 4.6% of total patient-visits occurred at a site that was different from the patients' original site of enrollment. Among those patients who were initiated on ART, only 8.4% of patient-visits occurring between the date of ART initiation and the date two years after the patient first became eligible for immunologic failure or second line-drugs took place at a site that was different from the patients' original site of ART initiation.

Table 2 presents descriptive statistics and ICCs for general health outcomes among all patient. The ICCs in Table 2 ranged from 0.0050 (95% CI: 0.0022, 0.0110) for receiving tuberculosis treatment and 0.0544 (0.0343, 0.0850). Table 3 presents descriptive statistics and ICCs for nutritional outcomes among all non-pregnant patients. The ICCs for nutritional outcomes ranged more widely than for the general health outcomes spanning from 0.0641, (95% CI: 0.0366, 0.1100) for overweight at baseline to 0.0009, (95% CI: 0.0003, 0.0030) for the 6-month cumulative incidence for obesity. For both general health outcomes and nutritional outcomes, ICCs for a given outcome tended to be higher at enrollment than for subsequent visits. However, among subsequent visits, the ICCs tended to increase with time since enrollment.

Table 4 presents descriptive statistics and ICCs for plasma lipid level outcomes among patents. Because fewer individuals provided data on plasma lipid level measurements, fewer sites met the criteria for inclusion in the estimation of the ICCs, and the confidence intervals for lipid level ICCs tended to be relatively large. In some cases, the confidence intervals for the ICCs could not be estimated; however, the point estimates of these ICCs were investigated and judged to be reasonable given site-specific data. The ICCs for lipid level outcomes tended to be smaller than the ICCs reported in Table 2, ranging from 0.0207 (95% CI: 0.0067, 0.0622) for prevalence of low HDL at enrollment to 0 for the prevalence of high

total cholesterol at 24 months, cumulative incidence of high LDL levels at 12 and 24 months, and change in ALT from baseline to 12 months. As in Table 2, the point estimate for the ICC of an outcome at enrollment tended to be higher than the ICC for that outcome over follow-up.

Table 5 presents descriptive statistics and ICCs for different definitions of immunologic failure among ART initiated patients. Cumulative incidences for immunologic failure were calculated starting from the first date of eligibility for immunologic failure, which occurs 168 days after ART initiation. Despite having similar clinical significance, the five definitions of immunological failure had relatively variable point estimates for the ICC, although their confidence intervals often overlapped substantially. The ICCs for the cumulative incidence of immunologic failure by two of the three single-item definitions, CD4+ cell count <100 and 50% drop in CD4+ count from peak value, decreased over time. In contrast, the ICCs for the cumulative incidence of immunologic failure defined as a return to pre-ART baseline CD4+ count or lower increased over time. Immunologic failure by the Tanzanian criteria and by any criteria, both of which are composite outcomes including at least one definition of immunologic failure for which ICCs increased over time as well as the definition of immunologic failure for which ICCs decreased over time, did not show a monotonic trend.

Table 6 presents descriptive statistics and ICCs for additional clinical outcomes among ART-initiated patients. ICCs ranged from 0.0707 (95% CI: 0.0448, 0.1099) for the 24-month cumulative incidence of non-adherence to 0 for the change in ALT IU/L 12 months from ALT initiation. As seen previously, ICCs for a given outcome tended to increase with time of ART initiation. However, ALT>40 IU/L and ALT>120 IU/L, the only outcomes in Table 6 for which prevalence at ART initiation was available, had lower ICCs for prevalence at ART initiation than for cumulative incidences over follow-up.

Discussion

This paper reports ICCs for key clinical outcomes among a large cohort of HIV-positive adults. This cohort allowed for the calculation of ICCs for many novel outcomes. Furthermore, while previous papers reporting ICCs for HIV-related outcomes relied exclusively on data available at baseline (18–20), this paper estimated ICCs using both cross-sectional and longitudinal data. Because most cRCTs focus on longitudinal outcomes, these ICCs may better reflect future researchers' chosen study designs than ICCs calculated from baseline data alone.

For many binary outcomes, the ICC for prevalence at baseline was larger than the ICCs calculated using longitudinal data. There are three explanations for this pattern. First, the ICC for a binary outcome is dependent on the probability of that outcome (35). All else being equal, we would expect the ICCs for prevalence at baseline to be greater than the ICCs for cumulative incidences whenever baseline prevalence was greater than later cumulative incidences, as was the case for many outcomes in our study. Second, when calculating the ICCs for incident outcomes, we excluded prevalent cases. Afterwards, the remaining population of at-risk patients at each clinic became more similar to each other than the initial

populations at each clinic had been, reducing both between-clinic variation and the ICC. Third, it has been noted that modeling time when calculating the ICC tends to meaningfully reduce ICC estimates (14). While time was not explicitly in our calculations, several of our outcomes, such as the cumulative incidences and changes from baseline values, investigated changes in patients' status from baseline. By looking at changes in patients' status over time, we were able to incorporate time into the definition of our outcome. This implicit modeling of time may also help explain why the ICCs for prevalence tended to be higher than ICCs for cumulative incidence and why the ICCs for baseline values tended to be higher than the ICCs for changes from baseline over time. Regardless of the precise mechanisms, the differences between ICCs calculated using baseline data and ICCs calculated using longitudinal data were often large enough to have substantial implications for sample size calculations, highlighting the importance of publishing ICCs for outcomes that are relevant for longitudinal study designs rather than ICCs calculated using baseline data alone.

The ICCs for the different definitions of cumulative incidence of immunologic failure did not demonstrate a consistent trend over time. While ICCs for the cumulative incidence of immunologic failure by the definitions of CD4+ cell count <100 and 50% drop in CD4+ count from peak value increased over time, the ICCs for the cumulative incidence of immunologic failure defined as a return to pre-ART baseline CD4+ count or lower decreased over time. While it is unclear why the trend for ICCs over time should be different for immunologic failure defined as a return to pre-ART baseline CD4+ count or lower than for most other outcomes included in this paper, the high 6-month cumulative incidence of return to pre-ART baseline CD4+ count or lower relative to the other single-item definitions of immunologic failure may play a role. For the immunologic failure defined by either Tanzanian criteria or by any criteria, the lack of a monotonic increasing trend in ICCs over time may reflect the fact that both outcomes include a return to pre-ART baseline CD4+ count or lower in their composite definition of immunologic failure.

The largest ICC observed in our study was for the 24-month cumulative incidence of non-adherence. This finding is consistent with previous observations that behavioral outcomes tend to have higher ICCs than physiologic outcomes. Our results are also similar to previously published estimates from Zhang et al. (20), who estimated ICCs from HIV clinics in Kenya, Namibia, and Tanzania. Their unadjusted estimates for ICCs for any missed medication does in the past 30 days as reported verbally (ICC=0.029, 95% CI: 0.014, 0.069) and using a visual analog scale, (ICC=0.041, 95% CI: 0.021, 0.095) overlap with our ICCs for ART non-adherence. Their confidence intervals for the ICC for CD4+ count <200 (ICC=0.019, 95% CI: 0.009, 0.048) also overlapped with our confidence intervals of the ICC for CD4+ cell count <100. While their unadjusted ICC for CD4+ count (ICC=0.017, 95% CI: 0.007, 0.043) was somewhat lower than our ICC for CD4+ count at baseline, the confidence intervals overlapped with our ICCs for change in CD4+ count 6, 12, and 24 months from enrollment.

Over the time periods included in our analysis, only 4.6% of patient-visits occurred at sites other than the site of enrollment among the general population of MDH adult patients, and only 8.4% of patient-visits occurred at sites other than the site of ART initiation among patients who initiated ART. Because this variation in visit site could influence the ICCs, we

removed visits that occurred at sites other than the site of enrollment or ART initiation and reran some of our analyses. After deleting those visits that took place other than at the site of enrollment or ART initiation, ICCs mostly decreased, usually by a little, but occasionally by a lot. This is somewhat surprising since mixing of patients between facilities should tend to dampen between-facilities variation in outcome rates, making them more alike to one another.

Although many ICCs reported in this paper appear small, sample size calculations, especially for binary outcomes, are sensitive to small changes in the ICC. Consider a hypothetical 2-armed cRCT conducted in Dar es Salaam designed to reduce the 24-month cumulative incidence of immunologic failure from 46% to 36%. Assuming equal sized intervention and control arms, a naïve sample size calculation assuming an ICC of zero would estimate that a study with 758 patients would achieve 80% power (36). However, if the true ICC for the study population were 0.0102, which reflects our estimate of the ICC of the 24-month cumulative incidence of immunologic failure by any definition and also approximates the mean of the ICCs reported in this paper, a study with 50 patients per cluster would require 1200 patients to achieve 80% power, over 1.5 times as many as would have been required in an individually randomized setting. A study with 100 individuals per cluster would require 1600 patients to achieve 80% power, which is over twice as many patients as were required in calculations that ignored the ICC. These scenarios demonstrate how failing to account for seemingly small ICCs can result in severely underpowered studies.

Because sample size calculations are sensitive to small changes in the ICC, we urge researchers to be cautious when selecting published ICCs to use in their sample size calculations. As demonstrated by the variation in point estimates of the ICCs for different definitions of immunologic failure, small differences in the definition of the outcome can meaningfully change the point estimates of ICCs. Therefore, we join other authors in recommending that researchers designing RCTs conduct sensitivity analyses to evaluate their anticipated power under the full range of ICCs suggested by the confidence intervals (9, 37).

This paper calculates the confidence intervals for ICCs using a formula that is based on a normality assumption. Because binary outcomes cannot satisfy this normality assumption, the confidence intervals reported in this paper are not strictly valid for binary outcomes. This normality assumption also may not be satisfied for all continuous outcomes. Because the calculations of ICC intervals can be very sensitive to violations of the assumptions of normality, these confidence intervals should be considered an approximation of the range of values that could be encountered in practice (38).

Donner and Klar (9) have previously advised against overestimating the stability of ICCs calculated from fewer than 40 clusters. Although 47 sites are included in this study, most of our ICCs were calculated using fewer than 40 sites due to the exclusion of sites with fewer than 5 events for binary outcomes, 10 measurements for continuous outcomes, or which were extreme outliers. The MDH clinics are part of a complex health system, and some sites serve few patients while others face special circumstances causing them to act as outliers.

Failing to use exclusion criteria sometimes resulted in unstable or implausible estimates for some ICCs. Despite this limitation, the MDH cohort is one of the largest cohorts of HIV-positive people, and few other cohorts are better suited to estimating these ICCs. For example, the median number of sites used in the calculation of our ICCs is greater than the total number sites available to Zhang et al. (20).

Our ICCs were calculated among adults attending CTCs in in Dar es Salaam, Tanzania. These findings will be most useful for researchers randomizing at the clinic level in urban sub-Saharan African settings, but may also be useful in other resource-limited settings. Researchers can also use our estimates to calculate coefficients of variation for binary outcomes, which have been used in alternative formulas of estimating sample sizes for cRCTs (39). For binary outcomes, the relationship between the coeffient of variation and the ICC is described using the following equation:

$$ICC = k^2 \left(\frac{\pi}{1 - \pi} \right)$$

where k is the coefficient of variation and π is the probability of the outcome (40). However, these ICCs cannot be generalized to all contexts. In particular, ICCs for binary outcomes can only be generalized to contexts with similar prevalence or cumulative incidences (35).

Conclusion

cRCTs provide unique opportunities to evaluate HIV-related interventions, especially for HIV treatment implementation research. However, researchers can effectively leverage this study design only if they have access to applicable ICCs needed to accurately predict the sample size needed to design well-powered, efficient studies. There is a critical need to provide future researchers with ICCs for a diverse range of HIV-related clinical outcomes. Despite some limitations, these estimates provide valuable information, especially given the current scarcity of ICCs for HIV-related outcomes. Future researchers conducting cRCTs should consider publishing ICCs for not only their primary outcomes but also for secondary outcomes to address this persistent gap in the literature.

Acknowledgments

List of Abbreviations

ART   antiretroviral treatment

CTC   care and treatment clinics

ICC	intra-cluster correlation coefficient
MDH	Management and Development for Health
PEPFAR	US President's Emergency Plan for AIDS Relief

Literature Cited

1. Global Report: UNAIDS report on the Global AIDS epidemic 2013. Geneva, Switzerland: World Health Organization; 2013.

2. Corbett EL, Makamure B, Cheung YB, Dauya E, Matambo R, Bandason T, et al. HIV incidence during a cluster-randomized trial of two strategies providing voluntary counselling and testing at the workplace, Zimbabwe. AIDS. 2007; 21(4):483–9. [PubMed: 17301567]

3. Boily MC, Masse B, Alsallaq R, Padian NS, Eaton JW, Vesga JF, et al. HIV treatment as prevention: considerations in the design, conduct, and analysis of cluster randomized controlled trials of combination HIV prevention. PLoS Med. 2012; 9(7):e1001250. [PubMed: 22807657]

4. Cori A, Ayles H, Beyers N, Schaap A, Floyd S, Sabapathy K, et al. HPTN 071 (PopART): a cluster-randomized trial of the population impact of an HIV combination prevention intervention including universal testing and treatment: mathematical model. PLoS One. 2014; 9(1):e84511. [PubMed: 24454728]

5. Selke HM, Kimaiyo S, Sidle JE, Vedanthan R, Tierney WM, Shen C, et al. Task-shifting of antiretroviral delivery from health care workers to persons living with HIV/AIDS: clinical outcomes of a community-based program in Kenya. J Acquir Immune Defic Syndr. 2010; 55(4):483–90. [PubMed: 20683336]

6. Chang LW, Kagaayi J, Nakigozi G, Ssempijja V, Packer AH, Serwadda D, et al. Effect of peer health workers on AIDS care in Rakai, Uganda: a cluster-randomized trial. PLoS One. 2010; 5(6):e10923. [PubMed: 20532194]

7. Ayles HM, Sismanidis C, Beyers N, Hayes RJ, Godfrey-Faussett P. ZAMSTAR, The Zambia South Africa TB and HIV Reduction Study: design of a 2×2 factorial community randomized trial. Trials. 2008; 9(1):63. [PubMed: 18992133]

8. Pagel C, Prost A, Lewycka S, Das S, Colbourn T, Mahapatra R, et al. Intracluster correlation coefficients and coefficients of variation for perinatal outcomes from five cluster-randomised controlled trials in low and middle-income countries: results and methodological implications. Trials. 2011; 12:151. [PubMed: 21672223]

9. Donner A, Klar N. Pitfalls of and controversies in cluster randomization trials. Am J Public Health. 2004; 94(3):416–22. [PubMed: 14998805]

10. Hayes, RJ.; Moulton, LH. Cluster randomised trials. Boca Raton: CRC Press; 2009.

11. Murray, DM. Design and analysis of group-randomized trials. New York: Oxford University Press; 1998.

12. Donner A, Klar N. Cluster randomization trials in epidemiology: theory and application. J Stat Plan Inference. 1994; 42(1–2):37–56.

13. Cornfield J. Randomization by group: a formal analysis. Am J Epidemiol. 1978; 108(2):100–2. [PubMed: 707470]

14. Murray DM, Blitstein JL. Methods To Reduce The Impact Of Intraclass Correlation In Group-Randomized Trials. Eval Rev. 2003; 27(1):79–103. [PubMed: 12568061]

15. Campbell MK, Piaggio G, Elbourne DR, Altman DG, Group C. Consort 2010 statement: extension to cluster randomised trials. BMJ. 2012; 345:e5661. [PubMed: 22951546]

16. Ivers NM, Taljaard M, Dixon S, Bennett C, McRae A, Taleban J, et al. Impact of CONSORT extension for cluster randomised trials on quality of reporting and study methodology: review of random sample of 300 trials, 2000-8. BMJ. 2011; 343:d5886. [PubMed: 21948873]

17. Pals SL, Wiegand RE, Murray DM. Ignoring the group in group-level HIV/AIDS intervention trials: a review of reported design and analytic methods. AIDS. 2011; 25(7):989–96. [PubMed: 21487252]

18. Pals SL, Beaty BL, Posner SF, Bull SS. Estimates of intraclass correlation for variables related to behavioral HIV/STD prevention in a predominantly African American and Hispanic sample of young women. Health Educ Behav. 2009; 36(1):182–94. [PubMed: 19188372]

19. Glassman JR, Potter SC, Baumler ER, Coyle KK. Estimates of Intraclass Correlation Coefficients From Longitudinal Group-Randomized Trials of Adolescent HIV/STI/Pregnancy Prevention Programs. Health Educ Behav. 2015; 42(4):545–53. [PubMed: 25626433]

20. Zhang J, Pals SL, Medley A, Nichols C, Bachanas P, van Zyl D, et al. Parameters for sample size estimation from a group-randomized HIV prevention trial in HIV clinics in sub-Saharan Africa. AIDS Behav. 2014; 18(12):2359–65. [PubMed: 24146070]

21. Li N, Spiegelman D, Drain P, Mwiru RS, Mugusi F, Chalamilla G, et al. Predictors of weight loss after HAART initiation among HIV-infected adults in Tanzania. AIDS. 2012; 26(5):577–85. [PubMed: 22156968]

22. Hawkins C, Chalamilla G, Okuma J, Spiegelman D, Hertzmark E, Aris E, et al. Sex differences in antiretroviral treatment outcomes among HIV-infected adults in an urban Tanzanian setting. AIDS. 2011; 25(9):1189–97. [PubMed: 21505309]

23. Hawkins C, Christian B, Ye J, Nagu T, Aris E, Chalamilla G, et al. Prevalence of hepatitis B co-infection and response to antiretroviral therapy among HIV-infected patients in Tanzania. AIDS. 2013; 27(6):919–27. [PubMed: 23196935]

24. Li N, Manji KP, Spiegelman D, Muya A, Mwiru RS, Liu E, et al. Incident tuberculosis and risk factors among HIV-infected children in Tanzania. AIDS. 2013; 27(8):1273–81. [PubMed: 23343909]

25. Liu E, Armstrong C, Spiegelman D, Chalamilla G, Njelekela M, Hawkins C, et al. First-line antiretroviral therapy and changes in lipid levels over 3 years among HIV-infected adults in Tanzania. Clin Infect Dis. 2013; 56(12):1820–8. [PubMed: 23449270]

26. Makubi A, Okuma J, Spiegelman D, Hawkins C, Darling AM, Jackson E, et al. Burden and Determinants of Severe Anemia among HIV-Infected Adults: Results from a Large Urban HIV Program in Tanzania, East Africa. J Int Assoc Provid AIDS Care. 2015; 14(2):148–55. [PubMed: 23792708]

27. Muya AN, Geldsetzer P, Hertzmark E, Ezeamama AE, Kawawa H, Hawkins C, et al. Predictors of Nonadherence to Antiretroviral Therapy among HIV-Infected Adults in Dar es Salaam, Tanzania. J Int Assoc Provid AIDS Care. 2015; 14(2):163–71. [PubMed: 24966305]

28. Semu H, Zack RM, Liu E, Hertzmark E, Spiegelman D, Sztam K, et al. Prevalence and Risk Factors for Overweight and Obesity among HIV-Infected Adults in Dar es Salaam, Tanzania. J Int Assoc Provid AIDS Care. 2014

29. The United Republic of Tanzania MoHaSW. , editor. National guideline for the management of HIV and AIDS, National AIDS Control Programme (NACP). 3rd. 2008.

30. Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach. World Health Organization; 2010.

31. Eveleth PB. Physical Status: The Use and Interpretation of Anthropometry. Report of a WHO Expert Committee. Am J Hum Biol. 1996; 8(6):786–787.

32. El-Khatib Z, Katzenstein D, Marrone G, Laher F, Mohapi L, Petzold M, et al. Adherence to drug-refill is a useful early warning indicator of virologic and immunologic failure among HIV patients on first-line ART in South Africa. PLoS One. 2011; 6(3):e17518. [PubMed: 21408071]

33. Hankinson SE, Manson JE, Spiegelman D, Willett WC, Longcope C, Speizer FE. Reproducibility of plasma hormone levels in postmenopausal women over a 2–3-year period. Cancer Epidemiol Biomarkers Prev. 1995; 4(6):649–54. [PubMed: 8547832]

34. Hertzmark, E.; Spiegelman, D. The SAS ICC9 Macro. Cambridge, MA: Channing Laboratory, Harvard University; 2010. Available at: https://www.hsph.harvard.edu/donna-spiegelman/software/icc9/

35. Gulliford MC, Adams G, Ukoumunne OC, Latinovic R, Chinn S, Campbell MJ. Intraclass correlation coefficient and outcome prevalence are associated in clustered binary data. J Clin Epidemiol. 2005; 58(3):246–51. [PubMed: 15718113]

36. Rosner, B. Fundamentals of biostatistics. Cengage Learning; 2010. p. 381-389.

37. Kerry SM, Bland JM. Statistics notes: The intracluster correlation coefficient in cluster randomisation. BMJ. 1998; 316(7142):1455–1460. [PubMed: 9572764]

38. Ionan AC, Polley MY, McShane LM, Dobbin KK. Comparison of confidence interval methods for an intra-class correlation coefficient (ICC). BMC Med Res Methodol. 2014; 14:121. [PubMed: 25417040]

39. Hayes RJ, Bennett S. Simple sample size calculation for cluster-randomized trials. Int J Epidemiol. 1999; 28(2):319–26. [PubMed: 10342698]

40. Thomson A, Hayes R, Cousens S. Measures of between-cluster variability in cluster randomized trials with binary outcomes. Stat Med. 2009; 28(12):1739–51. [PubMed: 19378266]

Table 1

Distribution of patients and patient visits by Care and Treatment Clinic (CTC) of among patients enrolled between 1 October 2004 and 30 September 2012 (K=47)

CTC	Patients N (%)	Patient-Visits N (%)	ART Patients N (%)	ART Patient-Visits N (%)
1	78 (0.1%)	334 (0.01%)	67 (0.1%)	277 (0.02%)
2	3224 (3%)	64984 (3%)	2060 (3%)	65943 (4%)
3	16550 (15%)	383809 (17%)	11428 (15%)	307166 (17%)
4	25 (0.02%)	118 (0.01%)	23 (0.03%)	93 (0.01%)
5	83 (0.1%)	288 (0.01%)	64 (0.1%)	196 (0.01%)
6	7655 (7%)	151134 (7%)	5307 (7%)	109195 (6%)
7	143 (0.1%)	515 (0.02%)	80 (0.1%)	257 (0.01%)
8	1016 (1%)	13601 (1%)	757 (1%)	13228 (1%)
9	994 (1%)	9643 (0.4%)	804 (1%)	8219 (0.5%)
10	9193 (8%)	303903 (13%)	7063 (10%)	242948 (14%)
11	41 (0.04%)	173 (0.01%)	29 (0.04%)	129 (0.01%)
12	163 (0.1%)	792 (0.03%)	109 (0.1%)	560 (0.03%)
13	78 (0.1%)	4425 (0.2%)	297 (0.4%)	13599 (1%)
14	1536 (1%)	22541 (1%)	1003 (1%)	21354 (1%)
15	904 (1%)	16584 (1%)	586 (1%)	20562 (1%)
16	81 (0.1%)	301 (0.01%)	68 (0.1%)	235 (0.01%)
17	278 (0.3%)	3070 (0.1%)	158 (0.2%)	2769 (0.2%)
18	181 (0.2%)	1925 (0.1%)	446 (1%)	15390 (1%)
19	12 (0.01%)	20 (0.001%)	2 (0.003%)	2 (0.0001%)
20	63 (0.1%)	286 (0.01%)	51 (0.1%)	220 (0.01%)
21	10257 (9%)	201851 (9%)	7054 (10%)	132293 (8%)
22	185 (0.2%)	10402 (0.5%)	511 (1%)	27529 (2%)
23	308 (0.3%)	3401 (0.1%)	165 (0.2%)	2553 (0.1%)
24	294 (0.3%)	7929 (0.3%)	533 (1%)	21657 (1%)
25	509 (0.5%)	13556 (1%)	505 (1%)	23576 (1%)
26	240 (0.2%)	2399 (0.1%)	56 (0.1%)	555 (0.03%)
27	18917 (17%)	350279 (15%)	11930 (16%)	237488 (14%)
28	233 (0.2%)	987 (0.04%)	146 (0.2%)	610 (0.03%)
29	11 (0.01%)	38 (0.002%)	9 (0.01%)	29 (0.002%)
30	130 (0.1%)	513 (0.02%)	104 (0.1%)	404 (0.02%)
31	157 (0.1%)	1813 (0.1%)	127 (0.2%)	1986 (0.1%)
32	10184 (9%)	210227 (9%)	6145 (8%)	115198 (7%)
33	2247 (2%)	41575 (2%)	1539 (2%)	33912 (2%)
34	83 (0.1%)	1857 (0.1%)	324 (0.4%)	17523 (1%)
35	3792 (3%)	57410 (3%)	2710 (4%)	39141 (2%)
36	21 (0.02%)	92 (0.004%)	19 (0.03%)	90 (0.01%)
37	17001 (16%)	381128 (17%)	10147 (14%)	258708 (15%)
38	57 (0.1%)	179 (0.01%)	55 (0.1%)	181 (0.01%)

CTC	Patients N (%)	Patient-Visits N (%)	ART Patients N (%)	ART Patient-Visits N (%)
39	12 (0.01%)	44 (0.002%)	6 (0.01%)	23 (0.001%)
40	94 (0.1%)	332 (0.01%)	56 (0.1%)	219 (0.01%)
41	30 (0.03%)	153 (0.01%)	26 (0.04%)	127 (0.01%)
42	73 (0.1%)	315 (0.01%)	39 (0.1%)	211 (0.01%)
43	85 (0.1%)	410 (0.02%)	38 (0.1%)	163 (0.01%)
44	658 (1%)	9268 (0.4%)	417 (1%)	5238 (0.3%)
45	610 (1%)	10596 (0.5%)	471 (1%)	9692 (1%)
46	103 (0.1%)	637 (0.03%)	64 (0.1%)	974 (0.1%)
47	731 (1%)	10298 (0.4%)	264 (0.4%)	5980 (0.3%)
TOTAL	**109,320**	**229,6135**	**73,862**	**1,758,402**

Table 2

Intra-cluster correlations (ICCs) for general health outcomes, by site of MDH enrollment

Outcome	% or Mean (SD)	n/N N	Sites	ICC (95% CI)
All Cause Mortality				
6 mo. cumulative incidence	8%	8873/106973	28	0.0084 (0.0045, 0.0155)
12 mo. cumulative incidence	10%	10261/106973	28	0.0096 (0.0053, 0.0175)
24 mo. cumulative incidence	11%	11746/108117	30	0.0128 (0.0074, 0.0223)
Loss to Follow-Up				
6 mo. cumulative incidence	3%	2730/105495	21	0.0023 (0.0009, 0.0060)
12 mo. cumulative incidence	17%	18210/108416	34	0.0123 (0.0067, 0.0223)
24 mo. cumulative incidence	26%	28062/108416	34	0.0256 (0.0151, 0.0432)
CD4+ Count				
Value at enrollment	266 (247)	87229	44	0.0544 (0.0343, 0.0850)
Change from enrollment to 6 mo.	74 (202)	46473	29	0.0022 (0.0007, 0.0065)
Change from enrollment to 12 mo.	98 (222)	42930	27	0.0122 (0.0048, 0.0309)
Change from enrollment to 24 mo.	135 (247)	35639	27	0.0486 (0.0266, 0.0873)
Receiving Tuberculosis Treatment				
Prevalence at enrollment	10%	10166/99430	32	0.0297 (0.0176, 0.0495)
6 mo. cumulative incidence[1]	6%	4996/87219	29	0.0050 (0.0022, 0.0110)
12 mo. cumulative incidence[1]	7%	6000/88261	29	0.0076 (0.0035, 0.0163)
24 mo. cumulative incidence[1]	8%	6955/88996	30	0.0093 (0.0045, 0.0193)

[1]Excludes prevalent cases at baseline

Table 3

Intra-cluster correlations (ICCs) for nutritional outcomes by site of MDH enrollment among non-pregnant patients

Outcome	% or Mean (SD)	n/N N	Sites	ICC (95% CI)
Severe Anemia (hemoglobin<8.5 g/dL)				
Prevalence at enrollment	20%	11936/60652	31	0.0048 (0.0024, 0.0098)
6 mo. cumulative incidence[1]	10%	5827/57144	24	0.0060 (0.0021, 0.0169)
12 mo. cumulative incidence[1]	11%	7073/61885	25	0.0082 (0.0033, 0.0198)
24 mo. cumulative incidence[1]	13%	8376/65127	26	0.0094 (0.0043, 0.0204)
Hemoglobin (g/dL)				
Value at enrollment	10 (2)	65619	43	0.0181 (0.0085, 0.0383)
Change from enrollment to 6 mo.	1 (2)	28736	28	0.0074 (0.0026, 0.0205)
Change from enrollment to 12 mo.	1 (2)	25782	27	0.0250 (0.0119, 0.0518)
Change from enrollment to 24 mo.	1 (3)	21241	26	0.0258 (0.0123, 0.0533)
Underweight (BMI<18.5)				
Prevalence at enrollment	25%	20897/84601	29	0.0281 (0.0159, 0.0492)
6 mo. cumulative incidence[1]	11%	6916/63658	22	0.0059 (0.0027, 0.0130)
12 mo. cumulative incidence[1]	14%	8968/66069	25	0.0067 (0.0032, 0.0141)
24 mo. cumulative incidence[1]	16%	10983/66818	25	0.0066 (0.0031, 0.0136)
Overweight (BMI ≥ 25)				
Prevalence at enrollment	22%	18516/84631	30	0.0641 (0.0366, 0.1100)
6 mo. cumulative incidence[1]	10%	7244/69500	26	0.0022 (0.0007, 0.0072)
12 mo. cumulative incidence[1]	17%	12013/71533	28	0.0112 (0.0076, 0.0263)
24 mo. cumulative incidence[1]	23%	16553/72489	29	0.0259 (0.0131, 0.0506)
Obesity (BMI ≥ 30)				
Prevalence at enrollment	6%	5360/84390	26	0.0130 (0.0065, 0.0258)
6 mo. cumulative incidence[1]	3%	2609/82013	23	0.0009 (0.0003, 0.0030)
12 mo. cumulative incidence[1]	5%	4523/84757	25	0.0013 (0.0005, 0.0036)
24 mo. cumulative incidence[1]	8%	7006/85716	25	0.0029 (0.0011, 0.0072)
BMI				
Value at enrollment	22 (5)	83594	31	0.0528 (0.0287, 0.0950)
Change from enrollment to 6 mo.	1 (3)	57564	31	0.0122 (0.0056, 0.0265)
Change from enrollment to 12 mo.	2 (4)	48218	27	0.0234 (0.0114, 0.0475)
Change from enrollment to 24 mo.	2 (4)	49302	27	0.0159 (0.0068, 0.0031)

[1]Excludes prevalent cases at baseline

Table 4

Intra-cluster correlations (ICCs) for plasma lipid levels by site of MDH enrollment

Outcome	% or Mean (SD)	n/N N	Sites	ICC (95% CI)
Dyslipidemia [1]				
Prevalence at Enrollment	45%	17093/38046	26	0.0152 (0.0069, 0.0330)
Prevalence at 6 mo.	44%	3654/8290	21	0.0057 (0.0018, 0.0181)
Prevalence at 12 mo.	43%	3066/7074	16	0.0091 (0.0032, 0.0254)
Prevalence at 24 mo.	47%	2468/5215	17	0.0141 (0.0056, 0.0353)
Triglycerides (mg/dL)				
Value at enrollment	134 (86)	36504	26	0.0107 (0.0044, 0.0257)
Change from enrollment to 6 mo.	−10 (90)	4801	15	0.0025 (0.0004, 0.0141)
Change from enrollment to 12 mo.	−8 (96)	3916	11	0.0022 (0.0003, 0.0169)
Change from enrollment to 24 mo.	3 (104)	2868	13	0.0047 (0.0011, 0.0196)
High Triglycerides (>150 mg/dL)				
Prevalence at Enrollment	30%	10796/36476	24	0.0072 (0.0030, 0.0174)
Prevalence at 6 mo.	20%	1622/7945	16	0.0049 (0.0015, 0.0159)
Prevalence at 12 mo.	20%	1375/6754	12	0.0083 (0.0028, 0.0241)
Prevalence at 24 mo.	24%	1182/4982	14	0.0131 (0.0045, 0.0375)
Total Cholesterol (mg/dL)				
Value at enrollment	150 (63)	37436	26	0.0070 (0.0027, 0.0180)
Change from enrollment to 6 mo.	14 (70)	4980	15	0.0066 (0.0022, 0.0201)
Change from enrollment to 12 mo.	19 (70)	4090	11	0.0099 (0.0029, 0.0334)
Change from enrollment to 24 mo.	17 (71)	3034	13	0.0151 (0.0048, 0.0467)
High Total Cholesterol (>200 mg/dL)				
Prevalence at Enrollment	15%	5554/37324	21	0.0039 (0.0012, 0.0126)
Prevalence at 6 mo.	19%	1552/8063	14	0.0007 (0.0001, 0.0081)
Prevalence at 12 mo.	22%	1537/6997	15	0.0011 (0.0001, 0.0107)
Prevalence at 24 mo.	25%	1273/5136	14	0
LDL (mg/dL)				
Value at enrollment	88 (44)	8999	20	0.0147 (0.0057, 0.0371)
Change from enrollment to 6 mo.	1 (34)	1409	9	0.0121 (0.0031, 0.0455)
Change from enrollment to 12 mo.	4 (35)	949	8	0.0046 (0.0002, 0.0800)
Change from enrollment to 24 mo.	3 (51)	567	7	0.0173 (0.0016, 0.1649)
High LDL (>130mg/dL)				
Prevalence at Enrollment	11%	1014/8802	11	0.0075 (0.0026, 0.0220)
Prevalence at 6 mo.	13%	500/3767	9	0.0025 (0.0004, 0.0138)
Prevalence at 12 mo.	15%	537/3638	10	0
Prevalence at 24 mo.	16%	430/2636	10	0
HDL (mg/dL)				
Value at enrollment	36 (18)	9061	20	0.0161 (0.0058, 0.0439)
Change from enrollment to 6 mo.	14 (20)	1463	9	0.0029 (0.0003, 0.0296)

Outcome	% or Mean (SD)	n/N N	Sites	ICC (95% CI)
Change from enrollment to 12 mo.	17 (20)	1020	8	0.0121 (0.0022, 0.0647)
Change from enrollment to 24 mo.	12 (28)	589	7	0.0066 (0.0003, 0.1438)
Low HDL (<40 mg/dL)				
Prevalence at Enrollment	64%	5804/9069	21	0.0207 (0.0067, 0.0622)
Prevalence at 6 mo.	34%	1367/3963	13	0.0041 (0.0010, 0.0168)
Prevalence at 12 mo.	26%	975/3711	9	0.0043 (0.0010, 0.0188)
Prevalence at 24 mo.	29%	775/2696	10	0.0072 (0.0019, 0.0273)

[1]TG 150 mg/dL, or TC 200 mg/dL, or LDL-c 130mg/dL, or HDL-c<40 mg/dL

Table 5

Intra-cluster correlations for immunologic failure outcomes (ICCs) by site of ART-initiation among patients initiated on ART

Outcome	%	n/N	Sites	ICC (95% CI)
CD4+ cell count<100				
6 mo. cumulative incidence[1]	11%	3820/35497	25	0.0088 (0.0043, 0.0180)
12 mo. cumulative incidence[1]	14%	5471/33539	25	0.0087 (0.0043, 0.0176)
24 mo. cumulative incidence[1]	17%	6964/39927	26	0.0106 (0.0056, 0.0201)
50% drop in CD4+ count from peak value				
6 mo. cumulative incidence[1]	11%	3781/35353	24	0.0033 (0.0013, 0.0085)
12 mo. cumulative incidence[1]	18%	7060/39091	28	0.0086 (0.0039, 0.0189)
24 mo. cumulative incidence[1]	27%	10909/39967	28	0.0253 (0.0131, 0.0481)
Return to pre-ART baseline CD4+ count or lower				
6 mo. cumulative incidence[1]	23%	7554/33223	25	0.0206 (0.0105, 0.0403)
12 mo. cumulative incidence[1]	30%	11083/36426	27	0.0117 (0.0057, 0.0240)
24 mo. cumulative incidence[1]	37%	13638/37201	27	0.0095 (0.0045, 0.0197)
Immunologic failure by Tanzanian Criteria[2]				
6 mo. cumulative incidence[1]	25%	8897/35535	26	0.0137 (0.0067, 0.0275)
12 mo. cumulative incidence[1]	34%	13445/39091	28	0.0075 (0.0034, 0.0162)
24 mo. cumulative incidence[1]	43%	17355/39967	28	0.0123 (0.0061, 0.0246)
Immunologic failure by any criteria[3]				
6 mo. cumulative incidence[1]	29%	10230/35568	28	0.0186 (0.0093, 0.0370)
12 mo. cumulative incidence[1]	38%	14744/39100	29	0.0096 (0.0045, 0.0204)
24 mo. cumulative incidence[1]	46%	18489/39976	29	0.0102 (0.0050, 0.0207)

[1] Cumulative incidences are calculated from the date of eligibility for immunologic failure which occurs 168 days after ART initiation.

[2] 50% drop in CD4+ count from peak value, or return to pre-ART baseline CD4+ count or lower after 6 months on ART

[3] CD4+ Count <100, 50% drop in CD4+ count from peak value or return to pre-ART baseline CD4+ count or lower after 6 months on ART

Table 6

Intra-cluster correlations (ICCs) by site of ART-initiation among patients initiated on ART

Outcome	%	n/N	Sites	ICC (95% CI)
Non-Adherence [1]				
6 mo. cumulative incidence	59%	43389/73228	43	0.0161 (0.0090, 0.0286)
12 mo. cumulative incidence	69%	50911/73268	44	0.0374 (0.0223, 0.0622)
24 mo. cumulative incidence	75%	55183/73272	44	0.0707 (0.0448, 0.1099)
Eligibility for 2ND Line ART [2]				
6 mo. cumulative incidence [3]	5.9%	2692/46012	23	0.0027 (0.0011, 0.0065)
12 mo. cumulative incidence [3]	11%	5076/47381	25	0.0084 (0.0042, 0.0168)
24 mo. cumulative incidence [3]	16%	7619/48346	27	0.0225 (0.0124, 0.0405)
Hepatotoxicity ALT>40 IU/L				
Prevalence at ART initiation	14%	5675/41909	26	0.0038 (0.0014, 0.0101)
6 mo. cumulative incidence [4]	21%	7683/37094	26	0.0129 (0.0064, 0.0259)
12 mo. cumulative incidence [4]	25%	9870/40163	28	0.0230 (0.0123, 0.0426)
24 mo. cumulative incidence [4]	28%	11694/41293	28	0.0385 (0.0216, 0.0678)
ALT>120 IU/L				
Prevalence at ART initiation	0.8%	278/36791	9	0.0004 (0.0001, 0.0023)
6 mo. cumulative incidence [4]	3%	1049/40080	19	0.0011 (0.0004, 0.0031)
12 mo. cumulative incidence [4]	3%	1290/43359	20	0.0014 (0.0005, 0.0038)
24 mo. cumulative incidence [4]	3%	1504/44854	21	0.0020 (0.0007, 0.0056)
ALT (IU/L)				
Value at enrollment	29 (29)	36663	32	0.0047 (0.0022, 0.0102)
Change from initiation to 6 mo.	−2 (54)	22236	23	0.0002 (0.0000, 0.0021)
Change from initiation to 12 mo.	−3 (64)	19599	26	0
Change from initiation to 24 mo.	−4 (34)	16408	24	0.0008 (0.0002, 0.0034)
Weight Loss >5% after ART initiation [5]				
6 mo. cumulative incidence	23%	16039/70180	38	0.0079 (0.0039, 0.0159)
12 mo. cumulative incidence	28%	19887/70436	38	0.0154 (0.0081, 0.0291)
24 mo. cumulative incidence	33%	23357/70465	38	0.0297 (0.0169, 0.0514)

[1] The number of days late to an appointment or an ART pick-up visit was 5% or more of the total days between scheduled appointments or ART pick-up visits.

[2] 50% drop in CD4+ count from its peak value and return to pre-ART CD4+ count or lower which occurs after 168 days on ART or a viral load greater than 10,000 after 168 days on ART

[3] Cumulative incidences are calculated from the date of eligibility for second line eligibility, 168 days after ART initiation.

[4] Excludes prevalent cases at baseline

[5] Excludes pregnant women