ICAP Journal Club

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Article

Barnabas RV, Szpiro AA, van Rooyen H, et al for the Delivery Optimization of Antiretroviral Therapy (DO ART) Study Team. **Community-based antiretroviral therapy versus standard clinic-based services for HIV in South Africa and Uganda (DO ART): a randomised trial.** *Lancet Glob Health*. 2020;8(10):e1305-e1315. https://doi.org/10.1016/S2214-109X(20)30313-2

Study Summary

The Delivery Optimization of Antiretroviral Therapy (DO ART) Study was a multicenter, household-randomized trial that compared HIV treatment outcomes among people living with HIV (PLHIV) receiving community-based antiretroviral therapy (ART) to standard clinic-based ART services.

Study Setting

- Rural and peri-urban areas of high and medium HIV prevalence, including 16 communities in South Africa and six communities in Uganda.
- Communities had a low per-capita income (<$2 USD per day) and public clinics that offered universal access to ART at no cost.

Methods

- Following a community-mobilization campaign, participants were recruited through HIV testing at community locations and at home. Participants could also be referred from clinics offering HIV testing and community-based distribution of HIV self-test kits.
- PLHIV were eligible to participate if they were ≥18 years old, resided in the participating communities, had not taken ART in the past 3 months and were clinically stable, defined as a CD4 cell count >100 cells/μL, World Health Organization (WHO) stage 1-3, not pregnant, normal renal function, and no symptoms of active tuberculosis (TB). Detectable viral load (VL) was added as an inclusion criterion one year after the study was activated.
- PLHIV received point-of-care testing to stage their HIV and assess clinical eligibility, including CD4 cell count, pregnancy testing, creatinine, and baseline HIV VL using dried blood spot.
- PLHIV who were not eligible for clinical reasons or pregnancy were referred and linked to clinic-based services.
- Eligible PLHIV with detectable VL were randomly assigned (1:1:1) to either the community, hybrid, or clinic groups. Eligible participants in the same household were randomly assigned to the same group to prevent crossover.
- Services for participants in the community-based ART group included:
    - Same-day ART initiation in the community, with a follow-up phone call seven days after initiation to ask about symptoms, ART side effects, and adverse events.

    - In-person follow-up visits in a mobile van, parked at a known location, at month 1, 3, 6, 9, and 12 for ART refills, clinical monitoring, counseling, and assessment of adverse events and social harms.
    - ART was dispensed for one month, two months, and then every three months thereafter. Trimethoprim-sulfamethoxazole prophylaxis was dispensed according to country guidelines and isoniazid preventive therapy was provided from month 1.
    - Participants received appointments for their mobile visits, with an automated text message reminder the week before their visit. Participants were able to reschedule visits by text message, request additional ART supply if travelling, and nominate someone else to collect their medication. The mobile service was also regularly available on evenings and weekends.
    - Participants who missed visits were contacted and their visit rescheduled.
    - As part of clinical monitoring, participants received point-of-care creatinine testing to monitor renal function and completed a questionnaire to screen for symptoms of ART adverse events, TB, and other common opportunistic infections.
    - Plasma VL was assessed at month 6 and results were returned via text message, including next steps, without mentioning HIV to protect confidentiality (e.g., "All is going well. Keep up the good work." or "Please contact us for more information.").
    - Participants in the community-based ART group were administratively linked to a clinic and their files kept up to date. Those who required additional clinical services were referred for care and followed up until they were linked to a clinic.
- Participants in the hybrid group were counseled to notify the study team once they had initiated ART at the clinic, after which they had community-based monitoring and refills, following the same procedures as the community-based ART group. Until notification of ART initiation, they received quarterly phone calls to enquire about ART status and to record adverse events.
- Participants in the clinic group were referred to local clinics for ART initiation, monitoring, and refills per national guidelines. They received quarterly telephone calls to document ART initiation and adverse events.
- Trained nurses and supervised lay counselors conducted study activities including ART initiation, refills, and monitoring.
- Participants completed a baseline questionnaire, after which social harms and adverse events were assessed at every in-person visit and with every telephone call. Chart abstraction was done for all participants to capture any additional clinical events and test results.
- All participants completed an in-person exit visit 12 months after random assignment, which included a plasma VL measurement and a questionnaire regarding their experience accessing care.
- The primary trial endpoints were 1) the proportion of participants who achieved VL suppression (<20 copies/mL) at month 12 and 2) the cost per person virally suppressed in the community-based group, assessed through activity-based micro-costing.
- Secondary outcomes included safety as assessed through adverse event reporting and clinical chart abstraction, and viral suppression among men.
- The primary analyses were by modified intention-to-treat, excluding participants who were virally suppressed at baseline. Sensitivity analyses were done including those who were virally suppressed at baseline, and using the WHO threshold for viral suppression of <1000 copies/mL.

Study Population and Follow-up

- Between May 2016 and March 2019, 8,265 people were tested for HIV and 2,479 (30%) tested positive. Of these, 2,393 (97%) completed screening and 1531 participants were randomly assigned: 514 to the clinic group, 509 to the hybrid group, and 508 to the community-based group.
- Of the 862 individuals who were ineligible for randomization, 68% were virally suppressed at baseline, 8% reported currently being on ART, 9% screened positive for TB symptoms, 4% had a CD4 cell count of <100 cells/μL, and 3% were pregnant.
- In the community-based ART group, at least 82% of participants completed each visit (months 1, 3, 6, and 9) and 95.8% of all randomized participants contributed a VL endpoint.
- Of the 71 participants lost to follow-up, 32% were in the clinic group, 45% in the hybrid group, and 23% in the community-based group. The most common reason participants were lost to follow-up was moved (50%), followed by withdrew (17%) and died (13%); 20% were lost to follow-up for unknown reasons.
- In total, 1,315 were included in the modified intention-to-treat analyses; 446 in the clinic group, 442 in the hybrid group, and 427 in the community group. Of these, the primary VL endpoint was available for 95%.
- Among participants in the primary modified intention-to-treat analysis, median age at baseline was 32 years (interquartile ratio 27–40); 51% were men, 68% had completed secondary education or higher, and 59% were unemployed. Most participants were asymptomatic and clinically stable, with 89% designated as WHO clinical stage I, 66% with a CD4 cell count ≥350 cells/μL and 95% had normal renal function.

Primary Outcomes

- Participants in the community-based ART group had increased viral suppression compared to the clinic group (74% vs. 63%, relative risk [RR] 1.18, 95% confidence interval [CI] 1.07-1.29; p=0.0005) and the hybrid approach was non-inferior to the clinic group (68% vs 63%, RR 1.08, 0.98-1.19; p for non-inferiority=0.0049).
- Similar results were seen in sensitivity analyses including those with suppressed VL at baseline and using the WHO threshold for viral suppression.
- In South Africa, the estimated annual cost per person virally suppressed was $402-422 in the clinic group and $325-390 in the community-based group. In Uganda the estimated annual cost per person virally suppressed was $214 in the clinic group and $275 in the community-based group.

Secondary Outcomes

- Compared to standard clinic care, viral suppression was significantly increased among men with both the community ART (73% vs. 54%, RR 1.34, 95% CI 1.16-1.55; p<0.0001) and hybrid strategies (66% vs. 54%, RR 1.19, 1.02-1.40; p=0.026).
- Viral suppression was similar for men (73%) and women (75%) in the community-based ART group, whereas gender differences were seen in the clinic group, with 54% of men and 73% of women achieving viral suppression.
- Serious adverse events occurred in 20 (1%) participants; eight in the clinic group, five in the hybrid group, and seven in the community group. Of these, 14 (70%) were considered related

or possibly related to HIV, including seven in the clinic group, one in the hybrid group, and six in the community group.
- Social harms related to trial participation were reported by two participants, both in the community-based group.

Critical Analysis

The multicenter, randomized DO ART study found that providing all ART-related services in the community, with the use of a mobile van, improved viral suppression one year after ART initiation compared to standard clinic-based services. The improvement in viral suppression was especially notable in men, and there were no major safety concerns with community-based services. The hybrid approach of ART initiation at the clinic, followed by monitoring and refills in the community, was non-inferior to clinic-based ART, suggesting that this could be an alternative approach to standard clinic-based care.

The following points should be considered when interpreting the study findings:
- Because of the study design, the study team and participants were not blinded to the ART delivery method. However, the laboratory staff who assessed the primary outcome were blinded to participant allocation.
- It is possible that additional changes to the standard of care at the study clinics made during the study period (e.g., fast-track ART) improved viral suppression in the clinic-based group. However, an analysis looking at date of enrollment did not change the primary finding for viral suppression.
- The community-based ART services included a number of client-centered changes from standard clinic care beyond location of services, including expanded operating hours, automated appointment reminders, flexibility in scheduling, and measures to maintain privacy. Therefore, it is not possible to isolate which component of the intervention had the most impact on viral suppression.
- The use of a mobile application during community-based services facilitated task shifting by ensuring provision of standardized care in accordance with clinical algorithms and national guidelines. Communication with the participants also relied heavily on mobile phone coverage. This could make the intervention difficult to replicate in settings with fewer resources and less cellular coverage.
- The use of point-of-care testing was central to determining eligibility for community-based ART and monitoring for adverse events and treatment response, however this may not be widely available in all settings, which limits the generalizability of findings.
- Although community-based ART resulted in improved viral suppression, a quarter of participants still did not achieve this outcome, which suggests that additional services may be needed to meet the needs of this group.
- The clinic-based costs were calculated using an estimate from the literature and were not directly measured in this study.

Implications

This randomized trial in high and medium HIV prevalence settings in South Africa and Uganda provides evidence that community-based HIV services including same-day ART initiation, mobile van monitoring, and ART refills, increases viral suppression among PLHIV compared with standard clinic-based services. The benefits of community-based ART were especially pronounced among men and helped to close the gender gap in viral suppression. While community-based services may require initial investments, the costs of such services must be weighed against the potential individual and community health benefits of achieving viral suppression. With the recent emphasis on person-centered care, this intervention provides a model of community-based care that programs can consider to improve retention and viral suppression.

This article synopsis was written by Cassia Wells. Share your thoughts on this article or suggest an article for Journal Club by emailing her at caw2208@columbia.edu.