TITLE PAGE

Re-engagement of HIV-infected children lost to follow up after active mobile phone tracing in a rural area of Mozambique

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SUMMARY

Introduction: Retention in care and re-engagement of loss to follow-up (LTFU) patients is a priority challenge in pediatric HIV care. We aimed to assess whether a telephone-call active tracing program facilitated re-engagement in care (RIC) in the Manhiça District Hospital, Mozambique.

Methods Telephone tracing of LTFU children was performed from July 2016 to March 2017. Both ART (antiretroviral treatment) and preART patients were included in this study. LTFU was defined as not attending the clinic for ≥120 days after last attended visit. Reengagement was determined 3-months after attempt to contact.

Results: total of 144 children initially identified as LTFU entered the active tracing program and 37 were reached by means of telephone tracing. RIC was 57% (95% CI, 39–72%) among children who could be reached versus 18% (95% CI, 11–26%) of those who could not be reached (p=0.001).

Conclusion: Telephone tracing could be an effective tool for facilitating reengagement in pediatric HIV care. However, the difficulty of reaching patients is an obstacle that can undermine the program.

TEXT

Introduction

Each step in the pediatric HIV care cascade presents challenges, leading to high rates of loss to follow-up (LTFU) and early mortality that exceed those reported in adults(1–3). Retention in care and treatment is necessary to achieve and maintain viral suppression (4). Continuous care allows detection of medication toxicity, treatment failure and the need for dosage/drug modifications, and provides social support (5–8). In Mozambique, one of the countries most affected by the epidemic, the 12-month retention rate among children under the age of 15 newly initiating antiretroviral treatment (ART) is around 70%(9).

SMS-text reminders for caregivers of HIV-infected children have been effective in increasing medical appointment attendance in Cameroon (10). However, little data explains the effects of phone calls on re-engagement in care (RIC) of pediatric HIV patients who were LTFU.

We aimed to assess whether a phone-call based active tracing program facilitated RIC of both ART and preART HIV children who were LTFU in the Manhiça District Hospital (MDH) in Southern Mozambique.

Materials and methods

Study setting

The study was conducted at the Centro de Investigação em Saúde de Manhiça (CISM), a semi-rural area in Southern Mozambique with a high HIV burden of disease(11). The CISM

collaborates closely with the Manhiça District Hospital (MDH), a public hospital offering free HIV services. HIV-infected children are followed-up in a pediatric clinic and seen every 3 months until the age of 15, when they are referred to the adult clinic. At the time of the study, for children over 5 years of age, ART eligibility was defined as CD4 count below 500 cell/mm^3 or HIV WHO stage III or IV; the first line of treatment was azidothymidine(AZT) + lamivudine (3TC) + nevirapine (NVP)/efavirenz (EFV). Universal treatment was recommended for all HIV-infected children under 5 and first line was AZT+3TC+NVP/ lopinavir (LPVr)(12).

Study design and procedures

This is a programmatic evaluation of the first 9 months (July 2016 to March 2017) of an Active Tracing Program (ATP) implemented at the MDH. This analysis was nested in a larger prospective pediatric cohort of HIV positive children < 15 years in care at the MDH. Data from clinic visits are routinely collected and entered into the MDH HIV pediatric cohort database (MDHIVPed).

The evaluation included all HIV-positive children < 15 years among whom HIV care was initiated at the MDH between February 2013 and March 2017. Both preART and ART patients were included in this study. Children were included in the ATP if considered LTFU at any time between July 2016 and March 2017. Children LTFU were identified monthly from the MDHIVPed and caregivers were contacted by telephone using the contact information that was registered in the patient chart on enrollment in HIV care. If the caregiver or child was reached by the ATP, the counselor provided a telephone counseling session, inquired about the reason for missed appointment and rescheduled the appointment. If the child returned to the clinic, an ATP counselor and a clinician from the MDH conducted the clinic visit. All the ATP information was collected in a specific questionnaire in electronic format in Open Data Kit

software 1.4 (ODK) (13)during the visit and uploaded into a database in REDCap (Research Electronic Data Capture) Software 5.7.3 (14). For the patients included in this study, phone based tracing in the context of this study was the only intervention to promote or incentivize retention applied.

Study definitions

LTFU was defined as not having attended the clinic for ≥120 days following last visit among patients considered alive and not transferred to another unit. Time of LTFU was calculated as the number of days from last clinic visit until ATP enrollment.

Patients reached by the ATP were defined as those whose caregiver received a phone call and communicated with the ATP counselor.

Patients with successful RIC were defined as HIV positive children who were LTFU and returned for a clinic visit within 3 months after being enrolled in the ATP.

Statistical considerations

Data were analyzed using Stata statistical software version 14.2 (Stata Corp., College Station, Texas, USA). We performed descriptive analysis of clinical and socio-demographic variables on entry into the ATP. Medians and interquartile ranges (IQR) were calculated to describe continuous variables, and categorical variables were expressed using frequencies. Differences between patients who could be reached and who could not be reached by telephone tracing were assessed using χ^2 and Fisher's exact test for categorical variables and Wilcoxon test for continuous variables. Patients not reached by means of telephone tracing included patients with absent telephone numbers in charts and those who could not be reached by the ATP counselor.

The proportion of patients who were re-engaged in care was the quotient of children re-engaged in care and those LTFU.

We performed univariate and multivariable analyses to determine the associations between clinical and socio-demographic patient characteristics and the primary outcome of RIC. Unadjusted and adjusted odds ratios were estimated. All associations with a *p*-value <0.2 in the univariate analysis were included in a multivariate logistic regression model, which was adjusted for sex and age at time of the enrollment. Variables with a *p*-value of <0.2 but with > 30% missing data were excluded from the final multivariate regression model.

Ethics statement

Children and caregivers in the prospective MDH HIV pediatric cohort signed an informed consent approved by the Mozambican National Bioethics Committee and the Barcelona Hospital Clinic Institutional Review Board. The specific active tracing activities were developed under the national recommendations and the district health services.

Results

Study profile and population characteristics

Care was initiated in a total of 422 children [average age, 4.9 (4.2 SD) years] at the MDH between February 2013 and March 2017. Of those, 269 children were flagged as potential LTFU between July 2016 and March 2017 in the MDHIVPed. Of these, 125 (46%) were identified as non-LTFU after reviewing the medical charts and were excluded from the ATP (Figure 1). Most exclusions were because of health facility transfer (N=56; 45%) or death (N=12; 9%). A total of 144 children met the inclusion criteria [median age at ATP enrollment,

8.37 years (IQR: 3.74–11.33); number of male children, 59%]. However, in 54 (37%) patients, telephone tracing was not attempted because no telephone number was registered in the chart (Figure 1). Telephone tracing was attempted for 90 children, and was unsuccessful for 53 (58%), primarily due to invalid telephone numbers.

Of 37 children successfully reached, 3 were reported as deaths, 2 had self- transferred to another health clinic and 2 had missed an appointment without fulfilling LTFU definition. (Figure 1). When assessing the main reasons for children discontinuing HIV care, caregivers reported forgetting about appointments (50%), moving residence (23%) and ill caregiver (7%), among others. The baseline descriptive characteristics of children who could be reached and those who could not be reached by means of telephone tracing were comparable (Table 1).

Intervention effect and factors associated with reengagement in care

RIC occurred in 21 of 37 [57% (95% CI 39%-72%)] of children LTFU reached through the ATP and in 19 of 107 [18% (95% CI 11%-26%)] of those not reached by the ATP. Table 2 shows the results of the univariate and multivariate analysis evaluating the association of variables with RIC for those patients LTFU included in the tracing program. Increased age at ATP enrollment, lower CD4 at enrollment in care, orphaned, reached by telephone tracing, fewer months of LTFU and more months in care were significantly associated with RIC in the univariate analysis.

In the multivariate model, the following three variables showed a statistically significant association with RIC; age at ATP enrollment [adjusted odds ratio (AOR) 1.11, 95% CI 1.01 - 1.24; *p*-value 0.036], time LTFU (in months) (AOR 0.76, 95% CI 0.60 - 0.96; *p*-value 0.021) and children who were reached by telephone tracing (AOR 7.20, 95% CI 2.27 – 22.78; *p*-value 0.001) (Table 2).

Discussion

The results of this study show that among HIV-infected children enrolled in care at the MDH, the telephone numbers of a high number, 107 (74%), in the chart were not working, reducing the potential impact of ATP. Importantly, in 54 of 107 cases (50.5%), telephone tracing was not attempted due to missing telephone number and in 44 (41.1%) cases, the registered number was invalid. Other studies in sub-Saharan Africa have shown logistical problems in telephone tracing programs in adults HIV patients owing to incomplete, outdated or erroneous telephone numbers on patients' files or lost/disconnected cell phone numbers (15). This may be an even greater problem for tracing children dependent on a caregiver, as disconnected mobile phone service may indicate patient deaths(15) or in our case, caregiver death or change in caregiver. Results of home tracing studies in HIV-infected patients vary in terms of patients reached (16–18). While a study in Malawi could reach 73% of all HIV LTFU patients of all ages(16), a South African study could reach only 31% adults with tuberculosis or HIV lost to care (17). However several studies combining telephone and home tracing could reach 85% of LTFU adults patients with HIV or tuberculosis (18) and 79% of HIV LTFU children(19), respectively. Therefore, multi-method tracing approach could improve the effectiveness to reengage HIV LTFU children, although further studies would be needed to evaluate the cost-benefit and long-term sustainability.

Telephone tracing was associated with reengagement among HIV-infected children LTFU. A total of 57% (95% CI 39%-72%) of cases that could be reached by the ATP reengaged in care and had 7-fold greater odds of RIC than those who could not be reached. Similar percentages were found in a home tracing program in South Africa (61%)(17) and a combined telephone-home tracing in Kenya (59%) (18), and slightly higher percentages were described Malawi (74%) (16). However, these studies included adults(16–18) and patients with tuberculosis lost to care (17,18).

Our study is one of the few addressing the predictors and/or risk factors of RIC following ATP among children LTFU. We have shown that in addition to ATP, time spent LTFU was associated with RIC. For each additional month of LTFU, the likelihood of RIC decreased (AOR 0.76, 95% CI 0.60 - 0.96; *p*-value 0.021). This inverse relationship between time spent LTFU and probability of RIC highlights the importance of early tracing programs soon after abandonment of care. Older children had higher probabilities of RIC in our study (AOR 1.11, 95% CI 1.01-1.24; *p*-value 0.036). Taking into account these findings as well as those from several studies (20–22) that indicate that younger children have a higher risk of LTFU and death, retention efforts should be increased in young children.

Although gender was not concluded as an indicator of RIC in our study, a study published in 2010 in Malawi, including patients of all ages, found women more likely to be RIC after LTFU(16). In our study, 71 % of caregivers reached were female thus not allowing conclusion. However, the caregiver gender might be important since the ultimately, they are the decision-makers regarding the child's healthcare. Several studies(16,23) have reported that patients in whom ART was initiated were more likely to return to the clinic than those in whom ART was never initiated. A possible explanation is that these patients likely have a greater understanding of the importance of ART compared with those who have never been on treatment. In this study, only 15% of participants were not on ART, limiting our ability to explore this association. We have also taken into account the idea that the proportion of patients defaulting in clinic may somehow differ to those defaulting in ART. In this study, we were not able to differentiate between the two, as we included all patients in whom care was initiated defaulting in clinic, regardless of ART use.

Residence-clinic distance has been documented as a barrier to follow-up in many African settings among HIV-positive individuals, pediatric and adult alike(24), but we did not see associations with RIC. Determinants of LTFU and RIC could in fact be different. Other important variables such as patient/caregiver work schedules' interference with long wait times for appointments, as well as the presence of social support, could impact RIC. Qualitative studies have shown structural and social factors also affect adult retention(25).

Reasons for missing clinical appointments may vary between settings. In our study, the main reported reason for LTFU was forgotten appointment (50%). Thus, mobile phone-based appointment-reminders for caregivers could potentially decrease LTFU, as demonstrated in other studies(10). In any case, our study shows the need to improve phone detail accuracy for mobile-phone interventions. Another reason frequently reported for LTFU was change of residence (23%). This is in line with other studies showing that HIV-positive individuals with a history of mobility are less likely to be retained at successive stages of the HIV treatment cascade (26). Ultimately, it should be noted that 8% of the patients located in our study had died. Other studies found even higher mortality (2,16) which highlights the importance of implementing strategies to reduce LTFU rates and trace patients who abandon care. Further studies are needed to understand the issues that arise from calling the caregiver of a child who has died.

This study has several limitations. The program located a low percentage of patients LTFU reached by the ATP. However, no significant differences were found between the baseline characteristics of patients who could be reached and those who could not, reducing the risk of selection bias. In addition, although our study was small, we clearly identified important

risk factors for RIC. A larger sample size of children with similar characteristics could increase the power and thus validity and generalizability of results.

In conclusion, active telephone tracing is a potential strategy to facilitate re-engagement in HIV care; however, every effort should be made to record correct numbers, including alternative/multiple numbers to maximize the patients reached.

Competing interests: We declare no competing interests.

Authors' contributions:

Conceived and designed the study: ELV, LDF, SFL, EB, DN. Implemented the study: LDF, SM, SFL, EB, supervised by ELV and DN. Analyzed the data: ELV, OA, DN. Wrote the paper: ELV, TMH, SFL. All authors contributed to refinement of the study protocol and approved the final manuscript.

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