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LOST TO FOLLOW-UP: FAILURE TO ENGAGE CHILDREN IN CARE IN THE FIRST THREE MONTHS OF DIAGNOSIS

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Abstract

Loss to follow-up (LTFU) is a critical factor in determining clinical outcomes in HIV treatment programs. Identifying modifiable factors of LTFU is fundamental for designing effective patient retention interventions. We analyzed factors contributing to children LTFU from a treatment

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program to identify those that can be modified. A case-control study involving 313 children was used to compare the sociodemographic and clinical characteristics of children LTFU (cases) with those remaining in care (controls) at a large pediatric HIV care setting in Botswana. We traced children through caregiver contacts and those we found, we conducted structured interviews with patients' caregivers. Children < 5 years were nearly twice as likely as older children to be LTFU (57·8% versus 30·9%, p<0·01). Approximately half (47·6%, n=51) of LTFU patients failed to further engage in care after just one clinic visit, as compared to less than 1% (n=2) in the control group (p<0·01). Children LTFU were more likely than controls to have advanced disease, greater immunosuppression, and not to be receiving ART. Among interviewed patient caregivers, psychosocial factors (e.g. stigma, religious beliefs, child rebellion, disclosure of HIV status) were characteristic of patients LTFU, but not of controls. Socioeconomic factors (e.g. lack of transportation, school-related activities, forgetting appointments) were cited predominantly by the controls. Pediatric patients and their caregivers need to be targeted and engaged at their initial clinic visit, with special attention to children <5 years. Possible interventions include providing psychosocial support for issues that deter patients from engaging with the clinic. Collaboration with community-based organizations focused on reducing stigma may be useful in addressing these complex issues.

Keywords

HIV; pediatric; loss to follow-up; psychosocial factors; socioeconomic factors

Introduction

Loss to follow-up (LTFU) is used in the treatment of HIV/AIDS to define patients who have not presented for routine clinical evaluations for more than 180 days since their last clinic visits (Braitstein et al., 2010; Chi et al., 2011; Geng et al., 2010; Weigel et al., 2011; Yiannoutsos et al., 2008). LTFU is a critical barrier to providing effective patient care and hinders evaluating treatment programs, sometimes biasing outcome estimates (Bisson & Stringer, 2009; Fenner et al., 2010). Success of treatment programs will therefore depend on how well patients are retained in care (Gwynn et al., 2015; Ojwang et al., 2015). Patients on antiretroviral therapy (ART) who become LTFU are more likely to develop drug-resistant virus than are those who remain on ART, which in turn reduces the number of effective treatment options, particularly where access to alternative antiretroviral (ARV) medications may be limited (Mullen et al., 2002). Rosen, Fox, & Gill (2007) found that only 62% of patients in resource-constrained treatment settings were retained after 2 years of treatment.

Among children, HIV progresses more rapidly and they are more vulnerable to negative outcomes including death, compared to adults (Evans et al., 2013; Nachega et al., 2009; Nglazi et al., 2012). Without access to life-saving ART and regular medical supervision, HIV-infected children experience disease progression with mortality of 26–45% by age one year, 45–53% by age two years and 50–62% by age five years (Newell, Brahmbhatt, & Ghys, 2004; Spira, et al., 1999) therefore engaging and retaining children in care is essential for preventing mortality.

Reported risk factors for becoming LTFU include lack of transportation, work, child-care responsibilities, and unreported transfer to another clinic (Coleman et al., 2007; Fleishman et al., 2012; Geng et al., 2010). Other authors have found that LTFU of children is influenced by the family structure, including orphan status (Kamali et al., 1996), disclosure to the patient of their HIV status (Vreeman et al., 2010), or excessive waiting time at clinic (Alamo et al., 2012). Understanding the socioeconomic, clinical and systemic factors that contribute to LTFU is fundamental to designing effective patient retention interventions and evaluating the potential impact of global ART scale-up (Braitstein et al., 2011; Geng et al., 2010; Zachariah, Van Damme, Arendt, Schmit, & Harries, 2011).

HIV-infected children have largely been under-treated (World Health Organization, 2008). In 2012, only 24–32% of children in need of HIV/AIDS treatment had access to life-saving medication worldwide (UNAIDS, 2014; van Dijk, Moss, Hamangaba, Munsanje, & Sutcliffe, 2014). Children are particularly vulnerable because of their diminished capacities to make autonomous decisions regarding their healthcare (Allen & Marshall, 2008) and their dependence on adults for administration of their medications and transportation to the clinics (Leroy et al., 2013).

We aimed to determine the factors that contribute to LTFU among HIV-infected children. Specifically, we wanted to evaluate the following factors with relation to LTFU: (1) stage of HIV infection, (2) enrollment into ART, and (3) social and economic factors.

Methods

Study Setting and Design

This study was conducted at the Baylor-Botswana Children's Clinical Center of Excellence, BBCCCOE (henceforth, The Clinic) in Gaborone, Botswana, May – August 2012. We conducted a case control study to compare patients who had been LTFU (cases) with those remaining in active care (controls), based on the date of their last clinic visit. We defined cases as the patients listed as active in the Electronic Medical Records (EMR) database but had not attended The Clinic for more than 6 months and their whereabouts unknown to The Clinic. The un-matched controls were defined as the active patients who had continued to be treated in the clinic and did not miss appointments.

We queried the EMR to extract the following patient information: name, computer-generated unique ID, date of first and last visits to The Clinic, phone and physical contact information and relationship of primary caregiver. Clinical information was extracted separately from participant clinical records and included the World Health Organization (WHO) Clinical Staging of HIV/AIDS disease, ARV status and baseline HIV RNA (viral load) levels. For children older than 5 years and adolescents, absolute $CD4^+$ lymphocyte (CD4) cell counts were collected. For those younger than 5 years, CD4+ lymphocyte percentages were used. The degree of immunosuppression was categorized according to the Botswana National HIV/AIDS Treatment guidelines, 2008 version (Ministry of Health - Botswana, 2008).

Sampling and Data Collection

The sample size of 326 subjects was calculated on a 1:2 ratio of cases to controls to have 80% power with an alpha level of 0.05 to detect a 10% difference between cases and controls, and based on an expected percentage prevalence of advanced clinical stage being 25·7% and 12·6% for the cases and controls, respectively, as described in literature (Bisson et al., 2008; Braitstein et al., 2010). We factored in an estimated 15% non-response rate, as LTFU may be characterized mostly by those who are unreachable or decline to participate.

We attempted to reach study cases and controls first by telephone using their primary caregivers' telephone numbers on record. We tried to trace those not reachable by telephone by going to the last home address recorded in the EMR. The caregivers that were selected to participate in the study and were contacted had several days to consider the invitation to participate, and then a follow-up call was made. Those who agreed to participate were scheduled for interviews at their home or at The Clinic, at their convenience. No incentives were provided. Interviewers obtained informed consent from all primary caregivers and assent from children older than 10 years, as recommended by the local Institutional Review Board (IRB). For the young children under 10, we interviewed their caregiver with the child present and participating, as one interview schedule. Interviews were guided by a structured questionnaire on basic demographic characteristics (e.g., household income, household size, employment status); their most recent interaction with the Clinic, including mode of transportation and time required to get to the Clinic; their experiences with the health system; and their difficulties in attending clinics. Socioeconomic surrogate factors included food supplementation status, guardian employment status, and mode of transport to clinic.

Two bilingual data collectors were trained on using the questionnaire and study forms, handling the study documents, and maintaining confidentiality. Interviews were administered in Setswana or English, depending on the respondent's preference, and the standardized questionnaire forms were back-translated to English when applicable. Data were entered into Epi Info™; thereafter records were spot-checked on a random basis (Trochim & Donnely, 2008). Open-ended responses were coded into general and short themes. STATA 12.0 (StataCorp, College Station, TX, USA) was used for all data analysis. We used student's t-test for our test of significance to compare cases and controls with a p-value of < 0·05 considered statistically significant. IRB approvals were granted by the Botswana Ministry of Health's (MoH's) Health Research and Development Committee (HRDC), Baylor College of Medicine and the University of Texas' Health Committee for Protection of Human Subjects.

Results

As of May 2012, The Clinic had a total of 2386 active patients (female =1259, 52·7%). Inclusion criteria identified 1850 HIV-infected patients, on ART or not, aged 1 to 18 years, who had attended The Clinic. Their mean age was 10·9 years (SD = 4·55), including 901 females (48·7%). Children aged 1–5 years numbered 209 (11·30%), their mean age was 2·9 years (SD = 1·46), and 110 (52·63%) were females. Children older than 5-years numbered 1641 (mean age =12·2 years; SD = 3·25). Results were stratified by age groups because of the greater vulnerability of young children for disease progression and for becoming LTFU.

To examine the association of having advanced clinical disease with being LTFU, we used the records of all patients LTFU (n = 107), and compared the demographic and clinical conditions with those of 206 controls randomly selected from the pool of 1722 active patients, yielding a total of 313 children's records reviewed. Characteristics of the joint sample are presented in table 1. When all patients were considered, there was a significant difference in the age distribution between cases and controls: children 1–5 years old were twice as likely to be LTFU as those aged 5–18 years.

Of 275 children aged 5 to 18 years, 115 (41·8%) had baseline absolute CD4-count results recorded in the EMR database (table 2). Baseline clinical laboratory data were not available for many children as many were enrolled before the institution of the EMR database. At enrollment, there was no statistically significant difference in the mean absolute CD4 cell count of controls and cases at 673 cells/μL and 691 cells/μL respectively. For children aged 5 to 18 years with accessible baseline CD4 measurements, most (n=80; 69·6%) were mildly immunosuppressed. However, more children with severe immune deficiency had become LTFU (31·8% compared to 14·1% among controls, P = 0·047). Among the 275 participants, approximately 34% had plasma HIV RNA (viral load) levels measured prior to initiation of ART. Lack of viral load may be due to lack of availability of test or due to initiation before the EMR was instituted. Mean pre-ART viral load levels were higher for patients LTFU than for controls (Table 2). LTFU patients were more likely to be severely immunocompromised, to have advanced disease, and to have a higher viral load, and more than three times less likely to be on ART when compared to active patients.

Overall, more than half of those children who had been staged based on clinical features were classified as having advanced or severe disease, so were eligible for initiation of ART (table 2). Children who became LTFU were more likely to have stage 3 or 4 disease than were controls (72% versus 55%); however, LTFU cases were less likely to have been staged (data not shown).

All of the children younger than 5 years old who remained in care were started on ART, but only 9% of those who became LTFU received ART (table 3). The likelihood of ART being initiated seems to be related to the length of time that the child remained engaged with The Clinic: all those who remained in care had been followed for at least 6 months, none of those who became LTFU had been followed for more than 6 months. The vast majority of those who became LTFU had only one visit to The Clinic.

Of the children identified as LTFU, we were able to contact the caregivers of only 15, seven of whom agreed to participate in an interview, one declined, and seven children were reported to be deceased. We also contacted 206 controls who agreed to participate in an interview. A total of 213 interviews (7 cases and 206 controls) lasting twenty minutes on average were completed and table 4 depicts their socio-demographic characteristics. The gender distribution was not too different overall. Most children in both cases and controls were from a single mother guardian relationship (57% and 47% respectively). Some 14% of cases and 19% of controls received food supplementation, an indicator of household socio-economic status.

Table 5 describes how patients accessed the clinic, factors interfering with appointments, and suggestions for improvements. All LTFU cases (100%) said that they had difficulties affecting their attending The Clinic, whereas only 18% of the controls did. Forty-four interviewees listed 55 clinic-access difficulties/challenges. Caregivers of the patients who were LTFU cited a number of psychosocial issues (e.g., belief that child is well/healed, caregiver's fear of stigmatization, issues regarding the disclosure of the patient's HIV status to the child or to others), but no such responses were expressed by the controls. Conversely, controls cited lack of transportation as a hindrance to their regular clinic attendance; the cases did not identify transportation as a difficulty. Moreover, lack of transportation among the controls did not translate into their being LTFU. Caregivers of the controls cited the need to attend to other responsibilities as hindering their ability to keep clinic appointments. We did not probe further what these responsibilities were.

All respondents said they received medication during their last visits to The Clinic (data not shown). This question did not distinguish between antiretroviral medications used for treatment and other medications used prophylactically or medications prescribed for a non-HIV related illness. Approximately 57% of cases LTFU stated that they were not on any medication at the time of the interview, compared to just 1% of controls. When asked, the respondents noted changes that could be made at The Clinic to make it easier for them to attend clinic (Table 5). The controls expressed a desire for a reduction in waiting times, whereas the LTFU group wanted a reduction in the frequency of refill days. Both groups had a number of responses classified as "other needs" that included desire for weekend clinic operation, students to be given priority to see doctors so that they could attend school, elimination of language barriers between patient caregiver and some doctors, training of new staff to reduce waiting times, library for use during waiting times, and building of hostels where children could receive care and also attend school.

Discussion

The objective of this study was to examine factors associated with retention of HIV-infected children in treatment and to identify factors, both clinical and experiential, associated with being LTFU. Our analysis revealed that during their initial clinic visits most patients did not provide adequate contact information, hindering efforts to trace those LTFU. A possible remedy to this would be to ensure that each patient's contact information is reviewed and updated at every clinic visit and having a second or even third alternative confidante's contact information is recorded. This can be a labor-intensive undertaking and may involve task shifting among clinic employees. Indeed, studies have suggested that its worth exploring task shifting to non-physician health care workers and lay workers can be part of strategy to improve access to care (De Schacht, et al., 2014), and in our case, retain patients in care.

The barriers to regular clinic attendance cited most commonly included lack of transportation to and from the clinic, caregiver forgetting the check-up dates, and school-related activities that conflicted with the clinic calendar. We lumped together these singleton explanations of barriers to going to clinic, as important as we believe they were, but we did not probe an in-depth inquiry of this question, and therefore we did not get an elaboration of

the individual factors. It is important to explore these in detail in future studies. Other reasons included child rebellion, religious beliefs, denial of HIV status, social stigma, and disclosure issues. Barriers themselves were not our greatest concern: whether those barriers translated into a patient being LTFU as an outcome was the focus of our questions. Transportation costs were the most cited barrier among the respondents, similar to other studies (Ware et al., 2013; A. P. Hardon et al., 2007; Rosen, Ketlhapile, Sanne, & DeSilva, 2007; Meyer-Rath & Richter, 2007; Mukherjee, Ivers, Leandre, Farmer, & Behforouz, 2006; Tuller et al., 2010). However, it was not cited as the predominant reason that prevented clinic attendance among those LTFU. If lack of transportation is economically driven, then how the active patients were able to overcome the difficulty and the cases were not should be probed further. Mapping the addresses of potential patients LTFU to see if they are clustered would allow for more efficient deployment of an outreach team and/or providing transportation to clinic. If economic barriers had been perceived as a problem, providing monetary incentives (or in kind) to subsidize the household income would likely ensure compliance with treatment. Other programs – such as those for TB patients – have used incentives successfully (Chua, Lim, Ng, Chee, & Wang, 2015). After all, the cost of incentive is minimal compared to the cost of one life lost or the cost of the treatment.

LTFU occurring mostly after the first clinic visit or entirely within the first 6 months indicates a failure to engage with the clinic. The first visit appears to be the most critical point for establishing a patient retention plan. Previous studies have suggested using patient navigators – human resources to help provide effective communication between patient and their providers (Bradford, Coleman, & Cunningham, 2007; Cheever, 2007; Fleishman et al., 2012) – as a remedy for failure to engage. We propose that attention should be given at the initial visit to address personal concerns and that the outreach team is best suited to help the patient express concerns that might arise. Special attention should be given to the children younger than 5 years old, who predominantly became LTFU after their first clinic visit and are most vulnerable to mortality. Ditekemena et al. (2014) documented similar findings.

Although socioeconomic issues were common on both arms of the study, psychosocial rather than socioeconomic factors were cited exclusively by the patients LTFU as a barrier to their regular clinic attendance. This response indicates that interventions should pay special attention to psychosocial issues, as they also have been identified in other studies (Bygrave et al., 2012). This finding could be attributed to Botswana's status as a middle-income nation with better access infrustructure than would be the case in many low-income nations.

Phone calls made prior to appointments would help ensure that patients remember their scheduled appointments, but due to cost constraints only those who miss appointments are currently contacted. Scheduling patients for clinic visits should take into consideration conflicts with school events such as sports and examinations, which were cited as reasons for missed appointments and, in turn, could reveal the transitory nature towards being LTFU. This finding corroborates other study findings (A. Hardon et al., 2006; Ware et al., 2013).

Our study was not sufficiently powered to detect the level of importance of each factor that may have affected patients' regular clinic attendance, but the varied response to factors hindering clinic attendance reveals that these concerns need to be addressed. It is not clear if

these issues are just factors to improve their overall clinic experiences or are barriers to attending clinic.

Also, our study was limited by the small sample size of cases traced and interviewed, which precluded conducting a more robust analysis to evaluate the relationships. We anticipated this as a major handicap, knowing that populations that are LTFU may actually be difficult ones to trace and interview. We employed mixed methods of both qualitative and quantitative data collection to triangulate information from different sources.

The psychosocial nature of the barriers to clinic attendance reported by caregivers of patients LTFU suggests that collaboration between program developers and community faith-based organizations is needed to strategize interventions. This approach will help address the belief issues that hinder effective treatment, and find common ground whereby treatment programs and patient beliefs can work concurrently.

Conclusion

LTFU has an obvious bearing on clinical outcomes. Children who are sicker at the time of diagnosis and then become LTFU represent a failure of the healthcare system and/or the caregivers to detect these children early as being in need of particular attention. Some children became LTFU before they had completed the clinical and immunologic staging process, previously a prerequisite for ART initiation. More recent guidance from the World Health Organization emphasizes starting ART among children regardless of clinical or immunologic stage, particularly for infants and children younger than 5 years of age (World Health Organization, 2015). There is need for more education to health care providers and caregivers about focusing additional attention to these children to keep them in therapy.

The successful strategies for patient-retention programs for HIV-infected patients will be those that address both the individual needs of patients struggling to remain in care and the general needs of the larger, responsive population. Operationally, this approach requires devoting more human resources towards capturing as much contact information as possible during the initial visit, updating patient contact information at every opportunity and patient-reminder efforts. Devoting additional resources to boost engagement in care has been suggested elsewhere in the literature (Bygrave et al., 2012). Greater emphasis should be placed on the initial visit to the clinic, particularly for children younger than 5 years of age, when as our study has shown, they fail to engage clinically. Identifying potential psychosocial issues early and linking caregivers to community-based resources may improve engagement and long-term retention in care.

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References

Alamo ST, Colebunders R, Ouma J, Sunday P, Wagner G, Wabwire-Mangen F, Laga M. Return to normal life after AIDS as a reason for lost to follow-up in a community-based antiretroviral

treatment program. Journal of Acquired Immune Deficiency Syndromes. 2012; 60(2):e36–45. DOI: 10.1097/FTD.0b013e3182526e6a [PubMed: 22622076]

Allen D, Marshall ES. Children with HIV/AIDS: A vulnerable population with unique needs for palliative care. Journal of Hospice & Palliative Nursing. 2008; 10(6):359–367. DOI: 10.1097/01.NJH.0000319193.39648.b1

Bisson GP, Rowh A, Weinstein R, Gaolathe T, Frank I, Gross R. Antiretroviral failure despite high levels of adherence: Discordant adherence-response relationship in Botswana. Journal of Acquired Immune Deficiency Syndromes. 2008; 49(1):107–110. DOI: 10.1097/QAI.0b013e3181820141 [PubMed: 18667926]

Bisson GP, Stringer JS. Lost but not forgotten--the economics of improving patient retention in AIDS treatment programs. PLoS Medicine. 2009; 6(10):e1000174.doi: 10.1371/journal.pmed.1000174 [PubMed: 19859529]

Bradford JB, Coleman S, Cunningham W. HIV system navigation: An emerging model to improve HIV care access. AIDS Patient Care and STDs. 2007; 21(Suppl 1):S49–58. DOI: 10.1089/apc.2007.9987 [PubMed: 17563290]

Braitstein P, Katshcke A, Shen C, Sang E, Nyandiko W, Ochieng VO, … Ayaya S. Retention of HIV-infected and HIV-exposed children in a comprehensive HIV clinical care programme in western Kenya. Tropical Medicine & International Health. 2010; 15(7):833–841. DOI: 10.1111/j.1365-3156.2010.02539.x [PubMed: 20487430]

Braitstein P, Songok J, Vreeman RC, Wools-Kaloustian KK, Koskei P, Walusuna L, … Yiannoutsos C. "Wamepotea" (they have become lost): Outcomes of HIV-positive and HIV-exposed children lost to follow-up from a large HIV treatment program in western Kenya. Journal of Acquired Immune Deficiency Syndromes. 2011; 57(3):e40–46. DOI: 10.1097/QAI.0b013e3182167f0d [PubMed: 21407085]

Bygrave H, Mtangirwa J, Ncube K, Ford N, Kranzer K, Munyaradzi D. Antiretroviral therapy outcomes among adolescents and youth in rural Zimbabwe. PloS One. 2012; 7(12):e52856.doi: 10.1371/journal.pone.0052856 [PubMed: 23285204]

Cheever LW. Engaging HIV-infected patients in care: Their lives depend on it. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2007; 44(11):1500–1502. DOI: 10.1086/517534 [PubMed: 17479949]

Chi BH, Yiannoutsos CT, Westfall AO, Newman JE, Zhou J, Cesar C, … Thiebaut R. Universal definition of loss to follow-up in HIV treatment programs: A statistical analysis of 111 facilities in Africa, Asia, and Latin America. PLoS Medicine. 2011; 8(10):e1001111.doi: 10.1371/journal.pmed.1001111 [PubMed: 22039357]

Chua APG, Lim LKY, Ng H, Chee CBE, Wang YT. Outcome of grocery voucher incentive scheme for low-income tuberculosis patients on directly observed therapy in Singapore. Singapore Medical Journal. 2015; 56(5):274–279. DOI: 10.11622/smedj.2015054 [PubMed: 25788246]

Coleman S, Boehmer U, Kanaya F, Grasso C, Tan J, Bradford J. Retention challenges for a community-based HIV primary care clinic and implications for intervention. AIDS Patient Care and STDs. 2007; 21(9):691–701. DOI: 10.1089/apc.2006.0205 [PubMed: 17919096]

De Schacht C, Lucas C, Mboa C, Gill M, Macasse E, Dimande SA, … Guay L. Access to HIV prevention and care for HIV-exposed and HIV-infected children: a qualitative study in rural and urban Mozambique. BMC Public Health. 2014; 14(1240):1–12. DOI: 10.1186/1471-2458-14-1240 [PubMed: 24383435]

Ditekemena J, Luhata C, Bonane W, Kiumbu M, Tshefu A, Colebunders R, Koole O. Antiretroviral treatment program retention among HIV-infected children in the Democratic Republic of Congo. PLOS ONE. 2014; 9(12):1–16. DOI: 10.1371/journal.pone.0113877

Evans D, Menezes C, Mahomed K, Macdonald P, Untiedt S, Levin L, … Maskew M. Treatment outcomes of HIV-infected adolescents attending public-sector HIV clinics across Gauteng and Mpumalanga, South Africa. AIDS Research and Human Retroviruses. 2013; 29(6):892–900. DOI: 10.1089/AID.2012.0215 [PubMed: 23373540]

Fenner L, Brinkhof MW, Keiser O, Weigel R, Cornell M, Moultrie H, … Davis M. Early mortality and loss to follow-up in HIV-infected children starting antiretroviral therapy in Southern Africa. Journal of Acquired Immune Deficiency Syndromes. 2010; 54(5):524–532. DOI: 10.1097/QAI.0b013e3181e0c4cf [PubMed: 20588185]

Fleishman JA, Yehia BR, Moore RD, Korthuis PT, Gebo KA. Establishment, retention, and loss to follow-up in outpatient HIV care. Journal of Acquired Immune Deficiency Syndromes. 2012; 60(3):249–259. DOI: 10.1097/QAI.0b013e318258c696 [PubMed: 22531758]

Geng EH, Bangsberg DR, Musinguzi N, Emenyonu N, Bwana MB, Yiannoutsos CT, … Martin JN. Understanding reasons for and outcomes of patients lost to follow-up in antiretroviral therapy programs in Africa through a sampling-based approach. Journal of Acquired Immune Deficiency Syndromes. 2010; 53(3):405–411. DOI: 10.1097/QAI.0b013e3181b843f0 [PubMed: 19745753]

Gwynn RC, Fawzy A, Viho I, Wu Y, Abrams EJ, Nash D. Risk factors for loss to follow-up prior to ART initiation among patients enrolling in HIV care with CD4+ cell count ≥ 200 cells/μL in the multi-country MTCT-Plus Initiative. BMC Health Services Research. 2015; 15(247):1–10. DOI: 10.1186/s12913-015-0898-9 [PubMed: 25603697]

Hardon, A.; Davey, S.; Gerrits, T.; Hodgkin, C.; Irunde, H.; Kgatlwane, J.; … Laing, R. From access to adherence: The challenges of antiretroviral treatment. 2006. Retrieved from http://www.who.int/medicines/publications/challenges_arvtreatment15Aug2006.pdf

Hardon AP, Akurut D, Comoro C, Ekezie C, Irunde HF, Gerrits T, … Laing R. Hunger, waiting time and transport costs: Time to confront challenges to ART adherence in Africa. AIDS Care. 2007; 19(5):658–665. DOI: 10.1080/09540120701244943 [PubMed: 17505927]

Kamali A, Seeley JA, Nunn AJ, Kengeya-Kayondo JF, Ruberantwari A, Mulder DW. The orphan problem: Experience of a sub-Saharan Africa rural population in the AIDS epidemic. AIDS Care. 1996; 8(5):509–515. DOI: 10.1080/09540129650125470 [PubMed: 8893902]

Leroy V, Malateste K, Rabie H, Lumbiganon P, Ayaya S, Dicko F, … Dabis F. Outcomes of antiretroviral therapy in children in Asia and Africa: A comparative analysis of the IeDEA pediatric multiregional collaboration. Journal of Acquired Immune Deficiency Syndromes. 2013; 62(2):208–219. DOI: 10.1097/QAI.0b013e31827b70bf [PubMed: 23187940]

Meyer-Rath G, Richter M. User fees, transport costs, and the ethics of exemption: How free is free ART? The South African Journal of HIV Medicine. 2007; 8(2):52–56.

Ministry of Health - Botswana. Botswana national HIV/AIDS treatment guidelines: 2008 version. 2008. Retrieved from http://www.who.int/hiv/pub/guidelines/botswana_art.pdf

Mukherjee JS, Ivers L, Leandre F, Farmer P, Behforouz H. Antiretroviral therapy in resource-poor settings. Decreasing barriers to access and promoting adherence. Journal of Acquired Immune Deficiency Syndromes. 2006; 43(Suppl1):S123–126. DOI: 10.1097/01.qai.0000248348.25630.74 [PubMed: 17133195]

Mullen J, Leech S, O'Shea S, Chrystie IL, Du Mont G, Ball C, … Easterbrook P. Antiretroviral drug resistance among HIV-1 infected children failing treatment. Journal of Medical Virology. 2002; 68(3):299–304. DOI: 10.1002/jmv.10203 [PubMed: 12226814]

Nachega JB, Hislop M, Nguyen H, Dowdy DW, Chaisson RE, Regensberg L, … Maartens G. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in southern Africa. Journal of Acquired Immune Deficiency Syndromes. 2009; 51(1): 65–71. DOI: 10.1097/QAI.0b013e318199072e [PubMed: 19282780]

Newell ML, Brahmbhatt H, Ghys PD. Child mortality and HIV infection in Africa: A review. AIDS. 2004; 18(Suppl 2):S27–34.

Nglazi MD, Kranzer K, Holele P, Kaplan R, Mark D, Jaspan H, … Bekker LG. Treatment outcomes in HIV-infected adolescents attending a community-based antiretroviral therapy clinic in South Africa. BMC Infectious Diseases. 2012; 12(21):1–7. DOI: 10.1186/1471-2334-12-21 [PubMed: 22214291]

Ojwang V, Penner J, Blat C, Agot K, Bukusi E, Cohen C. Loss to follow-up among youth accessing outpatient HIV care and treatment services in Kisumu, Kenya. AIDS Care. 2015; :1–8. DOI: 10.1080/09540121.2015.1110234

Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: A systematic review. PLoS Medicine. 2007; 4(10):e298.doi: 10.1371/journal.pmed.0040298 [PubMed: 17941716]

Rosen S, Ketlhapile M, Sanne I, DeSilva MB. Cost to patients of obtaining treatment for HIV/AIDS in South Africa. South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde. 2007; 97(7):524–529. [PubMed: 17805455]

Spira R, Lepage P, Msellati P, Van de Perre P, Leroy V, Simonon A, … Dabis F. Natural history of Human Immunodeficiency Virus Type 1 Infection in children: a five-year prospective study in Rwanda. Pediatrics. 1999; 104(5):e56. [PubMed: 10545582]

Trochim, W.; Donnely, J. Analysis. In: Baird, M.; Staudt, M.; Stranz, M.; Leonard, K., editors. The research methods knowledge base. 3. Cengage Learning; 2008. p. 251-281.

Tuller DM, Bangsberg DR, Senkungu J, Ware NC, Emenyonu N, Weiser SD. Transportation costs impede sustained adherence and access to HAART in a clinic population in southwestern Uganda: A qualitative study. AIDS and Behavior. 2010; 14(4):778–784. DOI: 10.1007/s10461-009-9533-2 [PubMed: 19283464]

UNAIDS. Children and HIV Fact Sheet. Geneva, Switzerland: UNAIDS; 2014. Retrieved from http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/unaidspublication/2014/FactSheet_Children_en.pdf

van Dijk JH, Moss WJ, Hamangaba F, Munsanje B, Sutcliffe CG. Scaling-up access to antiretroviral therapy for children: A cohort study evaluating care and treatment at mobile and hospital-affiliated HIV clinics in rural Zambia. PLoS ONE. 2014; 9(8):e104884.doi: 10.1371/journal.pone.0104884 [PubMed: 25122213]

Vreeman RC, Nyandiko WM, Ayaya SO, Walumbe EG, Marrero DG, Inui TS. The perceived impact of disclosure of pediatric HIV status on pediatric antiretroviral therapy adherence, child well-being, and social relationships in a resource-limited setting. AIDS Patient Care and STDs. 2010; 24(10):639–649. DOI: 10.1089/apc.2010.0079 [PubMed: 20836704]

Ware NC, Wyatt MA, Geng EH, Kaaya SF, Agbaji OO, Muyindike WR, … Agaba PA. Toward an understanding of disengagement from HIV treatment and care in sub-Saharan Africa: A qualitative study. PLoS Medicine. 2013; 10(1):e1001369.doi: 10.1371/journal.pmed.1001369 [PubMed: 23341753]

Weigel R, Hochgesang M, Brinkhof MW, Hosseinipour MC, Boxshall M, Mhango E, … Phiri S. Outcomes and associated risk factors of patients traced after being lost to follow-up from antiretroviral treatment in Lilongwe, Malawi. BMC Infectious Diseases. 2011; 11(31):1–8. DOI: 10.1186/1471-2334-11-31 [PubMed: 21199579]

World Health Organization. Towards universal access: Scaling up priority HIV/AIDS interventions in the health sector. 2008. Retrieved from http://www.who.int/hiv/mediacentre/key_messages_A4_en.pdf

World Health Organization. Guideline on when to start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV. Geneva: World Health Organization; 2015 Sep.

Yiannoutsos CT, An MW, Frangakis CE, Musick BS, Braitstein P, Wools-Kaloustian K, … Kimaiyo S. Sampling-based approaches to improve estimation of mortality among patient dropouts: Experience from a large PEPFAR-funded program in western Kenya. PloS One. 2008; 3(12):e3843.doi: 10.1371/journal.pone.0003843 [PubMed: 19048109]

Zachariah R, Van Damme W, Arendt V, Schmit JC, Harries AD. The HIV/AIDS epidemic in sub-Saharan Africa: Thinking ahead on programmatic tasks and related operational research. Journal of the International AIDS Society. 2011; 14(Suppl 1):S1–S7. DOI: 10.1186/1758-2652-14-S1-S7

Table 1

Characteristics of children analyzed in the BBCCCOE clinic in Gaborone, Botswana

	Totals	All N (%) 313	Cases N (%) 107 (34.2)	Controls N (%) 206 (65.8)	*p*
Gender	**313**				
Female		148 (47·3)	50 (46·7)	98 (47·6)	0·89
Male		165 (52·7)	57 (53·3)	108 (52·4)	
Age	**313**				
Under 5 year olds		38 (12·1)	22 (20·6)	16 (7·8)	<0·01
Over 5 year olds		275 (87·9)	85 (79·4)	190 (92·2)	
Mean age (SD)	**313**				
Overall mean age (SD)		10·8 (4·5)	9·3 (4·9)	11·7 (4·0)	<0·01
Under 5 year olds, mean (SD)		2·3 (1·2)	2·1 (1·2)	2·6 (1·3)	0·24
Over 5 year olds, mean (SD)		12·1 (3·4)	11·1 (3·8)	12·5 (3·1)	<0·01
Retention	**313**				
Under 5 year olds		38 (12·1)	22 (20·6)	16 (7·8)	<0·01
Over 5 year olds		275 (87·9)	85 (79·4)	190 (92·2)	
Length of enrollment	313				
1 visit		53 (16·9)	51 (47·7)	2 (0·9)	<0·01
< 6 months		34 (10·9)	26 (24·3)	8 (3·8)	
> 6 months		226 (72·2)	30 (28·0)	196 (95·1)	

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Table 2

Clinical characteristics of children (n=275) aged 5 – 18 years whose medical records were analyzed, in Gaborone, Botswana

	Totals	All N (%)	Cases 85 (%)	Controls 190 (%)	*p*
Baseline CD4 cell counts classifications (cells/μL)	**115**				
Mild Immunosuppression (>350)		80 (69·6)	28 (63·6)	52 (73·2)	0·04
Advanced (200–349)		11 (9·6)	2 (4·6)	9 (12·7)	
Severe (<200)		24 (20·9)	14 (31·8)	10 (14·1)	
Absolute CD4 cell counts	115		44	71	
Mean (SD)		679 (544)	691 (628)	673 (489)	0·86
Duration of clinic attendance	275				
Number with CD4 measures		115	44	71	
Duration in days (SD)		1489 (1260)	406(604)	21601082	<0·01
Number without CD4 measures		160	41	119	
Duration in days (SD)		1044 (1000)	157 (312)	1350 (973)	<0·01
Viral load	**275**				
# with baseline viral load		94	42	52	
Mean (SD) baseline viral load (*in logs*)		5·10 (0·75)	5·33 (0.70)	4.92 (0·74)	<0·01
# without baseline viral load		181	43	138	
WHO staging of HIV infection	249				
I and II		101 (40·6)	17 (27·9)	84 (44·7)	0·02
III and IV		148 (59·4)	44 (72·1)	104 (55·3)	
Patient on ART	275				
Yes		208 (75·6)	24 (28·2)	184 (96·8)	<0·01
No		67 (24·4)	61 (71·8)	6 (3·2)	
Patient not on ART (cells/μL)	62				
Mild Immunosuppression (>350)		56 (90·3)	51(89·5)	5(100·0)	1·00
Advanced (200–350)		2 (3·2)	2 (3·5)	0(0·0)	
Severe (< 200)		4 (6·5)	4 (7·0)	0(0·0)	
Length of enrollment	275		85	190	
Mean days (SD)		1325 (1936)	594 (2965)	1653 (1086)	<0·01
Duration enrolled at Clinic	275				

	Totals	All N (%)	Cases 85 (%)	Controls 190 (%)	*p*
1 visit		33 (12·0)	31 (36·5)	2 (1·1)	<0·01
< 6 months		32 (11·6)	24 (28·2)	8 (4·2)	
> 6 months		210 (76·4)	30 (35·3)	180 (94·7)	

Table 3

Clinical characteristics of children (n=38) aged < 5 years whose medical records were analyzed at BBCCCOE clinic in Gaborone, Botswana

	Totals 38	All N (%)	Cases 22 (%)	Controls 16 (%)	*p*
CD4 %	17		6	11	
Mean (SD)		20 (12)	17 (13)	22 (12)	0·47
CD4% classification	17				
Mild Immunosuppressed (>=20%)		7 (18·4)	1(4·6)	6 (37·5)	0·16
Advanced Immunosuppressed (<20%)		10 (26·3)	5 (22·7)	5 (31·3)	
Duration of clinic attendance	38				
# with CD4% measures		17	6	11	
Duration in days (SD)		518 (480)	13 (18)	794 (363)	<0·01
# without CD4% measures		21	16	5	
Duration in days (SD)		283 (555)	1 (0·00)	1186 (454)	<0·01
WHO staging	31				
I		18 (58·1)	10 (66·7)	8 (50·0)	0·44
II		1(3·2)	1 (6·7)	0 (0·0)	
III		5(16·1)	1 (6·7)	4 25·0)	
IV		7 (22·6)	3 (20·0)	4 (25·0)	
Patient on ART	38				
Yes		18 (47·4)	2 (9·1)	16 (100·0)	<0·01
No		20 (52·6)	20 (90·9)	0 (0·0)	
Length of enrollment	38		22	16	
Mean days (SD)		388·2 (529·6)	4·1 (10·2)	916·3 (421·8)	<0·01
# of clinic visits	38				
1 visit		20 (52·6)	20 (90·9)	0 (0·0)	<0·01
< 6 months		2 (5·3)	2 (9·1)	0 (0·0)	
> 6 months		16 (42·1)	0 (0·0)	16 (100·0)	

Table 4

Demographic and social characteristics of children (n=213) attending BBCCCOE Clinic, in Gaborone, Botswana

	Totals 213	All N (%)	Cases 7 (%)	Controls 206 (%)
Mean Age in yrs. (SD)		11·71 (4.0)	12 (4·6)	11·69 (4.0)
Gender				
Female		98 (46·1)	4 (57·2)	94 (45·6)
Male		115 (53·9)	3 (42·8)	112 (54·4)
Household (HH) size	213			
Small HH (less than 5 members)		112 (52·6)	2 (28·6)	110 (53·4)
Medium HH (5–10 members)		81 (38·0)	3 (42·8)	78 (37·9)
Large HH (more than 10 members)		20 (9·4)	2 (28·6)	18 (8·7)
Primary guardian	213			
Father & Mother		32 (15·0)	0 (0·0)	32 (15·5)
Father only		11 (5·2)	0 (0·0)	11 (5·3)
Mother only		100 (46·9)	4 (57·1)	96 (46·6)
Siblings		9 (4·2)	0 (0·0)	9 (4·4)
Other relatives		57 (26·8)	3 (42·9)	54 (26·2)
Lives in SoS[1] Care facility		4 (1·9)	0 (0·0)	4 (1·9)
Orphan status	181			
Both parents alive		33 (18·2)	2 (28·6)	31 (17·8)
Both parents dead		58 (32·0)	2 (28·6)	56 (32·2)
One dead parent, other alive		15 (8·3)	1 (14·3)	14 (8·0)
Other		4 (2·2)	0 (0·0)	4 (2·3)
Unknown		71 (39·3)	2 (28·6)	69 (39·7)
Guardian employment status	211			
Yes		67 (31·5)	3 (42·9)	64 (31·4)
No		144 (67·6)	4 (57·1)	140 (68·6)
Guardian education level	213			
Never went to school		4 (1·9)	1 (14·3)	3 (1·5)
Primary (≤ 8 years)		48 (22·5)	3 (42·9)	45 (21·8)
Secondary (≤ 12 years)		143 (67·1)	3 (42·9)	140 (68·0)
Tertiary/College (≥ 12 years)		15 (7·0)	0 (0·0)	15 (7·2)
Other		3 (1·4)	0 (0·0)	3 (1·5)
Number of HH members working	213			
1 member		85 (39·9)	3 (42·9)	82 (39·8)
2 members		65 (30·5)	2 (28·6)	63 (30·6)
3 members		14 (6·6)	0 (0·0)	14 (6·8)
>=4 members		10 (4·7)	1 (14·3)	9 (4·4)
None		35 (16·4)	1 (14·3)	34 (16·5)
N/A (lives in [1] SoS)		4 (1·9)	0 (0·0)	4 (1·9)

	Totals 213	All N (%)	Cases 7 (%)	Controls 206 (%)
Food supplementation	213			
Yes		41 (19·3)	1 (14·3)	40 (19·4)
No		172 (80·7)	6 (85·7)	166 (80·6)

[1] SoS: A facility that takes care of orphaned, destitute and abandoned children

Table 5

Psychosocial and socioeconomic factors among children (n=213) attending BBCCCOE clinic, in Gaborone, Botswana

	Total 213	All N (%)	Cases 7 (%)	Controls 206 (%)
Mode of transport to HIV clinic	213			
Walking		7 (3·3)	0 (0·0)	7 (3·4)
Public Transport (bus or '*combi*')		179 (84·0)	7 (100·0)	172 (83·5)
Private Car		27 (12·7)	0 (0·0)	27(13·1)
Travel time to Pediatric HIV clinic	213			
< 10 minutes		8 (3·7)	0 (0·0)	8 (3·9)
10 – 30 minutes		57 (26·8)	0 (0·0)	57 (27·7)
30 – 60 minutes		93 (43·7)	3 (42·9)	90 (43·7)
> 1 hour		55 (25·8)	4 (57·1)	51 (24·8)
Do you encounter difficulties to attend the clinic?	213			
Yes		44 (20·7)	7 (100·0)	37 (18·0)
No		169 (79·3)	0 (0·0)	169 (82·0)
What kinds of difficulties affect your attending clinic? (*More than one answer accepted*)	55			
Caregiver-related commitment		10 (22·7)	2 (28·6)	8 (21·6)
Lack of transport		17 (38·6)	1 (14·2)	16 (43·2)
Forgot check-up dates		10 (22·7)	0 (0·0)	10 (22·7)
Child rebellion		2 (4·5)	2 (28·6)	0 (0·0)
Denial of HIV status		4 (9·0)	4 (57·1)	0 (0·0)
Non-disclosure issues		2 (4·5)	2 (28·6)	0 (0·0)
School-related activities		8 (18·2)	0 (0·0)	8 (21·6)
Religious beliefs		1 (2·3)	1 (14·2)	0 (0·0)
Believes child is well		1 (2·3)	1 (14·2)	0(0·0)
Have difficulties prevented you from clinic attendance?	44			
Yes		25 (56·8)	7 (100·0)	18 (48·7)
No		19 (43·2)	0 (0·0)	18 (51·3)
Ways difficulties prevented your clinic attendance *(more than one answer accepted)*	28			
Attended to other caregiver commitments		12 (48·0)	1 (14·3)	11 (61·1)
Believes child is well/healed		2 (8·0)	2 (28·6)	0 (0·0)
Caregiver stigmatized		2 (8·0)	2 (28·6)	0 (0·0)
Child rebellion		1 (4·0)	1 (14·3)	0 (0·0)
Lacked Transport		8 (32·0)	0 (0·0)	8 (44·4)
Concerns about patient HIV status disclosure		2 (8·0)	2 (28·6)	0 (0·0)
Chose to attend to school activities		1 (4·0)	0 (0·0)	1 (0·0)
Are there changes at clinic that will make it easier for you to attend clinic?	213			
Yes		72 (33·8)	4 (57·1)	68 (33·0)
No		141 (66·2)	3 (42·9)	138 (67·0)

	Total 213	All N (%)	Cases 7 (%)	Controls 206 (%)
Name the changes that will make it easier for you to attend clinic	99			
Reduce clinic and/or pharmacy waiting time		44 (44·4)	0 (0·0)	44 (47·3)
Reduce frequency of refill days		8 (8·1)	1 (16·7)	7 (7·5)
Continuity of being seen by same clinician		1 (1·0)	0 (0·0)	1 (1·1)
Increase family clinic services		2 (2·0)	0 (0·0)	2 (2·2)
Provide afternoon appointment option		3 (3·0)	0 (0·0)	3 (3·2)
Other needs		41 (41·4)	5 (83·3)	36 (38·7)
Registration of next visit during last visit	213			
Yes		200 (93·9)	7(100·0)	193 (93·7)
No		13 (6·1)	0 (0·0)	13 (6·3)
Is patient currently on medication? (%)	213			
Yes		206 (96·7)	3 (42·9)	203 (98·5)
No		7 (3·3)	4 (57·1)	3 (1·5)