High loss to follow-up of children on antiretroviral treatment in a primary care HIV clinic in Johannesburg, South Africa

Nomathemba Chandiwana, MBChB, MPHa, b, Shobna Savary, MSC(Med)b, Matthew Chersich, MBChb, PhDa, Elizabeth Kachingwe, MSc(Med)a, Bulelani Makhathini, BCSc, Lee Fairlie, MBChb, FC Paeds, MMEDa

Abstract
Outcomes of HIV-infected children have improved dramatically over the past decade, but are undermined by patient loss to follow-up (LTFU). We assessed patterns of LTFU among HIV-infected children receiving antiretroviral treatment (ART) at a large inner-city HIV clinic in Johannesburg, South Africa between 2005 and 2014.

Demographic and clinical data were extracted from clinic records of children under 12 years. Differences between characteristics of children retained in care and LTFU were assessed using Wilcoxon rank sum tests or Pearson χ2 tests. Cox proportional hazard models then identified characteristics associated with LTFU.

Of 135 children, the median age at ART initiation was 21.5 months (IQR: 6.3–47.7) with a median follow-up time of 3.3 years (IQR: 1.4–5.0). The incidence rate of LTFU was 10.8 per 100 person-years (95% CI: 8.2–14.4); cumulatively 36% of children were LTFU.

Almost a third (n=39) of children missed a clinic visit, but then returned to care; 77% of these were eventually LTFU. In total, 18% of children had elevated viral loads after 6 or more months of ART. Older age at ART initiation (18–59 months: aHR 1.6, 95% CI: 3.9–14.2) and ever missing a clinic visit (aHR 7.4 95% CI: 3.9–14.2) were independent predictors of LTFU.

High rates of LTFU were observed in this primary care clinic. Risks for LTFU included older age (>18 months old) and missed clinic visits. Identifying children who miss scheduled visits and developing strategies directed at retaining them in care is critical to improving long-term pediatric HIV outcomes.

Abbreviations: aHR = adjusted hazard ratio, ART = antiretroviral therapy, CCA = cumulative clinic adherence, CD4 = T-lymphocyte cell bearing CD4 receptor, CI = confidence interval, EFV = efavirenz, HIV = human immunodeficiency virus, IeDEA-SA = International Epidemiologic Database to Evaluate AIDS Southern Africa, IQR = interquartile range, LTFU = loss to follow-up, NVP = nevirapine, PI = protease inhibitor, WHO = World Health Organization.

Keywords: antiretroviral treatment, HIV-infected children, loss to follow-up, primary care clinic, South Africa

1. Introduction
The remarkable success in treatment of HIV-infected children has altered pediatric HIV from being a progressively fatal disease to a manageable chronic condition. Scale-up of early infant HIV diagnosis, coupled with increased access to pediatric HIV care and treatment across sub-Saharan Africa, where over 90% of children living with HIV reside,[1] has improved survival and reduced mortality in the past decade. Consequently, many perinatally HIV-infected children are surviving into adolescence and adulthood.[2–4] In addition, an International Epidemiologic Database to Evaluate AIDS Southern Africa (IeDEA-SA) multicohort analysis showed that, compared with 2006, by 2010, children under 16 years had fewer markers of advanced clinical disease at the start of treatment, and had improved growth, lower levels of anaemia and higher baseline CD4 counts at antiretroviral therapy (ART) initiation.[5]

Despite these notable achievements,[5] challenges remain throughout the treatment cascade, particularly in maintaining viral suppression and retaining patients in long-term care.[6–8] Opportunities to retain children within the cascade are missed at each step and the risk of mortality is especially high in the first 90 days following ART initiation.[10–12] Several studies in sub-Saharan Africa describe high rates of loss to follow-up (LTFU) once children have entered care.[6–9] In Kenya, the rate of LTFU among HIV-infected children was 14.2 per 100 children years post initiation, with being severely immunocompromised as the only risk factor for LTFU (adjusted hazard ratio (aHR): 2.2, 95% CI: 1.51–3.12).[13,14] Leroy et al.[15] combined the pediatric IeDEA cohort data from Africa and Asia, and reported an overall LTFU rate of 12% after 18 months on ART and a cumulative mortality of about 6%, with the highest LTFU rate reported from West-Africa (16%). In this analysis, risk factors for LTFU included being under 1 year at ART initiation, advanced disease, not initiating a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based...
regimen, and obtaining care from a public sector clinic.\textsuperscript{14} Similarly, a recent systematic review of 12 studies reporting retention rates among HIV-infected children found that LTFU ranged from 5% to 29% one year after ART initiation; with risks of attrition linked to younger age, more severe immunocompromise and a shorter period on ART. Of concern, among the children who were lost to follow-up, 27% had died.\textsuperscript{15}

Missed clinic visits are associated with poor ART outcomes in adults; these include poor CD4 count recovery, failure to suppress virologically, and increased mortality in the short and long terms.\textsuperscript{16,17} Few studies, however, have examined the rates and consequences of clinic nonattendance among children. Somewhat surprisingly, in contrast with adult studies, in Western Kenya, Nyandiko et al report that children with greater adherence to clinic visits, scored as cumulative clinic adherence (CCA) to visits, were at higher risk for mortality and LTFU at 3 and 6 months post-ART initiation. However, by 24 months, higher CCA was associated with lower mortality and LTFU.\textsuperscript{18} This initially increased risk in mortality and LTFU was attributed to those children with more severe immune suppression, likely with late presentation, being given more frequent appointments and families being more adherent to these visits.\textsuperscript{18}

Achieving high rates of retention is central to the UNAIDS “90-90-90” targets,\textsuperscript{19} especially that 90% of HIV-infected people will receive sustained ART and 90% will have viral load suppression.\textsuperscript{20} In this study, we used routine clinic data to describe LTFU and identify high-risk groups among children receiving ART in inner-city Johannesburg, South Africa.

2. Methods

2.1. Study design, setting, and population

We conducted a retrospective record review of children on ART who attended a public sector primary care clinic between January 2005 and December 2014. The clinic is located in a densely populated urban setting in Johannesburg that is characterized by high levels of migration.\textsuperscript{21} It is operated by the South African Department of Health and supported by the Wits Reproductive Health and HIV Institute (Wits RHI), and provides free ART, primary care services, and psychosocial support to both adult and pediatric HIV patients. HIV-infected children who were ≤12 years at the time of their last visit and on either a standard first-line or second-line ART regimen were included in the analysis. Ethical clearance for this study was granted by the University of the Witwatersrand Human Research Ethics Committee. Approval for conducting the study was given by the Johannesburg Health District Research Committee.

2.2. Study variables and definitions

Patient data were extracted from medical records, from the visit at which ART was initiated until any of the following time-points: last clinic visit, LTFU or transfer out. Information on patient mortality among those LTFU had not been systematically collected. Data extracted included patient demographics, WHO clinical staging, absolute CD4 count, CD4 percentage, HIV plasma viral load, ART treatment history, and clinic visit history.

Children were initiated on a protease inhibitor (lopinavir/ritonavir (LPV/r)) regimen if <3 years of age, or a NNRTI-based regimen, usually efavirenz, but occasionally nevirapine, if they were ≥3 years. The nucleoside reverse transcriptase inhibitors used before 2010 included stavudine and lamivudine, with stavudine replaced with abacavir after 2010. Children were switched to a second-line ART regimen, when indicated, according to the national guidelines.\textsuperscript{22,23} A missed clinic visit was defined as nonattendance at the clinic >30 days but <90 days after the scheduled visit date, followed by a return to the clinic. Reasons for missed visits were not captured in most records.

Children with WHO stage 3 or 4 disease were considered to have advanced clinical disease. HIV viral load tests and CD4 counts were performed by the National Health Laboratory Service. HIV viral loads conducted post ART initiation were classified in 2 ways: virologically suppressed (<400 copies/mL) or not (≥400 copies/mL); and ever had an elevated viral load (>1000 copies/mL) or not (<1000 copies/mL). Virological failure was defined as 2 or more consecutive viral loads >1000copies/mL. Immune suppression was defined according to the age of the child: children <5 years with a CD4% <15% and children ≥5 years with a CD4 absolute count of <200cells/μL were classified as severely immune suppressed; children <5 years with a CD4% of 15% to 24% and children ≥5 years with a CD4 absolute count 200 to 499cells/μL as moderately immune suppressed; and children <5 years with a CD4% of ≥25% and children ≥5 years with a CD4 absolute count of ≥500cells/μL as immunologically normal.\textsuperscript{24} The primary outcome was LTFU, defined as no clinical contact ≥90 days after the date of a scheduled clinic visit or pharmacy refill.

2.3. Statistical analysis

Patient characteristics are presented overall and stratified by status at last clinic visit (retained in care or LTFU). All continuous variables were not normally distributed based on histograms and normal quantile plots, and thus were summarized using medians and compared using Wilcoxon rank-sum tests. Categorical variables, presented as proportions, were compared using the χ² test. Follow-up time was calculated as the person-time accrued from date of ART initiation to the earliest of date of last visit if LTFU, or date of last follow-up visit or transfer out before December 31, 2014.

Associations between patient characteristics and status at last visit were assessed using Cox proportional hazard models. Models included variables considered a priori to affect the probability of LTFU (i.e., age at ART initiation and ever missed a clinic visit) and all variables with P ≤.2 in univariate analyses. Backward elimination was used to select the most parsimonious model. Hazard proportionality was assessed by analysis of scaled Schoenfeld residuals. Kaplan–Meier survival curves showing the cumulative probability of LTFU were stratified by age group at ART initiation and ever missed a clinic visit. Survival curves were compared using log rank tests with follow-up time truncated at 5 years. Statistical analyses were performed using STATA (Statacorp, LP), version 13.1.

3. Results

3.1. Characteristics of cohort at ART initiation

Among the 135 HIV-infected children included in the study, 50.4% were female, and the median age at ART initiation was 21.5 months (Table 1). At ART initiation, 52 (54.2%) children were classified as WHO clinical stage 3 or 4, and 30.3% had severe immune suppression. The median CD4 percentage was 19.4% (IQR, 13.6–34.2) and 15 (19.5%) children had viral loads above 1 million copies/mL. Approximately half of the children,
73 of 135 (54.1%) initiated ART on a LPV/r-based regimen, with the remainder initiating efavirenz- or nevirapine-based regimens.

### 3.2. Outcomes at last visit

By the last visit, the median age was 6.9 years (IQR, 3.9–8.9), the median follow-up time was 3.3 years (IQR, 1.4–5.0). The number of children with severe immune suppression at their last visit decreased to 2.2%. Four (3.0%) children changed to a second-line regimen. About 13% (15/114) of children did not have follow-up viral loads available in their clinic records. Of those with results, 4 (4.0%) experienced virological failure and 18 (18.4%) ever had an elevated viral load at any time post ART initiation (Table 1). Those who ever had an elevated viral load were more likely to have moderate immune suppression (odds ratio: 3.89, 95% CI: 1.55–9.5) at their last visit compared with those with viral load suppression.

Of the 135 children, 114 (84%) were in care for more than 6 months post-ART initiation. Over the whole follow-up period, the overall incidence rate of LTFU was 10.8 per 100 person-years (95% CI, 8.2–14.4); while 1-year retention was 88% (95% CI: 80–92) and 86 (64%) were retained in care at the clinic or transferred to another facility at last follow-up. Children who were retained in care did not have significantly different demographic and clinical characteristics at ART initiation compared with those LTFU (Table 1). Children who were LTFU were, however, more likely to have a better WHO clinical stage (1 or 2) compared with those who were retained in care (79.2% vs 54.5%, P = .04). Thirty percent of children had ever missed a clinic visit. Children who were LTFU were more likely to have ever missed a clinic visit than those retained in care (68.2% vs 10.5%, P < .001).

As shown in the Kaplan–Meier survival curves (Fig. 1), up until 1 year after ART initiation, all age groups appeared to have similar probabilities for LTFU, but from 1 year post initiation onward, older children had a higher probability of LTFU (Fig. 1A). Four years after ART initiation, the cumulative probabilities of LTFU were 0.22, 0.36, and 0.48 among children <18 months, 18 to 59 months, and ≥60 months old at ART initiation, respectively (log rank P = .18; Fig. 1A). The Kaplan–Meier cumulative probability for LTFU in those who missed a visit rose to 0.51 at 3 years post initiation and increased further to 0.80 5-years post-ART initiation, compared to about 0.06 and 0.11, respectively, for children who had never missed a visit (log rank test P < .001; Fig. 1B).

A total of 94 (70%) children were included in the final multivariate cox proportional hazards model as the rest did not have data available for all the variables included. Compared with children <18 months old at ART initiation, older children aged 18 to 59 months (aHR: 5.2, 95% CI: 1.7–15.3) and those 60 months and older (aHR: 8.3, 95% CI: 1.6–41.9) were more likely to be LTFU post-ART initiation. Similarly, children who ever missed a clinic visit were more likely to be LTFU (aHR: 7.4, 95% CI: 3.9–14.2). Children who ever presented with an elevated viral load were less likely to be LTFU (aHR: 0.2, 95% CI: 0.04–0.8) (Table 2).
adherence to clinic visits in the first 6 months after initiation, most likely because these children were at greater risk for morbidity and mortality and thus were monitored more closely. In our study, children who were LTFU were more likely to have WHO stage 1 or 2 disease, suggesting that in relatively well, older children retention in care is problematic. Less intensive services may be provided for asymptomatic older children as they are at lower risk of opportunistic infection such as TB and may be in better clinical health. This sense of urgency regarding younger children is likely also perceived by caregivers, resulting in improved compliance with clinic visits and perhaps medication adherence. As children get older and enter the school system, it may be more difficult to comply with clinic visits. We also found that missed clinic visits were associated with LTFU, which highlights that in routine programmes, it is not sufficient to focus only on aspects of HIV care, such as elevated viral loads and virological failure, but that ongoing intensive efforts are required to retain children in care. More intensive enquiry into reasons for missed visits and interventions to reduce these and link children back into care coupled with step-up adherence counselling is necessary. These interventions are challenging to implement in already over-burdened primary care settings and this is a potential pitfall of decentralized care. Of interest, we found that having an increased viral load was protective of LTFU, which could be secondary to more frequent clinic visits and increased intensity of adherence counselling in children who had increased viral load. It is also possible that this is the result of bias, with children retained in care being more likely to have an increased viral load at some point in their disease course than those with shorter durations of care.

Children form a relatively small percentage of the overall HIV burden, but are the most vulnerable in terms of morbidity and mortality. Decentralization of pediatric HIV care with ART initiation in nurse-managed rather than specialist physician-led care, has resulted in good treatment outcomes, including high rates of retention in care. In a prospective cohort study from Zimbabwe, only 4% of children aged 6 to 15 years were LTFU 18 months post ART initiation, although only 64% of children were virally suppressed. Attention is needed to ensure that, in the long run, the care provided by decentralized services is not hampered by inadequate clinical and psychosocial support for patients in these often under resourced, high volume, primary care settings. Innovative linking and tracing programmes need to be developed and scaled up to optimize retention throughout the treatment cascade. Children are dependent on an adult caregiver to access care and to administer medications, and complex social and health-related issues including poor health or loss of the caregiver, financial constraints, issues of stigma, and disclosure are likely to contribute to missed visits and LTFU. Interventions to improve long-term pediatric retention in HIV care may include aligning the follow-up visits of children and their caregivers, and improved psychosocial support for older children and their caregivers. Community health workers hold great promise in all aspects of HIV-related and HIV-unrelated health care and indeed form part of the facility-based tracing teams in South Africa’s primary health care re-engineering programme. Ahmed et al demonstrated a 6-fold increase in the number of HIV-infected children linked into care using trained community health care workers in Malawi. Adherence programmes for caregivers of children and for older children themselves, such as adherence clubs or family clubs, require
further exploration. Furthermore, clinics should consider offering tailored services for families and children attending school, such as after hours and weekend clinical services. Implementation and scale-up of practices which address barriers to retention (including caregiver, health care system, and institutional barriers) is important as, although fewer children are vertically HIV-infected as a result of successful PMTCT interventions, early initiation with increased survival will still result in substantial numbers of children requiring lifelong ART.

Our study had several limitations. The study’s retrospective design and reliance on medical records collected primarily for patient care rather than for research, led to missing data and possible information bias. In particular, anthropometric measurements and other clinical data had not been systematically recorded and there was no data on caregiver characteristics, which are likely to influence retention. Any attempts made to trace children who were LTFU and the outcomes of these attempts, including any deaths, were also not recorded. While our findings may be relevant to pediatric care in similar settings, larger studies are needed to more fully investigate challenges with decentralized care and the reasons for poor engagement of HIV-infected children in these services. Similarly, more comprehensive and multidisciplinary approaches are required to identify the factors affecting the adherence to ART, especially in children above 18 months.

### 5. Conclusion

This retrospective review of a routine pediatric HIV clinic found that a high percentage of children were LTFU after ART initiation. One of the main predictors for LTFU was ever having missed a clinic visit; where 77% of children who had ever missed a visit were eventually lost to follow-up. Older children were also more likely to be LTFU, likely highlighting adherence issues once children enter the school system; these children require a more innovative approach to retention in care. These findings should prompt interventions to raise adherence, but also discussion with caregivers around the barriers to clinic attendance and potential solutions thereof. At a programme level, more dynamic, comprehensive, innovative, and multidisciplinary approaches could help retain HIV-infected children and adolescents in care and these require evaluation and then scale-up if successful.

### Table 2

| Characteristics | Unadjusted hazard ratio (95% CI) | \( P \) | Adjusted hazard ratio (95% CI) (N = 94) | \( P \) |
|-----------------|---------------------------------|------|--------------------------------------|------|
| Female          | 1                               |      | 1                                    |      |
| Male            | 1.0 (0.6–1.3)                   | .87  | 1                                    |      |
| Age group at ART initiation |                      |      | 1                                    |      |
| <18 mo          | 1                               |      | 1                                    |      |
| 18–59 mo        | 1.5 (0.8–2.9)                   | .18  | 5.16 (1.7–15.3)                      | .003 |
| ≥60 months      | 2.0 (1.1–8.2)                   | .10  | 8.3 (1.6–41.9)                       | .010 |
| WHO stage at ART initiation |                  |      |                                       |      |
| II              | 1                               |      | 1                                    |      |
| III/N           | 0.6 (0.3–1.2)                   | .14  |                                       |      |
| Immune suppression at ART initiation |                  |      |                                       |      |
| Normal          | 1                               |      |                                       |      |
| Moderate        | 1.1 (0.5–2.6)                   | .81  |                                       |      |
| Severe          | 0.9 (0.4–2.4)                   | .91  |                                       |      |
| Plasma viral load at ART initiation in copies/mL |                  |      |                                       |      |
| <10,000         | 1                               |      |                                       |      |
| 10,000–100,000  | 0.4 (0.1–1.7)                   | .20  |                                       |      |
| ≥100,000        | 0.92 (0.3–2.7)                  | .91  |                                       |      |
| ART regimen at initiation |                  |      |                                       |      |
| EFV and NVP-based | 1                        |      |                                       |      |
| PI-based        | 1.8 (1.1–3.2)                   | .04  |                                       |      |
| Ever missed clinic visit since ART initiation |                  |      |                                       |      |
| No              | 1                               |      | 1                                    | .001 |
| Yes             | 7.2 (3.8–13.8)                  | <.01 | 11.0 (4.4–28.1)                      |      |
| Ever had elevated viral load (>1000 copies/mL) after ART initiation |          |      | 1                                    |      |
| No              | 1                               |      |                                       |      |
| Yes             | 0.4 (0.1–1.4)                   | .15  | 0.2 (0.04–0.8)                       | .022 |
| Regimen switch  | 1                               |      |                                       |      |
| No              | 0.2 (0.1–1.4)                   | .09  |                                       |      |
| Age at last visit |                      |      |                                       |      |
| < 5 y           | 1                               |      |                                       |      |
| ≥ 5 y           | 0.33 (0.16–0.69)                | .01  |                                       |      |
| WHO clinical stage at last visit |                  |      |                                       |      |
| II              | 1                               |      |                                       |      |
| III/N           | 0.32 (0.11–0.94)                | .04  |                                       |      |

\(\text{ART} = \text{antiretroviral treatment}, \text{EFV} = \text{efavirenz}, \text{NVP} = \text{nevirapine}, \text{PI} = \text{protease inhibitor (lopinavir/ritonavir)}\).
Methodology: Nomathemba Chandiwana, Shobna Sawry, Elizabeth Kachingwe.

Project administration: Nomathemba Chandiwana, Matthew Chersich, Lee Fairlie.

Software: Nomathemba Chandiwana, Elizabeth Kachingwe.

Visualization: Nomathemba Chandiwana.

Writing – original draft: Nomathemba Chandiwana, Shobna Sawry, Matthew Chersich, Lee Fairlie.

Writing – review & editing: Nomathemba Chandiwana, Shobna Sawry, Elizabeth Kachingwe, Matthew Chersich, Lee Fairlie.

Author contributions

Conceptionalization: Nomathemba Chandiwana, Bulelani Makhathini, Lee Fairlie.

Data curation: thini, Lee Fairlie.

Formal analysis: Nomathemba Chandiwana, Shobna Sawry, Matthew Chersich, Elizabeth Kachingwe.

Investigation: Nomathemba Chandiwana.

Methodology: Nomathemba Chandiwana, Shobna Sawry, Elizabeth Kachingwe.

Project administration: Nomathemba Chandiwana, Matthew Chersich, Lee Fairlie.

Software: Nomathemba Chandiwana.

Visualization: Nomathemba Chandiwana.

Writing – original draft: Nomathemba Chandiwana, Shobna Sawry, Matthew Chersich, Lee Fairlie.

Writing – review & editing: Nomathemba Chandiwana, Shobna Sawry, Elizabeth Kachingwe, Matthew Chersich, Lee Fairlie.

References

[1] UNAIDS. Global report: UNAIDS report on the global AIDS epidemic. Geneva, Switzerland 2013.
[2] Judd A, Doerholt K, Tsekey PA, et al. Morbidity, mortality, and response to treatment by children in the United Kingdom and Ireland with perinatally acquired HIV infection during 1996–2006: planning for teenage and adult care. Clin Infect Dis 2007;45:198–24.
[3] Davies MA, Gibb D, Turkova A. Survival of HIV-1 vertically infected children. Curr Opin HIV AIDS 2016;11:435–64.
[4] Ferrand RA, Corbett EL, Wood R, et al. AIDS among older children and adolescents in Southern Africa: projecting the time course and magnitude of the epidemic. AIDS 2009;23:2039–46.
[5] Davies MA, Phiri S, Wood R, et al. Temporal trends in the characteristics of children at antiretroviral initiation in four Southern African countries: the IeDEA-SA Collaboration. PLoS One 2013;8(8):e70137.
[6] Woldebenet SA, Jackson D, Goga AE, et al. Missed opportunities for early infant HIV diagnosis: results of a national study in South Africa. J Acquir Immune Defic Syndr 2015;68:26–32.
[7] Sengayi M, Dwane N, Marinda E, et al. Predictors of loss to follow-up among children in the first and second years of antiretroviral treatment in Johannesburg, South Africa. Global Health Action 2013;6:19248.
[8] Beaum K, Kabue MM, McCollum ED, et al. Inadequate coordination of maternal and infant HIV services detrimentally affects infant diagnosis outcomes in Lilingwe, Malawi. J Acquir Immune Defic Syndr 2011;56:122–8.
[9] Vermund SH, Blevins M, Moon TD, et al. Poor clinical outcomes for HIV infected children on antiretroviral therapy in rural Mozambique: need for program quality improvement and community engagement. PLoS One 2014;9(9):e110116.
[10] Davies MA, May M, Bolton-Moore C, et al. Prognosis of children with HIV-1 infection starting antiretroviral therapy in Southern Africa: a collaborative analysis of treatment programs. Pediatr Infect Dis J 2014;33:608–16.
[11] Britstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet 2006;367:817–24.
[12] Fener A, Brinkhof MW, Kreier O, et al. Early mortality and loss to follow-up in HIV-infected children starting antiretroviral therapy in Southern Africa. J Acquir Immune Defic Syndr 2010;54:524–32.
[13] Britstein P, Katschke A, Shen C, et al. Retention of HIV-infected and HIV-exposed children in a comprehensive HIV care programme in Western Kenya. Trop Med Int Health 2010;15:833–41.
[14] Leroy V, Malaste K, Rabie H, et al. Outcomes of antiretroviral therapy in children in Asia and Africa: a comparative analysis of the IeDEA pediatric multicentre collaboration. J Acquir Immune Defic Syndr 2013;62:208–19.
[15] Abuogi LL, Smith C, McFarland EJ. Retention of HIV-infected children in the first 12 months of anti-retroviral therapy and predictors of attrition in resource limited settings: a systematic review. PLoS One 2016;11:e0156506.
[16] Muguve MM, Logu PK, Wilig JH, et al. Missed visits and mortality among patients establishing initial outpatient HIV treatment. Clin Infect Dis 2009;49:248–56.
[17] Brennan AT, Maskew M, Sanne I, et al. The importance of clinic attendance in the first six months on antiretroviral treatment: a retrospective analysis at a large public sector HIV clinic in South Africa. J Int AIDS Soc 2010;13:49.
[18] Nyandiko W, Vreeman R, Liu H, et al. Nonadherence to clinic appointments among HIV-infected children in an ambulatory care program in western Kenya. J Acquir Immune Defic Syndr V 63 2013; e49–55.
[19] UNAIDS. 90-90-90 - An Ambitious Treatment Target to Help End the AIDS Epidemic. Geneva, Switzerland 2014.
[20] UNAIDS. Ambitious Treatment Targets: Writing the Final Chapter of the AIDS Epidemic. Geneva, Switzerland 2014.
[21] Rees H, Delany-Morotew S, Scorgie F, et al. At the heart of the problem: health in Johannesburg’s Inner-City. BMC Public Health 2017;17:1–6.
[22] National Department of Health. The South African Antiretroviral Therapy Treatment Guidelines 2010. Pretoria, South Africa 2010.
[23] National Department of Health Guidelines for Management of HIV in Children. Pretoria, South Africa 2004.
[24] WHO. Antiretroviral therapy of HIV infection in infants and children. Towards universal access: recommendations for a public health approach. Geneva, Switzerland 2010.
[25] Davies MA, Keiser O, Technau K, et al. Outcomes of the South African National Antiretroviral Treatment Programme for children: the IeDEA Southern Africa collaboration. S Afr Med J 2009;99:730–7.
[26] Turker M, Davies MA, Mapani MK, et al. Outcomes of infants starting antiretroviral therapy in Southern Africa, 2004–2012. J Acquir Immune Defic Syndr 2015;69:593–601.
[27] Marston M, Bequet R, Zaba B, et al. Net survival of perinatally and postnatally HIV-infected children: a pooled analysis of individual data from sub-Saharan Africa. Int J Epidemiol 2011;40:385–96.
[28] Tene G, Lahuerta M, Teasdale C, et al. High retention among HIV-infected children in Rwanda during scale-up and decentralization of HIV care and treatment programs, 2004 to 2010. Pediatr Infect Dis J 2013;32:e341–7.
[29] Kabue MM, Buck WC, Wanless SR, et al. Mortality and clinical outcomes in HIV-infected children on antiretroviral therapy in Malawi, Lesotho, and Swaziland. Pediatrics 2012;130(6):e191–9.
[30] Penazzato M, Prendergast A, Tierney J, et al. Effectiveness of antiretroviral therapy in HIV-infected children under 2 years of age. Cochrane Database Syst Rev 2012;7:Cd004772.
[31] Bigna JJ, Noubiap JJ, Plottel CS, et al. Factors associated with non-adherence to scheduled medical follow-up appointments among Cameroonian children requiring HIV care: a case-control analysis of the usual-care group in the MORE CARE trial. Infect Dis Poverty 2014;3:44.
[32] UNAIDS/HEF Factsheet 2015. 2015/UNAIDS.
[33] Violanti A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med 2008;359:2333–44.
[34] McHugh G, Simms V, Daju E, et al. Clinical outcomes in children and adolescents initiating antiretroviral therapy in decentralized healthcare settings in Zimbabwe. J Int AIDS Soc 2017;20:21843.
[35] Fairall L, Bachmann MO, Lombard C, et al. Task shifting of antiretroviral treatment from doctors to primary-care nurses in South Africa (STRETCH): a pragmatic, parallel, cluster-randomised trial. Lancet 2012;380:889–98.
[36] Murray KR, Dulli LS, Ridgeway K, et al. Improving retention in HIV care among adolescents and adults in low- and middle-income countries: a systematic review of the literature. PLoS One 2012;12:e0184879.
[37] Harries AD, Zachariah R, Lawn SD, et al. Strategies to improve patient retention on antiretroviral therapy in sub-Saharan Africa. Trop Med Int Health 2010;15(suppl 1):70–5.
[38] Phelps BR, Ahmed S, Amzel A, et al. Linkage, initiation and retention of children in the antiretroviral therapy cascade: an overview. AIDS 2013;27(supp 2):S207–213.
[39] Ahmed S, Kim MH, Sugandhi N, et al. Beyond early infant diagnosis: case finding strategies for identification of HIV-infected infants and children. AIDS 2013;27(suppl 2):S235–245.

[40] Martin S, Elliott-DeSorbo DK, Wolters PL, et al. Patient, caregiver and regimen characteristics associated with adherence to highly active antiretroviral therapy among HIV-infected children and adolescents. Pediatr Infect Dis J 2007;26:61–7.

[41] Castro M, Gonzalez I, Perez J. Factors related to antiretroviral therapy adherence in children and adolescents with HIV/AIDS in Cuba. MEDICC Rev 2015;17:35–40.

[42] Grimsrud A, Barnabas RV, Ehrenkranz P, et al. Evidence for scale up: the differentiated care research agenda. J Int AIDS Soc 2017;20(suppl 4):22024.

[43] Mayosi BM, Lawn JE, van Niekerk A, et al. Health in South Africa: changes and challenges since 2009. Lancet 2012;380:2029–43.

[44] le Roux K, le Roux I, Mbewu N, et al. The role of community health workers in the re-engineering of primary health care in Rural Eastern Cape. S Afr Fam Pract 2015;57:116–20.

[45] Nsibande D, Doherty T, Ilumba P, et al. Assessment of the uptake of neonatal and young infant referrals by community health workers to public health facilities in an urban informal settlement, KwaZulu-Natal, South Africa. BMC Health Serv Res 2013;13:47.

[46] Marcos Y, Phelps BR, Bachman G. Community strategies that improve care and retention along the prevention of mother-to-child transmission of HIV cascade: a review. J Int AIDS Soc 2012;15:17394.