Late antiretroviral therapy initiation and associated factors among children on antiretroviral therapy at University of Gondar Comprehensive Specialized Hospital, Gondar, Northwest Ethiopia: a cross-sectional study

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Abstract

Objective: Highly active antiretroviral therapy reduces HIV related morbidity and mortality dramatically. Despite this fact, late ART initiation poses poor treatment outcome in pediatrics. However, the information is scarce in Ethiopia. Therefore, the study was aimed at determining the burden of late ART initiation and its associated factors among children on ART. Cross-sectional study was conducted among 422 children selected by simple random sampling. Patient charts were reviewed using pretested and structured data abstraction tool. Binary logistic regression model was fitted.

Results: A total of 402 child records with a completeness rate of 95.3% were included. The overall proportion of late antiretroviral therapy initiation among children on antiretroviral therapy was 53.2% (95% CI 48.5–58.4%). Under-5 years of age [AOR: 2.165 (95% CI 1.341, 3.495)], rural residence [AOR: 1.825 (95% CI 1.052, 3.166)], taking non-ART medication [AOR: 2.237 (95% CI 1.212, 4.130)], past opportunistic infection [AOR: 2.548 (95% CI 1.554, 4.178)], unmarried caregiver [AOR: 1.618 (95% CI 1.023, 2.559)], male caregiver [AOR: 1.903 (95% CI 1.026–3.527)] and null ANC visit [AOR: 1.721 (95% CI 1.077, 2.752)] were significantly associated factors. There is high burden of late ART initiation in children. Thus, focus should be started from pregnancy.

Keywords: Children, Ethiopia, Late ART initiation, University of Gondar Comprehensive Specialized Hospital

Introduction

Highly active antiretroviral therapy (HAART) is a combination of three or more antiretroviral drugs that substantially minimize HIV related morbidity and mortality [1]. However, late antiretroviral therapy (ART) initiation remains a major problem in the world, especially in low income countries [2]. It increases child morbidity, hospitalization and mortality [3]. Most children on ART faced treatment failure due to initiating ART at low CD4 count [4]. Nowadays, children on treatment encountered many challenges as in CD4 cell depletion, impaired CD4 recovery, increased mortality within a year of initiation, decreased life expectancy, and increased death at home before medical advice or ART initiation. These were due to high rates of late ART initiation [5, 6].

Despite progressive improvement in ART coverage, there is still high burden of late ART initiation in developing countries like 54.4% in Uganda [7, 8], 68.2% in South African [9], 48% in Mozambique [10] and 58.3% in Addis Ababa, Ethiopia [11].

Different strategies were employed to overcome it as in World Health Organization (WHO) frequently updated ART eligibility criteria [12]; but it remains high in developing countries [13]. In addition, shorter waiting time, supportive counseling and free charge prophylaxis were implemented. Nonetheless, it has not significantly
reduced yet. Moreover, it contravenes the 2020 Ethiopia's 90% ART coverage plan.

Late HIV diagnosis [14], being maternal orphan [15, 16], parental lower education and unemployment have highly determined late ART initiation [7] in children. Though, socio-demographic characteristics were clearly described in different literatures, clinical characteristics like HIV status of parents, year of initiation, relation to children and other treatment related characteristics were not clearly stated.

Furthermore, information on associated factors is scarce in the study area. Therefore, the study aimed to determine late ART initiation and its associated factors among children on ART. The study helps higher officials, managers and health policy makers to take appropriate measures. Furthermore, the findings of this study will serve as baseline for future researches.

Main text

Methods and materials

Study design, period and setting

An institution-based cross-sectional study was conducted from March, 28/2017 to April, 28/2017 at University of Gondar Comprehensive Specialized Hospital (UoGCSH) ART clinic.

Population and selection criteria

All HIV positive children <15 years who had been enrolled in HAART at UoGCSH ART clinic from January 1st 2007 to December 30th 2016 were the study population. Complete child records available at patient database were included in the study.

Sampling technique and procedures

Totally, 617 children were enrolled in ART from January 1st 2007 to December 30th 2016. About 422 child records were taken by simple random sampling using computer generated random numbers. Finally, 402 charts were fulfilled the inclusion criteria and analyzed in the study.

Data collection tools and procedures

Data were collected by three ART expert nurses using data extraction tool.

Operational definitions

Late ART initiation (YES/NO): initiation of ART at CD4 count or percent of <250 cells/mm³ for children ≥ 5 years; <15% (350 cells/mm³) total lymphocyte count for children 3–5 years; below 20% (750 cells/mm³) for 12–35 months children and below 25% (1500 cells/mm³) for children 11 months and below [7, 17]; Or initiate ART at WHO stage 3 or 4 [6, 10].

Data quality control

One day training was given for data collectors. Pre-test was done at UoGCSH on 22 child records. Data retrieval was monitored and checked daily by investigators. Data were entered using EPI Info-7 which reduces data entry errors.

Data processing and analysis

We used SPSS-20 for data analysis. Standard deviations, means, medians and inter-quartile ranges were used for data summarization. Texts and tables were used for data presentation. Variables with P-value <0.2 were entered into multivariable analysis. Logistic regression model was fitted. Finally, variables with P-value <0.05 were considered statistically significant with late ART initiation.

Results

Socio-demographic characteristics of children on ART

A total of 402 child records with completeness rate of 95.3% were included in the study. The mean age of children at ART initiation was 74.2 months in that 17 (4.2%) were < 11 months, 73 (18.2%) were from 12 to 35 months, 80 (19.9%) were from 36 to 60 months and 232 (57.7%) were above 5 years. From all children on ART, 208 (51.7%) were females by sex, 308 (76.6%) were urban by residence and 327 (81.3%) were living with their parents.

Baseline socio-demographic characteristics of caregivers’ of children on ART

From all caregivers, 81.8% were females, 84.8% were under 40 years, 70.9% of them were mothers, 62.2% of both parents are alive, about 84.1% were unemployed, and 50.7% were married; 52% and 51.1% of caregiver’s HIV status were unknown and HIV positive on ART respectively (Table 1).

Baseline clinical and treatment related characteristics of children on ART

From all children on ART, 72.4% were stayed below 6 months from test to enrollment to care, 74.4% had no other medication than ART, 53.2% had no past opportunistic infection before/at enrollment to care, 83.6% had no any TB treatment history, 80.6% had no any chronic diseases, 33.8% had WHO stage I during HIV test confirmed; whereas 42.7% had WHO stage III and IV at the time of ART initiation and 79.8% were initiated ART with CD4 count >250 cells/mm³; whereas 50.7% were initiated with CD4 percent >25% (Table 2).

Late ART initiation among children on ART

The overall proportion of late ART initiation among 402 children on ART was 53.2% (95% CI 48.5–58.4%). Of these, 47.2% were by WHO stage III and IV only, 71
Factors associated with late ART initiation among children on ART

In the multivariable analysis, age of children, child residence, any non-ART medication, past opportunistic

Table 1 Baseline socio-demographic characteristics of caregivers for children on ART at University of Gondar Comprehensive Specialized Hospital, 2017 (n = 402)

| Variables                           | Frequency (n) | Percentage (%) |
|-------------------------------------|---------------|----------------|
| Age                                 |               |                |
| < 40 years                          | 341           | 84.8           |
| ≥ 40 years                          | 61            | 15.2           |
| Sex                                 |               |                |
| Male                                | 73            | 18.2           |
| Female                              | 329           | 81.8           |
| Marital status                      |               |                |
| Married                             | 204           | 50.7           |
| Unmarried                           | 198           | 49.3           |
| Occupation                          |               |                |
| Employed                            | 64            | 15.9           |
| Unemployed                          | 338           | 84.1           |
| Relation to child                   |               |                |
| Mother                              | 285           | 70.9           |
| Father                              | 41            | 10.2           |
| Other relative                      | 76            | 18.9           |
| Antenatal history                   |               |                |
| No                                  | 133           | 46.7           |
| Yes                                 | 152           | 53.3           |
| PMTCT                               |               |                |
| No                                  | 123           | 77.4           |
| Yes                                 | 36            | 22.6           |
| Parental survival status            |               |                |
| Mother alive only                   | 77            | 19.1           |
| Father alive only                   | 30            | 7.5            |
| Both alive                          | 250           | 62.2           |
| Neither alive                       | 45            | 11.2           |
| HIV status of caregiver             |               |                |
| Positive                            | 174           | 43.3           |
| Negative                            | 19            | 4.7            |
| Unknown                             | 209           | 52             |
| Caregiver on ART                    |               |                |
| No                                  | 85            | 48.9           |
| Yes                                 | 89            | 51.1           |

n = sample size included in the analysis

(33.2%) were by both WHO staging and CD4 count/percentage, and 42 (19.6%) were by CD4 count/percent only. The median CD4 count and percentage at initiation of ART were 415.5 cells/mm³ (IQR: 363–446) and 26% (IQR: 23–27) respectively. Over the years, the proportion of late ART initiation decreases inconsistently from 53.6% (2007–2009) to 44.4% (2015–2016).

Table 2 Baseline clinical and treatment related characteristics of children on ART at University of Gondar Comprehensive Specialized Hospital, 2017 (n = 402)

| Variables                              | Frequency (n) | Percentage (%) |
|----------------------------------------|---------------|----------------|
| Duration between HIV test confirmed and enrollment |               |                |
| < 6 months                             | 291           | 72.4           |
| 6–12 months                            | 46            | 11.4           |
| > 12 months                            | 65            | 16.2           |
| Any medication before ART initiation   |               |                |
| No                                     | 299           | 74.4           |
| Yes                                    | 103           | 25.6           |
| Past OP at enrollment                  |               |                |
| No                                     | 214           | 53.2           |
| Yes                                    | 188           | 46.8           |
| Cotrimoxazole prophylaxis              |               |                |
| No                                     | 42            | 10.4           |
| Yes                                    | 360           | 89.6           |
| INH prophylaxis                        |               |                |
| No                                     | 338           | 84.1           |
| Yes                                    | 64            | 15.9           |
| TB treatment history                   |               |                |
| No                                     | 336           | 83.6           |
| Yes                                    | 66            | 16.4           |
| Chronic disease                        |               |                |
| No                                     | 324           | 80.6           |
| Yes                                    | 78            | 19.4           |
| Immunization status                    |               |                |
| Appropriate for age                    | 323           | 80.3           |
| Not appropriate for age                | 67            | 16.7           |
| Not Immunized                          | 12            | 3              |
| WHO stage at HIV test                  |               |                |
| I                                      | 136           | 33.8           |
| II                                     | 133           | 33.1           |
| III                                    | 98            | 24.4           |
| IV                                     | 35            | 8.7            |
| Functional status (≥ 5 years)          |               |                |
| Working                                | 120           | 47.8           |
| Ambulatory/bedridden                   | 131           | 52.2           |
| Developmental milestone (< 5 years)    |               |                |
| Appropriate ranges for age             | 116           | 76.8           |
| Developmental delay/regression         | 35            | 23.2           |
| CD4 count (≥ 5 years)                  |               |                |
| < 250 cells/mm³                        | 50            | 20.2           |
| ≥ 250 cells/mm³                       | 198           | 79.8           |
| CD4 percentage (≤ 5 years)             |               |                |
| < 15%                                  | 37            | 24.0           |
| 15–25%                                 | 39            | 25.3           |
| > 25%                                  | 78            | 50.7           |
| WHO stage at ART initiation            |               |                |
| I                                      | 94            | 23.4           |
| II                                     | 136           | 33.8           |
| III                                    | 130           | 32.3           |
infection, antenatal history, sex and marital status of caregiver were significantly associated with late ART initiation.

The odds of being late initiated for ART among children < 5 years were 2 times more likely [AOR: 2.165 (95% CI 1.341–3.495)] as compared to those > 5 years of age.

The odds of being late ART initiated among rural children were almost two times more likely [AOR: 1.825 (95% CI 1.052–3.166)] as compared to urban residents.

The odds of late ART initiation among children experienced past opportunistic infection before ART initiation were 2.5 times more likely [AOR: 2.548 (95% CI 1.554–4.178)] as compared to those who had not.

Besides, the odds of being late ART initiated among children who took medication before ART initiation was 2 times more likely [AOR: 2.237 (95% CI 1.212–4.130)] as compared to those who had not taken.

Additionally, the odds of late ART initiation among children from male caregivers were nearly 2 times more likely [AOR: 1.903 (95% CI 1.026–3.527)] as compared to children from female caregivers.

Moreover, the odds of late ART initiation among children from unmarried caregivers were 1.6 times more likely [AOR: 1.618 (95% CI 1.023–2.559)] as compared to children from married caregivers.

Finally, children from mothers who had no ANC follow up increases the odds of late ART initiation by 1.7 times [AOR: 1.721 (95% CI 1.077–2.752)] as compared to children from mothers who attended ANC (Table 3).

**Discussion**

In this study, the overall proportion of late ART initiation among children on ART was 53.2% (95% CI 48.5–58.4%). It is in line with studies of Uganda 54.4% [7], Kenya 53% [18] and Addis Ababa, Ethiopia 58.3% [11]. Conversely, the finding is higher than a study in Mozambique 48% [10]. This discrepancy might be explained by large sample size and done in district hospital using follow up study in Mozambique.
It is due to high transportation cost, inaccessibility of ART service and tedious long distance traveling to reach health facilities.

Those children who took medication before ART were two times more likely to initiate ART lately as compared to those who don't. A Zambian study indicates that concurrent treatment like TB was associated with late ART initiation [19] since it causes fear of pill burden and advanced disease.

Similarly, those children who had a past opportunistic infection before or at enrollment were nearly two and half times more likely to initiate ART lately as compared to those who didn't have it. It is supported by a study from South Africa [9] in that the principle of treating opportunistic infection first may delay initiation of ART.

The odds of late ART initiation among children from unmarried caregivers were nearly two times as compared to children from married caregiver. It is supported by a Mozambique study in that being single was significantly associated with late ART initiation [23], since married caregivers were more stable and brought their children early for HIV testing and ART initiation.

The odds of late ART initiation among children from male caregiver were two times higher as compared to those from female caregiver. Studies of Kenya and Zimbabwe [24, 25] supported this finding in that male caregiver had extra activities out of home and engaged to run out economic affairs in the household than to carryout child rearing duties. Additionally, females have a chance of access to information about early diagnosis and initiation of ART for their children during family planning service, vaccination and antenatal follow up.

The odds of late ART initiation among children born from mothers who have null ANC visit were nearly two times more likely as compared to those from fully attended mothers. It is supported with an Ethiopia study [26] in that mothers who had antenatal follow up have excellent chance of learning about mother-to-child transmission of HIV, its early diagnosis and initiation of ART for their children.

### Implications for clinical practice and research

This finding indicates that emphasis should be given for children who are under-5 years, rural residents, take any medicine before ART, experience past opportunistic infections, and for those from unmarried caregivers, male caregivers and mothers with null ANC visits. In line with this, researchers need to development and implement a risk prediction tool for identifying children with HIV that are likely to start ART lately. Moreover, clinicians should
have a high index of suspicion in children with the aforementioned significant factors.

Conclusion
There is high burden of late ART initiation among children on ART at UoGCSH. Age of children below 5 years, rural residence, any medication before ART initiation, presence of past opportunistic infection, null ANC follow up, unmarried and male caregivers were factors associated with late ART initiation among children on ART.

Limitation
Since we used secondary data, variables like disclosure status, income and educational status were missed due to data incompleteness. Additionally, psychosocial issues of caregiver and children haven’t been addressed with this study.

Abbreviations
AIDS: acquired immune deficiency syndrome, ANC: antenatal care; AOR: adjusted odds ratio; ART: anti-retroviral therapy; CD4: cluster differentiation 4; COR: crude odds ratio; HAART: highly active anti-retroviral therapy; HIV: human immunodeficiency virus; INH: isonicotinic acid hydrazide; OIs: opportunistic infections; PMTCT: prevention of mother to child transmission; TB: tuberculosis; UoGCSH: University of Gondar Comprehensive Specialized Hospital; WHO: World Health Organization.

Authors’ contributions
GMB: conceived the idea, wrote the proposal, and participated during data collection. TB: tuberculosis; UoGCSH: University of Gondar Comprehensive Specialized Hospital; WHO: World Health Organization.

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Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
Data will be made available to readers upon a reasonable request to the corresponding author.

Consent for publication
For this article, there is no individual human participant in that the consent for publication is not applicable here.

Ethics approval and consent to participate
Ethical clearance was obtained from the Institutional Review Board (IRB) of University of Gondar on behalf of the Ethical Review Committee of School of Nursing. Permission letter was obtained from University of Gondar Comprehensive Specialized Hospital Management. Information in the data abstraction tool was non-identifying and anonymous. The files of entered data in the software and the final result of this study were tied with strong passwords. The overall confidentiality and privacy of the information was kept safe throughout the whole process of the research work.

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References
1. Poudel KC, Buchanan DR, Poudel-Tandukar K. Delays in antiretroviral therapy initiation among HIV-positive individuals: results of the positive living with HIV study. Glob Health Action. 2016;9:13500.
2. Kiiribubunakul S, Boetiger D, Lee MP, Omar SF, Tanuma J, Ng OT, et al. Trends of CD4 cell count levels at the initiation of antiretroviral therapy over time and factors associated with late initiation of antiretroviral therapy among Asian HIV-positive patients. J Int AIDS Soc. 2014;17(11):18804.
3. Ford N, Kranzer K, Hilderbrand K, Jouquet G, Goemaere E, Vlahakis N, et al. Early initiation of antiretroviral therapy and associated reduction in mortality, morbidity and defaulting in a nurse-managed, community cohort in Lesotho. AIDS. 2010;24(17):2645–50.
4. Bacha T, Tilahun B, Worku A. Predictors of treatment failure and time to detection and switching in HIV infected Ethiopian children receiving first line anti-retroviral therapy. BMC Infect Dis. 2012;12(1):197.
5. Lewis J, Walker AS, Castro H, De Rossi A, Gibb DM, Giaquinto C, et al. Age and CD4 count at initiation of antiretroviral therapy in HIV-infected children: effects on long-term T-cell reconstitution. J Infect Dis. 2012;205(4):548–56.
6. Zanoni BC, Phungula T, Zanoni HM, France H, Feeney ME. Risk factors associated with increased mortality among HIV infected children initiating antiretroviral therapy (ART) in South Africa. PLoS ONE. 2011;6(7):e22706.
7. Nabukenya JMS. Outcomes of late initiation of antiretroviral therapy in Ugandan-HIV-infected children treated at Mildmay Jajja home: University of Limpopo (Medunsa Campus); 2011.
8. Boender TS, Sigaloff KC, Kayiwa J, Musime V, Calis JC, Hamers RL, et al. Barriers to initiation of pediatric HIV treatment in Uganda: a mixed-method study. AIDS Res Treat. 2012;2012:817506.
9. Feucht U, Kinzer M, Kruger M. Reasons for delay in initiation of antiretroviral therapy in a population of HIV-infected South African children. J Trop Pediatr. 2007;53(6):398–402.
10. Vermund SH, Blevins M, Moon TD, José E, Molina L, Tique JA, 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(10):e101116.
11. Asfawesen G, Solomie J, Birsat T, Berhanu G, Mebratu B, Rahlenbeck S. Outcome in a paediatric cohort receiving ART in Addis Abeba, Ethiopia. Acta Paediatr. 2011;100(8):1164–7.
12. Lahueria M, Ue F, Hoffman S, Elul B, Kulkarni SG, Wu Y, et al. The problem of late ART initiation in sub-Saharan Africa: a transient aspect of scale-up or a long-term phenomenon? J Health Care Poor Underserved. 2013;24(1):359.
13. Nash D, Wu Y, Elul B, Hoos D, El Sadr W. Program-level and contextual-level determinants of low-median CD4+ cell count in cohorts of persons initiating ART in eight sub-Saharan African countries. AIDS. 2011;25(12):1523.
14. Wolbers M, Bucher H, Furrer H, Rickenbach M, Cavassini M, Weber R, et al. Delayed diagnosis of HIV infection and late initiation of antiretroviral therapy in the Swiss HIV Cohort Study. HIV Med. 2008;9(6):397–405.
15. Mokgatle MM, Madiba S. The burden of disease on HIV-infected orphaned and non-orphaned children accessing primary health facilities in a rural district with poor resources in South Africa: a cross-sectional survey of primary caregivers of HIV-infected children aged 5–18 years. Infect Dis Poverty. 2015;4(1):18.

16. Mokgatle MM, Abasho DC. Treatment outcomes of antiretroviral therapy among pediatric patients in a Zewditu Memorial Hospital, Addis Ababa, Ethiopia. Pula Botswana J Afr Stud. 2016;30(1):139–49.

17. Minister of Health. Government of Lesotho. National guidelines on the use of antiretroviral therapy for HIV prevention and treatment. 4th ed. 2014.

18. Lahuerta M, Lima J, Elul B, Okamura M, Alvim MF, Nuwagaba-Biribonwoha H, et al. Patients enrolled in HIV care in Mozambique: baseline characteristics and follow-up outcomes. J Acquir Immune Defic Syndr. 2011;58(3):e75.

19. Sutcliffe CG, van Dijk JH, Muleka M, Munsanje J, Thuma PE, Moss WJ. Delays in initiation of antiretroviral therapy among HIV-infected children in rural Zambia. Pediatr Infect Dis J. 2016;35(4):e107–12.

20. Bolton-Moore C, Mubiana-Mbewe M, Cantrell RA, Chintu N, Stringer EM, Chi BH, et al. Clinical outcomes and CD4 cell response in children receiving antiretroviral therapy at primary health care facilities in Zambia. JAMA. 2007;298(16):1888–99.

21. Edmonds A, Yotebieng M, Lusiana J, Matumona Y, Kitetele F, Napravnik S, et al. The effect of highly active antiretroviral therapy on the survival of HIV-infected children in a resource-deprived setting: a cohort study. PLoS Med. 2011;8(6):e1001044.

22. Posse M, Meheus F, Van Asten H, Van Der Ven A, Baltussen R. Barriers to access to antiretroviral treatment in developing countries: a review. Trop Med Int Health. 2008;13(7):904–13.

23. Lahuerta M, Lima J, Nuwagaba-Biribonwoha H, Okamura M, Alvim MF, Fernandes R, et al. Factors associated with late antiretroviral therapy initiation among adults in Mozambique. PLoS ONE. 2012;7(5):e37125.

24. Geng EH, Hunt PW, Dier O, Kimayo S, Sorni GR, Okong P, et al. Trends in the clinical characteristics of HIV-infected patients initiating antiretroviral therapy in Kenya, Uganda and Tanzania between 2002 and 2009. J Int AIDS Soc. 2011;14(1):46.

25. Makumbe B. Factors associated with paediatric ART uptake in Bindura and Guruve districts, Zimbabwe 2015-2016.

26. Kebede B, Gebreyehu A, Jain S, Sun S, Haubrich R. Delay in early infant diagnosis and high loss to follow-up among infant born to HIV-infected women in Ethiopia. World J AIDS. 2014;4(04):402.